215. Determination of the Absolute Configuration of Dimethyl (2*S*,3*S*)-2-Allyl-3-hydroxyglutarate: A Chiral Building Block for Preparing Branched-Chain Nucleoside Analogues

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A yeast-catalyzed reduction of dimethyl (2*S*,3*S*)-2-allyl-3-hydroxyglutarate is the key step in the preparation of bis-homo, branched-chain nucleoside analogues. To establish unambiguously the stereochemical course of the microbial reaction, the product has been converted to a derivative esterified with camphanoyl chloride, and a crystal structure of the derivative solved.

Introduction. – We have been interested for some time in the synthesis of enantiomerically pure, branched-chain nucleosides as building blocks for the synthesis of oligonucleotide analogues bearing dimethylenesulfone linking groups replacing the phosphodiester linkages found in natural oligonucleotides [1–2]. These are potential 'antisense' oligonucleotide analogues sought for their ability to block the translation of mRNA molecules with sequence specificity [3–6]. One potentially attractive route to these molecules (*Scheme 1*) starts with an ester of 3-oxoglutaric acid, and uses non-fermenting yeast in the first step to yield an enantiomerically enriched intermediate.

Yeast is often used to reduce β-keto esters to prepare functionalized chiral building blocks in synthesis [7–10]. However, because yeast contains enzymes with differing stereospecificities that reduce such substrates, it is difficult to predict in advance the absolute configurations of the reduced products. For example, it was reported that although the prediction according to *Prelog*'s rule [11] would give the (*S*)-configuration for γ- and δ-hydroxy acids obtained by yeast reduction, the compounds were found to have (*R*)-configuration [12]. Furthermore, *Sih* and coworkers have proposed a model to predict the absolute configuration of reduction product α-substituted β-keto ester [13]. This model cannot be used with esters of 3-oxoglutaric acid (such as in *Scheme 1*) because of the two different β-keto ester moieties in the substrate, either of which could be the 'reference' ester group in the model.

Thus, before implementing the route, it was essential to obtain an unambiguous proof of the absolute configuration of the reduction product. We report such an analysis involving the correlation of dimethyl (2*S*,3*S*)-2-allyl-3-hydroxyglutarate (**1**) produced by yeast-mediated reduction of the corresponding ketone and a derivative whose camphanoyl derivative yielded suitable crystals.

Results. – Dimethyl 2-allyl-3-oxoglutarate was prepared by allylation of the dimethyl 3-oxoglutarate using MeONa as a base in MeOH. This gave a mixture of monoallylated product, 2,4-diallylated product, and starting material in a ratio of 1:1,5:1. This mixture

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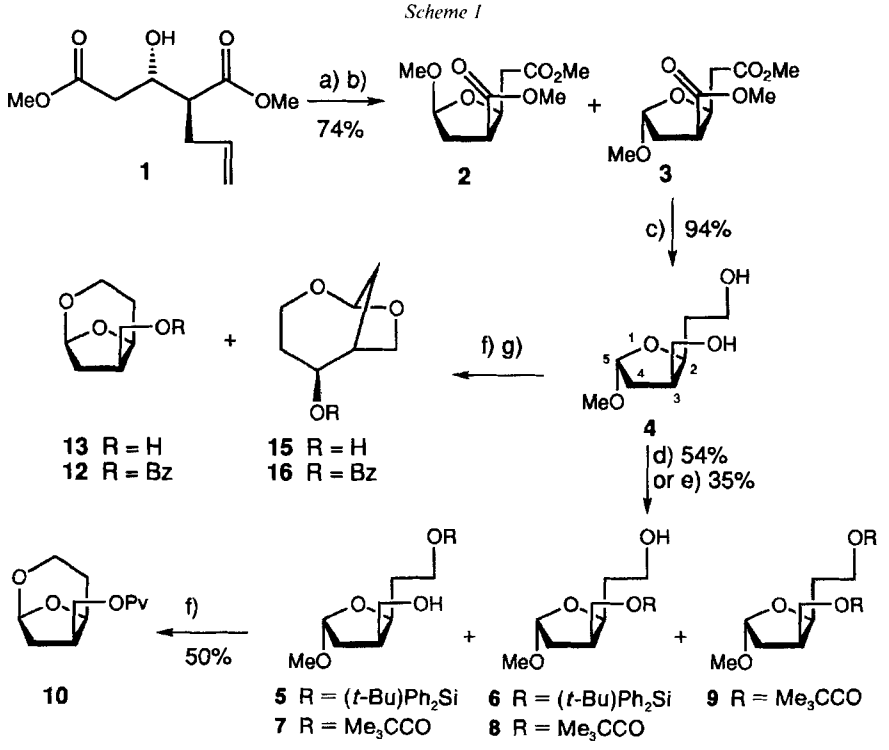
was used directly in the yeast-reduction step, yielding **1** in 44% yield. The ratio of **1** to its enantiomer was in excess of 96:4, determined by ^{1}H-NMR spectroscopy in the presence of the chiral shift reagent [Eu(hfc)$_3$] and by chiral-phase GC. The ratio **1** to its diasteroisomer (presumably with the (2*R*,3*S*)-configuration based on precedents with related compounds) was 94:6 (GC/MS) [14].

The enantiomerically enriched 3-hydroxy ester **1** was then employed in the synthesis of the branched-chain sugar analogues (*Scheme 1*). Ozonolysis of **1** in MeOH at low temperature followed by reduction with Me_2S yielded a mixture of hemiacetals, which were treated at reflux in the same solution with dry cation-exchange resin (*Dowex 50W X8*, H^+ form) to give two epimeric acetals in a ratio of 6:1. The minor isomer was isolated in crystalline form from Et_2O/pentane; the major isomer was isolated in pure form as an oil by chromatography of the mother liquor. Absolute configurations at the acetal centers of **2** and **3** were not assigned. The combined yield of isolated compounds was 74%.

Reduction of the major anomer with $LiAlH_4$ afforded diol **4** in 94% yield. A variety of experimental conditions using sterically demanding protecting groups where then investigated in an effort to differentiate the two OH groups of **4**. (*tert*-Butyl)dimethylsilyl chloride, dimethoxytrityl chloride, and trityl chloride each provided only very low yields of the corresponding monoprotected compounds. With (*t*-Bu)Ph_2SiCl, a 3:1 mixture of monoprotected compounds **5** and **6** was obtained in 35% combined yield [15]. The

Scheme 1



a) O_3, MeOH, −78°, SMe_2. b) *Dowex*, reflux. c) $LiAlH_4$, Et_2O, r.t. d) Me_3CCOCl, pyridine, 0°. e) (*t*-Bu)Ph_2SiCl_3, imidazole, CH_2Cl_2, 0°. f) *Dowex*, MeCN, reflux. g) BzCl, pyridine.

predominant isomer was assigned structure **5** by correlation to the monobenzoyl compound **11**, whose ^{1}H-NMR spectrum was readily assigned. Sequential treatment of **5** with benzoyl chloride and $Bu_4N^+F^-$ under standard conditions gave **11** in 71% yield (two steps; *Scheme 2*). The CH_2OBz ^{1}H-NMR signals of **11**, identified by their downfield shifts, were both of double *doublet* multiplicity (4.22 and 4.36 ppm), confirming the assignment of structures to **5** and **6**.

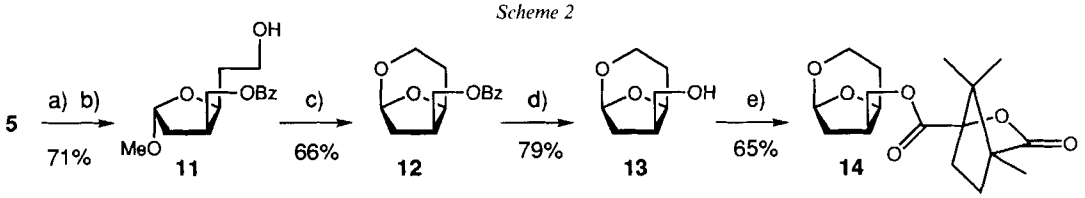
Slow addition of pivaloyl chloride to **4** in pyridine at 0° afforded an inseparable 6.4:1 (GC/MS) mixture **7**/**8** in 53% yield, together with the diprotected derivative **9**, in 17% yield [16][2]). The structures of **7** and **8** were assigned from the chemical shifts of the CH_2OH ^{1}H-NMR signals of the major isomer, which were themselves assigned based on their multiplicities. When the mixture of **7** and **8** was treated with dry cation-exchange resin (*Dowex 50W X8*, H^+) in refluxing MeCN, the fully protected branched-sugar analog **10** was obtained as a white powder in 50% yield. Since no other products were isolated from the *Dowex* treatment, an acyl-group migration must have taken place in **7** prior to cyclization (*Scheme 1*).

Another set of mono- and diprotected branched-chain sugar analogues was obtained from diol **4** (*Scheme 1*). Treatment of **4** with cation-exchange resin (*Dowex 50W X8*, H^+) in refluxing MeCN afforded an inseparable mixture of oily **13** and solid **15**. When the mixture was gently swirled with Et_2O and the solvent then removed, a pure portion of **15** crystallized. The OH groups of this mixture were protected with benzoyl chloride to afford **12** (15% yield, two steps) and **16** (56% yield, two steps), which were separated by flash chromatography. The major product from benzoylation was then hydrolyzed and gave a compound whose NMR spectra (^{1}H and ^{13}C) were identical to those of pure **15**. The ^{1}H-NMR chemical shifts of the H–C(5) signals, which appear at 4.05 ppm (*m*) in **15** and at 5.31 ppm (*dd*) in **16**, are particularly useful for structure assignment (*Scheme 1*).

Heating **11** in MeCN in the presence of cation-exchange resin (*Dowex 50W X8*, H^+) gave dioxabicyclooctane **12** in 66% yield, which in turn was hydrolyzed to the alcohol **13** (*Scheme 2*).

Although the reactions of **1**, **11**, and **15** with (–)-(1*S*)-camphanoyl chloride and (+)-camphorsulfonyl chloride gave the expected ester and sulfonates in good yields, neither derivative proved to be convenient for crystallographic analyses. Finally, ester **14** (*Scheme 2*), formed by reaction of alcohol **13** with (–)-(1*S*)-camphanoyl chloride, gave single crystals suitable for X-ray crystallographic studies (*Fig.*). These established the absolute configuration of the principal product of yeast reduction **1** as dimethyl (2*S*,3*S*)-2-allyl-3-hydroxyglutarate.

Scheme 2



a) BzCl, pyridine. b) TBAF, THF. c) *Dowex*, MeCN, reflux. d) NaOH, H_2O, THF, MeOH. e) (*S*)-Camphanoyl chloride, pyridine.

[2]) Interestingly, treatment of **9** with trimethylsilylated uracil under *Vorbrüggen* conditions [17] yielded a 9:1 mixture of epimers of the uridine analog in 72% yield. The structures of these isomers were not assigned.

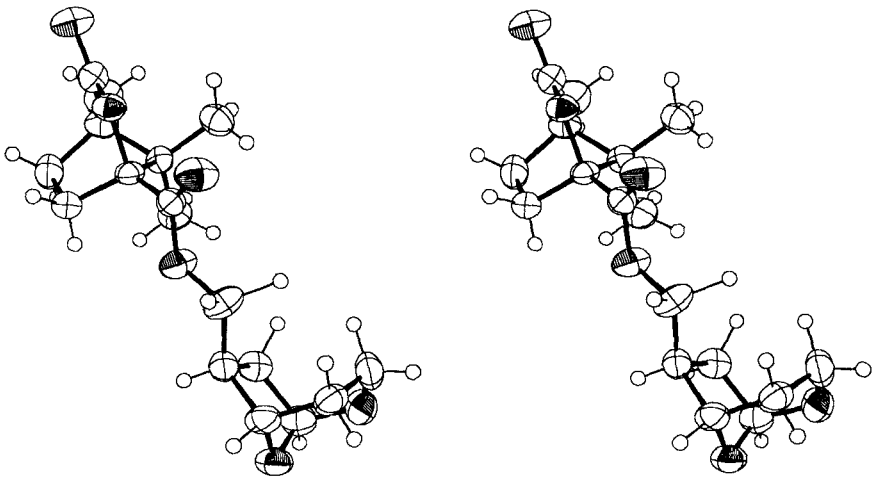


Figure. *Stereoscopic view of* **14**. Vibrational ellipsoids are drawn at the 50% level using ORTEP [18]. Orthorhombic space group $P2_12_12$, $Z = 4$ with cell dimensions $a = 6.185(2)$, $b = 13.345(5)$, $c = 21.812(9)$ Å. Intensities were measured at room temperature with an *Enraf Nonius CAD4* diffractometer equipped with a graphite monochromator (MoK_α, $\lambda = 0.7107$ Å). Of the 1693 independent reflections ($\theta < 25°$), 824 with $I > 3s(I)$ were used in the refinement. The structure was solved by direct methods with SHELXS-86 [19], and refined by full-matrix least-squares analysis [20]. Non-H-atoms were refined anisotropically. The positions of the H-atoms were calculated and refined isotropically in the final least-squares cycles. The weighting scheme used was $\sigma(F)^{-2}$. The refinement converged at $R = 0.032$, $R_w = 0.038$. Atomic positional and anisotropic displacement parameters for the non-H-atoms are deposited with the *Cambridge Crystallographic Data Centre*, Cambridge, England.

In summary, baker's yeast mediates a reduction of dimethyl 2-allyl-3-oxoglutarate gave dimethyl (2*S*,3*S*)-2-allyl-3-hydroxyglutarate. Further, the chiral building block thus obtained can be used in the synthesis of branched-chain sugar and nucleoside analogues.

Experimental Part

General. Experiments requiring anh. conditions were performed under Ar. Reactions were done at r.t. unless otherwise indicated. Solvents were *Fluka, p.a.*, and were used without purification unless mentioned otherwise. THF and Et_2O were distilled from K/benzophenone; MeCN was distilled from P_2O_5. M.p.: *Büchi 810* melting-point apparatus, not corrected. Optical rotations: *Perkin-Elmer 241* polarimeter at r.t. IR: *Perkin-Elmer 983* spectrophotometer. TLC: *Merck* silica gel F_{254} precoated plates; spots visualized by dipping the plates in a Ce–Mo staining reagent. Column chromatography: *Fluka* silica gel *60*, mesh size 0.040–0.063. As cation-exchange resin; *Dowex 50W X8* (H^+ form) was used. Anal. GC: *HP GC 5710A* with mass-spectral detector *5710B*. ^{1}H- and ^{13}C-NMR: *Varian XL 300*, *Varian EM-390*, or *Varian XL 200* spectrometer using DEPT for determination of the H substitution, all δ values in ppm relative to TMS and J in Hz. MS: *Hitachi-Perkin-Elmer RMU-6M*.

(2S,3S,5S)-5-Methoxy-3-(methoxycarbonyl)-2-[(methoxycarbonyl)methyl]tetrahydrofuran (**2**) *and (2S,3S,5R)-5-Methoxy-3-(methoxycarbonyl)-2-[(methoxycarbonyl)methyl]tetrahydrofuran* (**3**). A soln. of **1** (7.5 g, 34.4 mmol) in MeOH (200 ml) was cooled to −78° and treated with a stream of O_3 until a blue color persisted (2 h). The excess O_3 was then removed with a stream of dry N_2 (30 min), Me_2S (10 ml, 136 mmol) was added, and the soln. stirred under Ar, until no further peroxide was found (12 h). This mixture was refluxed with cation-exchange resin (*Dowex 50W X8*, H^+; 0.5 g) under open air (5 h). The resin was removed by filtration, and the solvents were removed *in vacuo*. GC/MS of the crude products showed a ratio of 1:6 for **2**:**3**. A large quantity of **2** could be separated by crystallization from Et_2O/pentane. The residue was chromatographed (Et_2O/hexane 5:3) to give **2**

(840 mg, 3.62 mmol, combined with that from crystallization) and **3** (5.06 g, 21.8 mmol) in 74% yield (for two steps). Compound **2** was crystallized from Et_2O/pentane.

Data of **2** *or* **3**: M.p.: 57°. $[\alpha]_D = +53.8$ ($c = 2.4$, $CHCl_3$). IR ($CHCl_3$): 3005, 2950, 1740, 1439, 1035. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.31–2.45 (*m*, 2 H–C(4)); 2.57 (*dd*, $J = 5.5, 15.7$, 1 H, CH_2–C(2)); 2.73 (*dd*, $J = 8.8, 15.7$, 1 H, CH_2–C(2)); 3.29 (*dt*, $J = 7.8, 9.3$, H–C(3)); 3.36 (*s*, MeO); 3.69 (*s*, CO_2Me); 3.71 (*s*, CO_2Me); 4.78 (*ddd*, $J = 5.5, 7.8, 8.8$, H–C(2)); 5.05 (*dd*, $J = 3.9, 5.8$, H–C(5)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 171.6 (*s*); 171.5 (*s*); 105.8 (*d*); 76.1 (*d*); 55.7 (*q*); 52 (*q*); 51.7 (*q*); 46.1 (*d*); 37.7 (*t*); 34.7 (*t*). MS: 231 ($[M - 1]^+$), 217, 201, 169, 159, 141, 127, 99, 81, 71, 59, 41, 29, 15. Anal. calc. for $C_{10}H_{16}O_6$ (232.23): C 51.72, H 6.94, O 41.34; found: C 51.37, H 6.95, O 41.24.

Data of **2** *or* **3**: $[\alpha]_D = -104.5$ ($c = 2.0$, $CHCl_3$). IR ($CHCl_3$): 3005, 2960, 1745, 1440, 1100, 1035. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.06 (*ddd*, $J = 1.7, 8.2, 13.5$, H–C(4)); 2.46 (*ddd*, $J = 5.3, 6.7, 13.5$, H–C(4)); 2.50–2.63 (*m*, CH_2–C(2)); 3.31–3.37 (*m*, H–C(3)); 3.34 (*s*, MeO); 3.68 (*s*, CO_2Me); 3.71 (*s*, CO_2Me); 4.70 (*dt*, $J = 6.3, 7.7$, H–C(2)); 5.12 (*dd*, $J = 1.7, 5.3$, H–C(5)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 172.9 (*s*); 171.0 (*s*); 104.4 (*d*); 74.7 (*d*); 54.9 (*q*); 51.9 (*q*); 51.8 (*q*); 45.2 (*d*); 36.6 (*t*); 35.9 (*t*). MS: 231 ($[M - 1]^+$), 217, 201, 169, 159, 141, 127, 99, 81, 71, 59, 41, 29, 15. Anal. calc. for $C_{10}H_{16}O_6$ (232.23): C 51.72, H 6.94, O 41.34; found: C 51.77, H 7.10, O 40.88.

(2S,3R,5R)-2-(Hydroxyethyl)-3-(hydroxymethyl)-5-methoxytetrahydrofuran (**4**). Diester **3** (5 g, 21.5 mmol) in Et_2O (50 ml) was added dropwise to a suspension of $LiAlH_4$ (1.650 g, 44 mmol, 2 equiv.) in Et_2O (50 ml) at r.t. under Ar. After being stirred overnight, the soln. was cooled to −78° and diluted dropwise with sat. Na_2SO_4 (6 ml). A white precipitate formed. MeOH/CH_2Cl_2 (200 ml, 5:95) was added, and the mixture was filtered through *Celite*. The *Celite* was extracted (30 min) with MeOH/CH_2Cl_2 (100 ml, 5:95), stirred, and removed by filtration. The org. fractions were combined and the solvents evaporated. The residue was dissolved in CH_2Cl_2 (200 ml), decanted to another flask, and the solvents were evaporated. The resulting product was taken up in Et_2O (100 ml) and decanted. The solvent was removed *in vacuo* to afford **4** (3.556 g, 94%) as a yellowish oil. $[\alpha]_D = -116.7$ ($c = 3.3$, $CHCl_3$). IR ($CHCl_3$): 3620, 3000, 2940, 1450, 1098, 1048. ^{1}H-NMR ($CDCl_3$): 1.76 (br. *s*, OH); 1.78–2.09 (*m*, 2 H–C(4), H–C(2)); 2.47–2.58 (*m*, H–C(3)); 2.69–2.79 (br. *s*, OH); 3.35 (*s*, MeO); 3.58 (*dd*, $J = 10, 5.9$, 1 H, CH_2–C(3)); 3.68 (*dd*, $J = 7.2, 10.2$, 1 H, CH_2–C(3)); 3.78–3.89 (*m*, C(2)–CH_2CH_2OH); 4.27 (*ddd*, $J = 4.7, 6.1, 9.0$, H–C(2)); 5.02 (*dd*, $J = 2.5, 5.3$, H–C(5)). ^{13}C-NMR ($CDCl_3$): 104.0 (*d*); 78.8 (*d*); 62.2 (*t*); 61.7 (*t*); 54.9 (*q*); 42.9 (*d*); 36.1 (*t*); 32.3 (*t*). MS: 175 ($[M - 1]^+$), 157, 145, 127, 118, 99, 81, 69, 55, 41, 29, 15.

*(2S,3R,5R)-2-{2-[(*tert*-Butyl)diphenylsilyloxy]ethyl}-3-(hydroxymethyl)-5-methoxytetrahydrofuran* (**5**) *and (2S,3R,5R)-4-{[(*tert*-Butyl)diphenylsilyloxy]methyl}-2-(2-hydroxyethyl)-5-methoxytetrahydrofuran* (**6**). (*t*-Bu)Ph_2SiCl (1.31 g, 4.77 mmol) was added dropwise at 0° over a period of 5 h to a soln. of **4** (720 mg, 4.09 mmol) and imidazole (552 mg, 8.08 mmol) in CH_2Cl_2 (20 ml). The mixture was warmed to r.t. and stirred overnight. The soln. was diluted with AcOEt (100 ml), washed with sat. $NaHCO_3$ (30 ml) and sat. NaCl (30 ml). The org. layer was dried ($MgSO_4$) and the solvents evaporated *in vacuo*. The residue was chromatographed (CH_2Cl_2/MeCN 9:1) to give **5** (450 mg, 1.08 mmol) and **6** (150 mg, 0.36 mmol) in a ratio of 3:1 in 35% (combined yield).

Data of **5**: IR ($CHCl_3$): 3660, 3440, 3000, 2960, 2935, 2860, 1520, 1430, 1390, 1360, 1035, 750. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.05 (*s*, *t*-Bu); 1.68–2.07 (2*m*, 2 H–C(4), CH_2–C(2), OH); 2.37–2.45 (*m*, H–C(3)); 3.32 (*s*, MeO); 3.51–3.66 (*m*, CH_2–C(3)); 3.76–3.87 (*m*, C(2)–CH_2CH_2OH); 4.25–4.31 (*m*, H–C(2)); 4.97 (distorted *t*, H–C(5)); 7.34–7.45 (*m*, 6 arom. H); 7.62–7.70 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 135.6 (*d*); 133.7 (*s*); 129.6 (*d*); 127.6 (*d*); 103.8 (*d*); 75.9 (*d*); 62.6 (*t*); 62.6 (*t*); 54.9 (*q*); 42.1 (*d*); 36.5 (*t*); 32.9 (*t*); 26.9 (*q*); 19.1 (*s*); MS: 414 (M^+), 413 ($[M - 1]^+$), 383, 365, 325, 295, 255, 229, 183, 169, 138, 109, 91, 81, 71, 41, 29, 15.

Data of **6**: ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.03 (*s*, *t*-Bu); 1.73–1.93 (*m*, 2 H–C(3), CH_2–C(2)); 2.35–2.72 (*m*, H–C(3), OH); 3.33 (*s*, MeO); 3.47–3.80 (*m*, C(2)–CH_2CH_2OH, CH_2–C(3)); 4.30 (*dd*, $J = 6.5, 13.7$, H–C(2)); 4.94 (*dd*, $J = 2.7, 4.8$, H–C(5)); 7.34–7.49 (*m*, 6 arom. H); 7.63–7.69 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 135.9 (*d*); 133.81 (*s*); 133.8 (*d*); 130.1 (*d*); 128.1 (*d*); 104.4 (*d*); 79.7 (*d*); 63.4 (*t*); 62.5 (*t*); 55.1 (*q*); 42.7 (*d*); 35.8 (*t*); 32.7 (*t*); 27.0 (*t*); 19.4 (*s*).

(2S,3R,5R)-3-(Hydroxymethyl)-5-methoxy-2-[2-(pivaloyloxy)ethyl]tetrahydrofuran (**7**), *(2S,3R,5R)-2-(Hydroxyethyl)-5-methoxy-3-[(pivaloyloxy)methyl]tetrahydrofuran* (**8**), *and (2S,3R,5R)-5-Methoxy-2-[(pivaloyloxy)ethyl]-3-[2-(pivaloyloxy)methyl]tetrahydrofuran* (**9**). Pivaloyl chloride (735 mg, 6.09 mmol) was added at 0° to a soln. of **4** (1 g, 5.68 mmol) in pyridine (30 ml) over 5 h. The mixture was warmed to r.t. and stirred overnight. The soln. was diluted with AcOEt (80 ml) and extracted first with sat. $NaHCO_3$ (20 ml) and then with NaCl (20 ml). The org. layer was dried ($MgSO_4$), the solvent removed by evaporation *in vacuo*, and the remaining pyridine removed under high vacuum. The residue was chromatographed (Et_2O/hexane 3:1) to give **7** and **8** (793 mg, 3.05 mmol, 53%) in a ratio of 6.4:1 (GC/MS) as colorless oil, and **9** (335 mg, 0.974 mmol, 17%) as a yellowish oil.

Data of **7**: ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.20 (*s*, *t*-Bu); 1.60–2.06 (*m*, OH, 2 H–C(4), CH_2–C(2)); 2.40–2.51 (*m*, H–C(3)); 3.33 (*s*, MeO); 3.59 (*dd*, $J = 6.2, 10.7$, 1 H, CH_2–C(3)); 3.67 (*dd*, $J = 6.2, 10.7$, 1 H, CH_2–C(3)); 4.14–4.29 (*m*, C(2)–CH_2, CH_2CH_2OH, H–C(3)); 4.95 (distorted *t*, $J = 3.9, 4.0$, H–C(5)). ^{13}C-NMR ($CDCl_3$, 75

MHz): 178.6 (*s*); 103.9 (*d*); 75.4 (*d*); 62.4 (*t*); 62.2 (*t*); 54.8 (*q*); 41.9 (*d*); 38.8 (*s*); 36.2 (*t*); 29.4 (*t*); 27.2 (*q*). IR ($CHCl_3$): 3620, 3510, 2975, 1720, 1480, 1290, 1165, 1100, 1040. MS: 260 (M^+), 259 ($[M-1]^+$), 229, 159, 127, 113, 99, 71, 57, 41, 29.

Data of **9**: $[\alpha]_D = +1.36$ ($c = 1.25$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.195 (*s*, *t*-Bu); 1.196 (*s*, *t*-Bu); 1.72–2.07 (2*m*, 2 H–C(4), CH_2–C(2)); 2.60–2.71 (*m*, H–C(4)); 3.32 (*s*, MeO); 3.96 (*dd*, $J = 7.3$, 11.2, 1 H, CH_2–C(3)); 4.05 (*dd*, $J = 7.3$, 11.2, 1 H, CH_2–C(8)); 4.14–4.29 (*m*, C(2)–CH_2CH_2OH, H–C(2)); 4.95 (*dd*, $J = 2.06$, 5.4, H–C(5)). ^{13}C-NMR ($CDCl_3$, 75 MHz): 178.4 (*s*); 178.3 (*s*); 103.6 (*d*); 75.0 (*d*); 63.7 (*t*); 62.0 (*t*); 54.7 (*q*); 39.0 (*d*); 38.7 (*s*); 36.2 (*t*); 29.6 (*t*); 27.2 (*q*). IR ($CHCl_3$): 2990, 1720, 1530, 1287, 1160, 1035. MS: 344 (M^+), 343 ($[M-1]^+$), 211, 183, 113, 84, 57, 41, 29.

(1S,5S,6R)-6-[(Pivaloyloxy)methyl]-2,8-dioxabicyclo[3.2.1]octane (**10**). A mixture **7**/**8** (6.4:1; 206 mg, 0.735 mmol) in MeCN (20 ml) was heated at reflux in the presence of cation exchange resin (*Dowex 50W X8*, H^+; 160 mg) for 4 h under open air. The cation-exchange resin (*Dowex 50W X8*, H^+) was recovered by filtration and the solvents evaporated. The residue was chromatographed (hexane/AcOEt 7:3) to yield **10** (85 mg, 0.373 mmol) in 50% yield as a white powder. M.p. 37°. $[\alpha]_D = -16.0$ ($c = 1.6$, $CHCl_3$). IR: 2980, 1722, 1480, 1280, 1160, 1100, 990, 950, 850. ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.2 (*s*, *t*-Bu); 1.40 (*dd*, $J = 3.7$, 13.9, H–C(4)); 1.84 (*dd*, $J = 6.6$, 13.7, H–C(4)); 2.23–2.43 (*m*, 2 H–C(7)); 2.68–2.82 (*m*, H–C(6)); 3.80–4.02 (*m*, 2 H–C(3)); 4.18 (*dd*, $J = 9.8$, 10.6, H–C(9)); 4.35–4.44 (*m*, H–C(9), H–C(5)); 5.47 (*d*, $J = 5.4$, H–C(1)). MS: 228 (M^+), 199, 169, 127, 85, 57.

(2S,3R,5R)-3-[(Benzoyloxy)methyl]-2-(2-hydroxyethyl)-5-methoxytetrahydrofuran (**11**). Benzoyl chloride (170 mg, 1.21 mmol) was added dropwise to a soln. of **5** (415 mg, 1 mmol) in pyridine (10 ml) at 0°. The soln. was warmed to r.t., stirred for 30 min, diluted with AcOEt (60 ml), and washed with sat. $NaHCO_3$ (20 ml) and sat. NaCl (20 ml). The org. layer was dried ($MgSO_4$), the solvents were evaporated, and the pyridine was removed under high vacuum. The crude product contaminated with *ca.* 10% benzoic acid was dissolved in THF (10 ml) and $Bu_4NF \cdot 3\,H_2O$ (608 mg, 193 mmol, *ca.* 2 equiv.) added. After 5 h, the mixture was quenched with MeOH (2 ml), the solvent was evaporated, and the residue was chromatographed with (Et_2O/hexane 3:1) giving **11** (200 mg, 0.714 mmol) in 71.4% yield (overall) as a white powder. M.p. 33°. IR ($CHCl_3$): 3620, 3530, 3000, 2960, 1720, 1450, 1315, 1275, 1100, 1065, 1030, 985, 965. ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.78–2.17 (*m*, 2 H–C(4), H–C(2), OH); 2.46 (*dd*, $J = 4.4$, 6.4, 1 H, CH_2–C(2)); 2.82 (*dt*, $J = 6.7$, 13.5, H–C(3)); 3.36 (*s*, MeO); 3.80–3.89 (*m*, CH(2)–CH_2CH_2(OH)); 4.22 (*dd*, $J = 6.8$, 11.1, 1 H, CH_2–C(3)); 4.36 (*dd*, $J = 6.2$, 11.1, 1 H, CH_2–C(3)); 4.38–4.42 (*m*, H–C(2)); 5.08 (*dd*, $J = 2.4$, 5.1, H–C(5)); 7.41–7.63 (*m*, 3 arom. H); 8.01–8.06 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 166.8 (*s*); 135.5 (*d*); 130.3 (*s*); 129.9 (*d*); 128.8 (*d*); 104.3 (*d*); 78.9 (*d*); 64.4 (*t*); 62.2 (*t*); 55.2 (*q*); 39.6 (*d*); 36.2 (*t*); 32.8 (*t*). MS: 280 (M^+), 249, 222, 189, 105, 84, 77, 39, 28. Anal. calc. for $C_{15}H_{20}O_5$ (280.32): C 64.27, H 7.19; found: C 64.27, H 7.01.

(1S,5S,6R)-6-[(Benzoyloxy)methyl]-2,8-dioxabicyclo[3.2.1]octane (**12**). Alcohol **11** (176 mg, 0.628 mmol) in MeCN (20 ml) was treated at reflux with dry cation-exchange resin (*Dowex 50W X8*, H^+; 158 mg) for 3 h (under open air). The cation-exchange resin (*Dowex 50W X8*, H^+) was removed by filtration, and the solvents were removed *in vacuo*. The residue was chromatographed (hexane/Et_2O 1:3) to yield **12** (103 mg, 0.415 mmol, 66%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.50 (*dd*, $J = 3.3$, 14.0, H–C(4)); 1.93 (*dd*, $J = 6.7$, 14.0, H–C(4)); 2.28–2.47 (*m*, 2 H–C(7)); 2.80–3.01 (*m*, H–C(6)); 3.83–4.08 (*m*, 2 H–C(3)); 4.40–4.50 (*m*, H–C(9), H–C(5)); 4.64 (*dd*, $J = 7.3$, 11.2, H–C(9)); 5.51 (*d*, $J = 5.4$, H–C(1)); 7.26–7.63 (*m*, 3 arom. H); 8.00–8.07 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 166.8 (*s*); 132.6 (*d*); 130.2 (*s*); 129.9 (*d*); 128.8 (*d*); 99.9 (*d*); 75.5 (*d*); 63.3 (*t*); 58.5 (*t*); 39.3 (*d*); 32.8 (*t*); 26.8 (*t*).

(1S,5S,6R)-6-(Hydroxymethyl)-2,8-dioxabicyclo[3.2.1]octane (**13**). NaOH (0.1N, 0.30 ml, 0.03 mmol) was added to a soln. of **12** (83 mg, 0.334 mmol) in MeOH/THF (4:5, 0.9 ml). After 15 min, pyridinium *Dowex* (40 mg) was added, and the pH brought to 6 with HCl (0.1N) soln. The cation-exchange resin (*Dowex 50W X8*, H^+) was removed by filtration, and the solvents were removed under high vacuum. The crude product was chromatographed (AcOEt) to yield **13** (38 mg, 0.264 mmol, 79%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.44–1.56 (*m*, H–C(4), OH); 1.81 (*dd*, $J = 6.6$, 13.8, H–C(4)); 2.22–2.42 (*m*, 2 H–C(7)); 2.59–2.72 (*m*, H–C(6)); 3.77–4.02 (*m*, 2 H–C(3), 2 H–C(9)); 4.43 (distorted *t*, $J = 5.0$, H–C(5)); 5.5 (*d*, $J = 5.4$, H–C(1)). MS: 126 ($[M-18]^+$), 113, 103, 98, 80, 70, 57.

(1S,5S,6R)-6-{[(1S)-Camphanoyloxy]methyl}-2,8-dioxabicyclo[3.2.1]octane (**14**). (−)-(*S*)-Camphanoyl chloride (50.5 mg, 0.233 mmol) in pyridine (0.2 ml) was added dropwise to a soln. of **13** (28 mg, 0.194 mmol) in pyridine (0.1 ml) at 0°. The soln. was stirred overnight, diluted with AcOEt (30 ml), and washed first with sat. $NaHCO_3$ (10 ml) and then with sat. NaCl (10 ml). The org. layer was dried ($MgSO_4$), the solvents were removed by evaporation *in vacuo*, and the residual pyridine was removed under high vacuum. The residue was chromatographed (CH_2Cl_2/MeCN 9:1) to yield **14** (41 mg, 0.126 mmol) in 65% yield as a white powder. The compound recrystallized from AcOEt/pentane as needles (after one week) from which a crystal structure was obtained. M.p.

138°. ^{1}H-NMR ($CDCl_3$, 200 MHz): 0.96 (*s*, Me); 1.06 (*s*, Me); 1.13 (*s*, Me); 1.35–1.44 (*m*, H–C(4)); 1.64–2.11 (*m*, H–C(5'), 2 H–C(4), H–C(6')); 2.26–2.49 (*m*, 2 H–C(7), H–C(6')); 2.73–2.86 (*m*, H–C(6)); 3.82–4.02 (*m*, 2 H–C(3)); 4.31–4.43 (*m*, H–C(9), H–C(5)); 4.56 (*dd*, J = 7.6, 11.2, H–C(9)); 5.48 (*d*, J = 5.8, H–C(1)). ^{13}C-NMR ($CDCl_3$, 50 MHz): 178 (*s*); 168 (*s*); 100 (*d*); 91 (*s*); 75 (*d*); 63.8 (*t*); 58.1 (*t*); 54.8 (*t*); 54.2 (*t*); 39 (*d*); 32.3 (*t*); 30.5 (*s*); 29 (*s*); 26.4 (*t*); 17 (*q*); 10 (*q*).

(1R,4S,5S)-5-(Benzoyloxy)-2,8-dioxabicyclo[4.2.1]nonane (**16**). Diol **4** (124 mg, 0.704 mmol) in MeCN (20 ml) was treated at reflux with dry cation-exchange resin (*Dowex 50W X8*, H^+; 80 mg) for 3 h. The cation-exchange resin (*Dowex 50W X8*, H^+) was recovered by filtration and the solvents were evaporated *in vacuo*. The residue was dried under high vacuum to give 87 mg of crude product. An attempt to separate the compounds at this stage failed. When the mixture was gently swirled with Et_2O, a pure portion of **15** could be obtained. The mixture was dissolved in pyridine (5 ml), and benzoyl chloride (100 µl, 0.868 mmol) at 0° was added dropwise. The soln. was stirred for 30 min at r.t., diluted with AcOEt (30 ml), washed with sat. $NaHCO_3$ (10 ml) and then with sat. NaCl (10 ml). The org. layer was dried ($MgSO_4$), the AcOEt was evaporated *in vacuo*, the remaining pyridine removed under high vacuum, and the residue chromatographed ($MeCN/CH_2Cl_2$ 1:9) to give **12** (26 mg, 0.104 mmol) in 14.9% yield as an oil, and **16** (98 mg, 0.395 mmol) in 56% yield as a white powder.

Data of (1R,4S,5S)-2,8-[4.2.1]bicyclononan-5-ol (**15**). M.p. 140°. ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.51 (*d*, J = 3.0, OH); 1.66–2.12 (*m*, H–C(9), 2 H–C(6)); 2.45 (*d*, J = 13.9, H–C(9)); 2.48–2.57 (*m*, H–C(4)); 3.64–3.74 (*m*, 2 H–C(3)); 3.82 (*dd*, J = 6.2, 9.0, H–C(7)); 3.94–4.06 (*m*, H–C(7), H–C(5)); 5.50 (*d*, J = 5.8, H–C(1)). ^{13}C-NMR ($CDCl_3$, 50 MHz): 102.5 (*d*); 70.5 (*t*); 69.5 (*d*); 58.8 (*t*); 42.9 (*d*); 34.5 (*t*); 28.6 (*t*). MS: 126 ([M – 18]$^+$), 98, 83, 70, 57.

Data of **16**. M.p. 64°. $[\alpha]_D = -38.4$ (c = 1.88, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.92–2.24 (*m*, H–C(9), 2 H–C(6)); 2.53 (*d*, J = 14.2, H–C(9)); 2.77–2.82 (*m*, H–C(4)); 3.78–3.91 (*m*, 2 H–C(3), H–C(7)); 4.05 (distorted, *t*, J = 12.8, 10.8, H–C(7)); 5.31 (*dd*, J = 3.8, 7.4, H–C(5)); 5.57 (*d*, J = 5.8, H–C(1)); 7.44–7.60 (*m*, 3 arom. H); 8.04–8.07 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 165.6 (*s*); 133.2 (*d*); 130.3 (*d*); 129.5 (*d*); 128.5 (*d*); 102.2 (*d*); 72.3 (*d*); 70.0 (*t*); 59.3 (*t*); 40.0 (*d*); 31.5 (*t*); 29.4 (*t*). IR ($CHCl_3$): 3000, 2960, 1715, 1270, 1108, 1062, 1030, 987, 948, 931, 900, 830. MS: 249 ([M + 1]$^+$), 248 (M^+), 231, 203, 189, 175, 157, 143, 126, 105, 96, 77, 51, 41, 39, 29. Anal. calc. for $C_{14}H_{16}O_4$ (248.28): C 67.73, H 6.50, O 25.78; found: C 67.38, H 6.54, O 25.78.

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