Synthesis of Tetracyclic Analogues of Calcitriol (1α,25-Dihydroxyvitamin D_3) with Side-Chain-Locked Spatial Orientations at C(20)

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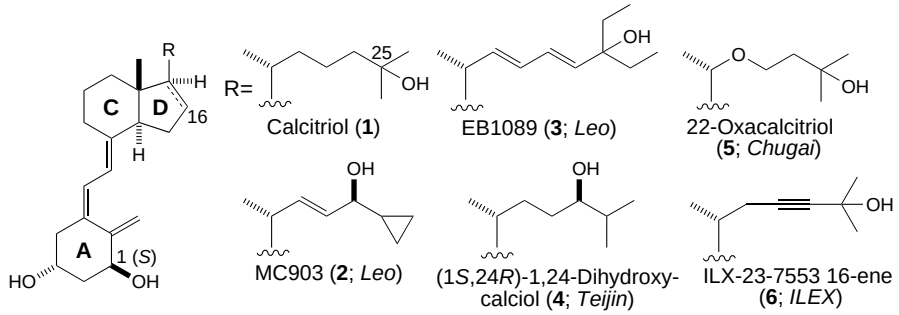
Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

We present our first results on the synthesis of a new class of conformationally restricted vitamin D analogues bearing an extra five-membered ring formed by linking C(18) and C(21). Two analogues of calcitriol (**1**) with unsaturations at the extra ring and the lateral chain were prepared. The triene system was introduced by the convergent *Wittig–Horner* approach developed by *Lythgoe* [8] and *F. Hoffmann-La Roche* [9]. The key steps in the preparation of the requisite fragments were: *i*) the long-distance functionalization of ketal **11** at C(18), *ii*) the ring closure on **15** through an intramolecular aldol condensation to give the α,β-unsaturated ketone **10**, and *iii*) the Pd-catalyzed installation of the side chains.

Introduction. – The current interest in the therapeutic properties of calcitriol (**1**; vitamin D_3 steroid hormone) and some of its analogues results from the ability of these compounds to control abnormal cellular processes by modulating cell differentiation, inhibiting cell proliferation, and regulating apoptosis [1]. Several analogues of **1** (**2**–**6**) are currently either marketed or in clinical trials for the treatment of skin diseases and cancer [1n–p][2].



One of our goals is directed toward the development of calcitriol analogues with high antiproliferative activity against a broad spectrum of cancer cells without causing significant calcemic effects. It has been postulated that **1** mediates a wide range of biological effects through a multi-step mechanism that includes binding of the vitamin

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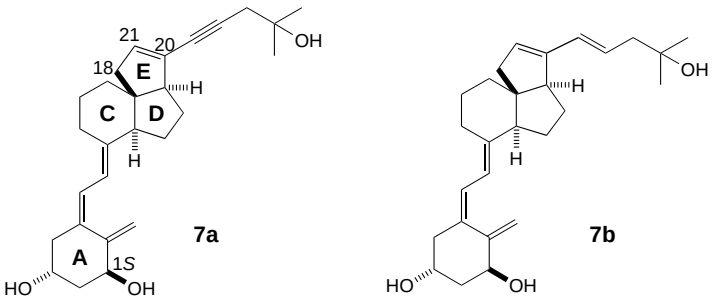
D receptor (VDR), heterodimerization of the VDR with the retinoic X receptor (RXR), and binding of the VDR–**1**–RXR complex to vitamin D responsive element (VDRE) sequences followed by transcription [3][10]. However, a more-detailed understanding of the mode of action of the natural hormone **1** is required in order to rationally design new analogues with selective properties [4].

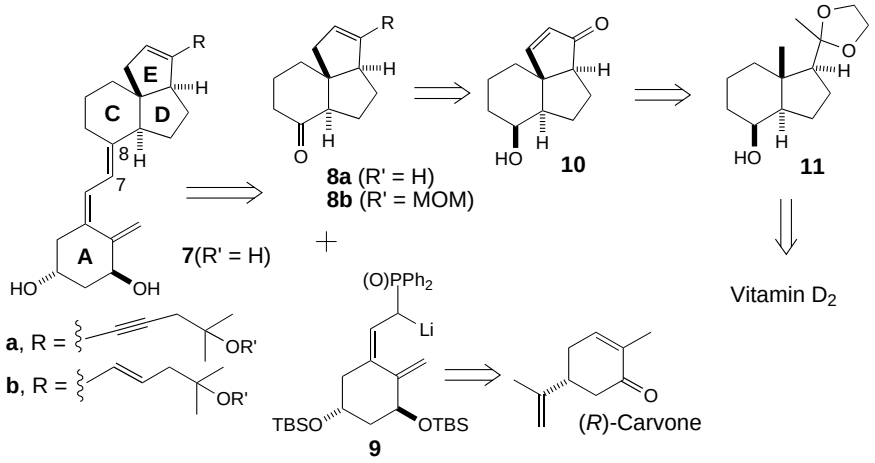
A few years ago, precise information on the shape of the biologically active conformation of **1** was unavailable due to problems encountered in the crystallization of the **1**–VDR complex. In addition, the study of the shape of the biologically active conformation of **1** was a difficult task due to the flexibility of the side chain, which can adopt numerous conformations of similar low-energy values. The gap in knowledge of structure–function relationships led us to systematically investigate structural modifications of **1** focusing the improvement of its activity as cancer-cell-growth inhibitor and as inducer of cancer-cell differentiation. More recently, X-ray-crystallographic studies have elicited the ligand-binding domain of VDR complexed to **1** and the plasma vitamin D binding protein (DBP) complexed to calcidiol. These structural features provide important tools for the design of a new generation of drugs with selective action [5].

To indirectly study the side-chain shape of the active calcitriol conformation, we started a research program directed toward the synthesis of analogues of **1** that possess side chains with locked spatial orientations. Our initial studies began with the synthesis of calcitriol analogues with either a double bond or the corresponding cyclopropane ring at C(17)–C(20), both of which lock the rotation of the side chain near the five-membered ring [6]. Some of these analogues were found to improve the biological profile of the natural vitamin D hormone for potential therapeutic applications, leading us to synthesize structurally related analogues of **1** with even higher degrees of unsaturation at the side chain [7] as well as a new class of calcitriol analogues with fixed torsion angles (C(16)–C(17)–C(20)–C(22) or C(16)–C(17)–C(20)–C(22)–C(23)–C(24)). As examples of the latter class of compounds, we describe here the synthesis of **7a** and **7b**, the structures of which are characterized by the presence of an additional five-membered ring (**E**) – formed by linking C(18) and C(21) – and side chains with locked spatial orientations at C(20).



General Retrosynthetic Analysis. – Our proposed route for the convergent synthesis of calcitriol analogues **7** is shown in *Scheme 1*. The projected approach for the introduction of the (*E*)–C(7)=C(8) bond is based on a *Wittig–Horner* coupling

Scheme 1



connecting the calcitriol subunit **8** with the known phosphine oxide anion **9** [1k,m]. This mild and popular approach to the vitamin D triene system was originally developed by *Lythgoe* [8] and subsequently improved by *F. Hoffmann-La Roche* [9]. It was envisaged that the ketone fragments **8a** and **8b** could be prepared from the α,β-unsaturated ketone **10** according to methods of *Sonogashira* [10] and *Stille* [11]. The formation of the sterically congested tricyclic ketone **10**, which is required for the convergent route, presents a more demanding challenge, particularly with regard to the formation of the five-membered ring *E*, which confers great conformational rigidity to the molecule. Ketal **11** has already been prepared in our laboratory from commercially available vitamin D_2 [12]. On this basis, we proceeded to attempt the synthesis of ketone **10**.

Synthesis of the α,β-Unsaturated Ketone 10. – Our plan for the construction of **10** involved an intramolecular aldol-type condensation on the masked aldehyde **12** (*Scheme 2*). Two approaches were then envisaged for the preparation of lactol **12** from ketal **11**. The first approach consisted of a four-step sequence: formation of intermediate **14** (X = I or AcO) by means of long-distance radical reaction on **11** ($Pb(OAc)_4$, $CaCO_3$, I_2, *hν*) [13][14][3]); oxidation of **14** to lactone **13** (CrO_3), and reduction of **13** followed by deprotection to **12**. The second option involved formation of lactol **12** by hydrolysis and deprotection of intermediate **14** (X = AcO). Considering the possibility of direct formation of lactol acetate **14** (X = AcO) by long-distance radical functionalization on **11**, we initially decided to explore this shorter route to **12**.

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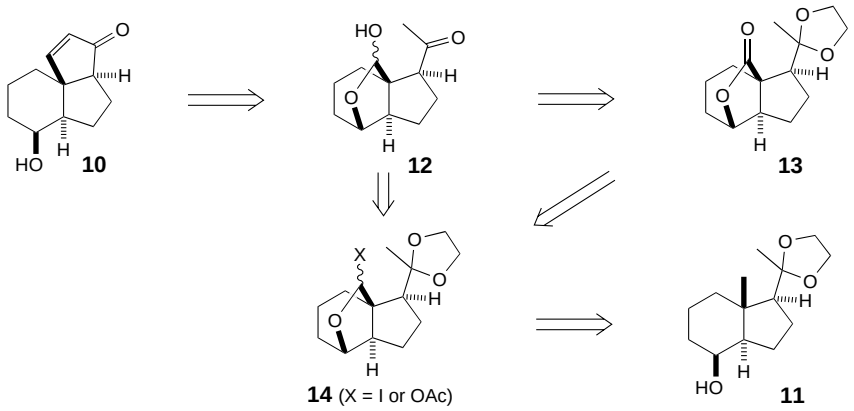
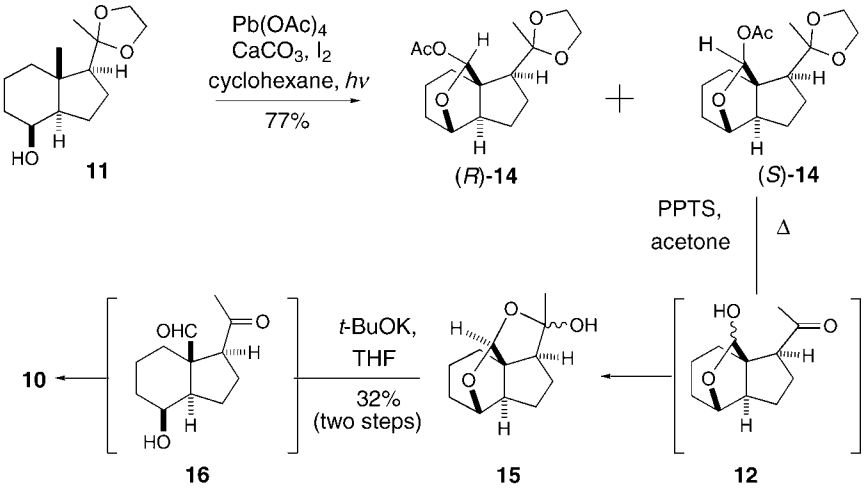
[3]) Some authors propose that long-distance radical functionalization provides iodides or lactols as intermediates [14a,b]. Other authors propose the direct formation of lactol acetates [14c].

Scheme 2



Irradiation of alcohol **11** (*Scheme 3*) in the presence of $Pb(OAc)_4$, I_2, and $CaCO_3$ in cyclohexane at 80° gave a mixture (*ca.* 3 :1) of the desired acetates (*R*)-**14** and (*S*)-**14** in a combined yield of 77%. The stereochemistry at C(10), of the two compounds was assigned on the basis of the steric interaction between the corresponding AcO group and the dioxolane ring.

Scheme 3

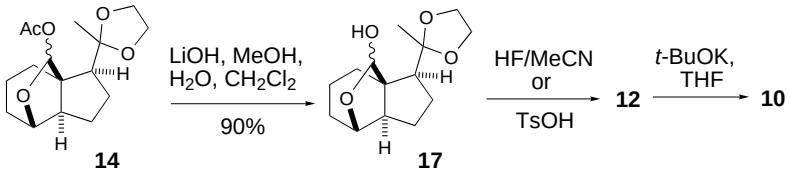


PPTS = pyridinium *p*-toluenesulfonate

Interestingly, treatment of this mixture of acetates with a catalytic amount of pyridinium *p*-toluenesulfonate in wet acetone induced deketalization to produce, presumably *via* **12**, lactol **15**, whose structure was proposed on the basis of ^{1}H-NMR data. Lactol **15**, which was prone to decomposition in the presence of silica gel, was immediately treated with *t*-BuOK to give in an intramolecular aldol condensation

followed by dehydration the key α,β-unsaturated ketone **10** (32% from acetate **14**). Attempts to improve the yield in **10** by following the sequence of reactions shown in *Scheme 4* were unsuccessful, presumably due to the extreme strain imposed by the tricyclic system. Similar results have recently been obtained during a triquinane-type synthesis [15].

Scheme 4

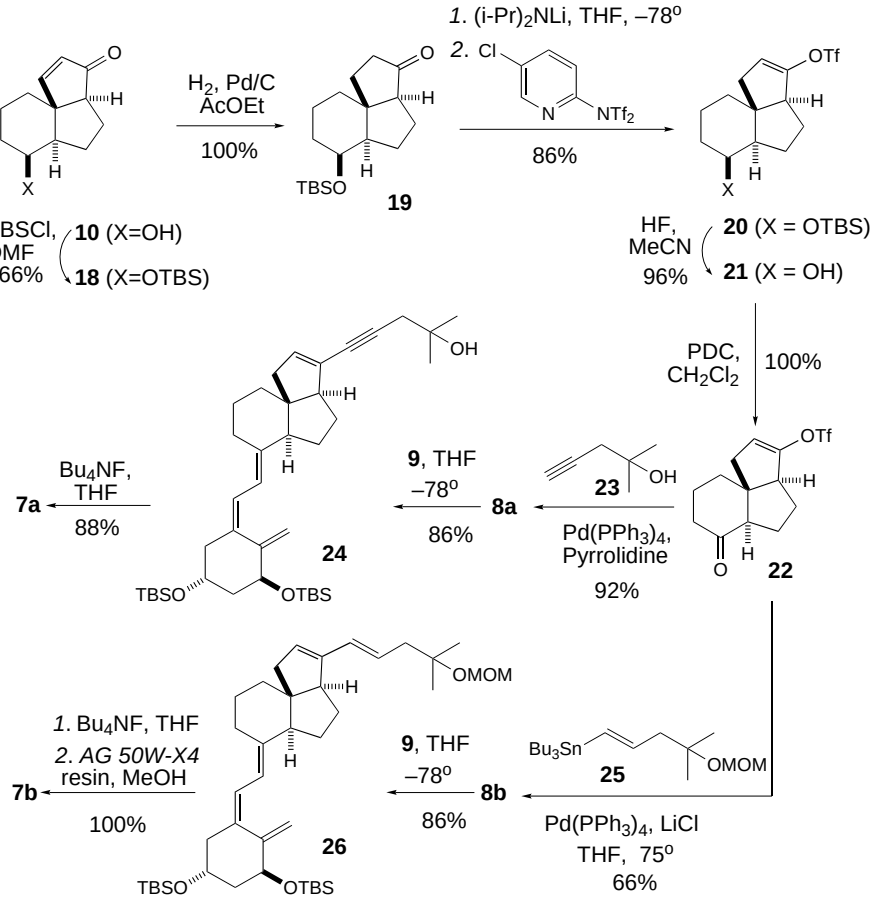


Synthesis of Calcitriol Analogues 7a and 7b. – Having obtained ketone **10**, our attention turned to the preparation of vinyl triflate **22** (*Scheme 5*), which is required for the introduction of the requisite side chains of target analogues **7a** and **7b**. Silylation of **10** with (*t*-Bu)Me_2SiCl [16] followed by catalytic hydrogenation of the cyclopentene double bond provided ketone **19** (two steps, 66%). Treatment of **19** with (i-Pr)$_2$NLi and reaction of the resulting kinetic enolate with *N*-(5-chloropyridin-2-yl)-1,1,1-trifluoro-*N*-(trifluoromethylsulfonyl)methanesulfonamide [17] afforded vinyl triflate **20**, which was converted to ketone **22** by sequential deprotection with HF and oxidation with pyridinium dichromate [18] (4 steps from **10**, 54% overall yield). Pd-Mediated *Sonogashira* cross-coupling of vinyl triflate **22** with 2-methyl-4-pentyn-2-ol (**23**) afforded the desired ketone **8a** in 92% yield. Vinyl triflate **22** was also coupled with known vinyl stannane **25** [19] under *Stille* conditions to produce the other fragment **8b** in 66% yield. The fragments **8a** and **8b** were individually coupled at $-78°$ with phosphine oxide anion **9** [20] to form stereoselectively the corresponding protected calcitriol analogues **24** and **26** (86% yield in both cases). These compounds were deprotected conventionally to the desired calcitriol analogues **7a** (88%) and **7b**.

Experimental Part

General Methods. All reactions involving oxygen- or moisture-sensitive compounds were carried out under dry Ar. Reaction temps. refer to external bath temps. All anh. solvents were distilled under Ar immediately prior to use. THF was distilled from Na/benzophenone, cyclohexane was distilled from $LiAlH_4$, AcOEt and (i-Pr)$_2$NH were distilled from CaH_2, and CH_2Cl_2 was distilled from P_2O_5. The anal. grade cation-exchange resin *AG 50W-X40* was supplied by *BioRad* and was washed with MeOH prior to use. Liquid reagents or solns. of reagents were added by syringe or *cannula*. Org. extracts were dried over anh. Na_2SO_4, filtered, and concentrated with a rotary evaporator at aspirator pressure (20–30 mm Hg). Reactions were monitored by TLC with aluminium-backed *Merck 60* silica-gel plates (0.2 mm); the chromatograms were visualized first with UV (254 nm) and then by immersion in a soln. of phosphomolybdic acid in MeOH (5%), followed by heating. Flash column chromatography (FC) [21] was performed with *Merck 60* (230–400 mesh) silica gel. M.ps.: measured in open capillary tubes, uncorrected. NMR Spectra: recorded at 250 (^{1}H) and 63 (^{13}C) MHz, in $CDCl_3$ solns., unless otherwise stated; chemical shifts (δ) in ppm, $CDCl_3$ (7.26 (^{1}H) or 77.0 (^{13}C)) as internal standard; coupling constants (J) in Hz. Distorsionless Enhancement by Polarization Transfer (DEPT) was used to assign C-atom types. MS: m/z (rel. %); EI: 70 eV.

Scheme 5



MOM = $MeOCH_2$; PDC: pyridinium dichromate, TBS = *t*-$BuMe_2Si$; Tf = CF_3SO_2

*(1*R*,2*S*,5*R*,6*R*,10*R*)- and (1*R*,2*S*,5*R*,6*R*,10*S*)-2-(2-Methyl-1,3-dioxolan-2-yl)-11-oxatricyclo[4.3.2.0^{1,5}]undec-10-yl Acetate* ((*R*)-**14** and (*S*)-**14**). A suspension of $Pb(OAc)_4$ (16.6 g, 37.45 mmol, 3 equiv.) and anh. $CaCO_3$ (3.75 g, 37.45 mmol, 3 equiv.) in anh. cyclohexane (150 ml) was stirred at 80° for 5 min. I_2 (4.12 g, 16.22 mmol, 1.3 equiv.) and a soln. of *(1*S*,3a*R*,4*S*,7a*S*)-2,3,3a,4,5,6,7,7a-octahydro-7a-methyl-1-(2-methyl-1,3-dioxolan-2-yl)inden-4(1*H*)-ol* (**11**; 3 g, 12.48 mmol, 1 equiv.) in anh. cyclohexane (30 ml) were added. The stirred violet mixture was irradiated (300-W tungstenlamp) for 3 h and thereupon turned colorless. The mixture was filtered, and the solid was washed with cyclohexane. The soln. was concentrated under vacuum to half volume and washed with sat. aq. $Na_2S_2O_3$ (200 ml) and H_2O (150 ml). The combined aq. phase was extracted with Et_2O (2 × 150 ml). The combined org. phase was dried, filtered, and concentrated under vacuum. FC of the residue (SiO_2, 3 × 10 cm, AcOEt/hexanes 1:9–3:7) provided (*R*)-**14** (2 g, 55%; R_f 0.45 (AcOEt/hexanes 4:6); colorless oil), and (*S*)-**14** (0.83 g, 22%; R_f 0.52 (AcOEt/hexanes 4:6); colorless oil).

Data of (*R*)-**14**: ^{1}H-NMR: 6.19 (*s*, H–C(10)); 4.14 (*d*, *J* = 4.5, H–C(6)); 3.80 (*m*, OCH_2CH_2O); 2.40 (*dd*, *J* = 13.0, 6.3, H–C(5)); 2.03 (*s*, MeC=O); 1.20 (*s*, Me). ^{13}C-NMR: 170.2 (C); 110.5 (C); 98.6 (CH); 79.3 (CH); 64.5 (CH_2); 63.4 (CH_2); 58.0 (CH); 53.8 (CH); 53.7 (C); 33.3 (CH_2); 30.9 (CH_2); 24.3 (CH_2); 24.1 (CH_2); 23.8 (Me); 21.0 (Me); 18.2 (CH_2). EI-MS: 281 (5, $[M - Me]^+$), 253 (2, $[M - Ac]^+$), 237 (12, $[M - OCH_2CH_2O]^+$), 209 (11), 193 (38, $[M - OCH_2CH_2O - Ac]^+$), 121 (100).

Data of (*S*)-**14**: ^{1}H-NMR: 6.11 (*s*, H–C(10)); 4.38 (*d*, *J* = 4.8, H–C(6)); 3.85 (*m*, OCH_2CH_2O); 2.00 (*s*, MeC=O); 1.22 (*s*, Me). ^{13}C-NMR: 169.3 (C); 110.2 (C); 98.0 (CH); 79.4 (CH); 63.7 (CH_2); 63.0 (CH_2); 55.7 (C); 55.3 (CH); 54.7 (CH); 34.7 (CH_2); 30.9 (CH_2); 26.2 (CH_2); 24.5 (CH_2); 23.5 (Me); 21.3 (Me); 18.2 (CH_2). FAB-MS: 237 (26, $[M - AcO]^+$), 194 (13), 193 (100), 176 (9).

*(3a*S*,5a*R*,6*S*,9a*R*)-3a,4,5,5a,6,7,8,9-Octahydro-6-hydroxycyclopenta[*c*]inden-3(3*H*)-one* (**10**). A stirred soln. of a mixture of (*S*)- and (*R*)-**14** (2.45 g, 8.35 mmol, 1 equiv.) and pyridinium *p*-toluenesulfonate 0.43 g, 2.12 mmol, 0.25 equiv.) in wet acetone (120 ml) was refluxed for 2 h. The cooled mixture was concentrated under vacuum, and the residue was dissolved in Et_2O (100 ml) and poured in H_2O (75 ml). The aq. phase was re-extracted with Et_2O (2 × 50 ml). The combined org. phase was dried, filtered, and concentrated under vacuum to give *(1*R*,3*RS*,4*S*,7*R*,8*R*,12*S*)-3-methyl-2,13-dioxatetracyclo[6.5.0.0^{4,8}.0^{7,12}]tridecan-3-ol* (**15**). ^{1}H-NMR: 5.57 (*s*, H–C(1)); 4.68 (br. *s*, H–C(12)); 1.44 (*s*, Me).

To a freshly prepared soln. of **15** in anh. THF (110 ml) *t*-BuOK (1.8 g, 16.01 mmol, 1.9 equiv.) was added. The mixture was stirred for 10 min, treated with a few drops of H_2O and then concentrated under vacuum. The residue was dissolved in Et_2O (60 ml) and washed with sat. aq. NaCl (40 ml). The combined org. phase was dried, filtered, and concentrated under vacuum. FC of the residue (SiO_2, 2 × 10 cm, AcOEt/hexanes 2:8–5:5) gave **10** (0.51 g, 2% for the two steps; R_f 0.45 (AcOEt/hexanes 6:4)). Colorless oil. ^{1}H-NMR: 8.20 (*d*, *J* = 5.8, H–C(1)); 6.02 (*d*, *J* = 5.8, H–C(2)); 4.26 (*m*, H–C(6)); 2.21 (br. *s*, OH); 2.19 (*dd*, *J* = 11.6, 1.6, H–C(3a)). ^{13}C-NMR: 212.5 (C); 171.5 (CH); 132.6 (CH); 67.9 (CH); 55.6 (C); 54.2 (CH); 51.4 (CH); 36.2 (CH_2); 33.3 (CH_2); 27.7 (CH_2); 24.9 (CH_2); 18.5 (CH_2). FAB-MS: 193 (100, $[M + H]^+$). EI-HR-MS: 192.1150 (calc. for $C_{12}H_{16}O_2$; found: 192.1144).

*(3a*S*,5a*R*,6*S*,9a*R*)-6-[[(*tert*-Butyl)(dimethyl)silyl]oxy]-3a,4,5,5a,6,7,8,9-octahydrocyclopenta[*c*]inden-3(3*H*)-one* (**18**). A soln. of **10** (2.1 g, 10.92 mmol, 1 equiv.), *t*-$BuMe_2SiCl$ (2.14 g, 14.20 mmol, 1.3 equiv.), and 1*H*-imidazole (1.7 g, 25.12 mmol, 2.3 equiv.) in anh. DMF (50 ml) was stirred at 60° for 24 h. The reaction was quenched by addition of H_2O (4 ml), and the resulting mixture was poured in ice-H_2O (250 ml). The aq. phase was extracted with Et_2O/hexanes 1:1 (5 × 100 ml). The combined org. phase was dried, filtered, and concentrated under vacuum. FC of the residue (SiO_2; 3 × 10 cm, AcOEt/hexanes 1:9–2:8) afforded **18** (2.19 g, 66%; R_f 0.52 (AcOEt/hexanes 1:4)). White solid. M.p. 70–72°. ^{1}H-NMR: 8.20 (*d*, *J* = 5.8, H–C(1)); 6.05 (*d*, *J* = 5.8, H–C(2)); 4.24 (*m*, H–C(6)); 2.23 (*dd*, *J* = 11.6, 1.7, H–C(3a)); 0.90 (*s*, *t*-Bu); 0.06 (*s*, MeSi); 0.91 (*s*, MeSi). ^{13}C-NMR: 212.4 (C); 171.6 (CH); 132.3 (CH); 68.9 (CH); 55.8 (C); 54.3 (CH); 52.1 (CH); 36.3 (CH_2); 33.9 (CH_2); 27.9 (CH_2); 25.8 (Me); 25.5 (CH_2); 18.7 (CH_2); 18.0 (C); –4.8 (Me); –5.2 (Me). EI-MS: 306 (4, M^+), 291 (2, $[M - Me]^+$), 250 (27), 249 (100, $[M - t\text{-Bu}]^+$), 157 (18), 129 (16), 91 (13), 75 (44). EI-HR-MS: 306.2015 (calc. for $C_{18}H_{30}O_2Si$; found: 306.2021). Anal. calc. for $C_{18}H_{30}O_2Si$: C 70.53, H 9.86; found: C 70.44, H 9.75.

*(3a*S*,5a*R*,6*S*,9a*R*)-6-{[(*tert*-Butyl)(dimethyl)silyl]oxy}decahydrocyclopenta[*c*]inden-3(3*H*)-one* (**19**). A stirred suspension of **18** (85 mg, 0.28 mmol) and a catalytic amount of Pd/C (5%) in anh. AcOEt (15 ml) was deoxygenated under vacuum and hydrogenated (balloon pressure) for 2 h. The mixture was filtered (*Celite*) and the residue was washed with AcOEt. The combined filtrate was concentrated under vacuum. FC of the residue (SiO_2; 1 × 7 cm, AcOEt/hexanes 1:9) gave **19** (85 mg, 100%; R_f 0.52 (AcOEt/hexanes)). White solid. M.p. 35–37°. ^{1}H-NMR (300 MHz): 4.12 (*m*, H–C(6)); 0.89 (*s*, *t*-Bu); 0.04 (*s*, MeSi); 0.02 (*s*, MeSi). ^{13}C-NMR (75 MHz): 222.8 (C); 68.6 (CH); 59 (CH); 51.8 (CH); 50.7 (C); 37.4 (CH_2); 34.2 (CH_2); 26.1 (CH_2); 26.0 (CH_2); 25.8 (Me); 24.9 (CH_2); 18.0 (C); 17.6 (CH_2); –4.8 (Me); –5.0 (Me). FAB-MS: 309 (37, $[M + H]^+$), 308 (16, $[M - OH]^+$), 291 (64, $[M - H_2O]^+$), 251 (14, $[M - t\text{-Bu}]^+$), 177 (21), 159 (100). Anal. calc. for $C_{18}H_{32}O_2Si$: C 70.07, H 10.45; found: C 70.01, H 10.75.

*(3a*S*,5a*R*,6*S*,9a*R*)-6-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-3a,4,5,5a,6,7,8,9-octahydro-1*H*-cyclopenta[*c*]inden-3-yl Trifluoromethanesulfonate* (**20**). Anh. $(i\text{-}Pr)_2NH$ (60 µl, 0.44 mmol, 1.5 equiv.) was added dropwise under stirring to a cold (–78°) soln. of BuLi in hexanes (180 µl, 0.44 mmol, 2.4M, 1.5 equiv.). The white solid of $(i\text{-}Pr)_2NLi$ was dissolved in anh. THF (1 ml). The soln. was stirred for 10 min, and a soln. of **19** (90 mg, 0.29 mmol, 1 equiv.) in anh. THF (3 ml) was added. The mixture was stirred at –78° for 2 h and than treated with *N*-(5-chloropyridin-2-yl)-1,1,1-trifluoro-*N*-(trifluoromethylsulfonyl)methanesulfonamide (140 mg, 0.35 mmol, 1.2 equiv.). The deep-red mixture was warmed to r.t., and then stirred for 20 min. The reaction was quenched by addition of a few drops of H_2O. The mixture was concentrated under vacuum, and the residue was purified by FC (SiO_2; 1 × 10 cm, hexanes) to afford **20** (110 mg, 86%; R_f 0.85 (hexanes)). Colorless oil. ^{1}H-NMR: 5.48 (*m*, H–C(2)); 4.16 (*m*, H–C(6)); 2.83 (*d*, *J* = 17.6, H–C(1)); 2.47 (*m*, H–C(3a)); 2.04 (*dd*, *J* = 17.6, 2.9, H–C(1)); 0.89 (*s*, *t*-Bu); 0.04 (*s*, MeSi); 0.02 (*s*, MeSi). ^{13}C-NMR: 151 (C); 118.6 (*q*, *J* = 320.7, CF_3); 116.6 (CH); 68.9 (CH); 52.8 (CH); 51.6 (CH); 51.4 (C); 37.4 (CH_2); 35.3 (CH_2); 34.4 (CH_2); 30.2 (CH_2); 27.5 (CH_2); 25.8 (Me); 18.0 (C); 17.1 (CH_2); –4.9 (Me); –5.1 (Me). FAB-MS: 441 (6, $[M + H]^+$), 440 (10, M^+), 439 (36,

$[M-H]^+$), 421 (6, $[M-F]^+$), 383 (19, $[M-t\text{-Bu}]^+$), 307 (36, $[M-SO_2CF_3]^+$), 175 (70), 159 (100), 154 (55), 136 (75),117 (64). Anal. calc. for $C_{19}H_{31}F_3O_4SSi$: C 51.82, H 7.05; found: C 52.22, H 7.11.

*(3a*S*,5a*R*,6*S*,9a*R*)-3a,4,5,5a,6,7,8,9-Octahydro-6-hydroxy-1*H*-cyclopenta[*c*]inden-3-yl Trifluoromethanesulfonate* (**21**). An aq. soln. of HF (48%, 4 drops) was added to a soln. of **20** (65 mg, 0.15 mmol, 1 equiv.) in MeCN (2 ml). The mixture was stirred for 2 h and then poured in an aq. sat. soln. of $NaHCO_3$ (5 ml). The aq. phase was extracted with Et_2O (3 × 5 ml). The combined org. phase was dried, filtered, and concentrated under vacuum. FC of the residue (SiO_2; 1 × 12 cm, AcOEt/hexanes 15:85) gave **21** (46 mg, 96%; R_f 0.50 (AcOEt/hexanes 3:7)). Colorless oil. ^{1}H-NMR: 5.46 (*m*, H–C(2)); 4.23 (*m*, H–C(6)); 2.77 (*d*, *J* = 17.4, H–C(1)); 2.50 (*m*, H–C(3a)); 2.12 (*dd*, *J* = 17.4, 2.9, H–C(1)). ^{13}C-NMR: 151.2 (C); 118.6 (*q*, *J* = 320.7, CF_3); 116.3 (CH); 68.6 (CH); 52.8 (CH); 51.3 (CH); 51.0 (C); 37.3 (CH_2); 35.3 (CH_2); 33.9 (CH_2); 30.3 (CH_2); 27.0 (CH_2); 17.0 (CH_2). EI-MS: 308 (2, $[M-H_2O]^+$), 280 (30), 175 (52), 157 (21), 147 (58), 69 (100). EI-HR-MS: 325.0721 (calc. for $C_{13}H_{16}F_3O_4S$; found: 325.0721).

*(3a*S*,5a*R*,9a*S*)-3a,4,5,5a,6,7,8,9-Octahydro-6-oxo-1*H*-cyclopenta[*c*]inden-3-yl Trifluoromethanesulfonate* (**22**). Pyridinium dichromate (80 mg, 0.21 mmol, 4.2 equiv.) and a catalytic amount of pyridinium *p*-toluenesulfonate were successively added to a soln. of **21** (15 mg, 0.05 mmol, 1 equiv.) in anh. CH_2Cl_2 (1.5 ml). The mixture was stirred in the dark for 5 h and then filtered (*Celite*), and the residue was washed with AcOEt. The filtrate was concentrated under vacuum, and the residue was purified by FC (SiO_2; 1 × 5 cm, AcOEt/hexanes 15:85) to give **22** (14 mg, 100%; R_f 0.60 (AcOEt/hexanes 3:7)). Colorless oil. ^{1}H-NMR: 5.48 (*m*, H–C(2)); 2.83 (*d*, *J* = 8.2, H–C(3a)); 2.58 (*dd*, *J* = 12.0, 4.0, H–C(5a)). ^{13}C-NMR: 210.2 (C); 149.5 (C); 118.5 (*q*, *J* = 320.7, CF_3); 115.3 (CH); 61.3 (CH); 57.0 (C); 52.5 (CH); 40.6 (CH_2); 35.9 (CH_2); 34.4 (CH_2); 29.9 (CH_2); 23.7 (CH_2); 23.1 (CH_2). EI-MS: 324 (18, M^+), 307 (8, $[M-OH]^+$), 192 (20), 191 (100), 163 (40). EI-HR-MS: 324.0643 (calc. for $C_{13}H_{15}F_{3\,O4}S$; found: 324.0641).

*(3a*S*,5a*R*,9a*S*)-3a,4,5,5a,8,9-Hexahydro-3-(4-hydroxy-4-methylpent-1-ynyl)-1*H*-cyclopenta[*c*]inden-6(7*H*)-one* (**8a**). *2-Methyl-pent-4-yn-2-ol* (**23**; 27 mg, 0.28 mmol, 3 equiv.) and a catalytic amount of $Pd(PPh_3)_4$ were succesively added to a soln. of **22** (30 mg, 0.09 mmol, 1 equiv.) in pyrrolidine (1 ml). The mixture was stirred for 30 min and then poured in a sat. aq. soln. of NH_4Cl (7 ml). The aq. phase was extracted with Et_2O (3 × 10 ml). The combined org. phase was dried, filtered, and concentrated under vacuum. FC of the residue (SiO_2; 1 × 10 cm, AcOEt/hexanes 2:8–4:6) **8a** (23 mg, 92%; R_f 0.50 (AcOEt/hexanes 1:1)). Colorless oil. ^{1}H-NMR (300 MHz): 5.78 (*m*, H–C(2)); 2.79 (*d*, *J* = 8.8, H–C(3a)); 2.59 (*dd*, *J* = 12.2, 4.4, H–C(14)); 2.51 (*s*, 2 H–C(3′)); 1.32 (*s*, 2 Me). ^{13}C-NMR (75 MHz): 211.2 (C); 133.9 (CH); 126.4 (C); 87.1 (C); 79.8 (C); 70.0 (C); 61.5 (CH); 58.6 (C); 58.2 (CH); 40.6 (CH_2); 39.3 (CH_2); 36.1 (CH_2); 34.9 (CH_2); 31.3 (CH_2); 28.5 (Me); 24.4 (CH_2); 22.9 (CH_2). EI-MS: 272 (4, M^+), 257 (3), 215 (17), 214 (100), 213 (5), 171 (26), 143 (29), 129 (38), 128 (34), 59 (86). EI-HR-MS: 272.1776 (calc. for $C_{18}H_{24}O_2$; found: 272.1768).

*(3a*S*,5a*R*,9a*S*)-3a,4,5,5a,8,9-Hexahydro-3-[(1*E*)-4-(methoxymethoxy)-4-methylpent-1-enyl]-1*H*-cyclopenta[*c*]inden-6(7*H*)-one* (**8b**). A soln. of **22** (25 mg, 0.08 mol, 1 equiv.), *tributyl[(*E*)-4-(methoxymethoxy)-4-methylpent-1-enyl]stannane* (**25**, 43 mg, 0.10 mmol, 1.25 equiv.), anh. LiCl (33 mg, 0.77 mmol, 9.5 equiv.), and a catalytic amount of $Pd(Ph_3P)_4$ in anh. THF (2 ml) was stirred at 75° for 4 h. The reaction was quenched by addition of H_2O (7 ml). The aq. phase was extracted with Et_2O (3 × 7 ml). The combined org. phase was dried, filtered, and concentrated under vacuum. The residue was purified by FC (SiO_2; 1 × 13 cm, AcOEt/hexanes 1:9–2:8) to give **8b** (16 mg, 66%; R_f 0.55 (AcOEt/hexanes 3:7)). Colorless oil. ^{1}H-NMR (300 MHz): 6.12 (*d*, *J* = 15.7, H–C(1′)); 5.53 (*m*, H–C(2′)); 5.38 (br. *s*, H–C(2)); 4.73 (*s*, OCH_2O); 3.36 (*s*, MeO); 2.88 (br. *d*, *J* = 9.9, H–C(3a)); 2.60 (*dd*, *J* = 11.5, 4.5, H–C(5a)); 1.21 (*s*, 2 Me–C(4′)). ^{13}C-NMR (75 MHz): 211.5 (C); 145.1 (C); 128.8 (CH); 127.2 (CH); 126.2 (CH); 91.0 (CH_2); 76.4 (C); 61.3 (Me); 59.6 (C); 55.0 (CH); 54.0 (CH); 45.5 (CH_2); 40.9 (CH_2); 38.7 (CH_2); 36.5 (CH_2); 31.6 (CH_2); 26.3 (Me); 26.2 (Me); 24.7 (CH_2); 23.3 (CH_2). EI-MS: 260 (51), 257 (21), 228 (32), 215 (35), 214 (100), 202 (23). EI-HR-MS: 318.2195 (calc. for $C_{20}H_{30}O_3$; found: 318.2196).

*(1*S*,3*R*,5*Z*,7*E*)-1,3-Bis{[(*tert*-butyl)(dimethyl)silyl]oxy}-20,21,22,22,23,23-hexadehydro-18,21-cyclo-9,10-secocholesta-5,7,10(19)-trien-25-ol* (**24**). A soln. of the lithium salt of *(2*Z*)-2-((3*S*,5*R*)-3,5-bis{[(*tert*-butyl)(dimethyl)silyl]oxy}-2-methylenecyclohexyliden)ethyl(diphenyl)phosphine oxide* (**9**) in THF was prepared by dropwise addition of a soln. of BuLi in hexanes (0.24 ml, 0.58 mmol) to a cooled (–78°), stirred soln. of **9** (409 mg, 0.70 mmol, 6 equiv.) in anh. THF (6.8 ml). The deep-red soln. was stirred for 1.5 h. To this cold soln. a soln. of **8a** (30 mg, 0.11 mmol, 1 equiv.) in anh. THF (3 ml) was added dropwise. The mixture was stirred in the dark at –78° for 9 h and at –40° for 1 h. The reaction was quenched by addition of H_2O (5 ml) and AcOEt (10 ml). The aq. phase was extracted with AcOEt (3 × 5 ml). The combined org. phase was washed with sat. aq. NaCl (5 ml), dried, filtered, and concentrated under vacuum. The residue was purified by FC (SiO_2; 1.5 × 14 cm, AcOEt/hexanes 1:99–5:95) to give **24** (60 mg, 86%; R_f 0.50 (AcOEt/hexanes 1:9)). Colorless oil. ^{1}H-NMR:

6.17, 6.02 (*AB*, $J = 11.3$, H–C(6), H–C(7)); 5.77 (*m*, H–C(21)); 5.19 (*m*, H–C(19)); 4.86 (*d*, $J = 2.3$, H–C(19)); 4.39 (*m*, H–C(1)); 4.18 (*m*, H–C(3)); 2.76 (*m*, H–C(14)); 2.62 (*d*, $J = 9.2$, H–C(17)); 2.51 (*s*, 2 H–C(24)); 2.44 (*dd*, $J = 13.3$, 3.6, H–C(18)); 2.21 (*dd*, $J = 13.1$, 7.1, H–C(18)); 2.21 (*dd*, $J = 13.1$, 7.1, H–C(18)); 1.32 (*s*, Me(26), Me(27)); 0.88 (*s*, 2*t*-Bu); 0.06 (*s*, 2 Me_2Si). ^{13}C-NMR: 148.3 (C); 141.1 (C); 135.5 (C); 135.3 (CH); 127.5 (C); 122.9 (CH); 117.2 (CH); 111.2 (CH_2); 86.1 (C); 81.0 (C); 71.9 (CH); 70.1 (C); 67.5 (CH); 58.2 (CH), 56.5 (CH); 55.5 (C); 45.9 (CH_2); 44.8 (CH_2); 39.8 (CH_2); 37.7 (CH_2); 35.2 (CH_2); 31.9 (CH_2); 28.6 (Me); 28.5 (CH_2); 25.8 (Me); 25.8 (Me); 25.3 (CH_2); 24.4 (CH_2); 18.2 (C); 18.1 (C); –4.6 (Me); –4.7 (Me); –4.8 (Me); –5.1 (Me).

*(1*S*,3*R*,5*Z*,7*E*)-20,21,22,22,23,23-Hexadehydro-18,21-cyclo-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol* (**7a**). A soln. of **24** (50 mg, 0.08 mmol, 1 equiv.) in anh. THF (9 ml) was treated with a soln. of Bu_4NF in THF (1M, 2 ml, 2 mmol, 25 equiv.). The mixture was stirred in the dark for 9 h. The reaction was quenched by addition of sat. aq. NH_4Cl (20 ml). The aq. phase was extracted with AcOEt (3 × 10 ml). The combined org. phase was dried, filtered, and concentrated under vacuum. FC of the residue (SiO_2; 1 × 10 cm, AcOEt/hexanes 2:3–4:1) gave **7a** (23 mg, 88%; R_f 0.60 (AcOEt)). White solid. ^{1}H-NMR: 6.31, 6.02 (*AB*, $J = 11.3$, H–C(6), H–C(7)); 5.77 (*m*, H–C(21)); 5.32 (*m*, H_E–C(19)); 4.99 (*m*, H_Z–C(19)); 4.43 (*m*, H–C(1)); 4.23 (*m*, H–C(3)); 2.77 (*m*, H–C(14)); 2.60 (*m*, H–C(17), H–C(18)); 2.50 (*s*, 2 H–C(24)); 2.31 (*dd*, $J = 13.3$, 6.3, H–C(18)); 1.32 (*s*, Me(26), Me(27)). ^{13}C-NMR: 147.6 (C); 143.2 (C); 135.2 (CH); 133.4 (C); 127.5 (C); 124.6 (CH); 116.3 (CH); 111.7 (CH_2); 86.2 (C); 80.9 (C); 70.6 (C); 70.1 (CH); 66.8 (CH); 58.2 (CH); 56.5 (CH); 55.6 (C); 45.1 (CH_2); 42.8 (CH_2); 39.8 (CH_2); 37.6 (CH_2); 35.1 (CH_2); 31.9 (CH_2); 28.7 (Me); 28.6 (CH_2); 25.4 (CH_2); 24.5 (CH_2). EI-MS: 408 (6, M^+), 391 (11), 390 (16), 372 (14), 279 (17), 171 (11), 167 (30), 149 (100). EI-HR-MS: 408.2664 (calc. for $C_{27}H_{36}O_3$; found: 408.2681).

*(1*S*,3*R*,5*Z*,7*E*,22*E*)-3-[(*tert*-Butyl)(dimethyl)silyl]oxy-20,21,22,23-tetradehydro-25-(methoxymethyoxy)-18,21-cyclo-9,10-secocholesta-5,7,10(19)-trien-1-yl (*tert*-Butyl)(dimethyl)silyl Ether* (**26**). A soln. of the lithium salt of **9** in THF was prepared by the dropwise addition of a soln. of BuLi in hexanes (0.16 ml, 0.40 mmol) to a cooled (–78°), stirred soln. of **9** (290 mg, 0.50 mmol, 3 equiv.) in anh. THF (4.8 ml). The deep-red soln. was stirred for 2 h. To this cold soln. was added dropwise a soln. of **8b** (50 mg, 0.17 mmol, 1 equiv.) in anh. THF (6 ml). The mixture was stirred in the dark at –78° for 4 h and at –40° for 1 h. The reaction was quenched by addition of H_2O (5 ml) and AcOEt (10 ml). The aq. phase was extracted with AcOEt (3 × 5 ml). The combined org. phase was washed with sat. aq. NaCl (5 ml), dried, filtered, and concentrated under vacuum. The residue was purified by FC (SiO_2; 1.5 × 9 cm, AcOEt/hexanes 1:99–5:95) to give **26** (97 mg, 86%; R_f 0.50 (AcOEt/hexanes 1:9)). Colorless oil. ^{1}H-NMR: 6.12 (*m*, H–C(6), H–C(7), H–C(22)); 5.53 (*m*, H–C(23)); 5.39 (*m*, H–C(21)); 5.20 (*m*, H–C(19*E*)); 4.88 (*m*, H–C(19*Z*)); 4.75 (*s*, OCH_2O); 4.39 (*m*, H–C(1)); 4.19 (*m*, H–C(3)); 3.38 (*s*, MeO); 2.76 (*m*, H–C(17), H–C(14)); 2.44 (*dd*, $J = 13.3$, 3.3, H–C(18)); 2.22 (*dd*, $J = 13.3$, 6.9, H–C(18)); 1.23 (*s*, Me(26), Me(27)); 0.89 (*s*, *t*-Bu); 0.88 (*s*, *t*-Bu); 0.07 (*s*, Me_2Si); 0.06 (*s*, Me_2Si). ^{13}C-NMR: 148.4 (C); 145.4 (C); 141.4 (C); 135.2 (C); 129.3 (CH); 127.3 (CH); 126.4 (CH); 123.0 (CH); 116.8 (CH); 111.1 (CH_2); 91.0 (CH_2); 71.8 (CH); 67.5 (CH); 56.2 (C); 56.1 (CH); 55.1 (CH); 53.7 (CH); 45.9 (CH_2); 45.5 (CH_2); 44.8 (CH_2); 39.1 (CH_2); 38.0 (CH_2); 32.1 (CH_2); 28.6 (CH_2); 26.3 (Me); 26.2 (Me); 25.8 (Me); 25.8 (Me); 25.7 (CH_2); 24.5 (CH_2); 18.3 (C); 18.1 (C); –4.7 (Me); –4.8 (Me); –5.1 (Me).

*(1*S*,3*R*,5*Z*,7*E*,22*E*)-20,21,22,23-tetradehydro-18,21-cyclo-9,10-secocholesta-5,7,10(19)-triene-1,3-diol* (**7b**). A soln. of **26** (45 mg, 0.07 mmol, 1 equiv.) in anh. THF (10 ml) was treated with a soln. of Bu_4NF in THF (1M, 1.5 ml, 1.5 mmol, 21 equiv.). The mixture was stirred in the dark for 15 h. The reaction was quenched by addition of sat. aq. NH_4Cl (20 ml). The aq. phase was extracted with AcOEt (3 × 10 ml). The combined org. phase was dried, filtered, and concentrated under vacuum. The residue was diluted with anh. MeOH (15 ml) and treated with cationic resin *AG 50W-X4* (800 mg). The mixture was stirred in the dark for 3 h and then filtered. The solids were washed with anh. AcOEt (4 × 20 ml). The soln. was concentrated under vacuum, and the residue was purified by FC (SiO_2; 1.5 × 10 cm, AcOEt/hexanes 2:8–7:3) to give **7b** (27 mg, 100%; R_f 0.50 (AcOEt/hexanes 8:2)). White solid. ^{1}H-NMR: 6.33, 6.03 (*AB*, $J = 11.3$, H–C(6), H–C(7)); 6.17 (*d*, $J = 15.7$, H–C(22), 5.53 (*m*, H–C(23)); 5.42 (*m*, H–C(21)); 5.32 (*m*, H–C(19*E*)); 5.00 (*m*, H–C(19*Z*)); 4.42 (*m*, H–C(1)); 4.22 (*m*, H–C(3)); 2.76 (*m*, H–C(17), H–C(14)); 2.58 (*dd*, $J = 13.3$, 3.1, H–C(18)); 2.34 (*dd*, $J = 13.3$, 6.4, H–C(18)); 2.25 (*d*, $J = 7.5$, 2 H–C(24)); 1.22 (*s*, Me(26), Me(27)). ^{13}C-NMR: 147.6 (C); 145.2 (C); 143.4 (C); 133.2 (C); 130.4 (CH); 127.8 (CH); 125.8 (CH); 124.7 (CH); 116.0 (CH); 111.6 (CH_2); 70.9 (CH); 70.6 (C); 66.8 (CH); 56.4 (C); 56.0 (CH); 53.7 (CH); 47.2 (CH_2); 45.1 (CH_2); 42.8 (CH_2); 39.1 (CH_2); 37.8 (CH_2); 32.0 (CH_2); 29.2 (Me); 29.1 (Me); 28.8 (CH_2); 25.8 (CH_2); 24.6 (CH_2). EI-MS: 410 (4 M^+), 393 (16), 392 (49), 374 (18), 334 (26), 200 (30), 155 (39), 129 (42), 59 (100). EI-HR-MS: 410.2820 (calc. for $C_{27}H_{38}O_3$; found: 410.2820).

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