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

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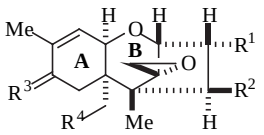
Abstract- The optically pure trichothecene *cis*-AB ring moiety (**1**) was synthesized starting from an optically pure butenolide (**7**) through the ring closing olefin metathesis for the formation of the A-ring and a Lewis acid mediated cyclization to the *cis*-fused tetrahedrochromane skeleton that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

Trichothecene mycotoxins, produced by a lot of species of imperfect fungi such as *Fusarium*, *Trichothcium* and *Myrothecium*, are a family of closely related sesquiterpenoids[1] that have been responsible for outbreaks of disease in human and farm animals due to the spoilage of cereal crops and other agricultural products.[2] Trichothecenes exhibit a wide array of biological activities such as anti-biotic, antibacterial and antiviral activity and insecticidal and phytotoxic behavior. In addition, many of them have cytotoxic and antitumor activities.[3] At the cellular level, trichothecenes inhibit protein synthesis in eukaryotic cell lines, resulting in inhibition of DNA synthesis.[4]



		R^1	R^2	R^3	R^4
Trichothecinol	A	OH	OOCOCH=CHMe-*Z*	O	H
	B	H	OCOCH=CHMe-*Z*	α-OH, β-H	H
	C	OH	OCOCH=CHMe-*Z*	α-OH, β-H	H
Trichothecin		H	OCOCH=CHMe-*Z*	O	H
Calonectrin		OAc	H	H, H	OAc

Figure 1. Structures of trichothecinols A-C, trichothecin and calonectrin

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

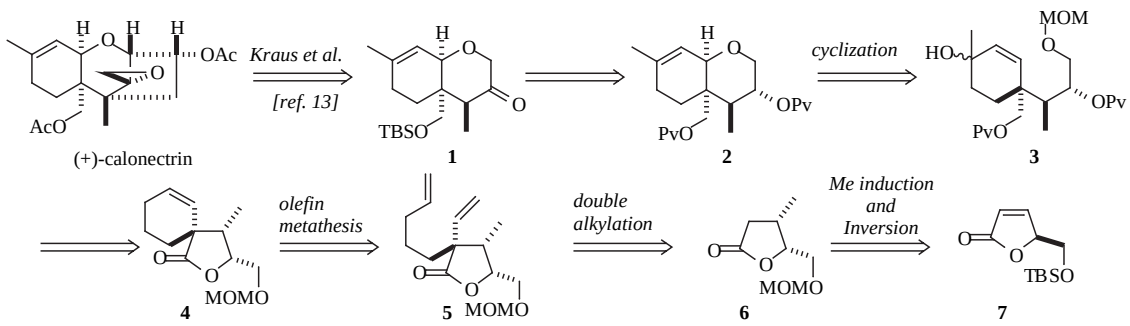
† We dedicate this paper to Professor Yuichi Kanaoka on the occasion of celebration of his 75th birthday.

A–C, together with the known analogues such as trichothecin (Figure 1).[5] 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-*O*-tetradecanoylphorbol-13-acetate in Raji cells, the EBV genome-carrying human lymphoblastoid cells.[6] The most active trichothecinol A suppressed the TPA-induced tumor promotion on mouse skin initiated with 7,12-dimethyl-benz(*a*)anthracene (DMBA) in mouse skin two-stage carcinogenesis experiments.[7] More recently it has been reported that trichothecinol A shows significant cytotoxicity against several human cell lines.[8]

A variety of synthetic studies of tricothecenes have appeared in the literature since the first total synthesis of trichodermin by the Colvin group.[9] Most of the synthetic trichothecenes have been obtained as racemates,[10] while several synthetic studies deal with the formation of these compounds in optically active form.[11] We describe herein an improved approach[12] starting from chiral butenolide to the optically pure trichothecene *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 *cis*-fused AB ring skeleton.

Synthetic strategy toward 1

The retrosynthesis for (+)-calonectrin begins with the established Kraus intermediate (**1**).[13] 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.[14]

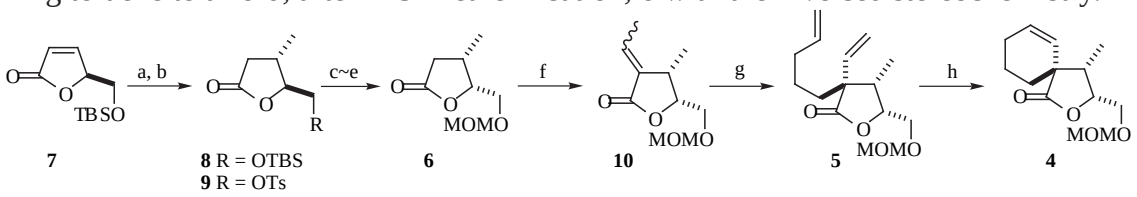


Scheme 1. Synthetic strategy for (+)-calonectrin from chiral butenolide

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.[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 debenzylated with hydrogen-5% Pd/C and then relactonized in refluxing toluene to afford, after MOM etherification, **6** with the inversed stereochemistry.

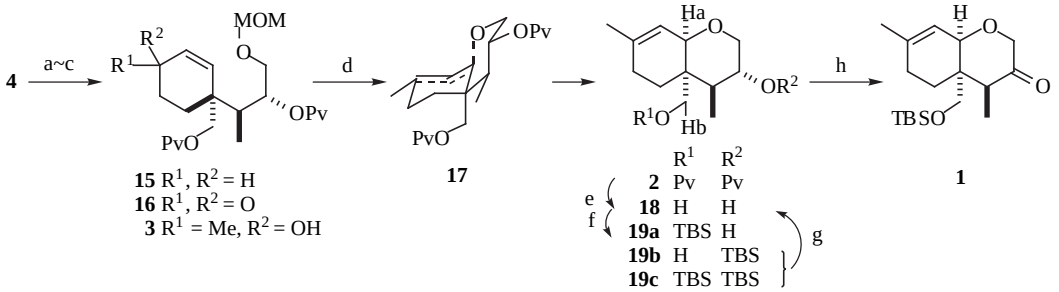


7 **8** R = OTBS **9** R = OTs **6** **10** **5** **4**

a) Me_2CuLi, Et_2O, -78 °C to -40 °C, 91% ; b) i) TBAF, THF, rt, 1 h, ii) TsCl, DMAP, py, rt, 18 h, 85% (2 steps); c) BnOLi, THF, 0 °C, 5 h, 80%; d) i) 5% Pd/C, H_2, Et_2O, rt, 2 h, ii) toluene, reflux, 13 h, 95% (2 steps); e) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, rt, 1 d, 86%; f) i) LDA, MeCHO, THF, -78 °C, 0.5 h, ii) MsCl, Et_3N, CH_2Cl_2, rt, 3 h, iii) DBU, benzene, 60 °C, 3 h, 86% (3 steps); g) LDA, HMPA, 1-bromo-5-pentene, THF, -78 °C to rt; h) $RuCl_2(=CHPh)(PCy_3)_2$, CH_2Cl_2, 67% (from **10**).

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 diasetereomeric mixture.[16] Ring-closing olefin metathesis[17] 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.



a) i) $LiAlH_4$, THF, 0 °C, 0.5 h, ii) PvCl, pyridine, 60 °C, 32 h, 88% **15**; b) CrO_3, pyridine, CH_2Cl_2, rt, 12 h, 67 % **16**; c) MeLi, THF, -78 °C, 15 min; d) $LiBF_4$, 2% H_2O/MeCN, 72 °C, 0.5 h, 79% (**2** from **16**); e) $LiAlH_4$, THF, rt, 20 min, 89% **18**; f) TBSCl, imidazole, DMF, rt, 1 h, 49% (**19a**), 12% (**19b**), 25% (**19c**); g) TBAF, THF, rt, 3 h, 83% **18**; h) PDC, CH_2Cl_2, rt, 24 h, 92 %.

Scheme 3. Synthesis of **1** by stereoselective cyclization

$LiAlH_4$ reduction of **4** followed by protection of the diol with pivaloyl chloride (PvCl) gave **15** in 88% yield, which was then oxidized with CrO_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[18] of $LiBF_4$ in 2% H_2O/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 *cis*-fused bicyclic structure of **2**. The intermediacy of the favorable **17** is responsible for the preferred formation of the *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]

EXPERIMENTAL[19]

(4*S*,5*S*)-5-(*tert*-Butyldimethylsilanyloxymethyl)-4-methyldihydrofuran-2-one (8)

A solution of **7**[20] (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% NH_4Cl in 23% NH_4OH (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, $CHCl_3$). IR (neat): 1780 cm^{-1}; ^1H 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, ddd, *J* = 5.4, 3.2, 3.2 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]

(4*S*,5*R*)-5-Methoxymethoxymethyl-4-methyldihydrofuran-2-one (6)

A colorless oil of $[\alpha]_D^{25}$ -23.0° (*c* 3.4, benzene). IR (neat): 1765 cm^{-1}; ^1H 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, ddd, *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 $C_8H_{14}O_4$: C 55.16; H 8.10. Found: C, 55.34; H 8.10. MS *m/z*: 174 (M^+).

(4*S*,5*R*)-3-Ethylidene-5-methoxymethoxymethyl-4-methyldihydrofuran-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 NH_4Cl 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 $NaHCO_3$. 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 $NaHCO_3$. 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); ^{13}C 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 $C_{10}H_{17}O_4$ 201.1127 (M^++1). Found: 201.1117.

(3*R*,4*S*,5*R*)-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 NH_4Cl and extracted with EtOAc. The organic layer was washed with 10% HCl and satd $NaHCO_3$. 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); ^{13}C 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 $C_{15}H_{25}O_4$ 269.1753 (M^++1). Found: 269.1743.

(3*R*,4*S*,5*R*)-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(tricychohexylphosphine) dicholoro 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 $[\alpha]_D^{25}$ -19.9° (*c* 2.9, $CHCl_3$). 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.

(1*R*,2*S*)-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_2O (5 drops), 15% NaOH (5 drops) and H_2O (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 diluted with EtOAc (30 mL) 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° (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^+).

(1*R*,2*S*)-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° (*c* 1.0, $CHCl_3$). IR (neat): 1730, 1680 cm^{-1}; ^{1}H NMR: 1.10 (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, dd, *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.

(3*R*,4*S*,4a*R*,8a*R*)-4a-(2,2-Dimethylpropionyloxymethyl)-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-2*H*-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 NH_4Cl and extracted with EtOAc. Concentration gave a pale yellow oil, which was treated with $LiBF_4$ in 2% H_2O/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 $[\alpha]_D^{25}$ -1.6° (*c* 3.0, $CHCl_3$). 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). ^{13}C 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 $C_{22}H_{37}O_5$ 381.2641 (M^++1). Found: 381.2636.

(3*R*,4*S*,4a*R*,8a*R*)-4a-Hydroxymethyl-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-2*H*-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 H_2O (0.08 mL), 15% NaOH (0.08 mL) and H_2O (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 $[\alpha]_D^{25}$ -7.6° (*c* 2.3, CH_3OH). IR (nujol): 3250, 2900 cm^{-1}; ^1H NMR (CD_3OD): 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); ^{13}C NMR (CD_3OD): 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 $C_{12}H_{21}O_3Si$ 213.1491 (M^++1). Found: 213.1501.

(3*R*,4*S*,4a*R*,8a*R*)-4a-(*tert*-Butyldimethylsilanyloxymethyl)-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-2*H*-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 NH_4Cl 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° (*c* 1.0, $CHCl_3$); IR (neat) 3400, 2960 cm^{-1}; ^1H 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 $C_{18}H_{35}O_5Si$ 327.2355 ($M+H^+$). Found: 327.2358.

19b: $[\alpha]_D^{25}$ -2.5° (*c* 0.7, EtOH); IR (neat): 3400, 2910 cm^{-1}; ^1H 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 $C_{18}H_{35}O_5Si$ 327.2355 (M^++1). Found: 327.2350.

19c: $[\alpha]_D^{25}$ -5.8° (*c* 1.6, $CHCl_3$); IR (neat): 2900, 2850 cm^{-1}; ^1H 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, dd, *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, dd, *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 $C_{24}H_{49}O_5Si_2$ 441.3220 (M^++1). Found: 441.3223.

(4*S*,4a*R*,8a*R*)-4a-(*tert*-Butyldimethylsilanyloxymethyl)-4,7-dimethyl-4a,5,6,8a-tetrahydro-4*H*-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° (*c* 0.8, $CHCl_3$). IR (neat): 1725cm^{-1}; ^1H 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 $C_{18}H_{33}O_5Si$: 325.2199 (M^++1). Found: 325.2195.

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