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Summary of Lecture Transcripts

Twenty Years of Naproxen Technology

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Abstract:

This review includes (1) a discussion of marketing and manufacturing of optically pure pharmaceuticals including naproxen, (2) an historical overview of Syntex naproxen manufacturing technology, (3) a comparison of classical resolution and asymmetric technologies specific to naproxen manufacture, (4) a cost comparison of naproxen starting materials, (5) data on the Syntex resolution technology and the impact of continuous process research and development on that technology, and (6) some environmental aspects of naproxen manufacturing.

I. Introduction: Marketing an Optically Pure Pharmaceutical

(*S*)-Naproxen is a nonsteroidal antiinflammatory drug introduced to the market by Syntex in 1976. The 1995 fiscal year sales of (*S*)-naproxen was $1.05 billion. The patent for (*S*)-naproxen expired in December of 1993. In 1991, prior to patent expiration, (*S*)-naproxen ranked fourth in sales of optically pure pharmaceuticals. Also on the list were the ACE inhibitors enalapril (first), captopril (second), and lisinopril (sixth), the hypolipemics lovastatin or mevinolin (third) and simvastatin (seventh), and the calcium antagonist and vasodilator diltiazem (fifth) (Table 1).

The structures of seven nonsteroidal antiinflammatories are presented in Figure 1. Of these seven, only naproxen is currently marketed exclusively in an optically pure form. A search for new asymmetric technology was driven by the anticipated expiration of the naproxen patent in 1993 and the potential to apply the technology to any of these related targets.

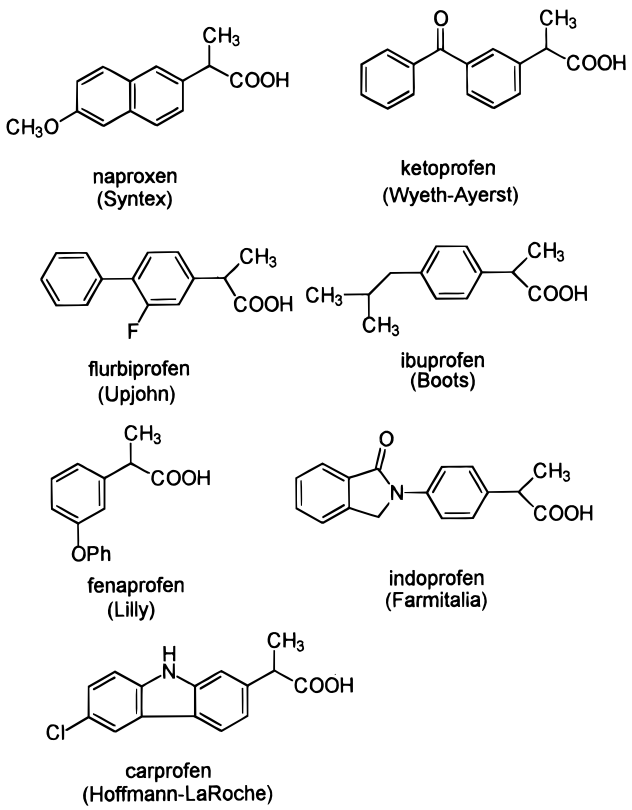

Figure 1. **Nonsteroidal antiinflammatories.**

Table 1. **World market for optically pure pharmaceuticals in 1991**

pharmaceutical	sales ($ million)
enalapril	1745
captopril	1580
lovastatin	1090
naproxen	971
diltiazem	912
lisinopril	630
simvastatin	400

II. Naproxen Manufacturing at Syntex: An Historical Overview

The first large-scale synthesis of naproxen produced 500 kg of material in 1970 (Scheme 1).[3] Friedel−Crafts acylation of 2-methoxynaphthalene (nerolin) afforded 2-acetyl-6-methoxynaphthalene (MAN), which was converted to a naphthylacetic acid by the Willgerodt reaction. α-Methylation yields the *d,l*-acid, which can be efficiently resolved using cinchonidine. This process had several unattractive features. First, the Friedel−Crafts acylation was not regiospecific, producing also the 1-isomer, which can be removed by crystallization. Second, aluminum hydroxide

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(3) Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, *13,* 203.

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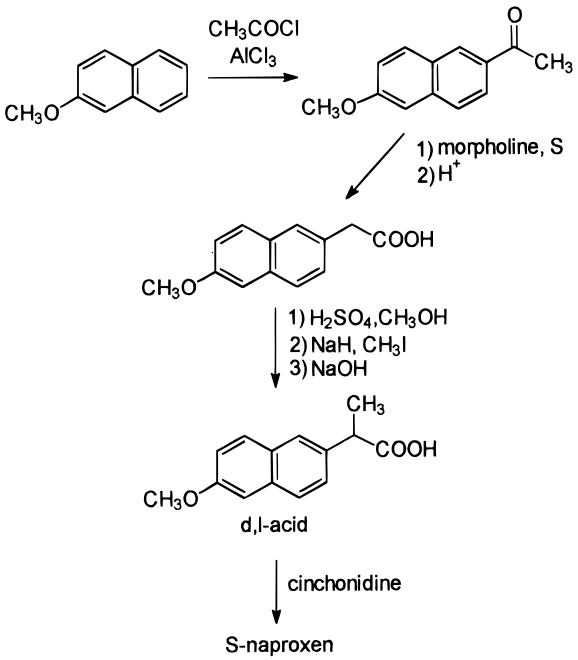
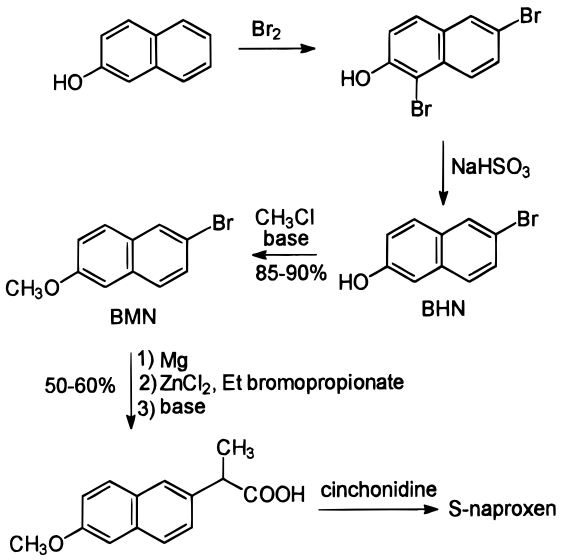
Scheme 1. **First large-scale naproxen process (500 kg)**



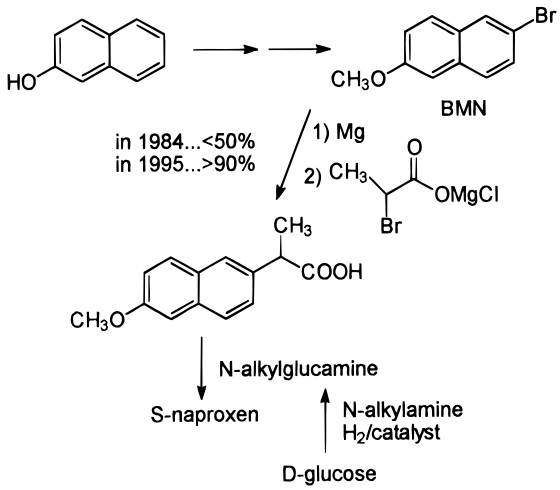
Scheme 2. **First large-scale manufacturing process, 1972−1975**



wastes were produced in significant quantity and were landfilled. Third, there were a number of undesirable reagents in the sequence: nitrobenzene (used in the acylation), ammonium sulfide (used in the Willgerodt reaction), sodium hydride, and methyl iodide.

All of these issues were addressed, and the first naproxen manufacturing process, in place in 1972−1975, was dramatically different (Scheme 2). β-Naphthol was brominated in methylene chloride to produce 1,6-dibromonaphthol. The labile bromine at the 1-position was removed with bisulfite. The resulting 2-bromo-6-hydroxynaphthalene (BHN) was methylated with methyl chloride in water−2-propanol. The yield of 2-bromo-6-methoxynaphthalene (BMN) was 85−90% from β-naphthol. BMN was converted to a Grignard reagent, which was transmetalated with zinc chloride and then the naphthylzinc coupled with ethyl bromopropionate. Hydrolysis of the ester yielded *d,l*-acid. The yield from BMN to *d,l*-acid was 50−60%. Again, resolution with

Scheme 3. **Second large-scale manufacturing process, 1976−1993**



cinchonidine was efficient (95%).

There were significant problems with this process as well. First, a stoichiometric amount of zinc chloride was required for the naphthylzinc coupling reaction. Large volumes of byproduct zinc hydroxide were filtered and landfilled. Second, the yield in the coupling reaction was low. Third, there were two undesirable side products in the coupling reaction. Reduction afforded 2-methoxynaphthalene (nerolin), which is volatile and has a "sweet grape" smell; odor complaints from the local community were common. A radical coupling reaction afforded a highly insoluble binaphthyl "dimer". Unacceptably large quantities of dimer were landfilled with the zinc waste.

The major problems in this first manufacturing process were associated with the naphthylzinc coupling reaction. An alternative coupling in the second manufacturing process, in place in 1976−1993, eliminated the zinc waste and minimized nerolin and dimer formation (Scheme 3). BMN was converted to the Grignard reagent, which was directly coupled with a salt of bromopropionic acid. As might be anticipated, this coupling reaction produced *d,l*-acid as one component of a complex mixture. In fact, production yields back in 1984 were less than 50%. A series of process improvements introduced in the past 10 years have increased the yield to greater than 90%! Cinchonidine was replaced by an *N*-alkylglucamine. Again, the resolution was efficient (>95%). The *N*-alkylglucamine, typically prepared by reductive amination of D-glucose, is both inexpensive and readily available.[4]

In 1988, the Syntex Technology Center staff at Boulder were charged with the task of evaluating all naproxen technology and then developing and implementing the lowest cost naproxen process. At that time, one-third of the total naproxen production cost was associated with the racemic acid and two-thirds of the production cost (primarily labor) was in the resolution−racemization. We concluded that there was little to gain in reducing the cost of *d,l*-acid. The real savings would come from a more streamlined resolution or from asymmetric technology which would circumvent the resolution.

(4) (a) Holton, P. G. U.S. 4,515,811, May 7, 1985. (b) Arnold, R. A.; Matthews, G. J. Ger. 2,805,488, Aug 17, 1978.

III. Industrial Syntheses of Optically Active Compounds Including Naproxen

Three general approaches to an optically active compound are (1) use of the chiral pool (α-amino acids, α-hydroxy acids, etc.), (2) separation of racemates (classical resolution, direct crystallization, kinetic resolution using an enzyme), and (3) asymmetric synthesis (noncatalytic, catalytic, enzyme mediated). There is precedent for large-scale manufacturing of optically active compounds using each of these approaches.

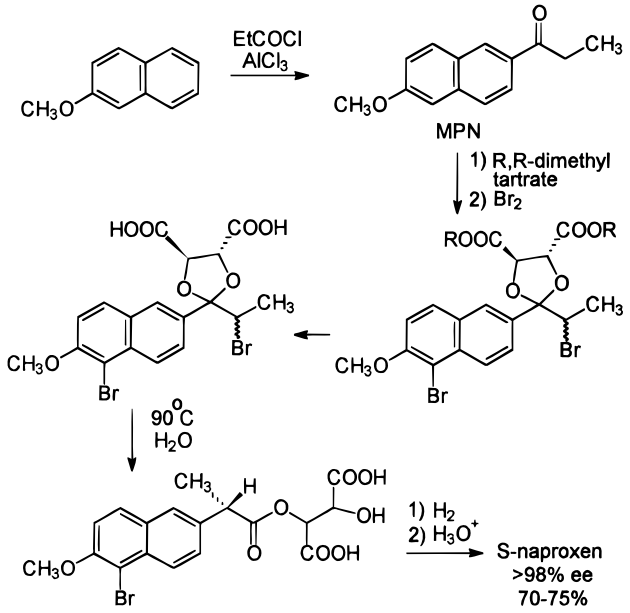
The large list of examples of manufacturing using chiral pool technology includes nafarelin acetate, ampicillin, and three ACE inhibitors. The decapeptide nafarelin acetate, effective in the treatment of endometriosis, is manufactured at Syntex using D-naphthylalanine. D-Phenylglycine is a key component of the antibiotic ampicillin. The top-selling ACE inhibitors, enalapril, captopril, and lisinopril, are all derived from L-proline.[5]

There is an even longer list of manufacturing processes incorporating a resolution. D-Biotin is resolved using ephedrine. Technology for resolution of (*S*)-naproxen using an *N*-alkylglucamine was already in place in the 1980s. There is considerable interest in optically pure (*S*)-ibuprofen, which is accessible by resolution with α-methylbenzylamine.[5]

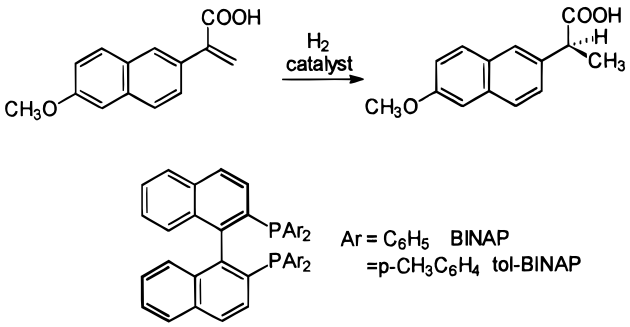
The least precedented manufacturing processes to obtain optically active targets employ asymmetric synthetic methods. The list of examples is small but compelling. A catalytic asymmetric hydrogenation is a key step in the manufacture of the antiparkinsonian drug L-DOPA, the antibiotic stabilizer cilistatin, and the nonnutritive sweetener aspartame. A catalytic asymmetric isomerization of an allylic amine to an enamine is the key step in Takasago's process for citronellol and L-menthol. Finally, catalytic asymmetric cyclopropanation using a chiral copper(I) salicylaldimine complex yields optically active pyrethroid insecticides.[6,7]

There are several asymmetric technologies specifically designed for naproxen manufacture.[8] The Zambon process is well-known (Scheme 4). 2-Methoxy-6-propionylnaphthalene (MPN) is prepared by Friedel−Crafts acylation of nerolin. Ketalization with (*R*,*R*)-dimethyl tartrate, bromination of the activated methylene, and ester hydrolysis yield a 92:8 mixture of diastereoisomers. Note that the 1-position is also labile in the bromination. This mixture of diastereoisomers rearranges on heating to 90 °C to produce an upgraded mixture of 1-bromonaproxen esters. Reductive cleavage of the 1-bromo substituent followed by ester hydrolysis affords (*S*)-naproxen (ee >98%). The yield from MPN is 70−75%.[9] Syntex management considered this process to be too complicated. There was also some concern about the mechanics of tartaric acid recycle. Finally, the problems associated with manufacture of MAN are also associated with manufacture of MPN: the regioisomer problem and generation of aluminum hydroxide wastes in he Friedel−Crafts acylation.

Scheme 4. **The Zambon process for naproxen manufacture**



Scheme 5. **Catalytic asymmetric hydrogenation for naproxen manufacture**

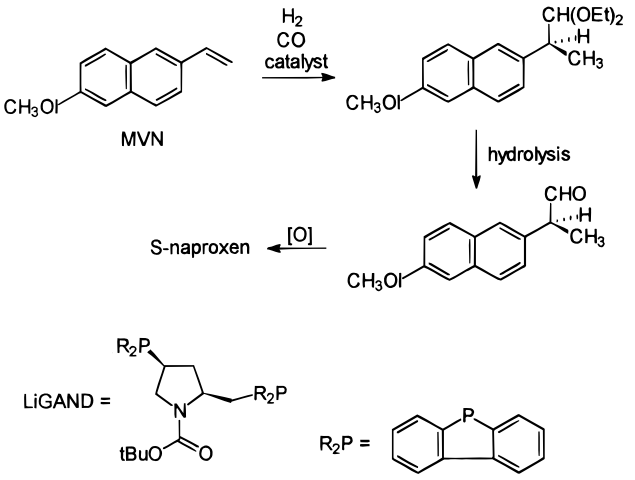


Catalytic asymmetric hydrogenation (Scheme 5) of a naphthacrylic acid using a ruthenium (*S*)-BINAP catalyst (135 atm) yields (*S*)-naproxen (ee >98%). A tol-BINAP-based catalyst will mediate hydrogenation at a significantly lower pressure (30 atm).[10] Such high pressures would necessitate a significant capital investment for any manufacturing facility. Perhaps of greater importance is the cost associated with the hydrogenation substrate, the naphthacrylic acid. Retrosynthetic analysis suggests the naphthylacetic acid or naphthylacetylene precursors which, in turn, might be derived from BMN or MAN.[11] In any event, manufacture of the naphthacrylic acid would involve at least two and more likely three process steps. We will discuss the cost of this and the other starting materials in Section IV.

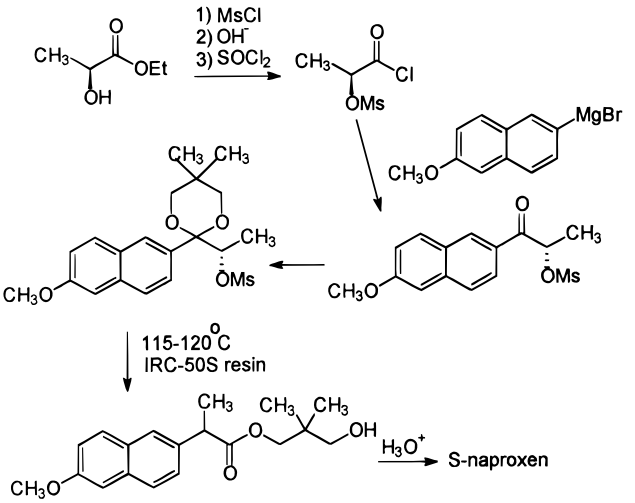
Catalytic asymmetric hydroformylation (Scheme 6) of 2-methoxy-6-vinylnaphthalene (MVN) using a rhodium catalyst with BINAPHOS ligand can produce an optically active aldehyde which on oxidation yields (*S*)-naproxen. There are several potential problems with this technology. First, the ligand must provide not only good stereoselectivity but also the correct regioselectivity. A linear aldehyde is

(5) Crosby, J. *Tetrahedron* **1991**, *47*, 4789.
(6) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
(7) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995.
(8) Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *Tetrahedron: Asymmetry* **1992**, *3*, 163.
(9) Giordano, C.; Castaldi, G.; Cavicchioli, S.; Villa, M. *Tetrahedron* **1989**, *45*, 4243.
(10) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174.
(11) Wagenknecht, J. H. U.S. 4,601,797, July 22, 1986.

Scheme 6. **Catalytic asymmetric hydroformylation for naproxen manufacture**



Scheme 7. **An asymmetric naproxen process from (*S*)-ethyl lactate**



often the major product of an alkene hydroformylation. Second, the branched aldehyde can racemize under the hydroformylation conditions. The racemization can be avoided by converting the aldehyde to an acetal *in situ* (with an orthoformate), but this approach necessitates an acetal hydrolysis later in the sequence.[12] Finally, there are the issues of cost, availability, and stability of MVN, which will be discussed in Section IV.

Other related technologies for naproxen manufacture from MVN can also be discussed in this context: catalytic asymmetric hydroesterification,[13] hydrocarboxylation,[14] or hydrocyanation.[15] These approaches have not received as much attention even though they may be more efficient in some respects.

All of the naproxen-specific technologies discussed thus far fall into the "asymmetric synthesis" category (noncatalytic or catalytic). One example of (*S*)-naproxen manufacture

(12) (a) Stille, J. K.; Su, H.; Brechot, P.; Parinello, G.; Hegedus, L. S. *Organometallics* **1991**, *10*, 1183. (b) Babin, J. E.; Whiteker, G. T. WO 93 03,839, March 4, 1993.
(13) Hiyama, T.; Wakasa, N.; Kusumoto, T. *Synlett* **1991**, 569.
(14) (a) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803. (b) Alper, H. Pct Int. Appl. WO 91 03,452, March 21, 1991.
(15) (a) RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 6265. (b) Casalnuovo, A. L.; RajanBabu, T. V. U.S. 5,175,335, Dec 29, 1992.

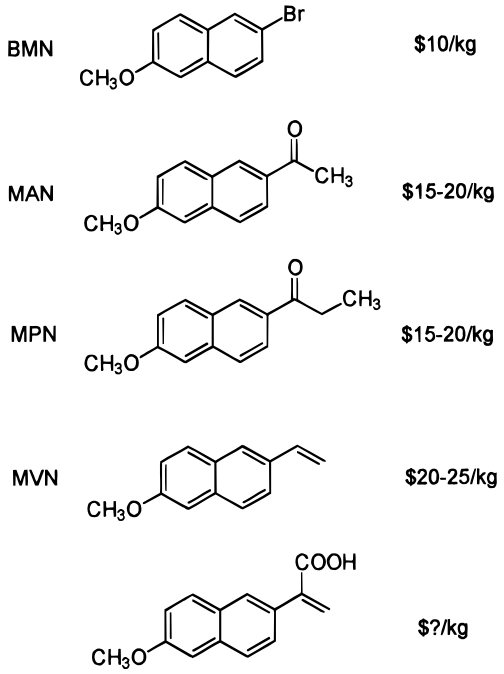


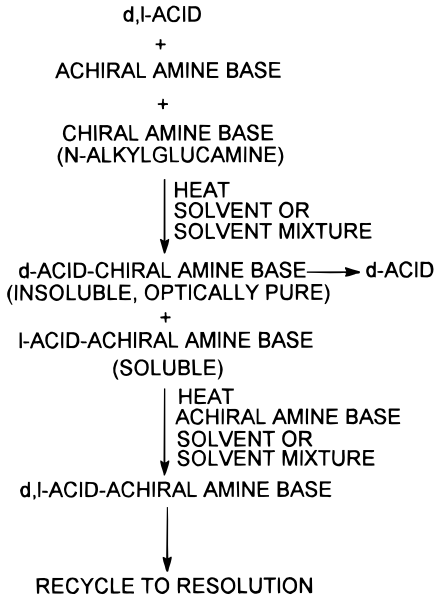
Figure 2. **Starting materials for naproxen manufacture.**

using the chiral pool approach was developed at Syntex in 1982 (Scheme 7). Ethyl lactate is one of a very few chiral compounds which can be used in stoichiometric quantity in a cost effective synthesis of (*S*)-naproxen. (*S*)-Ethyl lactate is converted to a mesylate. Ester hydrolysis and conversion of the acid to the acid chloride provides a chiral acylating agent. Acylation of the BMN-derived Grignard reagent yields an optically pure ketone. Ketalization with 2,2-dimethyl-1,3-propanediol, followed by rearrangement and ester hydrolysis, yields (*S*)-naproxen. The overall yield from BMN to (*S*)-naproxen is 75%.

IV. Cost Picture for Manufacture of Starting Materials

Several attractive processes for naproxen manufacture have been presented. The cost of starting materials becomes more critical as the efficiency of conversion to naproxen increases. The cost and availability of the starting materials for each of these processes should be compared (Figure 2). First, BMN is used in the Syntex manufacturing process and the asymmetric process using ethyl lactate. No cleanup to remove a regioisomer is required. Wastes generated are sodium bromide, hydrobromic acid, and methylene chloride. The cost of BMN is $10/kg. MAN was used in synthesis of the first 500 kg of naproxen in 1970. A cleanup is required to remove the 1-regioisomer generated in acetylation of nerolin. Aluminum hydroxide and methylene chloride are wastes generated in the acetylation. The cost of MAN is $15−20/kg. A similar cleanup and cost are associated with manufacture of MPN used in the Zambon process. MVN is used in hydroformylation, hydroesterification, hydrocarboxylation, and hydrocyanation. MVN can be manufactured in one or two steps from either MAN or BMN. MVN has significant polymerization potential. The cost of MVN is estimated at $20−25/kg. Finally, the naphthacrylic acid used in catalytic asymmetric hydrogenation can also be manufactured from either BMN or MAN. Using any precedented synthetic route and any cost estimation method,

Scheme 8. **The ideal case for a Pope Peachy resolution**



the naphthacrylic acid is projected to be several orders of magnitude more expensive than the other starting materials.

V. Syntex Resolution Technology and the Impact of Process Research and Development

The Syntex resolution technology approaches the ideal case for a Pope Peachy resolution (Scheme 8).[16] A mixture of 1 equiv of the *d,l*-acid, 0.5 equiv of an achiral amine base, and 0.5 equiv of a chiral amine base (the *N*-alkylglucamine) yields two salts. One is the insoluble salt of the *d*-acid and chiral amine base, the other the soluble salt of the *l*-acid and achiral amine base. The insoluble salt is filtered and the *d*-acid liberated. The mother liquor is heated. The achiral amine base catalyzes the racemization of the unwanted *l*-acid; the resulting salt of *d,l*-acid and the achiral amine is recycled to the resolution loop. The Syntex process has a first-pass diastereoisomer yield of 45−46% (optical purity ≥99%). The overall yield from the *d,l*-acid to (*S*)-naproxen is ≥95%. Finally, recovery of the resolving agent, the *N*-alkylglucamine, is ≥98% per cycle.

(16) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Wiley: New York, 1981.

Table 2. **Wastes associated with naproxen manufacturing**

substance	amount[a] (kg)
HBr	1.25
NaBr	1.05
$MgCl_2$	0.50
NaCl	0.60
$NaHSO_4$	0.75
CH_3OH	0.95

[a] Per kilogram of naproxen produced.

The combination of most accessible and least expensive starting material (BMN), an unusual and efficient Grignard coupling reaction, and this efficient resolution technology affords the lowest cost (*S*)-naproxen. The process today bears little resemblance to the process introduced in 1976. The cost competitiveness of the current process is a direct consequence of continuous process research and development during the past 20 years. In fact, the inflation-adjusted cost of (*S*)-naproxen today is only 25% of the 1974 cost!

VI. Environmental Health and Safety Aspects of Naproxen Manufacturing

Wastes associated with naproxen manufacturing are presented in Table 2. The annual emission of methylene chloride is 110 tons.

VII. Conclusion

After new drug launch, continuous process R & D will improve operations, reduce raw material and LOH costs, and address environmental concerns. From a long-range perspective, the end result of continuous process research and development will be a low-cost manufacturing process able to compete with generic manufacturers after patent expiration.

Acknowledgment is made to the men and women of Syntex Process R/D and Chemical Manufacturing who have worked on naproxen in the past 20 years.

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