Enantioselective Synthesis of (4*S*,*E*)-4-Methylhex-2-enoic Acid and (4*R*,*E*)-4-Methylhex-2-enoic Acid

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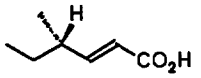
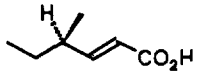
(+)-(4*S*,*E*)-4-Methylhex-2-enoic acid [(+)-**1**][1] is the key constituent of the peptide antibiotics leucinostatines possessing antibiotic, antitumoral, antibacterial and phytotoxic activities. Three syntheses have been reported[2] for (+)-**1**. In connection with our research programs to utilize optically active carbonates and sulfites as activating groups,[3] we were interested in the synthesis of (+)-**1**. Here we report an enantioselective synthesis of (+)-**1** and its enantiomer (−)-**1** based on S_N2' addition of organocuprates to chiral allylic cyclic carbonates.



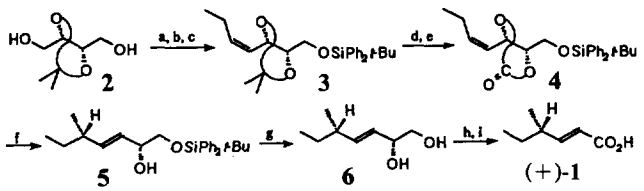
(+)-1



(-)-1

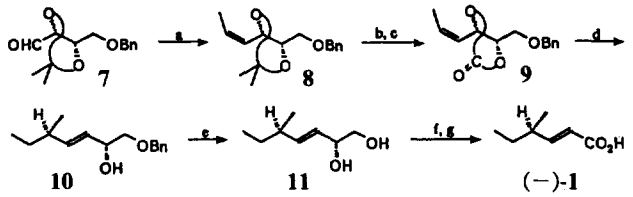
The acetonide **3**[4] was prepared from (2*S*,3*S*)-2,3-*O*-isopropylidenedioxy-1,4-butanediol **2**[5] in a three-step sequence *via* monosilylation, Swern oxidation[6] and Wittig olefination reaction. Deprotection of the acetonide followed by carbonylation with carbonyl diimidazole afforded the allylic cyclic carbonate **4**. Highly diastereoselective (>99%) S_N2' addition of **4** with MeMgBr, CuI (3 mol%), and $BF_3 \cdot Et_2O$ afforded the allylated compound **5**[4], which constitute the key step for the introduction of chirality. The diastereoselection was determined by NMR spectroscopy with a chiral shift reagent [^{1}H-NMR, 300 MHZ, chiral Eu(tfc)$_3$]. The exclusive (*E*)-stereochemistry was judged by ^{1}H-NMR (300 MHz) coupling constants of the two vinyl protons. Deprotection of the silyl group in **5** gave the diol **6**[4], which was transformed into the target compound, (+)-**1**[5], $[\alpha]_D^{25} = +47.8$ (*c* 0.12, $CHCl_3$), (lit.[1b] $[\alpha]_D^{20} = +49.7$) by oxidative cleavage with $NaIO_4$ followed by $NaClO_2$ oxidation (Scheme 1).

Alternatively, the enantiomer (−)-**1** was also synthesized



a) NaH, *t*-BuPh$_2$SiCl, DME, −20℃, 3 h (91%); b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78℃, 1 h (91%); c) *n*-BuLi, $Ph_3P^+CH_2CH_2CH_3Br^-$, THF, −78℃, 10 h (63%); d) 70% AcOH, 40℃, 5 h (89%); e) $CO(Im)_2$, CH_2Cl_2 rt, 10 min (93%); f) MeMgBr (2 equiv), CuI (3 mol%), $BF_3 \cdot Et_2O$ (1 equiv), THF, −78℃, 30 min (87%); g) (*n*-Bu)$_4$NF, THF, rt, 2 h (96%); h) $NaIO_4$, SiO_2, CH_2Cl_2, 1 h (89%); i) $NaClO_2$, *t*-BuOH, NaH_2PO_4, rt, 8 h (68%).

Scheme 1.



a) *n*-BuLi, $Ph_3P^+CH_2CH_2CH_3Br^-$, THF, −78℃, 10 h (75%); b) Dowex 50 W X 8 resin, MeOH, 45℃, 6 h (92%); c) $CO(Im)_2$, CH_2Cl_2, rt, 10 min (84%); d) EtMgBr (2 equiv), CuI (3 mol%), $BF_3 \cdot Et_2O$ (1 equiv), THF, −78℃, 30 min (75%); e) Na, NH_3 (1), THF, −78℃, 3 h (91%); f) $NaIO_4$, SiO_2, CH_2Cl_2, 1 h (90%); g) $NaClO_2$, *t*-BuOH, NaH_2PO_4, rt, 8 h (67%).

Scheme 2.

from 4-*O*-benzyl-2,3-isopropylidene-L-threose **7**[5b] by the similar methodology, which is shown in Scheme 2.

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References and Notes

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4. Satisfactory spectral and physical data were obtained for all new compound and are in accord with the assigned structure. Selected spectral data are as follows. (+)-**1**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H), 1.05 (d, 3H), 1.45 (m, 2H), 2.22 (m, 1H), 5.80 (d, 1H, J=16 Hz), 6.89 (dd, 1H, J=16.8 Hz), 12.25 (s, 1H). IR (neat) 3600-2400, 1685, 1640 cm^{-1}. $[\alpha]_D^{25} = +47.8$ (*c* 0.12, $CHCl_3$) (−)-**1**: $[\alpha]_D^{25} = -47.2$ (*c* 0.14, $CHCl_3$) **5**: TLC; SiO_2, EtOAc/hexane 1 : 3, R_f=0.71. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.82 (t, 3H, J=7.5 Hz), 0.96 (d, 3H, J=6.9 Hz), 1.08 (s, 9H), 1.26 (m, 2H), 2.05 (m, 1H), 3.56 (m, 1H), 3.65 (m, 1H), 4.20 (m, 1H), 5.35 (dd, 1H, J=15.5, 6.5 Hz), 5.62 (dd, 1H, J=15.5,

7.5 Hz), 7.38-7.46 (m, 6H), 7.67-7.70 (m, 4H). IR (neat) 3400, 3050, 2950 cm^{-1}, $[\alpha]_D^{25}=+8.0$ (*c* 0.15, $CHCl_3$). MS (m/e) 325 (M-*t*Bu), 269, 247, 199 (base peak), 181, 139, 135, 109, 57. **6**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.85 (t, 3H), 0.95 (d, 2H), 1.25-1.34 (m, 6H), 2.05 (m, 1H), 3.50 (m, 1H), 3.65 (m, 1H), 4.22 (m, 1H), 5.40 (dd, 1H), 5.65 (m, 1H). IR (neat) 3300, 2950 cm^{-1}, $[\alpha]_D^{25}=+1.82$ (*c* 0.17, $CHCl_3$). **10**: TLC; SiO_2, EtOAc/hexane 1 : 5, $R_f=0.33$, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86 (t, 3H, *J*=7.5 Hz), 0.97 (d, 3H, *J*=6.9 Hz), 1.27-1.37(m, 1H), 3.57 (dd, 1H, *J*=11.4, 7.8 Hz), 3.69 (dd, 1H, *J*=10, 3.6 Hz), 4.22 (m, 1H), 4.58 (s, 2H), 5.38 (ddd, 1H, *J*=15.5, 6.6, 1 Hz), 5.65 (ddd, 1H, *J*=15.5, 6.6, 1 Hz), 7.35 (s, 5H). **11**: $[\alpha]_D^{24}=-39.8$ (*c* 3.0, $CHCl_3$).

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Synthesis of Steroidal Cyclophosphamide, 2-Bis (2-chloroethyl)amino-2-oxo-6-(5α-cholestanyl)-1, 3,2-oxazaphosphorinane

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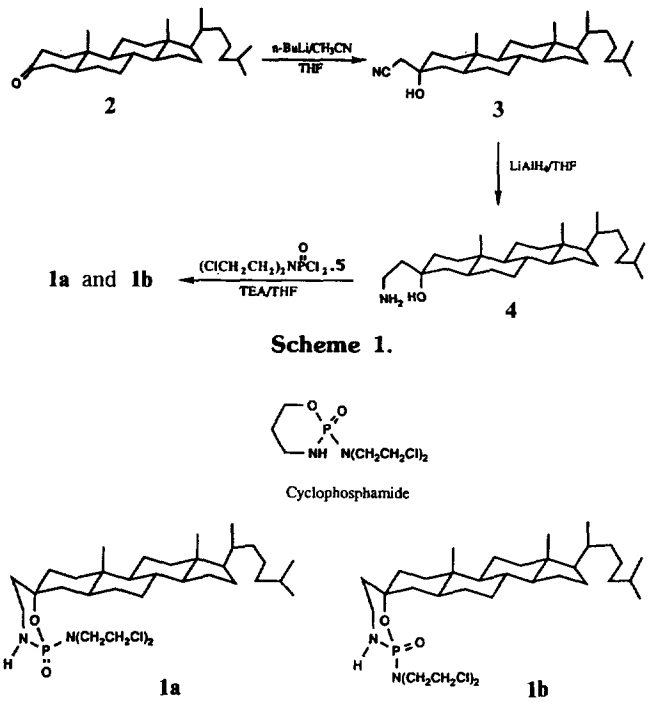
Cyclophosphamide and its analogues are important clinical agents in the treatment of cancer.[1] We have prepared steroidal cyclophosphamides (**1a** and **1b**). The approach used for the synthesis of **1a** and **1b** is outlined in Scheme 1. Treatment of cholestanone (**2**) with *n*-butyllithium and acetonitrile gave a 72.5% yield of β-hydroxynitrile derivative **3**[2], which was subsequently reacted with $LiAlH_4$ to give aminoethyl derivative **4**.[3] Cyclization of **4** with bis(2-chloroethyl)phosphoramidic dichloride (**5**) in the presence of 2 equiv. of Et_3N afforded crude mixtures of **1a** and **1b**, which were chromatographed on silica gel with EtOAc : CH_2Cl_2 : hexane = 2 : 2 : 1 to give analytically pure crystals of the faster (mp. 192-194℃) and slower (mp. 178-180℃) eluting diastereomers of **1a** and **1b** in 58% yield. Assignment of cyclophosphamide structures to the faster and slower eluting diastereomeric cyclization products has been suggested by the IR, ^{1}H-NMR, ^{31}P-NMR[4], and ^{13}C-NMR.

Our measurements of **1a** and **1b** indicated the ^{1}H-NMR chemical-shift difference between the NH resonances at 2.73 and 2.50 ppm for the faster and slower eluting diastereomers of **1a** and **1b**, respectively. The substantial deshielding (0.23 ppm) of N-H proton thus exhibited by the faster moving



Scheme 1.

compound **1a**, suggests more efficient intramolecular H-bonding to the adjacent P=O functionality. This difference in H-bonding was also founded in ^{13}C-NMR by the deshielding of chemical shift[41.9 ppm (-NH-CH_2-)] in the proposed **1a**, as opposed by the shielding of chemical shift [36.0 ppm (-NH-CH_2-)] in the proposed **1b**. These compounds may have a greater impact as anticancer agents by their lipophilicity. Compounds **1a** and **1b** were found no activity against Hepatoma cells[5].

Experimental

3-Cyanomethyl-5α-cholestan-3-ol (3). To a stirred solution of 1.6 M *n*-butyllithium in 9.5 m*l* (15 mmol) hexane, at −80℃ under nitrogen, was rapidly added a solution of 0.82 m*l* (15 mmol) of acetonitrile in 30 m*l* of anhydrous THF. After stirring for 1 hr, the resulting white suspension was treated with a solution of 3.0 g (7.5 mmol) **2** in 10 m*l* of THF. The cold-ice bath was removed and stirred for additional 10 min before it was poured into ice-water hydrochloric acid. The aqueous layer was extracted with three 50 m*l* portions of Et_2O. The combined ether extracts were dried($MgSO_4$) and evaporated in vaccuo, and the residual crude product was chromatographed on silica gel with CH_2Cl_2 as an eluent, and obtained 2.4 g (73% yield) of white solids. mp. 158-159 ℃; ^{1}H-NMR ($CDCl_3$) δ 2.6 (s, 2H, -CH_2CN), 0.6-2.0 (m, H steroid); IR (KBr) 3480 (-OH), 2930, 2255 (-CN), 1460, 1370, 1080, 1050 cm^{-1}.

3β-Aminoethylene-5α-cholestan-3-ol (4). To a stirred solution of 1.7 g (3.9 mmol) of **3** in 150 m*l* of anhydrous THF was added in small portions, 0.75 g (19.5 mmol) of lithium aluminum hydride. The mixture was refluxed with stirring for 17 hrs. After decomposing excess lithium aluminum hydride with 0.75 m*l* water and 2.3 m*l* of 20% NaOH, the mixture was filtered and filtrate was evaporated in vaccuo to obtain yellow oily residues (45% yield). All attempts

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