JOC The Journal of Organic Chemistry
Note
pubs.acs.org/joc

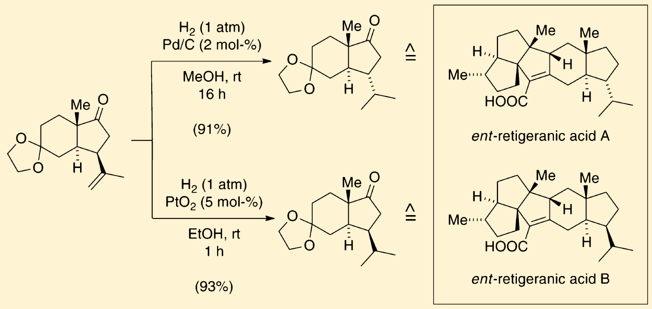
A Unified Approach to *trans*-Hydrindane Sesterterpenoids

Daniel T. Hog, Peter Mayer, and Dirk Trauner*

Fakultät für Chemie und Pharmazie, Ludwig-Maximilians-Universität München, and Munich Center of Integrated Protein Science, Butenandtstr. 5-13, 81377 München, Germany

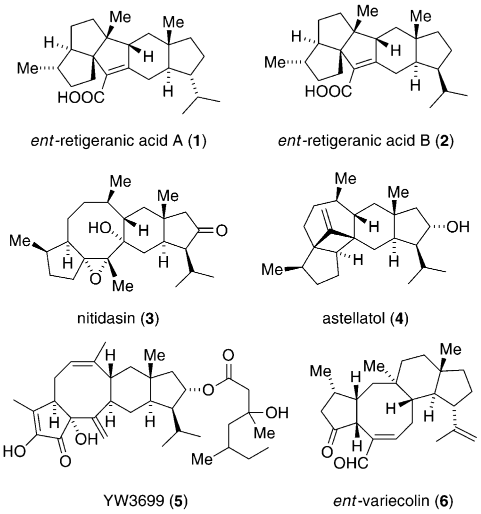
Ⓢ *Supporting Information*

ABSTRACT: A synthetic approach to several sesterterpenoids containing an isopropyl *trans*-hydrindane system is presented. Its most remarkable feature is the stereochemical diversification of a common precursor through the choice of different hydrogenation conditions.



Sesterterpenoids account for many beautiful natural products that continue to inspire synthetic chemists.[1] Being of considerable size, these molecules often show intricate ring systems and difficult to access oxygenation patterns, which renders them quite challenging targets. As a consequence, only a limited number of sesterterpenoids have been prepared by total synthesis,[2] and many attractive structures remain to be investigated in this respect.

Within the sesterterpenoid class, a small number of compounds contain a *trans*-hydrindane ring system bearing an angular methyl and an isopropyl group (Figure 1). The latter substituent either resides in a *trans*-relationship to the methyl group, as in retigeranic acid A (**1**),[3−5] or a *cis*-relationship, which is present in retigeranic acid B (**2**).[6] This configuration has also been found in several natural products that possess a further oxidized five-membered ring, such as nitidasin (**3**),[7] astellatol (**4**),[8,9] or YW3699 (**5**).[10] Another structurally related *trans*-hydrindane sesterterpenoid, variecolin (**6**),[11] exhibits an isopropenyl group and a different ring fusion pattern on the hydrindane portion. To facilitate comparison, retigeranic acids A (**1**) and B (**2**) as well as variecolin (**6**) are depicted in Figure 1 as their unnatural enantiomers. The absolute configurations of nitidasin (**3**), astellatol (**4**), and YW3699 (**5**) have not been established to date to the best of our knowledge.



ent-retigeranic acid A (**1**)　*ent*-retigeranic acid B (**2**)

nitidasin (**3**)　astellatol (**4**)

YW3699 (**5**)　*ent*-variecolin (**6**)

Figure 1. Molecular structures of selected sesterterpenoids bearing a *trans*-hydrindane moiety. The retigeranic acids A (**1**) and B (**2**) and variecolin (**6**) are depicted as their unnatural enantiomers.

Whereas retigeranic acid A (**1**) has been a popular synthetic target, as evidenced through successful total syntheses by Corey,[12] Paquette,[13,14] Hudlicky,[15,16] and Wender,[17] few approaches toward the other molecules shown in Figure 1 have been published to date. Tori et al. recently disclosed the preparation of the [5−8−6]-tricarbocyclic framework of YW3699 (**5**), a potent inhibitor of GPI anchor biosynthesis.[18] Furthermore, Piers[19,20] and Molander[21] have published studies toward the total synthesis of variecolin (**6**).

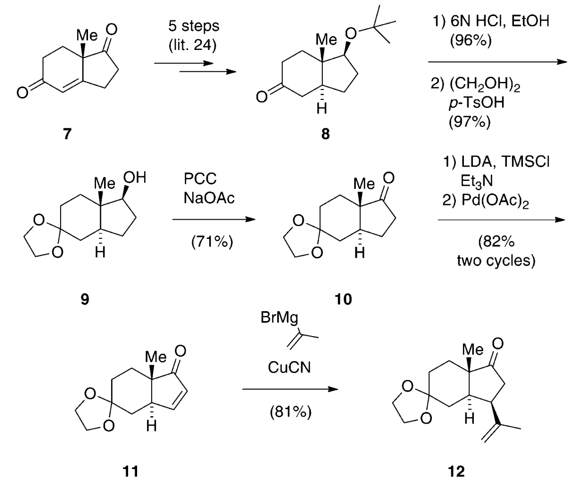
We now report an approach to the isopropyl hydrindane sesterterpenoids that involves a common bicyclic intermediate. Our synthetic manifold, which can be carried out in either enantiomeric series,[22] provides access to three *trans*-hydrindane building blocks, two of which could be incorporated into *ent*-retigeranic acids A (**1**) and B (**2**). The remaining one shows the correct oxygenation pattern to serve as a synthetic precursor to nitidasin (**3**), astellatol (**4**), and YW3699 (**5**).

Our pathway started from the readily available enantiopure diketone **7**,[23] which was converted into *trans*-hydrindane **8**[24] containing ca. 6% of the *cis*-isomer (Scheme 1). HCl-mediated cleavage of the *tert*-butyl ether, followed by protection of the carbonyl functionality as an acetal, provided secondary alcohol **9**, which in turn was oxidized with pyridinium chlorochromate

Received: April 25, 2012
Published: May 31, 2012

dx.doi.org/10.1021/jo300726z | *J. Org. Chem.* 2012, 77, 5838−5843

Scheme 1. Stereoselective Synthesis of Ketone 12

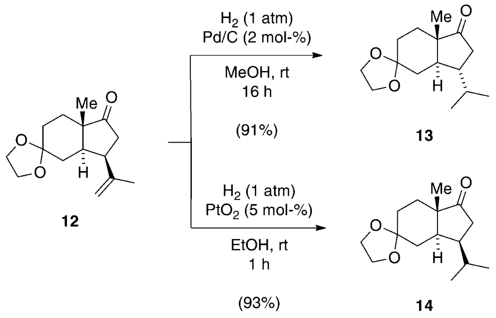


(PCC) to yield ketone **10**.[25,26] At this point, purification by recrystallization was possible, removing any traces of the *cis*-hydrindane. Ketone **10** was then oxidized under Saegusa−Ito conditions[21] to yield enone **11**, the structure of which was confirmed by X-ray crystallography (see the Supporting Information).[27]

Exposure of enone **11** to the higher order cyanocuprate prepared from isopropenylmagnesium bromide and CuCN resulted in the formation of isopropenyl hydrindanone **12** in 81% yield and as a single diastereomer. Two-dimensional NMR experiments indicated that this addition occurred from the *re*-side, i.e., syn to the angular methyl group. This unexpected stereochemical outcome was subsequently verified by X-ray crystallography (see the Supporting Information). It should be noted that Molander et al.[21] as well as Bull and Loedolff[28] observed similar stereoselectivities in synthetic studies directed toward variecolin (**6**) and a derivative of estrone, respectively.

Notably, the conjugate addition of an isopropyl cuprate gave only unsatisfactory results in our hands. Thus, we turned our attention to the seemingly straightforward hydrogenation of isopropenyl hydrindanone **12**. Exposure of alkene **12** to hydrogen in the presence of Pd/C gave rise to hydrindanone **13** (Scheme 2), which yielded suitable crystals for X-ray analysis (Figure 2). To our considerable surprise, ketone **13** possessed the (*R*)-configuration at the former allylic ring position. Presumably, this unexpected epimerization arises from the tendency of Pd/C to isomerize double bonds into more highly substituted positions prior to hydrogenation. This phenomenon has been observed before but has been rarely associated with the almost complete inversion of a stereocenter.[29−31] The reason for the stereoselectivity of the hydrogenation, which could occur at the stage of a tetrasubstituted double bond or an enone, is currently under investigation using theoretical calculations, as is the stereoselectivity of the initial conjugate addition. In both cases, the stereochemical outcome is not obvious from inspecting molecular models alone.

Scheme 2. Diastereoselective Synthesis of Epimeric Ketones 13 and 14 Utilizing Hydrogenation Catalysts as a Chemical Switch



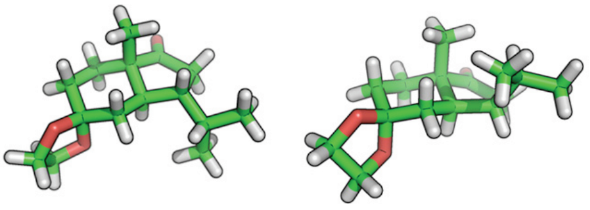
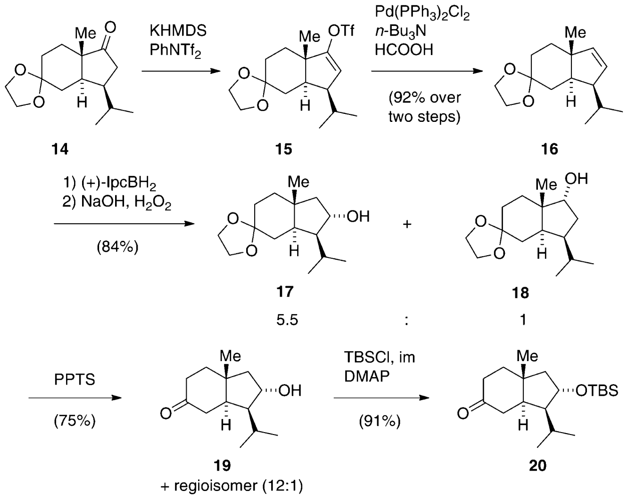


Figure 2. Crystal structures of hydrogenation products **13** and **14**.

Realizing that double-bond migration might be avoided with a different catalyst, we carried out the hydrogenation in the presence of PtO_2 (Scheme 2). Gratifyingly, a single diastereomer, hydrindanone **14**, was isolated under these conditions, possessing distinctly different spectroscopic data from the isomer obtained previously. This desired stereochemical outcome was again confirmed by X-ray crystallography, which unambiguously showed the isopropyl substituent residing in a *cis*-relationship to the angular methyl group (Figure 2).

With appreciable quantities of ketones **13** and **14** in hand, we then proceeded to correct the oxidation pattern on the five-membered ring. Trapping the potassium enolate of ketone **14** with $PhNTf_2$ yielded enol triflate **15**, which underwent facile Pd-catalyzed reduction to give alkene **16** (Scheme 3). The regio- and stereoselective hydroboration of cyclopentene **16**, however, proved to be more challenging than anticipated, especially in terms of its regioselectivity. After an extensive screen of conditions, we found that a matched chiral hydroboration reagent gave the most satisfying results. Treatment of alkene **16** with (+)-$IpcBH_2$,[32] followed by oxidative workup, gave the two isomeric alcohols **17** and **18** in a 5.5:1 ratio. A subsequent two-step protocol consisting of

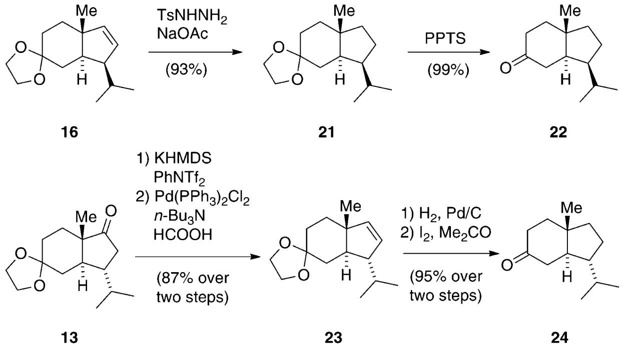
Scheme 3. Synthesis of Building Block 20 Suitable for Nitidasin (3), Astellatol (4), and YW3699 (5)



liberating the carbonyl functionality (→**19**) and protection of the alcohol as a TBS ether provided ketone **20** in pure form. The structure of this valuable building block for the synthesis of nitidasin (**3**), astellatol (**4**), and YW3699 (**5**) was also confirmed by X-ray crystallography (see the Supporting Information).

Next, we prepared building blocks suitable for *ent*-retigeranic acids A (**1**) and B (**2**) (Scheme 4). Interestingly, and in contrast with our earlier experiences, hydrogenation of cyclopentene **16** in the presence of PtO_2 resulted in partial epimerization. However, the use of diimide, generated in situ,[33] resulted in clean conversion to afford dioxolane **21** that was subsequently deprotected to yield ketone **22**.

Scheme 4. Syntheses of Building Blocks 22 and 24 Suitable for *ent*-Retigeranic Acids A (1) and B (2)



Its diastereomeric counterpart, ketone **24**, was accessible through an analogous reaction sequence. Transformation of ketone **13** into alkene **23** was conducted utilizing the same two-step protocol described above. Hydrogenation with Pd/C proceeded without incident with this substrate, and subsequent acetal cleavage gave hydrindanone **24**, an intermediate previously employed in both Corey's and Hudlicky's syntheses of retigeranic acid A (**1**).[34] The X-ray structure of compound **24** is presented in the Supporting Information.

In summary, we have synthesized three *trans*-hydrindane building blocks that might serve as valuable intermediates in the syntheses of several complex sesterterpenoids. Our study was marked by a high degree of stereochemical serendipity and emphasizes the importance of meticulous product analysis, even with seemingly straightforward reactions. Our work demonstates that the tenedency of double bonds to migrate during hydrogenation reactions, which is often unnoticed or seen as a nuisace, can be exploited in useful ways.

■ EXPERIMENTAL SECTION

(1′*S*,3a′*S*,7a′*S*)-7a′-Methyloctahydrospiro([1,3]dioxolane-2,5′-inden)-1′-ol (9). A mixture of *trans*-hydrindane **8** (30.4 g, 136 mmol) in EtOH/6 N HCl (7:1, 354 mL) was heated to reflux for 4 h. The pH was adjusted to 7 by addition of Na_2CO_3 at 0 °C, and the solvent was evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 (800 mL) and H_2O (200 mL). The organic layer was washed with saturated aqueous NaCl (200 mL) and dried (Na_2SO_4). Having evaporated the solvent under reduced pressure, purification by flash column chromatography (FCC) (silica, hexanes/EtOAc = 1:1) yielded alcohol **S1** (22.6 g, containing ca. 5% EtOAc, 96%) as colorless oil: R_f 0.16 (hexanes/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.74 (dd, J = 9.1, 8.2 Hz, 1H), 2.74−2.19 (m, 4H), 2.19−2.09 (m, 1H), 2.00 (m$_C$, 1H), 1.86 (brs, 1H), 1.76 (m$_C$, 1H), 1.69−1.34 (m, 4H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.7, 80.4, 44.8, 43.0, 42.5, 37.3, 34.8, 31.2, 25.4, 9.9; IR (ν/cm^{-1}) 3420, 2951, 2872, 1702, 1417, 1200, 1124, 1044; $[\alpha]_D^{20}$ +75.6 (c 1.00, CH_2Cl_2); HRMS-EI calcd for $C_{10}H_{16}O_2$ [M$^+$] 168.1145, found 168.1147.

A mixture of alcohol **S1** (22.6 g, 131 mmol), ethylene glycol (63.0 mL, 1.13 mol), and *p*-TsOH (2.50 g, 14.5 mmol) in benzene (500 mL) was heated to reflux for 2 h using a Dean−Stark trap. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (400 mL) at rt, and the aqueous layer was extracted with EtOAc (3 × 400 mL). The combined organic layers were washed with saturated aqueous NaCl (300 mL) and dried (Na_2SO_4), and the solvents were removed under reduced pressure. Purification by FCC (silica, hexanes/EtOAc = 3:2) yielded alcohol **9** (27.2 g, 97%) as pale yellow oil: R_f 0.45 (hexanes/EtOAc = 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.00−3.84 (m, 4H), 3.71 (dd, J = 8.8, 7.9 Hz, 1H), 2.18−2.06 (m, 1H), 1.79−1.42 (m, 9H), 1.39−1.22 (m, 2H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 110.1, 81.1, 64.4, 64.3, 42.6, 42.5, 35.8, 33.8, 31.2, 31.0, 25.0, 9.7; IR (ν/cm^{-1}) 3420, 2949, 2874, 1349, 1192, 1117, 1074, 1043, 944; $[\alpha]_D^{20}$ +18.8 (c 1.00, CH_2Cl_2); HRMS-EI calcd for $C_{12}H_{20}O_3$ [M$^+$] 212.1407, found 212.1405.

(3a′*S*,7a′*S*)-7a′-Methylhexahydrospiro([1,3]dioxolane-2,5′-inden)-1′(6′*H*)-one (10). To a suspension of PCC (68.0 g, 320 mmol) and NaOAc (52.0 g, 640 mmol) in CH_2Cl_2 (700 mL) at 0 °C was added dropwise a solution of alcohol **9** (27.2 g, 128 mmol) in CH_2Cl_2 (150 mL), and the mixture was stirred for 4 h at rt. After being filtered over a plug of silica, the solvents were removed under reduced pressure. Purification by FCC (silica, hexanes/EtOAc = 5:1) and subsequent recrystallization from hexanes yielded *trans*-hydrindane **10** (19.0 g, 71%) as a colorless crystalline solid: R_f 0.61 (hexanes/EtOAc = 1:1); mp 76.0−77.0 °C (hexanes); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.94 (m$_C$, 4H), 2.45 (ddd, J = 19.3, 8.8, 1.3 Hz, 1H), 2.14 (ddd, J = 19.2, 9.2, 9.2 Hz, 1H), 2.01 (dddd, J = 18.9, 13.0, 5.8, 3.8 Hz, 1H), 1.86 (dddd, J = 12.4, 8.9, 5.8, 1.1 Hz, 1H), 1.79−1.69 (m, 5H), 1.62 (m$_C$, 1H), 1.49 (m$_C$, 1H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 219.7, 109.6, 64.6, 64.4, 47.1, 42.8, 36.2, 35.6, 30.9, 28.7, 23.7, 12.3; IR (ν/cm^{-1}) 2924, 1730, 1118, 1066, 1036, 938; $[\alpha]_D^{20}$ +83.6 (c 1.00, CH_2Cl_2); HRMS-EI calcd for $C_{12}H_{18}O_3$ [M$^+$] 210.1250, found 210.1249.

(3a′*R*,7a′*S*)-7a′-Methyl-3a′,4′,7′,7a′-tetrahydrospiro([1,3]-dioxolane-2,5′-inden)-1′(6′*H*)-one (11). To a solution of freshly prepared LDA (86 mmol) in THF/hexanes (3.5:1, 154 mL) at −78 °C was slowly added a solution of ketone **10** (6.00 g, 28.6 mmol) in THF (30 mL). After the mixture was stirred for 45 min at −78 °C, Et_3N (18.0 mL, 129 mmol) was added followed by TMSCl (14.6 mL, 114 mmol). The solution was stirred for 30 min at −78 °C, and the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (50 mL) at 0 °C. The mixture was diluted with pentane (100 mL), and the aqueous layer was extracted with pentane (3 × 50 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure yielded crude silylenol ether **S2**.

To a solution of silylenol ether **S2** in CH_2Cl_2/MeCN (3:1, 132 mL) was added $Pd(OAc)_2$ (7.67 g, 31.5 mmol), and the solution was stirred at 37 °C for 4 h. The mixture was filtered over a plug of silica, and the solvents were evaporated under reduced pressure. Purification by FCC (silica, hexanes/EtOAc = 7:1 to 2:1) yielded enone **11** (4.10 g, 69%) as colorless crystalline solid along with starting material **10** (1.30 g, 22%).

A second cycle and additional reaction batches resulted in an overall transformation from ketone **10** (18.8 g, 89.5 mmol) to enone **11** (15.2 g) in 82% yield: R_f 0.50 (hexanes/EtOAc = 1:1); mp 127.5−129.5 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.38 (dd, J = 5.9, 1.8 Hz, 1H), 6.03 (dd, J = 5.9, 3.2 Hz, 1H), 4.00−3.92 (m, 4H), 3.04 (m$_C$, 1H), 1.96−1.86 (m, 3H), 1.82−1.74 (m, 2H), 1.69 (ddd, J = 13.2, 4.8, 4.8 Hz, 1H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 211.7, 160.6, 132.0, 109.7, 64.8, 64.3, 50.7, 48.1, 33.6, 31.7, 26.8, 19.4; IR (ν/cm^{-1}) 2963, 2934, 1699, 1180, 1134, 1092; $[\alpha]_D^{20}$ −67.2 (c 1.00, CH_2Cl_2); HRMS-EI calcd for $C_{12}H_{16}O_3$ [M$^+$] 208.1094, found 208.1097.

(3′*R*,3a′*R*,7a′*S*)-7a′-Methyl-3′-(prop-1-en-2-yl)-hexahydrospiro([1,3]dioxolane-2,5′-inden)-1′(6′*H*)-one (12).

To a suspension of CuCN (1.45 g, 16.2 mmol) in Et_2O (48 mL) at 0 °C was slowly added isopropenylmagnesium bromide (65 mL, 0.5 M in THF, 32.4 mmol). The resulting mixture was stirred for 30 min and subsequently cooled to −78 °C. A solution of enone **11** (1.50 g, 7.20 mmol) in THF (15 mL) was added slowly. After being stirred for 2 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (40 mL). The mixture was allowed to warm to rt and diluted with Et_2O (100 mL). After filtering over a pad of Celite, the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL) and dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. Purification by FCC (silica, hexanes/EtOAc = 7:1 to 5:1) yielded alkene **12** as colorless solid.

Combined FCC of several reactions batches resulted in an overall transformation from enone **11** (11.9 g, 57.2 mmol) to ketone **12** (11.5 g) in 81% yield: R_f 0.43 (hexanes/EtOAc = 3:1); mp 69.0−70.5 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.97 (s, 1H), 4.83 (s, 1H), 4.03−3.89 (m, 4H), 2.86 (m_C, 1H), 2.77 (dd, J = 19.7, 1.8 Hz, 1H), 2.49 (dd, J = 19.5, 9.2 Hz, 1H), 2.41−2.34 (m, 1H), 1.99−1.91 (m, 2H), 1.81 (s, 3H), 1.75 (ddd, J = 13.8, 13.8, 4.8 Hz, 1H), 1.68 (m_C, 1H), 1.63 (ddd, J = 13.1, 4.6, 2.6 Hz, 1H), 1.43 (ddd, J = 13.5, 13.5, 3.9 Hz, 1H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 220.6, 146.1, 112.3, 109.8, 64.7, 64.4, 47.1, 45.8, 42.2, 41.9, 35.7, 30.9 (2×), 24.9, 15.3; IR (ν/cm^{-1}) 2954, 2879, 1737, 1350, 1095, 1053; $[\alpha]_D^{20}$ +30.6 (c 1.00, CH_2Cl_2); HRMS-EI calcd for $C_{15}H_{22}O_3$ [M^+] 250.1563, found 250.1565.

(3′*R*,3a′*R*,7a′*S*)-3′-Isopropyl-7a′-methylhexahydrospiro([1,3]dioxolane-2,5′-inden)-1′(6′*H*)-one (13). To a solution of alkene **12** (250 mg, 1.00 mmol) in MeOH (10 mL) was added Pd/C (10% Pd, 20 mg, 19 μmol) and the solution was stirred under an atmosphere of H_2 (balloon, 1 atm) for 16 h. The reaction mixture was filtered over a pad of Celite, and the solvents were evaporated under reduced pressure. Purification by FCC (silica, hexanes/EtOAc = 4:1) and subsequent recrystallization from *n*-pentane provided pure ketone **13** (230 mg, 91%) as colorless solid: R_f 0.46 (hexanes/EtOAc = 3:1); mp 88.0−90.0 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.94 (m_C, 4H), 2.40 (m_C, 1H), 1.98−1.88 (m, 2H), 1.87−1.77 (m, 3H), 1.76−1.67 (m, 3H), 1.62 (m_C, 1H), 1.55−1.47 (m, 1H), 0.97 (s, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 219.0, 109.6, 64.6, 64.4, 48.8, 45.4, 41.9, 38.1, 33.9, 30.8, 29.0, 28.0, 22.0, 17.4, 13.5; IR (ν/cm^{-1}) 2960, 2875, 1737, 1141, 1122, 1046, 938; $[\alpha]_D^{20}$ +65.0 (c 1.00, CH_2Cl_2); HRMS-FAB calcd for $C_{15}H_{25}O_3$ [$(M + H)^+$] 253.1798, found 253.1793.

(3′*S*,3a′*R*,7a′*S*)-3′-Isopropyl-7a′-methylhexahydrospiro([1,3]dioxolane-2,5′-inden)-1′(6′*H*)-one (14). To a solution of alkene **12** (3.98 g, 15.9 mmol) in EtOH (300 mL) was added PtO_2 (181 mg, 800 μmol), and the suspension was purged with H_2 (balloon, 1 atm) for 60 min. The mixture was filtered over a pad of Celite, and the solvent was evaporated under reduced pressure. Purification by FCC (silica, hexanes/EtOAc = 5:1) yielded ketone **14** as colorless solid.

Combined FCC of several reactions batches resulted in an overall transformation from alkene **12** (10.7 g, 42.3 mmol) to ketone **14** (9.90 g) in 93% yield: R_f 0.46 (hexanes/EtOAc = 3:1); mp 65.5−67.0 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.00−3.87 (m, 4H), 2.48 (dd, J = 19.7, 2.4 Hz, 1H), 2.37 (dd, J = 19.7, 8.9 Hz, 1H), 2.28 (ddd, J = 13.8, 7.2, 3.2 Hz, 1H), 2.00 (dd, J = 13.7, 12.8 Hz, 1H), 1.91 (ddd, J = 12.7, 3.2, 2.2 Hz, 1H), 1.89−1.79 (m, 2H), 1.74−1.62 (m, 3H), 1.44 (ddd, J = 13.3, 13.3, 4.8 Hz, 1H), 1.04 (s, 3H), 0.96 (d, J = 6.0 Hz, 3H), 0.87 (d, J = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 220.7, 109.9, 64.6, 64.4, 46.5, 45.5, 43.5, 41.9, 35.8, 30.7, 30.6, 29.9, 23.7, 23.2, 15.9; IR (ν/cm^{-1}) 2954, 2879, 1740, 1472, 1346, 1139, 1113, 1102, 1086, 1045, 942; $[\alpha]_D^{20}$ +56.6 (c 1.00, CH_2Cl_2); HRMS-EI calcd for $C_{15}H_{24}O_3$ [M^+] 252.1720, found 252.1722.

(3′*R*,3a′*R*,7a′*R*)-3′-Isopropyl-7a′-methyl-3′,3a′,4′,6′,7′,7a′-hexahydrospiro([1,3]dioxolane-2,5′-indene) (16). To a solution of ketone **14** (3.00 g, 11.9 mmol) in THF (120 mL) at −78 °C was added dropwise KHMDS (33.4 mL, 0.5 M in toluene, 16.7 mmol), and the solution was stirred for 15 min. After addition of $PhNTf_2$ (6.37 g, 17.9 mmol), the mixture was stirred 10 min at −78 °C and an additional 30 min at 0 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl (40 mL), and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL) and dried ($MgSO_4$), and the solvents were removed under reduced pressure yielding crude enol triflate **15**.

To a solution of enol triflate **15** in DMF (30 mL) was added *n*-Bu_3N (8.47 mL, 35.7 mmol), HCOOH (1.12 mL, 29.8 mmol), and $Pd(PPh_3)_2Cl_2$ (334 mg, 476 μmol), and the suspension was stirred for 1 h at 75 °C. The mixture was quenched by adding H_2O (30 mL) at rt and filtered over a pad of Celite (washings with Et_2O). The aqueous layer was extracted with Et_2O (5 × 40 mL) and the combined organic layers were washed with 10% aqueous NaCl (3 × 75 mL) and dried ($MgSO_4$). Having evaporated the solvents under reduced pressure, purification by FCC (silica, pentane/Et_2O = 49:1 to 19:1) yielded alkene **16** (2.57 g, 92%) as colorless oil: R_f 0.32 (hexanes/EtOAc = 16:1); ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 5.86 (m_C, 1H), 5.81 (dd, J = 5.9, 2.8 Hz, 1H), 3.94−3.88 (m, 4H), 2.15 (ddd, J = 12.6, 7.6, 4.4 Hz, 1H), 2.06 (dddd, J = 9.9, 7.6, 2.8, 1.4 Hz, 1H), 1.90−1.84 (m, 2H), 1.79 (dd, J = 13.8, 5.1 Hz, 1H), 1.72 (dtt, J = 9.8, 6.6, 6.6 Hz, 1H), 1.64 (m_C, 1H), 1.56 (ddd, J = 12.5, 5.2, 2.4 Hz, 1H), 1.45 (m_C, 1H), 1.00 (d, J = 0.6 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H); ^{13}C NMR (CD_2Cl_2, 100 MHz): δ 142.2, 134.5, 110.8, 64.9, 64.7, 54.8, 48.8, 46.2, 35.4 (2×), 32.6, 30.3, 23.9, 22.6, 21.5; IR (ν/cm^{-1}) 3045, 2952, 2932, 2868, 1465, 1185, 1085; $[\alpha]_D^{20}$ −75.8 (c 1.00, CH_2Cl_2); HRMS-EI calcd for $C_{15}H_{24}O_2$ [M^+] 236.1771, found 236.1758.

(2′*S*,3′*S*,3a′*R*,7a′*R*)-3′-Isopropyl-7a′-methyloctahydrospiro([1,3]dioxolane-2,5′-inden)-2′-ol (17). To a solution of alkene **16** (550 mg, 2.33 mmol) in THF (60 mL) at 0 °C was added dropwise (+)-$IpcBH_2$ (3.5 mL, ca. 1 M in THF, 3.5 mmol),[32] and the mixture was stirred at rt for 30 min. MeOH (500 μL) was added at 0 °C followed by aqueous NaOH (3 N, 10 mL) and aqueous H_2O_2 (30%, 10 mL). After the mixture was heated to 55 °C for 40 min, saturated aqueous NH_4Cl (20 mL) was added at rt. The aqueous layer was extracted with Et_2O (3 × 30 mL), and the combined organic layers were washed with saturated aqueous NaCl (2 × 40 mL) and dried ($MgSO_4$). Having evaporated the solvents under reduced pressure, purification by FCC (silica, hexanes/EtOAc = 4:1) yielded alcohols **17** and **18** (5.5:1, 502 mg, 84%) as colorless oil. Analytical samples (colorless oils) were obtained by repeated FCC. The analytical sample of alcohol **18** contained ca. 14% of alcohol **17**.

Alcohol **17**: R_f 0.34 (hexanes/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.32 (m_C, 1H), 3.98−3.90 (m, 4H), 2.25 (ddd, J = 14.1, 10.5 Hz, 3.3 Hz, 1H), 2.01 (dd, J = 11.6, 7.1 Hz, 1H), 1.85 (m_C, 1H), 1.73−1.62 (m, 3H), 1.58 (m_C, 1H), 1.54 (ddd, J = 12.8, 4.7, 2.5 Hz, 1H), 1.48 (ddd, J = 10.4. 10.4, 4.3 Hz, 1H), 1.42 (m_C, 1H), 1.37 (brs, 1H), 1.22 (m_C, 1H), 1.00 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 110.4, 77.9, 64.5, 64.4, 57.2, 50.1, 46.9, 41.2, 36.9, 34.8, 30.8, 29.9, 24.1, 22.0, 19.1; IR (ν/cm^{-1}) 3418, 2950, 2876, 1457, 1289, 1193, 1111, 1095, 1035; $[\alpha]_D^{20}$ −1.3 (c 1.00, CH_2Cl_2); HRMS-EI calcd for $C_{15}H_{26}O_3$ [M^+] 254.1876, found 254.1879.

Alcohol **18**: R_f 0.31 (hexanes/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.99−3.92 (m, 4H), 3.74 (d, J = 5.1 Hz, 1H), 2.37 (ddd, J = 14.3, 9.8, 3.5 Hz, 1H), 2.00 (m_C, 1H), 1.93 (m_C, 1H), 1.85 (m_C, 1H), 1.82−1.71 (m, 4H), 1.69−1.64 (m, 1H), 1.63−1.58 (m, 1H), 1.36−1.27 (m, 2H), 0.90 (d, J = 6.4 Hz, 3H), 0.84 (s, 3H), 0.82 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 110.4, 79.0, 64.5, 64.4, 45.6, 44.9, 42.4, 38.5, 34.9, 30.8, 30.7, 29.6, 24.1, 22.3, 18.3; IR (ν/cm^{-1}) 3446, 2954, 2872, 1461, 1190, 1086, 1036; $[\alpha]_D^{20}$ −46.0 (c 0.50, CH_2Cl_2); HRMS-EI calcd for $C_{15}H_{26}O_3$ [M^+] 254.1876, found 254.1869.

(2*S*,3*S*,3a*R*,7a*R*)-2-Hydroxy-3-isopropyl-7a-methylhexahydro-1*H*-inden-5(6*H*)-one (19). To a solution of alcohols **17** and **18** (5.5:1, 495 mg, 1.95 mmol) in acetone/H_2O (10:1, 44 mL) was added PPTS (635 mg, 2.53 mmol), and the mixture was heated to reflux for 3 h. The pH was adjusted to 7 by adding $NaHCO_3$ at rt and the mixture was freed of acetone. The residue was diluted with Et_2O (80 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), aqueous HCl (1 N, 2 × 20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic layer was dried ($MgSO_4$), and the solvents were removed under reduced pressure. Purification by FCC (silica, hexanes/EtOAc = 4:1 to 2:1) yielded regioisomers **19** and **S3** (12:1, 307 mg, 75%) as a colorless solid. Analytical samples were obtained by repeated FCC.

Ketone **19**: colorless solid; R_f 0.22 (hexanes/EtOAc = 2:1); mp 52.5−54.5 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.42 (ddd, J = 9.4, 7.0, 4.9 Hz, 1H), 2.58 (ddd, J = 14.3, 3.4, 1.7 Hz, 1H), 2.44−2.30 (m, 4H), 2.10 (dd, J = 11.7, 7.0 Hz, 1H), 1.84 (ddd, J = 13.0, 7.1, 2.1 Hz, 1H), 1.73−1.67 (m, 1H), 1.62−1.55 (m, 3H), 1.31 (dd, J = 11.7, 9.3 Hz, 1H), 1.04 (d, J = 6.6 Hz, 3H), 1.04 (s, 3H), 0.94 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 212.0, 77.7, 56.6, 49.4, 48.6, 41.6, 40.9, 37.7, 37.2, 29.2, 24.2, 21.7, 19.1; IR (ν/cm^{-1}) 3406, 2955, 2932, 2871, 1703, 1462, 1388, 1034; $[\alpha]_D^{20}$ +72.0 (c 0.125, CH_2Cl_2); HRMS-EI calcd for $C_{13}H_{22}O_2$ [M$^+$] 210.1614, found 210.1613.

Regioisomer **S3**: colorless oil; R_f 0.28 (hexanes:EtOAc = 2:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.84 (d, J = 4.8 Hz, 1H), 2.63 (m_C, 1H), 2.54−2.36 (m, 4H), 2.06 (ddd, J = 14.7, 7.3, 4.7 Hz, 1H), 2.04−1.98 (m, 1H), 1.98−1.92 (m, 1H), 1.83 (dd, J = 14.8, 8.9 Hz, 1H), 1.64 (m_C, 1H), 1.59 (ddd, J = 12.7, 7.1, 2.4 Hz, 1H), 1.41 (brs, 1H), 1.00 (d, J = 0.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 212.6, 78.4, 45.5, 44.6, 44.2, 41.5, 38.8, 37.1, 30.1, 30.0, 24.1, 22.0, 18.4; IR (ν/cm^{-1}) 3434, 2957, 2894, 2874, 1698, 1466, 1386, 1234, 1171, 1031; $[\alpha]_D^{20}$ −9.2 (c 0.5, CH_2Cl_2); HRMS-EI calcd for $C_{13}H_{22}O_2$ [M$^+$] 210.1614, found 210.1614.

(2*S*,3*S*,3a*R*,7a*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-isopropyl-7a-methylhexahydro-1*H*-inden-5(6*H*)-one (20). To a solution of alcohols **19** and **S3** (12:1, 100 mg, 480 μmol) in DMF (6 mL) at 0 °C were added imidazole (122 mg, 1.80 mmol), DMAP (23 mg, 0.19 mmol), and TBSCl (181 mg, 1.20 mmol), and the mixture was stirred at rt for 16 h. The reaction was quenched by adding H_2O (15 mL) and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with 10% aqueous NaCl (3 × 15 mL) and dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. Purification by FCC (silica, hexanes/EtOAc = 70:1 to 30:1) yielded ketone **20** (141 mg, 91%) as colorless solid: R_f 0.23 (hexanes/EtOAc = 16:1); mp 49.5−51.0 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.36 (ddd, J = 8.8, 6.9, 4.2 Hz, 1H), 2.56 (ddd, J = 14.7, 3.6, 1.7 Hz, 1H), 2.43−2.36 (m, 2H), 2.35−2.28 (m, 2H), 1.98 (dd, J = 11.8, 6.9 Hz, 1H), 1.81 (ddd, J = 12.9, 7.1, 2.0 Hz, 1H), 1.71−1.63 (m, 2H), 1.58 (m_C, 1H), 1.27 (dd, J = 11.7, 8.8 Hz, 1H), 1.02 (s, 3H), 0.98 (d, J = 6.2 Hz, 3H), 0.91 (d, J = 6.0 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 212.3, 77.8, 56.5, 50.2, 48.1, 41.6, 40.9, 38.0, 37.3, 29.2, 26.0, 24.4, 21.9, 19.2, 18.0, −3.5, −4.7; IR (ν/cm^{-1}) 2956, 2929, 2857, 1711, 1472, 1254, 1106, 1073, 836; $[\alpha]_D^{20}$ +59.7 (c 0.33, CH_2Cl_2); HRMS-EI calcd for $C_{19}H_{36}O_2{}^{28}Si$ [M$^+$] 324.2479, found 324.2482.

(3′*S*,3a′*R*,7a′*S*)-3′-Isopropyl-7a′-methyloctahydrospiro([1,3]-dioxolane-2,5′-indene) (21). To a solution of alkene **16** (140 mg, 590 μmol) and NaOAc (556 mg, 6.80 mmol) in THF/H_2O (1:1, 18 mL) was added p-$TsNHNH_2$ (631 mg, 3.39 mmol), and the mixture was heated to 80 °C for 4 h. The reaction was quenched by addition of saturated aqueous K_2CO_3 (2 mL) at rt, and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. Purification by FCC (silica, pentane/Et_2O = 19:1 to 9:1) yielded *trans*-hydrindane **21** (130 mg, 93%) as a colorless oil: R_f 0.37 (hexanes/EtOAc = 16:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.02−3.88 (m, 4H,), 1.91−1.78 (m, 3H), 1.77−1.67 (m, 3H), 1.64−1.53 (m, 4H), 1.47 (dd, J = 11.8, 7.6 Hz, 1H), 1.32 (m_C, 1H), 1.13 (m_C, 1H), 0.89 (d, J = 6.3 Hz, 3H), 0.86 (s, 3H), 0.82 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 110.9, 64.4, 64.3, 48.4, 46.7, 41.0, 40.3, 37.2, 35.4, 31.3 (2×), 28.7, 24.1, 22.4, 17.9; IR (ν/cm^{-1}) 2950, 2873, 1464, 1356, 1289, 1190, 1115, 1096, 947; $[\alpha]_D^{20}$ −24.8 (c 0.25, CH_2Cl_2); HRMS-EI calcd for $C_{15}H_{26}O_2$ [M$^+$] 238.1927, found 238.1927.

(3*S*,3a*R*,7a*S*)-3-Isopropyl-7a-methylhexahydro-1*H*-inden-5(6*H*)-one (22). To a solution of dioxolane **21** (100 mg, 420 μmol) in acetone/H_2O (9:1, 10 mL) was added PPTS (137 mg, 546 μmol), and the reaction was heated to reflux for 3 h. The pH was adjusted to 7 by addition of $NaHCO_3$ at rt, and the mixture was freed of acetone. The residue was diluted with Et_2O (10 mL), and the mixture was washed with saturated aqueous $NaHCO_3$ (3 mL), HCl (2 N, 2 × 3 mL), and saturated aqueous $NaHCO_3$ (2 × 3 mL). The organic layer was dried ($MgSO_4$), and the solvents were removed under reduced pressure. Purification by FCC (silica, pentane/Et_2O = 20:1 to 9:1) yielded ketone **22** (80 mg, 99%) as colorless oil: R_f 0.29 (hexanes/EtOAc = 16:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.58 (ddd, J = 15.0, 4.1, 1.8 Hz, 1H), 2.47−2.40 (m, 2H), 2.31 (dddd, J = 16.3, 5.7, 1.8, 1.8 Hz, 1H), 1.97−1.88 (m, 2H), 1.86 (ddd, J = 12.9, 7.3, 1.9 Hz, 1H), 1.81−1.68 (m, 2H), 1.65−1.57 (m, 2H), 1.49 (ddd, J = 13.0, 13.0, 5.8 Hz, 1H), 1.19 (ddd, J = 11.8, 11.8, 8.4 Hz, 1H), 1.04 (s, 3H), 0.88 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 213.2, 50.2, 46.5, 42.3, 41.1, 39.9, 37.9, 37.6, 30.5, 29.3, 24.1, 22.1, 17.8; IR (ν/cm^{-1}) 2954, 2868, 1711, 1420, 1386, 1214, 1045; $[\alpha]_D^{20}$ +11.2 (c 0.25, CH_2Cl_2); HRMS-EI calcd for $C_{13}H_{22}O$ [M$^+$] 194.1665, found 194.1674.

(3′*S*,3a′*R*,7a′*R*)-3′-Isopropyl-7a′-methyl-3′,3a′,4′,6′,7′,7a′-hexahydrospiro([1,3]dioxolane-2,5′-indene) (23). To a solution of ketone **13** (380 mg, 1.51 mmol) in THF (25 mL) at −78 °C was added dropwise KHMDS (4.83 mL, 0.5 M in toluene, 2.41 mmol), and the solution was stirred for 15 min. After addition of $PhNTf_2$ (755 mg, 2.11 mmol), the mixture was stirred for an additional 30 min. The reaction was quenched by adding saturated aqueous NH_4Cl (10 mL), and the mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4). The solvents were removed under reduced pressure to yield crude enol triflate **S4**.

To a solution of enol triflate **S4** in DMF (10 mL) was added n-Bu_3N (1.07 mL, 4.53 mmol), HCOOH (140 μL, 3.78 mmol), and $Pd(PPh_3)_2Cl_2$ (53 mg, 80 μmol), and the mixture was stirred for 2 h at 75 °C. The reaction was quenched by adding H_2O (10 mL) at rt and the mixture was extracted with Et_2O (5 × 15 mL). The combined organic layers were washed with 10% aqueous NaCl (3 × 15 mL) and dried (Na_2SO_4), and the solvents were evaporated under reduced pressure. Purification by FCC (silica, pentane/Et_2O = 49:1 to 19:1) yielded alkene **23** (310 mg, 87%) as colorless oil: R_f 0.52 (hexanes/EtOAc = 7:1); ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 5.85 (dd, J = 5.8, 2.5 Hz, 1H), 5.66 (dd, J = 5.8, 1.5 Hz, 1H), 3.96−3.86 (m, 4H), 2.20 (m_C, 1H), 1.83−1.59 (m, 7H), 1.56−1.47 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 0.5 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 142.7, 132.9, 110.7, 64.8, 64.6, 52.2, 49.4, 46.5, 34.1 (2×), 32.2, 28.8, 22.3, 19.4, 16.8; IR (ν/cm^{-1}) 3043, 2945, 2872, 1119, 1082, 1054, 943; $[\alpha]_D^{20}$ +85.8 (c 1.00, CH_2Cl_2); HRMS-EI calcd for $C_{15}H_{24}O_2$ [M$^+$] 236.1771, found 236.1778.

(3*R*,3a*R*,7a*S*)-3-Isopropyl-7a-methylhexahydro-1*H*-inden-5(6*H*)-one (24). To a solution of alkene **23** (300 mg, 1.27 mmol) in n-pentane (15 mL) was added Pd/C (10% Pd, 33 mg, 25 μmol), and the suspension was stirred under an atmosphere of H_2 (balloon, 1 atm) for 16 h. The reaction mixture was filtered over a pad of Celite, and the solvents were removed under reduced pressure yielding crude ketal **S5**.

To a solution of ketal **S5** in acetone (15 mL) was added I_2 (86 mg, 0.34 mmol). The reaction was stirred for 10 min at rt and was then quenched by adding aqueous $Na_2S_2O_3$ (5 wt %, 10 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$). Having evaporated the solvents under reduced pressure, purification by FCC (silica, pentane/Et_2O = 24:1 to 19:1) yielded ketone **24** (234 mg, 95%) as colorless solid: R_f 0.55 (hexanes:EtOAc = 7:1); mp 64.5−66.0 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.44−2.36 (m, 2H), 2.31 (dddd, J = 16.5, 5.7, 1.9, 1.9 Hz, 1H), 2.15 (m_C, 1H), 1.90−1.79 (m, 2H), 1.67−1.58 (m, 2H), 1.57−1.44 (m, 4H), 1.21−1.14 (m, 1H), 0.99 (s, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 212.6, 50.2, 47.2, 42.8, 41.3, 38.3, 37.9, 37.2, 29.4, 25.1, 21.9, 18.1, 17.3; IR (ν/cm^{-1}) 2950, 2870, 1703, 1465, 1412, 1387, 1278, 1214, 1140; $[\alpha]_D^{20}$ +92.8 (c 0.50, CH_2Cl_2); HRMS-EI calcd for $C_{13}H_{22}O$ [M$^+$] 194.1665, found 194.1661.

ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra for compounds **9−14**, **16−24**, **S1**, and **S3** and X-ray data for compounds **10−14**, **20**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: dirk.trauner@cup.uni-muenchen.de.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the Fonds der Chemischen Industrie e. V. (Ph.D. scholarship to D.T.H.) for financial support. We thank D. Hager, P. Stawski, S. Strych, and R. Webster for helpful discussions as well as undergraduate researchers S. Rappenglück, T. M. Wildenhof, and M. Rossa for skillful experimental assistance.

REFERENCES

(1) Liu, Y.; Wang, L.; Jung, J. H.; Zhang, S. *Nat. Prod. Rep.* **2007**, *24*, 1401−1429 and further reviews in this series.

(2) For a recent review on synthetic approaches toward sesterterpenoids, see: Hog, D. T.; Webster, R.; Trauner, D. *Nat. Prod. Rep.* **2012**, *29*, 752−779.

(3) Rao, P. S.; Sarma, K. G.; Seshadri, T. R. *Curr. Sci.* **1965**, *34*, 9−11.

(4) Kaneda, M.; Takahashi, R.; Iiataka, Y.; Shibata, S. *Tetrahedron Lett.* **1972**, *13*, 4609−4611.

(5) Kaneda, M.; Takahashi, R.; Shibata, S. *Acta Crystallogr.* **1974**, *B30*, 358−364.

(6) Sugawara, H.; Kasuya, A.; Iiataka, Y.; Shibata, S. *Chem. Pharm. Bull.* **1991**, *39*, 3051−3054.

(7) Kawahara, N.; Nozawa, M.; Flores, D.; Bonilla, P.; Sekita, S.; Satake, M.; Kawai, K.-i. *Chem. Pharm. Bull.* **1997**, *45*, 1717−1719.

(8) Sadler, I. H.; Simpson, T. J. *J. Chem. Soc., Chem. Commun.* **1989**, 1602−1604.

(9) Sadler, I. H.; Simpson, T. J. *Magn. Reson. Chem.* **1993**, *30*, S18−S23.

(10) Wang, Y.; Dreyfuss, M.; Ponelle, M.; Oberer, L.; Riezman, H. *Tetrahedron* **1998**, *54*, 6415−6426.

(11) Hensens, O. D.; Zink, D.; Williamson, J. M.; Lotti, V. J.; Chang, R. S. L.; Goetz, M. A. *J. Org. Chem.* **1991**, *56*, 3399−3403.

(12) Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339−4341.

(13) Paquette, L. A.; Wright, J.; Drtina, G. J.; Roberts, R. A. *J. Org. Chem.* **1987**, *52*, 2960−2962.

(14) Wright, J.; Drtina, G. J.; Roberts, R. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1988**, *110*, 5806−5817.

(15) Hudlicky, T.; Radesca-Kwart, L.; Li, L.-q.; Bryant, T. *Tetrahedron Lett.* **1988**, *29*, 3283−3286.

(16) Hudlicky, T.; Fleming, A.; Radesca, L. *J. Am. Chem. Soc.* **1989**, *111*, 6691−6707.

(17) Wender, P. A.; Singh, S. K. *Tetrahedron Lett.* **1990**, *31*, 2517−2520.

(18) Mizutani, R.; Nakashima, K.; Saito, Y.; Sono, M.; Tori, M. *Tetrahedron Lett.* **2009**, *50*, 2225−2227.

(19) Piers, E.; Boulet, S. L. *Tetrahedron Lett.* **1997**, *38*, 8815−8818.

(20) Walker, S. D. Ph.D. Thesis, University of British Columbia, 2002.

(21) Molander, G. A.; Quirmbach, M. S.; Silva, L. F., Jr.; Spencer, K. C.; Balsells, J. *Org. Lett.* **2001**, *3*, 2257−2260.

(22) For this study, we opted to use the less expensive L-proline to synthesize diketone **7**.

(23) Hajos, Z. G.; Parrish, D. R. *Org. Synth.* **1985**, *63*, 26−31.

(24) 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.

(25) For a related reaction sequence, see: Cao, L.; Sun, J.; Wang, X.; Zhu, R.; Shi, H.; Hu, Y. *Tetrahedron* **2007**, *63*, 5036−5041.

(26) Ketone **10** has been prepared via an alternative route. However, no analytical data has been reported; see: Kotoku, N.; Tamada, N.; Hayashi, A.; Kobayashi, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3532−3535.

(27) CCDC 865613−865619 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(28) Bull, J. R.; Loedolff, M. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1269−1276.

(29) Smit, C.; Fraaje, M. W.; Minnaard, A. J. *J. Org. Chem.* **2008**, *73*, 9482−9485 and references cited therein.

(30) Siegel, S.; Smith, G. V. *J. Am. Chem. Soc.* **1960**, *82*, 6082−6087.

(31) For a report on the influence of pressure and catalyst on olefin isomerization, see: Hudlicky, M. Reductions in Organic Chemistry. *ACS Monograph* **1995**, *188*, 53−55.

(32) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *J. Org. Chem.* **1982**, *47*, 5074−5083.

(33) Webster, R.; Boyer, A.; Fleming, M. J.; Lautens, M. *Org. Lett.* **2010**, *12*, 5418−5421.

(34) Although different preparations of ketone **24** have been described,[15,16,35,36] no analytical data has been reported to date.

(35) Corey, E. J.; Engler, T. A. *Tetrahedron Lett.* **1984**, *25*, 149−152.

(36) Attah-Poku, S. K.; Chau, F.; Yadav, V. K.; Fallis, A. G. *J. Org. Chem.* **1985**, *50*, 3418−3419.