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THE SYNTHESIS OF (±)-ISOPTYCHANOLIDE BY APPLICATION OF THE α-ALKYNONE CYCLISATION

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Dedicated to Prof. Hans Wynberg at the occasion of his 65th birthday.

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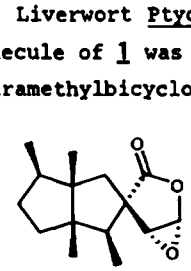
Abstract: The first synthesis of racemic isoptychanolide (2), a stereoisomer of natural ptychanolide (1), which differs in the configuration of the oxirane function, is reported. The key steps were an α-alkinone cyclisation (5 → 4, gas phase flow thermolysis at 620°), a stereoselective exo allylation of the enolate (F) derived upon desoxygenation and reduction of the enol ether 10, and elaboration of the two substituents at C(3) of the resulting 11 to afford the enol lactone 3. Epoxidation of the double bond of 3 took place from the side of C(2) (and not of C(4)), so that isoptychanolide (2) was formed. The configurations of all stereocentres in 2 were determined by an X-ray analysis.

INTRODUCTION

Ptychanolide (1), a sesquiterpene spiro-lactone of the pinguisane type, was isolated from the Liverwort *Ptychantus striatus* (Lehm. et Lindenb.) Nees by Takeda et al. in 1981[4]. The molecule of 1 was shown by X-ray analysis[5] to contain two novel substructures, an all-cis-tetramethylbicyclo[3.3.0]octane A and an α,α-disubstituted β,γ-epoxy-γ-lactone B[6].



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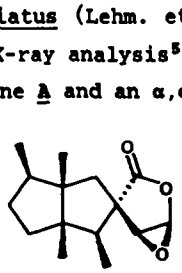

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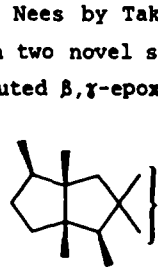
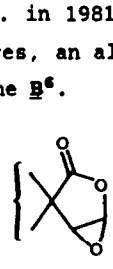


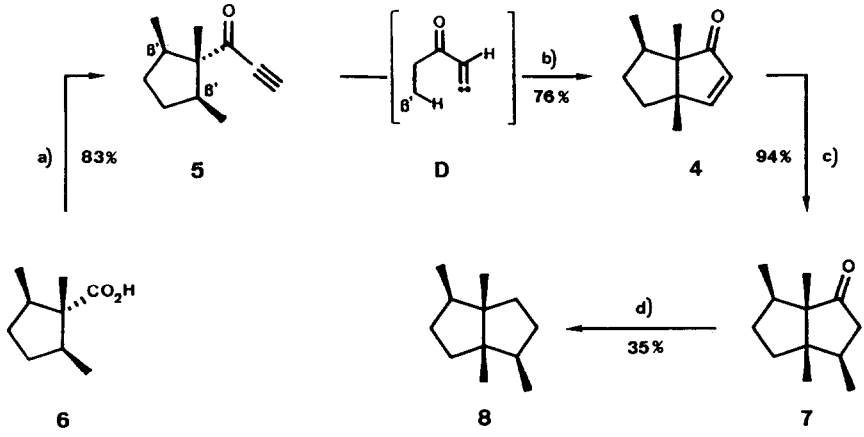
A



B

Isoptychanolide (2), which differs from the natural 1 in the configuration of the epoxide ring, has not been isolated so far. Our present approach to the ptychanolide skeleton, shown retrosynthetically in Chart 1, required methods for: a) the construction of the highly

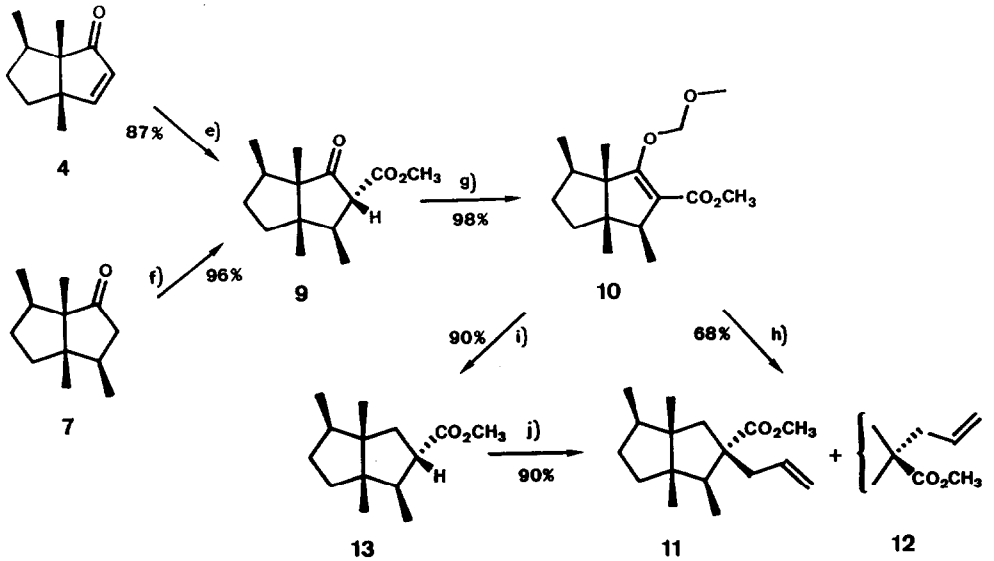
intermediate enolate **E** with CO_2 (method as in refs. 14 and 15) and obtained, after esterification with CH_2N_2, the β-keto ester **9** (87% from **4**) (Chart 3). The coupling constant



a) **i**: $SOCl_2$, **ii**: TMSC≡CTMS, $AlCl_3$, CH_2Cl_2, **iii**: $Na_2B_4O_7$ aq., MeOH, pH 8.5; b) distilled through a quarz tube at 620°; c) $LiCu(CH_3)_2$, Et_2O, -30° → 0°; d) K_2CO_3, $H_2NNH_2.H_2O$, TEG, 250°.

Chart 2

$J(3_{exo}H,4_{endo}H)$=12.3 in **9** showed the CH_3OOC group to be in the endo position (C(3) is SR relative to RS at C(1)). The same product **9** (96%) was obtained upon treatment of the tetramethylketone **7** with NaH (via the enolate **E**) and $(CH_3)_2CO_3$. In chloroform solution the

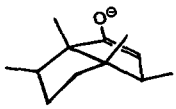


e) **i**: $LiCu(CH_3)_2$, Et_2O, -30° → 0°, **ii**: CO_2, -60°, **iii**: CH_2N_2; f) 4 NaH, $(CH_3)_2CO_3$, rfl.; g) NaH, HMPT, CH_3OCH_2Cl, r.t.; h) **i**: 4 Li, NH_3, THF, -78°, **ii**: CH_2=$CHCH_2Br$, -78°; i) 4 Li, NH_3, THF, -78°; j) **i**: LDA, THF, i-Pr_2NH, **ii**: CH_2=$CHCH_2Br$, -78°.

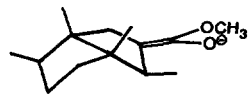
Chart 3

β-keto ester **9** exists exclusively in the keto form. The CH_3OOC group sits - probably under thermodynamic controll via the enol form - in the endo position (cf. ref. 15). The

elaboration of the γ-lactone moiety started with the O-alkylation of the β-keto ester **9** affording the methoxymethyl enol ether **10** (98%). The latter was reduced (in two consecutive steps) with 4 g. at. of Li in NH_3 at -78° for 1 min[16] (method as in ref. 17) to yield, after protonation, the saturated ester **13** (90%). The $J(3_{exo}H,2_{endo}H)$=11.5, $J(3_{exo}H,4_{endo}H)$=9.9, $J(3_{exo}H,4_{exo}H)$=8.3 couplings of H-C(3) showed that the CH_3OOC group of **13** is in the endo position (C(3) is RS relative to RS at C(1)). When the intermediate enolate **F** of this reduction of **10** was quenched with allyl bromide (method as in ref. 18), an (80:20)-mixture

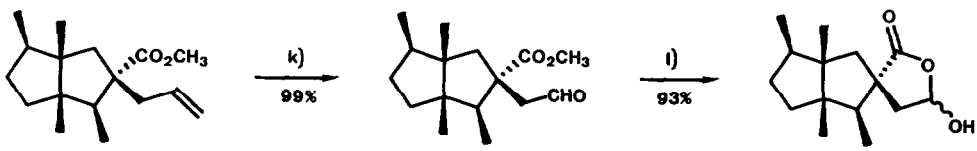


E



F

of the stereoisomeric allyl esters **11** and **12** (68%) was obtained (Chart 3). Treatment of the saturated ester **13** with LDA (via the enolate **F**) and then with allyl bromide similarly led to an (86:14)-mixture of **11** and **12** (90%). The configuration at C(3) of **11** (and thus of **12**) could not be determined at this stage. Only the X-ray analysis of isoptychanolide (**2**), which was the eventual product of our further synthesis from **11**, established the exo and endo position of the allyl and the CH_3OOC group, respectively, in **11** (and thus the reverse in **12**). Thus the (kinetically controlled) attack of the ester enolate **F** (made from **10** or from **13**) on allyl bromide occurs preferentially with its exo side (cf. also ref. 19). Preferred exo attack also applies to the (also kinetically controlled) protonation of the enolate **F** leading to **13**.



11 **14** **15**

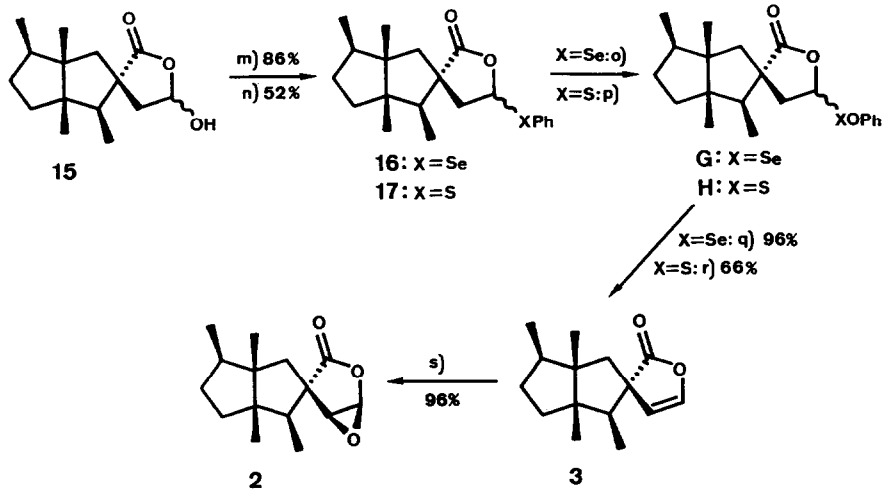
k) i: O_3, MeOH, -78°, ii: Me_2S; l) 1 N H_2SO_4, THF, 60°, or i: KOH, H_2O, MeOH, THF, ii: H_2SO_4, H_2O.

Chart 4

Ozonisation of the side chain double bond of **11** afforded the ester aldehyde **14** (99%) (Chart 4), which was cyclised to the pseudoacid **15** (93%) when treated with H_2SO_4. A similar yield of **15** was obtained by KOH saponification of **14** and subsequent acidification (method as in ref. 20).

Synthesis of Isoptychanolide (**2**) (Chart 5). Attempts at dehydrating the pseudoacid **15** by conventional methods gave only little or none of the enol lactone **3**, but the following two-step process was found to be efficient: The reaction of **15** with benzene selenol in the presence of a catalytic ammount of CH_3SO_3H at r.t. afforded the phenylseleno pseudoester **16** (86%). This was oxidised with ozone at -78° to the selenoxide **G**, which underwent a spontaneous syn elimination at r.t. within 2 h to give **3**; i-Pr_2NH was added to prevent

readdition of the eliminated phenylselenenic acid to the double bond (method as in ref. 21). An alternative method[22] via the phenylthio pseudoester 17 and the sulfoxide H produced only 34% of 3. The pseudoacid 15 and esters 16 and 17 (as well as probably G and H) were mixtures of C(3')-diastereoisomers (see Exper. Part). Finally, epoxidation of 3 afforded only one product (96%), m.p. 91-93°, with ^{1}H- and ^{13}C-NMR data similar to the ones of ptychanolide[23], m.p. 143-144°. The structure and, with it, the relative configuration of the synthetic



m) PhSeH, C_6H_6, cat. $MeSO_3H$, r.t.; n) PhSH, C_6H_6, cat. $MeSO_3H$, r.t.; o) O_3, CH_2Cl_2, -78°, p) MCPBA, $CHCl_3$, -20°; q) i-Pr_2NH, -78° → r.t., 2 h; r) $P(OMe)_3$, CCl_4, 75°, 2 days; s) MCPBA, CH_2Cl_2, r.t., 2 days.

Chart 5

(±)-isoptychanolide 2 was determined by an X-ray analysis[24] (Fig. 1). While this structure confirmed all the preceding arguments on the stereocontrol of our synthetic procedures, it also showed that the methyl group at C(2) had totally suppressed the epoxidation of the enol lactone from the desired side by steric hindrance and thus prevented the formation of 1.

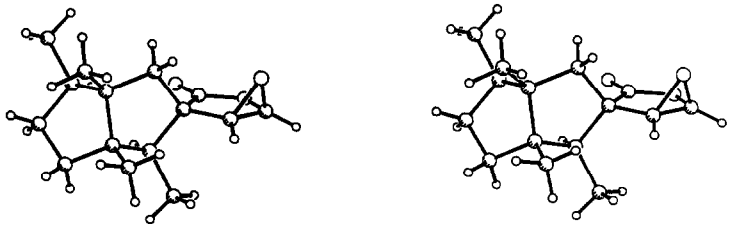


Figure 1. Stereoscopic view of the X-ray-determined structure of the isoptychanolide 2

This work was supported by the Swiss National Science Foundation and by Sandoz AG, Basel. We acknowledge the grant of a post-doctoral fellowship from the Legerlotz Fund to B.S.

EXPERIMENTAL

General Remarks. (See refs. 9 and 10) Chemical shifts and coupling constants (J) of ABX systems were assigned by first order analysis.

1. (1'r,2'RS,5'SR)-1',2',5'-Trimethylcyclopentylpropyn-1-one (5). The crude acid chloride obtained from 6[9] (5.46 g, 34.9 mmol) and $SOCl_2$ was treated with bis(trimethylsilyl)acetylene[12] to give 8.34 g of the crude trimethylsilylalkynone, which was desilylated directly[12] to yield, after bulb-to-bulb distillation at 120°/14 Torr, 4.78 g (83% based on 6) of 5 as a yellowish oil of ca. 96% purity (anal. GC (SE-52, 120°)). An analytical sample of 5 was obtained by column chromatography (Lobar A, hexane/EtOAc 98.5:1.5) followed by bulb-to-bulb distillation as a colourless oil. UV (ethanol): 212 (5200), 220 (3700). IR (film): 3260m, 2960s, 2880s, 2090s, 1670s, 1455w, 1385m, 1130m, 1065m, 1025m. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.16 (s, H-C(3)); 2.78-2.44 (m, H-C(2'), H-C(5')); 2.12-1.88 (m, 2 H); 1.46-1.18 (m, 2 H); 0.86 (s, CH_3-C(1')); 0.85 (d, J=6.8, CH_3-C(2'), CH_3-C(5')). MS (70 eV): 164 (1, M^+), 149 (5), 111 (71), 95 (20), 79 (12), 69 (100), 55 (46). Anal. calc. for $C_{11}H_{16}O$ (164.25): C 80.44, H 9.82; found: C 80.19, H 9.75.

2. (1RS,5RS,8SR)-1,5,8-Trimethylbicyclo[3.3.0]oct-3-en-2-one (4). Thermolysis of 5 (4.65 g, 28.3 mmol, purity 96%) at 620°/14 Torr for 6 h was carried out in the apparatus described in ref. 13. The crude oil from the cold trap was taken up in Et_2O, the solution dried over $MgSO_4$ and concentrated to give 4.20 g of dark brown oil. Bulb-to-bulb distillation at 110°/14 Torr afforded 3.54 g (76%) of 4 as a yellow semisolid of ca. 92% purity (anal. GC (SE-52, 130°)). An analytical sample of 4 was obtained by column chromatography (Lobar A, hexane/EtOAc 97.5:2.5) followed by bulb-to-bulb distillation as a colourless semisolid. UV (ethanol): 222 (8400). IR (film): 3080w, 3040w, 2960s, 2880s, 1710s, 1600m, 1470m, 1450m, 1385m, 1370w, 1345m, 1315w, 1270m, 1110m, 1050m, 840m, 735m. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.30 (d, J=5.6, H-C(4)); 6.02 (d, J=5.6, H-C(3)); 2.26-2.06 (m, 1 H); 1.86-1.54 (m, 2 H); 1.52-1.24 (m, 2 H); 1.18, 0.93 (both s, CH_3-C(5), CH_3-C(1)); 0.93 (d, J=6.8, CH_3-C(8)). MS (70 eV): 164 (53, M^+), 149 (85), 136 (10), 131 (18), 122 (63), 108 (36), 95 (100), 92 (28), 80 (38), 68 (47), 53 (31). Anal. calc. for $C_{11}H_{16}O$ (164.25): C 80.44, H 9.82; found: C 80.22, H 9.84.

3. (1RS,4SR,5RS,8SR)-1,4,5,8-Tetramethylbicyclo[3.3.0]octan-2-one (7). To a stirred suspension of CuI (12.05 g, 63.3 mmol) in Et_2O (100 ml), under N_2, at -30° was added

dropwise an 1.6 M solution of CH_3Li in Et_2O (63.0 ml, 100 mmol). After the solution was stirred for 15 min at -30°, a solution of 4 (3.46 g, 21.1 mmol) in Et_2O (20 ml) was added dropwise, the resulting yellow suspension was allowed to warm up to 0° within 20 min, stirred at this temperature for 10 min, cooled to -60°, treated with NH_4Cl (10 g) at once and then with H_2O (100 ml) and conc. aq. NH_4OH (100 ml). After stirring at r.t. for 16 h, the phases were separated and the aq. phase was extracted with Et_2O (3x 50 ml). The combined ether extracts were washed with H_2O and brine, dried over $MgSO_4$, filtered and the filtrate evaporated. Bulb-to-bulb distillation of the dark yellow oil at 115°/14 Torr afforded 3.57 g (94%) of 7 as a colourless oil of ca. 89% purity (anal. GC (SE-52, 130°)). An analytical sample of 7 was obtained by column chromatography (Lobar A, hexane/EtOAc 97.5:2.5) and bulb-to-bulb distillation. IR (film): 2970s, 2880s, 1735s, 1460m, 1420w, 1380m, 1180w, 1075m. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.53, (dd, J=18.2, 7.6, H-C(3)); 2.40-2.08 (m, 2 H); 2.06-1.60 (m, 3 H); 1.58-1.30 (m, 2 H); 0.97 (d, J=6.8, CH_3); 0.87 (d, J=6.6, CH_3); 0.83 (s, CH_3); 0.81 (s, CH_3). MS (70 eV): 180 (9, M^+), 152 (6), 138 (11), 123 (13), 109 (100), 95 (82), 81 (10), 67 (22), 55 (14). Anal. calc. for $C_{12}H_{20}O$ (180.29): C 79.94, H 11.18; found: C 80.21, H 11.23.

4. (1RS,2SR,5RS,6SR)-1,2,5,6-Tetramethylbicyclo[3.3.0]octane (8). A mixture of 7 (85 mg, 0.47 mmol), K_2CO_3 (250 mg), $H_2NNH_2.H_2O$ (0.25 ml) and triethyleneglycol (2 ml) was heated to 250° in a sealed tube for 6 h, cooled, diluted with H_2O (10 ml) and extracted with Et_2O (5x 1 ml). The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated to yield 30 mg (35%) of 8 as a colourless oil of ca. 92% purity (anal. GC (SE-52, 130°)). Its ^{1}H- and ^{13}C-NMR spectra were identical with the ones described[4,5], confirming the C_2-symmetry.

5. Methyl (1RS,3SR,4SR,5RS,8SR)-1,4,5,8-Tetramethyl-2-oxo-bicyclo[3.3.0]octan-3-carboxylate (9).

A. From 4. To a stirred suspension of CuI (6.59 g, 34.6 mmol) in Et_2O (80 ml), under N_2, at -30° was added dropwise an 1.6 M solution of CH_3Li in Et_2O (43.3 ml, 69.3 mmol). After the colourless solution was stirred for 15 min at -30°, a solution of 4 (4.72 g, 28.7 mmol) in Et_2O (40 ml) was added dropwise, the resulting yellow suspension was stirred for additional 3 h when the temperature gradually rose to 0°. The reaction mixture was cooled to -60°, a large excess of finely ground dry ice (ca. 80 g) was added at once and the stirring was continued for 90 min. The mixture was quenched at -10° with 3N HCl (pH 2), whereupon the temperature gradually rose to +5°. The resulting precipitate was filtered and the filtrate extracted with EtOAc (4x 40 ml). The colourless extracts were washed with water (2x 10 ml), dried over $MgSO_4$ and treated with an etheral solution of CH_2N_2 until the yellow colour persisted. The solvent was evaporated to yield 6.82 g of a yellow oil. Bulb-to-bulb distillation at 180°/14 Torr afforded 5.97 g (87%) of 9 as a ^{1}H-NMR pure, pale yellow oil, which solidified on standing. An analytical sample of 9 was obtained by column chromatography (Lobar A, hexane/EtOAc 97.5:2.5) and crystallisation from i-Pr_2O as colourless prisms, m.p. 55.1-55.9°. IR ($CHCl_3$): 2960s, 2880m, 1745s, 1720s, 1455m, 1440m, 1380m, 1370w, 1350w, 1340m, 1310m, 1280s, 1160s, 1140m, 1070w, 1040m, 1000w, 990w. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.77 (s, CH_3OOC-C(3)), 2.92 (d, J=12.3, H-C(3)); 2.68-2.36 (m, 2 H),

2.14-1.68 (m, 2 H); 1.64-1.34 (m, 2 H); 1.02 (d, J=6.6, CH_3-C(4)); 0.87 (d, J=7.0 CH_3-C(8)); 0.85, 0.84 (both s, CH_3-C(5), CH_3-C(1)). MS (70 eV): 238 (5, M^+), 210 (3), 20' (8), 151 (5), 138 (100), 123 (8), 109 (61), 95 (55), 79 (4), 69 (21), 55 (10). Anal. calc for $C_{14}H_{22}O_3$ (238.33): C 70.56, H 9.30; found: C 70.62, H 9.41.

B. From 7. A stirred mixture of 7 (3.45 g, 19.1 mmol), NaH (ca. 76 mmol, obtained by washin(3.34 g of ca. 55% oil dispersion of NaH 3x with pentane) and freshly distilled $(CH_3)_2CO_3$ (2' ml) was heated to reflux for 6 h. After cooling to r.t., the reaction mixture was poure(onto a mixture of 10% HCl (50 g) and ice (50 g) and extracted with Et_2O (3x 25 ml). Th(combined extracts were washed with brine, dried over $MgSO_4$, filtered and the filtrat(evaporated to yield 4.80 g of a yellow oil. Bulb-to-bulb distillation at 180°/14 Tor afforded 4.39 g (96%) of 9 as an ^{1}H-NMR pure, colourless solid, m.p. 52-54°.

6. Methyl (1RS,4RS,5RS,8SR)-2-Methoxymethyl-1,4,5,8-tetramethylbicyclo[3.3.0]oct-2-en-3-carboxylate (10). To a stirred solution of 600 mg (2.52 mmol) of 9 in HMPT (5 ml) was added Na (ca. 10 mmol), obtained by washing 440 mg of a ca. 55% dispersion of NaH in oil 3x wit pentane. The mixture was stirred for 30 min at r.t., cooled in an ice bath and treate(dropwise with 0.38 ml of chloromethylmethyl ether (403 mg, 5.1 mmol). After stirrin(overnight at r.t., the reaction mixture was poured onto ice-cold sat. $NaHCO_3$ (100 ml) an(extracted with pentane (3x 50 ml). The combined extracts were washed with water (50 ml), dried over $MgSO_4$ and evaporated to yield 755 mg of yellowish oil which, after bulb-to-bul distillation at 170°/14 Torr, afforded 700 mg (98%) of 10 as a ^{1}H-NMR pure colourless oil. An analytical sample of 10 was obtained by chromatography (Lobar A, hexane/EtOAc 99:1) an(bulb-to-bulb distillation. IR (film): 2950s, 2880m, 2830w, 1710s, 1620s, 1440m, 1390w, 1345m, 1320m, 1280w, 1250s, 1210s, 1170s, 1120m, 1100m, 1070m, 1025m, 990m, 930s, 805w, 790w. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.26, 5.14 (AB, J=5.8, 2 H-C(O,O)); 3.70 (s, CH_3OOC-C(3)); 3.50 (s, CH_3-OC); 2.63 (q, J=6.5, H-C(4)); 2.40-2.14 (m, 1 H); 1.84-1.50 (m, 3 H); 1.44-1.1((m, 1 H); 1.06-0.94 (m, 4 CH_3). MS (70 eV): 282 (2, M^+), 267 (2), 251 (1), 237 (8), 205 (3), 149 (3), 138 (4), 127 (6), 109 (20), 95 (6), 45 (100). Anal. calc. for $C_{16}H_{26}O_4$ (282.38): (68.06, H 9.28; found: C 67.98, H 9.31.

7. Methyl (1RS,2SR,3RS,5RS,6SR)-1,2,5,6-Tetramethylbicyclo[3.3.0]octan-3-carboxylate (13). To the well stirred blue solution made by dissolving powdered Li (67 mg, 9.8 mmol) for 7 mi in NH_3 (ca. 110 ml) at -78°, a THF solution of 10 (690 mg, 2.4 mmol, in 9.5 ml of THF) wa added at once at the same temperature and the resulting suspension was treated after 1 mi with solid NH_4Cl (5 g). After evaporation of the NH_3, toluene (60 ml) was added followed b 20 ml of H_2O, the organic layer was washed with 4% HCl and brine, dried over $MgSO_4$ an(evaporated to yield 496 mg (90%) of 13 as colourless oil of 90% purity (the 10% impurities consisted of 6 peaks, none exceeding 4%; anal. GC, BP-5, 50-250°). We could not find th (3SR)-diastereoisomer of 13 in the crude mixture. An analytical sample of 13 was obtained b column chromatography (Lobar A, hexane/EtOAc 97.5:2.5). IR (film): 2960s, 2870s, 1740s, 1450m, 1435m, 1380m, 1260w, 1195m, 1170s, 1145m, 1020w. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.67 (s, CH_3OOC-C(3)); 2.60-2.40 (m, H-C(3)); 2.28-1.98 (m, 2 H); 1.96-1.75 (m, 2 H); 1.74-1.50 (m, 2 H); 1.44-1.20 (m, 2 H); 0.87 (d, J=6.7, CH_3); 0.84 (d, J=6.9, CH_3); 0.75 (s, CH_3-C(1) an(

CH_3-C(5)). ^{1}H-NMR (400 MHz, $CDCl_3$) of the 2.60-1.50 region: 2.48 (ddd, J=11.5, 9.9, 8.3, H-C(3)); 2.16 (dq, J=11.5, 6.9, H-C(2)); 2.12-2.04 (m, 1 H); 1.96-1.74 (m, 2 H, including at 1.82 (dd, 13.3, 8.3, H_{exo}-C(4))); 1.72-1.47 (m, 2 H, including at 1.61 (dd, J=13.3, 9.9, H_{endo}-C(4))). MS (70 eV): 224 (12, M^+), 209 (52), 192 (7), 167 (62), 124 (41), 110 (75), 76 (53), 55 (86), 43 (100). Anal. calc. for $C_{14}H_{24}O_2$ (224.35): C 74.95, H 10.78; found: C 74.69, H 10.52.

8. Methyl (1RS,2RS,3RS,5RS,6SR)-1,2,5,6-Tetramethyl-3-2'-propenylbicyclo[3.3.0]octan-3-carboxylate (11).

A. From 10. To the well stirred blue solution made by dissolving powdered Li (45 mg, 6.5 mmol) for 7 min in NH_3 (ca. 75 ml) at -78°, a THF solution of 10 (447 mg, 1.6 mmol in 8.5 ml of THF) was added at once at the same temperature. After 1 min allyl bromide (5 ml, 60 mmol) was added at once and the resulting suspension was treated after 1 min with solid NH_4Cl (5 g). After evaporation of the NH_3, toluene (40 ml) was added followed by 20 ml of H_2O, the organic layer was washed with 4% HCl and brine, dried over $MgSO_4$ and evaporated to yield 456 mg of a colourless oil shown to contain 11 and 12 in the ratio of 80:20 (anal. GC (BP-5, 180°)). Column chromatography (Lobar B, hexane/EtOAc 99:1) afforded 142 mg (34%) of a colourless oil consisting of 11 and 12 in the GC ratio of 66:34 and 143 mg (34%) of 11 as a colourless oil, ca. 85% pure. An analytical sample of 11 was obtained by repeated column chromatography. IR (film): 3080w, 2960s, 2880m, 1735s, 1645w, 1460m, 1440m, 1380m, 1350w, 1320w, 1285w, 1210s, 1180m, 1160m, 1140m, 1060w, 995w, 920m. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.78-5.54 (m, H-C(2')); 5.15-4.95 (m, 2 H-C(3')), 3.64 (s, CH_3OOC-C(3)); 2.68-2.48 (m, 2 H); 2.40-1.10 (m, 8 H); 0.97 (d, J=7.4, CH_3); 0.85 (d, J=6.8, CH_3); 0.81, 0.72 (both s, CH_3-C(1), CH_3-C(5)). Anal. calc. for $C_{17}H_{28}O_2$ (264.41): C 77.22, H 10.67; found: C 77.20, H 10.87. Analysis of the above (80:20)-mixture of 11 and 12: ^{1}H-NMR (200 MHz, $CDCl_3$): Aside from all of the above mentioned signals of 11, the following signals of 12 could be seen: 3.64 (s, CH_3OOC-C(3)); 2.84-2.72 (m); 0.98 (d, J=7.3, CH_3); 0.89 (d, J=6.9, CH_3); 0.75 (s, CH_3). GC-MS (SE-54, 160°, 70 eV): GC-peak for 11: 264 (4, M^+), 246 (8), 232 (10), 223 (60), 205 (11), 191 (12), 181 (35), 163 (32), 148 (100), 138 (28), 127 (22), 124 (41), 109 (51), 95 (23), 81 (17), 67 (26), 55 (21); GC-peak for 12: 264 (6, M^+), 249 (6), 223 (91), 205 (43), 191 (8), 180 (82), 163 (52), 147 (26), 138 (40), 127 (31), 121 (100), 108 (12), 95 (39), 79 (26), 67 (42), 55 (36).

B. From 13. To a stirred solution of i-Pr_2NH (0.89 ml, 6.24 mmol) in THF (10 ml), under N_2, at -10° was added dropwise a 1.5 M solution of n-BuLi in hexane (2.5 ml, 3.75 mmol). After stirring the yellow solution for 10 min at -5°, it was cooled to -40° and a solution of 13 (701 mg, 3.12 mmol) in THF (1 ml) was added. The reaction mixture was allowed to warm up to 0° and stirred for 20 min at 0-10°, then cooled to -78° and treated with allyl bromide (0.8 ml, 9.36 mmol). After warming up slowly to r.t. and stirring overnight, the reaction mixture was poured into ice-cold 5% HCl (20 ml), the phases separated and the aqueous phase extracted with Et_2O (3x 5 ml). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the filtrate evaporated to yield a yellow oil, which after bulb-to-bulb distillation at 160°/14 Torr afforded 746 mg (90%) of colourless oil, which was shown to consist of 11 and 12 in the ratio of 86:14 (anal. GC (SE-52, 180°)).

9. Methyl (1RS,2RS,3SR,5RS,6SR)-1,2,5,6-Tetramethyl-3-2'-oxoethylbicyclo[3.3.0]octan-3-carboxylate (14). A slow stream of O_3 was bubbled through a stirred solution of 11 (186 mg, 0.70 mmol) in MeOH (40 ml) at -78° until the a slight blue colour persisted. After removal of the excess of O_3 with a stream of N_2, 5 ml of Me_2S was added and the reaction mixture was left at r.t. for 20 h. After evaporation of the solvents, the residue was dissolved in EtOAc (40 ml), washed with H_2O (2x 10 ml), 6N HCl (2x 10 ml), again with H_2O (3x 10 ml), dried over $MgSO_4$ and evaporated to yield 185 mg (99%) of 14 as ca. 89% pure colourless oil (anal. GC (BP-5, 180°)). An analytical sample of 14 was obtained by column chromatography (Lobar A, hexane/EtOAc 95:5). IR (film): 2960s, 2875s, 2730w, 1730s, 1455m, 1435m, 1380m, 1285m, 1245m, 1205s, 1180m, 1160m, 1135m, 1100m, 1065m. ^{1}H-NMR (200 MHz, $CDCl_3$): 9.68 (X of ABX, J_{AX}=0, J_{BX}=1.4, H-C(2')); 3.67 (s, CH_3OOC-C(3)); 2.99, 2.56 (AB of ABX, J_{AB}=17.4, J_{AX}=0, J_{BX}=1.4, 2 H-C(1')); 2.67 (d, J=14.4, H-C(4)); 2.40-1.16 (m, 6 H); 1.26 (d, J=14.4, [2.67] s, H-C(4)); 0.88 (d, J=7.3, CH_3); 0.87 (d, J=6.8, CH_3); 0.83, 0.73 (both s, CH_3-C(1), CH_3-C(5)). Anal. calc. for $C_{16}H_{26}O_3$ (266.38): C 72.14, H 9.84; found: C 71.90, H 9.87.

10. (1RS,2RS,3SR,5RS,6SR)-1,2,5,6-Tetramethylbicyclo[3.3.0]octane-3-spiro-5'-3'-hydroxy-2'--oxacyclopentan-1'-one (15). A solution of 14 (185 mg, 0.69 mmol) in THF (5 ml) and 1N H_2SO_4 (3 ml) was stirred for 2 days at 60°. The cooled reaction mixture was diluted with 60 ml of Et_2O/CH_2Cl_2 (5:1), washed with H_2O (4x 10 ml), dried over $MgSO_4$ and evaporated to yield 196 mg of a colourless oil. Column chromatography (Lobar A, hexane/EtOAc 8:2) afforded 163 mg (93%) of 15 as a colourless oil of ca. 93% purity (anal. GC (BP-5, 180°) one broad peak). An analytical sample of 15 was obtained after crystallisation from pentane as colourless plates, m.p. 88.4-90.5°; it was an 80:20-mixture (by ^{1}H-NMR) of the two C(3')-diastereoisomers of 15 of unknown configuration. IR (film): 3700-3050s (br.), 2960s, 2875s, 1760s, 1460m, 1380m, 1175m, 975m, 940m. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.88-5.74 (m, H-C(3')); 3.46 (d, J=5.2, OH, 0.2 H, exchangeable with D_2O)); 3.34 (dd, J=3.9, 1.2, OH, 0.8 H, exchangeable with D_2O); 2.63-1.21 (m, 10 H); 0.93-0.73 (m, 4 CH_3). MS (70 eV): 252 (0.7, M^+), 234 (3), 208 (58), 166 (24), 152 (21), 137 (18), 123 (20), 121 (39), 109 (100), 107 (26), 95 (18), 91 (17), 67 (19), 55 (22). Anal. calc. for $C_{15}H_{24}O_3$ (252.35): C 71.39, H 9.59; found: C 71.14, H 9.58.

11. (1RS,2RS,3SR,5RS,6SR)-1,2,5,6-Tetramethylbicyclo[3.3.0]octane-3-spiro-5'-3'-phenylseleno-2'-oxacyclopentan-1'-one (16). To a stirred suspension of 15 (50 mg, 0.2 mmol) and anh. $MgSO_4$ (50 mg) in benzene (0.6 ml) benzeneselenol 43 µl (0.4 mmol) was added, followed by one drop of CH_3SO_3H. The suspension was stirred at r.t. under N_2 for 24 h, filtered and the filtrate diluted with benzene (5 ml), washed with $NaHCO_3$ (2x 2ml), dried over $MgSO_4$ and evaporated to yield a yellow-orange oil, which was purified by PLC (hexane/EtOAc 9:1) to give 67 mg (86%) of 16 as a colourless oil, shown by anal. GC to consist of two C(3')-diastereoisomers of 16 of unknown configuration in the ratio of 64:36 (BP-5, 180-250°). IR (film): 3045w, 2955s, 2865m, 1775s, 1580w, 1480m, 1440m, 1380m, 1160s, 1115m, 1025m, 950m, 740m, 695m. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.72-7.58 (m, 2H); 7.40-7.24 (m, 3H); 5.83 (m, H-C(3')); 2.96 (m, ca. 0.5 H); 2.62-2.36 (m, ca. 1.5 H); 2.36-1.20 (m, 8 H); 0.90-0.56

(m, 4 CH_3). MS (70 eV, CI, iso-butane): 396 (2.5), 394 (16), 393 (64), 347 (12), 236 (17), 235 (100), 219 (11), 207 (19), 163 (18), 155 (9), 111 (21), 71 (19).

12. (1RS,2RS,3SR,5RS,6SR)-1,2,5,6-Tetramethylbicyclo[3.3.0]octane-3-spiro-5'-3'-phenylthio--2'-oxacyclopentan-1'-one (17). To a stirred solution of 15 (40 mg, 0.16 mmol) in benzene (1ml) thiophenol (1 ml) was added, followed by one drop of CH_3SO_3H, and reaction mixture was allowed to stand at r.t. for 6 h. After addition of 15 ml of 1N NaOH, the reaction mixture was extracted with Et_2O (3x 5 ml). The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated to yield 50 mg of a yellow oil, which after column chromatography (Lobar A, hexane/EtOAc 95:5) afforded 29 mg (52%) of 17 (a mixture of C(3')-diastereoisomers of unknown composition and configuration) as a colourless oil. IR (film): 3060w, 2960s, 2930s, 2870s, 1775s, 1585w, 1480m, 1440m, 1380m, 1160s, 1120m, 1025m, 945m, 910s, 735s, 690m. H-NMR (200 MHz, $CDCl_3$): 7.62-7.48 (m, 2 H); 7.42-7.30 (m, 3 H); 5.75-5.55 (m, H-C(3')); 3.04-2.86 (m, ca. 0.5 H), 2.66-1.20 (m, ca. 9.5 H); 0.95-0.66 (m, 4 CH_3).

13. (1RS,2RS,3RS,5RS,6SR)-1,2,5,6-Tetramethylbicyclo[3.3.0]octane-3-spiro-5'-2'-oxacyclo-pent-3'-en-1'-one (3).

A. From 16. A slow stream of O_3 was bubbled through a stirred solution of 16 (60 mg, 0.15 mmol) in CH_2Cl_2 (5 ml) at -78° until the slight blue colour persisted. After removal of the excess of O_3 with a stream of N_2, i-Pr_2NH (0.5 ml) was added to the solution containing G and the reaction mixture was left at r.t. for 2 h. After evaporation and column chromatography (Lobar A, hexane/EtOAc 95:5), 34.5 mg (96%) of 3 was obtained as a pale yellow oil of ca. 93% purity (anal. GC (BP-5, 180°). IR (film): 3120w, 2960s, 2870s, 1790s, 1620m, 1470m, 1455m, 1380m, 1325m, 1165m, 1125m, 1120m, 1105m, 1040m, 1025m, 970m, 740m. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.75 (d, J=3.5, H-C(3')); 5.59 (d, J=3.5, H-C(4')); 2.54-2.25 (m, 2 H); 2.10 (d, J=14.0, H-C(4)); 2.05-1.10 (m, 5 H) including at 1.54 (d, J=14.0, H-C(4)); 0.87 (d, J=7.0, CH_3); 0.84 (s, CH_3); 0.82 (s, CH_3); 0.71 (d, J=7.1, CH_3). GC-MS (BP-1, 75-200°, 70 eV): 234 (1, M^+), 137 (100), 123 (52), 109 (17), 96 (23), 81 (20), 67 (16), 41 (39).

B. From 17. A solution of 90% MCPBA (59 mg, 0.31 mmol) in $CHCl_3$ (1 ml) was added at -30° to a solution of 17 (108 mg, 0.31 mmol) in $CHCl_3$ (5 ml) and kept at -20° for 16 h. The reaction mixture was then washed with 1N NaOH (2x 1 ml), dried over $MgSO_4$ and evaporated to yield the crude sulfoxide H (105 mg) as a yellow oil, which was dissolved in CCl_4 (0.35 ml) and trimethylphosphite (73 µl, 0.62 mmol) and heated to 75° for 48 h. After evaporation and column chromatography (Lobar A, hexane/EtOAc 97.5:2.5), 48 mg (66%) of 3 was obtained as a colourless oil of 93% purity (anal. GC (SE-52, 180°)).

14. (1RS,2RS,3RS,5RS,6SR,3'SR,4'RS)-1,2,5,6-Tetramethylbicyclo[3.3.0]octan-3-spiro-5'-3',4'--epoxy-2'-oxacyclopentan-1'-one (Isoptychanolide (2)). A solution of 48 mg (0.20 mmol) of 3 and 90% MCPBA (200 mg, 1.16 mmol) was kept at r.t. for 48 h, washed with ice-cold 1N NaOH (1 ml), dried over $MgSO_4$ and evaporated to yield 49 mg (96%) of 2 as a colourless solid of 93% purity (anal. GC (SE-52, 180°)). An analytical sample of 2, m.p. 91-93°, was obtained after crystallisation from pentane. IR ($CHCl_3$): 3030w, 2970s, 2880s, 1795s, 1460m, 1405m, 1385m,

1325m, 1165m, 1155m, 1080s, 1070s, 1050m, 1015m, 985m, 860s. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.57 (d, J=2.2, H-C(3')); 3.79 (d, J=2.2, H-C(4')); 2.42 (q, J=7.6, H-C(2)); 2.35-2.15 (m, 1 H); 2.04 (d, J=14.2, H-C(4)); 2.00-1.80 (m, 2 H) including at 1.86 (d, J=14.2, ca. 1 H, H-C(4)); 1.74-1.24 (m, 3 H); 0.95 (s, CH_3); 0.91 (d, J=7.6, CH_3); 0.89 (s, CH_3); 0.88 (d, J=6.9; CH_3). ^{13}C-NMR (20 MHz, $CDCl_3$): 180.5 (s, C=O); 78.1 (d); 57.2 (d); 56.1 (s), 55.7 (s), 53.9 (s); 50.6 (d); 45.6 (t); 43.1 (d); 37.2 (t); 30.6 (t); 18.7 (q); 17.6 (q); 14.7 (q); 8.9 (q). GC-MS (BP-1, 75-200°, 70 eV): 250 (1, M^+), 235 (6), 221 (9), 205 (8), 193 (7), 175 (11), 153 (31), 135 (19), 121 (48), 109 (100), 95 (31), 67 (37), 41 (79). Anal. calc. for $C_{15}H_{22}O_3$ (250.34): C 71.97, H 8.86; found: C 72.22, H 8.64.

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