CHIRAL DRUG INTERACTIONS

Drug delivery systems, threats from generics, and FDA requirements all intersect the issue of chirality

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As worldwide annual sales of enantiomeric drugs get set to break through the $100 billion mark in 2000, the issue of chirality in drugs increasingly is interacting with other issues facing the drug industry and its suppliers. These issues include drug delivery systems, defenses against generic competition by drug innovators, Food & Drug Administration approval requirements, education of physicians, supply agreements, and production in India and China. Firms that have stakes in chirality in drugs—such as ChiroTech Technology, Chirex, Sepacor, and Oxford Asymmetry—must increasingly factor these issues into their business plans.

Such companies continue to be active in developing new enantioselective technology for chiral drug and intermediate production. They also scour universities to license patents granted to faculty. And firms involved with chirality and other fields of drug discovery and development form partnerships in various combinations.

The scorekeeper of the marketing progress of chiral drugs is Richard L. DiCicco, president of the consulting firm Technology Catalysts International, Falls Church, Va. He estimates the worldwide sales of single-isomer chiral drugs at $96.4 billion in 1998, 11% higher than 1997’s $86.8 billion.

DiCicco notes that chiral drugs for cardiovascular disease (CVD) increased only 8% in 1998, to $21.1 billion from $19.6 billion. Cardiovascular drugs include blood-pressure-lowering agents such as the “prils” and blood-cholesterol-lowering compounds like the “statins.” These drugs take their nicknames from the last syllables of their generic names, assigned by the U.S. Adopted Names Council, homosexual and middle class to being inner-city poor has limited sales of these expensive drugs. Future growth in antivirals will come from drugs against flu and various forms of hepatitis, he says.

Chiral respiratory drugs, which are mostly for asthma and allergic rhinitis (hay fever) grew 35% to $4.3 billion, DiCicco notes. The $1.1 billion increase resulted from the best-selling drug in the class—the chiral Claritin brand of loratadine marketed by Schering Corp., Kenilworth, N.J. On the other hand, the chiral steroids that are used in asthma are declining in sales. However, DiCicco holds out hope for future growth in chiral respiratory drugs because the incidence of both asthma and allergic rhinitis is rising in the population.

Two interrelated chirality issues that affect the drug industry involve the use of racemic switches as a strategy of drug life-cycle management and choosing whether to develop a chiral compound as a single isomer or as a racemate. A racemate is the redevelopment in single-isomer form of a chiral

Chicago. In particular, the 8% growth in the CVD class was fueled by the “blockbuster” Lipitor brand of atorvastatin marketed by Parke-Davis, Morris Plains, N.J. Lipitor has helped balance off the decline in sales of prils, which have begun to come off patent. A blockbuster is a drug that sells more than $1 billion per year.

Single-isomer drugs for the central nervous system (CNS) rose only 3% to $7.8 billion, DiCicco says. He ascribes the slow growth to the lack of new blockbusters, while selective serotonin reuptake inhibitors to treat depression are reaching maturity. He sees stronger growth in the future from the introduction of a single-isomer version of the Prozac brand of fluoxetine by Eli Lilly, Indianapolis. Also, the chiral “triptans” to treat migraine headaches will add growth.

Antiviral drugs grew an impressive 27% to $6.2 billion, but that was growth from a small base, DiCicco notes, and sales of protease inhibitors for human immunodeficiency virus (HIV) peaked in two years rather than the usual four or five. The changing demographics of people with AIDS from being primarily homosexual and middle class to being inner-city poor has limited sales of these expensive drugs. Future growth in antivirals will come from drugs against flu and various forms of hepatitis, he says.

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Chiral drug sales surge toward $100 billion per year

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>1997</th>
<th>1998</th>
<th>Annual change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>$21,031</td>
<td>$23,250</td>
<td>11%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>19,651</td>
<td>21,145</td>
<td>8</td>
</tr>
<tr>
<td>Hormones</td>
<td>9,903</td>
<td>11,585</td>
<td>17</td>
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<tr>
<td>Central nervous system</td>
<td>7,573</td>
<td>7,805</td>
<td>3</td>
</tr>
<tr>
<td>Cancer</td>
<td>6,913</td>
<td>7,605</td>
<td>10</td>
</tr>
<tr>
<td>Antiviral</td>
<td>4,893</td>
<td>6,220</td>
<td>27</td>
</tr>
<tr>
<td>Hematology</td>
<td>5,923</td>
<td>6,185</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory</td>
<td>3,159</td>
<td>4,255</td>
<td>35</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1,314</td>
<td>1,420</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>6,535</td>
<td>6,910</td>
<td>6</td>
</tr>
<tr>
<td>TOTAL</td>
<td>$86,795</td>
<td>$96,380</td>
<td>11%</td>
</tr>
</tbody>
</table>

Source: Technology Catalysts International
drug that was originally approved for marketing as a racemate.

In the reprocess of the system, a company may discover enough new information about a single isomer and/or its production to apply for patents. The new patents extend the life of the drug by up to 20 years because the racemate is already obsolete when its patent expires.

DiCicco says that drug companies are increasingly adopting racemic switches as a management strategy. The company first develops a chiral drug as a racemate, then patents and develops the single isomer.

For example, Forest Laboratories, New York City, received FDA approval for racemic citalopram for depression in 1998, while the Sisomer was already in clinical testing. If FDA approves (S)-citalopram in 2001, Forest will have exclusivity on that form until its patent runs out in 2009.

An alternative to a racemic switch in drug life-cycle management is development of a new drug delivery system. One example is the patented osmotic

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Racemic switches protect $9 billion of drug sales

- Citalopram $85 million
- Methylphenidate $200 million
- Omeprazole $4 billion
- Fluoxetine $3 billion
- Cisapride $1 billion
- Sibutramine $50 million
- Levofoxacin $1 billion

Source: Technology Catalysts International
wide have taken any kind of notice of the issue by FDA as a warning light. Research departments ever since have studied both isomers and decided to go with one. An obvious exception to the single-isomer approach is the case of ready interconvertibility of the enantiomers.

Such a case has arisen with the "glitazone" agents against diabetes. The glitazones are an important advance in Type II diabetes (also called adult-onset or non-insulin-dependent diabetes mellitus). One aspect of Type II diabetes is that the pancreas may still produce insulin, but cells are resistant to it. The glitazones restore sensitivity of cells to insulin; thus, they are adjuncts to insulin shots or oral drugs that stimulate insulin secretion.

The glitazones are 5-substituted 1,3-thiazolidine-2,4-diones. The C-5 is asymmetric, so the drugs can exist as at least one pair of enantiomers. But because C-5 is adjacent to a carbonyl group, the enantiomers racemize spontaneously in solution. Thus the pioglitazone approved by FDA for marketing by Eli Lilly and Takeda Pharmaceuticals America, New York City, and the rosiglitazone approved for marketing by SmithKline Beecham, Philadelphia, both in 1999, are marketed as racemates.

The troglitazone approved for marketing by Parke-Davis in 1997 has two asymmetric carbons and is marketed as a mix of four isomers. Besides C-5 of the thiazolidine ring, the second asymmetric atom is the 2-position of a chromane ring system, which is robust to racemization. Almost from the beginning, troglitazone has been plagued by potentially fatal liver damage in a small percentage of patients who take it. It is interesting to wonder whether the potential for liver damage lies in two of the four diastereoisomers, DiCicco adds.

Another issue that affects chirotechnology companies and their drug firm clients is exclusivity of supply agreements. The Federal Trade Commission (FTC) is expected to rule in November on its complaint that generic drug marketer Mylan Pharm-
Chemists report first solvent-dependent atropoisomerism

Atropoisomerism, the chirality caused by the inability of molecular groups to rotate freely about single bonds, is a familiar topic in medicinal chemistry. Students first hear of enantiomerism in hindered biphenyls in the sophomore organic course. Single isomers of hindered 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl (BINAP) are famous as catalyst ligands. And among natural products, the interlinked rings of the antibiotic vancomycin are permanently frozen in one chiral conformation.

But recently, chemists at Tokyo Institute of Technology and the research laboratories of Taisho Pharmaceutical Co. in Saitama, Japan, reported the first instance of an atropoisomerism in a natural product that is dependent on the solvent [J. Org. Chem., 64, 5371 (1999)]. In 1998, workers at Taisho isolated an antitumor antibiotic called FD-594 (shown here and on the cover) from a species of Streptomyces mold. The molecular structure takes the form of a trans-1,2-cyclohexanediol ring that forms a bridge between one xanthone and one 1-isochromanone ring system.

On the basis of circular dichroism spectrometry, nuclear magnetic resonance spectroscopy, and molecular mechanics calculations, organic chemistry professor Katsumi Kakinuma at Tokyo Tech and coworkers conclude that in chloroform the two hydroxyl groups of the cyclohexanediol ring each adopt equatorial conformations, orienting the six fused rings in a helix. In methanol, however, the entire molecule twists to the opposite helical sense, with the two hydroxyl groups axial. This leads to a large negative Cotton effect in chloroform, with a circular dichroism (Δε) of -33.9 at 279 nm, which changes to a large positive Cotton effect with Δε = 38.9 in methanol.

In 1983, organic chemistry professor Richard N. Armstrong of Vanderbilt University, Nashville, reported solvent-dependent atropoisomerism in 9,10-dihydroxy-9,10-dihydrophenanthrene. But FD-594’s atropoisomerism is the first incidence in nature. The Japanese workers don’t discuss implications for living systems, but it is interesting to speculate whether solvation microenvironments could lead to atropoisomeric changes in the body, with ensuing changes in pharmacological effects.

Many companies rely on an FDA publication called the “Orange Book” for such information, DiCicco says. This book lists approved drugs by active pharmaceutical ingredient, but also by patent and market exclusivity expiration. Still, generic companies can get far along in a costly development program before learning that there are patents in force.

DiCicco cites the example of the Rocephin brand of ceftriaxone, a chiral third-generation cephalosporin antibiotic. The Orange Book states that the Hoffmann-La Roche patent on ceftriaxone expires in 1999. But Germany’s Hoechst also discovered something new about ceftriaxone, patented its discovery, and licensed to Roche a patent that does not expire until 2005. This type of agreement is not listed in the Orange Book.

Yet another issue in chiral drugs is that companies in India and China now produce single-isomer intermediates and bulk active compounds. DiCicco says that in India the tactic is to buy enantioprocess chemistry elsewhere, validate the process in terms of FDA’s current good manufacturing practices (cGMP), and export single-isomer products to such patent-free countries as Argentina, Paraguay, Uruguay, and China. Meanwhile, the Indian companies use the experience to ready their plants for cGMP production and to export to Europe and North America when patents expire there.

In the case of China, one link is through what DiCicco
calls “forward-looking traders.” These non-Chinese companies furnish such essentials as financing, regulatory documentation called Drug Master Files, and cGMP production outside China for the final production steps. The second link is through Chinese chemists who immigrate to the West, start their own companies to forge links to Chinese producers, and furnish the same necessities.

The high rates of chiral and achiral drug discovery needed for financial success in the modern drug climate will bring a change to drug companies and even to FDA, DiCicco says. In the recent past, the word has been that many drug companies are giving up manufacturing to become discovery and marketing companies in an effort to concentrate on their core competencies. But DiCicco says that even discovery is no longer a core competency and can be farmed out to increase discovery rates.

The drug firms of the future will be marketing and information companies, he says. Part of the information component will be education of doctors. For example, as Forest Laboratories starts marketing (S)-citalopram and Eli Lilly sells (R)-fluoxetine, they must educate doctors about the importance of chirality.

A second part of the information component will be faster reaction to avoid wasteful me-too drug development. At present, DiCicco can point out seven competing triptans for migraine (five achiral and two chiral), six chiral statins for serum cholesterol, four chiral glitazones for diabetes, six sartans for high blood pressure (five achiral and one chiral), one achiral and three chiral selective serotonin reuptake inhibitors for depression, and four chiral nonnucleoside reverse transcriptase inhibitors and five chiral protease inhibitors for HIV.

In the future, DiCicco says drug companies will avoid such me-too proliferation by tracking their competitors’ product pipelines on a day-to-day basis rather than the month-to-month basis used at present. He predicts that this telescoping of the competitive intelligence time frame will affect publishers of such databases as ADIS, Pharma Projects, and IdDB, which tell what compounds are in clinical development and what phase they’re in.

Resolution still dominates

As they steer through the evolving environment of chiral issues, chirotechnolgy companies continue to acquire enantioselective technology by internal develop-
The Novartis technology uses a small number of cellulose chlorofomate groups to attach dimethylmaleimide side chains. Photolysis of the resulting resin cross-links cellulose chains by formation of 2 + 2 adducts between maleimide double bonds.

Eric Francotte, head of separations and physicochemical determinations at Novartis, described the licensed technology to the symposium Drug Analysis '98 in Brussels in May 1998. Francotte cited improved enantioselectivity, sample solubility, and loading capacity in preparative-scale enantioselective LC using a heptane-chloroform solvent—which is otherwise a fairly aggressive solvent toward derivatized cellulose.

Meanwhile, Regis Technologies has formed an alliance with MediChem Research, Lemont, Ill., for discovery of new chiral stationary phases for LC. MediChem will use Regis technology to produce libraries of chiral stationary phases. Clients of the two firms can send their racemates for screening with 200 to 300 such phases that MediChem already has. Then MediChem will synthesize libraries more closely suited to the racemate. Regis will produce the phase thus discovered in commercial quantities.

For its part, Regis has installed a new preparative chromatography pilot plant and applications laboratory. The laboratory operates under cGMP and can separate from milligrams to hundreds of kilograms.

Expositions, symposia highlight enantioselective technology

- Nov. 2-4, Conference on Pharmaceutical Ingredients, Frankfurt, Germany. For both the exposition and symposium, contact Miller Freeman, P.O. Box 200, 3600 AE Maarssen, The Netherlands; phone 31 346 559444, fax 31 346 573811; or T&G Food Ingredient Services, 4220 Commercial Way, Glenview, IL 60025; phone (847) 635-9960, fax (847) 635-6801.
- June 7-8, 2000, Chemical Specialities Europe '00. Lyons, France. For the exposition, contact DMG Business Media, 2 Queensway, Redhill, Surrey RH1 1QS, England; phone 44 1737 855297, fax 44 1737 855474. For the symposium, contact the British Association for Chemical Specialities, P.O. Box 435, Sutton, Surrey SM2 7RP, England; phone 44 181 6430689, fax 44 181 7707103.
Enantioselective Strecker reaction

The diagram shows a chemical reaction involving the Strecker reaction with an enantiomeric excess of 96% yield and 86% ee. The reaction involves the conversion of an aromatic amine into an amide with a high diastereomeric purity.

Logograms of active pharmaceutical ingredients and intermediates.

And Universal Pharma Technologies, which is a joint venture between Pharm-Eco Laboratories of Lexington, Mass., and UOP of Des Plaines, Ill., has formed an alliance with Artisan Industries, Waltham, Mass., to combine Artisan’s solvent-recycling technology with Universal Pharma’s simulated moving bed (SMB) enantioselective LC. The method moves a slug of racemate endlessly around a circular array of LC columns. At intervals, enantiomerically enriched sample is removed from the head and tail of the sample, and fresh racemate and solvent are added.

Universal Pharma provides contract research and cGMP production, including SMB, to drug industry clients. “The customers we service are particularly impressed with the inherent ability of the combined technologies to rapidly scale both chiral and achiral separations from gram to tonnage quantities,” states managing director Bob Byron.

In addition to enantioselective LC, kinetic resolution with enzymes continues to be attractive. Organic chemistry professor Jan-E. Bäckvall of Stockholm University in Sweden and coworkers have devised a dynamic kinetic resolution technique by combining the actions of a lipase enzyme and a transition-metal catalyst [J. Am. Chem. Soc., 121, 1645 (1999)].

In the kinetic resolution part of the process, the lipase catalyzes acylation of one enantiomer of a racemic alcohol much faster than the other enantiomer. The resolution is called dynamic because a ruthenium catalyst continuously racemizes the unwanted enantiomer of the alcohol, resulting in a theoretical conversion of 100% of the racemic alcohol to the ester of the desired enantiomer.

For example, the Swedish workers use a commercially available immobilized lipase from the fungus Candida antarctica to catalyze acetylation of racemic 2-octanol with p-chlorophenyl acetate. The isolated yield of (R)-2-octyl acetate is 80%, with an enantiomeric excess (ee) greater than 97%. This high enantiomeric excess with an aliphatic alcohol is noteworthy because the highest previous enantiomeric excess, from
asymmetric reduction of 2-octanone, was just 79%. The ligand for the ruthenium racemization catalyst is 2 moles of tetrphenylcyclopentadienol, which is made by reduction of commercially available “tetracyclone.”

In searches for lipases, chemists are generally limited to what nature provides. This is because not enough is known about substrate recognition to design good lipases by site-directed mutagenesis, directed evolution, or chemical modification.

But biotechnology professor Mats Holmquist at the Royal Institute of Technology, Stockholm, has been able to parley the amino acid sequences in two isozymes of Geotrichum candidum lipase, GCL I and II, into a superior hybrid lipase for his particular substrate [Org. Lett., 1, 763 (1999)]. Holmquist studies hydrolysis of ethyl 2-methyldecanoate, one of the 2-methyl branched acids that are raw materials for chiral drugs, pheromones, and liquid crystals.

Holmquist finds that GCL II is much more enantioselective than GCL I with respect to ethyl 2-methyldecanoate. He focuses on the “active site flap” region, consisting of amino acids 61 to 105, and the fatty acyl chain length specificity (FAS) region, consisting of amino acids 349 to 406. The upshot is a recombination of the FAS region of GCL II into GCL I to get a hybrid that is much more enantioselective than even GCL II.

Though resolution is used more in industrial production than asymmetric syntheses, asymmetric synthesis is often the method of choice. ChiroTech Technology, Cambridge, England, is an enantioselective technology company that uses its tool kit to develop processes for clients. ChiroTech was recently purchased by fellow
Combinatorial chemistry yields amino acid synthesis

\[
\begin{align*}
\text{H}_2\text{CO} &\quad \text{CH} = \text{NCH}[(\text{C}_6\text{H}_5)_{\text{2}}] \\
&\quad \text{CN} \\
\text{H}_2\text{CO} &\quad \text{H} \\
\text{H}_2\text{CO} &\quad \text{CO}_2\text{H} \\
\text{H}_2\text{CO} &\quad \text{NH}[(\text{C}_6\text{H}_5)_{\text{2}}] \\
\end{align*}
\]

80% yield >99% ee

Catalyst = Schiff base of salicylaldehyde with tripeptide of (S)-tert-leucine, (R)-2-amino-3-tert-butoxybutanoic acid, and glycine

Excess of the nonsteroidal anti-inflammatory agent naproxen, which is a chiral carboxylic acid. Phan dissolves naproxen of only 93.7% ee in aqueous sodium hydroxide and precipitates it out again with sulfuric acid in 99% ee.

Academic progress

Besides chemists in industry, academic chemists also devise asymmetric syntheses that become commercially important. These asymmetric syntheses are sometimes enantioselective versions of classic organic reactions. For instance, organic chemistry professor Franca Bigi of the University of Parma, Italy, has devised an asymmetric Friedel-Crafts reaction \([J. \text{Org. Chem.}, 64, 5004 \ (1999)].\) Reaction of \(\alpha\)-methyloxynaphtol with the (-)-\(\alpha\)-phenylimine ester of glyoxylic acid, catalyzed by titanium tetrachloride, yields \((S)-2\)-hydroxy-5-methoxymandelic acid in 97% yield and 94% ee.

Organic chemistry professors E. J. Corey of Harvard University and Amir H. Hoveyda of Boston College have re-

British firm Ascent, which plans to combine ChiroTech with its existing fine chemicals unit, Mitchell Cotts (C&EN, Oct. 4, page 11).

Mark J. Burk, head of catalysis at ChiroTech, has developed a commercial asymmetric hydrogenation for Pfizer, Sandwich, England \([J. \text{Org. Chem.}, 64, 3290 \ (1999)].\) The process uses \((R,E)\)-Me-DuPHOS, which is a chiral bis(tetramethylphospholide) ligand that ChiroTech licensed from DuPont and that Burk invented while he was a chemist at DuPont’s experimental station in Wilmington, Del. The product of the reaction is an intermediate in production of candesartan, which is Pfizer’s atrial natriuretic factor potentiator for treatment of high blood pressure and congestive heart failure. The yield of the hydrogenation is 97% in greater than 99% ee.

A high enantiomeric excess is certainly desirable for resolutions and asymmetric syntheses. Often, however, if a reaction achieves only a “very good” enantiomeric excess, it is possible to upgrade the enantiomeric excess by simple recrystallization or reprecipitation without use of asymmetric resolving agents or auxiliaries. As an example, research chemist Hao V. Phan of Albermarle Corp., Richmond, Va., invented and recently patented (U.S. 5,936,118) an enhancement of the enantiomeric
Catalyst has Lewis acid, base functions

In the Harvard synthesis, the Schiff base of benzaldehyde with benzhydrylamine reacts with hydrogen cyanide to give the N-benzhydrylamino nitrile corresponding to (R)-phenylglycine in 96% yield and 87% ee, with an enantiomeric guanidine as the catalyst [Org. Lett., 1, 157 (1999)]. The guanidine is itself made from 2 moles of (R)-phenylglycine.

In the Boston College synthesis, the substrate is the Schiff base of p-anisaldehyde and benzhydrylamine. That reacts with trimethylsilyl cyanide to give the amino nitrile corresponding to (S)-p-methoxyphenylglycine in 80% yield and greater than 99% ee [J. Am. Chem. Soc., 121, 4284 (1999)]. The catalyst, which was discovered by screening a library of peptide derivatives, is a Schiff base of salicylaldehyde with a tripeptide of (S)-tert-leucine, (R)-2-amino-3-tert-butoxybutanoic acid, and glycine.

In a related development, pharmacy professor Masakatsu Shibasaki at the University of Tokyo has developed a bifunctional Lewis acid-Lewis base asymmetric catalyst for reactions of trimethylsilyl cyanide with aldehydes [J. Am. Chem. Soc., 121, 2641 (1999)]. The catalyst is based on single-isomer binaphthol that also has diphenylphosphine oxide groups at the 3-positions of both naphthalene rings. Shibasaki completes the synthesis of the catalyst by reaction of that binaphthol with aluminum chloride so that the two oxygen atoms bind to an Al-Cl Lewis acid group.

In a reaction of trimethylsilyl cyanide with β-phenylpropionaldehyde, for example, the aluminum Lewis acid activates the aldehyde carbonyl group while the diphenylphosphine oxide Lewis base groups activate the cyanide nucleophile. The result is a 97% yield of (S)-2-hydroxy-4-phenylbutanenitrile in 97% ee.

Yet another achievement by Shibasaki is a direct catalytic asymmetric aldol reaction in which the ketone need not be first converted to an enol derivative [J. Am. Chem. Soc., 121, 4168 (1999)]. The catalyst is a trimer of a lithium-lanthanum salt of single-isomer binaphthol. For example, β-phenylpivalaldehyde reacts with methyl ethyl ketone to give the asymmetric catalyst for reactions of trimethylsilyl cyanide with aldehydes [J. Am. Chem. Soc., 121, 2641 (1999)]. The catalyst is based on single-isomer binaphthol that also has diphenylphosphine oxide groups at the 3-positions of both naphthalene rings. Shibasaki completes the synthesis of the catalyst by reaction of that binaphthol with aluminum chloride so that the two oxygen atoms bind to an Al-Cl Lewis acid group.
Direct catalytic asymmetric aldol

\[
\begin{align*}
\text{CH}_3 & \quad \text{C}_6\text{H}_5\text{CH}_2\text{COH} \\
+ & \\
\text{CH}_3 & \quad \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_3 \\
\text{Catalyst} & \\
\text{CH}_3 & \quad \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_3 \\
\end{align*}
\]

71% yield 94% ee

Catalyst = Li$_3$La$_3$(R-BINOL)$_3$
R-BINOL = (R)\-1,1\-Bi-2-naphthol

with various aldehydes and from hexanal with various ketones.

For further functionalization of single-isomer $\alpha$-amino acids, organic chemistry professor W. Roy Jackson of Monash University in Clayton, Australia, has devised a way to convert the amino groups to isocyanates without the use of phosgene [J. Org. Chem., 64, 3940 (1999)]. In a variation on the Mitsunobu ester synthesis, Jackson uses diisopropyl azodicarboxylate and tri-n-butylphosphine to mediate the reaction of L-phenylalanine ethyl ester with carbon dioxide. The yield of isocyanate is 69%.

Syntheses of many biologically important chiral compounds need a single-isomer 2-cyclohexenone with a functional group handle at the 5-position. In the past, chemists have made do with such naturally occurring compounds as carvone and pulegone. Both the Corey group at Harvard and that of biomolecular engineering professor Fumie Sato at Tokyo Institute of Technology have reported convenient syntheses of 5-silyl and 5-silyloxy derivatives.

One of the Harvard syntheses is of (5S)-trimethylsilyl-2-cyclohexenone. That synthesis begins with anisole, which is converted to a trimethylsilylcyclohexenol [Org. Lett., 1, 811 (1999)]. Asymmetry is introduced by a lipase, which acetylates one enantiomer prefer-
entially. Removal of the acetyl group, oxidation of the resulting alcohol, and isomerization of the double bond give the product.

The Harvard synthesis of the other enantiomer, 5R, starts with 2-cyclohexene, which is converted to a racemic 3-silylated cyclohexanol. Again, a lipase acetylates one enantiomer preferentially.

In the Tokyo Tech method, the starting material is ethyl (R)-γ-chloro-β-hydroxybutyrate, which is available commercially from Daiso Co., Osaka, Japan. Sato tacks two more carbon atoms onto the end of that molecule with a vinyl Grignard reagent [J. Am. Chem. Soc., 121, 3640 (1999)]. After converting the hydroxy to a tributylsilyloxy group, he cyclizes that product to (55S)-tributylsilyloxy-2-cyclohexenone. The (S)-hydroxybutyrate is also available from Daiso, and can serve as starting material for the opposite enantiomer.

These examples of enantioselective methods from academic laboratories may be harbingers of new technologies that could advance to commercial production. University-based technology is thus only one of the several issues with an impact on the field of chiral drugs. It is additive with other issues that include the interplay of racemic switches and drug delivery systems as means for innova
tors to fend off generic competition and the moves by countries such as India and China to increasingly acquire enantioselective technology for their own participation in chiral drugs.