ORGANIC LETTERS

2009
Vol. 11, No. 14
3136−3138

Efficient Asymmetric Total Syntheses of Cryptocarya Triacetate, Cryptocaryolone, and Cryptocaryolone Diacetate

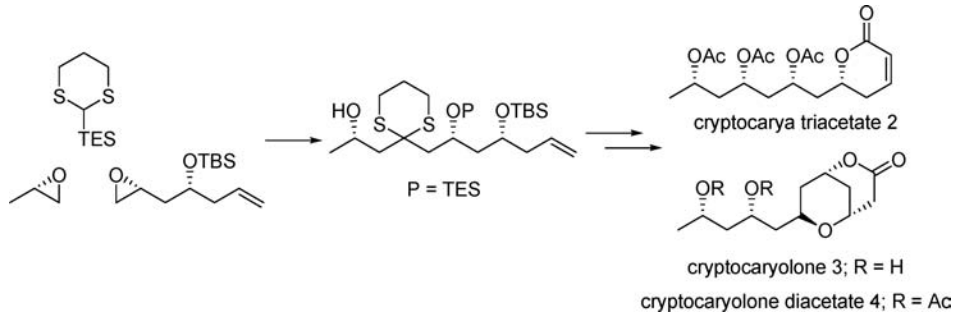
Xiaolei Wang,[†] Wenkuan Wang,[†] Huaiji Zheng,[†] Yingpeng Su,[†] Tuo Jiang,[†] Yongping He,[†] and Xuegong She*[,†,‡]

State Key Laboratory of Applied Organic Chemistry, Department of Chemistry, Lanzhou University, Lanzhou 730000, People's Republic of China, and State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, People's Republic of China

shexg@lzu.edu.cn

Received May 11, 2009

ABSTRACT



Concise and efficient asymmetric total syntheses of three substituted α-pyrone-type natural products have been accomplished via 7−9 steps from 5b in high overall yields, which involve linchpin coupling, ring-closing metathesis, and a tandem sequence of deacetylation and intramolecular oxa-Michael addition as the key steps.

Cryptocarya triacetate **2**, cryptocaryolone **3**, and cryptocaryolone diacetate **4** were isolated from the bark of a South African plant, *Cryptocarya latifolia*.[1] Related investigations showed that they have significant biological activities and medical properties, ranging from the treatment of headaches and morning sickness to that of cancer, pulmonary diseases, and various bacterial and fungal infections.[2] The absolute and relative stereochemistries of cryptocarya acetates **1** and **2** were determined by a combination of Mosher's ester and ^{13}C NMR/acetonide analysis.[3] The characteristic biological activities and the interesting architectures have stimulated synthetic efforts directed toward their total syntheses.[4] The first total syntheses of cryptocarya acetates **1** and **2** were accomplished by Nakata in 16 and 24 steps, respectively.[5] Subsequently, other synthetic approaches of **2**, **3**, and **4** were

[†] Lanzhou University.
[‡] Chinese Academy of Sciences.

(1) Drewes, S. E.; Schlapelo, B. M.; Horn, M. M.; Scott-Shaw, R.; Sandor, O. *Phytochemistry.* **1995**, *38*, 1427–1430.
(2) Sam, T. W.; Yeu, C. S.; Jodynis-Liebert, J.; Murias, M.; Bloszyk, E. *Planta Med.* **2000**, *66*, 199–205.
(3) Coleman, M. T.; Rivett, D. E. A.; Drewes, S. E.; Horn, M. M. *Phytochemistry* **1997**, *44*, 935–938.
(4) (a) Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem.* **2001**, *66*, 2512–2514. (b) Ghosh, A. K.; Bilcer, G. *Tetrahedron Lett.* **2000**, *41*, 1003–1006. (c) Boger, D. L.; Ichikawa, D.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161–4167. (d) Reddy, M. V. R.; Rearick, J. P.; Hoch, N.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 19–20. (e) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777–2780. (f) Garaas, S.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem.* **2002**, *67*, 2682–2685. (g) Gao, D.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 1069–1072. (h) Kumar, P.; Gupta, P.; Naidu, S. G. *Chem.—Eur. J.* **2006**, *12*, 1397–1402. (i) Georges, Y.; Ariza, X.; Garcia, J. *J. Org. Chem.* **2009**, *74*, 2008–2012.
(5) Jorgensen, K. B.; Suenaga, T.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8855–8858.

10.1021/ol901024t CCC: $40.75
Published on Web 06/19/2009

reported by O'Doherty in 13−15 steps while also corroborating the absolute configuration of both **3** and **4**.[6]

In context of our research in the synthesis of substituted α-pyrones, several of these natural products have been reported by our group.[7] Combined with our interest in designating a concise and efficient route to afford a *syn*-1,3-dihydroxyl unit via a multicomponent linchpin coupling and hydroxyl-directed s*yn*-reduction, herein we describe the total syntheses of cryptocarya triacetate **2**, cryptocaryolone **3**, and cryptocaryolone diacetate **4** (Figure 1) with high step economy.[8]

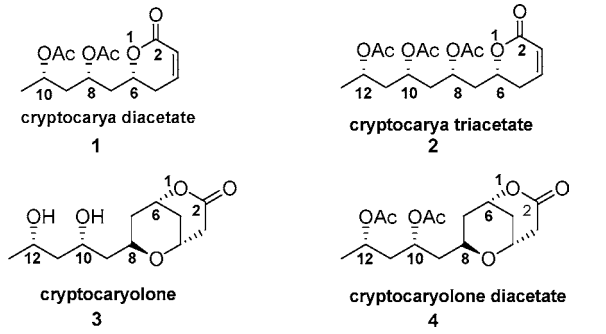
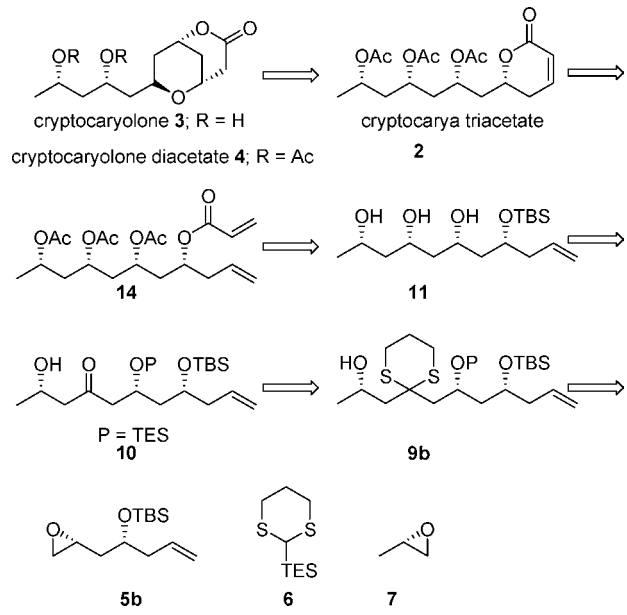


Figure 1. Structures of cryptocarya diacetate, cryptocarya triacetate, cryptocaryolone, and cryptocaryolone diacetate.

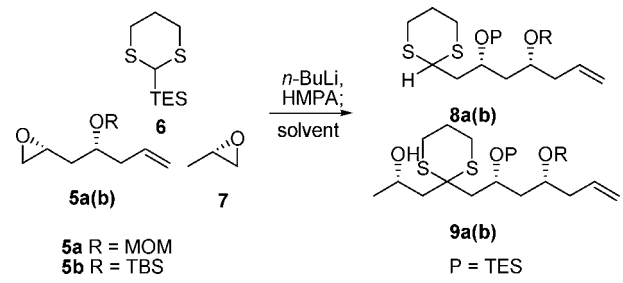
Our retrosynthetic analysis (Scheme 1) was inspired by Drewes' biosynthetic proposal. We envisioned that cryptocaryolone **3** could be accessed from cryptocaryolone **2** via a tandem deacetylation and intramolecular oxa-Michael addition process, which guaranteed the stereochemistry of the resulting dioxabicyclo[3.3.1]nonan-2-one unit. The unsaturated lactone moiety could be generated efficiently via the ring-closing metathesis of acrylate **14**, which in turn could be obtained from ketone **10**. The keto functionality in **10** would serve as an acyl equivalent junction in **9b** potentially suited to a Tietze[9]−Smith[10] linchpin convergence strategy—a multicomponent coupling of **5b**, **6**, and **7**.

Scheme 1. Retrosynthetic Anaylsis of Cryptocarya Triacetate, Cryptocaryolone, and Cryptocaryolone Diacetate



The synthesis of **9b** was initiated by a three-component linchpin coupling employing 2-triethylsilyl-1,3-dithiane **6** with two different epoxide electrophiles to construct unsymmetrical adducts. MOM epoxide **5a** was chosen to test the reactivity (Table 1). When the coupling was treated in THF

Table 1. Linchpin Coupling



entry	solvent	R	reaction conditions[a]	yield **8a(b)**	yield **9a(b)**
1	THF	MOM	a	58%	0%
2	Et_2O	MOM	a	86%	0%
3	THF/Et_2O (1/3)	MOM	b	79%	9%
4	THF/Et_2O (1/3)	MOM	c	71%	19%
5	THF/Et_2O (1/3)	TBS	c	5%	74%

[a] a: −78 °C, 1 h; **5**, then −40 °C, 1 h; −50 °C, HMPA, 15 min; **7**, −78 °C to rt, overnight. b: 0 °C, 10 min; **5**, then −35 °C, 1 h; −50 °C, HMPA, 15 min; **7**, −78 °C to rt, overnight. c: 0 °C, 10 min; **5**, then −35 °C, 1 h; HMPA and **7**, −50 °C to rt, overnight.

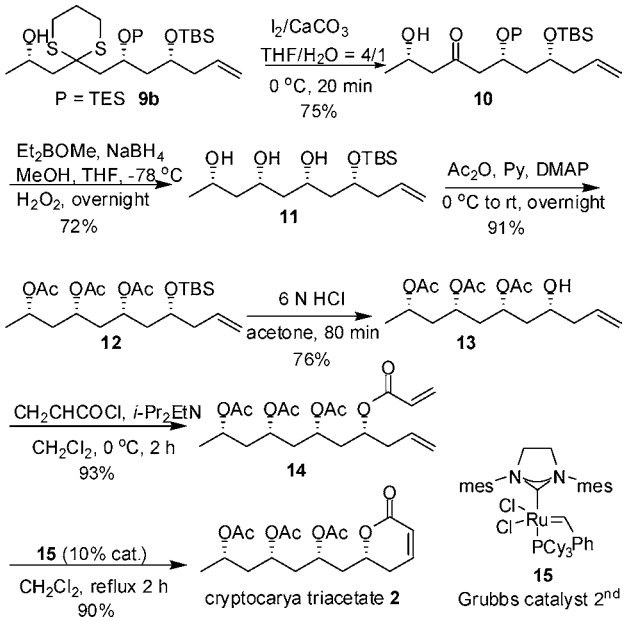
or Et_2O solvent, no desired product **9a** was observed (entries 1 and 2); on the contrary, when a mixed-solvent system was employed, a certain amount of **9a** was obtained in low yield

(6) Smith, C. M.; O'Doherty, G. A. *Org. Lett.* **2003**, *5*, 1959–1962.
(7) (a) Zhang, J.; Li, Y.; Wang, W.; She, X.; Pan, X. *J. Org. Chem.* **2006**, *71*, 2918–2921. (b) Xu, Y.; Huo, X.; Li, X.; Zheng, H.; She, X.; Pan, X. *Synlett.* **2008**, 1665–1668. (c) Su, Y.; Xu, Y.; Han, J.; Zheng, J.; Qi, J.; Jiang, T.; Pan, X.; She, X. *J. Org. Chem.* **2009**, *74*, 2743–2749.
(8) Wender, P. A., Miller, B. L. *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI: Greenwich, 1993; Vol. 2, pp 27−66.
(9) Tieze, L. F.; Gewert, J. A.; Jakobi, U. *Synlett* **1944**, *51*, 1–512.
(10) (a) Smith, A. B.; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365–377. (b) Smith, A. B.; Pitram, S. M.; Boldi, A. M.; Gaunt, M. J.; Sfouggatakis, C.; Moser, W. *J. Am. Chem. Soc.* **2003**, *125*, 14435–14445. (c) Smith, A. B.; Xian, M. *J. Am. Chem. Soc.* **2006**, *128*, 66–67. (d) Smith, A. B.; Zhuang, L.; Brook, C. S.; Boldi, A. M.; McBriar, M. D.; Moser, W. H.; Murase, N.; Nakayama, K.; Verhoest, P. R.; Lin, Q. *Tetrahedron Lett.* **1997**, *38*, 8667–8670. (e) Smith, A. B.; Zhuang, L.; Brook, C. S.; Lin, Q.; Moser, W. H.; Trout, R. E. L.; Boldi, A. M. *Tetrahedron Lett.* **1997**, *38*, 8671–8674. (f) Smith, A. B.; Lin, Q.; Nakayama, K.; Boldi, A. M.; Brook, C. S.; McBriar, M. D.; Moser, W. H.; Sobukawa, M.; Zhuang, L. *Tetrahedron Lett.* **1997**, *38*, 8675–8678. (g) Smith, A. B.; Pitram, S. M. *Org. Lett.* **1999**, *1*, 2001–2004. (h) Smith, A. B.; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783–786. (i) Smith, A. B.; Pitram, S. M.; Fuertes, M. J. *Org. Lett.* **2003**, *5*, 2751–2754. (j) Smith, A. B.; Kim, D. *Org. Lett.* **2004**, *6*, 1493–1495.

(entries 3 and 4). While TBS-protected substrate **5b**,[11] which can be prepared from 1,6-heptadien-4-ol via 4 steps, was used in linchpin coupling with **6** and **7**, disubstituted dithiane **9b** was successfully obtained in 74% yield (entry 5).

With the advanced intermediate **9b** in hand, removal of the dithiane, followed by hydroxyl-directed reduction of the resulting ketone **10**,[12] gave triol **11** in 72% yield (Scheme 2). Triol **11** was easily peracylated to provide triacetate olefin

Scheme 2. Synthesis of Cryptocarya Triacetate **2**

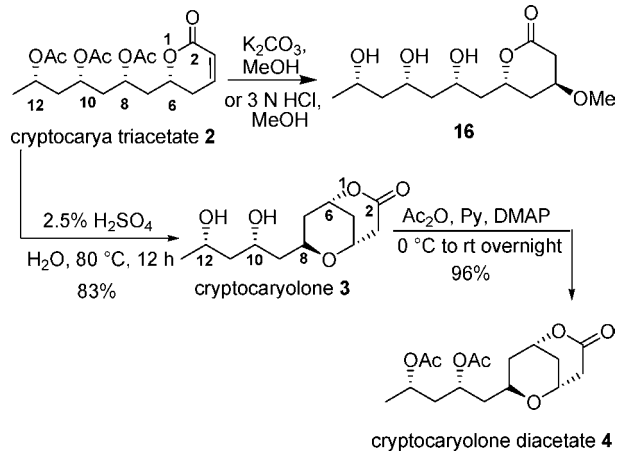


12 in 91% yield. Cleavage of the *O*-TBS protection of **12** under the treatment of 6 N aqueous HCl[13] resulted in alcohol **13**, while also a small amount of an acyl-migrated compound was observed. Coupling between alcohol **13** and acrylyl chloride proceeded smoothly to afford acrylate **14** in 93% yield, which underwent ring-closing metathesis utilizing the second-generation Grubbs' catalyst **15**[14] to furnish cryptocarya triacetate **3** in 90% yield.

According to our retrosynthetic analysis, a crucial tandem process combining deacylation and 1,4-oxa-Michael addition required considerable effort to facilitate the formation of the desired cryptocaryolone **3**. Under either basic or acidic conditions in organic protic solvent, such as K_2CO_3/MeOH and HCl/MeOH, MeOH performed as the *O*-nucleophile and

(11) Kim, Y.-J.; Tae, J. *Synlett* **2006**, *6*, 1–64.
(12) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155–158.
(13) Enders, D.; Dhulut, S.; Steinbusch, D.; Herrbach, A. *Chem.—Eur. J.* **2007**, *13*, 3942–3949.
(14) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784. (c) Trnka, T.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.

Scheme 3. Syntheses of Cryptocaryolone **3** and Cryptocaryolone Diacetate **4**



only lactone triol **16** was identified (Scheme 3). To our delight, when subjected to H_2O with a catalytic amount of H_2SO_4, cryptocarya triacetate **2** experienced global deacylation simultaneously followed by a spontaneous oxa-Michael addition of the free hydroxyl group at the C-8 position to the unsaturated lactone moiety to provide cryptocaryolone **3**. Cryptocaryolone **3** was then treated by Ac_2O/py to afford cryptocaryolone diacetate **4** in 96% yield. The analytical and spectral data of synthetic **2**, **3**, and **4** were in good agreement with those previously reported for cryptocarya triacetate **2**, cryptocaryolone **3**, and cryptocaryolone diacetate **4**.[1,6]

In summary, we have finished the concise and efficient asymmetric total syntheses of cryptocarya triacetate **2**, cryptocaryolone **3**, and cryptocaryolone diacetate **4** in 7−9 steps with 23%, 18%, and 18% overall yields, respectively. The stereogenic centers at C-8 and C-12 positions were economically constructed by a three-component linchpin coupling, while ring-closing metathesis (RCM) was also employed as a feasible choice for the formation of an unsaturated lactone moiety. Syntheses toward these three natural products further demonstrate the value of linchpin technology, substantiating the biosynthetic hypothesis raised by Drewes and allowing significant stereochemical flexibility to initiate structure−activity relationship studies.[1]

Acknowledgment. We are grateful for the generous financial support by the NSFC (QT program, 20872054, 20732002).

Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901024T