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An Enantioselective Route to (-)-$\Delta^{9(12)}$-Capnellene Employing Silyl Group Directed Stereo Control

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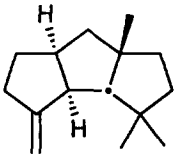
Abstract: A formal synthesis of a marine natural product (-)-$\Delta^{9(12)}$-capnellene has been achieved by employing silyl group directed stereo control, starting from (-)-2-methyl-4-trimethylsilyl-2-cyclopenten-1-one.

We have been interested in utilizing the silyl group directed stereo control for asymmetric synthesis and have synthesized some terpenes starting from a chiral building block, 5-trimethylsilyl-2-cyclohexen-1-one.[1] As an extension of the above work, we envisioned to apply the strategy, the silyl group directed stereo control, to a cyclopentenone system and targeted the development of a cyclopentenone-type chiral building block which is useful for the synthesis of some triquinanes.

In this paper we will report the synthesis of (-)-2-methyl-4-trimethylsilyl-2-cyclopenten-1-one (-)-**3** and its utilization for a formal asymmetric synthesis of (-)-$\Delta^{9(12)}$-capnellene (-)-**1**.

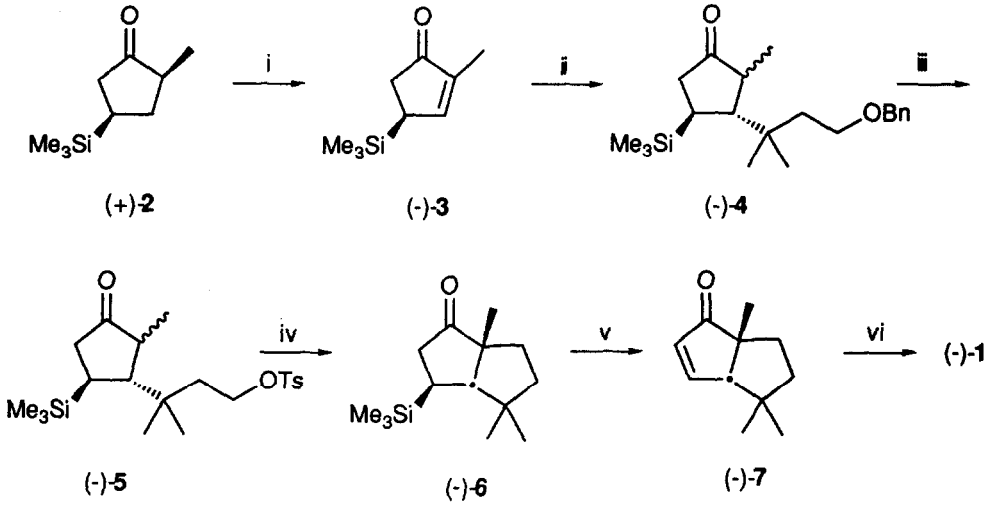


(-)-$\Delta^{9(12)}$-capnellene

(-)-**1**

(-)-$\Delta^{9(12)}$-Capnellene[2] found in the soft coral *Capnella imbricata* has received much synthetic attention, by virtue of its biological activity and interesting molecular architecture. A large number of racemic total syntheses have appeared, however, only two asymmetric total syntheses have been reported.[3]

By the method reported in a previous paper[4] (2*S*,4*R*)-2-methyl-4-trimethylsilylcyclopentanone (+)-**2** was prepared from (5*R*)-3-methyl-5-trimethylsilyl-2-cyclohexen-1-one in 55% overall yield. For the conversion of (+)-**2** into (-)-**3** via enol silyl ether, preferential formation of thermodynamically more stable enolate of (+)-**2** is necessary. Two methods, i.e., silylation via the regioselective enolate of (+)-**2** generated with diisopropylaminomagnesium bromide[5] and direct silylation of (+)-**2** with a combination of trimethylsilyl triflate and triethylamine,[6] were examined. The former method lacked reproducibility though it showed higher regioselectivity than the latter. Thus, silylation by the latter method and subsequent treatment of the crude enol silyl ether with a stoichiometric amount[7] of $Pd(OAc)_2$ gave cyclopentenone (-)-**3** in 74% overall yield from (+)-**2**. At the same time, 5-methyl-3-trimethylsilyl-2-cyclopentenone derived from regioisomeric enol silyl ether was isolated as a by-product in 14% yield. With the desired cyclopentenone-type chiral building block (-)-**3** in hand, we planned to synthesize the title compound via the Piers ketone **7**.[9]



i, (a) Me_3SiOTf, Et_3N, toluene, (b) $Pd(OAc)_2$, CH_3CN; ii, (a) $BnOCH_2CH_2C(Me)_2MgCl$ (**8**, 13 equiv.), CuBr·Me_2S (10%), HMPA (2 equiv.), Me_3SiCl (8 equiv.), THF, (b) KF, MeOH; iii, (a) H_2, Pd/C, EtOH, (b) TsCl, pyridine; iv, ^{t}BuOK, THF; v, (a) Me_3SiOTf, Et_3N, toluene, (b) NBS, THF, (c) TBAF, THF; vi, ref. 9.

Scheme 1.

1,4-Addition of 3-benzyloxy-1,1-dimethylpropylmagnesium chloride (**8**) to the enone in the presence of CuBr·SMe_2, hexamethylphosphoric triamide (HMPA), and chlorotrimethylsilane[10] gave slightly impure adduct (-)-**4** in 58-63% yield. Its ^{1}H- and ^{13}C-NMR showed that (-)-**4** was diastereomerically almost pure but contained a small amount of chromatographically inseparable impurity. Removal of the benzyl group by hydrogenolysis followed by tosylation furnished pure tosylate (-)-**5** in 40% overall yield from (-)-**3**. Treatment of (-)-**5** with *tert*-butoxide (^{t}BuOK) at 0 °C gave bicyclic ketone (-)-**6**, whose ^{13}C-NMR showed its diastereomeric homogeneity, in 85% yield. Conversion of (-)-**4** to (-)-**6** via methanesulfonate was also examined, however, the cyclization step was unsuccessful. Conversion of ketone (-)-**6** to its enol silyl ether with trimethylsilyl triflate in the presence of triethylamine and subsequent reaction with N-bromosuccimide (NBS) furnished α-bromo derivative of (-)-**6** which was treated with tetrabutylammmonium fluoride (TBAF) to give enone (-)-**7** in 61% overall yield. In this reaction, 4-trimethylsilyl derivative of (-)-**7**, which gave (-)-**6** quantitatively by hydrogenation, was obtained as a by-product in 10% yield. As the transformation of the Piers ketone (±)-**7** to (±)-**1** has already been established,[9] our synthesis constitutes the formal synthesis of (-)-$\Delta^{9(12)}$-capnellene.

Finally, we note that compound **3** can be a valuable intermediate in the synthesis of more complex triquinanes.

Experimental

Specific rotation was measured on a Horiba SEPA-200. IR was recorded on a Hitachi 260-50. ^{1}H- and ^{13}C-NMR were recorded on a JEOL JNM-EX 270 in $CDCl_3$.

(2*S*,4*R*)-2-Methyl-4-trimethylsilylcyclopentanone (+)-2: To a solution of (2*R*,3*R*,5*R*)-2,3-epoxy-3-methyl-5-trimethylsilylcyclohexanone (1.99 g, 10.1 mmol)[1c] in dry toluene (100 ml) was added BF_3·Et_2O (812 μl, 6.46 mmol), and the resulted solution was stirred under Ar at rt for 0.5 h. After addition of aqueous 6 M NaOH (10.1 ml, 60.6 mmol), the mixture was stirred vigorously for 10 min. Extraction with ether, removal of solvent, and purification by column chromatography (hexane:ether=4:1) gave (+)-**2** (1.34 g, 78%): oil; bp 120-135 °C (bath temp)/3.5 mmHg; $[\alpha]_D^{21}$ +153.5° (*c* 1.1, $CHCl_3$). ^{1}H-NMR: δ=0.02 (9H, s), 1.08 (3H, d, J=6.9 Hz), 1.21-1.33 (2H, m), 1.79-1.91 (1H, m), 2.09-2.39 (3H, m) ppm. ^{13}C-NMR: δ=-3.4, 14.0, 21.7, 33.9, 39.2, 45.9, 222.6 ppm. IR (neat): 1750 cm^{-1} (C=O). Found: C, 63.04; H, 10.68%. Calcd for $C_9H_{18}OSi$: C, 63.46; H, 10.65%.

(4*S*)-2-Methyl-4-trimethylsilyl-2-cyclopentenone (-)-3: To a solution of ketone (+)-**2** (302 mg, 1.78 mmol) in dry toluene (11 ml) were added triethylamine (546 μl, 3.92 mmol) and trimethylsilyl trifluoromethanesulfonate (688 μl, 3.56 mmol), and the mixture was stirred at room temperature overnight. Addition of saturated aqueous $NaHCO_3$ solution, extraction with CH_2Cl_2, and removal of the solvent under reduced pressure gave a mixture of regioisomeric enol silyl ethers. To a solution of the mixture in dry CH_3CN (10 ml) was added $Pd(AcO)_2$ (480

mg, 2.14 mmol). After 3 h stirring, the mixture was filtered through a short pad of celite and the filtrate was washed with CH_2Cl_2. Removal of the solvent and purification of the residue by column chromatography (hexane:ether=4:1) gave (-)-**3** (221 mg, 74%) and 5-methyl-3-trimethylsilyl-2-cyclopentenone (43 mg, 14%). (-)-**3**: oil; $[\alpha]_D^{22}$ -385.8° (*c* 1.1, $CHCl_3$). ^{1}H-NMR: δ=0.03 (9H, s), 1.78 (3H, dd, J=1.3, 2.3 Hz), 2.18-2.24 (1H, m), 2.27 (1H, d, J=19.5 Hz), 2.57 (1H, dd, J=6.6, 19.5 Hz), 7.40 (1H, dd, J=1.3, 2.6 Hz) ppm. ^{13}C-NMR: δ=-3.3, 10.1, 30.8, 37.3, 139.1, 162.5, 210.5 ppm. IR (neat): 1700 cm^{-1} (C=O). Found: C, 63.98; H, 9.60%. Calcd for $C_9H_{16}OSi$: C, 64.22; H, 9.58%. 5-Methyl-3-trimethylsilyl-2-cyclopentenone: oil; ^{1}H-NMR: δ=0.20 (9H, s), 1.17 (3H, d, J=7.6Hz), 2.24-2.36 (2H, m), 2.93-3.03 (1H, m), 7.32 (1H, t, J=2.0 Hz) ppm.

3-Benzyloxy-1,1-dimethylpropylmagnesium chloride (8): To a precooled (-78 °C) solution of 4-benzyloxy-2-butanone[11] (5.0 g, 28.1 mmol) in dry THF (110 ml) was added an ethereal solution of methyllithium (33.7 mmol) over a period of 0.5 h. After 0.5 h stirring at -78 °C, a saturated aqueous solution of NH_4Cl was added to the mixture. Usual workup and purification by column chromatography (hexane:ether=1:1) gave 4-benzyloxy-2-methyl-2-butanol (5.0 g, 91%). Bp 88-91 °C/0.02 mmHg. ^{1}H-NMR: δ=1.23 (6H, s), 1.80 (2H, t, J=5.9 Hz), 3.30 (1H, s), 3.71 (2H, t, J=5.9 Hz), 4.51 (2H, s), 7.25-7.40 (5H, m) ppm. A mixture of the alcohol (5.03 g, 25.9 mmol) and conc. HCl (15 ml) was stirred at rt for 1 h. Usual workup and column chromatography (hexane:ether=10:1) gave 1-benzyloxy-3-chloro-3-methylbutane (4.63 g, 84%). Bp 83-88 °C/0.25 mmHg. ^{1}H-NMR: δ=1.61 (6H, s), 2.11 (2H, t, J=6.8 Hz), 3.72 (2H, t, J=6.8 Hz), 4.51 (2H, s), 7.29-7.38 (5H, m) ppm. Preparation of a THF (20 ml) solution of **8** was carried out with Mg (2.19 g, 90.1 mmol) and the above chloride (4.25 g, 20 mmol) under the conventional conditions to give 0.55 M solution of the Grignard reagent.

(3*S*,4*R*)-3-(3-Benzyloxypropyl-1,1-dimethyl)-2-methyl-4-trimethylsilylcyclopentanone (-)-4: To a precooled (-78 °C) solution of CuBr·Me_2S (9.5 mg, 0.038 mmol) in dry THF (2 ml) were sequentially added the Grignard reagent **8** (1.27 mmol), HMPA (176 μl, 0.83 mmol), chlorotrimethylsilane (481 μl, 3.15 mmol), and enone (-)-**3** (63.7 mg in 2 ml of dry THF, 0.38 mmol). After stirring at that temperature for 50 min, another portion of the Grignard reagent (3.74 mmol) was added. The mixture was allowed to warm to 0 °C over a period of 10 h, and worked up in a usual manner. KF (592 mg, 10.2 mmol) was added to the residue in MeOH (5 ml), and the mixture was stirred at 40 °C for 2 h. Removal of solvent and subsequent purification by column chromatography (hexane:ether=8:1-5:1) gave (-)-**4** (101 mg) which contained a small amount of impurity. ^{1}H-NMR: δ=-0.03 (9H, s), 0.89 (3H, s), 0.90 (3H, s), 1.12 (3H, d, J=7.3 Hz), 1.35 (1H, dt, J=2.6, 12.9 Hz), 1.61 (2H, dt, J=1.3, 7.3 Hz), 1.67 (1H, dd, J=2.6, 5.3 Hz) ,2.1-2.2 (1H, m), 2.17 (1H, dd, J=2.6, 18.2 Hz), 2.59 (1H, ddd, J=2.0, 12.9, 18.2 Hz), 3.56 (2H, t, J=7.3 Hz), 7.2-7.4 (5H, m) ppm. ^{13}C-NMR: δ=-2.7, 17.0, 19.5, 23.8, 24.1, 37.0, 38.3, 40.0, 43.2, 54.5, 67.3, 73.2, 127.6, 127.7, 128.4, 138.4, 221.7 ppm. IR (neat): 1738 cm^{-1} (C=O).

(3*R*,4*S*)-3-(1,1-Dimethyl-3-toluenesulfonyloxypropyl)-2-methyl-4-trimethylsilylcyclopentanone (-)-5: To a solution of (-)-**4** (101 mg) dissolved in ethanol (3 ml) was added 10% Pd-C (48 mg), and the mixture was

stirred for 5 h under hydrogen atmosphere. Filtration of the reaction mixture through a short pad of celite, removal of the solvent, and purification by column chromatography (hexane:ether=2:1) gave the corresponding deprotected alcohol. To a solution of the alcohol in dry pyridine (4 ml) was added toluenesulfonyl chloride (83.5 mg, 0.438 mmol), and the solution was stirred overnight under Ar atmosphere. Usual workup and subsequent purification by column chromatography (hexane:ether=2:1) gave (-)-**5** [61.7 mg, 40% overall yield from (-)-**3**]: oil; $[\alpha]_D^{20}$ -38.3° (*c* 0.73, $CHCl_3$). ^{1}H-NMR: δ=-0.05 (9H, s), 0.85 (3H, s), 0.86 (3H, s), 1.07 (3H, d, J=7.3 Hz), 1.26 (1H, dt, J=2.3, 12.9 Hz), 1.58-1.64 (3H, m), 2.06 (1H, m), 2.15 (1H, dd, J=2.3, 18.1 Hz), 2.46 (3H, s), 2.51 (1H, ddd, J=2.0, 18.1, 19.1 Hz), 4.14 (2H, t, J=7.3 Hz), 7.36 (2H, d, J=8.3 Hz), 7.80 (2H, d, J=8.3 Hz) ppm. ^{13}C-NMR: δ=-2.8, 16.9, 19.4, 21.6, 23.4, 23.7, 36.9, 37.4, 39.8, 43.0, 54.3, 67.7, 127.9, 129.9, 133.2, 144.9, 220.8 ppm. IR (neat): 1740 cm^{-1} (C=O).

(1*R*,4*R*,5*S*)-1,6,6-Trimethyl-4-trimethylsilylbicyclo[3.3.0]octan-2-one (-)-6: To a cooled (0 °C) solution of tosylate (-)-**5** (110 mg, 0.268 mmol) in dry THF (20 ml) was slowly added a solution of t-BuOK in THF (2.0 ml, 0.4 M), and the reaction mixture was stirred for 50 min. Extraction with ether, removal of the solvent, and purification of the product by column chromatography (hexane:ether=20:1) gave (-)-**6** (54.5 mg, 85%): oil; bp 150-160 °C (bath temp)/3.0 mmHg; $[\alpha]_D^{19}$ -34.2° (*c* 1.1, $CHCl_3$). ^{1}H-NMR: δ=0.03 (9H, s), 0.90 (3H, s), 1.02 (3H, s), 1.17 (3H, s), 1.12-1.23 (1H, m), 1.38-1.63 (3H, m), 1.85 (1H, d, J=5.3 Hz), 1.93 (1H, dt, J=6.6, 13.2 Hz), 2.30 (1H, dd, J=8.6, 18.8 Hz), 2.43 (1H, dd, J=10.9, 18.8 Hz) ppm. ^{13}C-NMR: δ=-2.6, 18.5, 24.0, 25.9, 29.3, 35.8, 39.5, 40.8, 43.8, 56.9, 59.6, 225.0 ppm. IR (neat): 1740 cm^{-1} (C=O). Found: C, 70.13; H, 11.06%. Calcd for $C_{14}H_{26}OSi$: C, 70.52; H, 10.99%.

(1*R*,5*S*)-1,6,6-Trimethylbicyclo[3.3.0]oct-3-en-2-one (-)-7: To a dry toluene (2 ml) solution of ketone (-)-**6** (60.8 mg, 0.255 mmol) were added triethylamine (156 μl, 1.12 mmol) and trimethylsilyl trifluoromethanesulfonate (197 μl, 1.02 mmol), and then the reaction mixture was stirred under Ar atmosphere at rt overnight. Addition of aqueous $NaHCO_3$ solution, extraction with CH_2Cl_2, and removal of the solvent gave the corresponding enol silyl ether of (-)-**6**. To a dry THF (1 ml) solution of the silyl enol ether was added NBS (57.5 mg, 0.306 mmol) in dry THF (1.5 ml) at -78 °C, and the mixture was stirred at that temperature for 0.5 h. After addition of 1.0 M THF solution of TBAF (265 μl), the reaction mixture was allowed to warm to rt over a period of 2 h. Filtration of the mixture through a short pad of silica gel, removal of the solvent, and purification by TLC (hexane:ether=6:1) gave (-)-**7** (25.3 mg, 61%): oil; bp 120-130 °C (bath temp)/60 mmHg; $[\alpha]_D^{20}$ -167.6°(*c* 0.95, hexane); lit.[3b] $[\alpha]_D^{25}$ -191° (*c* 0.57, hexane). ^{1}H-NMR: δ=1.02 (3H, s), 1.12 (3H, s), 1.22 (3H, s), 1.18-1.39 (2H, m), 1.65 (1H, dt, J=6.6, 13.2 Hz), 1.88 (1H, dd, J=6.9, 13.2 Hz), 2.49 (1H, br s), 6.15 (1H, dd, J=1.6, 5.9 Hz), 7.59 (1H, dd, J=3.0, 5.9 Hz) ppm. ^{13}C-NMR: δ=23.7, 26.1, 28.9, 34.9, 38.5, 41.1, 54.7, 64.7, 133.2, 165.3, 215.6 ppm. IR (neat): 1710 cm^{-1} (C=O). Found: C, 79.98; H, 9.49%. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82%. The enantiomeric excess of this enone was examined on its 1,4-adduct with p-toluenethiol by HPLC using the chiral column CHIRALCEL OJ (Daicel Chemical Industries, Ltd.) and determined as 96% .

(1R,5S)-1,6,6-Trimethyl-4-trimethylsilyl-bicyclo[3.3.0]oct-3-en-2-one: oil; ^{1}H-NMR: δ=0.23 (9H, s), 0.77 (3H, s), 1.14 (3H, s), 1.18 (3H, s), 1.22-1.60 (3H, m), 1.82-1.86 (1H, m), 2.69 (1H, s), 6.30 (1H, s) ppm. ^{13}C-NMR: δ=-0.7, 25.2, 25.9, 29.7, 32.1, 41.9, 42.0, 57.6, 69.6, 141.5, 183.9, 215.8 ppm.

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