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Total Synthesis of (–)-Chokol A by an Asymmetric Domino Michael Addition–Dieckmann Cyclization[1]

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Abstract: A convergent and asymmetric total synthesis of (–)-chokol A was accomplished in six steps starting from the α,β-unsaturated ester (*E*)-**9** in an overall yield of 27% with an enantiomeric excess of 95%. The key step of this synthesis is the asymmetric tandem conjugate addition–Dieckmann cyclization of the higher-order cuprate **8** derived from vinyl bromide **7** with the α,β-unsaturated ester (*E*)-**9**.

Key words: antifungal agents, asymmetric synthesis, Michael addition, tandem reaction, total synthesis

(–)-Chokol A (**1**) is a fungitoxic, modified sesquiterpene[2] isolated from the stromata of timothy grass *Phleum pretense* infected by the pathogenic fungus *Epichloë typhina*. This antimycotic natural product was isolated for the first time in 1985 by Yoshihara et al.[3] (–)-Chokol A (**1**) and the more active chokols B (**2**), C (**3**), D (**4**), and G (**5**, Figure 1) have received special attention due to their fungitoxic properties.[4]

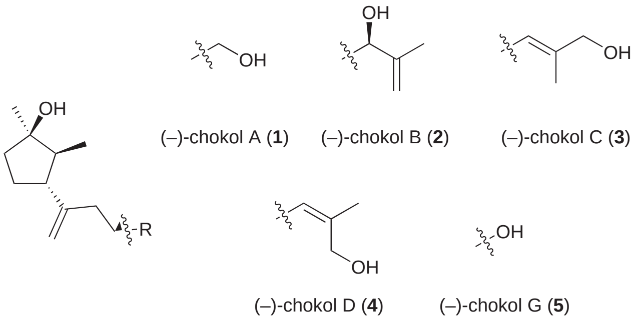


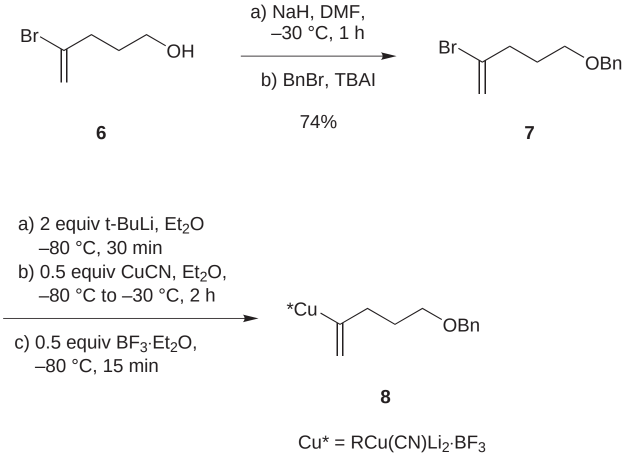
Figure 1 Representative members of the chokole family

Since the discovery of **1**, so far five racemic[5] and only four enantioselective[6] syntheses have been described for chokol A. In 1987 Mash[6a] presented the first asymmetric synthesis of (–)-chokol A (**1**). Key step of this synthesis was the diastereoselective cyclopropanation of a chiral ketal. The overall yield was 9% over 13 steps with an enantiomeric excess of approximately 80%. The last synthesis of (–)-chokol A (**1**) was described by Helmchen et al.[6d] in 1995. They converted the well-established 2-oxocyclopentenecarboxylate in six steps into the natural product (–)-**1** with an overall yield of 22% and ≥99%ee.

In 2004 we have reported the enantioselective synthesis of 2,3-disubstituted cyclopentanone derivatives via a combination of an asymmetric Michael addition and a Dieckmann cyclization.[7] This type of reaction belongs to the domino processes.[8]

Based on these results, an enantioselective synthesis of (–)-chokol A (**1**) was explored.

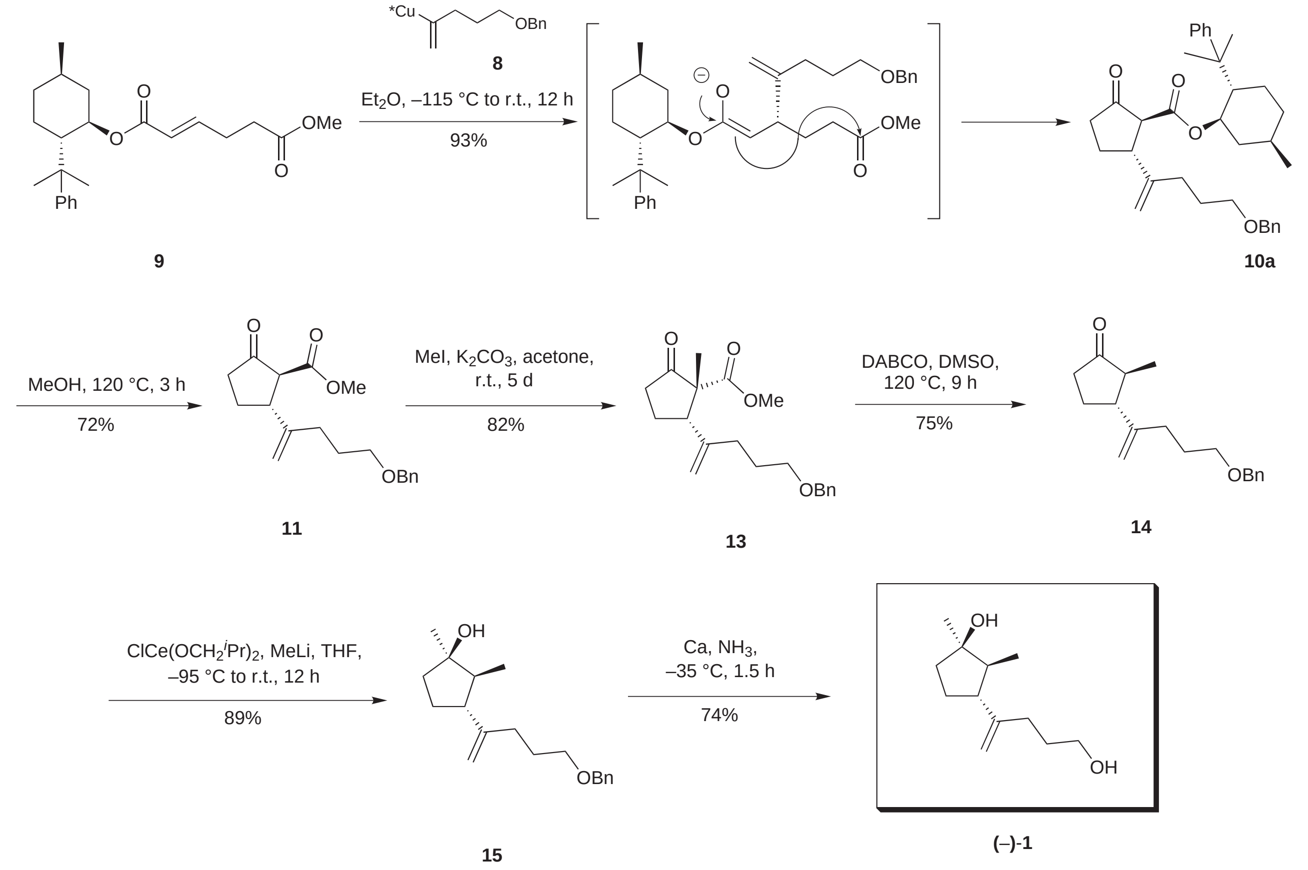
Starting the convergent synthesis with the benzylation of 2-bromo-5-hydroxypentene (**6**)[5d,9] (Scheme 1) following a protocol given by Gewald et al.[10] we obtained the bromo-vinyl building block **7**, which is essential for the synthesis of the higher-order cuprate **8**. Compound **7** was then treated with 2 equivalents of *tert*-butyllithium, followed by 0.5 equivalents of copper(I) cyanide and 0.5 equivalent of borontrifluoride in order to afford the cuprate **8**.



Scheme 1 Synthesis of the higher-order cuprate **8**

The α,β-unsaturated ester **9** (Scheme 2) was synthesized according to a formerly published route[7] by addition of (–)-phenylmenthol to 2-chloro-acetylchloride followed by a Michaelis–Arbuzov reaction with triethyl phosphite. The resulting diethoxy phosphonic ester was then converted into the α,β-unsaturated ester **9** via a Wittig–Horner reaction with methyl-4-oxo-butanoate. By employing this reaction sequence, we have generated the chiral Michael acceptor **9** in three steps with a yield of 83% over the whole sequence.

Addition of the cuprate **8** to the chiral ester **9** (Scheme 2) in diethyl ether at –115 °C gave after a Michael addition followed by a Dieckmann cyclization the cyclic β-keto



Scheme 2 Synthesis of (–)-chokol A (**1**)

ester **10a** with an excellent chemical yield of 93% and a diastereomeric excess of >98%.[11]

The cleavage of the chiral auxiliary was conducted by a transesterification with methanol at 120 °C in a sealed tube. This led to the methyl β-keto ester **11** in an acceptable yield of 72% with an excellent enantiomeric excess of >95%, whereby in a yield of 8% the retro-Dieckmann product and 84% of the enantiomerically pure (–)-phenylmenthol were recovered.

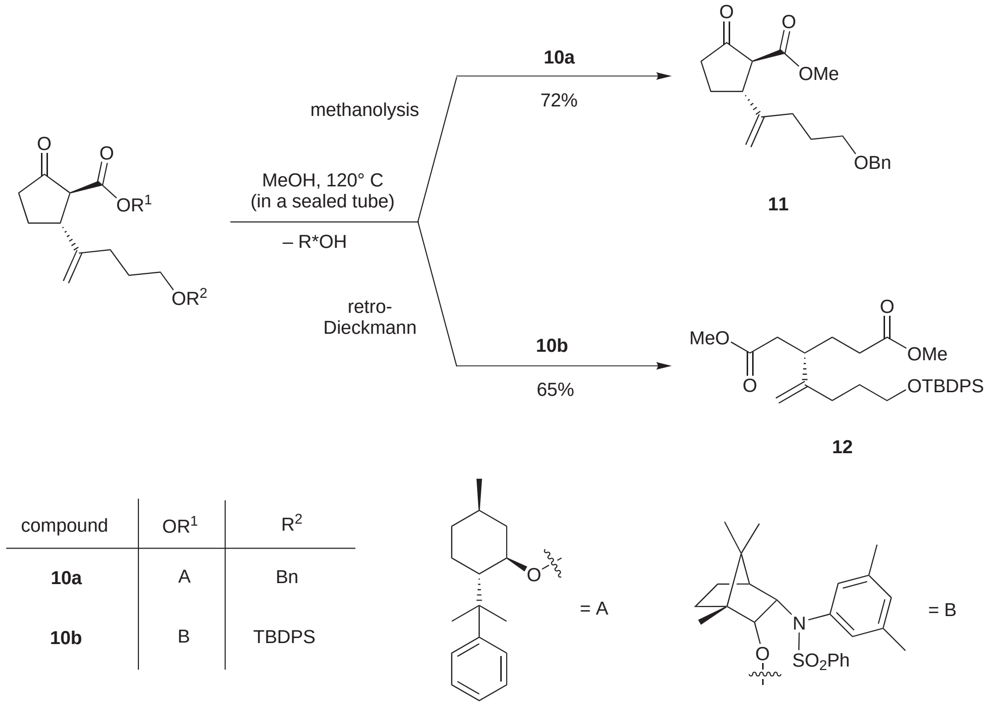
A comparable reaction with the substituted β-keto ester **10b** attached to the Helmchen reagent (Scheme 3) instead of (–)-phenylmenthol as chiral auxiliary and TBDPS as protecting group showed that the transesterification with methanol under the above-mentioned reaction conditions led to a retro-Dieckmann reaction. The substituted cyclopentanone **10b** underwent a ring-opening to the substituted dimethyl adipate **12** with additional recovering of the chiral camphor alcohol derivative.

After methylation with potassium carbonate and methyl iodide in acetone we obtained the 2,2′,3-trisubstituted cyclopentanone **13**. Compound **13** was then converted with 1,4-diaza-bicyclo[2.2.2]octane (DABCO) into dimethyl sulfoxide at 120 °C via a demethoxycarbonylation reaction[12] into the 2,3-disubstituted cyclopentanone **14**. Surprisingly the DABCO-initiated demethoxycarbonylation succeeded even without an α-proton between the C1 keto function and the ester, although this was postulated as a necessity for the feasibility of this reaction.[12b] In order to synthesize the tertiary alcohol at the C1 position we used cerium(III) reagents as nucleophiles, which were generated in situ from methyllithium and chlorocerium(III)dialkoxides. Best results were obtained by employing chlorocerium(III)di-neopentoxide for this reaction. Addition of this cerium(III) reagent afforded compound **15** after aqueous work-up in 89% yield with a diastereomeric excess of 88% (Table 1).

Table 1 Addition of Different Cerium(III) Reagents to **14**

Reagent	Yield of **14** (%)	de (%)
$MeCeCl_2$	91	63
$MeCe(Oi\text{-}Pr)_2$	83	79
$MeCe(Ot\text{-}Bu)_2$	85	82
$MeCe(OCH_2i\text{-}Pr)_2$	89	88

Because of their high steric demand and the oxophilic nature of cerium, the cerium(III) reagents are specially suited for addition reactions to carbonyl groups that easily undergo enolization.[13] The cleavage of the benzyl ether under mild conditions was then achieved by the use of calcium in liquid ammonia. The use of calcium in ammonia proved to be mild enough to cleave the benzyl ether without affecting the double bond. So finally, after column



compound	OR^1	R^2
10a	A	Bn
10b	B	TBDPS

Scheme 3

chromatography we isolated the natural product (–)-chokol A in 74% yield and the enantiomeric excess was determined to be ≥95% by comparing its optical rotation {$[\alpha]_D^{20}$ –56.2 (*c* 0.58, EtOH)} with the data reported earlier.[6]

Acknowledgment

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(11) **(1*S*,2*S*,1′*R*,2′*S*,5′*R*)-2-[1-(3-Benzyloxypropyl)vinyl]-5-oxocyclopentanecarboxylic Acid [5′-Methyl-2′-(1-methyl-1-phenylethyl)]cyclohexyl Ester (10a)**
To a solution of 2.55 g (10.0 mmol) 2-bromopentenylbenzyl ether (**7**) in 20 mL of abs. Et_2O 10.0 mL (20.0 mmol, 2 M solution in Et_2O) of *t*-BuLi was slowly added at –90 °C and stirred then at this temperature for 90 min. The resulting organolithium compound was then added at –80 °C via canula to a suspension of 0.45 g (5.0 mmol) copper(I) cyanide in 10 mL Et_2O and stirred then for 2 h until the temperature reached –30 °C and the suspension turned into a bright-green solution. After cooling the solution again to –80 °C 0.64 mL (5.0 mmol) $BF_3{\cdot}OEt_2$ were added by syringe and stirred for 15 min, whereupon the solution was cooled to –115 °C by an EtOH–dry ice bath. After reaching this temperature a degassed solution of 0.37 g (1.0 mmol) of the chiral ester **9** in 10 mL Et_2O was added (very) slowly to the solution of the higher order cuprate **8** and the resulting reaction solution was then stirred for 12 h under warming to r.t. For the work-up 30 mL of a sat. NH_4Cl solution were added to the black suspension, stirred for 2–3 min and then filtered over Celite®. After phase separation the aqueous phase was extracted 3 times with 25 mL portions of Et_2O. The combined organic phases were dried over $MgSO_4$ and concentrated with a rotary evaporator at 30 °C/13 mbar. The resulting residue was then purified via column chromatography over 200 g silica gel with PE–Et_2O = 2:1 as eluent, which gave 0.48 g (0.93 mmol, 93% yield) of the compound **10a** (Figure 2). The diastereomeric excess was determined to be >95% by ^{13}C NMR spectroscopy. $R_f = 0.35$ (PE–Et_2O = 2:1). ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.85$ (d, 3 H, -CH_3, $J = 6.3$ Hz), 1.18 (s, 3 H, -CH_3), 1.26 (s, 3 H, -CH_3), 1.34–2.39 (m, 18 H, H2–H4, H1′–H6′ and H2″–H3″), 2.86–2.88 (m, 1 H, H1), 3.5 (t, 2 H, H4″, $J = 6.2$ Hz), 4.52 (s, 2 H, -CH_2Ph), 4.76–4.83 (m, 2 H, C=CH_2), 7.06–7.50 (m, 10 H, 2 × Ph). ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 21.71$ (C5′–CH_3), 26.29 [C2′–C$(CH_3)_2$Ph], 26.56 (C3′), 26.83 [C2′–C$(CH_3)_2$Ph], 26.90 (C3″), 27.96 (C5′), 30.96 (C3), 31.25 (C2′), 34.48 (C4′), 38.09 (C4), 39.81 [C2′–C$(CH_3)_2$Ph], 41.22 (C2), 45.13 (C6′), 49.90 (C2′), 60.35 (C1), 69.66 (C4″), 72.91 (OCH_2Ph), 76.27 (C1′), 109.38 (C1″=CH_2), 124.90 ($C_{para,Ph}$), 125.42 ($C_{ortho,Ph}$), 127.48 ($C_{para,Bn}$), 127.55 ($C_{ortho,Bn}$), 127.92 ($C_{meta,Ph}$), 128.30 ($C_{meta,Bn}$), 138.42 ($C1_{Bn}$), 148.38 (C1″), 151.21 ($C1_{Ph}$), 167.49 (-CO_2R), 210.23 (C5). MS (EI, 70eV): *m/z* (%) = 516.4 (0.1) [M^+], 302.2 (52.0) [$M^+ - C_{16}H_{22}$], 119.1 (50.0) [Ph-$C(CH_3)_2^+$], 91.1 (100.0) [$C_7H_7^+$]. IR (film): 3020, 3005 (C=CH_2), 1745 (C=O), 1710 (-CO_2R), 1640 (C=C) cm^{-1}. $[a]_D^{20}$ +4.21 (*c* 1.13, $CHCl_3$). Anal. Calcd for $C_{34}H_{44}O_4$: C, 79.03; H, 8.58. Found: C, 78.90; H, 8.71.

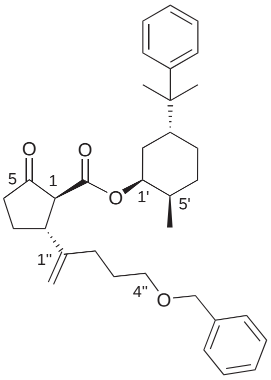

Figure 2

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