

Introduction

In 1848, Louis Pasteur, one of the pioneering stereochemists, recognized the omnipresence and significance of chirality, which prompted his famous statement that the universe is chiral (*l'univers est dissymétrique*).¹ Today, we know that chirality can indeed be encountered at all levels in nature – in the form of the elementary particle known as the helical neutrino, inherently chiral proteins, carbohydrates and DNA, or helical bacteria, plants and sea shells. Pasteur realized that chiral objects exist as a pair of enantiomorphous mirror images that are nonsuperimposable and related to each other like a right-handed and left-handed glove. At the molecular level, chirality gives rise to enantiomers that can exhibit strikingly different chemical and physical properties in a chiral environment. Many biologically active compounds, for example pharmaceuticals, agrochemicals, flavors, fragrances, and nutrients, are chiral, and more than 50% of today's top-selling drugs including Lipitor (cholesterol reducer, global sales in 2004: \$12.0 billion), Zocor (cholesterol reducer, \$5.9 billion), Plavix (antithrombic, \$5.0 billion) and Nexium (antiulcerant, \$4.8 billion) are sold as single enantiomers, Figure 1.1.

The increasing demand for enantiopure chemicals has been accompanied by significant progress in asymmetric synthesis^{2–8} and catalysis,^{9–14} and by the development of analytical techniques for the determination of the stereochemical purity of chiral compounds. Stereoselective analysis usually entails chiroptical measurements,¹⁵ NMR and mass spectroscopic methods,^{16–18} electrophoresis,¹⁹ chiral chromatography²⁰ or UV and fluorescence sensing assays,^{21–27} and it can provide invaluable information about the stability of chiral compounds to racemization and diastereomerization. A renowned example of a chiral drug that undergoes fast enantioconversion under physiological conditions is thalidomide (Thalidomid, Contergan) which was prescribed to pregnant women in the 1960s to alleviate morning sickness. One of the enantiomeric forms of thalidomide does indeed have sedative and anti-nausea effects, but the other enantiomer is a potent teratogen.ⁱ The racemic drug was approved in Europe for the treatment of pregnant women suffering from nausea and its use caused severe birth defects. Even formulation of the pure nontoxic (*R*)-enantiomer of thalidomide would have been unsafe because racemization takes place *in vivo* and the teratogenic (*S*)-enantiomer is rapidly generated in the human body, Scheme 1.1.ⁱⁱ

Since the thalidomide tragedy, the significance of the stereochemical integrity of biologically active compounds has received increasing attention and the investigation of the stereodynamic

ⁱTeratogenic agents interfere with embryonic development and cause congenital malformations (birth defects) in babies.

ⁱⁱDespite its inherent toxicity and stereochemical instability, thalidomide has recently been approved by the US Food and Drug Administration under a specially restricted distribution program for cancer therapy and for the treatment of the painful disfiguring skin sores associated with leprosy.

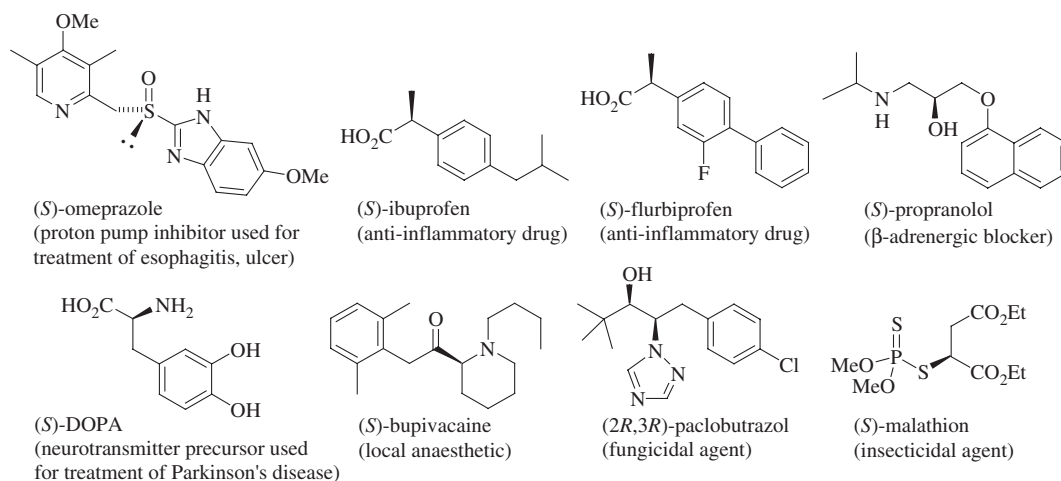
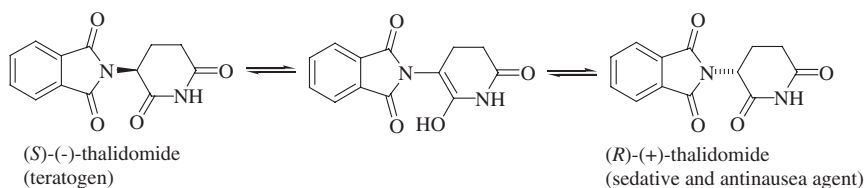


Figure 1.1 Structures of chiral pharmaceuticals and agrochemicals.



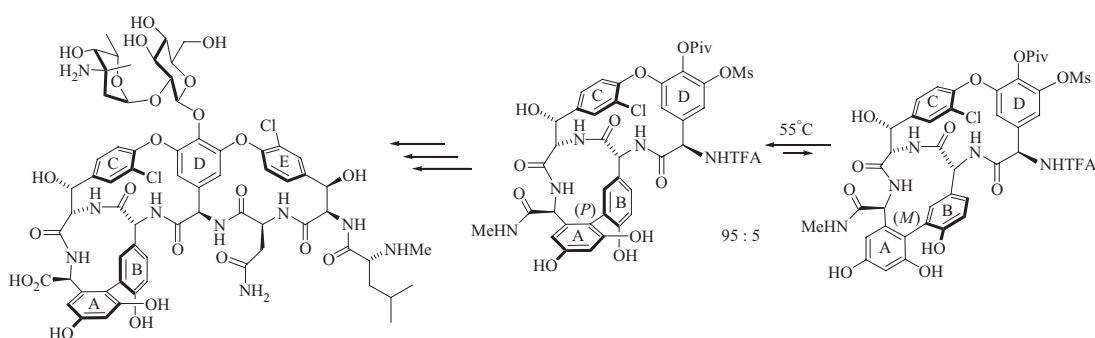
Scheme 1.1 Interconversion of the enantiomers of thalidomide.

properties of chiral molecules has become an integral part of modern drug development. For example, a variety of 2-arylpropionic acids including ibuprofen (Advil), naproxen (Aleve), ketoprofen (Oruvail), and flurbiprofen (Ansaid) has found widespread use as pain relievers and nonsteroidal anti-inflammatory drugs (NSAIDs). The anti-inflammatory activity of these profens resides primarily with the (*S*)-enantiomer.ⁱⁱⁱ The enantiomers of flurbiprofen possess different pharmacokinetic properties and show substantial racemization under physiological conditions. Although (*S*)-naproxen is the only profen that was originally marketed in enantiopure form, *in vivo* interconversion of the enantiomers of NSAIDs is an important issue in preclinical pharmacological and toxicological studies.²⁸ Another noteworthy example that underscores the significance of racemization of chiral drugs is the potent gastric acid secretion inhibitor omeprazole (Prilosec) which has been used in its racemic form for the treatment of esophagitis and ulcer.²⁹ The active form of this prodrug is an achiral sulfenamide derivative, and one could conclude that the presence of a chiral center in omeprazole does not affect its pharmacological activity. Nevertheless, the enantiomers of omeprazole have strikingly different pharmacokinetic profiles. The (*S*)-enantiomer of omeprazole affords higher bioavailability in humans because the (*R*)-form is more readily metabolized in the liver. To enhance the potency of this blockbuster drug, the pharmaceutical industry has launched esomeprazole (Nexium), the pure (*S*)-enantiomer of omeprazole.

The unique structure and mode of action of the antibiotic glycopeptide vancomycin (Vancocin) has fascinated synthetic and medicinal chemists alike. The antibacterial activity of vancomycin, *i.e.*,

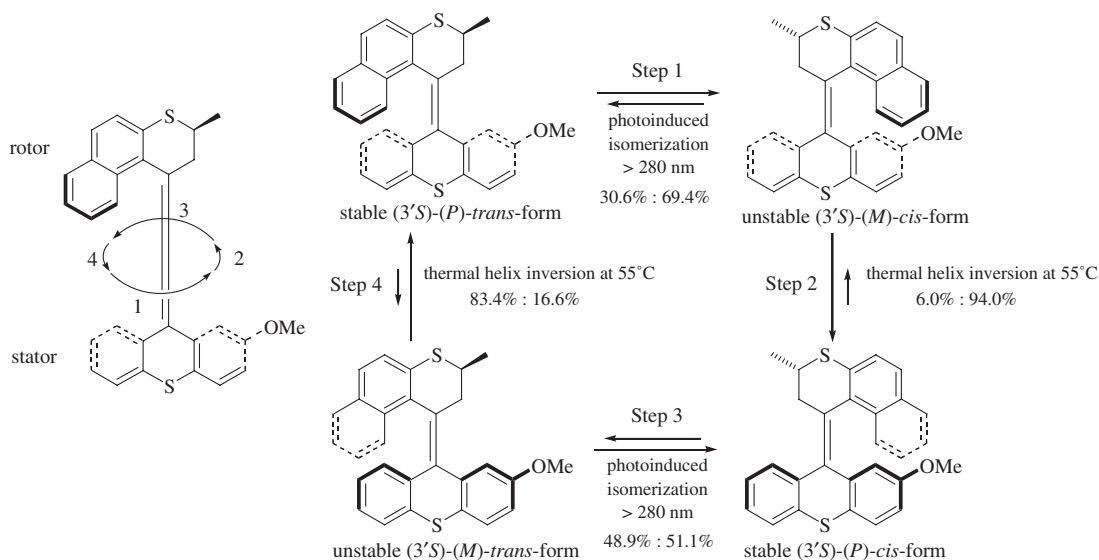
ⁱⁱⁱ Some (*S*)-profens have distinct ulcerogenic properties that are increased in the presence of the (*R*)-enantiomer.

its ability to inhibit cell wall biosynthesis, stems from its rigid macrocyclic structure which is crucial for effective recognition and binding to the terminal D-alanine-D-alanine sequence of bacterial peptides. The cup-shaped structure of vancomycin is a consequence of the chirality of the amino acids in conjunction with the chiral axis of the actinoidinic acid moiety consisting of aryl rings *A* and *B* and the planar chirality of aryl ethers *C* and *E*, Scheme 1.2. The stereodynamics of these chiral elements have played a pivotal role in the total synthesis of the vancomycin aglycon (the part of the glycopeptide lacking carbohydrate units).^{30–33} An intriguing example is Evans' synthesis of vancomycin from a bicyclic precursor bearing an unnatural (*M*)-actinoidinic acid moiety. Evans and coworkers recognized that the axial chirality of the atropisomeric actinoidinic acid unit is controlled by the global aglycon architecture, rather than by individual proximate stereogenic elements. They also realized that rotation about the central C–C bond between aryl rings *A* and *B* proceeds at ambient temperature and favors formation of the (*P*)-conformer with high selectivity. In fact, thermal equilibration at 55 °C results in atropisomerselective interconversion of the two diastereomeric tetrapeptides and establishes the desired axial chirality with 90% diastereomeric excess. This thermodynamically controlled transformation significantly enhances the overall efficiency of the total synthesis of vancomycin, Scheme 1.2. Similarly, Boger and others exploited thermally controlled atropisomerization reactions which have been strategically incorporated into several synthetic routes towards vancomycin and other complex antibiotics including teicoplanin.



Scheme 1.2 Structure of vancomycin (left), and stereoisomer interconversion favoring the formation of the natural (*P*)-diastereoisomer of a tetrapeptide precursor (right).

The unique stereodynamics of chiral compounds have paved the way to artificial machines and other molecular devices that lie at the interface of chemistry, engineering, physics, and molecular biology. The design of gears, rotors, switches, scissors, brakes, shuttles, turnstiles, and even motors showing unidirectional motion has certainly been inspired by the coordinated movement in biological systems such as muscle fibers, flagella and cilia.^{34–36} Feringa and coworkers developed light-driven molecular motors derived from sterically overcrowded chiral alkenes exhibiting thermal bistability and nondestructive read-out.^{37,38} The subtle interplay between the chiral center and the inherently helical conformation of this type of molecular motor provides control of the rotation about the carbon–carbon double bond in a series of thermally and photochemically initiated isomerization steps. In other words, both chirality and conformational flexibility are essential for unidirectional motion of the rotor around the stator, Scheme 1.3. The first isomerization step requires irradiation of UV light to a solution of the stable (*3'S*)-(*P*)-*trans*-form of the chiral alkene. This generates a photostationary state favoring 69.4% of the unstable (*3'S*)-(*M*)-*cis*-form that thermally relaxes to 94% of the stable (*3'S*)-(*P*)-*cis*-isomer in the second step. The same concept is exploited for photoisomerization of the (*3'S*)-(*P*)-*cis*-alkene to 48.9% of the (*3'S*)-(*M*)-*trans*-isomer



Scheme 1.3 Four isomerization steps of a unidirectional motor.

in the third step which is followed by thermal helix inversion to regenerate 83.4% of the (3'S)-(P)-*trans*-isomer in the final step. Since the interconverting isomers exist as mixtures obeying Boltzmann distributions and reversible reaction kinetics, this molecular motor is not rotating in an exclusively monodirectional sense. However, the discrete and synergetic photochemical and thermal isomerization reactions of the diastereomeric mixtures result in an overall clockwise motion observed from the stator.

Since the discovery of the ubiquity of chirality by Pasteur, stereochemistry has undoubtedly emerged as one of the most important and fascinating areas within the chemical sciences. Stereochemistry embraces a broad variety of closely intertwined static and dynamic aspects that are all related to the three-dimensional structure of molecules. While static stereochemistry deals with the spatial arrangement of atoms in molecules and the corresponding chemical and physical properties, dynamic stereochemistry emphasizes structural change and comprises asymmetric reactions as well as interconversion of configurational and conformational isomers. The few examples outlined above highlight both the significance of chirality and the fundamental role that dynamic stereochemistry plays in modern chemistry, spanning multiple disciplines from asymmetric synthesis and drug discovery to material sciences. The principles and applications of stereodynamic chemistry of chiral compounds are discussed in the chapters following.

REFERENCES

1. Pasteur, L. *Ann. Chim. Physique* **1848**, 24, 442-459.
2. Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E. *Stereoselective Synthesis in Methods of Organic Chemistry*, Houben-Weyl, Vol. 21a-21f, 4th ed., Thieme, Stuttgart, 1995.
3. Gawley, R. E.; Aubé, J. *Principles of Asymmetric Synthesis*, Tetrahedron Organic Chemistry Series, Elsevier, New York, 1996.
4. Ho, T.-L. *Stereoselectivity in Synthesis*, Wiley-VCH, New York, 1999.
5. Lin, G.-Q.; Li, Y.-M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*, Wiley-VCH, New York, 2001.
6. Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, 41, 2024-2032.

7. Song, C. E.; Lee, S.-G. *Chem. Rev.* **2002**, *102*, 3495-3524.
8. Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991-8035.
9. Jonathan, M. J. W. *Catalysis in Asymmetric Synthesis*, Sheffield Academic Press, Sheffield, 1999.
10. Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed., Wiley-VCH, New York, 2000.
11. Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008-2022.
12. Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187-2209.
13. Inanaga, J.; Furuno, H.; Hayano, T. *Chem. Rev.* **2002**, *102*, 2211-2225.
14. Mikami, K.; Terada, M.; Matsuzawa, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3554-3571.
15. Ding, K.; Shii, A.; Mikami, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 497-501.
16. Guo, J.; Wu, J.; Siuzdak, G.; Finn, M. G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1755-1758.
17. Evans, M. A.; Morcken, J. P. *J. Am. Chem. Soc.* **2002**, *124*, 9020-9021.
18. Markert, C.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2498-2500.
19. Reetz, M. T.; Kuhling, K. M.; Deege, A.; Hinrichs, H.; Belder, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 3891-3893.
20. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*, John Wiley & Sons, New York, 1994, pp. 214-274.
21. Pu, L. *Chem. Rev.* **2004**, *104*, 1687-1716.
22. Mei, X.; Wolf, C. *Chem. Commun.* **2004**, 2078-2079.
23. Zhao, J.; Fyles, T. M.; James, T. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 3461-3464.
24. Eelkema, R.; van Delden, R. A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5013-5016.
25. Mei, X.; Wolf, C. *J. Am. Chem. Soc.* **2004**, *126*, 14736-14737.
26. Tumambac, G. E.; Wolf, C. *Org. Lett.* **2005**, *7*, 4045-4048.
27. Folmer-Andersen, J. F.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **2005**, *127*, 7986-7987.
28. Leipold, D. D.; Kantoci, D.; Murray Jr., E. D.; Quiggle, D. D.; Wechter, W. J. *Chirality* **2004**, *16*, 379-387.
29. Lindberg, P.; Braendstroem, A.; Wallmark, B.; Mattsson, H.; Rikner, L.; Hoffman, K.-J. *Med. Res. Rev.* **1990**, *10*, 1-54.
30. Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700-2704.
31. Evans, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. I.; Trotter, B. W.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2704-3708.
32. Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Loiseleur, O.; Castle, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 3226-3227.
33. Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004-10011.
34. Kelly, T. R.; DeSilva, H.; Silva, R. A. *Nature* **1999**, *401*, 150-152.
35. Koumura, N.; Zijlstra, R. W. J.; van Delden, R. A.; Harada, N.; Feringa, B. L. *Nature* **1999**, *401*, 152-155.
36. Leigh, D. A.; Wong, J. K. Y.; Dehez, F.; Zerbetto, F. *Nature* **2003**, *424*, 174-179.
37. Koumura, N.; Geertsema, E. M.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 12005-12006.
38. Van Delden, R. A.; ter Wiel, M. K. J.; de Jong, H.; Meetsma, A.; Feringa, B. L. *Org. Biomol. Chem.* **2004**, *2*, 1531-1541.