Non-iterative Asymmetric Synthesis of C_{15} Polyketide Spiroketals

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The 2,2′-methylenebis[furan] (**1**) was converted to 1-{(4*R*,6*S*))-6-[(2*R*)-2,4-dihydroxybutyl]-2,2-dimethyl-1,3-dioxan-4-yl}-3-[(2*R*,4*R*)-tetrahydro-4,6-dihydroxy-2*H*-pyran-2-yl)propan-2-one ((+)-**18**) and its (4*S*)-epimer (−)-**19** with high stereo- and enantioselectivity (*Schemes 1–3*). Under acidic methanolysis, (+)-**18** yielded a single spiroketal, (3*R*)-4-{(1*R*,3*S*,4′*R*,5*R*,6′*S*,7*R*)-3′,4′,5′,6′-tetrahydro-4′-hydroxy-7-methoxyspiro[2,6-dioxabicyclo[3.3.1]nonane-3,2′-[2*H*]pyran]-6′-yl}butane-1,3-diol ((−)-**20**), in which both O-atoms at the spiro center reside in equatorial positions, this being due to the tricyclic nature of (−)-**20** (methyl pyranoside formation). Compound (−)-**19** was converted similarly into the (4′*S*)-epimeric tricyclic spiroketal (−)-**21** that also adopts a similar (3*S*)-configuration and conformation. Spiroketals (−)-**20**, (−)-**21** and analog (−)-**23**, *i.e.*, (1*R*,3*S*,4′*R*,5*R*,6′*R*)-3′,4′,5′,6′-tetrahydro-6′-[(2*S*)-2-hydroxybut-3-enyl]-7-methoxyspiro[2,6-dioxabicyclo[3.3.1]-nonane-3,2′-[2*H*]pyran]-4′-ol, derived from (−)-**20**, were assayed for their cytotoxicity toward murine P388 lymphocytic leukemia and six human cancer cell lines. Only racemic (±)-**21** showed evidence of cancer-cell-growth inhibition (P388, ED_{50}: 6.9 μg/ml).

Introduction. – A great variety of natural products of biological interest contain spiroketal subunits [1]. The 1,7-dioxaspiro[5.5]undecane and 1,6-dioxaspiro[4.5]decane ring systems are known in nature as simple derivatives [2a] (see also [2b], or, more frequently, the spiroketal is more highly oxidized, as exemplified by the milbemycin-avermectins [3], the polyether ionophores, and the phyllanthocin and related metabolites [4]. While the literature abounds in methods for the synthesis of such spiroketals and their thermodynamic aspects have been extensively studied [5], particular interest has been focused during the last decade on the two *AB* and *CD* spiroketal units found in the spongistatin class of compounds (see, *e.g.*, spongistatin 1) [6]. They appear to be the crucial pharmacophores for the unprecedented anticancer activity of these marine macrolides [7][2]).

We have published an approach to the *EF* rings of spongistatins embodying the trienic side chain [8]. In the present paper, we disclose a non-iterative approach to direct precursors of the *AB* and *CD* spiroketal moieties of spongistatins, based on our new methodology towards long-chain polyols [9]. Additionally, the newly synthesized spiroketals were evaluated against a mouse-leukemia cell line (P388) and six types of human-cancer cell lines [10].

We have shown that the chemistry developed by *Lautens* and co-workers (see, *e.g.*, [11]), *Hoffmann* and co-workers (see, *e.g.*, [12]), and later *Kaku* and co-workers [13],

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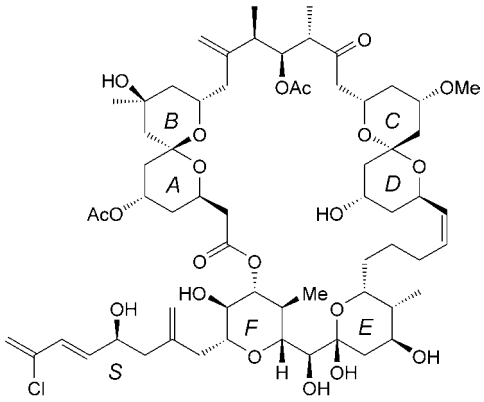
[2]) For the biological activity of the bis-tetrahydropyran, see [7h].

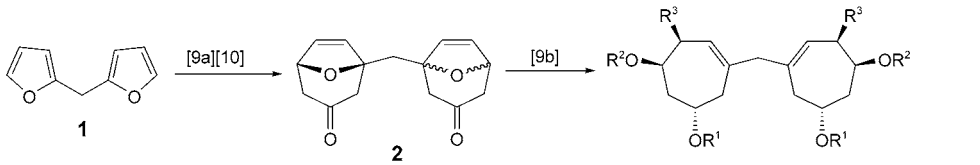


Spongistatin 1

who converted 8-oxabicyclo[3.2.1]oct-6-en-3-one into C_7 1,3-polyols and analogues [14], can be extended to the synthesis of a large number of stereoisomeric pentadecane-1,3,5,7,9,11,13,15-octols [9]. We have used also 8-oxabicyclo[3.2.1]oct-6-en-3-one derivatives in the stereoselective synthesis of *C*-disaccharides [15] and analogues of sialyl Lewis^x acid [16].

Results and Discussion. – As already reported, *meso*-**3** can be derived readily from 2,2′-methylenebis[furan] (**1**) *via* **2** (*Scheme 1*). The desymmetrization of *meso*-**3** was realized applying the *Sharpless* asymmetric dihydroxylation [17]. With *AD-mix*(α) (five times more concentrated than in the initially published *Sharpless* procedure [9]), we obtained (+)-**6** and (+)-**7** in 79% yield (*Scheme 2*). ^{19}F-NMR spectroscopy (^{13}C-^{19}F satellites) of *Mosher*'s esters **6M** and **7M** derived from (αS)-α-methoxy-α-(trifluoromethyl)benzeneacetyl chloride [18] showed (+)-**6** to have 98.4% ee and (+)-**7** 4% ee. Changing the substitution pattern of the carbocycles such as in **4** and **5** did not increase the diastereoselectivity (4:1) of the dihydroxylation. On the contrary, **4** gave a 3:1 mixture of diastereoisomeric diols (77% yield), and **5** a 1:1 mixture (22% yield) of diastereoisomeric diols. The absolute configuration of (+)-**6** was assumed to be opposite to that of the diol obtained with *AD-mix*(β) (5×), as the optical rotation was

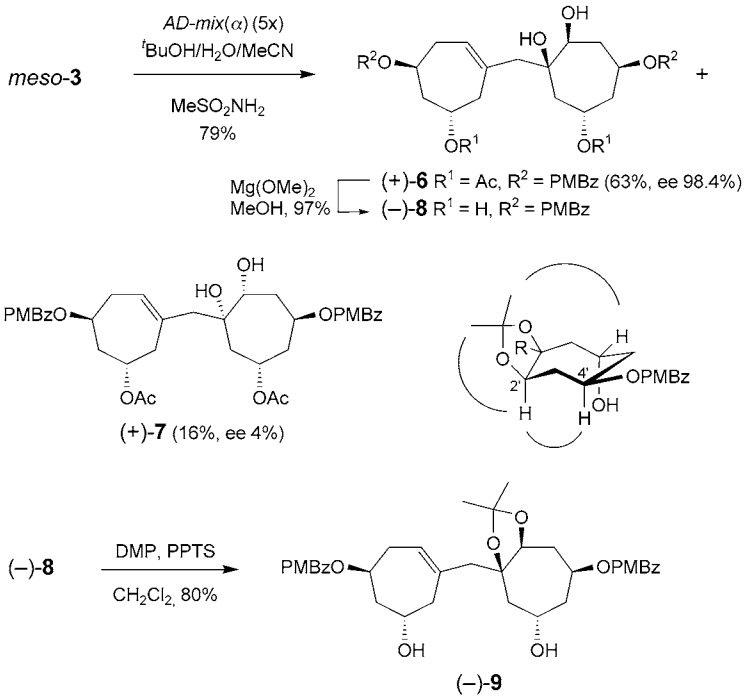
Scheme 1



meso-**3** R^1 = Ac, R^2 = PMBz, R^3 = H (6 steps, 67%)
4 R^1 = H, R^2 = PMBz, R^3 = H (7 steps, 65%)
5 R^1 = Ac, R^2 = TBDMS, R^3 = Cl (5 steps, 75%)

PMBz = 4-MeOC$_6$H$_4$CO, TBDMS = ^{t}BuMe$_2$Si

Scheme 2



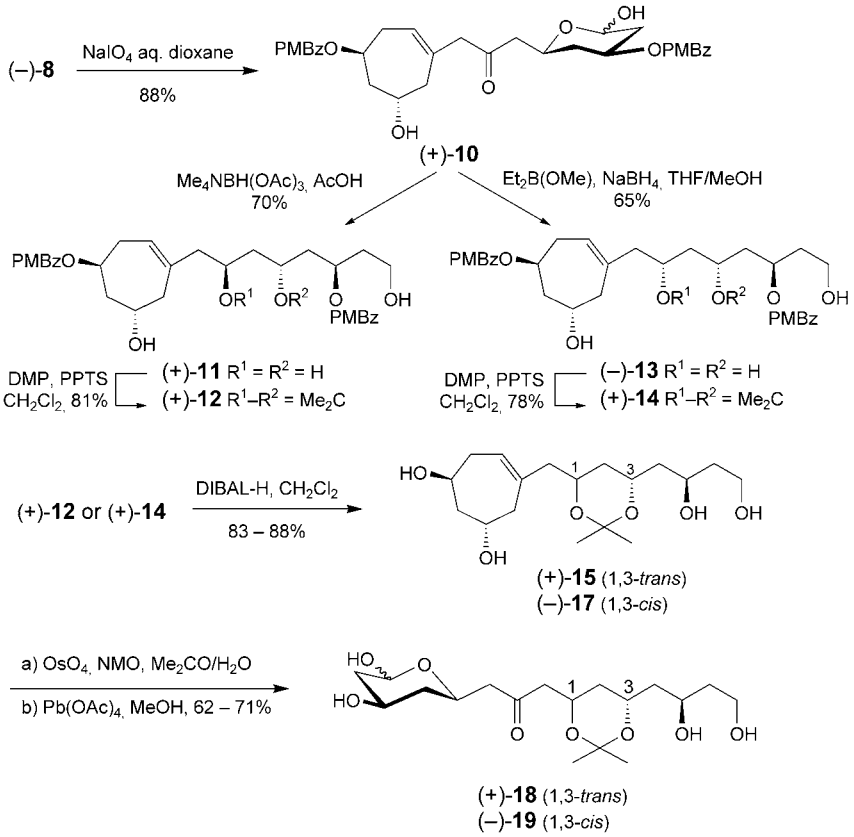
PMBz = 4-MeOC$_6$H$_4$CO, DMP = 2,2-dimethoxypropane, PPTS = pyridinium *p*-toluenesulfonate

of similar magnitude but of opposite sign. The relative configuration of the two diastereoisomers (+)-**6** and (+)-**7** was determined by the 2D ^{1}H-NMR NOESY experiments of acetonide (−)-**9**, which was obtained in two steps by deacetylation of (+)-**6** to tetrol (−)-**8**, followed by acetonide formation under standard conditions (*Scheme 2*). The ^{1}H-NMR spectrum of (−)-**9** implied a dipolar coupling of H−C(4′) with H−C(2′), which indicated clearly that, in the major diastereoisomer (+)-**6**, the C=C bond has been dihydroxylated from the face *cis* with respect to the (4-methoxybenzoyl)oxy group, in agreement with expectation [19].

Deacetylation of (+)-**6** with $Mg(OMe)_2$ in MeOH (→(−)-**8**), followed by treatment with $NaIO_4$ gave a mixture of anomeric hemiacetals (+)-**10** (*Scheme 3*). As already shown with the opposite series of enantiomers [9], hemiacetal (+)-**10** was reduced to *anti*-diol (+)-**11** (70%) under *Evans*'s conditions [20]. To increase the versatility of our methodology, the 1,3-*syn* diastereoisomer (−)-**13** was prepared by application of the *Narasaka*–*Prasad*–*Shapiro* method [21]. Acetonides (+)-**12** and (+)-**14** derived from (+)-**11** and (−)-**13**, respectively, showed ^{13}C-NMR signals expected for these products [22].

Reduction of (+)-**12** with DIBAL-H (diisobutylaluminium hydride) gave tetrol (+)-**15**. Dihydroxylation with OsO_4 (cat.) and *N*-methylmorpholine *N*-oxide (NMO),

Scheme 3

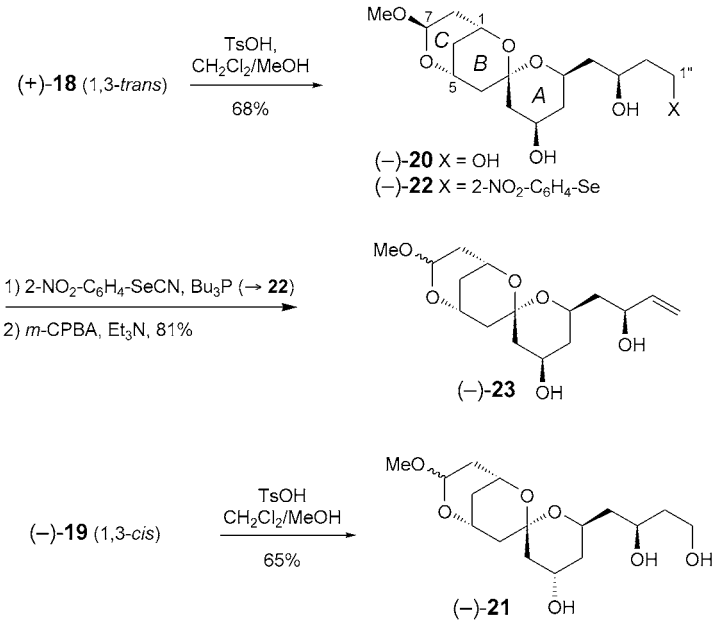


PMBz = 4-MeOC$_6$H$_4$CO, DMP = 2,2-dimethoxypropane, PPTS = pyridinium *p*-toluenesulfonate, DIBAL-H = diisobutylaluminium hydride, NMO = *N*-methylmorpholine *N*-oxide

followed by treatment with lead tetraacetate furnished (+)-**18** (1,3-*trans*). In a similar way, (+)-**14** was converted to (+)-**17** and then to (+)-**19** (1,3-*cis*). The crucial steps of spiroketalization of (+)-**18** and (–)-**19** were performed in pure MeOH/CH_2Cl_2 under acidic catalysis (TsOH). By ^{1}H-NMR, the reactions were complete after a few minutes at room temperature, and no change in products was observed after prolonged standing at 20° or heating to 60°. The ^{1}H-NMR spectra of the crude reaction mixtures showed that they contained a mixture of anomeric methyl acetals, their proportions varying slightly with the concentration of acid catalyst and the temperature of reaction. Flash chromatography allowed us to isolate pure (–)-**20** (68%) from the reaction of (+)-**18** (1,3-*trans*) and (–)-**21** (65%) from the reaction of (–)-**19** (1,3-*cis*). To the best of our knowledge, such tricyclic systems have never been reported before. The side chain of (–)-**20** was modified in the following way. Treatment of (–)-**20** with an excess of 2-NO_2–C_6H_4–SeCN and Bu_3P led to selective selenation of the primary-alcohol

function with formation of **22**, which underwent oxidative elimination with *m*-CPBA (3-chloroperbenzoic acid) [24] giving allylic alcohol (−)-**23** (*Scheme 4*).

Scheme 4



The structure of (−)-**20** was assigned as follows (see *Fig.*). The protons of cycle *C* and *B* were assigned through a 2D-NMR COSY-45 experiment. Due to its anomeric position, the proton H−C(7) is strongly deshielded (δ(H) 4.65, δ(C) 104.8) and can, thus, be easily identified. Starting from H−C(7), the other proton signals were assigned and their identities further confirmed by selective irradiation techniques. The remaining protons were assigned in a similar way. From the coupled ^{13}C-NMR spectra, the C(1″) center was identified unambiguously as the unique *t* in the *C*HOH region ($68 > \delta(C) > 53$) at δ(C) 61.0 (*t*, $^1J = 139$). A 2D-NMR HMQC experiment allowed us to find the corresponding protons CH_2(1″) at δ(H) 3.73 (*t*, $^3J = 7.5$, 2 H). Again, the 2D-NMR COSY-45 experiment allowed the assignments of the other protons of the side chain (CH_2(2″), H−C(3″), CH_2(4″)) and those from cycle *A* (H−C(6′), CH_2(5′), H−C(4′), CH_2(3′)). Selective irradiations were helpful to confirm these assignments. The absolute configuration (3*S*) of (−)-**20** could thus be determined by the 2D-NMR NOESY correlations (*Fig.*).

Two absolute configurations around the spiro center ((3*R*) or (3*S*)) are possible for the *AB* rings of (−)-**20**. For each absolute configuration, different conformations of the three cycles are possible *a priori*. Correlations of one of the H−C(9) protons with CH_2(3′) and H−C(4′) of cycle *A* are consistent with only the (3*S*) configuration. No dipolar couplings of H−C(8) or H−C(7) with CH_2(3′) and H−C(4′) (what would have been consistent with the opposite configuration (3*R*)) were observed (*Fig.*). Additionally, the correlations between H−C(5), H−C(1), H−C(3′), H−C(4), and

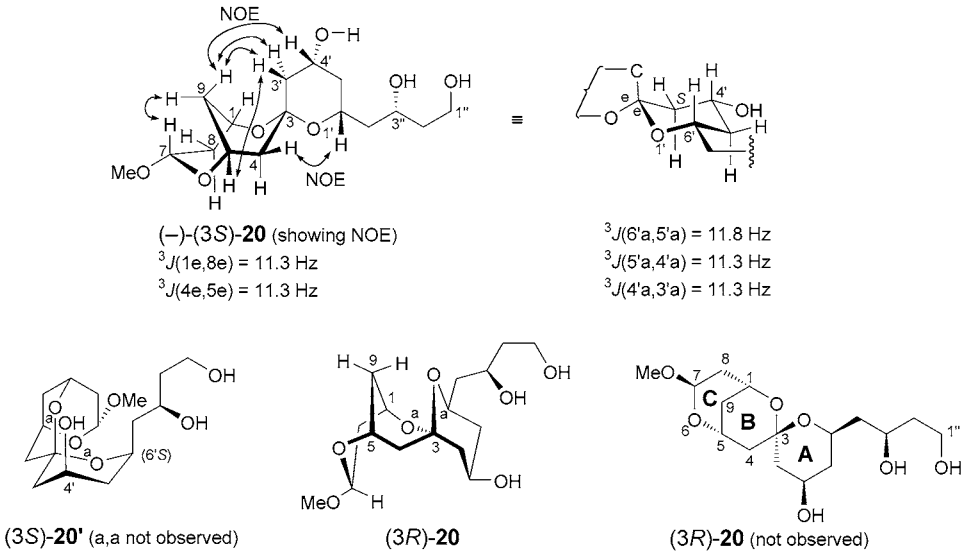


Figure. *Representations of spiroketal* **20** *in its (3S)-* (preferred) *and (3*R*)-configuration*

H–C(6′) are possible only for the (3*S*)-configuration (*Fig.*). While the correlation between H–C(5) and H–C(3′) would have been possible in the (3*R*)-configuration, the dipolar couplings between H–C(4) and H–C(6′) and between H–C(1) and H–C(3′) are not possible, as the corresponding protons point to opposite regions of space.

The conformation of the bicyclic moiety *BC* and cycle *A* of (–)-**20** could be established by H,H coupling constants between vicinal protons. For cycle *A*, the coupling constants indicate an axial-axial relationship between H–C(6′), 1 H–C(5′), H–C(4′), and 1 H–C(3′) ($^3J(6',5') = 11.8$ Hz and $^3J(5',4') = {}^3J(4',3') = 11.3$ Hz). Thus, cycle *A* in (–)-**20** adopts a chair conformation. For the bicyclic system *BC*, two characteristic ^3J(H,H) coupling constants indicate a boat conformation for both the *B* and *C* rings. $^3J(4,5) = 11.3$, $^3J(1,8) = 11.3$ Hz are only consistent with dihedral angles φ (H–C(1), H–C(8)) = φ (H–C(4), H–C(5)) $\approx 0°$, possible only for boat conformations [23]).

Substituted 1,7-dioxaspiro[5.5]undecanes can adopt different conformations; the relative populations of the different conformers depend on steric factors, anomeric and related effects, and intramolecular H-bonding. In the case of spiroketal (–)-**20**, both endocyclic O-atoms are disposed in equatorial position (e) relative to the other cycle (see *Fig.*) and, therefore, this structure is not stabilized by a conformational anomeric effect. The conformation (3*S*)-**20′** that disposes both endocyclic O-atoms in an axial positions (a) and which is stabilized by a double conformational anomeric effect would imply chair-chair conformation for its *AB* bicyclic moiety. This conformation is impeded by steric factors that override the stabilized anomeric effect, as both substituents on cycle *A* are disposed in unfavorable axial positions, and, additionally, the side chain of cycle *A* is subject to severe steric interaction with the *BC* moiety. The

formation of cycle *C* (pyranoside) seems to control the configuration of the spiroketal. The NMR data of (−)-**21** confirmed that this spiroketal adopts also the (3*S*)-configuration and a conformation similar to that of (−)-**20**.

The spiroketals (−)-**20**, (−)-**21**, (−)-**23**, and (±)-**21** were tested against the murine P388 lymphocytic leukemia cell line and six human cancer cell lines (pancreas (BXPX-3), breast (MCF-7), CNS Gliobl (SF 268), lung (NCI-H460), colon (KM20L2), and prostate (DU-145)). None of these displays any growth inhibition (GI_{50}) against the human cancer cell lines. While the enantiomerically pure (−)-**20**, (−)-**21**, and (−)-**23** were also inactive against the mouse leukemia cell line, the racemic mixture (±)-**21**[3]) displayed an effective median dose (ED_{50}) of 6.90 μg/ml, indicating potential activity of ED_{50} 3.45 μg/ml for (+)-**21**.

Conclusions. – Our non-iterative approach to the synthesis of long-chain polyols has now been adapted to the synthesis of precursors of the spiroketals of spongistatins. The versatility of our approach was further extended by the asymmetric dihydroxylation of *meso*-**3** with *AD-mix*(α) (5×) and the 1,3-*syn* diastereoselective reduction of hemiacetal (+)-**10** (→(−)-**13**). Unfortunately, and, as for simpler spiroketals [7a], the new tricyclic systems prepared in this study do not present significant anticancer activities.

We thank the *Swiss National Science Foundation* and the *Office Fédéral de l'Enseignement et de la Recherche* (Bern, European COSTD28/004/02 action) for financial support. We thank also Mr. *Martial Rey* and *Francisco Sepúlveda* for technical help. One of us (*G. R. P.*) also wishes to thank for financial support Grant RO1-CA90441-02-03 with the *Division of Cancer Treatment and Diagnosis*, *National Cancer Institute*, *Department of Health and Human Services* the *Arizona Disease Control Research Commission*, Dr. *Alec D. Keith*, the *Robert B. Dalton Endowment Fund* and for other assistance, Dr. *Jean-Charles Chapuis.*

Experimental Part

General. See [24]. Flash column chromatography (FC): *Merck* silica gel (230–400 mesh, No. 9385). TLC: silica gel (*Merck* aluminium foils). ^{1}H- and ^{13}C-NMR Spectra: assignments confirmed by coupled ^{13}C-NMR, 2D-COSY, HMQC, or HSQC, and when required, by 2D-NOESY; δ in ppm, *J* in Hz.

Cancer Assays. See [25].

*(1*S*,6*S*)-6-(Acetyloxy)-4-{{(1*R*,2*S*,4*S*,6*S*)-6-(acetyloxy)-1,2-dihydroxy-4-[(4-methoxybenzoyl)oxy]cyclohept-yl}methyl}cyclohept-3-en-1-yl 4-Methoxybenzoate* ((+)-**6**) *and (1*S*,6*S*)-6-(Acetyloxy)-4-{{(1*S*,2*R*,4*S*,6*S*)-6-(acetyloxy)-1,2-dihydroxy-4-[(4-methoxybenzoyl)oxy]cycloheptyl)methyl}cyclohept-3-en-1-yl 4-Methoxybenzoate* ((+)-**7**). A soln. of *meso*-**3** (14.5 g, 0.023 mol) and $MeSO_2NH_2$ (2.19 g, 0.023 mol) in 290 ml of H_2O/^{t}BuOH 1:1 with 10% of MeCN was cooled to 0° and *AD-mix*(α) (5×) (34.7 g, 1490 mg per mmol) was added portionwise under vigorous mechanical stirring. After 24 h stirring (TLC, CH_2Cl_2/MeOH 95:5), the mixture was diluted with AcOEt (200 ml) and quenched by addition of Na_2SO_3 (2.89 g, 0.023 mmol). After 1 h stirring, the aq. layer was extracted with AcOEt (3×400 ml). After drying ($MgSO_4$) of the org. phase, FC (silica gel, CH_2Cl_2/AcOEt 4:1) afforded starting material *meso*-**3** (493 mg) and (+)-**6**/(+)-**7** 4:1 (12.9 g, 79%) that was further separated by column chromatography (silica gel): 8.62 g of pure (+)-**6**, 1.39 g of (+)-**6**/(+)-**7**, and 1.86 g of pure (+)-**7**).

*Data of (+)-***6**: $[\alpha]_{589}^{25} = +56$; $[\alpha]_{577}^{25} = +60$; $[\alpha]_{546}^{25} = +67$; $[\alpha]_{435}^{25} + 122$; $[\alpha]_{405}^{25} = +156$ ($c = 0.20$, $CHCl_3$). UV (MeCN): 255 (21500), 207 (22300). IR (KBr): 3500, 2940, 2360, 1735, 1710, 1605, 1510, 1370, 1255, 1170, 1100, 1025, 770, 695, 615. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.98 (*m*, 1 MeOC_6H_4CO); 6.91 (*m*, 1 MeOC_6H_4CO); 5.63 (*t*, $^3J = 6.5$, H−C(3)); 5.38 (*dddd*, $^3J = 10.5$, 8.7, 6.0, 1.8, H−C(4′)); 5.27 (*m*, H−C(1)); 5.19 (*dddd*, $^3J = 10.5$, 9.0, 6.1, 2.6, H−C(6′)); 5.11 (*m*, H−C(6)); 3.85, 3.82 (2*s*, 2 *Me*OC_6H$_4$CO); 3.72 (br. *d*, $^3J = 10.7$, H−C(2′)); 2.65 (*m*, H−C(2)); 2.64 (*m*, H−C(7)); 2.57 (*d*, $^2J = 13.3$, 1 H, CH_2−C(4)); 2.48 (*dd*, $^2J = 15.0$, $^3J = 6.5$, H−C(2));

[3]) Prepared as (−)-**21**, but by using OsO_4/NMO in the oxidative step *meso*-**3**→(±)-**6**.

2.30 (*m*, 1 H–C(3′), 1 H–C(5), 1 H–C(7′)); 2.27 (*d*, ^2J = 13.3, 1 H, CH_2–C(4)); 2.20 (*m*, H–C(5)); 2.10 (*m*, H–C(7′)); 2.05, 2.01 (2*s*, 2 MeCO); 2.03 (*m*, 1 H–C(5′), 1 H–C(3′)); 1.81 (*dd*, ^2J = 14.7, ^3J = 10.5, 1 H–C(5′)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 170.6, 170.2 (2*s*, Me*C*O); 165.5 (*s*, 2 C, $MeOC_6H_4CO$); 163.4, 163.3 (2*s*, 2 C, $MeOC_6H_4CO$); 136.9 (*s*, C(4)); 131.6 (*d*, ^1J = 163, 4 C, $MeOC_6H_4CO$); 127.3 (*d*, ^1J = 162, C(3)); 122.6, 122.5 (2*s*, 2 C, $MeOC_6H_4CO$); 113.6 (*d*, ^1J = 161, 4 C, $MeOC_6H_4CO$); 74.3 (*s*, C(1′)); 73.0 (*d*, ^1J = 141, C(2′)); 68.7 (*d*, ^1J = 154, C(1)); 68.2 (*d*, ^1J = 137, C(6)); 68.1 (*d*, ^1J = 149, C(6′)); 66.9 (*d*, ^1J = 147, C(4′)); 55.4 (*q*, ^1J = 145, 2 C, *Me*OC_6H_4CO); 50.8 (*t*, ^1J = 127, *C*H_2–C(4)); 41.5, 40.9, 39.0, 38.6, 37.7 (5*t*, C(5), C(5′), C(7), C(7′), C(3′)); 32.3 (*t*, ^1J = 127, C(2)); 21.3 (*q*, ^1J = 130, 2 C, *Me*CO). CI-MS (NH_3): 673 (41, $[M+NH_4]^+$), 655 (8, $[M+H]^+$), 595 (8), 503 (18), 443 (11), 337 (13), 135 (100), 106 (2), 78 (26). Anal. calc. for $C_{35}H_{42}O_{12}$ (654.71): C 64.21, H 6.47, O 29.32; found: C 62.45, H 6.47 (corresponding to $C_{35}H_{42}O_{12}\cdot H_2O$: C 62.49, H 6.59).

*Data of (+)-***7**: $[\alpha]_{589}^{25} = +1$; $[\alpha]_{577}^{25} = +1$; $[\alpha]_{546}^{25} = +4$; $[\alpha]_{435}^{25} + 13$; $[\alpha]_{405}^{25} = +15$ (c = 0.11, CH_2Cl_2). UV (MeCN): 254 (34800), 208 (34500). IR (KBr): 3500, 2940, 1730, 1705, 1605, 1515, 1370, 1255, 1170, 1100, 1025, 845, 770, 610. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.99 (*m*, 1 $MeOC_6H_4CO$); 6.92 (*m*, 1 $MeOC_6H_4CO$); 5.64 (*t*, ^3J = 6.2, H–C(3)); 5.47 (*m*, H–C(4′)); 5.31 (*m*, H–C(1)); 5.10 (br. *t*, ^3J = 9.4, H–C(6)); 4.98 (br. *t*, ^3J = 9.4, H–C(6′)); 3.87, 3.86 (2*s*, 2 *Me*OC_6H_4CO); 3.85 (*m*, H–C(2′)); 2.74–2.56 (*m*, 2 H–C(5), 1 H–C(2)); 2.61 (*d*, ^2J = 13.5, 1 H, CH_2–C(4)); 2.48 (*m*, 1 H–C(2)); 2.46 (*d*, ^2J = 13.5, 1 H, CH_2–C(4)); 2.38–2.34 (*m*, 1 H–C(7′), 1 H–C(7), 1 H–C(3′)); 2.23–1.97 (*m*, 1 H–C(7), 1 H–C(3′), 2 H–C(5′)); 2.04, 1.79 (2*s*, 2 *Me*CO); 1.91 (*dd*, ^2J = 13.9, ^3J = 10.4, H–C(7′)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 171.1, 170.0 (2*s*, 2 C, Me*C*O); 165.2 (*s*, 2 C, $MeOC_6H_4CO$); 163.4 (*s*, 2 C, $MeOC_6H_4CO$); 136.2 (*s*, C(4)); 131.7, 131.6 (2*d*, ^1J = 163, 4 C, $MeOC_6H_4CO$); 127.8 (*d*, ^1J = 159, C(3)); 122.5 (*s*, 2 C, $MeOC_6H_4CO$); 113.6, 113.5 (2*d*, ^1J = 161, 4 C, $MeOC_6H_4CO$); 73.8 (*s*, C(1′)); 71.1 (*d*, ^1J = 141, C(2′)); 68.8 (*d*, ^1J = 149, C(1)); 68.2 (*d*, ^1J = 149, C(6)); 67.6 (*d*, ^1J = 149, C(4′)); 66.4 (*d*, ^1J = 149, C(6′)); 55.4 (*q*, ^1J = 143, 2 C, *Me*OC_6H_4CO); 47.7 (*t*, ^1J = 125, *C*H_2–C(4)); 43.1 (*t*, ^1J = 133, C(7′)); 41.5 (*t*, ^1J = 130, C(7)); 41.1 (*t*, ^1J = 130, C(5′)); 39.6 (*t*, ^1J = 125, C(5)); 35.6 (*t*, ^1J = 124, C(3′)); 31.8 (*t*, ^1J = 127, C(2)); 21.3, 20.9 (2*q*, ^1J = 129, 2 C, *Me*CO). CI-MS (NH_3): 673 (3, $[M+NH_4]^+$), 655 (1, $[M+H]^+$), 595 (4), 443 (4), 337 (7), 185 (7), 135 (81), 106 (100), 78 (25). Anal. calc. for $C_{35}H_{42}O_{12}$ (654.71): C 64.21, H 6.47, O 29.32; found: C 62.44, H 6.44 (corresponding to $C_{35}H_{42}O_{12}\cdot H_2O$: C 62.49, H 6.59).

*(1*S*,2*R*,4*S*,6*S*)-4-(Acetyloxy)-2-{[(4*S*,6*S*)-6-(acetyloxy)-4-[(4-methoxybenzoyl)oxy]cyclohept-1-en-1-yl]-methyl}-2-hydroxy-6-[(4-methoxybenzoyl)oxy]cycloheptyl (α*R*)-α-Methoxy-α-(trifluoromethyl)benzeneacetate* (**6M**). To a soln. of (+)-**6** (24.6 mg, 0.036 mmol) in dry CH_2Cl_2 (1 ml) was added dropwise Et_3N (10 µl, 0.072 mmol), *N*,*N*-dimethylpyridin-4-amine (one crystal), and (+)-(*S*)MTPACl ((α*S*)-α-methoxy-α-(trifluoromethyl)benzeneacetyl chloride; 7 µl, 0.036 mmol). After 3 h (TLC, CH_2Cl_2/MeOH 95:5), the reaction was quenched with sat. $NaHCO_3$ soln. (2 ml). The aq. phase was extracted with Et_2O (2 × 2 ml) and the org. layers were dried ($MgSO_4$). The ee was measured on the crude, which was further purified by FC (silica gel, Et_2O/light petroleum ether 1:1): **6M** (31 mg, 99%); 98.3% ee by ^{19}F-NMR, 97.6% by ^{1}H-NMR (MeO *s* of the minor diastereoisomer compared with the ^{13}C satellite peaks of the MeO *s* of the major diastereoisomer). $[\alpha]_{589}^{25} = +12$; $[\alpha]_{577}^{25} = +48$; $[\alpha]_{546}^{25} = +72$; $[\alpha]_{435}^{25} = +110$; $[\alpha]_{405}^{25} = +145$ (c = 0.07, CH_2Cl_2). UV (MeCN): 265 (18800), 252 (21300), 216 (15800). IR (KBr): 2955, 2845, 1780, 1715, 1605, 1580, 1520, 1450, 1420, 1370, 1315, 1260, 1170, 1100, 1025, 850, 770, 735, 700, 615. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.98 (*m*, 1 $MeOC_6H_4CO$); 7.55 (*m*, 2 H, *Ph*C(CF_3)(MeO)CO); 7.38 (*m*, 3 H, *Ph*C(CF_3)(MeO)CO); 6.91 (*m*, 1 $MeOC_6H_4CO$); 5.43 (*t*, ^3J = 6.3, H–C(6)); 5.34 (*m*, H–C(1), H–C(4′)); 5.21 (*dddd*, ^3J = 2.3, 6.3, 8.6, 10.4, 1 H–C(4)); 5.04 (*m*, H–C(6′)); 5.01 (*dd*, ^3J = 2.8, 10.4, H–C(2′)); 3.84, 3.87 (2*s*, 2 *Me*OC_6H_4CO); 3.57 (*s*, PhC(CF_3)(*Me*O)CO); 2.65–1.70 (*m*, 2 H–C(3′), 2 H–C(5′), 2 H–C(7′), 2 H–C(7), 2 H–C(5), 2 H–C(3), CH_2–C(2)); 2.05, 2.03 (2*s*, 2 *Me*CO). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 170.5, 170.3 (2*s*, 2 C, Me*C*O); 166.6, 166.3 (2*s*, 2 C, $MeOC_6H_4CO$); 165.4 (*s*, PhC(CF_3)(MeO)*C*O); 163.6, 163.4 (2*s*, 2 C, $MeOC_6H_4CO$); 135.1 (*s*, C(1′)); 132.3 (*d*, ^1J = 162, 4 C, $MeOC_6H_4CO$); 130 (*d*, ^1J = 161, 2 C, *Ph*C(CF_3)(MeO)CO); 128.4 (*s*, 1 C, *Ph*C(CF_3)(MeO)CO); 128.1 (*d*, ^1J = 162, 2 C, *Ph*C(CF_3)(MeO)CO); 128.0 (*d*, ^1J = 162, C(2′)); 127.6 (*d*, ^1J = 162, 1 C, *Ph*C(CF_3)(MeO)CO); 124.3 (*s*, Ph*C*(CF_3)(MeO)CO); 122.6, 122.2 (2*s*, 2 C, $MeOC_6H_4CO$); 113.6 (*d*, ^1J = 161, 4 C, $MeOC_6H_4CO$); 78.3 (*d*, ^1J = 140, C(6′)); 74.1 (*s*, C(2)); 68.8, 68.3 (*d*, ^1J = 142, 140, C(6), C(4)); 68.0 (*d*, ^1J = 151, C(1)); 66.1 (*d*, ^1J = 149, C(4′)); 55.1 (*q*, ^1J = 138, 2 C, *Me*OC_6H_4CO); 48.9 (*t*, ^1J = 129, CH_2–C(2)); 42.0, 40.8, 38.3, 38.0, 33.9, 31.4 (8*t*, C(3′), C(5′), C(7′), C(3), C(5), C(7)); 21.2 (*q*, ^1J = 162, 2 C, *Me*CO). ^{19}F-NMR (376.7 MHz, $CDCl_3$ + CCl_3F): −71.36 (*s*, 3 F, CF_3); −71.54 (*s*, 3 F, CF_3) for the minor diastereoisomer. CI-MS (NH_3): 888 (100, $[M+H_4]^+$), 654 (21), 570 (12), 334 (31), 294 (16), 252 (89), 152 (29), 135 (53), 91 (23). Anal. calc. for $C_{45}H_{49}F_3O_{14}$ (870.87): C 62.06, H 5.67, F 6.55, O 25.72; found: C 61.97, H 5.65.

*(1*R*,2*S*,4*R*,6*R*)/(1*S*,2*R*,4*S*,6*S*)-4-(Acetyloxy)-2-{[(4*S*,6*S*)/(4*R*,6*R*)-6-(acetyloxy)-4-[(4-methoxybenzoyl)oxy]-cyclohept-1-en-1-yl]methyl}-2-hydroxy-6-[(4-methoxybenzoyl)oxy]cycloheptyl (α*R*)-α-Methoxy-α-(trifluoro-methyl)benzeneacetate* (**7M**). As described for **6M**, with (+)-**7** (20 mg, 0.029 mmol), CH_2Cl_2 (1 ml), Et_3N

(8 µl, 0.058 mmol), DMAP (one cristal), and (+)-(*S*)-MTPACl (6 µl, 0.029 mmol): **7M** (31 mg, 99%); 4% ee by ^{19}F-NMR; the data were also photocopied, and the traces cut and weighted: 1% ee. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.07, 7.98 (2*m*, 8 H, $MeOC_6H_4CO_3$) 7.54 (2*m*, 4 H, *Ph*C(CF_3)(MeO)CO); 7.54 (2*m*, 6 H, *Ph*(CF_3)(MeO)CO); 6.94, 6.90 (2*m*, 8 H, $MeOC_6H_4CO$); 5.62, 5.53 (2*t*, ^3J = 6.2, 6.2, 2 H, H–C(2′)); 5.41, 5.34–5.26, 5.13–4.89 (3*m*, 8 H, H–C(4′), H–C(6), H–C(6′), H–C(4)); 3.86, 3.85, 3.85, 3.84 (4*s*, 12 H, *Me*OC_6H_4CO); 3.57, 3.52 (2*s*, 6 H, PhC(CF_3)(*Me*O)CO); 3.20–1.9 (*m*, 28 H, 7 CH_2); 2.02, 2.01, 1.80, 1.78 (4*s*, 12 H, MeCO). ^{19}F-NMR (376.7 MHz, $CDCl_3$ + CCl_3F): −71.49 (*s*, 3 F, CF_3); −71.43 (*s*, 3 F, CF_3) for the minor diastereoisomer. CI-MS (NH_3): 888 (100, $[M+NH_4]^+$), 654 (14), 570 (10), 334 (62), 294 (32), 252 (82), 170 (87), 135 (46), 105 (18), 91 (26), 77 (10).

*(1*S*,6*S*)-6-Hydroxy-4-{{(1*R*,2*S*,4*S*,6*S*)-1,2,6-trihydroxy-4-[(4-methoxybenzoyl)oxy]cycloheptyl}methyl}cyclohept-3-en-1-yl 4-Methoxybenzoate* ((−)-**8**). To a soln. of (+)-**6** (4 g, 6.1 mmol) in anh. MeOH (200 ml) was added dropwise 0.65M $Mg(OMe)_2$ (76 ml, 49 mmol) in MeOH. The reaction was complete within 5 h (TLC, CH_2Cl_2/MeOH 95:5) and was quenched with oxalic acid (4.4 g, 49 mmol). The soln. was stirred for 10 min and, without stirring, cooled to 0° for 1 h. The soln. was filtered over a *Celite* pad and the filtrate evaporated: (−)-**8** (3.34 g, 97%) as a white solid pure enough for the next step. For analysis, the product was purified by FC (silica gel, CH_2Cl_2/MeOH 92:8). $[\alpha]^{25}_{589} = -9$; $[\alpha]^{25}_{577} = -10$; $[\alpha]^{25}_{546} = -10$; $[\alpha]^{25}_{435} = -16$; $[\alpha]^{25}_{405} = -19$ (c = 0.28, CH_2Cl_2). UV (MeCN): 254 (14500), 202 (11800). IR (KBr): 3510, 3335, 2940, 2845, 1705, 1695, 1605, 1510, 1460, 1420, 1320, 1285, 1255, 1170, 1120, 1105, 1020, 985, 845, 770, 695, 665, 605. ^{1}H-NMR (400 MHz, CD_3OD): 7.95 (*m*, 1 $MeOC_6H_4CO$); 6.98 (*m*, 1 $MeOC_6H_4CO$); 5.63 (*t*, ^3J = 6.7, 1 H–C(3)); 5.25–5.19 (*m*, H–C(1), H–C(4′)); 4.25 (*dddd*, ^3J = 9.5, 5.0, 4.9, 2.7, H–C(6)); 4.12 (*m*, H–C(6′)); 3.86, 3.84 (*s*, 2 *Me*OC_6H_4CO); 3.53 (*dd*, ^3J = 10.9, 2.5, H–C(2′)); 2.69 (*dd*, ^2J = 14.8, ^3J = 9.5, 1 H–C(5)); 2.66 (*d*, ^2J = 12.7, 1 H, CH_2–C(4)); 2.61–2.51 (*m*, 1 H–C(5), 2 H–C(2)); 2.34 (*ddd*, ^2J = 13.3, ^3J = 10.9, 10.9, 1 H–C(3′)); 2.21 (*d*, ^2J = 12.8, 1 H, CH_2–C(4)); 2.26–2.14 (*m*, 2 H–C(7), 1 H–C(7′), 1 H–C(5′)); 2.03 (*dd*, ^3J = 8.2, 6.2, 1 H–C(7′)); 1.98 (*m*, 1 H–C(3′)); 1.61 (*dd*, ^2J = 14.5, ^3J = 10.5, 1 H–C(5′)). ^{13}C-NMR (100.6 MHz, CD_3OD): 165.5 (*s*, 2 C, $MeOC_6H_4CO$); 165.1 (*s*, 2 C, $MeOC_6H_4CO$); 139.6 (*s*, C(4)); 132.5 (*d*, ^1J = 170, 4 C, $MeOC_6H_4CO$); 127.6 (*d*, ^1J = 158, C(3)); 124.1 (*s*, 2 C, $MeOC_6H_4CO$); 114.8 (*d*, ^1J = 162, 4 C, $MeOC_6H_4CO$); 76.0 (*s*, C(1′)); 74.0 (*d*, ^1J = 138, C(2′)); 70.5, 70.4 (2*d*, ^1J = 159, C(1), C(4′)); 67.1 (*d*, ^1J = 139, C(6′)); 64.4 (*d*, ^1J = 143, C(6)); 56.0 (*q*, ^1J = 144, 2 C, *Me*OC_6H_4CO); 50.8 (*t*, ^1J = 128, *C*H_2–C(4)); 45.8 (*t*, ^1J = 127, C(7)); 45.0 (*t*, C(5′)); 43.4 (*t*, ^1J = 115, C(7′)); 41.6 (*t*, C(5)); 38.5 (*t*, ^1J = 127, C(3′)); 34.4 (*t*, ^1J = 127, C(2)). CI-MS (NH_3): 588 (7, $[M+NH_4]^+$), 419 (3), 277 (25), 152 (44), 135 (100), 107 (36). Anal. calc. for $C_{31}H_{38}O_{10}$ (570.64): C 65.25, H 6.71, O 28.04; found: C 65.19, H 6.79.

*(3*aS*,5*S*,7*S*,8*aR*)-Hexahydro-7-hydroxy-8a-{[(4*S*,6*S*)-6-hydroxy-4-[(4-methoxy)benzoyl)oxy]cyclohept-1-en-1- yl}methyl}-2,2-dimethyl-4*H*-cyclohepta[*d*]-1,3-dioxol-5-yl 4-Methoxybenzoate* ((−)-**9**). To a soln. of (−)-**8** (20 mg, 0.037 mmol) was added pyridinium *p*-toluenesulfonate (PPTS; 1 mg, $3.7 \cdot 10^{-3}$ mmol) and a soln. of 20% 2,2-dimethoxypropane/acetone (1 ml). The reaction was complete after 4 h at 60° (TLC, CH_2Cl_2/MeOH 95:5). Evaporation and purification by FC (silica gel, CH_2Cl_2/MeOH 95:5) afforded (−)-**9** (18 mg, 80%). White foam. $[\alpha]^{25}_{589} = -18$; $[\alpha]^{25}_{577} = -30$; $[\alpha]^{25}_{546} = -34$; $[\alpha]^{25}_{435} = -56$; $[\alpha]^{25}_{405} = -65$ (c = 0.11, CH_2Cl_2). IR (KBr): 3435, 2935, 1705, 1605, 1515, 1460, 1380, 1280, 1255, 1170, 1105, 1030, 850, 770, 730, 695, 610. UV (MeCN): 252 (40700), 207 (34200). ^{1}H-NMR (400 MHz, $CDCl_3$; numbering of (−)-**8**): 8.04 (*d*, ^3J = 9.1, 2 H, $MeOC_6H_4CO$); 7.91 (*d*, ^3J = 8.6, 2 H, $MeOC_6H_4CO$); 6.91 (*d*, ^3J = 9.1, 2 H, $MeOC_6H_4CO$); 6.89 (*d*, ^3J = 8.6, 2 H, $MeOC_6H_4CO$); 5.75 (*dd*, ^3J = 5.4, 8.1, 1 H–C(3)); 5.37 (br. *m*, H–C(4′)); 5.22 (*tt*, ^3J = 2.7, 9.7, H–C(1)); 4.34 (br. *d*, ^3J = 8.6, H–C(6)); 4.23 (br. *s*, H–C(6′)); 4.16 (*d*, ^3J = 6.4, H–C(2′)); 3.86 (2*s*, 2 *Me*OC_6H_4CH); 2.72 (*t*, ^3J = 6.4, 2 H–C(3′)); 2.68 (*m*, 1 H–C(5)); 2.53 (*m*, 2 H–C(2)); 2.56–2.32 (*m*, 1 H–C(7), 1 H–C(7′), 1 H–C(5′), CH_2–C(4)); 2.00–1.80 (*m*, 1 H–C(7), 1 H–C(5′), 1 H–C(5), 1 H–C(7′)); 1.55, 1.44 (2*s*, Me_2CO_2). ^{13}C-NMR (100.6 MHz, $CDCl_3$; numbering of (−)-**8**): 165.6, 165.4 (*s*, 2 C, $MeOC_6H_4CO$); 163.2 (2*s*, 2 C, $MeOC_6H_4CO$); 136.9 (*s*, C(4)); 131.8, 131.5 (2*d*, ^1J = 163, 4 C, $MeOC_6H_4CO$); 127.3 (*d*, ^1J = 156, C(3)); 123.1, 123.0 (2*s*, 2 C, $MeOC_6H_4CO$); 113.5, 113.4 (2*d*, ^1J = 163, 4 C, $MeOC_6H_4CO$); 107.5 (*s*, Me_2CO_2); 83.6 (*s*, C(1′)); 82.5 (*d*, ^1J = 144, C(2′)); 68.3 (*d*, ^1J = 151, C(1)); 68.1 (*d*, ^1J = 151, C(4′)); 66.6 (*d*, ^1J = 145, C(6′)); 63.5 (*d*, ^1J = 145, C(6)); 55.4 (*q*, ^1J = 145, 2 C, *Me*OC_6H_4CO); 53.7 (*t*, ^1J = 128, *C*H_2–C(4)); 46.8 (*t*, ^1J = 127, C(5)); 44.2, 44.0 (*t*, ^1J = 127, 2 C, C(7), C(5′)); 39.8 (*t*, ^1J = 125, C(2)); 34.3 (*t*, ^1J = 130, C(3′)); 31.8 (*t*, ^1J = 125, C(7′)); 27.8, 26.2 (2*q*, ^1J = 125, *Me*$_2$$CO_2$). CI-MS ($NH_3$): 629 (4, $[M+NH_4]^+$), 335 (13), 227 (6), 183 (23), 135 (100). Anal. calc. for $C_{34}H_{42}O_{10}$ (610.70): C 66.87, H 6.93, O 26.20; found: C 67.06, H 7.10.

*(2*R *and 2*S*,4*S*,6*S*) Tetrahydro-2-hydroxy-6-{3-[(4*S*,6*S*)-6-hydroxy-4-[(4-methoxybenzoyl)oxy]cyclohept-1-en-1-yl]-2-oxopropyl}-2*H*-pyran-4-yl 4-Methoxybenzoate* ((+)-**10**). To a soln. of (−)-**8** (1.77 g, 3.1 mmol) in dioxane (40 ml) was added a soln. of $NaIO_4$ (9 ml, 5.58 mmol) in H_2O (660 mg per 5 ml). After stirring overnight (TLC, CH_2Cl_2/MeOH 95:5), the soln. was diluted with sat. NaCl soln. (20 ml) and extracted with

AcOEt (3×75 ml). The org. phase was dried (Na_2SO_4) and evaporated: 1.74 g (99%) of crude (+)-**10**. Purification by FC (silica gel, CH_2Cl_2/MeOH 98:2) afforded pure anomer mixture (+)-**10** (1.55 g, 88%). White solid. $[\alpha]_{589}^{25} = +35$; $[\alpha]_{577}^{25} = +37$; $[\alpha]_{546}^{25} = +40$; $[\alpha]_{435}^{25} = +66$; $[\alpha]_{405}^{25} = +79$ ($c = 0.13$, CH_2Cl_2). UV (MeCN): 264 (11100), 246 (12700), 214 (10400). IR (KBr): 3425, 2935, 1715, 1605, 1510, 1420, 1260, 1170, 1105, 1030, 850, 770, 700, 615. ^{1}H-NMR (400 MHz, $CDCl_3$)[4]: 7.99 (*m*, 1 MeOC_6H_4CO); 6.92 (*m*, 1 MeOC_6H_4CO); 5.71 (*t*, $^3J = 6.6$, H–C(2″)); 5.50 (*m*, 2 H, H–C(4)(α/β), H–C(2)(α)); 5.25 (*m*, 1 H, H–C(4″)); 5.16 (*tt*, $^3J = 11.5$, 4.6, 1 H, H–C(4)(α/β)); 4.89 (br. *d*, $^3J = 9.3$, 1 H, H–C(2)(β)); 4.65 (*m*, 1 H, H–C(6)(α/β)); 4.16 (*m*, 1 H, H–C(6″)); 4.06 (*m*, 1 H, H–C(6)(α/β)); 3.87, 3.85 (*s*, 6 H, *Me*OC_6H_4CO); 3.37 (*d*, $^2J = 16.2$, 1 H, H–C(1′)); 3.32 (*d*, $^2J = 16.2$, 1 H, H–C(1′)); 2.94 (*dd*, $^2J = 15.5$, $^3J = 9.1$, 1 H, H–C(3′)); 2.81 (*dd*, $^2J = 15.5$, $^3J = 9.5$, 1 H, H–C(3′)); 2.60–2.44 (*m*, 4 H, H–C(3″), H–C(7″)); 2.43–2.36 (*m*, 2 H, H–C(3)(α/β)); 2.34–2.07 (*m*, 6 H, H–C(5″), H–C(5)(α/β), H–C(3)(α/β)); 1.74 (*ddd*, $^2J = 11.8$, $^3J = 3.4$, 3.4, H–C(5)(α/β)); 1.61–1.43 (*m*, H–C(5)(α/β), H–C(3)(α/β). ^{13}C-NMR (100.6 MHz, $CDCl_3$)[4]): 208.5 (*s*, C(2′)); 165.6, 165.5 (*s*, 2 C, MeOC_6H_4CO); 163.3 (*s*, 2 C, MeOC_6H_4CO); 133.7 (*s*, C(1″)); 131.6 (*d*, $^1J = 163$, 4 C, MeOC_6H_4CO); 127.0 (*d*, $^1J = 156$, C(2″)); 123.0, 122.7 (2*s*, 2 C, MeOC_6H_4CO); 113.6 (*d*, $^1J = 162$, 4 C, MeOC_6H_4CO); 94.2, 92.3 (2*d*, $^1J(\beta) = 189$, $^1J(\alpha) = 167$, C(2)); 68.7 (*d*, C(4)); 68.5 (*d*, C(4″)); 68.4 (*d*, C(6)(β)); 66.7 (*d*, C(4)); 65.7 (*d*, C(6″)); 64.3 (*d*, C(6)(α)); 55.4 (*q*, $^1J = 145$, 2 C, *Me*OC_6H_4CO); 55.0, 54.6 (*t*, C(1′)); 47.9, 47.4 (2*t*, $^1J = 128$, C(3′)); 44.6 (*t*, $^1J = 127$, C(5″)); 39.6 (*t*, $^1J = 125$, C(7″)); 38.1, 37.2 (C(3)); 36.2, 35.6 (C(5)); 33.3 (*t*, $^1J = 128$, C(3″)). CI-MS (NH_3): 586 (4, $[M + NH_4]^+$]), 568 (4, $[M + H]^+$), 399 (20), 301 (10), 251 (10), 229 (9), 170 (57), 135 (100).

*(1*S*,6*S*)-6-Hydroxy-4-{(2*S*,4*R*,6*R*)-2,4,8-trihydroxy-6-[(4-methoxybenzoyl)oxy]octyl}cyclohept-3-en-1-yl 4-Methoxybenzoate* ((+)-**11**). To a soln. of (+)-**10** (1.83 g, 3.2 mmol) in AcOH (40 ml) was added $Me_4NBH(OAc)_3$ (12.7 g, 48.2 mmol). After 24 h under stirring (TLC, CH_2Cl_2/MeOH 9:1), the AcOH was completely evaporated, and a mixture of H_2O and crushed ice (50 ml) was added slowly to the residue. After 10 min under stirring, solid $NaHCO_3$ (4 g) was added portionwise, and the soln. was stirred for another 20 min. After extraction of the aq. phase with AcOEt (5×50 ml), the org. layer was dried (Na_2SO_4), and the product was deposited on silica gel. Purification by FC (silica gel, CH_2Cl_2/MeOH 95:5) afforded (+)-**11** (1.28 g, 70%). White solid. $[\alpha]_{589}^{20} = +22$; $[\alpha]_{578}^{20} = +12$; $[\alpha]_{546}^{20} = +13$; $[\alpha]_{436}^{20} = +8$; $[\alpha]_{365}^{20} = +8$ ($c = 0.14$, CH_2Cl_2). UV (MeCN): 254 (45300), 201 (53000). IR (KBr): 3360, 2940, 1685, 1605, 1510, 1460, 1420, 1255, 1170, 1120, 1025, 845, 770, 695. ^{1}H-NMR (400 MHz, CD_3OD): 7.96 (*m*, 1 MeOC_6H_4CO); 6.90 (*m*, 1 MeOC_6H_4CO); 5.65 (*t*, $^3J = 6.7$, H–C(3)); 5.48 (*dddd*, $^3J = 8.6$, 8.6, 5.2, 4.3, H–C(6′)); 5.17 (*m*, H–C(1)); 4.68 (*m*, H–C(6)); 4.09 (*m*, H–C(2′)); 3.98 (*m*, H–C(4′)); 3.85, 3.83 (*s*, 2 *Me*OC_6H_4CO); 3.76–3.62 (*m*, 2 H–C(8′)); 2.59 (*dd*, $^2J = 14.8$, $^3J = 7.4$, 1 H–C(5)); 2.50, 2.46 (*m*, 1 H–C(5), 2 H–C(2)); 2.29 (*ddd*, $^2J = 13.6$, $^3J = 6.2$, 3.4, 1 H–C(7)); 2.18 (*dd*, $^2J = 13.1$, $^3J = 2.7$, 1 H–C(1′)); 2.07 (*d*, $^2J = 13.1$, 1 H–C(1′)); 2.11–2.03 (*m*, 1 H–C(7′), 1 H–C(7)); 1.94 (*dddd*, $^2J = 7.9$, $^3J = 5.2$, 5.2, 5.2, 1 H–C(7′)); 1.86–1.83 (*m*, 2 H–C(5′)); 1.64–1.61 (*m*, 2 H–C(3′)). ^{13}C-NMR (100.6 MHz, CD_3OD): 167.4, 165.6 (2*s*, 2 C, MeOC_6H_4CO); 163.6, 163.3 (2*s*, 2 C, MeOC_6H_4CO); 139.2 (*s*, C(4)); 131.8, 131.5 (2*d*, $^1J = 164$, 165, 4 C, MeOC_6H_4CO); 124.2 (*d*, $^1J = 155$, C(3)); 122.9, 122.1 (2*s*, 2 C, MeOC_6H_4-CO); 113.7, 113.5 (*d*, $^1J = 161$, 4 C, MeOC_6H_4CO); 69.5 (*d*, $^1J = 145$, C(2′)); 69.4 (*d*, $^1J = 145$, C(6′)); 68.6 (*d*, $^1J = 151$, C(1)); 66.2 (*d*, $^1J = 149$, C(6)); 65.2 (*d*, $^1J = 140$, C(4′)); 58.6 (*t*, $^1J = 140$, C(8′)); 55.4 (*q*, $^1J = 145$, 2 C, *Me*OC_6H_4CO); 48.4 (*t*, $^1J = 122$, C(1′)); 44.7 (*t*, $^1J = 122$, C(7)); 42.8 (*t*, $^1J = 119$, C(3′)); 42.7 (*t*, $^1J = 122$, C(5′)); 39.6 (*t*, $^1J = 121$, C(5)); 38.0 (*t*, $^1J = 120$, C(7′)); 33.5 (*t*, $^1J = 122$, C(2)). CI-MS (NH_3): 590 (10, $[M + NH_4]^+$), 573 (69, $[M + H]^+$), 421 (6), 297 (25), 233 (18), 135 (100), 92 (25). Anal. calc. for $C_{31}H_{40}O_{10}$ (572.65): C 65.02, H 7.04, O 27.94; found: C 64.99, H 7.00.

*(1*S*,6*S*)-6-Hydroxy-4-{{(4*S*,6*R*)-6-{(2*R*)-4-hydroxy-2-[(4-methoxybenzoyl)oxy]butyl}-2,2-dimethyl-1,3-dioxan-4-yl}methyl}cyclohept-3-en-1-yl 4-Methoxybenzoate* ((+)-**12**). To a soln. of (+)-**11** (1.28 g, 2.23 mmol) in 50% 2,2-dimethoxypropane/acetone (40 ml), was added PPTS (56 mg, 0.22 mmol). After 24 h under stirring (TLC, CH_2Cl_2/MeOH 95:5), the soln. was evaporated, the crude product dissolved in CH_2Cl_2/MeOH 98:2 (20 ml), and PPTS added (56 mg, 0.22 mmol). The selective deprotection of the acetal at C(4‴) was followed by TLC to keep the acetonide intact. The reaction was quenched by addition of solid $NaHCO_3$ (100 mg), and the product purified by FC (silica gel, CH_2Cl_2/MeOH 95:5): (+)-**12** (1.11 g, 81%). White foam. $[\alpha]_{589}^{25} = +30$; $[\alpha]_{577}^{25} = +30$; $[\alpha]_{546}^{25} = +37$; $[\alpha]_{435}^{25} = +71$; $[\alpha]_{405}^{25} = +92$ ($c = 0.18$, CH_2Cl_2). UV (MeCN): 252 (20200), 210 (13400). IR (KBr): 3450, 2935, 1705, 1605, 1510, 1260, 1170, 1105, 1030, 850, 770, 695, 610. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.01–7.94 (*m*, 1 MeOC_6H_4CO); 6.94–6.88 (*m*, 1 MeOC_6H_4CO); 5.63 (*t*, $^3J = 6.6$, H–C(3)); 5.46 (*dddd*, $^3J = 9.8$, 9.8, 3.2, 3.2, H–C(2‴)); 5.16 (*dddd*, $^3J = 9.7$, 9.7, 3.9, 3.8, H–C(1)); 4.06 (*m*, H–C(6)); 3.99 (*m*, H–C(4″)); 3.91 (*m*, H–C(6″)); 3.86, 3.84 (*s*, 2 *Me*OC_6H_4CO); 3.79–3.55 (*m*, 2 H–C(4‴)); 2.91 (br. *s*, OH–C(4‴)); 2.53 (br.

[4]) α refers to anomeric OH (axial) and β to anomeric OH (equatorial).

s, OH–C(6)); 2.51–2.42 (*m*, 2 H–C(2), 2 H–C(5)); 2.26–2.09 (*m*, 2 H–C(7), 2 H–C(1′)); 1.98–1.87 (*m*, 1 H–C(3‴), 1 H–C(1‴)); 1.81–1.72 (*m*, 1 H–C(3‴), 1 H–C(1‴)); 1.64 (*ddd*, ^2J = 21.7, ^3J = 12.8, 8.9, 1 H–C(5″)); 1.63 (*ddd*, ^2J = 21.7, ^3J = 12.8, 9.0, 1 H–C(5″)); 1.31, 1.14 (*s*, Me_2C(2″)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 167.0, 165.5 (2*s*, 2 C, MeOC_6H_4CO); 163.5, 163.2 (2*s*, 2 C, MeOC_6H_4CO); 137.5 (*s*, C(4)); 131.6, 131.5 (2*d*, ^1J = 164, 4 C, MeOC_6H_4CO); 123.9 (*d*, ^1J = 167, C(3)); 123.1, 122.2 (2*s*, 2C, MeOC_6H_4CO); 113.7, 113.5 (*d*, ^1J = 161, 4 C, MeOC_6H_4CO); 100.8 (*s*, C(2″)); 68.7 (*d*, ^1J = 151, C(1)); 68.3 (*d*, ^1J = 149, C(2‴)); 66.9 (*d*, ^1J = 143, C(4″)); 65.9 (*d*, ^1J = 143, C(6)); 63.0 (*d*, ^1J = 143, C(6″)); 58.2 (*t*, ^1J = 140, C(4‴)); 55.4 (*q*, ^1J = 145, 2 C, *Me*OC_6H_4CO); 45.9 (*t*, ^1J = 120, C(1′)); 44.8 (*t*, ^1J = 120, C(7)); 40.9 (*t*, ^1J = 131, C(1‴)); 40.6 (*t*, ^1J = 128, C(5)); 38.4 (*t*, ^1J = 126, C(5″)); 38.2 (*t*, ^1J = 126, C(3‴)); 33.1 (*t*, ^1J = 128, C(2)); 24.4, 24.3 (2*q*, ^1J = 128, 2 C, Me_2C(2″)). CI-MS (NH_3): 613 (15, $[M+H]^+$), 555 (66), 401 (8), 279 (58), 135 (100). Anal. calc. for $C_{34}H_{44}O_{10}$ (612.72): C 66.65, H 7.24, O 26.11; found: C 66.64, H 7.19.

(1S,6S)-6-Hydroxy-4-{(2R,4R,6R)-2,4,8-trihydroxy-6-[(4-methoxybenzoyl)oxy]octyl}cyclohept-3-en-1-yl 4-Methoxybenzoate ((−)-**13**). A soln. of (+)-**10** (200 mg, 0.35 mmol) in anh. THF/MeOH 4:1 (2 ml) was cooled to −78° and a 1M Et_2BOMe in THF (1.75 ml, 1.75 mmol) was added dropwise. After 2 h, the soln. was allowed to warm to −20°, and $NaBH_4$ (40 mg, 1.05 mmol) was added. Two further amounts of $NaBH_4$ (40 mg, 1.05 mmol) were added every 2 h until the reaction was almost complete (TLC, CH_2Cl_2/MeOH 9:1). After dilution with AcOEt (8 ml), the reaction was quenched with AcOH (200 µl) and H_2O (8 ml). The soln. was neutralized by addition of $NaHCO_3$, the aq. layer extracted with AcOEt (4 × 4 ml), the org. soln. dried (Na_2SO_4), and the product deposited on silica gel. Purification by FC (silica gel, CH_2Cl_2/MeOH 95:5) afforded (−)-**13** (130 mg, 65%). White solid. $[\alpha]_{589}^{20} = -12$; $[\alpha]_{578}^{20} = -16$; $[\alpha]_{546}^{20} = -19$; $[\alpha]_{436}^{20} = -25$; $[\alpha]_{365}^{20} = -47$ (*c* = 0.03, $CHCl_3$). UV (MeCN): 265 (13000), 248 (14900), 214 (12200). IR (KBr): 3405, 2935, 1705, 1605, 1510, 1420, 1260, 1170, 1105, 1030, 850, 770, 700, 610. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.97 (*m*, 1 MeOC_6H_4CO); 6.91 (*m*, 1 MeOC_6H_4CO); 5.70 (*dd*, ^3J = 7.7, 5.9, H–C(3)); 5.48 (*m*, H–C(6′)); 5.12 (*dddd*, ^3J = 10.3, 10.3, 2.8, 2.8, H–C(1)); 4.20 (br. *s*, H–C(6)); 4.05 (*m*, H–C(2′)); 3.91 (*m*, H–C(4′)); 3.86, 3.85 (2*s*, 2 *Me*OC_6H_4CO); 3.70 (*m*, 2 H–C(8′)); 2.45 (*m*, 2 H–C(5), 2 H–C(2), 1 H–C(7)); 2.10 (*d*, ^3J = 6.7, 2 H–C(1′)); 1.98–1.93 (*m*, 2 H–C(7′), 1 H–C(7)); 1.81 (*dd*, ^3J = 6.4, 6.4, 2 H–C(5′)); 1.57 (*m*, 2 H–C(3′)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 167.1, 165.5 (2*s*, 2 C, MeOC_6H_4CO); 163.5, 163.2 (2*s*, 2 C, MeOC_6H_4CO); 137.4 (*s*, C(4)); 131.8, 131.5 (2*d*, ^1J = 163, 4 C, MeOC_6H_4CO); 124.9 (*d*, ^1J = 154, C(3)); 122.9, 122.2 (2*s*, 2 C, MeOC_6H_4CO); 113.6, 113.4 (2*d*, ^1J = 166, 4 C, MeOC_6H_4CO); 69.2 (*d*, ^1J = 147, C(6′)); 68.5 (2*d*, ^1J = 141, C(4′), C(2′)); 68.2 (*d*, ^1J = 152, C(1)); 65.9 (*d*, ^1J = 143, C(6)); 58.5 (*t*, ^1J = 143, C(8′)); 55.4, 55.3 (2*q*, ^1J = 144, 2 C, *Me*OC_6H_4CO); 48.4 (*t*, ^1J = 128, C(1′)); 44.9 (*t*, ^1J = 133, C(7)); 43.1 (*t*, ^1J = 126, C(5′)); 42.5 (*t*, ^1J = 126, C(3′)); 38.0 (*t*, ^1J = 127, C(7′)); 36.5 (*t*, ^1J = 123, C(5)); 34.1 (*t*, ^1J = 126, C(2)). CI-MS (NH_3): 590 (23, $[M+NH_4]^+$), 573 (100, $[M+H]^+$), 421 (6), 297 (17), 233 (7), 135 (74), 92 (19). Anal. calc. for $C_{31}H_{40}O_{10}$ (572.65): C 65.02, H 7.04, O 27.94; found: C 64.99, H 6.87.

(1S,6S)-6-Hydroxy-4-{[(4R,6R)-6-{(2R)-4-hydroxy-2-[(4-methoxybenzoyl)oxy]butyl}-2,2-dimethyl-1,3-dioxan-4-yl]methyl}cyclohept-3-en-1-yl 4-Methoxybenzoate ((+)-**14**). To a soln. of (−)-**13** (1.00 g, 1.74 mmol) in 50% 2,2-dimethoxypropane/acetone (10 ml) was added PPTS (44 mg, 0.17 mmol) at 0°. After stirring overnight (TLC, CH_2Cl_2/MeOH 95:5), the soln. was evaporated and the residue dissolved in CH_2Cl_2/MeOH 97:3 (10 ml) in the presence of additional PPTS (22 mg, 0.08 mmol). The selective deprotection of the acetal at C(4″) was followed by TLC (CH_2Cl_2/MeOH 95:5) to avoid complete deprotection. After 10 min, the reaction was quenched with $NaHCO_3$ (80 mg), and the product was deposited on silica gel. Purification by FC (silica gel, CH_2Cl_2/MeOH 95:5) afforded (+)-**14** (1.06 g, 78%). White foam. $[\alpha]_{589}^{25} = +9$; $[\alpha]_{577}^{25} = +5$; $[\alpha]_{546}^{25} = +3$; $[\alpha]_{435}^{25} = +3$; $[\alpha]_{405}^{25} = +2$ (*c* = 0.20, CH_2Cl_2). UV (MeCN): 251 (37400), 209 (28900). IR (KBr): 3460, 1705, 1605, 1510, 1460, 1420, 1380, 1260, 1170, 1105, 1030, 975, 850, 770, 695, 615. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.97 (*m*, 1 MeOC_6H_4CO); 6.92 (*m*, 1 MeOC_6H_4CO); 5.64 (*dd*, ^3J = 6.6, 6.6, H–C(3)); 5.48 (*m*, H–C(2‴)); 5.16 (*dddd*, ^3J = 8.8, 8.8, 3.4, 3.4, 1 H–C(1)); 4.06 (*m*, H–C(6)); 3.99 (*m*, H–C(4′), H–C(6″)); 3.86, 3.84 (2*s*, 2 *Me*OC_6H_4CO); 3.69–3.57 (*m*, 2 H–C(4‴)); 2.45 (*m*, 2 H–C(5), 2 H–C(2)); 2.29 (*ddd*, ^2J = 13.3, ^3J = 6.2, 3.4, H–C(7)); 2.21 (*dd*, ^2J = 13.9, ^3J = 7.3, 1 H–C(1′)); 2.15 (*dd*, ^2J = 13.9, ^3J = 4.8, 1 H–C(1′)); 2.05 (*ddd*, ^2J = 13.3, ^3J = 8.8, 2.8, 1 H–C(7)); 1.95 (*dddd*, ^2J = 14.4, ^3J = 9.3, 5.6, 3.6, 1 H–C(3‴)); 1.88–1.74 (*m*, 1 H–C(5″), 1 H–C(3‴), 2 H–C(1‴)); 1.45 (*ddd*, ^2J = 12.9, ^3J = 2.5, 2.5, 1 H–C(5″)); 1.36, 1.27 (2*s*, Me_2C(2″)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 166.9, 165.4 (2*s*, 2 C, MeOC_6H_4CO); 163.6, 163.2 (2*s*, 2 C, MeOC_6H_4CO); 136.4 (*s*, C(4)); 131.7, 131.5 (2*d*, ^1J = 164, 4 C, MeOC_6H_4CO); 125.3 (*d*, ^1J = 161, C(3)); 123.1, 122.2 (2*s*, 2 C, MeOC_6H_4CO); 113.7, 113.5 (2*d*, ^1J = 161, 4 C, MeOC_6H_4CO); 99.1 (*s*, C(2″)); 68.4 (*d*, ^1J = 125, C(1)); 68.3 (*d*, ^1J = 133, C(2‴)); 67.1 (*d*, ^1J = 131, C(4″)); 65.8 (*d*, ^1J = 135, C(6)); 65.5 (*d*, ^1J = 141, C(6″)); 58.3 (*t*, ^1J = 140, C(4‴)); 55.4 (*q*, ^1J = 145, 2 C, *Me*OC_6H_4CO); 46.8 (*t*, ^1J = 121, C(1′)); 44.8 (*t*, ^1J = 120, C(7)); 41.6 (*t*, ^1J = 127, C(1‴)); 38.8 (*t*, ^1J = 126, C(5)); 38.2 (*t*, ^1J = 125, C(3‴)); 36.8 (*t*, ^1J = 128, C(5″)); 33.6 (*t*, ^1J = 126,

C(2)); 29.9, 19.3 (2*q*, ^1J = 126, 123, 2 C, $Me_2C(2'')$). CI-MS (NH_3): 613 (5, $[M+H]^+$), 555 (30), 279 (70), 233 (7), 135 (100). Anal. calc. for $C_{34}H_{44}O_{10}$ (612.72): C 66.65, H 7.24, O 26.11; found: C 66.62, H 7.34.

*(1*S*,3*S*)-5-{[(4*S*,6*S*)-6-[(2*R*)-2,4-Dihydroxybutyl]-2,2-dimethyl-1,3-dioxan-4-yl]methyl}cyclohept-5-ene-1,3-diol* ((+)-**15**). A soln. of CH_2Cl_2 (30 ml) containing (+)-**12** (1.11 g, 1.81 mmol) was cooled to −78°, and 1M DIBAL-H in CH_2Cl_2 (5.1 ml, 5.10 mmol) was added dropwise over 10 min (*the hydride supplied by* Sigma-Aldrich *gave better results than the one from* Fluka). The same quantity of reagent was added two more times, after 1 h intervals, while the temp. rose to −30°. After 7 h overall reaction time, the mixture was cooled to −78°, and the reaction was quenched with MeOH (50 ml). The soln. was stirred for 1 h 20 and then evaporated. The product was left over silica gel. FC (silica gel, CH_2Cl_2/MeOH 9:1) afforded (+)-**15** (548 mg, 88%). White solid. $[\alpha]_{589}^{25}$ = +32; $[\alpha]_{577}^{25}$ = +32; $[\alpha]_{546}^{25}$ = +38; $[\alpha]_{435}^{25}$ = +63; $[\alpha]_{405}^{25}$ = +80 (*c* = 0.05, MeOH). UV (MeCN): 255 (1200), 212 (2200). IR (KBr): 3380, 2935, 1690, 1605, 1510, 1445, 1380, 1260, 1225, 1165, 1095, 1035, 940, 905, 810, 735, 700. ^{1}H-NMR (400 MHz, CD_3OD): 5.54 (*t*, ^3J = 6.9, H−C(6)); 4.10 (*dtd*, ^3J = 2.5, 7.4, 10.4, H−C(4″)); 4.06–3.83 (*m*, H−C(1), H−C(3), H−C(6′), H−C(2‴)); 3.78 (*t*, ^3J = 6.4, 2 H−C(4‴)); 2.40 (*m*, 2 H−C(4)); 2.32 (*m*, 2 H−C(7)); 2.25 (*dd*, ^3J = 7.4, ^2J = 13.8, 1 H−C(1′)); 2.17 (*dd*, ^3J = 5.9, ^2J = 13.8, 1 H−C(1′)); 2.02 (*m*, 2 H−C(2)); 1.72–1.47 (*m*, 2 H−C(5″), 2 H−C(1‴), 2 H−C(3‴)); 1.37, 1.35 (2*s*, $Me_2C(2")$). ^{13}C-NMR (100.6 MHz, CD_3OD): 139.0 (*s*, C(2″)); 125.9 (*d*, ^1J = 155, C(6)); 102.5 (*s*, C(5)); 67.7, 67.5, 67.3, 67.1 (4*d*, ^1J = 144, 143, 144, 144, 4 C, C(3), C(1), C(6″), C(2‴)); 65.7 (*d*, ^1J = 146, C(4″)); 60.9 (*t*, ^1J = 140, C(4‴)); 50.8 (*t*, C(2)); 48.5 (*t*, ^1J = 125, C(1′)); 45.6 (*t*, ^1J = 123, C(5″)); 42.4, 42.3 (2*t*, ^1J = 124, 124, C(4), C(3‴)); 40.4 (*t*, ^1J = 127, C(1‴)); 37.3 (*t*, ^1J = 122, C(7)); 26.1, 26.0 (2*q*, ^1J = 126, 2 C, *Me*$_2$C(2″)). CI-MS (NH_3): 362 (32, $[M+NH_4]^+$), 345 (100, $[M+H]^+$), 287 (79), 267 (27), 203 (11), 121 (34), 83 (17). Anal. calc. for $C_{18}H_{32}O_6$ (344.45): C 62.77, H 9.36, O 27.87; found: C 62.65, H 9.27.

*(1*S*,3*S*)-5-{[(4*R*,6*S*)-6-[(2*R*)-2,4-Dihydroxybutyl]-2,2-dimethyl-1,3-dioxan-4-yl]methyl}cyclohept-5-ene-1,3-diol* ((+)-**17**). As described for (+)-**15**, with (+)-**14** (500 mg, 0.81 mmol), CH_2Cl_2 (15 ml), and 1M DIBAL-H in CH_2Cl_2 (2.2 ml, 2.2 mmol). After quenching with MeOH (25 ml), the soln. was stirred for 1 h at 20° in the presence of silica gel and then evaporated. FC (silica gel, CH_2Cl_2/MeOH 9:1) gave (+)-**17** (231 mg, 83%). White foam. $[\alpha]_{589}^{20}$ = +3; $[\alpha]_{578}^{20}$ = +5; $[\alpha]_{546}^{20}$ = +5; $[\alpha]_{436}^{20}$ = +15; $[\alpha]_{365}^{20}$ = +30 (*c* = 0.04, MeOH). UV (MeCN): 201 (9200). IR (KBr): 3385, 2990, 2940, 1650, 1430, 1385, 1265, 1200, 1165, 1090, 1040, 980, 930, 870, 735. ^{1}H-NMR (400 MHz, CD_3OD): 5.50 (*t*, ^3J = 6.5, H−C(6)); 4.15 (*ddt*, ^3J = 2.9, 5.5, 11.3, H−C(4″)); 4.06 (*dtd*, ^3J = 2.3, 6.4, 13.5, H−C(6″)); 3.96–3.86 (*m*, H−C(1), H−C(3), H−C(2‴)); 3.67 (*t*, ^3J = 6.4, 2 H−C(4‴)); 2.34 (*dd*, ^3J = 6.1, 14.5, 2 H−C(2)); 2.28 (*t*, ^3J = 6.5, 2 H−C(7)); 2.20 (*dd*, ^3J = 6.4, ^2J = 13.5, 1 H−C(1′)); 2.10 (*dd*, ^3J = 6.1, ^2J = 13.5, 1 H−C(1′)); 1.97 (*t*, ^3J = 5.6, 2 H−C(4)); 1.62 (*m*, 2 H−C(3‴)); 1.51 (*m*, 2 H−C(1‴)); 1.46, 1.32 (2*s*, $Me_2C(2")$); 1.12 (*m*, 2 H−C(5″)). ^{13}C-NMR (100.6 MHz, CD_3OD): 137.2 (*s*, C(5)); 125.6 (*d*, ^1J = 155, C(6)); 100.0 (*s*, C(2″)); 67.7 (*d*, ^1J = 138, C(6″)); 67.3 (*d*, ^1J = 142, C(4″)); 66.7, 66.5, 66.0 (3*d*, ^1J = 141, 144, 140, C(3), C(1), C(2‴)); 60.1 (*t*, ^1J = 144, C(4‴)); 49.8 (*t*, C(1′)); 49.2 (*t*, C(4)); 45.4 (*t*, ^1J = 125, C(1‴)); 41.5 (*t*, ^1J = 123, C(3‴)); 41.2 (*t*, ^1J = 125, C(2)); 38.5 (*t*, ^1J = 126, C(5″)); 36.6 (*t*, ^1J = 126, C(7)); 30.5, 20.2 (2*q*, ^1J = 126, 2 C, *Me*$_2$C(2″)). CI-MS (NH_3): 362 (47, $[M+NH_4]^+$), 345 (100, $[M+H]^+$), 305 (23), 287 (72), 267 (19), 121 (26), 83 (22). Anal. calc. for $C_{18}H_{32}O_6$ (344.45): C 62.77, H 9.36, O 27.87; found: C 62.64, H 9.16.

*1-{(4*R*,6*S*)-6-[(2*R*)-2,4-Dihydroxybutyl]-2,2-dimethyl-1,3-dioxan-4-yl}-3-[(2*R*,4*R*)-tetrahydro-4,6-dihydroxy-2*H*-pyran-2-yl]propan-2-one* ((+)-**18**). To a soln. of (+)-**15** (548 mg, 1.59 mmol) in acetone/H_2O 8:1 (30 ml) containing NMO (644 mg, 4.77 mmol) at 20° was added 0.1M OsO_4 in CCl_4 (6.36 ml, 0.64 mmol). After 24 h stirring, the soln. was quenched with Na_2SO_3 (600 mg, 4.77 mmol) and MeOH (5 ml). After 2 h stirring, the soln. was dried (Na_2SO_4) and evaporated. The residue, a 1:1 diastereoisomer mixture, was used without further purification for the next step.

To a soln. of the dihydroxylated product (601 mg, 1.59 mmol) in MeOH (30 ml) was added $Pb(OAc)_4$ (3.52 g, 7.95 mmol) at 20°. The reaction was complete after 10 min and quenched with $NaHCO_3$ (133 mg, 1.59 mmol) and Na_2SO_3 (200 mg, 1.59 mmol). After evaporation, the product was left over silica gel. FC (silica gel, CH_2Cl_2/MeOH 9:1) provided (+)-**18** (374 mg, 62%; over 2 steps) as a *ca.* 1:1 mixture of anomers. Whitish-yellow foam. $[\alpha]_{589}^{20}$ = +64 (*c* = 0.02, MeOH). UV (MeCN): 200 (4390). IR (KBr): 3410, 2935, 1705, 1650, 1555, 1385, 1255, 1220, 1165, 1120, 1050, 985, 810, 765, 695. ^{1}H-NMR (400 MHz, CD_3OD): 5.26 (*d*, ^3J = 2.7, 0.5 H, H_{eq}−C(6)); 4.64 (*dd*, ^3J = 2.2, 9.7, 0.5 H, H_{ax}−C(6)); 4.28 (*tt*, ^3J = 5.9, 9.7, H−C(4″)); 4.11–4.02 (*m*, H−C(2‴)); 4.04 (*m*, H−C(4)); 3.91–3.82 (*m*, H−C(6″), H−C(2)); 3.68 (*t*, ^3J = 6.5, 2 H−C(4‴)); 2.80–2.65 (*m*, 2 H−C(1′)); 2.65–2.53 (*m*, 2 H−C(3′)); 2.10, 1.88 (*m*, 2 H−C(3)); 1.96 (*m*, 2 H−C(5)); 1.70–1.54 (*m*, 2 H−C(3‴), 2 H−C(5″)); 1.54–1.36 (*m*, 2 H−C(1‴)); 1.32 (*s*, $Me_2C(2")$). ^{13}C-NMR (100.6 MHz, CD_3OD)[4]): 206.6 (*s*, C(2′)); 102.6 (*s*, C(2″)); 96.2, 94.2 (2*d*, ^1J = 157, 166, C(6)(*α*/*β*)); 70.1, 68.0 (2*d*, ^1J = 144, 143, C(2)(*α*/*β*)); 67.2 (*d*, ^1J = 143, C(6″)); 66.0, 64.6 (2*d*, ^1J = 138, 139, C(4″)(*α*/*β*)); 65.5 (*d*, ^1J = 145, C(2‴)); 65.3 (*d*, ^1J = 147, C(4″)); 60.9 (*t*, ^1J = 140, C(4‴)); 50.8 (*t*, ^1J = 129, C(1′)); 50.2 (*t*, ^1J = 127, C(3′)); 45.5 (*t*, ^1J = 124,

C(1‴)); 43.9, 42.8 (2*t*, ^1J = 126, 125, C(3)(*α*/*β*)); 42.4 (*t*, ^1J = 125, C(3‴)); 41.8, 41.2 (2*t*, ^1J = 125, 123, C(5)(*α*/*β*)); 40.3 (*t*, ^1J = 129, C(5″)); 25.9 (*q*, ^1J = 127, *Me*$_2$C(2″)). CI-MS (NH_3): 394 (1, $[M+NH_4]^+$), 377 (1, $[M+H]^+$), 322 (6), 283 (10), 168 (5), 149 (4), 127 (11), 105 (12), 81 (100). Anal. calc. for $C_{18}H_{32}O_8$ (376.45): C 57.43, H 8.57, O 34.00; found: C 57.39, H 8.37.

*1-{(4*S*,6*S*)-6-[(2*R*)-2,4-Dihydroxybutyl]-2,2-dimethyl-1,3-dioxan-4-yl}-3-[(2*R*,4*R*)-tetrahydro-4,6-dihydroxy-2*H*-pyran-2-yl]propan-2-one* ((−)-**19**). To a soln. of (+)-**17** (60 mg, 0.17 mmol) in Me_2CO/H_2O 8:1 (3 ml) was added NMO (70 mg, 0.5 mmol) and 0.1M OsO_4 in CCl_4 (700 µl, 0.064 mmol). The reaction was complete after one night (TLC, CH_2Cl_2/MeOH 9:1). The mixture was diluted with MeOH (3 ml) and quenched by addition of $Na_2S_2O_5$ (58 mg, 0.35 mmol). After 2 h stirring, the soln. was dried (Na_2SO_4), filtered over a *Celite* pad, and evaporated.

To a soln. of the dihydroxylated product (65 mg, 0.17 mmol) in dry MeOH (3 ml) was added portionwise $Pb(OAc)_4$ (377 mg, 0.85 mmol). After 30 min (TLC, CH_2Cl_2/MeOH 9:1), the mixture was treated with $NaHCO_3$ (20 mg), and the product was deposited on silica gel. FC (silica gel, CH_2Cl_2/MeOH 9:1) gave (−)-**19** (45 mg, 71%; over 2 steps) as a *ca.* 1:1 anomer mixture. Yellowish foam. $[\alpha]_{589}^{20} = -30$; $[\alpha]_{578}^{20} = -25$; $[\alpha]_{546}^{20} = -20$; $[\alpha]_{436}^{20} = -15$; $[\alpha]_{365}^{20} = -10$ (*c* = 0.02, MeOH). IR (KBr): 3385, 2940, 1710, 1575, 1385, 1265, 1200, 1165, 1095, 980, 935, 875. ^{1}H-NMR (400 MHz, CD_3OD): 5.26 (*d*, ^3J = 3.5, 0.5 H, H_{eq}−C(6)); 4.66 (*dd*, ^3J = 1.7, 9.4, 0.5 H, H_{ax}−C(6)); 4.42 (*m*, H−C(6″)); 4.18 (*ddt*, ^3J = 2.3, 5.3, 8.2, H−C(4″)); 4.07 (*dddd*, ^3J = 4.7, 9.4, 11.2, 11.8, 0.5, H−C(4)); 3.92 (*dtd*, ^3J = 3.5, 8.2, 12.3, H−C(2‴)); 3.82 (*m*, H−C(2)); 3.75 (*dtd*, ^3J = 4.3, 10.8, 11.6, 0.5, H−C(4)); 3.66 (*t*, ^3J = 6.5, 2 H−C(4‴)); 2.79–2.58 (*m*, 2 H−C(1′)); 2.56–2.48 (*m*, 2 H−C(3′)); 2.07 (*ddd*, ^3J = 2.2, 4.3, ^2J = 11.9, 1 H−C(5)); 1.95 (*m*, 1 H−C(3)); 1.87 (*ddd*, ^3J = 2.2, 4.3, ^2J = 11.9, 1 H−C(5)); 1.61 (*m*, 2 H−C(3‴)); 1.52 (*m*, 2 H−C(1‴)); 1.46, 1.28 (2*s*, Me_2C(2″)); 1.52, 1.16 (2*m*, 2 H−C(5″)); 1.08 (*m*, 1 H−C(3)). ^{13}C-NMR (100.6 MHz, CD_3OD): 206.2 (*s*, C(2′)); 100.0 (*s*, C(2″)); 95.3, 93.3 (2*d*, ^1J = 167, 161, C(6)); 69.2 (*d*, ^1J = 140, C(2)); 67.2, 63.8 (2*d*, ^1J = 138, 140, C(4)); 67.1 (*d*, ^1J = 138, C(4″)); 66.9, 65.2 (*d*, ^1J = 144, 142, C(6″)); 66.0 (*d*, ^1J = 133, C(2‴)); 60.1 (*t*, ^1J = 137, C(4‴)); 50.7 (*t*, ^1J = 126, C(1′)); 50.5 (*t*, ^1J = 126, C(3′)); 45.4 (*t*, ^1J = 124, C(1‴)); 43.0, 41.9 (2*t*, ^1J = 129, 124, C(5)); 41.4 (*t*, ^1J = 123, C(3‴)); 40.9, 40.5 (2*t*, ^1J = 127, 130, C(3)); 38.2 (*t*, ^1J = 128, C(5″)); 30.5, 20.0 (2*q*, ^1J = 126, Me_2C(2″)). CI-MS (NH_3): 394 (8, $[M+NH_4]^+$), 376 (13, M^+), 359 (62), 341 (47), 319 (53), 301 (68), 283 (100), 265 (43), 185 (21), 134 (47). Anal. calc. for $C_{18}H_{32}O_8$ (376.45): C 57.43, H 8.57, O 34.00; found: C 57.26, H 8.57.

*(3*R*)-4-{(1*R*,3*S*,4′*R*,5*R*,6′*S*,7*R*)-3′,4′,5′,6′-Tetrahydro-4′-hydroxy-7-methoxyspiro[2,6-dioxabicyclo[3.3.1]nonane-3,2′-[2*H*]pyran]-6′-yl}butane-1,3-diol* ((−)-**20**). To a soln. of (+)-**18** (50 mg, 0.13 mmol) in CH_2Cl_2/MeOH 1:1 (1 ml) at 20° was added TsOH (2.9 mg, 0.013 mmol). After 1 h (TLC, CH_2Cl_2/MeOH 9:1), the reaction was quenched with $NaHCO_3$ (30 mg), and the product was deposited on silica gel. FC (silica gel, CH_2Cl_2/MeOH 9:1) afforded (−)-**20** (29 mg, 68%). White foam. $[\alpha]_{589}^{25} = -53$; $[\alpha]_{577}^{25} = -47$; $[\alpha]_{546}^{25} = -29$; $[\alpha]_{435}^{25} = -27$; $[\alpha]_{405}^{25} = -24$ (*c* = 0.13, MeOH). UV (MeCN): 195 (550). IR (KBr): 3555, 2925, 2850, 1450, 1390, 1370, 1250, 1180, 1120, 1030, 965, 880, 805, 735. ^{1}H-NMR (400 MHz, CD_3OD): 4.65 (*dd*, ^3J = 3.2, 7.0, H−C(7)); 4.06 (*tt*, ^3J = 4.8, 11.3, H−C(4′)); 4.03 (*m*, H−C(3″)); 3.99 (*tt*, ^3J = 11.8, 3.2, H−C(6′)); 3.88 (*ddt*, ^3J = 2.7, 4.3, 11.3, H−C(5)); 3.80 (*ddt*, ^3J = 2.7, 5.9, 11.3, H−C(1)); 3.73 (*t*, ^3J = 7.5, 2 H−C(1″)); 3.35 (*s*, MeO−C(7)); 2.00 (*m*, 1 H−C(5′), 1 H−C(4″)); 1.91 (*m*, 1 H−C(3′), 1 H−C(9)); 1.78, 1.71 (2*m*, 2 H−C(8)); 1.74 (*m*, 2 H−C(2″)); 1.64 (*m*, 1 H−C(4)); 1.55 (*m*, 1 H−C(4)); 1.30 (*t*, ^2J = ^3J = 11.8, 1 H−C(4″)); 1.29 (*m*, 1 H−C(5′)); 1.14–1.13 (*m*, 1 H−C(9), 1 H−C(3′)). ^{13}C-NMR (100.6 MHz, CD_3OD): 104.8 (*d*, ^1J = 161, C(7)); 101.1 (*s*, C(3)); 67.5 (*d*, ^1J = 161, C(6′)); 67.3 (*d*, ^1J = 162, C(5)); 67.0 (*d*, ^1J = 142, C(1)); 65.9 (*d*, ^1J = 144, C(3″)); 65.7 (*d*, ^1J = 142, C(4′)); 61.0 (*t*, ^1J = 139, C(1″)); 53.9 (*q*, ^1J = 142, MeO−C(7)); 46.3 (*t*, ^1J = 127, C(4″)); 46.2 (*t*, ^1J = 127, C(5′)); 46.0 (*t*, ^1J = 127, C(4)); 42.9 (*t*, ^1J = 128, C(3′)); 42.6 (*t*, ^1J = 130, C(2″)); 42.5 (*t*, ^1J = 128, C(9)); 40.5 (*t*, ^1J = 126, C(8)). CI-MS (NH_3): 333 (7, $[M+H]^+$), 318 (25, $[M+H-Me]^+$), 301 (17, $[M-MeO]^+$), 283 (76, $[M-H_2O-MeO]^+$), 265 (55), 75 (100). Anal. calc. for $C_{16}H_{28}O_7$ (332.39): C 57.82, H 8.49, O 33.69; found: C 57.89, H 8.42.

*(3*R*)-4-{(1*R*,3*S*,4′*S*,5*R*,6′*R*)-3′,4′,5′,6′-Tetrahydro-4′-hydroxy-7-methoxyspiro[2,6-dioxabicyclo[3.3.1]nonane-3,2′-[2*H*]pyran]-6′-yl}butane-1,3-diol* ((−)-**21**). As described for (−)-**20**, with (−)-**19** (24 mg, 0.063 mmol), CH_2Cl_2/MeOH 1:1 (500 µl), and TsOH (14.5 mg, 0.063 mmol) (quenching with $NaHCO_3$ (10 mg)): (−)-**21** (13 mg, 65%). White solid. $[\alpha]_{589}^{25} = -28$; $[\alpha]_{577}^{25} = -32$; $[\alpha]_{546}^{25} = -32$; $[\alpha]_{435}^{25} = -59$; $[\alpha]_{405}^{25} = -71$ (*c* = 0.17, MeOH). UV (MeCN): 201 (750). IR (KBr): 3420, 2930, 2850, 1650, 1435, 1395, 1370, 1260, 1235, 1160, 1120, 1035, 965, 895, 840, 735. ^{1}H-NMR (400 MHz, $CDCl_3$)[5]: 4.65 (*dd*, ^3J = 4.1, 5.9, H−C(7)); 4.22 (br. *t*, ^3J = 10.5, H−C(5)); 4.08 (*m*, H−C(6′)); 4.05 (*m*, H−C(3″)); 4.02 (*m*, H−C(1)); 3.99 (br. *t*, ^3J = 11.4, H−C(4′)); 3.73 (*t*, ^3J = 6.2,

[5]) *α* refers to (7*R*) and *β* to (7*S*) configuration.

2 H–C(1″)); 3.36, 3.33 (2*s*, 3 H, MeO–C(7)(α/β)); 1.99–1.83 (*m*, 1 H–C(8), 1 H–C(3′), 1 H–C(5′), 1 H–C(4″)); 1.75–1.45 (*m*, 2 H–C(4), 1 H–C(8), 2 H–C(9), 2 H–C(2″), 1 H–C(3′)); 1.25 (*m*, 1 H–C(4″)); 1.20 (*q*, $^2J = {}^3J = 11.4$, 1 H–C(5′)). ^{13}C-NMR (100.6 MHz, $CDCl_3$)[5]): 104.2 (*d*, $^1J = 161$, C(7)); 100.2 (*s*, C(3)); 67.1 (*d*, $^1J = 143$, C(4′)); 66.1, 66.0 (2*d*, $^1J = 148$, 143, C(1), C(3″)); 64.5 (*d*, $^1J = 146$, C(6′)); 61.8 (*d*, $^1J = 143$, C(5)); 60.0 (*t*, $^1J = 142$, C(1″)); 54.1, 53.0 (2*q*, $^1J = 143$, *Me*O–C(7)(α/β)); 45.0, 44.9 (2*t*, $^1J = 125$, 125, C(9), C(5′)); 41.8, 41.6 (2*t*, $^1J = 122$, 130, C(8), C(3′)); 41.0 (*t*, $^1J = 129$, C(4″)); 39.4 (2*t*, $^1J = 126$, C(4), C(2″)). CI-MS (NH_3): 350 (16, $[M + NH_4]^+$), 333 (40, $[M + H]^+$), 318 (63, $[M + H - Me]^+$), 301 (56, $[M - MeO]^+$), 283 (100, $[M - H - H_2O - MeO]^+$), 265 (48), 167 (9), 95 (18), 75 (71). Anal. calc. for $C_{16}H_{28}O_7$ (332.39): C 57.82, H 8.49, O 33.69; found: C 56.38, H 8.58 (corresponding to $C_{16}H_{28}O_7 \cdot 1/2\ H_2O$: C 56.29, H 8.56).

*(1*R*,3*S*,4′*R*,5*R*,6′*R*)-3′,4′,5′,6′-Tetrahydro-6′-[(2*S*)-2-hydroxybutyl-3-enyl]-7-methoxyspiro[2,6-dioxabicyclo[3.3.1]nonane-3,2′-[2*H*]pyran]-4′-ol* ((−)-**23**). Under Ar, (−)-**20** (25 mg, 0.075 mmol) and 2-nitrophenyl selenocyanate (170 mg, 0.75 mmol) were dissolved in dry THF (500 µl). At 20°, tributylphosphine (185 µl, 0.75 mmol) was added dropwise. After 6 h (TLC, CH_2Cl_2/MeOH 9:1), MeOH (1 ml) was added, and the solvents were evaporated. FC (silica gel, CH_2Cl_2/MeOH 98:2) afforded the selenated compound **22** (35 mg, 97%) as a deep yellow oil, contaminated with tributylphosphine. The phosphine could be removed by several FCs or eliminated by oxidation in the next step.

A soln. of the crude selenated compound **22** (20 mg, 0.038 mmol) in dry THF (500 µl) was cooled to −78°, and Et_3N (10 µl, 0.076 mmol) was added dropwise, followed by 3-chloroperbenzoic acid (27 mg, 0.152 mmol). After 3 h, additional 3-chloroperbenzoic acid (27 mg, 0.152 mmol) was added. After 2 h (TLC, CH_2Cl_2/MeOH 95:5), the mixture was diluted with MeOH (1 ml) and treated with Na_2SO_3 (40 mg) and $NaHCO_3$ (40 mg) while the soln. was allowed to warm up to r.t. The product was deposited on silica gel and purified by FC (silica gel, CH_2Cl_2/MeOH 98:2 → 95:5): (−)-**23** (10 mg, 86%). Slightly yellowish foam. $[\alpha]_{589}^{25} = -12$; $[\alpha]_{577}^{25} = -17$; $[\alpha]_{546}^{25} = -19$; $[\alpha]_{435}^{25} = -20$; $[\alpha]_{405}^{25} = -37$ (*c* = 0.10, MeCN). UV (MeCN): 249 (940). IR (KBr): 3420, 2925, 2865, 1705, 1650, 1605, 1515, 1430, 1380, 1260, 1170, 1100, 1030, 805, 735, 705. ^{1}H-NMR (400 MHz, $CDCl_3$)[5]): 5.90 (*ddd*, $^3J = 5.4$, 10.4, 16.2, H–C(3″)); 5.30 (*m*, 1 H–C(4″)); 5.10 (*dd*, $^3J = 10.4$, $^2J = 1.7$, 1 H–C(4″)); 4.64 (*m*, H–C(7)); 4.36 (*m*, H–C(2″)); 4.12 (*tt*, $^3J = 5.8$, 10.8, H–C(4′)); 4.05 (*m*, H–C(5)); 3.84 (*m*, H–C(6′)); 3.71 (*m*, H–C(1)); 3.33, 3.28 (2*s*, 3 H, MeO–C(7)(α/β)); 2.09 (*m*, 1 H–C(3′), 1 H–C(4)); 1.97 (*m*, 1 H–C(4)); 1.92 (*m*, 1 H–C(9), 1 H–C(5′)); 1.82–1.68 (*m*, 2 H–C(8), 1 H–C(1″)); 1.61 (*m*, 1 H–C(1″)); 1.46 (*m*, 1 H–C(3″)); 1.40–1.19 (*m*, 1 H–C(5′), 1 H–C(9)). ^{13}C-NMR (100.6 MHz, $CDCl_3$)[5]): 140.7 (*d*, $^1J = 152$, C(3″)); 114.0 (*t*, $^1J = 155$, C(4″)); 100.9, 100.7 (2*d*, $^1J = 168$, 168, C(7)(α/β)); 99.1 (*s*, C(3)); 68.6 (*d*, $^1J = 146$, C(2″)); 64.6, 64.5 (2*d*, $^1J = 135$, 141, C(6′), C(1)); 64.4, 64.1 (2*d*, $^1J = 139$, 138, C(5), C(4′)); 53.0, 51.2 (2*q*, $^1J = 148$, 148, MeO–C(7)(α/β)); 44.4, 44.0 (2*t*, $^1J = 126$, 128, C(3′), C(5′)); 42.6 (*t*, $^1J = 132$, C(1″)); 40.8, 40.6 (2*t*, $^1J = 128$, 126, C(9), C(4)); 37.7 (*t*, $^1J = 127$, C(8)). CI-MS (NH_3): 316 (100, $[M + D]^+$), 300 (49, $[M + H - Me]^+$), 283 (28, $[M - MeO]^+$), 235 (29), 81 (26), 75 (69). HR-MS-ESI (MeOH): 369.1896 ($C_{16}H_{26}O_6 + MeOH + Na]^+$, $C_{17}H_{30}NaO_7^+$; calc. 369.1889.

REFERENCES

[1] T. L. B. Boivin, *Tetrahedron* **1987**, *43*, 3309; F. Perron, K. F. Albizati, *Chem. Rev.* **1989**, *89*, 1617; V. Vaillancourt, N. E. Pratt, F. Perron, K. F. Albizati, *Total Synth. Nat. Prod.* **1992**, 533; N. Haddad, Z. Abramovich, I. Ruhman, *Recent Res. Develop. Org. Chem.* **1997**, *1*, 35.

[2] a) R. Baker, R. H. Herbert, *Nat. Prod. Rep.* **1984,** *1,* 299; b) W. M. Kitching, J. A. Lewis, M. T. Fletcher, R. A. I. Drew, C. J. Moore, W. Francke, *J. Chem. Soc., Chem. Commun.* **1986,** 853 and ref. cit. therein.

[3] H. Mishima, M. Kurabayashi, C. Tamura, *Tetrahedron Lett.* **1975**, *10*, 711; R. W. Burg, B. M. Miller, J. Birnbaum, S. A. Currie, R. Hartman, Y. L. Kong, R. L. Monaghan, G. Olson, I. Putter, J. B. Tunac, H. Wallick, E. O. Stapley, R. Oiwa, S. Omura, *Antimicrob. Agents Chemother.* **1979**, *15*, 361; H. Mrozik, P. Eskola, M. H. Fisher, *Tetrahedron Lett.* **1982**, *23*, 2377.

[4] S. M. Kupchan, E. J. La Voie, A. R. Branfman, B. Y. Fei, W. M. Bright, R. F. Bryan, *J. Am. Chem. Soc.* **1977**, *99*, 3199.

[5] P. Deslongschamps, D. D. Rowan, N. Pothier, T. Sauve, J. Saunders, *Can. J. Chem.* **1981**, *59*, 1105; P. Deslongschamps, D. D. Rowan, N. Pothier, J. Saunders, *Can. J. Chem.* **1981**, *59*, 1122.

[6] G. R. Pettit, Z. A. Cichacz, F. Gao, C. L. Herald, M. R. Boyd, *J. Chem. Soc., Chem. Commun.* **1993**, 1116; G. R. Pettit, C. L. Herald, Z. A. Cichacz, F. Gao, J. M. Schmidt, M. R. Boyd, N. D. Christie, F. E. Boettner, *J. Chem. Soc., Chem. Commun.* **1993**, 1805; G. R. Pettit, Z. A. Cichacz, F. Gao, C. L. Herald, M. R. Boyd, J. M. Schmidt, J. N. A. Hooper, *J. Org. Chem.* **1993**, *58*, 1302; G. R. Pettit, C. L. Herald, Z. A. Cichacz, F.

Gao, M. R. Boyd, N. D. Christie, J. M. Schmidt, *Nat. Prod. Lett.* **1993**, *3*, 239; G. R. Pettit, Z. A. Cichacz, C. L. Herald, F. Gao, M. R. Boyd, J. M. Schmidt, E. Hamel, R. Bai, *J. Chem. Soc., Chem. Commun.* **1994**, 1605; M. Kobayashi, S. Aoki, H. Sakai, N. Kihara, T. Saski, I. Kitagawa, *Chem. Pharm. Bull.* **1993**, *41*, 989; M. Kobayashi, S. Aoki, I. Katagawa, *Tetrahedron Lett.* **1994**, *35*, 1243; M. Kobayashi, S. Aoki, K. Gato, I. Kitagawa, *Chem. Pharm. Bull.* **1996**, *44*, 9714.

[7] a) A. B. Smith, III, V. A. Doughty, C. Sfouggatakis, C. S. Bennett, J. Koyanagi, M. Takeuchi, *Org. Lett.* **2002**, *4*, 783; b) I. Paterson, M. J. Coster, *Tetrahedron Lett.* **2002**, *43*, 3285; c) M. T. Crimmins, J. D. Katz, D. G. Washburn, S. P. Allwein, L. F. McAtee, *J. Am. Chem. Soc.* **2002**, *124*, 5661; d) P. Quayle, *Ann. Rep. Prog. Chem.: Org. Chem.* **1999**, *95*, 235; e) J. Pietruszka, *Angew. Chem., Int. Ed.* **1998**, *37*, 2629 and ref. cit. therein; f) A. B. Smith, R. M. Corbett, G. R. Pettit, J.-C. Chapuis, J. M. Schmidt, E. Hamel, M. K. Jung, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2039; g) F. M. Uckun, C. Mao, A. O. Vassilev, S. T. Jan, H. Huang, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 541; F. M. Uckun, S. T. Jan, C. Mao, H. Huang, *Tetrahedron Lett.* **2000**, *41*, 1699; F. M. Uckun, PCT/US99/14747, 2000, 1. F. M. Uckun, *Curr. Pharm. Design* **2001**, *7*, 1627; h) S. A. Hermitage, A. Murphy, S. M. Roberts, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1635; A. B. Smith III, Q. Lin, G. R. Pettit, J. C. Chapuis, J. M. Schmidt, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 567.

[8] S. Lemaire-Audoire, P. Vogel, *Tetrahedron Lett.* **1998**, 39, 1345; S. Lemaire-Audoire, P. Vogel, *J. Org. Chem.* **2000**, *65*, 3346.

[9] a) M.-E. Schwenter, P. Vogel, *Chem.–Eur. J.* **2000**, *6*, 4091; b) M.-E. Schwenter, P. Vogel, *J. Org. Chem.* **2001**, *66*, 7869.

[10] K. T. Meilert, M.-E. Schwenter, Y. Shatz, S. R. Dubbaka, P. Vogel, *J. Org. Chem.* **2003**, *68*, 2964.

[11] M. Lautens, P. Chiu, *Angew. Chem., Int. Ed.* **1993**, *32*, 281; M. Lautens, R. Aspiotis, *J. Am. Chem. Soc.* **1996**, *118*, 10930; M. Lautens, S. Ma, *Tetrahedron Lett.* **1996**, *37*, 1727.

[12] H. M. R. Hoffmann, R. Dunkel, *Tetrahedron* **1997**, *53*, 14929; H. Kim, H. M. R. Hoffmann, *Eur. J. Org. Chem.* **2000**, 2195.

[13] H. Kaku, M. Tanaka, Y. Norimine, Y. Miyashita, H. Suemune, K. Sakai, *Tetrahedron: Asymmetry* **1997**, *8*, 195.

[14] J. Mann, *Tetrahedron* **1986**, *42*, 4611; A. Hosomi, Y. Tominga, '[4 + 3]-Cycloadditions', Ed. I. Fleming, Pergamon Press. Oxford, 1991; Vol. 5, p. 593; J. H. Rigby, C. F. Pigge, *Org. React.* **1997**, *51*, 351; C. P. Dell, *J. Chem. Soc., Perkin Trans. 1.* **1998**, 3873; M. Harmata, *Recent Res. Develop. Org. Chem.* **1997**, *1*, 523; M. Harmata, *Acc. Chem. Res.* **2001**, *34*, 595; A. El-Wareth, A. O. Sarhan, *Curr. Org. Chem.* **2001**, *5*, 827.

[15] D. Turner, P. Vogel, *Synlett* **1998**, 304.

[16] F. Carrel, P. Vogel, *Tetrahedron: Asymmetry* **2000**, *11*, 4661.

[17] H. C. Kolb, M. S. Vannieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.

[18] J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543.

[19] E. J. Corey, A. Guzmann-Perez, *J. Am. Chem. Soc.* **1995**, *117*, 10805; E. J. Corey, A. Guzman-Perez, *Tetrahedron Lett.* **1997**, *38*, 5941.

[20] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560.

[21] M. J. Shapiro, S. Russel, *Helv. Chim. Acta* **1986**, *69*, 803; M. J. Shapiro, K. Prasad, *Tetrahedron Lett.* **1987**, *28*, 155; K. Narasaka, F.-C. Pai, *Tetrahedron*, **1984**, *40*, 2233.

[22] S. D. Rychnovsky, B. N. Rogers, T. I. Richardson, *Acc. Chem. Res.* **1998**, *31*, 9.

[23] A. P. Marchand, 'Stereochemical Applications of NMR Studies in Rigid Bicyclic Systems', Verlag Chemie International, Deerfield Beach, 1982; W. Simon, E. Pretsch, J. Seibl, 'Spectral Data for Structure Determination of Organic Compounds', Springer Verlag, 1989.

[24] K. Kraehenbuel, S. Picasso, P. Vogel, *Helv. Chim. Acta* **1998**, *81*, 1439.

[25] M. R. Boyd, *Principles Practice Oncology* **1989**, *3*, 1.

Received February 7, 2004