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TETRAHEDRON: *ASYMMETRY*

# A new route to (2*S*,4*R*)- and (2*R*,4*S*)-4-hydroxypipecolic acid

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**Abstract**

Both enantiomers of *cis*-4-hydroxypipecolic acid have been prepared by asymmetric synthesis using (*S*)- or (*R*)-glycidol as the chiral source, and involving a stereoselective hydrogenation of a six-membered cyclic imine. The latter is obtained by reduction and cyclization of a cyano β-hydroxy ketone. 

## 1. Introduction

(2*S*,4*R*)-4-Hydroxypipecolic acid **1**, isolated from the leaves of *Calliandra pittieri* and *Strophantus scandeus*,[1] is a cyclic amino acid whose synthesis has been actively studied over recent years owing to its biological properties. Indeed, the amide derivative of **1** is incorporated in the structure of palinavir **2**, a member of a new class of potent inhibitors of the human immunodeficiency virus (HIV) protease.[2] Moreover, the (2*R*,4*S*)-enantiomer of **1** is an intermediate in the preparation of 4-(phosphonoalkyl)-piperidine-2-carboxylic acid **3** called CGS 20281 which is one of the most potent and selective competitive NMDA (*N*-methyl-D-aspartic acid) receptor antagonists,[3] and could thus have potential interest in certain CNS disorders such as treatment of epilepsy.

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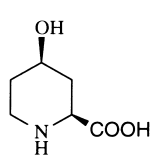
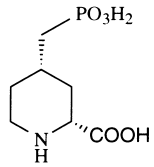
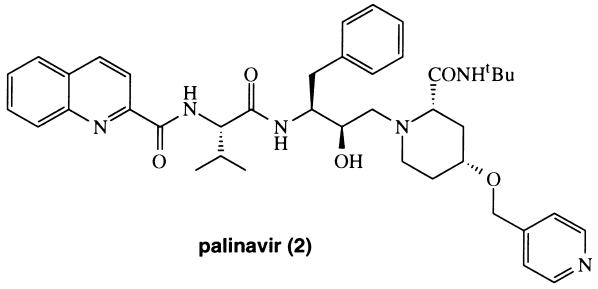



(2*S*,4*R*)-1




(2*R*,4*S*)-3
CGS 20281



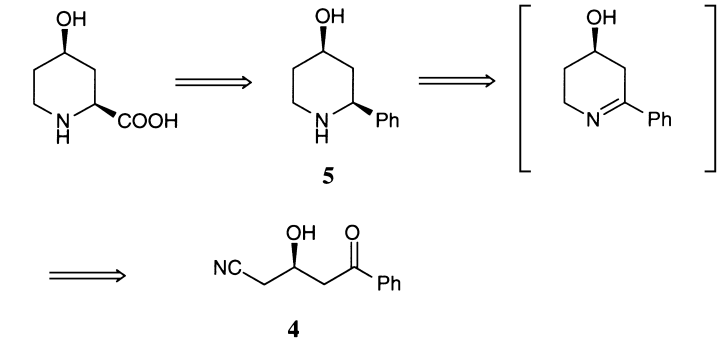

palinavir (2)

Since the first synthesis of pure enantiomeric (−)-**1** by Clarck-Lewis and Mortimer,[4] achieved by chemical transformation of (−)-*trans*-4-hydroxypipecolic acid (obtained from leaves of *Acacia oswaldii*), few total syntheses of **1** in non-racemic form have been described. Fujita et al.[5] started from L-lysine as chiral material, and obtained a mixture of *cis*- (80%) and *trans*- (20%) 4-hydroxypipecolic acid. Golubev et al.[6] used L-aspartic acid as starting material, involving an intramolecular Michael addition leading to the cyclic amino acid; however, the use of hexafluoroacetone as the protecting group made the synthesis rather expensive. The iminium ion cyclization of chiral homoallylic amine has been exploited to achieve an asymmetric synthesis of both enantiomers of **1**, but diastereomeric separation was necessary.[7] The more recent enantioselective synthesis was due to Di Nardo and Varela,[8] with D-glucoheptono-1,4-lactone as starting product. Nevertheless, at one step of their preparation, they required a separation of isomeric products resulting in a loss of yield. Here, we wish to describe an alternative route to piperidinic compound **1**, using the commercially available (*S*)-glycidol as the chiral source.

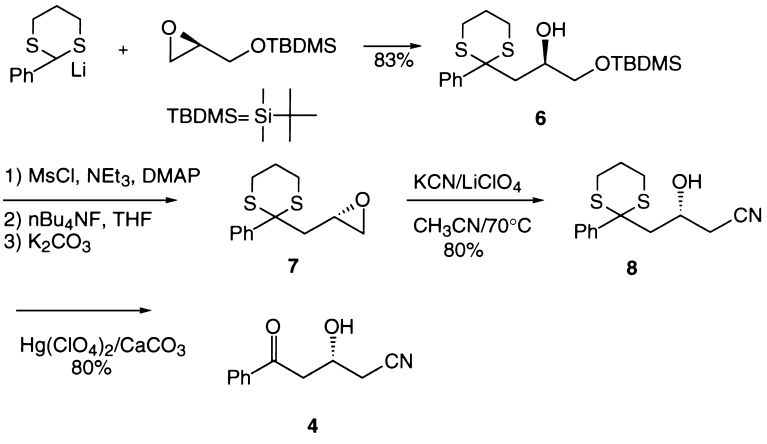
## 2. Results and discussion

A retrosynthetic analysis for **1**, as shown in Scheme 1, indicated that the cyano ketone **4** could be an intermediate to access the target compound. Indeed, the phenyl group constitutes a potential acid function,[9] while the cyano group, upon reduction and further imine formation, could be submitted to a stereoselective hydrogenation to afford 4-hydroxy-1-phenyl piperidine **5**, according to the model proposed for such cyclic imine reduction.[10] Consequently, we investigated the preparation of **4**. The latter was obtained from (*R*)-glycidyl *tert*-butyldimethylsilyl ether[11] as indicated in Scheme 2.

Condensation of 2-lithio-2-phenyl-1,3-dithiane with (*R*)-glycidyl *tert*-butyldimethylsilyl ether gave the alcohol **6** in 83% yield. However, the next step proved more troublesome. The initial idea was to convert **6** to the epoxide **7** via the corresponding diol. However, all the attempts to achieve this transformation, in particular the use of Sharpless conditions [$MeC(OMe)_3$, $PPTS/Me_3SiCl/K_2CO_3$][12] and the monotosylation (direct or through a cyclic stannylene intermediate) followed by base-induced cyclization,[13] gave the desired product with poor yield (about 30%). These results may be explained by the nucleophilic character of the sulfur atom. Finally, **7** has been isolated in good yield (77%) by the following procedure: mesylation of the secondary alcohol, selective deprotection of the primary alcohol




Scheme 1.



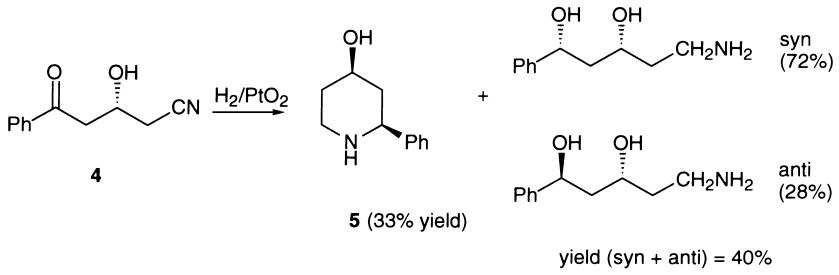

Scheme 2.

by tetrabutylammonium fluoride and basic treatment with $K_2CO_3$. In the next step, epoxide **7** was reacted with KCN in the presence of $LiClO_4$, which were the best conditions to access the cyano alcohol **8** (80%).[14] Hydrolysis of the dithioketal group by means of $Hg(ClO_4)_2$ gave the β-hydroxy ketone **4** in 80% yield.[15]

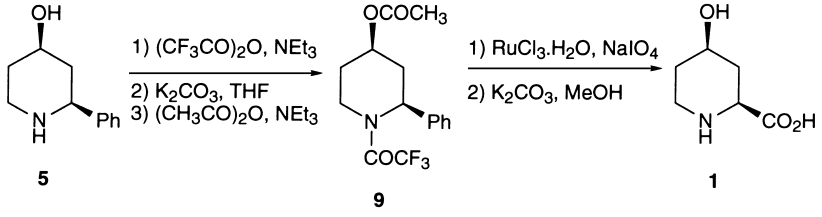
With **4** in hand, we then turned our attention towards the ring closure of the latter, which constituted the crucial step of the synthesis. For this purpose, **4** was submitted to catalytic hydrogenation using Pd or $Pd(OH)_2$. Unfortunately, in addition to non-reproductible results, the major isolated product was identified as phenyl-1-piperidine. Such β-elimination of the OH group and total hydrogenation has already been observed by Varela et al.[8] Finally, $PtO_2$ turned out to be a better catalyst to perform this conversion (no trace of the C-2 epimer was detected by $^1H$ NMR), although the yield was modest (33%). This was due to the reduction of ketone, which probably occurred before imine formation, affording a mixture of diols (Scheme 3).

The next few steps for the transformation of **5** into **1** involved selective and differential protection for the hydroxy and amino groups. This was accomplished in the following manner and without purification of the intermediates: complete protection by treatment with trifluoroacetic anhydride, selective deprotection of the hydroxy group with $K_2CO_3$ in THF, and protection of the latter as the acetate yielding **9** in 82% yield (Scheme 4).

After oxidation of the phenyl group by sodium periodate in the presence of ruthenium chloride hydrate, and full deprotection in basic medium, **1** was obtained in 60% yield. As expected, specific rotation




Scheme 3.




Scheme 4.

and spectral properties were in full agreement with the literature.[2,16] The (2*R*,4*S*)-enantiomer of **1** was prepared in a similar manner starting from (*R*)-glycidol.

In conclusion, we have developed a new practical method which allows access to both enantiomers of *cis*-4-hydroxypipecolic acid, using as non-racemic chiral starting material either (*R*)- or (*S*)-glycidol, and which does not require any separation of diastereomers.

## 3. Experimental

Infrared spectra were taken on an FT Nicolet 210 spectrometer. $^{1}$H NMR and $^{13}$C NMR spectra were recorded at 200 and 50 MHz, respectively, in $CDCl_3$ unless specified otherwise, using a Bruker AC-200 E apparatus. Chemical shifts are expressed in ppm from internal TMS. Mass spectra were recorded with a 70 eV ionizing voltage; ammonia was used for chemical ionization. Melting points were determined on a Kofler apparatus and are uncorrected. Flash chromatography was performed using silica gel 60 (Merck, 230–400 mesh). Optical rotations were measured on a Perkin–Elmer 141 polarimeter.

### *3.1. (2*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-(1,3-dithian-2-yl)-4-phenyl-2-butanol **6***

A 1.6 M solution of *n*-BuLi in hexanes (17.2 mL, 27.5 mmol) was added to a stirred solution of 2-phenyl-1,3-dithiane (4.91 g, 25 mmol) in dry THF (100 mL) at −25°C under an inert atmosphere. The solution was stirred at the same temperature for 2 h and (*R*)-glycidyl *tert*-butyldimethylsilyl ether (4.7 g, 25 mmol) diluted in THF (20 mL) was added dropwise. The reaction mixture was stirred for 5 h, quenched with saturated aqueous $NH_4Cl$, diluted with $H_2O$, and extracted with EtOAc. The extract was washed with water and saturated NaCl, dried over $MgSO_4$, and concentrated to give a residue which was purified by flash chromatography (cyclohexane:AcOEt, 90:10) to give the alcohol **6** as an oil (8 g, 83%): $[\alpha]_D^{22}=-10$ (c 1.2, $CH_2Cl_2$); $^{1}$H NMR (200 MHz, $CDCl_3$) δ 0.0 (s, 6H), 0.86 (s, 9H), 1.85–2.0 (m, 10H), 2.15–2.34 (m, 2H), 2.55 (d, J=3.2 Hz, 1H), 2.68–2.78 (m, 4H), 3.33 (d, J=5.8 Hz, 2H), 3.70–3.85 (m, 1H), 7.20–7.43 (m, 3H), 7.90–7.98 (m, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ −5.6, 18.0, 24.6, 25.7, 27.3,

27.6, 47.7, 57.0, 66.8, 68.5, 127.0, 128.3, 128.4, 141.6; MS (EI) m/z 384 ($M^+$, 6.1%), 327 ($[M-C_4H_9]^+$, 15%), 209 ($[M-C_8H_{19}SiO_2]^+$, 10%), 195 ($[M-C_9H_{21}SiO_2]^+$, 15%), 117 (100%).

### 3.2. (2S)-4-(1,3-Dithian-2-yl)-1,2-epoxy-4-phenylbutane **7**

To an ice cold solution of **6** (7.7 g, 20 mmol), triethylamine (4.18 mL, 30 mmol) and 4-dimethylaminopyridine (120 mg, 1 mmol) in anhydrous dichloromethane (100 mL) under a stream of argon was added dropwise methanesulfonyl chloride (1.70 mL, 22 mmol). The solution was stirred for 3 h, diluted with dichloromethane (50 mL) and washed successively with water, 5% aqueous HCl and saturated aqueous $NaHCO_3$. The solution was dried ($MgSO_4$) and concentrated to give a crude product which was used without purification. Thus, the above mesylate was diluted in anhydrous THF (80 mL) and the solution was cooled to 0°C. A 1 M THF solution of tetrabutylammonium fluoride (containing 5% water, 24 mL, 24 mmol) was added dropwise. The mixture was stirred for 1 h at the same temperature (the disappearance of the starting material was checked by TLC), after which time $K_2CO_3$ (5.52 g, 40 mmol) was added and the solution was stirred for additional 12 h at room temperature. The next day, water (100 mL) was added and the solution was extracted with ethyl acetate (2×60 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to give a residue which was purified by flash chromatography (cyclohexane:AcOEt, 85:15) to give the epoxide **7** (3.9 g, 77%): $[\alpha]_D^{22}$=+8.7 (c 1, $CH_2Cl_2$); $^1$H NMR (200 MHz, $CDCl_3$) δ 1.84–2.16 (m, 4H), 2.24–2.46 (m, 2H), 2.54–2.88 (m, 4H), 2.88–3.04 (m, 1H), 7.20–7.48 (m, 3H), 7.88–8.08 (m, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 24.7, 27.4, 27.5, 47.0, 47.9, 48.3, 57.4, 127.2, 128.5, 128.6, 141.3; MS (EI) m/z 252 ($M^+$, 30%), 195 ($[M-C_3H_5O]^+$, 100%).

### 3.3. (3R)-5-(1,3-Dithian-2-yl)-3-hydroxy-5-phenylpentanenitrile **8**

A solution of **7** (3.8 g, 15 mmol) in acetonitrile (40 mL) was treated with potassium cyanide (1.47 g, 22.58 mmol) and lithium perchlorate (2.40 g, 22.58 mmol). The resulting reaction mixture was stirred at 70°C for 8 h, and then cooled at room temperature, diluted with water and extracted with ethyl acetate (2×40 mL). The extract was dried ($MgSO_4$), filtered, and evaporated under vacuum to afford a brown oil. Purification by flash chromatography (cyclohexane:EtOAc, 60:40) gave the cyano alcohol **8** as a solid (3.36 g, 80%): $[\alpha]_D^{22}$=+36.5 (c 1.4, $CH_2Cl_2$); mp 80°C; $^1$H NMR (200 MHz, $CDCl_3$) δ 1.90–2.04 (m, 2H), 2.20–2.60 (m, 4H), 2.64–3.04 (m, 5H), 4.04–4.20 (m, 1H), 7.25–7.50 (m, 3H), 7.85–7.96 (m, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 24.4, 26.0, 27.3, 27.7, 50.2, 56.4, 64.6, 117.1, 127.7, 127.9, 129.0, 141.0; MS (EI) m/z 279 ($M^+$, 79%), 205 (31%), 195 (37%), 172 (52%), 103 (100%); IR (nujol) $\nu_{max}$ 3456 (br), 2930, 2900, 2250 $cm^{-1}$.

### 3.4. (3R)-3-Hydroxy-5-oxo-5-phenylpentanenitrile **4**

A mixture of **8** (3.36 g, 12 mmol), $CaCO_3$ (12 g, 120 mmol), and $Hg(ClO_4)_2$ (9.58 g, 24 mmol) in THF (120 mL) and $H_2O$ (30 mL) was stirred at room temperature for 2 h and then filtered through a short column of Celite using EtOAc (100 mL). Water was added (100 mL) and the solution was extracted. The extract was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to give a residue which was purified by flash chromatography (cyclohexane:AcOEt, 6:4) yielding **4** as an oil (1.82 g, 80%): $[\alpha]_D^{22}$=−41.7 (c 1.07, $CH_2Cl_2$); $^1$H NMR (200 MHz, $CDCl_3$) δ 2.69 (AB system part of ABX, $J_{AB}$=16.8 Hz, 2H), 3.54 (AB system part of ABX, J not measurable, 2H), 3.96 (d, J=3.8 Hz, 1H), 4.45–4.65 (m, 1H), 7.40–7.65 (m, 3H), 7.85–7.95 (m, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 25.0, 43.5, 63.7, 117.4, 127.9,

128.6, 133.7, 135.9, 198.7; MS (EI) m/z 190 ($MH^+$, 19.7%), 172 (17.7%), 105 (100%); IR (neat) $\nu_{max}$ 3500 (br), 2250, 1770, 1600 $cm^{-1}$.

### 3.5. (2S,4R)-2-Phenylpiperidine-4-ol **5**

The hydroxyketone **4** (1.13 g, 5.97 mmol) was dissolved in EtOH (30 mL), and $PtO_2$ (83% Pt, 60 mg) was added. Hydrogen (1 atm) was applied, and the reaction mixture was stirred at room temperature for 12 h. After filtration through Celite, the solvent was evaporated. The crude oil obtained was purified by flash chromatography ($CH_2Cl_2$:MeOH, 60:40) to afford **5** as a pale yellow solid (0.35 g, 33%): $[\alpha]_D^{22}=-10.9$ (c 0.53, MeOH); mp 101–102°C; $^1$H NMR (200 MHz, $CDCl_3$) δ 1.40–1.60 (m, 2H), 1.93–2.16 (m, 2H), 2.46 ($s_{broad}$, 2H), 2.76 (dt, J=2.6 Hz and J=12.3 Hz, 1H), 3.10–3.26 (m, 1H), 3.60 (dd, J=2.38 and J=11.48 Hz, 1H), 3.65–3.84 (m, 1H), 7.20–7.40 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$) 29.6, 35.2, 43.7, 44.9, 60.1, 69.4, 126.5, 127.2, 128.4, 143.6; MS (CI, $NH_3$) m/z 195 ($M+NH_4^+$, 4%), 178 ($MH^+$, 100%).

### 3.6. N-Trifluoroacetyl-(2S,4R)-4-acetoxy-2-phenylpiperidine **9**

To an ice cold solution of aminoalcohol **5** (0.3 g, 1.69 mmol) in $CH_2Cl_2$ (25 mL) containing $Et_3N$ (1.4 mL, 10 mmol) and dimethylaminopyridine (10 mg, 0.08 mmol) was added via a syringe through a septum trifluoroacetic anhydride (0.95 mL, 6.77 mmol). After stirring at 23°C for 12 h, water was added and the solution was extracted, dried over $MgSO_4$, filtered, and evaporated. The crude product obtained was diluted in THF (25 mL) and $K_2CO_3$ (0.46 g, 3.38 mmol) was added. The mixture was stirred for 12 h. Water was added and the reaction mixture was extracted with $CH_2Cl_2$. After drying over $MgSO_4$, the solution was filtered and placed into a one-neck 100 mL round bottomed flask. Triethylamine (0.94 mL, 6.8 mmol) and dimethylaminopyridine (10 mg, 0.08 mmol) were added before cooling to 0°C. Acetic anhydride (0.32 mL, 3.39 mmol) was added via a syringe through a septum and the solution was stirred at room temperature for 12 h. Water was added and the solution was extracted. The solution was dried over magnesium sulfate, filtered, and evaporated to give an oil which was purified by flash chromatography (cyclohexane:AcOEt, 80:20) to give the protected aminoalcohol **9** as a colorless oil (0.44 g, 82%): $[\alpha]_D^{22}=-45.5$ (c 1.05, $CH_2Cl_2$); $^1$H NMR (400 MHz, $C_6D_6$, 60°C) δ 1.26 (s, 3H), 1.28–1.37 (m, 2H), 1.56 (ddd, J=3.1, 6.6, 15.2 Hz, 1H), 2.39–2.46 (m, 1H), 3.2 ($dt_{broad}$, J not measurable, 1H), 3.79 (m, 1H), 4.72 (quint, J=3.5 Hz, 1H), 5.48 (m, 1H), 6.90–6.98 (m, 3H), 7.03–7.08 (m, 2H); $^{13}$C NMR (100 MHz, $C_6D_6$, 60°C) δ 19.8, 29.4, 31.2, 36.7, 52.4, 66.1, 117.2 (q, J=287 Hz, $CF_3$), 125.2, 126.4, 128.4, 139.0, 156.2, 168.8; MS (CI, $NH_3$) m/z 333 ($M+NH_4^+$, 100%), 316 ($MH^+$, 1.5%); IR (nujol) $\nu_{max}$ 1745, 1700, 1600 $cm^{-1}$.

### 3.7. (2S,4R)-4-Hydroxypipecolic acid **1**

Compound **9** (0.4 g, 1.27 mmol) was placed into a flask equipped with a magnetic stirrer and containing 2 mL of carbon tetrachloride, 2 mL of acetonitrile, and 3 mL of water. Sodium periodate (4.07 g, 19 mmol) and ruthenium chloride hydrate (13 mg, 0.06 mmol) were added and the solution was vigorously agitated overnight. On the next day, the solution was filtered through a Celite pad and rinsed several times with dichloromethane. The dark solution was dried over magnesium sulfate, filtered, and concentrated. The crude acid thus obtained was diluted in methanol (15 mL); potassium carbonate (1.05 g, 7.6 mmol) was added, and the mixture was stirred at room temperature for 12 h. The solution was concentrated and acidified with 1 M HCl. Purification was performed over a column of Dowex 50W-X8 resin (100–200

mesh, 20 g) eluted with 5% $NH_4OH$ under a light pressure. The ninhydrin positive fractions were combined and evaporated in vacuo to give a solid which was recrystallized from hot 25% water in EtOH. Evaporation and drying under vacuum over $P_2O_5$ gave pure (2*S*,4*R*)-**1** as a solid (0.11 g, 60%): $[\alpha]_D^{22}=-17.2$ (c 1.05, $H_2O$), lit.[2] $[\alpha]_D^{25}=-23.5$ (c 1, $H_2O$); mp 269°C dec; $^1H$ NMR (400 MHz, $D_2O$) $\delta$ 1.47–1.59 (m, 2H), 2.04–2.09 (m, 1H), 2.38–2.44 (m, 1H), 2.95 (dt, J=3.1, 13.2 Hz, 1H), 3.42 (ddd, J=2.7, 4.4, 13.2 Hz, 1H), 3.60 (dd, J=3.2, 12.9 Hz, 1H), 3.88 (tt, J=4.4, 11 Hz, 1H); $^{13}C$ NMR (50 MHz, $D_2O$) $\delta$ 31.0, 35.8, 42.5, 58.9, 66.6, 174.4; MS (CI, $NH_3$) m/z 163 ($M+NH_4^+$, 40%), 146 ($MH^+$, 100%).

## References


1. (a) Romeo, J. T.; Swain, L. A.; Bleecker, A. B. *Phytochemistry* **1983**, *22*, 1615. (b) Schenk, V. W.; Schutte, H. R. *Flora* **1963**, *153*, 426.
2. Gillard, J.; Abraham, A.; Anderson, P. C.; Beaulieu, P. L.; Bogri, T.; Bousquet, Y.; Grenier, L.; Guse, I.; Lavallée, P. *J. Org. Chem*. **1996**, *61*, 2226.
3. Ornstein, P. L.; Schoepp, D. D.; Arnold, M. B.; Leander, J. D.; Lodge, D.; Paschal, J. W.; Elzey, T. *J. Med. Chem*. **1991**, *34*, 90.
4. Clarck-Lewis, J. W.; Mortimer, P. I. *J. Chem. Soc*. **1961**, 189.
5. Fujita, Y.; Kollonitsch, J.; Witkop, B. *J. Am. Chem. Soc*. **1965**, *87*, 2030.
6. Golubev, A.; Sewald, N.; Burger, K. *Tetrahedron Lett*. **1995**, *36*, 2037.
7. Skiles, J. W.; Giannousis, P. P.; Fales, K. R. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 963.
8. Di Nardo, C.; Varela, O. *J. Org. Chem*. **1999**, *64*, 6119.
9. Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem*. **1981**, *46*, 3936.
10. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; p. 209.
11. (a) Lai, M.-t.; Oh, E.; Shih, Y.; Liu, H.-w. *J. Org. Chem*. **1992**, *57*, 2471. (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem*. **1998**, *63*, 6776.
12. Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.
13. Byun, H.-s.; Sadlofsky, J. A.; Bittman, R. *J. Org. Chem*. **1998**, *63*, 2560.
14. Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett*. **1991**, *32*, 4775.
15. Mori, Y.; Asai, M.; Okumura, A.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5299.
16. Esch, P. M.; Boska, I. M.; Hiemstra, H.; de Boer, R. F.; Speckamp, W. N. *Tetrahedron* **1991**, *47*, 4039.