Total Synthesis of the Archaebacterial C_{40}-Diol and its Enantiomer Based on(*R*)-5-Acetoxy-4-methylpentanoic Acid

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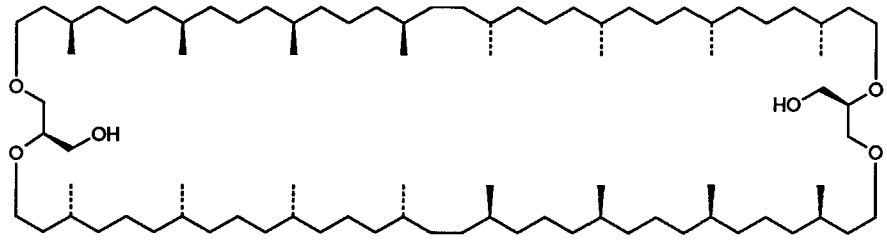
Optically pure archaebacterial C_{40}-diol **2a** and its enantiomer **2b** have been synthesized in 17 steps and *ca.* 2% overall yield using a readily available (*R*)-5-acetoxy-4-methylpentanoic acid as the single chiral building block.

The so-called 'archaebacterial C_{40}-diol' **2a** with eight chiral centres is a key structural component of the diglyceryl tetraether **1**, a common lipid constituent in the thermoacidophiles and methanogenes.[1] The absolute (3*R*, 7*R*, 11*S*, 15*S*, 18*S*, 22*S*, 26*R*, 30*R*)-configuration of the natural diol **2a** has been established by Heathcock's total synthesis realized in 30 steps and 0.4% overall yield. [1,2] For the creation of the desired chirality he used an 'aldol-Claisen strategy' including aldol reaction of α,β-unsaturated aldehydes with Evans chiral enolates and subsequent Ireland–Claisen rearrangement of the allylic esters which resulted in 1,5-stereoselection. The same approach was also employed for the synthesis of the (15*R*, 18*R*)-diastereoisomer of **2a**.[2] Here we report a total synthesis of the natural C_{40}-diol **2a** and a (3*S*, 7*S*, 11*R*, 15*R*, 18*R*, 22*R*, 26*S*, 30*S*)-enantiomer **2b** based on the single chiral building block, easily available (*R*)-5-acetoxy-4-methylpentanoic acid **3**,[3] which has already been used by us in the preparation of some methyl-branched biologically-active compounds.[4,5]



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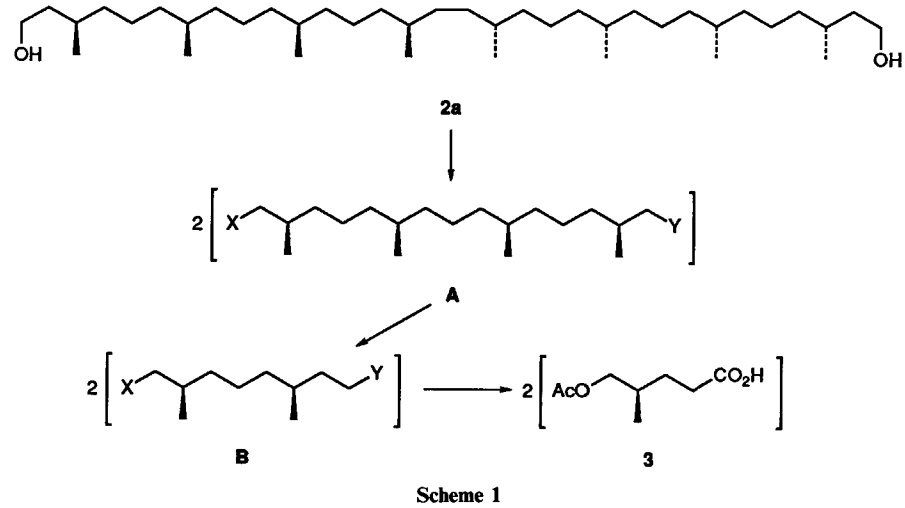
Retrosynthetic analysis of a C_2-symmetric molecule **2a** (Scheme 1) demonstrates the possibility of its construction by coupling of two (nor)diterpenoid units **A**, which, in turn, can be prepared from two monoterpenoid fragments **B**. The latter can apparently be presented as a combination of two molecules of **3**.

A similar consideration for the enantiomer **2b** (Scheme 2) shows an even simpler synthetic plan based on the same acetoxyacid **3** by sequential creation of mono- and diterpenoid fragments **D** and **C** of this molecule.

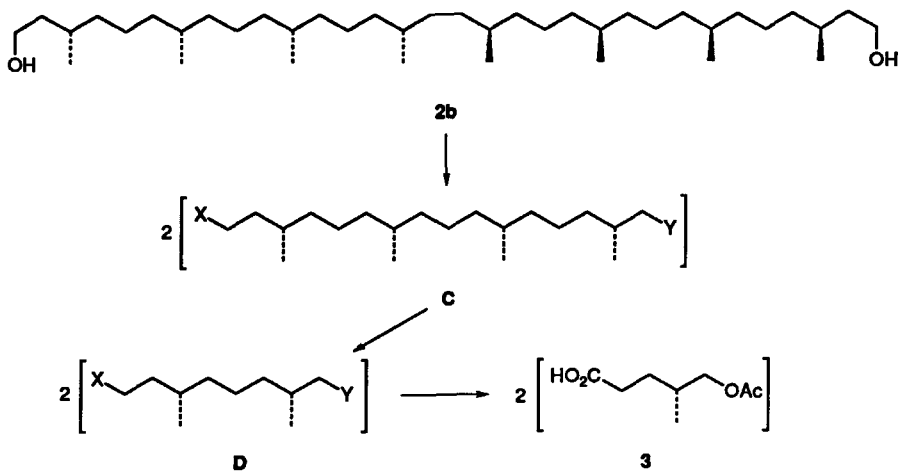
For the synthesis of the isomer **2a** (Scheme 3) the acid **3** was initially transformed into the known monochiral C_5-bromides **4**[4] and **5**.[6] Coupling of the latter with the Grignard reagent, prepared from **4**, in the presence of dilithium tetrachlorocuprate[7] smoothly led to the monoterpenoid acetate **6**‡, which can be easily converted to each of the C_{10}-components necessary for the preparation of the intermediate **A** in the retrosynthetic scheme. For this purpose, ester **6** was hydrolysed and the resulting alcohol **7** transformed into bromide **9** by standard method using *p*-toluenesulfonate **8**. In contrast, hydroboration–oxidation of olefin **6** gave the alcohol **10**, which was converted into bromoacetate **11** using carbon tetrabromide and triphenylphosphine. Dilithium tetrachlorocuprate-catalysed coupling of the bromoester **11** with the Grignard reagent derived from the bromide **9**, furnished the C_{20}-acetate **12**, with four centres, in high yield. Hydroboration–oxidation of the latter followed by Jones oxidation of the resulting alcohol **13** afforded the acetoxy



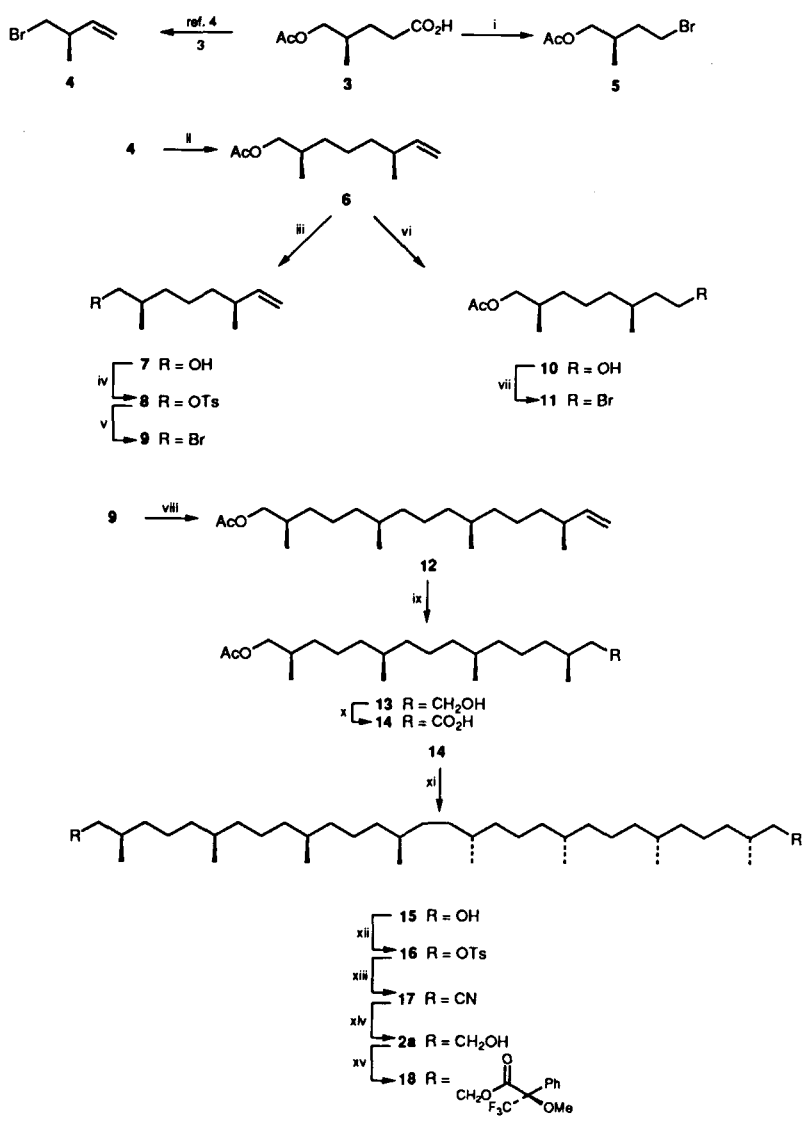
Scheme 1

† Professor Alexander Moiseenkov, Corresponding Member of the Russian Academy of Sciences, Renowned scientist and Butlerov Prize winner, died on the 1st November 1992.

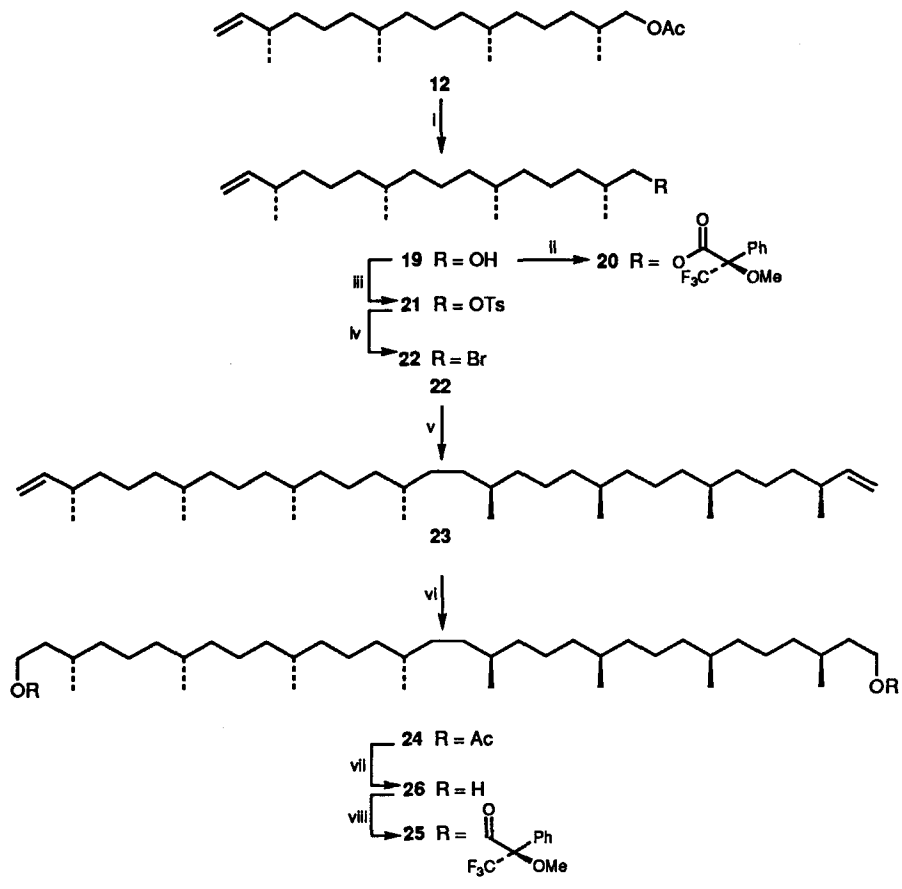
‡ All new compounds gave satisfactory spectroscopic and analytical data.



Scheme 2



Scheme 3 *Reagents and conditions*: i, HgO (red), Br_2, CCl_4, 65 °C, 1 h (81%); ii, Mg, Et_2O, then **5**, Li_2CuCl_4, THF, −70 → ~25 °C, 3 h (59%); iii, KOH, MeOH/H_2O, ~25 °C, 1 h (97%); iv, Ph_3CH, BuLi, Et_2O/HMPA, then TsCl, −20 → ~25 °C, 25 min; v, NaBr, DMF, 60 °C, 4 h (99% from **7**); vi, 9-BBN, THF, ~25 °C, 1 h, then AcONa, 30% H_2O_2, H_2O, 35 °C, 1 h (59%); vii, CBr_4, Ph_3P, Py, THF, ~25 °C, 24 h (82%); viii, Mg, THF, then **11**, Li_2CuCl_4, THF, −70 → ~25 °C, 3 h (69%); ix, 9-BBN, THF, ~25 °C, 1 h, then AcONa, 30% H_2O_2, H_2O, 35 °C, 1 h (82%); x, 4 mol dm^{-3} H_2CrO_4, Me_2CO, −10 °C, 1.5 h (96%); xi, e^-, MeONa, MeOH, ~ 25 °C, ~2 h, then KOH, ~25 °C, 30 min (70%); xii, TsCl, Py, $CHCl_3$, ~25 °C, 12 h; xiii, NaCN, DMSO, 60 °C, 12 h (64% from **15**); xiv, Bu^i_2AlH hexane, −40 → 0 °C, 30 min, then $LiAlH_4$, Et_2O, 0 °C, 30 min (69%); xv, (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA), DMAP, DCC, CH_2Cl_2, ~25 °C, 12 h (98%)



Scheme 4 *Reagents and conditions*: i, KOH, $MeOH/H_2O$, ~25 °C, 1 h (97%); ii, (*R*)-MTPA, DMAP, DCC, CH_2Cl_2, ~25 °C, 12 h (98%); iii, Ph_3CH, BuLi, Et_2O/HMPA, then TsCl, −20 → ~25 °C, 25 min; iv, NaBr, DMF, 60 °C, 6 h (98% from **19**); v, Mg, THF, then $AgNO_3$, ~25 °C, 10 h (74%); vi, 9-BBN, THF, ~25 °C, 1 h, then NaOH, 30% H_2O_2, H_2O, 35 °C, 1 h, then Py, Ac_2O, DMAP, CH_2Cl_2, ~25 °C, 2 h (59%); vii, KOH, $MeOH/H_2O$, ~25 °C, 2 h (100%); viii, (*R*)-MTPA, DMAP, DCC, CH_2Cl_2, ~25 °C , 12 h (99%)

acid **14**, which was subjected to Kolbe electrolysis to give C_{38}-diol **15** containing all the eight necessary chiral centres of the desired configuration. The final homologization step was accomplished by a sequence involving tosylation of the diol **15**, conversion of the di-*p*-toluenesulfonate **16** to dinitrile **17**, its reduction with diisobutylaluminium hydride, and further reduction of the intermediate aldehyde with lithium aluminium hydride to give the target compound **2a**, $[\alpha]_D^{26}+3.6°$ (*c* 1.5, chloroform). Both optical rotation and spectral data§ of the product thus obtained correspond to that reported earlier[1,2]: $[\alpha]_D+1.9°$ (*c* 0.97, chloroform); for the natural product[1]: $[\alpha]_D+4.8\pm0.63°$ (*c* 0.3, chloroform).

Synthesis of the enantiomer **2b** (Scheme 4) was started with diterpenoid acetate **12**, which initially was converted into bromide **22** using alcohol **19** and toluenesulfonate **21** in a way similar to the above transformation of **6** into **9**. Oxidative dimerization of the Grignard reagent, derived from bromide **22**, with silver nitrate afforded the C_{40}-diolefin **23** in unexpectedly high yield (74%), *cf*.[2] Finally, hydroboration–oxidation of **23** furnished the desired product **2b**, $[\alpha]_D^{31}-3.2°$ (*c* 1.0, chloroform), having the same spectral (IR, ^1H and ^{13}C NMR) data as the isomer **2a**.

§ ^1H NMR δ (400 MHz, $CDCl_3$): 0.85 (d, 18H, CH_3, *J* 7 Hz), 0.90 (d, 6H, CH_3, *J* 7 Hz), 1.05–1.45 (m, 48H, CH_2, CH), 1.5–1.7 (m, 4H, HC-2, HC-31), 3.70 (m, 4H, HC-1, HC-32); ^{13}C NMR δ (100 MHz, $CDCl_3$): 19.69 (3-CH_3 and 30-CH_3), 19.74 (15-CH_3 and 18-CH_3), 19.77 (7-CH_3 and 26-CH_3), 19.79 (11-CH_3 and 22-CH_3), 24.37 (C-5 and C-28), 24.47 (C-9 and C-24), 24.49 (C-13 and C-20), 29.55 (C-3 and C-30), 32.81 (C-7 and C-26, C-11 and C-22), 33.07 (C-15 and C-18), 34.32 (C-16 and C-17), 37.33 (C-10 and C-23), 37.40 (C-6 and C-27), 37.42 (C-4 and C-29, C-8 and C-25), 37.50 (C-12 and C-21), 37.56 (C-14 and C-19), 39.99 (C-2 and C-31), 61.27 (C-1 and C-32).

The optical purity of both enantiomers **2a** and **2b** corresponds to that of the starting monochiral compound **3** and is higher than 98%, because each step of the synthesis was carried out without affecting its chiral centre. The ^1H and ^{19}F NMR data of Mosher esters **18**, **20** and **25** prepared from alcohols **2a**, **19** and **2b**, respectively, can serve as an additional confirmation of the high optical purity of these products. Each NMR spectrum shows the presence of the one diastereoisomer only, *cf*.[2]

In conclusion, a total 17-step syntheses of the archaebacterial C_{40}-diol **2a** (1.5% overall yield) and its enantiomer **2b** (2.5% overall yield) has been developed based on a readily available monochiral building block **3**.

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Received: Moscow, 24th December 1992
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