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Asymmetric Synthesis of (R)-3,3-Dimethyl-2-hydroxy-γ-butyrolactone en route to the Formal Synthesis of Calcium D-pantothenate

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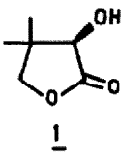
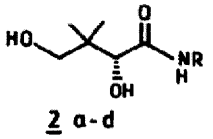
Abstract : An efficient asymmetric protocol for the synthesis of (R)-3,3-dimethyl-2-hydroxy- γ-butyrolactone, a crucial intermediate for the synthesis of calcium D-pantothenate and several other compounds is described, where the requisite chirality is incorporated by Sharpless asymmetric epoxidation reaction.

(R)-3,3-Dimethyl-2-hydroxy-γ-butyrolactone (R-pantolactone; 1) is an important intermediate in the synthesis of D-pantothenic acid (part of coenzyme A) enroute to calcium D-pantothenate[1] (2a, Vit.B group), D-panthenol[2] (2b, bactericide), D-pantetheine[3] (2c, growth factor) and D-pantoyl taurine[4] (2d, bacterial growth inhibitor). Compound 1 has also been extensively used as a chiral auxillary[5] and chiral building block[6] in the synthesis of natural products. Importance of (R)-pantolactone (1) has earlier resulted in the development of its synthesis involving resolution[7] (chemical or enzymatic) of (±) 1[1] or reduction[8] (microbial or enantioselective) of 3,3-dimethyl-2-oxo- -butyrolactone as the key step. Herein, we report an efficient asymmetric route for the synthesis of 1 enroute to the formal synthesis of calcium D-pantothenate (2a), making use of Sharpless asymmetric epoxidation as the key step for the introduction of the lone stereocentre in 1.



1



2 a-d

a R = $CO_2]_2Ca$

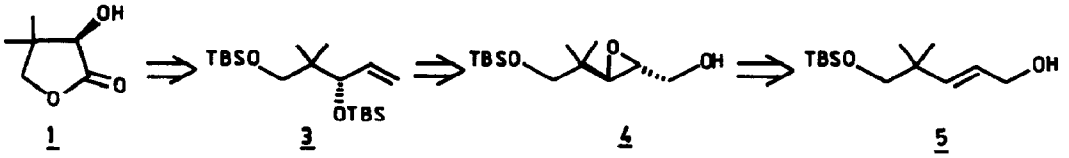
b R = OH

c R = O, N, H, SH

d R = SO_3H

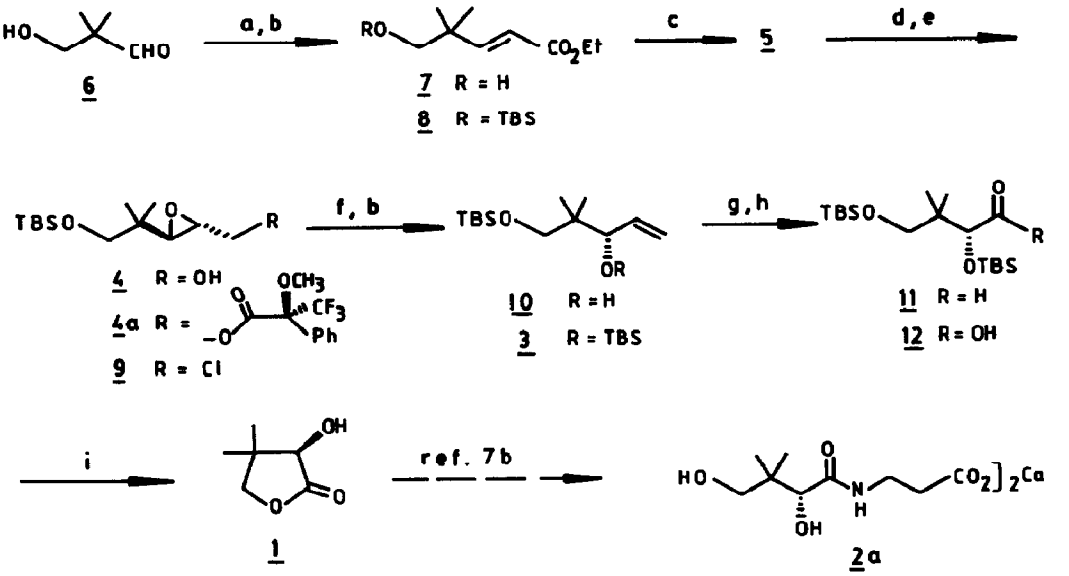
Antithetic analysis of 1 (scheme 1) indicated that the acid functionality could be efficiently derived by the oxidation of the terminal olefin in 3. The allylic carbinol 3 in turn would be effectively formed by a regioselective ring opening of the chiral oxirane methanol 4, while the epoxy alcohol 4 could be prepared from the allylic alcohol 5 by Sharpless asymmetric epoxidation reaction. Thus the main strategy in the incorporation of chirality would be accomplished through the asymmetric epoxidation.

Scheme - 1



Accordingly, the requisite allylic alcohol 5 (scheme 2) was made in 3 steps from the known[7] 2,2-dimethyl-3-hydroxy propionaldehyde (6). Thus Wittig olefination of 6 (prepared from the aldol condensation of isobutyraldehyde with 37% formalin in presence of K_2CO_3) with (carbethoxymethylene)triphenylphosphorane in benzene at reflux gave ester 7[9] in 78% yield. Compound 7 on silylation with TBDMSCl in presence of imidazole in DMF gave silylated

Scheme - 2



a) $Ph_3P{=}CHCO_2Et$, benzene, 80°C; b) TBDMSCl, imidazole, DMF; c) DIBAL-H, DCM, -10°C; d) (-)DIPT, TBHP, TIP, DCM; e) Ph_3P, CCl_4, 80°C; f) Sodium sand, ether; g) O_3, Ph_3P, DCM, -78°C; h) $NaClO_2$, NaH_2PO_4, H_2O_2, aq. CH_3CN, 0-10°C; i) PTSA, $CHCl_3$, 60°C.

product in 81% yield. Subsquently reduction of the ester 8 with DIBAL-H in DCM at -20°C afforded 5 (74%). The crucial Sharpless[10] asymmetric epoxidation on allylic alcohol 5 with TBHP in presence of (-)DIPT and TIP in DCM at -20°C in 2h furnished the epoxy alcohol 4 in 75% yield, $[\alpha]_D$ + 13.67° (c 1.03, $CHCl_3$), whose optical purity (98% ee) was determined from the ^1H and ^{19}F NMR (400 MHz) spectra of the corresponding Mosher ester 4a, thereby

achieving the incorporation of lone stereocentre that is present in **1**. Compound **4** on reaction with triphenyl phosphine in CCl_4 at reflux gave chloride **9** in 85% yield. The regioselective ring opening of **4** with pulverised sodium in ether at room temperature furnished allylic carbinol **10** (88%), $[\alpha]_D$-15.94° (c 1.6, $CHCl_3$). The hydroxy functionality in **10** was protected on treatment with TBDMSCl in presence of imidazole in DMF to give **3** (79%), $[\alpha]_D$ -12.6° (c 1.35, $CHCl_3$), whose ^1H NMR spectrum (200 MHz) indicated the chemical shifts for the terminal olefinic protons at δ 5.1 to 5.32 (m, 2H) and 5.85 to 6.0 (m, 1H). The terminal olefin in **10** was transformed into the acid by a two step sequence. Accordingly, ozonolysis of **10** in DCM at -78°C followed by quenching with Ph_3P gave the aldehyde **11** which on subsequent oxidation[11] with sodium chlorite and H_2O_2 in presence of NaH_2PO_4 in aq. CH_3CN at 0-10°C afforded acid **12** in 68% yield, $[\alpha]_D$ +10.1° (c 0.64, $CHCl_3$). Finally compound **12** on treatment with tetrabutyl ammonium fluoride in THF underwent simultaneous desilylation and lactonisation reaction and afforded (R)-pantolactone (**1**) in 78% yield as a hygroscopic solid, $[\alpha]_D$ -49.07° (c 1.2, H_2O), [lit.[7] $[\alpha]_D$ -50.7° (c 2.05, H_2O)], whose ^1H NMR spectrum (200 MHz) indicated the chemical shifts for H-2 at δ 4.11 as a singlet while H-4,4' at δ 4.0 as AB quartet, $J_{4,4'}$ = 8.5 Hz. Since the conversion of **1** to **2a** is a well documented[7b] procedure in literature, synthesis of **1** formally constitutes the total synthesis of calcium D-pantothenate (**2a**).

In conclusion, it is pertinent to mention that the present protocol provides an efficient approach for the synthesis of (R)-pantolactone (**1**) and related compounds.

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