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Practical and Versatile Syntheses of Angular Hydroxymethylated Decalones

Young-Ger Suh*, Hwa-Soon Kim, P. Raja kumar, Nam-Song Choi, and Jae-Kyung Jung

College of Pharmacy, Seoul National University, San 56-1, Shinrim-Dong
Kwanak-Gu, Seoul 151-742, Korea

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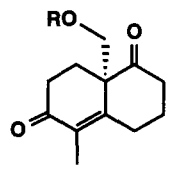
Abstract: The practical and versatile syntheses of angular hydroxymethylated decalones as potential synthetic intermediates for terpenoids are described. Particularly angular hydroxymethylated bicyclodecanedione **1** has been synthesized in 45 % overall yield from methyl 2,6-dimethoxy-1,4-dihydrobenzoate *via* six step sequence.

The angular hydroxymethylated decalones have been importantly utilized as the versatile synthetic intermediates in many biologically or structurally interesting natural products.[1] Accordingly, synthesis of the highly functionalized decalins with angular hydroxymethyl group continues to be current research objective[2] due to the versatile synthetic utilities of the angular hydroxymethyl group such as modulations of stereo and regiochemistries as well as its functional diversity although the chemistries related to the angular methylated decalins are quite well established.[3] The excellent synthetic utilization of the angular hydroxymethyl group has been also demonstrated in steroid chemistry.[4]



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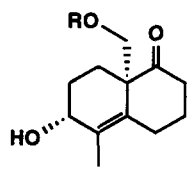

2

R = H or TBS

In conjuction with the syntheses of bioactive terpenoids as our ongoing project, we have looked for a practical and concise synthetic route to the angular hydroxymethylated decalones **1** and **2** which are highly potential intermediates in a wide range of terpenoid syntheses. However, a few previously reported procedures for angular hydroxymethylated decalones were considered to have limitations for a wide synthetic utility in terms of yield, reproductivity, conciseness or large scale operation. In this regard, we have initially developed a significantly efficient procedure for the known intermediate **7** by modification of Mander's procedure.[2c] The ester **7** could be conveniently obtained from the dihydrobenzoate **3a** rather than **3b** by only three step sequence. Treatment of the ester enolate of **3a** with silyloxyallyl iodide **4**,[5] followed by desilylation using tetrabutylammonium fluoride afforded the alkylation product **5**. Upon treatment of **5** with *p*-toluenesulfonic

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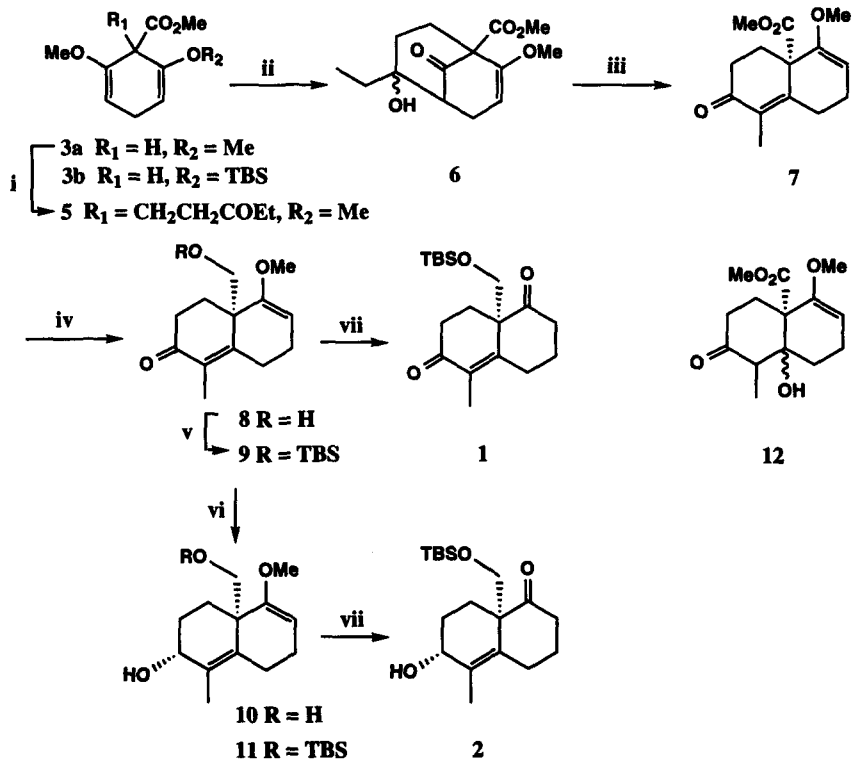
acid, the initial aldol product **6** as a diastereomeric mixture was obtained in an almost quantitative yield.[6] It is noteworthy that these reaction conditions selectively demethylate one of the two enol ether groups of **5** and the extra steps required for selective monosilyl ether protection for the silyl ether **3b**[2c] are consequently avoided. The difficult conversion of aldol **6** to enone **7** which limits the utilities of this approach was successfully achieved by employing K_2CO_3 in the presence of molecular sieves. The presence of pulverized 4 Å molecular sieves for dehydration of the recyclized product **12** was found to be crucial[7] for high yield. Moreover, the reluctant dehydration of the undesired isomer due to the unfavorable stereochemistry for dehydration has been overcome by development of this procedure.[8] For the conversion of keto ester **7** to the desired decalone **1**, the ester function of **7** was directly reduced to alcohol without protecting keto group. Treatment of **7** with LDA followed by DIBAL reduction of the resulting enolate anion afforded the keto alcohol **8** in 80 % yield along with the diol **10**. Employing excess LDA or variation of the reaction temperature did not eliminate the formation of the diol **10**. Protection of the keto alcohol **8** with TBSCl followed by reduction of the resulting keto ether **9** with $NaBH_4$ in the presence of $CeCl_3.7H_2O$ provided the alcohol **11** as a single diastereomer.[9] Finally, demethylation of **9** and **11** with *p*-toluenesulfonic acid in acetone at 0 °C gave the decalones **1** and **2** in almost quantitative yield.



Scheme 1. Reagents and conditions: i) LDA, THF, -70 °C, EtC(OTMS)=$CHCH_2I$ (**4**) / CH_3CN, workup then *n*-Bu_4NF, THF, 75 % ii) PTSA, acetone, 0 °C, 92 % iii) K_2CO_3, MeOH, pulverized 4 Å molecular sieves, 86 % iv) LDA, DIBAL, toluene / hexane (1 : 1), -20 °C, 80 % v) TBSCl, imidazole, DMF, 100 % vi) $NaBH_4$, $CeCl_3.7H_2O$, EtOH, 0 °C, 99 % vii) PTSA, acetone, 0 °C, 94 % for **1**, 95 % for **2**

In conclusion, we have developed a concise and practical syntheses of the angular hydroxymethylated decalones **1** and **2** which are highly useful synthetic intermediates. It should be also noted that these syntheses could be carried out even in decagram scale.

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EXPERIMENTAL

Unless noted otherwise, all reactions were performed under an argon atmosphere. Column chromatography was performed using silica gel 60 (230-400 mesh, Merck) with indicated solvents. Melting points were measured on a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. ^{1}H and ^{13}C-NMR spectra were recorded on either a JEOL JNM-GCX 400 or JEOL JNM-LA 300 spectrophotometer as solutions in deuteriochloroform ($CDCl_3$). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated chloroform ($CHCl_3$). MS spectra were obtained on VG Trio-2 GC-MS instrument. High resolution MS spectra were obtained on HP 5890 Series II.

Methyl 2,6-dimethoxy-1-(3'-oxopentyl)-2,5-cyclohexadiene-1-carboxylate (5) To a stirred solution of diisopropyl amine (3.7 ml, 28.2 mmol) in THF (60 ml) at -78 °C was slowly added *n*-butyllithium (16.6 ml of 1.6 M in hexane, 26.5 mmol). After stirring for 30 min, a solution of methyl 2,6-dimethoxy-2,5-cyclohexadiene-1-carboxylate (**3**)[2c] (4.38 g, 22.1 mmol) in THF (75 ml) was added and then the reaction mixture was stirred for further 2 h at the same temperature. In the meantime, 1-iodo-3-trimethylsiloxypent-2-ene (**4**) as the alkylating agent was prepared as follows. To a solution of anhydrous sodium iodide (6.50 g, 43.4 mmol) in dry CH_3CN (60 ml) was added ethyl vinyl ketone (4.5 ml, 45.0 mmol). After stirring for 15 min, chlorotrimethylsilane (5.2 ml, 41.0 mmol) was added and the reaction mixture was stirred for another 15 min to give **4** a pale yellow solution. The iodopentene **4** was added to the reaction mixture at -78 °C and stirred for 1 h. The resulting reaction mixture was then added to water (100 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic layer was washed with water (3 x 20 ml) and brine (3 x 30 ml), dried over $MgSO_4$ and concentrated. The residue was chromatographed (ethyl acetate-hexane, 1 : 6) to give 12 g of the crude alkylation product. The enol silyl ether as an alkylation product was dissolved in THF (100 ml) and treated with tetrabutylammonium fluoride (30.0 ml of 1.0 M solution in THF, 30.0 mmol) at 20 °C for 5 min. After normal workup with ethyl acetate followed by chromatography (ethyl acetate-hexane, 1 : 4) afforded **5** as a white solid (4.68 g, 75 %, two steps). mp109 °C (*lit.*[2c], mp108-109 °C).

***Exo*- and *endo*-Methyl 6-ethyl-6-hydroxy-2-methoxy-9-oxobicyclo[3.3.1]non-2-ene-1-carboxylate (6)** To a solution of PTSA (0.1 g, catalytic amount) in acetone (100 ml) at 0 °C was slowly added the keto ester **5** (5.4 g, 19.2 mmol) in several portions and stirred for 12 h at the same temperature. After addition of saturated $NaHCO_3$ solution (20 ml), the mixture was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was washed with water (2 x 20 ml) and brine (2 x 30ml), dried over $MgSO_4$ and concentrated to give a pale yellow oil. The residue was chromatographed (ethyl acetate-hexane, 1 : 2) to afford the *exo* isomer as a white solid (4.15 g, 81 %; mp139 °C, *lit.*[2c] mp137-139 °C) and the *endo* isomer (580 mg, 11 %) as a colorless oil. The unseparated ketol mixture **6** can be routinely obtained in 92 to 95% yields.

Methyl 4-methoxy-8-methyl-7-oxo-1,5,6,7-tetrahydro-4a(2*H*)-naphthalenecarboxylate (7) The diastereomeric mixture of **6** (4.0 g, 14.9 mmol) and anhydrous K_2CO_3 (740 mg, 5.35 mmol) and freshly pulverized 4 Å molecular sieves (2.0 g) in dry MeOH (80 ml) was stirred at room temperature for 2 days. The reaction mixture was filtered over celite, diluted with water (150 ml) and then extracted with ethyl acetate (3 x 100 ml). The combined extracts were washed with brine (2 x 30 ml), dried over $MgSO_4$ and concentrated to give a yellow oil, which was chromatographed (ethyl acetate-hexane, 1 : 4) to afford **7** (3.2 g, 86 %) as a white solid. mp 85 °C (*lit.*[2c], mp 84-85 °C).

4a-(Hydroxymethyl)-5-methoxy-1-methyl-4,4a,7,8-tetrahydro-2(3*H*)-naphthalenone (8) To a stirred solution of diisopropyl amine (1.4 ml, 10.2 mmol) in a mixture of toluene-hexane (6 ml of 1 : 1 mixture) at -20 °C was slowly added *n*-butyl lithium (6.2 ml of 1.6 M solution in hexane, 9.9 mmol) and the mixture was stirred for 30 min. A solution of the enone ester **7** (1.0 g, 4.0 mmol) in a mixture of toluene-hexane (14 ml of 1 : 1 mixture) was added and the reaction mixture was stirred for an additional 1 h at the same temperature. After addition of DIBAL (8.8 ml of 1 M solution in toluene, 8.8 mmol), the mixture was stirred at - 20 °C for 1 h and then quenched with water (10 ml). The mixture was extracted with ethyl acetate (3 x 100 ml) and the combined organic layer was washed with brine (2 x 50 ml), dried over $MgSO_4$ and concentrated to give a pale yellow oil, which was chromatographed (ethyl acetate-hexane, 1 : 5 to 1 : 2) to give **8** (710 mg, 80 %) as a white solid and the diol **10** (160 mg, 18 %) as an oil. **Keto alcohol 8** mp 106-108 °C. IR (neat): 3330, 1675, 1640, 1470 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.84 (m, 1H), 3.86 (dd, 1H, J = 11.0, 4.6 Hz), 3.79 (dd, 1H, J = 11.0, 8.0 Hz), 3.54 (s, 3H), 2.81-2.77 (m, 1H), 2.65-2.52 (m, 2H), 2.46-2.01 (m, 4H), 1.80 (s, 3H), 1.77-1.64 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 198.3, 158.1, 157.6, 130.2, 94.6, 68.4, 54.8, 45.6, 33.6, 28.4, 27.2, 22.8, 10.9. MS (EI) *m/z*: 222 (M^+), 191, 177, 163, 149, 131, 115, 105, 91, 77. HRMS (EI) Calcd for $C_{13}H_{18}O_3$: 222.1256, Found: 222.1257. **Diol 10** IR (neat): 3260, 2980, 2960, 1660, 1640, 1480 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.67 (d, 1H, J = 6.8 Hz), 3.98 (br t, 1H, J = 7.2 Hz), 3.69 (q, 2H, J = 10.8 Hz), 3.46 (s, 3H), 2.52-1.18 (m, 8H), 1.71 (s, 3H). ^{13}C-NMR NMR ($CDCl_3$, 75 MHz): δ 157.6, 134.9, 131.1, 95.9, 70.9, 68.5, 55.0, 49.3, 26.7, 25.9, 24.8, 20.2, 11.4. MS (EI) *m/z*: 224 (M^+), 206, 193, 176, 161, 143, 128, 115, 105, 91, 77. This diol was fully characterized as *tert*-butyldimethylsilyl ether **11**.

4a-({[*tert*-Butyldimethylsilyl]oxy}methyl)-5-methoxy-1-methyl-4,4a,7,8-tetrahydro-2(3*H*)-naphthalenone (9) To a stirred solution of the keto alcohol **8** (320 mg, 1.44 mmol), imidazole (240 mg, 3.53 mmol) in dry DMF (5 ml) was added *tert*-butyldimethylsilyl chloride (256 mg, 1.70 mmol) and the reaction mixture was further stirred for 18 h at room temperature. After addition of water (20 ml), the mixture was extracted with ethyl acetate (2 x 50 ml). The combined organic layer was washed with water (2 x 10 ml) and brine (2 x 20 ml), dried over $MgSO_4$ and concentrated. The residue was chromatographed (ethyl acetate-hexane, 1 : 15) to give **9** (485 mg, 100 %) as a white solid. mp 42 °C. IR (neat): 2980, 2970, 1675, 1480 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.74 (dd, 1H, J = 5.6, 1.6 Hz), 3.89 (q, 2H, J = 11.2 Hz), 3.47 (s, 3H), 2.77-2.68 (m, 2H), 2.41-2.25 (m, 4H), 2.15-1.80 (m, 2H), 1.83 (s, 3H), 0.81 (s, 9H), 0.08 (s, 6H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 198.9, 158.4, 157.3, 130.0, 93.7, 68.9, 54.5, 45.9, 34.2, 30.6, 27.0, 25.7, 22.9, 18.0, 10.9, -5.7, -5.8. MS (EI) *m/z*: 336 (M^+), 321, 306, 279, 264, 249, 217, 191, 163, 131, 115, 89. HRMS (EI) Calcd for $C_{19}H_{32}O_3Si_1$: 336.2121, Found: 336.2121.

4a-({[*tert*-Butyldimethylsilyl]oxy}methyl)-5-methoxy-1-methyl-2,3,4,4a,7,8-hexahydro-2-naphthalenol (11) To a solution of the enone **9** (200 mg, 0.60 mmol) and $CeCl_3.7H_2O$ (177 mg, 0.48 mmol) in ethanol (20 ml) at 0 °C was added $NaBH_4$ (28 mg, 0.74 mmol). After stirring for 2 h, the reaction

mixture was warmed up to room temperature and then quenched with saturated NH_4Cl solution (10 ml). The reaction mixture was extracted with ether (3 x 50 ml) and the combined organic layer was washed with water (2 x 20 ml) and brine (10 ml), dried over $MgSO_4$ and concentrated. The residue was chromatographed (ethyl acetate-hexane, 1 : 5) to give the allylic alcohol **11** (200 mg, 99 %) as a colorless waxy solid. mp 74 °C. IR (neat): 3315 (broad), 2930, 2836, 1669, 1452 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.65 (dd, 1H, J = 5.9, 2.4 Hz), 3.90 (br s, 1H), 3.68 (q, 2H, J = 9.3 Hz), 3.42 (s, 3H), 2.51 (dd, 1H, J = 6.0, 3.9 Hz), 2.16-1.90 (m, 4H), 1.79 (s, 3H), 1.73-1.63 (m, 4H), 0.82 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 157.9, 134.1, 130.1, 94.5, 70.4, 69.6, 54.3, 45.5, 29.2, 25.9, 25.3, 23.9, 23.8, 18.3, 16.0, -5.5, -5.6. MS (EI) *m/z*: 338(M^+), 320, 263, 175, 159, 143. HRMS (EI) Calcd for $C_{19}H_{34}O_3Si_1$: 338.2277, Found: 338.2284.

8a-({[*tert*-Butyldimethylsilyl]oxy}methyl)-5-methyl-3,4,8,8a-tetrahydro-1,6(2*H*,7*H*)-naphthalenedione (1) To a solution of enol ether **9** (106 mg, 0.32 mmol) in acetone (3 ml) at 0 °C was added PTSA (5 mg, catalytic amount) and the reaction mixture was stirred for 30 min at the same temperature. After addition of saturated $NaHCO_3$ solution (3 ml), the reaction mixture was extracted with ethyl acetate (3 x 20 ml). The combined organic layer was washed with water (2 x 5 ml) and brine (5 ml), dried over $MgSO_4$ and concentrated to give a pale yellow oil. The residue was chromatographed (ethyl acetate-hexane, 1 : 10) to afford dione **1** (95 mg, 94 %) as a white solid. mp 50-52 °C. IR (neat): 1720, 1680, 1620, 1440, 1360, 1250, 1180, 980, 900 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.96 (d, 1H, J = 10.0 Hz), 3.84 (d, 1H, J = 10.0 Hz), 2.86 (dt, 1H, J = 12.0, 3.9 Hz), 2.66-2.29 (m, 4H), 2.27-1.95 (m, 5H), 1.81 (s, 3H), 0.83 (s, 9H), 0.00 (s, 6H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 209.8, 197.5, 156.0, 132.3, 67.4, 56.6, 38.5, 33.3, 28.3, 25.7, 25.6, 21.8, 18.0, 11.4, -5.7, -5.8. MS (EI) *m/z*: 322 (M^+), 307, 292, 265, 237, 207, 177, 149, 121, 89, 73. HRMS (EI) Calcd for $C_{14}H_{21}O_3Si_1$ (M^+-*t*Bu): 265.1260, Found: 265.1261.

8a-({[*tert*-Butyldimethylsilyl]oxy}methyl)-6-hydroxy-5-methyl-3,4,6,7,8,8a-hexahydro-1(2*H*)-naphthalenone (2) The hydroxy ether **2** was prepared from **11** by the same procedure described for **1** and chromatography (ethyl acetate-hexane, 1 : 5). Yield: 95 %. mp 70-72 °C. IR (neat): 3415, 2930, 1711, 1467, 1255, 1085, 1036, 1008, 835, 776 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.94 (d, 1H, J = 9.8 Hz), 3.92 (br s, 1H), 3.68 (d, 1H, J = 9.8 Hz), 2.69-2.53 (m, 2H), 2.38-2.27 (m, 2H), 2.07-1.95 (m, 2H), 1.85-1.48 (m, 5H), 1.76 (s, 3H), 0.82 (s, 9H), 0.00 (s, 6H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 211.0, 133.3, 133.1, 70.1, 67.3, 57.8, 38.8, 28.5, 25.7, 25.4, 24.6, 22.7, 18.1, 16.2, -5.6. MS (EI) *m/z*: 324 (M^+), 294, 279, 249, 237, 175, 162, 147, 133, 105, 89, 73. HRMS (EI) Calcd for $C_{18}H_{32}O_3Si_1$: 324.2121, Found: 324.2128.

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6. The yield of the initial aldol **6** was significantly improved to be almost quantitative by adding **5** in several portions to a stirred solution of *p*-toluenesulfonic acid in acetone at 0 °C.

7. The formation of keto alcohol **12** is avoided by this procedure and the dehydration product **7** was directly obtained in 86 % yield. For the related report, see: Heathcock, C. H.; Mahaim, C.; Schlecht, M. F.; Utawanit, T. *J. Org.Chem.* **1984**, *49*, 3264-3274.

8. Thus, the formation of the undesired isomer of keto alcohol **12** was totally prevented by use of molecular sieves. The aldol **6** should be dried enough prior to retro-aldol reaction.

9. The structure of **11** was confirmed by careful analysis of the spectral data of **11**. For the references related to the stereochemistry of the newly formed hydroxyl group of **11**, see: Kim, S; Fuchs, P. L. *J. Am. Chem. Soc.* **1993**, *115*, 5934-5940. Pelletier, S. W.; Chappell, R. L.; Prabhakar, S. *J. Am. Chem. Soc.* **1968**, *90*, 2889-2895. Hagiwara, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1987**, 1351-1353.