Total Asymmetric Synthesis of a New 9,12-Anhydroerythronolide Aglycone

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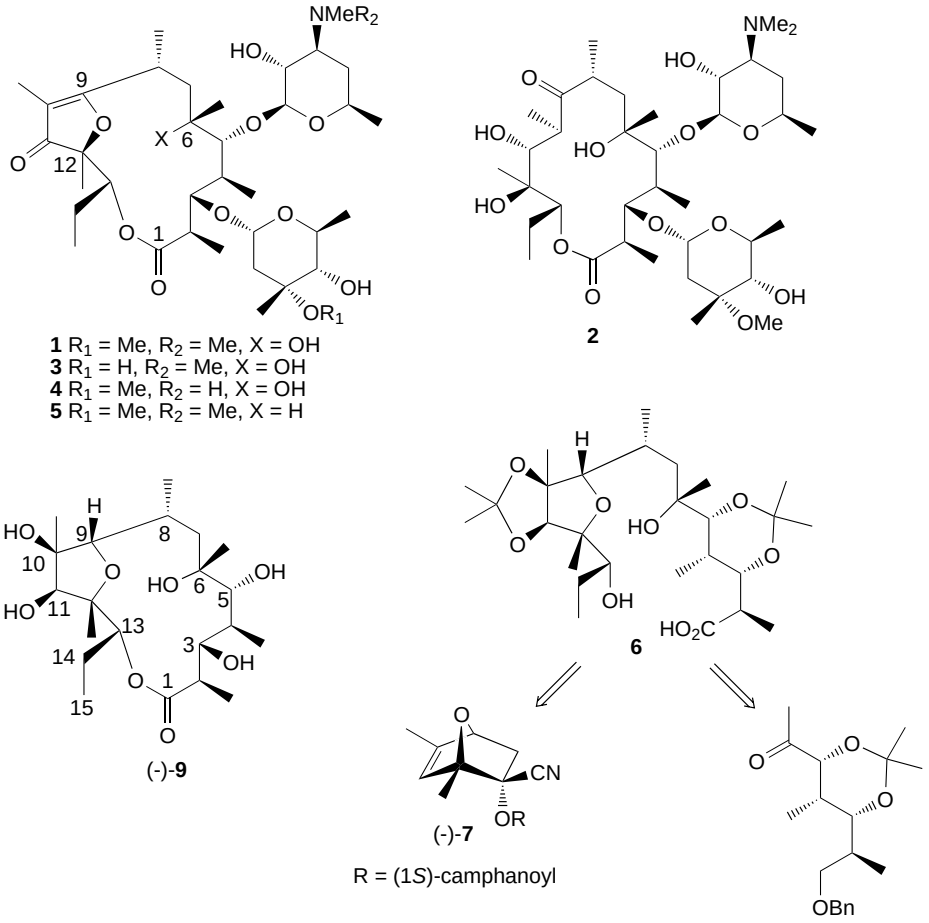
Two novel, potentially antimicrobial erythronolide aglycon analogs ((−)-**9** and (−)-**30**, respectively), which incorporate a large number of contiguous stereogenic centers, have been prepared by multistep synthesis from simple chirons. The chemistry presented demonstrates the power of the so-called 'naked sugars of the second generation' approach. As for the sporeamicins, our macrolides are 9,12-anhydroerythronolides, yet presenting a higher degree of complexity due to additional functional groups.

Introduction. – Evolution forces us to find new antibiotics [1]. This stimulates the search of new metabolites of microorganism and to apply chemistry to either mimic or modify them. Sporeamycin A (**1**), produced by *Saccharopolyspora* sp. L53-18A was isolated and characterized in 1992 by *Morishita* and co-workers [2]. It is active against *Gram*-positive bacteria [3]. Structurally, **1** is an analog of an oxidized form of erythromycins (*e.g.* erythromycin A: **2**) containing a 9,12-anhydro moiety. Sporeamycin B (**3**) [4] and C (**4**) [5] have also been isolated. In 1996, 6-deoxysporeamycin A (**5**) [6] was derived from 6-deoxyerythromycin A. The antibacterial spectrum of **5** is similar to that of erythromycin A, but it has a higher potency against susceptible streptococci. Other anhydrous derivatives of erythromycin A (**2**) such as the neotilides (8,9-anhydro-6,9-hemiacetals) have been described and were shown to stimulate gastrointestinal motility [7].

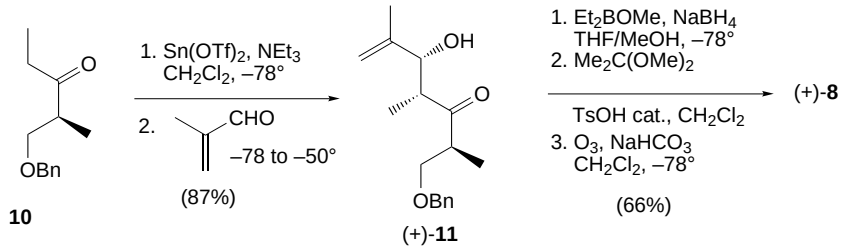
In a preliminary communication [8], we showed that the partially protected *seco*-acid of the 9,12-anhydroerythronolide aglycon **6** can be derived from the *Diels-Alder* adduct (−)-**7** of 2,4-dimethylfuran to 1-cyanovinyl (1′*S*)-camphanate (a 'naked sugar of the second generation' [9]) and (3*R*,4*S*,5*R*,6*S*)-7-benzyloxy-3,5-(isopropylidenedioxy)-4,6-dimethylheptane-2-one ((+)-**8**) [10]. We present now the details of these transformations and the conversion of the *seco*-acid to the corresponding macrolide **9**.

Results and Discussion. – The known methyl ketone (+)-**8** [10] was derived from *Paterson*'s chiron **10** [11]. Tin-aldol-reaction with an excess of methacrolein gave a mixture of diastereoisomeric allylic alcohols from which the pure *syn* aldol (+)-**11** could be isolated in 87% yield. Treatment of (+)-**11** with Et_2BOMe, followed by $NaBH_4$ in THF/MeOH at −78° [12] furnished a diol that was transformed *in situ* into its acetonide under standard conditions, the ozonolysis of which provided (+)-**8** in an overall yield of 66% (*Scheme 1*).

The conversion of (−)-**7** into the 7-oxanorbornanone derivative (−)-**12** (78%, 3 steps) has already been described [13]. The transformation of (−)-**12** into the 8-

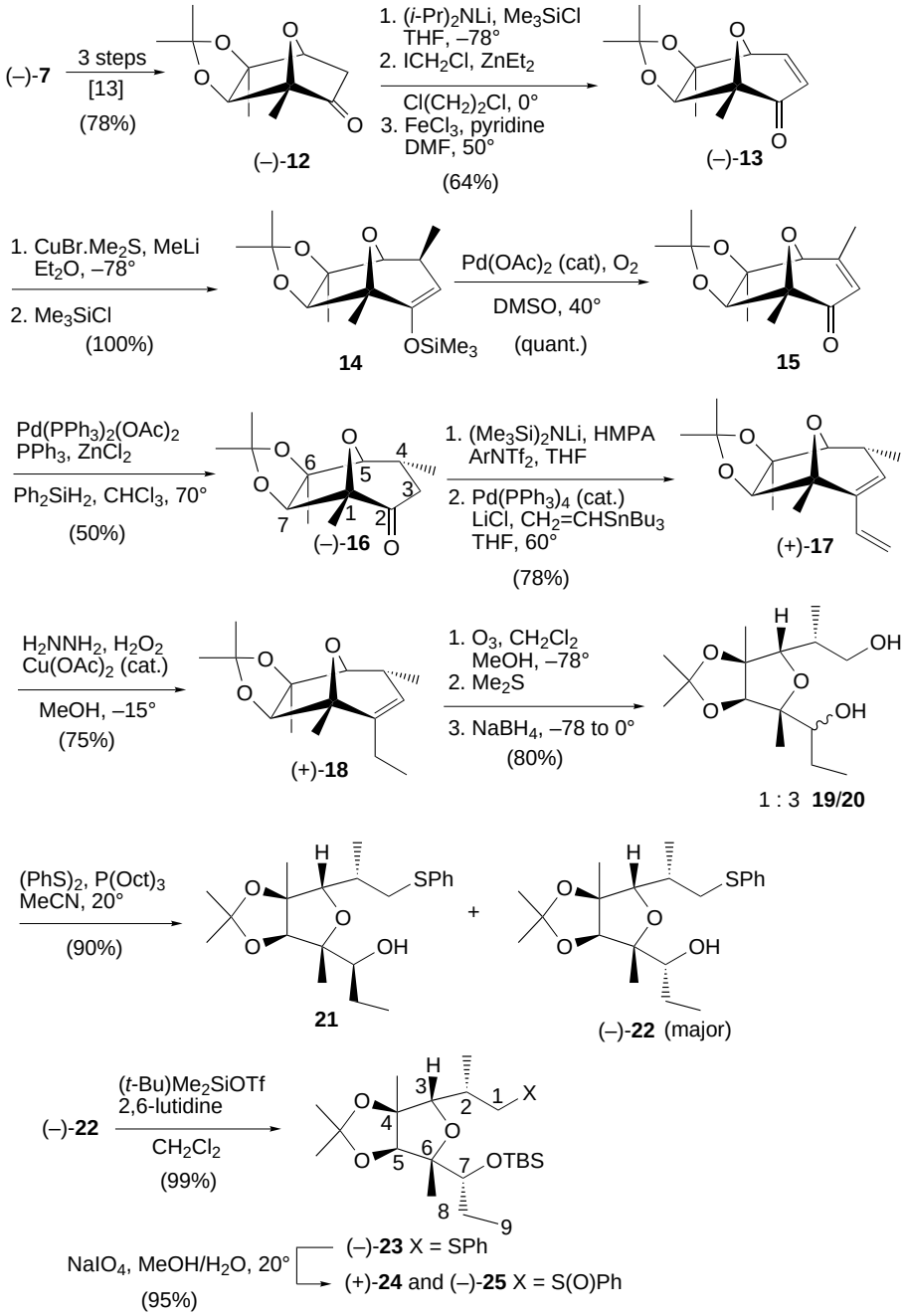


Scheme 1



oxabicyclo[3.2.1]oct-3-en-2-one (−)-**13** employs the cyclopropanation with ICH_2Cl and Et_2Zn [14] of the corresponding enoxysilane, obtained by quenching the lithium enolate with Me_3SiCl [15] (*Scheme 2*). The intermediate cyclopropane derivative was not isolated but directly submitted to oxidation with $FeCl_3$ in pyridine [16]. This

Scheme 2


(–)-7
3 steps
[13]
(78%)
(–)-12
1. (i-Pr)2NLi, Me3SiCl
THF, –78°
2. ICH2Cl, ZnEt2
Cl(CH2)2Cl, 0°
3. FeCl3, pyridine
DMF, 50°
(64%)
(–)-13
1. CuBr.Me2S, MeLi
Et2O, –78°
2. Me3SiCl
(100%)
14
OSiMe3
Pd(OAc)2 (cat), O2
DMSO, 40°
(quant.)
15
Pd(PPh3)2(OAc)2
PPh3, ZnCl2
Ph2SiH2, CHCl3, 70°
(50%)
(–)-16
1. (Me3Si)2NLi, HMPA
ArNTf2, THF
2. Pd(PPh3)4 (cat.)
LiCl, CH2=CHSnBu3
THF, 60°
(78%)
(+)-17
H2NNH2, H2O2
Cu(OAc)2 (cat.)
MeOH, –15°
(75%)
(+)-18
1. O3, CH2Cl2
MeOH, –78°
2. Me2S
3. NaBH4, –78 to 0°
(80%)
1 : 3 19/20
(PhS)2, P(Oct)3
MeCN, 20°
(90%)
21
(–)-22 (major)
(t-Bu)Me2SiOTf
2,6-lutidine
CH2Cl2
(99%)
(–)-22
OTBS
NaIO4, MeOH/H2O, 20°
(95%)
(–)-23 X = SPh
(+)-24 and (–)-25 X = S(O)Ph

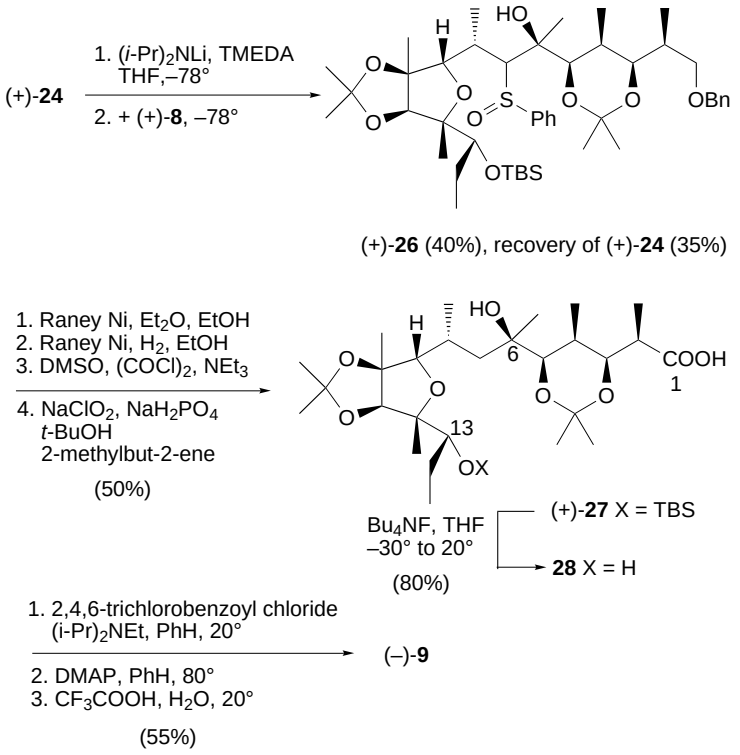
provided (−)-**13** in an overall yield of 64%. *Michael* addition of methylcuprate, followed by trapping the intermediate enolate with Me_3SiCl [17], gave the enoxysilane **14** quantitatively. Oxidation of **14** with O_2, catalyzed by $(AcO)_2Pd$ in DMSO [18], gave the enone **15** in quantitative yield. The latter was not purified but directly submitted to stereospecific *exo*-face hydrogenation with Ph_2SiH_2 in the presence of PPh_3, $ZnCl_2$, and a catalytic amount of a palladium catalyst [19] affording the ketone (+)-**16** (50% based on (+)-**13**). The relative *endo* configuration of its Me group at C(4) was confirmed by ^{1}H-NMR (^3J(H−C(4),H−C(5)) = 3.6 Hz [20]; see *Exper. Part*). (+)-**16** was converted into its enol trifluoracetate on treatment with LDA in THF at −78° and 2-[*N*,*N*′-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine [21], followed by direct *Stille* coupling [22] with tributyl(vinyl)stannane (LiCl, [Pd $(PPh_3)_4$], THF), providing the diene (+)-**17** in 78% yield. Selective reduction of the vinyl moiety was achieved on treating (+)-**17** with a large excess of hydrazine and H_2O_2 in the presence of $(OAc)_2Cu$ as a catalyst [23], furnishing the alkene (+)-**18** in 75% yield. Ozonolysis followed by reductive workup with Me_2S and with $NaBH_4$ provided a 1:3 mixture of the secondary alcohols **19** and **20**, respectively. Selective displacement of the primary alcohol moieties in both **19** and **20** was achieved by treatment with PhSSPh and trioctylphosphine in MeCN. This led to a 1:3 mixture of the compounds **21** and (−)-**22**, which were separated by flash chromatography (FC). The major alcohol (−)-**22** was silylated under standard conditions to yield the silyl ether (−)-**23** almost quantitatively. Oxidation of (−)-**23** with $NaIO_4$ resulted in a 3:2 mixture of the sulfoxides (+)-**24** and (−)-**25** (95% yield) which were separated by FC.

The major sulfoxide (+)-**24** was used in the condensation with the methyl ketone (+)-**8** (*Scheme 3*). The conjugate base of (+)-**24**, obtained by treatment with LDA and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in THF at −78°, reacted with (+)-**8** to give a mixture from which (+)-**26** was isolated in 40% yield together with 35% of the recovered ketone (+)-**8**. The relative configuration of the generated stereogenic center (tertiary alcohol) will be discussed below (*Figure 1*). Desulfurization of (+)-**26** was realized on treatment with *W2 Raney* Ni in ether/ethanol solution. Debenzylation by hydrogenolysis was catalyzed by the same Ni catalyst to give a primary alcohol. The latter was not isolated but directly submitted to *Swern* oxidation [24], then treated with $NaClO_2/NaH_2PO_4$, in *t*-BuOH and 2-methylbut-2-ene [25] generating the carboxylic acid (+)-**27** in 50% yield. Desilylation of (+)-**27** with Bu_4NF in THF gave **28** in 80% yield which was submitted to the *Yamaguchi* macrocyclization [26] in benzene (high dilution, slow addition of **28** through an automatic syringe). The crude macrolactone obtained was finally deprotected by acidic hydrolysis with aqueous TFA, and pure (−)-**9** was isolated in 55% yield by FC on silica gel.

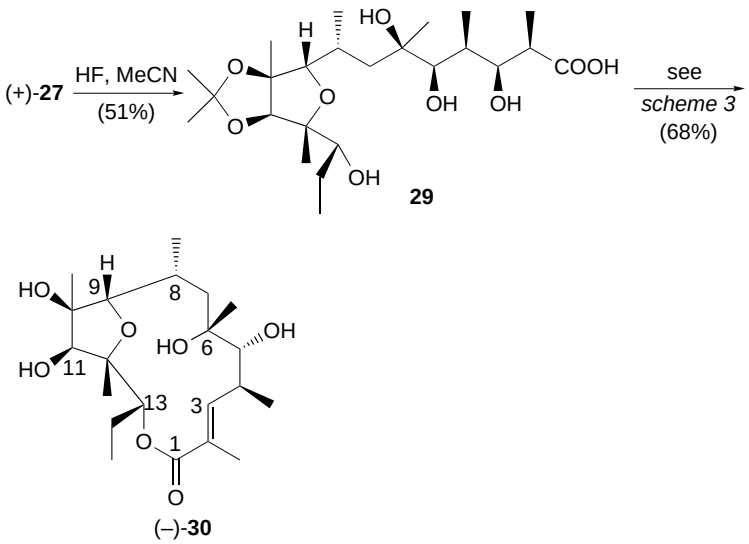
When the desilylation of (+)-**27** was performed with 40% aqueous HF in MeCN, the monoacetonide **29** was obtained in 51% yield. This compound was not fully characterized but submitted directly to the *Yamaguchi* macrolactonization giving (−)-**30** in 68% yield, a dehydrated analog of (−)-**9** (*Scheme 4*).

All new compounds described have been fully characterized by their spectral data, by elemental analysis, and by their mode of formation. The relative configuration at C(6) of (−)-**9** was established by both computer modelling and 2D-NOESY-^{1}H-NMR (*Figs. 1* and *2*). The *singlet* at 1.22 ppm showed cross-peaks with signals at 3.29 and 3.53 ppm (H−C(9) and H−C(11)) and was thus assigned to Me−C(10). The *singlet* at

Scheme 3



Scheme 4



1.09 ppm showed cross-peaks with signals at 3.29 and 4.98 ppm (H–C(9) and H–C(13)), and was thus assigned to Me–C(12). The remaining *singlet* at 1.16 ppm must be that of Me–C(6). Computer modelling with the calculation program Spartan gave two minimal conformations with enthalpy difference of 3.5 kcal/mol (*Figs. 1* and *2*). In the more stable one (conformation 1), the 2D-NOESY-^{1}H-NMR spectrum is expected to present cross-peaks between the signals of Me–C(6) (1.16 ppm) and of Me–C(8) (*doublet* at 1.04 ppm) on the one hand, and between the signals of H–C(2) (2.54–2.50 ppm) and that of H–C(5) (*doublet* at 3.16 ppm) on the other hand. These two significant cross-peaks were indeed observed in the 2D-NOESY-^{1}H-NMR spectrum of (–)-**9**. For the less stable conformation (conformation 2), a cross-peak between the signals of Me–C(6) (1.16 ppm) and that of H–C(9) (*doublet* at 3.29 ppm) should be present in the 2D-NOESY-^{1}H-NMR spectrum of (–)-**9**. This cross-peak was indeed observed. As this conformation should exist in a very low proportion, it gives a minor contribution to the coupling constants observed in the ^{1}H-NMR spectrum of (–)-**9**. These observations together with the calculated structure of (–)-**9** unequivocally establish the absolute configuration at C(6).

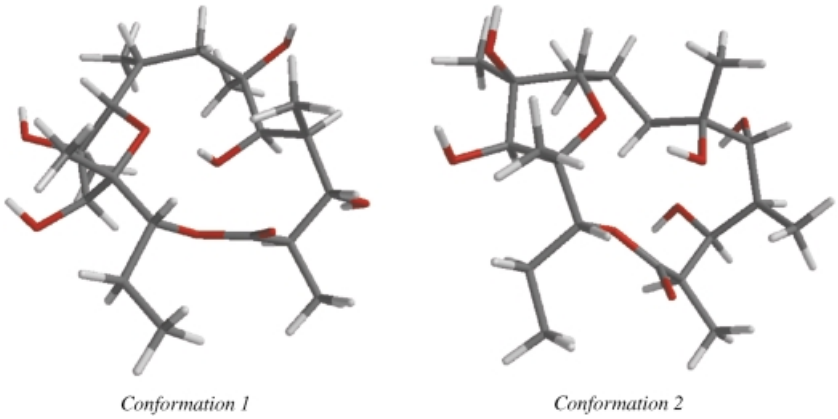


Fig. 1. *Calculated structure of* (–)-**9**

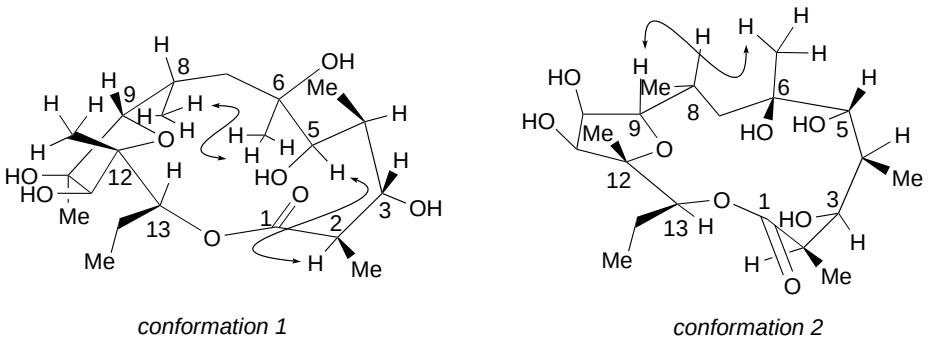


Fig. 2. *NOE Effects observed in* (–)-**9**. ^3J(H–C(2,3)) = 10.7 Hz; ^3J(H–C(3,4) = 0 Hz; ^3J(H–C(8,9)) = 11.1 Hz.

Conclusions. – Two new erythronolide aglycon analogs have been prepared starting from 'naked sugars of the second generation'. As for the sporeamicins, they are 9,12-anhydroerythronolides. However, they are more complex since they contain a 3,4-dihydroxy-2,4-dimethyltetrahydrofuran moiety. The chemistry presented demonstrates that 'naked sugars of the second generation' are suitable chirons for the construction of complex polypropionates containing a large number of contiguous stereogenic centers, including tertiary alcohols.[1])

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Experimental Part

General. See [28]. Signal assignments were confirmed by 2D COSY and NOESY ^{1}H-NMR experiments. Flash chromatography (FC) was performed on silica gel (SiO_2).

(2S,4R,5R)-1-(Benzyloxy)-5-hydroxy-2,4,6-trimethylhept-6-en-3-one ((+)-**11**). To a cooled ($-78°$) soln. of $Sn(OTf)_2$ (5 g, 11.97 mmol, 1.3 equiv.) and anh. Et_3N (2.1 ml, 14.74 mmol, 1.6 equiv.) in anh. CH_2Cl_2 (120 ml) was added **10** (1.9 g, 9.21 mmol) diluted in CH_2Cl_2. The mixture was stirred at $-78°$ for 2 h. Freshly distilled methacrolein (2.3 ml, 27.63 mmol) was added dropwise. After stirring for 2 h at $-78°$, the temp. was raised to $-50°$ for an additional hour. The mixture was poured into aq. pH 7 buffer (200 ml) and extracted with CH_2Cl_2 (3×200 ml). The combined org. layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by FC (petroleum ether/AcOEt 7:1) to yield 2.2 g (87%) of (+)-**11**. Colorless oil. $[\alpha]_{589}^{20} = 30.8$, $[\alpha]_{577}^{20} = 30.5$, $[\alpha]_{546}^{20} = 35.9$, $[\alpha]_{435}^{20} = 54.3$, $[\alpha]_{405}^{20} = 59.9$ ($c = 0.7$, $CHCl_3$). UV (MeCN): 205 (8240), 196 (8750). IR (film): 3475, 2975, 2935, 2876, 1700, 1455, 1375, 1100, 990, 905, 740, 700, 605. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.37–7.29 (*m*, 5 arom. H); 5.10 (*s*, H–C(7)); 4.95 (br. *s*, H–C(7)); 4.52 (*d*, ^3J(H–C(4,5)) = 2.5, H–C(5)); 4.50, 4.46 (2*d*, ^2J = 12.0, PhCH_2); 3.63 (*dd*, ^2J = 8.7, ^3J(H–C(1,2)) = 8.8, H–C(1)); 3.49 (*dd*, ^2J = 8.7, ^3J(H–C(1,2)) = 5.0, H–C(1)); 3.22–3.17 (*m*, H–C(2), HO–C(5)); 2.88 (*qd*, ^3J(H–C(4),Me–C(4)) = 6.9, ^3J(H–C(4,5)) = 2.5, H–C(4)); 1.64 (br. *s*, Me–C(6)); 1.06 (*d*, ^3J(H–C(4),Me–C(4)) = 6.9, Me–C(4)); 1.03 (*d*, ^3J(H–C(2),Me–C(2)) = 7.2, Me–C(2)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 218.1 (*s*, C(3)); 143.3 (*s*, C(6)); 137.5 (*s*, 1 arom. C); 128.4, 127.8, 127.7 (3*d*, ^1J(C,H) = 160, 161, 154, 5 arom. C); 111.4 (*t*, ^1J(C,H) = 157, C(7)); 73.5, 73.1 (2*t*, ^1J(C,H) = 142, 143 C(1), PhCH_2); 72.5 (*d*, ^1J(C,H) = 141, C(5)); 48.4 (*d*, ^1J(C,H) = 126, C(4)); 44.6 (*d*, ^1J(C,H) = 130, C(2)); 19.6 (*q*, ^1J(C,H) = 132, *Me*–C(6)); 13.6 (*q*, ^1J(C,H) = 129, *Me*–C(4)); 8.2 (*q*, ^1J(C,H) = 129, *Me*–C(2)). CI-MS (NH_3): 294 (9, $[M + NH_4]^+$), 277 (2, $[M + H]^+$), 259 (6), 207 (37), 91 (100, $[PhCH_2]^+$). Anal. calc. for $C_{17}H_{24}O_3$ (276.37): C 73.88, H 8.75; found: C 73.94, H 8.82.

(3R,4S,5R,6S)-7-(Benzyloxy)-3,5-(isopropylidenedioxy)-4,6-dimethylheptan-2-one ((+)-**8**). To a soln. of (+)-**11** (2.2 g, 7.96 mmol) in anh. THF/MeOH 4:1 (45 ml), cooled to $-78°$, Et_2BOMe (1M in THF, 10.4 ml, 10.35 mmol, 1.3 equiv.) was added, and the mixture was stirred for 15 min. $NaBH_4$ (423 mg, 11.14 mmol, 1.4 equiv.) was then added, and the mixture was stirred at $-78°$ for 1.5 h. AcOH (1 ml) was added dropwise and the soln. was poured into sat. aq. $NaHCO_3$ (150 ml). The aq. layer was extracted with AcOEt (4×150 ml). The combined org. layers were washed with brine (150 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a pale yellow oil, which was directly dissolved in CH_2Cl_2 (37.5 ml) and 4-(dimethylamino)pyridine (DMAP; 37.5 ml), containing TsOH (150 mg). The mixture was stirred at 20° overnight and concentrated *in vacuo*. Filtration over a pad of SiO_2 (petroleum ether/AcOEt 7:1) and evaporation afforded a yellow oil (2.4 g, 95% crude). The crude alkene (2.4 g, 7.55 mmol) was dissolved in anh. CH_2Cl_2 (300 ml) containing $NaHCO_3$ (1.2 g), and the mixture was cooled to $-78°$. The soln. was ozonolyzed for 15 min and Me_2S (15 ml) was added. The mixture was stirred at 0° for 1 h and then poured into H_2O (300 ml). The aq. layer was extracted with CH_2Cl_2 (2×200 ml). The combined org. extracts were washed with brine (150 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by FC (petroleum ether/Et_2O 4:1) to yield 1.68 g of (+)-**8** (66%, three steps). White solid. M.p. 40-41°. $[\alpha]_{589}^{20} = 30$, $[\alpha]_{577}^{20} = 30$, $[\alpha]_{546}^{20} = 35$, $[\alpha]_{435}^{20} = 63$, $[\alpha]_{405}^{20} = 79$ ($c = 1.0$, $CHCl_3$). UV (MeCN): 206 (8460). IR (KBr): 3065, 3030, 2990, 2940, 2880, 1720, 1455, 1385, 1350, 1200, 1160, 985, 915, 870,

[1]) For other syntheses of erythronolides and derivatives, see [27].

735, 700. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.38–7.28 (*m*, 5 arom. H); 4.49 (*s*, PhCH_2); 4.26 (*d*, ^3J(H–C(3,4)) = 2.6, H–C(3)); 3.75 (*dd*, ^3J(H–C(5,6)) = 9.6, ^3J(H–C(4,5)) = 2.0, H–C(5)); 3.39–3.31 (*m*, 2 H–C(7)); 2.17 (*s*, 3 H–C(1)); 2.16–2.14 (*m*, H–C(4)); 2.05–2.01 (*m*, H–C(6)); 1.49, 1.42 (2*s*, Me_2C); 1.05 (*d*, ^3J(H–C(4), Me–C(4)) = 6.6, Me–C(4)); 0.81 (*d*, ^3J(H–C(6), Me–C(6)) = 6.8, Me–C(6)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 209.9 (*s*, C(2)); 138.4 (*s*, 1 arom. C); 129.4, 127.6, 127.5 (3*d*, ^1J(C,H) = 160, 167, 162, 5 arom. C); 99.4 (*s*, Me_2C); 79.4 (*d*, ^1J(C,H) = 137, C(3)); 75.2 (*d*, ^1J(C,H) = 138, C(5)); 73.2 (*t*, ^1J(C,H) = 141, PhCH_2); 71.3 (*t*, ^1J(C,H) = 140, C(7)); 35.0 (*d*, ^1J(C,H) = 127, C(6)); 32.4 (*d*, ^1J(C,H) = 129, C(4)); 29.9, 19.3 (2*q*, ^1J(C,H) = 129, 123, Me_2C); 27.2 (*q*, ^1J(C,H) = 128, C(1)); 14.6 (*q*, ^1J(C,H) = 127, *Me*–C(4)); 6.4 (*q*, ^1J(C,H) = 126, *Me*–C(6)). CI-MS (NH_3): 321 (4, $[M+H]^+$), 277 (10), 263 (4), 245 (13), 155 (9), 127 (7), 91 (100, $[PhCH_2]^+$). Anal. calc. for $C_{19}H_{28}O_4$ (320.43): C 71.25, H 8.80; found: C 70.98, H 8.69.

(1S,5S,6S,7S)-6,7-(Isopropylidenedioxy)-1,6-dimethyl-8-oxabicyclo[3.2.1]oct-3-en-2-one ((−)-**13**). (−)-**12** (8.3 g, 39.10 mmol), dissolved in anh. THF (90 ml), was added dropwise to a soln. of (i-Pr)$_2$NLi (1.1 equiv., prepared from 6.62 ml of (i-Pr)$_2$NH and 31 ml of BuLi, 1.6M in hexane) in anh. THF (90 ml), cooled to −78°. The mixture was stirred at −78° for 1 h. Then, Me_3SiCl (8.4 ml, 66.5 mmol, 1.7 equiv.) was added dropwise. The temp. was raised to 0°. After 3 h, the soln. was concentrated *in vacuo*. The residue was taken up in pentane (100 ml) and the Li salts were removed by filtration. This operation was repeated twice to give a pale yellow oil (10.9 g, 97% crude). Then, $ClCH_2I$ (11.13 ml, 153.12 mmol, 4 equiv.) was added to a cooled (0°) soln. of Et_2Zn (1.1M in toluene, 69 ml, 76.56 mmol, 2 equiv.) and $Cl(CH_2)_2Cl$ (170 ml). The crude silyl enol ether (10.9 g, 38.28 mmol), dissolved in $Cl(CH_2)_2Cl$ (60 ml), was added dropwise, and the mixture was stirred at 0° for 4 h. The mixture was poured into sat. aq. NH_4Cl soln. (150 ml) and extracted with Et_2O (3 × 150 ml). The combined org. layers were washed with brine (80 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was taken up in DMF (120 ml) and transferred *via* cannula into a cooled (0°) soln. of $FeCl_3$ (18.3 g, 113.4 mmol, 3 equiv.) in DMF (180 ml). Pyridine (6.2 ml, 75.6 mmol, 2 equiv.) was added and the mixture was stirred at 50° for 4.5 h. The soln. was poured into 1M aq. HCl soln. (300 ml) and extracted with pentane/ether 5:1 (4 × 250 ml). The combined org. extracts were washed with 1M aq. HCl soln. (150 ml), brine (200 ml), dried ($MgSO_4$), and evaporated. The residue was purified by FC (petroleum ether/Et_2O 5:1 to 1:1) to yield 5.6 g of (−)-**13** (64%, 3 steps). White solid. M.p. 83–84°. $[\alpha]_{589}^{20} = -285$, $[\alpha]_{577}^{20} = -305$, $[\alpha]_{546}^{20} = -380$, $[\alpha]_{435}^{20} = -1380$, $[\alpha]_{405}^{20} = -1565$ (c = 1.1, CH_2Cl_2). UV (MeCN): 232 (9070), 193 (7290). IR (KBr): 2985, 2860, 1695, 1370, 1240, 1205, 1180, 1100, 1075, 1045, 940. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.26 (*dd*, ^3J(H–C(3,4)) = 9.8, ^3J(H–C(4,5)) = 5.1, H–C(4)); 6.06 (*d*, ^3J(H–C(3,4)) = 9.8, H–C(3)); 4.52 (*d*, ^3J(H–C(4,5)) = 5.1, H–C(5)); 4.14 (*s*, H–C(7)); 1.55, 1.52, 1.49, 1.46 (4*s*, Me–C(1), Me–C(6), Me_2C). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 197.6 (*s*, C(2)); 151.6 (*d*, ^1J(C,H) = 164, C(4)); 128.4 (*d*, ^1J(C,H) = 171, C(3)); 116.3 (*s*, Me_2C); 93.7 (*s*, C(6)); 89.6 (*s*, C(1)); 88.9 (*d*, ^1J(C,H) = 157, C(7)); 79.4 (*d*, ^1J(C,H) = 167, C(5)); 27.7, 26.8, 23.0, 14.6 (4*q*, ^1J(C,H) = 130, 126, 126, 129, *Me*–C(1), *Me*–C(6), Me_2C). CI-MS (NH_3): 225 (11, $[M+H]^+$), 209 (2), 179 (3), 124 (7), 111 (100). Anal. calc. for $C_{12}H_{16}O_4$ (224.25): C 64.27, H 7.19; found: C 64.29, H 7.19.

(1S,4R,5S,6S,7S)-6,7-(Isopropylidenedioxy)-1,4,6-trimethyl-8-oxabicyclo[3.2.1]octan-2-one ((−)-**16**). A complex of CuBr·DMS (7.2 g, 71.35 mmol, 1.6 equiv.) was suspended in anh. Et_2O (100 ml) and cooled to −78°. MeLi (1.6M in Et_2O, 83.6 ml, 133.77 mmol, 3 equiv.) was added dropwise, and the mixture was stirred at −78° for 30 min. The enone (−)-**13** (10 g, 44.59 mmol), dissolved in anh. Et_2O (40 ml), was added dropwise. After 30 min, Me_3SiCl (9.4 ml, 75.80 mmol, 1.7 equiv.) was added and the mixture was warmed to 20° over 3.5 h. The soln. was poured into sat. aq. NH_4Cl soln. (600 ml) and extracted with Et_2O (3 × 500 ml). The combined org. extracts were washed with H_2O (200 ml), brine (200 ml), dried ($MgSO_4$), and concentrated *in vacuo* to afford **14** as a pale yellow oil (13.9 g, 100%, crude).

Data of the intermediate **14** (*(1S,4S,5S,6S,7S)-6,7-(isopropylidenedioxy)-1,4,6-trimethyl-2-(trimethylsilyloxy)-8-oxabicyclo[3.2.1]oct-2-ene*): IR (film): 2985, 1655, 1450, 1375, 1225, 1160, 845, 755. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.57 (*d*, ^3J(H–C(3,4)) = 4.9, H–C(3)); 4.03 (*s*, H–C(7)); 3.84 (*s*, H–C(5)); 2.12–2.04 (*m*, H–C(4)); 1.51, 1.50, 1.42, 1.31 (4*s*, Me_2C, Me–C(1), Me–C(6)); 1.12 (*d*, ^3J(H–C(4),Me–C(4)) = 6.9, Me–C(4)); 0.21 (*s*, Me_3Si). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 153.6 (*s*, C(2)); 113.1 (*s*, Me_2C); 104.1 (*d*, ^1J(C,H) = 157, C(3)); 93.3 (*s*, C(1)); 90.7 (*d*, ^1J(C,H) = 153, C(7)); 88.0 (*s*, C(6)); 87.2 (*d*, ^1J(C,H) = 131, C(5)); 30.8 (*d*, ^1J(C,H) = 125, C(4)); 27.6, 22.9, 20.4 (3*q*, ^1J(C,H) = 125, 126, 122, Me_2C, *Me*–C(1), *Me*–C(6)); 14.5 (*q*, ^1J(C,H) = 127, *Me*–C(4)); 0.2 (*q*, ^1J(C,H) = 116, Me_3Si). CI-MS (NH_3): 312 (100, M^+), 297 (4), 211 (7), 197 (22), 183 (16), 170 (10), 149 (3), 96 (31), 85 (15). Anal. calc. for $C_{13}H_{28}O_4Si$: C 61.50, H 9.03, Si 8.99; found: C 61.65, H 9.15, Si 8.91.

The crude silyl enol ether **14** (13.9 g, 44.48 mmol) was dissolved in DMSO (300 ml) and $[Pd(OAc)_2]$ (3.0 g, 13.34 mmol, 0.3 equiv.) was added. The soln. was saturated with O_2 and heated to 40° for 2 d, purging three times per day with O_2. The mixture was poured into cooled (0°) H_2O (450 ml) and extracted with Et_2O (4 × 400 ml). The combined org. extracts were washed with H_2O (200 ml), dried ($MgSO_4$), and concentrated *in*

vacuo. FC (petroleum ether/AcOEt 5:1 to 3:1) afforded a pale yellow oil (8 g, 75%), which was dissolved in $CHCl_3$ (240 ml). $ZnCl_2$ (5.9 g, 43.65 mmol, 1.3 equiv.), Ph_2SiH_2 (16.9 ml, 91.67 mmol, 2.1 equiv.), PPh_3 (1.15 g, 4.37 mmol, 0.1 equiv.) and $[Pd(PPh_3)_2(OAc)_2]$ (3.3 g, 4.37 mmol, 0.1 equiv.) were successively added. The mixture was stirred at 70° for 4 h, then diluted with CH_2Cl_2 (400 ml), and washed with H_2O (2 × 100 ml). The org. layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by FC (petroleum ether/Et_2O 9:1) to yield 5.36 g (50%, 3 steps) of (−)-**16**.

*Data of (−)-***16**: Colorless oil. $[\alpha]_{589}^{20} = -35$, $[\alpha]_{577}^{20} = -38$, $[\alpha]_{546}^{20} = -47$, $[\alpha]_{435}^{20} = -127$, $[\alpha]_{405}^{20} = -202$ ($c = 1.9$, $CHCl_3$). UV (MeCN): 195 (4520). IR (film): 2985, 2935, 1725, 1380, 1215, 1085, 820. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.09 (*dd*, ^3J(H−C(4,5) = 3.6, ^4J(H−C(3,5)) = 2.2, H−C(5)); 4.08 (*s*, H−C(7)); 2.6 (*ddd*, ^2J = 19.2, ^3J(H−C(3,4) = 6.3, ^3J(H−C(3,5)) = 2.2, H−C(3)); 2.56 (*m*, H−C(4)); 2.06 (*dd*, ^2J = 19.2, ^3J(H−C(3,4)) = 7.6, H−C(3)); 1.66, 1.53, 1.48, 1.33 (4*s*, Me_2C, Me−C(1), Me−C(6)); 1.13 (*d*, ^3J(H−C(4), Me−C(4)) = 7.2, Me−C(4)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 206.1 (*s*, C(2)); 113.6 (*s*, Me_2C); 92.4 (*s*, C(6)); 89.9 (*d*, ^1J(C,H) = 136, C(7)); 89.7 (*s*, C(1)); 86.6 (*d*, ^1J(C,H) = 130, C(5)); 42.3 (*t*, ^1J(C,H) = 126, C(3)); 35.6 (*d*, ^1J(C,H) = 127, C(4)); 29.4, 27.9, 23.0 (3*q*, ^1J(C,H) = 127, 123, 124, Me_2C, *Me*−C(1), *Me*−C(6)); 13.8 (*q*, ^1J(C,H) = 129, *Me*−C(4)). CI-MS (NH_3): 240 (3, M^+), 225 (77), 207 (12), 189 (19), 164 (8), 135 (19), 111 (70), 97 (82), 85 (100). Anal. calc. for $C_{13}H_{20}O_4$ (240.30): C 64.98, H 8.39; found: C 64.94, H 8.46.

*(1*R*,4*R*,5*S*,6*S*,7*S*)-6,7-2-Ethenyl-(Isopropylidenedioxy)-1,4,6-trimethyl-8-oxabicyclo[3.2.1]oct-2-ene* ((+)-**17**). The ketone (−)-**16** (4 g, 16.64 mmol), dissolved in anh. THF (50 ml), was added to a cooled (−78°) soln. of $(Me_3Si)_2NH$ (6.94 ml, 33.29 mmol, 2 equiv.), BuLi (1.6M in hexane, 20.8 ml, 33.29 mmol, 2 equiv.) and HMPA (5.8 ml, 33.29 mmol, 2 equiv.) in anh. THF (120 ml). The mixture was stirred at −78° for 2 h. Then, 2-[*N*,*N*′-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (13 g, 33.29 mmol, 2 equiv.) was added and the temp. was raised to −30° over 2 h. The soln. was poured into H_2O (250 ml) and extracted with Et_2O (3 × 200 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Filtration over a pad of SiO_2 (petroleum ether/AcOEt 6:1) and evaporation afforded a colorless oil (6 g, 97%). In a flame-dried *Schlenk* tube, LiCl (2.05 g, 48.33 mmol, 3 equiv.), $[Pd(PPh_3)_4]$ (373 mg, 0.322 mmol, 0.02 equiv.) and the crude triflate (6 g, 16.11 mmol) were dissolved in anh. THF (90 ml). Tributyl(vinyl)stannane (5.17 ml, 17.72 mmol, 1.1 equiv.) was added and the mixture was stirred at 60° for 12 h. The soln. was diluted with pentane (250 ml), washed with H_2O (40 ml) and brine (40 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by FC (petroleum ether/Et_2O 7:1) to give 3.25 g (78%, 2 steps) of (+)-**17**. Colorless oil. $[\alpha]_{589}^{20} = 19.7$, $[\alpha]_{577}^{20} = 26.9$, $[\alpha]_{546}^{20} = 36.1$, $[\alpha]_{435}^{20} = 39.3$, $[\alpha]_{405}^{20} = 46.1$ ($c = 0.4$, CH_2Cl_2). UV (MeCN): 238 (5570), 196 (3740). IR (film): 2985, 1620, 1455, 1375, 1340, 1255, 1180, 1160, 1115, 1095, 1075, 985, 955, 870, 840. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.07 (*dd*, ^3J = 17.3, 11.0, vinyl CH); 5.68 (*d*, ^3J(H−C(3,4) = 7.6, H−C(3)); 5.28 (*d*, ^3J = 17.3, CH_2 vinyl), 5.02 (*d*, ^3J = 11.0, vinyl CH_2); 4.04 (*s*, H−C(7)); 3.91 (br. *s*, H−C(5)); 2.12 (*m*, H−C(4)); 1.52, 1.47, 1.42, 1.41 (4*s*, Me_2C, Me−C(1), Me−C(6)); 1.19 (*d*, ^3J(H−C(4), Me−C(4)) = 7.1, Me−C(4)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 139.8 (*s*, C(2)); 134.2 (*d*, ^1J(C,H) = 153, C(3)); 128.2 (*d*, ^1J(C,H) = 157, vinyl CH); 114.4 (*t*, ^1J(C,H) = 151, vinyl CH_2); 112.0 (*s*, CMe_2), 93.8 (*s*, C(6)); 92.3 (*d*, ^1J(C,H) = 157, C(7)); 93.8 (*s*, C(1)); 86.3 (*d*, ^1J(C,H) = 140, C(5)); 34.7 (*d*, ^1J(C,H) = 127, C(4)); 28.6, 27.6, 25.1, 17.0 (4*q*, ^1J(C,H) = 126, 130, 128, 127, Me_2C, *Me*−C(1), *Me*−C(6)); 15.6 (*q*, ^1J(C,H) = 127, *Me*−C(4)). Anal. calc. for $C_{15}H_{22}O_3$ (250.34): C 71.97, H 8.86; found: C 71.88, H 8.75.

*(1*R*,4*R*,5*S*,6*S*,7*S*)-2-Ethyl-6,7-(isopropylidenedioxy)-1,4,6-trimethyl-8-oxabicyclo[3.2.1]oct-2-ene* ((+)-**18**). Soln. *A*: H_2O_2 (35% in H_2O, 172 ml) in MeOH (500 ml). *Procedure:* $Cu(OAc)_2$ (0.001M, 4.12 ml) was added to a soln. of the diene (+)-**17** (3.2 g, 12.78 mmol) in MeOH (1.2 l). The mixture was cooled to −15° and every 8 min, soln. *A* (67 ml) and hydrazine (80% in H_2O, 3.3 ml) were added simultaneously. After 10 additions, the mixture was stirred at −15° for 1.5 h. H_2O (250 ml) was added, and the soln. was concentrated to a volume of 500 ml. The aq. layer was extracted with pentane/Et_2O 2:1 (3 × 500 ml). The combined org. extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by FC (petroleum ether/Et_2O, 6:1) to yield 2.4 g (75%) of (+)-**18**. Colorless oil. $[\alpha]_{589}^{20} = 84$, $[\alpha]_{577}^{20} = 87$, $[\alpha]_{546}^{20} = 99$, $[\alpha]_{435}^{20} = 174$, $[\alpha]_{405}^{20} = 213$ ($c = 1.2$, $CHCl_3$). UV (MeCN): 196 (6950). IR (film): 2980, 2935, 1650, 1460, 1375, 1245, 1110, 1060, 870. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.28 (*m*, H−C(3)); 3.98 (*s*, H−C(7)); 3.90 (br. *s*, H−C(5)); 2.12 (*m*, H−C(4)); 2.11–2.01, 1.99–1.81 (2*m*, CH_2); 1.53, 1.50, 1.42, 1.35 (4*s*, Me_2C, Me−C(1), Me−C(6)); 1.13 (*d*, ^3J(H−C(4),Me−C(4)) = 7.2, Me−C(4)); 1.05 (*t*, ^3J = 7.3, *Me*CH_2). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 141.2 (*s*, C(2)); 123.9 (*d*, ^1J(C,H) = 156, C(3)); 112.0 (*s*, CMe_2); 93.8 (*s*, C(1)); 92.4 (*d*, ^1J(C,H) = 156, C(7)); 87.1 (*d*, ^1J(C,H) = 151, C(5)); 84.2 (*s*, C(6)); 34.5 (*d*, ^1J(C,H) = 126, C(4)); 28.8, 27.8, 25.4 (3*q*, ^1J(C,H) = 123, 124, 122, Me_2C, *Me*−C(1), *Me*−C(6)); 24.3 (*t*, ^1J(C,H) = 123, CH_2); 16.2 (*q*, ^1J(C,H) = 123, *Me*−C(4)); 11.8 (*q*, ^1J(C,H) = 122, *Me*CH_2). CI-MS (NH_3): 270 (93, $[M + NH_4]^+$), 253 (100, $[M + H]^+$), 195 (24), 123 (17). Anal. calc. for $C_{15}H_{24}O_3$ (252.35): C 71.39, H 9.59; found: C 71.41, H 9.60.

*(1*S*)-1-((3a*R*,4*S*,6*R*,6a*S*)-3a,4,6,6a-Tetrahydro-6-{(1*S*)-1-[1-methyl-2-(phenylthio)]ethyl}-2,2,4,6a-tetramethyl-2*H*-furo[3,4-*d*][1,3]dioxol-4-yl)propan-1-ol* ((−)-**22**). A stream of O_3 was passed through a cooled (−78°) soln. of (+)-**17** (1.57 g, 6.23 mmol) in anh. CH_2Cl_2/MeOH 4:1 (250 ml) for 10 min. The soln. was purged with O_2 for 2 min, and Me_2S (90 µl, 12.46 mmol, 2 equiv.) was added. After stirring for 5 min at −78°, $NaBH_4$ (473 mg, 12.46 mmol, 2 equiv.) was added, and the mixture was stirred for 1 h at 0°. The soln. was poured into 1M aq. HCl soln. (250 ml) and extracted with CH_2Cl_2 (2 × 200 ml). The combined org. extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by CC (petroleum ether/AcOEt 2:1 to 1:2) to afford a white solid (1.44 g, 80%) as an inseparable mixture of the diols **19** and **20**, respectively. To a soln. of the crude diols (1.44 g, 4.99 mmol) in MeCN (90 ml) were added PhSSPh (3.27 g, 14.97 mmol, 3 equiv.) and Oct_3P (8.9 ml, 19.96 mmol, 4 equiv.), and the soln. was stirred at 20° for 3 h. The mixture was diluted with Et_2O (300 ml) and washed with 2M aq. NaOH soln. (2 × 200 ml). The aq. layers were re-extracted with Et_2O (150 ml each). The combined org. extracts were washed with brine (200 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by FC (AcOEt/petroleum ether 1:5): 428 mg of **21** (22%) and 1.29 g of (−)-**22** (68%). Colorless oils.

Data of the Major Isomer (−)-**22**: $[\alpha]_{589}^{20} = -18$, $[\alpha]_{577}^{20} = -18$, $[\alpha]_{546}^{20} = -20$, $[\alpha]_{435}^{20} = -28$, $[\alpha]_{405}^{20} = -36$ (c = 1.0, $CHCl_3$). UV (MeCN): 201 (8570). IR (film): 3495, 2985, 2935, 1585, 1480, 1455, 1380, 1255, 1210, 1115, 1060, 740. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.35, 7.27, 7.15 (3*m*, 5 arom. H); 4.31 (*s*, H−C(5)); 3.50 (*d*, ^3J(H−C(8,7)) = 10.3, H−C(7)); 3.41–3.35 (*m*, 1 H−C(9), H−C(3)); 2.66 (*dd*, ^2J = 12.6, ^3J(H−C(9,8)) = 8.9, 1 H−C(9)); 2.32 (br. *s*, HO−C(3)); 1.86 (*ddq*, ^2J = 13.1, ^3J(H−C(3,2)) = 10.3, ^3J(H−C(2,1)) = 6.5, H−C(2)); 1.65 (*dm*, ^2J = 13.1, H−C(2)); 1.53, 1.38, 1.35, 1.15 (4*s*, Me_2C, Me−C(6), Me−C(4)); 1.45–1.33 (*m*, H−C(8)); 1.10 (*d*, ^3J(H−C(8),Me−C(8)) = 7.1, Me−C(8)); 1.05 (*t*, ^3J(H−C(2,1)) = 6.5, 3 H−C(1)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 137.4 (*s*, 1 arom. C); 128.7, 128.4, 125.4 (3*d*, ^1J(C,H) = 161, 162, 162, 5 arom. C); 114.4 (*s*); 88.4 (*s*, C(6)); 88.2 (*d*, ^1J(C,H) = 155, C(5)); 84.8 (*d*, ^1J(C,H) = 144, C(7)); 84.7 (*s*, C(4)); 77.6 (*d*, ^1J(C,H) = 132, C(3)); 38.2 (*t*, ^1J(C,H) = 142, C(9)); 33.3 (*d*, ^1J(C,H) = 129, C(8)); 27.9, 26.7 (2*q*, ^1J(C,H) = 127, 126, 2 Me); 24.1 (*t*, ^1J(C,H) = 126, C(2)); 19.3, 16.3 (2*q*, ^1J(C,H) = 127, 128, 2 Me); 14.9 (*q*, ^1J(C,H) = 130, *Me*−C(8)); 11.0 (*q*, ^1J(C,H) = 122, C(1)). CI-MS (NH_3): 398 (32, $[M+NH_4]^+$), 381 (100, $[M+H]^+$), 321 (11), 263 (32), 123 (22). Anal. calc. for $C_{21}H_{32}O_4S$ (380.55): C 66.28, H 8.48, S 8.43; found: C 66.36, H 8.43, S 8.40.

*(3a*R*,4*S*,6*R*,6a*S*)-4-{(1*S*)-1-[1-(*tert*-Butyl)dimethylsilyloxy]propyl}-3a,4,6,6a-tetrahydro-6-{(1*S*)-1-[1-methyl-2-(phenylthio)]ethyl}-2,2,4,6a-tetramethyl-2*H*-furo[3,4-*d*][1,3]dioxole* ((−)-**23**). To a cooled (0°) soln. of (−)-**22** (920 mg, 2.42 mmol) in anh. CH_2Cl_2 (44 ml), 2,6-lutidine (843 µl, 7.26 mmol, 3 equiv.) and (*t*-Bu)Me_2SiO-SO_2CF_3 (945 µl, 1.7 equiv.) were added. After stirring at 0° for 1 h, the soln. was poured into a 2M aq. NaOH soln. (80 ml) and extracted with $CHCl_3$ (3 × 80 ml). The combined org. extracts were washed with 1M aq. HCl soln. (80 ml), brine (50 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by FC (petroleum ether/AcOEt 10:1) to give 1.18 g (99%) of (−)-**23**. Colorless oil. $[\alpha]_{589}^{20} = -20$, $[\alpha]_{577}^{20} = -22$, $[\alpha]_{546}^{20} = -25$, $[\alpha]_{435}^{20} = -43$, $[\alpha]_{405}^{20} = -51$ (c = 1.9, $CHCl_3$). UV (MeCN): 254 (10760), 196 (16910). IR (film): 2930, 1585, 1460, 1380, 1255, 825, 765, 740, 670. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.37, 7.27, 7.15 (3*m*, 5 arom. H); 4.23 (*s*, H−C(5)); 3.46 (*d*, ^3J(H−C(2,3)) = 10.2, H−C(3)); 3.41 (*dd*, ^2J = 13.3, ^3J(H−C(1,2)) = 2.7, H−C(1)); 3.38 (*dd*, ^3J(H−C(7,8)) = 6.9, 3.6, H−C(7)); 2.64 (*dd*, ^2J = 13.3, ^3J(H−C(1,2)) = 9.1, H−C(1)); 1.85–1.75 (*m*, H−C(2), 1 H−C(8)); 1.54 (*s*, Me); 1.47 (*m*, 1 H−C(8)); 1.35, 1.25, 1.17 (3*s*, 3 Me); 1.07 (*d*, ^3J(H−C(2),Me−C(2)) = 6.5, Me−C(2)); 1.01 (*t*, ^3J(H−C(8,9)) = 7.5, H−C(9)); 0.89 (*s*, (*t*-Bu)); 0.12, 0.10 (2*s*, Me_2Si). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 137.6 (*s*, 1 arom. C); 128.7, 128.3, 125.2 (3*d*, ^1J(C,H) = 160, 154, 161, 5 arom. C); 113.7 (*s*); 90.0 (*d*, ^1J(C,H) = 155, C(5)); 87.9 (*s*, C(4)); 84.6 (*d*, ^1J(C,H) = 141, C(3)); 84.1 (*s*, C(6)); 78.4 (*d*, ^1J(C,H) = 140, C(7)); 38.2 (*t*, ^1J(C,H) = 141, C(1)); 33.0 (*d*, ^1J(C,H) = 130, C(2)); 28.1 (*t*, ^1J(C,H) = 126, C(8)); 26.0 (*q*, ^1J(C,H) = 119, (*t*-Bu)); 19.5 (*s*, C); 18.3, 15.0 (2*q*, ^1J(C,H) = 126, 128, 4 Me)); 14.6 (*q*, ^1J(C,H) = 127, *Me*−C(2)); 11.2 (*q*, ^1J(C,H) = 129, C(9)); −3.8, −4.1 (2*q*, ^1J(C,H) = 118, 118, Me_2Si). CI-MS (NH_3): 495 (32, $[M+H]^+$), 403 (100), 345 (17), 271 (15), 229 (22). Anal. calc. for $C_{27}H_{46}O_4SSi$ (494.81): C 65.54, H 9.37, S 6.48; found: C 65.50, H 9.29, S 6.47.

*(3a*R*,4*S*,6*R*,6a*S*)-4-{(1*S*)-1-[1-(*tert*-Butyl)dimethylsilyloxy]propyl}-3a,4,6,8a-tetrahydro-2,2,4,6a-tetramethyl-6-{(1*S*)-1-methyl-2-(phenylsulfinyl)]ethyl}-2*H*-furo[3,4-*d*]dioxole* ((+)-**24** and (−)-**25**). To a soln. of (−)-**23** (565 mg, 1.14 mmol) in MeOH/H_2O 28:1.6 (*v*/*v*), $NaIO_4$ (1.37 mmol, 1.2 equiv.) was added, and the mixture was stirred at 20° for 12 h. The soln. was poured into H_2O (60 ml) and extracted with $CHCl_3$ (4 × 60 ml). The combined org. extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by FC (petroleum ether/ether 2:1) to yield 325 mg (55%) of (+)-**24** and 126 mg (40%) of (−)-**25**. Colorless oils.

Data of (+)-**24**: $[\alpha]_{589}^{20} = 30.7$, $[\alpha]_{577}^{20} = 48.4$, $[\alpha]_{546}^{20} = 65.8$, $[\alpha]_{435}^{20} = 125.8$, $[\alpha]_{405}^{20} = 156.4$ (c = 0.8, CH_2Cl_2). UV (MeCN): 215 (15430). IR (film): 2935, 2865, 1735, 1465, 1375, 1255, 1215, 1160, 1025, 940, 900, 860, 835, 775, 750. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.67–7.65, 7.56–7.49 (2*m*, 5 arom. H); 4.22 (*s*, C(3a)); 3.44 (*d*, ^3J = 10.0, H−C(6));

3.38 (*dd*, ^3J = 6.7, 4.0, EtC*H*); 3.02 (*d*, ^2J = 13.2, 1 H, SCH_2); 2.37 (*dd*, ^2J = 13.2, ^3J = 10.5, 1 H, SCH_2); 2.34–2.26 (*m*, SCH_2CH); 1.75–1.67, 1.48–1.44 (2*m*, MeCH_2); 1.42, 1.38, 1.31, 1.15 (4*s*, 4 Me); 1.28 (*d*, ^3J = 6.3, *Me*CHCH$_2$S); 0.96 (*t*, ^3J = 7.5, *Me*CH_2); 0.90 (*s*, (*t*-Bu)); 0.09 (*s*, Me_2Si). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 144.7 (*s*, 1 arom. C); 130.8, 129.2, 124.0 (3*d*, ^1J(C,H) = 164, 162, 161, 5 arom. C); 113.9 (*s*, C(2)); 89.9 (*d*, ^1J(C,H) = 151, C(3a)); 87.9 (*s*, C(6a)); 84.7 (*d*, ^1J(C,H) = 143, C(6)); 84.3 (*s*, C(4)); 78.2 (*d*, ^1J(C,H) = 150, Et*C*H); 61.4 (*t*, ^1J(C,H) = 143, SCH_2); 29.0 (*d*, ^1J(C,H) = 130, SCH_2CH); 28.1, 26.6 (2*q*, ^1J(C,H) = 128, 128, 2 Me); 26.1 (*q*, ^1J(C,H) = 130, (*t*-Bu)); 25.7 (*t*, ^1J(C,H) = 129, *C*H_2Me); 20.1, 17.3 (2*q*, ^1J(C,H) = 127, 129, 2 Me); 18.3 (*s*, 1 C); 15.2 (*q*, ^1J(C,H) = 130, *Me*CHCH$_2$S); 11.0 (*q*, ^1J(C,H) = 127, CH_2Me); −3.9 (*q*, ^1J(C,H) = 116, Me_2Si). CI-MS (NH_3): 511 (7, $[M+H]^+$), 453 (20, $[M-(t\text{-Bu})]^+$), 395 (6), 337 (24), 125 (30), 73 (100). Anal. calc. for $C_{27}H_{46}O_5SSi$ (510.81): C 63.49, H 9.08; found: C 63.60, H 9.15.

Data of (−)-**25**: $[\alpha]_{589}^{20} = -11.0$, $[\alpha]_{577}^{20} = -18.3$, $[\alpha]_{546}^{20} = -30.7$, $[\alpha]_{435}^{20} = -81.0$, $[\alpha]_{405}^{20} = -115.3$ (*c* = 0.3, CH_2Cl_2). UV (MeCN): 195 (16960). IR (film): 2990, 2955, 2935, 2850, 1740, 1460, 1380, 1255, 1115, 835, 775, 750. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.73–7.70, 7.58–7.53 (2*m*, 5 arom. H); 4.14 (*s*, C(3a)); 3.34 (*d*, ^3J = 10.1, H−C(6)); 3.32 (*dd*, ^3J = 5.2, 3.9, Et*CH*); 3.05 (*dd*, ^2J = 13.1, ^3J = 2.3, 1 H, SCH_2); 2.72 (*dd*, ^2J = 13.1, ^3J = 10.4, 1 H, SCH_2); 1.78–1.73 (*m*, SCH_2CH); 1.70–1.63, 1.44–1.40 (2*m*, MeCH_2); 1.29, 1.24, 1.19, 1.13 (4*s*, 4 Me); 1.18 (*d*, ^3J = 6.5, *Me*CHCH$_2$S); 0.92 (*t*, ^3J = 7.0, *Me*CH_2); 0.89 (*s*, (*t*-Bu)); 0.08, 0.03 (2*s*, Me_2Si). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 144.2 (*s*, 1 arom. C); 131.2, 129.2, 124.5 (3*d*, ^1J(C,H) = 162, 163, 164, 5 arom. C); 114.0 (*s*, C(2)); 89.6 (*d*, ^1J(C,H) = 152, C(3a)); 87.6 (*s*, C(6a)); 84.6 (*d*, ^1J(C,H) = 137, C(6)); 84.2 (*s*, C(4)); 78.2 (*d*, ^1J(C,H) = 160, Et*C*H); 60.5 (*t*, ^1J(C,H) = 142, SCH_2); 29.2 (*d*, ^1J(C,H) = 137, SCH_2CH); 28.0, 26.6 (2*q*, ^1J(C,H) = 127, 129, 2 Me); 26.0 (*q*, ^1J(C,H) = 122, (*t*-Bu)); 25.6 (*t*, ^1J(C,H) = 128, *C*H_2Me); 19.4, 18.1 (2*q*, ^1J(C,H) = 125, 127, 2 Me); 18.3 (*s*, 1 C); 15.3 (*q*, ^1J(C,H) = 131, *Me*CHCH$_2$S); 10.9 (*q*, ^1J(C,H) = 128, CH_2Me); −4.1 (*q*, ^1J(C,H) = 114, Me_2Si). CI-MS (NH_3): 511 (100, $[M+H]^+$), 453 (36, $[M-(t\text{-Bu})]^+$), 395 (11), 325 (42), 251 (13), 173 (55), 73 (70). Anal. calc. for $C_{27}H_{46}O_5SSi$ (510.81): C 63.49, H 9.08; found: C 63.95, H 9.28.

*(1S,3S,4R,5S,6R,7S)-(8-(Benzyloxy)-1-((3aS,4R,6S,6aR)-6-{(1S)-1-[1-(*tert*-butyl)dimethylsilyloxy]propyl}-3a,4,6,6a-tetrahydro-2,2,3a,6-tetramethyl-2*H*-furo[3,4-*d*][1,3]dioxol-4-yl)-4,6-(isopropylidenoxy)-2-(phenylsulfinyl)-1,3,5,7-tetramethyloctan-3-ol* ((+)-**26**). In a flame-dried *Schlenk* tube, BuLi (1.5M in hexane, 418 µl, 0.627 mmol, 1.6 equiv.) was added to a cooled (−60°) soln. of i-Pr_2NH (105 µl, 0.745 mmol, 1.9 equiv.) in anh. THF (8 ml). After stirring for 15 min at −60°, the mixture was cooled to −78°, and a cooled (−78°) soln. of (+)-**24** (200 mg, 0.392 mmol) in anh. THF (1 ml) was added dropwise. After 2 min, TMEDA (94 µl, 0.627 mmol, 1.6 equiv.) was added, followed by a cooled (−78°) soln. of (+)-**8** (163 mg, 0.510 mmol, 1.3 equiv.) in anh. THF (1 ml). After stirring for 5 min at −78°, the soln. was poured into sat. aq. NH_4Cl soln. (20 ml) and extracted with AcOEt (3 × 20 ml). The combined org. extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by FC (petroleum ether/AcOEt 15:1 to 3:1) to give 130 mg (40%) of (+)-**26** and 70 mg (35%) of recovered (+)-**24**, resp. Colorless oil. $[\alpha]_{589}^{20} = 5.6$, $[\alpha]_{577}^{20} = 4.7$, $[\alpha]_{546}^{20} = 4.9$, $[\alpha]_{435}^{20} = 10.2$, $[\alpha]_{405}^{20} = 11.4$ (*c* = 0.5, CH_2Cl_2). UV (MeCN): 273 (15030), 260 (12720), 217 (11413). IR (film): 3285, 2935, 2855, 1455, 1380, 1260, 1205, 1115, 1070, 1015, 945, 870, 835, 775, 740, 700. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.92–7.90, 7.42–7.39, 7.36–7.30 (3*m*, 10 arom. H); 7.00 (br. *s*, HO−C(3)); 4.52 (*s*, CH_2Ph); 4.35 (*s*, EtCHCC*H*); 4.05 (*d*, ^3J = 10.1, S(CH)$_2$C*H*); 3.60 (*d*, ^3J = 2.2, H−C(4)); 3.46 (*dd*, ^3J = 6.7, 3.9, Et*CH*); 3.33 (*dd*, ^2J = 10.0, ^3J = 3.8, H−C(8)); 3.26 (*dd*, ^2J = 10.0, ^3J = 5.9, H−C(8)); 2.86 (br. *s*, H−C(2)); 2.83 (*dd*, ^3J(H−C(6,7)) = 9.7, ^3J(H−C(5,6)) = 1.4, H−C(6)); 2.57–2.53 (*m*, H−C(1)); 1.80–1.70 (*m*, H−C(7), H−C(5), 1 H, CH_2Me); 1.67 (*d*, ^3J(H−C(1),Me−C(1)) = 6.8, Me−C(1)); 1.61, 1.42, 1.40, 1.27 (4*s*, 2 Me_2C); 1.56–1.43 (*m*, 1 H, CH_2Me); 1.21 (br. *s*, S(CH)$_3$C*Me*, EtCHC*Me*); 0.99 (*t*, ^3J = 7.5, CH_2Me); 0.97 (*d*, ^3J(H−C(5),Me−C(5)) = 6.7, Me−C(5)); 0.93 (*s*, (*t*-Bu)); 0.88 (*d*, ^3J(H−C(7), Me−C(7)) = 6.7, Me−C(7)); 0.56 (*s*, Me−C(3)); 0.12 (*s*, Me_2Si). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 143.5, 138.7 (2*s*, 2 arom. C); 130.4, 129.2, 128.4, 127.8, 127.6 (5*d*, 10 arom. C); 114.7, 98.7 (2*s*); 90.3 (*d*, ^1J(C,H) = 149, EtCHC*C*); 89.0 (*s*, C(3)); 85.3, 83.5 (2*s*, S(CH)$_3$*C*, EtCH*C*); 84.0 (*d*, ^1J(C,H) = 158, S(CH)$_2$*C*); 78.3 (*d*, ^1J(C,H) = 139, Et*C*H); 78.0 (*d*, ^1J(C,H) = 141, C(4)); 76.7 (*d*, ^1J(C,H) = 141, C(6)); 73.3 (*t*, ^1J(C,H) = 142, *C*H_2Ph); 71.3 (*t*, ^1J(C,H) = 143, C(8)); 64.4 (*d*, ^1J(C,H) = 144, C(2)); 34.4 (*d*, ^1J(C,H) = 123, C(7)); 33.3 (*d*, ^1J(C,H) = 128, C(1)); 30.7 (*d*, ^1J(C,H) = 126, C(5)); 29.8, 28.1, 26.8 (3*q*, ^1J(C,H) = 129, 3 Me); 26.1 (*q*, ^1J(C,H) = 119, (*t*-Bu)); 25.9, 20.9, 19.2 (3*q*, ^1J(C,H) = 127, 126, 128, 3 Me); 24.3 (*t*, ^1J(C,H) = 128, *C*H_2Me); 18.4 (*s*, 1 C); 15.8 (*q*, ^1J(C,H) = 126, Me); 14.9, 14.8 (2*q*, ^1J(C,H) = 122, 122, *Me*−C(7), *Me*−C(1)); 10.8 (*q*, ^1J(C,H) = 120, CH_2Me); 7.5 (*q*, ^1J(C,H) = 121, *Me*−C(5)); −3.9, −4.1 (2*q*, ^1J(C,H) = 117, 116, Me_2Si). CI-MS (NH_3): 832 (74, $[M+H]^+$), 774 (10, $[M-(t\text{-Bu})]^+$), 688 (77), 629 (28), 427 (100), 235 (47), 91 (50, $[PhCH_2]^+$). Anal. calc. for $C_{46}H_{74}O_9SSi$: C 66.47, H 8.97; found: C 66.78, H 8.79.

*(2S,3R,4S,5R,6S,8S)-8-((3aS,4R,6S,6aR)-6-{(1S)-1-[1-(*tert*-Butyl)dimethylsilyloxy]propyl}-3a,4,6,6a-tetrahydro-2,2,3a,6-tetramethyl-2*H*-furo[3,4-a][1,3]dioxol-4-yl)-6-hydroxy-3,5-(isopropylidenoxy)-2,4,6,8-tetramethyloctanoic acid* ((+)-**27**). To a soln. of (+)-**26** (100 mg, 0.12 mmol) in Et_2O/EtOH 7:3 (*v*/*v*) *W2 Raney* Ni

(500 mg) was added, and the mixture was vigorously stirred at 20° for 15 h. Filtration over a pad of SiO_2 (AcOEt) and concentration *in vacuo* afforded a colorless oil (86 mg, 100%, crude), which was taken up in EtOH (8 ml). *W2 Raney* Ni (400 mg) was added, and the mixture was vigorously stirred under H_2 (1 bar) at 20° for 12 h. Filtration over a pad of SiO_2 (AcOEt) and concentration *in vacuo* afforded the corresponding alcohol (88%, crude, 2 steps), that was oxidized as follows: DMSO (37 µl, 0.526 mmol, 5 equiv.) was added to a cooled (−78°) soln. of oxalyl chloride (22 µl, 0.252 mmol, 2.4 equiv.) in anh. CH_2Cl_2 (4 ml). After stirring for 15 min at −78°, a soln. of the above intermediate (65 mg, 0.105 mmol) in anh. CH_2Cl_2 (2 ml) was added dropwise. After stirring for 30 min at −78°, Et_3N (150 µl) was added, and the temp. was raised to −30°. After 5 min, the soln. was poured into H_2O (15 ml) and extracted with AcOEt (4 × 15 ml). The combined org. extracts were washed with H_2O (20 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was taken up in *t*-BuOH (4 ml) and 2-methylbut-2-ene (78 µl). A soln. of NaH_2PO_4 (182 mg, 1.172 mmol, 11.6 equiv.) and $NaClO_2$ (137 mg, 1.515 mmol, 15 equiv.) in distilled H_2O (4 ml) was added, and the mixture was stirred at 20° for 2 h. The soln. was poured into brine (15 ml) and extracted with AcOEt (4 × 15 ml). The combined org. extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by FC (CH_2Cl_2/MeOH 15:1) to yield 38 mg (50%, 4 steps) of (+)-**27**. Colorless oil. $[\alpha]_{589}^{20} = 10.8$, $[\alpha]_{577}^{20} = 12.5$, $[\alpha]_{546}^{20} = 22.9$, $[\alpha]_{435}^{20} = 40.1$, $[\alpha]_{405}^{20} = 62.7$ ($c = 0.3$, CH_2Cl_2). UV (MeCN): 262 (10050), 212 (4750). ^{1}H-NMR (400 MHz, $CDCl_3$): 4.20 (*s*, $(Me_2C)OCH$); 3.92 (*dd*, ^3J(H−C(2,3)) = 8.9, ^3J(H−C(3,4)) = 0.9, H−C(3)); 3.59 (*d*, ^3J(H−C(4,5)) = 1.9, H−C(5)); 3.38 (*d*, ^3J = 10.2, OCHC(8)); 3.37 (*dd*, ^3J = 7.5, 3.0, EtC*H*); 2.73–2.69 (*m*, H−C(2)); 1.89–1.86 (*m*, H−C(4), H−C(8)); 1.80–1.61 (*m*, 1 H−C(7), 1 H, MeCH_2); 1.49–1.29 (*m*, 1 H−C(7), 1 H, MeCH_2); 1.53, 1.48, 1.44, 1.41 (4*s*, 2 Me_2C); 1.35, 1.23, 1.15 (3*s*, Me−C(6), $(Me_2C)OCMe$, EtCHC*Me*); 1.26 (*d*, ^3J(H−C(2),Me−C(2)) = 6.9, Me−C(2)); 1.04 (*d*, ^3J(H−C(4),Me−C(4)) = 6.9, Me−C(4)); 0.98 (*d*, ^3J(H−C(8),Me−C(8)) = 6.6, Me−C(8)); 0.95 (*t*, ^3J = 6.9, *Me*CH_2); 0.92 (*s*, (*t*-Bu)); 0.12, 0.11 (2*s*, Me_2Si). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 177.0 (*s*, C(1)); 113.4, 99.7 (2*s*, 2 Me_2C); 90.0 (*d*, $(Me_2C)OCH$); 86.7 (*d*, OCHC(8)); 80.0 (*d*, C(5)); 78.4 (*d*, EtCH); 76.1 (*d*, C(3)); 87.6, 84.9, 72.7 (3*s*, C(6), $(Me_2C)OCMe$, EtCHC); 46.0 (*t*, C(7)); 41.2 (*d*, C(2)); 31.5, 27.6 (2*d*, C(4), C(8)); 29.8, 28.1, 26.5 (3*q*, 3 Me); 26.0 (*q*, Me_3C); 25.0 (*t*, MeCH_2); 23.2, 19.3, 18.6 (3*q*, 4 Me); 18.3 (*q*, *Me*−C(8)); 17.5 (*s*, 1 C); 14.1 (*q*, *Me*−C(2)); 11.1 (*q*, *Me*CH_2); 7.0 (*q*, *Me*−C(4)); −3.6, −4.3 (2*q*, Me_2Si). CI-MS (NH_3): 649 (100, $[M + NH_4 + 1]^+$), 632 (87, $[M + H + 1]^+$), 574 (53), 429 (45), 73 (48). Anal. calc. for $C_{33}H_{62}O_9Si$ (630.93): C 62.82, H 9.90; found: C 63.01, H 9.98.

*(1*R*,2*R*,5*R*,6*S*,7*S*,8*R*,9*R*,11*R*,12*R*,13*S*,14*S*)-2-Ethyl-6,8,9,13,14-pentahydroxy-1,5,7,9,11,13-hexamethyl-3,15-dioxabicyclo[10.2.1]pentadecan-4-one* ((−)-**9**). To a cooled (−30°) soln. of (+)-**27** (15 mg, 24 µmol) in anh. THF (1 ml), Bu_4NF (1M in THF, 150 ml) was added dropwise, and the mixture was allowed to react at 20° for 1 h. The solvent was evaporated, and the residue was filtered over a pad of SiO_2 (AcOEt). Concentration *in vacuo* afforded a pale yellow oil (**28**, 10 mg, 80%, crude), which was directly engaged in the macrolactonization. The *seco*-acid **28** (10 mg), was dissolved in a 0.4M soln. of i-Pr_2NEt (1.45 ml, 0.580 mmol, 30 equiv.) in benzene. A 0.4M soln. of 2,4,6-trichlorobenzoyl chloride (967 µl, 0.387 mmol, 20 equiv.) was added dropwise. After stirring for 3 h at 20°, the soln. was diluted with PhH (11 ml) and added through a syringe pump over 24 h to a refluxing soln. of 4-(Me_2N)-pyridine (118 mg, 0.967 mmol) in benzene (20 ml). The mixture was cooled to 20° and a sat. aq. soln. of $NaHCO_3$ (25 ml) was added to dissolve the white precipitate. The layers were separated and the aq. layer was extracted with AcOEt (3 × 25 ml). The combined org. extracts were washed with brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was filtered over a pad of SiO_2 (AcOEt/petroleum ether 1:2) and concentrated *in vacuo*. The crude macrolactone (8 mg, 16.03 µmol) was stirred for 1 h at r.t. in 80% aq. CF_3COOH (1 ml). The solvent was evaporated and the residue was purified by FC (CH_2Cl_2/MeOH 15:1) to give 4.5 mg (55%, 2 steps) of (−)-**9**. Colorless oil. $[\alpha]_{589}^{20} = -0.2$, $[\alpha]_{577}^{20} = -1.0$, $[\alpha]_{546}^{20} = -2.0$, $[\alpha]_{435}^{20} = -6.5$, $[\alpha]_{405}^{20} = -9.0$ ($c = 0.2$, MeOH). UV (MeCN): 265 (10620), 258 (11450), 215 (3820). IR (film): 3475, 2970, 2940, 1750, 1465, 1370, 1215, 1185, 1140, 1030, 990, 920, 640, 615. ^{1}H-NMR (400 MHz, CD_3CN): 4.98 (*dd*, ^3J = 11.2, 2.4, H−C(2)); 3.69 (*d*, ^3J(H−C(5,6)) = 10.7, H−C(6)); 3.53 (*s*, H−C(14)); 3.29 (*d*, ^3J(H−C(11,12)) = 11.1, H−C(12)); 3.16 (*d*, ^3J(H−C(7,8)) = 1.9, H−C(8)); 2.54–2.50 (*m*, H−C(5)); 2.18–2.15 (*m*, H−C(7)); 2.00–1.97 (*m*, H−C(11)); 1.73–1.67 (*dm*, ^2J = 14.7, 1 H, MeCH_2); 1.62–1.56 (*m*, 1 H, MeCH_2, 2 H−C(10)); 1.22 (*s*, Me−C(13)); 1.16 (*s*, Me−C(9)); 1.13 (*d*, ^3J(H−C(5),Me−C(5)) = 6.8, Me−C(5)); 1.09 (*s*, Me−C(1)); 1.04 (*d*, ^3J(H−C(11),Me−C(11)) = 6.2, Me−C(11)); 1.01 (*d*, ^3J(H−C(4),Me−C(7)) = 6.9, Me−C(7)); 0.85 (*t*, ^3J = 7.4, *Me*CH_2). ^{1}H-NMR (400 MHz, CD_3OD): 5.02 (*dd*, ^3J = 11.0, 2.4, H−C(2)); 3.75 (*d*, ^3J(H−C(2,3)) = 10.8, H−C(6)); 3.59 (*s*, H−C(14)); 3.33 (masked, H−C(12)); 3.20 (*d*, ^3J(H−C(7,8)) = 1.0, H−C(8)); 2.57–2.53 (*m*, H−C(5)); 2.18 (*qd*, ^3J(H−C(7),Me−C(7)) = 6.8, ^3J(H−C(7,8)) = 1.0, H−C(7)); 2.07–1.99 (*m*, H−C(11)); 1.77–1.64 (*m*, MeCH_2); 1.50–1.37 (*m*, 2 H−C(10)); 1.27 (*s*, Me−C(13)); 1.22 (*s*, Me−C(9)); 1.21 (*d*, ^3J(H−C(5),Me−C(5)) = 7.1, Me−C(5)); 1.17 (*s*, Me−C(1)); 1.09 (*d*, ^3J(H−C(11),Me−C(11)) = 6.2, Me−C(11)); 1.08 (*d*, ^3J(H−C(7),Me−C(7)) = 6.8, Me−C(7)); 0.91 (*t*, ^3J = 7.3, 2 *Me*CH_2). ^{13}C-NMR

(100.6 MHz, CD_3OD): 175.2 (*s*, C(4)); 87.6 (*d*, C(14)); 84.7 (*d*, C(2)); 83.2, 75.8, 74.1 (3*s*, C(1), C(9), C(13)); 80.7 (*d*, C(12)); 78.7 (*d*, C(6)); 78.1 (*d*, C(8)); 46.0 (*t*, C(10)); 42.3 (*d*, C(5)); 38.1 (*d*, C(7)); 31.8 (*d*, C(11)); 30.6 (*q*, *Me*–C(1)); 24.2 (*q*, *Me*–C(9)); 23.7 (*q*, *Me*–C(13)); 21.7 (*t*, Me*C*H_2); 16.3 (*q*, *Me*–C(11)); 15.4 (*q*, *Me*–C(5)); 11.2 (*q*, *Me*–C(7)); 7.8 (*q*, *Me*CH_2). CI-MS (NH_3): 419 (58, $[M+H]^+$), 401 (61, $[M-H_2O+1]^+$), 383 (95), 360 (16), 294 (29), 242 (23), 167 (24), 125 (66), 98 (29), 83 (100). Anal. calc. for $C_{21}H_{38}O_8$ (418.52): C 60.27, H 9.15; found: C 60.40, H 9.17.

*(1*R*,2*R*,7*S*,8*R*,9*R*,11*R*,12*R*,13*S*,14*S*)-2-Ethyl-8,9,13,14-tetrahydroxy-1,5,9,7,11,13-hexamethyl-3,15-dioxabicyclo[10.2.1]pentadec-5-ene-4-one* ((–)-**30**). HF (40% in H_2O, 60 µl) was added dropwise to a cooled (0°) soln. of (+)-**27** (18 mg, 28.53 µmol) in MeCN (1 ml). After 15 min, the mixture was allowed to react at 20° for 1.5 h. Sat. aq. $NaHCO_3$ soln. (6 ml) was added until pH 8 was reached. Then, the mixture was re-acidified with 1M aq. HCl soln. (5 ml). The mixture was extracted with AcOEt (4 × 12 ml), and the combined org. extracts were dried ($MgSO_4$) and concentrated *in vacuo*. FC (CH_2Cl_2/MeOH 10:1) afforded the intermediate **29** (white foam, 7 mg, 51%), which was directly engaged in the macrolactonization. The *seco*-acid **29** (7 mg, 15 µmol) was dissolved in i-Pr_2NH (0.4M soln. in PhH, 1.1 ml, 0.440 mmol, 30 equiv.) and a soln. of 2,4,6-trichlorobenzoyl chloride (0.4M in PhH, 734 µl, 0.294 mmol, 20 equiv.) was added dropwise. The mixture was stirred at 20° for 3 h. The soln. was diluted with benzene (8.5 ml) and added through a syringe pump over 23 h to a refluxing soln. of DMAP (90 mg) in benzene (15 ml). The mixture was cooled to 20°, and sat. aq. $NaHCO_3$ soln. (20 ml) was added to dissolve the white precipitate. The layers were separated, and the aq. layer was extracted with AcOEt (3 × 20 ml). The combined org. extracts were washed with brine (15 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was filtered over a pad of SiO_2 (AcOE/petroleum ether 1:3) and concentrated *in vacuo* to give a pale yellow oil, which was immediately exposed to 80% aq. CF_3CO_2H (1 ml) for 1 h at r.t. The solvent was evaporated, and the residue was purified by FC (MeCN/25% aq. NH_3 7:1) to give 4 mg (68%, 2 steps) of (–)-**30**. Colorless oil. $[\alpha]_{589}^{20}=-2$, $[\alpha]_{577}^{20}=-15$, $[\alpha]_{546}^{20}=-34$, $[\alpha]_{435}^{20}=-79$, $[\alpha]_{405}^{20}=-103$ ($c=0.1$, MeOH). UV (MeCN): 273 (13330), 214 (3460). IR (film): 3055, 2985, 2870, 1690, 1585, 1555, 1425, 1405, 1290, 1200, 1115, 1025, 930, 815, 755, 695, 665. ^{1}H-NMR (400 MHz, CD_3OD): 685 (*dd*, ^3J(H–C(6,7)) = 6.5, ^4J(H–C(6,8)) = 1.3, H–C(6)); 4.32 (br. *d*, ^3J(H–C(7,8)) = 3.0, H–C(8)); 3.46 (*s*, H–C(14)); 3.27 (*dd*, ^3J = 10.4, 1.7, H–C(2)); 3.22 (*d*, ^3J(H–C(11,12)) = 9.5, H–C(12)); 2.68–2.66 (*m*, H–C(7)); 2.08–1.96 (*m*, H–C(11)); 1.91 (br. *s*, Me–C(5)); 1.65–1.60 (*m*, H–C(10), 1 H, MeCH_2); 1.41–1.35 (*m*, H–C(10), 1 H, MeCH_2); 1.29 (*s*, *Me*–C(9), –C(13)); 1.14 (*d*, ^3J(H–C(7),Me–C(7)) = 7.0, Me–C(7)); 1.12 (*d*, ^3J(H–C(11),Me–C(11)) = 6.3, Me–C(11)); 1.11 (*s*, Me–C(5)); 1.05 (*t*, ^3J = 7.3, *Me*CH_2). ^{13}C-NMR (100.6 MHz, CD_3OD): 171.6 (*s*, C(4)); 151.6 (*d*, C(6)); 129.5 (*s*, C(5)); 89.2 (*d*, C(14)); 88.4 (*d*, C(12)); 83.6 (*d*, C(2)); 82.6 (*d*, C(8)); 88.8, 80.0, 77.0 (3*s*, C(1), C(9), C(13)); 49.6 (*t*, C(10)); 34.9 (*d*, C(7)); 33.2 (*d*, C(11)); 27.9, 26.0, 24.7 (3*q*, *Me*–C(9), *Me*–C(13), *Me*–C(1)); 21.3 (*t*, Me*C*H_2); 19.3 (*q*, *Me*–C(5)); 16.9 (*q*, *Me*–C(7)); 15.8 (*q*, Me–C(11)); 14.2 (*q*, *Me*CH_2). CI-MS (NH_3): 401 (100, $[M+H]^+$, 294 (7), 223 (10), 123 (15). Anal. calc. for $C_{21}H_{36}O_7$ (400.51): C 62.98, H 9.06; found: C 62.96, H 9.08.

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