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"AN EFFICIENT SYNTHESIS OF ETHYL (R)-2-HYDROXY-4-PHENYLBUTYRATE: A USEFUL INTERMEDIATE IN THE SYNTHESIS OF CONVERTING ENZYME INHIBITORS"

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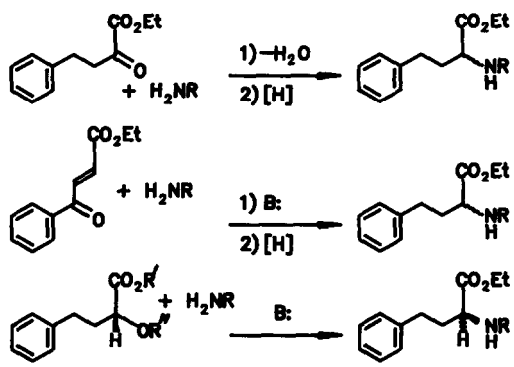
Abstract: Optically pure Ethyl (R)-2-hydroxy-4-phenylbutyrate has been synthesized stereoselectively in 24% overall yield.

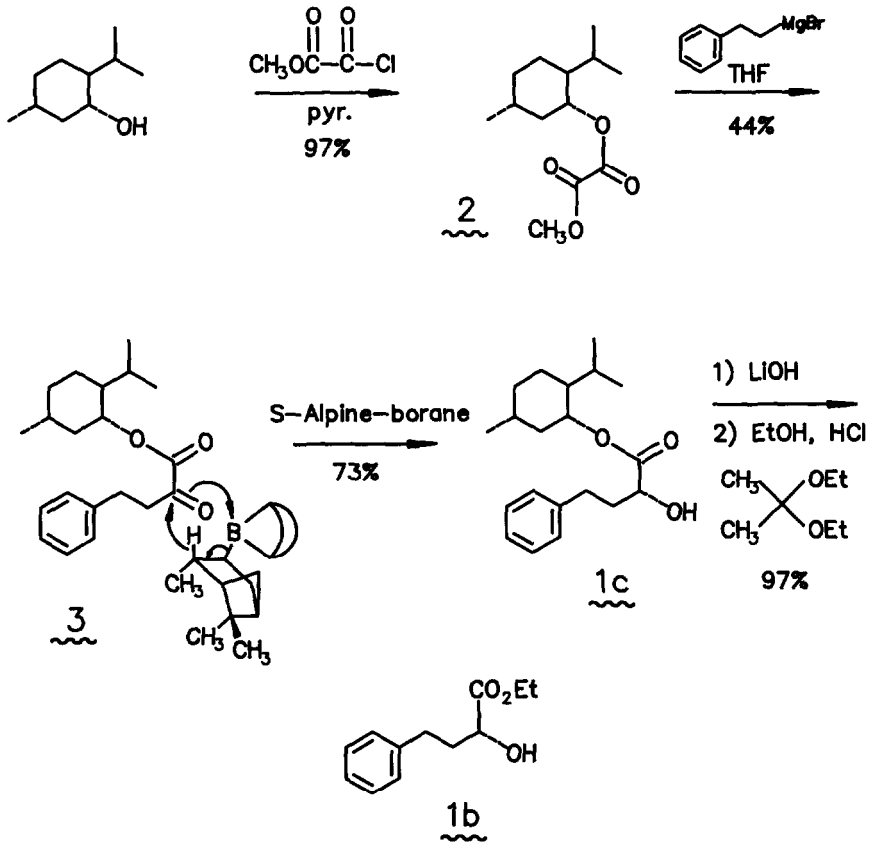
The recent discovery of potent inhibitors of angiotensin-converting enzyme (ACE) which incorporate the ethyl N-substituted-(S)-2-amino-4-phenylbutyrate moiety as a common structural element[1] has prompted the development of varied methods for the stereoselective introduction of this residue. This goal has been successfully achieved through the reduction of Schiff-bases derived from an amine and ethyl 2-oxo-4-phenylbutyrate[2] and through conjugate addition of amines to ethyl 4-oxo-4-phenylcrotonate[3] followed by reduction (Scheme 1). Perhaps the most stereospecific, versatile, and efficient approach, however, is the S_N2 displacement of (R)-triflate 1a by amines.[3] This reaction has the advantage of consistently providing the desired (S)-amino ester derivative resulting from stereospecific inversion in high yield (>90%).

Scheme 1



1a R' = Et, R'' = $-SO_2CF_3$
1b R' = Et, R'' = H
1c R' = L-menthyl, R'' = H

Scheme 2



The major disadvantage to the latter coupling method is the preparation of the requisite (R)-alcohol 1b. Alcohol 1b has been separated from the racemic mixture as its L-menthyl ester, 1c. Crystallization of the desired (R)-diastereomer is tedious, slow, and proceeds in low yield.[4] Once enriched, alcohol 1c can be recrystallized to a high degree of purity from alcohol-water and converted to ethyl ester 1b in high yield.

We now wish to describe a highly stereoselective and direct synthesis of (R)-hydroxy menthyl ester 1c which makes the displacement of (R)-triflate 1a practical and an attractive alternative method for the preparation of ACE inhibitors incorporating this residue (Scheme 2). L-menthol was condensed with methyl chloroglyoxylate in 2:1 CH_2Cl_2/pyridine to afford mixed oxalate 2 in 97% yield (bp = 95°C @ 0.02 mmHg, $[\alpha]_D^{20}$ = +77.6°). Mixed oxalate 2 was then treated with an equivalent of phenethylmagnesium bromide[5] at -20°C in THF to yield α-keto ester 3 as a crystalline solid (mp = 51-53°C, $[\alpha]_D^{20}$ = -66.4°)[6] in 44% yield. Stereoselective reduction of keto ester 3 with (S)-Alpine-borane[7] proceeded in high optical yield and gave the desired (R)-hydroxy menthyl ester 1c in 73% purified yield (mp = 85-86.5°C, $[\alpha]_D^{20}$ = -63.1°, lit.[4] $[\alpha]_D^{20}$ = -65.4°). Saponification of menthyl ester 1c (LiOH, EtOH) and re-esterification (EtOH, HCl gas, 2,2-diethoxypropane) gave ethyl (R)-2-hydroxy-4-phenylbutyrate in 97% yield (bp 120°C @ 1.0 mmHg, $[\alpha]_D^{20}$ = -21.7°, lit.[3] $[\alpha]_D^{20}$ = -22.1°).

Reduction of α-keto ester 3: A solution of 160 mL (80 mmol) of 0.5N S-Alpine Borane (Aldrich Chem. Co.) was concentrated to 50 mL at reduced pressure. The concentrated solution was placed under N_2 atmosphere, cooled to 0°C, and treated with 17.9 g (56.5 mmol) of α-keto ester 3. The resulting orange solution was allowed to stand at 0°C for 5 days. Acetaldehyde was added to decompose the excess reagent and the volatiles were removed by Kugelrohr distillation (70°C @ 1.0 mmHg). The crude residue was dissolved in ether, cooled in an ice bath and 4.8 mL (80 mmol) of ethanol amine was added in dropwise fashion over 10 minutes. The mixture was filtered through 75 mL of silica gel and the filtrate was recrystallized from hexane to give 11.2 g (62.3% yield) of (R)-hydroxy ester 4. The mother liquors were flash chromatographed (12:1 hexane/EtOAc) and crystallized to give an additional 2.0 g of 4 (41.5 mmol, 73.4% total yield, m.p. 85-86.5°C): IR (KBr) 3450, 2950, 2920, 2850, 1725, 1450, 1100 cm^{-1}; NMR ($CDCl_3$) δ 7.25 (m, 5H); 4.79 (dt, 1H, J_d = 4.5 Hz, J_t = 10.5 Hz); 4.17 (ddd, 1H, J_a = 4.5 Hz, J_b = 6.4 Hz, J_c = 7.5 Hz); 2.92 (d, 1H, J = 5.3 Hz); 2.82 (ddd, 1H, J_a = 7 Hz, J_b = 11 Hz, J_c = 18 Hz); 2.67 (ddd, 1H, J_a = 4.9 Hz, J_b = 10.8 Hz, J_c = 18 Hz); 2.0 (m, 4H); 1.7 (m, 2H); 1.46 (m, 3H); 1.03 (m, 2H); 0.92 (d, 6H, J = 7 Hz); 0.76 (d, 3H, J = 7 Hz). $[\alpha]_D^{20}$ = -63.1° (C = 0.85, $CHCl_3$).
Calcd. for $C_{20}H_{30}O_3$: %C = 75.46, %H = 9.50; Found: %C = 75.13, %H = 9.59.

This process provides (R)-α-hydroxy ester 1b in 24% overall yield starting from L-menthol. The Grignard addition to mixed oxalate 2 proceeds well without using a large excess of oxalate. The direct formation of the L-menthol ester 3 allows for easy optical resolution of the reduction products. An exact optical yield is not available for the chiral reduction but it is believed to exceed 80% de. Since the S_N2 displacement of R-triflate 1a by amines occurs in high yield (>90%), this method would be of particular utility where the amine used is not readily available.

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