52. Synthesis of (±)-Pyrenolide B

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In the synthesis of the title compound **12**, the important intermediate **7** was obtained in good yield from the easily available ethyl 5,5-ethylenedioxy-2-oxocyclohexane-1-carboxylate (**1**) *via* ring enlargement of the bicyclic enol ether **5** (*Scheme*). Its reduction ($NaBH_4$, $CeCl_3$ in EtOH) and subsequent protection with (*t*-Bu)Me_2Si resulted in the highly functionalized ten-membered lactone **9**. Introduction of the (*Z*)-configurated double bond, followed by deprotection and elimination of H_2O, gave (±)-pyrenolide B (**12**) in 16% overall yield.

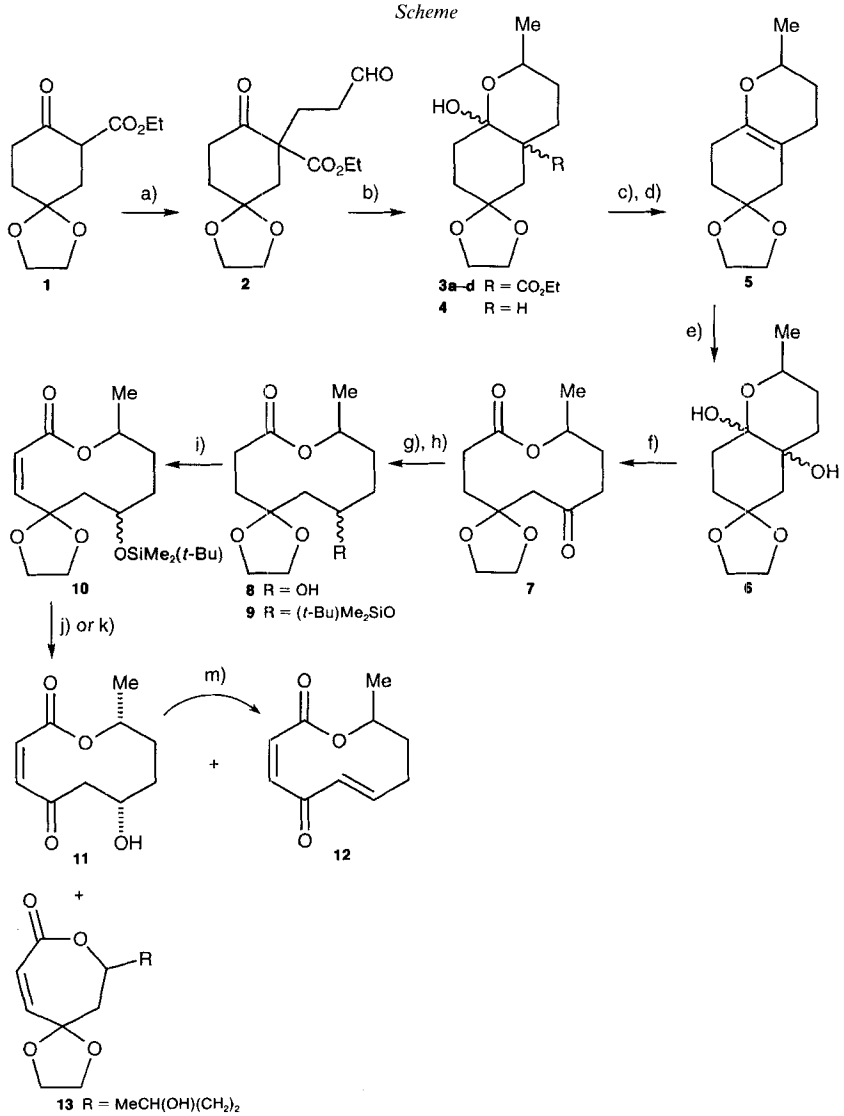
1. Introduction. – In the course of our studies on the use of α-activated cycloalkanones as starting materials for ring-enlargement reactions, we have acquired an intimate insight into the mechanistics and the scope of such transformations and have prepared a number of medium- and large-size cyclic ketones, lactones, and lactams. Some of these compounds have successfully served as precursors for natural products [1] such as the structurally simple ketones and lactones muscone [2], 15-pentadecanolide [3], (–)-(*R*)-phoracantholide I [4], (+)-(*S*)-15-hexadecanolide [5], dihydrorecifeiolide [6], and the lactone antibiotic A 26771 B [7], as well as the macrocyclic compound muscopyridine [8], and the spermidine alkaloids inandenin-10-ol, inandenin-10-one, and oncinotine [9].

In continuing our investigation of the ring-enlargement procedure [6], using the oxidative cleavage of the bridge of bicyclic enol ethers to acquire the macrocycle [10] [11], we designed a straightforward synthesis of (±)-pyrenolide B (**12**), starting from the readily available 2-oxocyclohexanecarboxylate derivative **1** [12] (*Scheme*). (–)-Pyrenolide B was isolated by *Nukina et al.* [13] from *Pyrenophora teres* (IFO 7508), a phytopathogenic fungus in 1980. The general interest in morphogenic substances lies in their phytotoxic properties. Pyrenolide B (**12**), for example, inhibits the growth of rice seedlings. So far, the compound has been synthesized twice, both syntheses being based on ring-enlargement reactions [14] [15].

2. Results and Discussion. – The ring-enlargement precursor **5**, required for the construction of (±)-pyrenolide B (**12**), was synthesized from **1** using a procedure similar to that described earlier for the preparation of (±)-dihydrorecifeiolide I [6]. The carboxylate **1** was initially reacted with acrylaldehyde to produce the *Michael*-addition product **2** (*Scheme*). Bu_4NF was found to be a most effective catalyst for this transformation. When the reaction was performed in the presence of 2% Bu_4NF at –70°, the desired product was obtained in almost quantitative yield. Subsequent treatment of the aldehyde **2** with excess of $Me_2Ti(i\text{-}PrO)_2$ gave rise to a mixture of the four cyclic hemiacetals **3a–d** (80%

[1]) Part of the planned Ph. D. thesis of *A. M.*

Scheme



a) 1. Acrylaldehyde, Bu_4NF (kat.), THF; 2. 2% aq. AcOH. b) $TiMe_2(i\text{-}PrO)_2$, THF. c) 0.5M aq. KOH soln., EtOH. d) Camphorsulfonic acid, Δ, toluene. e) Monoperoxyphthalic acid, 'wet' Et_2O. f) $Pb(OAc)_4$, benzene. g) $NaBH_4$, 0.4M $CeCl_3 \cdot 7\ H_2O$ in EtOH, THF. h) 2,6-Dimethylpyridine, (*t*-Bu)Me_2Si triflate, CH_2Cl_2, −50°. i) 1. LDA; 2. PhSeBr; 3. 0.1M aq. HCl soln., THF; 4. O_3, $(i\text{-}Pr)_2NH$, CH_2Cl_2. j) PPTS, 'wet' acetone. k) CF_3COOH, CH_2Cl_2. m) *Burgess* reagent, MeCN.

yield) wherefrom the major isomer **3a** (2*R**,4a*R**,8a*S**) was easily separated by flash chromatography and examined by single-crystal X-ray analysis. Heating the mixture of all four isomers **3a–d** with KOH in an aqueous EtOH solution delivered quantitatively deethoxycarbonylation products of the constitution **4**, which were dehydrated to the

desired bicyclic enol ether **5** in 70% yield by refluxing the compounds in the presence of camphorsulfonic acid in toluene.

The oxidative cleavage of the bridge in **5** to obtain finally the oxo-lactone **7** was performed using a two-step procedure as originally described by *Borowitz et al.* [11]. The reaction of **5** with 'wet' monoperoxyphthalic acid leading to diol **6** (73%) was followed by the oxidation of this intermediate with $Pb(OAc)_4$ to afford quantitatively the ring-enlarged product **7**. The direct conversion of compound **5** into **7** by oxidation with *meta*-chloroperbenzoic acid, permanganate, pyridinium chlorochromate, or by ozonolysis was not advantageous, giving rise to only 44% of the desired product at its best.

The important intermediate **7** was fully characterized by IR, ^{1}H-, ^{13}C-NMR, and mass spectra, as well as elemental analysis. The molecular formula was supported by the CI-MS with the sole signals at m/z 260 (100 rel. %) and 243 (42 rel. %) for the $[M + NH_4]^+$ and the $[M + H]^+$ ions, respectively. Characteristic for the two CO groups in the structure of **7** were found the COO and CO stretching vibrations at 1720 and 1675 cm^{-1} in the IR and the signals for the corresponding C-atoms at 207.4 (ketone) and 171.3 ppm (lactone) in the ^{13}C-NMR spectrum. Additionally, it was possible to assign all proton signals in the ^{1}H-NMR spectrum by means of ^{1}H,^{1}H-NOESY and ^{1}H,^{1}H-COESY experiments [16].

Oxo-lactone **7** was reduced with the *Luche* method [17] – using $NaBH_4$ and $CeCl_3$ in EtOH – to the hydroxy-lactone **8** (86%) which was protected as a (*t*-Bu)Me_2Si ether by treatment with (*t*-Bu)Me_2Si triflate in the presence of 2,6-dimethylpyridine at −50° (97% of **9**). The addition of $CeCl_3$ to $NaBH_4$ in the reduction step was important due to the low reactivity of the ten-membered cyclic oxo-lactone **7**. The use of the highly reactive (*t*-Bu)Me_2Si triflate as the silylating reagent, which reacts at low temperature, was crucial for the protection step to avoid intramolecular translactonization, as it was observed in similar systems under basic conditions. To introduce the double bond in α-position to the lactone C=O group, compound **9** was subsequently α-selenylated and oxidized. After selenoxide elimination, 67% of α,β-unsaturated lactone **10** were obtained. The introduction of the C=C bond proceeded with high (*Z*)-selectivity, which was confirmed on the basis of ^{1}H-NMR data (J_{vic} = 11.7 Hz). This is contrasting the assumption of *Asaoka et al.* [15], who feared that such a C=C bond introduction would deliver the (*E*)-configurated product, and, therefore, introduced the corresponding (*Z*)-configurated C=C bond in protected form early in their preparation of pyrenolide B (**12**).

The synthesis of pyrenolide B (**12**) was completed by deprotection of the masked C=O and OH groups followed by elimination of H_2O (*Scheme*). Treatment of lactone **10** with CF_3COOH in CH_2Cl_2 afforded directly a mixture of the desired product **12** (22%) and the alcohol **11** (52%). The latter compound was transferred separately into the final product **12** in 79% yield (overall 63% from **10**) by the action of the *Burgess* reagent [18]. Heating alternatively precursor **10** with pyridinium *para*-toluene sulfonate (PPTS) in 'wet' acetone at reflux afforded no pyrenolide B (**12**) but solely alcohol **11** (68%) together with ring-contracted product **13** (14%). It is interesting to note that the reaction of the two diastereoisomers of **10** (*cis* and *trans*, ratio *ca.* 4:1) delivered in both reactions the single isomer **11** (the *cis*-product), indicating that the corresponding *trans*-product might be more reactive leading to pyrenolide B (**12**), the translactonization product **13**, or to decomposition under the reaction conditions.

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Experimental Part

1. *General.* All experiments were carried out under N_2. All reagents used were of high commercial quality. Solvents for CC were distilled prior to use. TLC: Silica gel *60*, F_{254} (*Merck*). CC: Silica gel *60* (*Merck*, 0.040–0.063 mm). M.p.: *Mettler FP 5*. The m.p. of mixtures of diastereoisomers are not given. UV: *Hewlett-Packard '8452 A Diode Array'*; in MeOH; λ_{max} in nm ($\log\varepsilon$). IR: *Perkin-Elmer 297*; $\tilde{\nu}$ in cm^{-1} in KBr. ^{1}H-NMR: *Bruker AC 300* (300 MHz); in $CDCl_3$; chemical shifts in ppm as δ values relative to $CDCl_3$ (δ = 7.26 ppm, *J* in Hz); *Bruker AM 400* (400 MHz) for decoupling experiments. ^{13}C-NMR: *Varian XL 200* (50.4 MHz); in $CDCl_3$; internal standard: $CDCl_3$ (δ(C) = 77.0 ppm, *t*, ^1J(C,D) = 31.5 Hz). CI-MS: *Finnigan SSQ 700* or *Finnigan MAT 90*; *m/z* (rel.%); chemical ionisation (CI) with NH_3 as reactant gas. X-Ray analysis: *Rigaku AFC5R*. The X-ray data of the compounds **3a**, **11**, and **12** are deposited at the *Cambridge Crystallographic Data Centre*.

2. *Ethyl 5,5-(Ethylenedioxy)-1-(3-oxopropyl)-2-oxocyclohexane-1-carboxylate* (**2**). To a soln. of 0.96 ml of Bu_4NF (1M in THF) and 11.0 g (48.2 mmol) of *ethyl 5,5-(ethylenedioxy)-2-oxocyclohexane-1-carboxylate* (**1**) in 100 ml of THF at $-70°$ were added slowly 3.8 ml (57.8 mmol) of acrylaldehyde. It was allowed slowly to warm up to 23°, and stirring was continued for 12 h. The mixture was quenched with 2.4 ml of 2% aq. AcOH soln. and filtered through a plug of SiO_2 with Et_2O/hexane 2:1. Evaporation of the solvent and drying at 10^{-2} mbar gave 14.11 g of crude **2** as a viscous oil. Except of a small amount for the spectroscopic data, the product was used without further purification in the next step. M.p. 44.2–47.1° (Et_2O/hexane). IR: 2735 (CHO), 1725 (CO_2), 1715 (CO, CHO), 1450, 1365, 1300, 1255. ^{1}H-NMR: 9.73 (*s*, CHO); 4.25, 4.17 (*AB* of *ABX*$_3$, J_{AB} = 10.8, $J_{AX} = J_{BX}$ = 7.1, MeC*H*$_2$); 4.06–3.93 (*m*, OCH_2CH_2O); 3.12–3.00 (*m*, 1 H); 2.77–2.66 (*m*, 1 H); 2.60 (*dt*, *J* = 13.9, 1.6, 1 H–C(6)); 2.47 (*dt*, *J* = 14.5, 4.2, 1 H); 2.36–2.24 (*m*, 1 H); 2.14–1.97 (*m*, 3 H); 1.90–1.80 (*m*, 1 H); 1.76 (*d*, *J* = 13.9, 1 H–C(6)); 1.29 (*t*, X_3 of *ABX*$_3$, *J* = 7.1, Me). ^{13}C-NMR: 206.9 (*s*, C(2)); 200.9 (*d*, CHO); 171.9 (*s*, CO_2); 106.5 (*s*, C(5)); 65.0, 64.3 (2*t*, OCH_2CH_2O); 61.5 (*t*, MeCH_2O); 57.2 (*s*, C(1)); 42.4, 39.5, 37.7, 35.3, 27.4 (5*t*, 5 C); 13.9 (*q*, Me). CI-MS: 302 (100, $[M + NH_4]^+$), 285 (47, $[M + 1]^+$), 267 (39, $[M + 1 - H_2O]^+$). Anal. calc. for $C_{14}H_{20}O_6$ (284.31): C 59.14, H 7.09; found: C 59.41, H 7.18.

3. *Ethyl 3,4,4a,5,6,7,8,8a-Octahydro-8a-hydroxy-2-methylspiro[2H-[1]benzopyran-6,2'-dioxolane]-4a-carboxylate* (**3a–d**). To an ice-cooled soln. of 1.87 ml (6.33 mmol) of (i-PrO)$_4$Ti in 20 ml of THF were added dropwise 0.68 ml (6.33 mmol) of $TiCl_4$. The soln. turned immediately yellow. After stirring for 1 h at 23°, the mixture was cooled to –78°, and 15.9 ml (25.3 mmol) of MeLi (*ca.* 1.6M in Et_2O) were added slowly over 30 min. The clear yellow soln. turned meanwhile to an orange suspension. The temp. was raised to $-30°$ and the suspension cleared up to a deep red soln. Compound **2** (1.80 g, 6.33 mmol) in 10 ml of THF was added to the mixture, and, after 3 h stirring at $-10°$, 9 ml of 20% aq. KF soln. were added. Instantly, a fine colorless precipitate was formed, which was filtered off on a column with $MgSO_4/SiO_2/MgSO_4$ with Et_2O as eluent. Evaporation of the solvent yielded 2.12 g of a crude oily product which was sufficiently pure for further transformation. Purification of a sample by CC (70 g SiO_2, Et_2O/hexane 13:6) afforded **3a** and **3b–d**.

Data of **3a**: M.p. 92.1–94.3° (Et_2O/hexane). IR: 3460 (OH), 1695 (CO_2), 1450, 1390, 1310. ^{1}H-NMR: 4.90 (*s*, OH); 4.28–4.09 (*m*, H–C(2), MeCH_2O); 4.03–3.77 (*m*, OCH_2CH_2O); 2.26 (*d*, *J* = 13.6, 1 H–C(5)); 2.21–1.93 (*m*, 4 H); 1.84–1.78 (*m*, 1 H); 1.62–1.46 (*m*, 4 H); 1.30 (*t*, *J* = 7.1, *Me*CH$_2$O); 1.17 (*d*, *J* = 6.2, Me). ^{13}C-NMR: 178.4 (*s*, CO_2); 108.5 (*s*, C(6)); 95.0 (*s*, C(8a)); 65.1 (*d*, C(2)); 64.5, 64.2 (2*t*, OCH_2CH_2O); 60.8 (*t*, MeCH_2O); 47.4 (*s*, C(4a)); 36.6, 35.1, 32.3, 29.0, 27.6 (5*t*, 5 C); 21.6 (*q*, Me); 14.0 (*q*, *Me*CH$_2$O). CI-MS: 300 (12, $[M + NH_4 - H_2O]^+$), 283 (100, $[M + 1 - H_2O]^+$). Anal. calc. for $C_{15}H_{24}O_6$ (300.35): C 59.98, H 8.05; found: C 60.20, H 8.10.

Data of **3b–d** (ratio *ca.* 1:1:2; determined by integration of the Me groups in the ^{1}H-NMR spectrum): IR (film): 3450 (OH), 1735, 1715 (CO_2), 1450, 1370, 1300. ^{1}H-NMR: 4.83 (*s*, OH); 4.21–4.01 (*m*, H–C(2), MeCH_2O); 3.97–3.72 (*m*, OCH_2CH_2O); 3.00–1.38 (*m*, 20 H); 1.29–1.19 (*m*, *Me*CH$_2$O); 1.14, 1.10, 1.09 (3*d*, *J* = 6.2, Me). ^{13}C-NMR: 176.6, 173.5, 172.2 (3*s*, CO_2); 108.1, 107.7, 106.6 (3*s*, C(6)); 97.6, 95.6, 94.1 (3*s*, C(8a)); 69.2, 67.9, 66.3 (3*d*, C(2)); 64.9, 64.8, 64.5, 64.2, 64.1, 63.8 (6*t*, OCH_2CH_2O); 61.3, 61.1, 59.9, 57.8 (4*t*, MeCH_2O); 48.8, 48.6 (2*s*, C(4a)); 41.8, 40.6, 40.0, 37.8, 35.2, 33.9, 33.1, 32.6, 31.5, 31.2, 30.9, 29.9, 29.2, 28.7, 28.1 (15*t*, 15 C); 23.3, 22.1, 21.7 (3*q*, Me); 14.1, 13.9 (2*q*, *Me*CH$_2$O). CI-MS: 318 (12, $[M + NH_4]^+$), 301 (4, $[M + 1]^+$), 300 (16, $[M + NH_4 - H_2O]^+$), 283 (100, $[M + 1 - H_2O]^+$). Anal. calc. for $C_{15}H_{24}O_6$ (300.35): C 59.98, H 8.05; found: C 60.25, H 7.86.

4. *3,4,4a,5,6,7,8,8a-Octahydro-2-methylspiro[2H-[1]benzopyran-6,2'-dioxolane]-8a-ol* (**4**). To a soln. of 100 mg (0.33 mmol) of **3a–d** in 1.5 ml of EtOH were added 1.3 ml of 0.5M aq. KOH soln., and the mixture was heated 1.5 h at reflux. The dark yellow soln. was poured on brine and extracted with Et_2O. The combined org. layers were washed with brine, dried ($MgSO_4$), and evaporated: 72 mg (95%) of a yellow oil which was used in the next step without further purification. To obtain the spectroscopic data, a small amount was purified by bulb-to-bulb distillation (air bath: 80–100°/10^{-3} mbar). IR: 3440 (OH), 1450, 1365, 1300, 1250. ^{1}H-NMR (CD_3OD), (2

diastereoisomers *ca.* 4:1): 4.13–4.06 (*m*, H–C(2)); 3.95–3.87 (*m*, OCH_2CH_2O); 2.27–1.18 (*m*, 11 H); 1.11, 1.09 (2*d*, $J = 6.2$, Me). ^{13}C-NMR (CD_3OD): 110.1 (*s*, C(6)); 96.7 (*s*, C(8a)); 67.2, 67.0 (2*d*, C(2)); 65.3, 65.2 (2*t*, OCH_2CH_2O); 41.1 (*d*, C(4a)); 39.2, 37.9, 36.8, 36.6 (4*t*, 4 C); 36.3 (*d*, C(4a)); 34.8, 33.0, 32.6, 28.2, 26.1, 24.6 (6*t*, 6 C); 22.3, 22.1 (2*q*, Me). CI-MS: 246 (3, $[M + NH_4]^+$), 229 (1, $[M + 1]^+$), 228 (6, $[M + NH_4 - H_2O]^+$), 211 (100, $[M + 1 - H_2O]^+$). Anal. calc. for $C_{12}H_{20}O_4$ (228.29): C 63.14, H 8.83; found: C 63.39, H 8.66.

5. *3,4,5,6,7,8-Hexahydro-2-methylspiro[2H-[1]benzopyran-6,2′-dioxolane]* (**5**). In a flask fitted with a *Dean-Stark* water trap, 2.5 g (11.0 mmol) of **4** and 51 mg (0.2 mmol) of camphorsulfonic acid were dissolved in 100 ml of toluene and refluxed for 30 min. The soln. was evaporated, the yellow residue dissolved in Et_2O, and washed (3 ×) with a sat. aq. $NaHCO_3$ soln., H_2O, and brine. Drying (Na_2SO_4) and evaporation yielded 2.42 g of a yellow liquid. After CC (75 g SiO_2, hexane/Et_2O 1:1), 1.24 g (54%) of **5** and 870 mg (35%) of **4** were isolated. The reaction was repeated with the recovered **4** but chromatographed on basic Al_2O_3 (*Woelm*, activity I) instead of SiO_2 resulting in an additional 358 mg of **5**. Total yield of **5**: 1.6 g (70%). IR (film): 1700 (C=C, enol ether), 1450, 1380, 1370. ^{1}H-NMR: 4.10–3.89 (*m*, OCH_2CH_2O); 3.87–3.77 (*m*, H–C(2)); 2.24–2.06 (*m*, 4 H); 2.02–1.84 (*m*, 1 H); 1.77–1.67 (*m*, 4 H); 1.58–1.42 (*m*, 1 H); 1.19 (*d*, $J = 6.3$, Me). ^{13}C-NMR: 145.6 (*s*, C(8a)); 108.2 (*s*, C(6)); 101.0 (*s*, C(4a)); 71.2 (*d*, C(2)); 64.4, 64.3 (2*t*, OCH_2CH_2O); 38.7, 31.1, 29.6, 26.2, 25.4 (5*t*, 5 C); 21.2 (*q*, Me). CI-MS: 211 ($[M + 1]^+$). Anal. calc. for $C_{12}H_{18}O_3$ (210.27): C 68.55, H 8.63; found: C 68.84, H 8.78.

6. *3,4,4a,5,6,7,8,8a-Octahydro-2-methylspiro[2H-[1]benzopyran-6,2′-dioxolane]-4a,8a-diol* (**6**). To a soln. of 4.37 g (20.8 mmol) of **5** in 40 ml of Et_2O were added 100 ml (27 mmol) of a 0.27M monoperoxyphthalic acid soln. in 'wet' Et_2O (freshly prepared). Vigorous stirring was continued for 26 h at 23°. The precipitated phthalic acid was filtered off, the org. layer washed with sat. aq. $NaHCO_3$ soln., and the aq. layer rewashed with CH_2Cl_2. After combining and drying (Na_2SO_4) of all org. extracts, followed by evaporation, 5.08 g of a yellow oil were obtained. The crude product was purified by CC (150 g SiO_2, Et_2O/hexane 10:1): 3.70 g (73%) of **6**, colorless oil, which crystallized upon standing at 4°. IR: 3480 (OH), 1435, 1380, 1370. ^{1}H-NMR (2 diastereoisomers *ca.* 3:1): 4.22, 3.11 (2*s*, OH, with D_2O exchanged); 4.21–4.09 (*m*, H–C(2)); 4.05–3.90 (*m*, OCH_2CH_2O); 2.37 (*d*, $J = 14.0$, H–C(5)); 2.27–1.33 (*m*, 10 H); 1.19, 1.14 (2*d*, $J = 6.3$, Me). ^{13}C-NMR: 109.4, 109.3 (2*s*, C(6)); 96.9, 96.1 (2*s*, C(8a)); 71.5, 71.4 (2*s*, C(4a)); 66.3, 65.4 (2*d*, C(2)); 64.5, 64.4, 64.2, 64.1 (4*t*, OCH_2CH_2O); 41.5, 39.4, 33.4, 32.0, 31.8, 31.6, 31.5, 31.0, 30.8, 28.0 (10*t*, 10 C); 21.5, 21.3 (2*q*, Me). CI-MS: 244 (31, $[M + NH_4 - H_2O]^+$), 227 (100, $[M + 1 - H_2O]^+$), 209 (10, $[M + 1 - 2\,H_2O]^+$). Anal. calc. for $C_{12}H_{20}O_5$ (244.29): C 59.00, H 8.25; found: C 58.87, H 8.11.

7. *10-Methyl-1,4,9-trioxaspiro[4.9]tetradecane-8,13-dione* (**7**). To a soln. of 3.48 g (14.25 mmol) of **6** in 75 ml of benzene were added 9.48 g (31.37 mmol) of $Pb(OAc)_4$. After vigorous stirring of the white suspension at 23° for 2 h, 15 ml of EtOH were poured into the soln., and, after another 15 min, the excess $Pb(OAc)_4$ was filtered off and washed with benzene. The yellow filtrate was evaporated to give a sticky residue which was purified by CC (100 g SiO_2, Et_2O/hexane 5:1) yielding 3.44 g (99.5%) of **7**. M.p. 106.8–108.2° (Et_2O). IR: 1720 (CO_2), 1675 (CO), 1440, 1415, 1355, 1265, 1230. ^{1}H-NMR: 4.99–4.88 (*m*, H–C(10)); 4.00–3.87 (*m*, OCH_2CH_2O); 3.85–3.75 (*m*, OCH_2CH_2O); 2.85 (*d*, $J = 17.0$, H–C(14)); 2.49 (*dd*, $J = 17.0$, 1.3, H–C(14)); 2.45–2.34 (*m*, 2 H–C(7), H–C(6), H–C(12)); 2.23–2.08 (*m*, H–C(12), H–C(11)); 1.89 (*pseudo ddt*, $J = 14.3$, 7.3, 2.9, H–C(11)); 1.64–1.53 (*m*, H–C(6)); 1.19 (*d*, $J = 6.3$, Me). *Decoupling experiments:* Irrad. at 4.99–4.88: 1.89 (*ddd*, $J = 14.3$, 7.3, 2.9), 1.19 (*s*); irrad. at: 2.85: 2.49 (*d*, $J = 1.4$); irrad. at: 1.19: 4.93 (*dd*, $J = 10.0$, 2.9). ^{13}C-NMR: 207.4 (*s*, C(13)); 171.3 (*s*, C(8)); 107.8 (*s*, C(5)); 71.7 (*d*, C(10)); 64.7, 63.8 (2*t*, OCH_2CH_2O); 49.6, 39.9, 33.6, 30.5, 29.1 (5*t*, 5 C); 19.4 (*q*, Me). CI-MS: 260 (100, $[M + NH_4]^+$), 243 (42, $[M + 1]^+$). Anal. calc. for $C_{12}H_{18}O_5$ (242.27): C 59.49, H 7.49; found: C 59.78, H 7.68.

8. *13-Hydroxy-10-methyl-1,4,9-trioxaspiro[4.9]tetradecan-8-one* (**8**). To 1.77 g (7.32 mmol) of **7** in 40 ml of 0.4M ethanolic $CeCl_3 \cdot 7\,H_2O$ soln., 0.55 g (14.64 mmol) of $NaBH_4$ were added in small portions. After 6 h, the soln. was diluted with H_2O and neutralized with 0.1M aq. HCl soln. under ice-cooling. The mixture was extracted with CH_2Cl_2 and sat. aq. *Rochelle* salt soln. The combined org. layers were washed with brine, dried (Na_2SO_4), and chromatographed (100 g SiO_2, Et_2O/hexane 6:1): 1.53 g (86%) of **8**. IR: 3530 (OH), 1730 (CO_2), 1445, 1355, 1325. ^{1}H-NMR (2 diastereoisomers *ca.* 5:1): 5.05–5.02 (*m*, 0.2 H–C(10)); 5.02–4.90 (*m*, 0.8 H–C(10)); 4.26–4.16 (*m*, 0.2 H–C(13)); 4.05–3.85 (*m*, OCH_2CH_2O); 3.77–3.68 (*m*, 0.8 H–C(13)); 3.09, 2.96 (2*s*, OH); 2.61 (*d*, $J = 14.9$, H–C(14)); 2.55–1.38 (*m*, 9 H); 1.30, 1.29 (2*d*, $J = 6.5$, Me). *Decoupling experiment:* Irrad. at 5.05–5.02, 5.02–4.90: 1.30, 1.29 (2*s*). ^{13}C-NMR: 173.7 (*s*, C(8)); 112.3 (*s*, C(5)); 73.2, 71.7 (2*d*, C(10)); 68.0, 67.3 (2*d*, C(13)); 64.8, 64.7, 64.5, 64.2 (4*t*, OCH_2CH_2O); 41.1, 40.2, 33.3, 32.8, 31.2, 31.0, 30.9, 30.1 (8*t*, 8 C); 21.5, 18.1 (2*q*, Me). CI-MS: 262 (100, $[M + NH_4]^+$), 245 (21, $[M + 1]^+$), 244 (20, $[M + NH_4 - H_2O]^+$), 227 (25, $[M + 1 - H_2O]^+$), 178 (7), 145 (6). Anal. calc. for $C_{12}H_{20}O_5$ (244.29): C 59.00, H 8.25; found: C 58.74, H 8.33.

9. *13-[(* tert-*Butyl)dimethylsilyloxy]-10-methyl-1,4,9-trioxaspiro[4.9]tetradecan-8-one* (**9**). To a soln. of 2.5 g (10.2 mmol) of **8** and 2.4 ml (20.5 mmol) of 2,6-dimethylpyridine in 50 ml of CH_2Cl_2 at $-50°$ were added 3.5 ml (15.3 mmol) of (*t*-Bu)Me_2Si triflate. The mixture was allowed to warm up to 23° within 1 h, then it was diluted with CH_2Cl_2 and extracted with H_2O and 10 ml of 0.1M aq. HCl soln. After washing with brine and drying (Na_2SO_4), the solvent was removed to yield 4.89 g of a yellowish liquid. CC (100 g SiO_2, hexane/Et_2O 6:1) and removal of the remaining volatile impurities at high vacuum (air bath: 100°/10^{-4} mbar) afforded 3.56 g (97%) of **9**, a colorless slightly viscous oil. IR (film): 1730 (CO_2), 1440, 1355, 1245. ^{1}H-NMR (2 diastereoisomers *ca.* 4:1): 4.98–4.94 (*m*, 0.25 H–C(10)); 4.92–4.84 (*m*, 0.75 H–C(10)); 4.15–4.07 (*m*, 0.25 H–C(13)); 3.94–3.74 (*m*, OCH_2CH_2O): 3.73–3.65 (*m*, 0.75 H–C(13)); 2.48–2.28 (*m*, 3 H); 2.13–1.73 (*m*, 3 H); 1.69–1.42 (*m*, 4 H); 1.24, 1.23 (2*d*, $J = 6.5$, Me); 0.84, 0.82 (2*s*, *t*-Bu); 0.06, 0.05, 0.02, 0.00 (4*s*, Me_2Si). *Decoupling experiment:* Irrad. at 4.98–4.84: 1.24, 1.23 (2*s*). ^{13}C-NMR: 173.6, 171.6 (2*s*, C(8)); 110.8, 110.4 (2*s*, C(5)); 72.6, 71.1 (2*d*, C(10)); 68.7, 68.0 (2*d*, C(13)); 64.6, 64.3, 63.9, 63.7 (4*t*, OCH_2CH_2O); 41.2, 40.3, 35.7, 34.2, 33.4, 31.3, 30.9, 30.8, 29.5 (9*t*, 9 C); 25.9, 25.8 (2*q*, Me_3C); 21.1, 18.0 (2*q*, Me); 17.9 (*s*, Me_3C); −4.3, −4.4, −4.6, −4.7 (4*q*, Me_2Si). CI-MS: 376 (31, $[M + NH_4]^+$), 359 (100, $[M + 1]^+$), 261 (5, $[M + NH_4 - (t\text{-Bu})Me_2Si]^+$), 244 (52, $[M + 1 - (t\text{-Bu})Me_2Si]^+$), 227 (59, $[M + 1 - (t\text{-Bu})Me_2SiOH]^+$). Anal. calc. for $C_{18}H_{34}O_5Si$ (358.55): C 60.30, H 9.56; found: C 60.56, H 9.34.

10. *13-[(* tert-*Butyl)dimethylsilyloxy]-10-methyl-1,4,9-trioxaspiro[4.9]tetradec-6-en-8-one* (**10**). To a soln. of 9.48 mmol of LiN(i-Pr)$_2$ (freshly prepared from 1.39 ml (9.83 mmol) of (i-Pr)$_2$NH and 7.07 ml (9.48 mmol) of 1.34M BuLi in hexane) in 70 ml of THF at $-78°$, 2.52 g (7.02 mmol) of **9** in 20 ml THF were added over 20 min. After 2 h, it was cooled to −100°, and 1.82 g (7.73 mmol) of PhSeBr and 0.85 ml (7.02 mmol) of 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one in 20 ml of THF were added in one portion. The yellow soln. was stirred for another 2 h, while it was warmed up to 23°. It was evaporated, the residue treated with 0.1M aq. HCl soln., and extracted with Et_2O/pentane 1:1. The org. layers were washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated to give 3.67 g of a crude yellow oil. CC (180 g SiO_2, hexane/Et_2O 15:1) afforded 3.24 g (90%) of the phenylselenylated compound as a yellow oil. Subsequently, 744 mg (1.45 mmol) of the latter product were ozonized at $-78°$ in 40 ml of CH_2Cl_2, followed by addition of 0.48 ml (3.37 mmol) of (i-Pr)$_2$NH. The cooling bath was removed and the temp. raised to 23°, whereby the color of the soln. turned to yellow. Washing with 0.1M aq. HCl soln., sat. aq. $NaHCO_3$ soln., and brine, drying (Na_2SO_4), and CC (20 g SiO_2, hexane/Et_2O 15:1) afforded 383 mg (74%) of **10** as a mixture of diastereoisomers (ratio *ca.* 4:1). The pure major diastereoisomer was obtained by repetitive CC and was used for the spectroscopic data. M.p. 50.7–53.4°. UV: 201 (3.8). IR: 1730 (CO_2), 1620 (C=C), 1470, 1460, 1440, 1375. ^{1}H-NMR: 6.04, 5.80 (*AB*, $J = 11.7$, H–C(6), H–C(7)); 4.74–4.65 (*m*, H–C(10)); 3.93–3.69 (*m*, OCH_2CH_2O, H–C(13)); 2.68 (*dd*, $J = 14.6$, 10.7, 1 H–C(14)); 2.11–1.81 (*m*, 1 H–C(14), another 3 H); 1.56–1.44 (*m*, 1 H); 1.27 (*d*, $J = 6.2$, Me); 0.83 (*s*, *t*-Bu); 0.01, 0.00 (2*s*, Me_2Si). ^{13}C-NMR (400 MHz): 166.9 (*s*, C(8)); 144.1 (*d*, C(6)); 124.3 (*d*, C(7)); 107.7 (*s*, C(5)); 74.5 (*d*, C(10)); 68.3 (*d*, C(13)); 64.2, 63.6 (2*t*, OCH_2CH_2O); 42.9, 33.9, 29.2 (3*t*, 3 C); 25.8 (*q*, Me_3C); 20.8 (*q*, Me); 18.0 (*s*, Me_3C); −4.8 (*q*, Me_2Si). CI-MS: 374 (29, $[M + NH_4]^+$), 357 (100, $[M + 1]^+$), 242 (63, $[M + 1 - (t\text{-Bu})Me_2Si]^+$), 225 (35, $[M + 1 - (t\text{-Bu})Me_2SiOH]^+$), 180 (14), 159 (7), 102 (47). Anal. calc. for $C_{18}H_{32}O_5Si$ (356.53): C 60.64, H 9.05; found: C 60.54, H 9.09.

11. *7,8,9,10-Tetrahydro-7-hydroxy-10-methyl-2*H*-oxecine-2,5(6*H*)-dione (***11***) and 7-(3-Hydroxybutyl)-1,4,8-trioxaspiro[4.6]undec-10-en-9-one* (**13**). In a flask with 150 mg (0.42 mmol) of **10** dissolved in 5 ml of 'wet' acetone 35.2 mg (0.14 mmol) of PPTS were added. The mixture was refluxed for 10 h, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2, washed with sat. aq. $NaHCO_3$ soln. and brine, and dried (Na_2SO_4). After removal of the solvent *in vacuo*, the remaining 84 mg of crude product were purified by CC (4 g SiO_2, Et_2O/hexane 6:1): 57 mg (68%) of **11** and 14 mg (14%) of **13**.

Data of **11**: M.p. 98.3–101.1° (Et_2O/hexane). UV: 202 (4.0). IR: 3490 (OH), 1715 (CO_2), 1670 (CO), 1610 (C=C), 1415, 1365, 1325. ^{1}H-NMR: 6.44, 6.02 (*AB*, $J = 12.0$, H–C(3), H–C(4)); 5.20–5.14 (*m*, H–C(10)); 3.78–3.50 (br. *m*, H–C(7), OH); 2.96 (*dd*, $J = 17.4$, 2.15, 1 H–C(6)); 2.64 (*dd*, $J = 17.4$, 4.7, 1 H–C(6)); 1.95–1.88 (*m*, 2 H); 1.71–1.61 (*m*, 1 H); 1.54–1.46 (*m*, 1 H); 1.21 (*d*, $J = 6.5$, Me). *Decoupling experiment:* Irrad. at 5.20–5.14: 1.21 (*s*). ^{13}C-NMR: 206.2 (*s*, C(5)); 162.8 (*s*, C(2)); 142.2 (*d*, C(4)); 125.6 (*d*, C(3)); 71.3, 71.2 (2*d*, C(10), C(7)); 45.1 (*t*, C(6)); 28.6, 28.0 (2*t*, C(8), C(9)); 19.3 (*q*, Me). CI-MS: 216 (100, $[M + NH_4]^+$), 199 (11, $[M + 1]^+$). Anal. calc. for $C_{10}H_{14}O_4$ (198.22): C 60.59, H 7.12; found: C 60.30, H 7.34.

Data of **13**: UV: 203 (4.0). IR ($CHCl_3$): 3610 (OH), 1700 (CO_2), 1630 (C=C), 1445, 1390. ^{1}H-NMR: 6.03 (*dd*, $J = 12.4$, 1.7, H–C(11)); 5.92 (*d*, $J = 12.3$, H–C(10)); 4.47–4.39 (*m*, H–C(7)); 4.01–3.86 (*m*, OCH_2CH_2O); 3.81–3.73 (*m*, H–C(3′)); 2.27 (*dd*, $J = 15.4$, 8.9, H–C(6)); 2.08 (br. *d*, $J = 15.5$, H–C(6)); 1.88–1.22 (*m*, 5 H); 1.15 (*d*, $J = 6.3$, Me). *Decoupling experiment:* Irrad. at 4.47–4.39: 1.15 (*d*). ^{13}C-NMR: 169.0 (*s*, C(9)); 140.8 (*d*, C(11)); 121.5 (*d*, C(10)); 106.1 (*s*, C(5)); 75.2 (*d*, C(7)); 67.3 (*d*, C(3′)); 65.5, 64.7 (2*t*, OCH_2CH_2O); 43.7 (*t*, C(6)); 34.1, 31.2

(2*t*, 2 C); 23.6 (*q*, Me). CI-MS: 260 (100, $[M + NH_4]^+$), 243 (21, $[M + 1]^+$). Anal. calc. for $C_{12}H_{18}O_5$ (242.27): C 59.49, H 7.49; found: C 59.54, H 7.29.

12. *(±)-9,10-Dihydro-10-methyl-2*H*-oxecine-2,5(8*H*)-dione* ((±)-*Pyrenolide B*, **12**). *Method A:* To a soln. of 24 mg (0.12 mmol) of **11** in 1 ml of MeCN were added 34 mg (0.14 mmol) of $MeO_2C\bar{N}SO_2\dot{N}Et_3$ (*Burgess* reagent) dissolved in 2 ml of MeCN. The mixture was stirred at 60° for 24 h, poured on H_2O, extracted with Et_2O, dried (Na_2SO_4), and purified by CC (2.5 g SiO_2, hexane/Et_2O 4:1) to afford 17 mg (79%) of (±)-**12**.

Method B: A soln. of 114 mg (0.32 mmol) of **10** and 7 drops of CF_3COOH were stirred for 3 d. The mixture was neutralized with Na_2HPO_4 and filtered through a plug of SiO_2. The crude product was dissolved in hexane/Et_2O 4:1, wherefrom 33 mg (52%) of **11** precipitated. The mother liquor was chromatographed (3 g SiO_2, hexane/Et_2O 4:1) to give 13 mg (22%) of **12**. Compound **11** was also transferred into **12** by the action of the *Burgess* reagent (see above). M.p. 81.4–83.6° ([15]: 84–84.5°). UV: 237 (3.8), 219 (3.8), λ_{min} = 229 (3.7). IR: 1725 (CO_2), 1660 (CO), 1605 (C=C), 1450, 1440, 1375. ^{1}H-NMR: 6.56, 6.03 (*AB*, *J* = 12.5, H–C(3), H–C(4)); 6.50 (*ddd*, *J* = 16.3, 11.4, 3.2, H–C(7)); 5.91 (*dd*, *J* = 16.4, 2.4, H–C(6)); 5.17–5.06 (*m*, H–C(10)); 2.52–2.42 (*m*, 1 H); 2.28–2.14 (*m*, 1 H); 1.97–1.75 (*m*, 2 H); 1.24 (*d*, *J* = 6.4, Me). ^{13}C-NMR: 197.5 (*s*, C(5)); 167.1 (*s*, C(2)); 148.2 (*d*, C(4)); 134.8 (*d*, C(3)); 133.0 (*d*, C(7)); 128.0 (*d*, C(6)); 73.5 (*d*, C(10)); 35.6 (*t*, C(8)); 31.2 (*t*, C(9)); 21.2 (*q*, Me). CI-MS: 198 (100, $[M + NH_4]^+$), 181 (5, $[M + 1]^+$). Anal. calc. for $C_{10}H_{12}O_3$ (180.20): C 66.65, H 6.71; found: C 66.70, H 6.73.

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