An Analysis On The Development of Bulk Pharmaceutical Industry In China Mainland and Taiwan

A Thesis

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By

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Declaration

I hereby declare that this thesis summarizes my own work carried out since my registration for the degree of master of Philosophy in July, 1996, and that is has not been previously included in a thesis, dissertation or report presented to this or any other institution for a degree, diploma, or other qualification.

Liu, Wen-Ching

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Chapter 1 Introduction

The pharmaceutical industry has been booming in the 20th century. It is considered to be related to the social welfare. Although it is part of the specialty chemical industries, it has direct connection with human health and life extension. Therefore, it is not influenced by the economies. The operations, marketing and product development of pharmaceutical industry are different from the other industries because pharmaceutical products emphasize on their safety, efficacy, patent protection and trade marks. The characteristics of pharmaceutical industry are as follows:

1. *A "High quality software" industry*

   Like telecommunication industry, it requires creativity, tremendous knowledge and information in order to produce pharmaceutical products. Therefore, it can be considered as another "High quality software" industry.

2. *Dependence on the government policies*

   The success of pharmaceutical industry is somewhat related to the government medical policies. Especially after the launch of national health insurance policy and the impact of upcoming free import of pharmaceuticals, how government supports the pharmaceutical industry becomes really important for its growth.

3. *Monitored by the government health agency*

   Because pharmaceuticals are directly related to the human health, their safety, quality, production and sales are highly regulated by the government health agency in order to protect the people.

4. *High risk business*

Innovation is the driving force for the development of pharmaceutical industry. New drug discovery requires lots of money and is time consuming. Moreover, the return on investment is not guaranteed. Although making generic drug would require less time and money than developing a new drug, oftentimes the market price dramatically drops because of patent expiration and intense competition from other generic makers.

5. *Research involves different high-tech disciplines*

New drug development is usually for the treatment of diseases with unmet medical needs or for the improvement of current drugs. It does not matter whether it is new chemical entity, new use or new process, all research involves organic chemistry, chemical engineering, biochemistry, pharmacology, physiology, toxicology, pathology, and clinical studies.

6. *Monopoly of worldwide market*

Because of the patent protection, a pharmaceutical company that develops a new drug can monopolize the worldwide market through its worldwide sale forces. Even after the new drug patent expired and its generic drugs introduced, the original new drug developing company usually still has the market advantage and high profit due to the product's trade mark image. However, for the next five years, because of the health insurance cost containment policy in each country and the general acceptance of generic drugs by consumers, it is predicted that the generic drug market will grow 14% annually.

7. *Production by small quantities but with many items*

Currently there are over 4000 pharmaceuticals with over 1000 in common use. Usually, the production quantity of each drug is small except some antibiotics and vitamins.

Therefore, most of the bulk pharmaceutical companies are using multi-purpose production facilities to produce several bulk drugs. Recently, in order to lower the production cost of bulk drugs because of the pressure of drug cost containment policy, bulk drug production has gradually changed to global contract manufacturing. Also, pharmaceutical companies like to market many items based on different dosage forms from the same bulk drug.

Generally speaking, pharmaceutical industry includes: bulk drug, western medicine, and Chinese medicine. From the up-, middle-, and down-stream point of view, the structure of pharmaceutical industry is as follows:

Up-stream: Materials for preparation of pharmaceuticals. It includes natural products and chemicals.

Middle-stream: Bulk drug and herbal material. Based on the source, different starting material has different production methods. For example, if it is from the natural products, the main production technologies involve extraction, separation and purification. If it is from the chemicals, the production technologies include organic synthesis and purification.

Down-stream: The bulk drug or herbal material is formulated to different dosage forms such as oral tablets or capsules, oral liquids, topical ointments or creams, and injectables in order to be administered to the patients.

Chapter 2 Worldwide Bulk Pharmaceutical Markets

Section 1 Worldwide Pharmaceutical Markets

1. The merger trend of multinational companies

After multinational pharmaceutical companies started the merger in 1989, it has since shaken up the whole pharmaceutical industry. It was predicted that because of the keen competition, there will be only the largest twenty mega companies which can survive eventually. This merger trend will cause revolutional change of the global pharmaceutical industry. For example, in 1995, Glaxo bought Wellcome with US$ 15 billion; Hoechst bought Marion Merrell Dow with US$ 7.1 billion; and Swedish company Pharmacia merged with US company Upjohn. In March 1996, Sandoz merged with Ciba Geigy to form Novartis.

2. The pharmaceutical industry has gradually out of the "Drug cost containment" nightmare

In early 1990's, each government issued "Drug cost containment" policy in order to balance the budgets. The pharmaceutical industry has had a long period of adjustment. However, from the growing market at present, it seems that the future growth potential is pretty bright.

In 1994, worldwide pharmaceutical market increased 8%, among them, prescription drugs grew 6% and OTC drugs rose 10%. The situation was improving compared with only 5% increase in 1993. If according to the district, major developed countries like US, United Kingdom and Germany grew 6~8%. Japan also had 2% increase. Worldwide pharmaceutical markets grew 8% up to September 1995. Among them, US had 10%, Spain had 11%, United Kingdom had 8%, Germany had 7%, and Japan had 9% increase.

3. Biopharmaceuticals are emerging

Sales of major biopharmaceuticals in 1995 were US$ 6.8 billion with the first three being Erythropoietin (US$ 1.65 billion), Heptatis B vaccine (US$ 1 billion), and Granulocyte Colony Stimulating FACTO (US$ 0.94 billion). It is estimated that by 2000, worldwide sales of biotechnology products will reach US$ 15 billion, accounted for 17% of the pharmaceuticals.

Section 2 The Pharmaceutical Market in Different Regions

1. The Pharmaceutical Market of US

The performance of pharmaceutical industry in US is on the top list among all the manufacturing industries. Also, US pharmaceutical industry is far ahead of those in other countries. The main reason is because of the successful result of new drug discovery. For the last thirty years, one fourth of the new drugs came from US. However, the cost of new drug development is continuously increasing. For example, in 1995, it increased 4.2 times from 1984. Also, new drug sales declined recently. The research-based US pharmaceutical companies have to cut down their R&D projects for the next 3~4 years in order to reduce the cost.

For the last five years the total employees of US pharmaceutical companies were about 184,000 people. Among them, 25% were manufacturing of bulk pharmaceuticals. The US-based pharmaceutical companies manufactured 25% of pharmaceuticals in Europe and 10% in Japan. Because of the incentive policies of Puerto Rico, many large US pharmaceutical companies had manufacturing facilities in Puerto Rico in order to be benefited by its tax incentives (country tax, island tax, tax exemption in US Tax Law, and profit tax exemption), rental incentives of industrial land, and other supports from Puerto Rico. Therefore, the global competitiveness of US pharmaceutical companies had increased tremendously.

Table 1 Investments of Foreign Pharmaceutical Companies in Puerto Rico

Employees	Companies	
>2500	• Baxter International	• Johnson & Johnson
1500~2499	• Abbott Laboratories Inc. • Warner-Lambert Co.	• Bristol-Myers Squibb
1000~1499	• American Cyanamid • Schering-Plough Co.	• American Home Products
500~999	• Allergan • Hoffmann-LaRoche • Pfizer • Upjohn Co.	• Eli Lilly and Co. • Monsanto • SmithKline Beecham

Source: Puerto Rico Economic Development Office

The pharmaceutical market of US in 1995~1996 had the following characteristics:

- The generic drug market was growing

US was No. 1 in pharmaceutical sales with 31% of the worldwide market share. However, because of the influence of private healthcare sector such as Pharmacy Benefit Management (PBM)* and Health Maintenance Organization (HMO), drug costs were under tremendous pressure to be lowered down. The cost of brand name drugs had already down due to "cost containment policy". On the other hand, market of less expensive OTC and generic drugs had been growing steadily. For example, the patent of antiulcer drug cimetidine (brand name: Tagamet) of SmithKlein Beecham (SKB) just went expired, its OTC and generic versions were immediately on the market. Likewise, drugs with the same mechanism of action (H2 antagonist), ranitidine (brand name: Zantac, Glaxo) and famotidine (brand name: Pepcid, Merck), also went into OTC and generic.

PBM provides a list of less expensive but equally effective drugs, after screened by experts, to medical care organizations for the reimbursement reference. This will protect the public from unnecessary medical costs. One who wants to join PBM has to pay the annual due according to the rules. One can also join various medical care programs based on each person's needs. For instance, diabetic patients may join a whole set program with diet control item in it.

- The private healthcare organizations HMO and PBM had completed the medical care cost containment plans

  Since Merck, Eli Lilly, and SKB merged with healthcare organizations in 1993~1994, the market share of PBM or HMO had increased from 21% in 1988 to 71% in 1996. On the contrary, the percentage of patients who paid the healthcare costs by themselves had decreased from 70% to 17%. The expand of healthcare sectors like PBM or HMO is expected. Another point is that mail order medical service has been becoming important.

According to US government's survey, the US generic drug market was US$ 4.9 billion in 1994. Comparing with US$ 4 billion in 1993, it increased dramatically. Generic drug market accounted for 16% of the US pharmaceutical market in 1994, a 2% increase compared with 1993. It is predicted that by 2000 sales of generic drugs will reach US$ 9.5 billion. Also, in the next 15 years patents of brand name drugs with total sales over US$ 34 billion will be expired. Generic drug companies will have plenty of rooms to compete in this market. In addition, due to the cost containment policy and the expand of healthcare sectors (might increase 85% after 1997), generic drug market will account for more than 20% of the pharmaceutical market.

2. *The Pharmaceutical Market of Europe*

Although the seven major countries of Western Europe have had drug cost containment policy in place since 1990, the pharmaceutical market grew steadily, with 3% increase in 1994 and 6% in 1995.

Table 2 The Growth Rate of Pharmaceutical Market in Western Europe

Country	1994 Growth Rate	1995 Growth Rate
Germany	6%	7%
France	4%	5%
United Kingdom	8%	8%
Italy	-6%	4%
Spain		11%

Source: Yakugyo Jiho

From the above data, European countries had already out of the "drug cost containment policy" nightmare. However, generic drugs will still play important role in the presence of this cost containment policy.

- Germany

In 1994, pharmaceutical sales of Germany were 22 billion DM (US$ 15.7 billion). Generic drugs accounted for 36.6% of the healthcare pharmaceuticals, but only for 28.2% (ca. 8.7 billion DM) of the expenditure. Sixty-nine percent of the most common used drug, Diclofenac, was generic. The biggest sale was Nifedipine with 653 million DM (US$ 460 million) and generic had 81.9% of the share.

- United Kingdom

Pharmaceutical industry was the most profitable industry in UK. The pharmaceutical market was US$ 6.97 billion in 1994, shared by Glaxo (12.07%), Astra (6.38%), SKB

(5.02%), Ciba (3.42%), and American Home (3.22%). After Glaxo merged with Wellcome, its market share became 15%.

- France

Pharmaceutical sales of France were US$ 10.9 billion in 1994. Generic drug market only accounted for 3.3% of the pharmaceutical market. Foreign companies had 55% share of the market (US 21% and other European countries 34%). In 1993, there were 68,500 employees with 10,500 people in bulk drug manufacturing.

3. *The Pharmaceutical Market of Asia-Pacific Region*

According to a statistical figure published by US PhRMA, pharmaceutical sales of Asia-Pacific region were ca. US$ 70~71.5 billion in 1994. Japan had the largest market with US$ 53.5 billion annual sales. Mainland China was the second with US$ 9.3 billion. South Korea was the third with US$ 3.6 billion, and then India (US$ 2.2 billion), Taiwan (US$ 1.3 billion), Pakistan (US$ 1 billion), Philippines (US$ 980 million), Indonesia (US$ 820 million), Thailand (US$ 670 million), and Singapore (US$ 105 million).

In 1994, pharmaceutical sales of Japan were 5333.6 billion Yen, a 0.6% decrease compared with 1993 (because of the drug cost containment policy, with average lowering rate 5%). But due to the currency exchange rate, the sales were US$ 53.5 billion when exchanged to US dollars. It thus increased 9.9% and accounted for 20.9% of the worldwide market. The total medical products' market was 6800 billion Yen (US$ 67 billion), equivalent to 15% of the GDP.

From the present developing trend of Mainland China, it was estimated that by 2000 pharmaceutical sales will reach US$ 20 billion. Although Mainland China has the largest population, 90% are farmers and not really covered by the health insurance. Only if those farmers' income increases dramatically, then pharmaceutical sales will rise.

Because of the economic development in Asia-Pacific region and improvement of the living standard, the pharmaceutical market of Asia-Pacific region has become important. It is the third largest one, only next to US and Europe. Western multinational companies are eagerly competing for the pharmaceutical market of Asia-Pacific region. They are building new manufacturing plants (joint venture, control stocks, or solely own, etc.). For example, Johnson & Johnson already had either joint venture or solely owned enterprise in Mainland China, Japan, Korea, Taiwan, Thailand, and Singapore. J & J will heavily invest in Mainland China and Japan due to their market sizes. It is going to manufacture popular brand name drugs like gastrointestinal drugs, antifungals, and anti-diarrhea drugs. Other companies like Squibb, Merck, and Glaxo are also stepping into the Asian-Pacific markets.

There is big difference in the sales of therapeutic categories among each Asian-Pacific countries. For countries of slow economic development, the most popular items are antibiotics and vaccines. For economy more developed countries such as Japan, Korea, Taiwan, and Singapore, the popular items are similar to those of western countries, e.g., cardiovascular drugs, hospital use antibiotics, antiulcer drugs, and cholesterol lowering agents. The Asian-Pacific pharmaceutical sales in the 21st Century are expected to rise to over US$ 100 billion.

Table 3 Worldwide Pharmaceutical Market Analysis in 1994

(Unit: US$ 100 million)

District	Sales	Share of Worldwide Market	Growth Rate in 1994
North America	791	30.9%	6.0%
Europe	779	30.4%	6.3%
Japan	535	20.9%	9.9%
Asia-Pacific	181	7.1%	13.6%
Latin America	175	6.8%	8.6%
Others	106	4.2%	13.1%
Total	2562	100%	7.6%

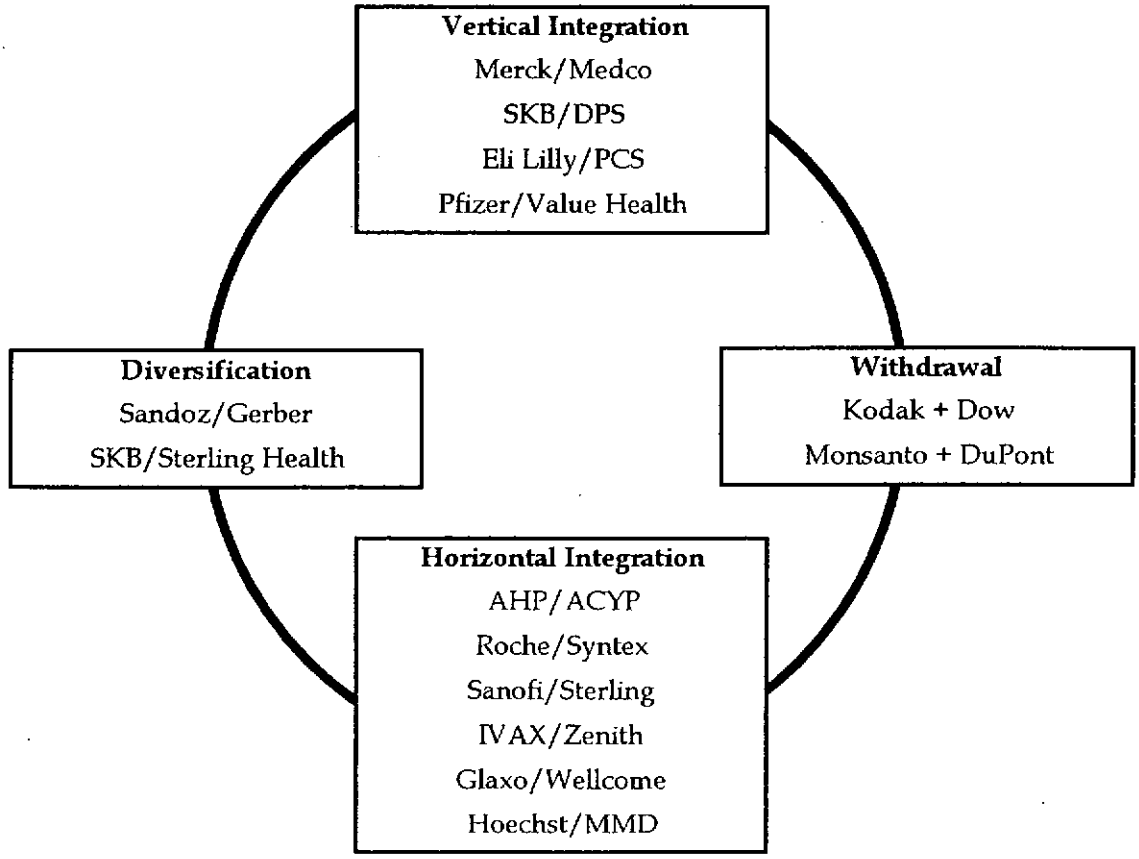
Source: PMSI; ITIS (DCB)

Section 3 The Strategies of Worldwide Pharmaceutical Industries

1. The Big Mergers will Decline

The mergers in 1994~1995 are described in Table 4. It includes the vertical integration between manufacturing companies and sales sectors and horizontal integration due to the advantage of locations, generic or OTC drug sales, etc. In addition, there are cases for diversification purpose.

Table 4 1994~1995 Pharmaceutical Companies mergers



Source: Yakugyo Jiho

There were also cases such as Merck or SKB, after they spent huge money to buy other companies, they sold off part of the companies in order to pay back the bank loans. Same thing happened to American Home Products (AHP) and American Cyanamid (ACY) merger as well as Sandoz and Gerber merger.

- Glaxo & Wellcome merger: strengthen and broaden the product lines

  Glaxo bought Wellcome with US$ 15 billion for strengthening and broadening its product lines. In early 1995, sales of Glaxo product Zantac decreased 3%. Its management was eager to strengthen other product areas. Wellcome's main product lines were in infectious diseases and cancer area. Its R&D directions had little overlap with Glaxo's. Therefore, in order to leverage both companies' strength and product lines as well as to achieve win-win for both companies, Glaxo finally merged with Wellcome. However, previously Glaxo had 45,000 employees and Wellcome had 17,000. They decided to cut back 15,000~17,000 jobs to reduce the cost.

- Hoechst Marion Roussel & Marion Merrell Dow merger: increase sales of generic drugs

  The main purpose of Hoechst Marion Roussell and Marion Merrell Dow merger was to increase sales of generic drugs in Europe. For the next five years there are several patents of blockbuster drugs going to be expired. The generic drug markets of European countries like Germany, United Kingdom, and France are estimated to have 12% annual growth rate until 2000. Marion Merrell Dow was selling generic drugs for the European company Cox and the largest US generic drug sales company Rugby-Darby.

- Pharmacia & Upjohn merger: increase the product lines and sales territories

  The merger of Pharmacia and Upjohn will increase the product lines and sales territories because of little overlap. The major product lines of Pharmacia were anticancers, metabolic disease drugs, and ophthalmic drugs and the major sales territories were Europe and Japan. The major product lines of Upjohn, however, were gynecological drugs, antiinfectives, an CNS drugs and the major sales territory was US.

- Ciba & Sandoz merger: reduce the R&D overlap

The merger of Ciba and Sandoz to becoming the world second largest pharmaceutical company not only increases the product lines but reduces their R&D overlap. Table 5 shows the summary of the reasons behind all the mergers.

Table 5 The Reason Behind the Big Mergers

Merging Companies	Reasons
Glaxo & Wellocme	strengthen and broaden the product lines
HMR & MMD	increase sales of generic drugs
Pharmacia & Upjohn	increase the product lines and sales territories
Ciba & Sandoz	reduce the R&D overlap

2. *Major Changes in Therapeutic Drugs*

- Proton pump inhibitors are replacing H2 antagonists as antiulcer drugs

The patent of SKB H2 antagonist antiulcer agent cimetidine went expired, thus its worldwide market share dropped 2% and US market share lost 5%.

The price of Glaxo's ranitidine also went down. However, the market shares of proton pump inhibitors omeprazole and lansoprazole increased 2% and 4%, respectively.

- The major therapeutic drugs in the future will be cardiovascular drugs, cholesterol lowering agents, and proton pump inhibitor antiulcers

The biggest change of worldwide drug market from 1993 to 1994 were that sales of proton pump inhibitor antiulcer drug omeprazole (brand name: Losec, Astra) increased from US$ 1.64 billion to US$ 2.24 billion and sales of the antidepressant drug fluoxetine (brand name: Prozac, Lilly) grew from US$ 1.15 billion to US$ 1.58 billion. On the contrary,

sales of cimetidine went down from US$ 1.2 billion to US$ 1.04 billion because of patent expiration. Sales of same mechanism drug, ranitidine, were still No. 1 with US$ 4.11 billion, a 14% increase compared with 1993.

Among the first twenty world's best-selling drugs in 1994, there were eight cardiovascular drugs and four antiulcer drugs. The growth rate of proton pump inhibitor antiulcer drugs increased 40.6% in 1994. It was predicted that cardiovascular drugs, cholesterol lowering agents, and proton pump inhibitor antiulcer drugs will be the major therapeutic drugs in the future.

Section 4 The Performance of Some Multinational Companies

Although under the cost containment policy, each multinational company still achieved its performance objectives in 1994 due to sales volumes except Glaxo Wellcome. Pharmaceutical sales of Merck, Glaxo Wellocme, Roche, Pfizer, Eli Lilly, J & J, and Takeda had all double-digit growth from the previous year. As for the profits, Merck, Hoechst, Pfizer, and Eli Lilly had over 50%, almost two times's growth. However, sales of Sandoz, Ciba, and Bayer and profits of Glaxo Wellcome did not meet the expectations.

1. *Merck: Sales of major products were encouraging*

After Merck bought the pharmacy benefit management company Medco in November 1993, sales grew 43% in 1994 (7% increase excluding Medco). Its net profit after tax also increased 12%. Sales of major products like enalapril, lisinopril, lovastatin, simvastatin, Prilosec (brand name of omeprazole), and finasteride were pretty good and sales of pharmaceuticals in 1994 were US$ 13.25 billion.

2. *Glaxo: Contributions from the major products like Zantac*

On May 1, 1995, Glaxo changed its name to Glaxo Wellcome. From July 1994 to June 1995, Glaxo was trying to increase product sales volumes for minimizing the effect of worldwide cost containment policy. Because of the major products like Zantac, Ventolin, and Beclovent, Glaxo's worldwide sales were still on the top list. However, Glaxo's net profit was greatly affected due to the Wellcome merger spending of 700 million pounds and the annual loan interests of ca. 100 million pounds. Sales of pharmaceuticals in 1994 were US$ 10.23 billion.

3. *Roche-Syntex merger*

Since the merger of Roche and Syntex in October 1994, sales of Rocephin, Roaccutane, Inhibace, and Roferon-A grew steadily. In 1994, pharmaceutical sales were US$ 6.1 billion.

4. *Pfizer: Total sales of six major products increased 44%*

Pfizer's sales in 1994 broke the record. Total sales of major products like Zithromax, Norvasc, Diflucan, Procardia XL, and Zoloft increased 44%, reaching US$ 2.7 billion. Procardia XL had US$ 1.18 billion of sales. Norvasc had a 85% increase and cardiovascular drugs, company's major products, had 20% of growth. In 1994, pharmaceutical sales were over US$ 5.8 billion.

5. *Eli Lilly: Sales of fluoxetine increased 39%*

Although sales only increased 20% in 1994 due to the effect of cost containment policy, sales volumes grew 11%. Sales of Prozac (chemical name fluoxetine) were US$ 1.7 billion, a 39% increase. Eli Lilly bought PCS Health System, a pharmacy benefit management company, in the hope to help the future sales. Sales of pharmaceuticals in 1994 were US$ 5.25 billion.

6. *Smith-Klein Beecham: Contributions from the Tagamet HB OTC switch*

The huge increase (119.7%) of sales (US$ 511 million) of the selective serotonin reuptake inhibitor antidepressant drug Paxil and the increase (30%) of sales (US$ 391 million) of antiarthritic drug Relifex (chemical name nabumetone) made up the effect of 47% decrease of Tagamet sales due to patent expiration. However, OTC Tagamet sales increased 51% and the profit grew 73%. Even excluding the profit of Sterling Health, SKB still had 21% of profit in 1994. Tagamet HB OTC switch certainly had its contributions to it. Sales of pharmaceuticals in 1994 were US$ 5.53 billion.

Table 6 The Leading Pharmaceutical Companies in 1994

(Unit: US$ million, %)

'95	'94	'93	Company	Total Sales	Pharmaceutical Sales	Profit	R&D Expenditure
2	1	1	Merck & Co. (US)	14,969	13,247 (88.5)	4,415 (29.5)	1,230 (8.2)
1	2	2	Glaxo Wellcome (UK)	10,225	10,225 (100)	2,324 (22.7)	1,915 (18.7)
5	3	3	Bristol-Myers Squibb (US)	11,984	6,970 (58.2)	2,641 (22.0)	1,108 (9.2)
3	4	4	Hoechst (Ger)	30,587	6,332 (20.7)	1,428 (4.7)	2,076 (6.8)
6	5	5	Roche (Swi)	10,783	6,097 (56.5)	1,941 (18.0)	1,705 (15.8)
7	6	7	Pfizer (US)	8,281	5,811 (70.2)	2,089 (25.2)	1,139 (13.8)
8	7	6	SmithKline Beecham (UK)	9,298	5,532 (59.5)	1,894 (20.4)	951 (10.2)
13	8	9	Sandoz (Swi)	11,603	5,261 (45.3)	1,792 (15.4)	1,195 (10.3)
10	9	12	Eli Lilly (US)	5,711	5,248 (91.9)	1,286 (22.5)	838 (14.7)
11	10	13	Johnson & Johnson (US)	15,734	5,158 (32.8)	2,681 (17.0)	1,278 (8.1)
14	11	8	Ciba (Swi)	16,121	5,149 (31.9)	1,995 (12.4)	1,572 (9.8)
4	12	11	American Home Products (US)	8,966	4,980 (55.5)	2,029 (22.6)	817 (9.1)
12	13	15	Takeda (Jap)	7,550	4,856 (64.3)	932 (12.3)	657 (8.7)
	14	10	Bayer (Ger)	26,756	4,273 (6.0)	1,995 (7.5)	1,957 (7.3)
15	15	16	Rhone-Poulenc Rorer (Fr.)	4,174	4,174 (100)	570 (13.7)	600 (14.4)
	17	18	Sankyo (Jap)	5,411	3,908 (72.2)	874 (16.2)	463 (8.6)
	18	26	Shionogi (Jap)	3,574	3,574 (100)	243 (6.8)	265 (7.4)
	22	27	Yamanouchi (Jap)	3,760	3,051 (81.1)	871 (23.2)	374 (9.9)
	27	30	Fujisawa (Jap)	2,779	2,423 (87.2)	252 (9.1)	357 (12.8)
	28	32	Daiichi (Jap)	2,491	2,364 (94.9)	196 (7.9)	311 (12.5)
	30	36	Eisai (Jap)	2,527	2,242 (88.7)	383 (15.2)	334 (13.2)
	34	34	Sumitomo (Jap)	2,156	1,967 (91.3)	164 (7.6)	146 (6.8)
	35	37	Taisho (Jap)	2,063	1,878 (91.0)	457 (22.2)	183 (8.9)

Source: SCRIP, Pharmaceutical Company League Table 1995.

Table 7 The Change of Worldwide Pharmaceutical Market

(Unit: 100 million pound, %)

	1990	1991	1992	1993
US	220 (27.4)	268 (28.7)	326 (29.5)	400 (30.8)
Japan	150 (18.7)	174 (18.6)	199 (18.0)	280 (21.5)
France	61 (7.6)	65 (7.0)	82 (7.4)	90 (6.9)
Germany	64 (8.0)	72 (7.7)	95 (8.6)	80 (6.2)
Italy	60 (7.5)	68 (7.3)	68 (6.1)	60 (4.6)
UK	28 (3.5)	31 (3.3)	36 (3.3)	40 (3.1)
Subtotal	583 (72.7)	678 (72.6)	806 (72.9)	950 (73.1)
Spain	22 (2.7)	25 (2.7)	30 (2.7)	
Canada	18 (2.2)	22 (2.4)	24 (2.2)	
Brazil	15 (1.9)	14 (1.5)		
Central & South America				80 (6.2)
Korea	11(1.4)		18 (1.6)	
Mexico		14.5 (1.5)		
Other Asia-Pacific Region				60 (4.6)
South Africa, Middle East				20 (1.5)
Australia				10 (0.8)
Others	153 (19.1)	181 (19.4)	228 (20.6)	180 (13.8)
Total	802 (100)	934 (100)	1,106 (100)	1,300 (100)

* The No. in the brackets indicate "% of market share"

Source: Glaxo annual report; Yakuhyo Jiho annual report

Section 5 World Market Trend on Generic Bulk Drugs

1. Why Is There A Demand For Generic Drugs?

In recent years, most of the nations are cutting budget on their medicare system. The budget reduction seriously affect the buying power of the consumers and hence more and more consumers gradually shift their preferences toward buying generic drugs that are nearly as potent yet less expensive than the brandname products. From an economic point of view, competitions from the generics would drive the market price down and increase the availability of the products. Of course, each nation is liable to set strict guidelines and monitor the quality of the generics to ensure the safety of consumers. Only through this framework the consumers would gain the maximum benefit from the existence of generic drugs.

2. Response from Well Known Drug Makers

Due to the fast growth in the demand for generics, a number of brandname drug makers are also making adjustment to the trend. Thus, not only are they makers of brandname products, they are also makers of generics.

Table 8 Generic Companies Owned by Brand Drug Companies

Brand Drug Company	Generic Drug Company
American Home Product	ESI-Lederle Pharma and Elkins-Sinn
Wyeth-Ayerst	Pan-Efeka
Boehringer Ingelheim	Roxane
Bristol-Meyers Squibb	Apothecan
Ciba-Geigy	Geneva Pharmaceuticals
DuPont Merck Pharmaceutical	DuPont Multi-Source Products
Hoechst-Celanese/Marion Merrell Dow	Copley Pharmaceutical
Merck & Co.	West Point Pharma
Phone-Poulenc Rorer	Arcola Laboratories
Sandoz Pharmaceuticals	Creighton Products
Sanofi Winthrop	Kanetta Pharmaceutical
Schering-Plough	Warrick Pharmaceuticals
SmithKline-Beecham	Penn Labs
Stiefel	Glades
Roche-Syntex	Hamilton Pharma
Upjohn	Greenstone
Warner-Lambert	Warner Chilcott Laboratories
Zenecca	IPR

3. *Market Situation of Generic Drugs*

The use of generic drugs are most popular in the following three regions: the United States, Japan, and European Union.

- The United States

In the U.S. generic drugs have always had a steady growth since 1989, as shown in Table 9:

Table 9 Analysis of Market Share for Generic Drug in U.S.A.

(Unit: Billion USD)

	Sales			Growth Rate(X+1)/X			Share		
	Generic	Brand	Total	Generic	Brand	Total	Generic	Brand	Total
1994	6.35	56.34	62.68	38.8%	4.3%	7.0%	10.1%	89.9%	100.0%
1993	4.57	54.00	58.58	23.9%	3.9%	5.3%	7.8%	92.2%	100.0%
1992	3.69	51.96	55.65	3.6%	19.3%	18.1%	6.6%	93.4%	100.0%
1991	3.56	43.56	47.12	3.2%	13.4%	12.5%	7.6%	92.4%	100.0%
1990	3.45	38.43	41.88	5.4%	12.5%	11.9%	8.2%	91.8%	100.0%
1989	3.27	34.16	37.43				8.7%	91.3%	100.0%

Source: IMS America

From the statistics, it is clear that the demand for generics are on a sharp rise while the brandname product is, although steady, somewhat less drastic.

In 1995 overall sales of the generic drugs in the U.S. totaled up to 8.2 billion US dollars, a 10% growth from 1994. In Table 10, the 1995 total sales of generic drugs in the U.S. are shown. The top 10 makers together accounted for 26% of the total marketshare, whereas the top 20 makers as a whole owns 40% of the total share:

Table 10 1995 Sales of Generic Drug Manufacturers in U.S.A.

(Unit: Million USD)

	Originator	Sales	Growth Rate(+/- %)
Mylan	Independent	685	+86
Key Pharmaceutical	Schering-Plough	407	+19
Geneva Pharm	Ciba-Geigy	401	+12
RPR Pharm	Rhone-Poulenc	380	+ 9
Schein Pharm	Independent	365	- 1
Rugby Labs	Hoechst	356	- 5
Lederle Rx	American Cyanamid	348	- 3
Ortho Pharm	J & J	334	- 5
Abbot Hospital	Abbott	304	0
Forest Pharm	Independent	281	+28
Top 10 Total		3861 (26%)	
Next 10 Total		1992 (14%)	
Total Others		9156 (60%)	
Non-Originator Total		15009 (100%)	+10

The total sales in year 2006 is expected to exceed 20 billion US dollars, with an average of 9.5% growth, as shown below:

Table 11 2006 Estimated Market of Generic Drug in U.S.A.

(Unit: Thousand USD)

	Sales	Growth Rate
1989	3,274,400	na
1990	3,451,700	5.4%
1991	3,562,700	3.2%
1992	3,690,900	3.6%
1993	4,571,800	23.9%
1994	6,350,075	38.9%
1995E	8,369,365	31.8%
1996E	9,501,492	13.5%
1997E	10,851,432	14.2%
1998E	11,438,892	5.3%
1999E	12,782,774	11.8%
2000E	14,080,651	10.2%
2001E	14,777,287	4.9%
2002E	15,948,735	7.9%
2003E	17,150,732	7.5%
2004E	18,864,763	10.0%
2005E	20,923,009	10.9%
2006E	22,919,895	9.5%
Total	177,602,468	11.3% (12-year Ave.Growth Rate)

Source: Retail & Hospital Market Analysis 1996, Dillon Read.

- JAPAN

In Japan where the consumers still prefer the more expensive brandname drugs, the current market share for the generics is quite small, 5~7%. However, since the Japanese government is earnestly reducing the price of drugs, a huge growth in the demand for generic drugs is expected.

- EU

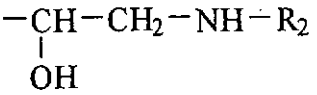
In European Union, generic drugs already enjoys a good market share at 15% which is accounted for 6 billion US dollars. These figures are expected to grow rapidly. Based on the growth rate, the total sales in year 2000 is expected to reach US$10.7 billion.

Section 6 World Market Hot Generic Bulk Drugs' Scheme

1. Antihypertensives

(1) β - Adrenergic Blocking Agents

Figure 2-6-1. 1st Generation β - Blocking Agents

Basic Scheme : 

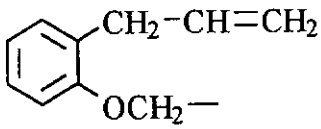
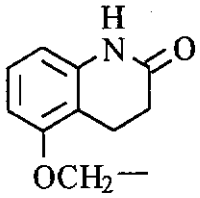
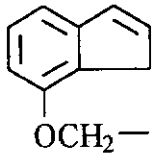
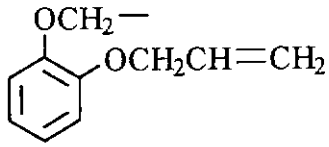
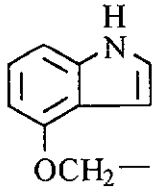
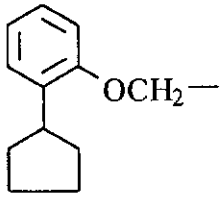
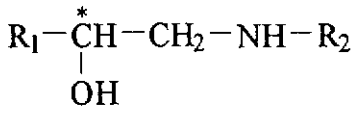
Drug Name	R_1	R_2
Alprenolol		$-CH(CH_3)_2$
Carteolol		$-C(CH_3)_3$
Indenolol		$-CH(CH_3)_2$
Oxprenolol		$-CH(CH_3)_2$
Pindolol		$-CH(CH_3)_2$
Penbutolol		$-CH(CH_3)_2$

Figure 2-6-2. 2nd Generation β - Blocking Agents

Basic Scheme : 

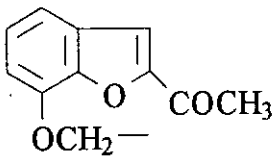
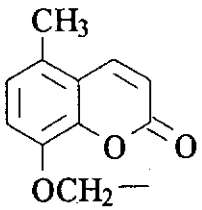
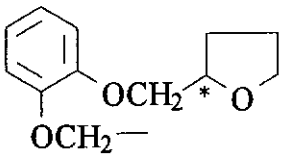
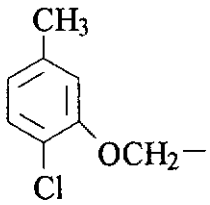
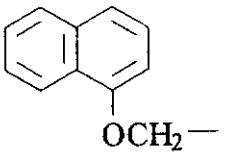
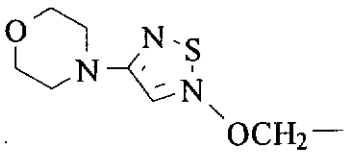
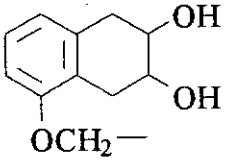
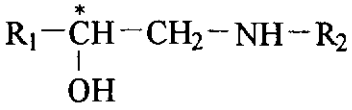
Drug Name	R_1	R_2
Befunolol		$-CH(CH_3)_2$
Bucumolol		$-C(CH_3)_3$
Bufetolol		$-C(CH_3)_3$
Bupranolol		$-C(CH_3)_3$
Propranolol		$-CH(CH_3)_2$
Timolol		$-C(CH_3)_3$
Nadolol		$-C(CH_3)_3$

Figure 2-6-3. 3rd Generation β - Blocking Agents

Basic Scheme : 

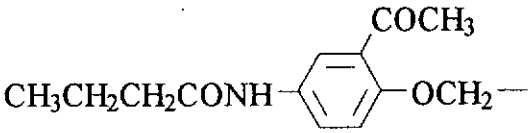
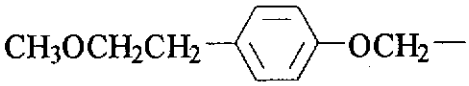
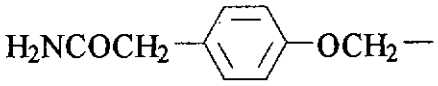
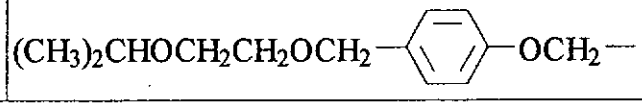
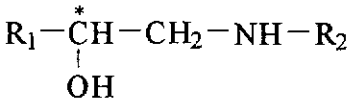
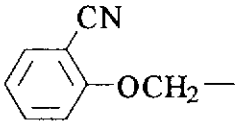
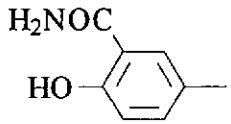
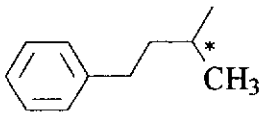
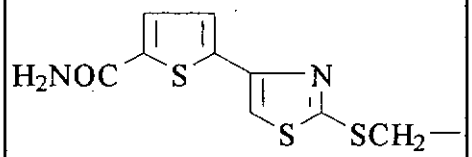
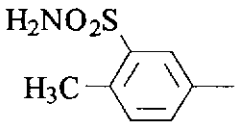
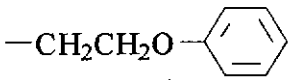
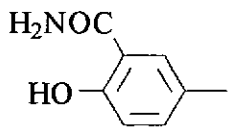
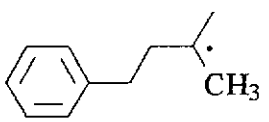
Drug Name	R_1	R_2
Acebutolol		$-CH(CH_3)_2$
Metoprolol		$-CH(CH_3)_2$
Atenolol		$-CH(CH_3)_2$
Bisoprolol		$-CH(CH_3)_2$

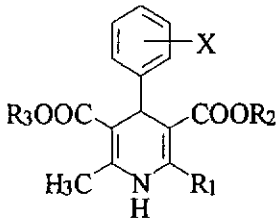
Figure 2-6-4. 4th Generation β - Blocking Agents

Basic Scheme : 

Drug Name	R_1	R_2
Bunitrolol		$-C(CH_3)_3$
Labetalol		
Arotinolol		$-C(CH_3)_3$
Amosulalol		
Dilevalol		

(2) Calcium Channel Blocker

Figure 2-6-5. 1,4-Dihydropyridine Derivatives



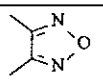
Drug Name	X	R_1	R_2	R_3
Nifedipine	2-NO_2	$-CH_3$	$-CH_3$	$-CH_3$
Nitrendipine	3-NO_2	$-CH_3$	$-C_2H_5$	$-CH_3$
Nisoldipine	2-NO_2	$-CH_3$	$-CH_2CH(CH_3)_2$	$-CH_3$
Nicardipine	3-NO_2	$-CH_3$	$-CH_2CH_2N(CH_3)(CH_2C_6H_5)$	$-CH_3$
Nimodipine	3-NO_2	$-CH_3$	$-CH_2CH_2OCH_3$	$-CH(CH_3)_2$
Nilvadipine	3-NO_2	$-CN$	$-CH_3$	$-CH(CH_3)_2$
Manidipine	3-NO_2	$-CH_3$	$-CH_2CH_2-N$ piperazine $N-CH(C_6H_5)_2$	$-CH_3$
Amlodipine	2-Cl	$-CH_2OCH_2CH_2NH_2$	$-C_2H_5$	$-CH_3$
Felodipine	2-Cl 3-Cl	$-CH_3$	$-C_2H_5$	$-CH_3$
Benidipine	3-NO_2	$-CH_3$	N-benzyl-piperidine	$-CH_3$
Barnidipine	3-NO_2	$-CH_3$	$-CH_2-C_6H_5$	$-CH_3$
Darodipine		$-CH_3$	$-C_2H_5$	$-C_2H_5$
Isradipine		$-CH_3$	$-CH(CH_3)_2$	$-CH_3$
Niludipine	3-NO_2	$-CH_3$	$-CH_2CH_2OC_3H_7$	$-CH_2CH_2OC_3H_7$

Figure 2-6-6. Benzothiazepine Derivatives

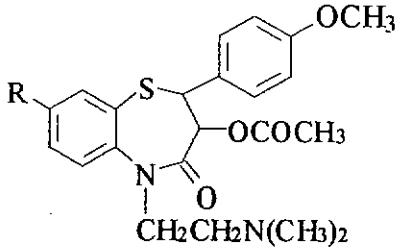
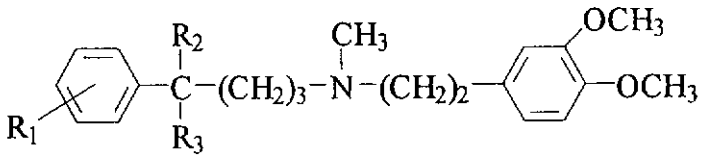
Basic Scheme	Drug Name	R
	**Diltiazem**	—H
	Clentiazem	—Cl

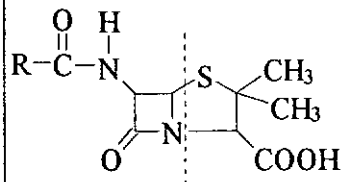
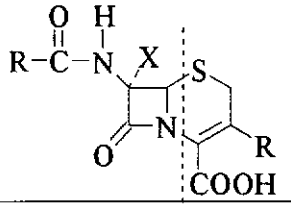
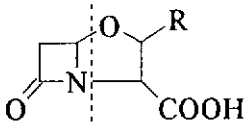
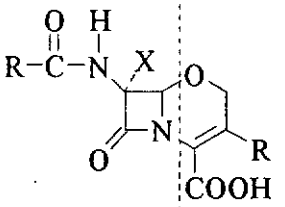
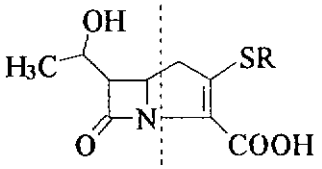
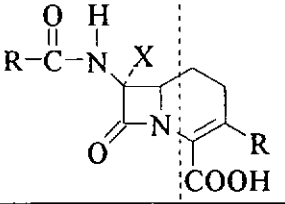
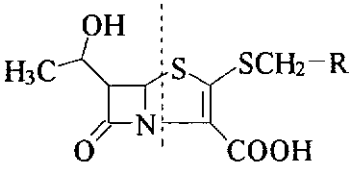
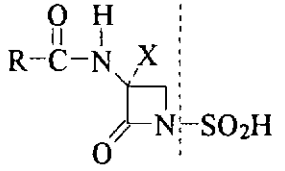
Figure 2-6-7. Phenylalkylamine Derivatives



Drug Name	R_1	R_2	R_3
Verapamil	3,4-$(OCH_3)_2$	$-CH(CH_3)_2$	$-CN$
Gallopamil	3,4,5-$(OCH_3)_3$	$-CH(CH_3)_2$	$-CN$
Tiapamil	3,4-$(OCH_3)_2$	$-SO_2(CH_2)_3SO_2^-$	

2. β - Lactam Series Antibiotics

Figure 2-6-8. β - Lactam Series Antibiotics

General Name	Basic Scheme	General Name	Basic Scheme
Penam Penicillin Series		**Cephem** Cephalosporin Series	
Oxapenam		**Oxacephem**	
Carbapenem		**Carbacephem**	
Penem		**Monobactam**	

(1) Cephalosporin Series

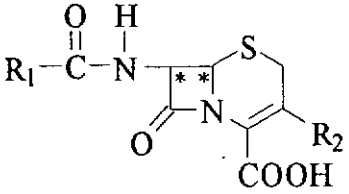


Figure 2-6-9. Cephalosporin Series 1st Generation (Inject)

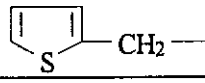
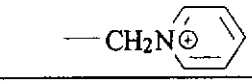
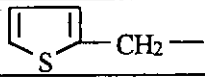
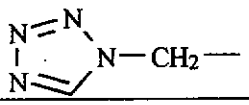
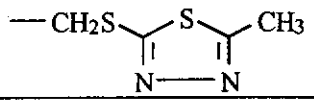
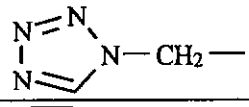
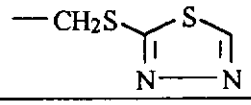
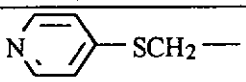
Drug Name	R_1	R_2
Cephaloridine		
Cephalothin		$-CH_2OCOCH_3$
Cefazolin		
Ceftezole		
Cephapirin		$-CH_2OCOCH_3$
Cephacetrile	$CN-CH_2-$	$-CH_2OCOCH_3$

Figure 2-6-10. Cephalosporin Series 1st Generation (Oral)

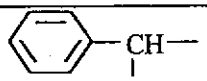
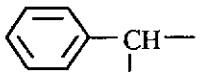
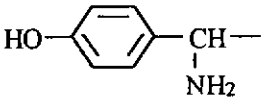
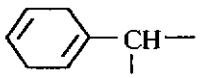
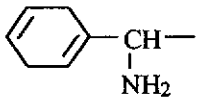
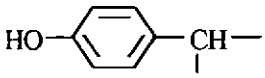
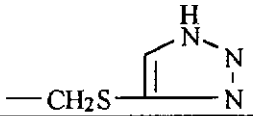
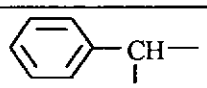
Drug Name	R_1	R_2
Cephaloglycin		$-CH_2OCOCH_3$
Cephalexin		$-CH_3$
Cefadroxil		$-CH_3$
Cefroxadine		$-OCH_3$
Cephradine		$-CH_3$
Cefatrizine		
Cefaclor		$-Cl$

Figure 2-6-11. Cephalosporin Series 2nd Generation (Inject)

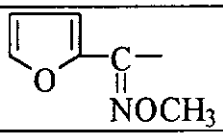
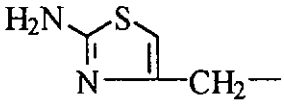
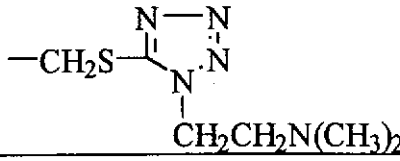
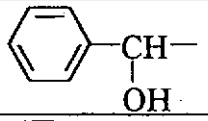
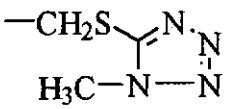
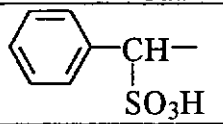
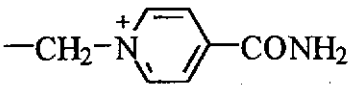
Drug Name	R_1	R_2
Cefuroxime		$-CH_2OCONH_2$
Cefotiam		
Cefamandole		
Cefsulodin		

Figure 2-6-12. Cephalosporin Series 2nd Generation (Oral)

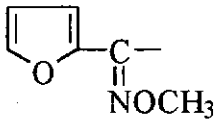
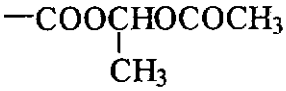
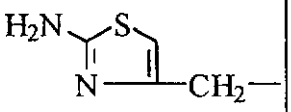
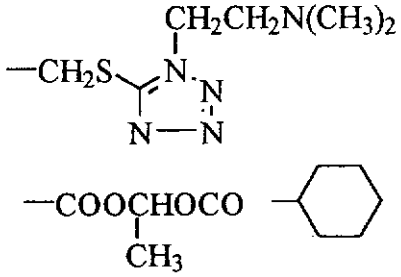
Drug Name	R_1	R_2
Cefuroxime Axetil		$-CH_2OCONH_2$ 
Cefotiam Hexetil		

Figure 2-6-13. Cephalosporin Series 3rd Generation (Inject)

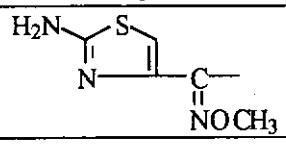
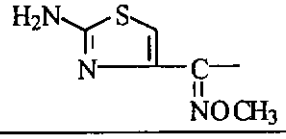
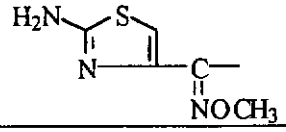
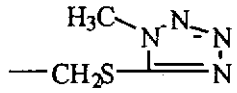
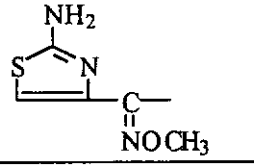
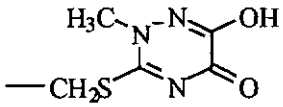
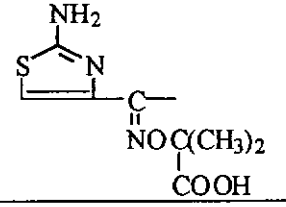
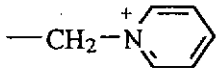
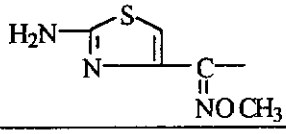
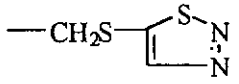
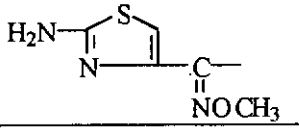
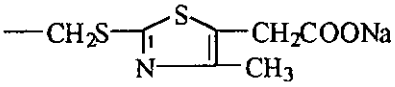
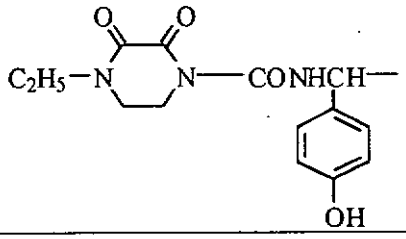
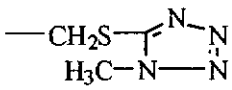
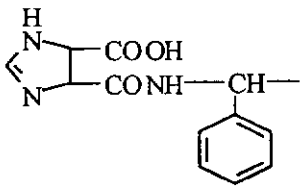
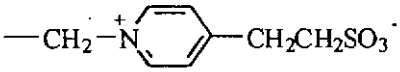
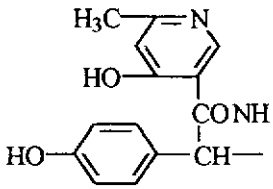
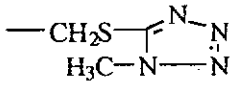
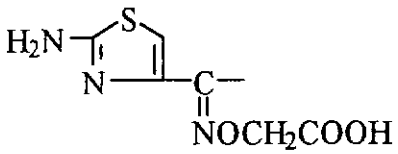
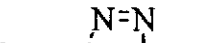
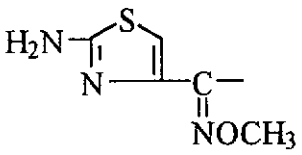
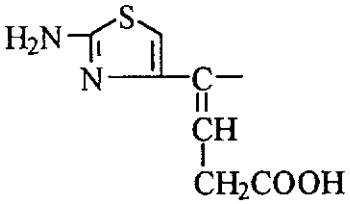
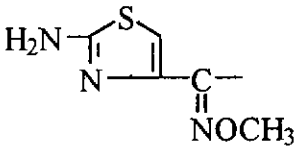
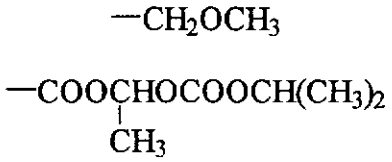
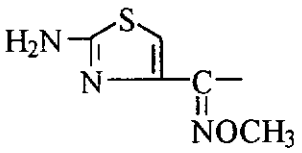
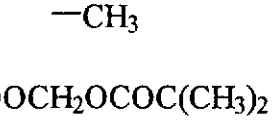
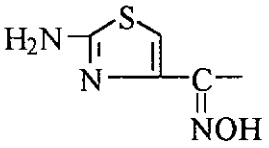
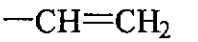
Drug Name	R_1	R_2
Cefotaxime		
Ceftizoxime		
Cefmenoxime		
Ceftriaxone		
Ceftazidime		
Cefuzonam		
Cefodizime		
Cefoperazone		
Cefpimizole		
Cefpiramide		

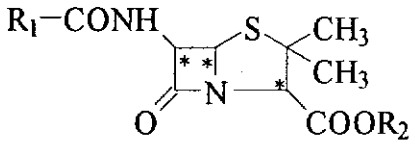
Figure 2-6-14. Cephalosporin Series 3rd Generation (Oral)

Drug Name	R_1	R_2
Cefixime		
Cefteram Pivoxil		
Ceftibuten		
Cefpodoxime Proxeti		
Cefetamet Pivoxi		
Cefdinir		

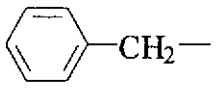
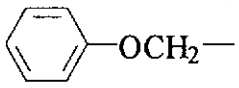
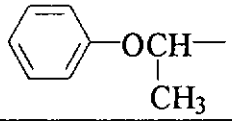
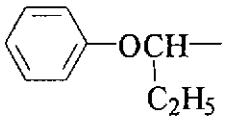
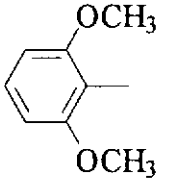
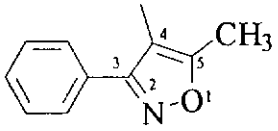
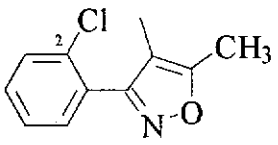
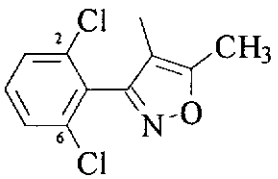
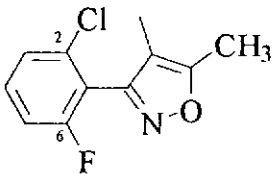
(2) Penicillin Series

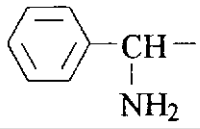
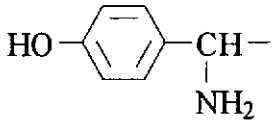
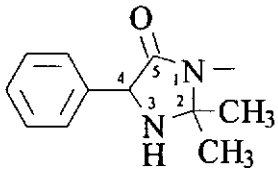
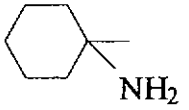
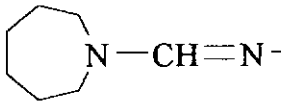
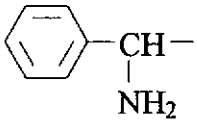
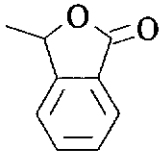
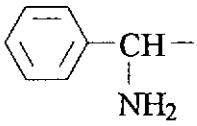
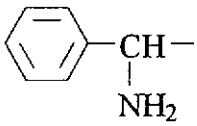
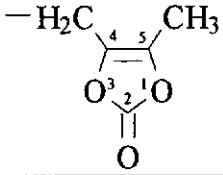
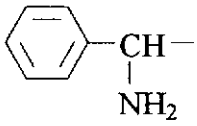
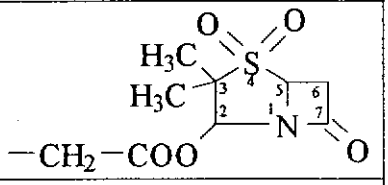
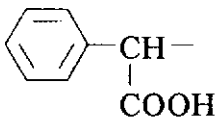
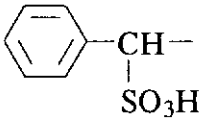
Figure 2-6-15. Penicillin Series Derivatives

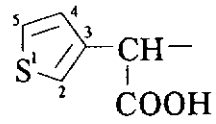
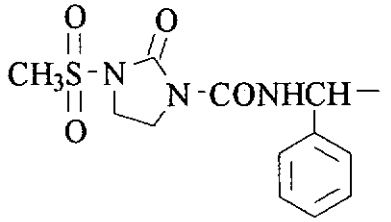
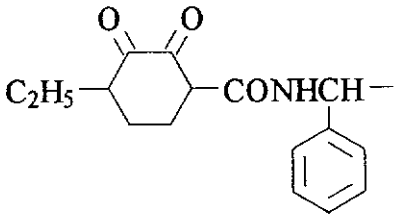
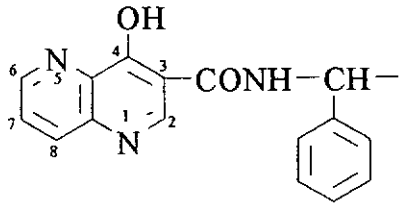
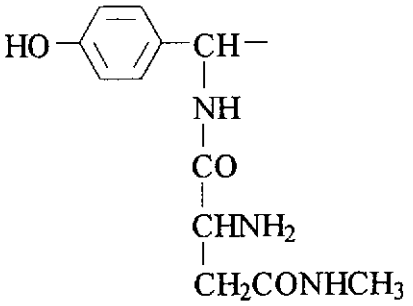
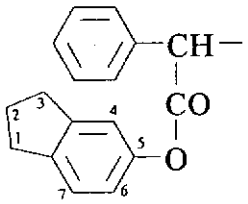
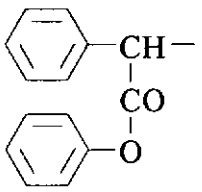
Basic Scheme :



● Oral
○ Inject.
◎ Oral.Inject

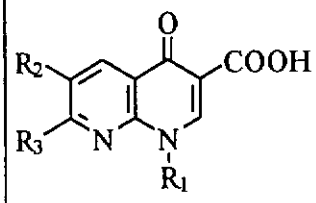
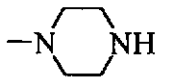
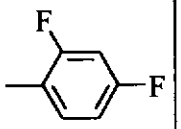
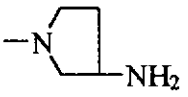
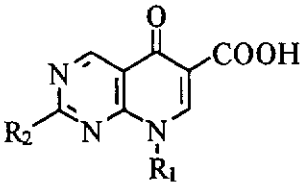
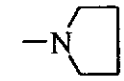
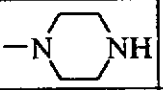
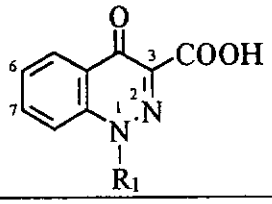
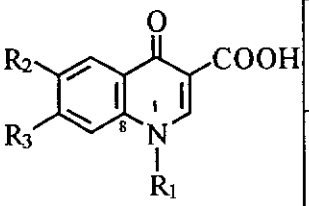
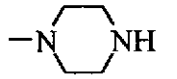
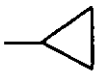
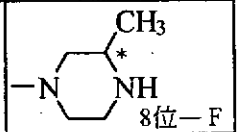
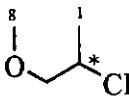
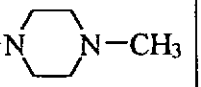
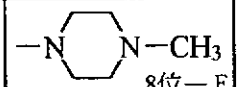
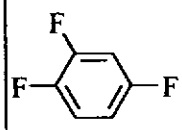
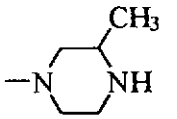
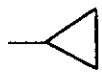
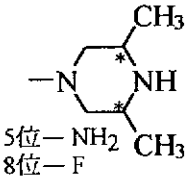
Drug Name	R_1	R_2
○**Benzylpenicillin**		—H
●**Phenoxymethylpenicillin**		—H
●**Phenethicillin**		—H
●**Propicillin**		—H
●**Methicillin**		—H
◎**Oxacillin**		—H
◎**Cloxacillin**		—H
●**Dicloxacillin**		—H
●**Flucloxacillin**		—H

Drug Name	R_1	R_2
◎**Ampicillin**		−H
●**Amoxicillin**		−H
◎**Hetacillin**		−H
●**Ciclacillin**		−H
●**Pivmecillinam**		$-CH_2OC_2C(CH_3)_3$
●**Talampicillin**		
●**Bacampicillin**		$-CHOCOOC_2H_5$ CH_3
●**Lenampicillin**		
●**Sultamicillin**		
○**Carbenicillin**		−H
○**Sulbenicillin**		−H

Drug Name	R_1	R_2
○**Ticarcillin**		—H
○**Mezlocillin**		—H
○**Piperacillin**		—H
○**Apalcillin**		—H
○**Aspoxicillin**		—H
●**Carindacillin**		—H
●**Carfecillin**		—H

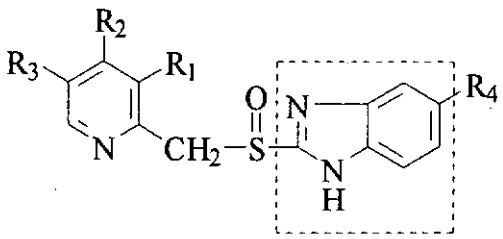
3. Pyridoncarbonic Acid Series Synthetic Antibacterial

Figure 2-6-16. Pyridoncarbonic Acid Derivatives

Basic Scheme	Drug Name	R_1	R_2	R_3
	**Nalidixic Acid**	$-C_2H_5$	$-H$	$-CH_3$
	Enoxacin	$-C_2H_5$	$-F$	
	Tosufloxacin		$-F$	
	**Piromidic Acid**	$-C_2H_5$		
	Pipemidic Acid	$-C_2H_5$		
	**Cinoxacin**	$-C_2H_5$		
	**Norfloxacin**	$-C_2H_5$	$-F$	
	Ciprofloxacin		$-F$	
	Lomefloxacin	$-C_2H_5$	$-F$	 8位— F
	Ofloxacin		$-F$	
	Fleroxacin	$-CH_2CH_2F$	$-F$	 8位— F
	Temafloxacin		$-F$	
	Sparfloxacin		$-F$	 5位— NH_2 8位— F

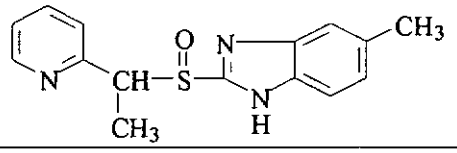
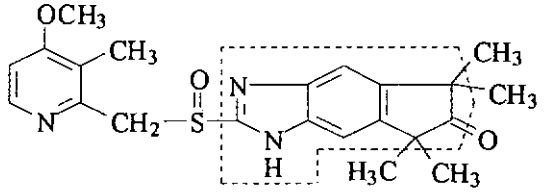
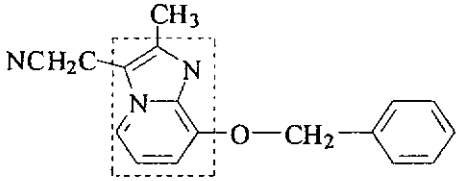
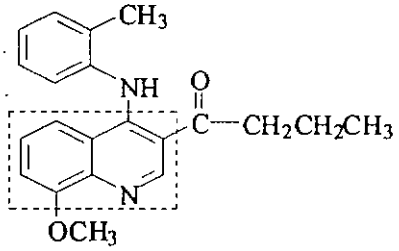
4. H/K Adenosine Triphophatase （ ATPase ） Inhibitor

Figure 2-6-17. Omeprazole Type Basic Scheme



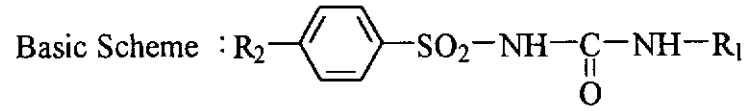
Drug Name	R_1	R_2	R_3	R_4
Omeprazole	$-CH_3$	$-OCH_3$	$-CH_3$	$-OCH_3$
Timoprazole	$-H$	$-H$	$-H$	$-H$
Lansoprazole	$-CH_3$	$-OCH_2CF_3$	$-H$	$-H$
Pantoprazole	$-OCH_3$	$-OCH_3$	$-H$	$-OCF_2H$
E-3810	$-CH_3$	$-O(CH_2)_3-OCH_3$	$-H$	$-H$
B-823-08	$-CH_3$	$-OCH_3$	$-H$	$-CF_3$

Figure 2-6-18. Others ATPase Inhibitor

Drug Name	Scheme
H83/88	
Ro-18-5364	
SCH-28080	
SK & F-96067	

5. Oral Hypoglycemic Drugs

Figure 2-6-19. Sulfonylurea Derivatives

Basic Scheme : 

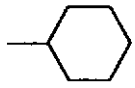
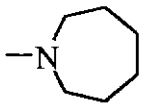
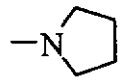
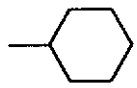
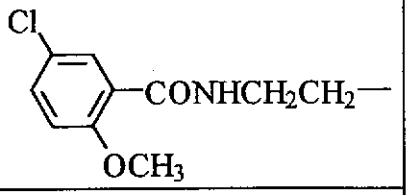
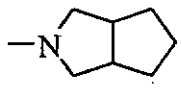
Drug Name	R_1	R_2
Tolbutamide	$-CH_2(CH_2)_2CH_3$	CH_3-
Chlorpropamide	$-CH_2CH_2CH_3$	Cl—
Acetohexamide		CH_3CO-
Tolazamide		CH_3-
Glyclopyramide		Cl—
Glibenclamide		
Gliclazide		CH_3-

Figure 2-6-20. Sulfonamide Derivatives

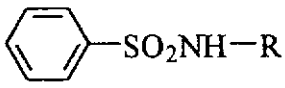
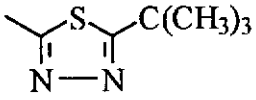
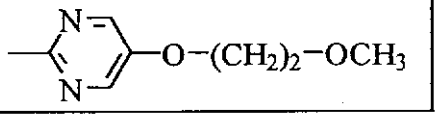
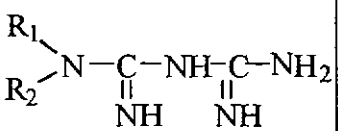
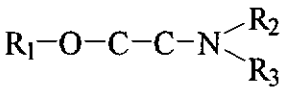
Basic Scheme	Drug Name	R
	**Glybuzole**	
	Glymidine	

Figure 2-6-21. Biguanide Derivatives

Basic Scheme	Drug Name	R_1	R_2
	**Phenformin**	—H	$-CH_2CH_2-$ 
	Buformin	—H	$-(CH_2)_3CH_3$
	Metformin	$-CH_3$	$-CH_3$

6. H_1 Antihistamine

Figure 2-6-22. Aminoallkylether Derivatives

Basic Scheme : 

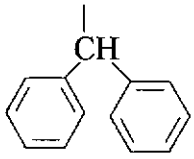
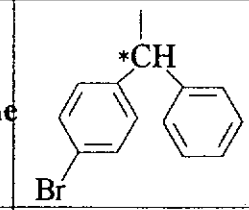
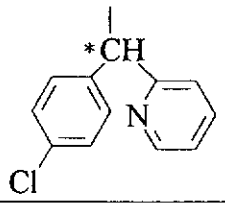
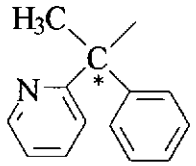
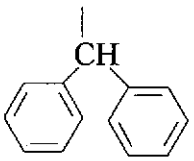
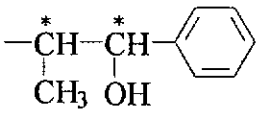
Drug Name	R_1	R_2	R_3
Diphenhydramine		$-CH_3$	$-CH_3$
Bromodiphenhydramine		$-CH_3$	$-CH_3$
Carbinoxamine		$-CH_3$	$-CH_3$
Doxylamine		$-CH_3$	$-CH_3$
Difeterol		$-CH_3$	

Figure 2-6-23. Piperazines Derivatives

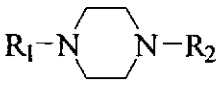
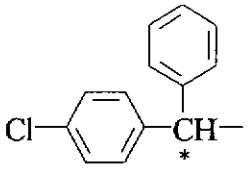
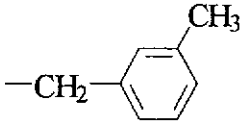
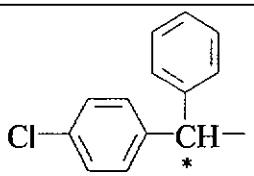
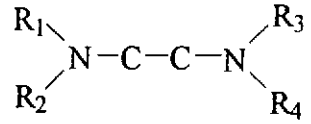
Basic Scheme	Drug Name	R_1	R_2
	**Meclizine**		
	Chlorcyclizine		$-CH_3$

Figure 2-6-24. Ethylenediamines Derivatives

Basic Scheme :



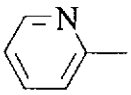
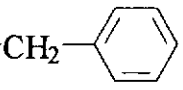
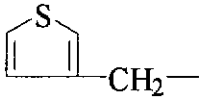
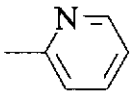
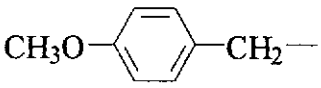
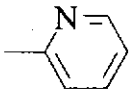
Drug Name	R_1	R_2	R_3	R_4
Tripelennamine			$-CH_3$	$-CH_3$
Thenyldiamine			$-CH_3$	$-CH_3$
Pyrilamine			$-CH_3$	$-CH_3$

Figure 2-6-25. Allkylamines Derivatives

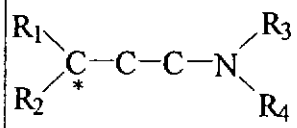
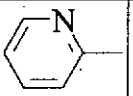
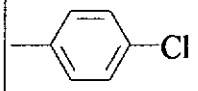
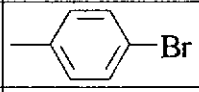
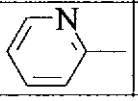
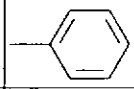
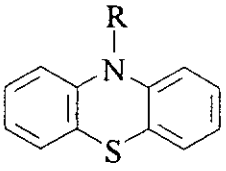
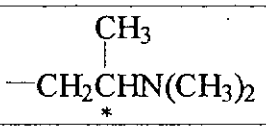
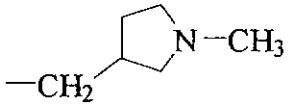
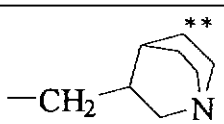
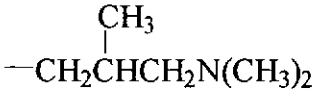
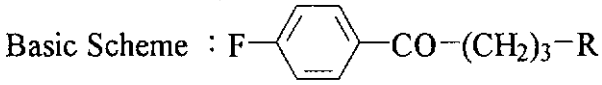
Basic Scheme	Drug Name	R_1	R_2	R_3	R_4
	**Chlorpheniramine**			$-CH_3$	$-CH_3$
	Brompheniramine			$-CH_3$	$-CH_3$
	Pheniramine			$-CH_3$	$-CH_3$

Figure 2-6-26. Phenothiazines Derivatives

Basic Scheme	Drug Name	R
	**Promethazine**	
	Methdilazine	
	Mequitazine	
	Alimemazine	

7. Antipsychotic Drugs

Figure 2-6-27. Buthrophenones Derivatives

Basic Scheme : 

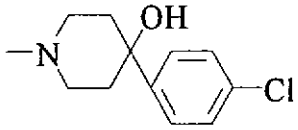
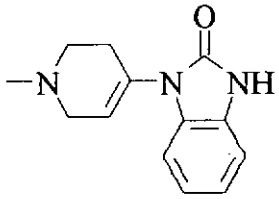
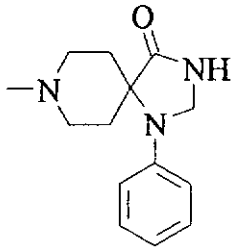
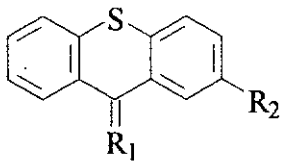
Drug Name	R
Haloperidol	
Droperidol	
Spiperone	

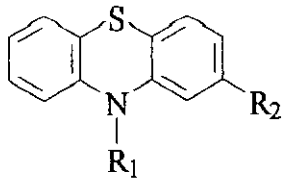
Figure 2-6-28. Thioxanthenes Derivatives

Basic Scheme : 

Drug Name	R_1	R_2
Chlorprothixene	$=CH(CH_2)_2-N(CH_3)_2$	$-Cl$
Thiothixene	$=CH(CH_2)_2-N$  $-CH_3$	$-SO_2N(CH_3)_2$
Flupentixol	$=CH(CH_2)_2-N$  $-(CH_2)_2-OH$	$-CF_3$

Figure 2-6-29. Phenothiazines Derivatives

Basic Scheme :



Drug Name	R_1	R_2
Promazine	$-(CH_2)_3-N(CH_3)_2$	$-H$
Chlorpromazine	$-(CH_2)_3-N(CH_3)_2$	$-Cl$
Trifluprомazine	$-(CH_2)_3-N(CH_3)_2$	$-CF_3$
Levomepromazine	$-CH_2CH(CH_3)CH_2-N(CH_3)_2$	$-OCH_3$
Promethazine	$-CH_2CH(CH_3)N(CH_3)_2$	$-H$
Prochlorperazine	$-(CH_2)_3-$N(piperazine)$-CH_3$	$-Cl$
Trifluoperazine	$-(CH_2)_3-$N(piperazine)$-CH_3$	$-CF_3$
Perphenazine	$-(CH_2)_3-$N(piperazine)$-(CH_2)_2OH$	$-Cl$
Fluphenazine	$-(CH_2)_3-$N(piperazine)$-(CH_2)_2OH$	$-CF_3$
Thioridazine	H_3C-N(piperidine)$-(CH_2)_2-$	$-SCH_3$
Propericiazine	$-(CH_2)_3-$N(piperidine)	$-CN$

8. Antidepressants

Figure 2-6-30. Dibenzocycloheptadiene Derivatives

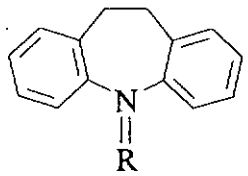
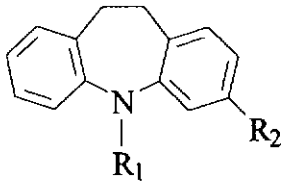
Basic Scheme	Drug Name	R
	**Amitriptyline**	$=CHCH_2CH_2N(CH_3)_2$
	Nortriptyline	$=CHCH_2CH_2-NH-CH_3$

Figure 2-6-31. Iminodibenzyl Derivatives

Basic Scheme :



Basic Scheme	R_1	R_2
Imipramine	$-(CH_2)_3-N(CH_3)(CH_3)$	$-H$
Desipramine	$-(CH_2)_3-NH-CH_3$	$-H$
Clomipramine	$-(CH_2)_3-N(CH_3)(CH_3)$	$-Cl$
Trimipramine	$-CH_2CH(CH_3)CH_2-N(CH_3)(CH_3)$	$-H$
Lofepramine	$-(CH_2)_3-N(CH_3)(CH_2CO-C_6H_4-Cl)$	$-H$

Chapter 3 The Bulk Pharmaceutical Industry of Mainland China

Section 1 The Status of China's Pharmaceutical Industry

In the international bulk pharmaceutical market Mainland China has been an active producer of generic drugs. On certain drugs, China's annual output even exceeds that of the US, EU, and Japan. In fact, in many cases, China has become one of the dominant producers in the world, particulary in the field of pencillins and vitamines. The current status of China's pharmaceutical industry is described below:

A. The manufacturing status of bulk pharmaceuticals in Mainland China in 1995

- The bulk pharmaceuticals are divided according to therapeutic effects into 15 items with total 534 drugs.
- From the bulk drug production volumes and manufacturer's production scale, one will be able to analyze whether there is room to compete with and whether there is a niche present.

B. The leading 30 imported bulk drugs in Mainland China in 1993 and 1994

- From the import trend one may know what Mainland China needs and whether Taiwan can provide it.

C. The performance and major products of the leading 30 bulk pharmaceutical companies and joint venture companies

- After understanding the performance and technology advantage of the leading 30 companies, one knows where to seek technical collaboration or how to compete in sales.

D. Investigations of the cooperation possibilities of both sides's bulk pharmaceutical industries

- Based on the informations provided from the above A, B and C items as well as the present status of Taiwan bulk pharmaceutical industry, one will be able to study the possibilities of cooperation between both sides.

Because Chinese government publishes their industrial financial informations after 24 months, one can only obtain the related informations of 1994 even from the Scrip Reports "The Chinese Pharmaceutical Market Guide 1996" published by PJB Publications Ltd. and SPAC Information Center. Also, due to the huge areas covered, minor errors of statistical numbers are inevitable. Therefore, these numbers can be seen as a trend and as a reference for strategic planning of Taiwan bulk pharmaceutical industry.

US dollar is used as currency unit for the sake of readers. If needed, please refer to the following tables of US dollar and RMB exchange rate and the inflation rate of Mainland China.

Table 12 Currency Exchange Rate (1983/1996)

Year	US$ = RMB
1983	1.9809
1984	2.7957
1985	3.2015
1986	3.4528
1987	3.7221
1988	3.7221
1989	3.7651
1990	4.7832
1991	5.3234
1992	5.5146
1993	5.7620
1994	8.6187
1995	8.3100
1996	8.2900

Source: International Financial Statistics Yearbook 1992;

International Financial Statistics April 1994;

International Financial Statistics July 1995;

The Chinese Pharmaceutical Market Guide 1996 (SCRIP Report). Vol.1, XV.

Table 13 Inflation Rate in Mainland China (1979/1994)

Year	General Price Index of Retail Sales	Retail Price Index of Consumer Goods
1979	102.0	102.1
1980	106.0	107.1
1981	102.4	102.6
1982	101.9	101.9
1983	101.5	101.2
1984	102.8	101.7
1985	108.8	109.7
1986	106.0	106.5
1987	107.3	107.4
1988	118.5	119.0
1989	117.8	117.5
1990	102.1	101.6
1991	102.9	102.9
1992	105.4	105.6
1993	113.2	113.0
1994	121.7	124.1

Source: State Pharmaceutical Administration of PR China;

The Chinese Pharmaceutical Market Guide 1996 (SCRIP Report). Vol.1, XV.

Pharmaceutical industry in China has gone through a lot of changes since the economic reform policy took place in 1978. Most significantly was the pro-active attitude traditionally held by the communist government had been changed gradually into a free-for-all market economy. About 3600 pharmaceutical companies had to face with a tough environment of competition. As a result between the year 1993 and 1995 over 200 companies went bankrupt.

Another 150 or so were merged with other companies. It is predicted that another 200 or so may be either merged or closed within the next 1~2 years.

Sales of traditional Chinese medicine (TCM) and western medicine (including bulk and generic drugs) in 1990~1994 are as follows:

Table 14 Pharmaceutical Sales of Mainland China in 1990~1994

(Unit: US$ 100 million)

	1990	1991	1992	1993	1994
TCM	19.05	20.29	22.81	24.21	13.27
WM	31.66	33.21	37.74	40.11	25.49
TCM: WM	1: 1.66	1: 1.64	1: 1.65	1: 1.66	1: 1.92

Source: Development in TCM Sector, (1994), China TCM Publishing House;

The Chinese Pharmaceutical Market Guide 1996 (SCRIP Report). Vol.1, P.22.

The export values and volumes as well as the production quantities of bulk pharmaceuticals are also shown below:

Table 15 The Export Value of Bulk Pharmaceuticals in 1992~1995

(Unit: US$ million)

Year	1992	1993	1994	1995
Export Value	531.33	716.88	1,095.18	1,333.74

Source: 1. China Pharmaceutical Industry Present and Future Symposium (1996)

2. The Chinese Chemical Industry Development Guide 1996. P.210

Table 16 The Export and Production Volumes of Bulk Drugs in 1994~1995

(Unit: tons)

	1994			1995		
	% of Total Export Volumes	Export Volumes	Production Volumes	% of Total Export Volumes	Export Volumes	Production Volumes
Antipyretic Analgesic	30.89%	18,783	34,213	22.50%	16,321	33,240
Vitamins	25.33%	15,402	20,702	27.70%	20,093	25,760
Antibiotics	19.50%	11,857	26,887	17.60%	12,766	29,551
Sulfonamides	5.60%	3,405	10,195	7.8%	5,658	13,667
Others	18.68%	11,359		24.40%	17,699	
Total	100.00%	60,807		100.00%	72,536	

Source: 1. China Pharmaceutical Industry Present and Future Symposium (1996)

2. The Chinese Chemical Industry Development Guide 1996. P.210

Section 2 The Status of China Bulk Pharmaceuticals Production in 1995

Mainland China produces over 1300 bulk drugs in 24 major classes. The more common 15 classes are described below according to their therapeutic categories:

	Therapeutic Category
1	Anti-infectives
	(1) Antibiotics
	(2) Sulfonamides
	(3) Furfurans
	(4) Tuberculostatics
	(5) Antileprotics
	(6) Antifungals
	(7) Antivirals
	(8) Others (including Quinolones)
2	Analgesics & Anti-inflammatory
3	Vitamins
4	Antiparasitics
5	Contraceptives & Hormones
6	Anticancers
7	Cardiovascular
8	Respiratory
9	Neurological
10	Digestive System
11	Endocrinological
12	Hemotological
13	Anesthetics
14	Antihistamines & Antidotes
15	Biochemicals

1. Anti-infectives:

(1) *Antibiotics*

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Acetylspiramycin	2,038.086	14
Amikacin	254.295	9
Amoxicillin	26.031	3
Amphotericin	0.005	1
Ampicillin	2,179.364	15
Benzylpenicillin G Potassium	1,119.413	8
Benzylpenicillin G Sodium	2,615.899	11
Capreomycin	0.765	1

Carbemicillin	1.104	1
Cefalexin	39.464	4
Cefatrizine	1.191	2
Cefazolin Sodium	17.241	2
Cefoperazone	0.471	1
Cefotaxime	9.028	4
Cefradine	20.239	3
Ceftazidime	0.040	1
Ceftriaxone Sodium	1.555	1
Chloramphenicol	2,504.775	10

Chloramphenicol Palmitate	13.740	1
Chlortetracycline	2,435.592	4
Clindamycin	33.772	10
Cloxacillin	3.395	1
Dihydro Streptomycin	261.663	2
Doxycycline Hydrochloride	114.143	3
Erythromycin	1,174.792	12
Erythromycin Bisulfate	12.867	1
Erythromycin Estolate	79.248	4
Erythromycin Lactobionate	23.693	2
Erythromycin Succinate	35.841	4

Fosfomycin	92.612	1
Gentamycin	1,114.263	30
Griseofulvin	160.340	2
Kanamycin	1,094.859	9
Kanamycin (Base)	570.050	1
Kitasamycin	362.120	8
Lincomycin	1,367.234	16
Lomefloxacin	0.011	1
Meleumycin	382.595	10
Metacycline Hydrochloride	25.419	3
Mezlocillin Sodium	0.013	1
Mioronomicine Sulfate	94.455	5
Neomycin	166.242	4

Nystatin	26.320	1
Oxacillin Sodium	29.713	3
Oxytetracycline	29,335.142	44
Oxytetracycline Hydrochloride	1,617.724	13
Piperacillin	44.055	3
Procaine Benzylpenicillin	384.383	3
Ribostarmycin	0.777	1
Rifamdin	39.087	3
Rifampicin	559.231	12
Rifamycin SV-Na	380.150	2
Rifapentine	6.000	1
Sisomicin (Bu)	161.140	2
Spectinomycin	0.399	1

Streptomycin Sulfate	1,228.742	5
Sulbactam Sodium	1.481	3
Tetracycline	1,588.963	10
Tetracyclline Hydrochloride	4,676.109	12
Thiamphenical	58.331	4
Tobramycin	0.671	4
Vancomycin Hydrochloride	0.049	1

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.847-857)

(2) *Sulfonamides*

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Ciprofloxacin Lactate	19.215	4
Sulfacetamide Sodium	720.550	1
Sulfadiazine	3,144.178	6
Sulfadiazine Silver	2.716	2
Sulfadiazine Sodium	460.050	1
Sulfadoxine	861.840	2
Sulfaguanidine	25,414.163	7
Sulfamethazine Sodium	1,662.609	4
Sulfamethazone	11,403.475	7
Sulfamethoxazole	4,471.834	14

Sulfanilamide	7,350.150	3
Sulfasalazine	114.000	1
Sulfathiazole	4,357.550	1
Sulfathiazole Sodium	30.000	1
Trimethoprim	1,408.382	16

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.858-860)

(3) *Furfurans*

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Furazdidone	7,847.671	11
Nitrofurantion	194.518	2
Nitrofurazone	16.873	2

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.861)

(4) *Tuberculostatics*

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Ethambutol	31.328	2
Isoniazid	267.625	2
Para-aminosalicylate Sodium	119.430	1
Pasiniazide	0.018	1
Profionamide	4.030	1
Pyrazinamide	162.453	4

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.862)

(5) *Antileprotics*

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Dapsone	2.610	1

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.863)

(6) *Antifungals*

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Bifonazine	2.500	1
Clotrimazole	41.429	6
Dequalin Chloride	0.100	1
Econyzole	1.162	2
Flucylosine	0.050	1
Ithranol	0.008	1
Ketoconazole	2.760	1
Miconazole	0.300	1
Miconazole Nitrate	9.893	3

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.864)

(7) *Antivirals*

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Acyclovir	0.343	2
Amantadine Hydrochloride	33.812	2
Moroxydine Hydrochloride	2,175.210	7
Ribavirin	91.406	5
Vidarabine	0.050	1

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.865)

(8) *Others (Including Quinolone)*

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Baicalin	0.300	1
Berberine Bisulfate	2.000	1
Berberine Hydrochloride	101.664	8
Berberine Tannas	0.200	1

Ciprofloxacin	226.843	9
Cyclosporin A	2.033	3
Enorxacin	2.915	4
Houttuynin	8.855	2
Matrine Tannas	2.900	1
Norfloxacin	5,202.792	16
Ofloxacin	19.869	6
Oridonin	10.410	1
Pipemidic Acid	191.735	3
Taurine	2,037.248	6

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.866-867)

2. Analgesics & Antiinflammatory

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Acetyl Salicylic Acid	8,892.566	8
Allopurinol	0.195	1
Amidopyrine	595.350	10
Analgin	8,826.230	13
Antipyrin	144.754	4
Aspirin-DL-Lysine	9.700	1
Benorylate	466.327	3
Clofenamic Acid	0.500	1
Dextropropoxyphene	1.031	1
Diclofenac	924.737	13
Fenbufen	17.120	1
Fortanodyn	1.430	1

Glucoside Tripterygh	0.024	1
Ibuprofen	1,609.022	3
Indolacine	0.156	1
Indomethacin	249.305	4
Ketoprofen	20.932	1
Lappaconifine HBr	0.098	1
Levopropoxyphene	0.252	1
Marasmic	60.500	2
Mefenamic Acid	131.581	4
Methocarbamol	51.742	1
Nabumetone	13.470	3
Naproxen	93.746	8
Nefopam Hydrochloride	12.230	3
Oxaprozin	4.500	1
Paracetamol	34,832.151	19
Phenacetin	6,511.452	7

Phenoxyprofen	0.435	1
Phenprobamate	19.625	2
Phenylbutazone	153.138	2
Piroxicam	28.064	4
Pizotifene	0.037	1
Probenecid	3.010	1
Rotundine	0.492	1
Sodium Salicylate	190.755	1
Sulindac	0.400	1
Tripterygll Hyproglauce	19.200	1

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.868-872)

3. Vitamins

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Acetomenaphthone	4.537	1
Adenine	0.100	1
Calciferol	.887	2
Calcium Pantothenate	17.954	1
Cobamamide	0.114	1
Crude Vitamin A	17.350	1
Crude Vitamin E	75.376	2
Cyanocobalamin	0.634	2
Folic Acid	394.232	3
Fursultiamine	83.700	2

Nicotinamide	133.504	3
Nicotinic Acid	560.532	5
Phytonadione	0.300	1
Riboflavino Phosphatis	0.534	1
Rutin	3,897.721	5
Sulfonium Chloride	54.611	5
Thiamine Mononitrate	3,266.039	8
Vitamin A Acetate	175.299	2
Vitamin B2	351.346	8
Vitamin B6	985.938	6
Vitamin C	29,289.493	16
Vitamin C90	79.000	1
Vitamin C-97	178.170	1

Vitamin C-Calcium	61.122	2
Vitamin C-Sodium	559.684	2
Vitamin E Acetate	2,631.634	7
Vitamin E Nicotinate	9.408	3
Vitamin K_3	1.764	2

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.873-876)

4. Antiparasitics

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Albendazole	315.483	7
Arteannuin	2.173	2
Artemether	0.350	1
Artesunate	1.685	1
Chloroquine Diphosphate	1,084.815	6
Diethylcarbamazine Citrate	1,000.000	1
Fenbendazole	31.030	1
Fluprofen	194.850	1
Hydroxychloroquine	2.500	1
Levamisole Hydrochloride	495.662	5
Levamisole Phosphate	21.232	2

Mebendazole	56.309	2
Metronidazole	7,478.543	15
Niclosamide	18.200	1
Oxfendazole	11.030	1
Parazine	96.103	1
Piperazafe	133.579	4
Praziquante	15.512	2
Pyrantel Embonate	70.518	1
Pyrimethamine	4.332	1
Tetramisole Hydrochloride	139.520	2

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.877-879)

5. Contraceptives and Hormones

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Antiflamisonum	0.100	1
Beclometasone Dipropionate	0.057	1
Betamethasone Dipropionate	0.033	1
Clobetasol	0.141	1
Cortisone Acetate	7.560	1
Dehydroepiandrosterone Acetate	0.140	1
Dexamethasone Phosphate	1.520	1
Estradiol	0.216	1
Estradiol Benzoate	0.087	1
Estradiol Valerate	0.038	1
Ethinyloesteradiol	0.263	1
Ethisterone	0.667	3
Fluocinolone	0.400	1

Glibenclamide	0.350	1
Glipizide	0.026	1
Halcinonide	0.310	1
Hexestol	0.125	1
Hydrocortisone (Acetate)	80.137	7
Hydroxy Progesterone Caproate	19.650	1
Medroxyprogesterone	0.805	1
Megestrol	0.175	1
Methylstanazole	0.043	1
Methyltestosterone	1.412	2
Mifepristone	0.422	3
Nandrolone Phenpropionate	0.217	1
Nanofin Hydrochloride	15.033	2
Nenonoxynoe	4.259	1
Nilestriol	0.025	1
Norethisterone	0.821	2
Norgestrel	2.844	4

Phenformin Hydrochloride	7.595	3
Potassium Iodate	242.641	2
Prasterone	0.014	1
Prednisolone	16.043	6
Prednisone	113.634	12
Progesterol	16.111	4
Quinoestrol	0.173	1
Stilbestrol	1.160	1
Tapazole	0.403	1
Testosterone	0.105	1
Testosterone Propionate	1.188	1
Tolbutamide	53.416	3
Triamcinolone Acetonide	3.366	3
Triamcinolone Acetonide Acetate	0.009	1

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.880-884)

6. Anticancer

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Aminoglutethimide	0.074	1
Aminopterin	0.006	1
Ancitabine Hydrochloride	0.002	1
Azathioprine	1.504	2
Bimolane	100.160	3
Camptothecine (CPT)	0.014	2
Carboplatinum	0.029	2
Carmustine	0.002	1
Chlorambucil	0.002	1
Chlormethine Hydrochloride	0.013	1
Cisplatin	0.020	2
Cyclophosphamide	0.991	1
Cytarabine Hydrochloride	0.048	1

Doxorubicin Hydrochloride	0.009	1
Ehtyliminum	14.964	2
Etoposide	0.037	3
Floxuridine	0.010	1
Fluorouracil	10.503	2
Ftorafur	5.103	3
Hydroxyurea	2.000	1
Isophosphamide	0.143	1
Mercaptopurine	0.004	1
Methotrexate	0.009	1
Mitomycin	0.016	2
Nitrocaphane	0.001	1
Polyactin A	0.071	3
Tamoxifen	0.045	1
Thio-TEPA	0.002	1
Vincrisfine	0.400	2

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.885-887)

7. Cardiovascular

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Aluminium Clofibrate	8.076	1
Amiodarone	7.554	2
Benzamino Salicylamide Hydrochloride	0.240	1
Betahistine Hydrochloride	10.500	1
Captopril	18.381	4
Cinnarizine	4.380	2
Clofibrate	8.000	1
Clonidine Hydrochloride	0.032	2
Complamin	12.816	3
Cyclandelate	2.010	1
Deslanoside	0.001	1
Dibazol	8.300	1
Digoxin	0.022	1
Dihydralazine Sulfate	11.552	1
Diltiazem	0.312	1

Dobutamine Hydrochloride	1.120	1
Dopamine	0.161	2
Enalapril	0.145	1
Ethyl Linoleate	26.115	2
Gemfibrozil	9.166	2
Guanoxane Sulfate	1.000	1
Hesperidin	2,914.433	4
Isosorbide Dinitrate	5.389	2
Ketobemidone	5.770	2
Ligustrazine	5.400	1
Ligustrazine Phosphate	1.296	1
Maize Oil	2,015.622	5
Methyl Hesperidin	12.500	1
Mexiletine Hydrochloride	5.532	1
Minoxidil	1.100	1
Molsidomin	0.968	1
Nicardipine	0.054	1
Nicorandil	0.006	2
Nifedipine	15.164	8
Nimodipine	16.247	3

Nitrendipine	3.250	6
Nitroglycerin	0.520	1
Noradrenadline	0.043	1
Panax Notoginsenosides	0.393	1
Pentaerythnitol Tetranitrate	0.575	1
Pentoxifylline	9.076	1
Persontin	38.859	3
Phenoxybengamine	0.010	1
Phenoxybenzamide Hydrochloride	0.960	1
Phenoxybenzamine	0.069	2
Polysaccharide Sulphate	33.500	5
Prazosin Hydrochloride	0.002	1
Propafenone Hydrochloride	10.576	3
Timolol	0.068	3
Trapidile	0.940	1
Venoruton	369.606	12
Verapamil	0.882	1
Verticil	3.509	2

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.888-893)

8. Respiratory

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Aminophylline	288.688	8
Ammonium Chloride (medicinal)	1,340.160	3
Baipujun Zhi Ke Fen	11.870	1
Bengenin	12.146	3
Benproperane Phosphate	8.087	4
Benproperone Phosphate	2.019	1
Bromhexine Citrate	21.856	2
Carbetapentane	101.092	2
Carbocysteine	1.900	1
Chloperastine	9.640	2
Clenbuterol Hydrochloride	0.037	3
Clorprenaline Hydrochloride	1.552	1

D-Ephedrine Hydrochloride	712.175	13
Dioxopromethazine	7.034	4
Diprophylline	23.373	1
Ephedrine Hydrochloride	1,620.017	15
Guaiacol	21.000	1
Guaifenesin	86.733	1
Jranilast	0.108	1
L-Ephedrine Hydrochloride	907.842	15
Methyl-Ephedrine Hydrochloride	183.400	2
Potassium Guaiacolsulfonate	114.174	2
Potassium Iodium	15.696	3
Theophylline	590.424	6

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.894-897)

9. Neurological

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Aceglutamide	0.482	1
Alprazolam	0.175	4
Amfepramone Hydrochloride	5.681	1
Amitriptyline Hydrochloride	1.160	1
Ammonium Bromide	4.214	1
Ammonium Bromide (Medicinal)	386.400	2
Amobarbital	40.777	1
Aniracetam	2.901	1
Atraxin	27.000	1
Barbital	68.235	1
Benzhexol Hydrochloride	1.590	2
Caffeine	3,639.057	13
Caffeine Sodium Benzoate	9.248	1
Camphor	52.870	1

Carbamazepine	536.287	9
Carbidopa	0.016	1
Chlordiazepoxide	11.412	1
Chlorpromazine Hydrochloride	71.731	3
Chlorzoxazone	2.714	1
Clazopine	16.857	8
Clomipramine	0.150	1
Clonazepam	0.094	2
Diazepam	358.167	3
Doxapram	0.003	1
Doxepin	4.360	2
Dried Powder of Armillaria mellea	53.170	1
Estazolam	5.807	2
Grastrodine	12.256	2
Haloperidol	0.041	1
Levodopa	115.934	5
Lithium Carbonate	5.974	1
Lithium Carbonate (Medicinal)	38.100	1
Magnesium Valproate	0.721	1

Maprotiline	0.011	1
Nitrazepam	6.410	1
Orygazol	241.990	6
Perphenazine	1.084	2
Phenobarbital	327.608	3
Phenytoin Sodium	103.510	1
Piracetam	578.417	8
Primaclone	4.551	1
Pyrithioxine Hydrochloride	31.349	2
Secobarbital Sodium	0.585	1
Sodium Camphorsulfonate	24.400	1
Sodium Valproate	20.994	1
Sulpirid	29.610	2
Tardan	1.644	1
Tiapride	3.042	1
Triazolam	0.010	2
Valpromide	11.268	1

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.898-903)

10. Digestive System

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Albumin Tannate	33.000	1
Aluminium Hydroxide	463.905	3
Anisodamine	2.887	3
Armillarisin	5.880	1
Atropine	1.658	2
Belladonna Liquid Extract	13.476	1
Benactyzine	201.760	2
Biphenyldicarboxylate	0.359	3
Bisacodyi	0.021	1
Bismuth Lactate	67.580	1
Bismuth Potassium Citrate	0.860	1
Bismuth Subnitrate	69.162	2
Carbenoxolone Sodium	0.150	1

Cimetidine	377.819	9
Cinametic Acid	22.842	3
Cuscohygrine	0.051	1
Diacetyldiphenolisatin	0.028	1
Diisopropylamine Ascorbate	1.812	1
Diphenoxylate Hydrochloride	0.644	2
Famotidine	7.494	5
Filcilin	0.100	1
Glucurolactone	106.977	3
Heavy Magnesium Carbonate	113.000	1
Herieii	126.368	2
Hydroxymethyl Coumarin	5.000	2
Inosine	5,229.899	6
Inositol	255.165	4
Krestin	1.029	2

Lactobicillin	110.737	2
Lactulose	42.439	1
Licorzinc	2.690	1
Magnesium Hydroxide	160.420	2
Magnesium Oxide	6.600	1
Magnesium Salfate	1,629.190	2
Magnesium Trisillicate	37.825	1
Medicinal Magnesium Carbonate	208.025	1
Medicinal Sodium Bicarbonate	11,223.000	2
Oleanolic Acid	13.100	1
Omeperazole	0.045	2
Orazamide	0.520	1
Phenolphthalein	1,325.160	2
Piperidic Acid	55.920	1
Proglumide	17.978	3
Ranitidine	174.563	8
Silymarin	73.228	4

Sucralfate	249.924	3
Thioctic Acid	0.313	1
Trepibutone	0.398	4
Tripotassium Glycyrrhizinic Acid	1.128	2
Wei Mei Su	22.678	2

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.904-909)

11. Endocrinological

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Acetazolamide	27.774	1
Amiloride	3.050	1
Bumetanide	0.015	1
Dimethylbiguanide	3.286	1
Furosemide	2.440	1
Hydrochlorothiazide	120.345	1
Mannitol(Medicinal)	2,451.320	3
Spironolactone	1.906	1
Theobromine	123.306	2

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.910)

12. Hemotological

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Adrenosin	2.028	1
Aminocaproic Acid	69.351	2
Batylalcohol	1.301	2
Dextran	528.924	14
Etamsylate	158.116	4
Ferric Ammonium Citrate	528.100	3
Ferric Glycerophosphate	0.659	1
Ferrous Gluconate	1.560	1
Ferrous Sulfate	31.795	1
Ferrous Sulfate (Medicinal)	485.575	2
Iron Dextran	281.919	2
Leucoson	1.959	1
Polyglucose	3,484.272	6
Sodium Citrate for Injection	44.900	1
Transamic Acid	14.274	1
Warfarin Sodium	0.013	1

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.911-912)

13. Anesthetics

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Bupivacaine Hydrochloride	8.000	1
Galanthamine	0.010	2
Ketamine Hydrochloride	0.653	2
Lidocaine Hydrochloride	38.136	3
Procaine Hydrochloride	762.995	4
Piridostigmine	4.000	1
Sodium Oxybate	0.200	1
Succinylcholine Chloride	0.013	1

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.915)

14. Antihistamines and Antidotes

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Chlorphenamine Meleate	281.787	2
Cyproheptamine Hydrochloride	0.900	1
Decloxizine	7.411	1
Dimenhydrinate	30.935	3
Diphenhydramine Hydrochloride	1,674.496	2
Diphenidol	44.231	3
Ketotifen	0.326	2
Penicillamine	0.186	1
Phenylpropanolamine Hydrochloride	11.142	1
Pralidoximeiodide	9.053	1
Promethazine Hydrochloride	75.117	3
Sodium Cromoglycate	0.067	1
Sodium Nitrite (Medicinal)	5.810	1
Terfenadine	4.050	1

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.916-917)

15. Biochemical

(Unit: Metric Ton)

Generic Drug Name	Total Production	Nos of Manufacturer
Adrenocorticotropin (0.1bU)	0.518	1
Antaisu	80.400	1
Aprotinin (0.1bU)	31.744	1
Artifical Calculus	285.685	20
Chondroitin Sulfate	0.200	1
Chorionic Gonadotropin (0.1bU)	23.346	1
Chymotrypsin	0.019	1
Cod Liver Oil	1,337.600	1
Coenzyme A (0.1bU)	203.657	2
Dried Powder of Cordyceps Sinensis Sace	2.453	1
Dried Yeast	53,407.238	6
Gastric Mucin	34.775	4
Glycine	4,230.320	2

Hyaluronidase (0.1bU)	48.524	1
Insulin (0.1bU)	2.678	2
Lactasin	15.057	3
L-Cysteine Hydrochloride	1,016.300	1
L-Cysteine	901.453	4
L-Cysteine	892.713	4
L-Glutamic Acid	129.530	2
L-Isoleucine	115.540	2
L-Leucine	868.970	3
L-Lysine	59.149	2
L-Lysine Hydrochloride	8.831	1
L-Phenylalanine	110.000	1
L-Threonine	15.487	1
L-Tyrosine	20.000	1
Oxystin (0.1bU)	4.030	1
Pancreatin	199.297	4
Pepsin	43.351	5

Pituigan (0.1bU)	0.354	1
Protamine Sulfate	0.032	1
Sodium Cholate	73.050	1
Sodium Heparin (External)(0.1bU)	322.489	2
Sodium Heparin (Pure) (0.1bU)	2,680.444	5
Trypsin	0.003	1

Source: PRC Pharmaceutical Industry Database, 1996 edition. (P.918-922)

Chapter 4 The Bulk Pharmaceutical Industry in Taiwan

Section 1 A Highly Regarded Industry

In recent years, because of the growing environmental protection awareness and the escalating manufacturing cost, traditional chemical manufactures in Taiwan are fighting for survival. Therefore, the government is encouraging the chemical industry to develop high-tech, high value-added, and low waste production specialty chemicals. Among the specialty chemical industries, pharmaceutical industry is directly related to human health. Also, it is characterized as a high-tech and high value-added industry with worldwide market potential.

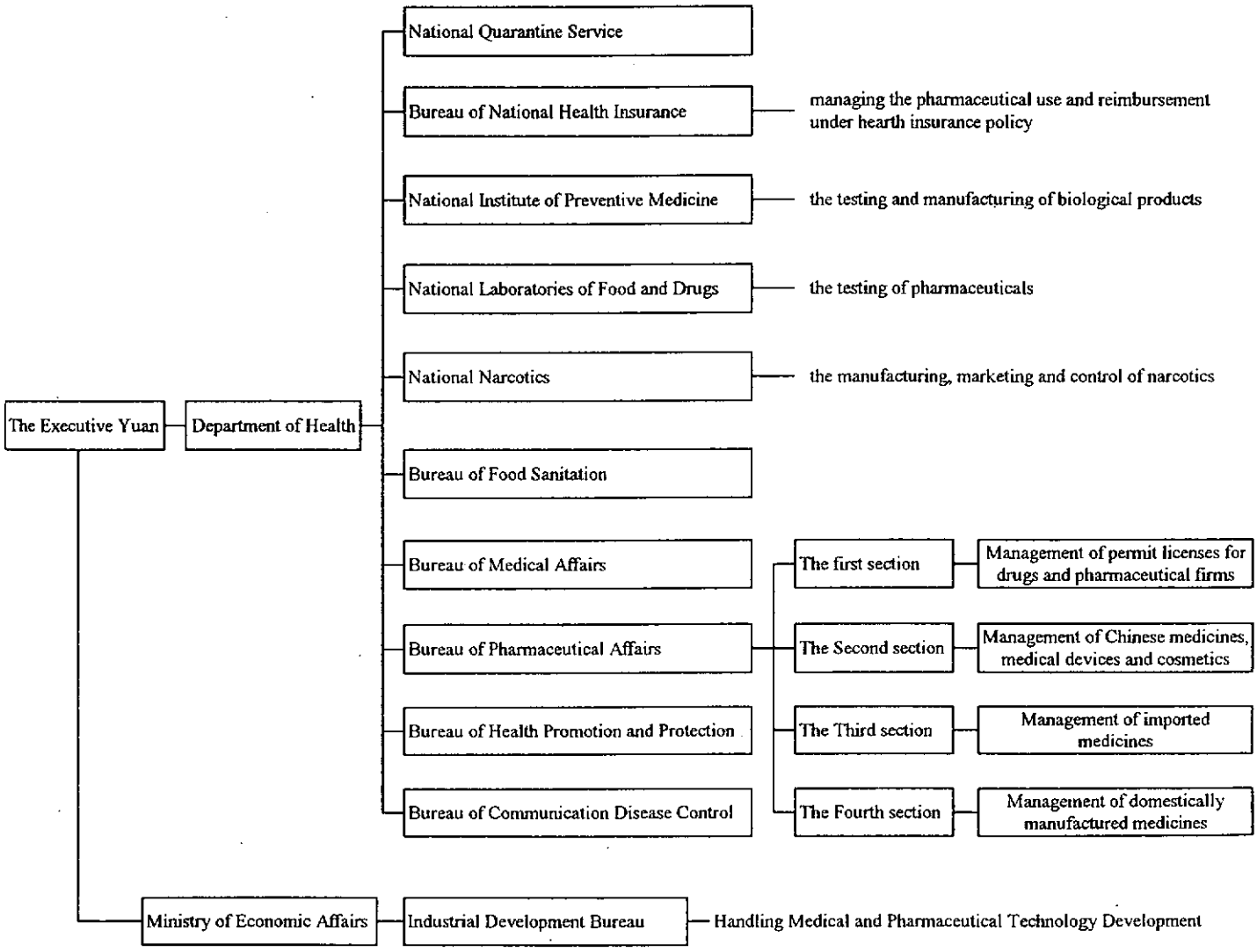
The pharmaceutical industry was designated to be one of the Ten New Priority Industries in Taiwan. Recently, pharmaceuticals (bulk drug, new drug, new dosage form) and modern Chinese medicine (new dosage form, new formulation, new indication) are among the promoting items for the plan of establishing Taiwan as the Asia-Pacific Manufacturing Center.

Section 2 Health Organization

In the government, the Bureau of Pharmaceutical Affairs under the Department of Health, the Executive Yuan handles most of the pharmaceutical relevant matters. There are four sections in the Bureau of Pharmaceutical Affairs in charge of the following affairs: management of permit licenses for drugs and pharmaceutical firms (the First Section); management of Chinese medicines, medical devices, and cosmetics (the Second Section); management of imported medicines (the Third Section); management of domestically manufactured medicines (the Fourth Section). Other pharmaceutical related organizations include: National Narcotics in charge of the manufacturing, marketing and control of narcotics; Bureau of National Health Insurance managing the

pharmaceuticals use and reimbursement under health insurance policy; National Institute of Preventive medicine handling the testing and manufacturing of biological products such as vaccines; National Laboratories of Foods and Drugs responsible for the testing of pharmaceuticals.

Table 17 Health Organization



One of the characteristics of pharmaceutical industry is the tight regulations of government agency. The goals of pharmaceutical control are to safeguard the use of medicines, to upgrade the quality of medicines and to bring up the level of local pharmaceutical industries to the international standard. Some major activities are as follows:

- Laws and regulations on pharmaceutical affairs
- Inspection of medicines and cosmetics and control of advertisements
- Registration and market approval of medicines and cosmetics and safety surveillance of new medicines
- Supervision of pharmaceutical industries
- Control of narcotics for medical use
- Control of pharmaceutical firms and the separation of dispensing practice from medical practice
- Control of drug abuse
- Computerization of pharmaceutical affairs

Considering the safety, efficacy, and quality, there are the following regulations in the Law of Pharmaceutical Affairs and the Law for the Sanitary Control of Cosmetics:

- All medicines (western and Chinese herbal medicines and medical devices) and cosmetics must apply in advance for registration and market approval following the guidelines for the registration and market approval of medicines issued by the Department. They can be manufactured, imported or sold only after permit licenses are issued.
- Permit licenses are good for five years, each extension can not be over five years.
- Factories that manufacture medicines should meet the GMP requirements (Chinese herbal medicines and bulk pharmaceuticals are not included).

- In 1993, the Law of Pharmaceutical Affairs gave a new definition to new drugs (including new chemical entity, new use, new formulation, or new dosage form, etc.), and indicated that new drugs should conduct clinical trials.
- Clinical trials have four stages:

  Phase I: in normal human volunteers 20 or more people

  Phase II: in a small number of subjects100 or more patients

  Phase III: in a few hundred or a few thousand patients

  Phase IV: post-marketing surveillance to see any side effects or other adverse reactions
- For the importation of new drugs, free sale certificates from at least three of the ten countries, Australia, Belgium, Canada, France, Germany, Japan, Sweden, Switzerland, UK and USA, should be submitted.
- To protect the patent rights of foreign new drugs in the Taiwan area and to promote research and development of domestic pharmaceutical industries, the Department of Health establish a safety surveillance system for new drugs. The surveillance period is seven years. Since August 1993, for the registration and market approval of new drugs, in addition to the documents required by the current regulations, reports of domestically conducted clinical trials should also be attached. In the first stage of surveillance (the first 5 years), agents and manufacturers, in applying for either the manufacturing or importation of common name medicines of similar preparation or dosage, must submit reports of domestically conducted clinical trials equivalent to that of the original manufacturer; in the second stage (the last two years), they should submit reports of bioequivalence tests conducted by either domestic or foreign laboratories authorized by the Department of Health.

Section 3 The Bulk Pharmaceutical Industry in Taiwan

1. History

Taiwan bulk pharmaceutical industry started from 1940's during the period of Japanese occupation. For example, Takeda Chemical Industries (Taiwan) Co. in Miao-Li manufactured tartaric acid for Japanese government and Taiwan Sheng Yao Co. in Hsin-Ying worked on cocaine extraction. After 1945, Taiwan pharmaceutical industry emphasized on manufacturing of formulated products. Most of the bulk pharmaceuticals were imported. Therefore, at that time the items, qualities, quantities, and prices of Taiwan's pharmaceutical products were determined by the source of bulk pharmaceuticals. Imported bulk pharmaceuticals controlled the development of whole Taiwan pharmaceutical industry.

The government recognized that developing the bulk pharmaceutical industry is the foundation of the entire pharmaceutical industry. In 1973, National Science Council supported the synthesis of more than ten bulk pharmaceuticals, including CNS drugs, sympathetic system drugs, diuretics, tonics, etc. All of these items were aimed at scale-up production. Although all the syntheses had been successively completed, due to the problems in industrial environment and mass production technology, most of the products had not been commercialized except for nicotinic acid, nicotinamide, and kainic acid.

In 1981, the promotion of bulk pharmaceutical industry was in charge by the "bulk Pharmaceutical Manufacturing Evaluation Committee" made of people from Ministry of Economic Affairs, Department of Health, Bureau of Agriculture, National Science Council, pharmaceutical industry, and academic institutes. For encouraging pharmaceutical companies to manufacture bulk pharmaceuticals, the "Implementation Plan to Promote the Production of Bulk Pharmaceuticals" was declared. Manufacturers were benefited from several policies such as a temporary curtail in registration for inspection and temporary halt in import. Eighteen products were manufactured during this period. Recently, because of the free trade and

entering WTO, the above "Implementation Plan" was abandoned after twelve years of execution.

In order to upgrade the pharmaceutical industry and reduce the impact of imports to the bulk pharmaceutical industry, for bulk drug items that a local pharmaceutical company can produce sufficient quantities by itself to supply the domestic market, the taxation rate of imports is 10%. From October 1994 until now, twenty-two bulk drugs are applicable by the above policy. As for the bulk drug items and intermediates that were not manufactured in Taiwan, they were tax-free.

The pharmaceutical industry was recently designated to be one of the Ten New Priority Industries in Taiwan's Six-Year National Development Plan. It is also among one of the industries in the Plans for promoting Taiwan to be the Asia-Pacific Manufacturing Center. The government has several incentive programs for promoting the bulk pharmaceutical industry, e.g., industrial technology development plan, new leading products development plan, development fund investment plan, and R&D incentive programs. It is hoped that through these programs, the bulk pharmaceutical industry can be upgraded and be competitive in the international market.

2. *The Present Status of Local Pharmaceutical Industry*

In 1994, Yung Shin Pharm. Co. invested NT$ 1 billion to build a new plant. In 1995, six companies including Cyanamid Taiwan Co. and China Chemical & Pharmaceutical Group had investment plans. Since 1996, big investment cases are declining, only Taiwan Biotech Co. and Scino Pharm, Inc. made investment with the help of Executive Yuan's Development Fund. It is particularly noted that the Scino Pharm, Inc. intends to invest NT$ 4.5 billion for building bulk pharmaceutical manufacturing plant in comply with FDA's requirements. Hopefully, these investments will bring bulk pharmaceuticals into international market. It is predicted that by 2000 the production value of Scino Pharm will reach NT$ 5 billion.

The list of local pharmaceutical companies with better net sales in 1995 is as follows:

Table 18 The Operation Status of Taiwan Pharmaceutical Companies in 1995

(Unit: NT)

Company	Assets (million)	Net Sales (million)	Sales Growth Rate (%)	Income beofre tax (thousand)	% of Net Income	Employee (No. of people)
San Yo Pharm. Ind.	195	3,276	7.30	425,135	12.97	194
CPCC	1,881	2,080	17.27	37,213	1.78	751
Yung Shin Pharm.	1,168	1,980	14.09	376,384	19.00	900
Taiwan Hoechst	62	1,483	-8.57			210
Novartis	1,017	1,201	-0.01			
Sintong Chem. Ind.	300	1,041	5.37	-112,482	-10.79	480
Lilly	16	872		95,765	10.98	191
Yuen Foong Chem. Ind.	180	842	15.08			
Standard Chem. & Pharm.	547	722	11.56	132,169	18.29	384
Fujisawa Pharm.	290	690	26.36	78,111	11.31	198
Grape King	869	676	-7.92	N.A.		N.A.
China Chem. Syn. Ind.	445	643	34.09			120
Boehringer Ingelheim	300	626	-0.74	75,934	12.12	207
Kingdom Pharm.	250	589	9.09	20,288	3.44	225
Swisspharma Taiwan	170	569	14.58	N.A.		62
Takeda Chem. Ind.	90	554	4.85	60,748	10.95	204
Taiwan Tung Yang Chem.	198	337		10,408	3.08	128
Nang Kuang Pharm.	180	293	0.31			155
Delta Synthetic	20	281	53.18	23,241	8.26	27
Min Tong Pharm.	120	270	19.51	N.A.		170
Taiwan Biotech.	266	195	9.51	-15,222	-7.78	37
Seven Star Pharm.	10	132	9.10	10,377	7.85	38

Source: China Credit Information Service Ltd.

The population in Taiwan is twenty-one million and four hundred thousand people. According to a report by IMS Taiwan Co., pharmaceutical sales in 1995 were NT$ 43.3 billion, a 13% increase compared with 1994. The above figure does not include sales of government's health stations, special health rooms, and dental clinics which account for ca. 5% of sales. Therefore, total pharmaceutical sales were about NT$ 45.5 billion. To the third quarter of 1996, pharmaceutical sales already reached NT$ 54.1 billion. Although it had double-digit growth, the pharmaceutical market in Taiwan was rather small, only 3.5% of the sales in Japan and 20% of the sales in Korea with a population of forty-five million.

For bulk pharmaceuticals, there are only about twenty companies in operation. It can be divided into three categories:

- Bulk pharmaceuticals only: Delta Synthetic, Seven Star Pharm., Syn-Tech Chem. & Pharm., Cheng Fong Chem., Taiwan Biotech., San Yueh Chem., Forever Chem., Prince Pharm., Su Chiang Chem. & Pharm., Siegfried Chem., Tainan Peng Lai Enterprise, etc.
- Bulk pharmaceuticals & formulation: China Chem. Syn. Ind., Kingdom Pharm., Yung Zip Chem. Ind., Kink Lab., Cyanamid Taiwan, Yuen Foong Chem. Ind., etc.
- Intermediates: Techco Chem., China Camphor, etc.

Table 19 The Operation Status of Taiwan Bulk Pharmaceutical Companies in 1995

(Unit: NT)

Company	Assets (million)	Net Sales (million)	Sales Growth Rate (%)	Income before Tax (thousand)	% of Net Income	Employee (No. of people)
China Chem. Syn. Ind.	445	643	34.09			120
China Camphor	142	358	16.12	550	0.15	76
Delta Synthetic	20	281	53.18	23,241	8.26	27
Taiwan Biotech.	266	195	9.51	-15,222	-7.78	37
Cheng Fong Chem.	101	191	11.02	7,260	3.79	51
Siegfried Chem.	200	191	-4.24	-21,700	-11.31	79
Yuen Foong Chem. Ind.	180	842	15.08			
Yung Zip Chem. Ind.	124	165	23.77	16,720	10.12	70
Seven Star Pharm.	10	132	9.10	10,377	7.85	38

Source: China Credit Information Service Ltd.

It is estimated that the total assets of Taiwan bulk pharmaceutical industries are ca. NT$ 2.5 billion with an average of NT$ 130 million/ company. Generally speaking, the bulk pharmaceutical industry belongs to small and medium enterprise. There are one-third of the companies with assets below NT$ 60 million, one-third between NT$ 60 million and 100 million, and one-third between NT$ 100 million and 300 million. Over 80% of the companies are with assets below NT$ 300 million.

According to a survey report in June 1996 conducted by Industrial Technology Information System (ITIS), the total employees of bulk pharmaceutical industries are ca. 700 people with 44% in manufacturing, 10% in sales, 13% in management, 8% in R&D, 10% in quality control, and 15% in others. The manpower ratio of R&D is rather low compared with the other developed countries. However, when comparing with other industries in Taiwan, the ratio is in the high range. As for the education background, 63% of the employees are below college level, 30% are college graduates, 4% have master degrees, and 2% have Ph. D. degrees.

The recent production, import and export values of bulk pharmaceuticals are as follows:

Table 20 Bulk Pharmaceutical Market in Taiwan

(Unit: NT$ 100 million)

Year	Production Value (A)	Export Value (B)	Import Value (C)	Market (A+B+C)
1991	15.9	4.25	31.20	42.85
1992	13.3	3.26	35.70	45.74
1993	27.1	5.91	39.96	61.15
1994	22.9	6.90	49.95	65.95
1995	28.4	8.93	49.48	68.95

Source: 1. Present and Future of Taiwan Pharmaceutical Industry DCB-IS-E-030 (82) P36-37

2. Present and Trend of Global Pharmaceutical Industry special report DCB-151-S303 (85) P61

The import value in 1995 decreased 0.9% compared with 1994. Antibiotic was the largest (52%) import item (The first three antibiotics were Cefaclor Monohydrate, Amikacin, and Cephalexin Monohydrate). Vitamin was next (25%). The export value in 1995 increased 29% compared with 1994. Antibiotic was also the largest export item, accounted for 16% of the total export value. As for the starting materials for manufacturing bulk drugs, 25.76% came from Japan according to a survey report by Union Chemical Laboratories of Industrial Technology Research Institute. Lacal compaines produced 17.88% and 27.38% came from Mainland China and India. Another 9.66% were from Germany.

3. *Important Bulk Pharmaceutical Products*

The bulk drugs which are registered and manufactured by indigenous bulk pharmaceutical companies are described in Table 21:

Table 21 Bulk Drugs Manufactured Indigenously

Therapeutic Categories	Items
CNS drugs	Alprazolam, Astemizole, Chlorpheniramine, Dextroamphentamine, Dyphylline, Fluoxetine, Phenindiamine, Theophylline.
Cardiovascular drugs	Alufibrate, Amlodipine, Atenolol, Captopril, Clonidine, Enalapril, Nicametate, Nifedipine, Probucol, Propranolol, Ubequinon.
Antiinflammatory analgesic	Acetaminophen, Diclofenac, Mefenamic Acid, Naproxen, Oxaprozin, Piroxicam, Sulpyrin.
Antiinfectives	Amoxicillin, Ampicillin, Aspoxicillin, Cefaclor, Cefadroxil, Cefalexin, Ceftriazine, Cefuroxime Axetil, Cephradine, Chloramphenicol, Ciprofloxacin, Colistine, Dextromycin, Dicloxacilline, Econazole, Erythromycin, Fluconazole, Flumequine, Miconazole, Nalidixic Acid, Norfloxacin, Oxolinic Acid, Oxytetracycline, Povidone, Rifampicin, Ronidazole, Sulfadiazine, Sulfamethomidine, Sulfamethoxazole, Thiamphenicol, Trimethoprim.
Cough medicines	Bromhexine, Cloperastine, Guaifenesin.
Gastrointestinal drugs	Antacids, Anethol Trithione, Arprinocid, Cimetidine, Crotamiton, Dimetridazole, Famotidine, Kainic Acid, Nicarbazine, Omeprazole, Ranitidine, Sucrafate, Urogastrone.
Local anesthetics	Bucetin, Lidocaine, Oxethazaine, Procaine, Xylocaine.
Muscle relaxants	Chlormezanone, Chlorzoxazone, Methocarbamol.
Antidiabetics	Glipizide, Glyburide.
Others	Benzalkonium Chloride, Melatonin, Propentofylline, Terbutaline Sulfate, Terfenadine.

4. *Research and Development*

There are about 150 bulk drugs which are manufactured indigenously, including antibiotics, vitamins, antiinflammatories, cardiovascular drugs, gastrointestinal drugs, CNS drugs, etc. Technically speaking, bulk drugs produced by organic synthesis usually can be manufactured without any difficulty. Several companies are investigating somewhat more advanced synthetic technologies such as high-pressure hydrogenation and organometallic reactions. Cyanamid Taiwan Co. uses fermentation to producing tetracyclines. China Camphor Co. uses chiral resolution technology to manufacturing D-phenylglycine. Although many manafacturing technologies are accessible in bulk drug production, the capability of technology development is still lacking.

The production chain of β-lactam antibiotics has been established. Technologies for preparing chiral drugs such as antihypertensives (Captopril, Enalapril, Timolol, Diltiazem), cholesterol lowering agents (Lovastatin, Pravastatin), and antiinflammatories (Naproxen) are under development.

There are lots of overlap among the R&D directions in the bulk pharmaceutical industries. For example:

China Chem. Syn. Ind.:	antihypertensives, cholesterol lowering agents, antibiotics, CNS drugs, gastrointestinal agents, antiinflammatories, etc.
Yung Zip Chem. Ind.:	cholesterol lowering agents, antibiotics, gastrointestinal agents, antiinfectives, antihypertensives, anticancer drugs, etc.
Syn-Tech Chem. & Pharm.:	cholesterol lowering agents, gastrointestinal agents, antibacterials, antihypertensives, muscle relaxants, antacids, etc.

Sintong Chem. Ind.:	antibiotics, cholesterol lowering agents
Taiwan Biotech:	antibiotics
Kingdom Pharm.:	anticancer drugs, antihypertensives, antibiotics, antacids
Everlight Chem. Ind.:	prostaglandins, antiinflammatories, cardiovascular drugs

As for the new drug discovery, the main R&D activities are in academia, especially at universities with pharmacy and chemistry departments. Compounds from natural product isolation and purification or from organic synthesis are sent for pharmacological screenings. With the financial help by National Science Council and matching fund by local pharmaceutical industries, several compounds have been sent to screening centers abroad for preclinical studies, e.g., anticancers (Kingdom Pharm. and Yung Shin Pharm.), antiarrhythmic (CPCC), antihypertensive agent (Purzer Pharm.), antiviral (Yung Shin Pharm.), etc.

Section 4 Evaluating Taiwan's Bulk Pharmaceutical Industry

During the last two decades, Taiwan has become one of the world's most dynamic economic forces. In an island that has a population of 21 million people and has little or no natural resources, what Taiwan has accomplished is indeed an economic miracle. Of course, along with the growth of the economy come several growing pains such as inflation, pollution, rising labor cost, etc. All these problems have rendered Taiwan less competitive and have driven many labor intensive businesses, which used to be Taiwan's core industries, out of Taiwan. As Taiwanese manufacturers are gradually abandoning these traditional business, they are laying their eyes on the highly profitable, technology oriented industries, one of which being the pharmaceutical industry.

- *Advantages*

1. Strong Support from Taiwanese Government

Determined to build up a prosperous pharmaceutical industry that will be an important integral in the Asia-Pacific Manufacture Center, the Taiwanese government has designated the pharmaceutical industries as one of its Ten New Priority Industries. As an attempt to stimulate the development of Taiwan's pharmaceutical industry, numerous R&D incentive plans have been designed. Some of the most important plans include "industrial technology development plan", "new leading products development plan", development fund investment plan", etc.

2. Assistance from Non-profitable Research Institutes

Because only a handful of Taiwanese drug manufacturers has adequate R&D capabilities, non-profitable research institutes have become a source for technology and information. Two of the most important research institutes in Taiwan are UCL and DCB, which are partially financially supported by Taiwanese government. In many occasions, these institutes have assisted drug manufacturers in the development of key knowhows. Some of the well known projects include the synthesis of enalapril, diltiazem, fluconazole, terfenadine, etc. More importantly, for years these well equipped and well organized institutes have served as the hotbed for the future engineers and managers of the private enterprises.

3. Strong Interest and Ambition from Taiwanese Drug Manufacturers

Over the years, Taiwan has built an excellent drug formulation industry. There also were some small scale bulk pharmaceutical productions. However, the quantity was very small that are insignificant.

In recent years, lured by the enormous profit of the bulk drugs, several drug formulators have included the manufacture of bulk pharmaceutical into their business activities. Some of the renounced companies include C&P, Sheng Ta, and Taiwan Cyanamide. In addition,

not only the drug formulators are showing interests, manufacturers from other industry such as specialty chemical, dye-stuff, and agrochemical are also getting involved in the bulk pharmaceutical business. These companies are expected to become the cornerstone of Taiwan's bulk pharmaceutical industry.

- *Disadvantages*

1. Inability to Deal with Intellectual Property Rights

The growing awareness of intellectual property right has handcuffed on the generic makers' ability to enter the world pharmaceutical market. Even the slightest patent infringement could make years of effort fruitless. Patents and lawsuits are the Achilles' heel for most Taiwanese companies, as they are usually inexperienced in dealing with patents and copyrights.

2. Shortage in Human Resources

According to ITIS's statistics, the total work force in Taiwan's pharmaceutical industry is about 700 people altogether. Of these 700 some personnel, only a very small fraction is experienced in the field of bulk pharmaceutical industry. This shortage of trained personnel may give Taiwan's pharmaceutical industry problems in the researching, manufacturing and sales of pharmaceutical products.

3. Lack of Integration among Manufacturers

At the moment, there are a few dozens of bulk pharmaceutical producers in Taiwan. Oftentimes, these manufacturers are making the same products and competing in the same market. In order to reduce cost, maintain high product quality, avoid competition in Taiwan market, and increase competitiveness in the world market, integrating these manufacturers into strategetic alliances may be needed.

4. No Interest in the Development of New Drugs

To develop a new drug from scratch would require enormous human resources and captial investment. Moreover, it is a rather time consuming process, as a new drug would take a dozen of years before it could finally hit the market. Most importantly, the risk is very high as there is no guarantee that the drug will be successful. The high risk and the long investment return period have made Taiwanese drug producers unwilling to participate in new drug development.

5. Competitions from Third World Countries

Competitions from third world countries may pose the biggest threat to Taiwan's drug industry. Having the advantages of low labor cost and production cost, products from these countries could give Taiwan a run in the fight for market share and profit.

Section 5 What Taiwan Can Do

Despite the weaknesses it has, Taiwan's pharmaceutical industry still have a good chance to flourish. There are several measures Taiwan can implement to solidify its position in global pharmaceutical market.

- Intellectual Property Rights

1. Strengthen the ability in R&D

Taiwan has a number of institutions that are solid in fundamental chemistry and enough funding for both R&D and capital investment. The industy may work closely with these insititutes to develop new manufacturing knowhows that are unrestricted by patents.

2. Establish Patent Related Legal Services

Taiwanese government could establish offices or services which provides legal advice on problems pertaining to intellectual property rights.

3. Seek for Technology Transfer

Taiwan's pharmaceutical industry may either purchase the needed technology from the patent assignees or pursuit for joint venture with the bearer of the needed technoloy in Taiwan.

- Human Resources

1. Promote interaction between industry and research institutes

Research institutes may assist pharmaceutical industry in several ways:

a. Personnel training
b. Technological consultation
c. Collaboration in the development of key technologies

2. Promote interaction between Taiwan and major pharmaceutical producing nations

Taiwan's pharmaceutical industry may actively participate in multi-nation (or cross-nation) research project. Interactions with experts from other nation could help Taiwan's pharmaceutical industry learn the global trends in market and technology.

- Global Market

1. Establish Overseas Alliance

Overseas alliance can be formed via joint-venture, buyout, brokerage and merger. The formation of alliance would help Taiwan find overseas distribution channels.

2. Establish overseas R&D groups or plants

This will give companies more flexibility in selling their products into overseas market, as companies will have a better ideals on the rules and regulations and also have a better grasp of market information.

3. Seek for the Assistance from Taiwan's Overseas Offices

Taiwanese government has trade offices in most of the nations. These offices are excellent channels for market informations. Most importantly, they may offer some insightful legal advices.

- Strategic Integration

1. Form Strategic Alliances with Other Chemical Manufacturers

Taiwan has several chemical related industries, such as agrochemical, dye-stuff, and specialty chemical, that could be the suppliers of the important intermediates or OEM partners. Combining the up-stream, middle-stream, and down-stream together can avoid unnecessary investment in R&D and facilities.

2. Collaborate in R&D Works

Undoubtedly, both UCL and DCB are excellent research institutes. All have state of art facilities and capable researchers. Unfortunately there are many overlaps and too little interaction between the two. As a matter of fact, in many cases, they are competing on the same research topic. Perhaps the two ought to cooperate more often in order to save resources.

- Increase Effort in New Drug Development

1. Establish New Drug Development Institutes

There is a need to establish an institute that specializes in new drug development. This institute can also cooperate with other overseas research institutes in the development of new drugs and may serve as a link in bringing new ideas and technologies into Taiwan.

2. Promote Traditional Herbal Medicines

With its annual sales topping US$ 3.0 billion, traditional herbal medicines are gaining more recognitions worldwide. For instance, in the US alone, the annual sales totals up to 3 billion US dollars. Because of westerners' preference in the potency of one active ingredient and the convenience of capsules, pills, or tablets, the identification and isolation of the main active ingredient may be the direction for traditional herbal medicine. More importantly, the isolated active ingredient may help drug companies and research institutes design new generation drugs.

Section 6 Opportunities for Taiwan

1. Growing Demand for Generics

In recent years, the sales of generic drugs is demonstrating a double digit growth annually. This may be the best timing for Taiwanese makers to enter the market and capture significant marketshare with high quality, reasonably priced generic products.

2. Growing Interest in Integration and Strategic Alliance

For many years, Taiwan's pharamceutical makers had very little cooperation among themselves and most of the time were competing against each others in the Taiwanese market. The term "stragetic alliance" was almost non-existent. Nowadays, however, the trend is gradually changing, as more and more producers are starting to cooperate through merger or partnership in production with latter being the most common.

3. The Return of Pharmaceutical Specialists from Overseas

In the 70's and 80's, thousands of Taiwanese students went to the U.S. for a higher education. Most of them later ended up working in the U.S. industries, particularly in the R&D field. In early 90's when the US was facing an economic slowdown which forced many U.S. companies to cutback on R&D spendings and restructure, many of these specialists returned to Taiwan. These specialists may provide the much needed experiences and the key knowhows for the bulk pharmaceutical makers.

4. Growing Acceptance in Traditional Herbal Medicine

Often being labeled as voodoo or superstition, herbal medicine or tradtional medical practices have long been overlooked by the western world. However, recently herbal medicines are drawing substantial attentions from western scientists and health departments, as

in many occasions they have proven to be effective remedies and dietary supplement. This has breathed a new life into the traditional herbal medicine, particularly in the identification and extraction of active ingredient contained in the herbal medicines.

Section 7 Possible Threats

1. Multinationals' Involvement in the Generic Pharmaceutical Market

Realzing the potential in the rapid growth of the generic market, many multinationals are getting their act in this business by selling their own generics either through establishing their own generic divisions or buying out other generic makers.

2. Rising Production Cost

The rapid economic boom in Taiwan has raised Taiwan's standards of living. However, along also comes the rise in labor cost which renders Taiwan less competitive in labor intensive industries. Under this circumstance, Taiwan's bulk pharmaceutical industry has to upgrade its technology level and find its fields of expertise in order to avoid competing in the low value, low technology products.

3. Dependence on Incentives from the Government

Goverment offered incentives are interim measures designed to encourage the development of an industry. However, some applications have a different idea, as they tend to use the funding for other purposes. For instance, Taiwan's government has agreed to a NT$4 billion investment funding recently. Suprisingly, nobody involved in this plan is experienced in drugs R&D nor in full scaled production. The government officials were simply blinded by the sugar coating created by the predicted lucrative profit return and pursuaded by the intimate relation between the applicant and bureaucrat. The passing of this investment plan confuses many genuine drug manufacturers and will encourage other immoral firms to follow suite.

Section 8 The Future

According to Taiwan government's forcast, by year 2002 Taiwan's pharmaceutical output would total up to NT$110 billion. Within this stunning figure, the total output of bulk pharmaceuticals was forecasted at NT$50 billion. However, other evaluations disagree with these figures. For example, DCB reported that in 1995 the total output in Taiwan's bulk pharmaceutical product was NT$2.4 billion. Assuming an average 10.3% growth could be achieve between year 1995~2000, the total in year 2000 would be a mere NT$4.6 billion, which is lightyears away from the forecasted NT$50 billion! This projected NT$50 billion has become a controversial issue and been extensively debated in many symposia and conferences. In order to obtain a more realistic forecast, it becomes necessary to evaluate the status and strength of Taiwan's pharmaceutical industry.

In order for Taiwan's bulk pharmaceutical output to reach NT$50 billion in 2002 from NT$2.8 billion in 1995, the average growth has to reach 51.8%. Even at a lower number of NT$25 billion, the required annual growth rate is 37.4%. Under Taiwan's current economic strength, this high growth rate may be very difficult to achieve. For example, in the recent years, the electronic sectors, particularly in the semiconductor, telecommunication, and computer industries, have been the most dynamic and profitable industries inTaiwan. The growth rate in the semiconductor industry is 18.6%, followed by the telecommunication and the computer industry at 15.2% and 12.7%, respectively.

Under the current growth of 10.3%, to reach NT$50 billion may be unrealistic. Even the inclusion of Scino Pharma's projected output of NT$5 billion by year 2000 would not be enough to propel the figure to NT$50 billion. It would require about 10 more investments like that of Scino Pharma in order to reach the target. Based on the current growth rate and the expected output from Scino Pharmaceutical, NT$12 billion by year 2002 may be a more realistic figure. However, with the ever changing market situation, the reflux of overseas pharmaceutical specialists and the acknowledgement of traditional herbal medicine, the pharmaceutical industry in Taiwan still has a bright future.

Chapter 5 Where Taiwan May Go

Section 1 How to Make the Right Choice

Regardless the industries, picking out a right product is a difficult process. Many parameters have to be considered, yet profitability is not guaranteed. Because of the hugh investment involved, the pharmaceutical industry requires a very high stake. A minor misjudgement could translate into a loss of millions of dollars. Hence, it is very important to choose the right product and plan out the right direction ahead of time. Usually, the selections are made via either one of the two routes:

- Product-Directed

  This method may be the most widely adopted route. It is based on the current market situation of one particular drug. Since it follows the market trend closely, manufacturers who adopt this method would invariably face competitions from the other generic makers. Therefore, it is impossible to generate high profit under this circumstance.

- Technology-Directed

  There are three major factors in determining the value of a drug: advanced pharmacology, high technology added value, and patent. Since achieving all these three factors requires high investment in both human resources and capital, technology-directed method may be a good way to reduce competitions from the also-rans and help drug firms maintaining the drug price at a profitable level. Unfortunately, this method has a long investment return period which would deter manufacturers who are less established.

Section 2 Drugs with Good Market Potential

Table 22 Drugs with Good Market Potential and Their Patent Expiration Dates

Generic Drug Name	Brand Name	Originator	Indicator	Expire Date
Acyclovir	Zovirax	Wellcome	Antivirals	1997, 04
Alprazolam	Xanax	Upjohn	Antidepressants	1993, 10
Allopurinol	Zolyprim	Wellcome	Gout Preparation	1988, 11
Amoldipine Besylate	Norvase	Pfizer	Cardiotonics	2003, 02
Amirinon Lactate	Inocor Lactate	Winthrop	Cardiotonics	1998, 04
Apraclonidine HCl	Iopidine	Alcon	Autonomic Drugs	2002, 05
Aspoxycillin	Doyle	Tanabe	Antibiotics	1996, 12
Astemizole	Hismanal	J & J	Antihistamine	1999, 10
Atenolol	Tenormin	ICI	b-Blocker	1989, 03
Atracirium Beslate	Tracrium	Wellcome	Muscle Relaxants	1996, 12
Azithromycin	Zithromax	Pfizer	Antibiotics	2002, 01
Benazepril HCl	Cibacen	Ciba Geigy	ACE Inhibitor	2002, 10
Betamethasone	Diprolene	Schering	Corticosteroids	2001, 12
Bupropion HCl	Wellbutrin	Wellcome	Antidepressant	2000, 07
Buspirone	Buspar	BMS	Anxiolytics	1999, 01
Bumetanide	Bumex	Roche	Diuretics	1993, 02
Calcitriol	Rocaltrol	Roche	Vitamins D_3	2000, 07
Captopril	Capoten	Squibb	ACE Inhibitors	1996, 02
Carbamazepine	Tegretol	Ciba Geigy	Antiseizure	2000, 10
Carteolol HCl	Mikelan	Otsuka	b-Blocker	Expired
Cefaclor	Ceclor	Eli Lilly	Antibiotics	1992, 09
Cefixime	Cefspan	Fujizawa	Antibiotics	1998, 05
Ceftriaxone	Rocephin	Hoffmann	Antibiotics	1999, 04
Cefuroxime Axetil	Ceftin	Glaxo	Antibiotics	2000, 12
Cefuroxime Sodium	Zinacef	Glaxo	Antibiotics	1993, 10
Cephradine Oral	Velosef	Squibb	Antibiotics	1986, 02
Chloromezanone	Tensolax	Winthrop	Muscle Relaxants	Expired
Cinoxacin	Cinobac	Dista	Antibacterials	1989, 01
Ciprofloxacin	Ciprobay	Bayer	Antibiotics	2002, 10
Clarithromycin	Karicid	Abbott	Antibiotics	2003, 06
Clonazepam	Rivotril	Roche	Anxiolytics	1994, 02
Cloxazolam	Sepazon	Sankyo	Anxiolytics	1990, 06
Clozapine	Clozaril	Sandoz	Tranquilizer	1994, 09
Cromolyn Sodium	Intal	Fisons	Antiasthmatics	1989, 08
Crotamiton	Euraxil	Ciba Geigy	Antiinfectives	1968, 06
Diazepam	Valium	Roche	Anxiolytics	1985, 02
Digoxin	Lanoxicaps	Wellcome	Cardio	1995, 05
Diltiazem HCl	Cardizem	Marion Labs.	Antianginal	1988, 02
Dobutamine	Dobutrex	Eli Lilly	Autonomic Drugs	1993, 10
Doxazosin Mesylate	Cardura	Pfizer	a-Blocker	1998, 02
Econazole Nitrate	Pevison	Cilag	Antifungals	1992, 12
Enalapril Maleate	Vasotec	Merck	Antihypertensives	2001, 09

Esmolol HCl	Brevibloc	Anaquert	Antihypertensives	2000, 06
Etodolac	Lodine	American Home	Antiarthritic	1997, 02
Famotidine	Pepcid	Merck	Antiulceratives	2000, 08
Felodipine	Plendil	Astra	Antihypertensives	1999, 06
Fluconazole	Diflucan	Pfizer	Antifungals	2000, 11
Flumazenil	Mazicon	Roche	Antidotes	2003, 03
Fluoxetine	Prozac	Eli Lilly	Antidepressants	1994, 04
Flutamide	Eulexin	Scherings	Antineoplastics	2001, 05
Fluticasone	Cutivate	Glaxo	Corticosteroids	2002, 03
Fosinopril Sodium	Monopril	Bristol Myers	Antidepressants	2000, 05
Gadopentetic Acid	Magnevist	Berlex	Diagnostic Drugs	2004, 03
Gemfibrozil	Lopid	Parke Davis	Antihyperlipidamic	1993, 01
Glibenclamide	Diabeta	Hoechst	Antidiabetics	1992, 04
Glipizide	Glucotrol	Pfizer	Antidiabetics	1992, 04
Hydralazine HCl	Apresoline	Ciba Geigy	Antihypertensives	Expired
Indeloxazine HCl	Elen	Yamonouchi	Cerebral Metabolics	1996, 04
Iohexol	Omnipaque	Sterling	Contrast Agent	1994, 05
Isotretinoin	Accutane	Roche	Acne Drug	2001, 08
Isradipine	Dynacirc	Sandoz	Antihypertensives	2003, 08
Ketoconazole	Nizoral	Janssen	Antifungals	1999, 06
Ketorolac	Lodine	Wyeth	Antiinflammatory	1995, 05
Ketazolam	Solatran	SKF & Beecham	Anxiolytics	1989, 06
Lansorprazole	Prevacid	Takada	Antiulcer	2005, 04
Levamisole HCl	Ergamisol	Janssen	Anthelmintics	2003, 06
Lisinopril	Zestril	ICI	Cardiovasculator	2001, 12
Indomethacin	Indocid	Merck	Antipyretics	1984, 05
Lomefloxacin	Maxaquin	Searle	Antibacterials	2005, 05
Loperamide HCl	Imodium	J & J	Antidiartheal	1990, 01
Lorazepam	Ativan	Wyeth	Anxiolytics	1994, 04
Loratidine	Clarithin	Schering	Antihistamine	1998, 06
Lovastatin	Mevacor	Merck	Atherosclerosis	1999, 10
Meclofenamic Acid	Meclomen	Parke Davis	Antiinflammatory	1993, 07
Methocarbamol	Robaxin	Robins Rowell	Muscle Relaxants	Expired
Methyldopa	Aldomet	MSD	Antihypertensives	2000, 09
Metoclopramide HCl	Reglan	A. H. Robins	Antiemetics	2002, 08
Metolazone	Mykrox	Fisons	Diuretics	2002, 05
Metoprolol	Lopressor	Ciba Geigy	b-Blocker	1993, 12
Miconazole	Monistat	J & J	Antifungals	1990, 02
Midazolam	Dormicum	Roche	Anxiolytics	1999, 12
Misoprostol	Cytotec	Searles	Antiulcers	2000, 07
Mitoxantrone HCl	Novantrone	Lederle	Antineoplastics	2000, 07
Mometasone	Elocon	Schering	Corticosteroids	2001, 09
Nabumetone	Relafen	Smithkline	Antiinflammatory	1994, 12
Naftifine HCl	Naftin	Allergan	Antifungals	2000, 08
Nalidixic Acid	Negacide	Windthrop	Antibacterials	Expired
Nicardipine	Cardene	Syntex	Ca Channel Blocker	1993, 10
Nicotine	Habitrol	Ciba Geigy	Natidotes	2003, 06

Nifedipine	Procardia	Pfizer	Antianginal	1991, 01
Nimodipine	Nimotop	Miles	Cardiotonics	2002, 09
Nisoldipine	Baymycard	Bayer	Cardiotonics	1996, 06
Nizatidine	Axid	Eli Lilly	Antiulceratives	2000, 05
Norfloxacin	Noroxin	Merck	Antibacterials	1998, 05
Nordazepam	Calmday	Will	Anxiolytics	1982, 06
Octreotide	Sandostatin	Eli Lilly	Antineoplastics	2002, 07
Ofloxacin	Tarivid	Daiichi	Antibacterials	2000, 05
Olsalazine Sodium	Dipentum	Kabi	Antiinflammatory	2004, 08
Omeprazole	Prilosec	Merck	Antiulceratives	2000, 05
Ondansetron HCl	Zofran	Glaxo	Antiemetics	2004, 09
Oxaprozin	Daypro	Searle	Antiinflammatory	1997, 10
Oxazepam	Serax	Wyeth	Anxiolytics	2003, 10
Oxazolam	Serenal	Sankyo	Anxiolytics	1990, 06
Paroxetine	Paxil	Smithkline	Anxiolytics	1994, 06
Pentoxyfylline	Trental	Hoechst Russel	Vasotherapeutic	1997, 05
Piperacillin	Pipril	Lederle	Antibiotics	Expired
Piroxicam	Feldene	Pfizer	Antiinflammatory	1989, 07
Pravastatin	Mevalotin	Sankyo	Atherosclerosis	1999, 08
Prazosin	Hypovase	Pfizer	a-Blocker	1995, 05
Propentofylline	Hoxtol	Hoechst	Vasotherapeutic	1996, 04
Propranolol HCl	Inderal	ICI	b-Blocker	2003, 06
Ramipril	Tritace	American Hoechst	Antihypertensives	2005, 01
Ranitidine	Zantac	Glaxo	Antiulcers	1997, 06
Salbutamol	Ventolin	Glaxo	Bronchodiator	1991, 05
Sertraline HCl	Zoloft	Pfizer	Anxiolytics	2002, 07
Simvastatin	Zocor	Merck	Atherosclerosis	2005, 12
Somatrem	Protropin	Genentech	Hormone	2004, 04
Somatropin	Humatrope	Eli Lilly	Growth Hormone	2004, 04
Sulconazole	Exelderm	Tanabe	Antifungals	1996, 10
Sulindac	Clinoril	Merck	Analgesic	1989, 04
Sumatriptan	Imitrex	Glaxo	Antimigraine	2003, 06
Temazepam	Restoril	Sandoz	Anxiolytics	2008, 07
Terazosin HCl	Hytrin	Abbott	a-Blocker	2000, 05
Terbinafine HCl	Lamisil	Sandoz	Antibiotics	2005, 07
Terbutaline Sulfate	Brethine	Ciba Geigy	Bronchodiator	1994, 03
Terconazole	Fungistate	Eli Lilly	Antifungals	2001, 11
Terfenadine	Seldane	Marion	Antihistamine	1994, 06
Ticlopidine	Ticlid	Syntex	Cardiovasculars	2005, 10
Timolol	Blocadren	Merck	Cardiovasculars	1989, 04
Triazolam	Halcion	Upjohn	Anxiolytics	1993, 10
Verapamil	Calan SR	Knoll	Ca Channel Blocker	1989, 12
Vincristine Sulfate	Oncovin	Eil Lilly	Antineoplastics	2003, 10
Zidovudine	Retrovir	Wellcome	Antivirals	2005, 02

Source: IMS Patent international.

Table 23 The Present Status and the Future of World's Pharmaceutical Market

Generic Drug Name	1994 Estimated			2005 Predict		
	Sales Volume (Ton)	Price (USD/kg)	Sales Value (US$mil)	Sales Volume (Ton)	Price (USD/kg)	Sales Value (US$mil)
Acyclovir	380	300	114	840	200	168
Alprazolam	4	1,000	4	4	700	3
Amlodipine	4	1,500	6	3	800	2
Amoxicillin	5,650	72	407	11,000	66	726
Ampicillin(Oral+Inj.)	6,180	68	420	5,000	65	325
Atenolol	360	60	22	350	50	18
Beclomethasone	4	5,000	20	5	4,000	20
Captopril	250	350	88	200	220	44
Carbamazepine	n/a	50	n/a	n/a	50	n/a
Cefaclor	505	1,050	530	400	800	320
Cefadroxil	410	200	82	400	160	64
Cefalexin	1,700	150	255	1,800	130	234
Cefixime	75	1,200	90	65	800	52
Cefotaxime	99	700	69	41	400	17
Cefotiam	56	700	39	44	450	20
Cefpodoxime Proxetil	38	1,100	42	20	800	16
Ceftazidime	96	1,200	116	108	800	86
Ceftriaxone	104	1,400	145	106	1,000	106
Cefuroxime Axetil	150	1,000	150	170	700	119
Cefuroxime Na (Inj.)	78	800	62	100	500	50
Ciclosporin	24	10,000	240	40	4,000	160
Cimetidine	1,250	35	44	1,100	30	33
Ciprofioxacin	465	100	47	700	70	49
Cisapride	16	2,000	32	24	1,000	24
Clarithromycin	150	300	45	250	200	50
Clavulanic Acid(+Amoxicillin)	205	1,400	287	320	800	256
Diclofenac	575	45	26	520	40	21
Diltiazem	550	280	154	600	200	120
Enalapril	80	750	60	100	400	40
Erythromycin	2,200	90	198	3,500	100	350
Famotidine	55	300	17	60	200	12
Flomoxef	21	1,200	25	10	800	8
Fluconazole	11	1,200	13	30	600	18
Fluoxetine	16	800	13	25	300	8
Frusemide	280	60	17	250	60	15
Gemfibrozil	1,050	100	105	1,350	90	122
Glibenclamide	22	200	4	25	200	5
Ibuprofen	9,350	15	140	14,000	15	210
Idebenone	29	1,200	35	14	900	13
Imipenem (+Cilastatin)	20	2,000	40	20	1,000	20
Iohexol	850	n/a	n/a	800	n/a	n/a

Iopamidol	800	n/a	n/a	650	n/a	n/a
Ipratropium Bromide	0	10,000	3	0	10,000	4
Isotretinoin	7	5,000	34	12	5,000	60
Ketoconazole	85	350	30	94	250	23
Ketorolac	5	2,000	10	4	900	4
Ketotifen	6	2,000	12	9	1,500	14
Lisinopril	43	1,800	77	50	500	25
Loratidine	5	2,500	13	10	1,500	15
Lorazepam	22	1,500	33	19	750	14
Lovastatin	69	15,000	1,035	130	4,000	520
Metoprolol	180	100	18	150	80	12
Midazolam	3	1,000	6	6	1,000	6
Minocycline	71	1,100	78	67	700	47
Nabumetone	380	200	76	650	120	78
Naproxen	1,640	90	148	2,000	60	120
Nicardipine	80	250	20	30	100	3
Nicergolone	24	700	17	15	400	6
Nifedipine	230	50	12	250	40	10
Nizatidine	107	250	27	120	150	18
Ofloxacin	135	320	43	150	200	30
Omeprazole	47	2,000	94	80	800	64
Ondansetron	1	6,000	3	1	1,000	1
Oxatomide	36	400	15	17	250	4
Paracetamol	55,000	6	330	65,000	6	390
Paroxetine	7	1,000	7	23	450	10
Pentoxifylline	1,100	90	99	900	80	72
Piroxicam	30	100	3	20	80	2
Pravastatin	26	20,000	520	40	5,000	200
Propanolol	260	20	5	180	16	3
Ranitidine	1,280	90	124	1,500	60	90
Salbutamol	28	200	6	35	160	6
Sertraline	62	1,000	62	90	400	36
Simvastatin	18	20,000	360	45	5,000	225
Sodium Cromoglycate	16	1,000	16	18	1,000	18
Sulbactam	65	500	33	85	400	34
Tamoxifen	35	700	25	60	500	30
Tegafur (+ Uracil)	22	300	7	15	240	4
Teprenone	100	170	17	90	100	9
Terfenadine	195	180	35	250	140	35
Theophylline	900	10	9	1,000	10	10
Ticlopidine	263	180	47	300	160	48
Timolol	5	2,500	13	5	2,000	10
Verapamil	590	140	83	500	130	65

Source: Michael Barber and Associates, CHEMICA Useful Book 1995.

Section 3 Strategic Products: Product-Directed

1. Cephalosporins (β-Lactams Antibiotics)

In the recent years, Taiwan's pharmaceutical industry has devoted into the synthesis of cephalosporins. This particular field perhaps is the most established in Taiwan's pharmaceutical industry, as a well integrated network between the intermediate makers and bulk drug makers has already been developed and executed. With the growing demand for antibiotics in the Southeast Asian countries and the lack of competition from the Chinese producers, Taiwan may concentrate its effort in the development of β-lactams and become the prominent supplier for these products. The current Taiwan manufacturers of β-lactams are as follows:

Penicillin G:	China Chem. Syn. Ind.
7-ADCA:	Techco Chem.
6-APA:	China Chem. Syn. Ind. and Yuen Foong
D-Phenylglycine:	China Camphor
Cefaclor:	Taiwan Biotech, Yung Zip, and Kuo Ching
Cephradine:	Taiwan Biotech
Cefatrizine:	China Chem. Syn. Ind.
Cephadroxyl:	China Chem. Syn. Ind. and Taiwan Biotech
Amoxycillin:	China Chem. Syn. Ind., Yuen Foong, and Kingdom
Ampicillin:	China Chem. Syn. Ind., Yuen Foong, and Kingdom

Taiwan's progress in the synthesis of β-lactams has drawn interests from Japanese pharmaceutical manufacturers who are looking for a reliable Taiwanese partner in the OEM business. These Japanese have emphatically visited the facilities and evaluated the capabilities of several major manufacturers in Taiwan. It is widely believed that the formation of strategic alliance with the Japanese may accelerate and solidify Taiwan's development in the market of cephalosporins.

In spite of Taiwan's boom in the this particular field, there are two problems Taiwan's cephalosporins industry cannot overlook. First of all, Taiwan lacks a strong domestic support in the supply of penicillin or its derivatives that are the essential starting raw materials for cephalosporins. At the moment, Taiwan still relies heavily on foreign sources. This renders Taiwan's cephalosporins industry susceptible to the change in pricing and the shortage in the supply of penicillins. Although there have been talks on establishing a penicillin production plant in Taiwan, to actually build one from scratch is very difficult, as the time and resources required will be enormous.

Another problem is the decline of cephalosporins pricing worldwide. According SCRIP's prediction on the future of cephalosporins market, the pricing on the existing products is expected to drop:

Table 24 1995 - 1998 Prices Prediction o f Antibiotics Market

(Unit: USD)

Price (USD)/Unit	1995	1996	1997	1998
Penicillin GK(bu)	23	20	18	16
6 -APA (Kg)	78	68	62	56
Ampicillin Trihydrate (Kg)	72	68	63	58
Amoxicillin Trihydrate (Kg)	74	71	65	61
7 - ADCA (Kg)	145	145	140	135
Cefalexin Monohydrate (Kg)	150	150	145	140

Source: Scrip No. 2094, 1996 P.27,

In order to extend the life of Taiwan's cephalosporins industry, it is very important to develop new generation products which are high in commercial values and limited in number of supplier. With the gaining preference of orally administered formulation, Cefixime and other orally administrable cephalosporins are perhaps the most promising products for Taiwan.

2. Antiulceratives

Peptic ulcers are the deterioration of the mucous member of the stomach or duodenum caused by acid and pepsin. Since peptic ulcers often associate with excessive secretion of acid, the saying "no acid, no ulcer" may well describes the relation between peptic acid and peptic ulcers. In another word, when the balance between factors promoting ulcers overwhelm factors protecting the stomach's mucosal lining is disturb, thus ulcers form. Although a temporary relief may be achieved through the administering of antacids, other more effective treatments are more widely employed as treatments to ulcers.

Commonly used antiulceratives may be divided into the following categories:

1. M1 blocking agents: pirenzepine
2. Prostaglandins: misoprostol
3. H_2 blocking agents: cimetidine and ranitidine
4. ATPase inhibitors: omeprazole and lansoprazole
5. Antisecretory drugs: xylamide

Of these agents, both the H_2 antagonist and ATPase inhibitors are preferred as they provide both the long term and short term relief. Because of their effectiveness, they are of high market value and are perhaps ideal generic products. Although they may achieve similar results, each type of drugs has its own distinctive characteristics:

- H_2 blocking agents

  These drugs inhibit acid secretion by blocking the histamine H_2 receptors in the parietal cell.

  Advantages

  1. It can inhibit acid secretion.
  2. It does not influence the activity of pepsin.
  3. It does not inhibit the secretion of enzyme.

4. It does not influence Cytochrome P-450.

Disadvantage

1. Effective in promoting the healing of peptic ulcer, but recurrence may still occur.
2. These drugs cannot be administered by women who are pregnant or breast feeding their infants and patients with kidney or liver problems.
3. These drugs may confuse symptoms from hepatic cancers.

- ATPase inhibitors

ATPase inhibitors works by inhibit the proton (acid) pump, the enzyme H+K+ATPase, which is located in the apical secretory membrane of the parietal cell.

Advantages

1. It can completely suppress the secretion of acid in the stomach.
2. It has a long duration of action.
3. It is the most effective drug for treating gastrinoma (Zollinger-Ellison syndrome).
4. It may be used as an alternative treatment for peptic ulcer if H_2 histamine antagonists fail.

Disadvantages

1. These drugs cannot be administered by women who are pregnant or breast feeding their infants and patients with kidney or liver problems
2. These drugs may confuse symptoms from hepatic cancers.

As mentioned in chapter 2, proton pump inhibitors are replacing the H2 antagonists in the pharmaceutical market. For instance, after Smith Klein Beecham's patent on cimetidine had expired, cimetidine lost 2 percent of its global market share and 5% in the U.S. market. With its patent about to expire in 1997, rantidine's market share is also expected to take a huge dive.

While the H_2 antagonists are losing their market share, proton pump inhibitors such as omeprazole and lansoprazole have gaining a higher market share, from 20% in 1994 to 24% in 1995. Of all the proton pump inhibitors, omeprazole has done particularly well, as its total sales in 1994 grew from US$1.64 billion in 1993 to US$2.24 billion. The consistent growth of the proton pump inhibitors have demonstrated proton pump inhibitors' potential in the global pharmaceutical market.

Of all the antiulcerative drugs in the market, omeprazole draws a lot of attention among the pharmaceutical makers in Taiwan. Both the DCB and Chemical Research Center have already announced their plans in the process development of omeprazole which drew the interest from Ching-ta, Everhope and Kingdom. Although omeprazole appeals to the Taiwanese pharmaceutical makers, there are several shortcomings associated with omeprazole:

1. Omeprazole is very well protected by its patent. By-passing the patent would be very difficult.
2. The quality of omeprazole largely depends on the oxidation of sulfide to sulfoxide.
3. The selection of oxidating agent greatly affect the production cost of omeprazole.
4. The intermediate is difficult to obtain. Its synthesis involves multiple steps processes and requires strong acid as a reactant which is very difficult to handle.
5. Omeprazole is sold in pellets, which increases the production cost and adds complexity to the synthesis steps.
6. Omeprazole's price is dropping and there has been a steady supply from China.

Having all these factors influencing the market price of omeprazole, it seems omeprazole may not be a suitable product for strategic development. However, with the altering preference from H_2 antagonist to proton pump inhibitors and the growing market share, proton pump inhibitors' market potential cannot be overlooked. The following table shows the sales of proton pump inhibitors in the past five years.

Table 25 PPIs , By Value, World Market Prediction

(Unit: Million, USD)

	Area	1994	1995	1996	1997	1998
Omeprazole (Losec ; Astra) (Prilosec ; Merck)	EU	880	960	1010	105	1120
	USA	540	650	740	850	970
	Japan	46	50	50	52	54
	Others	394	465	545	625	715
	Total	1860	2125	2345	2577	2859
Lansoprazole (Prevacid ; TAP)	EU	64	85	105	125	145
	USA	0	10	50	75	100
	Japan	55	70	85	100	110
	Others	1	5	8	10	12
	Total	120	170	248	310	367
Pantoprazole (SmithKline Beecham)	EU	5	75	165	250	375
	Others	2	25	50	75	125
	Total	7	100	215	325	500
PPIs Global Market,	Total	1987	2395	2808	3212	3726

Source: Japan Pharma Time Annual Report 1995

According to the above table, the future of proton pump inhibitors look very promising. Since there are already many players in the omeprazole market, it may be wise to select other proton pump inhibitors to avoid engaging in fierce competitions. From the market trend and technical background, lansoprazole may be the most ideal item for strategic development. One of the reasons is that lansoprazole is similar to omeprazole, from a chemist point of view. The technology for omeprazole may perhaps be used to synthesize lansoprazole. Secondly, having these two compounds together may offer a wider product range for the maker (or makers).

3. Cardiovascular Drugs

Of the top 20 drugs in 1994, eight of them are cardiovascular drugs. As shown by this statistics, cardiovascular drugs may have the best market potential of all drugs. Based on how the drugs interact with human body, cardiovascular drugs may be divided into the following seven classes:

1. Diuretics: Thiazides derivatives that include furosemide and spironolactone.
2. Sympatholytic agents: These include methyldopa and colnidine which interact with central neural system; reserpine and cuanethidine that interact with peripheral neural system; and β-blockers such as atenolol, timolol, propranolol, nadolol and metoprolol that interact with symphatholytic neural system.
3. Vasodilators (ACE inhibitors): These include captoril, enalapril, lisinopril, perindopril, quinapril, ramipril, delapril, and fopsinopril.
4. Calcium Channel Blockers: These include diltiazem, nifedipine, nicardipine, lsradipine, felodipine, and verapamil.
5. Antihypertensive: These include nitroprusside, diazoxide, trimethaphan, camsylate and clonidine.
6. Ganglionic blocking agent: This class is represented by mecamylamine.
7. MAO inhibitor: This class is represented by pargyline.

According to the sales records of all drugs in global market, β-blockers, ACE inhibitors, and calcium channel blockers are the most often prescribed.

Since cardiovascular drugs interact with human hearts, therefore brandname loyalty is a very important factor, as products from renounced pharmaceutical makers are preferred. Although the market for these drugs look enormously profitable, in reality there is very little room for the generic products. Moreover, the specifications on these drugs are rather strict. Besides the

usual USP or BP standards on chemical properties, physical properties such as particle size are also greatly emphasized. As a result, it is very difficult for generic makers to prosper in the particular market.

With the support from the Ministry of Economics, Union Chemical Laboratory and several pharmaceutical makers in Taiwan are jointly developing a number of cardiovascular drugs.

1. β-blockers

   UCL and Sheng-Ta have successfully co-developed the manufacturing process of atenolol. A patent has been also granted. Currently Sheng-Ta is manufacturing and selling atenolol. Furthermore, research efforts on timolol and propranolol are being started.

2. ACE inhibitors

   Efforts have been concentrated on the development of captopril, enalapril, and lisinopril. The synthesis processes on captopril and enalapril have been developed by UCL. Although these processes are not yet optimized for mass scale production, they do give good results in lab scale production. As compared to UCL's progress in captopril and enalapril, DCB's development of linsinopril is less satisfactory. Since lisinopril has three chiral centers, it would require a solid background in asymmetric synthesis which DCB is unfamiliar with. As a result, DCB's progress has been delayed.

3. Calcium channel blockers:

   Since the scaled-up production of nifedipine in 1993, China Chemical Synthesis and UCL continue to develop the manufacturing steps on the 1,4-dihydroxypyridine derivatives such as nicardipine, nitrendipine, nisoldipine, etc. Furthermore, in 1996 these two

parties announced the joint research plan on amlodipine, a treatment for Alzheimer disease. Since amlodipine is an analog of 1,4-dihydroxypyridine derivatives, the extensive experience CCS and UCL already have in the synthesis of nifedipine, nicardipine, nitrendipine and nisoldipine may accelerate the progress.

Taiwanese pharmaceutical industry has already exerted much effort in the development of cardiovascular drugs. Under this circumstance, it is unecessary to pick out a strategic product from this pool. Until Taiwanese makers are familar with asymmetric synthesis and organometallic reaction, it may be wise to focus on the manufacturing of captopril and enalapril presently.

Section 4 Strategic Products: ProductsTechnology-Directed

1. Hydrogenation

Hydrogenation is one of the key technologies in drug synthesis. It is an important step in the manufacture of many highly valued drugs such as clarithromycin, dobutamine, etodolac, terbutaline, etc. Because conducting hydrogenation requires special equipment and specialized knowledge and extreme caution, most chemcial manufacturers in Taiwan usually avoid using hydrogen by taking other alternative routes, such as using NaBH4 as a reducing agent, which are more costly than hydrogenation. Perhaps an answer to this problem is to gather several companies to establish a company which specializes in hydrogenation toll conversion services. This may help Taiwan's pharmaceutical manufacturers solve the problem associated with hydrogenation and also help reducing the production cost.

Among all the Taiwanese companies that are experienced in hydrognation, there are two companies that stand out: Taiwan's Catalysis Research Center and Kuo Ching Chemical Co., Ltd. Each of the two organizations is well established and is unique in this field of expertise. For decades, Catalysis Research Center is perhaps

Kuo Ching's success in the stereoselective manufacture of naproxen via asymmetric hydrogenation has broken a new ground in Taiwan. This may be a niche technology for Taiwan.

2. Organo-metallic Reactions

Organo-metallic reactions are very important to organic synthesis. They are often used in the introduction of basic functional groups onto a molecule. Although these reactions are often done in laboratory, they are very sparingly used in Taiwan's chemical industry because of the harsh reaction conditions and extreme cautions needed. Under this circumstance, many products that require organo-metallic reactions in their manufacturing processes are given up. For example, DCB successfully developed the manufacturing processes for terfenadine and fluconazole. Since no manufacturer in Taiwan has the capability to conduct organo-metallic reaction in large scale. and as a result DCB was forced to use alternative routes which are more costly than organo-metallic reactions. In order for Taiwan's pharmaceutical industry to grow, developing the capability of conducting organo-metallic reactions in large scale is a must.

3. Asymmetric Synthesis

With the growing interest in optically pure compounds, the asymmetric synthesis has become a hot technology for chemists to pursuit. In the moment, the desired products may be obtained through the following two methods: optical resolution and asymmetric catalysis. Other new technologies are also being explored. Most importantly, there is no dominant player in this

field which makes it anyone's game. Given the fact that over 40% of the drugs are sold in racemic form. The lucractive market makes the development of asymmetric synthesis extremely important. At the moment, Taiwan's chemical industries still lack the capability in asymmetric synthesis. Fortunately the research instititues in Taiwan are assiduously studying these technologies. The chemical industries may work together with research institutes to co-develop these technologies which may be the niche knowhow for Taiwan's pharmaceutical industry.

Chapter 6 Working Together

Section 1 Possible Strategic Alliance between China Mainland and Taiwan in the Synthesis of Generic Drugs

As the statistical data and market information have shown, there are significant advancement in the pharmaceutical industries in both China Mainland and Taiwan . Unfortunately, due to lack of interaction and integration, there are too many similarities in the product ranges which resulted in stiff competitions in the market. Consequently, what used to be a golden goose egg would become a rotten egg.

From a technical point of view, each industry has its own forte and also its own weakness. For example, China has a well developed fermentation industry in which Taiwan trails far behind. On the other hand, Taiwan has a well established formulation industry in which China lacks experience and knowhow. Therefore, by joining the two sides together and establishing a strategic alliance, both industries could be benefitted enormously.

In this chapter, we will analyze advantages and disadvantages of the two industries and formulate possible strategies for collaboration:

A. Anti-infectives

a. Antibiotics

1. Because of its strong background in fermentation, China has become a dominate producer in the manufacturing of antibiotics, particularly in penicillins, tetracyclines, macrolides and aminoglucosides.
2. Because of its experience in organic synthesis, Taiwan takes the lead in the synthesis of cephalosprions. More importantly, Taiwan is self-sufficient in the key intermediates

such as 7-ADCA and 6-APA for penicillins and cephalosprions. This is one area where China lags behind.

3. Because most of the producers in Taiwan are not equipped with clean room facitlities, the cephalosporins industry is somewhat limited.
4. Owning a clean room facilities would allow manufacturers to synthesize high value cephalosporins and avoid competitions.
5. Several antibiotics that are of low market value can be modified and synthesized into high value antibiotics.

   Take amoxycillin for example. Its current market price ranges from US$70~72.00/kg. Its derivative, aspoxicillin, has a much higher market value, around US$650.00/kg.
6. One probable area of interest may be the development of new generation marcolides, which has been highly tauted by SCRIP for its vast market potential.

b. Sulfonamides

1. The sulfonamides are synthetic bateriostatic antimicrobial agents with a wide antibacterial spectrum encompassing most gram-positive and many gram-negative organisms. Because some of the sulfonamides are readily soluble in urine, they are often used in the treatment of urinary tract infections. However, when continuously adminstered, sulfonamides will become less effective as macroorganisms are quick to develop resistance. This shortcoming limits the usage of sulfonamides and makes them relatively inexpensive antiinfective agents.
2. Because of their low economic values, there are very little incentives in the development and the production of sulfonamides.

c. Antifungal Agents

1. Most of the antifungal agents produced in China are relatively old generation products.

2. In the U.S. and most European countries, triazoles such as Bifonazole, Fluconazole, Itraconazole, Ketoconazole, Miconazole and Tioconazole are more widely used. Of them all, Fluconazole is the most touted.
3. Another triazole antifungal angent worth mentioning is Ketoconazole, also known as Nizoral. Its market price is around US$300/kg and market competition is low. Most importantly, its patent will expire in 1999.

d. Antiviral Agents

1. Among all the antiviral agents, Acyclovir is the most highly touted. Its current market price is around US$230/kg.
2. The most difficult problem in the manufacture of Acyclovir is Acyclovir's low solubility. It often renders the reaction imcomplete and makes the purifcation of end product rather difficult.

e. Quinolone Antibiotics

1. Since the discovery of the first and second generation quinolone antibiotics, the third generation drug has already been well established. Based on the functional groups, there are two major classes of quinolones:

   1) Single fluorinated

   2) Multifluorinated

   The presence of fluorine and piperazinyl greatly enhances the potency of these quinolones. As a result, they are also called "fluoroquinolones".
2. In China, the manufature of quinolones is well established. This may due to the fact that the synthesis of quinolones are relatively easy as compared to β-lactams which requires strong support of biotechnology whereas the quinolones does not.
3. There are a handful of quinolones manufacturers in Taiwan. However, their activities are pretty much restricted in the final-step synthesis of the final drug from the

intermediates produced in China, which puts Taiwanese manufacturers in a disadvantage.

B. Analgesic & Anti-inflammatory

1. There are plentiful of drugs under this category. They are usually distinguished in the following classes:
   1) Salicylates (e.g. aspirin)
   2) p-Aminophenol derivatives (e.g. acetaminophen)
   3) Ergot derivatives (e.g. ergotamine)
   4) Pyrazolones (e.g. phenylbutazone)
   5) Non-steroidal Anti-inflammatory drugs (e.g. ibuprofen)
   6) Gold complex (e.g. aurothioglucose)
   7) Penicillamine
   8) Anti-gout agents (e.g. clochicine)
   9) Miscillaneous (e.g. ethoheptazine)
2. There are several major producers of these drugs in China due to the simplicity in synthesis. For example, acetyl salicylic acid, analgin, diclofenac, ibuprofen, paracetamol, phenacetin are all produced in large scales, sometimes exceeding 1,000 mt per annual. There are also quite a few producers in Taiwan. Produced drugs include acetaminophen, diclofenac, mefenamic acid, naproxen, oxaprozin, piroxicam and sulpyrin.
3. The market for analgesic & anti-inflammatory is huge and consumer brandname loyality is limited. More importantly, most of them are off-patent already. This gives a strong incentives for generic makers.
4. The industrial manufacturing process of naproxen via asymmetric hydrogenation has already been successfully developed by Kuo Ching Chemical Co., Ltd. in Taiwan. Perhaps other Taiwan generic makers can cooperate with Kuo Ching in the manufacture of other analgesic & antiinflammatory drugs such as propionic acid derivatives and pyrazolones.

C. Vitamines

Because of China's strong background in fermentation technology, besides penicillins, vitamines have become a major industry in China. As compared to China, Taiwan lags far behind in this particular category.

D. Antiparasitics

Because of their low economic values, there is currently no producers in Taiwan. No significant manufacturer was found in China also.

E. Contraceptives & Hormones

1. Interestingly, since the Chinese are very experienced in the development and use of steroids, the synthesis of hormones, particularly in female hormones, is very well established.
2. There are two major types of female hormones: estrogens and progestins. All of them are derived from steroidal compounds.
3. Birth control drugs can be divided into three categories: steroidal contraceptives, ovulatory agents, and prostaglandins.
4. For safety reasons, tough regulations have been established to prevent the cross contamination of hormones with other non-related drugs and personnel contact. Moreover, the synthesis of these drugs would require high technology. These two problems make the synthesis of hormones rather expensive. However, because of their low dosage requirement and high economic value, they are especially suitable for small or medium size plants.

F. Antineoplastic Drugs

1. Antineoplastic drugs can be separated into the following categories:
   1) Alkylating agents
   2) Antimetabolites

3) Inorganic ions

4) Hormones

5) Antitumor antibiotics

6) Plant alkaloids

7) Enzymes

8) Biological Response Modifiers

2. Like hormones, antineoplastic drugs are of high economic values and ideal for small scale production plants, particularly in Taiwan. For instance, Everlight of Taiwan has a R&D group that is focused in the development testosterone suppressing agent. This may drive Taiwan's drug manufacturing technology to a higher plateau.

G. Cardiovascular Drugs

1. Cardiovascular drugs include: cardioactive glycosides, antiarrhythmic agents, antihypertensive drugs, antianginal drugcoronary vasodilators, prophylaxis of atherosclerosis-hyolipemic drug, agents used in hypotension and shock and peripheral vasodilators.

2. Due to the huge market demand, cardiovascular drugs have long been the focus of drug makers worldwide. China has a relatively strong industry in the production of cardiovascular drugs which covers all the classes mentioned in 1. Taiwanese manufacturers specializes only in two areas: antihypertensive drugs and antianginal drugs. Insider's information has shown that Sheng Ta is already producing lovastatin and in process of developing the manufacturing process of paravastatin.

3. Of all the cardiovascular drugs, there are a few that may possess great potential:

1) 1,4-dihydropyridine

Research efforts have been made in both China Mainland and Taiwan yet no industrial scale production has been made in either area.

2) β-blockers

The key technology in the synthesis of β-blockers is resolution. Neither China nor Taiwan is well experienced in this field. Since there is little market competition in β-blockers, perhaps this may give some incentitives for development.

3) ACE inhibitors

The core technology is asymmetric synthesis. Several Taiwanese companies and institutions have expressed interest in ACE inhibitors. In China there are limited productions of captopril (a total of 18 mt in 1996). At the moment, China still rely heavily on imported drugs to fulfill its demand.

4) Brandname loyalty is a very important factor in the marketing of cardiovascular drugs. This makes generics difficult to compete in the market.

H. Respiratory Drugs

1. The most frequently used respiratory drugs include: antitussives, expectorants, mucolytics, bronchodilators, and antiasmatic drugs. Most of these drugs are relatively of low market value, except for bronchodilators, and antiasmatic drugs.
2. In China, the synthesis of xanthine derivatives is quite matured. The major products are aminophylline (289 mt/year), diprophylline (23 mt/year), and theophylline (590 mt/year).
3. Taiwan is inexperienced in this particular area. Perhaps Taiwan generic makers could concentrate on isoproterenol derivatives.

Section 2 Choosing the Right Drugs

To select one drug that is worthy the effort to research and develop from a huge pool that contains hundreds of drugs is a rather difficult task. Most importantly, the selective process has to take account the ability of either China or Taiwan's capability in technology and financial status. In this thesis, the main goal is to find out which ones would be the most ideal to pursue and to propose possible synthesis route for these drugs.

Two of the most important credentials in the selection process are the market status of the drug and the technology to synthesis the drug. A drug having a huge market usually spells profitability. On the other hand, having a crucial technology usually guarantees the availability of the product. These two factors pretty much govern the value of the drugs and have to compliment each other to succeed in the market.

One good example is diclofenac. Diclofenac sodium had been one of the top 20 best selling drugs in the world during the past five years. With the vast market it had, diclofenac sodium is a very attractive product. However, its production technology is quite easy to imitate. Upon the expiration of diclofenac sodium's patent in the early 1980's, numerous generic producers, particularly from China and India, began to appear and the generic products started to compete in the market. As a result, the price dwindled and fell from US$100.-/kg down to US$20.-/kg. At this price level, achieving profitability was very difficult, so the less capable makers eventually went out of business. At the moment, there are approximatlely 20 major producers worldwide. Most of them are at break even point rather than making a huge profit.

From the aforementioned example, it is clear that choosing a right product requires good knowledge in the market and technology. Under this circumstance, what can China Mainland and Taiwan do and in which direction should they proceed?

Given the fact that both China Mainland and Taiwan have good chemical synthesis capability yet have little ability in the marketing of new drugs, it is the best for both parties to focus on the development of generic drugs. Based on the production technology and the market status, 9 generic drugs were screened out:

1. albuterol,
2. amlodipine,
3. fluconazole,
4. fluoxetine,
5. ketoprofen,
6. lisinopril,
7. omeprazole,
8. paroxetine,
9. sertraline,

They are based on the following distinctions: market size, expired date, technology feasibility, and the amount of investment:

1. High market volume

All of these 9 drugs are in the top 200 prescription drugs in the United States where the consumption volume of drugs is the highest among all nations. The huge market would offer high incentives for generic makers to follow suit.

Table 26 The US market ranking of the selected drugs from 1995 to 1997

Drugs	1995[1]	1996[2]	1997[3]
albuterol	10,22,141,157	29,35,102,148,190	18,80,107,108,162,200
amlodipine	23	15	10
fluconazole	111	72	65
fluoxetine	9	6	5
ketoprofen	189	189	189
lisinopril	17,50	18,52	20,53,172
omeprazole	21	12	7
paroxetine	34	27	17
sertraline	13	10	11

Source: 1. Pharmacy Times, April 1996.

2. American Druggist, February 1997.

3. American Druggist, February 1998.

2. Approaching patent expiration date

These 9 drugs either have their patents expired or about to expire. This advantage would give generic maker a shorter turnover period for their investment in the development of the key technology and the establishment of key market. Most importantly, this will make generic immune from the binding of patent laws and possible court cases.

Besides, considering the Laboratory work (1-2 years), Pilot test (1-2 years), and the manufacture process (2-3 years), we think the products' patents expire from 2000 to 2005 will be very suitable for us to develop soon.

Table 27 The expiration dates of the chosen 9 drugs

Drugs	Expiration Date[1]	Expiration Date[2]
albuterol	May 1995	
amlodipine	Feb. 2003	2007
fluconazole	Nov. 2000	2004
fluoxetine	Apr. 1994	2001
ketoprofen	expired	expired
lisinopril	Dec. 2001	2001
omeprazole	May 2000	2001
paroxetine	June 1994	2005
sertraline	July 2002	2005

Source: 1. IMS Patent report

2. A. Southworth, Generic Pharmaceuticals 1996 Edition, Financial Times. Pharmaceutical & Healthcare Publishing. P.45

3. New technology fesibility

According to the current chemical synthetic technology, most products manufactured in China Mainland and Taiwan are within three steps from the raw material. The profit of these products are quite limited. In the next 10 years, we should develop new process within 5-7 steps from raw material for the selected products. This would allow makers to reduce the fixed costs and also the variable cost, such as labor, utilities, and waste treatment. This reduction would translate into price advantage against competition from other generic makers.

High-tech products, especially the high purity pharmaceutical chemicals, will be the new target for the chemical industries of both parties. We believe that the technology capability of the two parties are higher than the other developing countries, and the manufacturing cost are lower than western countries and Japan. The aforementioned 9 targets will be the best choice to be the strongest competitive products with the brand name drugs.

4. Low investment requirement

Ordinarily it would take about US$100millions for the development of a drug from the lab to the commercial scale production. To develop a generic drug would reqire about US$3millions to US$15millions. Since the size of the drug manufacturers in China Mainland and Taiwan are either small or intermediate, it is wise to set the focus at the development of generic drugs.

Above 4 considerations will tell us why we select these 9 drugs. Next the possible synthesis steps for these 9 drugs are proposed:

1. Albuterol

(Bronchodilator)

Technical Information

Albuterol

The key technolog synthesis of albuterol is to prepare its α-amino-β-hydroxyethyl side chain. Based on our review, there are four methodologies to build up such functionality.

1: Nucleophilic substitution of α-carbonylhalide by t-butylamine.

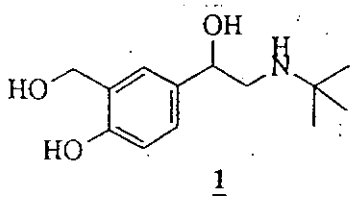
2: Reductive amination of the corresponding aldehyde.

3: Reduction of the corresponding amide.

4: Ring opening of the corresponding epoxide by by t-butylamine.

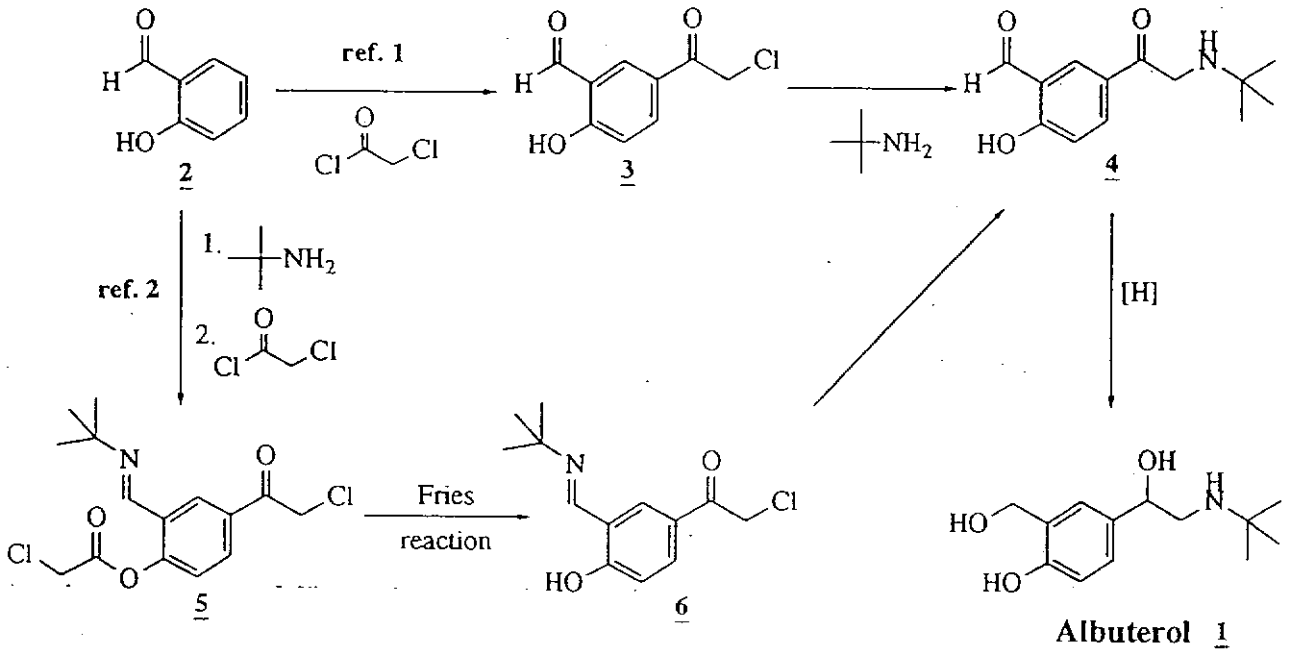
Among the above methods, the last one seems more efficient than the others because the aldehyde 25 is readily available, and the synthetic scheme is relatively straight forward without much of the complication from the side reaction.

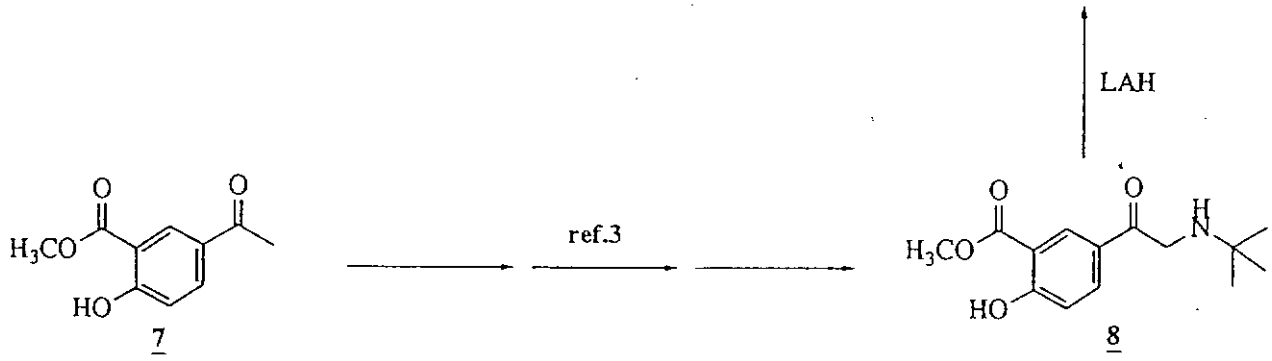
Albuterol:

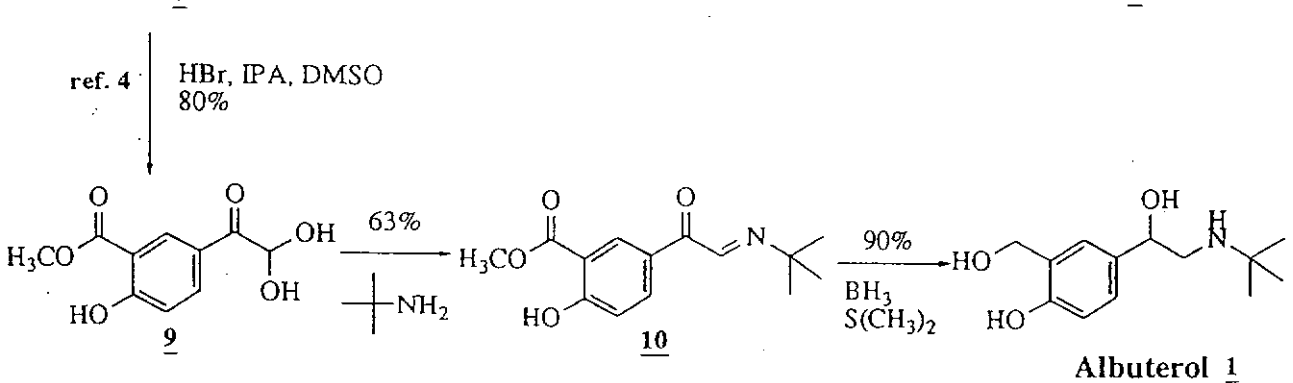


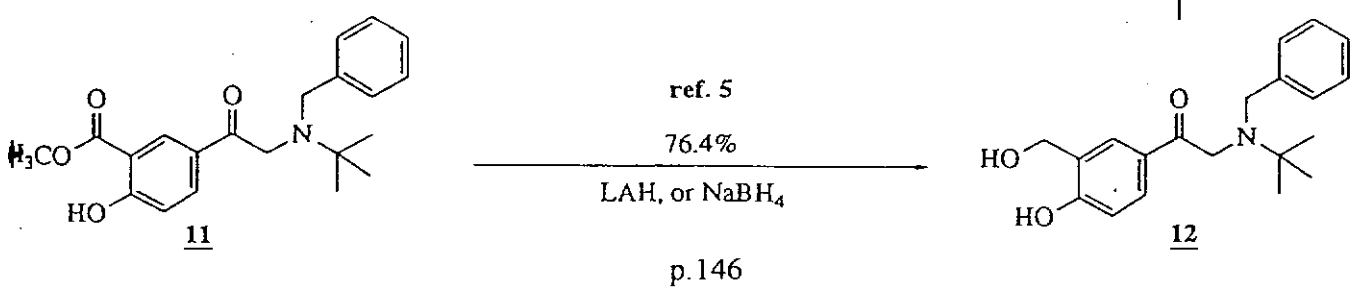
1

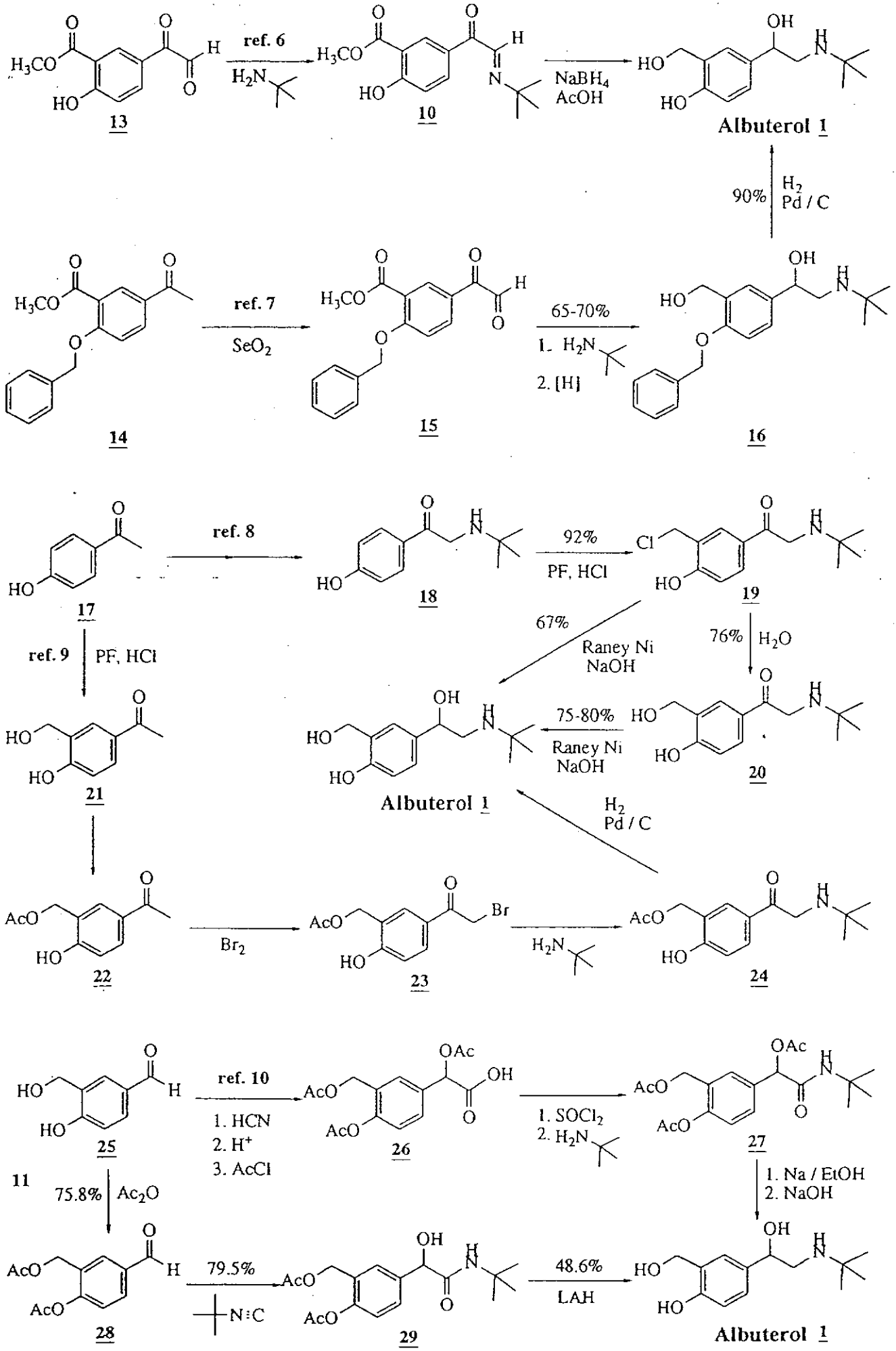
Bronchodilator
Tocolytic
Allen; Hanburys
28 tons/year, 200 USD/Kg

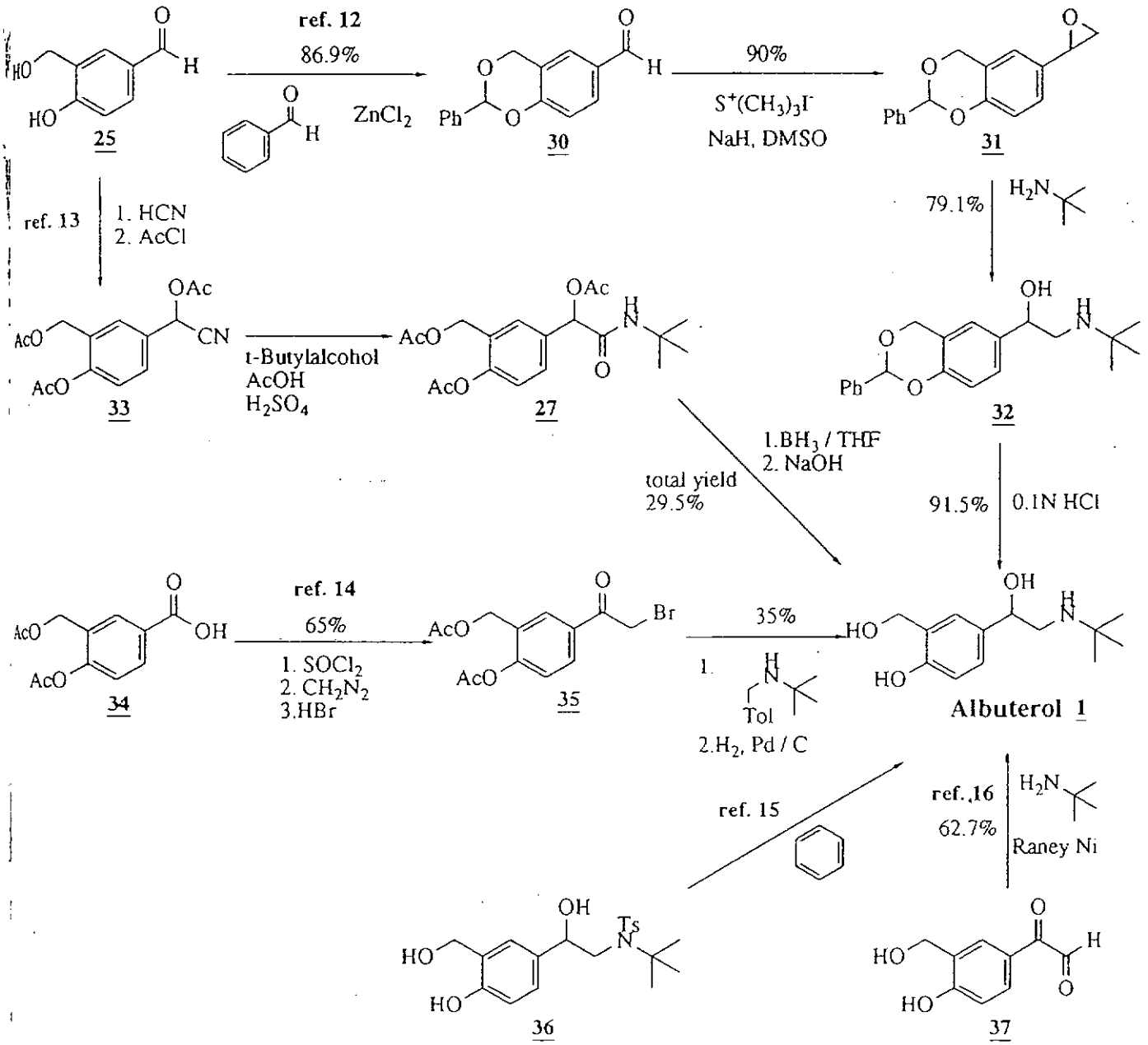









13
ref. 6
10
NaBH4
AcOH
Albuterol 1
90%
H2
Pd / C
14
ref. 7
SeO2
15
65-70%
1. H2N
2. [H]
16
17
ref. 8
18
92%
PF, HCl
19
ref. 9
PF, HCl
67%
Raney Ni
NaOH
76%
H2O
21
75-80%
Raney Ni
NaOH
20
Albuterol 1
H2
Pd / C
22
Br2
23
H2N
24
25
ref. 10
1. HCN
2. H+
3. AcCl
26
1. SOCl2
2. H2N
27
11
75.8%
Ac2O
1. Na / EtOH
2. NaOH
28
79.5%
N≡C
29
48.6%
LAH
Albuterol 1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86.9%
ZnCl2
90%
S+(CH3)3I-
NaH, DMSO
25
30
31
ref. 13
1. HCN
2. AcCl
79.1%
H2N
33
t-Butylalcohol
AcOH
H2SO4
27
32
1.BH3 / THF
2. NaOH
total yield
29.5%
91.5%
0.1N HCl
ref. 14
65%
1. SOCl2
2. CH2N2
3.HBr
35%
1.
Tol
2.H2, Pd / C
34
35
Albuterol 1
ref. 15
ref. 16
62.7%
Raney Ni
36
37

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5. *US Pat.* 3,644,353 **1972**.
6. *Japan Kokai* 74 72,227 **1974**.
7. *Japan Kokai* 75 130,732 **1975**.
8. a. *Czech* 176,846 **1979**.; b. *Czech* 185,080 **1980**.
9. *US Pat.* 3,642,896 **1972**.
10. *Span. ES* 459,339 **1979**.
11. *Japan Kokai* 75 52,038 **1975**.
12. *Japan Kokai* 74 52,037 **1975**.
13. *Japan Kokai* 78 02,442 **1978**.
14. *Ger. Offen* 2,340,189 **1975**.
15. *US Pat.* 3,956,390 **1976**.
16. *Japan Kokai* 73 103,535 **1973**.

2. Amlodipine

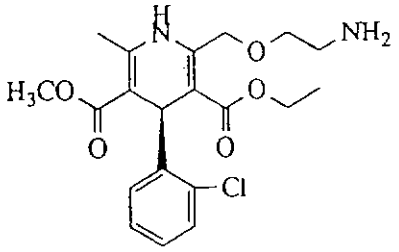
(Antianginal; Antihypertensive)

Technical Information

Amlodipine

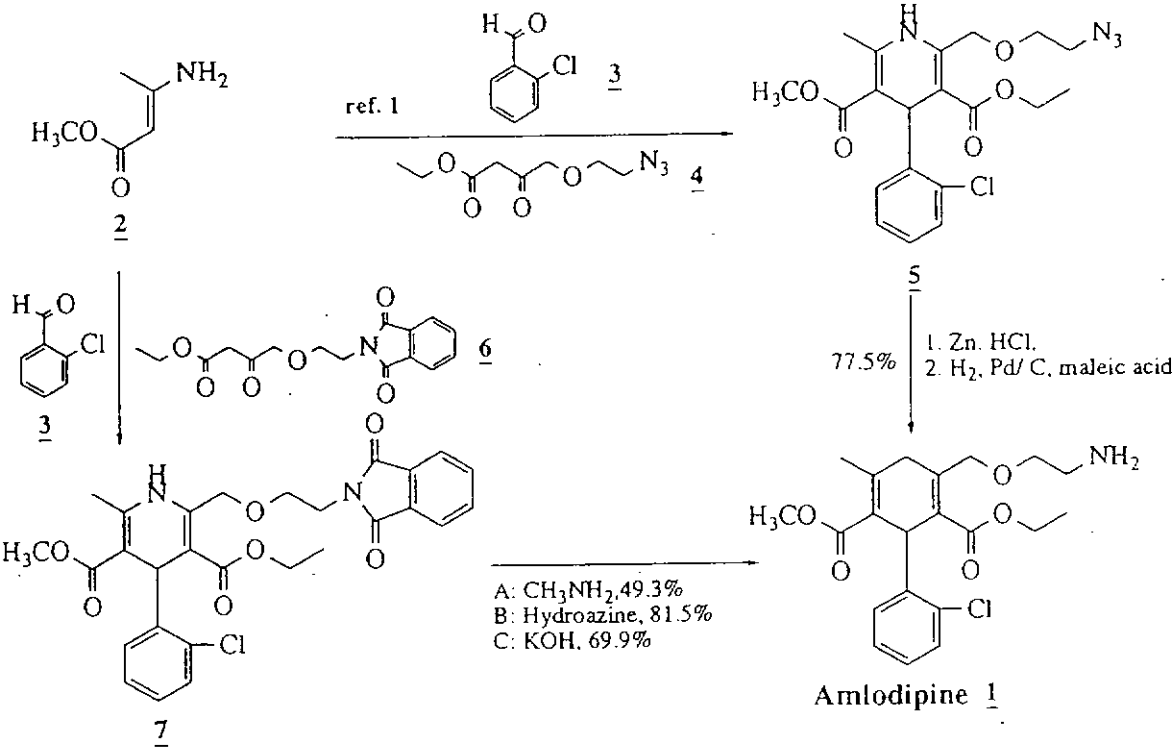
The key technology in the synthesis of amlodipine is to prepare its pyridine skeleton. Based on our review, the pyridine ring is assembled by 2-cholorobenzaldehyde, ethyl β -aminocrotonate, and a β-ketoester with various γ-alkoxyl substituent. Subsequent deprotection of the amino group would give the desired product, amlodipine. The *s*-isomer of amlodipine can be resolves through fractional crystallization from its salt with chiral acids, such as camphanic acid and tartaric acid.

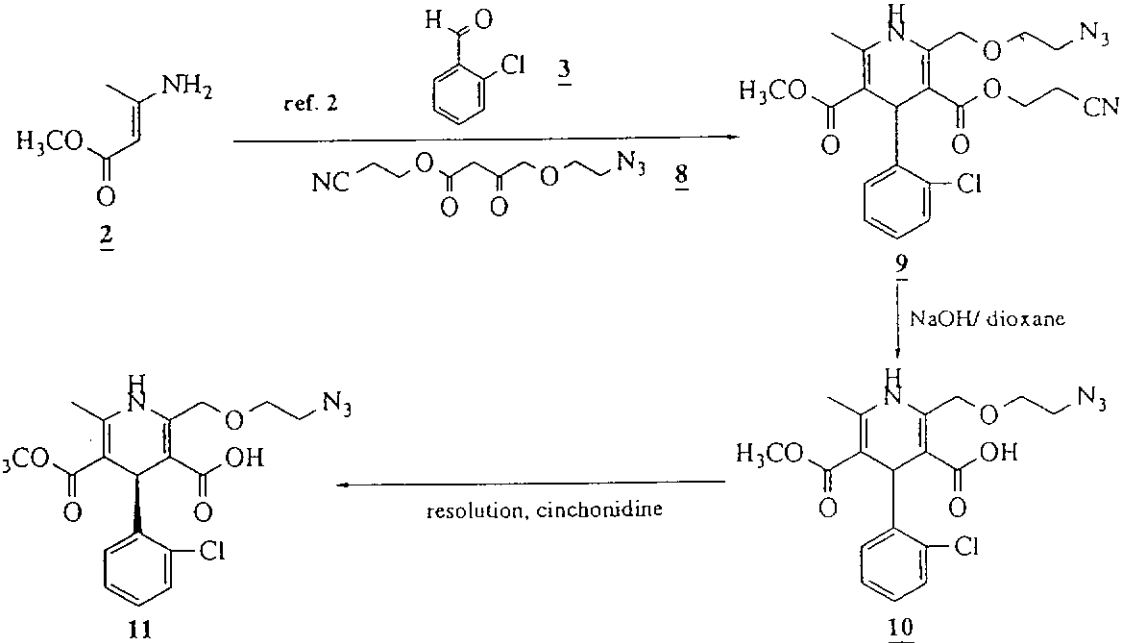
Amlodipine

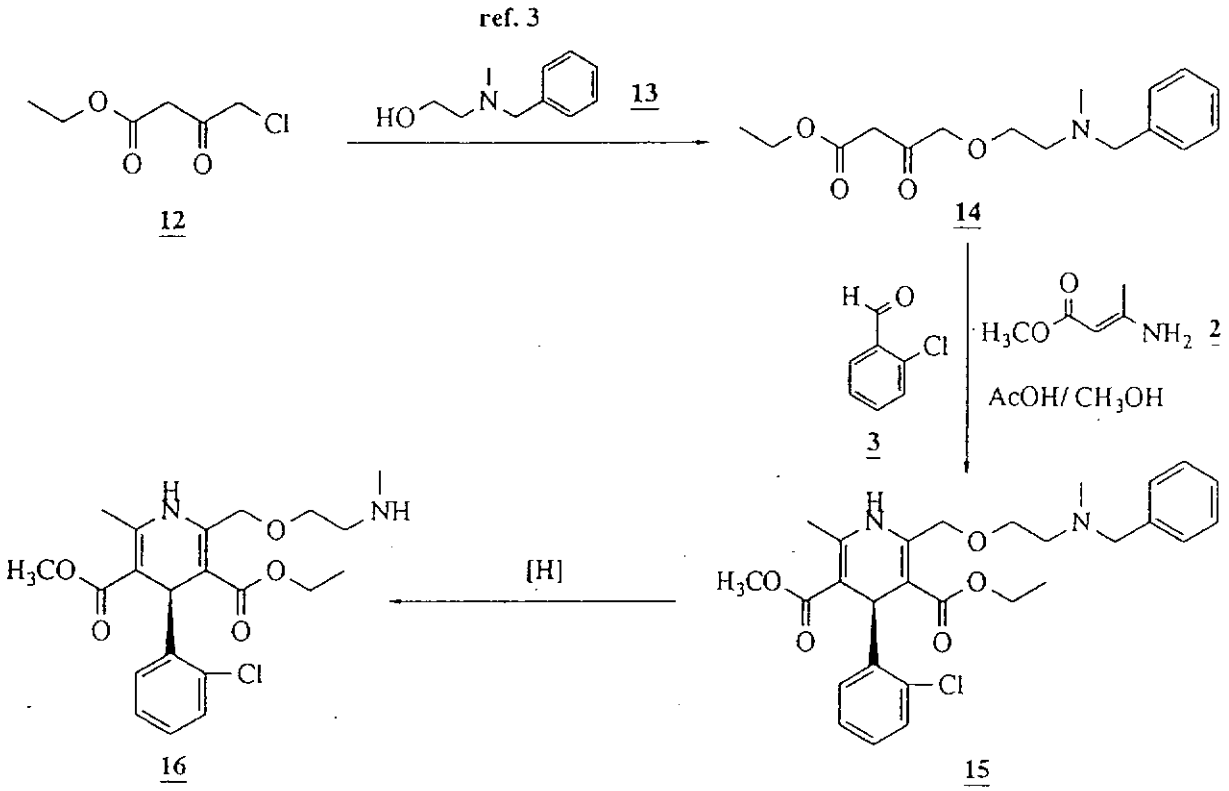


1

Antianginal
Antihypertensive
Pfizer
4 tons/year, 1500 USD/Kg







Resolution ((S)-form = (-) - enantiomer)

resolution agents:	1. (1S) - Camphanic acid	**ref. 4**
	2. (S) - methoxy-2-phenylethanol	**ref. 4**
	3. L or D - tartaric acid / DMSO	**ref. 5**

Other methods ref. 6

References:

1. a. *US Pat.* 4,572,909 **1986.**; b. *J. Med. Chem. 29*, 1696, **1986**.
2. *Brit. UK Pat. Appl. GB* 2,233,974 **1991**.
3. a. *US Pat.* 4,572,909 **1986.**; b. *Eur. Pat. Appl. EP* 89,167 **1983**.
4. *J. Med. Chem. 35*, 3341, **1992**.
5. *PCT Int. Appl. WO* 9,525,722 A1 28 Sep **1995**.
6. a. *Eur. Pat. Appl. EP* 132,375 **1985.**; b. *US Pat. Appl.* 463,095 **1983.**

3. Fluconazole

(Antifungal Agent)

Technical Information

Fluconazole

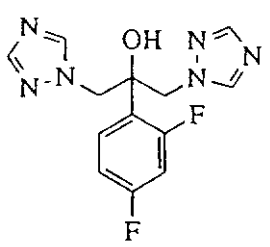
The key technology in the synthesis of fluconazole is to prepare the tertiary alcohol. Based on our review, the three alkyl or aryl groups are assembled through the following methods.

1: Grignard addition to the corresponding ketone

2: Bis-hydroxylation of the corresponding olefin.

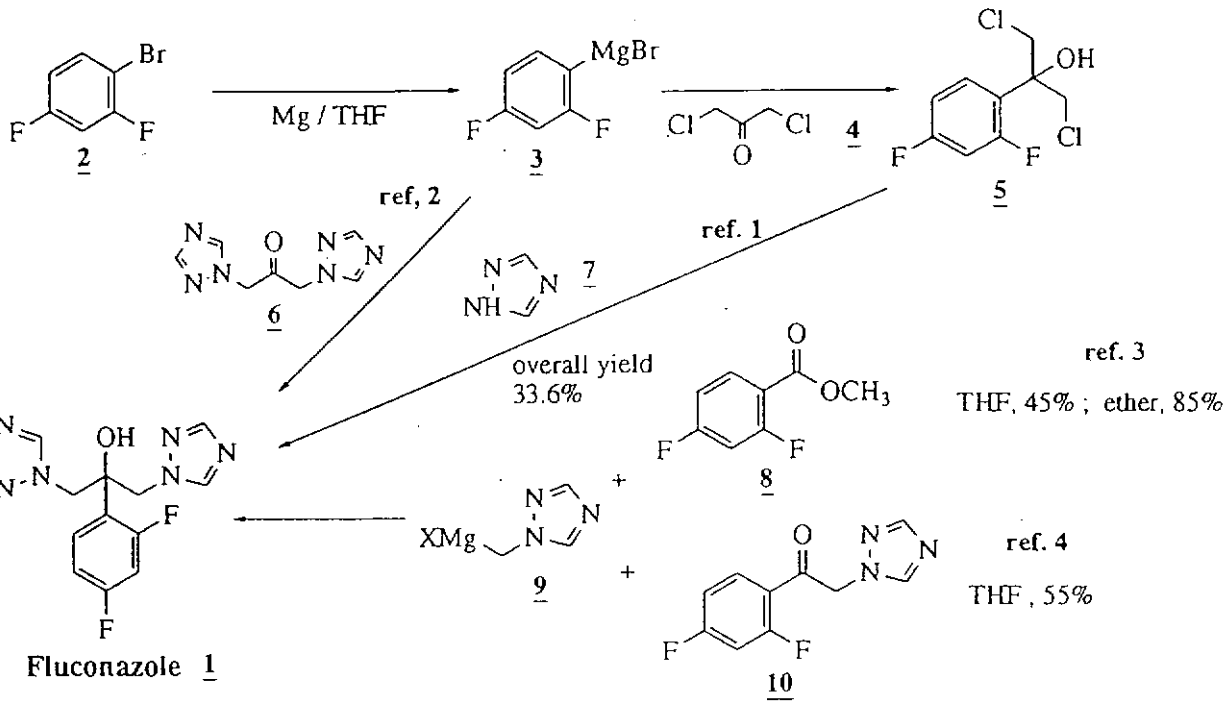
3: Wittig reaction of the corresponding ketone and sulfur yilid, and subsequent ring opening of the epoxide.

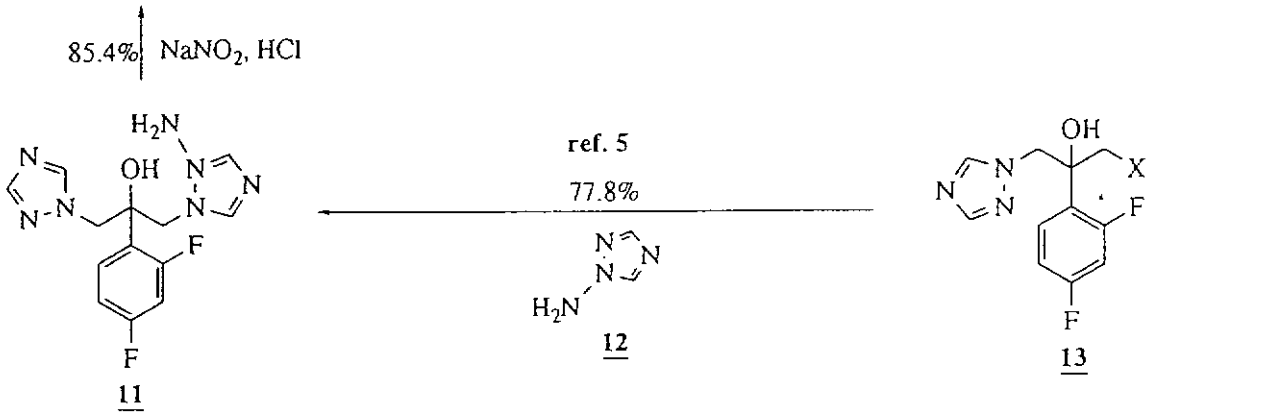
Fluconazole:

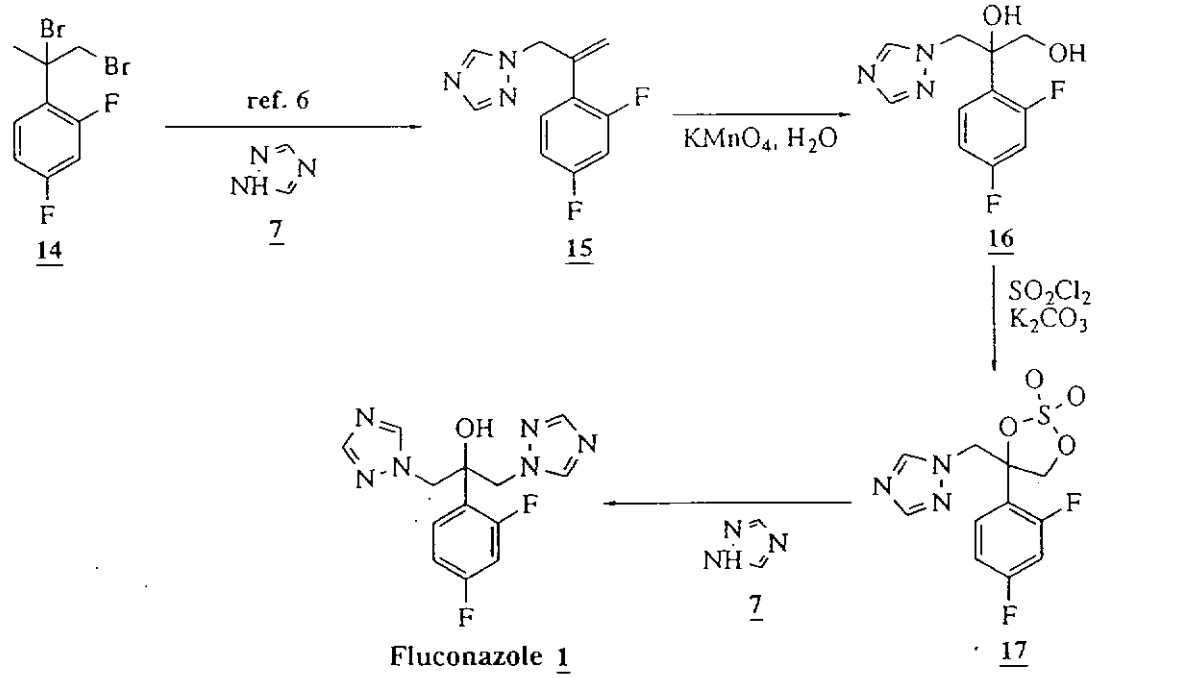


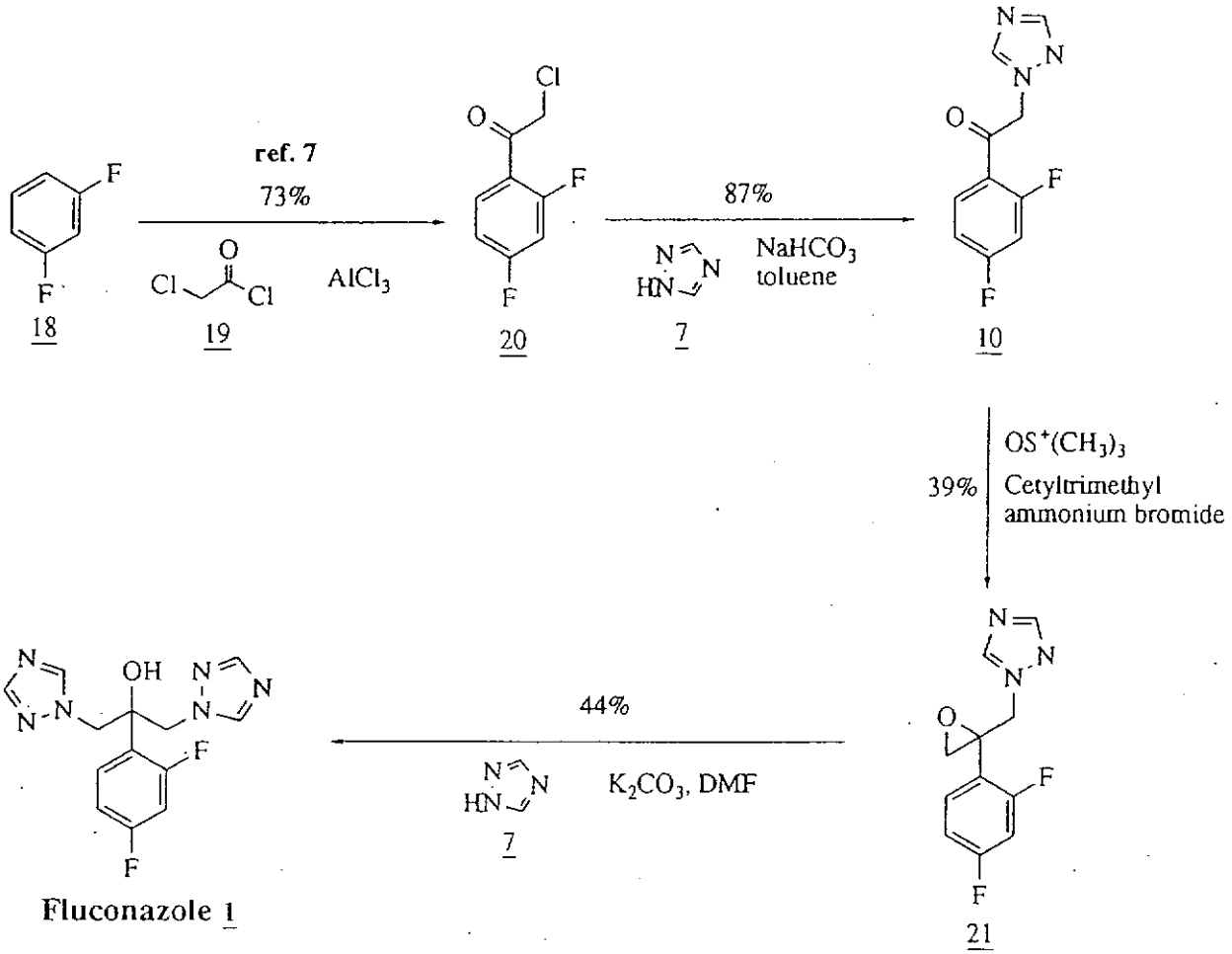
1

Antifungal
Pfizer
11 tons/tear, 1200 USD/Kg








ref. 7
73%
AlCl3
87%
NaHCO3
toluene
18
19
20
7
10
OS+(CH3)3
39%
Cetyltrimethyl
ammonium bromide
44%
K2CO3, DMF
7
21
Fluconazole 1

References:

1. *Zhongguo Yiyao Gongye Zazhi 21(4)*, 152, **1990**.
2. *Span. ES* 549,020 **1986**.
3. *Span. ES* 549,021 **1986**.
4. *Span. ES* 549,684 **1986**.
5. *Can. Pat. Appl. CA* 2,051,281 **1993**.
6. *PCT Int. Appl. WO* 96 20181 A1 4 Jul **1996**.
7. *US Pat.* 4,404,216 **1983**.

4. Fluoxetine

(Antidepressant Agent)

Technical Information

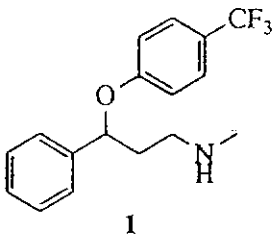
Fluoxetine

The key technology in the synthesis of fluoxetine is to prepare the benzilic phenyl ethyl. Based on our review, most of the current strategies are through the reduction of the bezoketone, converting the hydroxyl group into a leaving group, and replace with *p*-trifluoromethylpheoxide. Another important route is the arylation of the hydroxyl group by 1-choloro-4-trifluoromethylbenzene though nucleophilic substitution.

Recently, chiral s-form fluoxetine are found to be more efficient than its enantiomer.

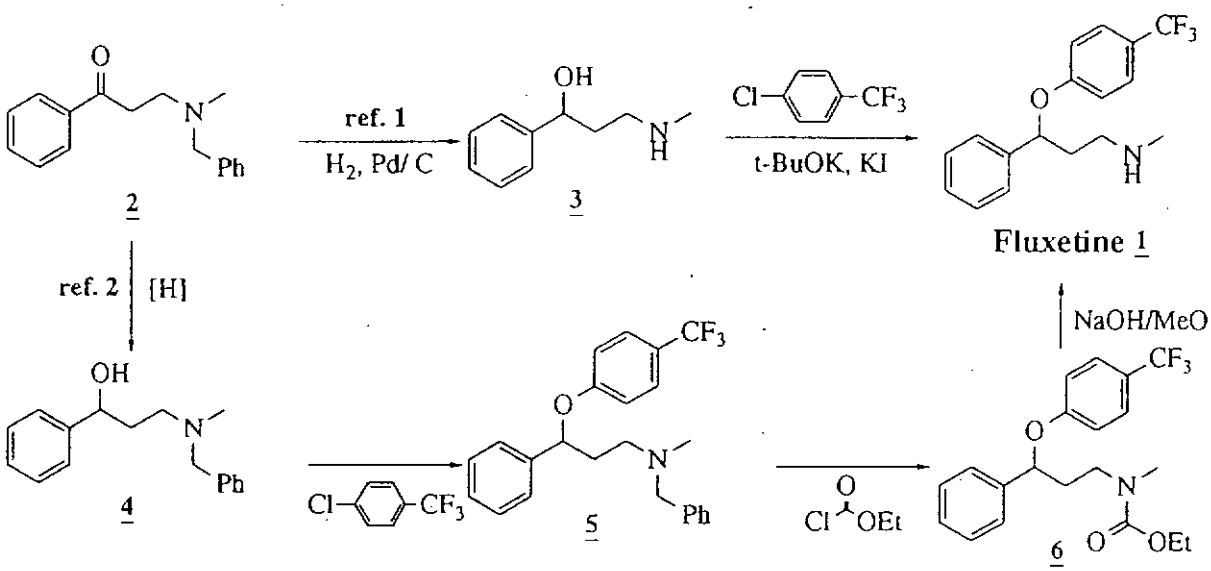
Besides the traditional resolution of the racemic fluoxetine, asymmetric reduction of the bezoketone is also a important way to prepare optically pure s-fluoxetine. In fact the chiral reduction of aryl ketone has became a hot subject for academic and industrial researchers working in the asymmetric synthesis area.

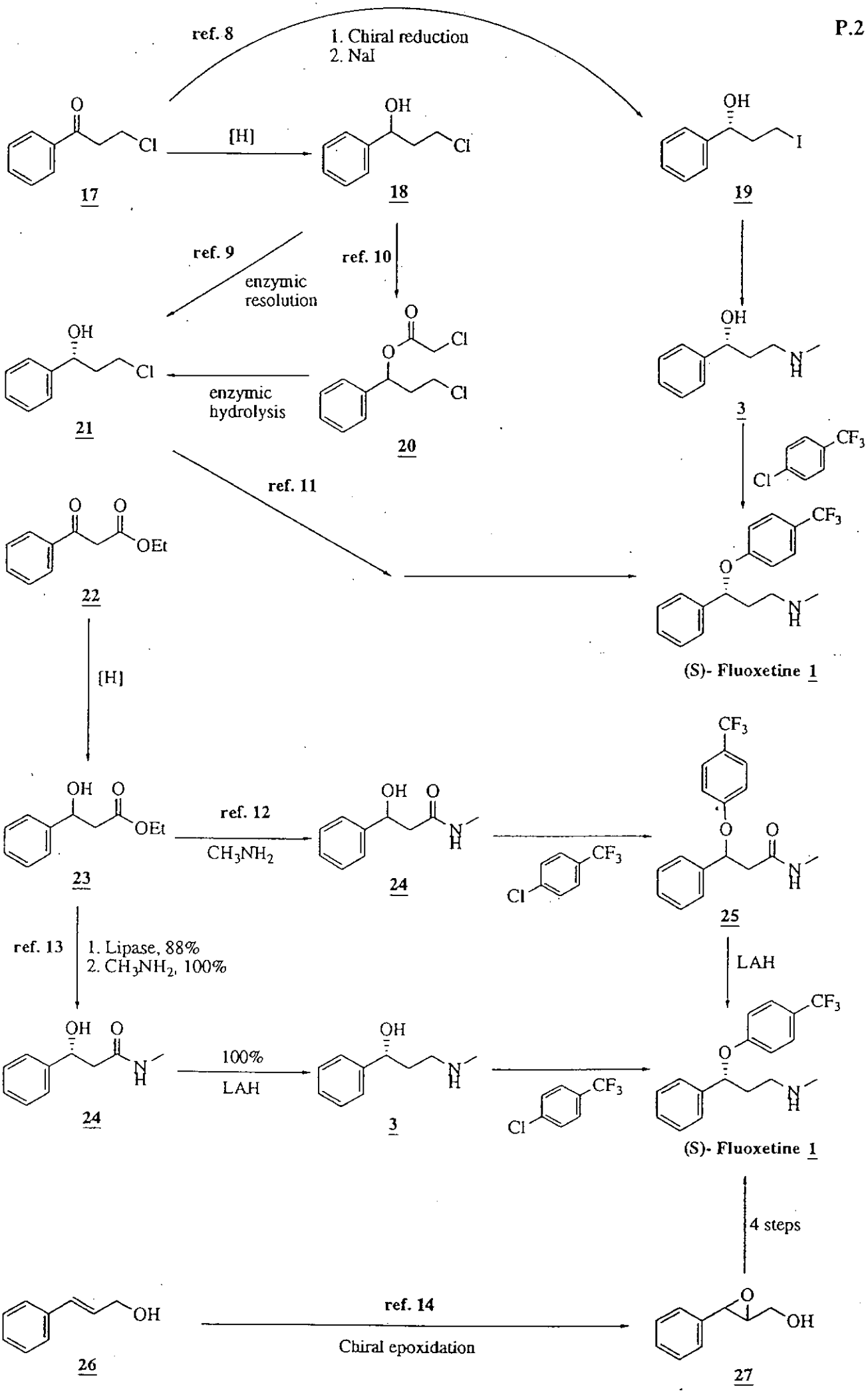
Fluoxetine



1

Antidepressant
Lilly
16 tons/tear, 800 USD/Kg




ref. 8
1. Chiral reduction
2. NaI
[H]
17
18
19
ref. 9
enzymic resolution
ref. 10
21
enzymic hydrolysis
20
3
ref. 11
22
(S)- Fluoxetine 1
[H]
23
ref. 12
CH3NH2
24
25
ref. 13
1. Lipase, 88%
2. CH3NH2, 100%
LAH
100%
LAH
24
3
(S)- Fluoxetine 1
4 steps
ref. 14
Chiral epoxidation
26
27

References:

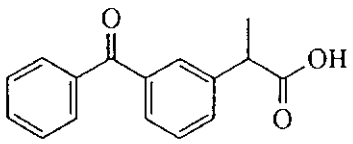
1. *Finn. FI* 81,083 **1990**.
2. *Eur. Pat. Appl. EP* 617,006.
3. *US Pat.* 4,018,895.
4. *Eur. Pat. Appl. EP* 529,842 **1993**.
5. *T.L .* 33, 6845, **1992**.
6. a. *PCT Int. Appl. WO* 92 13,452 **1992**.; b. *US Appl.* 650,385 **1991**.
7. a. *US Pat.* 5,104,899.; b. *Span. ES* 556,009 **1987**.
8. *J. Med. Chem. 31(7),* 1412, **1988**.
9. *Tetrahedron : Asym. 3(4),* 525, **1992**.
10. *Ger. Offen. DE* 4 123,253 **1993**.
11. *T.L. 30,* 5207, **1989**.
12. *Tetrahedron 48(33),* 6769, **1992**.
13. *Jpn. Kokai Tokkyo Koho JP* 04 05,268 **1992**.
14. *PCT Int. Appl. WO* 93 09,769 **1993**.

5. Ketoprofen

(Anti-inflammatory; Analgesic)

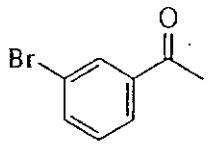
Technical Information

Ketoprofen



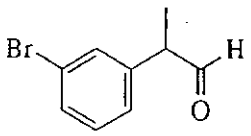
1

Anti-inflammatory
analgestic
Rhone-Poulenc



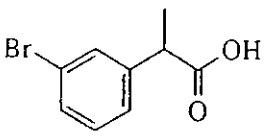
2

1. $S^+(CH_3)_3$
2. Al_2O_3
82.7%

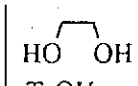


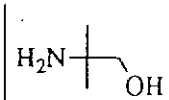
3

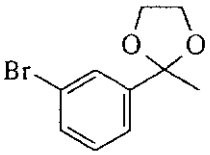
ref. 1
NaOCl
95.2%



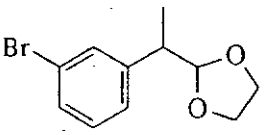
4

ref. 2
96.17%

TsOH

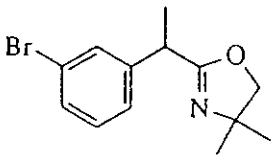
89.3%




11



8

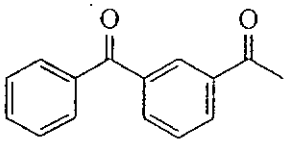


5

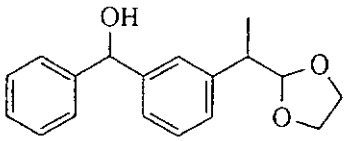
ref. 3
64%
1. Mg
2. PhCHO
3. HClO, Bu_4NHSO_3

88.1%
1. Mg
2. PhCHO

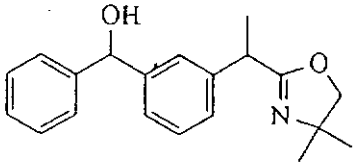
1. Mg
2. PhCHO



12



9

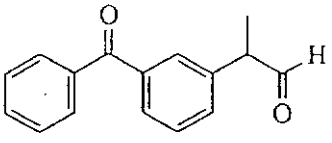


6

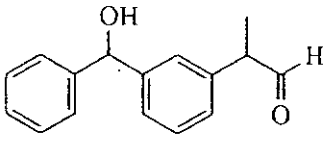
ref. 4
1. $BrCH_2CO_2Et$, 72%
2. NaOH

HCl

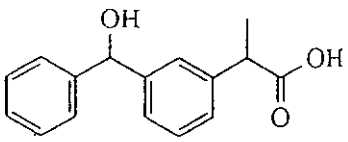
93.1%
HCl



13



10

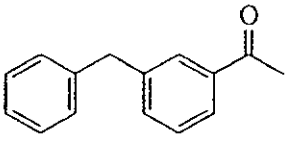


7

$KMnO_4$

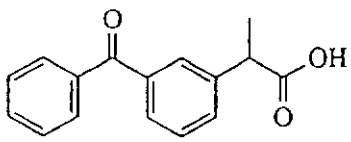
$KBrO_3$, HOAc
80.9%

ref.5
86.8%
[O]

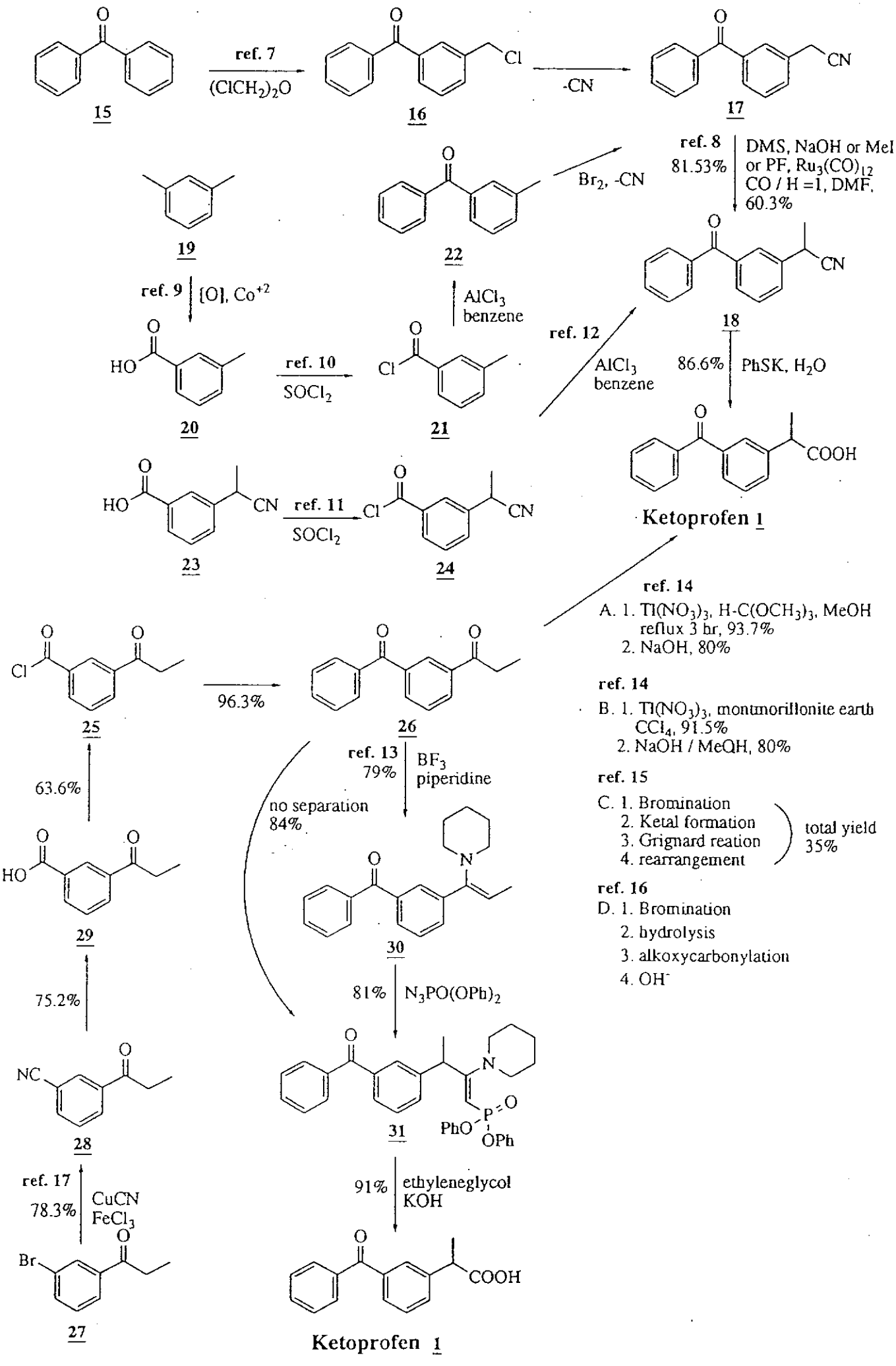


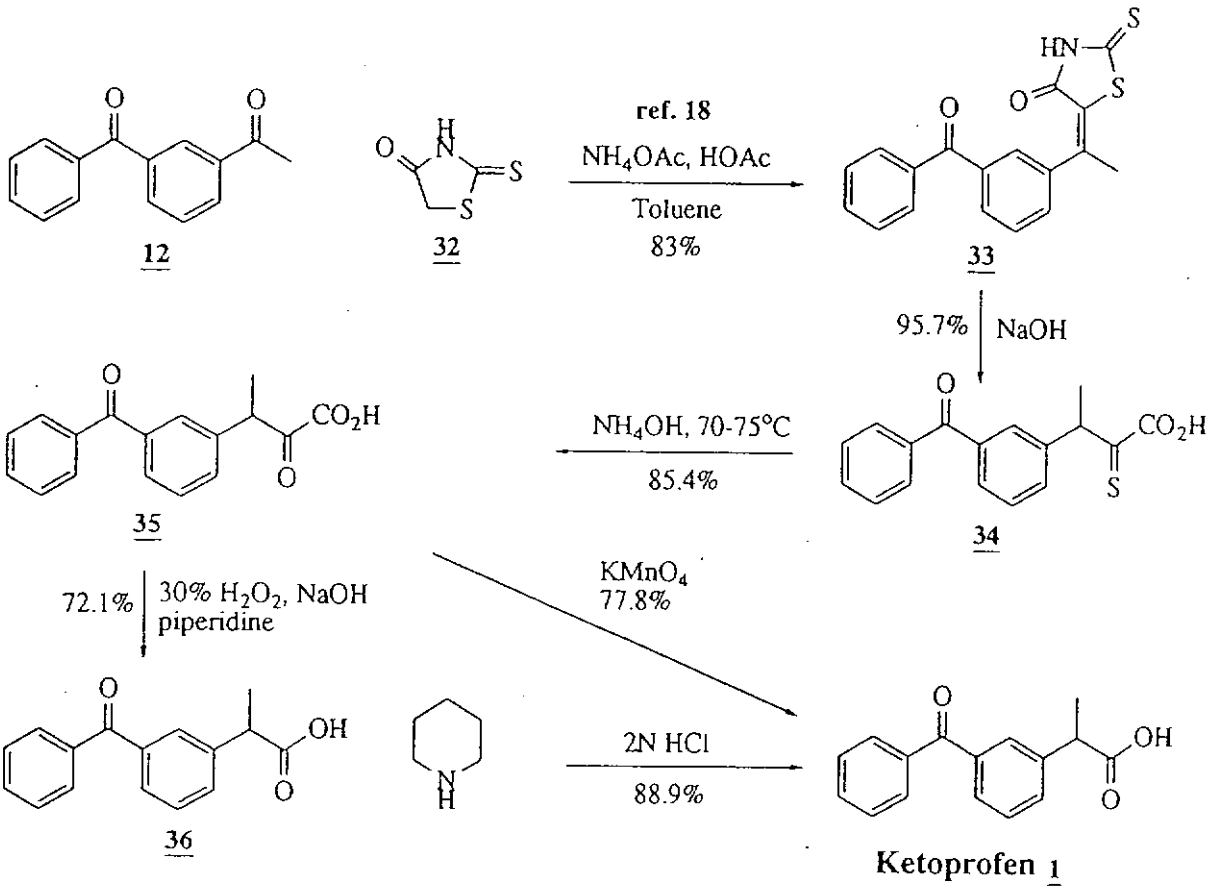
14

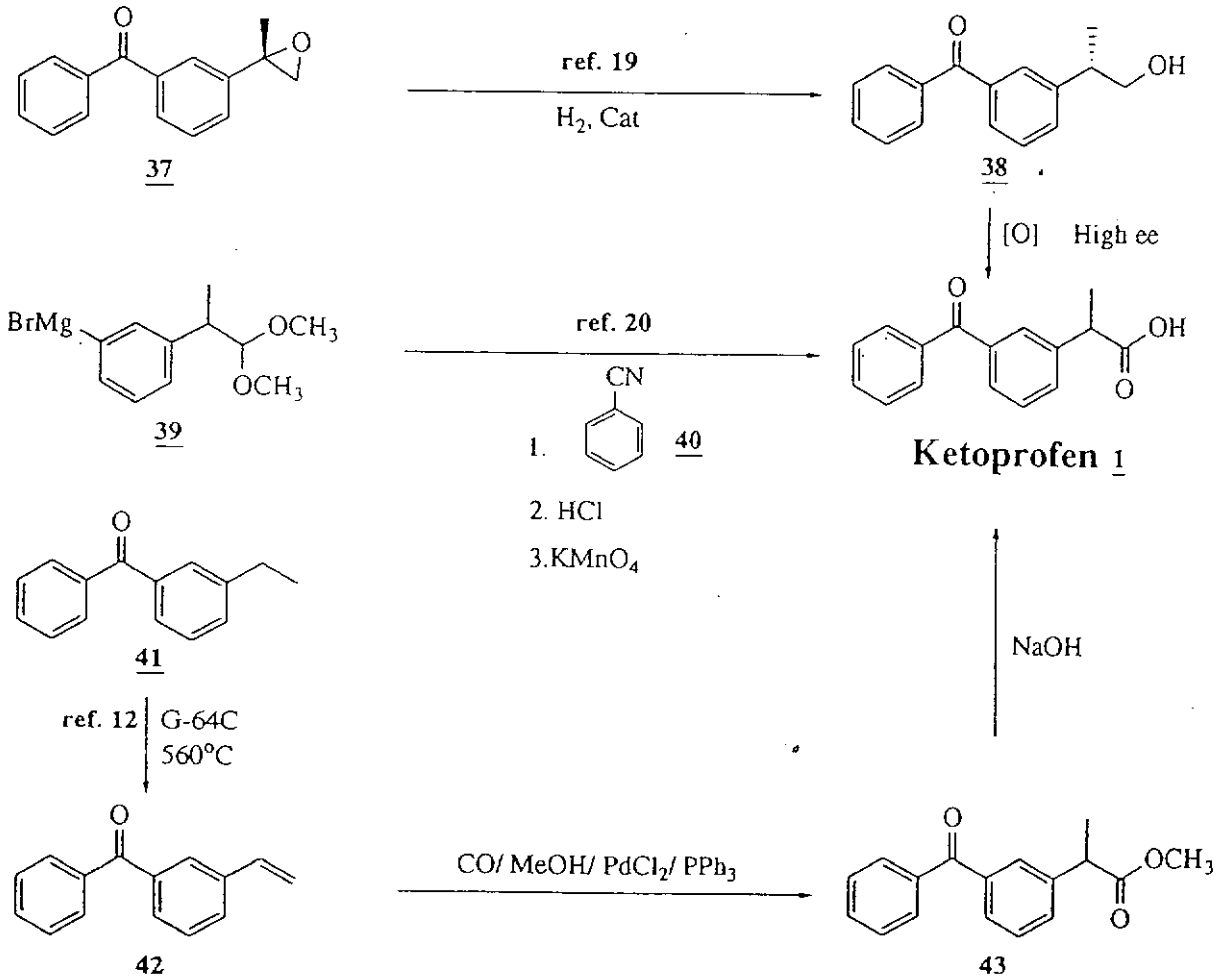
ref. 6
1.$ClCH_2CO_2Et$ / NaOEt
2.NaOH, 72%
3.$KMnO_4$, 69%

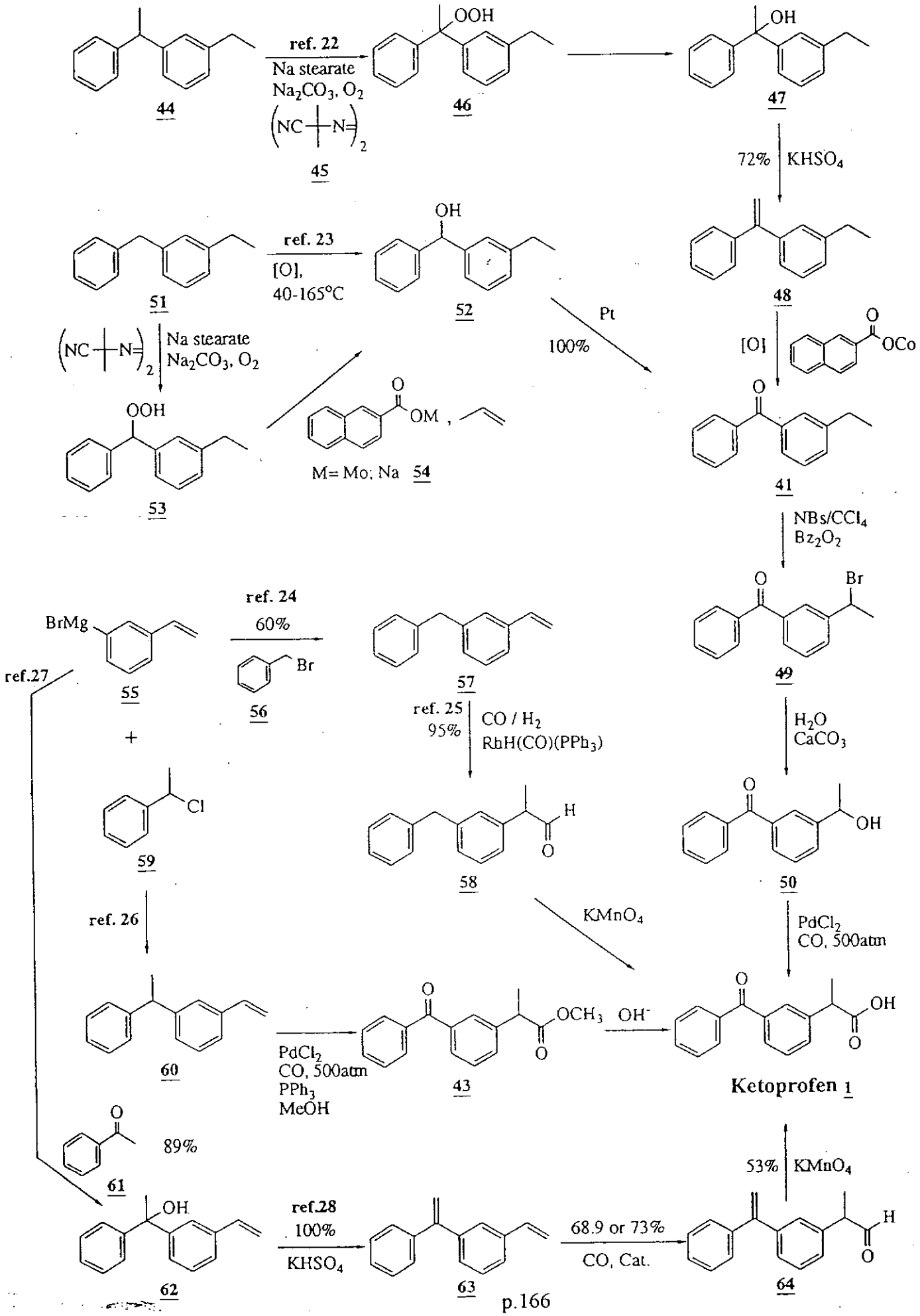


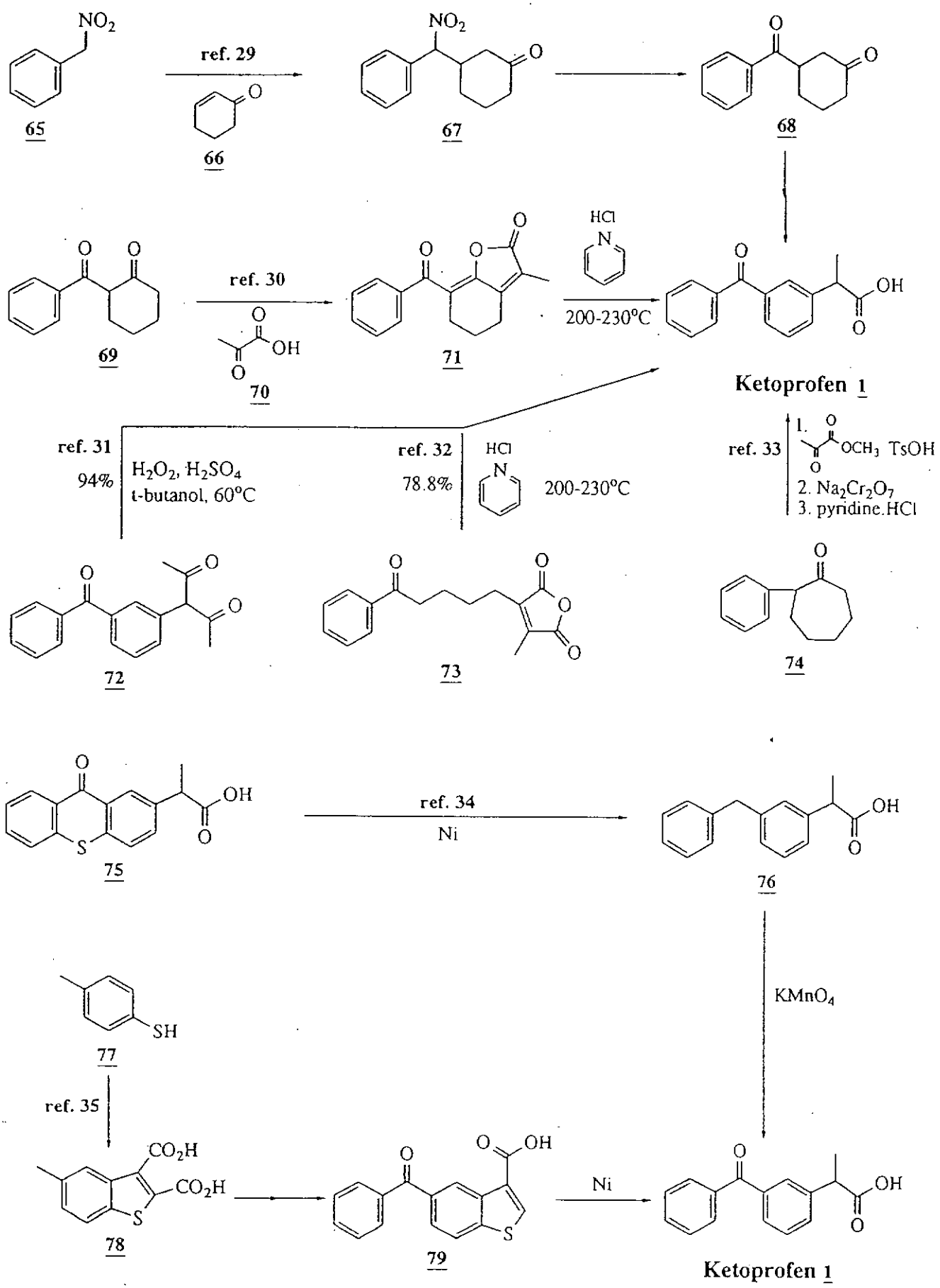
Ketoprofen 1

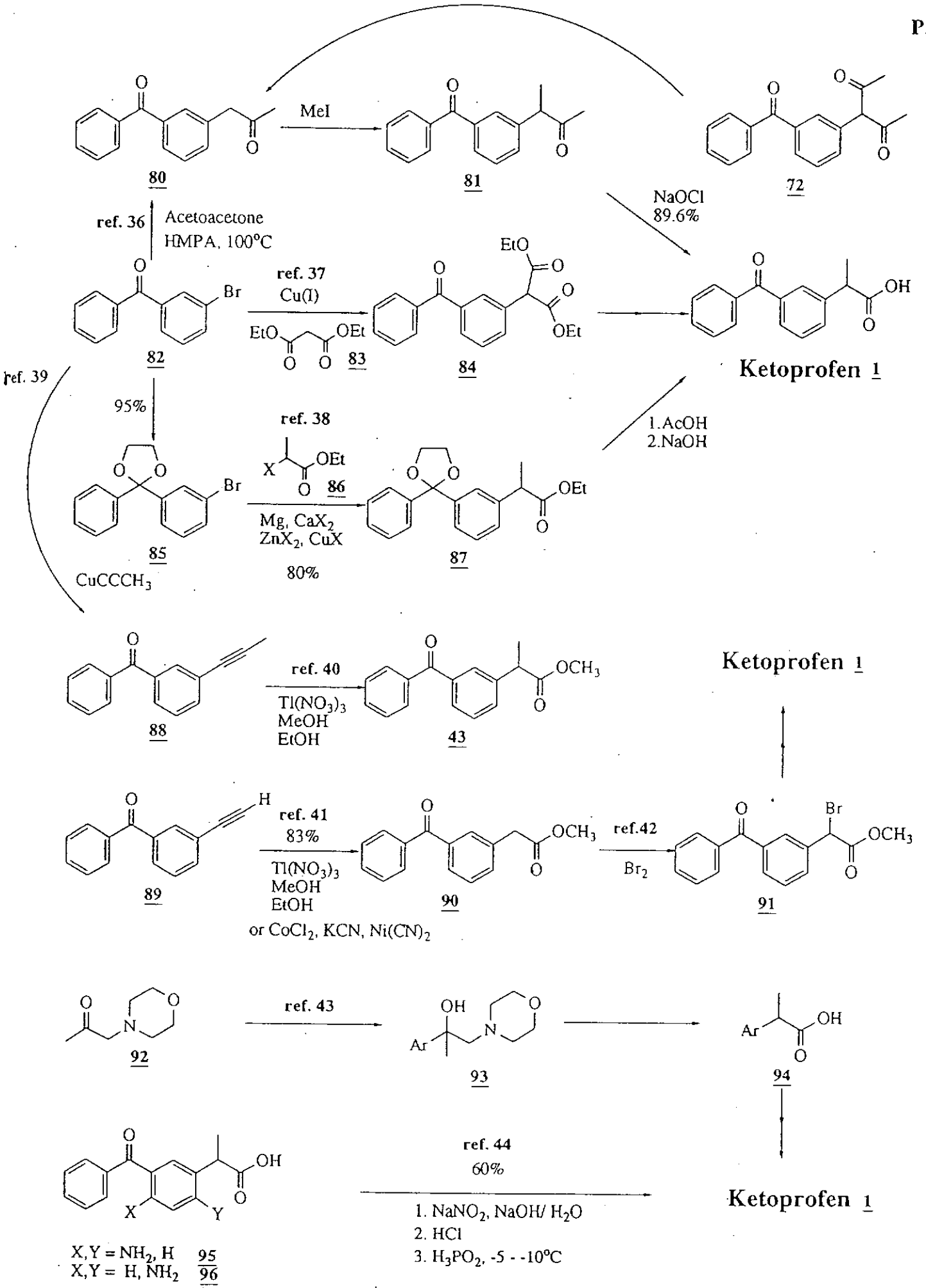

15
ref. 7
$(ClCH_2)_2O$
16
Cl
-CN
17
CN
ref. 8
81.53%
DMS, NaOH or MeI
or PF, $Ru_3(CO)_{12}$
CO / H =1, DMF,
60.3%
19
22
Br_2, -CN
18
CN
ref. 9
[O], Co^{+2}
$AlCl_3$
benzene
ref. 12
$AlCl_3$
benzene
86.6%
PhSK, H_2O
20
HO
ref. 10
$SOCl_2$
21
Cl
COOH
Ketoprofen 1
23
HO
CN
ref. 11
$SOCl_2$
24
Cl
CN
ref. 14
A. 1. $Tl(NO_3)_3$, $H\text{-}C(OCH_3)_3$, MeOH
reflux 3 hr, 93.7%
2. NaOH, 80%
ref. 14
B. 1. $Tl(NO_3)_3$, montmorillonite earth
CCl_4, 91.5%
2. NaOH / MeOH, 80%
ref. 15
C. 1. Bromination
2. Ketal formation
3. Grignard reation
4. rearrangement
total yield
35%
ref. 16
D. 1. Bromination
2. hydrolysis
3. alkoxycarbonylation
4. OH^-
25
Cl
96.3%
26
63.6%
29
HO
ref. 13
79%
BF_3
piperidine
no separation
84%
30
N
75.2%
81%
$N_3PO(OPh)_2$
28
NC
31
N
PhO
OPh
ref. 17
78.3%
CuCN
$FeCl_3$
91%
ethyleneglycol
KOH
27
Br
COOH
Ketoprofen 1

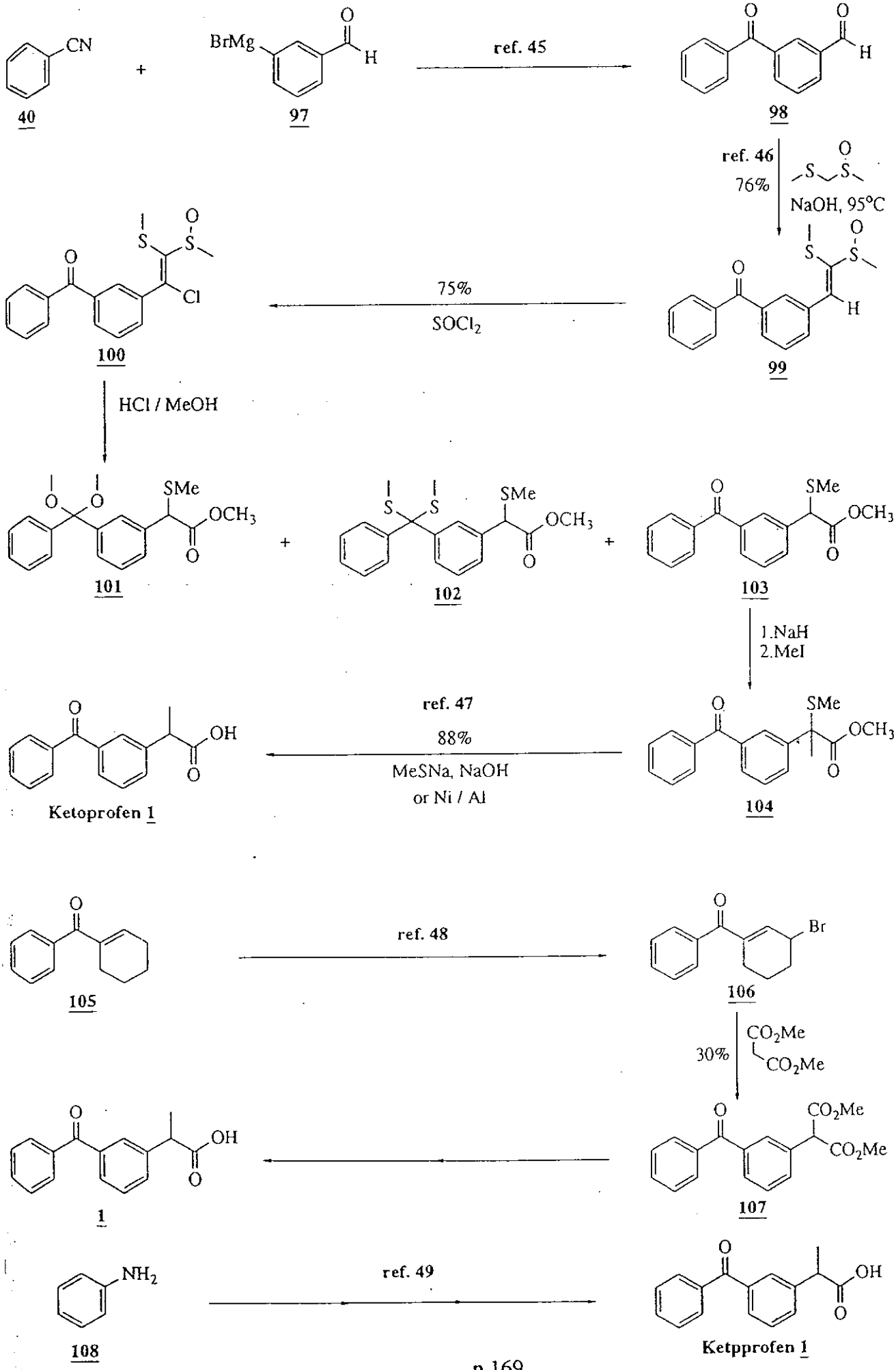

12
32
ref. 18
NH4OAc, HOAc
Toluene
83%
33
95.7%
NaOH
35
NH4OH, 70-75°C
85.4%
34
72.1%
30% H2O2, NaOH
piperidine
KMnO4
77.8%
36
2N HCl
88.9%
Ketoprofen 1

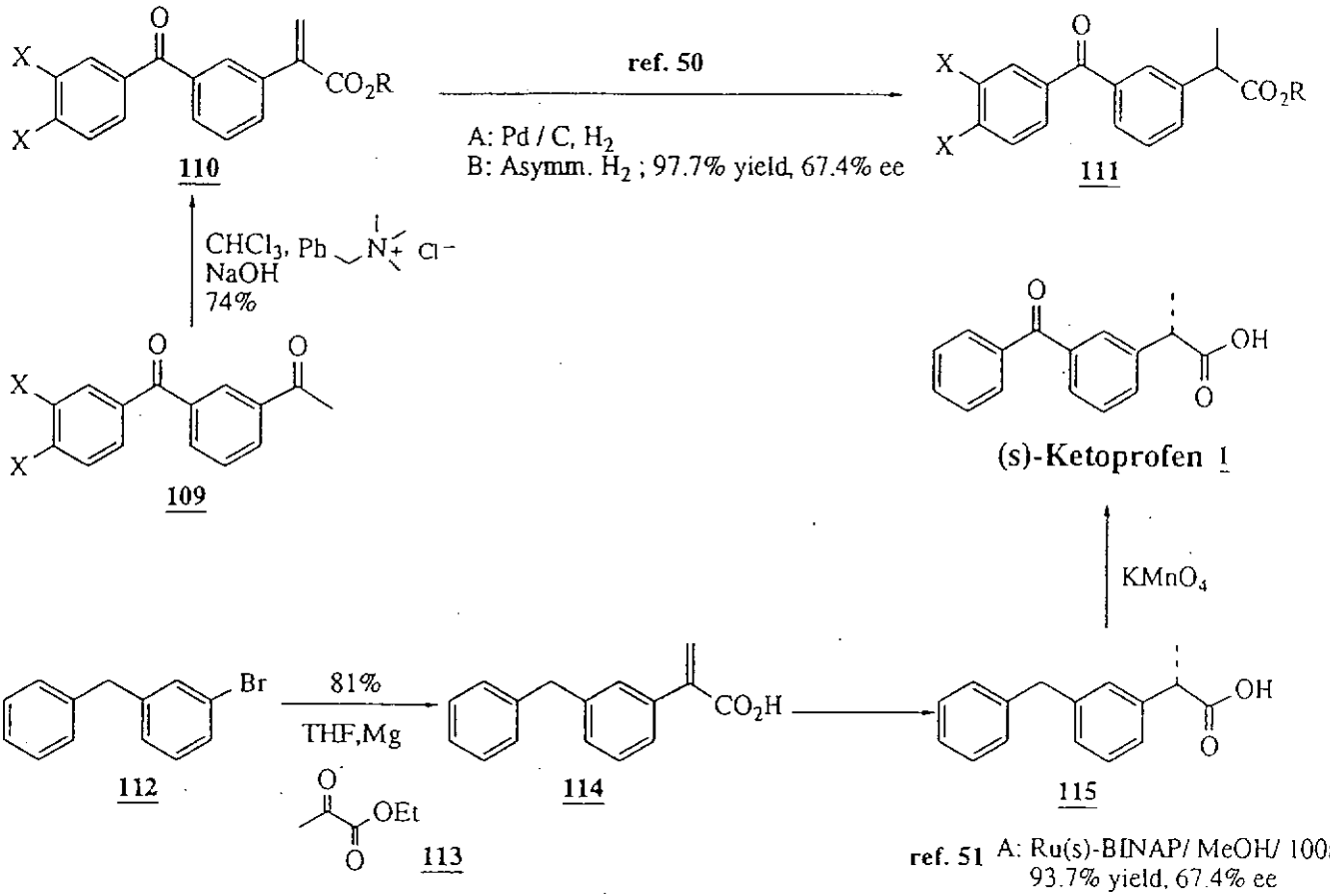

37
ref. 19
H2, Cat
38
[O] High ee
39
ref. 20
CN
1.
40
2. HCl
3.KMnO4
Ketoprofen 1
41
NaOH
ref. 12
G-64C
560°C
42
CO/ MeOH/ PdCl2/ PPh3
43


ref. 22
Na stearate
Na_2CO_3, O_2
45
44
46
47
72% $KHSO_4$
48
ref. 23
[O],
40-165°C
51
52
Pt
100%
[O]
Na stearate
Na_2CO_3, O_2
53
M= Mo; Na 54
41
NBs/CCl_4
Bz_2O_2
ref. 24
60%
55
56
57
49
ref. 25
95%
CO / H_2
$RhH(CO)(PPh_3)$
H_2O
$CaCO_3$
59
58
50
ref. 26
$KMnO_4$
$PdCl_2$
CO, 500atm
60
$PdCl_2$
CO, 500atm
PPh_3
MeOH
43
OH^-
Ketoprofen 1
89%
61
53% $KMnO_4$
ref.28
100%
$KHSO_4$
62
63
68.9 or 73%
CO, Cat.
64

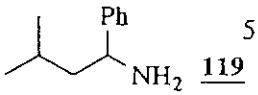

NO2
65
ref. 29
66
NO2
67
68
69
ref. 30
70
71
HCl
200-230°C
Ketoprofen 1
ref. 31
94%
H2O2, H2SO4
t-butanol, 60°C
ref. 32
78.8%
HCl
200-230°C
ref. 33
1. OCH3 TsOH
2. Na2Cr2O7
3. pyridine.HCl
72
73
74
75
ref. 34
Ni
76
KMnO4
77
ref. 35
78
79
Ni
Ketoprofen 1


MeI
80
81
72
ref. 36
Acetoacetone
HMPA, 100°C
NaOCl
89.6%
ref. 37
Cu(I)
82
83
84
Ketoprofen 1
ref. 39
95%
ref. 38
86
1.AcOH
2.NaOH
85
87
Mg, CaX2
ZnX2, CuX
80%
CuCCCH3
88
ref. 40
Tl(NO3)3
MeOH
EtOH
43
Ketoprofen 1
89
ref. 41
83%
Tl(NO3)3
MeOH
EtOH
or CoCl2, KCN, Ni(CN)2
90
ref.42
Br2
91
92
ref. 43
93
94
ref. 44
60%
1. NaNO2, NaOH/ H2O
2. HCl
3. H3PO2, -5 - -10°C
Ketoprofen 1
X,Y = NH2, H 95
X,Y = H, NH2 96


CN
BrMg
O
H
ref. 45
40
97
98
ref. 46
76%
NaOH, 95°C
75%
SOCl2
100
99
HCl / MeOH
SMe
OCH3
101
102
103
1.NaH
2.MeI
ref. 47
88%
MeSNa, NaOH
or Ni / Al
OH
Ketoprofen 1
104
105
ref. 48
Br
106
CO2Me
30%
107
1
NH2
ref. 49
108
Ketpprofen 1



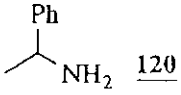
Resolution: resolution agents

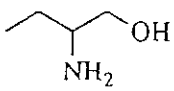
ref. 55 a.  55-75% yield, 99% ee(+) **119**

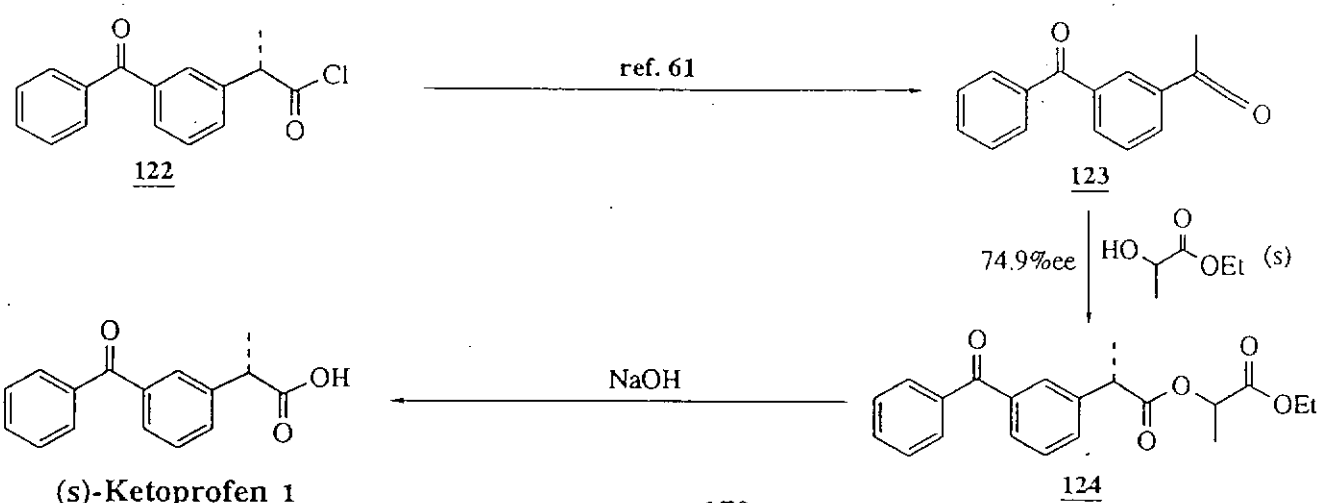
ref. 56 b. Enzymic resolution >99%ee

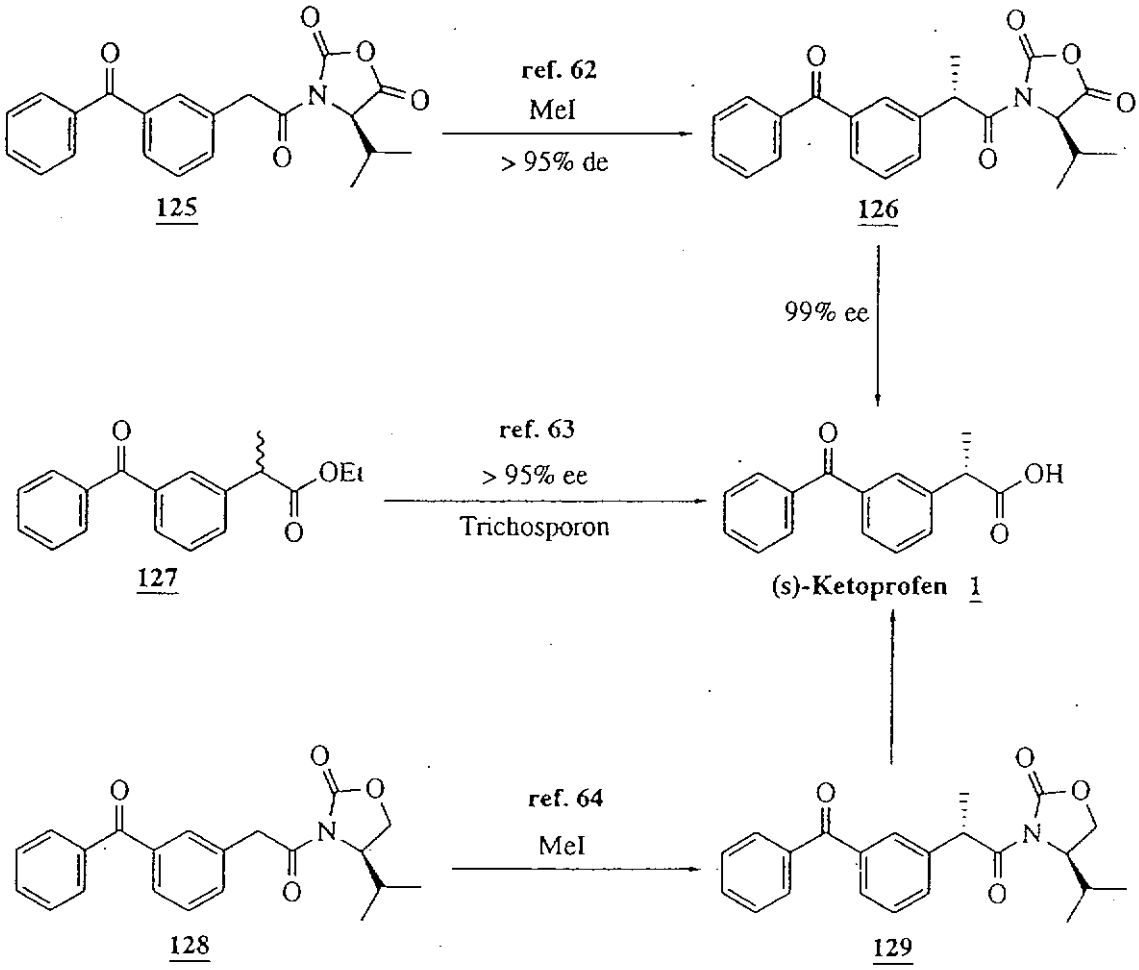
ref. 57 c. Cinchonidine 44% yield, 86%ee; 31% yield, 97%ee

ref. 58 d. (R)-ketoprofen $\xrightarrow{NaOH}$ (R,S)-ketoprofen

ref. 59 e.  44% yield, >99%ee **120**

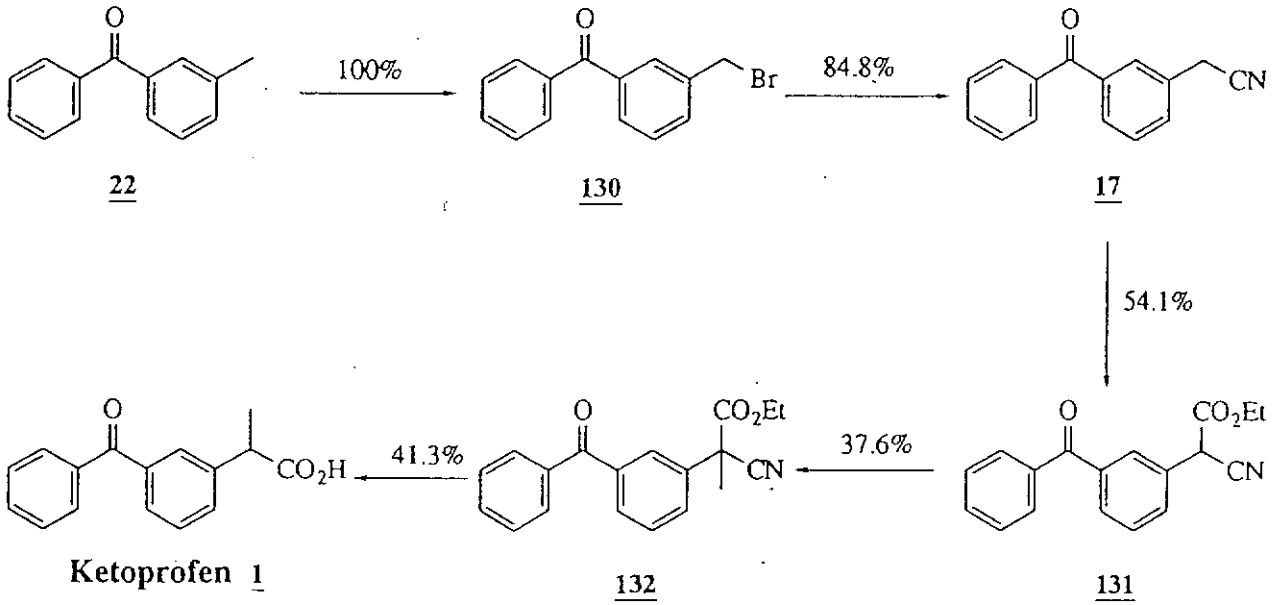
ref. 60 f.  **121**



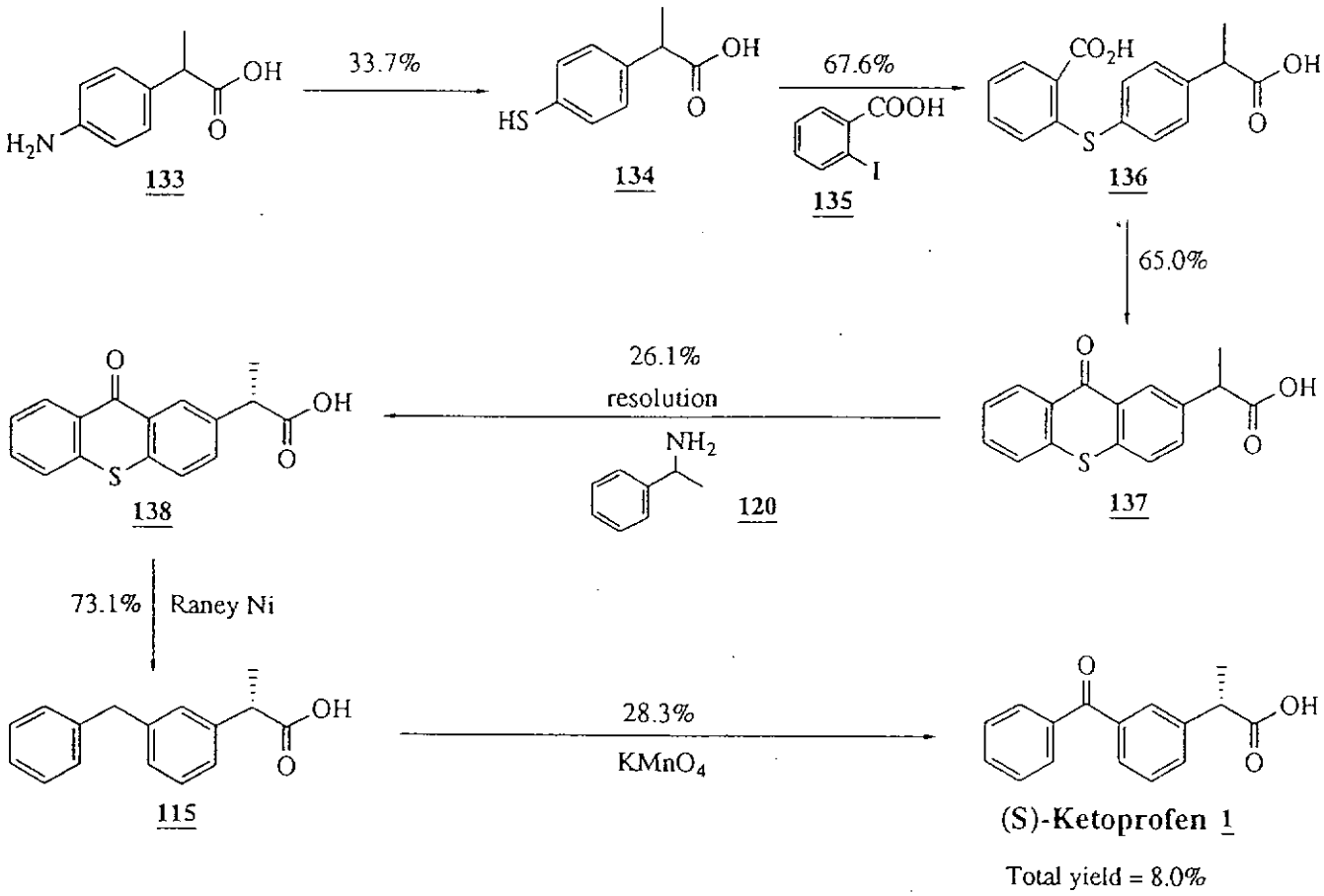


125 126 127 (s)-Ketoprofen 1 128 129

A.



B. (s)-ketoprofen



Total yield = 8.0%

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6. Lisinopril

(Antihypertensive Agent)

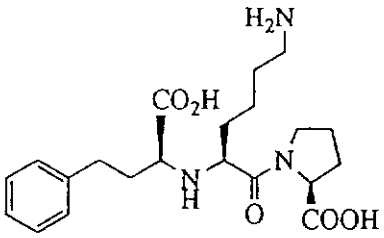
Technical Information

Lisinopril

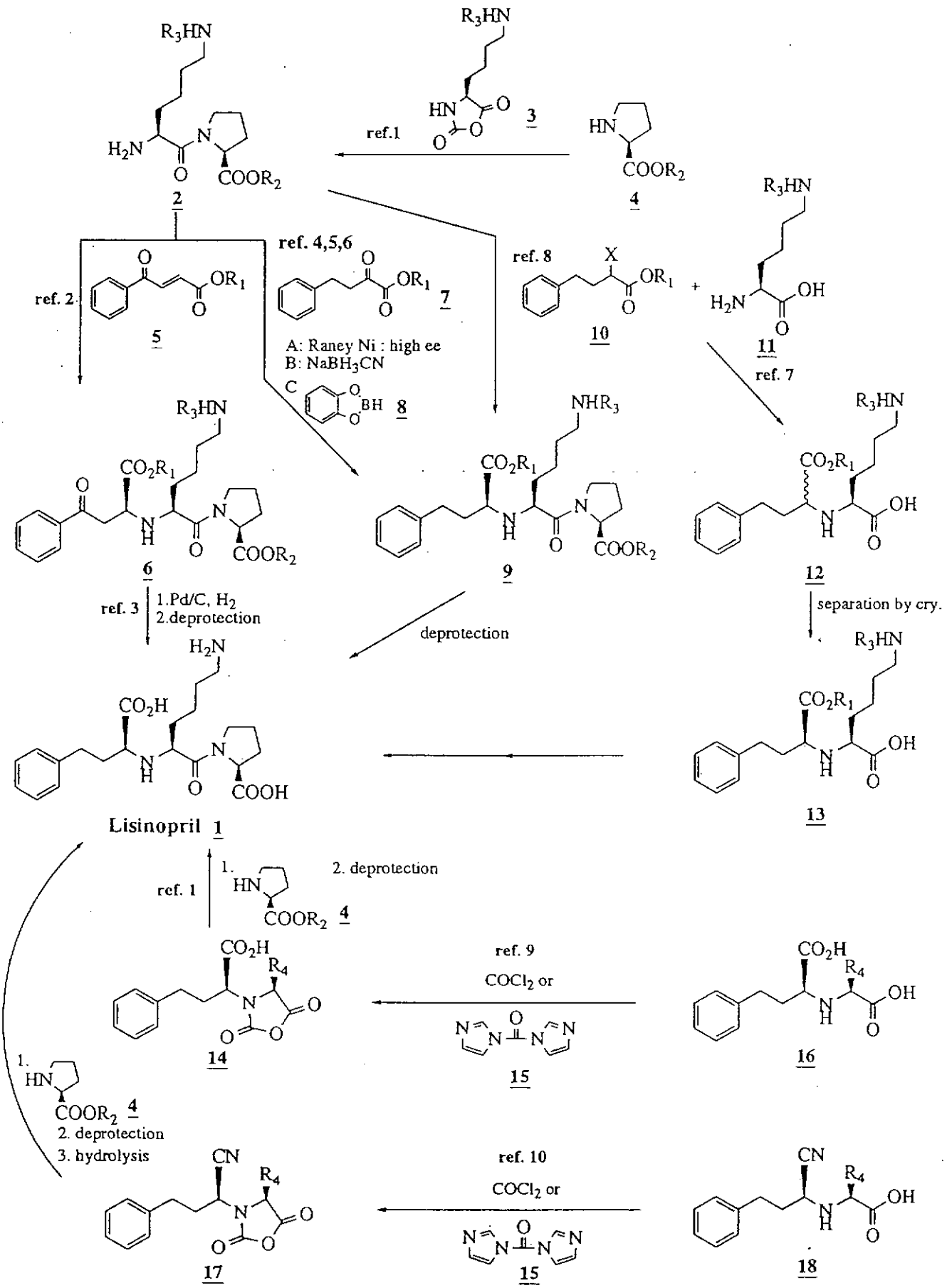
Lisinopril is made through the assembling of the three amino acids, including proline, lysine, and homophenylalanine. Because homoalanine is not from natural source. If we first assemble proline and lysine together, the homoalanine part can be prepared by either Michael addition to enone or by reductive amination or the corresponding α-ketoester. Up to date, the industrial technology to acquire chiral version of lisinopril is still based on the fractional crystallization of the diastereoisomers.

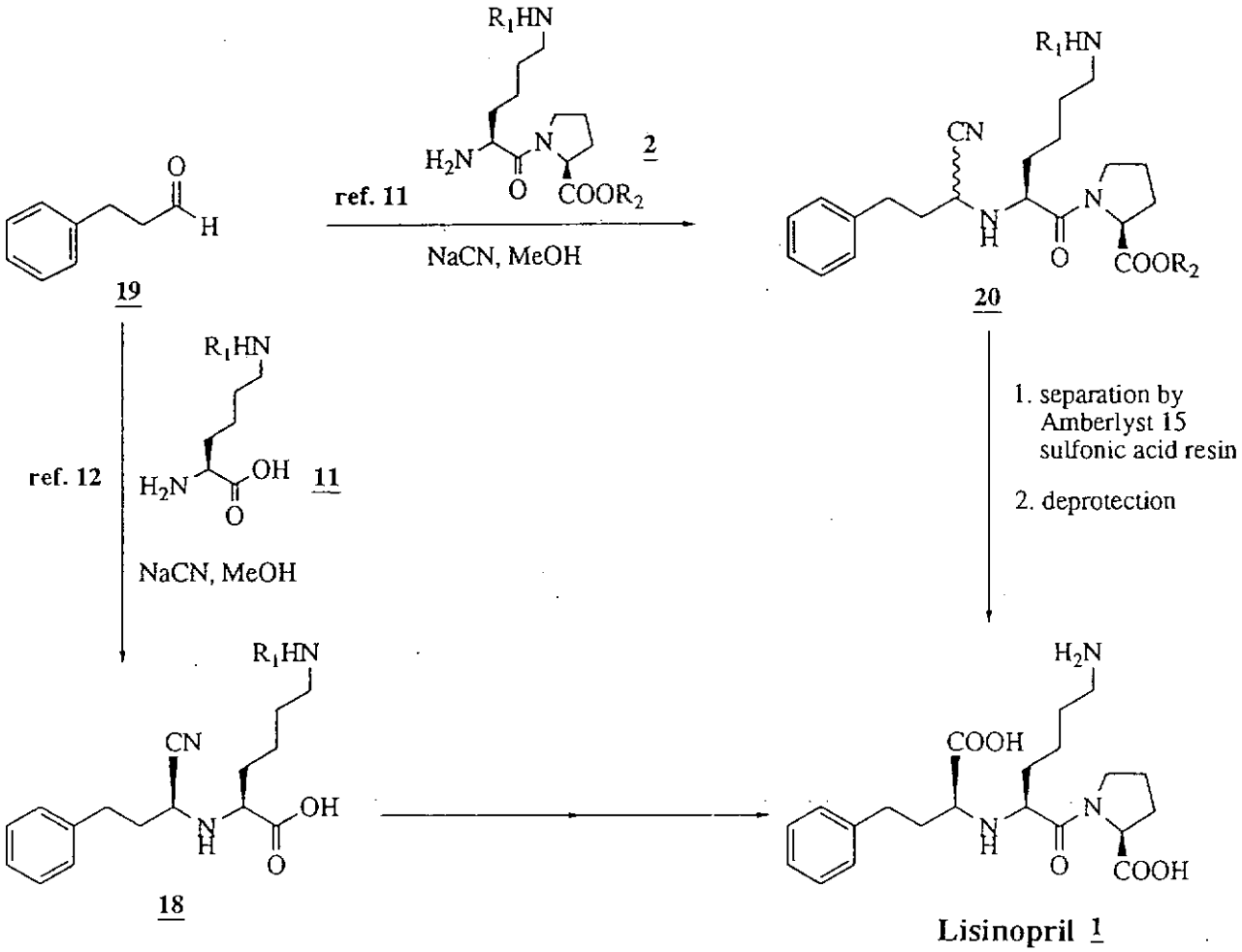
Lisinopril

Antihypertensive
Merck
43 tons/year, 1800 USD/Kg



1





other methods:

1. From D-α-hydroxyphenylbutanoic acid **ref. 13**
2. Reviews **ref. 14**

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12. *Eur. Pat. Appl. EP* 336,368 **1989**.
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7. Omeprazole

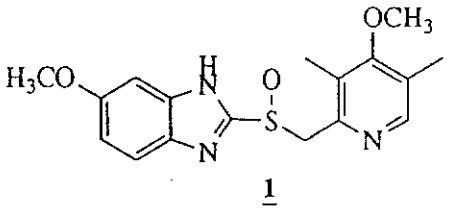
(Antiulcerative Agent)

Technical Information

Omeprazole

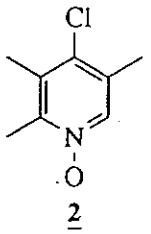
The first important thing in the manufacture of omeprazole is to ensure the resource of 2,3,5-trimethylpyridine, which can be obtained through careful distillation of coal tar. According to the literature, the sulfur atom can be first connected to the benzene diamine or the pyridine counterpart. However, we think the more feasible way is to couple the benzene diamine moiety and the pyridine part thorough a thiocarbonate, if the trimethylpridine can be obtained in cheap price(under 50USD/Kg).

Omeprazole



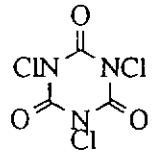
1

Antiulcerative
in treatment of Zollinger-Ellison syndrome
AB Hassle
47 tons/year, 2000 USD/Kg

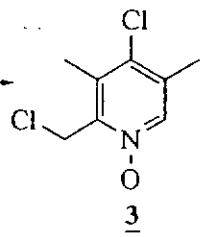


2

ref. 1

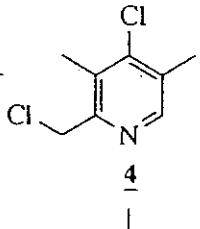


trichlorocyanuric acid



3

PCl_3



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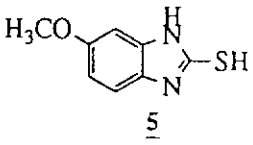

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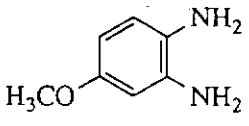

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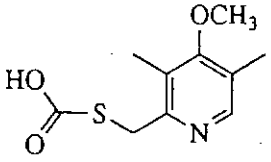
+



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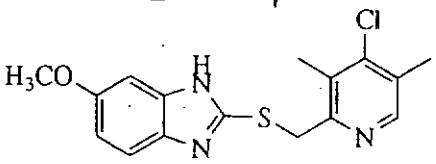
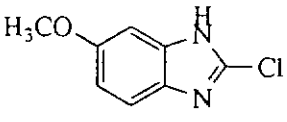
ref. 2



6

$NaOCH_3$



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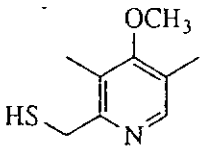
+



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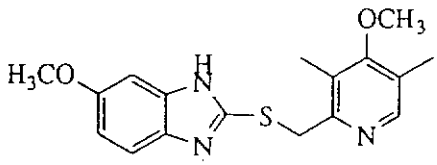
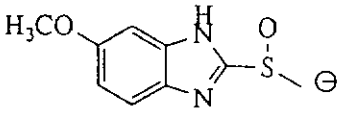
ref. 3



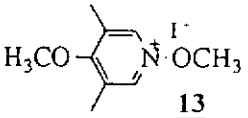
7

[O]



12

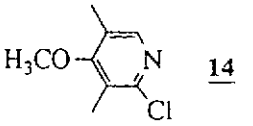
ref. 4



13

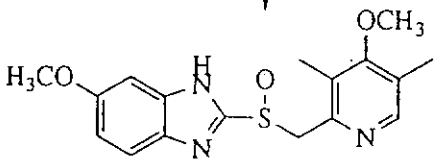
72%

ref. 5

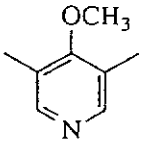


14

82%



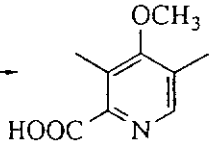
Omeprazole 1



15

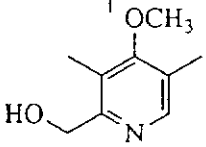
ref. 6

1. NaCN, TMS
2. HCl



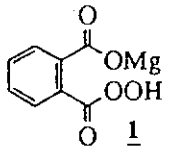
16

LAH



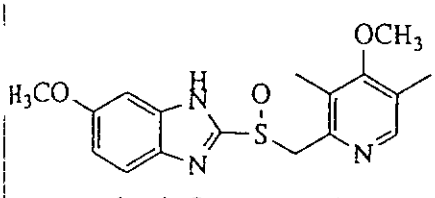
17

Sulfide 7 —[O]→ Sulfoxide 1

1. $PhIO / Ac_2O$ **ref. 7**
2. MCPBA **ref. 8**
3. H_2O_2 / V_2O_5 / t-Butanol **ref. 9**
4. hv **ref. 10**
5.  92% **ref. 11**

1

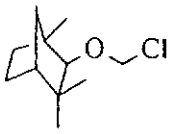
6. Vanadyl(acetylacetonate), H_2O_2, 90% **ref. 12**



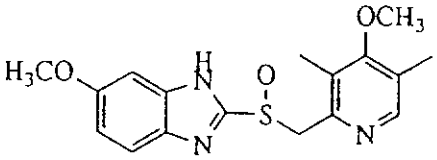
(+,-)-Omeprazole 1

ref. 13

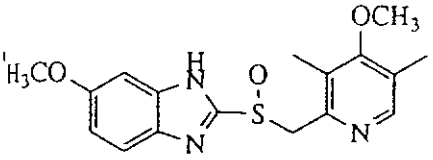
(+)- Fenchylchloromethylrther



18



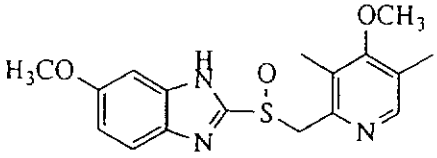
(+)-Omeprazole 1



(+,-)-Omeprazole 1

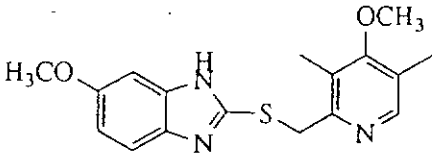
ref. 14

Bioreduction: Proteus Vulgaris



(+)-Omeprazole 1

+



Other methods: ref. 15

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8. Paroxetine

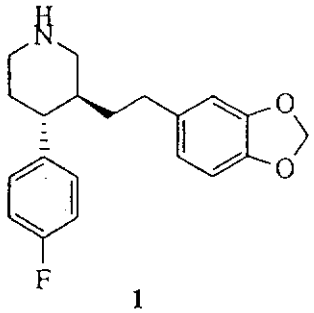
(Antidepressant Agent)

Technical Information

Paroxetine

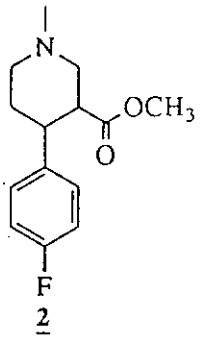
The key technology to acquire the paroxetine is to make the 3-carboxy-4-phenylpiperidine basic skeleton. Generally, the 3-carboxy group was reduces into alcohol, and the hydroxyl group was then replaced by the protected 3,4-dihydroxybenzyl moiety. The final deprotection step can be completed by acylation and subsequent hydrolysis.

Paroxetine



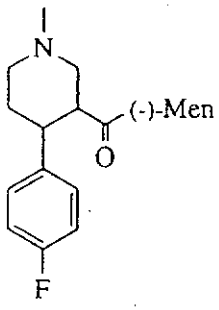
1

Antidepressant
Beecham
7 tons/year, 1000 USD/Kg



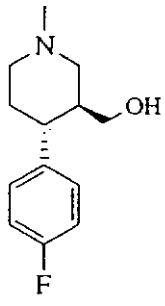
2

ref. 1
1. $SOCL_2$
2. (-)-menthol
75%



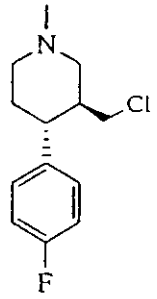
3

1. HBr / EtOH
2. LAH



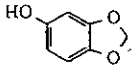
4

$SOCl_2$
90%

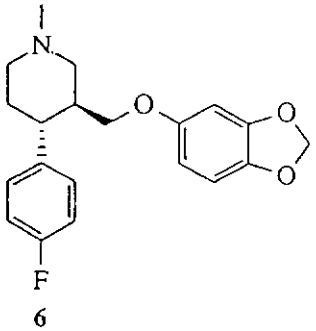


5

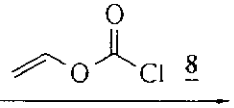
27.1% Na / Methanol



7

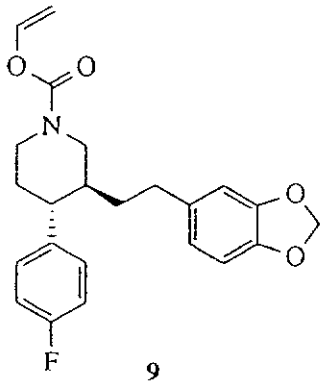


6



8

74.1%



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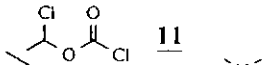
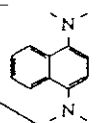


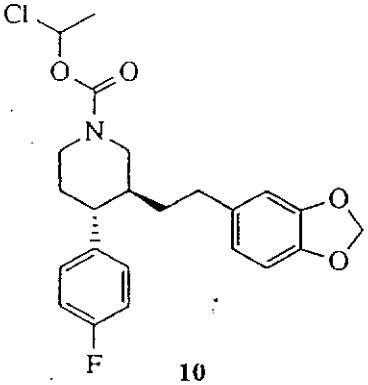
11



12

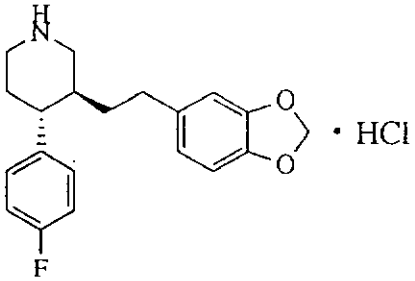
Toluene ; 92%
CH_2Cl_2 ; 74.1%

$HCl_{(g)}$

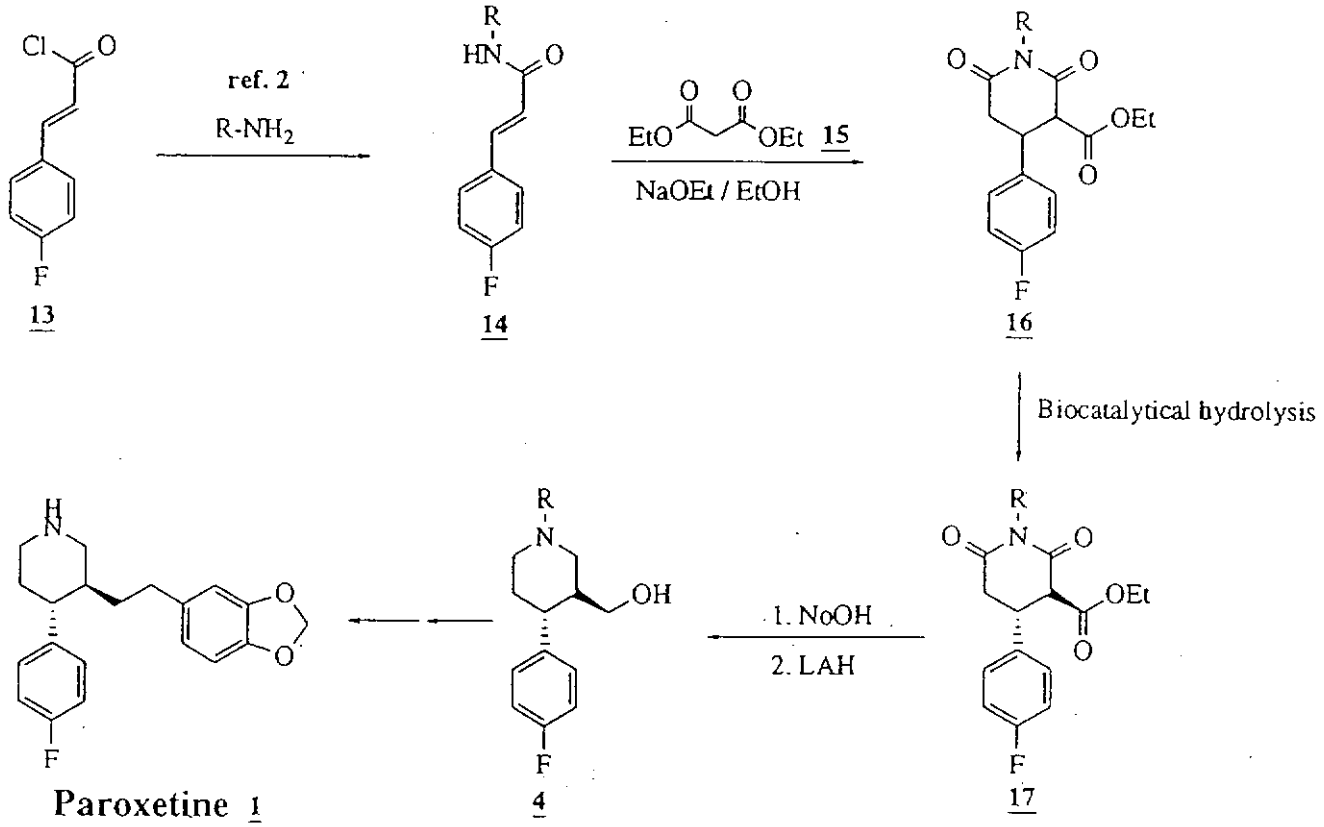


10

MeOH
100%

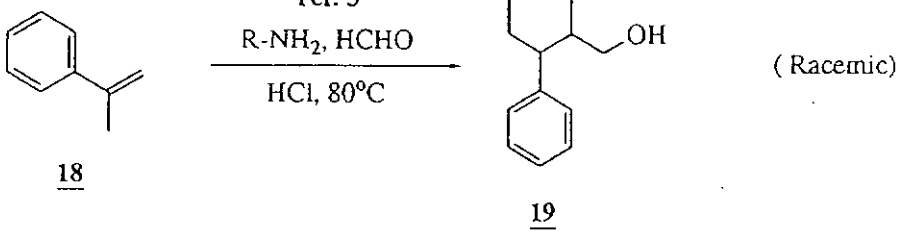


Paroxetine 1 . HCl



13 14 16 17 4

Paroxetine 1



18 19 (Racemic)

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9. Sertraline

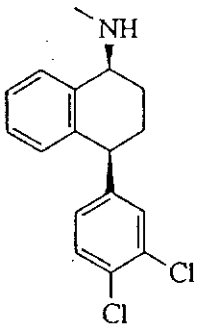
(Antidepressant Agent)

Technical Information

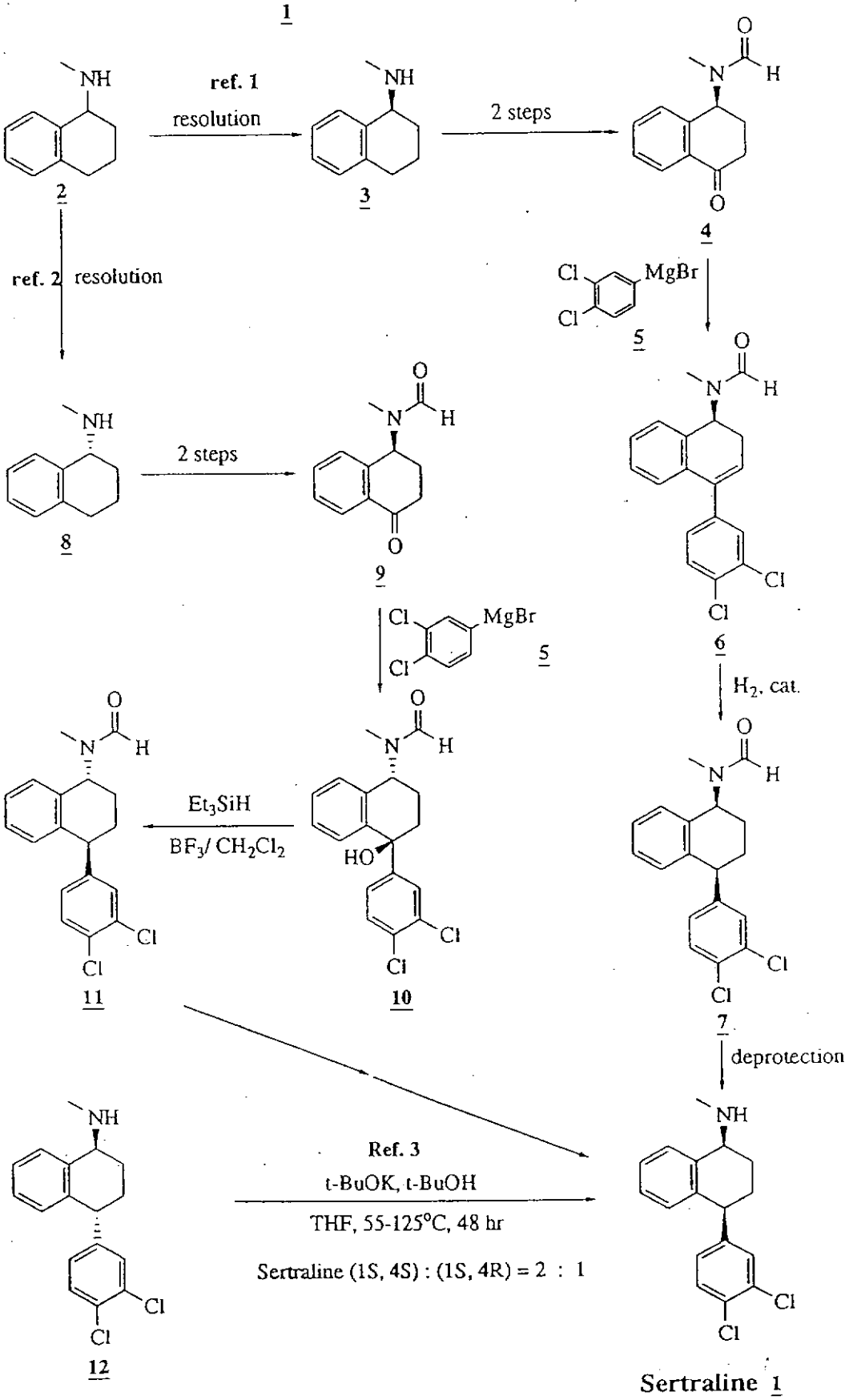
Sertraline

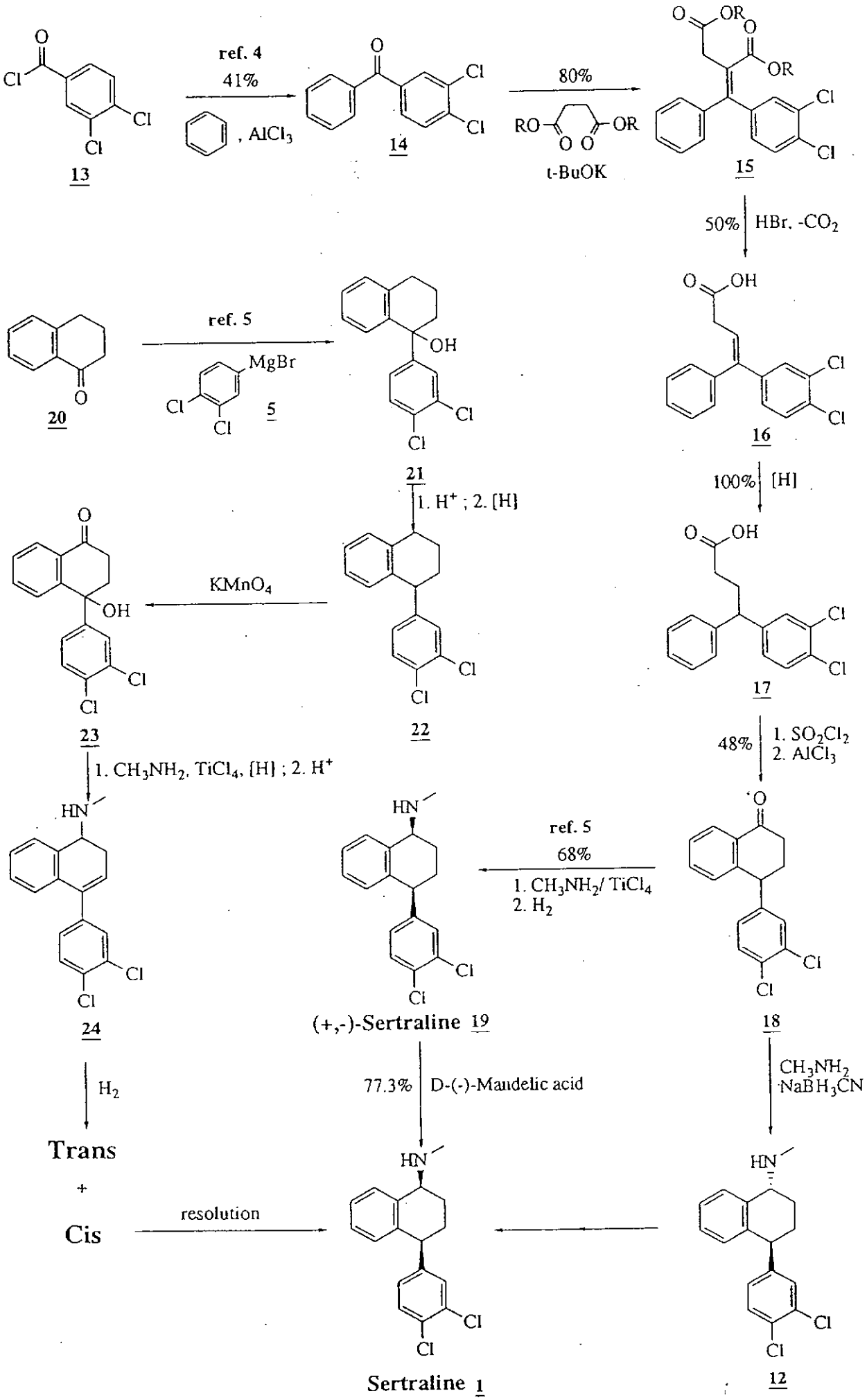
The current technology to acquire the sertraline can be started from 1,2,3,4-tetrahydronaphthalene. Transformation of the benzilic carbon to carbonyl group or aminocarbon by sequential oxidation. Generally, the carbonyl functionality is attacked by aryl Grignard reagent, followed by proper reduction process can lead to the 1-amino-4-aryl-2,3-dihydronaphthalene system. After some elaboration on the substituents, the desired sertraline can be obtained in good yield.

Sertraline



Antidepressant
Pfizer
62 tons/year, 1000 USD/Kg




13
ref. 4
41%
, AlCl3
14
80%
RO OR
O O
t-BuOK
15
50% HBr, -CO2
16
100% [H]
17
48% 1. SO2Cl2 2. AlCl3
18
ref. 5
68%
1. CH3NH2/ TiCl4
2. H2
(+,-)-Sertraline 19
77.3% D-(-)-Mandelic acid
Sertraline 1
CH3NH2
NaBH3CN
12
20
ref. 5
MgBr
5
21
1. H+ ; 2. [H]
22
KMnO4
23
1. CH3NH2, TiCl4, [H] ; 2. H+
24
H2
Trans
+
Cis
resolution

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