101. Synthetic Studies towards Pseurotin A

Part 3[1])

Synthesis of a Related Highly Functionalized γ-Lactone

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Dedicated to *Albert Eschenmoser* on the occasion of his 70th birthday

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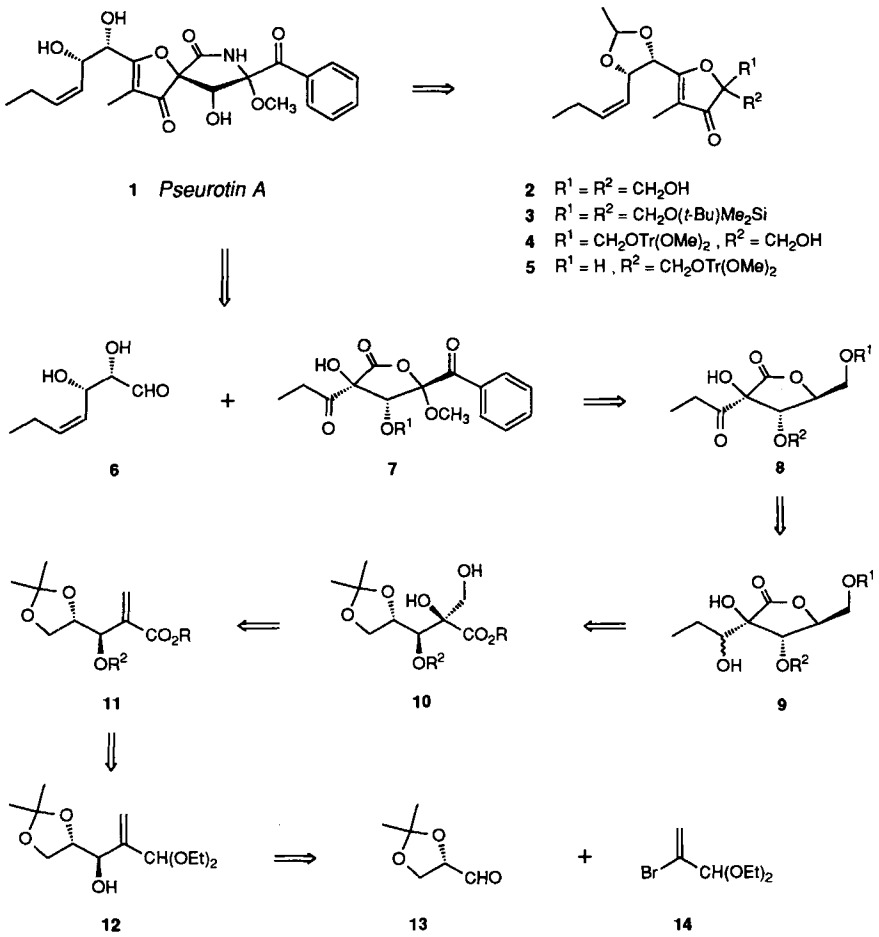
A new general concept for the total synthesis of pseurotin A (**1**), a secondary metabolite of *Pseudeurotium ovalis* STOLK, which possesses a highly substituted 1-oxa-7-azaspiro[4.4]nonane skeleton, is presented. A key intermediate of the planned reaction sequence is the functionalized γ-lactone **8**. The corresponding protected compound **52** was prepared using (*S*)-*O*,*O*-isopropylideneglyceraldehyde (**13**) and the bromoacetal **14** as starting material. γ-Lactone **52** was obtained in enantiomerically pure state in ten steps. It possesses the desired configuration.

Introduction. – The pseurotins are a small family of secondary microbial metabolites which have been isolated from cultures of *Pseudeurotium ovalis* STOLK. The isolation, spectral data, and chemical properties as well as biosynthetic studies on the main component, pseurotin A (**1**), have been already reported [2]. Pseurotin A (**1**) possesses a novel highly substituted 1-oxa-7-azaspiro[4.4]nonane skeleton and five chiral centers. First approaches towards the total synthesis of the unique spirocyclic system of pseurotin A (**1**) have been focused on the preparation of various substituted 2*H*-furan-3-ones **2**–**5** corresponding to the 'western' moiety of the natural product as suitably functionalized intermediates [1] [3] (*Scheme 1*). Although differentiation in the protection of the two primary OH groups of **2** was achieved, the aldehyde obtained by oxidation of the remaining primary OH group proved to be unstable. It decarbonylated immediately yielding **5**. Also the subsequent deprotection of **5** and conversion of the CH_2OH group into an aldehyde or carboxyl group proved to be very difficult [1]. Therefore, we decided to change the strategy for the synthesis of pseurotin A (**1**). Accordingly, we envisaged to elaborate first the 'eastern' part of the molecule by the construction of a suitable precursor of the γ-lactam to which the 'western' side chain with the simultaneous formation of the furanone moiety could be attached. The retrosynthetic analysis for the realization of the new concept is outlined in *Scheme 1*. The key intermediate is the highly functionalized γ-lactone **8**, possessing three chiral centers with the required configuration. Starting from this building block, it should be possible to elaborate the desired γ-lactam system. The next step is the conversion of **8** into **7**. Subsequent aldol condensation of **7** with the unsaturated dihydroxyaldehyde **6**, which had been prepared earlier [3], would complete

[1]) Part 2: [1].

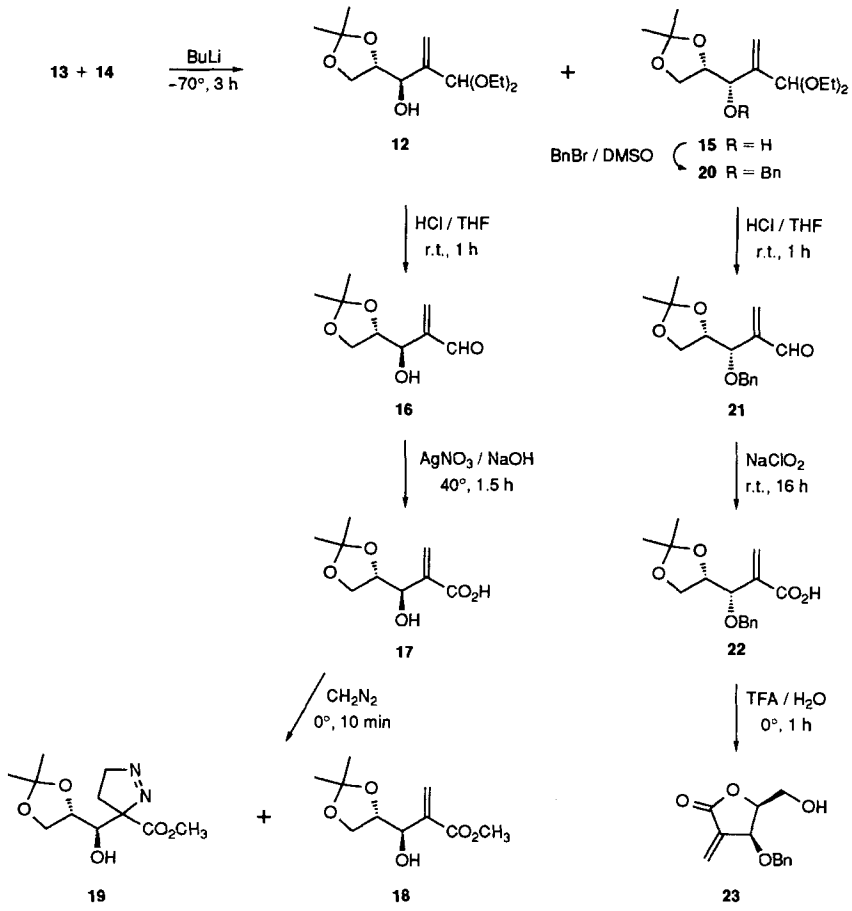
Scheme 1



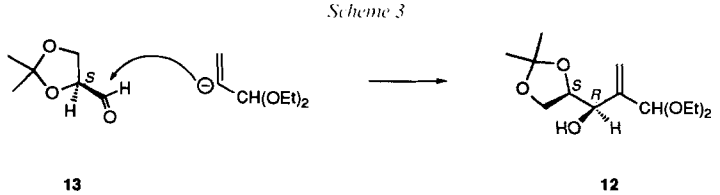
the synthesis of **1**. γ-Lactone **8** is obtained from ester **10** *via* **9** by oxidation and a *Grignard* alkylation. Dihydroxy ester **10** is generated from the α-methylidene-substituted ester **11** by stereoselective dihydroxylation. The latter is accessible from acetal **12** which is the product of the reaction of (*S*)-*O*,*O*-isopropylideneglyceraldehyde (**13**) with bromoacetal **14**. (*S*)-Glyceraldehyde provides the β-OH group of **12** possessing the desired configuration. In this paper, the stereoselective synthesis of γ-lactone **8**, or more specifically, of the protected γ-lactone **52** is described.

Results and Discussion. – Treatment of (*S*)-*O*,*O*-isopropylideneglyceraldehyde (**13**) [4] with 2-bromo-3,3-diethoxyprop-2-ene (**14**) [5] in the presence of BuLi in THF at −70° gave a mixture of the diastereoisomers **12** and **15** in a ratio of 7:3 (total yield 70%) after chromatographic separation (silica gel; *Scheme 2*). The predominant formation of **12** can

Scheme 2



Scheme 3



be explained assuming that the glyceraldehyde derivative acts as a 'template' to control the steric course of the attack of the anion generated from **14** (*Scheme 3*). The determination of the configuration as described in [6] was unsatisfactory. However, the absolute configuration of **12** and **15** could be established using the ^{13}C-NMR method described for γ-alkoxy-β-hydroxy-α-methylidene esters and analogs [7].

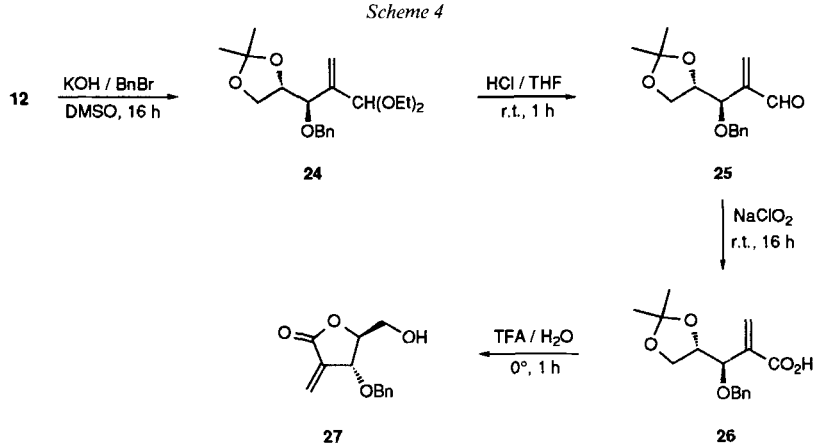
The signals of C(2), C(3), C(4), and C(5) of the '*anti*'(*u*)-isomer **12** appear at higher field as compared with those of the '*syn*'(*l*)-isomer **15**. This behavior can be explained by assuming intramolecular H-bonding between

OH–C(3) and the alkoxy group at C(4). Therefore, the '*anti*'-isomer is sterically more congested, and the signals of C(2) and C(5) are shifted upfield. The higher steric compression is probably also responsible for the upfield shift of the signals of C(3) and C(4).

Acetal **12** was converted to the free aldehyde **16** with 1% HCl in THF in quantitative yield (*Scheme 2*). Oxidation of **16** with $AgNO_3$ and NaOH [8] at 40° yielded carboxylic acid **17** (84%). The subsequent conversion to methyl ester **18** with CH_2N_2 proceeded only with low yield, because the main product was the 4,5-dihydro-3*H*-pyrazole derivative **19**.

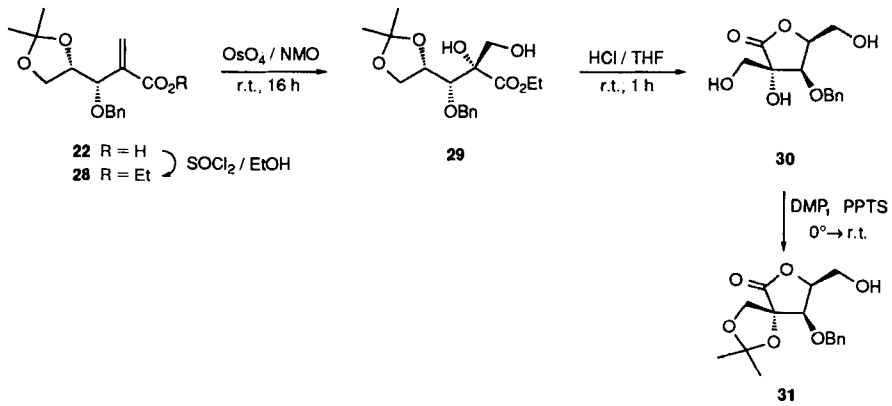
Before further reactions were carried out with ester **18**, the undesired isomer **15** was used to explore the best conditions for the planned reactions. After benzyl protection of the free OH group (→ **20**) and acetal deprotection as described for **16**, aldehyde **21** was smoothly oxidized to carboxylic acid **22** with $NaClO_2$, 2-methylbut-2-ene, *t*-BuOH, and NaH_2PO_4 according to *Bal et al.* [9] (*Scheme 2*). By treatment with aqueous CF_3COOH at 0°, **22** cyclized to γ-lactone **23**. When this reaction sequence was applied to the benzyl derivative **24** of compound **12**, aldehyde **25** and carboxylic acid **26** were obtained in good yields, but γ-lactone **27** proved to be unstable (*Scheme 4*); rapid polymerization took place.

Scheme 4

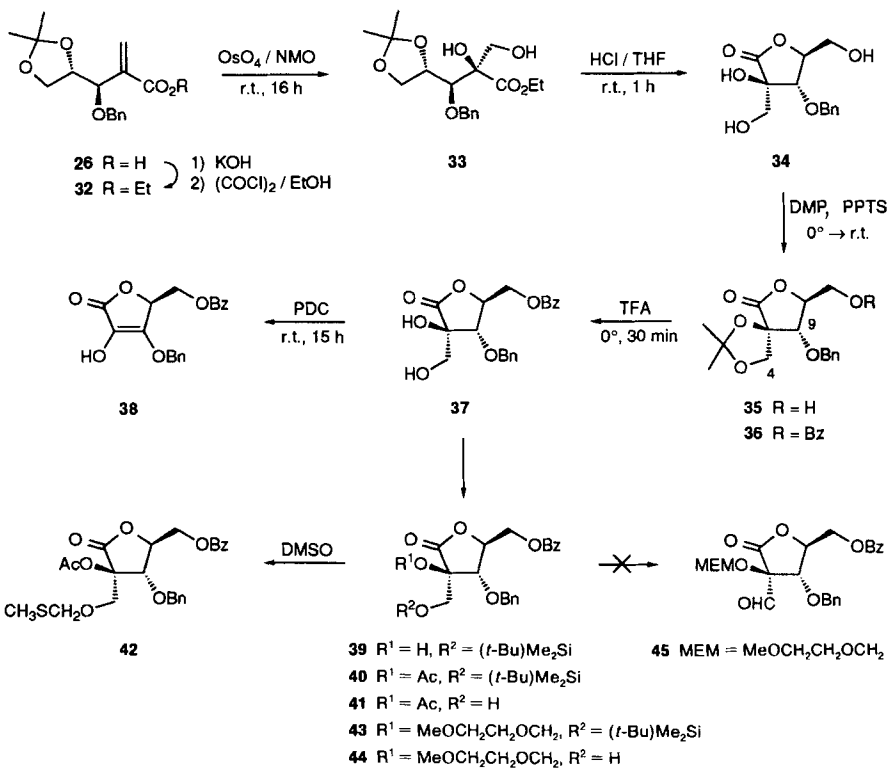


To prevent polymerization of the γ-lactone, it was decided to dihydroxylate the C=C bond of the corresponding acid prior to the lactonization. Thus, **22** was converted to ethyl ester **28** by treatment with either $SOCl_2$ [10a] or $(COCl)_2$ [10b]. But the yields were poor, even after applying several other methods [11]. Dihydroxylation of **28** was then effected using *N*-methylmorpholine *N*-oxide (NMO) with a catalytic amount of OsO_4 to give the dihydroxy ester **29** in excellent yield (*Scheme 5*). Regarding the configuration of **29**, it is known that osmylation of allylic ethers or alcohols in general occurs with high facial selectivity introducing the new OH groups in '*anti*'-position to the preexisting alkoxy or OH group as demonstrated, *e.g.* by *Kishi* and coworkers [12], and *Ikemoto* and *Schreiber* [13]. However, upon osmylation of γ-alkoxy-β-hydroxy-α-methylidene esters, the new OH groups are generally directed to a '*syn*'-position to the preexisting OH group, as shown by *Scolastico* and coworkers [14]. Dihydroxy ester **29** was then transformed as usual to γ-lactone **30** which was protected by an isopropylidene group (→ **31**) for spectral analyses. Similarly, acid **26** yielded, *via* **32** and **33**, γ-lactone **34** and its isopropylidene

Scheme 5



Scheme 6



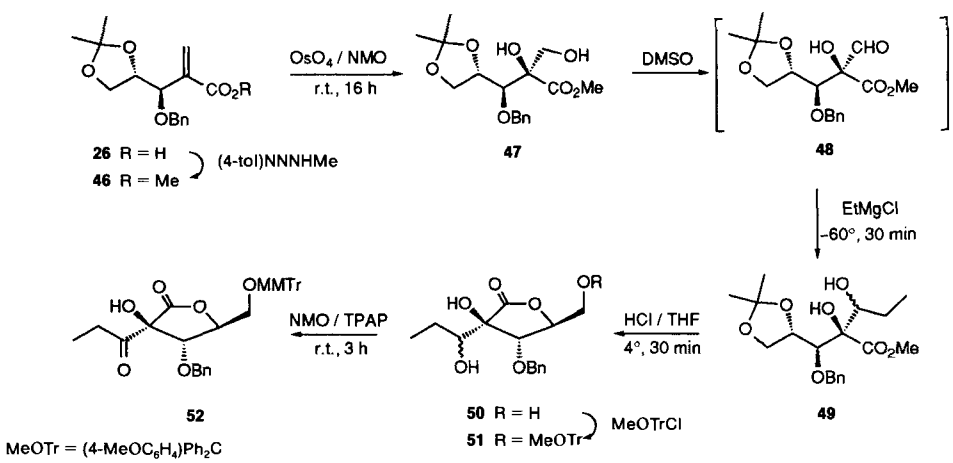
derivative **35** (*Scheme 6*). The configuration of the γ-lactones was established by measuring the NOE's in the ^{1}H-NMR spectra. Irradiation of H–C(9) at 4.83 ppm of **35** led to a large enhancement of the signal of one of the protons of PhCH_2 and not of one of CH_2(4). Thus, osmylation of analogs of γ-alkoxy-β-hydroxy-α-methylidene ethyl esters with a

protected or unprotected β-OH group can lead to '*syn*'-orientation of the new OH groups with respect to the preexisting OH or alkoxy group.

The next steps, the conversion of the CH_2OH group of **34** into a formyl group proved to be very difficult without selective protection of the various OH groups. The acetonide **35** was first benzoylated (→ **36**) and the isopropylidene group removed with aqueous CF_3COOH to give diol **37** in excellent yield. Treatment of the latter with pyridinium dichromate (PDC) or pyridinium chlorochromate (PCC) [15] did not yield the desired aldehyde but enol lactone **38** (*Scheme 6*). Therefore, the tertiary OH group of **37** needed to be protected by an Ac group *via* **39** and **40** (see *Exper. Part*) before attempts were undertaken to oxidize the primary OH group. Treatment of the resulting monohydroxy compound **41** with DMSO, $SOCl_2$ or $(CF_3CO)_2O$ and Et_3N in CH_2Cl_2 according to *Swern* and coworkers [16] did not give the expected aldehyde but thioacetal **42**. Neither application of dipyridine chromium(VI)oxide (*Collins*) [17] nor of *Dess-Martin* periodinane [18] was successful. Oxidation of the (2-methoxyethoxy)methyl (MEM)-protected monohydroxy compound **44** (obtained from **39** *via* **43**) did not yield aldehyde **45** either.

Finally, success was attained, when the problem of the preparation of an β,γ-dialkoxy-α-methylidene ester was solved in a satisfactory manner. Treatment of carboxylic acid **26** with 3-methyl-1-(4-tolyl)triazene in Et_2O according to *White et al.* [19] yielded methyl ester **46** (98%; *Scheme 7*). Dihydroxylation with OsO_4 gave diol **47** in nearly

Scheme 7



quantitative yield. The subsequent oxidation by the *Swern* method failed but was successful when $SOCl_2$ was replaced by $(CF_3CO)_2O$ [16]. The aldehyde **48** obtained was treated with EtMgCl at –60° to give dihydroxy ester **49** in 53% yield; thus, the desired extension of the chain by two C-atoms has been achieved prior to lactonization. As mentioned earlier, this C_3 unit is required for the attachment to aldehyde **6** of the 'western' part of the natural product **1** [3] and for the construction of the spirocyclic system according to the synthetic concept presented in *Scheme 1*. By treatment of **49** with HCl in THF, selective removal of the protecting isopropylidene group, hydrolysis of the methyl ester, and

subsequent lactonization was achieved (98% yield). The primary OH group of the resulting trihydroxy-γ-lactone **50** was selectively protected with the (4-methoxyphenyl)-diphenylmethyl (MeOTr) group to give dihydroxy lactone **51**. Oxidation to the target keto lactone **52** was successful neither by *Swern*'s nor by *Dess-Martin*'s method. It was achieved by treating **51** with tetrapropylammonium perruthenate (TPAP), a reagent developed by *Griffith* and *Ley* [20].

By the synthesis of the γ-lactone **52** the key intermediate **8** of our synthetic plan has become available in ten steps with correct configuration and excellent overall yield.

Financial support of these investigations by the *Swiss National Science Foundation* is gratefully acknowledged.

Experimental Part

General. Moisture-sensitive reactions were carried out in flame-dried glass ware under Ar or N_2. Org. extracts were dried (Na_2SO_4) and evaporated below 40°. Anal. samples were dried overnight under reduced pressure or over P_2O_5. TLC: silica gel *60 F254* (*Merck*; detection with UV light, I_2, 10% H_2SO_4 in MeOH, or $KMnO_4$ soln. $KMnO_4$ (2.0 g), Na_2CO_3 (4.0 g), H_2O (100 ml)). Column chromatography (CC): silica gel *60* (0.063–0.200 mm; *Merck* or *Chemische Fabrik Uetikon*); FC = flash chromatography. IR: *Perkin-Elmer-781* IR spectrometer; $\tilde{\nu}$ in cm^{-1}. NMR: *Varian-EM-360* (^1H, 60 MHz), *Varian-Gemini-300* (^1H, 300 MHz; ^{13}C, 75 MHz), or *Varian-VXR-400* (^1H, 400 MHz; ^{13}C, 101 MHz) spectrometer; δ in ppm downfield from internal $SiMe_4$ (= 0 ppm), J in Hz. MS: *VG-70-250* spectrometer; Cl with NH_3. PE = petroleum ether.

(3R,4S)- and (3S,4S)-2-(Diethoxymethyl)-4,5-[(1-methylethylidene)dioxy]pent-1-en-3-ol (**12** and **15**, resp.). To a soln. of 2-bromo-3,3-diethoxyprop-1-ene (**14**; 2.09 g, 10 mmol) in dry THF, 1.6M BuLi in hexane (6.25 ml) was added dropwise under Ar at −70°. After 15 min, 10 mmol of (*S*)-*O*,*O*-isopropylideneglyceraldehyde (**13**) were added. The mixture was stirred for 3 h at −70°, then warmed to r.t., poured into a buffer soln. (pH 7), and extracted with Et_2O. The org. extract was dried (Na_2SO_4) and evaporated: **12**/**15**. The mixture was separated by FC (hexane/AcOEt 5:1): 1.29 g of **12** and 0.53 g of **15** (combined yield 70%). Colorless liquids.

12: $[\alpha]_D^{23} = -8.1$ ($c = 0.47$, $CHCl_3$). IR (film): 3470, 2980, 2930, 2880, 1380, 1370, 1250, 1210, 1155, 1110, 1060, 930, 850. ^1H-NMR (300 MHz, $CDCl_3$): 1.19–1.28 (*2t*, $J = 7.0$, 2 $MeCH_2O$); 1.36, 1.44 (*2s*, Me_2C); 3.07 (br., OH); 3.43–3.54 (*m*, 1 $MeCH_2O$); 3.60–3.73 (*m*, 1 $MeCH_2O$); 3.90–4.00 (*m*, $CH_2(5)$); 4.35–4.40 (*m*, H–C(3), H–C(4)); 4.87 (*s*, $(EtO)_2CH$); 5.35 (*s*, 1 H–C(1)); 5.43 (*s*, 1 H–C(1)). ^{13}C-NMR (75 MHz, $CDCl_3$): 15.2; 25.3; 26.7; 62.6; 62.9; 65.7; 71.3; 77.4; 103.9; 109.7; 116.3; 144.4.

15: $[\alpha]_D^{23} = +11.6$ ($c = 3.7$, $CHCl_3$). IR (film): 3460, 2980, 2930, 2890, 1380, 1370, 1250, 1210, 1155, 1110, 1060, 930, 845. ^1H-NMR (300 MHz, $CDCl_3$): 1.23 (*2t*, $J = 7.1$, 2 $MeCH_2O$); 1.38, 1.46 (*2s*, Me_2C); 2.95 (br., OH); 3.45–3.57 (*m*, 1 $MeCH_2O$); 3.60–3.74 (*m*, 1 $MeCH_2O$); 3.75–4.02 (*2m*, $CH_2(5)$); 4.15 (*d*, $J = 6.6$, H–C(3)); 4.36 (*dd*, $J = 12.9$, 6.6, H–C(4)); 4.92 (*s*, $(EtO)_2CH$); 5.35 (*s*, 1 H–C(1)); 5.38 (*s*, 1 H–C(1)). ^{13}C-NMR (75 MHz, $CDCl_3$): 15.2; 25.5; 26.8; 62.7; 63.0; 66.6; 73.4; 78.6; 103.1; 110.0; 117.1; 145.0.

(3S,4S)-3-(Benzyloxy)-2-(diethoxymethyl)-4,5-[(1-methylethylidene)dioxy]pent-1-ene (**20**). To a stirred soln. of **15** (134 mg, 0.51 mmol) in DMSO (1 ml) at r.t., 3 equiv. of KOH (86 mg, 1.53 mmol) were added in portions under Ar. After 2 h, 1.5 equiv. of benzyl bromide (91 µl, 0.77 mmol) were added, and the mixture was stirred at r.t. for 16 h. After neutralizing and extracting with Et_2O, the extract was dried and evaporated and the residue purified by CC (silica gel; PE/AcOEt 9:1): **20** (162 mg, 90%). Colorless oil. IR (film): 3100, 3070, 3040, 2980, 2940, 2880, 1455, 1380, 1370, 1255, 1210, 1160, 1070, 935, 850, 735, 700. ^1H-NMR (300 MHz, $CDCl_3$): 1.15–1.25 (*2t*, $J = 7.0$, 2 $MeCH_2O$); 1.36, 1.39 (*2s*, Me_2C); 3.40–3.50 (*m*, 1 $MeCH_2O$); 3.55–3.70 (*m*, 1 $MeCH_2O$); 3.73 (*t*, $J = 6.8$, 1 H–C(5)); 3.92 (*t*, $J = 6.8$, 1 H–C(5)); 3.96 (*d*, $J = 7.7$, H–C(3)); 4.36 (*q*, $J = 6.8$, H–C(4)); 4.45 (*A* of *AB*, $J_{AB} = 12.3$, 1 H, $PhCH_2$); 4.64 (*B* of *AB*, $J_{AB} = 12.3$, 1 H, $PhCH_2$); 4.84 (*s*, $(EtO)_2CH$); 5.32 (*s*, 1 H–C(1)); 5.53 (*s*, 1 H–C(1)); 7.20–7.40 (*m*, $PhCH_2$). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.8; 25.2; 26.3; 62.0; 62.9; 65.7; 70.1; 77.5; 80.0; 100.9; 109.1; 117.3; 127.1; 127.5; 127.9; 138.1; 142.5.

2-{(1R,2S)-1-Hydroxy-2,3-[(1-methylethylidene)dioxy]propyl}prop-2-enal (**16**). To a soln. of **12** (1.80 g, 6.9 mmol) in THF (50 ml) under Ar, 6 ml of 1% HCl soln. were added dropwise at r.t. The mixture was stirred for 1 h, neutralized, and extracted with Et_2O. The extract was dried (Na_2SO_4) and evaporated: **16** (1.30 g, quant.). Colorless liquid. IR (film): 3450, 2980, 2960, 2930, 2870, 1695, 1635, 1455, 1380, 1370, 1250, 1215, 1155, 1110, 1065,

960, 845. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.33, 1.43 (2*s*, Me_2C); 4.66–3.17 (*m*, H–C(1'), H–C(2'), CH_2(3')); 6.17 (*s*, 1 H–C(3)); 6.57 (*s*, 1 H–C(3)); 9.50 (*s*, H–C(1)).

2-{(1S,2S)-1-(Benzyloxy)-2,3-[(1-methylethylidene)dioxy]propyl}prop-2-enal (**21**). As described for **16**, with **20** (635 mg, 1.8 mmol): **21** (500 mg, quant.). Colorless oil. IR (film): 3090, 3060, 3040, 2980, 2940, 2870, 1690, 1450, 1380, 1370, 1250, 1210, 1150, 1070, 960, 900, 840, 730, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.34, 1.39 (2*s*, Me_2C); 3.77 (*dd*, J(3'a,2') = J(3'a,3'b) = 6.6, H_a–C(3')); 3.90 (*dd*, J(3'b,2') = J(3'a,3'b) = 6.6, H_b–C(3')); 4.26 (*q*, J = 6.6, H–C(2')); 4.40 (*A* of *AB*, J_{AB} = 12.0, 1 H, PhCH_2); 4.45 (*d*, J = 5.4, 1 H, H–C(1')); 4.56 (*B* of *AB*, J_{AB} = 12.0, 1 H, PhCH_2); 6.29 (*s*, 1 H–C(3)); 6.62 (*s*, 1 H–C(3)); 7.25–7.35 (*m*, *Ph*CH_2); 9.62 (*s*, H–C(1)). ^{13}C-NMR (75 MHz, $CDCl_3$): 25.4; 26.1; 30.2; 65.3; 71.4; 74.2; 77.2; 109.7; 127.6; 128.3; 136.8; 137.6; 146.5; 193.3.

2-{(1R,2S)-1-Hydroxy-2,3-[(1-methylethylidene)dioxy]propyl}prop-2-enoic Acid (**17**). To a soln. of NaOH (1.39 g, 34.8 mmol) in H_2O (20 ml), a mixture of $AgNO_3$ (1.43 g, 8.4 mmol) and **16** (1.10 g, 5.9 mmol) in 50% EtOH (13 ml) was added dropwise under Ar at 40° over 1.5 h. The mixture was stirred for 1 additional h at 40°, filtered and acidified to pH 3. Extraction with Et_2O, drying (Na_2SO_4), and evaporation gave **17** (1.00 g, 84%). Colorless liquid. IR (film): 3450, 2980, 2960, 2930, 2870, 2680, 2600, 1720, 1630, 1430, 1380, 1370, 1250, 1225, 1150, 1100, 1065, 960, 845.

2-{(1S,2S)-1-(Benzyloxy)-2,3-[(methylethylidene)dioxy]propyl}prop-2-enoic Acid (**22**). To a stirred soln. of **21** (350 mg, 1.27 mmol) in *t*-BuOH (30 ml) and 2-methylbut-2-ene (7 ml) at r.t., a soln. of $NaClO_2$ (0.9 g, 10.0 mmol) and NaH_2PO_4 (0.9 g, 7.5 mmol) in H_2O (10 ml) was added dropwise over 10 min under Ar. After stirring overnight, dilute aq. NaOH soln. was added (pH → 9), and the soln. was evaporated. The residue was redissolved in H_2O (30 ml) and the mixture washed with hexane (2 × 15 ml). The aq. layer was acidified to pH 3 and extracted with Et_2O and the extract dried and evaporated: **22** (363 mg, 98%). Colorless oil. IR (film): 3430, 3200, 3100, 3060, 3030, 2980, 2930, 2870, 2700, 2580, 1700, 1630, 1450, 1380, 1370, 1250, 1210, 1150, 1070, 960, 850, 735, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.36, 1.40 (2*s*, Me_2C); 3.82 (*t*, J = 6.6, 1 H–C(3')); 3.96 (*t*, J = 6.6, 1 H–C(3')); 4.36 (*q*, J = 6.4, H–C(2')); 4.43 (*A* of *AB*, J_{AB} = 12.0, 1 H, PhCH_2); 4.44 (*d*, J = 6.9, H–C(1')); 4.64 (*B* of *AB*, J_{AB} = 12.1, 1 H, PhCH_2); 6.08 (*s*, 1 H–C(3)); 6.60 (*s*, 1 H–C(3)); 7.25–7.35 (*m*, *Ph*CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): 25.4; 26.1; 65.3; 71.3; 76.8; 77.4; 110.0; 127.8; 128.4; 130.4; 137.0; 137.6; 170.5.

Methyl 2-{(1R,2S)-1-Hydroxy-2,3-[(1-methylethylidene)dioxy]propyl}propenoate (**18**) *and Methyl 4,5-Dihydro-3-{(1R,2S)-hydroxy-2,3-[(1-methylethylidene)dioxy]propyl}-3H-pyrazole-3-carboxylate* (**19**). To a stirred soln. of **17** (80 mg, 0.4 mmol) in Et_2O (10 ml), excess diazomethane in Et_2O was added at 0° and stirred for 10 min. Evaporation and FC (silica gel) gave **19** (55 mg, 53%) and **18** (30 mg, 35%).

18: IR (film): 3460, 2980, 2930, 2880, 1720, 1630, 1440, 1380, 1370, 1250, 1210, 1150, 1110, 1060, 960, 840. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.35, 1.45 (2*s*, Me_2C); 3.79 (*s*, MeO); 3.93 (*d*, J = 6.3, CH_2(3')); 4.35 (*q*, J = 6.0, H–C(4)); 4.54 (*d*, J = 5.5, H–C(3)); 6.00 (*s*, 1 H–C(3)); 6.37 (*s*, 1 H–C(3)). ^{13}C-NMR (101 MHz, $CDCl_3$): 25.0; 26.6; 52.0; 65.1; 71.1; 76.6; 109.7; 127.6; 138.0; 166.5.

19: IR (film): 3450, 2980, 2950, 2930, 2890, 1730, 1555, 1440, 1380, 1370, 1260, 1215, 1150, 1120, 1060, 980, 885, 870, 840, 800. ^{13}C-NMR (101 MHz, $CDCl_3$): 21.5; 25.3; 26.1; 52.8; 66.8; 71.5; 75.0; 78.8; 102.0; 110.0; 169.3.

(4S,5S)-4-(Benzyloxy)-4,5-dihydro-5-(hydroxymethyl)-3-methylidene-3H-furan-2-one (**23**). Carboxylic acid **22** (100 mg, 0.34 mmol) was added to CF_3COOH (7 ml) and H_2O (1 ml) under Ar at 0° and stirred for 1 h. The mixture was neutralized and extracted with Et_2O, the extract dried (Na_2SO_4) and evaporated and the residue submitted to FC (silica gel; PE/AcOEt 9:1): **23** (68 mg, 85%). Colorless oil. IR (film): 3200, 2930, 2900, 2840, 1770, 1670, 1460, 1410, 1350, 1280, 1240, 1160, 1120, 1070, 750, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.56 (br., OH); 3.88–4.04 (*m*, CH_2OH); 4.54 (*A* of *AB*, J_{AB} = 11.7, 1 H, PhCH_2); 4.59 (*m*, H–C(5)); 4.69 (*B* of *AB*, J_{AB} = 11.6, 1 H, PhCH_2); 4.72 (*d*, J = 6.0, H–C(4)); 5.87 (*s*, 1 H, CH_2=C(3)); 6.42 (*s*, 1 H, CH_2=C(3)); 7.30–7.40 (*m*, *Ph*CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): 61.0; 71.2; 74.8; 80.2; 125.9; 127.8; 128.3; 128.7; 135.4; 136.5; 164.4.

(3R,4S)-3-(Benzyloxy)-2-(diethoxymethyl)-4,5-[(1-methylethylidene)dioxy]pent-1-ene (**24**). As described for **20**, with **12** (610 mg, 2.35 mmol): pure **24** (750 mg, 91%). Colorless oil. IR (film): 3090, 3070, 3040, 2980, 2940, 2880, 1455, 1380, 1370, 1250, 1210, 1160, 1130, 1070, 930, 850, 735, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.17–1.28 (*m*, 2 *Me*CH_2O); 1.34, 1.42 (2*s*, Me_2C); 3.40–3.72 (2*m*, 2 MeCH_2O); 3.90–4.07 (*m*, H–C(3), CH_2(5)); 4.24 (*q*, J = 6.3, H–C(4)); 4.41 (*A* of *AB*, J_{AB} = 11.7, 1 H, PhCH_2); 4.60 (*AB*, J_{AB} = 11.8, 1 H, PhCH_2); 4.90 (*s*, $(EtO)_2CH$); 5.45 (*s*, 1 H–C(1)); 5.54 (*s*, 1 H–C(1)); 7.25–7.35 (*m*, *Ph*CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): 15.1; 25.4; 26.5; 61.3; 62.8; 66.5; 71.1; 78.2; 78.6; 101.3; 109.3; 115.6; 127.6; 127.8; 128.3; 138.4; 144.0.

2-{(1R,2S)-1-(Benzyloxy)-2,3-[(1-methylethylidene)dioxy]propyl}prop-2-enal (**25**). As described for **21**, with **24** (500 mg, 1.43 mmol): **25** (400 mg, 100%). Colorless oil. IR (film): 3090, 3060, 3030, 2980, 2930, 2870, 1690, 1450, 1380, 1370, 1250, 1210, 1155, 1070, 960, 840, 735, 700.

2-{(1R,2S)-1-(Benzyloxy)-2,3-[(1-methylethylidene)dioxy]propyl}prop-2-enoic Acid (**26**). As described for **22**: **26** (550 mg, 98%). Colorless oil. IR (film): 3460, 3320, 3080, 3040, 3000, 2940, 2880, 2660, 2600, 1700, 1630, 1450, 1380, 1370, 1260, 1220, 1160, 1080, 970, 850, 750, 700.

Ethyl 2-{(1S,2S)-1-(Benzyloxy)-2,3-[(1-methylethylidene)dioxy]propyl}prop-2-enoate (**28**). $SOCl_2$ (16 µl, 0.22 mmol) was added under Ar to a stirred mixture of **22** (57 mg, 0.2 mmol) and pyridine (45 µl, 0.56 mmol) in CH_2Cl_2 (3 ml) at r.t. The mixture was stirred for 20 min, then EtOH was added and the mixture stirred at r.t. for 10 h. After transferring into 50 ml of Et_2O, the mixture was washed with aq. $NaHCO_3$ and NH_4Cl soln., dried (Na_2SO_4), and evaporated. The residue was purified by FC (silica gel; PE/AcOEt 9:1): **28** (15 mg, 23%). Colorless oil. IR (film): 3090, 3060, 3030, 2980, 2930, 1720, 1630, 1450, 1380, 1370, 1260, 1210, 1150, 1090, 1070, 850, 735, 700. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.31 (*t*, *J* = 7.0, *Me*CH_2O); 1.35, 1.38 (2*s*, Me_2C); 3.75–3.93 (2*m*, CH_2(3′)); 4.22 (*q*, *J* = 7.0, MeCH_2O); 4.35 (*dd*, *J* = 12.5, 6.7, H–C(2′)); 4.44 (*A* of *AB*, J_{AB} = 11.9, 1 H, PhCH_2); 4.48 (*d*, *J* = 6.7, H–C(1′)); 4.62 (*B* of *AB*, J_{AB} = 11.9, 1 H, PhCH_2); 5.96 (*s*, 1 H–C(3)); 6.43 (*s*, 1 H–C(3)); 7.30–7.35 (*m*, *Ph*CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$): 14.2; 25.5; 26.2; 60.9; 65.4; 71.2; 77.2; 77.5; 109.7; 127.6; 127.7; 128.3; 137.9; 138.0; 166.3.

Ethyl (2S,3R,4S)-3-(Benzyloxy)-2-hydroxy-2-(hydroxymethyl)-4,5-[(1-methylethylidene)dioxy]pentanoate (**29**). To a mixture of *N*-methylmorpholine *N*-oxide (14.9 mg, 0.11 mmol) and 0.1 ml of 0.04M OsO_4 in *t*-BuOH in acetone/H_2O 8:1 (1 ml), a soln. of **28** (18 mg, 0.055 mmol) in acetone/H_2O 8:1 (1 ml) was added. The mixture was stirred overnight at r.t., then Na_2SO_3 (35 mg, 0.22 mmol) was added. After stirring for 1 additional h, the mixture was evaporated and the crude product purified by FC (silica gel; PE/AcOEt 9:1): **29** (18 mg, quant.). Colorless oil. IR (film): 3460, 3090, 3060, 3030, 2980, 2920, 1730, 1450, 1380, 1370, 1250, 1210, 1200, 1150, 1100, 1020, 920, 850, 730, 700. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.28 (*t*, *J* = 7.1, *Me*CH_2O); 1.36, 1.44 (2*s*, Me_2C); 1.70 (*s*, OH); 2.30 (*s*, OH); 3.71 (*A* of *AB*, J_{AB} = 12.0, 1 H, CH_2OH); 3.76 (*d*, *J* = 6.0, H–C(3)); 3.78 (*B* of *AB*, J_{AB} = 12.0, 1 H, CH_2OH); 3.86 (*dd*, *J*(5a,5b) = 8.3, *J*(5a,4) = 7.3, H_a–C(5)); 4.04 (*dd*, *J*(5b,5a) = 8.3, *J*(5b,4) = 6.4, H_b–C(5)); 4.24–4.29 (*m*, MeCH_2O); 4.37 (*m*, H–C(4)); 4.62 (*A* of *AB*, J_{AB} = 11.4, 1 H, PhCH_2); 4.84 (*AB*, J_{AB} = 11.4, 1 H, PhCH_2); 7.25–7.38 (*m*, *Ph*CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$): 14.1; 25.5; 26.3; 62.4; 65.1; 66.3; 75.1; 76.0; 80.2; 80.6; 109.0; 127.7; 128.0; 128.3; 128.4; 137.9; 173.3.

(3S,4R,5S)-4-(Benzyloxy)-4,5-dihydro-3-hydroxy-3,5-bis(hydroxymethyl)-3H-furan-2-one (**30**). To a stirred soln. of **29** (19.4 mg, 0.06 mmol) in THF (1.5 ml), 2 drops of conc. HCl were added under Ar at r.t. After 1 h, the mixture was cooled to 0°, neutralized, and extracted with Et_2O. The extract was dried (Na_2SO_4) and evaporated and the residue submitted to FC (silica gel; PE/AcOEt 9:1): pure **30** (16 mg, quant.). Colorless oil. IR (film): 3560, 3300, 3140, 2940, 2870, 1770, 1450, 1400, 1330, 1190, 1110, 1090, 1070, 1040, 1010, 980, 930, 880, 740, 700. ^{1}H-NMR (400 MHz, (D_6)acetone): 3.85–3.95 (*m*, O*H*CH_2–C(3), O*H*CH_2–C(5)); 4.07 (*dd*, J_{gem} = 5.1, J_{vic} = 6.4, 1 H, OHCH_2–C(5)); 4.18 (*dd*, J_{gem} = 5.1, J_{vic} = 6.2, 1 H, OHCH_2–C(5)); 4.26 (*d*, *J* = 4.3, H–C(4)); 4.74 (*A* of *AB*, J_{AB} = 11.2, 1 H, PhCH_2); 4.76–4.81 (*m*, H–C(5)); 4.85 (*B* of *AB*, J_{AB} = 11.2, 1 H, PhCH_2); 5.16 (*s*, OH–C(3)); 7.28–7.45 (*m*, *Ph*CH_2). ^{13}C-NMR (101 MHz, (D_6)acetone): 60.6; 61.7; 74.8; 81.8; 83.0; 128.6; 128.6; 128.9; 129.2; 139.0; 175.4.

(5S,8S,9R)-9-(Benzyloxy)-2,2-dimethyl-8-(hydroxymethyl)-1,3,7-trioxaspiro[4.4]nonan-6-one (**31**). To a stirred soln. of **30** (15 mg, 0.056 mmol) in 2,2-dimethoxypropane (DMP; 3 ml), toluene-4-sulfonic acid (PPTS; 1 mg) was added at 0°. After warming to r.t., the mixture was stirred overnight. The mixture was then washed with aq. $NaHCO_3$ soln. and extracted with Et_2O. The extract was dried (Na_2SO_4) and evaporated and the residue submitted to FC (silica gel; PE/AcOEt 9:1): **31** (16 mg, 93%). Colorless crystals. M.p. 65–66.5°. IR (KBr): 3450, 3050, 3020, 2980, 2920, 1780, 1445, 1380, 1365, 1330, 1235, 1205, 1175, 1130, 1045, 840, 730, 690. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.53, 1.57 (2*s*, Me_2C); 1.80 (br., OH); 3.81 (*A* of *AB*, J_{AB} = 11.6, 1 H, CH_2OH); 3.85 (*B* of *AB*, J_{AB} = 11.6, 1 H, CH_2OH); 4.16 (*A* of *AB*, J_{AB} = 9.3, 1 H–C(4)); 4.37 (*d*, *J* = 7.3, H–C(9)); 4.58 (*m*, H–C(8)); 4.59 (*B* of *AB*, J_{AB} = 9.2, 1 H–C(4)); 4.62 (*A* of *AB*, J_{AB} = 11.4, 1 H, PhCH_2); 4.86 (*B* of *AB*, J_{AB} = 11.4, 1 H, PhCH_2); 7.35–7.43 (*m*, *Ph*CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$): 25.3; 26,7; 60.3; 67.3; 74.0; 78.3; 79.8; 82.8; 112.4; 128.1; 128.5; 128.7; 136.7; 174.7.

Ethyl 2-{(1R,2S)-1-(Benzyloxy)-2,3-[(1-methylethylidene)dioxy]propyl}prop-2-enoate (**32**). To a stirred soln. of **26** (205 mg, 0.70 mmol) in EtOH (5 ml), KOH (39.3 mg, 0.70 mmol) was added under Ar at 0°. Removal of the solvent and drying overnight under vacuum yielded a salt which was dissolved in benzene (6 ml) and DMF (1 drop). Oxalyl chloride (72 µl, 0.84 mmol) was added dropwise and the mixture stirred for 5 min at r.t., followed by the addition of pyridine (56 µl, 0.70 mmol) and EtOH (6 ml). After 2 h, the mixture was diluted with Et_2O (50 ml), the org. phase washed with aq. NH_4Cl and $NaHCO_3$ soln., dried (Na_2SO_4), and evaporated, and the residue purified by FC (silica gel; PE/AcOEt 9:1): **32** (135 mg, 60%). Colorless oil. IR (film): 3090, 3060, 3030, 2980, 2930, 1720, 1630, 1450, 1380, 1370, 1250, 1210, 1150, 1070, 960, 850, 740, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.31 (*t*, *J* = 7.0, *Me*CH_2O); 1.32, 1.39 (2*s*, Me_2C); 3.90–4.04 (*m*, MeCH_2O); 4.18–4.28 (*m*, H–C(2′), CH_2(3′)); 4.43 (*A* of

AB, J_{AB} = 11.7, 1 H, PhCH_2); 4.45 (*d*, *J* = 6.0, H–C(1')); 4.56 (*B* of *AB*, J_{AB} = 11.7, 1 H, PhCH_2); 5.96 (*s*, 1 H–C(3)); 6.42 (*s*, 1 H–C(3)); 7.25–7.38 (*m*, *Ph*CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.1; 25.2; 26.3; 60.8; 66.2; 71.3; 77.5; 78.0; 109.5; 126.7; 127.6; 127.7; 128.3; 137.8; 139.1; 166.1.

*Ethyl (2*R*,3*S*,4*S*)-3-(Benzyloxy)-2-hydroxy-2-(hydroxymethyl)-4,5-[(1-methylethylidene)dioxy]pentanoate* (**33**). As described for **29**, with **32** (155 mg, 0.48 mmol): **33** (157 mg, 99%). Colorless oil. IR (film): 3450, 3080, 3060, 3020, 2980, 2930, 2900, 1740, 1450, 1380, 1370, 1250, 1200, 1150, 1100, 920, 875, 845, 730, 695. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.23 (*t*, *J* = 7.1, *Me*CH_2O); 1.36, 1.43 (2*s*, Me_2C); 3.75 (*A* of *AB*, J_{AB} = 11.5, 1 H, CH_2OH); 3.81 (*B* of *AB*, J_{AB} = 11.5, 1 H, CH_2OH); 4.00–4.15 (*m*, H–C(3), CH_2(5)); 4.11 (*q*, *J* = 7.1, 1 H, MeCH_2O); 4.21 (*q*, *J* = 7.1, 1 H, MeCH_2O); 4.22–4.32 (*m*, H–C(4)); 4.55 (*A* of *AB*, J_{AB} = 11.3, 1 H, PhCH_2); 4.85 (*B* of *AB*, J_{AB} = 11.3, 1 H, PhCH_2); 7.20–7.35 (*m*, *Ph*CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.1; 25.3; 26.4; 62.4; 64.9; 65.4; 75.4; 76.1; 79.9; 80.1; 108.3; 127.5; 127.7; 128.3; 137.9; 173.0.

*(3*R*,4*S*,5*S*)-4-(Benzyloxy)-4,5-dihydro-3-hydroxy-3,5-bis(hydroxymethyl)-3*H*-furan-2-one* (**34**). As described for **30**, with **33** (119 mg, 0.37 mmol): **34** (97 mg, quant.). Colorless oil. IR (film): 3420, 3060, 3040, 2940, 2880, 1780, 1500, 1460, 1370, 1325, 1195, 1160, 1120, 1050, 920, 740, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.55 (*s*, OH); 3.70 (*s*, OH); 3.80–4.00 (*m*, 2 CH_2OH); 4.28–4.35 (*m*, H–C(4), H–C(5)); 4.56 (*A* of *AB*, J_{AB} = 11.5, 1 H, PhCH_2); 4.74 (*B* of *AB*, J_{AB} = 11.5, 1 H, PhCH_2); 4.85 (*s*, OH); 7.22–7.32 (*m*, *Ph*CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): 60.4; 62.7; 73.3; 78.4; 80.5; 81.0; 128.0; 128.1; 128.5; 136.9; 176.6.

*(5*R*,8*S*,9*S*)-9-(Benzyloxy)-2,2-dimethyl-8-(hydroxymethyl)-1,3,7-trioxaspiro[4.4]nonan-6-one* (**35**). As described for **31**, with **34** (870 mg, 3.24 mmol): **35** (926 mg, 92%). Colorless crystals. M.p. 73–73.5°. IR (KBr): 3430, 3060, 3030, 2990, 2930, 2880, 1795, 1450, 1380, 1375, 1320, 1240, 1210, 1180, 1110, 1070, 1035, 850, 750, 700. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.55, 1.60 (2*s*, Me_2C); 1.96 (br., OH); 3.65 (*m*, 1 H, CH_2OH); 3.89 (*m*, 1 H, CH_2OH); 4.09 (*d*, *J* = 8.7, 1 H–C(4)); 4.12 (*m*, H–C(8)); 4.34 (*d*, *J* = 7.7, H–C(9)); 4.61 (*A* of *AB*, J_{AB} = 11.4, 1 H, PhCH_2); 4.66 (*d*, *J* = 8.7, 1 H–C(4)); 4.85 (*B* of *AB*, J_{AB} = 11.4, 1 H, PhCH_2); 7.30–7.45 (*m*, *Ph*CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$): 25.4; 26.4; 60.6; 66.3; 73.5; 77.8; 80.1; 84.0; 112.7; 128.1; 128.4; 128.6; 136.8; 174.2.

*[(5*R*,8*S*,9*S*)-9-(Benzyloxy)-2,2-dimethyl-6-oxo-1,3,7-trioxaspiro[4.4]non-8-yl]methyl Benzoate* (**36**). To a stirred soln. of **35** (240 mg, 0.77 mmol) and 4-(dimethylamino)pyridine (378 mg, 3.1 mmol) in CH_2Cl_2 (10 ml), benzoyl chloride (180 µl, 1.55 mmol) was added dropwise under Ar at 0°. The mixture was stirred overnight at r.t. and then evaporated and the residue purified by FC (silica gel; PE/AcOEt 9:1): **36** (315 mg, 99%). Colorless oil. IR (KBr): 3060, 3040, 3000, 2940, 2880, 1800, 1730, 1600, 1450, 1385, 1375, 1315, 1270, 1230, 1175, 1110, 1060, 850, 710. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.54, 1.59 (2*s*, Me_2C); 4.12 (*d*, *J* = 8.8, 1 H–C(4)); 4.24 (*d*, *J* = 6.7, H–C(9)); 4.37–4.44 (*m*, H–C(8), 1 H of CH_2OBz); 4.52–4.62 (*m*, 1 H of CH_2OBz); 4.62 (*A* of *AB*, J_{AB} = 11.4, 1 H, PhCH_2); 4.67 (*d*, *J* = 8.8, 1 H–C(4)); 4.82 (*B* of *AB*, J_{AB} = 11.4, 1 H, PhCH_2); 7.23–7.35 (*m*, 5 arom. H); 7.42 (*m*, 2 arom. H); 7.57 (*m*, 1 arom. H); 7.97 (*m*, 2 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 25.3; 26.3; 62.3; 66.3; 73.3; 77.6; 78.4; 83.5; 112.8; 128.2; 128.4; 128.4; 128.6; 129.1; 129.6; 129.7; 133.3; 136.3; 165.8; 173.6.

*[(2*S*,3*S*,4*R*)-3-(Benzyloxy)tetrahydro-4-hydroxy-4-(hydroxymethyl)-5-oxofuran-2-yl]methyl Benzoate* (**37**). A soln. of **36** (16 mg, 0.039 mmol) in CF_3COOH/H_2O 1:1 (1 ml) was stirred at 0° under Ar for 30 min. The mixture was neutralized and extracted with Et_2O, the extract washed with brine, dried (Na_2SO_4), and evaporated. FC (silica gel; PE/AcOEt 9:1) gave **37** (13 mg, 90%). Colorless oil. IR (film): 3450, 3060, 3040, 2940, 2880, 1785, 1725, 1450, 1275, 1110, 1070, 740, 710. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.30 (*s*, OH); 3.97 (*A* of *AB*, J_{AB} = 11.9, 1 H, CH_2OH); 4.04 (*B* of *AB*, J_{AB} = 11.9, 1 H, CH_2OH); 4.35 (*d*, *J* = 7.9, H–C(3)); 4.35 (*dd*, *J* = 5.4, 12.9, 1 H, CH_2OBz); 4.58–4.62 (*m*, H–C(2), 1 H of CH_2OBz); 4.63 (*A* of *AB*, J_{AB} = 11.6, 1 H, PhCH_2); 4.80 (*B* of *AB*, J_{AB} = 11.5, 1 H, PhCH_2); 7.23–7.35 (*m*, 5 arom. H); 7.42 (*m*, 2 arom. H); 7.55 (*m*, 1 arom. H); 7.96 (*m*, 2 arom. H). ^{13}C-NMR (101 MHz, $CDCl_3$): 62.4; 63.1; 73.5; 77.7; 78.1; 80.5; 128.3; 128.5; 128.6; 128.7; 129.1; 129.8; 133.4; 136.2; 165.9; 175.6.

*[(2*S*)-4-(Benzyloxy)-2,5-dihydro-4-hydroxy-5-oxofuran-2-yl]methyl Benzoate* (**38**). To a stirred soln. of **37** (11 mg, 0.03 mmol) in CH_2Cl_2 (1 ml), pyridinium dichromate (13.4 mg, 0.036 mmol) was added under Ar. After stirring for 15 h at r.t., the mixture was washed with aq. NH_4Cl soln. and brine and extracted with Et_2O. The extract was dried (Na_2SO_4) and evaporated. FC (silica gel; PE/AcOEt 9:1) yielded **38** (7 mg, 69%). Colorless oil. IR (film): 3450, 3070, 3040, 2960, 2930, 1790, 1730, 1455, 1375, 1315, 1275, 1120, 1070, 1030, 710, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.17 (br., OH); 4.52–4.65 (*m*, H–C(2), CH_2OBz); 5.22 (*A* of *AB*, J_{AB} = 12.3, 1 H, PhCH_2); 5.30 (*m*, J_{AB} = 12.3, 1 H, PhCH_2); 7.23–7.35 (*m*, 5 arom. H); 7.40 (*m*, 2 arom. H); 7.56 (*m*, 1 arom. H); 7.91 (*m*, 2 arom. H). ^{13}C-NMR (101 MHz, $CDCl_3$): 65.9; 68.0; 69.4; 128.4; 128.4; 128.6; 128.7; 129.7; 129.8; 133.2; 134.7; 150.2; 166.2; 172.1; 198.1.

*[(2*S*,3*S*,4*R*)-3-(Benzyloxy)-4-{[(*tert*-butyl)dimethylsilyloxy]methyl}tetrahydro-4-hydroxy-5-oxofuran-2-yl]methyl Benzoate* (**39**). A mixture of **37** (211 mg, 0.57 mmol), (*tert*-butyl)chlorodimethylsilan (95 mg, 0.63 mmol), and 1*H*-imidazole (93 mg, 1.37 mmol) in dry DMF (1.5 ml) was stirred under Ar at r.t. overnight. After diluting with Et_2O, the mixture was washed with aq. NH_4Cl soln. and brine, the extract dried (Na_2SO_4) and evaporated,

and the residue submitted to FC (silica gel; PE/AcOEt 9:1): pure **39** (265 mg, 97%). Colorless oil. IR (film): 3450, 3060, 3035, 2960, 2930, 2880, 2860, 1800, 1720, 1660, 1450, 1270, 1200, 1100, 1030, 840, 780, 710. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.08 (*s*, Me_2C); 0.90 (*s*, *t*-Bu); 3.46 (*s*, OH); 3.83 (*A* of *AB*, J_{AB} = 9.7, 1 H, CH_2OSi); 4.08 (*B* of *AB*, J_{AB} = 9.7, 1 H, CH_2OSi); 4.30 (*d*, *J* = 8.5, H–C(3)); 4.31–4.38 (*m*, 1 H, CH_2OBz); 4.55–4.62 (*m*, 1 H, CH_2OBz); 4.61 (*A* of *AB*, J_{AB} = 11.8, 1 H, $PhCH_2$); 4.60–4.68 (*m*, H–C(2)); 4.83 (*B* of *AB*, J_{AB} = 11.8, 1 H, $PhCH_2$); 7.22–7.35 (*m*, 5 arom. H); 7.40 (*m*, 2 arom. H); 7.55 (*m*, 1 arom. H); 7.94 (*m*, 2 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): –5.2; –5.0; 18.8; 26.3; 63.1; 64.2; 73.6; 78.0; 78.9; 80.5; 128.7; 128.8; 129.0; 129.0; 129.0; 129.1; 129.9; 130.3; 133.9; 137.3; 166.2; 176.2.

*[(2S,3S,4R)-4-Acetoxy-3-(benzyloxy)-4-{[(*tert*-butyl)dimethylsilyloxy]methyl}tetrahydro-5-oxofuran-2-yl]methyl Benzoate* (**40**). A mixture of **39** (244 mg, 0.51 mmol), 4-(dimethylamino)pyridine (246 mg, 2.02 mmol), and benzoyl chloride (72.5 µl, 1.02 mmol) in CH_2Cl_2 (10 ml) was stirred under Ar at 0° for 5 h. The mixture was diluted with Et_2O and the extract washed with aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated. Purification by FC (silica gel; PE/AcOEt 9:1) gave **40** (254 mg, 95%). Colorless oil. IR (film): 3080, 3040, 2960, 2930, 2880, 2860, 1800, 1750, 1725, 1600, 1585, 1450, 1370, 1315, 1270, 1240, 1185, 1110, 1060, 835, 780, 745, 710. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.00 (*s*, Me_2Si); 0.81 (*s*, *t*-Bu); 1.93 (*s*, Ac); 3.79 (*A* of *AB*, J_{AB} = 8.8, 1 H, CH_2OSi); 4.14 (*B* of *AB*, J_{AB} = 8.9, 1 H, CH_2OSi); 4.35–4.57 (*m*, CH_2OBz, 1 H of $PhCH_2$); 4.55 (*d*, *J* = 3.3, H–C(3)); 4.56–4.62 (*m*, H–C(2)); 4.70 (*B* of *AB*, J_{AB} = 8.0, 1 H, $PhCH_2$); 7.18–7.25 (*m*, 5 arom. H); 7.33 (*m*, 2 arom. H); 7.47 (*m*, 1 arom. H); 8.00 (*m*, 2 arom. H). ^{13}C-NMR (101 MHz, $CDCl_3$): –6.0; –5.8; 20.5; 25.6; 62.6; 62.8; 73.4; 76.9; 78.2; 82.0; 127.9; 128.2; 128.2; 128.3; 128.5; 128.5; 129.3; 129.9; 133.1; 136.6; 166.1; 168.8; 171.1.

[(2S,3S,4R)-4-Acetoxy-3-(benzyloxy)tetrahydro-4-(hydroxymethyl)-5-oxofuran-2-yl]methyl Benzoate (**41**). A soln. of **40** (230 mg, 0.44 mmol) and Bu_4NF (277 mg, 0.88 mmol) in THF (5 ml) was stirred at r.t. under Ar for 20 min. The mixture was diluted with Et_2O and the extract washed with aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated. FC (silica gel; PE/AcOEt 9:1) yielded **41** (175 mg, 96%). Colorless oil. IR (film): 3440, 3060, 3040, 2960, 2880, 1790, 1750, 1725, 1600, 1450, 1380, 1320, 1270, 1230, 1110, 1060, 920, 750, 710, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.10 (*s*, Ac); 3.91 (*s*, OH); 4.30–4.63 (2*m*, CH_2OH, 1 H of CH_2OBz, H–C(2), H–C(3)); 4.62 (*A* of *AB*, J_{AB} = 11.5, 1 H, $PhCH_2$); 4.65 (*B* of *AB*, J_{AB} = 11.8, 1 H of CH_2OBz); 4.84 (*B* of *AB*, J_{AB} = 11.5, 1 H, $PhCH_2$); 7.20–7.34 (*m*, 5 arom. H); 7.41 (*t*, *J* = 7.6, 2 arom H); 7.56 (*t*, *J* = 7.8, 1 arom. H); 7.92 (*d*, *J* = 7.3, 2 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.6; 62.1; 63.6; 73.2; 76.9; 77.3; 80.0; 128.2; 128.3; 128.4; 128.5; 129.1; 129.7; 133.3; 136.1; 165.8; 170.6; 173.8.

[(2S,3S,4R)-4-Acetoxy-3-(benzyloxy)tetrahydro-4-[(methylthio)methoxymethyl]-5-oxofuran-2-yl]methyl Benzoate (**42**). A soln. of trifluoroacetic anhydride (16 µl, 0.12 mmol) in dry CH_2Cl_2 (1 ml) was cooled to –60°, and DMSO (11 µl, 0.154 mmol) was added dropwise. After 10 min, a soln. of **41** (32 mg, 0.077 mmol) in a small amount of dry CH_2Cl_2 was added slowly, and the mixture was stirred for 20 min. Et_3N (54 µl, 0.39 mmol) was added, and after 20 min, the cooling bath was removed. After an additional 10 min, H_2O (10 ml) was added, the mixture extracted with Et_2O, and the extract washed with aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated. FC (silica gel; PE/AcOEt 9:1) gave **42** (17 mg, 47%). Colorless oil. IR (film): 3060, 3030, 2960, 2920, 2880, 1790, 1750, 1725, 1600, 1450, 1380, 1360, 1310, 1270, 1225, 1175, 1110, 1070, 1025, 910, 740, 710. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.09, 2.19 (2*s*, MeS, Ac); 4.37 (*A* of *AB*, J_{AB} = 11.7, 1 H, OCH_2–C(4)); 4.43 (*dd*, *J* = 5.4, 13.2, 1 H, OCH_2–C(2)); 4.51 (*d*, *J* = 6.8, H–C(3)); 4.58–4.64 (*m*, H–C(2), 1 H of OCH_2–C(2)); 4.66 (*A* of *AB*, J_{AB} = 11.7, 1 H, SCH_2O); 4.75 (*B* of *AB*, J_{AB} = 11.7, 1 H, OCH_2–C(4)); 4.79 (*B* of *AB*, J_{AB} = 11.7, 1 H, SCH_2O); 4.82 (*A* of *AB*, J_{AB} = 11.2, 1 H, $PhCH_2$); 4.86 (*B* of *AB*, J_{AB} = 11.3, 1 H, $PhCH_2$); 7.25–7.33 (*m*, 5 arom. H); 7.44 (*m*, 2 arom. H); 7.59 (*m*, 1 arom. H); 7.97 (*m*, 2 arom. H). ^{13}C-NMR (101 MHz, $CDCl_3$): 14.7; 20.8; 61.5; 62.5; 71.0; 73.2; 77.8; 78.4; 81.4; 128.2; 128.5; 128.5; 128.5; 128.7; 129.2; 129.8; 133.5; 136.3; 165.9; 169.8; 171.2.

*[(2S,3S,4R)-3-(Benzyloxy)-4-{[(*tert*-butyl)dimethylsilyloxy]methyl}tetrahydro-4-[(2-methoxyethoxy)-methoxy]-5-oxofuran-2-yl]methyl Benzoate* (**43**). A mixture of **39** (90 mg, 0.19 mmol), (2-methoxyethoxy)methyl chloride (MEMCl; 42 µl, 0.37 mmol), and $(i\text{-}Pr)_2NEt$ (95 µl, 0.56 mmol) in dry CH_2Cl_2 (1 ml) was stirred overnight at r.t. under Ar. The mixture was diluted with Et_2O, the org. phase washed with aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated, and the residue submitted to FC (silica gel; PE/AcOEt 9:1): **43** (100 mg, 92%). Colorless oil. IR (film): 3080, 3040, 2960, 2940, 2900, 2870, 1800, 1730, 1610, 1555, 1275, 1120, 1030, 840, 780, 715, 700.

[(2S,3S,4R)-3-(Benzyloxy)tetrahydro-4-(hydroxymethyl)-4-[(2-methoxyethoxy)methoxy]-5-oxofuran-2-yl]methyl Benzoate (**44**). As described for **41**, from **43** (110 mg, 0.19 mmol). After chromatography, **44** (80 mg, 92%) was obtained. IR (film): 3450, 3080, 3040, 2960, 2940, 2900, 2870, 1800, 1730, 1460, 1280, 1120, 1070, 1030, 840, 780, 715. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.15 (br., OH); 3.34 (*s*, MeO); 3.55 (*t*, *J* = 5.0, OCH_2CH_2O); 3.72 (*t*, *J* = 5.0, OCH_2CH_2O); 3.92 (*A* of *AB*, J_{AB} = 14.3, 1 H, CH_2OH); 4.18 (*B* of *AB*, J_{AB} = 14.3, 1 H, CH_2OH); 4.28–4.66 (*m*, H–C(2), H–C(3), CH_2OBz); 4.62 (*A* of *AB*, J_{AB} = 11.6, 1 H, $PhCH_2$); 4.82 (*B* of *AB*, J_{AB} = 11.5, 1 H,

PhCH_2); 4.83 (*s*, OCH_2O); 7.20–7.33 (*m*, 5 arom. H); 7.41 (*m*, 2 arom. H); 7.56 (*m*, 1 arom. H); 7.95 (*m*, 2 arom. H). FAB-MS (+KCl): 499 ([*M* + K]$^+$), 461 ([*M* + 1]$^+$), 242, 184, 142, 91, 59.

Methyl 2-{(1R,2S)-1-(Benzyloxy)-2,3-[(1-methylethylidene)dioxy]propyl}prop-2-enoate (**46**). A mixture of **26** (80 mg, 0.27 mmol) and (4-Tol)NNNHMe (48.3 mg, 0.32 mmol) in Et_2O (2 ml) was stirred overnight under Ar at r.t. The mixture was washed with 5% aq. AcOH soln., aq. NH_4Cl soln., and brine, dried (Na_2SO_4), and evaporated. CC (silica gel; PE/AcOEt 9:1) gave **46** (82 mg, 98%). Colorless oil. IR (film): 3070, 3030, 2990, 2930, 2860, 1725, 1635, 1520, 1450, 1440, 1380, 1370, 1260, 1210, 1155, 1070, 850, 820, 735, 700.

Methyl (2R,3S,4S)-3-(Benzyloxy)-2-hydroxy-2-(hydroxymethyl)-4,5-[(1-methylethylidene)dioxy]pentanoate (**47**). As described for **29**, **46** (1.00 g, 3.27 mmol): **47** (1.10 g, 99%). Colorless oil. IR (film): 3450, 3090, 3060, 3030, 2990, 2950, 2930, 1750, 1500, 1450, 1435, 1375, 1250, 1210, 1160, 1090, 1050, 910, 865, 840, 800, 735, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.35, 1.42 (2*s*, Me_2C); 2.97 (*s*, OH); 3.67 (*s*, CO_2Me); 3.75 (*m*, H–C(5)); 3.76 (*A* of *AB*, J_{AB} = 9.3, 1 H, CH_2OH); 3.86 (*s*, OH); 4.11 (*m*, 1 H–C(5)); 4.04 (*B* of *AB*, J_{AB} = 9.4, 1 H, CH_2OH); 4.05 (*d*, *J* = 6.5, H–C(3)); 4.26 (*m*, H–C(4)); 4.52 (*A* of *AB*, J_{AB} = 11.2, 1 H, PhCH_2); 4.81 (*B* of *AB*, J_{AB} = 11.2, 1 H, PhCH_2); 7.20–7.35 (*m*, *Ph*CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): 25.0; 26.2; 52.7; 64.7; 65.2; 75.2; 75.9; 79.8; 81.2; 108.1; 127.5; 127.7; 127.9; 128.2; 128.3; 137.7; 173.2.

Methyl (2R,3S,4S)-3-(Benzyloxy)-2-hydroxy-2-(1-hydroxypropyl)-4,5-[(1-methylethylidene)dioxy]pentanoate (**49**). A soln. of trifluoroacetic anhydride (666 µl, 4.78 mmol) in dry CH_2Cl_2 (1 ml) was cooled to −60°, and DMSO (352 µl, 4.95 mmol) was carefully added under Ar. After 10 min, a soln. of **47** (280 mg, 0.825 mmol) in a small amount of dry CH_2Cl_2 was added slowly, and the mixture was stirred for 20 min. Et_3N (1.39 ml, 10 mmol) was added and the mixture stirred an additional 20 min at −60°. A soln. of EtMgCl (10 mmol) in Et_2O was added dropwise at −60°. After 30 min, the cooling bath was removed and, after 10 min, H_2O (10 ml) was added. The mixture was extracted with Et_2O, the extract washed with aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated, and the residue submitted to FC (silica gel; PE/AcOEt 9:1): **49** (160 mg, 53%). Colorless oil. IR (film): 3470, 3100, 3070, 3040, 3000, 2940, 2890, 1750, 1500, 1455, 1440, 1380, 1250, 1220, 1160, 1110, 1060, 865, 845, 740, 700.

(3R,4S,5S)-4-(Benzyloxy)-4,5-dihydro-3-hydroxy-5-(hydroxymethyl)-3-(1-hydroxypropyl)-3H-furan-2-one (**50**). A soln. of **49** (160 mg, 0.435 mmol) in THF (5 ml) was cooled to 4°, and 5 drops of conc. HCl were added under Ar. After stirring for 30 min, the mixture was neutralized and extracted with Et_2O and the extract washed with aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated: **50** (127 mg, 98%). Colorless oil. IR (film): 3450, 3090, 3060, 3030, 2960, 2940, 2880, 1775, 1500, 1450, 1370, 1320, 1250, 1180, 1150, 1100, 910, 740, 700.

(3R,4S,5S)-4-(Benzyloxy)-4,5-dihydro-3-hydroxy-3-(1-hydroxypropyl)-5-{[(4-methoxyphenyl)diphenylmethoxy]methyl}-3H-furan-2-one (**51**). To a soln. of **50** (81 mg, 0.27 mmol) in pyridine (2 ml), monomethoxytrityl chloride (83 mg, 0.27 mmol) was added at r.t. After stirring for 2 days under Ar, pyridine was removed by evaporation, the residue extracted with Et_2O, and the extract washed with aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated. FC (silica gel; PE/AcOEt 9:1) gave **51** (142 mg, 93%). Colorless oil. IR (film): 3550, 3060, 3040, 2940, 2880, 1790, 1610, 1510, 1450, 1300, 1250, 1180, 1150, 1080, 1035, 835, 750, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.05 (*t*, *J* = 7.2, *Me*CH_2CH); 1.34–1.47 (*m*, 1 H, MeCH_2CH); 1.76–1.89 (*m*, 1 H, MeCH_2CH); 2.40 (*d*, *J* = 8.5, CHO*H*); 3.16 (*dd*, *J* = 4.2, 11.1, 1 H, OCH_2–C(5)); 3.49 (*dd*, *J* = 2.5, 11.1, 1 H, OCH_2–C(5)); 3.78 (*s*, MeO); 3.81 (*m*, *CH*OH); 3.83 (*m*, MeCH_2C*H*); 4.30–4.36 (*m*, H–C(5)); 4.39 (*A* of *AB*, J_{AB} = 11.5, 1 H, PhCH_2); 4.42 (*d*, *J* = 7.6, H–C(4)); 4.58 (*B* of *AB*, J_{AB} = 11.5, 1 H, PhCH_2); 6.83 (*d*, *J* = 8.8, 2 arom. H); 7.13–7.42 (3*m*, 15 arom. H). ^{13}C-NMR (101 MHz, $CDCl_3$): 10.5; 24.5; 55.2; 62.2; 73.6; 74.0; 78.8; 79.8; 82.0; 86.7; 113.3; 127.1; 128.0; 128.0; 128.0; 128.0; 128.3; 128.3; 128.3; 128.3; 128.4; 128.6; 130.3; 134.9; 136.4; 143.6; 143.8; 158.7; 175.0.

(3R,4S,5S)-4-(Benzyloxy)-4,5-dihydro-3-hydroxy-5-{[(4-methoxyphenyl)diphenylmethoxy]methyl}-3-(1-oxopropyl)-3H-furan-2-one (**52**). Tetrapropylammonium perruthenate (TPAP; 2 mg) was added under Ar at r.t. to a mixture of **51** (55 mg, 0.098 mmol), *N*-methylmorpholine *N*-oxide (20.5 mg, 0.15 mmol), and molecular sieves (4 Å) in CH_2Cl_2 (1 ml). After stirring for 3 h, the mixture was diluted with Et_2O and the org. phase washed with aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated. FC (silica gel; PE/AcOEt 9:1) gave **52** (45 mg, 82%). Colorless oil. IR (film): 3540, 3060, 3040, 2980, 2960, 2940, 2880, 1790, 1730, 1610, 1510, 1450, 1300, 1250, 1180, 1150, 1100, 1030, 830, 750, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.12 (*t*, *J* = 7.0, *Me*CH_2); 2.54–2.68 (*q*, *J* = 7.0, 1 H, MeCH_2); 2.72–2.86 (*q*, *J* = 7.0, 1 H, MeCH_2); 3.21 (*dd*, *J* = 4.2, 10.9, 1 H, OCH_2–C(5)); 3.52 (*dd*, *J* = 2.8, 10.9, 1 H, OCH_2–C(5)); 3.78 (*s*, MeO); 4.32 (*A* of *AB*, J_{AB} = 11.4, 1 H, PhCH_2); 4.41 (*s*, OH); 4.45 (*d*, *J* = 6.7, H–C(4)); 4.47 (*B* of *AB*, J_{AB} = 11.5, 1 H, PhCH_2); 4.56–4.63 (*m*, H–C(5)); 6.84 (*d*, *J* = 9.8, 2 arom. H); 7.07–7.41 (3*m*, 16 arom. H).

REFERENCES

[1] X. Shao, M. Dolder, Ch. Tamm, *Helv. Chim. Acta* **1990,** *73,* 483.

[2] P. Bloch, Ch. Tamm, P. Bollinger, T.J. Petcher, H.P. Weber, *Helv. Chim. Acta* **1976,** *59,* 133; T.J. Petcher, H.P. Weber, P. Bloch, Ch. Tamm, *ibid.* **1976,** *59,* 137; P. Bloch, Ch. Tamm, *ibid.* **1981,** *64,* 304.

[3] M. Dolder, X. Shao, Ch. Tamm, *Helv. Chim. Acta* **1990,** *73,* 63.

[4] Ch. Hubschwerlen, *Synthesis* **1986,** 962.

[5] A.B. Smith, III, P.A. Levenberg, P.J. Jerris, R.M. Scarborough, Jr., P.M. Wovkulich, *J. Am. Chem. Soc.* **1981,** *103,* 1501.

[6] J.C. Depezay, Y. Le Merrer, *Tetrahedron Lett.* **1978,** 2865; *Carbohydr. Res.* **1980,** *83,* 51.

[7] L. Banfi, D. Potenza, G.S. Ricca, *Org. Magn. Reson.* **1984,** *22,* 224.

[8] J.A. Marshall, N. Cohen, *J. Org. Chem.* **1965,** *30,* 3475.

[9] B.S. Bal, W.E. Childers, Jr., H.W. Pinnick, *Tetrahedron* **1981,** 2091.

[10] a) F. Matsuda, M. Yanagiya, T. Matsumoto, *Tetrahedron Lett.* **1982,** 4043; S. Wolfe, J.C. Godfrey, C.T. Holdrege, Y.G. Perron, *Can. J. Chem.* **1968,** *46,* 2549; b) P.J. Beeby, *Tetrahedron Lett.* **1977,** 3379; A. Wissner, C.V. Grudzinskas, *J. Org. Chem.* **1978,** *43,* 3972.

[11] J.S. Grossert, W.M.N. Ratnayake, T. Swee, *Can. J. Chem.* **1981,** *59,* 2617; E.P. Boden, G.E. Keck, *J. Org. Chem.* **1985,** *50,* 2394; M.K. Dhaon, R.K. Olsen, K. Ramasamy, *ibid.* **1982,** *47,* 1962; L. Anzalone, J.A. Hirsch, *ibid.* **1985,** *50,* 2607; N.B. Lortte, J.H. Brown, Jr., *ibid.* **1958,** *24,* 261; R.V. Stevens, N. Beaulieu, W.H. Chan, A.R. Daniewski, T. Takeda, A. Waldner, P.G. Williard, U. Zutter, *J. Am. Chem. Soc.* **1986,** *108,* 1039.

[12] J.K. Cha, W.J. Christ, Y. Kishi, *Tetrahedron* **1984,** *40,* 2247.

[13] N. Ikemoto, S.L. Schreiber, *J. Am. Chem. Soc.* **1992,** *114,* 2524.

[14] A. Bernardi, M.G. Beretta, L. Colombo, C. Gennari, G. Poli, C. Scolastico, *J. Org. Chem.* **1985,** *50,* 4442; A. Bernardi, S. Cardani, C. Scolastico, R. Villa, *Tetrahedron* **1988,** *44,* 491.

[15] E.J. Corey, G. Schmidt, *Tetrahedron Lett.* **1979,** 399; E.J. Corey, J.W. Suggs, *ibid.* **1975,** 2647.

[16] A.J. Mancuso, S.-L. Huang, D. Swern, *J. Org. Chem.* **1978,** *43,* 2480; S.L. Huang, K. Omura, D. Swern, *Synthesis* **1978,** 297; A.J. Mancuso, D. Swern, *ibid.* **1981,** 165.

[17] L.C. Collins, W.W. Hess, F.J. Frank, *Tetrahedron Lett.* **1968,** 3363.

[18] D.B. Dess, J.C. Martin, *J. Org. Chem.* **1983,** *48,* 4155; *J. Am. Chem. Soc.* **1991,** *113,* 7277.

[19] E.H. White, A.A. Baum, D.E. Eitel, 'Organic Syntheses', J. Wiley & Sons, New York–London–Sydney–Toronto, 1973, Coll. Vol. 5, p. 797.

[20] W.P. Griffith, S.V. Ley, G.P. Whitcombe, A.D. White, *J. Chem. Soc., Chem. Commun.* **1987,** 1625; W.P. Griffith, S.V. Ley, *Aldrichim. Acta* **1990,** *23,* 13.