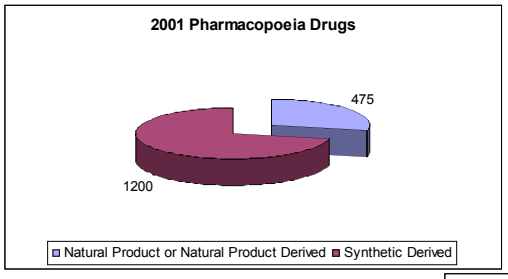
Role of Stereochemistry in Drug Development

Kevin Cusack
3/22/2006
University of Pittsburgh Lecture

Special thanks to Donald Konopacki

Abbott
A Promise for Life

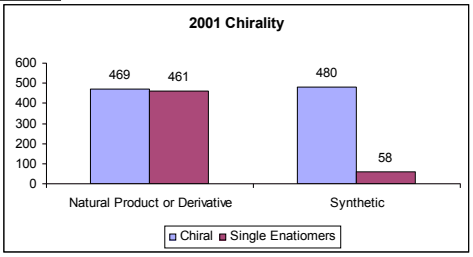
Drug Development of Stereoisomers



Of 1675 Drugs in *Pharmacopoeia* (2001), most are natural products

Of 480 Synthetics in *Pharmacopoeia* (2001), most are not single enantiomers

- ***Sales exceed $100B***



Abbott
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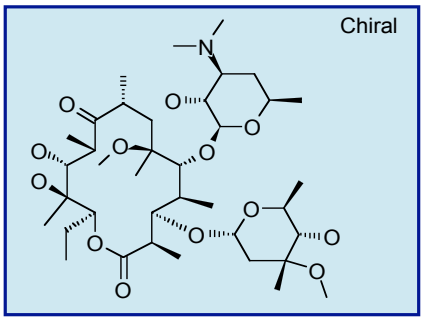
Abbott Natural Product Based - Clarithromycin



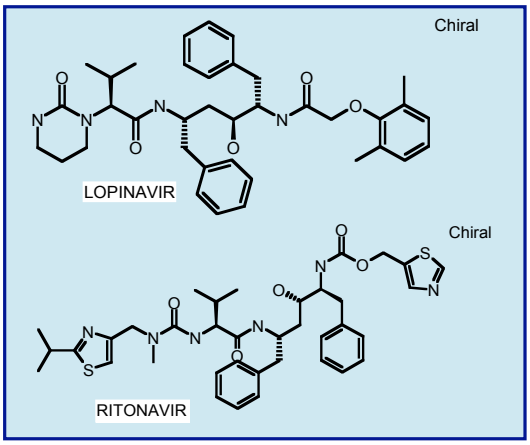
Antibiotic (antibacterial)

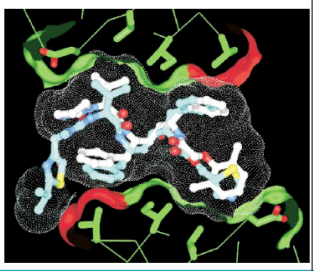
Polypeptide synthesis inhibitor

Derivative of erythromicin (*streptomyces erythreus*)

See Woodward synthesis, JACS, 1981, 103, 3210, 3213, 3215

Abbott Amino Acid Based Drugs

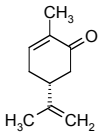




Should we be concerned with stereochemistry?

Enantiomers often show distinct receptor binding profiles

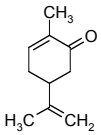
Olfactory receptor:



d-Carvone

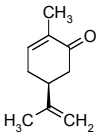
Caraway seed (rye)

Dill seed oil



dl-Carvone

Gingergrass oil

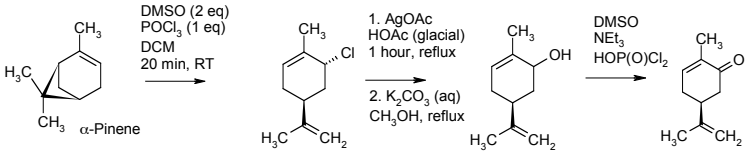


l-Carvone

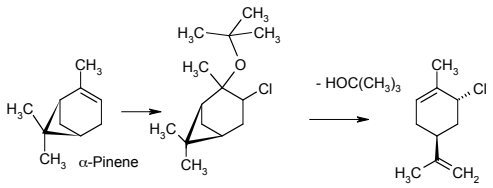
Spearmint

Originally published 08/30/04, last revised 10/25/04, at http://www.sciencecases.org/alice/alice.asp

Synthesis of Carvone via Pinene

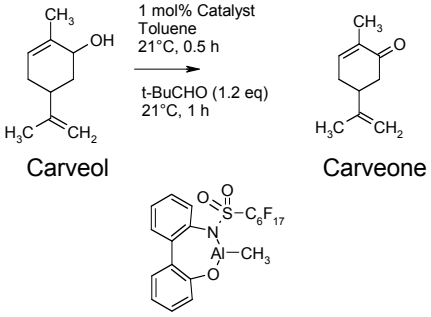


LIU H J, NYANGULU J M, TETRAHEDRON LETT 30(38),5097-5098(1989) Based on notes in related 1950 paper JACS (1950), 72, 2381.



Only occurs with undistilled t-butyl hypochlorite

Oxidative Routes via Carveol



Carveol Carveone

OOI T, OTSUKA H, MIURA T, ICHIKAWA H, MARUOKA K, ORG LETT 4(16),2669-2672(2002).
MULDOON J, BROWN S N, ORG LETT 4(6),1043-1045(2002).
HIRANO M, KOBAYASHI T, MORIMOTO T, SYNTHETIC COMMUN 24(13),1823-1831(1994).

Other Advantages of Single Enantiomers in Pharmaceuticals

Enantiomers can show distinct receptor binding profiles

- Reduction of total dose
- Simpler dose-response relationships
- Reduction in inter-patient PK/ADME
- Reduction in toxicity from inactive stereoisomer

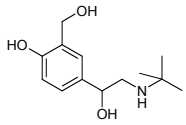
However, this view is too simplistic as it assumes that *all desirable or undesirable properties reside in one enantiomer*.

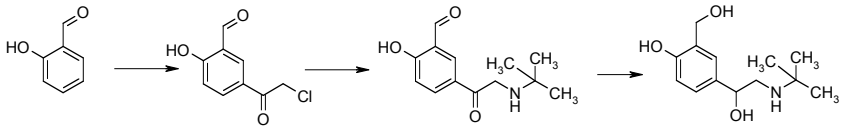
Caveat: *In vitro* binding studies may not predict *in vivo* clinical outcome

Opposing Effects of Enantiomers

Albuterol: Bronchodilator for treatment of asthma

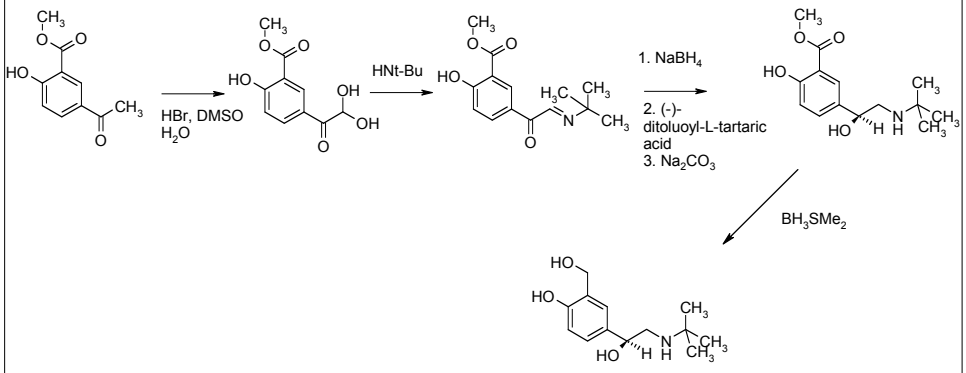
- R-isomer has 100x affinity for β_2–adrenoceptors
- S-isomer activates muscarinic receptors- opposes beneficial effects of R-isomer
- Potentcy of R-isomer is greater than expected by extrapolation of racemate





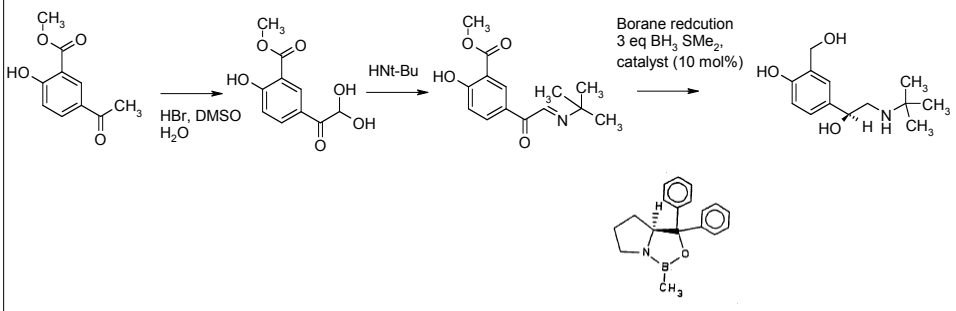
A short synthesis of albuterol. Synthesis (1988), (12), 966-8

Resolution of Benzoate with Chiral Acid



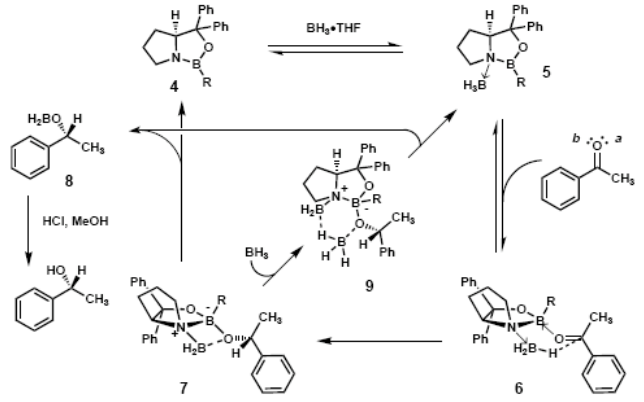
Enantioselective preparation of optically pure albuterol. U.S. (1996), U.S. 5,399,765

Iminoketone Synthesis



Gao, Yun; Hong, Yaping; Zepp, Charles M. **Asymmetric synthesis of (R)- and (S)-arylethanolamines from imino ketones.** U.S. (1995), US 5442118 A

Proposed Mechanism



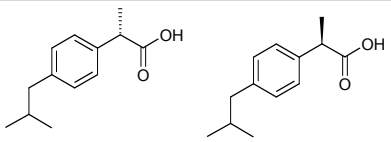
Scheme 5. Proposed mechanism for the catalytic enantioselective reduction of ketones by oxazaborolidines 4.

Corey, Helal; *Angew. Chem. Int. Ed. Eng.*, 37, (1998), 1986

Is racemate ever preferred?

Ibuprofen: Anti-inflammatory

- S-enantiomer responsible for activity
  - Inhibits PG synthetase
- R-enantiomer undergoes metabolic chiral inversion
- Racemate is more effective than predicted by *in vitro* binding studies



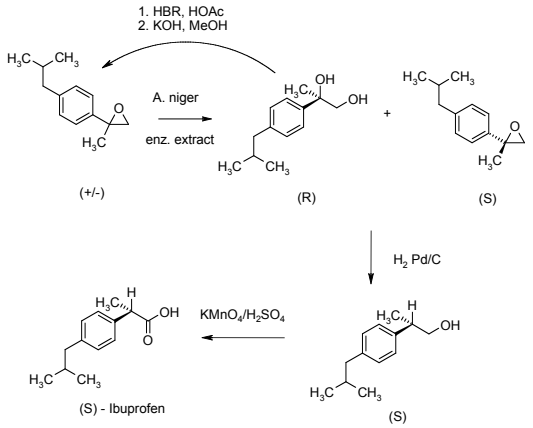
(*S*)-(+)-Ibuprofen
Active

(*R*)-(-)-Ibuprofen
Inactive

A case where a single enantiomer offers no clinical advantage, only the racemate was in clinical use…but there is a wealth of literature on single isomer preparation…

Agents and Actions, 1989, 27, 3/4, 455-457

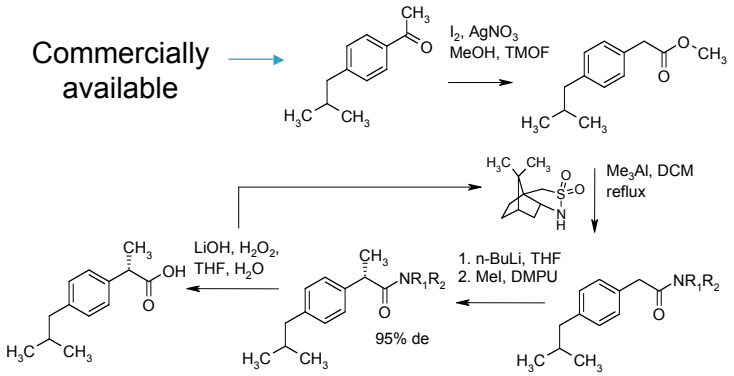
Synthesis of Ibuprofen via Enzymatic Hydrolysis



Microbiological Transformations 43. Epoxide Hydrolases as Tools for the Synthesis of Enantiopure α-Methylstyrene Oxides: A New and Efficient Synthesis of (S)- Ibuprofen

Journal of Organic Chemistry (1999), 64(14), 5029-5035

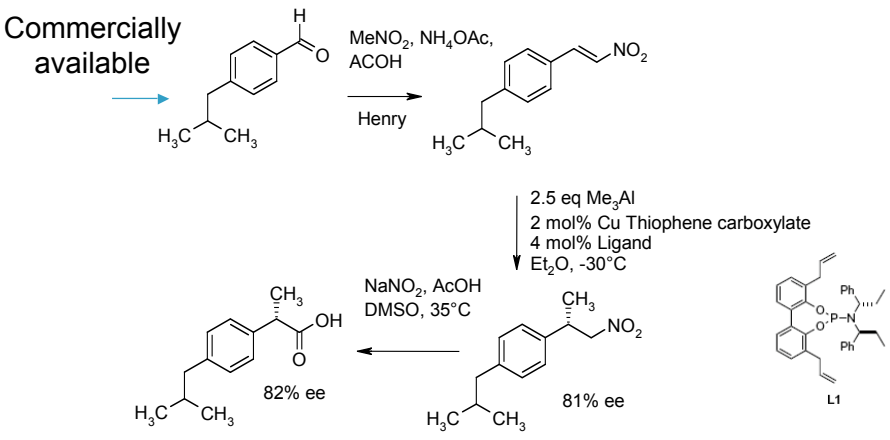
Ibuprofen via N-acylboranesultam



Oppolzer, Wolfgang; Rosset, Stephane; De Brabander, Jef. **Asymmetric synthesis of ibuprofen via diastereoselective alkylation of a homochiral N-acylbornanesultam.**

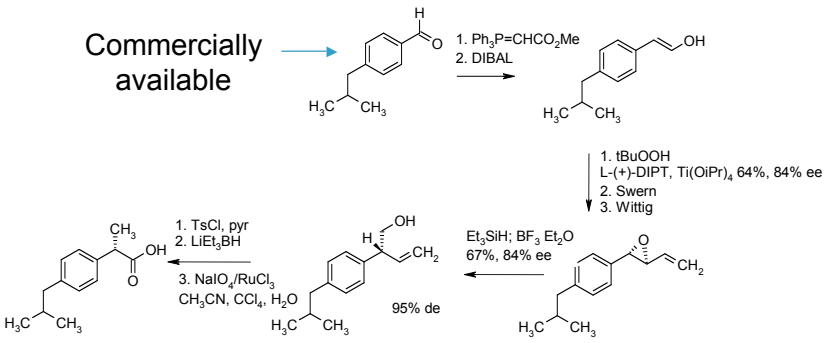
Tetrahedron Letters (1997), 38(9), 1539-1540

Ibuprofen via 1,4 Addition to Nitroalkene



Cu-catalyzed asymmetric 1,4-addition of Me3Al to nitroalkenes. Synthesis of (+)- ibuprofen.
Tetrahedron Letters (2005), 46(9), 1529-1532

Ibuprofen via Stereospecific Rearrangement

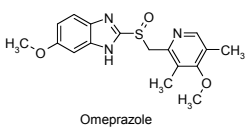


Stereospecific rearrangements of optically active 2-aryl-3-ethenyloxiranes to give optically active β -ethenylbenzeneethanols: benzyl vs. allyl cations and an efficient synthesis of (S)- ibuprofen.

Tetrahedron Letters (1997), 38(15), 2605-2608

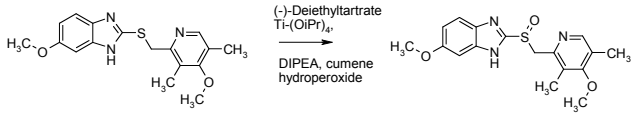
Omeprazole – Example of Non-Carbon Chirality

Histamine Blocker:



Omeprazole

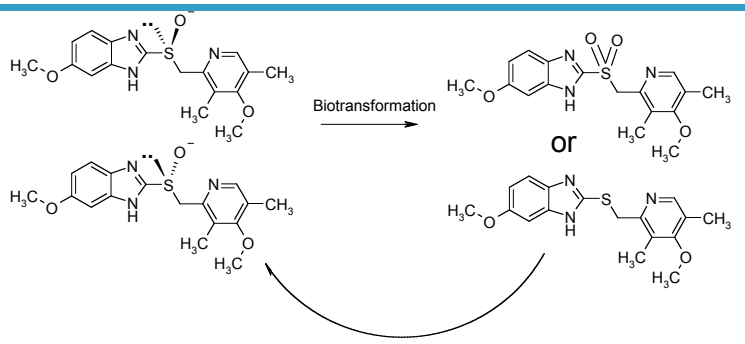
Enantioselective synthesis is described for example in Euro. J. Biochem. 166 (1987) 453 and US 5,948,789. Disadvantages of these methods are that strict control of conditions is to be maintained and strict control of quantities of oxidizing agents is required for avoiding oxidation of desired sulfoxide to sulfone impurity. Moreover, the crystallization from the reaction mixture of a stereoisomer of the sulfoxide is difficult.



A process for the preparation of substituted (pyridinylmethylsulfinyl)benzimidazole enantiomers.
Parthasaradhi Reddy, Bandi; Rathnakar Reddy, Kura; Raji Reddy, Rapolu; Muralidhara Reddy, Dasari.

WO 2003-IN384 20031205

Enzymatic Routes to Omeprazole



Enantioselective preparation of pharmaceutically active sulfoxides by bioreduction
WO 95-SE1416 19951127
Enantioselective preparation of pharmaceutically active sulfoxides by biooxidation.
WO 95-SE1415 19951127

Microbial synthesis of a proton pump inhibitor by enantioselective oxidation of a sulfide into its corresponding sulfoxide by Cunninghamella echinulata MK40
Biotechnology Letters (2001), 23(15), 1217-1222

Pharmacokinetics

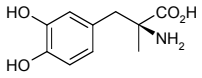
Stereospecificity can alter adsorption, elimination and cellular transport of drugs

Factors which can effect PK/ADME:

- Different protein binding profiles
- Stereoselective cellular transport
  - Accumulation of drug at specific site
- Genetic differences in expression of metabolic enzymes
  - Example: CYP2D6 expressed as 2 phenotypes- extensive and poor metabolizers

α-Methyldopa

Ocular hypotensive for reducing intraocular pressure in treatment of glaucoma



L-α-methyldopa

- Stereoselective cellular transport
  - Initial entry rate of L-isomer is 4.5 x D-isomer
  - C_{max} of L-isomer >2x D-isomer
  - AUC: L-isomer > D-isomer
- Stereoselective accumulation of L vs. D isomer in rabbit aqueous humour (compartment responsible for therapeutic action)

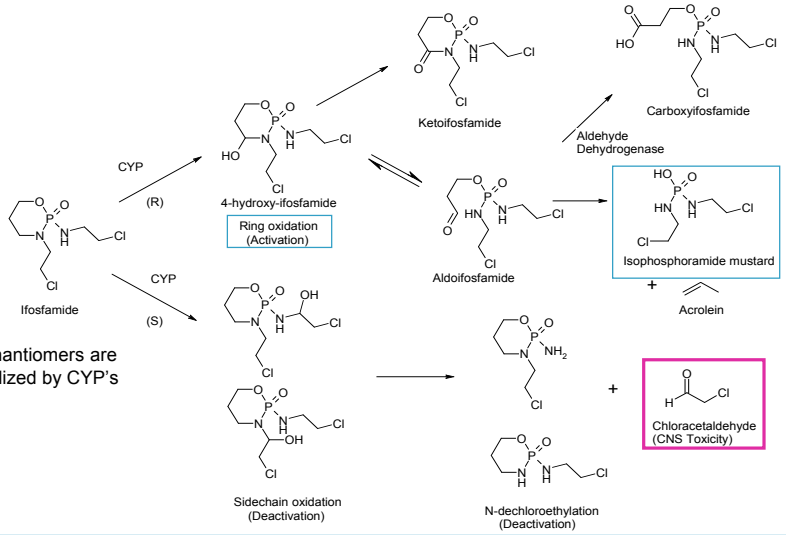
Table 1. Aqueous humour kinetics of L-α-methyldopa and D-α-methyldopa in the rabbit after intravenous injection of 10 mg/kg (Auclair *et al.*, 1988)

	L-α-methyldopa	D-α-methyldopa
C_{max} (μM)	25.2 ± 2.9	11.3 ± 2.5*
T_{max} (min)	51 ± 9	60 ± 10
Initial entry rate (nM/min)	783 ± 91	169 ± 31*
Elimination half-life (min)	109 ± 10	84 ± 9
AUC (μM●min)	3665 ± 438	1378 ± 171*

*$p < 0.01$; $n = 6$.

- D-isomer has even distribution in tissue fluids
- Only S-isomer (L) is metabolized and may explain pharmacological profile
  - Metabolized to α-methyldopamine and/or α-methylnorepinepherine (Alices story)

Stereospecific Biotransformation: Metabolism of Anticancer pro-drug Ifosamide

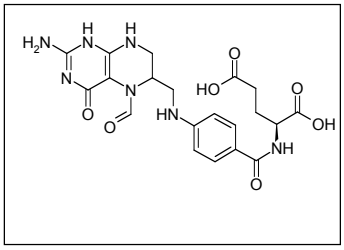


Both enantiomers are metabolized by CYP's

Clinical Issues

Therapeutic Drug Monitoring

Distinct biochemical properties between enantiomers in racemate can compromise accuracy of plasma drug monitoring

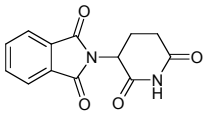


- Leucovorin: Reduced form of folic acid used to rescue patients treated with folate antagonists
- Monitoring of leucovorin levels crucial ensure adequate rescue
- S-enantiomer is active and is rapidly taken into cells
- R-enantiomer is inactive and does not enter cells
- Plasma levels reflect amount of inactive enantiomer
- Difficult to correlate plasma levels with pharmacological effect

Toxicology

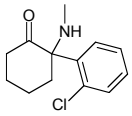
Many chiral drugs have undesirable characteristics associated with a specific enantiomer

Thalidomide



- R-Enantiomer: Sedative
- S-Enantiomer: Teratogen

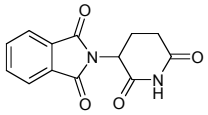
Ketamine



- S-Enantiomer: Anesthetic
- R-Enantiomer: Hallucinogen

Thalidomide Story

Thalidomide



• R-Enantiomer: Sedative
• S-Enantiomer: Teratogen

• Approved in Germany as a sedative in 1957 (UK, Canada, Australia followed)

• Based on animal studies in mice (insensitive to teratogenic effects *in utero*

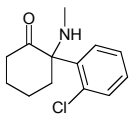
• Less potential for death than barbituates

• Later approved as effective anti-emetic in pregnant women

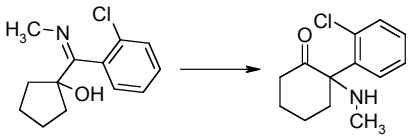
• Reports of deformed babies emerged by 1956. Drug withdrawn in 1961.

Ketamine Synthesis

Ketamine



• S-Enantiomer: Anesthetic
• R-Enantiomer: Hallucinogen



PRZEM CHEM 64(10),478-480(1985). IN POLISH

Scenarios for Development of Enantiopure Chiral Drugs

1. ***De novo* development**
2. **"Chiral switch": Existing racemate to single enantiomer**

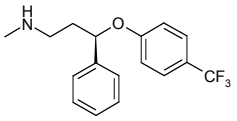
A patent is attainable if either or both enantiomers are sufficiently pharmacologically different from the racemate. Often the racemate is protected but the enantiomers are not.

Selection Invention: Selects a group of individual novel members from a previously known class based on superior properties

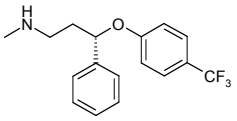
Rules for Patentability of Selection Invention

1. Must show substantial advantage
2. All members must possess it
3. Special properties must be defined in clear terms in specification
4. Must be peculiar to the selected group (those skilled in the art would not expect to find a large number with these properties in original group

Example: Fluoxetine . HCl (Prozac- Eli-Lily)



(*S*)-(+)-Fluoxetine



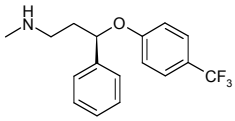
(*R*)-(-)-Fluoxetine

Biological and pharmacological activity were the same in their trials therefore Lily didn't consider it advantageous to seek patents for the individual enantiomers as anti-depressants

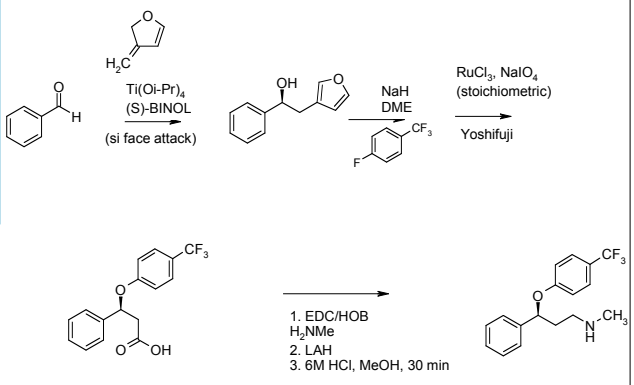
• **Sepracor was granted patents for (*S*)-(+)-Fluoxetine for migraine headaches and (*R*)-(-)-Fluoxetine for depression**

(*S*)-(+)-Fluoxetine	(*R*)-(-)-Fluoxetine
• Doesn't have certain side effects (anxiety, insomnia, nervousness) • Faster onset of action • Increased response rate • Effective for treatment of migraine headaches	• Short half life • Short duration of action • Effective anti-depressant • Effective appetite suppressant

Synthesis of (S)-(+)-Fluoxetine

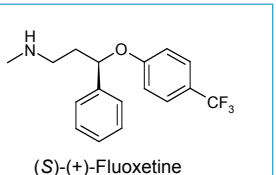


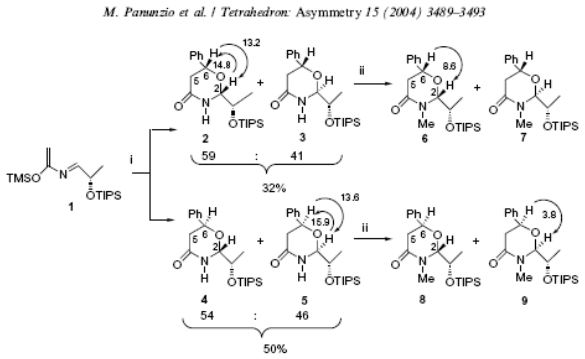
(*S*)-(+)-Fluoxetine



Miles, *et al*, Tetrahedron, (2001), *57*, 9925

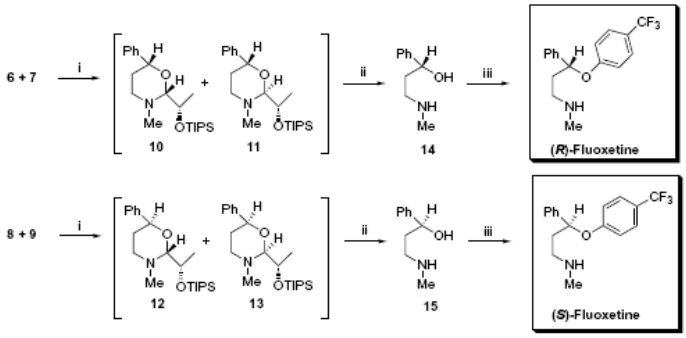
Synthesis of (S)-(+)-Fluoxetine





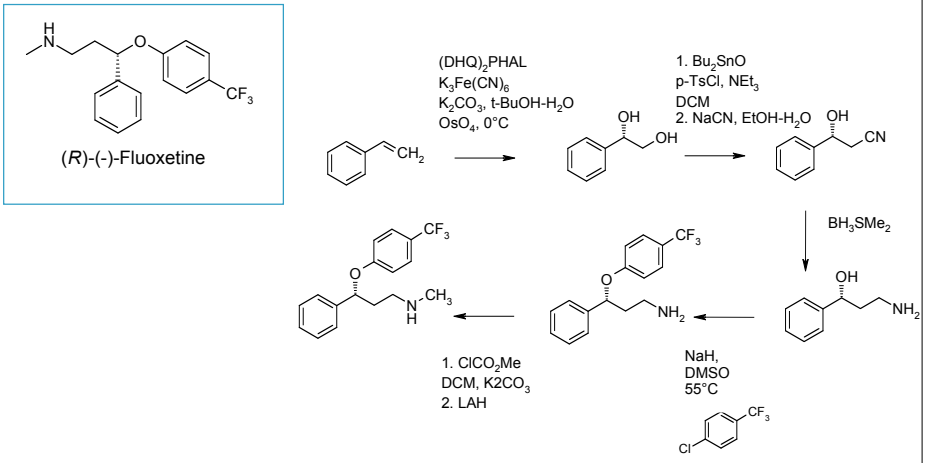
(i) BF_3, PhCHO, CH_2Cl_2, −78 °C to rt; (ii) LiHDSA, MeI, THF, 0°C.

Completion of synthesis



(i) Ph_2SiH_2, $RhH(CO)(PPh_3)_3$; (ii) HCl_{aq}; (iii) 4-Cl-Benzotrifluoride, NaH, DMSO,

Synthesis of (R)-(-)-Fluoxetine



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