A General Route to the Monomeric Subunits of the Macrotetrolides – A Short Synthesis of Methyl Nonactate☆

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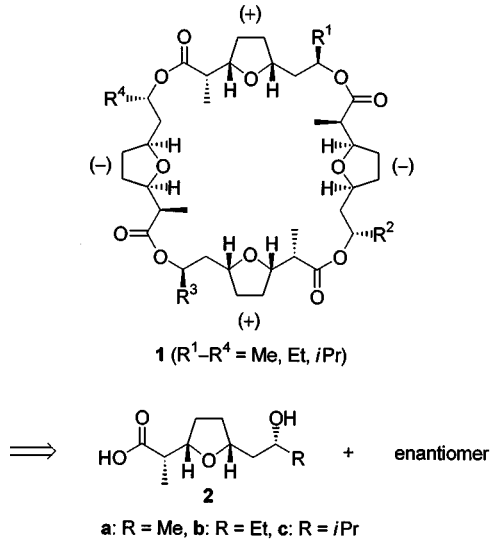
A highly stereoselective and flexible sultone route to actic acids, the monomeric subunits of the macrotetrolides, has been developed and exemplified for nonactic acid (**2a**). Due to the extensive application of tandem transformations, only six steps were needed to secure methyl nonactate (**20**) from furan.

The macrotetrolides **1**, also known as actins or nactins, have been isolated from various *Streptomyces* cultures (Scheme 1)[1]. These neutral ionophores[2] display pronounced antibacterial[3], insecticidal[4], as well as immunosuppressive[5] activities. An unusual feature of the structurally elucidated macrotetrolides **1** is the alternating sequence[6] of (+) and (−) enantiomers of the monomeric subunits **2**. With respect to an efficient synthesis of actins **1**, including the achiral S_4-symmetrical members such as nonactin (R^1-R^4 = Me)[7] and tetranactin (R^1-R^4 = Et)[8], an enantioselective preparation of both enantiomers of the actic acids **2**[9] is thus required. Though several syntheses of nonactic acid (**2a**)[10] and some reports on the synthesis of its homologs[8][11] have been published, a short and general access to **2** was still highly desirable in view of the biological activities associated with the actins. Here we give a full account of a practical route to methyl nonactate[12] which emerged from our studies on intramolecular Diels−Alder reactions of vinylsulfonates and the synthetic elaboration of the resultant sultones[13].

Scheme 1

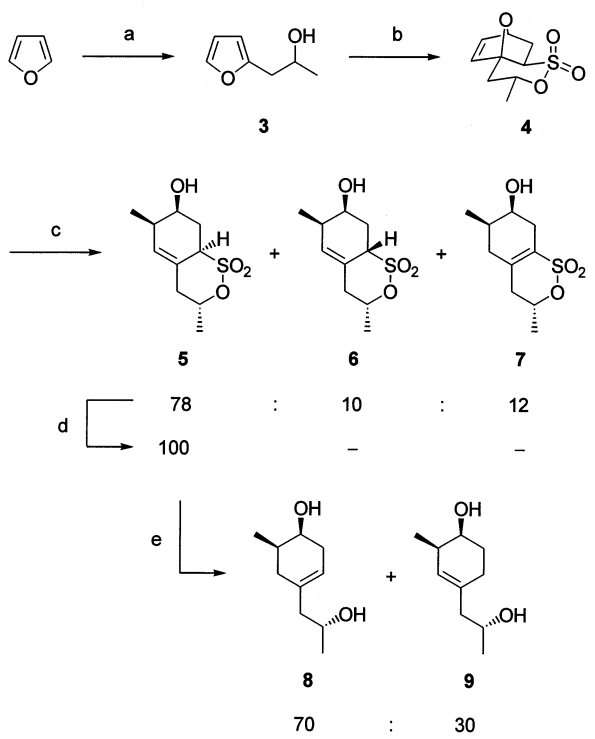


Lithiation of furan, followed by alkylation with epoxypropane yielded alcohol **3** that was subjected to a tandem esterification/cycloaddition with ethenesulfonyl chloride (Scheme 2). Out of four possible diastereomers, only the *exo* adduct **4** with an equatorial alkyl group on a chair δ-sultone was obtained[14]. A subsequent treatment of **4** with two equivalents of methyllithium induced a tandem elimination/alkoxide-directed 1,6-addition to give a mixture of sultones **5**−**7**. Although the alkoxide-directed C−C coupling involved in this transformation occurred with complete regio- and diastereoselectivity, a product mixture was formed due to a less selective protonation of the intermediate allyllithium species produced upon 1,6-addition. A subsequent equilibration with catalytic amounts of potassium *tert*-butoxide resulted in complete conversion of the minor isomers **6** and **7** to the thermodynamically most stable allylic sultone **5**[15]. We first envisioned to convert **5** into nonactic acid (**2a**) by reductive desulfurization[16] followed by an oxidative alkene cleavage. However, upon reaction of **5** with sodium in liquid ammonia, the undesired olefin regioisomer **8** was preferentially formed[15].

Nevertheless, the required position of the double bond for an oxidative scission is already present in the allylic sultone **5** and thus, cleavage of the olefin prior to reductive removal of the sulfur function was an alternative (Scheme 3). A first series of experiments toward this end including ozonization of **5** using oxidative or reductive workup procedures met with failure. Likewise, ozonolysis of silyl ether **10** followed by treatment with dimethyl sulfide could not be used for elaboration of **5**, since it was accompanied by a facile intramolecular aldol reaction to give the spiro compound **11**[17] as a single diastereomer. On the other hand,

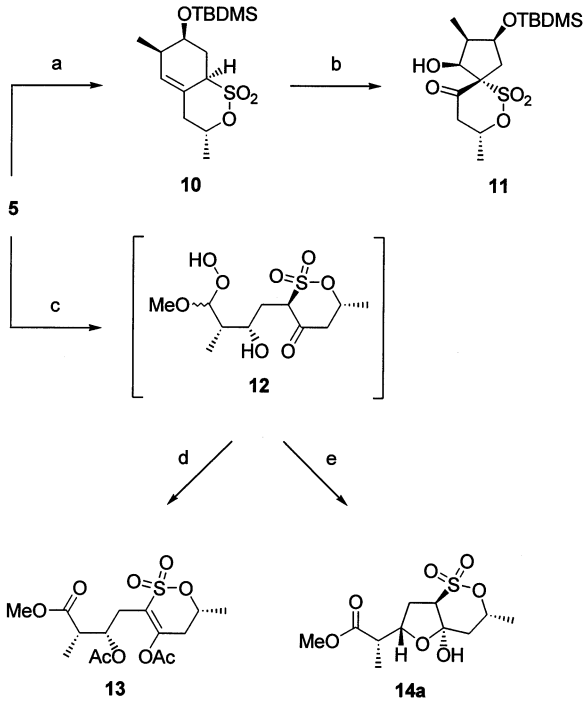
  1434−193X/98/1010−2073 $ 17.50+.50/0

Scheme 2



(a) i. BuLi, THF, −78°C; ii. epoxypropane, −78°C to room temp., 65%; (b) CH_2=$CHSO_2Cl$, Et_3N, THF, 0°C to room temp., 90%; (c) i. MeLi (2 equiv.), THF, −78°C to 0°C; ii. sat. aqueous NH_4Cl, −78°C to room temp., 54%; (d) cat. *t*BuOK, toluene, room temp., 77%; (e) Na, NH_3, THF, −60°C, 95%.

Scheme 3



(a) TBDMSCl, imidazole, cat. DMAP, DMF, room temp., 93%; (b) i. O_3, CH_2Cl_2, −78°C; ii. Me_2S, −78°C to room temp., 68%; (c) O_3, $NaHCO_3$, CH_2Cl_2, MeOH, −78°C; (d) Et_3N (13 equiv.), Ac_2O, 0°C to room temp., 61% of **13** from **5**; (e) pyridine (2 equiv.), Ac_2O (1 equiv.), CH_2Cl_2, 0°C to room temp., 69% of **14a** from **5**.

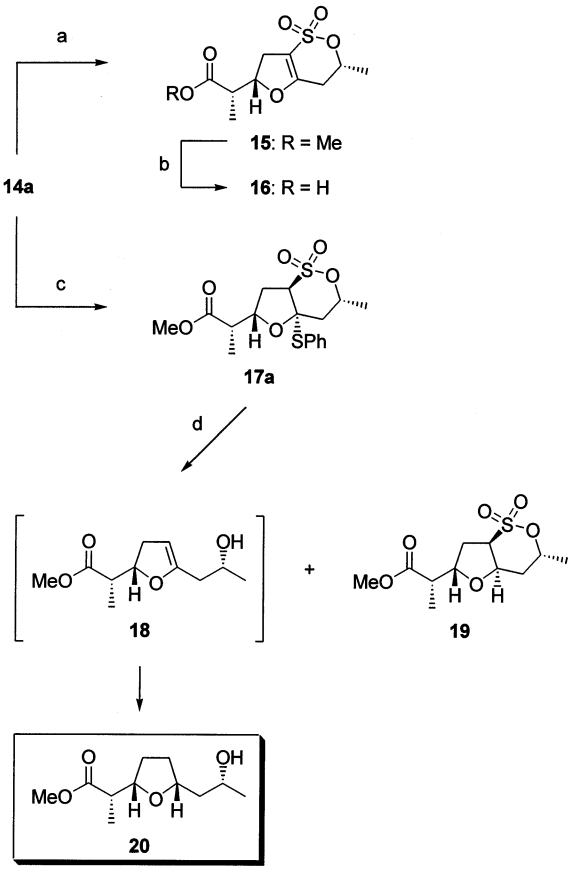
ozonolysis of **5** with eliminative workup[18] was successful, provided proper conditions were chosen. As anticipated, the primary ozonide from **5** obviously undergoes a regioselective cycloreversion with formation of the carbonyl oxide function distal to the electron-withdrawing sulfonate moiety. Subsequent trapping of the carbonyl oxide with methanol leads to intermediate **12**. Using an excess of acetic anhydride and triethylamine[18b] for workup, only the diacetate **13** was formed, whereas only the desired hemi-acetal **14a** was produced with one equivalent of acetic anhydride for chemoselective acylation of the hydroperoxy group and two equivalents of pyridine[18c] as the base. The relative configuration of **11**[17] and **14a**[12] was unambiguously established by X-ray diffraction analysis.

With **14a** in hand, we planned to convert this hemi-acetal to an α,β-unsaturated sultone that was supposed to lead to a hydroxyalkyl-substituted 2,3-dihydrofuran (cf. **18**) by a subsequent reductive cleavage of the vinylic C−S bond[16a]. Upon treatment of **14a** with mesyl chloride and triethylamine, a nearly quantitative elimination to give methyl ester **15** took place that was readily saponified to acid **16** with the aid of pig liver esterase (Scheme 4). However, all attempts to achieve a reductive desulfurization of either **16** or **15** only led to complex mixtures. As an alternative, we then investigated the reductive elimination of a suitable derivative of hemi-acetal **14a**. Indeed, a Lewis acid catalyzed exchange of the hydroxy group in **14a** against a phenylthio group[19] in **17a**, again characterized by X-ray diffraction analysis[12], smoothly set the stage for a chemoselective reductive cleavage of both C−S bonds in one operation. To our delight, upon treatment of **17a** with Raney nickel[20], methyl nonactate (**20**) was directly obtained. Presumably, first a reductive elimination occurs to give a 2,3-dihydrofuran[21] **18**, which in turn is immediately hydrogenated by the hydrogen adsorbed within the Raney nickel nearly exclusively (**20**/6-*epi*-**20**[7c][22] = 96:4) from the sterically less hindered π face. In addition to **20**, a smaller amount of sultone **19** was isolated, which proved to be completely inert to Raney nickel reduction in a separate experiment.

Gratifyingly, one can even skip the equilibration of the mixture of sultones **5**−**7**, all of which have the desired relative configuration at the three stereogenic centers still present in **20** and two of which, **5** and **6**, have the double bond in the position needed for further elaboration, with an increase in total yield (Scheme 5). Upon ozonolysis, only the trisubstituted olefins **5** and **6** were attacked, while the vinylic sultone **7** could easily be separated from the two diastereomeric methyl esters **14** (**14a**/**14b** = 93:7), both of which led to methyl nonactate (**20**) via a single 2,3-dihydrofuran **18**. Saponification of **20** to nonactic acid (**2a**) is known[7b] and thus, our sultone route from furan to **20** consisting of only six steps due to the extensive application of tandem transformations[23] also constitutes the shortest synthesis of acid **2a** with excellent stereocontrol.

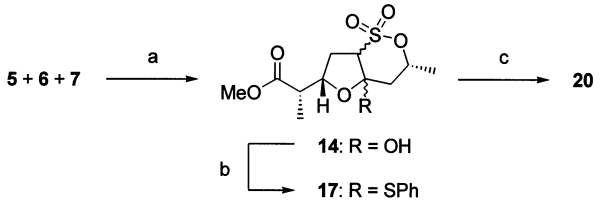
Since the tricyclic compounds corresponding to sultone **4** with an Et or *i*Pr substituent instead of the Me group

Scheme 4



(a) MsCl, Et_3N, CH_2Cl_2, 0°C, 98%; (b) PLE, pH 7 buffer, H_2O, acetone, room temp., 98%; (c) PhSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, room temp., 95%; (d) Raney Ni, EtOH, room temp., 51% of **20**, 34% of **19**.

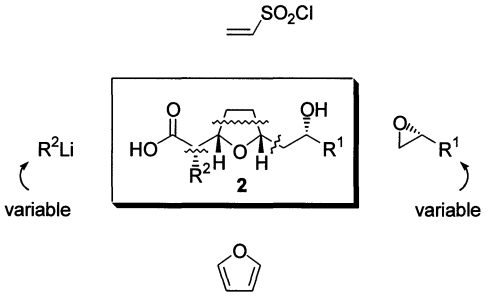
Scheme 5



(a) i. O_3, $NaHCO_3$, CH_2Cl_2, MeOH, −78°C; ii. pyridine (2 equiv.), Ac_2O (1 equiv.), CH_2Cl_2, room temp., 66%; (b) PhSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, room temp., 93%; (c) Raney Ni, EtOH, room temp., 51% of **20**, 32% of **19**.

are readily prepared in an analogous fashion[14], and alkyl groups other than Me are smoothly introduced by tandem elimination/alkoxide-directed 1,6-addition with **4**[15], this reaction sequence offers a general access to all naturally occurring actic acid homologs **2a**−**c** as well as unnatural analogs. Scheme 6 illustrates how the hydroxy acids **2** can now be assembled from four simple building blocks: furan, an epoxide, ethenesulfonyl chloride, and an organolithium reagent. Moreover, an enantioselective synthesis is at hand, since a large variety of the requisite enantiomerically pure epoxides which react with lithiated furan to the starting materials[7b][14] for the tandem esterification/Diels−Alder reaction is readily available in both enantiomeric forms[24][25].

Scheme 6



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Experimental Section

For general experimental information, see ref.[26].

Sultone **4**[14]: White needles, m.p. 124°C (ether), R_f = 0.35 (ethyl acetate/petroleum ether, 1:1). − IR (KBr): $\tilde{\nu}$ = 1364 cm^{-1}, 1173 (SO_2OR). − ^1H NMR ($CDCl_3$): δ = 1.49 (d, *J* = 6.4 Hz, 3 H), 1.82 (dd, *J* = 7.9, 12.3 Hz, 1 H), 2.29 (dd, *J* = 11.2, 15.4 Hz, 1 H), 2.39 (dd, *J* = 2.8, 15.4 Hz, 1 H), 2.53 (ddd, *J* = 3.6, 4.6, 12.3 Hz, 1 H), 3.10 (dd, *J* = 3.4, 7.9 Hz, 1 H), 4.99 (ddq, J_d = 2.8, 11.2 Hz, J_q = 6.4 Hz, 1 H), 5.19 (dd, *J* = 1.7, 4.7 Hz, 1 H,), 6.05 (d, *J* = 5.6 Hz, 1 H), 6.57 (dd, *J* = 1.7, 5.6 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 20.61 (q), 29.19 (t), 34.47 (t), 56.43 (d), 77.40 (d), 78.67 (d), 88.21 (s), 135.52 (d), 139.95 (d). − MS (GC/MS, 70 eV); *m/z* (%): 216 (0.5) [M^+], 201 (0.3) [$M^+ - CH_3$], 135 (8) [$CH_3CHOSO_2CHCH_2^+$], 108 (95) [$M^+ - CH_2CHSO_3H$], 81 (100) [$C_5H_5O^+$]. − $C_9H_{12}O_4S$ (216.26): calcd. C 49.99, H 5.59; found C 49.71, H 5.39.

Silyl Ether **10**: To a solution of alcohol **5**[15] (599 mg, 2.58 mmol) in dry DMF (20 ml), a solution of DMAP (132 mg, 1.09 mmol), TBDMSCl (540 mg, 3.59 mmol), and imidazole (497 mg, 7.31 mmol) was added with stirring. The mixture was stirred overnight, poured into sat. aqueous NH_4Cl (20 ml), and neutralized with 2 N HCl. The aqueous layer was extracted with ether (4 × 20 ml), and the combined organic layers were washed with 2 N HCl (40 ml), sat. aqueous $NaHCO_3$ (40 ml), and brine (40 ml). After drying with magnesium sulfate and removal of the solvent in vacuo, the crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:6) to give 831 mg of **10** (93%), white crystals, m.p. 102°C, R_f = 0.44. − IR (KBr): $\tilde{\nu}$ = 1354 cm^{-1}, 1172 (SO_2OR). − ^1H NMR ($CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.89 (s, 9 H), 1.05 (d, *J* = 7.2 Hz, 3 H), 1.41 (d, *J* = 6.2 Hz, 3 H), 2.03−2.41 (m, 5 H), 3.80 (m_c, 1 H), 3.90 (ddd, *J* = 4.8, 4.8, 11.8 Hz, 1 H), 4.67 (ddq, J_d = 3.6, 12.4 Hz, J_q = 6.2 Hz, 1 H), 5.82 (m_c, including J_d = 6.2 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = −4.85 (q), −4.75 (q), 13.41 (q), 18.06 (s), 20.76 (q), 24.63 (t), 25.71 (q), 35.65 (d), 40.20 (t), 59.54 (d), 67.80 (d), 80.88 (d), 125.49 (s), 134.62 (d). − MS (GC/MS, 70 eV); *m/z* (%): 289 (11) [$M^+ - C_4H_9$], 105 (100) [M^+ − HOTBDMS − $CH_3CH_2OSO_2$], 75 (20) [$(CH_3)_2Si{=}OH^+$], 73 (7) [$(CH_3)_3Si^+$], 57 (6) [$C_4H_9^+$]. − $C_{16}H_{30}O_4SSi$ (346.56): calcd. C 55.45, H 8.73; found C 55.72, H 8.97.

Keto Sultone **11**: A solution of sultone **10** (140 mg, 0.40 mmol) in dry CH_2Cl_2 (14 ml) was cooled to −78°C and ozonized with oxygen-free ozone[27] until the mixture turned blue. Excess ozone

was removed by purging with argon. Dimethyl sulfide (2.5 ml) was added, and the mixture was stirred for 1 h at −78°C and 24 h at room temperature. Excess dimethyl sulfide and CH_2Cl_2 were removed by distillation, and the residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:8) to give 103 mg of **11** (68%), white solid, m.p. 78−80°C, R_f = 0.42. − IR (KBr): $\tilde{\nu}$ = 3442 cm^{-1} (OH), 1728 (C=O), 1361, 1182, 1172 (SO_2OR). − ^1H NMR ($CDCl_3$): δ = 0.10, (s, 3 H), 0.18 (s, 3 H), 0.89 (s, 9 H), 1.11 (d, J = 7.2 Hz, 3 H), 1.54 (d, J = 6.0 Hz, 3 H), 2.25 (dd, J = 4.5, 15.5 Hz, 1 H), 2.31 (m_c, 1 H), 2.73 (dd, J = 2.6, 14.7 Hz, 1 H), 3.03 (dd, J = 12.4, 14.7 Hz, 1 H), 3.03 (d, J = 15.5 Hz, 1 H), 3.53 (d, J = 11.7 Hz, 1 H, O*H*), 4.27 (m_c, 1 H), 4.53 (dd, J = 4.5, 11.7 Hz, 1 H), 4.73 (ddq, J_d = 2.6, 12.4 Hz, J_q = 6.0 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = −3.87 (q), −3.44 (q), 8.73 (q), 17.89 (s), 20.89 (q), 25.67 (q), 34.31 (t), 43.77 (d), 47.04 (t), 75.31 (d), 77.60 (d), 80.57 (d), 83.43 (s), 193.89 (s). − MS (GC/MS, 70 eV); *m/z* (%): 379 (4) [M^+ + 1], 378 (3) [M^+], 363 (2) [$M^+ - CH_3$], 321 (100) [$M^+ - C_4H_9$], 75 (45) [$(CH_3)_2Si{=}OH^+$], 73 (16) [$(CH_3)_3Si^+$], 57 (15) [$C_4H_9^+$]. − $C_{16}H_{30}O_6SSi$ (378.55): calcd. C 50.77, H 7.99; found C 50.90, H 7.83.

Diacetate **13**: To a solution of sultone **5**[15] (100 mg, 0.43 mmol) in methanol (2 ml) and CH_2Cl_2 (8 ml) was added $NaHCO_3$ (190 mg, 2.25 mmol). After cooling to −78°C, the mixture was ozonized until it turned blue. Excess ozone was removed by purging with argon, and the mixture was allowed to warm to room temperature. Benzene (10 ml) was added, the mixture was filtered, and the solvents were removed at 0°C in vacuo behind a safety shield. The solid residue was taken up in acetic anhydride (3 ml) and triethylamine (0.8 ml, 5.71 mmol) at 0°C. After stirring for 12 h at room temperature, the solution was diluted with diethyl ether (50 ml), washed successively with 0.1 N HCl (10 ml), H_2O (10 ml), sat. aqueous $NaHCO_3$ (10 ml), H_2O (10 ml), and dried with $MgSO_4$. Concentration in vacuo and purification of the residue by flash chromatography (ethyl acetate/petroleum ether, 4:5) gave 99 mg of **13** (61%), white needles, m.p. 118°C, R_f = 0.21. − IR (KBr): $\tilde{\nu}$ = 1775 cm^{-1}, 1731, 1724 (C=O), 1358, 1347 (SO_2OR), 1251 (C−O), 1183, 1171 (SO_2OR). − ^1H NMR ($CDCl_3$): δ = 1.20 (d, J = 7.2 Hz, 3 H), 1.51 (d, J = 6.2 Hz, 3 H), 2.02 (s, 3 H), 2.26 (s, 3 H), 2.57 (dd, J = 3.3, 17.9 Hz, 1 H), 2.67−2.93 (m, 4 H), 3.70 (s, 3 H), 5.04 (ddq, J_d = 3.3, 12.0 Hz, J_q = 6.2 Hz, 1 H), 5.34 (m_c, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 12.33 (q), 20.25 (q), 20.66 (q), 20.85 (q), 26.25 (t), 35.56 (t), 42.36 (d), 51.82 (q), 71.81 (d), 75.48 (d), 125.05 (s), 152.78 (s), 167.65 (s), 170.17 (s), 173.07 (s). − MS (GC/MS, 70 eV); *m/z* (%): 378 (8) [M^+], 347 (1) [$M^+ - OCH_3$], 346 (2) [$M^+ - HOCH_3$], 43 (100) [$OCCH_3$]. − $C_{15}H_{22}O_9S$ (378.40): calcd. C 47.61, H 5.86; found C 47.82, H 5.95.

Hemi-acetal **14a** *by Oxidative Cleavage of Sultone* **5**: To a solution of sultone **5**[15] (400 mg, 1.72 mmol) in methanol (3 ml) and CH_2Cl_2 (12 ml) was added $NaHCO_3$ (500 mg, 6.0 mmol). After cooling to −78°C, the mixture was ozonized until it turned blue. Excess ozone was removed by purging with argon, and the mixture was allowed to warm to room temperature. Benzene (10 ml) was added, the mixture was filtered, and the solvents were removed at 0°C in vacuo behind a safety shield. The solid residue was taken up in CH_2Cl_2 (4 ml), and treated at 0°C with acetic anhydride (0.16 ml, 1.72 mmol) and pyridine (0.28 ml, 3.44 mmol). After stirring for 12 h at room temperature, the solution was diluted with diethyl ether (50 ml), washed successively with 0.1 N HCl (10 ml), H_2O (10 ml), sat. aqueous Na_2CO_3 (10 ml), H_2O (10 ml), and dried with $MgSO_4$. Concentration in vacuo and purification of the residue by flash chromatography (ethyl acetate/petroleum ether, 4:5) gave 352 mg of **14a** (69%), white needles, m.p. 106°C, R_f = 0.21. − IR (KBr): $\tilde{\nu}$ = 3454 cm^{-1} (OH), 1714 (C=O), 1381, 1361 (SO_2OR), 1274 (s, C−O), 1179 (SO_2OR). − ^1H NMR ($CDCl_3$): δ = 1.27 (d, J = 7.2 Hz, 3 H), 1.44 (d, J = 6.3 Hz, 3 H), 2.08 (dd, J = 11.8, 14.8 Hz, 1 H), 2.26 (ddd, J = 0.8, 2.0, 14.9 Hz, 1 H), 2.47 (ddd, J = 7.3, 9.2, 14.1 Hz, 1 H), 2.62−2.73 (m, 2 H), 3.62 (d, J = 7.3 Hz, 1 H), 3.73 (s, 3 H), 4.31 (m_c, 1 H, O*H*), 4.65 (m_c, 1 H), 4.75 (ddq, J_d = 2.0, 11.8 Hz, J_q = 6.3 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 14.76 (q), 20.25 (q), 29.42 (t), 41.11 (t), 45.56 (d), 52.10 (q), 65.68 (d), 77.03 (d), 81.65 (d), 104.50 (s), 175.53 (s). − MS [GC/MS, 70 eV, after silylation with *N,O*-bis(trimethylsilyl)acetamide]; *m/z* (%): 351 (4) [$M^+ - CH_3$], 335 (8) [$M^+ - OCH_3$], 319 (32) [$M^+ - CH_3OH - CH_3$], 279 (32) [$M^+ - CH_3CHCO_2CH_3$], 245 (16) [$M^+ - HOSi(CH_3)_3 - OCH_3$], 75 (65) [$(CH_3)_2Si{=}OH^+$], 73 (100) [$(CH_3)_3Si^+$]. − $C_{11}H_{18}O_7S$ (294.32): calcd. C 44.89, H 6.16; found C 44.98, H 6.13.

Hemi-Acetal **14** *(2 Diastereomers) by Oxidative Cleavage of the Mixture of Sultones* **5 + 6 + 7**: The procedure for preparation of **14a** from **5** was applied. From the mixture of sultones **5** + **6** + **7**[15] (234 mg, 1.01 mmol) in methanol (2 ml) and CH_2Cl_2 (8 ml) containing $NaHCO_3$ (250 mg, 3 mmol) was obtained after eliminative workup with acetic anhydride (0.09 ml, 1.01 mmol) and pyridine (0.16 ml, 2.02 mmol) followed by purification as described above 196 mg of **14** (66%), R_f = 0.21, with a ratio **14a**/**14b** = 93:7 according to capillary GC analysis, and 27 mg of **7** (9%), white crystals, m.p. 115°C, R_f = 0.17.

Hemi-Acetal **14b**: MS [GC/MS, 70 eV, after silylation with *N,O*-bis(trimethylsilyl)acetamide]; *m/z* (%): 351 (5) [$M^+ - CH_3$], 335 (2) [$M^+ - OCH_3$], 319 (9) [$M^+ - CH_3OH - CH_3$], 279 (14) [$M^+ - CH_3CHCO_2CH_3$], 245 (6) [$M^+ - HOSi(CH_3)_3 - OCH_3$], 75 (63) [$(CH_3)_2Si{=}OH^+$], 73 (100) [$(CH_3)_3Si^+$].

Sultone **7**: IR (KBr): $\tilde{\nu}$ = 3535 cm^{-1} (OH), 1320, 1176 (SO_2OR). − ^1H NMR ($CDCl_3$): δ = 1.02 (d, J = 6.7 Hz, 3 H), 1.46 (d, J = 6.2 Hz, 3 H), 1.70−1.83 (m, 1 H), 1.94−2.24 (m, 3 H), 2.30−2.74 (m, 4 H), 4.03 (m_c, 1 H), 5.00 (ddq, J_d = 3.1, 11.9 Hz, J_q = 6.2 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 17.02 (q), 20.59 (q), 30.87 (t), 31.64 (d), 33.09 (t), 36.87 (t), 67.30 (d), 77.54 (d), 126.23 (s), 140.89 (s). − MS (GC/MS, 70 eV); *m/z* (%): 232 (14) [M^+], 214 (50) [$M^+ - H_2O$], 150 (6) [$M^+ - H_2O - SO_2$], 124 (2) [$M^+ - CH_3CHOSO_2$], 93 (100), 58 (67) [$C_3H_6O^+$]. − $C_{10}H_{16}O_4S$ (232.08): calcd. C 51.71, H 6.94; found C 51.70, H 6.91.

Methyl Ester **15**: To a solution of hemi-acetal **14a** (327 mg, 1.11 mmol) and triethylamine (0.98 ml, 7.02 mmol) in CH_2Cl_2 (15 ml) cooled to 0°C was added mesyl chloride (0.40 ml, 5.16 mmol) over a period of 5 min under argon. After stirring at 0°C for 1 h, the mixture was treated with sat. aqueous $NaHCO_3$ (15 ml), diluted with CH_2Cl_2 (15 ml), and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 ml). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (ethyl acetate/petroleum ether, 4:5) gave 301 mg of **15** (98%), white needles, m.p. 69°C, R_f = 0.37. − IR (KBr): $\tilde{\nu}$ = 1735 cm^{-1} (C=O), 1341, 1329 (SO_2OR), 1211 (C−O), 1188 (SO_2OR). − ^1H NMR ($CDCl_3$): δ = 1.20 (d, J = 6.9 Hz, 3 H), 1.54 (d, J = 6.4 Hz, 3 H), 2.39 (dddd, J = 1.2, 2.5, 3.7, 17.7 Hz, 1 H), 2.51 (dddd, J = 2.7, 2.7, 11.0, 17.9 Hz, 1 H), 2.79 (m_c, 1 H), 2.89 (dddd, J = 1.0, 2.9, 7.2, 14.1 Hz, 1 H), 3.15 (dddd, J = 2.4, 2.4, 10.3, 14.1 Hz, 1 H), 3.72 (s, 3 H), 4.96 (ddq, J_d = 3.8, 11.0 Hz, J_q = 6.2 Hz, 1 H), 5.02 (ddd, J = 7.2, 7.6, 10.3 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 12.24 (q), 20.34 (q), 29.91 (t), 31.64 (t), 44.04 (d), 52.00 (q), 76.63 (d), 84.52 (d), 106.61 (s), 161.94 (s), 173.13 (s). − MS (GC/MS, 70 eV); *m/z* (%): 276 (16) [M^+], 245 (8) [$M^+ - OCH_3$], 217 (28) [$M^+ - CO_2CH_3$], 189 (47) [$M^+ - CH_3CHCO_2CH_3$], 88 (100) [$CH_3CH_2CO_2CH_3^+$]. − $C_{11}H_{16}O_6S$ (276.31): calcd. C 47.82, H 5.84; found C 47.81, H 5.93.

Acid **16**: To a solution of methyl ester **15** (160 mg, 0.58 mmol) in acetone (2 ml) was added aqueous phosphate buffer pH 7 (0.05 M, 20 ml) and pig liver esterase (3 mg). The mixture was stirred for 3 h at room temperature, while pH 7 was maintained by addition of 0.2 N NaOH. Extraction with ethyl acetate (20 × 10 ml), drying with $MgSO_4$, and removal of the solvent in vacuo left 149 mg of **16** (98%), colorless crystals, m.p. 100−102°C. Due to the instability of the product, it was immediately subjected to the reduction experiments mentioned in the text. − ^{1}H NMR ($CDCl_3$): δ = 1.22 (d, *J* = 6.9 Hz, 3 H), 1.54 (d, *J* = 6.4 Hz, 3 H), 2.34−2.56 (m, 2 H), 2.78−2.83 (m_c, 2 H), 3.15 (dd, *J* = 10.3, 14.1 Hz, 1 H), 4.90−5.06 (m, 2 H).

S,O-Acetal **17a** *from Hemi-Acetal* **14a**: To a solution of hemiacetal **14a** (440 mg, 1.50 mmol) in CH_2Cl_2 (3 ml) was added thiophenol (1 ml) and $BF{\cdot}Et_2O$ (0.21 ml, 1.72 mmol) under argon. After stirring for 1 h at room temperature, the solution was treated with sat. aqueous $NaHCO_3$ (3 ml) and extracted with CH_2Cl_2 (5 × 5 ml). The combined organic layers were washed with brine (5 ml) and dried with $MgSO_4$. Removal of the solvent in vacuo and purification of the residue by flash chromatography (ethyl acetate/petroleum ether, 1:6) gave 549 mg of **17a** (95%), white solid, m.p. 98°C, R_f = 0.20. − IR (KBr): $\tilde{\nu}$ = 1735 cm^{-1} (C=O), 1361 (SO_2OR), 1265 (C−O), 1175 (SO_2OR), 765 (Ph). − ^{1}H NMR ($CDCl_3$): δ = 1.20 (d, *J* = 6.9 Hz, 3 H), 1.33 (d, *J* = 6.4 Hz, 3 H), 2.16−2.18 (m, 2 H), 2.62 (ddd, *J* = 7.2, 9.5, 14.1 Hz, 1 H), 2.83 (dd, *J* = 6.9, 14.1 Hz, 1 H), 3.11 (dq, J_d = 10.5 Hz, J_q = 7.2 Hz, 1 H), 3.76 (s, 3 H), 3.82 (d, *J* = 7.2 Hz, 1 H), 4.76−4.93 (m, 2 H), 7.32−7.44 (m, 3 H), 7.53−7.59 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 14.02 (q), 20.19 (q), 31.71 (t), 41.45 (t), 46.81 (d), 51.83 (q), 65.10 (d), 78.11 (d), 83.30 (d), 95.37 (s), 129.23 (d), 129.64 (d), 130.04 (s), 136.11 (d), 174.66 (s). − MS (GC/MS, 70 eV); *m/z* (%): 355 (5) [$M^+ - OCH_3$], 278 (14) [$M^+ - CH_3CHOSO_2$], 277 (100) [$M^+ - SPh$], 245 (60) [$M^+ - PhSH - OCH_3$], 109 (74) [PhS^+], 108 (8) [$CH_3CHOSO_2^+$]. − $C_{17}H_{22}O_6S_2$ (386.49): calcd. C 52.83, H 5.74; found C 52.72, H 5.61.

S,O-Acetals **17** *(2 Diastereomers) from Hemi-Acetals* **14**: The procedure for preparation of **17a** from **14a** was applied. From the mixture (**14a**/**14b** = 93:7) of hemi-acetals **14** (153 mg, 0.52 mmol) in CH_2Cl_2 (2 ml), thiophenol (0.4 ml), and $BF_3{\cdot}Et_2O$ (0.08 ml, 0.66 mmol) was obtained after purification as described above 187 mg of **17** (93%). The ratio **17a**/**17b** could not be determined by capillary GC analysis due to partial decomposition.

Methyl Nonactate (**20**) *by Reductive Desulfurization of S,O-Acetal* **17a**: A neutral Raney Ni suspension (activity W-2) in EtOH was freshly prepared as follows[20]. Powdered nickel aluminum alloy (2 g, 30−50% Ni) was suspended in H_2O (20 ml) and cautiously treated with solid NaOH (2.6 g) in small portions without cooling. After an induction period of about 30−60 s, a vigorous reaction occurred. When the addition was complete, the suspension was stirred for further 30 min, filtered through a D4 funnel and washed with H_2O (3 ×) and subsequently with EtOH until neutral (***CAUTION:*** Do not completely remove EtOH from the suspension!). To this suspension of Raney Ni in EtOH was added *S,O*-acetal **17a** (207 mg, 0.54 mmol), and the resultant mixture was stirred for 12 h at room temperature. Filtration through silica gel (elution with ether) and flash chromatography (ether/ethyl acetate/petroleum ether, 1:2:2) yielded 59 mg of **20** (51%), R_f = 0.28, with a ratio **20**/6-*epi*-**20** = 96:4 according to capillary GC analysis, and 51 mg of **19** (34%), white solid, m.p. 113−115°C, R_f = 0.26.

Methyl Nonactate (**20**)[7c][22]: IR (KBr): $\tilde{\nu}$ = 3427 cm^{-1} (OH), 1739 (C=O). − ^{1}H NMR ($CDCl_3$): δ = 1.13 (d, *J* = 6.9 Hz, 3 H), 1.21 (d, *J* = 6.4 Hz, 3 H), 1.51−1.70 (m, 3 H), 1.75 (ddd, *J* = 4.1, 7.6, 14.5 Hz, 1 H), 1.94−2.07 (m, 2 H), 2.54 (dq, J_d = 8.4 Hz, J_q = 6.9 Hz, 1 H), 3.69 (s, 3 H), 3.95−4.03 (m, 1 H), 4.01−4.09 (m, including J_q = 6.4 Hz, 1 H), 4.09−4.18 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 13.41 (q), 23.05 (q), 28.71 (t), 30.56 (t), 42.83 (t), 45.22 (d), 51.63 (q), 65.17 (d), 78.13 (d), 80.98 (d), 175.20 (s). − MS [GC/MS, 70 eV, after silylation with *N,O*-bis(trimethylsilyl)-acetamide]; *m/z* (%): 273 (6) [$M^+ - CH_3$], 257 (4) [$M^+ - OCH_3$], 229 (38) [$M^+ - CO_2CH_3$], 201 (12) [$M^+ - CH_3CHCO_2CH_3$], 198 (40) [$M^+ - HOSi(CH_3)_3$], 157 (22) [$M^+ - CH_2CHCH_3OSi(CH_3)_3$], 125 (22) [$M^+ - CH_2CHCH_3OSi(CH_3)_3 - HOCH_3$], 117 (100), 111 (22) [$M^+ - CH_3CHCO_2CH_3 - HOSi(CH_3)_3$], 75 (32) [$(CH_3)_2Si{=}OH^+$], 73 (68) [$(CH_3)_3Si^+$]. − MS ($NH_3$-DCI); *m/z* (%): 234 (100) [$M + NH_4^+$], 217 (55) [$M + H^+$]. − $C_{11}H_{20}O_4$ (216.28): calcd. C 61.09, H 9.32; found C 60.82, H 9.19.

Minor Diastereomer 6-*epi*-**20**[7c][22]: MS [GC/MS, 70 eV, after silylation with *N,O*-bis(trimethylsilyl)acetamide]; *m/z* (%): 273 (3) [$M^+ - CH_3$], 229 (27) [$M^+ - CO_2CH_3$], 201 (19) [$M^+ - CH_3CHCO_2CH_3$], 198 (25) [$M^+ - HOSi(CH_3)_3$], 157 (22) [$M^+ - CH_2CHCH_3OSi(CH_3)_3$], 125 (22) [$M^+ - CH_2CHCH_3OSi(CH_3)_3 - HOCH_3$], 117 (100), 111 (22) [$M^+ - CH_3CHCO_2CH_3 - HOSi(CH_3)_3$], 75 (36) [$(CH_3)_2Si{=}OH^+$], 73 (88) [$(CH_3)_3Si^+$].

Sultone **19**: IR (KBr): $\tilde{\nu}$ = 1741 cm^{-1} (C=O), 1366 (SO_2OR), 1252 (C−O), 1168 (SO_2OR). − ^{1}H NMR ($CDCl_3$): δ = 1.15 (d, *J* = 6.9 Hz, 3 H), 1.42 (d, *J* = 6.4 Hz, 3 H), 1.87 (ddd, *J* = 3.1, 11.7, 15.0 Hz, 1 H), 2.04−2.16 (m, 2 H), 2.59 (dq, J_d = 7.2 Hz, J_q = 7.2 Hz, 1 H), 2.71 (dd, *J* = 7.2, 14.3 Hz, 1 H), 3.62 (dd, *J* = 4.5, 7.4 Hz, 1 H), 3.68 (s, 3 H), 4.43 (m_c, 1 H), 4.62 (m_c, 1 H), 5.04 (ddq, J_d = 1.9, 12.3 Hz, J_q = 6.4 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 13.08 (q), 20.59 (q), 31.41 (t), 33.63 (t), 45.26 (d), 51.73 (q), 59.64 (d), 76.53 (d), 77.88 (d), 79.93 (d), 174.22 (s). − MS (GC/MS, 70 eV); *m/z* (%): 247 (8) [$M^+ - OCH_3$], 219 (2) [$M^+ - CO_2CH_3$], 191 (11) [$M^+ - CH_3CHCO_2CH_3$], 109 (100). − MS (NH_3-DCI); *m/z* (%): 296 (100) [$M + NH_4^+$]. − MS (HR-EI): 278.0832 ($C_{11}H_{18}O_6S$, M^+: calcd. 278.0824).

Methyl Nonactate (**20**) *by Reductive Desulfurization of the Mixture of S,O-Acetals* **17**: The procedure for preparation of **20** from **17a** was applied. From the mixture of **17a** + **17b** (142 mg, 0.37 mmol) was obtained after purification as described above 41 mg of **20** (51%), with a ratio **20**/6-*epi*-**20** = 96:4 according to capillary GC analysis, and 33 mg of **19** (32%).

☆ Dedicated to Professor *Reinhard W. Hoffmann* on the occasion of his 65th birthday.

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[17] Crystal data for **11**: $C_{16}H_{30}O_6SSi$, M = 378.55, triclinic, space group $P\bar{1}$ (No. 2), a = 6.741(1), b = 12.232(1), c = 12.523(2) Å, α = 86.78(1), β = 74.82(1), γ = 89.22(1)°, V = 995.0(2) Å^3, Z = 2, D_c = 1.264 g cm^{-3}, μ = 22.6 cm^{-1}, empirical absorption correction via ψ-scan data (0.941 < C < 0.999), $F(000)$ = 408, colorless crystal with dimensions 0.35 × 0.3 × 0.15 mm, λ = 1.54178 Å, T = 223(2) K, Θ range 3.62 to 74.25°, index ranges $0 \le h \le 8$, $-15 \le k \le 15$, $-15 \le l \le 15$, 4436 reflections collected, 4075 independent [R_{int} = 0.066], full-matrix least-squares refinement on F^2, 227 parameters, GOF on F^2 1.085, final R indices [$I > 2\sigma(I)$] R = 0.044 and wR^2 = 0.126, largest difference peak and hole 0.31 and −0.44 eÅ^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101756. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(0)1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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