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SYNTHESIS of (4R)-4-((E)-2-BUTENYL)-4,N-DIMETHYL-L-THREONINE (MeBMT), THE CHARACTERISTIC AMINO ACID OF CYCLOSPORINE[1]

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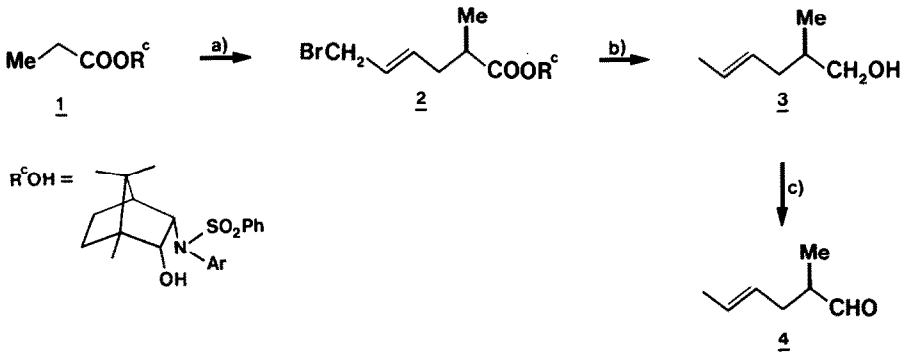
Summary: Aldol condensation of (2R,4E)-2-methyl-4-hexanal 4 with the lithium enolate of N,N,O-tris(trimethylsilyl)glycine produces exclusively the two erythro-isomers 5 and 6 (75:25), which are separated by medium pressure chromatography. Each diastereomer is transformed separately with complete Walden inversion into the oxazolines 9 and 10, which are N-methylated, reduced and hydrolyzed to give MeBmt 15 and its diastereomer 16, respectively.

The immunosuppressive cyclopeptide cyclosporine contains N-methylvaline, N-methylleucine, and MeBmt als "non-protein" amino acids. In the course of his synthesis of cyclosporine, R.M.Wenger prepared MeBmt in 24 steps starting from tartaric acid[2]. A few month ago, D.A.Evans described the preparation of MeBmt by means of an aldol condensation of a chiral isothiocyanoacetyl-oxazolidinone with chiral (2R,4E)-2-methyl-4-hexenal 4 under conditions of "double stereodifferentiation" using the tin triflate technique[3]. A recent synthesis by D.H.Rich utilized Sharpless' asymmetric epoxidation of (2E,5E)-heptadien-1-ol but required more steps than Evans' and our route and gave a product of only 94% ee through crystallization of a key intermediate[4].

In this communications we report a further total synthesis of MeBmt. In the key step, the two asymmetric centers at the 2- and 3-positions are formed from the chiral aldehyde 4 by exploitation of "Cram" control and the known erythro-selectivity of trisilylated glycines in aldol condensations[5]. Although the high diastereoselectivity of Evans' synthesis is not achieved, the starting material is more readily accessible and the reaction is considerably more simple to perform. The method requires only one chromatographic separation and leads directly to an N,O-protected derivative 12a,b that is suitable for use in further peptide syntheses. This sequence avoids the incomplete[4] epimerization of an oxazolidinone derivative used in the other syntheses[2,3,4].

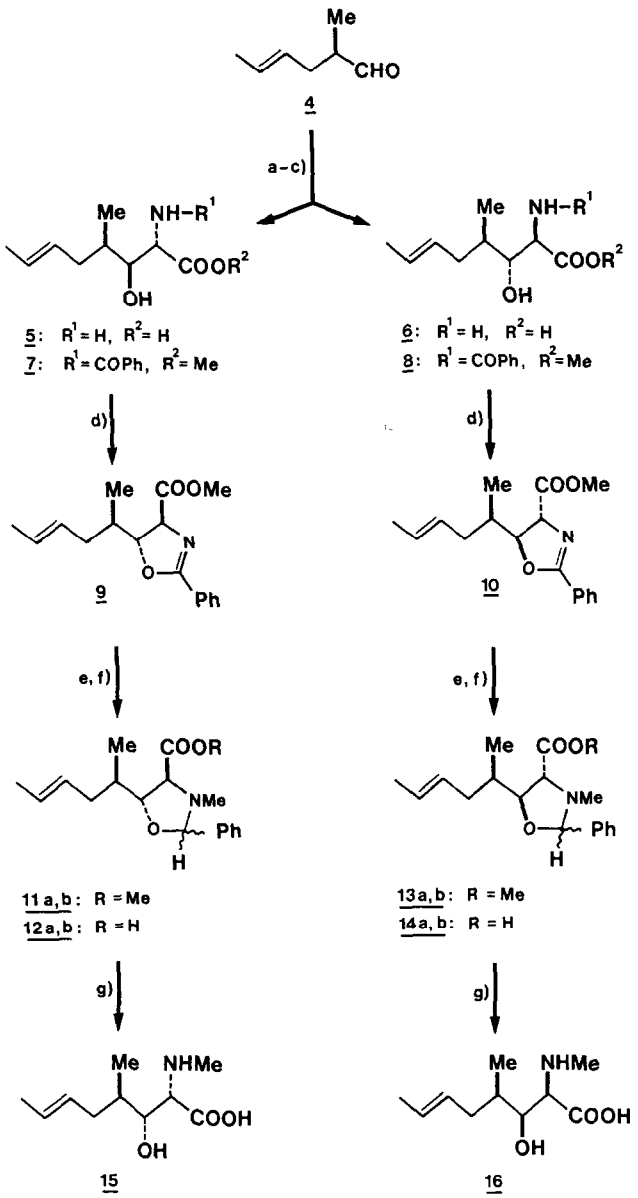
The aldehyde 4 was prepared according to G.Helmchen's method[6] as follows. The chiral propanoate 1 is enantioselectively alkylated by trans-1,4-dibromo-2-butene to give the (2R,4E)-6-bromo-2-methyl-4-hexenoate 2 (76% yield, 92% ee (HPLC)). The desired isomer is obtained in optically pure form after a single recrystallization (≥ 99% ee, (HPLC,NMR))[7]. Subsequent reduction of 2 with $LiAlH_4$ furnishes the alcohol 3 (97% yield) in one step and this is oxidized to the aldehyde 4 (91% yield) by Swern's method[8].



Scheme 1
a) 1 eq $LiN(i\text{-}C_3H_7)(c\text{-}C_6H_{11})$/THF/1 h, -80°C//3 eq $BrCH_2\text{-}CH{=}CH\text{-}CH_2Br$/ 4 h, -50° → -40°C//quenched with NH_4Cl/H_2O/-40°C; b) $LiAlH_4/Et_2O$/1 h/ 0°C; c) $(COCl)_2$/DMSO/NEt_3/-78°//1 h/-30°C

Aldol condensation of the aldehyde 4 with the lithium enolate of N,N,O-tris-(trimethylsilyl)glycine[9] finally produces the two erythro-isomers 5 and 6 exclusively (75:25, (HPLC)). The N-benzoyl methyl esters 7 and 8 of the latter can be separated easily by preparative medium pressure chromatography. Reaction of 7 with $SOCl_2$ leads to the oxazoline derivative 9 with inversion at C-3. The coupling constants of the protons H(C-4) and H(C-5) confirm the trans orientation of the substituents on the ring[10].

After N-methylation of 9 with methyl triflate and reduction of the resultant oxazolinium salt with $NaBH_4$, a 4:1 mixture of the oxazolidines 11a,b which are epimeric at position 2, is obtained. Weakly basic saponification of the ester functions in 11a,b gives rise to the stable half aminals 12a,b that can be used directly in peptide synthesis. Acid hydrolysis of 12a,b yields free MeBmt 15 (46% yield from 4). The previously not reported (2S,3S,4R)-MeBmt diastereomer 16 is obtained analogously from 6 (12% yield from 4). Data for compounds 3, 4 and 15 are in full agreement with those reported in literature[2,3,4]. All new compounds gave satisfactory spectral and analytical data[11].



Scheme 2

a) 2 eq LDA/THF/2 eq $(Me_3Si)_2N\text{-}CH_2\text{-}COOSiMe_3$/1 h, -78°C//1 eq 4/-78°C → 0°C, 12 h//HCl/EtOH/pH 3/5 min//pH 7. b) dioxane/H_2O = 1:1/2.5 eq $NaHCO_3$/2.1 eq PhCOCl/4 h/r.t.//evaporation to dryness/EtOAc extraction; c) MeOH/CH_2NH_2 (4 → 7,8, 68% yield); d) 7, 0.1 M in CH_2Cl_2/10 eq $SOCl_2$/0°/10 h, (96% yield); e) $CH_2Cl_2/MeOSO_2CF_3$/4 h/r.t. (quantitative)//EtOH abs./1 eq $NaBH_4$/1h/r.t.// phosphate buffer pH 8//EtOH evaporation//Et_2O extraction (11a,b 95% yield); f) 0.1 M in MeOH/1.05 eq 1N NaOH/4 h/r.t.; g) MeOH/1 N HCl/pH 5/30 min/r.t. (11a,b → 15, 98% yield)

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Notes and references

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11 ^{1}HNMR data (300 MHz, $CDCl_3$) if not otherwise indicated.
3: δ = 0.82 (s,3H), 0.83 (s,3H), 1.03 (s,3H), 1.07-1.15 (m,1H), 1.31 (d, 3H,J=7Hz), 1.7-1.76 (m,1H), 1.83-1.85 (m,1H), 2.07 (s,3H), 2.21-2.3 (m,2H), 2.3 (s,3H), 2.51-2.64 (m,2H), 3.95 (d,2H,J=6.6Hz), 4.20 (dd,1H, J=3.3, 8.7Hz), 5.38 (d,1H,J=8.7Hz), 5.79-5.84 (m,2H), 5.96 (br s,1H), 6.85 (br s, 1H), 6.97 (br s,1H), 7.28-7.4 (m,3H), 7.49-7.55 (m,1H). $[\alpha]_D^{20}$ = +1.79° (c = 11.8, CH_2Cl_2).
7: δ = 0.98 (d,3H,J=6.7Hz), 1.65 (dd,3H,J=0.8,5.8Hz), 1.66-1.76 (m,1H), 1.89-2.02 (m,1H), 2.17-2.24 (m,1H), 3.38 (br,1H), 3.67-3.8 (1H), 3.75 (s, 3H), 4.97 (dd, 1H,J=4.1,8.1Hz), 5.34-5.51 (m,2H), 7.26 (d,1H,J=8.1Hz), 7.36-7.51 (m,3H), 7.78-7.82 (m,2H). $[\alpha]_D^{20}$ = +32.9° (c = 0.9, CH_2Cl_2).
8: δ = 0.99 (d,3H,J=6.7Hz), 1.65 (d,3H,J=4.9Hz), 1.67-1.76 (m,1H), 1.91-2.03 (m,1H), 2.32-2.39 (m,1H), 3.24 (br,1H), 3.67 (dd,1H,J=2.8,9.3Hz), 3.79 (s,3H), 4.97 (dd,1H,J=2.8,7.5Hz), 5.36-5.54 (m,2H), 7.27 (d,1H,J= 7.5Hz), 7.31-7.54 (m,3H), 7.8-7.84 (m,2H). $[\alpha]_D^{20}$ = -37.8° (c = 1, CH_2Cl_2).
9: δ = 0.93 (d,3H,J=5.6Hz), 1.66 (dd,3H,J=0.9,5.8Hz), 1.86-2.04 (m,2H), 2.23-2.3 (m,1H), 3.8 (s,3H), 4.59 (d,1H,J=7.1Hz), 4.75 (dd,1H,J=6.5,7.1Hz), 5.38-5.53 (m,2H), 7.37-7.52 (m,3H), 7.97-8.01 (m,2H). $[\alpha]_D^{20}$ = +110.4° (c = 2.89, CH_2Cl_2).
10: δ = 0.97 (d,3H,J=6.7Hz), 1.65 (dd,3H,J=1.0,5.8Hz), 1.74-1.89 (m,1H), 1.91-2.01 (m,1H), 2.15-2.25 (m,1H), 3.79 (s,3H), 4.60 (d,1H,J=7.1Hz), 4.81 (dd,1H,J=5.3,7.1Hz), 7.37-7.52 (m,3H), 7.96-8.01 (m,2H). $[\alpha]_D^{20}$ = -142.5° (c = 0.92, CH_2Cl_2).
16 (D_2O): δ = 0.96 (d,3H,J=6.6Hz), 1.67 (d,3H,J=6.1Hz), 1.68-1.78 (m, 1H), 1.96-2.14 (m,2H), 2.75 (s,3H), 3.58 (d,1H,J=8.6Hz), 3.82 (dd,1H,J= 3.3,8.6Hz), 5.42-5.65 (m,2H). $[\alpha]_D^{20}$ = +9.2° (c = 0.56, pH 7 phosphate buffer).

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