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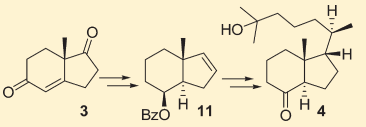
Total Synthesis of a CD-Ring: Side-Chain Building Block for Preparing 17-*epi*-Calcitriol Derivatives from the Hajos−Parrish Dione

Karol Michalak and Jerzy Wicha*

Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, 01-224 Warsaw, Poland

Supporting Information

ABSTRACT: An efficient synthesis of the key building block for 17-*epi*-calctriol from the Hajos−Parrish dione involving a sequence of diastereoselective transformation of the azulene core and the side-chain construction is presented.



The total synthesis of calcitriol (1α,25-dihydroxy-vitamin D_3, **1**, Scheme 1) and its congeners attracts a great deal of attention owing to the present and pending medical applications of these compounds.[1] In search for a modification of the calcitriol structure that would improve selectivity of action, we have recently synthesized 17-*epi*-calcitriol (**2**).[2,3] The synthesis commenced from 3β-hydroxyandrost-5-en-17-one and, in part, followed the classical vitamin D route through 17-*epi*-cholestane intermediates and a photolytic opening of the ring B. Although some improvements were developed, the synthesis included notoriously ineffectual steps (bromination−dehydrobromination, photolysis) that diminished the overall yield (4.80%, 23 steps).

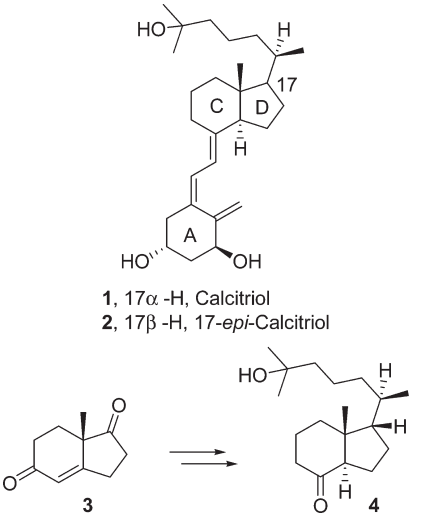
The promising biological activity of **2**, which proved to be more active in inhibiting proliferation human breast cancer MCF-7 than **1**, and the progress in the total synthesis of *trans*-hydrindan derivatives prompted us to revisit the synthesis. It was thought that **2**, and eventually other 17-*epi*-calicitriol analogues, could be efficiently synthesized from the Hajos−Parrish dione[4] **3**. Diastereoselective transformations of **3** are of interest on their own rights since this optically active 10-carbon compound, readily obtained by an organocatalytic route, provides an important augment of the natural chiral pool.[5]

The dione **3** was selectively reduced and the hydroxy group in the five-membered ring was protected as a *tert*-butyl ether to give **5** (Scheme 2), following the well-known procedure.[6] The *trans*-hydrindan intermediate **6** was then prepared from **5** by a sequence of reactions previously reported from this laboratory[7,8] amended to gram-scale operations (eight steps, 52% overall yield).

The benzoate **7** was subjected to an action of $CeCl_3 \cdot 7H_2O$ and NaI in acetonitrile[9] to provide alcohol **8** that was subsequently oxidized into ketone **9** (74% from **6**).

All our attempts to transform ketone **9** via its hydrazone into the respective vinyl iodide[10] which could be reduced into alkene **11** failed, presumably, because of inherent instability of the iodide. Eventually, the ketone **9** was transformed into enol triflate **10**, and this derivative was treated with tributylammonium formate in the presence of $Pd(PPh_3)_2(OAc)_2$ to afford **11** (86% in two steps).[11]

Scheme 1. Calcitriol, Its 17-*Epi* Derivative, and the Planned Synthetic Transformations



The usual modus operandi for cyclopropanation of alkene **11** would involve its reaction with ethyl diazoacetate induced by a rhodium[12] or palladium catalyst[2,13] [often $Pd(OAc)_2$ or $Rh_2(AcO)_4$]. After some experimentation, we have found that an inexpensive and easy to prepare copper catalyst,[14] $CuI \cdot P(OMe)_3$, gives the best results with regard to both the product purity and the yield. Thus, slow addition of ethyl diazoacetate (ca. 5 equiv) to a mixture of **11** and $CuI \cdot P(OMe)_3$ (10 mol %) in benzene, at reflux temperature, afforded the cyclopropane derivative **12** (as a mixture isomers, Scheme 3). A brief heating of the crude product with sodium methoxide in methanol affected trans-esterification, epimerization at the α-position to the alkoxycarbonyl group, and a cleavage of the benzoate linkage to

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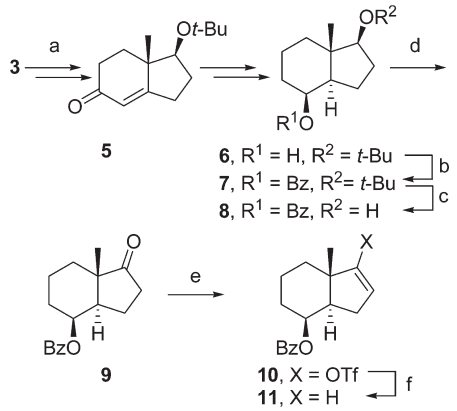
afforded **13** (80% yield from **11**). The hydroxy group in **13** was protected as a *tert*-butyldimethylsilyl derivative in the usual way to give **14**. The cyclopropane carboxylic ester moiety in **14** was then reduced with lithium in liquid ammonia−THF in the presence of *tert*-butyl alcohol.[15] The crude reduction product was reoxidized with the Jones' reagent to afford carboxylic acid **15** contaminated with a side product (less than 10% by ^{1}H NMR). Since the contamination could not be removed by chromatography at this stage, the crude acid was treated with diazomethane, and the ester **16** containing a side product (less than 10%) was used for a sterol side chain construction. Thus, treatment of **16** with LDA in THF−hexanes, at −78 °C, and then with methyl iodide (3.5 equiv) and HMPA (3.5 equiv) afforded selectively the methyl derivative (95% yield) to which the structure **17** was assigned[16] contaminated with a side product (less than 10%). The crude ester **17** was reduced with lithium aluminum hydride in THF and the product was purified by a careful chromatography on a silica gel column to give alcohol **18** (91% yield).

The alcohol **18** was converted into its tosylate, and the latter was allowed to react with a lithium acetylide, prepared from **19** and BuLi.[17] The derivative **20** was subjected to exhaustive catalytic hydrogenation to afford **21**. The protective TBS group in a sterically congested environment and the THP group were then removed by treatment of **21** with 40% HF in acetonitrile.[18] The diol **22** thus obtained, after column chromatography, was shown to be 97.5% pure by HPLC. Oxidation of **22** with PDC[19] afforded the hydroxy ketone **4** identical in all respects with the product obtained previously from a steroid starting material.[2]

In conclusion, the *trans*-hydrindan derivative **4**, being a key building block for the synthesis of 17-*epi*-calcitriol **2**, has been prepared from the Hajos−Parrish dione **3** in 24 steps, 14.97% overall yield. The method for transforming of **3** into **6** has been improved and amended to a gram-scale operations. The side chain has been attached to the olefin **11** using a cyclopropanation reaction induced by a Cu complex. The developed methods may serve for economic synthesis of 17-*epi*-calcitriol and analogues.

Scheme 2. Transformation of the Hajos−Parrish Dione (3) into the *trans*-Hydrindan Intermediate 11[a]

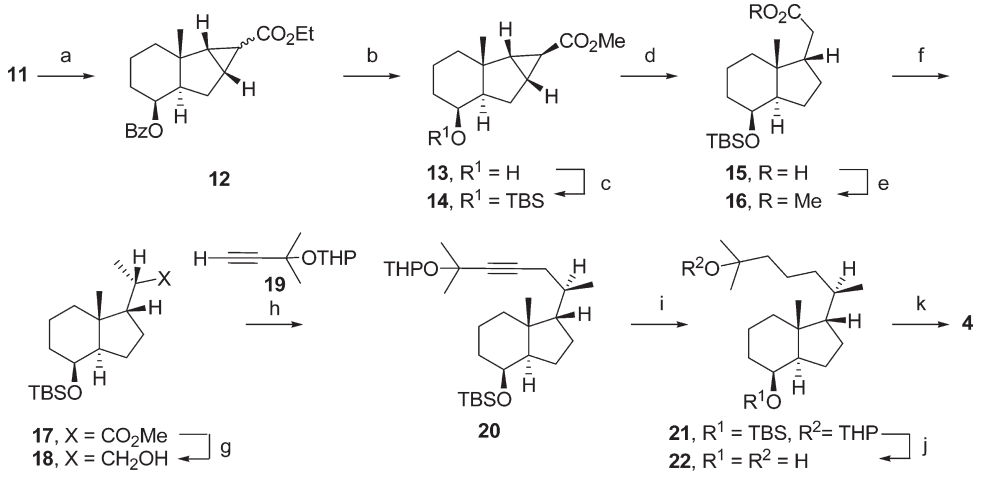


[a] Key: (a) refs [7] and ref.;[8] (b) BzCl, DMAP, Py, reflux, 1 h (52% from **3**); (c) $CeCl_3 \cdot 7H_2O$, NaI, MeCN, reflux, 2 h (100%); (d) Jones' reagent, acetone (86%); (e) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, rt, 6 h, 91%; (f) $Pd(PPh_3)_2(OAc)_2$, Bu_3N, HCO_2H, DMF, rt → 60 °C, 95%.

EXPERIMENTAL SECTION

NMR spectra were recorded in $CDCl_3$ solutions, ^{1}H at 200 MHz and ^{13}C at 50 MHz; chemical shifts are quoted on the δ scale, ppm, with the solvent signal as the internal standard ($CHCl_3$, ^{1}H NMR 7.26 ppm; $CDCl_3$, ^{13}C NMR 77.00 ppm). In the ^{13}C NMR spectra multiplicities of signals were assigned using the DEPT technique. High-resolution mass spectra (HRMS) were taken using EI technique, electrospray ionization (ESI), or liquid secondary ion mass spectroscopy (LSIMS). Column chromatography was performed on Merck silica gel 60, 230−400 mesh. TLC was performed on aluminum sheets, Merck 60F 254. Anhydrous solvents were obtained by distillation from benzophenone ketyl (THF), calcium hydride (CH_2Cl_2), or lithium aluminum hydride (ether). Commercially available hexanes (a mixture of isomers) was used. Air-sensitive

Scheme 3. Side-Chain Construction[a]



[a] Key: (a) $N_2CH_2CO_2Et$ (added dropwise), $CuI \cdot P(OMe)_3$ (10 mol %); (b) MeONa, MeOH, reflux, 1.5 h (80% from **11**); (c) TBSCl, DMAP, imidazole, DMF, 80 °C, 16 h (99%); (d) Li, *t*-BuOH−THF−liquid NH_3 and then Jones' oxidation (98% yield, ca. 90% pure, see the text); (e) CH_2N_2, Et_2O (89% yield, ca. 90% pure); (f) LDA, −78 °C and then MeI and HMPA, −78 °C, 16 h, 95%; (g) $LiAlH_4$, THF, chromatography (91%); (h) (1) TsCl, Py, (2) **19**, BuLi, 5 °C and then reflux, 4 days; (i) H_2, 10% Pd-on-carbon, $NaHCO_3$, reflux, 5 days; (j) 40% HF, MeCN, rt, 8 h, 72% from **18**; (k) PDC, CH_2Cl_2 (96%).

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reactions were performed in flame-dried glassware under argon. Organic solutions were evaporated in a rotary evaporator. Reagents were used as purchased. Microanalyses were performed at our analytical laboratory.

Gram-Scale Preparation of (1*S*,3a*R*,4*S*,7a*S*)-1-*tert*-butoxy-7a-methyloctahydro-1*H*-inden-4-ol benzoate (7) from the Hajos−Parrish Dione (3). The Hajos−Parrish dione (**3**, 3.00 g, 18.2 mmol) was transformed[6] into (1*S*,7a*S*)-1-*tert*-butoxy-7a-methyl-1,2,3,6,7,7a-hexahydro-5*H*-inden-5-one (**5**), and this product, without purification, was reduced following the Luche protocol.[7,20] Thus obtained (1*S*,5*S*,7a*S*)-1-*tert*-butoxy-7a-methyl-2,3,5,6,7,7a-hexahydro-1*H*-inden-5-ol[21] was epoxidized with *m*-CPBA[7] to afford (1a*S*,2*S*,4a*R*,5*S*,7a*R*)-1-*tert*-butoxy-4a-methyloctahydroindeno[3a,4-*b*]oxiren-2-ol. This crude product was dissolved in Et_2O (140 mL), and $NaBH_3CN$ (3.0 g, 47.8 mmol) was added. The mixture was stirred at rt while $BF_3 \cdot Et_2O$ (3.6 mL, 29.2 mmol) was added dropwise over 1 h. Stirring was continued for 1 h and then the mixture was poured into brine and satd aq $NaHCO_3$ (1:1, 100 mL). The organic layer was separated, washed consecutively with 2% aq NaOH (100 mL) and brine (50 mL), and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel (60 g, hexane−EtOAc, 3:1) to give (1*S*,3a*R*,4*R*,5*S*,7a*S*)-1-*tert*-butoxy-7a-methyloctahydro-1*H*-indene-4,5-diol (2.764 g, 63% yield from **3**). A mixture of this diol (2.764 g, 11.4 mmol), thiocarbonyldiimidazole (TCDI, 4.15 g, 23.3 mmol), and THF (20 mL) was heated under reflux for 3 h. After cooling, the solvent was evaporated, and the residue was chromatographed on silica gel (50 g, hexanes−EtOAc, 9:1) to give (3a*S*,5a*S*,6*S*,8a*R*,8b*R*)-6-*tert*-butoxy-5a,8a-dimethyloctahydro-3a*H*-indeno[4,5-*d*]dioxole-2-thione (2.909 g, 90%, 57% from **3**). A mixture of the latter product (2.909 g, 10.2 mmol), MeI (12 mL, 193 mmol), $NaHCO_3$ (0.5 g), and some Cu turnings was stirred and heated in a sealed ampule at 45 °C (an oil bath temperature) for 40 h. After cooling, the solid material was filtered off, and the filtrate was evaporated to dryness. The residue was chromatographed on silica gel (50 g, hexanes−EtOAc, 93:7) to give *O*-[(1*S*,3a*R*,4*R*,5*R*,7a*S*)-1-*tert*-butoxy-5-iodo-7a-methyloctahydro-1*H*-inden-4-ol] *S*-methyl thiocarbonate (4.062 g). This product was dissolved in THF (20 mL), and the solution was added dropwise, over ca. 15 min, to a suspension of $LiAlH_4$ (1.40 g, 36.8 mmol) in THF (100 mL) heated under reflux. Heating was continued for 15 min, and then the mixture was allowed to cool to rt. The reagent excess was destroyed with concd aq Na_2SO_4. The solid was filtered off and washed with EtOAc. The combined filtrate was evaporated to dryness to give alcohol **6**[7] containing a side product, ca. 5% by ^1H NMR (2.152 g), that was used for the next step without purification.

A mixture of crude **6** (1.026 g, ca. 4.53 mmol), pyridine (10 mL), DMAP (5 mg), and benzoyl chloride (0.785 mL, 6.8 mmol) was heated under reflux for 1 h. Water (0.5 mL) was then added, and the mixture was cooled to rt and diluted with EtOAc (30 mL). The solution was partitioned between water (100 mL) and hexanes (100 mL). The hexane layer was collected and washed consecutively with water, 5% HCl, water, and brine. After drying (Na_2SO_4), the solution was filtered through a pad of silica gel (ca. 3 g). The silica gel was washed with hexanes−EtOAc, 8:2 (15 mL), and the solvent was evaporated to give benzoate **7** (1.490 g, 52% from **3**). ^1H NMR: 2.1−1.0 (m, 11H) overlapping 1.09 (s, 3H), 1.15 (s, 9H), 3.40 (br t, 1H, J = 8.0 Hz), 5.40 (br d, 1H, J = 2.0 Hz), 7.60−7.36 (m, 3H), 8.12−8.02 (m, 2H). ^{13}C NMR: 13.1, 17.8, 22.3, 28.7, 30.1, 30.8, 37.2, 41.6, 46.7, 72.00, 72.2, 80.5, 128.3, 129.5, 130.8, 132.6, 166.4. MS EI (m/z): 330 (M^+, 1), 274 (18), 152 (89), 134 (57), 108 (41), 105 (100). HRMS: calcd for $C_{21}H_{30}O_3$ 330.21950, found: 330.22049.

(1*S*,3a*R*,4*S*,7a*S*)-1,4-Dihydroxy-7a-methyloctahydro-1*H*-indenyl 4-benzoate (8). A mixture of **7** (1.485 g, 4.49 mmol), $CeCl_3 \cdot 7H_2O$ (2.01 g, 5.4 mmol), NaI (0.81 g, 5.4 mmol), and MeCN (20 mL) was heated under reflux for 2 h. After the mixture was cooled to rt, a few crystals of Na_2SO_3 were added and the mixture was diluted with hexanes (100 mL). The solution was washed consecutively with water and brine, dried (Na_2SO_4), and filtered through a pad of silica gel (ca. 3 g). The silica gel was washed with hexanes−EtOAc (7:3, 50 mL). The combined filtrate was evaporated to give **8** (1.230 g, 100%). ^1H NMR: 1.0−2.1 (m, 11H) overlapping 1.01 (s, 3H), 3.65 (t, 1H, J = 8.0 Hz), 5.40 (br d, 1H, J = 2.2 Hz), 7.60−7.36 (m, 3H), 8.12−8.02 (m, 2H). ^{13}C NMR: 12.4, 17.6, 21.9, 29.3, 30.5, 36.6, 42.0, 46.6, 71.7, 81.5, 128.3, 129.5, 130.6, 132.7, 166.4. MS EI (m/z): 274 (M^+, 6), 230 (3), 169 (12), 152 (54), 134 (30), 108 (50), 105 (100). HRMS: calcd for $C_{17}H_{22}O_3$ 274.15689, found 274.15572.

(3a*R*,4*S*,7a*S*)-4-Hydroxy-7a-methyloctahydro-1*H*-inden-1-one Benzoate (9). Jones' reagent was added dropwise to a stirred solution of **8** (1.201 g, 4.38 mmol) in acetone (20 mL) at rt until the reagent color persisted. The mixture was stirred for a few additional min, and then the reagent excess was destroyed with *i*-PrOH (0.25 mL). The solution was diluted with hexanes (60 mL), and then Na_2SO_4 was added in portions until a well-separated greenish granulate solid was formed. The solution was decanted, and the solvent was evaporated. The residue was chromatographed on silica gel (25 g, hexanes−EtOAc, 9:1) to give **9** (1.031 g, 86%). ^1H NMR: 2.2−1.1 (m, 10H) overlapping 1.21 (s, 3H), 2.42−1.34 (m, 1H), 5.53 (br d, 1H, J = 1.6 Hz), 7.60−7.38 (m, 3H), 7.78−8.06 (m, 2H). ^{13}C NMR: 16.2, 17.3, 21.2, 30.5, 31.6, 35.1, 47.0, 47.4, 71.9, 128.4, 129.4, 130.3, 132.9, 166.1, 219.5. MS EI (m/z): 272 (M^+, 4), 244 (4), 167 (7), 150 (26), 122 (14), 108 (14), 105 (100). HRMS: calcd for $C_{17}H_{20}O_3$ 272.14124, found 272.14216.

(3a*R*,7*S*,7a*R*)-3a-Methyl-3a,4,5,6,7,7a-hexahydro-1*H*-inden-7-ol Benzoate (11). Tf_2O (0.81 mL, 4.9 mmol) was added dropwise to a mixture of **9** (1.021 g, 3.75 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (1.154 g, 5.6 mmol), and CH_2Cl_2 (20 mL) and stirred at rt. After 6 h, Et_3N (1.55 mL, 11 mmol) and hexanes (40 mL) were added. The mixture was stirred briefly and concentrated to a volume of ca. 10 mL. The upper layer was separated and transformed to a silica gel column (25 g). The column was eluted with hexanes (300 mL) to recover 2,6-di-*tert*-butyl-4-methylpyridine (1.132 g) and then with hexanes−EtOAc, 97:3 (400 mL) to give triflate **10** (1.372 g, 91%). A mixture of **10** (1.372 g, 3.40 mmol), $Pd(PPh_3)_2(OAc)_2$ (52 mg, 0.068 mmol, 2 mol %), Bu_3N (2.43 mL, 10.2 mmol), HCO_2H (≥99%, 0.32 mL, 8.5 mmol), and DMF (10 mL) was stirred at rt, the temperature was warmed to 60 °C (bath) in ca. 10 min, and stirring was continued for 20 min. After cooling, the mixture was diluted with EtOAc (30 mL) and poured into water. The product was extracted with hexanes (100 mL). The extract was washed with 1 N HCl, water, and brine and dried (Na_2SO_4). The solvent was evaporated, and the reside was chromatographed on silica gel (20 g, hexanes−EtOAc, 98:2) to give **11** (829 mg, 95%). ^1H NMR: 2.2−1.0 (m, 9H) overlapping 1.15 (s, 3H), 5.50 (br d, 1H, J = 2.4 Hz), 5.76−5.68 (m, 1H), 5.84−5.78 (m, 1H), 7.60−7.38 (m, 3H), 9.10−8.02 (m, 2H). ^{13}C NMR: 18.5, 19.6, 30.9, 31.4, 36.00, 44.8, 71.3, 128.3, 128.6, 129.5, 130.8, 132.6, 143.3, 166.4. MS LSIMS (m/z): 535 [$(2M + Na)^+$, 12], 279 [$(M + Na)^+$, 100]. HRMS: calcd for $C_{17}H_{20}O_2Na$ 279.13555, found 279.13681.

Methyl (1*S*,1a*S*,1b*R*,5*S*,5a*R*,6a*R*)-5-Hydroxy-1b-methyldecahydrocycloprop[*a*]indene-1-carboxylate (13). To a mixture of **11** (428 mg, 1.67 mmol) and $CuI \cdot P(OMe)_3$ (52 mg, 0.17 mmol, 10 mol %) in benzene (15 mL), heated under reflux, was added freshly distilled ethyl diazoacetate (0.87 mL, 8.4 mmol) in benzene (15 mL) over 5.5 h by means of a syringe pump via a cannula inserted through the condenser in such a manner that the reagent solution was dropping directly onto the surface of the mixture from the cold part of the condenser. After an additional 0.5 h, the mixture was allowed to cool, and then the solvent was evaporated. The residue was transferred with hexanes to a silca gel column (30 g, in hexanes). The column was eluted with hexanes−EtOAc 99:1 (500 mL) to recover the starting material contaminated with nonpolar side products (48 mg) and then with hexanes−EtOAc 94:6 (500 mL) to give ethyl ester **12** (616 mg). This product consisted of exo- and endo-isomers in a ratio of ca. 7:1 and ethyl

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diazoacetate decomposition products (ca. 15%) by ^{1}H NMR analysis. An analytical sample was prepared by stirring of a solution of a sample of this product in EtOH with palladium on carbon (5%) in hydrogen atmosphere (90 atm, rt, 20 h) and rechromatography. **12** (Main Isomer). ^{1}H NMR: 1.12 (dt, 1H, J = 2.8, 7.8 Hz), 2.1−1.2 (m, 11H) overlapping 1.25 (s, 3H) overlapping 1.26 (t, 3H, J = 7.2 Hz), 4.01 (q, 2H, J = 7.2 Hz), 5.44 (br.s, 1H), 7.62−7.36 (m, 3H), 8.10−7.97 (m, 2H). ^{13}C NMR: 14.3, 18.5, 20.2, 22.3, 23.5, 26.4, 30.7, 35.2, 37.8, 40.3, 43.3, 60.4, 71.3, 128.3, 129.5, 130.5, 132.8, 166.3, 173.7. MS LSIMS (m/z): 707 [(2M + Na]$^+$, 13), 365 [(M + Na]$^+$, 100). HRMS: calcd for $C_{21}H_{26}O_4Na$ 365.17233, found 365.17084. Minor Isomer, the Diagnostic Signal. ^{1}H NMR: 4.18 (q, 1H, J = 6.6 Hz). The crude **12** (582 mg) was dissolved in a solution of MeONa in MeOH, prepared from MeOH (5 mL) and sodium (140 mg). The mixture was heated under reflux for 1.5 h, cooled, and transferred with Et_2O (30 mL) into 3% aq HCl (80 mL). The product was extracted with a mixture of hexanes and EtOAc (1:1, 100 mL). The organic extract was washed with water and brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel (15 g, hexanes−EtOAc, 85:15) to give **13** (304 mg, 80% from **11**). ^{1}H NMR: 0.87 (ddd, 1H, J = 12.2, 6.2, 2.2 Hz), 1.9−1.1 (m, 11H) overlapping 1.14 (s, 3H), 3.64 (s, 3H), 4.14 (br s, 1H). ^{13}C NMR: 18.0, 20.1, 22.1, 23.7, 26.2, 34.0, 35.5, 38.4, 40.2, 43.9, 51.6, 68.7, 174.3. MS EI (m/z): 224 (M$^+$, 4), 206 (32), 191 (52), 175 (17), 147 (100). HRMS: calcd for $C_{13}H_{20}O_3$ 224.14124, found 224.14196.

Methyl (1*S*,1a*S*,1b*R*,5*S*,5a*R*,6a*R*)-5-(*tert*-Butyldimethylsilyloxy)-1b-methyldodecahydrocyclopropa[*a*]indene-1-carboxylate (14). A mixture of **13** (304 mg, 1.36 mmol), TBSCl (409 mg, 2.71 mmol), imidazole (369 mg, 5.43 mmol), DMAP (3 mg), and DMF (3 mL) was stirred at 80 °C (bath) for 16 h. After cooling, the mixture was diluted with Et_2O (25 mL) and poured into brine. The product was extracted with hexanes (50 mL). The extract was washed with water (2 × 25 mL) and brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel (10 g, hexanes−EtOAc, 99:1) to give **14** (456 mg, 99%). ^{1}H NMR: −0.01 (s, 3H), 0.00 (s, 3H), 0.87 (s, 9H) partly overlapping 0.86 − 0.72 (m, 1H), 1.11 (s, 3H), 1.7−1.1 (m, 11H), 3.63 (s, 3H), 4.06 (d, 1H, 0.8 Hz). ^{13}C NMR: −5.1, −4.8, 18.1, 18.2, 20.1, 22.6, 23.9, 25.8, 26.6, 34.6, 35.8, 38.6, 40.4, 44.2, 51.5, 68.8, 174.5. MS EI (m/z): 338 (M$^+$, 6), 323 (3), 281 (100), 206 (23), 175 (32), 147 (52), 133 (21), 105 (31). HRMS: calcd for $C_{19}H_{34}O_3Si$ 338.22772, found 338.22865.

[(1*S*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilyloxy)-7a-methyloctahydro-1*H*-inden-1-yl]acetic Acid (15). A mixture of *t*-BuOH−THF (3: 4, 7 mL) and a solution of **14** (456 mg, 1.35 mmol) in *tert*-BuOH−THF (1: 1, 8 mL) were consecutively added to a solution of Li (188 mg, 27 mg atom) in liquid NH_3 (25 mL) at reflux. After 30 min, an excess of Li was destroyed with solid NH_4Cl, and then ammonia was allowed to evaporate. The residue was dissolved in Et_2O (60 mL) and poured into water. The product was extracted with hexanes (60 and 30 mL). The combined extract was washed with water and brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was dissolved in acetone (15 mL). The solution was stirred at rt while Jones' reagent (2.67 M, 2 mL) was added in two portions. After 0.5 h, the reagent excess was destroyed with *i*-PrOH (1 mL), and some Na_2SO_4 was added. The solid was filtered off and washed with EtOAc. The combined filtrate was evaporated to dryness, and the residue was chromatographed on silica gel (15 g, hexanes−EtOAc, 8:2) to give **15** contaminated with a side product, less than 10% (by ^{1}H NMR)(432 mg, 98%). ^{1}H NMR: 0.00 (s, 3H), 0.01 (s, 1H), 0.88 (s, 9H), 1.04 (s, 3H), 2.1−1.1 (m, 13H), 2.50−2.30 (m, 1H), 4.01 (dd, 1H, J = 4.4, 2.0 Hz). ^{13}C NMR: −5.1, −4.8, 17.5, 18.1, 23.1, 24.2, 25.8, 27.5, 34.5, 34.7, 37.8, 42.4, 45.00, 47.4, 69.1, 180.3. MS EI (m/z): 326 (M$^+$, 2), 293 (2), 269 (64), 251 (25), 193 (36), 149 (53), 135 (100), 107 (11). HRMS: calcd for $C_{18}H_{34}O_3Si$ 326.22772, found 326.22752. Minor Side Product. ^{1}H NMR: 4.04−3.99 (m, 1H)

Methyl [(1*S*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilyloxy)-7a-methyloctahydro-1*H*-inden-1-yl]acetate (16). Diazomethane in Et_2O was added dropwise to a stirred solution of **15** (432 mg, 1.32 mmol) in Et_2O (15 mL) until a yellow color persisted. The reagent excess and the solvent were evaporated, and the residue was chromatographed on silica gel (4 g, hexane−EtOAc, 97:3) to give **16** contaminated with a side product, less than 10% (by ^{1}H NMR) (399 mg, 89%). ^{1}H NMR: −0.01 (s, 3H), 0.00 (s, 3H), 0.87 (s, 9H), 2.1−10.9 (m, 13H) overlapping 1.02 (s, 3H), 2.50−2.24 (m, 1H), 3.65 (s, 3H), 4.08 (br.d, 1H, J = 2.2 Hz). ^{13}C NMR: −5.1, −4.8, 17.5, 18.0, 23.1, 24.2, 25.8, 27.4, 34.5, 34.6, 37.8, 42.4, 45.2, 47.4, 51.4, 69.1, 174.2. MS EI (m/z): 340 (M$^+$, 1), 325 (1), 309 (3), 297 (5), 283 (56), 209 (38), 207 (22), 177 (28), 149 (53), 135 (100), 133 (67), 107 (14). HRMS: calcd for $C_{19}H_{36}O_3Si$ 340.24337, found 340.24347. Minor Side Product. ^{1}H NMR: 4.04−3.98 (m, 1H).

Methyl (2*S*)-2-[(1*S*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilyloxy)-7a-methyloctahydro-1*H*-inden-1-yl]propanoate (17). Ester **16** (386 mg, 1.14 mmol) in THF (5 mL) was added dropwise to a stirred at −78 °C solution of LDA in THF prepared from (*i*-Pr)$_2$NH (0.19 mL, 1.37 mmol), BuLi (2.17 M in hexanes, 0.63 mL, 1.37 mmol), and THF (5 mL). The mixture was stirred at −78 °C for 0.5 h, and then MeI (0.085 mL, 1.37 mmol) and HMPA (0.24 mL, 1.38 mmol) were consecutively added. Stirring was continued for 16 h (at −78 °C), and the solution was diluted with hexanes (20 mL) and poured into water. The mixture was extracted with hexanes (40 mL). The organic extract was washed consecutively with water and brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel (4 g, hexanes−EtOAc, 97:3) to give **17** contaminated with a side product, less than 10% (by ^{1}H NMR) (380 mg, 95%). ^{1}H NMR: −0.02 (s, 3H), −0.01 (s, 3H), 0.86 (s, 9H), 2.0−0.9 (m, 12H) overlapping 1.01 (s, 3H), 1.07 (d, 3H, J = 6.8 Hz), 2.19 (dq, 1H, J = 10.4, 6.8 Hz). 3.63 (s, 3H), 4.06 (br.d, 1H, J = 2.6 Hz). ^{13}C NMR: −5.1, −4.8, 17.1, 17.7, 18.1, 23.9, 24.7, 24.8, 25.8, 34.3, 34.6, 41.7, 42.9, 48.6, 51.2, 51.3, 69.2, 178.0. MS EI (m/z): 354 (M$^+$, 1), 339 (1), 323 (2), 311 (4), 297 (64), 223 (76), 221 (27), 191 (21), 163 (100), 135 (79), 133 (34), 107 (24). HRMS: calcd for $C_{20}H_{38}O_3Si$ 354.25902, found 354.25811.

Minor Side Product. ^{1}H NMR: 3.66 (s, 3H), 4.05−3.96 (m, 1H).

(1*S*,3a*R*,4*S*,7a*R*)-1-[(1*S*)-2-Hydroxy-1-methylethyl]-4-(*tert*-butyldimethylsilyloxy)-7a-methyloctahydro-1*H*-indene (18). $LiAlH_4$ (76 mg, 2 mmol) was added to a stirred solution of crude **17** (380 mg, 1.07 mmol) in THF (15 mL). After 15 min, the reagent excess was destroyed with satd aq Na_2SO_4, and the mixture was diluted with Et_2O (30 mL). The solid was filtered off and washed with Et_2O. The filtrate was evaporated to dryness, and the residue was chromatographed on silica gel (40 g, hexane−EtOAc, 96:4, (ca. 1200 mL) to give **18** (319 mg, 91%). ^{1}H NMR: −0.01 (s, 3H), 0.00 (s, 3H), 0.84 (d, 3H, J = 6.6 Hz), 0.87 (s, 9H), 1.00 (s, 3H), 2.0−1.1 (m, 13H), 3.25 (dd, 1H, J = 10.2, 7.2 Hz), 3.43 (dd, 1H, J = 10.2, 6.2 Hz), 4.06 (br.d, 1H, J = 2.2 Hz). ^{13}C NMR: −5.1, −4.7, 13.8, 17.7, 18.0, 21.2, 24.9, 24.9, 25.8, 34.9, 34.7, 36.1, 43.1, 49.1, 49.2, 68.4, 69.1. MS EI (m/z): 326 (M$^+$, 1), 311 (1), 283 (3), 269 (45), 193 (35), 177 (15), 175 (11), 135 (44), 121 (23), 109 (18), 107 (22), 95 (46), 93 (22), 83 (31), 81 (28), 75 (100). HRMS: calcd for $C_{19}H_{38}O_2Si$ 326.26411, found 326.26282.

[*O*-[2ξ-Tetrahydro-2*H*-pyranyl)oxy]-1-[(1*R*)-5-hydroxy-1,5-dimethylhex-3-ynyl]]-(1*S*,3a*R*,4*S*,7a*R*)-4-(*tert*-butyldimethylsilyloxy)-7a-methyloctahydro-1*H*-indene (20). TsCl (373 mg, 1.96 mmol) was added to a solution of **18** (319 mg, 0.98 mmol) in pyridine (8 mL) stirred at rt. After 16 h, the mixture was cooled to 0 °C, and water (0.5 mL) was added. The mixture was allowed to warm to rt (in ca. 20 min) and then diluted with Et_2O (20 mL) and poured into water. The product was extracted with hexanes (80 mL). The extract was washed with water and brine and dried (Na_2SO_4). The solvent was evaporated to give the crude tosylate (471 mg) that was used further without purification. This product was dissolved in dry dioxane (8 mL),

and the solution was combined with a solution of a lithium acetylenide prepared as follows: butyllithium (2.17 M in hexanes, 4.1 mL, 8.9 mmol) was added to a mixture of 2-[(1,1-dimethylprop-2-ynyl)oxy]tetrahydro-2*H*-pyran (**19**) (1.65 g) and dioxane (8 mL) stirred at 5 °C, and the mixture was allowed to warm to rt in ca. 20 min. The combined solution was heated under reflux for 4 days, cooled, and diluted with hexanes (100 mL). The solution was washed consecutively with water (100 mL) and brine, dried (Na_2SO_4), and clarified by filtration through a pad of silica gel (1 g). The silica gel was washed with hexanes−EtOAc (90:10, 30 mL). The filtrates were combined, and the solvent was evaporated. The residue was dried at 40 °C under vacuum (2 mmHg) for a few hours to give **20** (1.00 g). An analytical sample was purified by a repeated chromatography on silica gel (100 g per 1 g) eluting with hexanes−EtOAc (100:0.5). ^{1}H NMR: −0.01 (s, 3H), 0.00 (s, 3H), 0.87 (s, 9H) overlapping 0.89 (d, 3H, J = 7.4 Hz), 1.00 (s, 3H), 1.9−1.2 (m, 19H) overlapping 1.46 (s, 3H), 1.49 (s, 3H), 2.04 (t, 2H, J = 6.6 Hz), 3.40−3.54 (m, 1H), 4.02−3.88 (m, 1H), 4.06 (br.d, 1H, J = 2.0 Hz), 5.05 (dd, 1H, J = 6.0, 3.2 Hz). ^{13}C NMR: −5.1, −4.76, 16.80, 17.7, 18.0, 20.8, 21.6, 24.9 br, 25.5, 25.8, 27.0, 30.2, 31.1, 32.1, 33.5, 34.7, 34.8, 43.1, 48.9, 52.7, 63.4, 69.2, 71.4, 83.4, 84.0, 96.2. MS EI (m/z): 476 (M^+, 1), 475 (4), 317 (3), 265 (1), 251 (2), 243 (30), 187 (14), 161 (34), 159 (100), 147 (14), 135 (19), 133 (15), 121 (11), 119 (11), 109 (23), 107 (16), 105 (12). HRMS: calcd for $C_{29}H_{52}O_3Si$ 476.36857, found 476.36729.

***O*-[[2ξ-(Tetrahydro-2*H*-pyranyl)oxy]-1-[(1*R*)-5-hydroxy-1,5-dimethylhexyl]]-(1*S*,3a*R*,4*S*,7a*R*)-4-(*tert*-butyldimethylsilyloxy)-7a-methyloctahydro-1*H*-indene (21).** A mixture of crude **20** (1.0 g), EtOAc (10 mL), 10% palladium-on-carbon (45 mg), and $NaHCO_3$ (0. 1 g) was stirred under hydrogen atmosphere for 5 days at reflux temperature. The mixture was cooled and filtered through a pad of Celite, and the solid was washed with EtOAc. The filtrates were combined, and the solvent was evaporated to give **21** (1.031 g). Hydrogenation of the previously prepared analytical sample of **20** under an analogous conditions provided an analytical sample of **21**. ^{1}H NMR: −0.01 (s, 3H), 0.00 (s, 3H), 2.0−0.7 (m, 23H) overlapping 0.78 (d, 3H, J = 6.6 Hz), 0.87 (s, 9H), 0.98 (s, 3H), 1.18 (s, 3H), 1.19 (s, 3H), 3.50−3.36 (m, 1H), 4.02−3.88 (m, 1H), 4.05 (s, 1H), 4.74−4.66 (m, 1H). ^{13}C NMR: −5.1, −4.7, 16.8, 17.8, 18.1, 21.0, 21.4, 22.0, 25.0, 25.2, 25.5, 25.9, 26.3, 26.9, 32.6, 33.0, 33.1, 34.6, 34.6, 38.4, 42.2, 43.1, 49.0, 53.4, 53.5, 63.5, 69.3, 76.3, 93.9. MS LSIMS (m/z): 983 [(2M + Na)$^+$, 8), 503 [(M + Na)$^+$, 100]. HRMS: calcd for $C_{29}H_{56}O_3SiNa$ 503.3891, found 503.38751.

(1*S*,3a*R*,4*S*,7a*R*)-1-[(1*R*)-5-Hydroxy-1,5-dimethylhexyl]-7a-methyloctahydro-1*H*-inden-4-ol (22). HF (40%, 4 mL) was added to a solution of crude **21** (351 mg) in MeCN (20 mL) in a plastic container, and the mixture was stirred vigorously for 8 h at rt. The mixture was then partitioned between EtOAc (100 mL) and water (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ and then with brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel (20 g, hexanes−EtOAc, 85:15) to give **22** (68 mg, 72% yield from **18**). HPLC analysis (Nucleosil 50/5 column, hexane−EtOAc, 3:1, RI detector) indicated that this product was 97.5% pure (t_R = 13.60 min) with two contaminants: t_R = 15.32 min, 2.0% and t_R = 16.04 min, 0.5%. **21**. ^{1}H NMR: 0.79 (d, 3H, J = 6.4 Hz) partly overlapping 1.9−0.8 (m, 19H), 1.00 (s, 3H), 1.20 (s, 6H), 4.13 (br s, 1H). ^{13}C NMR: 16.7, 17.5, 21.2, 22.2, 24.3, 24.7, 29.2, 33.0, 32.6, 34.2, 38.2, 42.7, 44.2, 48.5, 53.3, 69.1, 71.0. MS LSIMS (m/z): 305 [(M + Na)$^+$, 85], 303 (100), 247 (65), 209 (70). HRMS: calcd for $C_{18}H_{34}O_2Na$ 305.2451, found 305.24584.

(1*S*,3a*R*,7a*R*)-1-[(1*R*)-5-Hydroxy-1,5-dimethylhexyl]-7a-methyloctahydro-1*H*-inden-4-one (4). PDC (30 mg, 0.08 mmol) was added to a solution of **22** (8.1 mg, 0.029 mmol) in CH_2Cl_2 (3 mL) and the mixture stirred at rt. After 2.5 h, the mixture was diluted with Et_2O (10 mL) and filtered through a pad of Celite. The filtrate was evaporated to dryness, and the residue was chromatographed on silica gel (1 g, hexanes−EtOAc, 80:20) to give **4** (7.8 mg, 96%) identical with a sample reported earlier.[2]

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: jwicha@icho.edu.pl.

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■ REFERENCES

(1) (a) Antony, P.; Sigueiro, R.; Huet, T.; Sato, Y.; Ramalanjaona, N.; Rodrigues, L. C.; Mourino, A.; Moras, D.; Rochel, N. *J. Med. Chem.* **2010**, *53*, 1159–1171. (b) Laverny, G.; Penna, G.; Uskokovic, M.; Marczak, S.; Maehr, H.; Jankowski, P.; Ceailles, C.; Vouros, P.; Smith, B.; Robinson, M.; Reddy, G. S.; Adorini, L. *J. Med. Chem.* **2009**, *52*, 2204–2213. (c) Glebocka, A.; Sokolowska, K.; Sicinski, R. R.; Plum, L. A.; DeLuca, H. F. *J. Med. Chem.* **2009**, *52*, 3496–3504. (d) Vrielynck, F.; Van Haver, D.; Vandewalle, M.; Verlinden, L.; Verstuyf, A.; Bouillon, R.; Croce, G.; De Clercq, P. *Eur. J. Org. Chem.* **2009**, *2009*, 1720–1737.

(2) Kurek-Tyrlik, A.; Michalak, K.; Wicha, J. *J. Org. Chem.* **2005**, *70*, 8513–8521.

(3) Kurek-Tyrlik, A.; Michalak, K.; Urbanczyk-Lipkowska, Z.; Wicha, J. *Tetrahedron Lett.* **2004**, *45*, 7479–7482.

(4) (a) Hajos, Z. G.; Parrish, D. R. German Patent Application, Jan 21, 1970; *Chem. Abstr.* **1971**; *75*, 129414r. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621. (c) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496–497.

(5) For recent synthetic applications of the Hajos−Parrish dione, see: (a) Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394–5397. (b) Cao, L.; Sun, J.; Wang, X.; Zhu, R.; Shi, H.; Hu, Y. *Tetrahedron* **2007**, *63*, 5036–5041. (c) Katona, B. W.; Rath, N. P.; Anant, S.; Stenson, W. F.; Covey, D. F. *J. Org. Chem.* **2007**, *72*, 9298–9307. (d) Reddy, T. J.; Bordeau, G.; Trimble, L. *Org. Lett.* **2006**, *8*, 5585–5588. (e) Arai, N.; Ui, H.; Omura, S.; Kuwajima, I. *Synlett* **2005**, 1691–1694. (f) Lajunen, M.; Koskinen, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, *9*, 1439–1443. (g) Yunus, U.; Iqbal, R.; Winterfeldt, E. *J. Heterocycl. Chem.* **2005**, *42*, 1079–1084. (h) Chapelon, A. S.; Moraleda, D.; Rodriguez, R.; Ollivier, C.; Santelli, M. *Tetrahedron* **2007**, *63*, 11511–11616.

(6) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675–681.

(7) Chochrek, P.; Wicha, J. *J. Org. Chem.* **2007**, *72*, 5276–5284.

(8) (a) Chochrek, P.; Wicha, J. *Org. Lett.* **2006**, *8*, 2551–2553. (b) Chochrek, P.; Kurek-Tyrlik, A.; Michalak, K.; Wicha, J. *Tetrahedron Lett.* **2006**, *47*, 6017–6020.

(9) (a) Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2005**, *7*, 427–430. (b) Chochrek, P.; Frelek, J.; Kwit, M.; Wicha, J. *J. Org. Chem.* **2009**, *74*, 7300–7308.

(10) Barton, D. H. R.; O'Brien, R. E.; Sternhell, S. *J. Chem. Soc.* **1962**, 470.

(11) (a) Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283–284. (b) Stang, P. J.; Hanack, M. C.; Subramanian, L. R. *Synthesis* **1982**, 85–126. (c) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 4821–4824.

(12) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919–939. Maas, G. *Chem. Soc. Rev.* **2004**, *33*, 183–190.
(13) (a) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssie, P. *J. Org. Chem.* **1980**, *45*, 695–702. (b) Majchrzak, M. W.; Kotełko, A.; Lombert, J. B. *Synthesis* **1983**, 469–470.
(14) House, H. O.; Fischer, W. F.; Gall, M.; McLaughlin, T. E.; Peet, N. P. *J. Org. Chem.* **1971**, *36*, 3429–3437.
(15) (a) Volkenburgh, R. v.; Greenlee, K. W.; Derfer, J. M.; Boord, C. E. *J. Am. Chem. Soc.* **1949**, *71*, 3595–3597. (b) House, H. O.; Blankley, C. J. *J. Org. Chem.* **1968**, *33*, 47–53.
(16) Wicha, J.; Bal, K. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1282–1288.
(17) Partridge, J. J.; Faber, S.; Uskoković, M. *Helv. Chim. Acta* **1974**, *57*, 764–770.
(18) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, *20*, 3981–3982.
(19) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2650.
(20) Luche, J.-L.; Rodriguez-Hahn, L.; Crabbe, P. *Chem. Commun.* **1978**, 601–602.
(21) Dauben, W. D.; Dietsche, T. J. *J. Org. Chem.* **1972**, *37*, 1212–1216.