STEREOSELECTIVE SYNTHESIS OF THE OPTICALLY PURE AB-RING MOIETY OF TRICHTOHECENE SESQUITERPENE (+)-CALONECTRIN†

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Abstract- The optically pure trichothecene cis-AB ring moiety (1) was synthesized starting from an optically pure butenolide (7) through the ring closing olefin metathesis for the formation of the A-ring and a Lewis acid mediated cyclization to the cis-fused tetrahedrochromane skeleton that had been converted to natural trichothecene, (+)-calonectrin.

Trichothecene mycotoxins, produced by a lot of species of imperfect fungi such as Fusarium, Trichothecium and Myrothecium, are a family of closely related sesquiterpenoids that have been responsible for outbreaks of disease in human and farm animals due to the spoilage of cereal crops and other agricultural products. Trichothecenes exhibit a wide array of biological activities such as antibiotic, antibacterial and antiviral activity and insecticidal and phytotoxic behavior. In addition, many of them have cytotoxic and antitumor activities. At the cellular level, trichothecenes inhibit protein synthesis in eukaryotic cell lines, resulting in inhibition of DNA synthesis.

Recently, we have isolated from Trichothecium roseum novel 12,13-epoxytrichothecenes, trichothecinol

† We dedicate this paper to Professor Yuichi Kanaoka on the occasion of celebration of his 75th birthday.
A–C, together with the known analogues such as trichothecin (Figure 1). Differently from trichothecin, new trichothecenes did not exhibit remarkable antifungal activity. However, it was found that they inhibit the induction of Epstein-Barr virus early antigen by 12-\textit{O}-tetradecanoylphorbol-13-acetate in Raji cells, the EBV genome-carrying human lymphoblastoid cells. The most active trichothecinol A suppressed the TPA-induced tumor promotion on mouse skin initiated with 7,12-dimethylbenz(\textit{a})anthracene (DMBA) in mouse skin two-stage carcinogenesis experiments. More recently it has been reported that trichothecinol A shows significant cytotoxicity against several human cell lines.

A variety of synthetic studies of trichothecenes have appeared in the literature since the first total synthesis of trichodermmin by the Colvin group. Most of the synthetic trichothecenes have been obtained as racemates, while several synthetic studies deal with the formation of these compounds in optically active form. We describe herein an improved approach starting from chiral butenolide to the optically pure trichothecene \textit{cis}-AB ring moiety (1) as a promising key intermediate of trichothecinols (Scheme 1). The synthesis is characterized by the use of ring closing olefin metathesis for the formation of the A ring and a Lewis acid mediated cyclization to the \textit{cis}-fused AB ring skeleton.

**Synthetic strategy toward 1**

The retrosynthesis for (+)-calonectrin begins with the established Kraus intermediate (1). The reduced oxidation state structure (2) is accessible by the stereoselective cyclization of the cationic intermediate derived from 3. The contiguous quaternary and tertiary chiral centers of 3 are available by the dialkylation of 6 followed by a ring-closing olefin metathesis of 5. The stereoselective methyl group introduction into 7 and following chirality inversion into 6 are possible by applying our old chemistry.

**Stereoselective synthesis of 1**

The conjugate addition reaction of 7 with lithium dimethylcuprate in ether at -78 °C proceeded stereoselectively to give 8 in 91% yield. The next task is the inversion of the original chiral center.
which played its role in introduction of the methyl group in the desired stereochemistry.\textsuperscript{15} Treatment with TBAF followed by tosylation provided 9. Treatment of 9 with lithium benzyl alkoxide in THF gave an epoxy-benzyl ester, which was then debenzyalted with hydrogen-5% Pd/C and then relactonized in refluxing toluene to afford, after MOM etherification, 6 with the inversed stereochemistry.

\[ \text{Scheme 2. Stereoselective synthesis of 4} \]

Stereoselective dialkylation was begun with ethylidenation to 10 followed by alkylation to give 5 as a major isomer of 10:1 diastereomeric mixture.\textsuperscript{16} Ring-closing olefin metathesis of 5 gave a spiro-annulated 4 in an overall yield of 67\% from 10. The stereochemistry of 4 was confirmed on the basis of NOESY measurement.

\[ \text{Scheme 3. Synthesis of 1 by stereoselective cyclization} \]

LiAlH\textsubscript{4} reduction of 4 followed by protection of the diol with pivaloyl chloride (PvCl) gave 15 in 88\% yield, which was then oxidized with CrO\textsubscript{3} in methylene chloride to an enone (16) in 67\% yield. Treatment of 16 with methyllithium in THF at -78 °C gave 3. Upon treatment of 3 under the conditions of LiBF\textsubscript{4} in 2\% H\textsubscript{2}O/MeCN at 72 °C unmasking of an alcoholic group from MOM ether and subsequent cyclization took place to give 2 as a sole product in 79\% overall yield from 16. The NOESY cross peak observed between Ha at 3.89 ppm and Hb at 3.66 ppm demonstrated the validity of the \textit{cis}-fused bicyclic structure of 2. The intermediacy of the favorable 17 is responsible for the preferred formation of the \textit{cis}-2. Completion of a formal total synthesis of calonectrin was carried out by reductive removal of pivaloyl group of 2 and following selective protection in a form of TBS ether (19a).
and then PDC oxidation, giving 1, the established synthetic intermediate. The NMR and MS spectra of 1 were in good agreement with those reported by Kraus.12

EXPERIMENTAL19

(4S,5S)-5-(tert-Butyldimethylsilanyloxymethyl)-4-methylidihydrofuran-2-one (8)
A solution of 720 (10 g, 46 mmol) in ether (50 mL) was added dropwise over 0.5 h at -78 °C to a solution of lithium dimethylcuprate in ether (100 mL), prepared from MeLi (138 mL, 138 mmol) and CuI (10 g, 69 mmol). The whole was stirred at -40 °C for 6 h. The reaction was quenched with 80% NH4Cl in 23% NH4OH (300 mL) and was allowed to stir at rt for 9 h. The aqueous layer was extracted with ether. Concentration and chromatography (ether/hexane = 1/4) gave 8 (10.9 g, 91%) as a colorless oil of $[\alpha]_D^{25}$ +18.6° (c 1.3, CHCl3). IR (neat): 1780 cm$^{-1}$; $^1$H NMR: 0.07 (6H, s), 0.89 (9H, s), 1.16 (3H, d, $J = 6.8$ Hz), 2.13 (1H, dd, $J = 17.0$, 7.0 Hz), 2.52 (1H, m), 2.77 (1H, dd, $J = 17.0$, 8.9 Hz), 3.72 and 3.84 (each 1H, dd, $J = 11.3$, 3.2 Hz), 4.09 (1H, dddd, $J = 14.0$, 8.9, 8.6, 7.0 Hz), 3.38 (3H, s), 3.74 (1H, dd, $J = 11.3$, 3.8 Hz), 3.78 (1H, dd, $J = 11.3$, 3.6 Hz), 4.58 (1H, dddd, $J = 14.0$, 3.8, 3.6 Hz), 4.62 (1H, d, $J = 6.4$ Hz), 4.65 (1H, d, $J = 6.4$ Hz); $^{13}$C NMR: -5.51, 5.45, 18.27, 18.96, 25.82, 31.55, 37.05, 63.73, 86.88, 176.80. Anal. Calcd for C_{38}H_{40}O_{5}: C, 55.15; H, 5.66. Found: C, 54.91; H, 5.67. CIMS m/z: 245 (M$^+$+1).

This compound (8) was converted to 6 via 9 under the reported procedure.15

(4S,5R)-5-Methoxymethoxymethyl-4-methylidihydrofuran-2-one (6)
A colorless oil of $[\alpha]_D^{25}$ -23.0° (c 3.4, benzene). IR (neat): 1765 cm$^{-1}$; $^1$H NMR: 1.16 (1H, d, $J = 7.0$ Hz), 2.35 (1H, dd, $J = 17.1$, 8.9 Hz), 2.58 (1H, dd, $J = 17.1$, 8.6 Hz), 2.76 (1H, dddd, $J = 14.0$, 8.9, 8.6, 7.0 Hz), 3.38 (3H, s), 3.74 (1H, dd, $J = 11.3$, 3.8 Hz), 3.78 (1H, dd, $J = 11.3$, 3.6 Hz), 4.58 (1H, dddd, $J = 14.0$, 3.8, 3.6 Hz), 4.62 (1H, d, $J = 6.4$ Hz), 4.65 (1H, d, $J = 6.4$ Hz); $^{13}$C NMR: 13.8, 32.4, 36.6, 36.6, 66.5, 81.1, 96.7, 176.9. Anal. Calcd for C_{38}H_{40}O_{5}: C, 55.16; H, 8.10. Found: C, 55.34; H 8.10. MS m/z: 174 (M$^+$).

(4S,5R)-3-Ethylidene-5-methoxymethoxymethyl-4-methylidihydrofuran-2-one (10)
To a stirred solution of LDA (1.2 mmol) in THF (4.5 mL) was added 6 (174 mg, 1.0 mmol) in THF (0.5 mL) at -78 °C. After 0.5 h, acetaldehyde (88 mg, 2.0 mmol) in THF (2 mL) was added to the mixture. After 0.5 h, the mixture was quenched with satd NH4Cl and extracted with EtOAc. Concentration gave a pale yellow oil. To a solution of the oil (230 mg) and triethylamine (152 mg, 1.5 mmol) in methylene chloride (3.0 mL) was added methanesulfonyl chloride (137 mg, 1.2 mmol) at 0 °C. After stirring at rt
for 3 h, the mixture was diluted with EtOAc and washed with 10% HCl and satd NaHCO₃. Concentration gave a pale yellow oil. To a solution of the oil (210 mg) in benzene (2 mL) was added DBU (152 mg, 1.0 mmol). The mixture was stirred at 60 °C for 3 h, diluted with EtOAc (30 mL), and washed with 10% HCl and satd NaHCO₃. Concentration and chromatography (EtOAc/hexane = 1/19) gave 10 (127 mg, 86%, E/Z mixture = 5/3 by NMR) as a colorless oil. IR (neat): 1750, 1670 cm⁻¹; ¹H NMR (major 10): 1.13 (3H, d, J = 7.0 Hz), 1.20 (3H, d, J=7.3 Hz), 1.91 (3H, dd, J = 7.3, 1.3 Hz), 3.28 (1H, m), 3.40 (3H, s), 3.64-3.83 (2H, m), 4.55-4.69 (1H, m), 6.76 (1H, dq, J = 7.3, 2.1 Hz); ¹³C NMR (major 10): 14.6, 19.0, 33.8, 36.6, 64.2, 84.2, 98.6, 133.1, 134.5, 170.5. HRCIMS: Calcd for C₁₀H₁₇O₄ 201.1127 (M⁺+1). Found: 201.1117.

(3R,4S,5R)-5-Methoxymethoxymethyl-4-methyl-3-pent-4-enyl-3-vinyldihydrofuran-2-one (5)

To a solution of LDA (1.2 mmol) in THF (4.5 mL) and HMPA (904 mg, 5.1 mmol) was added 10 (101 mg, 0.51 mmol) in THF (1 mL) at -78 °C. The mixture was stirred at -40 °C for 0.5 h. After addition of bromopentene (305 mg, 2.02 mmol) at -78 °C, the mixture was stirred at rt for 4 h and quenched with satd NH₄Cl and extracted with EtOAc. The organic layer was washed with 10% HCl and satd NaHCO₃. Concentration and chromatography (ether/hexane = 1/4) gave 5 (120 mg, 86%, 10:1 diastereomeric mixture by NMR) as a colorless oil. IR (neat): 1760, 1640 cm⁻¹; ¹H NMR (major 5): 0.99 (3H, d, J = 7.0 Hz), 1.44 (1H, m), 1.54 (1H, m), 1.66 (1H, m), 1.74 (1H, m), 2.04 (2H, m), 2.58 (1H, dq, J = 7.3, 7.0 Hz), 3.37 (3H, s), 3.66 (1H, dd, J = 11.0, 4.6 Hz), 3.70 (1H, dd, J = 11.0, 7.3 Hz), 4.63 (2H, s), 4.67 (1H, ddd, J = 7.3, 7.3, 4.6 Hz), 4.96-5.04 (2H, m), 5.40-5.48 (2H, m), 572-5.81 (2H, m); ¹³C NMR (major 5): 10.5, 23.4, 33.8, 35.8, 40.4, 52.7, 55.5, 66.5, 78.8, 96.7, 115.1, 117.8, 135.2, 138.0, 177.6. HRCIMS: Calcd for C₁₅H₂₅O₄ 269.1753 (M⁺+1). Found: 269.1743.

(3R,4S,5R)-3-Methoxymethoxymethyl-4-methyl-2-oxaspiro[4.5]dec-6-en-1-one (4)

A mixture of 5 (120 mg, 0.44 mmol) and benzylidenebis(tricyclohexylphosphine) dichloro ruthenium (32.6 mg, 0.04 mmol) in methylene chloride (300 mL) was stirred at rt for 18 h. Concentration and chromatography (EtOAc/hexane = 1/5) gave 4 (81 mg, 67% from 10) as a colorless oil of [α]D²⁵ -19.9° (c 2.9, CHCl₃). IR (neat): 1760 cm⁻¹; ¹H NMR: 1.01 (1H, d, J = 7.4 Hz), 1.60 (1H, m), 1.86-1.83 (2H, m), 1.93 (1H, m), 2.16–2.02 (2H, m), 2.46 (1H, dq, J = 7.4, 7.3 Hz), 3.39 (3H, s), 3.71 (1H, dd, J = 11.0, 4.6 Hz), 3.75 (1H, dd, J = 11.0, 6.7 Hz), 4.66 and 4.68 (each 1H, d, J = 6.7 Hz), 4.72 (1H, ddd, J = 7.3, 6.7,
4.6 Hz), 5.55 (1H, d, $J = 10.1$ Hz), 6.06 (1H, ddd, $J = 10.1, 3.7, 3.7$ Hz); $^{13}$C NMR: 10.6, 18.9, 24.3, 30.5, 42.5, 48.2, 55.4, 66.5, 78.4, 96.6, 124.0, 132.3, 180.1. HRCIMS: Calcd for C$_{15}$H$_{25}$O$_4$ 241.1440 (M$^+$+1). Found: 241.1441.

$(1R,2S)$-2-[1-(2,2-Dimethylpropionyloxymethyl)-(R)-cyclohex-2-enyl]-1-methoxymethoxymethyl-propyl 2,2-dimethylpropionate (15)

A mixture of 4 (81 mg, 0.34 mmol) and lithium aluminium hydride (39 mg, 1.01 mmol) in THF (1 mL) was stirred at 0 °C for 0.5 h, and treated successively with H$_2$O (5 drops), 15% NaOH (5 drops) and H$_2$O (15 drops). Filtration and concentration gave an oil, which was treated with pivaloyl chloride (121 mg, 1.01 mmol) in pyridine (0.5 mL) at 60 °C for 32 h and then washed with 10% HCl and satd NaHCO$_3$. Concentration and chromatography (EtOAc/hexane = 1/5) gave 15 (123 mg, 88%) as a colorless oil of $[\alpha]_D^{25} +16.0^\circ$ (c 2.9, CHCl$_3$). IR (neat): 1725 cm$^{-1}$; $^1$H NMR: 1.00 (3H, d, $J = 7.3$ Hz), 1.20 (18H, s), 1.65-1.51 (4H, m), 2.02-1.94 (m, 3H), 3.35 (3H, s), 3.43 (1H, dd, $J = 9.8, 6.7$ Hz), 3.48 (1H, dd, $J = 9.8, 6.4$ Hz), 3.82 and 4.12 (each 1H, d, $J = 11.7$ Hz), 4.58 and 4.59 (each 1H, d, $J = 6.7$ Hz), 5.30 (1H, d, $J = 6.7, 6.4, 1.0$ Hz), 5.39 (1H, d, $J = 10.1$ Hz), 5.87 (1H, ddd, $J = 10.1, 3.7, 3.7$ Hz); $^{13}$C NMR: 8.3, 18.9, 24.8, 26.5, 27.1, 38.1, 40.8, 55.3, 67.8, 68.5, 70.9, 96.3, 130.2, 177.4, 178.4. Anal. Calcd for C$_{20}$H$_{40}$O$_6$: C, 66.96; H 9.77. Found: C, 66.93; H, 9.79. MS m/z: 412 (M$^+$).

$(1R,2S)$-2-[1-(2,2-Dimethylpropionyloxymethyl)-(R)-4-oxocyclohex-2-enyl]-1-methoxymethoxy-methylpropyl 2,2-dimethylpropionate (16)

A mixture of 15 (760 mg, 1.84 mmol) and CrO$_3$-(pyridine)$_2$ (14.3 g, 55.3 mmol) in methylene chloride (30 mL) was stirred at rt for 24 h, and was diluted with EtOAc, and then washed with satd NaHCO$_3$, 10% HCl, and satd NaHCO$_3$. Concentration and chromatography (EtOAc/hexane = 1/2) gave 16 (525 mg, 67%) as an oil of $[\alpha]_D^{25} +17.8^\circ$ (c 1.0, CHCl$_3$). IR (neat): 1730, 1680 cm$^{-1}$; $^1$H NMR: 1.00 (3H, d, $J = 7.0$ Hz), 1.18 (9H, s), 1.21 (9H, s), 2.09-2.01 (2H, m), 2.29 (1H, m), 2.25-2.43 (2H, m), 3.35 (3H, s), 3.44 (1H, dd, $J = 9.8, 7.9$ Hz), 3.49 and 3.86 (each 1H, d, $J = 11.3$ Hz), 3.50 (1H, ddd, $J = 9.8, 5.8$ Hz), 4.59 and 4.61 (each 1H, d, $J = 6.4$ Hz), 5.26 (1H, ddd, $J = 7.9, 5.8, 5.8$ Hz), 6.07 and 6.75 (each 1H, dd, $J = 10.4$ Hz); $^{13}$C NMR: 8.4, 27.0, 27.1, 27.2, 33.5, 37.8, 38.9, 39.0, 42.1, 55.4, 66.6, 70.3, 96.5, 130.5, 153.6, 177.3, 178.1, 198.3. HRCIMS: Calcd for C$_{23}$H$_{39}$O$_7$ 426.2696 (M$^+$+1). Found: 426.2688.
(3R,4S,4aR,8aR)-4a-(2,2-Dimethylpropionyloxy)methyl)-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-2H-chromen-3-yl 2,2-dimethylpropionate (2)

To a solution of 16 (61 mg, 0.14 mmol) in ether (1.0 mL) was added MeLi in ether (0.38 mL, 0.45 mmol) at -78°C. The mixture was stirred for 15 min and was quenched with satd NH₄Cl and extracted with EtOAc. Concentration gave a pale yellow oil, which was treated with LiBF₄ in 2% H₂O/MeCN at 72 °C for 0.5 h and diluted with water (20 mL), and then extracted with EtOAc. Concentration and chromatography (EtOAc/hexane = 1/6) gave 2 (43 mg, 79%) as a colorless oil of [α]D²5 -1.6° (c 3.0, CHCl₃). IR (neat): 1730 cm⁻¹; ¹H NMR: 0.92 (3H, d, J = 7.0 Hz), 1.20 (9H, s), 1.23 (9H, s), 1.70 (3H, s), 1.88-2.09 (4H, m), 3.12 (1H, dd, J = 11.0, 11.0 Hz), 3.66 (1H, d, J = 5.0 Hz), 3.89 (1H, d, J = 12.5 Hz), 4.00 (1H, dd, J = 11.0, 5.0 Hz), 4.19 (1H, d, J = 12.5 Hz), 4.78 (1H, ddd, J = 11.0, 11.0, 5.0 Hz), 5.52 (1H, d, J = 5.0 Hz). ¹³C NMR: 10.2, 19.6, 23.2, 27.1, 27.2, 27.3, 38.8, 38.9, 39.7, 40.0, 65.1, 69.0, 70.8, 73.8, 119.0, 139.9, 178.0, 178.2. HRCIMS: Calcd for C₂₂H₃₇O₅ 381.2641 (M+²). Found: 381.2636.

(3R,4S,4aR,8aR)-4a-Hydroxymethyl-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-2H-chromen-3-ol (18)

A mixture of 2 (280 mg, 0.74 mmol) and lithium aluminum hydride (84 mg, 2.21 mmol) in THF (6 mL) was stirred at 0 °C for 0.5 h and was then quenched with H₂O (0.08 mL), 15% NaOH (0.08 mL) and H₂O (0.25 mL). Filtration, concentration, and chromatography (17% EtOH in EtOAc) gave 18 (139 mg, 89%) as colorless needles of mp 179-181 °C (EtOAc) and [α]D²5 -7.6° (c 2.3, CH₃OH). IR (nujol): 3250, 2900 cm⁻¹; ¹H NMR (CD₃OD): 1.21 (3H, d, J=6.7 Hz), 1.42 (1H, m), 1.68 (3H, s), 1.72 (1H, m), 3.09 (1H, dd, J = 10.7, 10.7 Hz), 1.89-2.97 (3H, m), 3.41 (1H, ddd, J = 10.7, 10.7, 5.2 Hz), 3.48 (2H, s), 3.45 and 3.47 (each 1H, d, J = 10.5 Hz), 3.74 (1H, d, J=5.8 Hz), 3.82 (1H, dd, J = 10.7, 4.9 Hz), 5.49 (1H, d, J = 5.8 Hz); ¹³C NMR (CD₃OD): 10.4, 20.9, 23.2, 28.3, 40.4, 41.5, 63.0, 69.4, 73.2, 75.3, 120.7, 140.5. HRCIMS: Calcd for C₁₂H₂₁O₃Si 213.1491 (M⁺). Found: 213.1501.

(3R,4S,4aR,8aR)-4a-(tert-Butyldimethylsilanyloxymethyl)-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-2H-chromen-3-ol (19a)

A solution of 18 (33 mg, 0.16 mmol), t-butyldimethylsilyl chloride (28 mg, 0.19 mmol) and imidazole (17.3 mg, 0.26 mmol) in DMF (1 mL) was stirred at rt for 1 h and was quenched with satd NH₄Cl and then extracted with EtOAc. Concentration and chromatography (EtOAc/hexane = 1/2) gave 19a (25 mg, 49%, a colorless oil), 19b (6 mg, 12%, an amorphous powder) and 19c (17 mg, 25 %, a colorless oil).
**19a:** $\alpha_d^{25} -3.2^\circ$ (c 1.0, CHCl$_3$); IR (neat) 3400, 2960 cm$^{-1}$; $^1$H NMR: -0.01 (3H, s), 0.00 (3H, s), 0.88 (9H, s), 1.02 (3H, d, $J = 7.0$ Hz), 1.36 (1H, br s), 1.41 (1H, m), 1.69 (3H, s), 1.73 (1H, m), 1.85 (1H, m), 1.94-2.00 (2H, m), 3.11 (1H, dd, $J = 10.7$, 10.7 Hz), 3.45 and 3.47 (each 1H, d, $J = 10.5$ Hz), 3.72 (1H, d, $J = 5.5$ Hz), 3.95 (1H, dd, $J = 10.7$, 4.9 Hz), 5.52 (1H, d, $J = 5.5$ Hz), 5.54 (1H, ddd, $J = 10.7$, 10.7, 4.9 Hz); $^{13}$C NMR: -4.8, 10.0, 18.2, 23.1, 25.9, 27.4, 40.1, 40.5, 63.1, 69.1, 72.3, 73.6, 119.8, 139.0. HRCIMS: Calcd for C$_{18}$H$_{35}$O$_5$Si 327.2355 (M+H$^+$). Found: 327.2358.

**19b:** $\alpha_d^{25} -2.5^\circ$ (c 0.7, EtOH); IR (neat): 3400, 2910 cm$^{-1}$; $^1$H NMR: 0.04 (3H, s), 0.56 (3H, s), 0.88 (9H, s), 0.98 (3H, d, $J = 7.0$ Hz), 1.43 (1H, m), 1.69 (3H, s), 1.76-2.01 (4H, m), 3.16 (1H, dd, $J = 10.4$, 10.4 Hz), 3.53 (1H, ddd, $J = 10.4$, 10.4, 4.9 Hz), 3.57 (2H, s), 3.75 (1H, d, $J = 5.5$ Hz), 3.85 (1H, dd, $J = 10.7$, 4.9 Hz), 5.55 (1H, d, $J = 5.0$ Hz); $^{13}$C NMR: -4.8, -4.2, 10.5, 18.0, 20.1, 23.2, 25.8, 27.4, 40.1, 40.3, 63.6, 69.4, 72.6, 73.4, 119.8, 139.3. HRCIMS: Calcd for C$_{18}$H$_{35}$O$_5$Si 327.2355 (M$^+$+1). Found: 327.2350.

**19c:** $\alpha_d^{25} -5.8^\circ$ (c 1.6, CHCl$_3$); IR (neat): 2900, 2850 cm$^{-1}$; $^1$H NMR: -0.01, (s, 3H) 0.00 (s, 3H), 0.03 (3H, s), 0.05 (3H, s), 0.88 (18H, s), 0.93 (3H, d, $J = 6.7$ Hz), 1.42 (1H, m), 1.68 (3H, s), 1.72 (1H, m), 1.85 (1H, m), 1.92-1.99 (2H, m), 3.42 (1H, d, $J = 10.1$ Hz), 3.10 (1H, d, $J = 10.4$, 10.4 Hz), 3.47 (1H, d, $J = 10.1$ Hz), 3.50 (1H, ddd, $J = 10.4$, 10.4, 4.9 Hz), 3.68 (1H, d, $J = 5.8$ Hz), 3.82 (1H, d, $J = 10.7$, 4.9 Hz), 5.55 (1H, d, $J = 5.8$ Hz); $^{13}$C NMR: -5.6, -4.7, -4.2, 10.6, 18.0, 18.3 x 2, 23.2, 25.9, 27.4, 40.1, 40.5, 63.6, 69.7, 72.7, 73.6, 119.8, 138.9. HRCIMS: Calcd for C$_{24}$H$_{49}$O$_5$Si$_2$ 441.3220 (M$^+$+1). Found: 441.3223.

(4S,4aR,8aR)-4a-(tert-Butyldimethylsilanyloxymethyl)-4,7-dimethyl-4a,5,6,8a-tetrahydro-4H-chromen-3-one (1)

To a solution of **19a** (10.3 mg, 0.032 mmol) in methylene chloride (0.5 mL) was added PDC (36.1 mg, 0.096 mmol) at rt. The mixture was stirred at rt for 24 h and filtrated. Concentration and chromatography (EtOAc/hexane = 1/4) gave 1 (9.5 mg, 92%) as a colorless oil of $\alpha_d^{25} +13.9^\circ$ (c 0.8, CHCl$_3$). IR (neat): 1725 cm$^{-1}$; $^1$H NMR: 0.04 (6H, s), 0.90 (9H, s), 1.03 (3H, d, $J = 6.7$ Hz), 1.36-1.51 (2H, m), 1.73 (3H, s), 1.78-2.96 (2H, m), 3.12 (1H, q, $J = 6.7$ Hz), 3.44 and 3.56 (each 1H, d, $J = 10.1$ Hz), 3.93 and 3.98 (each 1H, d, $J = 15.6$ Hz), 4.27 (1H, d, $J = 4.6$ Hz), 5.50 (1H, d, $J = 4.6$ Hz); $^{13}$C NMR: -5.6, 6.5, 18.2, 22.6, 23.3, 25.8, 26.9, 43.9, 45.7, 64.6, 71.4, 72.6, 119.7, 140.2, 212.4. HRCIMS: Calcd for C$_{18}$H$_{33}$O$_5$Si: 325.2199 (M$^+$+1). Found: 325.2195.
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REFERENCES AND NOTES


19. The extracts were washed with satd NaCl and dried over MgSO₄. Silica gel column chromatography was used. NMR was measured in CDCl₃ unless otherwise noted. Chemical shift was presented in ppm relative to internal TMS.