# A Novel Strategy for the Convergent Synthesis of 1,3,5,…-Polyols: Enone Formation, Asymmetric Dihydroxylation, Reductive Cleavage, Hydride Addition

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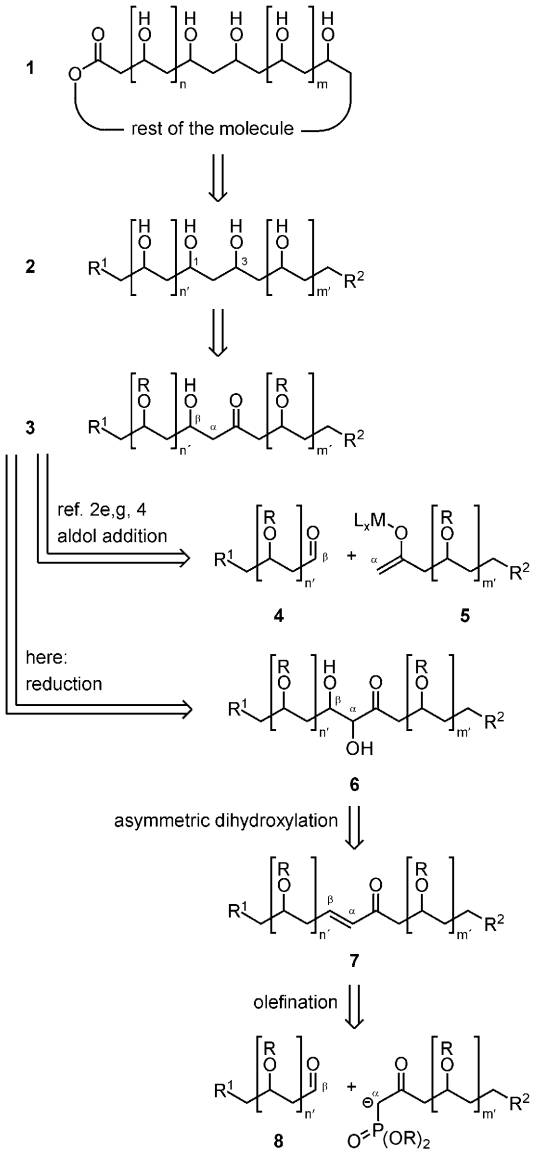
**Abstract:** Asymmetric dihydroxylation of α,β-unsaturated ketones provided α,β-dihydroxyketones with up to 100% ee. The $C^{\alpha}$–O bond of these intermediates or their bis-TMS ethers, acetonides, phenylborates or orthoformiates was cleaved with $SmI_2$, affording β-hydroxyketones. The latter can be reduced to furnish *syn*- or *anti*-configured 1,3-diols of any desired configuration.

**Key words:** defunctionalization, 1,3-diol, Horner–Wadsworth–Emmons olefination, β-hydroxy ketones, samarium iodide, α,β-unsaturated ketones

1,3,5,…-Polyols without substituents at $C^2$, $C^4$, $C^6$,… are the core structural feature of the polyol/polyene macrolide antibiotics **1** (Scheme 1).[1] This family of compounds comprises more than 200 members. Those representatives of which not only the constitution but also the configuration is known have received considerable attention in the synthetic community.[1,2] This is due to a desire of developing methodology for making such molecules in a stereocontrolled manner. In a longer perspective, the synthetic interest in polyol/polyene antibiotics **1** is motivated by the wish to understand the correlation (if any) between their 3D structure and their biological activity.

Preferably, extended stretches **2** of 1,3,5,…-polyols should emerge from a convergent strategy (Scheme 1). In state-of-the-art syntheses of 2,4,6,…-substituted 1,3,5,…-polyol building blocks, such convergency is typically due to the inclusion of β-hydroxyketone intermediates and their construction through 'complex aldol additions'.[3] β-Hydroxyketone intermediates **3** have been used en route to extended polyols **2**, too; they arose from the aldol addition of enolates **5** to aldehydes **4**[2e,g,4] or from a different approach.[5] Here we communicate a novel way of making polyols **2** via β-hydroxyketones **3**: by the α-defunctionalization of α,β-dihydroxyketones **6**. The latter stem from the asymmetric dihydroxylation[6] ('AD') of enones **7**, which, in turn, result from Horner–Wadsworth–Emmons olefinations of aldehydes **8** or from analogous Wittig reactions.

We started with the AD of the α,β-unsaturated ketone **9a** (Scheme 2). Trying to accelerate conversion, we utilized the so-called improved[7] rather than standard procedure,[8] i. e., employed 1 mol% $K_2OsO_2(OH)_4$ instead of 0.2 mol% and 5 mol% $(DHQD)_2PHAL$ instead of 1 mol%. Even so this reaction required 2.5 days at 0 °C to furnish diol α*S*,β*R*-**10a**[9] in 89% yield and with 100% ee[10] (after extractive work up and purification by flash chromatography on silica gel[11]). Hence, the reaction rate was somewhat lower and stereocontrol somewhat better than in the not too many known ADs of α,β-unsaturated ketones.[12–15]




**Scheme 1** Convergent approaches to 'skipped polyol' building blocks **2** of polyol/polyene macrolide antibiotics **1** via type-**3** β-hydroxyketone intermediates.

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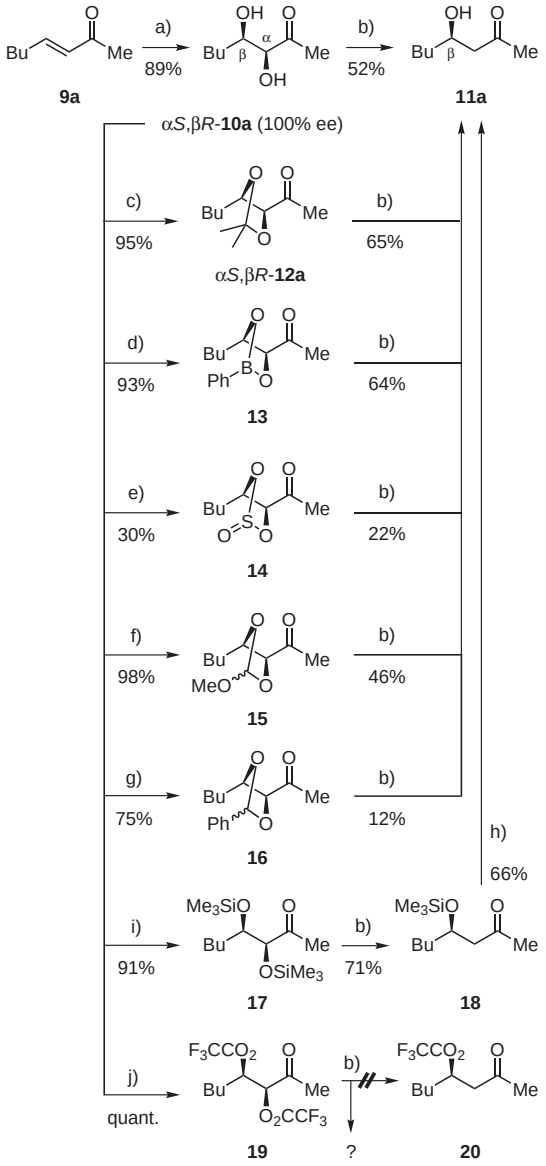
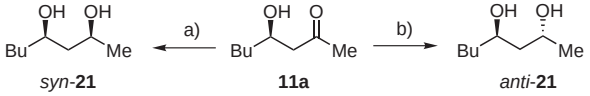



**Scheme 2** $SmI_2$-mediated α-reductions of a model α,β-dihydroxyketone and derivatives thereof. *Reagents and conditions*: a) $K_2OsO_2(OH)_4$ (1 mol%), $(DHQD)_2PHAL$ (5 mol%), $K_3Fe(CN)_6$ (3.0 equiv), $NaHCO_3$ (3.0 equiv), $K_2CO_3$ (3.0 equiv), *t*-BuOH–$H_2O$ 1:1 (v:v), 0 °C, 60 h; b) $SmI_2$ (2.1 equiv), THF, –78 °C, addition of substrate in THF–MeOH 2:1 (v:v), 50 min; –78 °C to r.t., 30 min; c) pyridinium *p*-toluenesulfonate (10 mol%), 2,2-dimethoxypropane, r.t., 24 h; PTSA (3 mol%), 22 h; d) phenylboronic acid (1.1 equiv), $CH_2Cl_2$, r.t., 24 h; e) $SOCl_2$ (1.1 equiv), DMF (5 mol%), $CH_2Cl_2$, 0 °C, 1 h; then r.t., 4 h; f) trimethyl orthoformiate (1.2 equiv), pyridinium *p*-toluenesulfonate (5 mol%), $CH_2Cl_2$, r.t., 3.3 d; g) benzaldehyde dimethylacetal (1.1 equiv), PTSA (5 mol%), $CH_2Cl_2$, r.t., 22 h; h) $Bu_4NF·3H_2O$ (3.6 equiv), THF, r.t., 6 h; i) $Et_3N$ (8 equiv), $Me_3SiCl$ (4 equiv), $CH_2Cl_2$, 0 °C, 3 h; j) $Na_2CO_3$ (0.8 equiv), trifluoroacetic anhydride (as a solvent), 0 °C, 10 min.

The $C^{\alpha}$–O bond of α,β-dihydroxyketone α*S*,β*R*-**10a** was cleaved by treatment with $SmI_2$[16] in THF–MeOH at –78 °C (50 min) to room temperature (30 min) furnishing β-hydroxyketone **11a** in 52% yield (Scheme 2, top row). It is plausible that this transformation entails the following steps: electron transfer (giving the ketyl), $C^{\alpha}$–O bond rupture, electron transfer (giving the α-desoxygenated enolate), and proton transfer from the cosolvent before the $E1_{cb}$ elimination of β-OH occurs.[17] Prior to the present study, reductive C–O bond cleavages in O=C–C–O-containing compounds have rarely concerned $C^{\alpha}$–OH groups: The only previously described defunctionalization of a simple α-hydroxyketone with $SmI_2$ in THF–MeOH proceeded with only 29% yield at –78 °C;[18] two related substrates could be defunctionalized by $SmI_2$ only in the presence of HMPA.[19,20] Activated – i. e., β,γ-unsaturated – α-hydroxyketones were defunctionalized by $SmI_2$ in pure THF[21] or in the presence either of HMPA.[21] or a proton source.[22] Apart from that, $SmI_2$-mediated C–O bond cleavage affected α-(sulfonyloxy)ketones,[18] α,β-epoxyketones,[23] α-(acyloxy)ketones,[18,24] α-(trialkylsiloxy)ketones,[18,21] and α-methoxyketones.[25] Conceptually related yet mechanistically distinct are the α-desoxygenations of α,β-epoxyketones and α,β-thiocarbonatoketones with $Na^+PhSeB(OEt)_3^-$[26] and $Bu_3SnH$,[27] respectively.

In an effort to enhance the efficiency of the defunctionalization α*S*,β*R*-**10a**→**11a**, we protected the OH groups of dihydroxyketone α*S*,β*R*-**10a** as derivatives α*S*,β*R*-**12a**–**17** (Scheme 2). Each of them plus $SmI_2$/THF/MeOH gave the desired β-hydroxyketone **11a**, too. The best-yielding $SmI_2$-mediated reductions started from bis(trimethylsilylether) **17** (→71% **18**), acetonide α*S*,β*R*-**12a** (→65% **11a**[28]), or phenyl boronate **13** (→64%). Orthoformiate **15** provided 46% of **11a**, sulfinate **14** 22%, and benzylidene acetal **16** just 12%. While bis(trifluoroacetate) **19** reacted rapidly with $SmI_2$ it gave none of the desired trifluoroacetate **20**. A fluorine-free diester analogue of diester **19** was not investigated. This was because optimally the reduction of such an ester would furnish a β-(acyloxy)ketone. The latter, from our experience, would be difficult to hydrolyze (→**11a**) because of competing reversal to compound **9a** through β-elimination of HOAc.




**Scheme 3** Synthesis of enantiomerically pure 1,3-diols **21**. *Reagents and conditions*: a) $BEt_3$ (1.1 equiv), THF–MeOH 4:1 (v:v), r.t., 1 h; then –78 °C, addition of **11a** in THF, 2 h; $NaBH_4$ (0.8 equiv), 16 h; 90% of the pure diastereomer; b) $Me_4NBH(OAc)_3$ (4.05 equiv), MeCN–AcOH 1:1 (v:v), r.t., 30 min; then –40 °C, addition of **11a** in MeCN, 1 h; then –20 °C, 14 h; 51% of the pure diastereomer.

We terminated our exploratory sequence by reducing β-hydroxyketone **11a** diastereoselectively (Scheme 3). The reliability of this step is a pre-requisite for using β-hydroxyketones as latent *syn*- and *anti*-1,3-diol motifs in synthesis. Among *syn*-selective β-hydroxyketone reductions[29–33] the unquestioned favorite is the Narasaka–Prasad procedure.[29] It relies on chelate formation with in situ formed diethylborinate followed by hydride delivery from $NaBH_4$ at –78 °C, furnishing diol diastereomer *syn*-**21** in 90% yield (after purification by flash chromatography[11]). From several *anti*-selective β-hydroxyketone reductions[34–39] we used Evans' OH-directed



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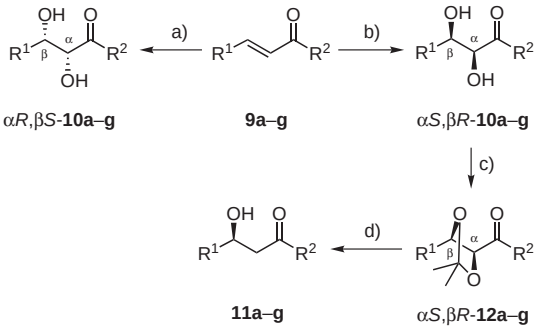
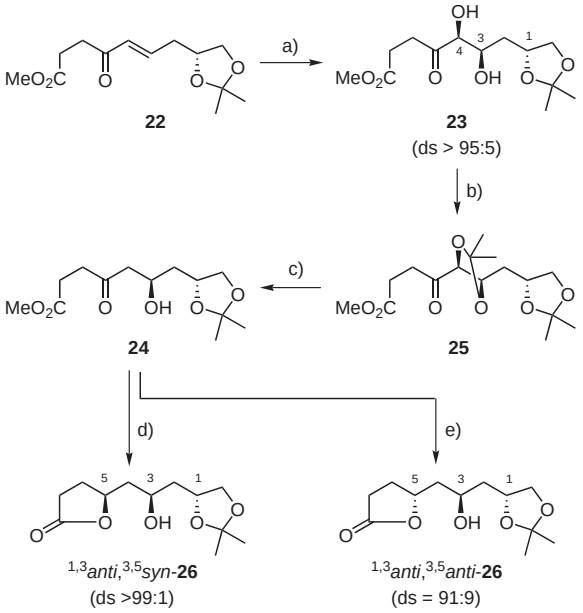
hydride delivery[34] for accessing diol diastereomer *anti*-**21** (51% yield, again after flash chromatography[11]).




**Scheme 4** Asymmetric dihydroxylations of α,β-unsaturated ketones; reductive cleavage of the derived α,β-dihydroxyketone acetonides. *Reagents and conditions*: a) $K_2OsO_2(OH)_4$ (1 mol%), $(DHQ)_2PHAL$ (5 mol%), $K_3Fe(CN)_6$ (3.0 equiv), $NaHCO_3$ (3.0 equiv), $K_2CO_3$ (3.0 equiv), $MeSO_2NH_2$ (0.0 or 1.0 equiv*), *t*-BuOH–$H_2O$ 1:1 (v:v), 0 °C; b) same* as (a) but using $(DHQD)_2PHAL$ (5 mol%); c) PTSA (3 mol%), 2,2-dimethoxypropane (as a solvent), r.t.; d) $SmI_2$ (2.1–4.5 equiv), THF, –78 °C; addition of **12a**–**g** in THF–MeOH 2:1 (v:v) during 20 min; another 15 min at –78 °C; –78 °C to r.t. within 30 min; *$MeSO_2NH_2$ was only employed in the preparations of dihydroxyketones α*R*,β*S*-**10a**, α*S*,β*R*-**10a**, α*R*,β*S*-**10c**, α*S*,β*R*-**10c**, and α*R*,β*S*-**10d**. For details, see Table 1.

Scheme 4 and Table 1 show that the AD of enone **9a** with $(DHQ)_2PHAL$ instead of $(DHQD)_2PHAL$ as the chiral auxiliary exhibits 99% ee vs. 100% ee in the latter case. The AD of several other enones **9b**–**g** proceeds with considerable enantiocontrol, too. Acetonide formation from the dihydroxyketone enantiomers α*S*,β*R*-**10a**–**g** only – because of their slightly superior enantiomeric purities – gave acetonides **12a**–**f** in high yields (94–100%) and somewhat less of the most volatile acetonide **12g** (81%). Combining these acetonides with 2.1–4.5 equivalents of $SmI_2$ in THF–MeOH and raising the temperature from –78 °C to ambient led to the desired defunctionalizations with the sole exception of compound **12f**: β-hydroxyketones **11a**–**e** and **g** were isolated with an average yield of 62%.




**Scheme 5** Synthesis of protected, enantiomerically pure 1,3,5-triols **25**. *Reagents and conditions*: a) $K_2OsO_2(OH)_4$ (1 mol%), $(DHQD)_2PHAL$ (5 mol%), $K_3Fe(CN)_6$ (3.0 equiv), $NaHCO_3$ (3.0 equiv), $K_2CO_3$ (3.0 equiv), $MeSO_2NH_2$ (1.0 equiv), *t*-BuOH–$H_2O$ 1:1 (v:v), 0 °C, 24 h; 90% [in a 74:26 mixture (w:w) with $MeSO_2NH_2$ which co-chromatographed with **23**; an analytically pure sample of **23** was obtained following the same procedure but in the absence of $MeSO_2NH_2$; however, the yield there was only 60%]; b) pyridinium *p*-toluenesulfonate (10 mol%), 2,2-dimethoxypropane (36 equiv), no additional solvent, r.t., 12 h; 82%; c) $SmI_2$ (3.0 equiv, prepared in situ), THF–MeOH 9:1 (v:v), –78 °C to r.t., 40 min; 90%; d) (i) $BEt_3$ (1.1 equiv), $NaBH_4$ (0.8 equiv), THF–MeOH 4:1 (v:v), –78 °C, 12 h; (ii) camphor sulfonic acid (10 mol%), $CH_2Cl_2$, r.t., 12 h; 91% over the 2 steps; e) (i) $Me_4NBH(OAc)_3$ (4.1 equiv), MeCN–AcOH 1:1 (v:v), –40 °C to –20 °C, 14 h; (ii) camphor sulfonic acid (10 mol%), $CH_2Cl_2$, r.t., 12 h; 94% over the 2 steps.

As demonstrated in Scheme 5, our sequence (1) enone formation, (2) AD, (3) $C^{\alpha}$–O bond cleavage, (4) hydride addition strategy is applicable in a structurally more complex environment without difficulty. Enone **22** was dihydroxylated by a modified AD mix-β™ in 90% yield and with complete diastereoselectivity. Transformation of the

**Table 1**

| Compd **9**–**12** | $R^1$ | $R^2$ | Yield of α*R*,β*S*-**10** (%) | ee of α*R*,β*S*-**10** (%)[a] | Yield of α*S*,β*R*-**10** (%) | ee of α*R*,β*S*-**10** (%)[a] | Yield of **11** (%) | Yield of α*S*,β*R*-**12** (%) |
|---|---|---|---|---|---|---|---|---|
| **a** | Bu | Me | 100 | 99 | 89 | 100 | 65 | 94 |
| **b** | Ph | Me | 72 | 97 | 77 | 98 | 44 | 100 |
| **c** | *i*-Pr | Me | 87 | 98 | 91 | 99 | 68 | 93 |
| **d** | Pr | Me | 100 | 98 | 95 | 99 | 59 | 94 |
| **e** | Pr | Bu | 93 | – | 82 | – | 71 | 95 |
| **f** | Pr | Ph | 93 | 91 | 89 | 87 | 6 | 95 |
| **g** | Pr | *i*-Pr | 83 | 94 | 60 | 98 | 66 | 81 |

[a] The ee values of compounds **10a**,**c**,**d**,**g** were determined by GLC, the ee of **10b** by GLC of the corresponding bis(trifluoroacetate), and the ee of **10f** by HPLC. No enantiomer separation was accomplished in the case of compound **10e**.



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resulting dihydroxyketone **23** into acetonide **25** (82%) set the stage for reductive cleavage by $SmI_2$–THF–MeOH. This afforded the ester-containing β-hydroxyketone **24**[40] in 90% yield. Narasaka–Prasad reduction[29] provided a *syn*-diol. Its acid-catalyzed lactonization led to the protected 1,3,5-triol[1,3]*anti*,[3,5]*syn*-**26** (91% yield, 100% stereocontrol). The triacetoxyborohydride reduction[34] of β-hydroxyketone **24** proceeded with complementary stereocontrol. After treatment of the resulting dihydroxyester with camphor sulfonic acid the [1,3]*anti*,[3,5]*anti* isomer of the protected 1,3,5-triol **26** was isolated (94% yield, 91:9 mixture with diastereomer[1,3]*anti*,[3,5]*syn*-**26**).

In conclusion we have established a straightforward synthesis of 1,3-diols with completely controlled stereostructure. The β-hydroxyketones obtained from the α,β-dihydroxyketone intermediates and stoichiometric to overstoichiometric amounts of $SmI_2$ (Scheme 2, Scheme 3, Scheme 4) should be susceptible to over-reduction by an excess of this reductant. Since such an over-reduction is conceivably diastereoselective,[38] it appears as if one might realize a one-pot synthesis of stereopure 1,3-diols from enantiomerically pure α,β-dihydroxyketones, ≥4 equivalents of $SmI_2$, THF, and a proton source like methanol or water. Studies towards this end are underway in our laboratory.

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(9) Compounds α*S*,β*R*-**10a–g**, α*R*,β*S*-**10a–g**, **11a–g**, α*R*,β*S*-**12c**, **13**, **15**, **17**, **18**, *syn*-**21**, and *anti*-**21** provided correct $^1$H NMR spectra and combustion analyses. Compounds α*S*,β*R*-**12a–g** except **c** were too volatile for combustion analysis and intermediates **14**, **16**, and **19** deemed not worth it; these compounds were characterized by $^1$H NMR and low-resolution mass spectra only.

(10) **(3*S*,4*R*)-3,4-Dihydroxy-2-octanone (α*S*,β*R*-10a).** At 0 °C, *trans*-3-octen-2-one (1.20 g, 1.38 mL, 9.51 mmol) was added to a stirred mixture of $K_2OsO_2(OH)_4$ (35.0 mg, 0.095 mmol, 1.0 mol%), $(DHQD)_2PHAL$ (370.0 mg, 0.475 mmol, 5.0 mol%), $NaHCO_3$ (2.40 g, 28.5 mmol, 3.0 equiv), $K_2CO_3$ (3.95 g, 28.5 mmol, 3.0 equiv), $MeSO_2NH_2$ (903 mg, 9.51 mmol, 1 equiv), and $K_3Fe(CN)_6$ (9.39 g, 28.5 mmol, 3.0 equiv) in *t*-BuOH (25 mL) and $H_2O$ (25 mL). After stirring for 60 h sat. aq $Na_2SO_3$ (120 mL) was added. The mixture was warmed to r.t. and extracted with EtOAc (3 × 70 mL). The combined organic extracts were washed with brine (60 mL) and dried over $MgSO_4$. Removal of the solvent in vacuo and purification of the residue by flash chromatography on silica gel[11] (column filling 5 cm × 20 cm, cyclohexane–EtOAc 1:2, 60 mL fractions) provided the title compound (fractions 5–8, 1.39 g, 89%) as a colorless oil. The ee was ≥99% according to chiral GC {CP-Chirasil-Dex CB 25 m × 0.25 mm catalog number CP7502; from 60 °C/10 min at 5 °C/min to 170 °C/20 min; 80 kPa, $t_R$ (major enantiomer) = 26.46 min; no compound eluted around $t_R$ = 25.71 min [which was the independently measured value of $t_R$ (minor enantiomer)]}. $^1$H NMR (500 MHz, TMS internal standard in $CDCl_3$): δ = 0.93 (t, $J_{8,7}$ = 7.1 Hz, 8-$H_3$), 1.34–1.42 (m, 7-$H_2$, 6-$H^1$), 1.44–1.50 (m, 6-$H^2$), 1.66 ($m_c$, presumably interpretable as ddd, $J_{5,4} = J_{5,6\text{-}H(1)} = J_{5,6\text{-}H(2)}$ = 6.9 Hz, 5-$H_2$), superimposed partly by 1.73 (br s, 4-OH), 2.28 (s, 1-$H_3$), 3.70 (br s, 3-OH), 3.95 (td, $J_{4,5}$ = 6.9 Hz, $J_{4,3}$ = 1.4 Hz, 4-H), 4.08 (d, $J_{3,4}$ = 1.5 Hz, 3-H). $[\alpha]_D^{20}$ +94.6 (*c* 0.45, $CHCl_3$). IR ($CDCl_3$): 3575, 3465, 2960, 2935, 2875, 2860, 1715, 1465, 1460, 1385, 1360, 1235, 1130, 1090, 935, 910, 885 cm$^{-1}$. Anal. Calcd for $C_8H_{16}O_3$ (160.2): C, 59.97; H, 10.07. Found: C, 59.68; H, 10.09.



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(40) **Methyl (6*R*)-7-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-hydroxy-4-oxoheptanoate (24).**
A suspension of 1,2-diiodoethane (2.062 g, 7.316 mmol, 3.0 equiv) and Sm powder 40 mesh (1.155 g, 7.316 mmol, 3.15 equiv) in THF (70 mL) was stirred at r.t. for 2 h. A deep-blue solution of $SmI_2$ was obtained. At –78 °C acetonide **25** (805 mg, 2.44 mmol) in THF–MeOH 2:1 (30 mL) was added within 10 min. After another 10 min, the mixture was warmed to r.t. and the reaction quenched 20 min later by the addition of aq HCl (1 M, 7.4 mL). The aqueous phase was separated and extracted with *t*-BuOMe (3 × 25 mL). The combined organic phases were washed successively with sat. aq $NaHCO_3$ (15 mL) and brine (12 mL) and dried over $MgSO_4$. Removal of the solvent in vacuo and purification of the residue by flash chromatography on silica gel[11] (column filling 3 cm × 20 cm, eluent = cyclohexane–EtOAc, 40:60) provided the title compound (fractions 8–24, 601 mg, 90%). $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.36 and 1.41 [2 × s, 2′-$(CH_3)_2$], AB signal ($\delta_A$ = 1.69, $\delta_B$ = 1.73, $J_{AB}$ = 13.1 Hz, in addition split by $J_{7\text{-}H(A),6}$ = 7.3 Hz,* $J_{7\text{-}H(A),4'}$ = 4.1 Hz,* $J_{7\text{-}H(B),4'}$ = 8.3 Hz,** $J_{7\text{-}H(B),6}$ = 4.9 Hz,** 7-$H_2$), presumably extreme AB signal where the 8 off-center signals are too small to be identified (so that $J_{AB}$ cannot be extracted) so that the best description is: 2.61 (dd, $J_{3\text{-}H(1),2\text{-}H(1)}$ = 6.6 Hz, $J_{3\text{-}H(1),2\text{-}H(2)}$ = 3.8 Hz), 2.62 (dd, $J_{3\text{-}H(2),2\text{-}H(2)}$ = 6.6 Hz,*** $J_{3\text{-}H(2),2\text{-}H(1)}$ = 2.7 Hz,*** 3-$H_2$), 2.68 and 2.76 (2 × $m_c$, 2-$H_2$, 5-$H_2$), 3.26 (d, $J_{OH,6}$ = 3.5 Hz, 6-OH), 3.57 (dd, $J_{gem}$ = $J_{5'\text{-}H(1),4'}$ = 7.8 Hz, 5′-$H^1$), 3.68 (s, 1-$OCH_3$), 4.09 (dd, $J_{gem}$ = 7.9 Hz, $J_{5'\text{-}H(2),\ 4'}$ = 6.1 Hz, 5′-$H^2$), 4.25–4.33 (m, 6-H, 4′-H); *, **, *** coupling constants exchangeable. $^{13}$C NMR [75 MHz, $CDCl_3$; APT spectrum, peak orientation 'up' ('+') for $CH_3$ and CH and 'down' ('–') for $CH_2$ and $C_{quat}$]: δ = '+' 25.67 and '+' 26.91 [2′-($CH_3$)$_2$], '–' 27.55 (C-2), '–' 37.80 (C-3), '–' 39.94 (C-7), '–' 49.66 (C-5), '+' 51.88 (1-$OCH_3$), '+' 65.46 (C-6), '–' 69.64 (C-5'), '+' 73.37 (C-4'), '–' 108.75 (C-2'), '–' 173.21 (C-1), '–' 209.34 (C-4). $[\alpha]_D^{20}$ –22.6 (*c* 1.92, $CHCl_3$). IR (film): 3490, 3015, 2985, 2945, 1735, 1715, 1435, 1415, 1370, 1215, 1165, 1060, 990, 870, 855 cm$^{-1}$. Anal. Calcd for $C_{13}H_{22}O_6$ (274.3): C, 56.92; H, 8.08. Found: C, 57.12; H, 7.99.

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