706, 605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.7–7.4 (m, 5 H), 5.6 (s, 2 H), 4.5 (m, 1 H), 4.1 (s, 2 H), 2.5–1.3 (m, 4 H), 0.8 (t, 3 H, J = 7 Hz); mass spectrum, m/z 251 (M^+), 250, 208, 141, 125, 108, 91, 77 (100). Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57. Found: C, 62.10; H, 7.03; N, 5.63.

3-Ethyl-1-(phenylsulfonyl)-3-pyrroline (2d). The same procedure as described above but with **1d** gave **2d** (68%) as an oil: IR (KBr) 3040, 2970, 2880, 1460, 1370, 1170, 1120, 720, 600, 570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.0–7.3 (m, 5 H), 5.3 (s, 1 H), 4.1 (s, 4 H), 1.8 (q, 2 H, J = 7 Hz), 0.9 (t, 3 H, J = 7 Hz); mass spectrum, m/z 237 (M^+), 236, 208, 141, 125, 96, 77 (100), 68. Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90. Found: C, 60.77; H, 6.40; N, 6.00.

3-Benzyl-1-(phenylsulfonyl)-3-pyrroline (2e). The same procedure as described above but with **1e** gave **2e** (97%): mp 82–84 °C; IR (KBr) 3080, 3050, 2970, 2930, 2880, 1615, 1460, 1340, 1165, 1095, 760, 750, 690, 630, 585 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.0–6.9 (m, 9 H), 5.2 (s, 1 H), 4.0 (s, 4 H), 3.2 (s, 2 H); mass spectrum, m/z 299 (M^+, 100), 208, 158, 141, 131, 115, 91, 77. Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.00; H, 5.77; N, 4.61.

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A Simple Route to (2*R*,3*R*,5*E*)-2-Hydroxy-3-methyl-5-heptenal: A Key Intermediate for MeBmt†

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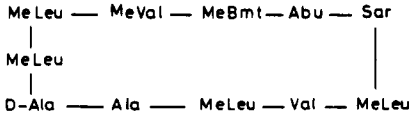
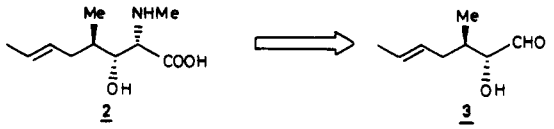
The efficacy of any synthetic protocol to the potent immunosuppressive agent, cyclosporine[1] (1), would largely depend on how efficiently large quantities of the unnatural β-hydroxy-α-amino acid, (4*R*)-4-[(*E*)-2-butenyl]-4,*N*-dimethyl-L-threonine (MeBmt) (2), present in the molecular structure of 1, are made available. Many synthetic routes to 2 have been reported.[2] The synthesis of 2 reported by Wenger,[2g] involving the highly stereocontrolled transformation of the key intermediate 3 into 2, is particularly interesting. However, the synthesis of 3 from diethyl (+)-tartrate required 18 steps including protecting–deprotecting of functional groups. Consequently we felt that an alternative but simple approach toward 3 could be derived, based on our[3a] findings that Sharpless epoxidation[3b] of 1-(benzyloxy)-3-buten-2-ol proceeds with a degree of efficiency.



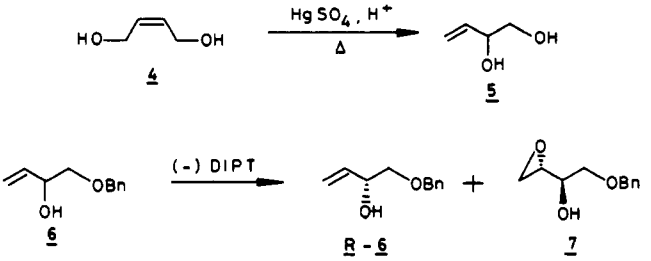
Cyclosporine 1



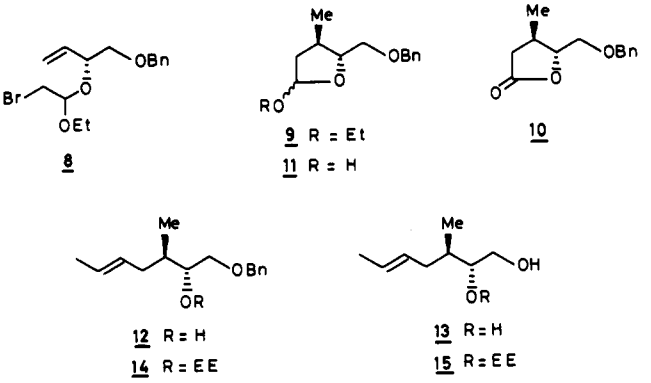
2 3

The starting material (5) was earlier prepared[3a] in our laboratory by one-step isomerization of *cis*-butene-1,4-diol (4) in the presence of catalytic amounts of mercuric sulfate and sulfuric acid in refluxing water for 1.5 h (Scheme I). Interestingly, now we observed that this isomerization could be more conveniently and rapidly effected in a microwave oven[4] in just 3 min (temperature of reaction mixture was ~50 °C), providing 5 in 60–70% yield. How the rate of the above rearrangement is enhanced by microwave irradiation could not reasoned with any proper explanation. However, we believe that due to high dielectric constant, water absorbs high microwave energy and being one of the reactants taking part in the reaction, concomitantly transfer this energy to the transition state to effect further reaction to occur rapidly.[5]

Scheme I



Scheme II



The kinetic resolution of the derived benzyl ether 6 (70%) under Sharpless condition[3,6] with (–)-diisopropyl tartrate (DIPT) as a chiral auxiliary led to the isolation of (*R*)-1-(benzyloxy)-3-buten-2-ol (*R*-6) (75% of theoretical yield, 95% ee)[3b] and (2*S*,3*S*)-1-(benzyloxy)-3,4-epoxybuten-2-ol (7).

Stork[7] and Ueno[8] have demonstrated that mixed bromo acetals derived from the allylic alcohols undergo stereoselective radical cyclization to form the *trans*-tetrahydrofuran derivative. Thus, compound *R*-6 was converted into the bromo acetal derivative 8 by the reaction with

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ethyl vinyl ether and *N*-bromosuccinimide at 0 °C. Subsequent treatment of **8** with freshly prepared tri-*n*-butyltin hydride containing azobisisobutyronitrile (AIBN) as catalyst in benzene at 65 °C for 4 h gave **9** in 70% yield. By adopting Grieco's procedure,[9] compound **9** was converted in one step into the γ-lactone **10**, which was fully characterized (Scheme II).

Hydrolysis of **9** with 3 N sulfuric acid afforded the hemiacetal **11**, which on Wittig reaction with ethyltriphenylphosphonium bromide by employing Schlosser's conditions[2a,10] gave the *E* olefin **12** in 61% yield. Removal of the benzyl group furnished the known diol **13**.[2g] Alternatively compound **12** was protected as ethoxyethyl derivative (**14**) by reacting with ethyl vinyl ether and pyridinium *p*-toluenesulfonate (PPTS) followed by hydrogenolysis with Li/NH_3 to afford **15**. Compound **15** was transformed[2g] into the key intermediate **3**.

Experimental Section

^1H nuclear magnetic resonance spectra were recorded at 80 or 90 MHz in $CDCl_3$. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co. (India). Thin-layer chromatography was performed on Merck 60 F-254 silica gel plates. Solvents were distilled before use, and petroleum ether refers to bp 60–80 °C. The microwave reaction was performed on Batliboi-Eddy microwave oven with power settings 1–7.

(±)-3-Butene-1,2-diol (5). A mixture of 6.00 g (68.1 mmol) of *cis*-butene-1,4-diol (**4**), 25 mg of mercuric sulfate, 0.035 g of concentrated H_2SO_4, and 2.5 mL of water was kept in a microwave oven with power setting at 1 for 3 min (temperature ca. 50 °C). After usual[3a] workup, 4.0 g (66%) of **5** was isolated by fractional distillation (bp 78–90 °C/15 mm).

(2*RS*,4*R*,5*R*)-5-[(Benzyloxy)methyl]-2-ethoxy-4-methyltetrahydrofuran (9). *N*-Bromosuccinimide (2.93 g, 16.45 mmol) was added to a solution of 2.50 g (14.04 mmol) of *R*-**6** and 1.30 g (18.05 mmol) of ethyl vinyl ether in 25 mL of CH_2Cl_2 at −10 °C. The mixture was stirred at 0 °C and filtered, and the filtrate was successively washed with 5% KOH and water, dried (Na_2SO_4), and concentrated to afford 3.80 g (82%) of **8** as an oil.

To a solution of 2.50 g (7.60 mmol) of **8** and a catalytic amount of azobisisobutyronitrile (AIBN) in dry benzene at 65 °C under nitrogen was added 2.21 g (7.60 mmol) of tri-*n*-butyltin hydride. The reaction was maintained at 65 °C for 4 h and then concentrated. The residue was purified by column chromatography on silica gel with low-boiling petroleum ether as eluent to give 1.33 g (70%) of **9** as an oil: ^1H NMR (80 MHz) δ 0.9–1.8 (m, 1 H), 2.1 (m, 2 H), 2.9–4.0 (m, 3 H), 4.52 (s, 2 H), 5.0 (m, 1 H), 7.25 (s, 5 H).

(4*R*,5*R*)-5-[(Benzyloxy)methyl]-3-methyltetrahydrofuran-2(3*H*)-one. A soluton of 0.217 g (0.868 mmol) of **9**, a catalytic amount of $BF_3{\cdot}OEt_2$, and 0.18 g (1.04 mmol) of *m*-chloroperbenzoic acid in 5 mL of CH_2Cl_2 was stirred at room temperature for 3 h. After workup, the crude product was purified on silica gel with ethyl acetate–petroleum ether (1:9) as eluent to give 0.155 g (81%) of **10** as a oil: $[\alpha]_D$ −16.7° (*c* 2.45, $CHCl_3$); ^1H NMR (80 MHz) δ 1.15 (d, 3 H, *J* = 6.5 Hz), 2.05–3.0 (m, 3 H), 3.85 (m, 2 H), 4.20 (m, 1 H), 4.50 (s, 2 H), 7.25 (s, 5 H); mass spectrum *m/z* 220 (M^+). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.27. Found: C, 70.7; H, 7.12.

(2*R*,3*R*,5*E*)-1-(Benzyloxy)-3-methyl-5-hepten-2-ol (12). A solution of 1.20 g (4.8 mmol) of **9**, 15 mL of methanol, and 4 mL of 3 N H_2SO_4 was stirred at room temperature for 12 h, neutralized with $BaCO_3$, and filtered through Celite. The filtrate was concentrated to give 0.92 g (86%) of **11**.

To a solution of 2.52 g (6.8 mmol) of ethyltriphenylphosphonium bromide in 20 mL of THF-OEt_2 (3:5) was added 2 mL of *n*-BuLi in hexane (2.8 M) at −70 °C. After 0.5 h, 0.85 g (3.82 mmol) of **11** dissolved in 5 mL of ether was introduced followed by the addition of 0.8 mL of *n*-BuLi. The reaction mixture was warmed to −30 °C at which 0.28 mL of *tert*-butyl alcohol and 0.43 g of potassium *tert*-butoxide were added. After being stirred at room temperature for 1.5 h, the solution was poured over water. The aqueous layer was repeatedly extracted with ether, and then combined extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with ethyl acetate–petroleum ether (1:9) as eluent to give 0.54 g (61%) of **12**, homogeneous on silver nitrate impregnated silica gel: TLC, $[\alpha]_D$ −4.5° (*c* 1.85, $CHCl_3$); ^1H NMR (90 MHz) δ 1.0 (d, 3 H, *J* = 7 Hz), 1.65 (d, 3 H, *J* = 5.3 Hz), 1.7–2.5 (m, 3 H), 2.35 (d, 1 H, D_2O exchangeable), 3.8 (m, 1 H), 3.95 (m, 2 H), 4.5 (s, 2 H), 5.75 (m, 2 H), 7.25 (s, 5 H). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.92; H, 9.40. Found: C, 76.76; H, 9.02.

(2*R*,3*R*,5*E*)-2-(1-Ethoxyethoxy)-3-methyl-5-hepten-1-ol (15). A solution of 0.45 g (1.92 mmol) of **12**, 140 mg of ethyl vinyl ether, and a catalytic amount of PPTS in 15 mL of CH_2Cl_2 was stirred at 0 °C for 2 h. The reaction mixture was concentrated to give 0.56 g (95%) of the crude **14**.

A solution of 0.306 g (1 mmol) of crude **14** in 10 mL of ether was added to 50 mL of condensed ammonia; 14 mg of lithium metal was added, and after 1 h solid NH_4Cl was introduced. The ammonia was allowed to evaporate, and the residue was partitioned between ether and water. The ethereal layer was dried (Na_2SO_4) and concentrated. The residue was purified on silica gel with ethyl acetate–petroleum ether (1:9) as eluent to give 0.18 g (83%) of the known **15**. The spectral properties of **15** are consistent with the reported values.[2g]

(2*R*,3*R*,5*E*)-3-Methyl-5-heptene-1,2-diol (13). The debenzylation of 0.20 g (0.85 mmol) of **12** was carried out with Li/NH_3 as described above to afford 0.10 g (81%) of **13**, as an oil: $[\alpha]_D$ −5.13° (*c* 0.9, $CHCl_3$) (lit.[2g] $[\alpha]_D$ −5.7° ($CHCl_3$)).

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An Improved and Practical Method for the Synthesis of Optically Active Diethyl Tartrate Dibenzyl Ether

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Tartaric acid (**1a**) is one of the most useful chiral building blocks of asymmetric synthesis.[1] Although methods for the preparation of tartrate derivatives having the two hydroxy groups protected by cyclic acetals have been developed,[2] protection by *O*-benzyl groups, which are more stable than acetals under acidic conditions, is not easily effected. It was believed that protection of the secondary alcohol groups of **1** with alkyl halides via alkoxy anions under strongly basic conditions would be accompanied by racemization of the two chiral centers or by elimination of the resulting alkoxy groups. To overcome this difficulty, Seeback and co-workers developed[3] a thallium alkoxide reagent for the protection of the hydroxy groups. However, a major drawback of this reagent is its severe toxicity and high price.

We now report a practical method for the large-scale preparation of the dibenzyl ether **2** using sodium hydride, tetrabutylamminoum iodide, and a catalytic amount of 18-crown-6 (Scheme I). The tartrate **1b** was deprotonated with slightly less than 2 equiv of sodium hydride at 0 °C in anhydrous tetrahydrofuran (THF). The resulting suspension was stirred for 30 min until evolution of hydrogen

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