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A Short Synthesis of (–)-Chokol A

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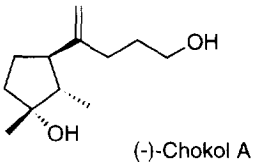
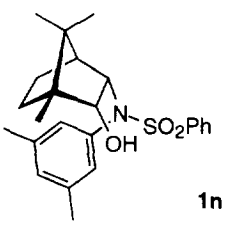
Abstract: (-)-Chokol A (**10**) was prepared in six steps (22% overall yield) via conjugate addition of a higher order cyanocuprate to the chiral 2-oxo-cyclopentenecarboxylate **2n**. After deprotection by transesterification the enantiomerically pure β-ketoester **5** was obtained which was transformed by α-methylation and subsequent decarbethoxylation to the cyclopentanone derivative **8**. Addition of methylcerium dichloride resulted in a mixture of **9a**, **9b** and **9c** (78:16:6), from which the main diastereomer **9a** was separated by MPLC. Finally desilylation of **9a** achieved (-)-chokol A (**10**).

(-)-Chokol A, a fungitoxic modified sesquiterpene isolated from stroma of the timothy *Phleum pratense* infected by the fungus *Epichloe typhina,* has shown biological activity against another pathogen of timothy, *Cladosporium plei.* Structure of this antibiotic was determined by spectroscopic methods[1] and later confirmed by syntheses of both the racemic[2-4] and the non-racemic[5-7] compounds. The first synthesis of racemic chokol A was carried out by Oppolzer[2] (13 steps, 3% overall yield). Shorter routes were later reported by Simpkins[3] (6 steps, 15% overall yield) and Groth[4] (5 steps, 24% overall yield). Routes to enantiomerically enriched material were developed by Mash[5] (80% ee) and Suzuki[6,7] (93% ee); however, an efficient synthesis of the enantiomerically pure compound is so far elusive. In connection with our program aiming at syntheses of biologically active natural products using auxiliary controlled conjugate additions[8-10] we considered (-)-chokol A a rewarding target and are now able to present a short and highly selective asymmetric synthesis of this antimycotic natural product.



(-)-Chokol A

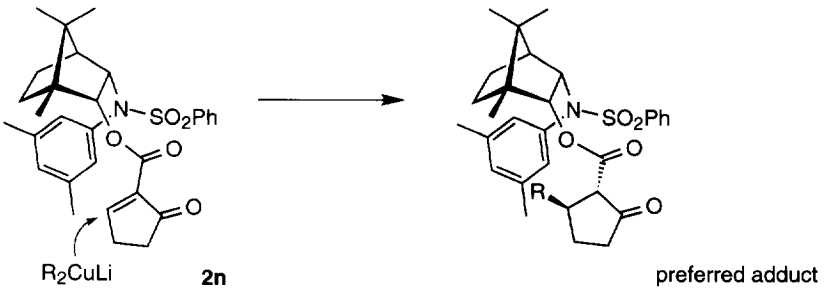


1n

Scheme 1

Key step of our route is the conjugate addition of an organocopper compound to the 2-oxo-cyclopentenecarboxylate **2n** of the concave chiral alcohol **1n** (Scheme 2); these additions generally proceed with extremely high diastereoselectivity (>98:2) and good yield (60-80%).[9,10]

Considering that the steric course of additions to such asymmetric shielded enoates can be rationalized by an attack of the organocopper reagent from the less hindered half-space of the *s-trans* enoate reactive species,[8-10] the addition of a nucleophilic side chain equivalent to **2n** was anticipated to give rise to the configuration of (-)-chokol A.



Scheme 2

The requisite side chain fragment 2-bromo-5-hydroxy-pentene (**3**) was prepared in two steps from readily available starting materials according to a procedure reported by Simpkins[3]. The terminal alcohol function of **3** was protected to give the *tert*-butyldiphenyl-silyl ether **4** (Scheme 3); this protecting group was expected to be stable against *tert*-BuLi (halogen-metal exchange reaction) and dilute acid (cleavage of the auxiliary) which would be necessary in the following steps.

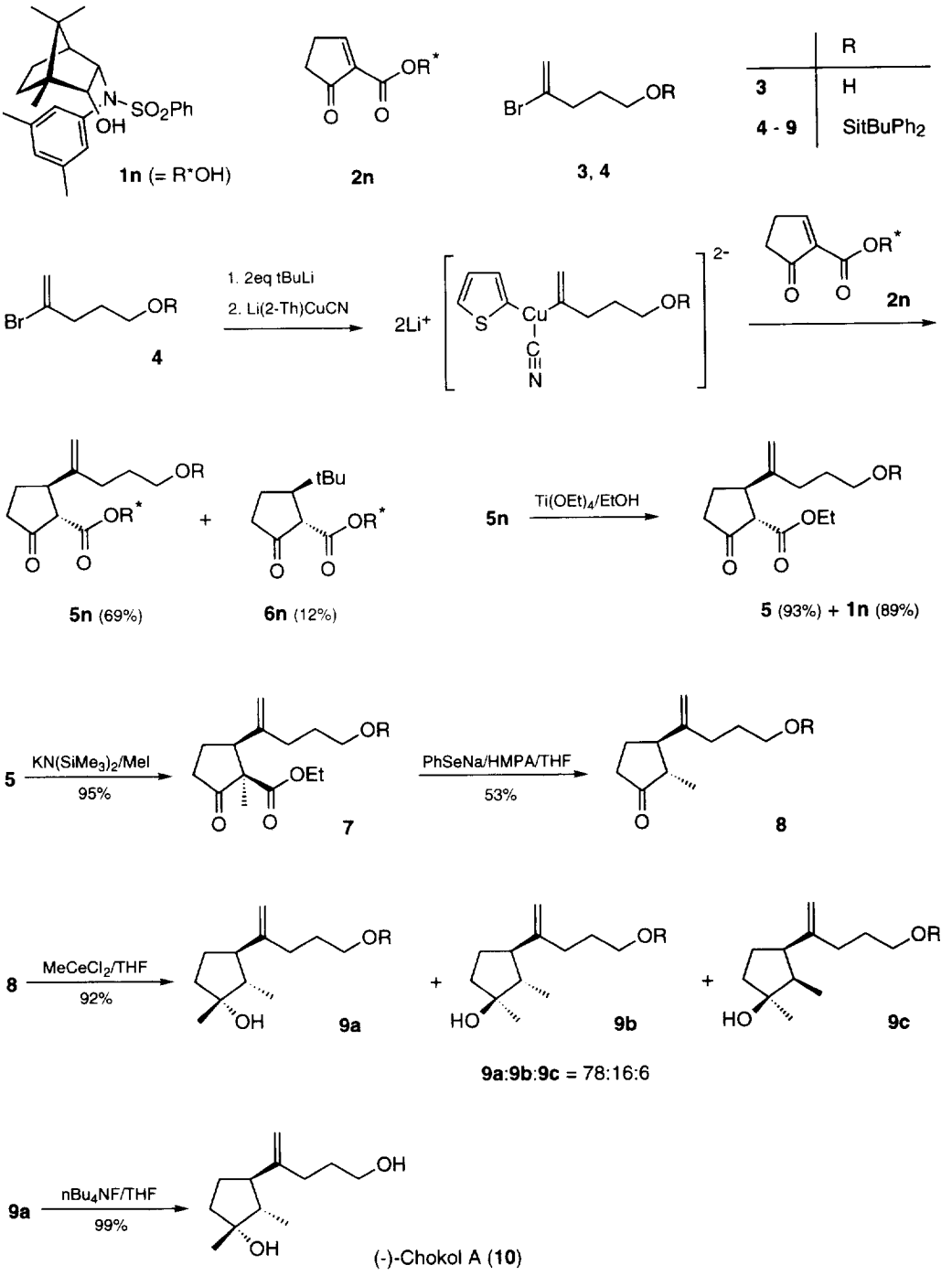
An organocopper reagent was prepared from bromide **4** by halogen-metal exchange and subsequent treatment with 2-thienylcyanocuprate according to a procedure of Lipshutz.[11] The resulting higher order cyanocuprate was treated with an equimolar amount of enoate **2n** to give a mixture of the desired addition product **5n** (69%) and a side product which after separation by flash chromatography was identified as the previously described *tert*-butyl adduct **6n** (12%).[10] No side products diastereomer to **5n** were detected by HPLC, ^1H and ^{13}C NMR, which indicated very high diastereoselectivity. This result is in agreement with our earlier report of high diastereoselection obtained in additions of simpler organocopper compounds to **2n**.[9,10]

Cleavage of the chiral auxiliary from the highly crowded cyclopentanoate **5n** was accomplished by $Ti(OEt)_4$ mediated transesterification,[12] which allowed to recover **1n** in 89% yield and gave the enantiomerically pure ethyl ester **5** in 93% yield.

α-Methylation of the β-ketoester **5** via the potassium enolate gave **7** as single product in excellent yield (95%). The configuration of **7** was established by analysis of the ^1H NMR resonance of the ring methine hydrogen (5-H, 1.93 ppm) and the α-methyl group (1.40 ppm). The shifts caused by vicinal *cis* or *trans* ester and methyl substituents were previously determined in similar β-ketoesters.[13] Good agreement with the published values[13] for the chemical shifts of methine hydrogen (2.0-2.7 ppm) and of the methyl group (1.43 ppm) indicated for **7** a *trans* disposition of the methine hydrogen and the ester group.

Decarbethoxylation of **7** first caused great difficulties, because under standard conditions (eg. $DMSO/H_2O/NaCl$)[14] the silyl group rather than the ethoxycarbonyl group was removed. However, selective cleavage of the ethyl ester and subsequent decarboxylation was enabled by the method of Liotta[15] using sodium phenylselenide in THF/HMPA which gave **8** in moderate yield (53%).

Completion of the synthesis required the addition of a methyl anion equivalent to the ketone **8**. This was achieved by addition of methylcerium dichloride.[16] The resulting mixture of diastereomeric alcohols (**9a:9b:9c** = 78.4:15.8:5.8; HPLC) was separated by medium pressure chromatography to give diastereomerically pure (>99.7%, HPLC) **9a** in 67% yield.


1n (= R*OH)
2n
3, 4
R
3 H
4 - 9 SitBuPh2
1. 2eq tBuLi
2. Li(2-Th)CuCN
4
2Li+
2n
5n (69%)
6n (12%)
5n
Ti(OEt)4/EtOH
5 (93%) + 1n (89%)
5
KN(SiMe3)2/MeI
95%
7
PhSeNa/HMPA/THF
53%
8
8
MeCeCl2/THF
92%
9a
9b
9c
9a:9b:9c = 78:16:6
9a
nBu4NF/THF
99%
(-)-Chokol A (10)

Scheme 3

After removal of the silyl ether protecting group by treatment of **9a** with tetrabutylammonium fluoride in THF (-)-chokol A was obtained in 99% yield (22% overall starting from **2n**). The synthetic material gave spectral data fully in accordance with the published data of the natural product.[1] The optical rotation {$[\alpha]_D^{20}$ = -61.68 (c = 1.07 in EtOH)} corresponded to the value expected[5-7] for enantiomerically pure (-)-chokol A.

In conclusion, this short synthesis of (-)-chokol A demonstrates the usefullness of asymmetric protected 2-oxo-cyclopentenecarboxylates as key intermediates in natural product syntheses. Extended antimycotic testing of the synthetic antibiotic, especially against human pathogen fungi, is enabled by the improved access.

EXPERIMENTAL SECTION

Melting points were determined with a Büchi glass capillary melting point apparatus (Dr. Tottoli) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured with a Bruker AC 300 using TMS as an internal standard. MPLC was performed with a Pharmacia pump (P-500), a Kronwald column (841x18.5 mm, Lichroprep Si 60, 15-25 µm), a Pharmacia single path monitor (UV-1, 254 nm) and a Pharmacia fraction collector (FRAC-200). The HPLC system consisted of a Kontron pump type 420, a Reodyne injection valve, a Merck column (250x4 mm, Lichrospher Si 60, 5 µm), a Kontron UV/VIS detector type 432 (detection at 254 nm), and a Kontron data system 450 for integration. GC chromatograms were performed at a Hewlett Packard chromatograph (HP 5890) using a capillary column (HP1, 23 m x 0.2 mm x 0.33 µm, crosslinked with methylsilicon); mass spectrometric detector (HP 5970 MSD). Optical rotations were measured on a Perkin Elmer 241 polarimeter. Microanalyses were determined at the Institute of Organic Chemistry, University of Heidelberg.

2-Bromo-5-*tert*-butyldiphenylsilyloxy-1-pentene (4)

A solution of 2-bromo-1-penten-5-ol (**3**)[3] (12.4 g, 67.8 mmol), imidazole (11.6 g, 170 mmol) and $tBuPh_2SiCl$ (20.6 g, 75 mmol) in DMF (150 ml) was stirred at 20 °C for 3h. Then water (100 ml) was added and the reaction mixture extracted with ether (300 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was distilled off *in vacuo*. Purification of the residue by flash chromatography (300 g, silica gel, hexane:EtOAc = 95:5) gave **4** (21.7 g, 79%), colourless oil, bp 155 °C/0.05 mbar. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.07 (s, 9H, tBu CH_3), 1.82 (m_c, 2H, 4-H), 2.58 (t, *J* = 7.3 Hz, 2H, 3-H), 3.70 (t, *J* = 6.1 Hz, 2H, 5-H), 5.40 (s, 1H, 1H), 5.56 (s, 1H, 1-H), 7.34-7.48 (m, 6H, aryl H), 7.62-7.73 (m, 4H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 19.22 (tBu C), 26.87 (tBu CH_3), 30.90 (C-4), 37.93 (C-3), 62.31 (C-5), 116.65 (C-1), 127.64 (SiAr C-3, C-5), 129.60 (SiAr C-4), 133.60 (SiAr C-1), 134.30 (C-2), 135.54 (SiAr C-2, C-6). GC: Injection port 200 °C, initial temp. 60 °C (5 min), increased (20 °C/min) to final temp. (250 °C), R_t = 19.94 min. MS (70 eV), *m/z* (%): 347 (32) [M^+-tBu·; ^{81}Br], 345 (29) [M^+-tBu·; ^{79}Br], 199 (29) [Ph_2SiOH^+]. Anal. Calcd for $C_{21}H_{27}BrOSi$: C, 62.51; H, 6.76; Br, 19.80. Found C, 62.74; H, 6.85; Br, 19.85.

Conjugate Addition to 2n

Bromide **4** (10.6 g, 26.3 mmol) dissolved in THF (100 ml) was treated with tBuLi (18.73 g, 50.0 mmol) at -78 °C for 2 h. The resulting reaction mixture was added to a precooled solution of lithium 2-thienylcyanocuprate (100 ml, 0.25 M in THF, 25 mmol, purchased from Aldrich) and stirred at -78 °C for 1 h. Then a solution of **2n** (13.0 g, 25.0 mmol) in THF (140 ml) was added and stirring was continued at -78 °C for 2 h. The reaction mixture was quenched with a solution of NH_4Cl (5%), stirred at 20 °C for 1 h and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent distilled off *in vacuo*. Purification of the residue by flash chromatography (1 kg, silica gel, hexane:EtOAc = 9:1) gave **5n** (14.58 g, 69%, R_f = 0.26), colourless crystals from hexane, mp 60 °C and **6n** (1.68 g, 12%, R_f = 0.22), colourless crystals from 2-PrOH, mp 184 °C.

(1R,2R,3S,4S)-{3-[N-Benzenesulfonyl-N-(3,5-dimethylphenyl)-amino]-2-bornyl}-(1S,5R)-5-(5-*tert*-butyl-diphenyl-silyloxy-1-penten-2-yl)-2-oxo-cyclopentanecarboxylate (5n)

^{1}H NMR (300 MHz, $CDCl_3$, ketone:enol = 77:23) δ(ketone) = 0.81 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 1.04 (s, 9H, tBu CH_3), 1.06 (s, 3H, CH_3), 1.00-1.30 (m, 3H), 1.65-1.93 (m, 4H), 2.01 (s, 3H, Ar–CH_3), 2.10-2.50 (m, 6H), 2.31 (s, 3H, Ar–CH_3), 3.48 (dt, *J* = 5.8 and 11.2 Hz, 1H, 5'-H), 3.59 (d, *J* = 11.2 Hz, 1H, 1'-H), 3.72 (t, *J* = 6.3 Hz, 2H, OCH_2), 4.28 (dd, *J* = 8.6 and 3.3 Hz, 1H, 3-H), 4.91 (s, 1H, =CH_2), 5.06 (s, 1H, =CH_2), 5.48 (d, *J* = 8.6 Hz, 1H, 2-H), 5.73 (s, 1H, NAr 2-H), 6.84 (s, 1H, NAr 4-H), 7.18 (s, 1H, NAr 6-H), 7.29-7.43 (m, 10H, SiArH, SO_2ArH), 7.49 (m_c, 1H, SO_2ArH), 7.63-7.72 (m, 4H, SiArH); δ(enol, separated signals) = 0.74 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.04 (s, 9H, tBu CH_3), 2.10 (s, 3H, Ar–CH_3), 2.20 (s, 3H, Ar–CH_3), 4.12 (dd, *J* = 8.6 and 3.3 Hz, 1H, 3-H), 4.69 (s, 1H, =CH_2), 4.83 (s, 1H, =CH_2), 5.43 (d, *J* = 8.6 Hz, 1H, 2-H), 6.19 (s, 1H, NAr 2-H), 6.74 (s, 1H, NAr 4-H), 6.80 (s, 1H, NAr 6-H), 10.60 (s, 1H, =C–OH). ^{13}C NMR (75 MHz, $CDCl_3$, ketone:enol = 85:15) δ(ketone) = 13.41 (CH_3), 19.16 (CH_3), 19.35 (CH_3), 19.49 (tBu C, C-5), 21.01 (Ar–CH_3), 21.13 (Ar–CH_3), 26.47 (C-6), 26.84 (tBu CH_3), 30.70 (C-3"), 30.97 (C-4"), 38.31 (C-3'), 45.30 (C-5'), 45.72 (C-7), 49.29 (C-4), 51.44 (C-1), 59.32 (C-3), 59.70 (C-1'), 63.62 (C-5"), 77.77 (C-2), 109.51 (C-1"), 127.50 (SiAr C-3, C-5), 128.04 (SO_2Ar C-3, C-5), 128.12 (SO_2Ar C-3, C-5), 129.28 (NAr C-4), 129.38 (SiAr C-4), 129.46 (NAr C-2), 130.41 (NAr C-6), 132.30 (SO_2Ar C-4), 134.10 (SiAr C-1), 135.50 (SiAr C-2, C-6), 137.01 (NAr C-3), 137.29 (NAr C-1), 138.19 (NAr C-5), 138.94 (SO_2Ar C-1), 148.47 (C-2"), 167.82 (COO), 210.52 (C-2'); δ(enol, separated signals) = 13.81 (CH_3), 19.39 (CH_3), 19.44 (CH_3), 30.26 (C-3"), 30.83 (C-4"), 31.29 (C-3'), 45.30 (C-7), 46.76 (C-5'), 50.16 (C-4), 50.89 (C-1), 59.05 (C-3), 63.83 (C-5"), 74.96 (C-2), 102.93 (C-1'), 107.65 (C-1"), 129.53 (NAr C-4), 132.50 (SO_2Ar C-4), 136.40 (NAr C-1), 137.14 (NAr C-3), 137.82 (NAr C-5), 139.63 (SO_2Ar C-1), 152.20 (C-2"), 169.04 (COO), 176.88 (C-2'). Anal. Calcd for $C_{51}H_{63}NO_6SSi$: C, 72.38; H, 7.52; N, 1.66; S, 3.78. Found C, 72.30; H, 7.79; N, 1.84; S, 3.97.

(1R,2R,3S,4S)-{3-[N-Benzenesulfonyl-N-(3,5-dimethylphenyl)-amino]-2-bornyl}-(1S,5R)-5-*tert*-butyl-2-oxo-cyclopentanecarboxylate (6n)

Physical and chemical data corresponded to previous published values.[10]

Transesterification of 5n

Ester **5n** (12.7 g, 15.0 mmol) and $Ti(OEt)_4$ (3.42 g, 15.0 mmol) were dissolved in ethanol (500 ml) and refluxed for 96 h. After removal of the solvent *in vacuo* the residue was dissolved in CH_2Cl_2 (300 ml), 1 M HCl (300 ml) was added and the mixture was stirred for 1 h at 20°C. The organic layer was separated, dried (Na_2SO_4) and the solvent distilled off at reduced pressure. After the main fraction of **1n** (3.86 g, 62%) was removed by crystallization from EtOH the residue was separated by flash chromatography (300 g, silica gel, CH_2Cl_2:hexane = 3:1) to give **5** (6.69 g, 93%, R_f = 0.42), as colourless oil and **1n** (1.65 g, 27%, R_f = 0.25), colourless crystals from EtOH, mp. 184 °C.

Ethyl-(1S,5R)-5-(5-*tert*-butyldiphenylsilyloxy)-1-penten-2-yl)-2-oxo-cyclopentanecarboxylate (5)

$[\alpha]_D^{20}$ = + 20.9 (*c* = 1.10, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.06 (s, 9H, tBu CH_3), 1.26 (t, *J* = 7.1 Hz, 3H, CH_3), 1.60-1.80 (m, 3H), 2.16 (t, *J* = 7.7 Hz, 2H, 3'-H), 2.20-2.54 (m, 3H), 3.16 (d, *J* = 11.4 Hz, 1H, 1-H), 3.20 (dt, *J* = 11.4 and 5.0 Hz, 1H, 5-H), 3.70 (t, *J* = 6.2 Hz, 2H, 5'-H), 4.19 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.84 (s, 2H, 1'-H), 7.35-7.47 (m, 6H, aryl H), 7.64-7.70 (m, 4H, aryl H). ^{13}C NMR (75 MHz,

$CDCl_3$) δ = 14.10 (CH_3), 19.14 (tBu C), 26.81 (tBu CH_3, C-4), 30.44 (C-3'), 30.87 (C-4'), 38.25 (C-3), 46.58 (C-5), 60.09 (C-1), 61.23 (OCH_2), 63.27 (C-5'), 109.41 (C-1'), 127.55 (SiAr C-3, C-5), 129.51 (SiAr C-4), 133.88 (SiAr C-1), 135.48 (SiAr C-2, C-6), 148.44 (C-2'), 168.99 (COO), 210.88 (C-2). GC: Injection port 200 °C, initial temp. 60 °C (5 min), increased (20 °C/min) to final temp. (250 °C), R_t = 32.57 min. MS (70 eV), *m/z* (%): 349 (86) [M^+-tBu·-H_2C=CH_2,-CO_2], 199 (100) [Ph_2SiOH^+]. Anal. Calcd for $C_{29}H_{38}O_4Si$: C, 72.75; H, 8.01. Found C, 72.57; H, 8.29.

Ethyl-(1R,5S)-5-(5-*tert*-butyldiphenyl-silyloxy-1-penten-2-yl)-1-methyl-2-oxo-cyclopentanecarboxylate (7)

β-Ketoester **5** (5.60 g, 11.7 mmol) dissolved in THF (160 ml) was reacted with a solution of $KN(SiMe_3)_2$ (23.4 ml, 0.50 M in toluene, 11.7 mmol) at -78 °C for 1 h. Then MeI (7.50 ml, 120 mmol) was added, the mixture was allowed to warm up to 20 °C and stirred for 2 h. A solution of NH_4Cl (5%, 200 ml) was added and extracted with ether. The organic layer was dried (Na_2SO_4) and the solvent distilled off *in vacuo*. Purification of the residue by flash chromatography (300 g, silica gel, hexane:ether = 9:1) gave **7** (5.47 g, 95%, R_f = 0.24), colourless oil. $[\alpha]_D^{20}$ = + 40.5 (*c* = 1.20, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ = 1.06 (s, 9H, tBu CH_3), 1.18 (t, *J* = 7.1 Hz, 3H, CH_3), 1.40 (s, 3H, CH_3 at C-1), 1.68-1.78 (m, 2H, 4'-H), 1.93 (m_c, 1H, 5-H), 2.08-2.40 (m, 4H, 4-H, 3'-H), 2.52-2.71 (m, 2H, 3-H), 3.68 (t, *J* = 6.3 Hz, 2H, 5'-H), 4.04 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.87 (s, 1H, 1'-H), 4.91 (s, 1H, 1'-H), 7.34-7.46 (m, 6H, aryl H), 7.64-7.70 (m, 4H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.03 (CH_3), 19.15 (tBu C), 20.18 (CH_3 at C-1), 24.58 (C-4), 26.82 (tBu CH_3), 30.96 (C-4'), 32.56 (C-3'), 37.58 (C-3), 53.84 (C-5), 59.81 (C-1), 60.89 (OCH_2), 63.38 (C-5'), 111.07 (C-1'), 127.57 (SiAr C-3, C-5), 129.53 (SiAr C-4), 133.89 (SiAr C-1), 135.51 (SiAr C-2, C-6), 146.92 (C-2'), 170.24 (COO), 215.69 (C-2). GC: Injection port 250 °C, initial temp. 120 °C (5 min), increased (20 °C/min) to final temp. (250 °C), R_t = 41.47 min. MS (70 eV), *m/z* (%): 199 (100) [Ph_2SiOH^+]. Anal. Calcd for $C_{30}H_{40}O_4Si$: C, 73.11; H, 8.20. Found C, 73.24; H, 8.34.

Decarbethoxylation of 7

Small pieces of sodium (460 mg, 20.0 mmol) were added to a solution of $(PhSe)_2$ (3.12g, 10.0 mmol) in dry THF (10 ml) and the mixture was refluxed for 12 h. Then dry HMPA (4 ml) and a solution of **6** (1.97 g, 4.0 mmol) in THF (6 ml) were added and refluxing was continued for 96 h. After a solution of NH_4Cl (5%, 100 ml) was added the mixture was extracted with ether, the organic layer was dried (Na_2SO_4) and the solvent distilled off *in vacuo*. Purification of the residue by flash chromatography (150 g, silica gel, hexane:acetone = 9:1) gave **8** (887 mg, 53%, R_f = 0.53), colourless oil and **7** (158 mg, 8%, R_f = 0.44), colourless oil.

(2S,3R)-3-(5-*tert*-Butyldiphenylsilyloxy-1-penten-2-yl)-2-methyl-cyclopentanone (8)

$[\alpha]_D^{20}$ = + 30.0 (*c* = 1.16, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ = 1.02 (s, 3H, CH_3), 1.06 (s, 9H, tBu CH_3), 1.52-1.80 (m, 4H), 2.00-2.18 (m, 4H), 2.26 (m_c, 1H), 2.40 (m_c, 1H), 3.71 (t, *J* = 6.3 Hz, 2H, 5'-H), 4.84 (s, 1H, 1'-H), 4.85 (s, 1H, 1'-H), 7.35-7.44 (m, 6H, aryl H), 7.64-7.70 (m, 4H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 12.45 (CH_3), 19.21 (tBu C), 26.87 (tBu CH_3), 27.44 (C-4), 29.89 (C-3'), 31.15 (C-4'), 37.30 (C-5), 48.17 (C-3), 51.39 (C-2), 63.44 (C-5'), 109.34 (C-1'), 127.60 (SiAr C-3, C-5), 129.57 (SiAr C-4), 133.98 (SiAr C-1), 135.55 (SiAr C-2, C-6), 149.27 (C-2'), 220.13 (C-1). GC: Injection port 250 °C, initial temp. 120 °C (5 min), increased (20 °C/min) to final temp. (250 °C), R_t = 25.44 min. MS (70 eV), *m/z* (%): 363 (100) [M^+-tBu·], 199 (99) [Ph_2SiOH^+]. Anal. Calcd for $C_{27}H_{36}O_2Si$: C, 77.07; H, 8.64. Found C, 77.00; H, 8.68.

Addition of Methylcerium dichloride to 8

$CeCl_3$ (3.45 g, 14.0 mmol) was suspended in THF (40 ml) at 20 °C, cooled to -78 °C, reacted with MeLi (7.90 ml, 1.60 M in ether, 12.6 mmol) and stirred at -78 °C for 1 h. Then a solution of **8** (1.47 g, 3.50 mmol) in THF (40 ml) was added and stirring was continued at -78 °C for 4 h. After a solution of NH_4Cl (5%) was added, the mixture was extracted with ether, the organic layer was dried (Na_2SO_4) and the solvent evaporated to give a mixture of isomers (1.55 g, **9a**:**9b**:**9c** = 78.4:15.8:5.8, HPLC). Separation by MPLC (841x18.5 mm, LiChroprep Si 60, 15-25 µm, hexane:EtOAc = 9:1, 500 ml/h, 8 runs) gave **9a** (1.02 g, 67%, **9a**:**9c** = 99.7:0.3, HPLC), **9b** (153 mg, 10%, HPLC pure) and **9c** (46 mg, 3%, **9c**:**9a** = 97.9:2.1, HPLC) as colourless oils. HPLC: hexane:EtOAc = 9:1, flow 1.0 ml/min, R_t(**9a**) = 20.30 min, R_t(**9c**) = 22.02 min, R_t(**9b**) = 28.82 min.

(1R,2S,3R)-3-(5-*tert*-Butyldiphenylsilyloxy-1-penten-2-yl)-1,2-dimethyl-cyclopentanol (9a)

$[\alpha]_D^{20}$ = − 23.2 (*c* = 1.02, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.85 (d, *J* = 6.6 Hz, 3H, CH_3 at C-2), 1.05 (s, 9H, tBu CH_3), 1.09 (s, 1H, OH), 1.27 (s, 3H, CH_3 at C-1), 1.41 (m_c, 1H, 5-H), 1.53 (dq, *J* = 11.2 and 6.6 Hz, 1H, 2-H), 1.66-1.78 (m, 4H, 4-H, 4'-H), 1.94 (m_c, 1H, 5-H), 2.05 (m_c, 3'-H), 2.37 (dt, *J* = 11.2 and 8.8 Hz, 1H, 3-H), 3.69 (t, *J* = 6.2 Hz, 2H, 5'-H), 4.72 (s, 1H, 1'-H), 4.76 (s, 1H, 1'-H), 7.34-7.45 (m, 6H, aryl H), 7.64-7.70 (m, 4H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 10.63 (CH_3 at C-2), 19.20 (tBu-C), 26.54 (CH_3 at C-1), 26.87 (tBu-CH_3), 28.54 (C-4), 29.80 (C-3'), 31.27 (C-4'), 39.96 (C-5), 47.50 (C-3), 51.98 (C-2), 63.65 (C-5'), 80.25 (C-1), 108.12 (C-1'), 127.57 (SiAr C-3, C-5), 129.48 (SiAr C-4), 134.07 (SiAr C-1), 135.54 (SiAr C-2, C-6), 151.37 (C-2'). Anal. Calcd for $C_{28}H_{40}O_2Si$: C, 76.99; H, 9.25. Found C, 76.76; H, 9.04.

(1S,2S,3R)-3-(5-*tert*-Butyldiphenylsilyloxy-1-penten-2-yl)-1,2-dimethyl-cyclopentanol (9b)

$[\alpha]_D^{20}$ = − 11.7 (*c* = 0.91, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.84 (d, *J* = 6.8 Hz, 3H, CH_3 at C-2), 1.05 (s, 9H, tBu CH_3), 1.14 (s, 3H, CH_3 at C-1), 1.26 (s, 1H, OH), 1.55 (m_c, 1H), 1.64-1.84 (m, 6H), 1.97-2.12 (m, 3H, 3-H, 3'-H), 3.69 (t, *J* = 6.4 Hz, 2H, 5'-H), 4.72 (s, 1H, 1'-H), 4.78 (s, 1H, 1'-H), 7.34-7.45 (m, 6H, aryl H), 7.64-7.70 (m, 4H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 12.89 (CH_3 at C-2), 19.19 (tBu-C), 23.37 (CH_3 at C-1), 26.86 (tBu CH_3), 27.90 (C-4), 29.71 (C-3'), 31.29 (C-4'), 40.51 (C-5), 48.46 (C-3), 52.31 (C-2), 63.61 (C-5'), 80.21 (C-1), 108.23 (C-1'), 127.56 (SiAr C-3, C-5), 129.48 (SiAr C-4), 134.02 (SiAr C-1), 135.53 (SiAr C-2, C-6), 151.22 (C-2'). Anal. Calcd for $C_{28}H_{40}O_2Si$: C, 76.99; H, 9.25. Found C, 77.20; H, 9.53.

(1R,2R,3R)-3-(5-*tert*-Butyldiphenylsilyloxy-1-penten-2-yl)-1,2-dimethyl-cyclopentanol (9c)

$[\alpha]_D^{20}$ = + 0.709, $[\alpha]_{436}^{20}$ = − 2.13 (*c* = 0.846, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.74 (d, *J* = 7.3 Hz, 3H, CH_3 at C-2), 1.05 (s, 9H, tBu CH_3), 1.26 (s, 1H, OH), 1.33 (s, 3H, CH_3 at C-1), 1.54-1.94 (m, 7H, 2-H, 4-H, 5-H, 4'-H), 2.00 (ddd, *J* = 15.6, 9.5 and 4.2 Hz, 1H, 3`-H), 2.13 (ddd, *J* = 15.6, 9.3 and 6.3 Hz, 1H, 3`-H), 2.63 (q, *J* = 9.0 Hz, 1H, 3-H), 3.68 (t, *J* = 6.4 Hz, 2H, 5'-H), 4.75 (s, 1H, 1'-H), 4.85 (s, 1H, 1'-H), 7.33-7.45 (m, 6H, aryl H), 7.64-7.70 (m, 4H, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 9.54 (CH_3 at C-2), 19.24 (tBu C), 25.65 (C-4), 26.89 (tBu CH_3), 29.56 (CH_3 at C-1), 31.13 (C-3'), 32.93 (C-4'), 39.34 (C-5), 45.53 (C-3), 47.38 (C-2), 63.70 (C-5'), 80.31 (C-1), 109.44 (C-1'), 127.60 (SiAr C-3, C-5), 129.53 (SiAr C-4), 134.11 (SiAr C-1), 135.58 (SiAr C-2, C-6), 150.16 (C-2'). Anal. Calcd for $C_{28}H_{40}O_2Si$: C, 76.99; H, 9.25. Found C, 76.69; H, 9.44.

Desilylation of 9a

A solution of nBu_4NF (4.0 ml, 1.1 M in THF, 4.4 mmol) was dropped to a solution of **9a** (940 mg, 2.15 mmol) in THF (20 ml) and the mixture was stirred at 20 °C for 1 h. After a solution of NH_4Cl (5%) was added, the mixture was extracted with ether, the organic layer was dried (Na_2SO_4) and the solvent evaporated. Separation of the residue by flash chromatography (20 g silica gel, ether) gave $tBuPh_2SiOH$ (550 mg, 99%) and (-)-Chokol A (420 mg, 99%) as colourless oils.

(-)-Chokol A (10)

$[\alpha]_D^{22}$ - 61.68 (*c* = 1.07, EtOH). ^1H NMR (300 MHz, $CDCl_3$) δ = 0.87 (d, *J* = 6.8 Hz, 3H, CH_3 at C-2), 1.15 (s, 1H, OH), 1.28 (s, 3H, CH_3 at C-1), 1.48-1.37 (m, 2H, 5-H, OH), 1.56 (dq, *J* = 11.3 and 6.8 Hz, 1H, 2-H), 1.70-1.80 (m, 4H, 4-H, 4'-H), 1.98 (m_c, 1H, 5-H), 2.07 (t, *J* = 7.6 Hz, 2H, 3'-H), 2.40 (dt, *J* = 11.3 and 9.1 Hz, 1H, 3-H), 3.68 (t, *J* = 6.4 Hz, 2H, 5'-H), 4.78 (d, *J* = 1.5 Hz, 1H, 1'-H), 4.80 (s, 1H, 1'-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 10.55 (CH_3 at C-2), 26.39 (CH_3 at C-1), 28.63 (C-4), 30.05 (C-3'), 30.99 (C-4'), 39.77 (C-5), 47.46 (C-3), 51.56 (C-2), 62.42 (C-5'), 80.13 (C-1), 108.02 (C-1'), 151.20 (C-2'). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.66; H, 11.20. Found C, 72.42; H, 10.96.

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