Total Synthesis of (–)-Chokol A by an Asymmetric Domino Michael Addition– Dieckmann Cyclization¹

Ulrich Groth,* Christian Kesenheimer, Paul Kreye

Fachbereich Chemie, Universität Konstanz, Universitätsstraße 10, Postfach M-720, 78457 Konstanz, Germany Fax +49(7531)884155; E-mail: ulrich.groth@uni-konstanz.de *Received 31 May 2006*

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 higherorder 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 sesquiterpene² 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 racemic⁵ and only four enantioselective⁶ 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.

SYNLETT 2006, No. 14, pp 2223–2226 Advanced online publication: 24.08.2006 DOI: 10.1055/s-2006-949653; Art ID: G16806ST © Georg Thieme Verlag Stuttgart · New York 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 route⁷ 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 reaction¹² 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(O <i>i</i> -Pr) ₂	83	79
MeCe(Ot-Bu) ₂	85	82
MeCe(OCH ₂ <i>i</i> -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



Scheme 3

chromatography we isolated the natural product (–)chokol A in 74% yield and the enantiomeric excess was determined to be \geq 95% by comparing its optical rotation {[α]_D²⁰ -56.2 (*c* 0.58, EtOH)} with the data reported earlier.⁶

Acknowledgment

The authors are grateful to Metallgesellschaft AG and Wacker AG for providing valuable starting materials. P.K. thanks the Cusanus-Werk – Bischöfliche Hochbegabtenförderung – for a doctoral fellowship.

References and Notes

- (a) Stereoselective Synthesis of Steroids and Related Compounds, IX. For part VIII, see: Groth, U.; Kalogerakis, A.; Richter, N. *Synlett* **2006**, 905. (b) Lanthanides in Organic Synthesis, part VI. For part V, see: Groth, U.; Kesenheimer, C.; Neidhöfer, J. *Synlett* **2006**, *12*, 1859.
- (2) Koshino, H.; Yoshihara, T.; Togiya, S.; Terada, S.; Tsukada, S.; Okuno, M.; Noguchi, A.; Sakamura, S.; Ichihara, A. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* 1989, 31, 244.
- (3) Yoshihara, T.; Togiya, S.; Koshino, H.; Sakamura, S.; Shimanuki, T.; Sato, T.; Tajimi, A. *Tetrahedron Lett.* 1985, 26, 5551.
- (4) Sakamura, S. In *Biologically Active Natural Products Potential Use in Agriculture*; Culter, H. G., Ed.; ACS Symposium Series, Vol. 380, Oxford University Press: New York, **1988**.

- (5) (a) Oppolzer, W.; Cunningham, A. F. *Tetrahedron Lett.* 1986, 27, 5467. (b) Lawler, D. M.; Simpkins, N. S. *Tetrahedron Lett.* 1988, 29, 1207. (c) Tanimori, S.; Ueda, T.; Nakayama, M. *Biosci. Biotechnol. Biochem.* 1994, 58, 1174. (d) Groth, U.; Halfbrodt, W.; Köhler, T.; Kreye, P. *Liebigs Ann. Chem.* 1994, 9, 885. (e) Deloux, L.; Srebnik, M. *Tetrahedron Lett.* 1996, 37, 2735.
- (6) (a) Mash, E. A. J. Org. Chem. 1987, 52, 4142. (b) Suzuki, T.; Sato, E.; Matsuda, Y.; Tada, H.; Koizumi, S.; Unno, K.; Kametami, T. J. Chem. Soc., Chem. Commun. 1988, 1531.
 (c) Suzuki, T.; Tada, H.; Unno, K. J. Chem. Soc., Perkins Trans. 1 1992, 2017. (d) Urban, E.; Knühl, G.; Helmchen, G. Tetrahedron 1995, 51, 13031. (e) For the enantioselective synthesis of (-)-chokol G, see: Kanada, R. M.; Tanaguchi, T.; Ogasawara, K. Chem. Commun. 1998, 1755.
- (7) Groth, U.; Halfbrodt, W.; Kalogerakis, A.; Köhler, T.; Kreye, P. Synlett 2004, 291.
- (8) For recent reviews on domino reactions, see: (a) Tietze, L. F. J. Heterocycl. Chem. 1990, 27, 47. (b) Tietze, L. F.; Beifuss, U. Angew. Chem., Int. Ed. Engl. 1993, 32, 131; Angew. Chem. 1993, 105, 137. (c) Tietze, L. F.; Bachmann, J.; Wichmann, J.; Burkhardt, O. Synthesis 1994, 1185. (d) Tietze, L. F. Chem. Ind. (London, U.K.) 1995, 453. (e) Tietze, L. F. Chem. Rev. 1996, 96, 115. (f) Tietze, L. F.; Modi, A. Med. Res. Rev. 2000, 20, 304. (g) Tietze, L. F.; Haunert, F. Domino Reactions in Organic Synthesis. An Approach to Efficiency, Elegance, Ecological Benefit, Economic Advantage and Preservation of our Resources in Chemical Transformations, In Stimulating Concepts in Chemistry; Shibasaki, M.; Stoddart, J. F.; Vögtle, F., Eds.; Wiley-VCH: Weinheim, 2000, 39-64. (h) Tietze, L. F.; Rackelmann, N. Pure Appl. Chem. 2004, 76, 1967. (i) Tietze, L. F.; Brasche, G.; Gericke, K. Domino Reactions in Organic Synthesis; Wiley-VCH: Weinheim, 2006.
- (9) For the synthesis of 2-bromo-5-hydroxypent-2-ene 7, see also: Lawler, D. M.; Simpkins, N. S. *Tetrahedron Lett.* 1988, 29, 1207.

Synlett 2006, No. 14, 2223-2226 © Thieme Stuttgart · New York

- (10) Gewald, K.; Jänsch, H. J. J. Prakt. Chem. 1973, 4, 779.
- (11) (1S,2S,1'R,2'S,5'R)-2-[1-(3-Benzyloxypropyl)vinyl]-5oxocyclopentanecarboxylic Acid [5'-Methyl-2'-(1methyl-1-phenylethyl)]cyclohexyl Ester (10a) To a solution of 2.55 g (10.0 mmol) 2-bromopentenylbenzyl ether (7) in 20 mL of abs. Et₂O 10.0 mL (20.0 mmol, 2 M solution in Et₂O) 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) BF₃·OEt₂ 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 Et₂O 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. NH₄Cl 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 Et₂O. The combined organic phases were dried over MgSO4 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 ¹³C NMR spectroscopy. $R_f = 0.35$ $(PE-Et_2O = 2:1)$. ¹H NMR (200 MHz, CDCl₃): $\delta = 0.85$ (d, 3 H, -CH₃, *J* = 6.3 Hz), 1.18 (s, 3 H, -CH₃), 1.26 (s, 3 H, -CH₃), 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, -CH₂Ph), 4.76–4.83 (m, 2 H, C=CH₂), 7.06– 7.50 (m, 10 H, 2 × Ph). ¹³C NMR (50.3 MHz, CDCl₃): $\delta = 21.71 (C5'-CH_3), 26.29 [C2'-C(CH_3)_2Ph], 26.56 (C3'),$



Figure 2

- 26.83 [C2'-C(CH₃)₂Ph], 26.90 (C3''), 27.96 (C5'), 30.96 (C3), 31.25 (C2'), 34.48 (C4'), 38.09 (C4), 39.81 [C2'-C(CH₃)₂Ph], 41.22 (C2), 45.13 (C6'), 49.90 (C2'), 60.35 (C1), 69.66 (C4''), 72.91 (OCH₂Ph), 76.27 (C1'), 109.38 (C1''=CH₂), 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 (-CO₂R), 210.23 (C5). MS (EI, 70eV): *m/z* (%) = 516.4 (0.1) [M⁺], 302.2 (52.0) [M⁺ C₁₆H₂₂], 119.1 (50.0) [Ph-C(CH₃)₂⁺], 91.1 (100.0) [C₇H₇⁺]. IR (film): 3020, 3005 (C=CH₂), 1745 (C=O), 1710 (-CO₂R), 1640 (C=C) cm⁻¹. [a]_D²⁰ +4.21 (*c* 1.13, CHCl₃). Anal. Calcd for C₃₄H₄₄O₄: C, 79.03; H, 8.58. Found: C, 78.90; H, 8.71.
- (12) (a) Parish, E. J.; Mody, N. V.; Hedin, P. A.; Miles, D. H. J. Org. Chem. 1974, 39, 1592. (b) Huang, B.-S.; Parish, E. J.; Miles, D. H. J. Org. Chem. 1974, 39, 2647. (c) For a review article about this topic, see: Krapcho, A. P. Synthesis 1982, 805.
- (13) Alcarez, C.; Groth, U. Angew. Chem., Int. Ed. Engl. 1997, 36, 2480.