Total Synthesis of 25-Hydroxy Vitamin D_3 Northern Portion, Involving Tandem Conjugate Additions

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New approaches to 25-hydroxy vitamin D building blocks **7** and **8** have been developed. Tandem acid-catalyzed conjugate addition of ketene acetal **2d** or **2c** and acceptors **3** and then **11** yielded **5b** (76% from **3**) or **22** (64%), respectively, with the proper relative configuration on C20, C17, and C13 (steroid numbering, all compounds are racemic). The *trans*-hydrindan ring junction in **16** and **27** has been secured by chirality transfer in palladium-catalyzed hydrogenolysis of formates **15** and **26**. Treatment of **16** with *N*-bromoacetamide followed by NaOH yielded a mixture of 8β,9β- and 8α,9α-epoxides **18** in a ratio of ca. 2:1, which was tosylated and reduced with lithium aluminum hydride without separation. The required diol **20** and its isomer **21** were obtained. In a complementary approach, **27** was oxidized into 8α,9α-epoxide **29** with a new reagent composed of *m*-CPBA, KF, and 2,6-di-*tert*-butyl-4-methylphenol. Opening of the epoxide ring in **29** with thiophenoxide anion followed by oxidation afforded dihydroxy sulfone **31**. The latter was reduced via the respective dimesylate, and then the protective benzyloxy group was removed yielding **8**.

1α,25-Dihydroxy vitamin D_3 (**1**, Scheme 1) or other vitamin D derivatives are used for the treatment of several human diseases, including various forms of hypocalcemia, osteoporosis, and psoriasis. There is strong evidence that the therapeutic potential of this class of compounds embraces also inhibition of proliferation of malignant cells and the immune system.[1] New and promising observations regarding the effect of vitamin D analogues in AIDS therapy and multiple sclerosis have also been published.[2,3] The need for large-scale preparation of **1** and a variety of its analogues has rendered a renewal of interest in vitamin D total synthesis.[4]

We have recently reported[5] a synthesis of a 1α,25-dihydroxy vitamin D_3 northern portion building block (rings C/D and the side chain), involving an acid-catalyzed (Michael−Mukaiyama) conjugate addition of ketene acetal **2a** (Scheme 1) and 2-methylcyclopent-2-en-1-one (**3**). The silyl enol ether **4a** that was generated in this reaction was further used for multistep construction of the ring C (starting from allylation of **4a**). These studies highlight the use of the conjugate addition[6] in the generation of a silyl enol ether (i.e., **4**), which can be utilized as a reactive intermediate in subsequent reactions. In continuation of work on vitamin D synthesis, it was of interest to examine reaction of silyl enol **4** (or its congeners) with methyl vinyl ketone and related Michael acceptors. Application of the "second" conjugate addition would allow for an approach to the key intermediate **5** in one step starting from three components (**2**, **3**, and MVK). Acid-catalyzed tandem conjugate addition has been executed in an intramolecular fashion on two previous occasions,[7] but there have been no literature reports of tandem *intermolecular* addition. Now we report a very short synthetic approach to the vitamin D building blocks **7** and **8** via the common intermediate[8] **6**. The latter was constructed in two steps in 64% yield (the previous synthesis: nine steps, 16% yield).

Results and Discussion

Reaction of ketene acetal **2b** with **3**[9] in the presence of trityl hexachloroantimonate[10] (5 mol %) followed by flash chromatography gave a mixture of **4b** (46% yield, Scheme 2) and **9a** (31%, a mixture of diastereomers). When this reaction was performed with addition of 0.9 molar equiv of MVK to the reaction mixture after the first conjugate addition, diketone **5b** (43%) and triketone **10** (10%) were isolated. The carbon skeleton of **5b** incorporates all carbon atoms needed to construct the target compounds (**7** and **8**), with the three contiguous asymmetric carbons in the proper relative configuration. However, the low yield of **5b** and formation of double Michael adduct **10**

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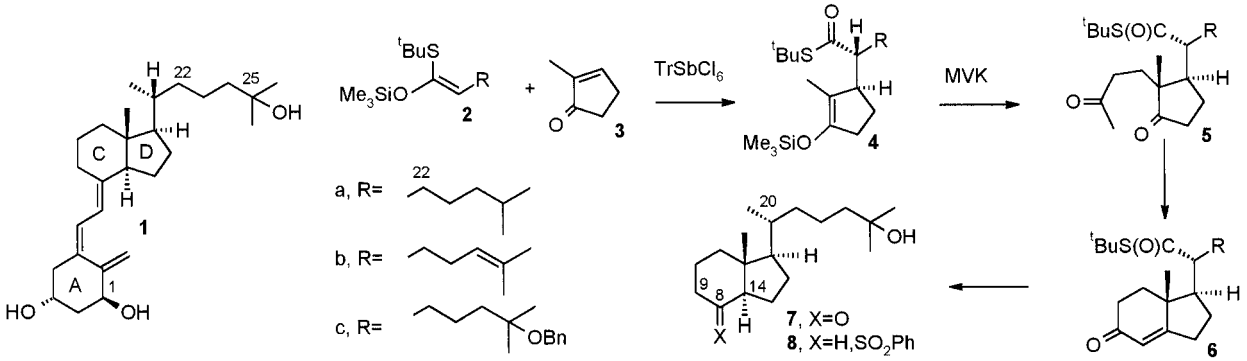
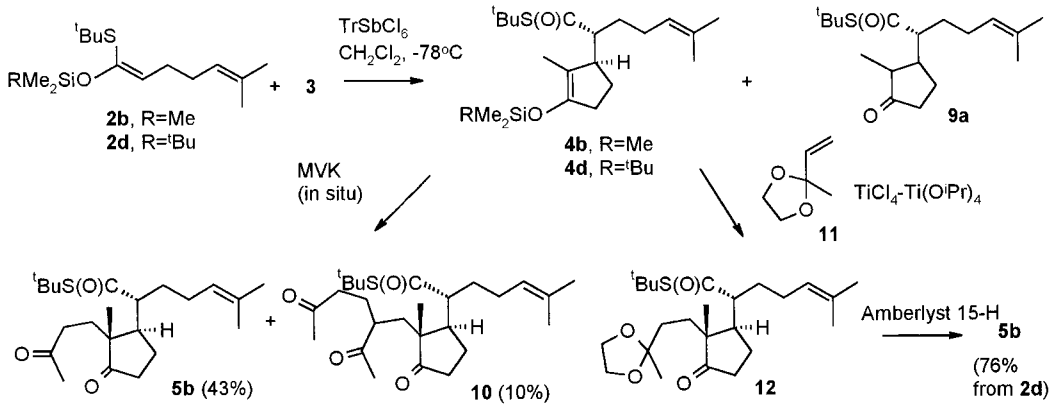
Scheme 1



Scheme 2



led us to suspect that polymerization of MVK was the source of the diminished yields.[11] In an attempt to inhibit polymerization of the reagent, we substituted 2-(triethylsilyl)but-3-en-2-one[12] and (*E*)-4-(phenylsulfonyl)but-3-en-2-one[13] for MVK in the reaction, but we observed no improvement in the isolated yields of the corresponding **5b** derivatives. A slightly better yield of **5b** (48%) in the reaction between **2b**, **3**, and MVK was obtained by addition of triphenylmethanol (0.7 molar equiv) as a sterically bulky proton source. Ultimately, we found that the reaction of **2b** and **3** followed by treatment of **4b** (nonisolated) with 3 molar equiv of ketal **11**[14] in the presence of $TiCl_4$/$Ti(O\text{-}i\text{-}Pr)_4$ (1 molar equiv of each) afforded **5b** in 64% yield from **3** after hydrolysis of ketal **12** with Amberlyst 15-H in wet acetone. The yield of **5b** could be further increased (76%) by using the less labile silylthioketene acetal **2d** (prepared using TBDMSCl) in the tandem conjugate addition reaction.

With dienone **5b** in hand we attempted the *trans*-hydrindan ring construction. Annulation using pyrrolidine in THF (Scheme 3) afforded ketol **13**, which was then dehydrated to give the crystalline α,β-unsaturated ketone **14**. The relative stereochemistry of **14** was confirmed to be 13*R**,17*R**,20*R** (steroid numbering) by single-crystal X-ray analysis.[15] Reduction of **14** with DIBAL yielded the diol (dr > 95:5), which was transformed to formate ester **15** without intervening purification. The formate **15** is a suitable substrate for stereoselective palladium-catalyzed hydrogenolysis with double-bond migration, developed by Tsuji and co-workers[16] for similar hydrindan derivatives and using $Pd(OAc)_2$ and Bu_3P in THF (rt). Under slightly modified conditions,[17] using $Pd(OAc)_2$ and 99% Bu_3P in dioxane at 60 °C, allylic formate **15** was converted to a mixture of **16** and **17** (2:1 ratio) with less than 5% of the C14 epimer of hydrindene **16**. Compounds **16** and **17** were isolated in 54% and 29% yields, respectively, by preparative HPLC. Our efforts to increase the yield of **16** by altering the concentration or the proportion of the reagents proved futile. Analogues of **15** with different substitution pattern at C21 (COS-*t*-Bu, $CH_2OTBDMS$, CH_3) reacted to afford mixtures of the respective 8-ene and conjugated diene in a similar ratio.[18] However, when different batches of nominally the same tributylphosphine[19] were employed in the reaction, the relative proportions of the desired product to conjugated diene were quite variable and ranged from ~1:1 to >3:1.

The use of allylic formate hydrogenolysis resulted in effective access to *trans*-hydrindan derivative **16**. To

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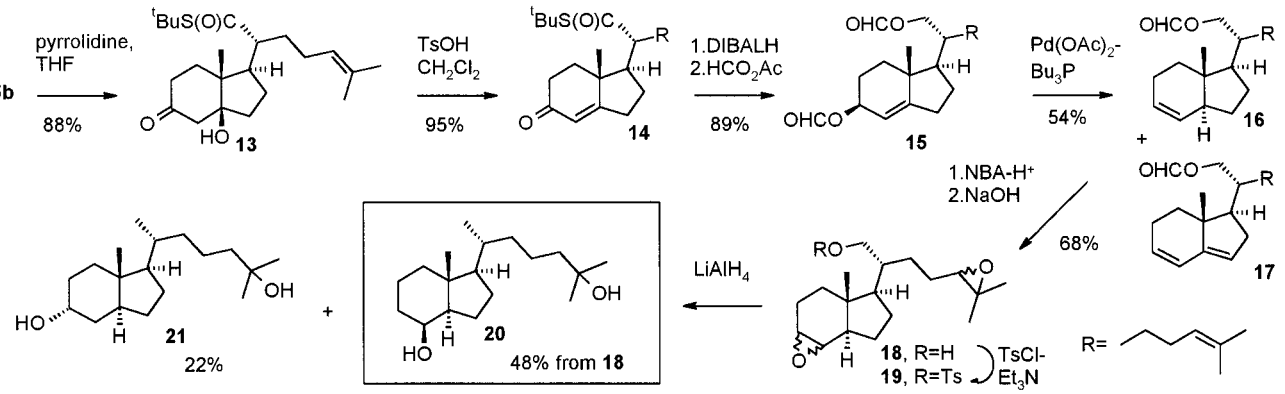
Scheme 3



introduce oxygen functionality at C8 and C25, we intended to simultaneously epoxidize the two double bonds in **16** and then to reductively open the epoxides. It is well documented that $LiAlH_4$ reduction of the 8β,9β-epoxy moiety in intermediates similar to **16** provides the respective 8β hydroxyl,[20] and we expected that reduction of the 24,25-epoxide would occur at the less substituted position (C24), which would place the hydroxyl group at C25.

For introduction of the 8β,9β-epoxide, **16** was treated with NBA and a catalytic amount of $HClO_4$ in aqueous dioxane (to generate bromohydrins) and then with aqueous NaOH.[20] A mixture of hydroxy epoxides **18** (Scheme 3) was obtained in 68% yield. The hydroxy group in **18** was tosylated, and the crude tosylate was reduced with an excess of $LiAlH_4$ in refluxing THF to provide a 2:1 mixture of diols **20** (48% yield) and **21** (22% yield). It was apparent that **21** was derived from 8α,9α-**18** and consequently that the mixture of epoxides **18** consisted of 8β,9β and 8α,9α isomers in a ratio of 2:1. Oxidation of **20** provided the 8-oxo derivative **7** in quantitative yield.[21] This synthetic route to **7** is exceptionally short (nine steps from **3**) owing to the three-component one-step construction of the intermediate **5b** and to simultaneous reduction of C−O bonds at C9, C21, and C24 in **19** and proceeds in a total yield of 10% (from **3**).

A serious drawback to the preparation of **7** is the unselective bromohydrin formation (**16** → **18**), which prompted us to redesign our approach for installation of a substituent at C8. Since in the preliminary experiments it was found that oxidation of the C8−C9 olefin of **16** with *m*-CPBA is completely selective[22] (yielding the 8α,9α-epoxide), we anticipated that the opening of the 8α,9α epoxide with thiophenolate anion would yield the respective 8β-(phenylthio)-9α-hydroxy derivative (diaxial epoxide opening), which could then be transformed into sulfone **8**. However, the presence of the second double bond (C24−C25) in the side chain of **16** posed an awkward regioselectivity problem in the epoxidation of the C8−C9 double bond. To avoid this complication, we undertook the preparation of **8** using a different side chain precursor.

The synthesis of sulfone **8** is illustrated in Scheme 4. Tandem conjugate addition of **2c** with **3** and then **11** gave **22** (64%) and its diastereomer at C20 (**23**, 5%) after chromatography. Pyrrolidine-induced annulation of **22** afforded a crystalline alcohol **24** that was transformed via enone **25** to diformate **26**. Hydrogenolysis of **26** (under the optimized reaction conditions with the best batch[19] of Bu_3P) followed by preparative HPLC afforded the *trans*-hydrindan derivative **27** and the corresponding diene **28** (see the Experimental Section) in 72 and 24% yields, respectively (vide supra).

Unexpectedly, the attempted epoxidation of **27** with *m*-CPBA in CH_2Cl_2 failed to yield **29**, instead providing a complex mixture of products resulting from partial cleavage of the benzyl ether and epoxide opening with *m*-chlorobenzoic acid. When the oxidation was conducted under biphasic conditions with aqueous $NaHCO_3$ as a buffer, the yield of the desired epoxide **29** improved to 45%. The use of a potassium fluoride suspension as buffer[23] allowed us to eliminate the epoxide-opening reaction, and when the epoxidation was performed with *m*-CPBA in the presence of KF and BHT[24] (as a free-radical inhibitor), a near quantitative yield in the transformation of **27** to **29** was achieved. Addition of sodium thiophenolate in refluxing ethanol to **29** provided the dihydroxythiophenyl derivative **30**, which was subsequently oxidized to sulfone **31**. In practice, no HPLC purification of **27** was needed. The allylic formate hydrogenolysis, epoxidation, and thiolate addition were carried out without purification of the intermediates; a 60% yield of **30** (after flash chromatography) was realized for these three steps. Sulfone **31** was then converted to **8** by deoxygenation of the C8 hydroxyl (MsCl and then $LiEt_3BH$, 98%, two steps) followed by hydrogenolysis of the benzyl ether. Hydroxy sulfone **8** was obtained in 23% overall yield from **3** (12 steps).

(19) Three batches of 99% tributylphosphine consecutively purchased in the period 1994−1996 from Strem Chemicals, Newburyport, MA, were used. The reagent was applied immediately after the ampule was opened. ^{31}P NMR spectra of all these products showed the presence of tributylphosphine oxide (less than 1%, δ 48.5 ppm, relative to phosphoric acid) and of trace contaminations with (1) δ 35, (2) δ 57.6 and (3) δ 133.3 ppm. No clear relation between the reactivity and the reagent NMR spectrum could be found. Several samples of 98% Bu_3P were virtually ineffective. All our attempts to purify Bu_3P by distillation over $LiAlH_4$ or K/Na alloy failed.

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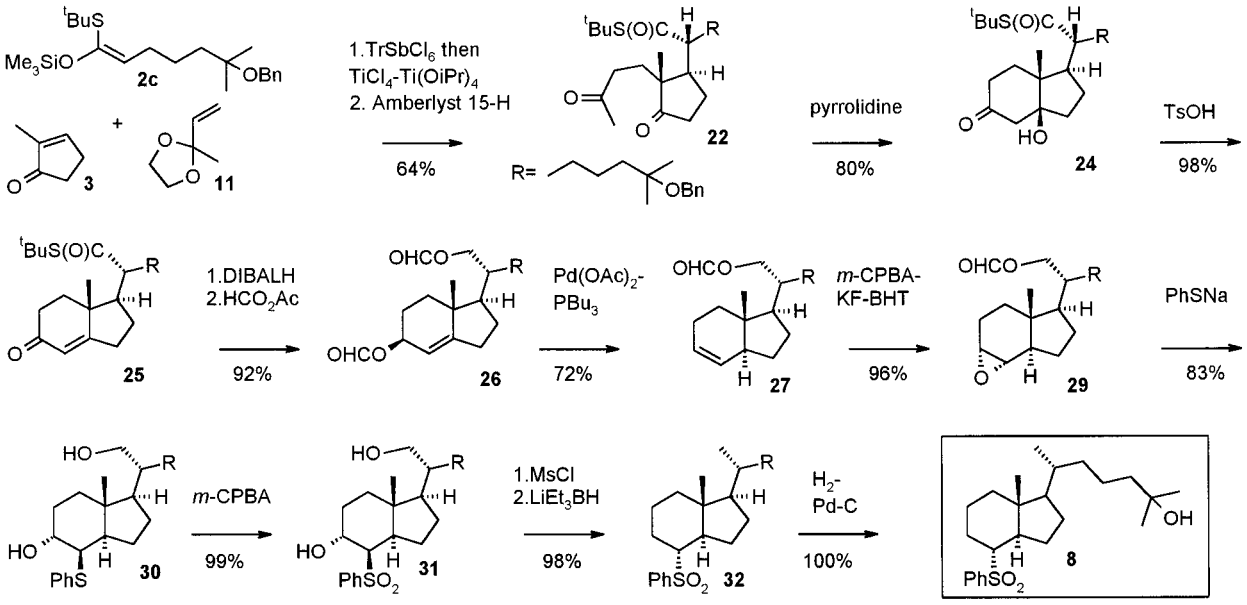
Scheme 4



In conclusion, a new approach to building blocks for total synthesis of 25-hydroxy vitamin D_3, **7** and **8**, has been presented. Tandem conjugate addition of ketene acetals **2** and two Michael−Mukaiyama acceptors, **3** and **11**, has been developed. The intermediate α,β-unsaturated ketones **14** and **25** were transformed into the corresponding *trans*-hydrindan derivatives (**16** and **27**, respectively) by means of stereoselective reduction of the carbonyl group and then palladium-catalyzed allylic formate (**15**, **26**) hydrogenolysis. A method for epoxidation of an ethylenic bond with *m*-CPBA in acid- and radical-sensitive system (**27**) has been developed

Experimental Section[25]

6-(Benzyloxy)-6-methylheptanethioic Acid *S*-*tert*-Butyl Ester.[26] *Caution! This preparation should be conducted in an efficient hood because of HCl and CO evolution in reaction with oxalyl chloride and the obnoxious odor of 2-methyl-2-propanethiol.* To a suspension of potassium salt of 6-(benzyloxy)-6-methylheptanoic acid (see the Supporting Information) (prepared by neutralization of the acid (37.5 g, 130 mmol) with methanolic KOH by phenolphthalein, evaporation of the solvent, and drying in high vacuum) in benzene (500 mL) was added oxalyl chloride (160 mmol, 14.0 mL) dropwise at 0 °C. The mixture was stirred for 1 h at room temperature and then heated at 80 °C for 20 min. The solvents were evaporated, and the residue was treated with a mixture of 2-methyl-2-propanethiol (14.6 mL, 130 mmol) and Et_3N (140 mmol, 19 mL) in CH_2Cl_2 (250 mL) at 0 °C. The mixture was set aside for 16 h and then diluted with hexane (300 mL), washed with 5% aqueous HCl, and water. The solvents were evaporated, and the residue was chromatographed on SiO_2 (200 g, hexanes−EtOAc 96:4) to give 36 g (86%) of 6-(benzyloxy)-6-methylheptanethioic acid *S*-*tert*-butyl ester: ^{1}H NMR (200 MHz) δ 7.37−7.15 (m, 5H), 4.38 (s, 2H), 2.45 (t, 2H, J = 7.1 Hz), 1.80−1.10 (m, 6H) overlapping 1.44 (s, 9H), 1.22 (s, 6H); ^{13}C NMR and DEPT (50 MHz) δ 200.1 (0), 139.7 (0), 128.1 (1), 127.1 (1), 126.9 (1), 74.9 (0), 63.5 (2), 47.6 (0), 44.4 (2), 40.1 (2), 29.7 (3), 26.0 (2), 25.5 (3), 23.1 (2); EIMS LSIMS *m*/*z* 345 ((M + Na)$^+$, 3), 323 ((M + H)$^+$, 30); HRMS LSIMS calcd for $C_{19}H_{31}O_2S$ (M + H)$^+$ 323.204 48, found 323.204 23.

6-(Benzyloxy)-1-(*tert*-butylsulfanyl)-6-methyl-1-[(trimethylsilyl)oxy]hept-1-ene (2c). To a solution of LDA [prepared from *i*-Pr_2NH (12.0 mL, 86 mmol), *n*-BuLi (1.6 M in hexane, 54 mL, 86 mmol), and THF (250 mL)] was added *tert*-butylthio 6-(benzyloxy)-6-methylheptanoate (23.0 g, 71 mmol) at −78 °C. The mixture was stirred at − 78 °C for 1 h, and then TMSCl (22.5 mL, 178 mmol) was added dropwise. The mixture was set aside at room temperature for 16 h, and then the solvent was evaporated. The residue was diluted with hexane containing 1% of Et_3N (150 mL) and filtered through a pad of SiO_2 (4 g, washed with hexane −1% Et_3N), and the solvent was evaporated to give **2c** (33.2 g, a mixture of isomers E:Z = ca. 8:1, 97%). (*E*)-**23**: ^{1}H NMR (200 MHz) δ 7.37−7.19 (m, 5H), 5.23 (t, 1H, J = 7.5 Hz), 4.41 (s, 2H), 2.21 (dt, 2H, J = 7.5, 7.2 Hz), 1.74−1.10 (m, 4H) overlapping 1.38 (s, 9H), 1.24 (s, 6H), 0.23 (s, 9H); ^{13}C NMR (50 MHz) δ 145.4 (0), 139.9 (0), 128.2 (1), 127.2 (1), 127.0 (1), 120.6 (1), 75.1 (0), 63.6 (2), 46.3 (0), 39.9, 31.7 (3), 29.6, 25.7 (3), 24.4, 0.3 (3) (*Z*)-**23**: ^{1}H NMR (200 MHz) δ 2.05 (dt, 2H, J = 7.0, 7.0 Hz), 1.35 (s, 9H); E:Z ratio 8:1 was determined by integrating of the signals at δ 1.35 and 1.38; ^{13}C NMR (50 MHz) δ 31.4, 0.7; LSIMS *m*/*z* 395 (20) (M + H)$^+$; HRMS LSIMS calcd for $C_{22}H_{39}O_2SSi$ (M + H)$^+$ 395.244 01, found 395.235 99.

(2*R,1′*R**,2′*S**)-6-(Benzyloxy)-6-methyl-2-[2-methyl-3-oxo-2-(3-oxobutyl)cyclopentyl]heptanethioic Acid *S*-*tert*-Butyl Ester (22).** To a stirred at −78 °C solution of **3** (1.15 mL, 11.7 mmol) and $TrSbCl_6$ (345 mg, 0.6 mmol) in CH_2Cl_2 (30 mL) was added **2c** (5.21 g, 13.2 mmol). After 1 h, **11** (4.37 g, 38.3 mmol) was added dropwise during 1.5 h, followed by a mixture of $TiCl_4$ (2.52 mL, 23.0 mmol), Ti(O-*i*-Pr)$_4$ (6.3 mL, 21.3 mmol), and CH_2Cl_2 (20 mL). After 2 h at −78 °C the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL), and hexane (50 mL) was added. The organic layer was separated and washed with 5% aqueous HCl and water. The solvent was evaporated, and the residue was dissolved in acetone (150 mL) containing Amberlyst 15-H (0.5 g). The mixture was stirred for 16 h and then filtered and evaporated. The residue was chromatographed on SiO_2 (85 g, hexanes−EtOAc 9:1 and then 4:1) to give (1) starting thioester (612 mg), (2) **9b** (327 mg, 7%), (3) **23** (288 mg, 5%), and (4) **22** (3.663 g,

(25) General experimental conditions are described elsewhere.[5] Materials were obtained from commercial suppliers and used without further purification unless stated otherwise. Organic extracts were dried over anhydrous Na_2SO_4, and solvents were evaporated on a rotary evaporator. Column chromatography was performed on Merck silica gel 60, 230−400 mesh, and TLC on Merck aluminum sheets, silica gel 60 S_{254}. Silica gel columns were deactivated by washing with hexane containing 5% of Et_3N and then with hexane.

(26) In the text vitamin D (steroid) numbering is used; however, in the Experimental Section compounds are named according to IUPAC nomenclature. IUPAC names were generated with the aid of the Beilstein AutoNom program.

64%). **9b**: ^{1}H NMR (200 MHz) δ (relative to TMS) 7.36−7.17 (m, 5H), 4.39 (s, 2H), 2.54−0.98 (m, 13H) overlapping 1.44 (s, 9H), 1.23 (s, 6H), 1.08 (d, 3H, J = 6.5 Hz); ^{13}C NMR and DEPT (50 MHz) δ 219.5 (0), 202.6 (0), 139.7 (0), 128.0 (1), 127.0 (1), 126.8 (1), 74.8 (0), 63.4 (2), 58.4 (1), 48.1 (1), 48.1 (0), 46.6 (1), 40.4 (2), 36.6 (2), 30.3 (2), 29.5 (3), 25.4 (3), 25.0 (2), 21.3 (2), 14.1 (3); EIMS LSIMS *m/z* 441 (10) $(M + Na)^+$, 419 (7) $(M + H)^+$; HRMS LSIMS calcd for $C_{25}H_{39}O_3S$ $(M + H)^+$ 419.261 99, found 419.261 94.

23: ^{1}H NMR (200 MHz) δ 7.34−7.15 (m, 5H), 4.38 (s, 2H), 2.76−0.80 (m, 16H) overlapping 2.07 (s, 3H), 1.41 (s, 9H), 1.22 (s, 6H), 0.98 (s, 3H); ^{13}C NMR and DEPT (50 MHz) δ 221.0 (0), 208.0 (0), 203.2 (0), 139.6 (0), 128.1 (1), 127.1 (1), 126.9 (1), 74.9 (0), 63.5 (2), 53.5 (1), 50.2 (1), 50.0 (0), 48.4 (0), 40.5 (2), 37.2 (2), 35.4 (2), 32.1 (2), 30.0 (3), 29.4 (3), 25.5 (3), 25.4 (3), 23.4 (2), 22.4 (2), 20.9 (2), 20.3 (3); EIMS LSIMS *m/z* 511 (100) $(M + Na)^+$ 489 (5) $(M + H)^+$; HRMS LSIMS calcd for $C_{29}H_{44}O_4SNa$ $(M + Na)^+$ 511.28580, found 511.28604.

22: mp 66−68 °C (hexane); ^{1}H NMR (200 MHz) δ (relative to TMS) 7.37−7.15 (m, 5H), 4.41 (s, 2H), 2.64−2.25 (m, 4H), 2.16−1.84 (m, 4H) overlapping 2.08 (s, 3H), 1.68−1.34 (m, 8H) overlapping 1.42 (s, 9H), 1.24 (s, 6H), 0.99 (s, 3H); ^{13}C NMR (50 MHz) δ 221.4 (0), 207.6 (0), 203.3 (0), 139.7 (0), 128.1 (1), 127.1 (1), 126.9 (1), 74.9 (0), 63.5 (2), 54.1 (1), 51.2 (0), 48.6 (0), 43.3 (1), 40.7 (2), 38.5 (2), 36.5 (2), 32.1 (2), 29.7 (3), 29.4 (3), 29.1 (2), 25.5 (3), 25.4 (3), 22.8 (2), 20.9 (2), 18.6 (3); EIMS LSIMS *m/z* 511 (24) $(M + Na)^+$, 489 (7) $(M + H)^+$; HRMS LSIMS calcd for $C_{29}H_{44}O_4SNa$ $(M + Na)^+$ 511.2858, found 511.2860. Anal. Calcd for $C_{29}H_{44}O_4S$: C, 71.27; H, 9.08. Found: C, 71.27; H, 9.27.

(2*R,1′*R**,3′a*S*,7′a*R**)-6-(Benzyloxy)-2-(3′a-hydroxy-7′a-methyl-5-oxooctahydroinden-1′-yl)-6-methyl-heptanethioic Acid *S*-*tert*-Butyl Ester (24).** A mixture of **22** (5.06 g, 10.3 mmol), THF (100 mL), and pyrrolidine (10 mL, 0.12 mol) was stirred at room temperature for 16 h, and the solvent was evaporated. The residue was chromatographed on SiO_2 (100 g, hexanes−EtOAc, 4:1) to give: (1) unchanged **22** (670 mg, 13%) and (2) **24** (3.55 g, 70%): mp 139 °C (hexane−acetone); ^{1}H NMR (200 MHz) δ 7.37−7.16 (m, 5H), 4.39 (s, 2H), 2.64−1.08 (m, 18H), overlapping 1.43 (s, 9H), 1.23 (s, 6H), 1.00 (s, 3H); ^{13}C NMR (50 MHz) δ 211.5 (0), 204.0 (0), 139.7 (0), 128.1 (1), 127.1 (1), 126.9 (1), 84.3 (0), 74.9 (0), 63.5 (2), 55.6 (1), 51.0 (2), 48.3 (0), 45.4 (0), 43.3 (1), 40.5 (2), 36.9 (2), 36.1 (2), 32.9 (2), 31.4 (2), 29.4 (3), 25.5 (3), 25.4 (3), 23.9 (2), 20.9 (2), 16.3 (3). Anal. Calcd for $C_{29}H_{44}O_4S$: C, 71.27; H 9.08. Found: C, 71.19; H, 8.97.

(2*R,1′*R**,7′a*R**)-6-(Benzyloxy)-6-methyl-2-(7′a-methyl-5′-oxo-2′,3′,5′,6′,7′,7′a-hexahydro-1′*H*-inden-1′-yl)heptanethioic Acid *S*-*tert*-Butyl Ester (25).** A solution of **27** (3.19 g, 6.5 mmol) and $TsOH·H_2O$ (160 mg, 0.8 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 16 h, and then the solvent was evaporated. The residue was chromatographed on SiO_2 (30 g, hexanes−EtOAc 4:1) to give **25** (3.01 g, 98%): mp 82−84 °C (MeOH); ^{1}H NMR (200 MHz) δ 7.36−7.16 (m, 5H), 5.70 (s, 1H), 4.39 (s, 2H), 2.69−0.90 (m, 16H) overlapping 1.43 (s, 9H), 1.22 (s, 6H), 1.13 (s, 3H); ^{13}C NMR (50 MHz) δ 203.1 (0), 198.8 (0), 177.8 (0), 139.7 (0), 128.1 (1), 127.1 (1), 126.9 (1), 121.6 (1), 74.9 (0), 63.5 (2), 54.4 (1), 51.9 (1), 48.4 (0), 44.6 (0), 40.6 (2), 35.3 (2), 33.3 (2), 33.1 (2), 29.5 (3), 28.2 (2), 25.7 (2), 25.4 (3), 21.0 (2), 16.3 (3); EIMS LSIMS *m/z* 493 (23) $(M + Na)^+$, 471 (27) $(M + H)^+$; HRMS LSIMS calcd for $C_{29}H_{43}O_3S$ $(M + H)^+$ 471.2933, found 471.292 56. Anal. Calcd for $C_{29}H_{42}O_3S$: C, 73.99; H, 9.00. Found: C, 73.76; H, 9.09.

(2*R,1′*R**,5′*S**,7′a*R**)-6-(Benzyloxy)-2-(5′-hydroxy-7′a-methyl-2′,3′,5′,6′,7′,7′a-hexahydro-1*H*-inden-1′-yl)-6-methylheptan-1-ol 1,5′-Diformate (26).** To a stirred, −78 °C solution of **25** (1.375 g, 2.92 mmol) in CH_2Cl_2 (90 mL) was added DIBALH (0.7 M in hexane, 16.5 mL, 11.5 mmol) over 0.5 h. The mixture was stirred at room temperature for 4 h and poured into 3% HCl. The product was extracted with CH_2Cl_2, and the solvent was evaporated. The residue was dried under high vacuum and then dissolved in benzene (30 mL) and treated with HCOOAc (2.4 mL) and DMAP (10 mg). The mixture was set aside for 16 h and then partitioned between water and hexane. The organic layer was washed with aqueous $NaHCO_3$ and water, and the solvent was evaporated. The residue was chromatographed on SiO_2 (30 g, hexanes−EtOAc 85:15) to give **26** (1.19 g, 92%): ^{1}H NMR (200 MHz) δ 8.08 (d, 1H, J = 1.1 Hz), 8.05 (s, 1H), 7.37−7.17 (m, 5H), 5.52−5.37 (m, 1H), 5.26 (s, 1H), 4.40 (s, 2H), 4.31 (dd, 1H, J = 11.3, 3.8 Hz), 4.08 (dd, 1H, J = 11.3, 5.4 Hz), 2.52−0.82 (m) overlapping 1.25 (s, 6H,), 1.01 (s, 3H); ^{13}C NMR (50 MHz) δ 161.1 (HCOO-1), 155.3 (0), 139.7 (0), 128.2 (1), 127.2 (1), 127.0 (1), 116.1 (1), 75.0 (0), 71.1 (1), 64.2 (2), 63.6 (2), 50.6 (1), 42.9 (0), 40.9 (2), 38.3 (1), 35.6 (2), 29.9 (2), 27.2 (2), 25.8 (2), 25.6 (3), 25.2 (2), 20.3 (2), 17.4 (3); EIMS LSIMS *m/z* 465 ((M + Na)$^+$, 15); HR LSIMS calcd for $C_{27}H_{38}O_5Na$ $(M + Na)^+$ 465.261 69, found 465.261 80.

(2*R*,1′*R*,3′a*S*,7′a*S*)-6-(Benzyloxy)-6-methyl-2-(7′a-methyl-2′,3′,3′a,6′,7′,7′a -hexahydro-1*H*-inden-1′-yl)heptan-1-ol Formate (27) and (2*R*,1′*R*),3′a*S*,7′a*R*)-6-(Benzyloxy)-6-methyl-2-(7′a-methyl-2′,6′,7′,7′a-tetrahydro-1*H*-inden-1′-yl)heptanol Formate (28). (a) To a solution of $Pd(OAc)_2$ (6 mg, 0.027 mmol) in dioxane[5] (2 mL) was added PBu_3 (Strem Chemicals,[19] batch C, see text, 0.032 mL, 0.128 mmol) followed, after 5 min, by **26** (314 mg, 0.71 mmol) in dioxane (4 mL). The mixture was heated at 65 °C for 1 h and then cooled and evaporated. The residue was dissolved in hexanes−EtOAc (4:1) and filtered through SiO_2 (2 g). The filtrate was evaporated and chromatographed on preparative HPLC column, ET 250/1″/20 Nucleosil 100-7, hexanes−EtOAc 95:5, 2 mL/min) to give **27** (204 mg, 72%) (R_f = 14.51 min) and **28** (65 mg, 24%) (R_f = 15.65 min). (b) To a solution of $Pd(OAc)_2$ (2.5 mg, 0.011 mmol) in THF[4] (0.5 mL) was added PBu_3 (0.011 mL, 0.045 mmol) followed, after 5 min, by **26** (82 mg, 0.19 mmol) in THF (2 mL). The mixture was heated under reflux for 1 h, and then it was cooled and the solvent was evaporated. The residue was dissolved in hexanes−EtOAc (4:1) and filtered through SiO_2 (3 g). The filtrate was evaporated to give a residue (69 mg, 93%) consisting of **27** and **28** in a ratio of 3.7:1 by HPLC.

27: ^{1}H NMR (200 MHz) δ 8.05 (s, 1H), 7.35−7.20 (m, 5H), 5.64−5.48 (m, 2H), 4.41 (s, 2H) overlapping 4.37 (dd, 1H, J = 11.2, 3.2 Hz), 4.14 (dd, 1H, J = 11.2, 5.5 Hz), 2.18−0.8 (m, 17H) overlapping 1.25 (s, 6H), 0.72 (s, 3H); ^{13}C NMR (50 MHz) δ 161.1 (1), 139.7 (0), 128.1 (1), 127.9 (1), 127.1 (1), 126.9 (1), 126.3 (1), 75.0 (0), 64.3 (2), 63.5 (2), 48.9 (1), 48.3 (1), 41.4 (0), 40.8 (2), 39.7 (1), 35.9 (2), 30.4 (2), 27.9 (2), 25.6 (3), 24.6 (2), 24.3 (2), 20.2 (2), 11.1 (3); EIMS *m/z* 398 (M^+, 0.2); HRMS calcd for $C_{26}H_{38}O_3$ (M^+) 398.282 09, found 398.282 01.

28: ^{1}H NMR (200 MHz) δ 8.07 (s, 1H), 7.37−7.18 (m, 5H), 6.18 (br d, 1H, J = 10 Hz), 5.79−5.67 (m, 1H), 5.38 (s, 1H), 4.42 (s, 2H) overlapping 4.38 (dd, 1H, J = 11.3, 1.9 Hz), 4.12 (dd, 1H, J = 11.3, 4.8 Hz), 2.44−1.10 (m, 14H) overlapping 1.26 (s, 6H,), 0.91 (s, 3H); ^{13}C NMR (50 MHz) δ 161.2 (1), 147.7 (0), 139.8 (0), 128.5 (1), 128.2 (1), 127.2 (1), 127.0 (1), 122.9 (1), 121.0 (1), 75.1 (0), 64.4 (2), 63.6 (2), 51.1 (1), 44.9 (0), 40.9 (2), 37.7 (1), 35.8 (2), 35.0 (2), 30.4 (2), 25.6 (3), 23.6 (2), 20.1 (2), 15.7 (3); EIMS *m/z* 396 (M^+, 0.3); HRMS calcd for $C_{26}H_{36}O_3$ (M^+) 396.266 44, found 396.266 43.

(2*R,1′*S**,1′a*S**,4′*R*,5′a*R**,7′*S**)-6-(Benzyloxy)-6-methyl-2-(3a-methyloctahydro-1-oxacyclopropa[*e*]inden-4-yl)heptan-1-ol Formate (29).** To a stirred solution of *m*-CPBA (86%, 243 mg, 1.22 mmol) in CH_2Cl_2 (8 mL), containing BHT (12 mg, 0.05 mmol) was added KF (88 mg, 1.51 mmol). The slurry was cooled to 0 °C, and then **27** (244 mg, 0.61 mmol) in CH_2Cl_2 (12 mL) was added. The mixture was stirred at 0 °C for 16 h, whereupon it was poured into saturated aqueous Na_2SO_3, and the product was extracted with CH_2Cl_2. The solvent was evaporated and the residue was chromatographed on SiO_2 (10 g, hexanes−EtOAc 9:1) to give **29** (244 mg, 96%): mp 42−44 °C (hexane); ^{1}H NMR (200 MHz) δ 8.03 (s, 1H), 7.37−7.17 (m, 5H), 4.40 (s, 2H), 4.30 (dd, 1H, J = 11.4, 3.3 Hz), 4.06 (dd, 1H, J = 11.4, 5.3 Hz), 3.14 (t, 1H, J = 3.3 Hz), 2.95 (d, 1H, J = 3.8 Hz), 2.16−0.79 (m, 17H) overlapping 1.24 (s, 6H,), 0.69 (s, 3H); ^{13}C NMR (50 MHz) δ 161.0 (1), 139.7 (0), 128.1 (1), 127.1 (1), 126.9 (1), 75.0 (0), 64.1 (2), 63.6 (2), 53.4 (1), 51.4 (1), 50.2 (1), 48.3 (1), 40.9 (2), 40.5 (0), 39.5 (1), 32.5 (2), 30.3

(2), 27.4 (2), 25.6 (3), 24.0 (2), 21.6 (2), 20.3 (2), 12.2 (3); EIMS *m*/*z*, 149 (27); LSIMS *m*/*z* 437 ($(M + Na)^+$, 45); HRMS LSIMS calcd for $C_{26}H_{38}O_4Na$ (M^+) 437.266 77, found 437.266 42. Anal. Calcd for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24. Found: C, 75.28, H, 9.42.

(2*R*,1′*R*,3′a*R*,4′*S*,5′*R*,7′a*R*)-6-(Benzyloxy)-2-[5-hydroxy-7a-methyl-4-(phenylthio)octahydroinden-1-yl]-6-methylheptan-1-ol (30). (a) To a solution of **29** (225 mg, 0.54 mmol) in EtOH (10 mL) was added PhSNa (0.9 M in EtOH, 1.8 mL, 1.62 mmol). The mixture was heated at reflux for 7 h and then cooled and poured into water. The product was extracted with toluene. The organic extract was washed with water, and the solvent was removed. The residue was chromatographed on SiO_2 (9 g, hexanes−EtOAc 6:4) to give **30** (223 mg, 83%): ^{1}H NMR (200 MHz) δ 7.39−7.13 (m, 10H), 4.41 (s, 2H), 4.05 (dd, 1H, J = 4.9, 2.3 Hz), 3.75−3.56 (m, 2H), 3.42 (dd, 1H, J = 2.1, 2.1 Hz), 2.34−2.05 (m, 2H), 1.97−1.13 (m, 15H) overlapping 1.25 (s, 6H,), 0.88 (s, 3H); ^{13}C NMR (50 MHz) δ 139.8 (0), 137.8 (0), 130.1 (1), 129.0 (1), 128.2 (1), 127.3 (1), 127.1 (1), 126.3 (1), 75.3 (0), 70.3 (1), 63.7 (2), 62.4 (2), 53.8 (1), 50.5 (1), 45.3 (1), 42.2 (0), 42.0 (1), 41.0 (2), 33.3 (2), 29.6 (2), 26.6 (2), 25.7 (3), 25.1 (2), 23.6 (2), 20.5 (2), 13.0 (3); EIMS *m*/*z* 496 (M^+, 25); HRMS calcd for $C_{31}H_{44}O_3S$ (M^+) 496.301 12, found 496.300 16.

(b) Directly from a Mixture of 27 and 28. To a stirred solution of *m*-CPBA (86%, 66 mg, 0.33 mmol) in CH_2Cl_2 (1 mL) containing BHT (3 mg, 0.012 mmol) was added KF (12 mg, 0.21 mmol). The slurry was cooled to 0 °C, and a mixture of **27** and **28** (66 mg, 3.3:1, respectively, by ^{1}H NMR) in CH_2Cl_2 (2 mL) was added. After being stirred at 0 °C for 16 h, the mixture was poured into saturated aqueous Na_2SO_3, and the product was isolated as described above and chromatographed on SiO_2 (3 g, hexanes−EtOAc 9:1). The main fraction (48 mg) consisting of **29** contaminated with 10−20% of unidentified side products was dissolved in EtOH (2 mL) and treated with PhSNa (0.9 M in EtOH, 0.35 mL, 0.32 mmol). The mixture was heated at reflux for 8 h, cooled, and poured into water. The product was extracted with toluene and chromatographed on SiO_2 (3 g, hexanes−EtOAc 6:4) to give **30** (41 mg, 60% yield from **26**).

(2*R*,1′*R*,3′a*R*,4′*S*,5′*R*,7′a*R*)-2-[4-(Benzenesulfonyl)-5-hydroxy-7a-methyloctahydroinden-1-yl]-6-(benzyloxy)-6-methylheptan-1-ol (31). To a stirred solution of **30** (220 mg, 0.44 mmol) in CH_2Cl_2 (15 mL) containing BHT (8 mg, 0.04 mmol) was added *m*-CPBA (86%, 237 mg, 1.19 mmol). After 1 h the mixture was poured into saturated aqueous Na_2SO_3, the product was isolated with CH_2Cl_2 and chromatographed on SiO_2 (12 g, hexanes−EtOAc, 1:1) to give **31** (231 mg, 99%): ^{1}H NMR (200 MHz) δ 7.93−7.82 (m, 2H), 7.66−7.47 (m, 3H), 7.36−7.18 (m, 5H), 4.39 (s, 2H), 4.14 (br s, 1H), 3.65 (br d, A part of AB q, 1H, J = 11.5 Hz), 3.57 (br d, 1H, B part of AB q, J = 11.5 Hz), 3.43 (br d, J = 4.0 Hz); 2.40−2.08 (m, 4H); 1.80−1.10 (m, 13H) overlapping 1.23 (s, 6H,), 1.05 (s, 3H); ^{13}C NMR (50 MHz) δ 141.2 (0), 139.6 (0), 133.3 (1), 129.1 (1), 128.2 (1), 127.8 (1), 127.3 (1), 127.0 (1), 75.3 (0), 68.4 (1), 64.7 (1), 63.6 (2), 62.1 (2), 50.0 (1), 45.5 (1), 42.0 (1), 40.9 (2), 40.8 (0), 33.2 (2), 29.4 (2), 26.6 (2), 26.2 (2), 25.6 (3), 22.9 (2), 20.5 (2), 13.3 (3); EIMS *m*/*z* 422 (1) $(M\text{-}OBn)^+$; HRMS calcd for $C_{24}H_{38}O_4S$ $(M - BnO)^+$ 422.249 83, found 422.250 39, calcd for $C_{24}H_{37}O_4S$ $(M - BnOH)^+$ 421.241 52, found 421.241 73, calcd for $C_{24}H_{36}O_3S$ $(M - BnO - H_2O)^+$ 404.236 06, found 404.234 40, calcd for $C_{24}H_{35}O_3S$ $(M - BnOH - H_2O)^+$ 403.227 86, found 403.227 20.

(6*R*,1′*R*,3′a*R*,4′*R*,5′*R*,7′a*R*)-2-(Benzyloxy)-6-[4-(benzenesulfonyl)-7a-methyloctahydroinden-1-yl]-2-methylheptane (32). To a solution of **31** (105 mg, 0.20 mmol) in CH_2Cl_2 (9 mL) containing Et_3N (0.26 mL, 1.88 mmol) was added MsCl (0.045 mL, 0.6 mmol) at −20 °C. The mixture was stirred for 0.5 h and then saturated aqueous $NaHCO_3$ (3 mL) and water were added. The respective mesylate was isolated with CH_2Cl_2, dissolved in THF (12 mL), and treated with $LiEt_3BH$ (0.9 M in THF, 1.8 mL, 1.62 mmol). The mixture was stirred at room temperature for 3 h and then poured into aqueous $NaHCO_3$. The product was isolated with CH_2Cl_2 and chromatographed on SiO_2 (5 g, hexanes−EtOAc 85:15) to give **32** (97 mg, 98%): ^{1}H NMR (200 MHz) δ 7.92−7.83 (m, 2H), 7.68−7.49 (m, 3H), 7.38−7.18 (m, 5H), 4.41 (s, 2H), 3.04 (ddd, 1H, J = 11.3, 11.3, 3.3 Hz), 2.14−0.82 (m, 17H) overlapping 1.25 (s, 6H,), 0.92 (d, 3H, J = 6.4 Hz), 0.70 (s, 3H); ^{13}C NMR (50 MHz) δ 139.8 (0), 138.3 (0), 133.2 (1), 128.8 (1), 128.6 (1), 128.1 (1), 127.2 (1), 126.9 (1), 75.2 (0), 63.7 (1), 63.5 (2), 55.0 (1), 48.1 (1), 44.6 (0), 40.7 (2), 38.7 (2), 36.3 (2), 35.4 (1), 27.9 (2), 27.3 (2), 25.7 (3), 25.3 (2), 21.1 (2), 20.2 (2), 18.7 (3), 11.8 (3); EIMS *m*/*z* 496 (M^+, 0.4); HRMS calcd for $C_{31}H_{44}O_3S$ (M^+) 496.301 11, found 496.300 65.

(6*R*,1′*R*,3′a*R*,4′*R*,7′a*R*)-6-[4-(Benzenesulfonyl)-7a-methyloctahydroinden-1-yl]-2-methylheptan-2-ol (8). A mixture of **32** (46 mg, 0.09 mmol), EtOH (95%, 6 mL), and Pd/C (10%) (5 mg) was stirred vigorously in a hydrogen atmosphere for 5 h. The catalyst was filtered off, the filtrate was evaporated, and the residue was chromatographed on SiO_2 (1 g, hexanes−EtOAc 7:3) to give **8** (38 mg, 100%): ^{1}H NMR (200 MHz) δ 7.89−7.81 (m, 2H), 7.68−7.49 (m, 3H), 3.02 (ddd, 1H, J = 11.3, 11.3, 3.3 Hz), 2.14−0.86 (m, 17H) overlapping 1.20 (s, 6H); 0.91 (d, 3H, J = 6.4 Hz), 0.68 (s, 3H); ^{13}C NMR (50 MHz) δ 138.3, 133.3, 128.9, 128.7, 71.0, 63.8, 55.0, 48.1, 44.6, 44.3, 38.7, 36.3, 35.5, 29.3, 29.2, 27.9, 27.4, 25.3, 21.1, 20.7, 18.7, 11.9. The product was identical with the authentic sample.[29]

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Supporting Information Available: Procedures for synthesis of the side-chain precursors, **2b,2d**, **4b,d**, **5b**, **9a**, **10**, and **12**−**21**, ORTEP projection of the X-ray structure of **14** and its crystallographic data, and ^{1}H and ^{13}C NMR spectra of compounds **2b**−**d**, **4b,d**, **5b**, **8**, **9b**, **10**, **12**−**18**, **21**, **23**, and **26**−**32** (70 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(27) Hahn, E. F. *J. Org. Chem.* **1973**, *38*, 2092−2094.

(28) This mixed anhydride was prepared in the following way: to Ac_2O (13 mL, 130 mmol), stirred at 0 °C, was added formic acid (100%, 6 mL, 159 mmol). The mixture was stirred at 60 °C for 2 h and cooled and stored under argon.

(29) Michalak, K.; Stepanenko, W.; Wicha, J. *Tetrahedron Lett.* **1996**, *37*, 7657−7658.