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First Total Synthesis of J_2 Isoprostane

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A stereoselective Julia−Lythgoe olefination followed by an efficient 1,3-allylic transposition of the C-9 hydroxyl group of compound **13** has allowed the first total synthesis of J_2 isoprostane (**1**), a recently discovered member of the growing isoprostane family. This elusive compound opens up numerous new avenues for the molecular biology of cyclopentenone prostaglandins which are endowed of intriguing biological effects such as antitumor, antiinflammatory, and antiviral activities. In principle, our approach is flexible enough to allow an easy synthesis of other isoprostanes of the J family following the same methodology.

Isoprostanes (IsoPs) are a family of eicosanoids formed in vivo from the free radical-initiated peroxidation of membrane-bound arachidonic acid independent of the cyclooxygenase enzyme.[1]

Lipid peroxidation can occur by either of two routes involving an endoperoxide mechanism or a dioxetane/endoperoxide mechanism.[2] Regardless of the mechanism responsible for their formation, isoprostanes exhibit two key structural features which distinguish them from common prostaglandins, namely the thermodinamically less stable cis stereochemistry of the two side chains on the five-membered ring and the formation of racemates. These are the notable differences between the enzymatic process and free-radical processes. Besides the well-known F_2-, D_2-, and E_2-IsoPs, in 1999 Morrow and Roberts[3] reported the formation in vivo of two new elusive cyclopentenone isoprostanes belonging to the A_2 and J_2 families which are formed presumably through dehydration of E_2- and D_2-IsoPs, respectively.[4] Representative examples of E_2-, A_2-, D_2-, and J_2-IsoPs are reported in Figure 1.

As a consequence of the nonenzymatic pathway, J_2-IsoP (**1**) is formed as a racemic mixture of two pairs of diastereomers: 15-J_{2c}-IsoP (**2**) and its enantiomer 15-*epi*-15-J_{2t}-IsoP (*ent*-**2**); and 15-J_{2t}-IsoP (**3**) and its enantiomer 15-*epi*-15-J_{2c}-IsoP (*ent*-**3**) (Figure 2).[5]

Cyclopentenone prostaglandins of the J_2 series have their own unique spectrum of biological effects, including antitumor activities, the inhibition of cell cycle progression, the suppression of viral replication, the apoptosis of cells, and the expression of stress-related genes in various cell types including human breast cancer cells. In addition, they also show an antiinflammatory effect, including inhibition of nuclear factor κB activation by inhibiting IκB kinase.[6]

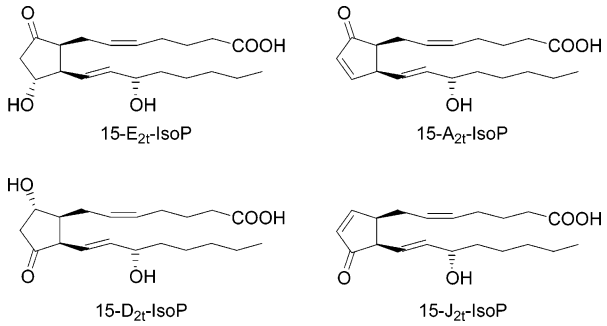

FIGURE 1.

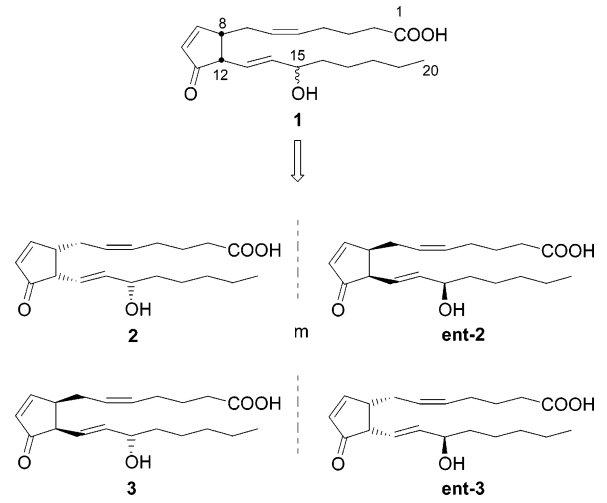

FIGURE 2. J_2 isoprostane family.

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(2) (a) Rokach, J.; Khanapure, S. P.; Hwang, S.-W.; Adiyaman, M.; Schio, L.; FitzGerald, G. A. *Synthesis* **1998**, *1*, 569. (b) Rokach, J.; Khanapure, S. P.; Hwang, S. W.; Adiyaman, M.; Lawson, J. A.; FitzGerald, G. A. *Prostaglandins* **1997**, *54*, 823.

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(5) Different nomenclature systems are used to name the Isops; we followed the Taber's indication: Taber, D. F.; Morrow, J. D.; Roberts, J. L., II *Prostaglandins* **1997**, *53*, 67.

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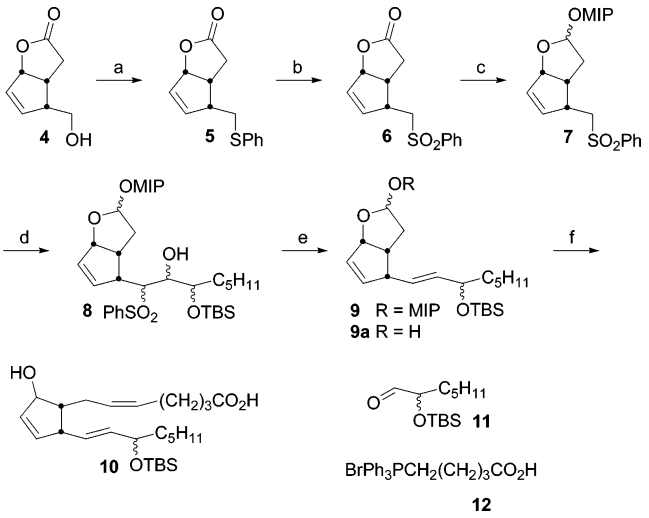
SCHEME 1[a]



[a] Reagents and conditions: (a) $(PhS)_2$, Bu_3P, pyridine, rt, 4.5 h, 92%; (b) H_2O_2, 10% mol of $(NH_4)_2MoO_4$, MeOH, 0 °C to rt, 16 h, 98%; (c) (1) DIBAL-*H*, DCM, −78 °C, 1.5 h, 97%; (2) 2-methoxypropene, PPTS, DCM, −20 to 0 °C, 1 h, 93%; (d) (1) BuLi, THF, −78 °C, 45 min; (2) **11** in THF, −78 °C, 2 h, 83%; (e) Na(Hg), 10% Na_2HPO_4, MeOH, −40 to −20 °C, 1.5 h, 80%. (f) (1) acetate buffe,r pH 4.15, THF−H_2O 3:2, 24 h, 82%; (2) **12**, t-BuOK, THF, rt, 20 min, then **9a** in THF, 2 h, 83%.

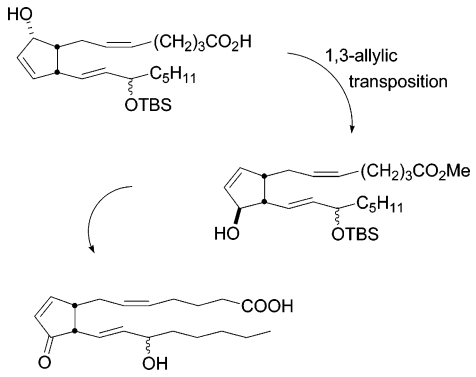
These intriguing properties make the investigation of the biological profiles of new cyclopentenone isoprostanes J_2 (**1**; J_2-IsoP) an important task. Unfortunately, a detailed evaluation of the biological activities of J_2-IsoP has been prevented by poor availability of pure compounds.[4] Thus, the chemical synthesis of J_2-IsoP is not only a highly challenging goal, but is the only way to gain enough material for biological studies.

In achieving this elusive target by total synthesis three main issues have to be considered, each presenting a daunting synthetic challenge: (i) the inherent difficulty in installing the two side chains with the thermodynamically less favored cis stereochemistry on the cyclopentenone ring,; (ii) the easy epimerization of the labile stereogenic centers C-8 and C-12, and (iii) the high tendency to dehydration of the C-15 hydroxyl group.[7] In this paper we report a simple and efficient solution to these problems and the first total synthesis of natural J_2-IsoP.

The initial part of the synthesis, involving the stereoselective construction of the cis-disubstituted cyclopentene moiety, is summarized in Scheme 1.

The pivotal point for this approach is the all-cis sulfone-lactone **6** available in multigram quantities, in a stereodefined fashion, from known lactone **4**.[8] In the event, lactone **4** was converted into the corresponding sulfide **5**, which was chemoselectively oxidized to sulfone **6** in 95% yield with H_2O_2 in the presence of a catalytic amount of $(NH_4)_2MoO_4$ in methanol at rt.[9] Reduction of lactone **6** with DIBAL-*H* gave the corresponding lactol in 99% yield, which was immediately protected as its 1-methyl-1-methoxyethyl ether (MIP) **7** in 93% yield upon exposure to 2-methoxypropene in the presence of a catalytic amount of PPTS.[10] The lower side chain was then installed taking advantage of the unique stereochemical features of the Julia−Lythgoe olefination.[11] We envisioned that this approach not only would allow the cis stereochemistry of sulfone **6** to be preserved, but also would give rise to the required stereodefined *E* Δ^{13} double bond. The crucial Julia−Lythgoe condensation was carried out by exposing the lithiated sulfone **7** to aldehyde **11**[12] (BuLi, THF, −78 °C 45 min, followed by addition of **11** in THF, −78 °C 2 h) to yield the desired hydroxysulfone **8** as a mixture of diastereomers in 80% yield. Reductive elimination of crude **8** with 10% sodium amalgam in the presence of Na_2HPO_4 in MeOH at −20 °C delivered the desired MIP-protected lactol **9** in 82% yield. The upper side chain was then installed by a Wittig condensation, using the well-known prostaglandin chemistry.[13] Thus, standard olefination of the aldehyde function released from acetal **9** (acetate buffer pH 4.15, THF/H_2O, 82%) with the nonstabilized Wittig reagent derived from phosphonium salt **12** smoothly gave the corresponding *Z* olefin **10** in 83% isolated yield. With the cyclopentenol **10** assembled in a stereocontrolled way, completion of the synthesis of J_2-Isop (**1**) required an allylic 1,3-transposition of the C-9 hydroxyl group followed by a manipulation of functional groups (Scheme 2).

SCHEME 2



There are a number of 1,3-allylic transposition reactions that, in pinciple, can provide the rearranged cyclopentenol **15**. However, after some experimentation, only the [2,3] sigmatropic rearrangement of secondary allyl selenoxides[14] was successfully applied to allylic alcohol **10**.[15]

In the event (Scheme 3), carboxylic acid **10** was first converted to the corresponding methyl ester **13** (CH_2N_2, Et_2O, 90%). Treatment of **13** with *o*-nitrophenyl seleno-

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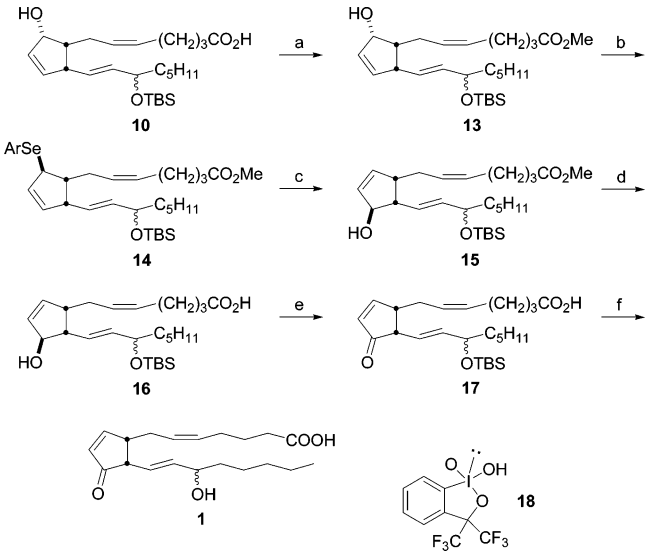
SCHEME 3[a]



[a] Reagents and conditions: (a) CH_2N_2, Et_2O, 0 °C, 90%; (b) *o*-nitrophenylselenocyante, Bu_3P, THF, rt, 2 h, 88%; (c) 30% H_2O_2, pyridine, THF, 0 °C, 18 h, 60%; (d) $Ba(OH)_2 \cdot 8H_2O$, MeOH, rt, 18 h, 80%; (e) **18**, AcOH, DCM, 0.5 h, rt, 84%; (f) aq 48% HF, MeCN, −20 °C, 4 h, 90%.

cyanate in the presence of tri-*n*-butylphosphine readily afforded the S_N2 selenide product **14** in 88% yield.[16] Subsequent oxidation of compound **14** with 30% H_2O_2 at 0 °C, in the presence of pyridine in THF, proceeded smoothly, producing the desired alcohol **15** in 60% yield. It should be pointed out that the stereochemical outcome of this crucial transposition has no consequence for our synthetic plan since one of the last steps requires the oxidation of the transposed allylic alcohol to the corresponding α,β-unsaturated ketone. Deprotection of methyl ester **15** with $Ba(OH)_2$ in MeOH (18 h, rt, 80%)[17] followed by mild oxidation of the sensitive cyclopentenol **16** with hydroxyiodinane oxide **18**[18] in DCM, in the presence of 1.2 equiv of AcOH, delivered the labile cyclopentenone **17** in 84%.

Finally, aqueous HF (aq 48% HF, MeCN, −20 °C, 4 h) mediated desilylation afforded synthetic J_2-IsoP **1** in 90% yield.[19]

The cis stereochemistry of the two side chains on the cyclopentenone ring was firmly established by Noesy experiments[20] and by comparing the ^{1}H NMR spectrum of natural PGJ_2 with that of synthetic J_2-IsoP. Moreover, the ^{1}H NMR olefinic signals at 5.65−5.50 of the lower side-chain double bond of PGJ2 were completely superimposable on those of J_2-IsoP (**1**), indicating a complete *E* stereoselectivity for the Julia−Lythgoe olefination. In conclusion, we have described the first synthesis of isoprostane J_2.

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(20) Irradiation of H-12 at δ 3.72 gave an enhancement of 3% of H-8 at δ 2.55.

Experimental Section

(3a*R,4*R**,6a*S**)-4-Phenylsulfanylmethyl-3,3a,4,6a-tetrahydrocyclopenta[*b*]furan-2-one (5).** To a stirred solution of lactone **4** (97 mg, 0.629 mmol) in 2.5 mL of dry THF under an argon atmosphere was added solid PhSSPh (412 mg, 1.887 mmol, 3 equiv), then the mixture was cooled to 0 °C in an ice bath and then Bu_3P (382 mg, 1.887 mmol, 3 equiv) was added dropwise. The ice bath was removed and the solution was stirred at room temperature for 4 h. Brine (7 mL) and DCM were then added to the reaction mixture and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic fractions were washed with brine and dried on $MgSO_4$. Evaporation under reduced pressure gave an oily residue that was purified by flash chromatography on silica gel (28 g). Elution with hexanes−EtOAc (8:2) gave sulfide **5** as a colorless oil (142 mg, 92%).

IR (liquid film) 3057, 2929, 1770, 1171, 1002, 742, 691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5−7.1 (m, 5H, Ph), 6.02 (dt, *J* = 5.7, 1.3 Hz, 1H), 5.9 (dt, *J* = 6.4, 2.4 Hz, 1H), 5.45 (dd, *J* = 1.6, 8.0 Hz, 1H), 3.28 (m, 1H), 3.12 (br t, *J* = 2.14, 6.0 Hz, 1H), 3.05 (d, *J* = 6.4 Hz, 1H), 2.86 (dt, *J* = 4.2, 11.8 Hz, 1H), 2.60 (dd, *J* = 9.6, 18.2 Hz, 1H), 2.45 (dd, *J* = 8.6, 18.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6 (0), 138.0 (1), 135.1 (0), 130.0 (1), 129.6 (1), 129.0 (1), 126.7 (1), 88.3 (1), 45.9 (1), 39.4 (1), 35.1 (2), 29.1 (2); EIMS (70 eV) *m*/*z* 246 (30) [M$^+$], 123 (100), 108 (20), 91 (10), 77 (30), 65 (20), 52 (12), 45 (25). Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.34; H, 5.76.

(3a*R,4*R**,6a*S**)-4-Benzenesulfonylmethyl-3,3a,4,6a-tetrahydrocyclopenta[*b*]furan-2-one (6).** Sulfide **5** (144 mg, 0.585 mmol) was dissolved in MeOH (5 mL) and cooled to 0 °C; to this solution were added solid $(NH_4)_2MoO_4$ (15 mg) and 30% H_2O_2 (650 μL). The temperature was allowed to reach rt and stirring was continued for 90 min. After addition of an additional 190 μL of 30% H_2O_2 the yellow slurry was stirred for an additional 16 h. The reaction was quenched by adding solid Na_2SO_3; after 40 min of stirring at room temperature, MeOH was removed by evaporation in vacuo and the residue was taken up in a saturated solution of NH_4Cl (6 mL) and DCM (10 mL). The aqueous phase was extracted with DCM (3 × 25 mL) and the organic layers were collected, washed with brine, and dried on $MgSO_4$. Evaporation in vacuo of the volatiles gave the crude sulfone (160 mg) that was purified by chromatography on silica gel (4 g) with hexanes−EtOAc (1:1) as eluent. Sulfone **6** was obtained as a pale yellow oil (159 mg, 98%).

IR (liquid film) 3060, 2980, 2940, 1770, 1450, 1410, 1370, 1310, 1150, 1090, 1020, 1000, 950, 775, 750, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, 2H, Ph), 7.80−7.65 (m, 1H, Ph), 7.65−7.50 (m, 2H, Ph), 5.95 (br s, 2H, H-5 and H-6), 5.45 (dd, *J* = 1.7, 8.1 Hz, 1H), 3.50−3.35 (m, 2H), 3.35−3.10 (m, 2H), 2.65−2.45 (m, 1H), 2.30 (dd, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8 (0), 139.0 (0), 136.2 (1), 134.2 (1), 130.9 (1), 129.5 (2 × 1), 127.9 (2 × 1), 87.9 (1), 56.7 (2), 40.3 (1), 29.8 (2), 29.2 (1); EIMS (70 eV) *m*/*z* 279 (3) [M + H]$^+$, 261 (13) [M − OH]$^+$, 233 (20), 217 (5), 137 (48), 125 (23), 109 (8), 91 (100), 77 (15), 65 (11), 51 (15), 39 (31). Anal. Calcd for $C_{14}H_{14}O_4S$: C, 60.42; H, 5.07; O, 22.99; S, 11.52. Found: C, 60.44; H, 5.09.

(3a*R,4*R**,6a*S**)-4-Benzenesulfonylmethyl-2-(1-methoxy-1-methylethoxy)-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan (7).** A stirred solution of sulfone **6** (150 mg, 0.539 mmol) in DCM (3.5 mL) was cooled to −78 °C and DIBAL-*H* (1 M in hexanes, 650 μL, 1.2 equiv) was added dropwise. Stirring was continued for an additional 1 h, then a saturated solution of NH_4Cl (2.6 mL) was added at −78 °C. The mixture was gradually warmed to room temperature, diluted with DCM (8 mL), and acidified with concentrated HCl. The aqueous layer was extracted with DCM (3 × 7 mL) and the combined organic phases were washed with H_2O and brine, and dried on $MgSO_4$. Evaporation in vacuo of the volatiles left the corresponding lactol (146 mg, 97%), 9:1 mixture of hemiacetals, as a white solid, mp 129−130 °C.

The crude lactol (139 mg, 0.496 mmol) was dissolved in dry DCM (7.6 mL) under an argon atmosphere and neat 2-methoxypropene (250 mg, 3.472 mmol, 7.0 equiv) was added. The solution was cooled to −20 °C and solid PPTS was added with stirring. The mixture was gradually warmed to 0 °C and stirring was continued for an additional 1 h. The reaction was quenched by adding solid $NaHCO_3$ at 0 °C. A saturated solution of $NaHCO_3$ (7 mL) was then added and the aqueous layer was extracted with DCM (3 × 15 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography of the oily residue (silica gel, hexanes−EtOAc, 75:25 → 70:30) afforded acetal **7** (163 mg, 93%) as a mixture of epimers. IR (liquid film) 2990, 1447, 1382, 1305, 1148, 1086, 1010, 905, 793, 746, 689 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3) δ 8.02−7.96 (m, 2H, Ph), 7.83−7.75 (m, 1H, Ph), 7.73−7.66 (m, 2H, Ph), 5.73 (dt, J = 5.6, 1.4 Hz, 1H, C*H*═), 5.67 (br d, J = 5.6 Hz, 1H, C*H*═), 5.36 (d, J = 4.8 Hz, 1H, H-6a), 5.05 (br d, J = 7.9 Hz, 1H, H-2), 3.39 (d, J = 6.7 Hz, 2H, CH_2SO_2Ph), 3.29−3.14 (m, 2H, H-3a and H-4), 3.12 (s, 3H, OCH_3), 1.79 (dd, J = 7.3, 12.0 Hz, 1H, H-3), 1.63 (ddd, J = 4.8, 10.6, 15.3 Hz, 1H, H-3′), 1.33 (s, 3H, CH_3), 1.25 (s, 3H, CH_3) [for the major anomer]; ^{13}C NMR (75 MHz, CD_3COCD_3) δ 141.4 (0), 135.0,* 134.7* (1), 133.93,* 133.89* (1), 130.6 (3 × 1), 129.29,* 129.14* (2 × 1), 101.2 (0), 98.96,* 98.32* (1), 89.57,* 88.41* (1), 58.69,* 57.37* (2), 49.07 (3), 43.9,* 43.2* (1), 40.95 (1), 36.12,* 35.94* (2), 27.57,* 27.25* (3), 25.4,* 25.2* (3) [the asterisk indicates doubled signals due to the presence of epimers]; ESI-MS (APCI) m/z 375 (100) $[M + Na]^+$. Anal. Calcd for $C_{18}H_{24}O_5S$: C, 61.34; H, 6.86; O, 22.70; S, 9.10. Found: C, 61.36; H, 6.88.

(3a*R,4*R**,6a*S**)-1-Benzenesulfonyl-3-(*tert*-butyldimethylsilanyloxy)-1-[2-(1-methoxy-1-methylethoxy)-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-4-yl]octan-2-ol (8).** Sulfone **7** (75 mg, 0.213 mmol) was dissolved in dry THF (1.2 mL) and cooled to −78 °C; after the solution was stirred for 10 min, ^{n}BuLi (2.5 M in hexanes, 100 μL, 0.256 mmol, 1.2 equiv) was added dropwise. After 45 min of stirring at the same temperature, the deep orange solution was slowly added via cannula with a solution of aldehyde **11** (69 mg, 0.256 mmol, 1.2 equiv) in dry THF (810 μL). After the solution was stirred at the same temperature for an additional 2 h, a saturated solution of NH_4Cl (2 mL) was added at −78 °C and the temperature was allowed to reach rt. The two layers were separated and the aqueous phase was extracted with DCM (3 × 6 mL). The organic phases were combined, washed with brine, dried on Na_2SO_4, and concentrated under reduced pressure. The crude adduct was filtered through a short pad of silica gel with hexanes−EtOAc (9:1) as eluent to afford pure hydroxysulfone **8** (106 mg, 83%), which was immediately used in the next step.

(1*E*,3a*R,4*S**,6a*S**)-*tert*-Butyl-{3-[2-(1-methoxy-1-methylethoxy)-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-4-yl]-1-pentylallyloxy}dimethylsilane (9).** Crude hydroxysulfone **8** (65 mg, 0.109 mmol) was dissolved in dry MeOH (3.7 mL) under an argon atmosphere. To the solution was added Na_2HPO_4 (375 mg) and the slurry was cooled to −40 °C; after 10 min of vigorous stirring, sodium amalgam (591 mg, 10% of Na) was slowly added portionwise in such a way as to keep the temperature below −40 °C. At the end of the addition, the temperature was raised to −20 °C and stirring was continued for an additional 1.5 h. The mixture was warmed to room temperature and filtered through a filter paper. Evaporation of volatiles in vacuo under 40 °C gave a residue that was partitioned between DCM (13 mL) and an aqueous saturated solution of $NaHCO_3$. The two phases were separated and the aqueous layer was extracted with DCM (3 × 8 mL). The organic phases were combined, washed with brine, dried on Na_2SO_4, and concentrated at reduced pressure. Flash column chromatography of the residue (silica gel; hexanes−Et_2O, 99:1 → 94:6) gave adduct **9** as a colorless oil (38 mg, 80%). IR (liquid film) 2930, 1463, 1370, 1251, 1146, 1075, 1018, 965, 836, 767 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3) δ 5.88−5.33 (m, 5H, H-1, H-2, H-5′, H-6′, and H-6a′), 5.06 (m, 1H, H-2′), 4.18 (br q, 1H, H-3), 3.52−3.37 (m, 1H, H-4′), 3.25−3.01 (m, 1H, H-3a′), 3.13 (s, 3H, OCH_3), 1.99−1.92 (m, 1H, H-3′), 1.75−1.67 (m, 1H, H-3″), 1.55−1.45 (m, 2H, H_2-4), 1.31 (br s, 6H, H_2-5, H_2-6, and H_2-7), 1.35 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 0.92 (overlapped s and t, 9H and 3H, respectively, $(CH_3)_3$−C−Si and H_3-8), 0.09 and 0.06 (s and s, 3H each, $(CH_3)_2$Si) [for the major anomer]; ^{13}C NMR (75 MHz, CD_3COCD_3) δ 136.4,* 136.3* (1), 135.8,* 135.6* (1), 133.2,* 133.0* (1), 130.2,* 129.3* (1), 101.2 (0), 99.5,* 99.3,* 98.7* (1), 90.5,* 90.1,* 89.1,* 88.9* (1), 76.4,* 74.9,* 74.5* (1), 55.3,* 54.6* (1), 49.0,* 48.8* (3), 44.4,* 44.1,* 43.9* (1), 39.6 (2), 36.7 (2), 32.9 (2), 26.0 (2), 23.7 (2), 27.6,* 27.3* (3), 26.6 (3 × 3), 25.4 (3), 19.1 (0), 14.7 (3), −3.6 (3), −4.2 (3) [an asterisk indicates doubled signals due to the presence of epimers]; ESI-MS (APCI) m/z 461 (100) $[M + Na]^+$. Anal. Calcd for $C_{25}H_{46}O_4Si$: C, 68.44; H, 10.57; O, 14.59; Si, 6.40. Found: C, 68.46; H, 10.55.

(5*Z*)-7-{(1*R,2*S**,5*S**)-2-[(1*E*)-3-(*tert*-Butyldimethylsilanyloxy)oct-1-enyl]-5-hydroxycyclopent-3-enyl}hept-5-enoic Acid (10).** MIP-acetal **9** (100 mg, 0.229 mmol) was dissolved in the solvent system THF−H_2O 3:2 (THF 11.4 mL, H_2O 7.6 mL); to this solution was added a buffer (pH ca. 4.75) of AcOH (231 mg, 3.85 mmol) and NaOAc (316 mg, 3.85 mmol) at room temperature with stirring. Stirring was continued for an additional 24 h at the same temperature; then another portion of AcOH was added (654 mg, 10.9 mmol) to adjust the pH at about 4.15, to accelerate deprotection of the acetal group. After 24 h of stirring, the mixture was quenched by adding a phosphate buffer solution (pH ca. 6.96) and solid NaCl, and it was diluted with Et_2O. The aqueous phase was extracted with Et_2O (3 × 15 mL); the combined organic layers were washed twice with brine (2 × 10 mL), dried on Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography of the residue (silica gel, hexanes−EtOAc, 9:1 → 8:2) afforded unreacted MIP-acetal **9** (13 mg) and the desired lactol **9a** (60 mg, 82% yield on recovered **9**) that was immediately used in the next step.

Solid (4-carboxybutyl)triphenylphosphonium bromide **12** (291 mg, 0.656 mmol, 4.0 equiv) was suspended in dry THF (2.1 mL) in a two-necked round-bottom flask under an argon atmosphere. To the suspension was added freshly sublimed potassium *tert*-butoxide (147 mg, 1.312 mmol, 8.0 equiv) portionwise at room temperature. After having been stirred for 20 min, the solution became deeply orange and lactol **9a** (60 mg, 0.164 mmol) in THF (1.6 mL) was cannulated dropwise at room temperature. Stirring was continued for an additional 2 h and the reaction was quenched by adding a saturated aqueous solution of NH_4Cl (10 mL) and acetic acid (85 mg, 1.05 equiv); Et_2O (13 mL) was added to the mixture and the organic layer was separated, whereas the aqueous phase was extracted with an additional Et_2O (3 × 13 mL). The organic phases were combined, dried on $MgSO_4$, filtered, and concentrated at reduced pressure. Flash column chromatography of the residue (silica gel; hexanes−EtOAc, 8:2) afforded acid **10** (61 mg, 83%) as a pale yellow oil, as a 1:1 mixture of epimers at the C-15 hydroxyl group. IR (liquid film) 3300−2600 (*OH* and *COOH*), 2928, 2856, 1713, 1462, 1253, 1065, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.08−5.96 (m, 2H), 5.64−5.48 (m, 1H), 5.48−5.32 (m, 3H), 4.52 (dd, J = 2.6, 5.3 Hz, 1H), 4.05 (br q, J = 6.4 Hz, 1H), 3.18 (m, 1H), 2.36 (br t, J = 6.7 Hz, 2H), 2.36−2.24 (m, 1H), 2.20−2.0 (m, 4H), 1.72 (quintuplet, J = 6.7 Hz, 2H), 1.56−1.38 (m, 2H), 1.28 (br s, 6H), 0.9 (s, 9H), 0.88 (t, J = 6.5 Hz, 3H), 0.08−0.02 (4s, 6H overall); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3 (0), 139.4 (1), 135.5 (1), 133.0 (1), 131.4 (1), 129.6 (1), 129.2 (1), 76.3 (1), 73.5 (1), 49.8,* 49.6* (1), 46.8 (1), 38.42,* 38.37* (2), 33.4 (2), 31.8 (2), 26.6 (2), 25.0 (2), 24.5 (2), 24.0 (2), 22.6 (2), 25.9 (3 × 3), 18.2 (0), 14.0 (3), −4.3 (3), −4.8 (3) [an asterisk indicates doubled signals due to the presence of epimers]; ESI-MS (negative ions) m/z 485 $[M + Cl^-]$, 449 $[M - H^-]$. Anal. Calcd for $C_{26}H_{46}O_4Si$: C, 69.28; H, 10.29; O, 14.20; Si, 6.23. Found: C, 69.35; H, 10.30.

(5*Z*)-7-{(1*R,2*S**,5*S**)-2-[(1*E*)-3-(*tert*-Butyldimethylsilanyloxy)oct-1-enyl]-5-hydroxycyclopent-3-enyl}hept-5-enoic Acid Methyl Ester (13).** A stirred solution of hydroxy acid **10** (274 mg, 0.608 mmol) in Et_2O (6 mL) was cooled in an ice bath and an ethereal solution of CH_2N_2 was added in excess. Evaporation of the volatiles left a residue (312 mg) that was purified by flash column chromatography (silica gel, hexanes−EtOAc, 96:4 → 9:1) to give the desired methyl ester **13** (254 mg, 90%) as a pale yellow oil. IR (liquid film) 3422, 2929, 1742, 1462, 1251, 1078, 968, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.09−5.95 (m, 2H, H-10 and H-11), 5.62−5.48 and 5.48−5.36 (2m, 1H and 3H, respectively, H-5, H-6, H-13, and H-14), 4.51 (dd, J = 2.4, 5.2 Hz, 1H, H-9), 4.04 (br q, J = 6.0 Hz, 1H, H-15), 3.68 (s, 3H, $COOCH_3$), 3.17 (m, 1H, H-12), 2.34 (t, J = 7.5 Hz, 2H, H_2-2), 2.34−2.25 (m, 1H, H-8), 2.20−2.01 (m, 4H, H_2-4 and H_2-7), 1.72 (quintuplet, J = 7.5 Hz, 2H, H_2-3), 1.57−1.39 (m, 2H, H_2-16), 1.39−1.19 (m, 6H, H_2-17, H_2-18, and H_2-19), 0.88 (s, 9H, $(CH_3)_3$−C−Si), 0.87 (t, 3H, H_3-20), 0.05 (s, 6H, $(CH_3)_2$Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5 (0), 139.8 (1), 135.9 (1), 133.6 (1), 131.9 (1), 129.85 (1), 129.8 (1), 76.7 (1), 73.9 (1), 51.9 (3), 50.2 (1), 47.3 (1), 39.8 (2), 33.9 (2), 32.2 (2), 27.2 (2), 25.4 (2), 25.2 (2), 24.4 (2), 26.3 (3 × 3), 18.6 (0), 14.4 (3), −3.8 (3), −4.3 (3); EIMS (70 eV) *m*/*z* 447 (3) $[M - OH]^+$, 407 (15), 389 (3), 375 (18), 357 (4), 315 (28), 301 (5), 265 (10), 241 (11), 201 (18), 169 (15), 143 (12), 131 (21), 117 (27), 105 (20), 91 (27), 75 (100), 55 (32), 41 (51). Anal. Calcd for $C_{27}H_{48}O_4Si$: C, 69.78; H, 10.41; O, 13.77; Si, 6.04. Found: C, 69.79; H, 10.40.

(5*Z*)-7-{(1*R,2*R**,5*S**)-2-[(1*E*)-3-(*tert*-Butyldimethylsilanyloxy)oct-1-enyl]-5-(2-nitrophenylselanyl)cyclopent-3-enyl}hept-5-enoic Acid Methyl Ester (14).** To a stirred solution of methyl ester **13** (93 mg, 0.20 mmol, 1.0 equiv) in dry THF (2.5 mL) under an argon atmosphere was added solid, freshly sublimed (*o*-nitrophenyl) selenocianate (68 mg, 0.30 mmol, 1.5 equiv), followed by nBu$_3$P (65 mg, 0.322 mmol, 1.61 equiv), cannulated dropwise at room temperature. Stirring was continued for an additional 60 min; the reaction mixture was then diluted with EtOAc, and the organic layer was separated and washed with a saturated solution of $NaHCO_3$ and then with brine. The combined organic phases were dried on $MgSO_4$, filtered, and concentrated in vacuo to give an oily, brown orange residue that was purified on silica gel. Elution with hexanes−EtOAc, 98:2 → 95:5, gave selenide **14** (115 mg, 88%) as a brown yellow oil. IR (liquid film) 2940, 2930, 2850, 1738, 1590, 1565, 1510, 1460, 1435, 1335, 1300, 1250, 1100, 1040, 980, 840, 780, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (dd, J = 1.4, 8.3 Hz, 1H, H−Ph), 7.71 (dt, J = 8.1, 1.4 Hz, 1H, H−Ph), 7.51 (td, J = 8.3, 1.4 Hz, 1H, H−Ph), 7.33 (td, J = 7.1, 1.2 Hz, 1H, H−Ph), 5.97−5.92 and 5.89−5.82 (m and m, 1H each, H-10 and H-11), 5.61−5.44 (m, 4H, H-5, H-6, H-13, H-14), 4.23 (br s, 1H, H-9), 4.11 (br q, J = 5.7 Hz, 1H, H-15), 3.68 (s, 3H, $COOCH_3$), 2.52−2.39 (m, 1H, H-12), 2.32 (t, J = 7.5 Hz, 2H, H_2-2), 2.32−2.17 (m, 1H, H-8), 2.17−2.02 (m, 4H, H_2-4 and H_2-7), 1.71 (quintuplet, J = 7.5 Hz, 2H, H_2-3), 1.55−1.39 (m, 2H, H_2-16), 1.39−1.16 (m, 6H, H_2-17, H_2-18, and H_2-19), 0.9 (s, 9H, $(CH_3)_3$−C−Si), 0.89 (t, 3H, H_3-20), 0.05 (s, 6H, $(CH_3)_2$Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3 (0), 147.6 (0), 135.16,* 135.04* (0), 137.7 (1), 136.7,* 136.6* (1), 133.7 (1), 131.2 (1), 130.7,* 130.5* (1), 129.3,* 129.2* (1), 127.7 (1), 126.8 (1), 125.9 (1), 73.8,* 73.7* (1), 51.9 (3), 51.0,* 50.9* (1), 49.9,* 49.7* (1), 48.9,* 48.8* (1), 38.8 (2), 33.9 (2), 32.2 (2), 28.0 (2), 27.2 (2), 25.3 (2), 25.2 (2), 23.0 (2), 26.3 (3 × 3), 18.7 (0), 14.4 (3), −3.8 (3), −4.3 (3) [an asterisk indicates doubled signals due to the presence of epimers]; ESI-MS (positive ions) *m*/*z* 673 (46) $[M + Na + H]^+$, 672 (100) $[M + Na]^+$, 670 (57) $[M + Na - 2H]^+$. Anal. Calcd for $C_{33}H_{51}NO_5SeSi$: C, 61.09; H, 7.92; N, 2.16; O, 12.33; Se, 12.17; Si, 4.33. Found: C, 61.11; H, 7.91; N, 2.12.

(5*Z*)-7-{(1*S,4*R**,5*S**)-5-[(1*E*)-3-(*tert*-Butyldimethylsilanyloxy)oct-1-enyl]-4-hydroxycyclopent-2-enyl}hept-5-enoic Acid Methyl Ester (15).** To a stirred solution of selenide **14** (128.5 mg, 0.198 mmol, 1.0 equiv) in dry THF (5 mL) under an argon atmosphere was added pyridine (62 mg) via a syringe at room temperature. The mixture was cooled to 0 °C and 30% v/v hydrogen peroxide (84 μL, 2.769 mmol, 14 equiv) was added dropwise. Stirring was continued at +7 °C for an additional 18 h. The reaction was then quenched with water and diluted with EtOAc; the aqueous phase was extracted with EtOAc and the combined organic layers were washed with a saturated solution of $NaHCO_3$ and brine, dried on $MgSO_4$, filtered, and evaporated in vacuo. Flash column chromatography of the residue (silica gel, hexanes−EtOAc, 9:1) afforded pure cyclopentenol **15** (55 mg, 60%). IR (liquid film) 3400, 2950, 2920, 2845, 1740, 1460, 1440, 1360, 1250, 1080, 1060, 1000, 980, 840, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98−5.90 and 5.87−5.78 (m and m, 1H each, H-9 and H-10), 5.64−5.53 and 5.44−5.34 (m and m, 2H each, H-5, H-6, H-13, and H-14), 4.64 (dd, J = 5.5, 12.5 Hz, 1H, H-11), 4.10 (br q, J = 6 Hz, 1H, H-15), 3.68 (s, 3H, $COOCH_3$), 2.93−2.81 and 2.73−2−62 (m and m, 1H each, H-8 and H-12), 2.31 (t, J = 7.5 Hz, 2H, H_2-2), 2.24−2.10 (m, 1H, OH), 2.10−1.97 and 1.97−1.81 (m and m, 2H each, H_2-4 and H_2-7), 1.69 (quintuplet, J = 7.5 Hz, 2H, H_2-3), 1.57−1.42 (m, 2H, H_2-16), 1.42−1.16 (m, 6H, H_2-17, H_2-18, and H_2-19), 0.91 (s, 9H, $(CH_3)_3$−C−Si), 0.89 (t, 3H, H_3-20), 0.05 (s, 6H, $(CH_3)_2$Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4 (0), 138.4,* 138.3* (1), 137.1,* 137.0* (1), 133.3 (1), 130.0 (1), 129.4 (1), 128.3,* 128.2* (1), 82.2,* 82.1* (1), 73.9,* 73.8* (1), 55.5,* 55.4* (1), 48.5,* 48.4* (1), 51.9 (3), 38.8 (2), 33.9 (2), 32.2 (2), 29.5,* 29.4* (2), 27.1 (2), 25.4 (2), 25.2 (2), 23.0 (2), 26.3 (3 × 3), 18.7 (0), 14.4 (3), −3.8 (3), −4.3 (3) [an asterisk indicates doubled signals due to the presence of epimers]; EIMS (70 eV) *m*/*z* 447 (2) $[M - OH]^+$, 407 (22), 389 (6), 375 (15), 357 (8), 305 (17), 265 (10), 241 (10), 229 (7), 183 (11), 169 (13), 157 (11), 143 (13), 129 (21), 117 (25), 105 (18), 91 (27), 75 (100), 55 (31). Anal. Calcd for $C_{27}H_{48}O_4Si$: C, 69.78; H, 10.41; O, 13.77; Si, 6.04. Found: C, 69.80; H, 10.39.

(5*Z*)-7-{(1*S,4*R**,5*S**)-5-[(1*E*)-3-(*tert*-Butyldimethylsilanyloxy)oct-1-enyl]-4-hydroxycyclopent-2-enyl}hept-5-enoic Acid (16).** Methyl ester **15** (20 mg, 43 μmol, 1.0 equiv) was dissolved in MeOH (0.8 mL) and solid $Ba(OH)_2 \cdot 8H_2O$ (54 mg, 172.1 μmol, 4.0 equiv) was added in a single portion. Stirring was continued for 18 h at room temperature, then the reaction mixture was diluted with brine and acidified with glacial acetic acid. EtOAc was added, the two phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed twice with brine, dried on $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography of the residue (silica gel; hexanes−EtOAc, 9:1 → 85:15) afforded the desired hydroxy acid **16** (15 mg, 80%) as a pale yellow oil. IR (liquid film) 3600−3200 (*OH* and *COOH*), 2960, 2920, 2850, 1710, 1460, 1250, 1080, 970, 840, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98−5.92 and 5.87−5.80 (m and m, 1H each, H-9 and H-10), 5.64−5.54 and 5.46−5.36 (m and m, 2H each, H-5, H-6, H-13, and H-14), 4.66 (dd, J = 5.5, 12.5 Hz, 1H, H-11), 4−19−4.04 (m, 1H, H-15), 2.94−2.81 and 2.73−2.62 (m and m, 1H each, H-8 and H-12), 2.36 (t, J = 7.4 Hz, 2H, H_2-2), 2.27−2.13, 2.12−2.0, and 1.99−1.80 (m, m, and m, 1H, 2H, 1H, respectively, H_2-4 and H_2-7), 1.70 (quintuplet, J = 7.4 Hz, 2H, H_2-3), 1.61−1.42 (m, 2H, H_2-16), 1.42−1.17 (m, 6H, H_2-17, H_2-18, and H_2-19), 0.91 (s, 9H, $(CH_3)_3$−C−Si), 0.89 (t, 3H, H_3-20), 0.05 (s, 6H, $(CH_3)_2$−Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.20*, 178.07* (0), 138.4,* 138.3* (1), 137.0,* 136.8* (1), 133.3 (1), 129.8 (1), 129.6 (1), 128.3,* 128.2* (1), 82.3,* 82.1* (1), 73.9 (1), 55.5,* 55.4* (1), 48.5,* 48.4* (1), 38.8,* 38.7* (2), 33.6,* 33.5* (2), 32.2 (2), 29.6,* 29.5* (2), 27.0 (2), 25.5,* 25.4* (2), 24.9 (2), 23.1 (2), 26.3 (3 × 3), 18.20,* 18.18* (0), 14.6,* 14.4* (3), −3.8 (3), −4.3 (3) [an asterisk indicates doubled signals due to the presence of epimers]; ESI-MS (positive ions) *m*/*z* 475 (97) $[M + Na + 2H]^+$, 473 (100) $[M + Na]^+$. Anal. Calcd for $C_{26}H_{46}O_4Si$: C, 69.28; H, 10.29; O, 14.0; Si, 6.23, 69. Found: C, 69.27; H, 10.28.

(5*Z*)-7-{(1*S,5*S**)-5-[(1*E*)-3-(*tert*-Butyldimethylsilanyloxy)oct-1-enyl]-4-oxo-cyclopent-2-enyl}hept-5-enoic Acid (17).** To a stirred solution of hydroxy acid **16** (30 mg, 66.6 μmol,

1.0 equiv) in dry DCM (6.7 mL) was added glacial acetic acid (5 mg ca., 79.9 μmol, 1.2 equiv) and solid periodinane **18** (29.4 mg, 73.2 μmol, 1.1 equiv) in a single portion. Stirring was continued for an additional 30 min to reaction completion. The mixture was then diluted with Et_2O, filtered on a short pad of silica gel-Celite, and concentrated under reduced pressure. Flash column chromatography of the residue (silica gel; hexanes−EtOAc, 9:1 → 7:3) afforded the desired cyclopentenone **17** (25 mg, 84%) as a pale yellow oil. IR (liquid film) 3600−3100 (*COOH*), 2930, 2857, 1713, 1589, 1463, 1360, 1257, 1197, 1140, 1111, 1083, 1005, 969, 836, 810, 776, 732 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3) δ 10.46 (br s, 1H, COO*H*), 7.81−7.73 and 7.68−7.59 (m and m, 1H, H-9), 6.21−6.15 and 6.13−6.09 (m and m, 1H, H-10), 5.72−5.39 (m, 4H, H-5, H-6, H-13, and H-14), 4.26−4.17 (m, 1H, H-15), 3.19 (d, J = 6 Hz, 1H, H-12), 2.55−2.27 (overlapped m and t, 1H and 2H, respectively, H-8 and H_2-2), 2.22−2.05 (m, 4H, H_2-4 and H_2-7), 1.74−1.61 (quintuplet, J = 7.4 Hz, 2H, H_2-3), 1.58−1.46 (m, 2H, H_2-16), 1.46−1.25 (m, 6H, H_2-17, H_2-18, and H_2-19), 0.91 (s, 9H, $(CH_3)_3$−C−Si), 0.89 (t, 3H, H_3-20), 0.05 (s, 6H, $(CH_3)_2Si$); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 207.9,* 207.8* (0), 173.9 (0), 166.7 (1), 139.6 (1), 132.7 (1), 131.2,* 131.1* (1), 128.0,* 127.9* (1), 124.6,* 124.4* (1), 73.6 (1), 52.8 (1), 46.0 (1), 38.7,* 38.6* (2), 33.1 (2), 32.1 (2), 29.4 (2), 26.9 (2), 25.0 (2), 24.7 (2), 22.8 (2), 25.8 (3 × 3), 18.2 (0), 13.8 (3), −4.4,* −4.5* (3), −5.0*, −5.1* (3) [an asterisk indicates doubled signals due to the presence of epimers]; ESI-MS (positive ions) m/z 472 (100) $[M + Na]^+$. HRMS calcd for $C_{26}H_{44}O_4Si$ 448.3009, found 448.3010.

(5*Z*)-7-[(1*S,5*S**)-5-((1*E*)-3-Hydroxyoct-1-enyl)-4-oxocyclopent-2-enyl]hept-5-enoic Acid (1).** Cyclopentenone **17** (59 mg, 0.131 mmol) was dissolved in CH_3CN (4.8 mL) in a Teflon test tube; the solution was cooled to −20 °C and 48% aq HF (245 μL) was added dropwise. The mixture was stirred for 4 h at the same temperature, then diluted with THF (7.2 mL, so that the THF−CH_3CN ratio was about 1.5:1) and quenched by addition of pH ca. 6.96 phosphate buffer (2 mL). The mixture was gradually warmed to room temperature and diluted with DCM. The aqueous phase was extracted with DCM (3 × 5 mL), and the combined organic layers were washed twice with water (2 × 3 mL) and twice with brine (2 × 3 mL), dried on $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography of the residue on reverse phase RP-18 with MeOH/H_2O (55:45) as eluent afforded 15-J_2-IsoP **1** (39 mg, 90%) as a pale yellow oil; IR (liquid film) 3600−3100 (*OH* and *COOH*), 2928, 1705, 1582, 1195, 734 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 7.69−7.61 (m, 1H, H-9), 6.15 (dd, J = 1.9, 5.7 Hz, 1H, H-10), 5.73−5.45 (m, 4H, H-5, H-6, H-13, and H-14), 4.19−4.08 (m, 1H, H-15), 2.90−2.79 (m, 1H, H-8), 2.69−2.61 (m, 1H, H-12), 2.49−2.23 and 2.23−2.03 (m and m, 4H and 2H, respectively, H_2-2, H_2-4, and H_2-7), 1.80−1.63 (m, 2H, H_2-3), 1.63−1.46 (m, 2H, H_2-16), 1.33 (br s, 6H, H_2-17, H_2-18, and H_2-19), 0.92 (br t, 3H, H_3-20); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 208.3,* 208.1* (0), 177.0,* 176.9* (0), 165.8,* 165.6* (1), 136.6,* 136.2* (1), 132.5 (1), 131.3 (1), 126.9,* 126.6* (1), 126.2 (1), 72.7,* 72.6* (1), 54.7,* 54.3* (1), 48.4,* 47.9* (1), 36.8 (2), 32.8 (2), 31.5 (2), 30.3 (2), 26.2 (2), 24.9 (2), 24.3 (2), 22.4 (2), 13.6 (3) [an asterisk indicates doubled signals due to the presence of epimers]; ESI-MS (APCI) m/z 315 (100) $[M - H_2O - H]^+$. HRMS calcd for $C_{20}H_{30}O_4$ 334.2144, found 334.2142.

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Supporting Information Available: ^1H NMR, ^{13}C NMR, and DEPT data for compounds **9**, **13**, **14**, **15**, and **16**, and ^1H NMR and ^{13}C NMR data for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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