Tetrahedron Letters 51 (2010) 1945–1946

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The first asymmetric total syntheses of both enantiomers of cryptocaryone

Hiromichi Fujioka *, Kenji Nakahara, Tomohiro Oki, Kie Hirano, Tatsuya Hayashi, Yasuyuki Kita †

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan

ARTICLE INFO

Article history:
Received 28 December 2009
Revised 26 January 2010
Accepted 28 January 2010
Available online 10 February 2010

Keywords:
Cryptocaryone
Chiral auxiliary
Intramolecular bromoetherification
CAN

ABSTRACT

The first asymmetric total syntheses of the (+)- and (−)-cryptocaryones are described. Removal of the acetal unit of the enone acetal **5**, which was obtained in our previous study from the cyclohexadiene acetal **3**, afforded the enone acetal **8** in a one-pot procedure. The acylation of **8** with cinnamoyl chloride and subsequent hydrolysis of the resulting acetal gave the lactol **11**. Its oxidation with NIS and tetra-*n*-butylammonium iodide (TBAI) finally furnished the natural (+)-cryptocaryone **2**. The same procedure from *ent*-**3** afforded the unnatural one **1**.

Cryptocaryone was first isolated from the root of *Cryptocarya bourdilloni* Gamb in 1972 and its structure was reported as a chalcone.[1] Its structure was revised in 1985 and its relative structure was determined as **1** by X-ray analysis.[2] In 2001, cryptocaryone having the same optical rotation was also obtained from the trunk bark of *Cryptocarya infectoria* (Bl.) Miq. and its absolute configuration was determined as **2** from an X-ray analysis of its analogue.[3] However, its absolute configuration is still confusing. For example, cryptocaryone was also isolated from *Cryptocarya rugulosa* in 2009 by Cardellina II and co-workers, and its structure was shown as **1**, although they did not mention its absolute configuration.[4] From a biological aspect, cryptocaryone was reported to show a cytotoxicity against the multi-drug resistant K562-DOX cells in 2001,[3] and quite recently, it was shown to be an inhibitor of the nuclear factor-κB (NF-κB) activity.[4] The NF-κB signaling pathway is active in many cancers and is a potent therapeutic target. Therefore, cryptocaryone is an important synthetic target in view of its biological properties.

In this Letter, we present the first asymmetric syntheses of compounds **1** and **2**, the enantiomers of each other (Fig. 1), in a concise manner with unambiguous determination of their absolute configurations by chemical synthesis.

During the course of our continuous efforts regarding natural product syntheses, we have recently succeeded in the intramolecular haloetherification of the cyclohexadiene acetal **3**,[5] easily obtained from the commercially available 1,4-cyclohexadiene and chiral (*R,R*)-hydrobenzoin in two steps and 75% overall yield, to afford the optically active cyclohexene acetal **4** with multiple chiral centers. One of its application to asymmetric syntheses of natural products was conducted via the cyclohexenone acetal **5** obtained from **4** by hydroboration–oxidation procedure (Scheme 1).[6]

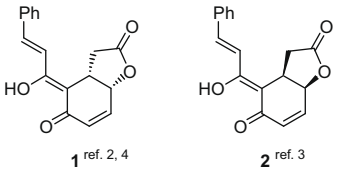
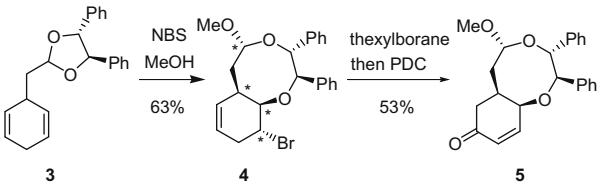


Figure 1. Structure of cryptocaryone.

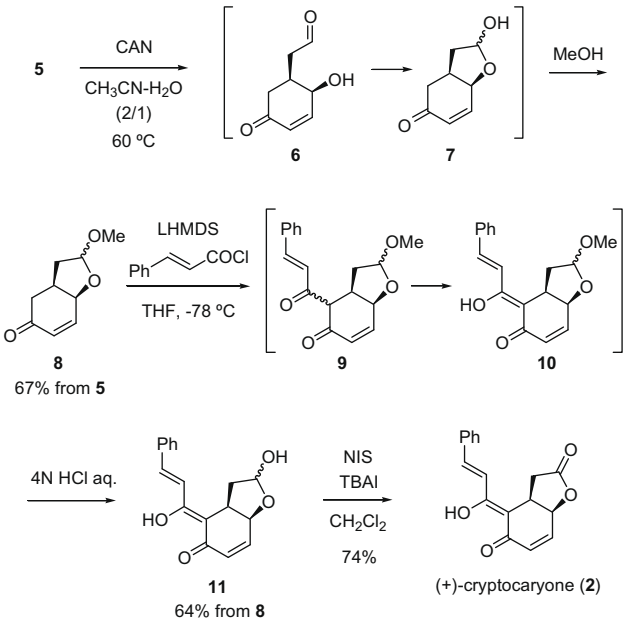
The cyclohexenone structure and its two asymmetric centers of **5** seemed to be a good precursor of those in structure **2**. Since the structures **1** and **2** are enantiomers of each other, we then studied the asymmetric syntheses of both enantiomers of cryptocaryone. The introduction of the side chain at the α′-position of the enone **5** was achieved using LHMDS and cinnamoyl chloride in good yield. However, the removal of the chiral auxiliary, the diphenylethyl unit, was unsuccessful. We then first removed the chiral auxiliary



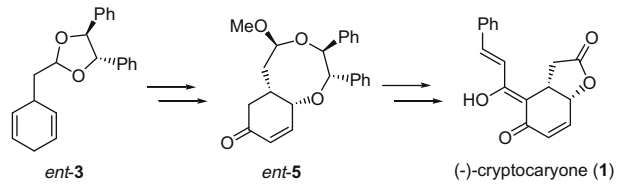
Scheme 1. Synthesis of the enone acetal **5** from the diene acetal **3**.

* Corresponding author. Tel.: +81 6 6879 8225; fax: +81 6 6879 8229.
E-mail address: fujioka@phs.osaka-u.ac.jp (H. Fujioka).
† Present address: College of Pharmaceutical Sciences, Ritsumeikan University, 1-1-1 Nojihigashi, Kusatsu, Shiga 525-8577, Japan.

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.01.101



Scheme 2. Asymmetric synthesis of (+)-cryptocaryone (**2**).



Scheme 3. Asymmetric synthesis of (−)-cryptocaryone (**1**).

and successively introduced the side chain as shown in Scheme 2. The treatment of **5** with CAN in CH_3CN–H_2O (2/1) at 60 °C allowed hydrolysis of an acetal unit[7] and subsequent removal of the diphenylethanol unit[8] to give the hydroxyl aldehyde **6**, which spontaneously cyclized to afford the lactol **7** as a diastereomeric mixture in a single operation. The lactol **7** was unstable and easily decomposed during evaporation and SiO_2 column chromatography. The treatment of the reaction mixture with MeOH then afforded the Me-ether **8** in 67% yield from **5** in a one-pot operation via the lactol **7**. It is proposed that the lactol **7** converted to the corresponding acetal **8**[10] by the Brønsted acid generated from CAN and MeOH.[9] Acylation at the α′-position of the enone unit of **8** with LHMDS and cynnamoyl chloride produced the diketone **9**, which was spontaneously converted to the enol form **10**. Acidic workup then afforded the lactol **11**[10] (64% yield from **8** in a one-pot operation). Although usual oxidants such as PCC and PDC gave poor results, the oxidation of the lactol unit with NIS and tetra-*n*-butylammonium iodide (TBAI)[11] finally furnished the structure **2**[10] in 74% yield. In addition to the physical data (^{1}H NMR, ^{13}C NMR, IR, HRMS), the agreement of its optical rotation with the natural cryptocaryone ($[\alpha]_D^{25.0}$ +761.8 (*c* 0.69, $CHCl_3$), (lit. $[\alpha]_D$ +776.6 (*c* 2, $CHCl_3$),[1a] $[\alpha]_D^{25}$ +770.7 (*c* 0.99, $CHCl_3$)[3]) indicated that the absolute configuration of the natural one is structure **2**.

For confirmation, the structure of **1** was also synthesized (Scheme 3). Thus, the same procedure from the *ent*-**3**,[5c] prepared from 1,4-cyclohexadiene and (*S*,*S*)-hydrobenzoin, afforded the structure **1** of cryptocaryone via *ent*-**5**. The optical rotation of **1** showed the opposite sign from the natural one ($[\alpha]_D^{24.9}$ −727.7 (*c* 1.00, $CHCl_3$)). From these facts, the structure of **1** was confirmed to be an enantiomer of the natural one.

In conclusion, we accomplished the first asymmetric syntheses of the natural and unnatural cryptocaryones from the commercially available 1,4-cyclohexadiene in a total of seven steps with a 7.9% overall yield. Furthermore, the information about the absolute structure of the natural one was presented by chemical synthesis.

Acknowledgments

This work was financially supported by Grant-in-Aid for Scientific Research (A) and (B) and Grant-in-Aid for Scientific Research for Exploratory Research from Japan Society for the Promotion of Science.

References and notes

1. (a) Govindachari, T. R.; Parthasarathy, P. C. *Tetrahedron Lett.* **1972**, *13*, 3419–3420; (b) Govindachari, T. R.; Parthasarathy, P. C.; Desai, H. K.; Shanbhag, M. N. *Tetrahedron* **1973**, *29*, 3091–3094.
2. Maddry, J. A.; Joshi, B. S.; Newton, M. G.; Pelletier, S. W.; Parthasarathy, P. C. *Tetrahedron Lett.* **1985**, *26*, 5491–5492.
3. Dumontet, V.; Gaspard, C.; Hung, N. V.; Fahy, J.; Tchertanov, L.; Sévenet, T.; Guéritte, F. *Tetrahedron* **2001**, *57*, 6189–6196.
4. Meragelman, T. L.; Scudiero, D. A.; Davis, R. E.; Staudt, L. M.; McCloud, T. G.; Cardellina, J. H., II; Shoemaker, R. H. *J. Nat. Prod.* **2009**, *72*, 336–339.
5. (a) Fujioka, H.; Kotoku, N.; Sawama, Y.; Nagatomi, Y.; Kita, Y. *Tetrahedron Lett.* **2002**, *43*, 4825–4828; (b) Fujioka, H.; Kotoku, N.; Sawama, Y.; Kitagawa, H.; Ohba, Y.; Wang, T.-L.; Nagatomi, Y.; Kita, Y. *Chem. Pharm. Bull.* **2005**, *53*, 952–957; (c) Fujioka, H.; Sawama, Y.; Kotoku, N.; Ohnaka, T.; Okitasu, T.; Murata, N.; Kubo, O.; Li, R.; Kita, Y. *Chem. Eur. J.* **2007**, *13*, 10225–10238.
6. Fujioka, H.; Ohba, Y.; Nakahara, K.; Takatsuji, M.; Murai, K.; Ito, M.; Kita, Y. *Org. Lett.* **2007**, *9*, 5605–5608.
7. For deprotection of acetals by CAN, see: (a) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Markó, I. E. *Tetrahedron Lett.* **1999**, *40*, 1799–1802; (b) Markó, I. E.; Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C. *Angew. Chem., Int. Ed.* **1999**, *38*, 3207–3209; (c) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C.; Markó, I. E. *Tetrahedron* **2003**, *59*, 8989–8999.
8. For the method using CAN, see: (a) Fujioka, H.; Ohba, Y.; Hirose, H.; Murai, K.; Kita, Y. *Org. Lett.* **2005**, *7*, 3303–3306; (b) Fujioka, H.; Hirose, H.; Ohba, Y.; Murai, K.; Nakahara, K.; Kita, Y. *Tetrahedron* **2007**, *63*, 625–637.
9. Pachamuthu, K.; Vankar, Y. D. *J. Org. Chem.* **2001**, *66*, 7511–7513.
10. Spectral data of compound **8** (ca. 2:1 diastereomeric mixture): colorless oil; IR (KBr): 1682, 1101, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.55–1.85 (1H, m), 2.01–2.06 (1H, m), 2.47–2.66 (2H, m), 2.84–2.91 (1/3H, m), 2.97–3.05 (2/3H, m), 3.35 (1H, s), 3.35 (2H, s), 4.73–4.76 (1H, m), 5.01 (2/3H, d, *J* = 5.0 Hz), 5.07 (1/3H, dd, *J* = 5.9, 4.1 Hz), 5.98 (1/3H, d, *J* = 10.1 Hz), 6.00 (2/3H, d, *J* = 10.5 Hz), 6.70 (2/3H, dd, *J* = 10.1, 3.2 Hz), 6.78 (1/3H, dd, *J* = 10.1, 2.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 34.9, 36.6, 37.8, 37.9, 38.0, 38.1, 54.9, 55.7, 73.0, 74.1, 104.6, 106.2, 128.9, 129.3, 145.8, 148.1, 197.5, 197.7; LRMS (EI): *m*/*z* 168 (M^+); HRMS (EI): calcd for $C_9H_{12}O_3$: 168.0786; found 168.0788. Spectral data of compound **11** (ca. 4:1 diastereomeric mixture): yellow amorphous; IR (KBr): 3376, 1630, 1557 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.89–1.96 (1H, m), 2.28 (4/5H, dd, *J* = 12.8, 7.3 Hz), 2.63–2.70 (1/5H, m), 3.49 (1H, br s), 3.55–3.62 (1/5H, m), 3.86–3.94 (4/5H, m), 4.93 (1/5H, d, *J* = 8.2 Hz), 5.12 (4/5H, d, *J* = 8.7 Hz), 5.56 (4/5H, d, *J* = 4.6 Hz), 5.66 (1/5H, t, *J* = 5.0 Hz), 6.04 (4/5H, d, *J* = 10.1 Hz), 6.06 (1/5H, d, *J* = 9.6 Hz), 6.45 (4/5H, dd, *J* = 10.1, 2.3 Hz), 6.67 (1/5H, d, *J* = 10.1 Hz), 6.84 (1/5H, d, *J* = 15.6 Hz), 6.98 (4/5H, d, *J* = 15.6 Hz), 7.32–7.58 (5H, m), 7.71 (1/5H, d, *J* = 15.6 Hz), 7.73 (4/5H, d, *J* = 15.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.6, 37.0, 41.4, 42.1, 75.0, 75.3, 96.3, 98.2, 104.7, 105.4, 117.7, 117.8, 127.3, 128.0, 128.1, 128.9, 129.0, 130.0, 130.1, 135.1, 135.2, 140.8, 141.0, 143.7, 146.7, 173.0, 174.1, 186.5, 187.1; LRMS (FAB): *m*/*z* 285 (MH^+); HRMS (FAB): calcd for $C_{17}H_{17}O_4$: 285.1127; found 285.1122. Spectral data of compound **2** ((+)-cryptocaryone): yellow solid; $[\alpha]_D^{25.0}$ +761.8 (*c* 0.69, $CHCl_3$); IR (KBr): 1778, 1630, 1556 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.62 (1H, dd, *J* = 17.4, 12.3 Hz), 2.79 (1H, dd, *J* = 17.4, 8.6 Hz), 3.94–4.04 (1H, m), 5.48 (1H, dd, *J* = 8.8, 2.0 Hz), 6.26 (1H, dd, *J* = 10.3, 1.8 Hz), 6.60 (1H, d, *J* = 10.1 Hz), 6.77 (1H, d, *J* = 15.4 Hz), 7.41–7.58 (5H, m), 7.77 (1H, d, *J* = 15.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.9, 35.3, 76.1, 103.3, 116.7, 128.2, 129.1, 130.1, 130.6, 134.8, 140.0, 142.4, 174.1, 174.4, 185.8; LRMS (FAB): *m*/*z* 283 (MH^+); HRMS (FAB): calcd for $C_{17}H_{15}O_4$: 283.0971; found 283.0958.
11. Hanessian, S.; Wong, D. H.; Therien, M. *Synthesis* **1981**, 394–396.