JOC The Journal of Organic Chemistry

Featured Article

pubs.acs.org/joc

A Convergent and Stereocontrolled Cycloaddition Strategy toward Eudesmane Sesquiterpenoid: Total Synthesis of (±)-6β,14-Epoxyeudesm-4(15)-en-1β-ol

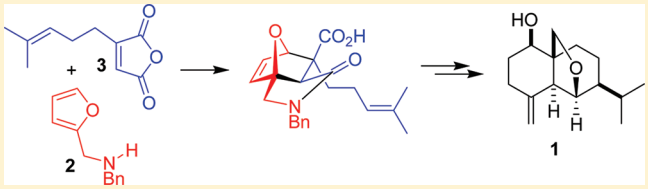
Cui-Cui Wang[†] and Wei-Dong Z. Li*[,†,‡]

[†]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

[‡]State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

Supporting Information

ABSTRACT: We present in this report the development of a convergent and highly stereocontrolled cycloaddition strategy toward the synthesis of C-1, C-6, and C-14 tris-oxygenated eudesmane sesquiterpenoids. This approach was demonstrated in the first total synthesis of (±)-6β,14-epoxyeudesm-4(15)-en-1β-ol (**1**), a structurally unique ethereal eudesmane sesquiterpenoid, via an effective Diels–Alder construction of a compact functionalized tricycle intermediate from readily available *N*-benzylfurfurylamine (**2**) and homoprenyl maleic anhydride (**3**) as the C_5 and C_{10} building blocks, respectively.



INTRODUCTION

Eudesmane sesquiterpenoids are classic targets in natural product synthesis[1] because of their diverse structural types[2] and wide range of biological properties.[3] Recent reports[4] in this field prompted us to disclose our recent efforts in the development of a novel strategic approach toward the stereocontrolled total synthesis of multiple oxygenated eudesmane sesquiterpenoids. Our previous studies[5] in this context have resulted in a general approach based on the assembly of functionalized oxabicyclo[2.2.1]heptane templates,[6] which was demonstrated in the total synthesis of the C-1- and C-6-oxygenated eudesmanoids (Figure 1).[5] This

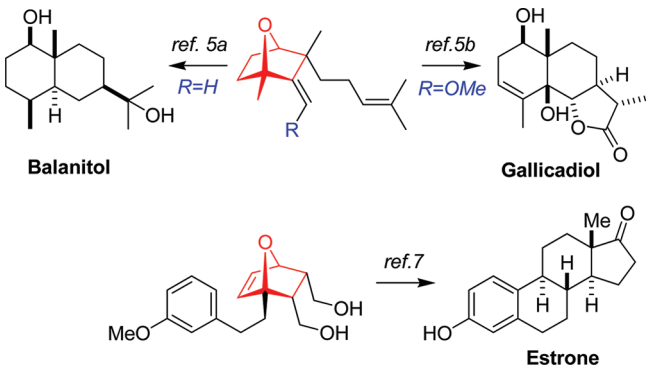


Figure 1. Template strategy based on oxabicyclo[2.2.1]heptane.

template approach was also extended recently to a novel synthesis of estrone in our laboratory.[7] In view of the frequent occurrence of the C-14-hydroxylated eudesmane sesquiterpenoids (i.e., euonyminol, Figure 2) of biological significance[8] and lack of a general synthetic approach,[1c,8b] we decided to investigate new methods of general application.

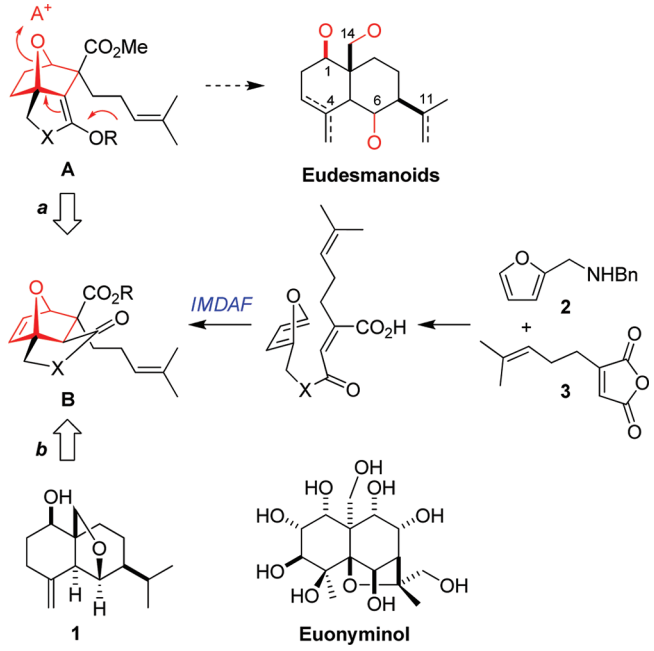


Figure 2. Cycloaddition strategy and structure of **1**.

In alignment with our previous oxabicyclic template approach, we have explored the possibility of a tandem epoxy-ring-opening/cation-π cyclization (arrows in Figure 2a) of a cyclic ketene acetal (X = O) or aminal (X = NR) precursor **A**, which might be accessed from **B** via a facile intramolecular Diels–Alder furan (IMDAF) cyclocondensation.[9] Although the

Received: March 20, 2012
Published: April 16, 2012

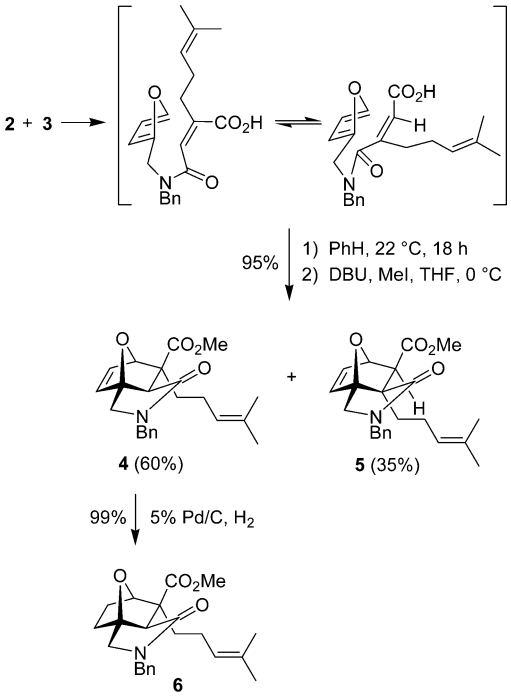
   dx.doi.org/10.1021/jo300556r | J. Org. Chem. 2012, 77, 4217–4225

initially anticipated tandem construction was not realized due to the failure of preparing the corresponding tricyclic precursor **A** (Figure 2a), we have developed an alternative convergent and stereocontrolled approach for the synthesis of the C-1, C-6, and C-14 tris-hydroxylated eudesmane sesquiterpenoids based on the IMDAF cyclocondensation of *N*-benzylfurfurylamine (**2**) and homoprenyl maleic anhydride (**3**) as the C_5 and C_{10} building blocks, respectively, which was demonstrated (Figure 2b) in the first total synthesis of (±)-6*β*,14-epoxyeudesm-4(15)-en-1*β*-ol (**1**), a novel type of eudesmane sesquiterpenoid with a unique C-6/C-14 ethereal linkage isolated from *Erigeron philadelphicus* by Kikuchi and co-workers[10] in 2003.

RESULTS AND DISCUSSION

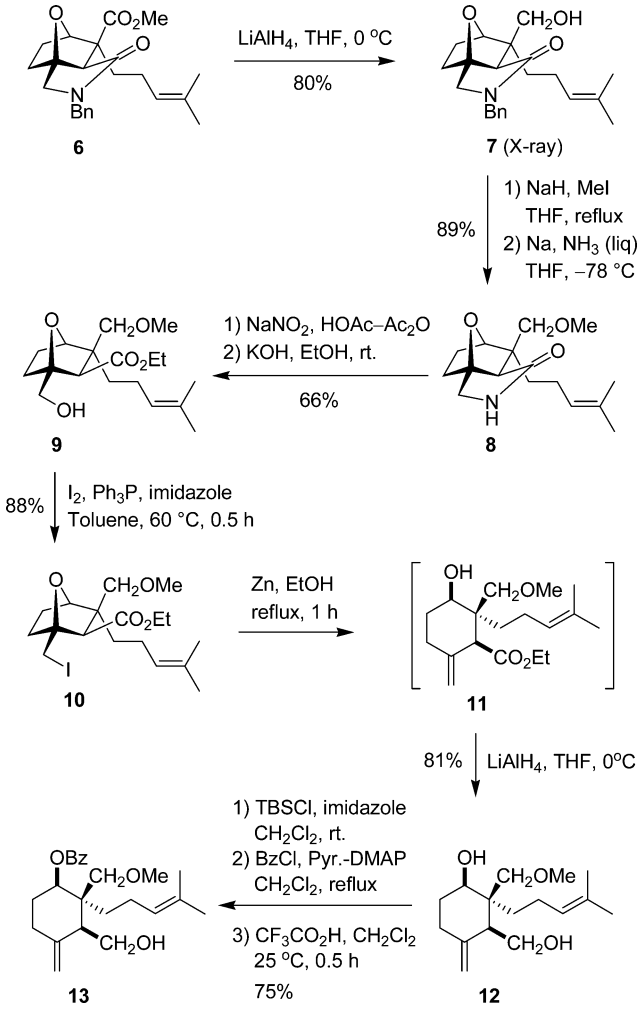
As shown in Scheme 1, the synthesis commenced from the cyclocondensation of **2** and **3**.[9d,e] Ammonolysis of homoprenyl maleic anhydride (**3**)[11] with *N*-benzylfurfurylamine (**2**)[9e] in benzene at ambient temperature was followed by methylation of the resulting carboxylic acid products to afford the desired IMDAF cycloadduct **4** (60%) and its regioisomer **5** (35%), via presumably a kinetically favorable *N*-tethered IMDAF cycloaddition process.[12] To our delight, an effective regioselective catalytic hydrogenation of tricyclic diene **4** was achieved in ethyl acetate with 5% Pd/C as the catalyst (balloon pressure, ambient temperature, 0.5 h) to give tricyclic methyl ester **6** quantitatively.

Scheme 1. Synthesis of Tricycle 6 via the IMDAF Cycloaddition



With readily available highly functionalized tricyclic ester **6** in hand, further transformation to the eudesmane system was undertaken. As depicted in Scheme 2, hydride reduction of **6** with $LiAlH_4$ in THF at 0 °C gave alcohol **7** in good yield, whose structure was unambiguously confirmed by a single-crystal X-ray analysis.[13] Methyl ether formation of **7** was followed by reductive *N*-debenzylation[14] to give methyl ether **8**, which was converted into the hydroxyl ester **9** effectively via the corresponding *N*-nitroso intermediate according to known protocol.[15] Iodination of **9** followed by reductive cleavage of the epoxy bridge of iodide **10** with zinc[16] and further hydride reduction of the resulting intermediary ester **11** furnished diol **12** in 81% overall yield. Benzoate **13** was obtained readily from diol **12** in 75% overall yield via a routine hydroxyl protecting group manipulation.

Scheme 2. Conversion of 6 → 13

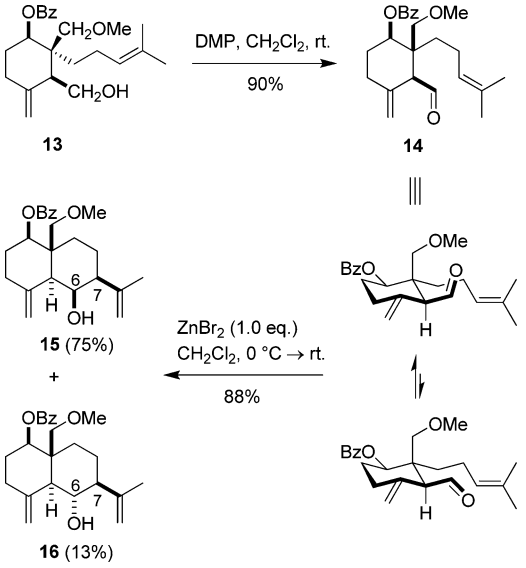


Stereocontrolled construction of the eudesmane system via carbonyl–ene cyclization[17] is shown in Scheme 3. Oxidation of benzoate **13** with DMP afforded aldehyde **14** in 92% yield, which was subjected to the carbonyl–ene cyclization mediated by $ZnBr_2$[5b] to give alcohol **15** (75%) as the major diastereoisomer along with its C-6 epimer **16** (13%).[18] X-ray structural analysis of **15** revealed the stereochemistry at the C-6 and C-7 as shown.[13] Apparently, the conformational preference (Scheme 3) of the cyclization precursor **14** is responsible for the observed diastereoselectivity (ca. 6:1).

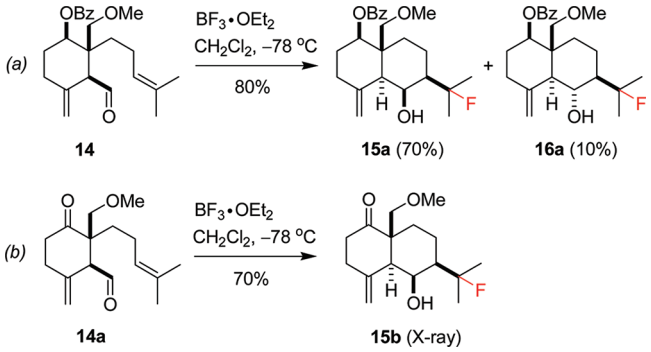
Other Lewis acids (such as $SnCl_4$ or $EtAlCl_2$) could also promote the desired cyclization of **14** → **15**, but in less satisfactory yields (ca. 30%). Interestingly, BF_3 etherate was found to promote a stereoselective Prins-type cyclization of **14** leading to the formation of fluorinated alcohol **15a** (70%) as the major product along with its minor epimer **16a** in an overall yield of 80% (Scheme 4a).[19] Analogously, Prins-type cyclization of 1-keto aldehyde **14a** mediated by BF_3 etherate gave solely fluoride **15b** in 70% yield (Scheme 4b).[13]

dx.doi.org/10.1021/jo300556r | J. Org. Chem. 2012, 77, 4217–4225

Scheme 3. Carbonyl−Ene Cyclization of Aldehyde 14



Scheme 4. Prins Cyclization of 14 and 14a Mediated by $BF_3{\cdot}OEt_2$

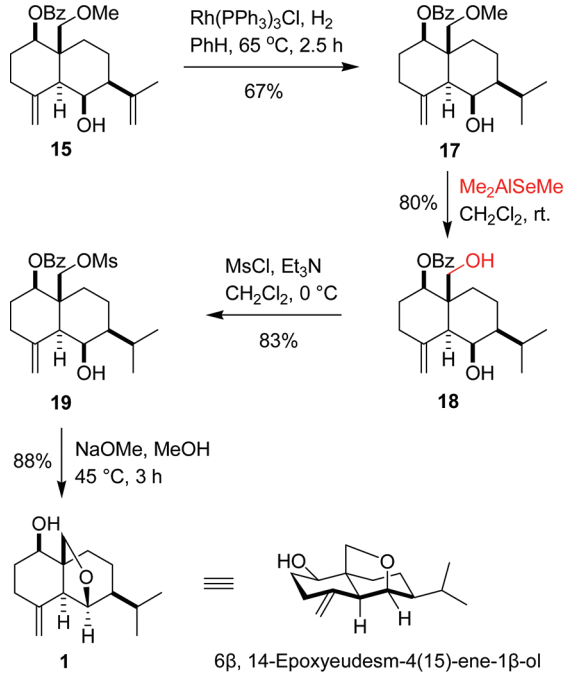


The stage was now set to complete the total synthesis of **1** from **15**. As outlined in Scheme 5, regioselective catalytic hydrogenation of diene **15** using Wilkinson's catalyst[20] in warm benzene gave the desired alcohol **17** in 67% yield. Effective *O*-demethylation[21] of **17** was achieved by treatment with a freshly prepared *n*-heptane solution of $Me_2AlSeMe$[23] to give diol **18** in 80% yield. Mesylation of the primary C-14 hydroxyl of **18** was followed by the treatment of the resulting mesylate **19** with NaOMe in warm MeOH to furnish the racemic 6*β*,14-epoxyeudesm-4(15)-en-1*β*-ol (**1**) in 73% yield. The synthetic **1** exhibits spectroscopic properties identical with those of natural **1** reported.[10]

CONCLUSION

In summary, we have developed a convergent strategy for the stereocontrolled construction of multioxygenated eudesmane sesquiterpenoids via a facile IMDAF cyclocondensation. The first total synthesis of (±)-6*β*, 14-epoxyeudesm-4(15)-ene-1*β*-ol (**1**) was achieved from readily accessible functionalized IMDAF cycloadduct **6** in 14 steps. Some noteworthy transformations in the synthetic sequence include: (1) regioselective catalytic hydrogenation of **4** → **6** and **15** → **17** and (2) effective *O*-demethylation of **17** mediated by a readily available chemical reagent $Me_2AlSeMe$. Further developments of this approach toward the synthesis of polyoxygenated

Scheme 5. Total Synthesis of 1



sesquiterpenoids as well as asymmetric method are underway in our laboratory.

EXPERIMENTAL SECTION

3-(4-Methylpent-3-en-1-yl)furan-2,5-dione (3). (1) In a flame-dried, nitrogen-flushed round-bottom flask were added freshly grounded magnesium turnings (3.84 g, 160 mmol) and Et_2O (50 mL). To the above mixture was then added a solution of homoprenyl iodide[24] (31.5 g, 150 mmol) in Et_2O (100 mL) dropwise and a crystal of iodine. The reaction mixture was refluxed for 1.5 h and cooled to room temperature. The above prepared Grignard reagent was then added dropwise to a suspension of cuprous bromide−dimethyl sulfide complex (24.67 g, 120 mmol) in THF (240 mL) at −40 °C. The resulting solution was stirred at −40 °C for 2 h and then cooled to −78 °C, and freshly distilled DMAD (14.2 g, 100 mmol) in THF (100 mL) was added dropwise to give a dark red-brown mixture. After 1 h, the reaction mixture was quenched with a saturated solution of ammonium chloride (100 mL, adjusted to pH 8 with ammonia) and allowed to warm to room temperature. After 30 min, the mixture was partitioned between water and ether. The aqueous layer was extracted with ethyl acetate (2 × 500 mL), and the combined organic extracts were washed with an additional saturated aqueous NH_4Cl solution (300 mL) and brine (300 mL) and dried over Na_2SO_4. Concentration in vacuo gave a crude oil. Purification by flash column chromatography on silica gel (petroleum ether/EtOAc, 15:1) gave dimethyl 2-(4-methylpent-3-enyl)maleate (17.2 g, 76 mmol) in 76% yield as a colorless oil: R_f = 0.5 (petroleum ether:EtOAc = 4:1); IR (film) ν_{max} 2954, 2921, 1732, 1650, 1438, 1372, 1268, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.58 (3H, s), 1.67 (3H, s), 2.14−2.18 (2H, m), 2.35 (2H, t, J = 7.6 Hz), 3.70 (3H, s), 3.81 (3H, s), 5.05 (1H, t, J = 7 Hz), 5.80 (1H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 25.5, 25.6, 34.4, 51.7, 52.2, 119.3, 121.9, 133.3, 150.2, 165.4, 169.3 ppm; HRMS (ESI) calcd for $C_{12}H_{19}O_4$ 227.1278, found for $[M + H]^+$ 227.1272. (2) To a mixture of dimethyl 2-(4-methylpent-3-enyl)maleate (17.2 g, 76.0 mmol) in THF−H_2O (150 mL, 1: 1) was added aqueous 4.0 M LiOH (76 mL, 304 mmol), and the mixture was stirred at 50 °C for 2 h and then cooled to 0 °C. The reaction mixture was acidified with 10% HCl at 0 °C and extracted with ether (6 × 250 mL). The combined organic extracts were washed with brine (250 mL), dried over Na_2SO_4, and concentrated in vacuo to give an oil, which was taken in 150 mL of toluene. The solvent was slowly removed by

dx.doi.org/10.1021/jo300556r | J. Org. Chem. 2012, 77, 4217−4225

distillation. The last traces of solvent were removed in vacuo, leaving **3** (11 g, 61.1 mmol, 80% yield) as a yellowish oil. The crude **3** was used in the next step without further purification. Compound **3**: R_f = 0.55 (petroleum ether/EtOAc = 4:1); IR (film) ν_{max} 1843, 1772, 1246, 894 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.62 (3H, s), 1.71 (3H, s), 2.35 (2H, q, J = 7.2 Hz), 2.56 (2H, td, J = 1.8 Hz, 7.2 Hz), 5.07 (1H, m), 6.59 (1H, t, J = 1.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 25.3, 25.6, 26.1, 121.2, 128.7, 134.6, 153.2, 164.0, 165.9 ppm; HRMS (ESI) calcd for $C_{10}H_{12}NaO_3$ 203.0684, found for $[M + Na]^+$ 203.0687.

Methyl 2-Benzyl-7-(4-methylpent-3-en-1-yl)-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylate (4) and Methyl 2-Benzyl-7a-(4-methylpent-3-en-1-yl)-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylate (5). To a mixture of **3**[11] (7.70 g, 42.7 mmol) in 43 mL of benzene was added a solution of compound **2**[9e] (7.98 g, 42.7 mmol) in 43 mL of benzene at room temperature. After the reaction mixture was stirred for 18 h and evaporated under reduced pressure at 30 °C, the resulting residue was taken in 95 mL of THF, to which was added DBU (9.56 mL, 64 mmol) at 0 °C. After the reaction mixture was stirred for 15 min, MeI (5.32 mL, 85.4 mmol) was added, stirring was continued for 15 min at 0 °C, and then 30 mL of H_2O was added to terminate the reaction. The aqueous layer was extracted with ethyl acetate (2 × 250 mL), and the combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was taken in a solution of petroleum ether/EtOAc (5: 1, 50 mL). Cycloadduct **5** (5.69 g, 14.9 mmol, 35% yield) was crystallized after 2 days. The filtrate was evaporated under reduced pressure to give a residue, which was subjected to repeated column chromatography on silica gel eluting with petroleum ether/EtOAc (5: 1) to give cycloadduct **4** (9.76 g, 25.6 mmol, 60% yield) as a colorless oil. Compound **4**: R_f = 0.5 (petroleum ether/EtOAc = 1:1); IR (film) ν_{max} 2946, 2923, 1730, 1689, 1431, 1360, 1219, 738, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (1H, td, J = 4.8 Hz, 12.8 Hz), 1.61 (3H, s), 1.66 (3H, s), 1.86−1.91 (1H, m), 1.99−2.04 (1H, m), 2.18 (1H, td, J = 4.8 Hz, 13.2 Hz), 2.33 (1H, s), 3.57 and 3.74 (ABq, 2H, J = 12 Hz), 3.81 (3H, s), 4.32 and 4.65 (ABq, 2H, J = 15 Hz), 5.03 (1H, t, J = 6.8 Hz), 5.20 (1H, s), 6.49 (2H, s), 7.23−7.35 (5H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 24.6, 25.6, 37.2, 46.7, 48.3, 52.2, 56.3, 57.7, 83.8, 88.6, 123.1, 127.6, 127.9 (2C), 128.8 (2C), 132.5, 135.5, 136.1, 136.5, 170.7, 173.2 ppm; HRMS (ESI) calcd for $C_{23}H_{28}NO_4$ 382.2013, found for $[M + H]^+$ 382.2010. Compound **5**: R_f = 0.6 (petroleum ether: EtOAc = 1: 1); mp 122−124 °C ; IR (film) ν_{max} 2920, 2855, 1735, 1686, 1432, 1168, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.302−1.473 (2H, m), 1.55 (3H, s), 1.65 (3H, s), 2.11 (2H, dd, J = 8 Hz, 16.8 Hz), 2.30 (1H, s), 3.54 and 3.85 (ABq, 2H, J = 11.6 Hz), 3.79 (3H, s), 4.75 and 4.74 (ABq, 2H, J = 15 Hz), 4.97−5.00 (1H, m), 5.07 (1H, d, J = 2 Hz), 6.41 (1H, d, J = 6 Hz), 6.50 (1H, dd, J = 1.6 Hz, 5.6 Hz), 7.24−7.33 (5H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 23.5, 25.5, 37.2, 46.6, 47.5, 51.7, 52.0, 60.4, 80.6, 90.8, 123.1, 127.5, 128.0 (2C), 128.6 (2C), 132.3, 133.5, 136.1, 137.1, 172.5, 173.0 ppm; HRMS (ESI) calcd for $C_{23}H_{28}NO_4$ 382.2013, found for $[M + H]^+$ 382.2010.

Methyl 2-Benzyl-7-(4-methylpent-3-en-1-yl)-1-oxooctahydro-3a,6-epoxyisoindole-7-carboxylate (6). A mixture of compound **4** (5.00 g, 13.1 mmol) and 5% Pd/C (500 mg) in 150 mL of AcOEt was stirred under hydrogen atmosphere (1 atm). After 35 min at rt, ^1H NMR indicated that diene **4** was completely consumed. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure to give **6** (5.00 g, 13.1 mmol, 99%) as a yellowish oil. Compound **6** was used directly in the next step without purification. Compound **6**: R_f = 0.5 (petroleum ether/EtOAc = 1:1); IR (film) ν_{max} 2948, 1731, 1691, 1430, 1351, 1218, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.55 (1H, td, J = 4.4 Hz, 13.2 Hz), 1.61 (3H, s), 1.66 (3H, s), 1.68−1.99 (5H, m), 2.01−2.12 (1H, m), 2.25 (1H, td, J = 4.8 Hz, 12.4 Hz), 2.38 (1H, s), 3.42 and 3.53 (ABq, 2H, J = 11.6 Hz), 3.76 (3H, s), 4.41 and 4.54 (ABq, 2H, J = 15 Hz), 4.73 (1H, d, J = 4.8 Hz), 5.10 (1H, t, J = 6.8 Hz), 7.24−7.33 (5H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 24.8, 25.5, 25.6, 29.6, 36.2, 46.5, 48.7, 52.0, 59.9, 61.5, 82.3, 86.3, 123.2, 127.4, 127.9 (2C), 128.7 (2C), 132.4, 136.1, 171.4, 172.6 ppm; HRMS (ESI) calcd for $C_{23}H_{30}NO_4$ 384.2169, found for $[M + H]^+$ 384.2158.

2-Benzyl-7-(hydroxymethyl)-7-(4-methylpent-3-en-1-yl)-hexahydro-3a,6-epoxyisoindol-1(4*H*)-one (7). To a stirred solution of **6** (2 g, 5.22 mmol) in dry THF (70 mL) was added $LiAlH_4$ (397 mg, 10.44 mmol) portionwise at 0 °C. After being stirred for 10 min, the reaction mixture was quenched by addition of powdered $Na_2SO_4{\cdot}10H_2O$ and filtered through Celite. The solid residue was washed with AcOEt four times. The combined filtrate and washings were combined. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (6:1) to give compound **7** (1.48 g, 4.18 mmol, 80% yield) as white crystals. Compound **7**: R_f = 0.65 (petroleum ether/EtOAc = 1:1); mp 118−119 °C ; IR (film) ν_{max} 3378, 2963, 2926, 1660, 1431, 1348, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (1H, dt, J = 4.4 Hz, 16.4 Hz), 1.63 (3H, s), 1.71 (3H, s), 1.65−1.87 (4H, m), 1.98−2.05 (1H, m), 2.16−2.20 (1H, m), 2.30 (1H, s), 2.43 (1H, dt, J = 4.8 Hz, 13.2 Hz), 3.47 (ABq, 2H, J = 11.8 Hz), 3.62 (1H, t, J = 11.8 Hz), 3.82 (1H, d, J = 12 Hz), 4.08 (1H, d, J = 5.6 Hz), 4.48 and 4.54 (ABq, 2H, J = 14.8 Hz), 4.67 (1H, dd, J = 2.8 Hz, 11.6 Hz), 5.12 (1H, t, J = 7.2 Hz), 7.22−7.37 (5H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 23.3, 25.2, 25.7, 29.2, 34.1, 46.7, 49.6, 55.9, 62.6, 64.5, 82.2, 87.4, 124.0, 127.7, 127.9 (2C), 128.8 (2C), 131.8, 135.6, 174.7 ppm; HRMS (ESI) calcd for $C_{22}H_{30}NO_3$ 356.2220, found for $[M + H]^+$ 356.2212. X-ray crystallographic data of **7**:[13] $C_{22}H_{29}NO_3$, FW 355.46, monoclinic, space group $P2(1)/c$, a = 10.0388(3) Å, b = 18.6942(5) Å, c = 10.7459(3) Å, α = 90°, β = 98.5760(10)°, γ = 90.00°, Z = 4, d_{calcd} = 1.184 g/cm^3, $R_1(I > 2\sigma(I))$ = 0.0388, wR_2 = 0.0960.

7-(Methoxymethyl)-7-(4-methylpent-3-en-1-yl)hexahydro-3a,6-epoxyisoindol-1(4*H*)-one (8). (1) To a stirring mixture of NaH (162 mg, 6.76 mmol) in 5 mL of THF was added a solution of alcohol **7** (1.2 g, 3.38 mmol) in 15 mL of THF at room temperature under nitrogen atmosphere. After the reaction mixture was stirred for 30 min, MeI (0.63 mL, 10.14 mmol) was added, and the solution was brought to reflux. After being refluxed for 1 h, the reaction mixture was cooled to room temperature, and the mixture was quenched by addition of 2 mL of H_2O. The mixture was extracted with ethyl acetate (2 × 60 mL), and the combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (6:1) to give the corresponding methyl ether derivative (1.21 g, 3.28 mmol, 97% yield) as white crystals: R_f = 0.7 (petroleum ether/EtOAc = 1:1); mp 76−78 °C; IR (film) ν_{max} 2920, 2874, 1684, 1425, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (1H, dt, J = 4.4 Hz, 12.4 Hz), 1.60−1.76 (4H, m), 1.63 (3H, s), 1.71 (3H, s), 1.92−1.97 (1H, m), 2.10−2.23 (2H, m), 2.21 (1H, s), 3.28 (1H, d, J = 9.2 Hz), 3.36 (3H, s), 3.38 and 3.46 (ABq, 2H, J = 11.6 Hz), 3.85 (1H, d, J = 9.2 Hz), 4.42−4.51 (3H, m), 5.17 (1H, t, J = 7.2 Hz), 7.22−7.36 (5H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 24.2, 24.4, 25.6, 30.1, 33.9, 46.3, 49.3, 53.0, 58.9, 58.91, 71.8, 81.5, 86.9, 124.0, 127.4, 127.8 (2C), 128.7 (2C), 131.5, 136.1, 171.7 ppm; HRMS (ESI) calcd for $C_{23}H_{32}NO_3$ 370.2377, found for $[M + H]^+$ 370.2381. (2) To a solution of liquid NH_3 (ca. 40 mL) were added portionwise chips of Na (935 mg, 40.65 mmol) at −78 °C with stirring. After the solution was stirred for 10 min at the same temperature, a mixture of the above prepared methyl ether (1.50 g, 4.07 mmol) in dry THF (20 mL) was added dropwise at −78 °C with stirring. The stirring was continued for 10 min at −78 °C. The mixture was quenched with satd aqueous NH_4Cl solution. The resulting mixture was stirred for 30 min at room temperature and extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (1:1) to give compound **8** (1.04 g, 3.74 mmol, 92% yield) as white crystals. Compound **8**: R_f = 0.4 (EtOAc); mp 136−139 °C; IR (film) ν_{max} 2965, 2917, 1687, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (1H, dt, J = 4.4 Hz, 12.4 Hz), 1.60 (3H, s), 1.68 (3H, s), 1.63−1.79 (4H, m), 1.91−1.99 (1H, m), 2.02−2.1 (1H, m), 2.1 (1H, s),

dx.doi.org/10.1021/jo300556r | J. Org. Chem. 2012, 77, 4217−4225

2.14−2.22 (1H, m), 3.28 (1H, d, J = 9.6 Hz), 3.34 (3H, s), 3.53 and 3.61 (ABq, 2H, J = 11.2 Hz), 3.78 (1H, d, J = 9.2 Hz), 4.47 (1H, d, J = 4.8 Hz), 5.16 (1H, dt, J = 1.6 Hz, 7.2 Hz), 6.20 (1H, br) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 24.3, 24.6, 25.7, 30.3, 34.1, 45.3, 53.0, 57.8, 58.9, 71.8, 81.6, 90.0, 124.4, 131.6, 175.4 ppm; HRMS (ESI) calcd for $C_{16}H_{26}NO_3$ 280.1907, found for $[M + H]^+$ 280.1911.

Ethyl 1-(Hydroxymethyl)-3-(methoxymethyl)-3-(4-methylpent-3-en-1-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxylate (9). To a mixture of lactam **8** (810 mg, 2.9 mmol) in HOAc (4 mL) and acetic anhydride (12 mL) was added sodium nitrite (600 mg, 8.7 mmol). The reaction mixture turned yellow immediately, and a brown gas escaped. After th emixture was stirred at rt for 30 min, the solvents were evaporated and the remaining solid was taken in EtOAc (100 mL) which was washed with saturated aqueous $NaHCO_3$ (4 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. To remove residual acetic acid from the crude product the reaction mixture was concentrated after the addition of toluene, providing sufficiently pure *N*-nitrosolactam. To a solution of this *N*-nitrosolactam in EtOH (6 mL) was added 3 mL of 1 M potassium hydroxide solution in ethanol (3.2 mmol). The resulting dark brown reaction mixture was stirred for 20 min at room temperature and then poured into saturated aqueous $NaHCO_3$ (5 mL) at 0 °C. The aqueous layer was extracted with EtOAc (2 × 50 mL), and the organic layers were washed with brine and subsequently dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (4: 1) to give compound **9** (624 mg, 1.91 mmol, 66% yield) as an oil. Compound **9**: R_f = 0.5 (petroleum ether/EtOAc = 1:1); IR (film) ν_{max} 3458, 2975, 2927, 1732, 1449, 1376, 1181, 1157, 1107, 1041, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7.2 Hz), 1.48−1.60 (2H, m), 1.61 (3H, s), 1.69 (3H, s), 1.69−1.1.79 (2H, m), 1.82−1.91 (2H, m), 1.94−1.99 (1H, m), 2.00−2.08 (1H, m), 2.34 (1H, s), 2.57 (1H, br), 3.32 (3H, s), 3.33 and 3.47 (ABq, 2H, J = 9.4 Hz), 3.86 (1H, d, J = 11.6 Hz), 4.04−4.14 (3H, m), 4.20 (1H, d, J = 5.2 Hz), 5.12 (1H, t, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 17.5, 23.5, 25.1, 25.6, 32.9, 34.5, 54.6, 58.6, 59.4, 60.2, 62.2, 71.9, 81.2, 88.2, 124.1, 131.6, 171.3 ppm; HRMS (ESI) calcd for $C_{18}H_{31}O_5$ 327.2166, found for $[M + H]^+$ 327.2161.

Ethyl 1-(Iodomethyl)-3-(methoxymethyl)-3-(4-methylpent-3-en-1-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxylate (10). To a solution of hydroxyl compound **9** (1.61 g, 4.94 mmol) in dry toluene (30 mL) were added Ph_3P (1.94 g, 1.94 mmol), imidazole (1.18 g, 17.3 mmol), and I_2 (1.88 g, 7.41 mmol). The mixture was heated to 60 °C and stirred for 25 min at this temperature, after which 2 mL of H_2O was added to quench the reaction. The aqueous layer was extracted with EtOAc (2 × 75 mL), and the organic layers were washed with satd $Na_2S_2O_3$ solution and brine and subsequently dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (15: 1) to give compound **10** (1.89 g, 4.35 mmol, 88% yield) as an oil. Compound **10**: R_f = 0.5 (petroleum ether/EtOAc = 4:1); IR (film) ν_{max} 2927, 2926, 1729, 1375, 1164, 1107 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, t, J = 7.2 Hz), 1.50 (1H, dt, J = 5.2 Hz, 13.2 Hz), 1.62 (3H, s), 1.71 (3H, s), 1.63−1.72 (1H, m), 1.74−1.82 (2H, m), 1.85−1.97 (3H, m), 2.04−2.10 (1H, m), 2.50 (1H, s), 3.22 (3H, s), 3.24 (1H, d, J = 9.2 Hz), 3.42 (2H, dd, J = 6.8 Hz, 9.2 Hz), 3.84 (1H, d, J = 9.6 Hz), 3.86−4.20 (2H, m), 4.38 (1H, d, J = 5.2 Hz), 5.12 (1H, t, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.2, 14.2, 17.6, 23.4, 25.4, 25.6, 34.5, 37.2, 55.1, 58.7, 59.7, 60.2, 71.8, 82.7, 87.0, 124.1, 131.7, 170.7 ppm; HRMS (ESI) calcd for $C_{18}H_{30}IO_4$ 437.1183, found for $[M + H]^+$ 437.1173.

3-(Hydroxymethyl)-2-(methoxymethyl)-4-methylene-2-(4-methylpent-3-en-1-yl)cyclohexanol (12). To a mixture of iodo compound **10** (1.0 g, 2.29 mmol) in EtOH (70 mL) and H_2O (2.8 mL) was added Zn dust (5.96 g, 91.7 mmol), and the mixture was refluxed for 1 h. After completion of the reaction, the mixture was filtered through a pad of Celite and washed with AcOEt (50 mL), and all of the solvent was evaporated to give the crude ester **11**. The resulting crude ester **11** was then taken in dry THF (20 mL), to which was added $LiAlH_4$ (522 mg, 13.74 mmol) portionwise at 0 °C. After being stirred for 1 h at room temperature, the mixture was quenched by addition of powdered $Na_2SO_4{\cdot}10H_2O$ and filtered through Celite. The residual cake was washed with AcOEt four times. The filtrate and washings were combined. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (5: 1) to give compound **12** (500 mg, 1.86 mmol, 81% yield) as an oil. Compound **12**: R_f = 0.3 (petroleum ether/EtOAc = 2:1); IR (film) ν_{max} 3259, 3068, 2930, 2810, 1644, 1449, 1108, 1104, 983, 889 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (1H, dt, J = 5.2 Hz, 12.4 Hz), 1.54 (1H, dt, J = 4.8 Hz, 12.4 Hz), 1.67 (3H, s), 1.71 (3H, s), 1.71−1.74 (2H, m), 1.79−1.90 (2H, m), 1.92−1.99 (1H, m), 2.04−2.12 (1H, m), 2.22−2.25 (1H, m), 2.50−2.58 (1H, m), 2.81 (1H, br), 3.34 (3H, s), 3.43 and 3.58 (ABq, 2H, J = 9.6 Hz), 3.72 (1H, dd, J = 3.6 Hz, 11.2 Hz), 3.79 (1H, t, J = 4.0 Hz), 3.88 (1H, dd, J = 3.6 Hz, 7.2 Hz), 4.79 (1H, s), 4.93 (1H, s), 5.08 (1H, t, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 21.5, 25.6, 28.6, 30.1, 33.8, 44.1, 51.2, 59.2, 62.0, 71.1, 75.7, 111.5, 124.2, 131.6, 147.1 ppm; HRMS (ESI) calcd for $C_{16}H_{29}O_3$ 269.2111, found for $[M + H]^+$ 269.2116.

3-(Hydroxymethyl)-2-(methoxymethyl)-4-methylene-2-(4-methylpent-3-en-1-yl)cyclohexyl Benzoate (13). To a solution of diol **12** (466 mg, 1.74 mmol) in DCM (8 mL) was added imidazole (266 mg, 3.92 mmol) and TBSCl (394 mg, 2.61 mmol). The mixture was stirred for 30 min and extracted with EtOAc (50 mL), and the organic layer was washed with H_2O and brine and subsequently dried over Na_2SO_4. After evaporation of the solvent, the residue was taken in dry DCM (8 mL) and Py (8 mL). To this solution were added DMAP (208 mg, 1.70 mmol) and BzCl (478 mg, 3.40 mmol). The mixture was brought to reflux, and the stirring was continued for 5 h. H_2O (2 mL) was added to quench the reaction. The mixture was extracted with EtOAc (2 × 50 mL) and the organic layers were washed with brine and subsequently dried over Na_2SO_4. After evaporation of the solvent, the residue was taken in wet DCM (15 mL), to which was added CF_3CO_2H (0.5 mL). After being stirred for 0.5 h, H_2O (5 mL) was added. The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic layers were washed with brine and subsequently dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (8: 1) to give compound **13** (485 mg, 1.305 mmol, 75% yield) as an oil. Compound **13**: R_f = 0.3 (petroleum ether/EtOAc = 4:1); IR (film) ν_{max} 3417, 2926, 2812, 1716, 1274, 1107, 712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (2H, t, J = 8.4 Hz), 1.59 (3H, s), 1.67 (3H, s), 1.82 (2H, br), 1.89−2.05 (3H, m), 2.16 (1H, td, J = 4.4 Hz, 14 Hz), 2.41−2.46 (2H, m), 3.27 (3H, s), 3.38 (2H, dd, J = 9.2 Hz, 12 Hz), 3.81 (1H, dd, J = 4.4 Hz, 10.8 Hz), 4.03 (1H, t, J = 10.0 Hz), 4.96 (1H, s), 5.05 (1H, s), 5.09 (1H, t, J = 7.2 Hz), 5.24 (1H, t, J = 3.6 Hz), 7.48 (2H, t, J = 8.0 Hz), 7.59 (1H, t, J = 7.6 Hz), 8.03 (2H, d, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 21.6, 25.7, 26.9, 27.1, 33.3, 43.8, 51.6, 59.2, 60.2, 71.7, 73.2, 113.7, 124.1, 128.6 (2C), 129.5 (2C), 130.3, 131.8, 133.1, 145.1, 165.8 ppm; HRMS (ESI) calcd for $C_{23}H_{33}O_4$ 373.2373, found for $[M + H]^+$ 373.2380.

3-Formyl-2-(methoxymethyl)-4-methylene-2-(4-methylpent-3-en-1-yl)cyclohexyl Benzoate (14). To a solution of alcohol **13** (305 mg, 0.82 mmol) in DCM (10 mL) was added DMP (869 mg, 2.05 mmol), and the mixture was stirred at room temperature for 30 min. After completion of the reaction, H_2O (3 mL) was added, the aqueous layer was extracted with EtOAc (2 × 40 mL), and the combined organic layers were washed with brine and subsequently dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (15: 1) to give compound **14** (279 mg, 0.75 mmol, 92% yield) as an oil. Compound **14**: R_f = 0.6 (petroleum ether/EtOAc = 4:1); IR (film) ν_{max} 2925, 2869, 1718, 1270, 1105, 712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (2H, m), 1.62 (3H, s), 1.69 (3H, s), 1.89−2.07 (4H, m), 2.29 (1H, d, J = 14 Hz), 2.60 (1H, dt, J = 6 Hz, 14 Hz), 3.07 (1H, s), 3.27 (3H, s), 3.46 and 3.56 (ABq, 2H, J = 9.6 Hz), 4.86 (1H, s), 5.08−5.11 (2H, m), 5.31 (1H, t, J = 2.8 Hz), 7.47 (2H, t, J = 7.6 Hz), 7.58 (1H, t, J = 7.2 Hz), 7.96 (2H, J = 7.2 Hz), 9.99 (1H, d, J = 2.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 21.5, 25.7, 26.2, 27.6, 33.1,

dx.doi.org/10.1021/jo300556r | J. Org. Chem. 2012, 77, 4217−4225

45.7, 59.1, 60.6, 71.7, 72.7, 115.2, 123.7, 128.6 (2C), 129.6 (2C), 130.0, 132.2, 133.2, 141.0, 165.8, 201.6 ppm; HRMS (ESI) calcd for $C_{23}H_{31}O_4$ 371.2217, found for $[M + H]^+$ 371.2212.

5β-Hydroxy-8a-(methoxymethyl)-4-methylene-6-(prop-1-en-2-yl)decahydronaphthalen-1-yl Benzoate (15) and 5α-Hydroxy-8a-(methoxymethyl)-4-methylene-6-(prop-1-en-2-yl)decahydronaphthalen-1-yl Benzoate (16). To a solution of aldehyde 14 (173 mg, 0.47 mmol) in dry DCM (10 mL) was added a solution of $ZnBr_2$ (105 mg, 0.47 mmol) in DCM (1.05 mL) at 0 °C under nitrogen atmosphere. After being stirred for 1 h at room temperature, H_2O (2 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic extracts were washed with brine and subsequently dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (15: 1) to give compound **15** (130 mg, 0.35 mmol, 75% yield) as white crystals and compound **16** (22 mg, 0.06 mmol, 13% yield) as white crystals. Compound **15**: R_f = 0.45 (petroleum ether/EtOAc = 4:1); mp 141−143 °C ; IR (film) ν_{max} 3402, 2926, 2853, 1716, 1450, 1270, 1110, 1097, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28−1.38 (1H, m), 1.48−1.50 (1H, m), 1.62−1.73 (1H, m), 1.84 (3H, s), 1.92−2.00 (3H, m), 2.10−2.14 (1H, m), 2.33−2.45 (2H, m), 3.42 (3H, s), 3.69 and 3.84 (ABq, 2H, J = 9.6 Hz), 4.16 (2H, d, J = 9.6 Hz), 4.23 (2H, d, J = 9.6 Hz), 4.74 (1H, s), 4.90 (1H, s), 4.95 (1H, dd, J = 4.4 Hz, 12.0 Hz), 5.01 (1H, d, J = 1.2 Hz), 5.46 (1H, J = 2.0 Hz), 7.45−7.49 (2H, m), 7.56−7.60 (1H, m), 8.04 (2H, dd, J = 1.2 Hz, 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 22.3, 28.1, 34.0, 34.2, 42.6, 49.6, 52.3, 59.4, 67.5, 73.5, 81.9, 110.6, 111.1, 128.4 (2C), 129.6 (2C), 130.4, 133.0, 144.7, 147.0, 165.9 ppm; HRMS (ESI) calcd for $C_{23}H_{30}NaO_4$ 393.2036, found for $[M + Na]^+$ 393.2032. X-ray crystallographic data of **15**:[13] $C_{23}H_{30}O_4$, FW 370.47, monoclinic, space group $P2(1)/c$, a = 14.6915(18) Å, b = 12.6135(16) Å, c = 11.3554(14) Å, α = 90°, β = 104.3130(10)°, γ = 90.00°, Z = 4, d_{calcd} = 1.207 g/cm^3, $R_1(I > 2\sigma(I))$ = 0.0454, wR_2 = 0.1112. Compound **16**: R_f = 0.3 (petroleum ether/EtOAc = 4:1); mp 91−94 °C; IR (film) ν_{max} 3526, 2932, 2891, 1714, 1272, 1111, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (1H, dt, J = 4.0 Hz, 12.8 Hz), 1.51 (1H, dd, J = 3.6 Hz, 13.6 Hz), 1.71−1.86 (5H, m), 1.96−2.02 (2H, m), 2.05−2.12 (2H, m), 2.28−2.32 (2H, m), 2.44 (1H, dd, J = 5.2 Hz, 13.2 Hz), 3.38 (3H, s), 3.53 and 3.60 (ABq, 2H, J = 10.2 Hz), 4.08 (1H, t, J = 10.0 Hz), 4.91 (3H, s), 4.99 (1H, dd, J = 4.8 Hz, 12.0 Hz), 5.07 (1H, s), 7.44 (2H, t, J = 7.6 Hz), 7.55 (1H, t, J = 7.4 Hz), 8.05 (2H, d, J = 8.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 25.5, 28.5, 32.9, 34.5, 44.6, 53.5, 59.4, 66.4, 72.0, 77.2, 80.6, 108.9, 112.8, 128.3 (2C), 129.7 (2C), 130.6, 132.8, 143.6, 146.9, 166.2 ppm; HRMS (ESI) calcd for $C_{23}H_{30}NaO_4$ 393.2036, found for $[M + Na]^+$ 393.2037.

8a-(Methoxymethyl)-4-methylene-5-oxo-6-(prop-1-en-2-yl)-decahydronaphthalen-1-yl Benzoate (12a). To a mixture of compound **15** or **16** (15 mg, 0.04 mmol) in DCM (1 mL) were added silica (40 mg) and PCC (33 mg, 0.154 mmol). After being stirred for 5 h under reflux, the reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (15: 1) to give compound **12a** (9 mg, 0.024 mmol, 61% yield) as white crystals. Compound **12a**: R_f = 0.65 (petroleum ether/EtOAc = 4:1); mp 144−146 °C ; IR (film) ν_{max} 2981, 2930, 2875, 2813, 1715, 1268, 1109, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (3H, s), 1.75−1.85 (3H, m), 2.05−2.20 (2H, m), 2.27−2.41 (3H, m), 2.77 (1H, s), 2.98 (1H, dd, J = 6.4 Hz, 12.8 Hz), 3.27 (3H, s), 3.65 (2H, dd, J = 9.6 Hz, 15.6 Hz), 4.73 (1H, s), 4.93 (1H, s), 5.15 (1H, dd, J = 4.8 Hz, 11.2 Hz), 5.20 (1H, s), 6.00 (1H, s), 7.46 (2H, t, J = 7.6 Hz), 7.59 (1H, t, J = 7.6 Hz), 8.02 (2H, d, J = 8.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 27.8, 29.0, 35.0, 35.4, 49.3, 55.3, 58.2, 59.3, 73.1, 79.7, 113.4, 114.2, 128.4 (2C), 129.6 (2C), 130.1, 133.1, 139.0, 144.2, 165.9, 205.3 ppm; HRMS (ESI) calcd for $C_{23}H_{28}NaO_4$ 391.1880, found for $[M + Na]^+$ 391.1874.

6-(2-Fluoropropan-2-yl)-5β-hydroxy-8a-(methoxymethyl)-4-methylenedecahydronaphthalen-1-yl Benzoate (15a) and 6-(2-Fluoropropan-2-yl)-5α-hydroxy-8a-(methoxymethyl)-4-methylenedecahydronaphthalen-1-yl Benzoate (16a). To a solution of aldehyde **14** (18 mg, 0.05 mmol) in dry DCM (3 mL) was added a solution of 1 M $BF_3{\cdot}Et_2O$/DCM (0.05 mL, 0.05 mmol) at −78 °C under nitrogen atmosphere. After the solution was stirred for 5 min at that temperature, saturated $NaHCO_3$ (1 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic extracts were washed with brine and subsequently dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (15: 1) to give compound **15a** (11 mg, 0.036 mmol, 70% yield) as white crystals and compound **16a** (2 mg, 0.005 mmol, 10% yield) as white crystals. Compound **15a**: R_f = 0.5 (petroleum ether/EtOAc = 4:1); mp 132−134 °C; IR (film) ν_{max} 3388, 2927, 2853, 1710, 1452, 1273, 1094, 1065, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30−1.40 (1H, m), 1.41 (3H, d, J = 22.8 Hz), 1.46 (3H, d, J = 22.8 Hz), 1.60−1.69 (2H, m), 1.81−1.89 (1H, m), 1.92−1.99 (2H, m), 2.02 (1H, s), 2.05−2.18 (1H, m), 2.32−2.43 (2H, m), 3.44 (3H, s), 3.70 and 3.81 (ABq, 2H, J = 9.4 Hz), 4.28 (1H, d, J = 10.4 Hz), 4.53 (1H, d, J = 10.4 Hz), 4.93 (1H, dd, J = 4.8 Hz, 12.0 Hz), 5.02 (1H, s), 5.44 (1H, d, J = 1.6 Hz), 7.47 (2H, t, J = 7.6 Hz), 7.59 (1H, t, J = 7.2 Hz), 8.03 (2H, d, J = 8.0 Hz) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.94 (d, J_{C-F} = 7.5 Hz), 24.9 (d, J_{C-F} = 24 Hz), 26.0 (d, J_{C-F} = 24 Hz), 28.1, 34.1, 34.3, 42.5, 52.1 (d, J_{C-F} = 19.5 Hz), 52.6, 59.5, 66.6 (d, J_{C-F} = 9 Hz), 73.9, 81.9, 98.2 (d, J_{C-F} = 165 Hz), 111.2, 128.5 (2C), 129.6 (2C), 130.3, 133.1, 144.5, 165.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −132.3 to −132.7 (m) ppm; HRMS (ESI) calcd for $C_{23}H_{32}FO_4$ 391.2280, found for $[M + H]^+$ 391.2276. Compound **16a**: R_f = 0.3 (petroleum ether/EtOAc = 4:1); mp 116−117 °C; IR (film) ν_{max} 3598, 3472, 3418, 2976, 2935, 2888, 1714, 1452, 1376, 1271, 1112, 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40−1.44 (1H, m), 1.43 (3H, d, J = 23.4 Hz), 1.48 (3H, d, J = 23.4 Hz), 1.55−1.60 (1H, m), 1.75−1.85 (3H, m), 2.03 (1H, d, J = 9.6 Hz), 2.06−2.12 (1H, m), 2.19−2.32 (2H, m), 2.42−2.46 (1H, m), 2.95 (1H, d, J = 20.0 Hz), 3.35 (3H, s), 3.49 and 3.58 (ABq, 2H, J = 10.2 Hz), 4.31 (1H, t, J = 9.6 Hz), 4.94 (1H, s), 4.97 (1H, dd, J = 4.8 Hz, 12.0 Hz), 5.08 (1H, s), 7.43 (2H, t, J = 8.0 Hz), 7.54 (1H, d, J = 7.2 Hz), 8.05 (2H, d, J = 8.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2 (d, J_{C-F} = 8 Hz), 23.5 (d, J_{C-F} = 25 Hz), 26.8 (d, J_{C-F} = 25 Hz), 29.6, 33.0, 34.6, 44.0, 52.1 (d, J_{C-F} = 16 Hz), 54.3, 59.4, 67.0, 72.2, 80.6, 101.6 (d, J_{C-F} = 160 Hz), 109.0, 128.3 (2C), 129.7 (2C), 130.6, 132.9, 143.2, 166.1 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −128.4 to −128.7 (m) ppm; HRMS (ESI) calcd for $C_{23}H_{32}FO_4$ 391.2280, found for $[M + H]^+$ 391.2258.

2-(Methoxymethyl)-6-methylene-2-(4-methylpent-3-en-1-yl)-3-oxocyclohexanecarbaldehyde (14a). To a solution of alcohol **12** (134 mg, 0.5 mmol) in DCM (8 mL) was added DMP (848 mg, 2 mmol), and the resulting mixture was stirred at room temperature for 30 min. After completion of the reaction, H_2O (3 mL) was added, the aqueous layer was extracted with EtOAc (2 × 40 mL), and the combined organic layers were washed with brine and subsequently dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (15: 1) to give compound **14a** (119 mg, 0.45 mmol, 90% yield) as an oil. Compound **14a**: R_f = 0.5 (petroleum ether/EtOAc = 4: 1); IR (film) ν_{max} 2965, 2923, 1783, 1718, 1447, 1382, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.55 (3H, s), 1.56−1.67 (6H, m), 1.90−1.95 (1H, m), 2.40−2.54 (4H, m), 3.26 (3H, s), 3.53 and 3.60 (ABq, 2H, J = 10 Hz), 3.70 (1H, s), 5.01−5.03 (1H, m), 5.15 (1H, s), 5.24 (1H, s), 9.57 (1H, d, J = 2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 21.9, 25.6, 30.1, 34.3, 37.9, 53.4, 59.1, 64.5, 70.3, 118.6, 123.1, 132.6, 137.1, 197.9, 210.4 ppm; HRMS (ESI) calcd for $C_{16}H_{24}NaO_3$ $[M + Na]^+$ 287.1618, found for 287.1622.

6-(2-Fluoropropan-2-yl)-5-hydroxy-8a-(methoxymethyl)-4-methyleneoctahydronaphthalen-1(2*H*)-one (15b). To a solution of aldehyde **14a** (13 mg, 0.05 mmol) in dry DCM (3 mL) was added a solution of 1 M $BF_3{\cdot}Et_2O$ in DCM (0.05 mL, 0.05 mmol) at −78 °C under nitrogen atmosphere. After the solution was stirred for 5 min at that temperature, saturated $NaHCO_3$ (1 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic extracts were washed with brine and subsequently dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with

dx.doi.org/10.1021/jo300556r | J. Org. Chem. 2012, 77, 4217−4225

petroleum ether/EtOAc (15:1) to give compound **15b** (10 mg, 0.035 mmol, 70% yield) as white crystals. Compound **15b**: R_f = 0.65 (petroleum ether/EtOAc = 2:1); mp 107−110 °C; IR (film) ν_{max} 3398, 2952, 2923, 2853, 1459, 1377, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27−1.36 (1H, m), 1.44 (3H, d, J = 23.0 Hz), 1.50 (3H, d, J = 23.0 Hz), 1.57−1.68 (1H, m), 1.72−1.78 (1H, m), 1.86 (1H, td, J = 3.6 Hz, 13.2 Hz), 1.99 (1H, s), 2.11 (1H, dt, J = 3.2 Hz, 14.0 Hz), 2.34−2.49 (3H, m), 2.62−2.73 (2H, m), 3.27 (3H, s), 3.67 (1H, dd, J = 1.2 Hz, 10.0 Hz), 3.92 (1H, d, J = 10.0 Hz), 4.61 (1H, s), 5.14 (1H, d, J = 1.2 Hz), 5.35 (1H, d, J = 1.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8 (d, J_{C-F} = 3 Hz), 26.0 ($2CH_3$, d, J_{C-F} = 25 Hz), 27.7, 35.7, 38.8, 50.1 (d, J_{C-F} = 19 Hz), 52.7, 53.3, 59.3, 67.8 (d, J_{C-F} = 3 Hz), 73.3, 99.4 (d, J_{C-F} = 160 Hz), 111.4, 143.3, 211.6 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −144.2 to −144.5 (m) ppm; HRMS (ESI) calcd for $C_{16}H_{26}FO_3$ 285.1861, found for $[M + H]^+$ 285.1857. X-ray crystallographic data of **15b**:[13] $C_{16}H_{25}FO_3$, FW 284.36, triclinic, space group P-1, a = 7.924(3)Å, b = 9.569(4) Å, c = 13.406(5) Å, α = 74.476(4)°, β = 80.638(4)°, γ = 77.042(4)°, Z = 2, d_{calcd} = 0.995 g/cm^3, $R_1(I > 2\sigma(I))$ = 0.0502, wR_2 = 0.1436.

5-Hydroxy-6-isopropyl-8a-(methoxymethyl)-4-methylene-decahydronaphthalen-1-yl Benzoate (17). To a solution of compound **15** (31 mg, 0.086 mmol) in benzene (5 mL) was added $Rh(PPh_3)_3Cl$ (16 mg, 0.017 mmol) and the mxiture degassed with hydrogen three times. The resulting mixture was stirred at 65 °C under hydrogen (1 atm) for 2.5 h. The solvent was removed in vacuo, and the residue was further purified by a flash column chromatography on silica gel with petroleum ether/EtOAc (20:1) to give compound **17** (22 mg, 0.059 mmol, 67% yield) as white crystals. Compound **17**: R_f = 0.5 (petroleum ether/EtOAc = 4:1); mp 125−128 °C; IR (film) ν_{max} 3412, 2923, 2853, 1719, 1269, 1103, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82−0.85 (1H, m), 0.86 (3H, d, J = 7.2 Hz), 0.99 (3H, d, J = 6.8 Hz), 1.28 (1H, dt, J = 5.2 Hz, 13.2 Hz), 1.50−1.69 (4H, m), 1.92−1.97 (2H, m), 2.01−2.06 (1H, m), 2.31−2.42 (2H, m), 3.41 (3H, s), 3.68 and 3.79 (ABq, 2H, J = 9.2 Hz), 4.20 (1H, d, J = 10.4 Hz), 4.38 (1H, d, J = 10.4 Hz), 4.92 (1H, dd, J = 4.8 Hz, 12.4 Hz), 5.02 (1H, s), 5.46 (1H, d, J = 1.6 Hz), 7.47 (2H, t, J = 7.8 Hz), 7.56−7.60 (1H, m), 8.03 (2H, d, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 20.9, 22.3, 28.1, 28.9, 34.2, 34.5, 42.2, 49.8, 52.4, 59.3, 66.9, 73.8, 82.1, 111.1, 128.4, 129.5, 130.3, 133.0, 145.0, 165.9 ppm; HRMS (ESI) calcd for $C_{23}H_{32}NaO_4$ 395.2193, found for $[M + Na]^+$ 395.2190.

8-Hydroxy-1-methyl-7-(prop-1-en-2-yl)octahydro-1*H*-1,4a-(epoxymethano)naphthalen-4-yl Benzoate (17a) and 8a-(Methoxymethyl)-4-methyl-6-(prop-1-en-2-yl)-1,2,6,7,8,8a-hexahydronaphthalen-1-yl Benzoate (17b).[21] (1) $AlCl_3$-mediated conditions: To a mixture of $AlCl_3$ (40 mg, 0.3 mmol) and $^nBu_4NI$ (111 mg, 0.3 mmol) in CH_3CN (1.5 mL) and Py (0.024 mL, 0.3 mmol) was added a solution of **15** (11 mg, 0.03 mmol) in CH_3CN (2 mL) at room temperature under nitrogen atmosphere. The mixture was stirred for 3 days, and water (0.5 mL) was added to quench the reaction. The mixture was extracted with EtOAc (2 × 15 mL), and the combined organic extracts were washed with brine and subsequently dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (petroleum ether/AcOEt = 20:1−8:1) to give compound **17a** (4 mg, 0.011 mmol, 38% yield) as an oil and **17b** (5 mg, 0.014 mmol, 45% yield) as a labile yellowish oil. (2) BBr_3-mediated conditions: To a solution of **15** (11 mg, 0.03 mmol) in DCM (2 mL) was added a solution of BBr_3 (0.15 mmol in 0.5 mL of DCM) at −78 °C under nitrogen atmosphere. After being stirred for 5 min at this temperature, saturated $NaHCO_3$ (1 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (2 × 15 mL), and the combined organic extracts were washed with brine and subsequently dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (petroleum ether/AcOEt = 20:1−8:1) to give compound **17a** (4 mg, 0.011 mmol, 38% yield) as an oil and **17b** (5 mg, 0.014 mmol, 45% yield) as a labile yellowish oil. Compound **17a**: R_f = 0.2 (petroleum ether/EtOAc = 4:1); IR (film) ν_{max} 3424, 2923, 2853, 1715, 1452, 1273, 1112, 1024, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35−1.46 (1H, m), 1.49 (3H, s), 1.54 (1H, d, J = 3.6 Hz), 1.58−1.68 (2H, m), 1.77−1.80 (1H, m), 1.83 (3H, s), 1.86−1.96 (4H, m), 2.05−2.16 (1H, m), 2.41 (1H, s), 3.99 (1H, d, J = 8.0 Hz), 4.17 (2H, d, J = 8.0 Hz), 4.81 (1H, s), 4.95 (1H, s), 5.00 (1H, dd, J = 6.0 Hz, 10.4 Hz), 7.45 (2H, t, J = 8.0 Hz), 7.57 (1H, t, J = 7.6 Hz), 8.02 (2H, d, J = 8.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 20.5, 22.6, 25.9, 27.1, 39.1, 46.7, 48.2, 53.3, 65.9, 70.6, 79.6, 83.0, 111.4, 128.4 (2C), 129.6 (2C), 130.3, 133.0, 146.7, 166.1 ppm; HRMS (ESI) calcd for $C_{22}H_{29}O_4$ 357.2060, found for $[M + H]^+$ 357.2064. Compound **17b**: R_f = 0.7 (petroleum ether/EtOAc = 4:1); IR (film) ν_{max} 3412, 2928, 2874, 2812, 1716, 1450, 1274, 1112, 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (1H, td, J = 4.0 Hz, 9.2 Hz), 1.74 (3H, s), 1.81 (3H, s), 2.30 (2H, dt, J = 3.6 Hz, 13.2 Hz), 2.39−2.51 (1H, m), 2.60 (2H, dt, J = 5.6 Hz, 16.8 Hz), 2.90 (1H, t, J = 8.4 Hz), 3.38 (3H, s), 3.50 and 3.68 (ABq, 2H, J = 10.2 Hz), 4.77 (2H, d, J = 6.4 Hz), 5.08 (1H, dd, J = 6.0 Hz, 10.4 Hz), 5.48 (1H, d, J = 4.4 Hz), 5.68 (1H, d, J = 2.4 Hz), 7.44 (2H, t, J = 7.6 Hz), 7.55 (1H, t, J = 7.6 Hz), 8.10 (2H, d, J = 8.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 20.3, 24.0, 29.1, 29.6, 41.4, 44.4, 59.6, 74.1, 77.7, 110.0, 121.5, 128.2 (2C), 128.3, 128.5, 129.8 (2C), 132.6, 132.8, 137.6, 149.5, 166.3 ppm.

5-Hydroxy-8a-(hydroxymethyl)-6-isopropyl-4-methylenede-cahydronaphthalen-1-yl Benzoate (18). An n-heptane solution of $Me_2AlSeMe$ (1 M) was prepared similarly to the procedure of Corey and co-workers.[23] To dry Se powder (440 mg, 5.5 mmol) was added a 1 M solution of Me_3Al in n-heptane (5 mL, 5 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was refluxed for 5 h, cooled to room temperature, and kept for 2 h. This freshly prepared clear solution was used directly in the following demethylation reaction. Thus, to a mixture of **17** (12 mg, 0.032 mmol) in dry DCM (2.5 mL) was added a freshly prepared 1 M solution of $Me_2AlSeMe$ in n-heptane (0.32 mL, 0.32 mmol) at room temperature under nitrogen atmosphere. The mixture was then refluxed for 3 h, to which was added powdered $Na_2SO_4{\cdot}10H_2O$ portionwise at 0 °C to quench the reaction. The mixture was extracted with EtOAc (2 × 20 mL), and the combined organic extracts were washed with brine and subsequently dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (8:1) to give compound **18** (9 mg, 0.026 mmol, 80% yield) as white crystals: R_f = 0.2 (petroleum ether/EtOAc = 4:1); mp 117−119 °C; IR (film) ν_{max} 3300, 2927, 2853, 1716, 1272, 1112, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, d, J = 6.8 Hz), 0.95−1.00 (1H, m), 1.01 (3H, d, J = 6.8 Hz), 1.18−1.26 (2H, m), 1.55−1.65 (4H, m), 1.90−2.05 (4H, m), 2.31−2.44 (1H, m), 2.45−2.50 (1H, m), 3.98 and 4.09 (ABq, 2H, J = 11.6 Hz), 4.45 (1H, s), 4.94 (1H, dd, J = 5.8 Hz, 11.2 Hz), 4.98 (1H, d, J = 1.2 Hz), 5.17 (1H, d, J = 1.6 Hz), 7.45 (2H, t, J = 7.6 Hz), 7.55−7.59 (1H, m), 8.03 (2H, d, J = 1.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 21.0, 21.9, 28.1, 28.8, 33.6, 34.0, 42.9, 49.3, 51.7, 63.4, 67.7, 82.1, 109.2, 128.4 (2C), 129.6 (2C), 130.3, 133.0, 146.1, 166.0 ppm; HRMS (ESI) calcd for $C_{22}H_{30}NaO_4$ 381.2042, found for $[M + Na]^+$ 381.2021.

5-Hydroxy-6-isopropyl-4-methylene-8a-(((methylsulfonyl)-oxy)methyl)decahydronaphthalen-1-yl Benzoate (19). To a mixture of **18** (6 mg, 0.017 mmol) in dry DCM (2 mL) were added Et_3N (0.05 mmol, 0.007 mL) and a 0.5 M solution of MsCl in DCM (0.07 mL, 0.034 mmol) at 0 °C under nitrogen atmosphere. After the mixture was stirred for 10 min, H_2O (1 mL) was added. And the mixture was extracted with EtOAc (2 × 15 mL), the combined organic extracts were washed with brine and subsequently dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (8: 1) to give compound **19** (6 mg, 0.014 mmol, 83% yield) as white crystals: R_f = 0.4 (petroleum ether/EtOAc = 2:1); mp 138−140 °C; IR (film) ν_{max} 3552, 2938, 2870, 1712, 1351, 1275, 1173, 1116, 979, 954, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, d, J = 6.4 Hz), 0.99 (3H, d, J = 6.8 Hz), 1.23−1.28 (2H, m), 1.48−1.69 (5H, m), 1.98−2.05 (2H, m), 2.21 (1H, td, J = 3.2 Hz, 10.8 Hz), 2.36 (1H, dt, J = 6.0 Hz, 13.6 Hz), 2.50 (1H, td, J = 2.4 Hz, 12.0 Hz), 3.01 (3H, s), 4.42 (1H, s), 4.53 (1H, d, J = 10.8 Hz), 4.99 (1H, s), 5.02 (1H, t,

dx.doi.org/10.1021/jo300556r | J. Org. Chem. 2012, 77, 4217−4225

J = 5.6 Hz), 5.06 (1H, d, J = 10.8 Hz), 5.13 (1H, s), 7.45 (2H, t, J = 7.6 Hz), 7.56 (1H, t, J = 7.6 Hz), 8.12 (2H, d, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.4, 21.0, 27.8, 28.6, 31.9, 33.9, 36.9, 42.5, 49.6, 51.3, 67.7, 68.8, 80.6, 109.8, 128.4 (2C), 129.9 (2C), 130.2, 133.1, 144.3, 166.3 ppm; HRMS (ESI) calcd for $C_{23}H_{36}NO_6S$ 454.2258, found for $[M + NH_4]^+$ 454.2246.

(±)-6β,14-Epoxyeudesm-4(15)-en-1β-ol (1). To a mixture of **19** (4 mg, 0.009 mmol) in MeOH (0.5 mL) was added a methanol solution of NaOMe (0.28 mL, 0.1 M, 0.028 mmol) at room temperature. After the mixture was stirred for 3 h at 45 °C, H_2O (0.5 mL) was added to the reaction mixture. The resulting mixture was extracted with EtOAc (2 × 15 mL), and the combined organic extracts were washed with brine and subsequently dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (6:1) to give compound **1** (2 mg, 0.008 mmol, 88% yield) as white crystals: R_f = 0.4 (petroleum ether/EtOAc = 2:1); mp 88−90 °C; IR (film) ν_{max} 3406, 2932, 2868, 1450, 1013, 889, 846, 666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.892 (3H, d, J = 6.8 Hz), 0.963 (3H, d, J = 6.8 Hz), 1.063 (1H, ddd, J = 13.6, 8.4, 5.2 Hz), 1.30−1.47 (3H, m), 1.59−1.65 (2H, m), 1.75−1.81 (1H, m), 1.93−1.98 (1H, m), 1.99 (1H, br s), 2.02−2.09 (1H, m), 2.14−2.19 (1H, m), 2.38 (1H, td, J = 3.4 Hz, 12.8 Hz), 3.61 (1H, d, J = 8 Hz), 3.82 (1H, dd, J = 8 Hz, 2.0 Hz), 3.84 (1H, dd, J = 11.6, 5.6 Hz), 4.57 (1H, s), 4.89 (2H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 20.9, 23.5, 30.4, 32.7, 33.6, 35.7, 49.1, 49.6, 54.0, 69.8, 74.2, 77.6, 107.3, 144.0 ppm; HRMS (ESI) calcd for $C_{15}H_{24}NaO_2$ 259.1669, found for $[M + Na]^+$ 259.1674.

■ ASSOCIATED CONTENT

Supporting Information

Detailed tabular X-ray crystallographic data and CIF files for **7**, **15**, and **15b**, copies of ^{1}H and ^{13}C NMR spectra for compounds **3**−**10**, **12**−**19**, **12a**, **14a**, **15a**,**b**, **16a**, **17a**,**b**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel/Fax: 0086-(0)22-23494613. E-mail: wdli@nankai.edu.cn.

■ ACKNOWLEDGMENTS

We are grateful to Miss Yu-Jie Liu (Lanzhou University) for technical assistance during the early stage of this research. We thank the National Natural Science Foundation (21132006) for financial support. The Cheung Kong Scholars program and the Outstanding Scholars program of Nankai University are gratefully acknowledged.

■ REFERENCES

(1) For general reviews on sesquiterpene synthesis, see: (a) Heathcock, C. H. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1973; Vol. 2, pp 197−558. (b) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1983; Vol. 5. (c) Spivey, A. C.; Weston, M.; Woodhead, S. *Chem. Soc. Rev.* **2002**, *31*, 43.

(2) Wu, Q.-X.; Shi, Y.-P.; Jia, Z.-J. *Nat. Prod. Rep.* **2006**, *23*, 699.

(3) For general reviews, see: (a) Munoz, O.; Penazola, A.; Gonzales, A. G.; Ravelo, A. G.; Bazzocchi, I. L.; Alvarenga, N. L. In *Studies in Natural Product Chemistry*; Atta-ür-Rahman, Ed.; Elsevier Science Publisher: Amsterdam, 1996; Vol. *18*, pp 739−783. (b) Fraga, B. M. *Nat. Prod. Rep.* **2007**, *24*, 1350.

(4) (a) Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289. (b) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824.

(5) (a) Zhang, Z.; Li, W.-D. Z.; Li, Y.-L. *Org. Lett.* **2001**, *3*, 2555. (b) Li, W.-D. Z.; Gao, Z.-H. *Org. Lett.* **2005**, *7*, 2917.

(6) For recent reviews on the natural occurrence and synthetic utilities of the 7-oxabicyclo[2.2.1]heptane derivatives, see: (a) Vogel, P.; Cossy, J.; Plumet, J.; Arjona, O. *Tetrahedron* **1999**, *55*, 13521. (b) Schindler, C. S.; Carreira, E. M. *Chem. Soc. Rev.* **2009**, *38*, 3222.

(7) Xue, Y.-P.; Li, W.-D. Z. *J. Org. Chem.* **2011**, *76*, 57.

(8) For a review on agarofuran sesquiterpenoids, see: (a) Gao, J.-M.; Wu, W.-J.; Zhang, J.-W.; Konishi, Y. *Nat. Prod. Rep.* **2007**, *24*, 1153. For a notable synthetic approach, see: (b) White, J. D.; Shin, H.; Kim, T.-S.; Cutshall, N. S. *J. Am. Chem. Soc.* **1997**, *119*, 2404.

(9) For a seminal work, see: (a) Parker, K. A.; Adamchuk, M. R. *Tetrahedron Lett.* **1978**, *19*, 1689. For reviews, see: (b) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (c) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179. For recent examples, see: (d) Murali, R.; Scheeren, H. W. *Tetrahedron Lett.* **1999**, *40*, 3029. (e) Murali, R.; Rao, H. S. P.; Scheeren, H. W. *Tetrahedron* **2001**, *57*, 3165. (f) Boonsompat, J.; Padwa, A. *J. Org. Chem.* **2011**, *76*, 2753 and references cited therein.

(10) Iijima, T.; Yaoita, Y.; Kikuchi, M. *Chem. Pharm. Bull.* **2003**, *51*, 545.

(11) Prepared by an analogous procedure according to: Scholte, A. A.; Eubanks, L. M.; Poulter, C. D.; Vederas, J. C. *Bioorg. Med. Chem.* **2004**, *12*, 763.

(12) Ammonolysis of **3** and the subsequent IMDAF were fast and reversible at higher temperature, which will lead to thermodynamic rearrangement of **4** to **5** according to Scheeren's study (ref 9e). In fact, the cycloadduct **4** will isomerized gradually to adduct **5** even at room temperature.

(13) See the Supporting Information for detailed X-ray crystallographic data.

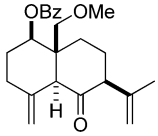
(14) (a) Kim, M. Y.; Starrett, J. E., Jr.; Weinreb, S. M. *J. Org. Chem.* **1981**, *46*, 5383. (b) Webster, F. X.; Millar, J. G.; Silverstein, R. M. *Tetrahedron Lett.* **1986**, *27*, 4941.

(15) Benningshof, J. C. J.; Blaauw, R. H.; van Ginkel, A. E.; van Maarseveen, J. H.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1693.

(16) (a) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990. (b) Yadav, J. S.; Sreedhar, P.; Srihari, P.; Sarma, G. D.; Jagadeesh, B. *Synthesis* **2008**, 1460.

(17) For previous examples, see: (a) Schwartz, M. A.; Growell, J. D.; Musser, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 4361. (b) Marshall, J. A.; Wuts, P. G. M. *J. Am. Chem. Soc.* **1978**, *100*, 1627.

(18) Oxidation of **15** and **16** with PCC led to the *same* 6-keto product **12a**.

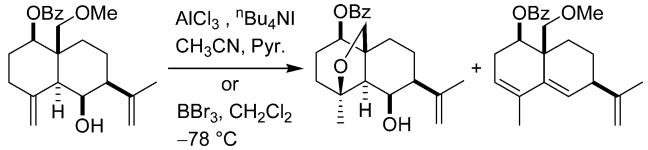


12a

(19) For a general review on the Prins reaction, see: (a) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 527−561. For recent examples, see: (b) Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2008**, *130*, 13177. (c) Luo, H.-Q.; Hu, X.-H.; Loh, T.-P. *Tetrahedron Lett.* **2010**, *51*, 1041 and references therein. We are grateful to one of the reviewer's critical corrections on the structural characterization of **15a** and **16a**.

(20) (a) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711. (b) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917.

(21) Other attempted *O*-demethylation of **15** with $AlCl_3$ (i.e., Akiyama, T.; Shima, H.; Ozaki, S. *Tetrahedron Lett.* **1991**, *32*, 5593) or BBr_3 led to a product mixture of cyclic ether **17a** and *labile* dehydration product **17b**[22] in moderate yields:



15 **17a** (30~45%) **17b** (40~45%)

(22) For similar 1β-hydroxyeudesm-3,5-diene derivatives, see: (a) Cabrera, E.; Garcia-Granados, A.; Quecuty, M. A. *Phytochemistry* **1988**, *27*, 183. (b) Weyerstahl, P.; Marschall, H.; Splittgerber, U.; Wolf, D. *Flavour Fragr. J.* **2000**, *15*, 153.
(23) Prepared according to: Kozikowski, A. P.; Ames, A. *J. Org. Chem.* **1978**, *43*, 2735. For an analogous preparation of $Me_2AlTeMe$ as a reagent chemical and use in organic synthesis, see: Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Tetrahedron Lett.* **2005**, *46*, 4589.
(24) (a) Biernacki, W.; Gdula, A. *Synthesis* **1979**, 37. (b) Enders, D.; Schüßeler, T. *Synthesis* **2002**, 2280.