ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

A Short, Protecting Group-Free Total Synthesis of Bruceollines D, E, and J

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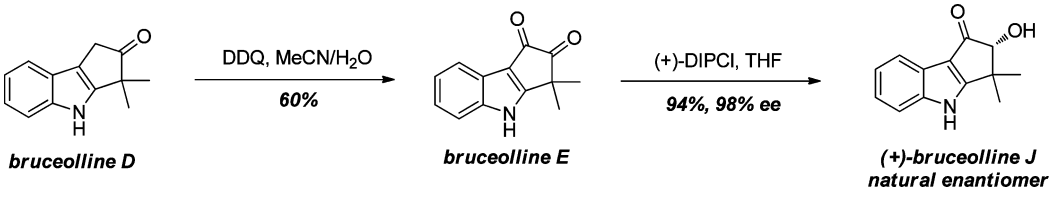
Received July 19, 2013

ABSTRACT



A short, protecting group-free total synthesis of bruceollines D, E, and J has been achieved. The enantioselective reduction of bruceolline E with β-chlorodiisopinocampheylborane delivers both the natural and unnatural enantiomers of bruceolline J in excellent yields and enantioselectivities. Reduction with baker's yeast and sucrose was shown to provide the unnatural enantiomer of bruceolline J in 98% ee.

The bruceolline family of natural products is comprised of various structurally related cyclopent[*b*]indole and cathan-6-one alkaloids which have been isolated from the root wood of *Brucea mollis* Wall. var. *tonkinensis* Lecomte (Figure 1).[1] *Brucea mollis* and *B. javanica* are native to southwestern China and traditionally used for the treatment of various parasitic diseases including malaria.[2] Despite the potential medicinal utility, both the biological evaluation and synthetic investigations have been limited.[3]

As a part of our longstanding interest in the synthesis of fused indoles and cyclopent[*b*]indole natural products,[4] we were intrigued by the possibility of developing a short synthesis that could allow successive access to bruceollines D (**5**), E (**6**), and J (**9**) without the need for protecting groups.

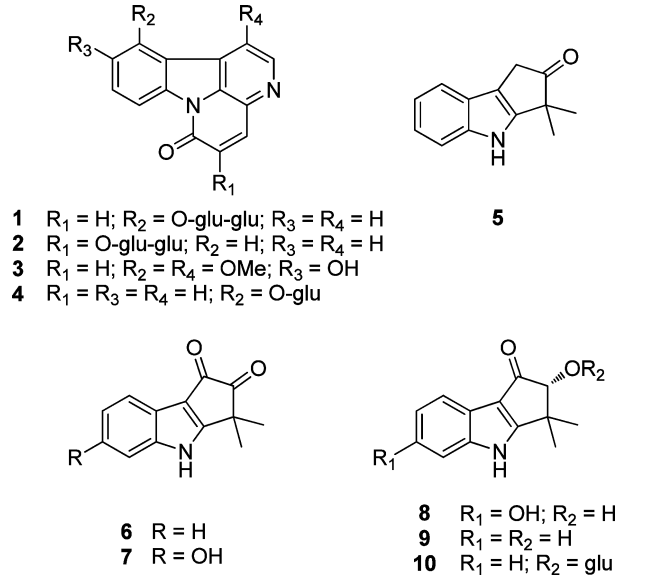


Figure 1. Bruceolline natural products.

Our initial attempt to construct bruceolline D (**5**) utilized phenylhydrazine and dione **12** through Fischer indolization

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(1) (a) For a review of natural products isolated from *Brucea* plants, see: Liu, J.-H.; Jin, H.-Z.; Zhang, W.-D.; Yan, S.-K.; Shen, Y.-H. *Chem. Biodiversity* **2009**, *6*, 57–70. (b) For the isolation of bruceollines A and B, see: Ouyang, Y.; Koike, K.; Ohmoto, T. *Phytochemistry* **1994**, *36*, 1543–1546. (c) For the isolation of bruceollines C and G, see: Ouyang, Y.; Mitsunaga, K.; Koike, K.; Ohmoto, T. *Phytochemistry* **1995**, *39*, 911–913. (d) For the isolation of bruceollines D–F, see: Ouyang, Y.; Koike, K.; Ohmoto, T. *Phytochemistry* **1994**, *37*, 575–578. (e) For the isolation of bruceollines H–N, see: Chen, H.; Bai, J.; Fang, Z.-F.; Yu, S.-S.; Ma, S.-G.; Xu, S.; Li, Y.; Qu, J.; Ren, J.-H.; Li, L.; Si, Y.-K.; Chen, X.-G. *J. Nat. Prod.* **2011**, *74*, 2438–2445.

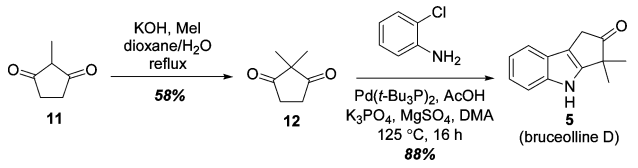
(2) (a) Guo, Z.; Vangapandu, S.; Sindelar, R. W.; Walker, L. A.; Sindelar, R. D. *Curr. Med. Chem.* **2005**, *12*, 173–190. (b) Muhammad, I.; Samoylenko, V. *Expert Opin. Drug Discovery* **2007**, *2*, 1065–1084.

(3) For the only synthesis of bruceolline E to date, see: Jordan, J. A.; Gribble, G. W.; Badenock, J. C. *Tetrahedron Lett.* **2011**, *52*, 6772–6774.

(4) Gribble, G. W. *Pure Appl. Chem.* **2003**, *75*, 1417–1432.

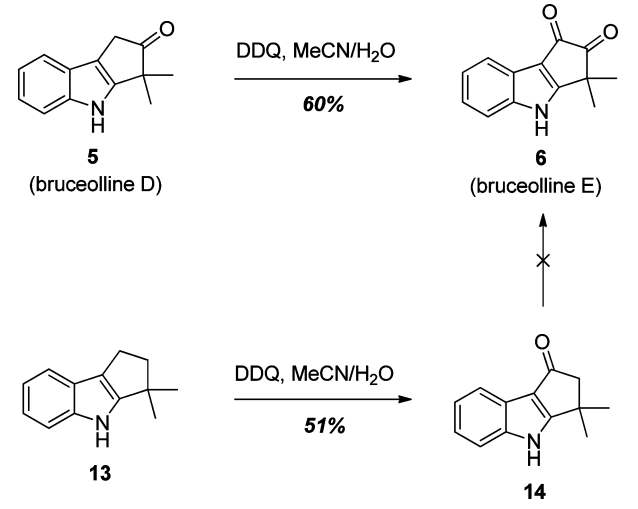
10.1021/ol402042f

Scheme 1. Synthesis of Bruceolline D



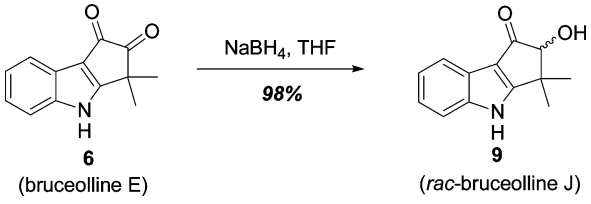
chemistry even though a report by Dashkevich[5] indicated yields may be low due to both thermal instability and acid sensitivity of the target compound. Indeed, despite screening numerous conditions (including recently reported cyclizations in low melting mixtures) we were never able to achieve yields above 35%.[6] In addition to problems with the stability of the product, formation of the unproductive bis-hydrazone tended to be more competitive than initially suspected.[7] We turned instead to palladium-catalyzed cyclization conditions reported by Nazaré and co-workers.[8] To our delight, the cyclization of *o*-chloroaniline with dione **12** proceeded smoothly to provide bruceolline D (**5**) in 88% yield (Scheme 1). The structure was confirmed by X-ray crystallography.[9]

Scheme 2. Synthesis of Bruceolline E



Oxidation of bruceolline D (**5**) to bruceolline E (**6**) proved straightforward by treatment of **5** with DDQ in aqueous acetonitrile (Scheme 2).[10] An alternative synthesis of bruceolline E (**6**) was investigated which involved Fischer or palladium-catalyzed cyclization to indole **13** and subsequent DDQ oxidation to indolone **14**. Unfortunately, attempts to convert the indolone directly to bruceolline E (**6**) via selenium dioxide oxidation without protection of the indole NH were unsuccessful, typically returning unreacted starting material.[11] Protection of **14** at this stage would intercept the route used in the only previous synthesis of bruceolline E (**6**).[3] With bruceolline E (**6**) in hand, we turned our focus to the selective monoreduction of the dione moiety to furnish racemic bruceolline J (**9**). As expected, the ketone was reduced rapidly and selectively in the presence of the vinylogous amide with none of the possible bis-reduction product detected (Scheme 3). A variety of reductants worked well including sodium borohydride, borane-dimethyl sulfide, and catecholborane. The structure was confirmed by X-ray crystallography.[12]

Scheme 3. Synthesis of *rac*-Bruceolline J



With the first total synthesis of racemic bruceolline J (**9**) complete, we turned our attention to effecting an enantioselective reduction and obtaining both the natural and unnatural enantiomers. Initial testing with the venerable CBS reduction was disappointing. Both catalytic and stoichiometric versions of the reaction gave poor enantioenrichment due to the overly competitive background reduction (Table 1, entries 1–3).[13] Although the CBS–catecholborane system has been shown to promote enantioselective reductions at low temperatures, only a trace of product was observed after 12 h at −78 °C (Table 1, entry 4).[14] As foreshadowed by a literature precedent of related substrates, the dione proved to be too hindered for Alpine Borane to furnish any of the desired product, even after 10 days at room temperature.[15]

β-Chlorodiisopinocampheylborane[16] (DIPCl) delivered the most promising result from the initial screen (Table 1,

(5) Dashkevich, S. N. *Chem. Heterocycl. Cmpds.* **1978**, *14*, 109.

(6) Conditions tested included HCl, H_2SO_4, polyphosphoric acid (PPA), and buffered phosphoric acid. For the unsuccessful low melting mixture Fischer indolization conditions, see: Gore, S.; Baskaran, S.; König, B. *Org. Lett.* **2012**, *14*, 4568–4571.

(7) Interestingly, both high dilutions and changing solvents failed to significantly alter the distribution of hydrazone formation. The low melting mixtures (ref 6) favored the monohydrazone more than any other tested condition; however, the cyclization itself did not proceed.

(8) Nazare, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 4526–4528.

(9) Lopchuk, J. M.; Gribble, G. W.; Jasinski, J. P. *Acta Crystallogr.* **2013**, *E69*, o1043.

(10) Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213–1216.

(11) Gribble, G. W.; Barden, T. C.; Johnson, D. A. *Tetrahedron* **1988**, *44*, 3195–3202.

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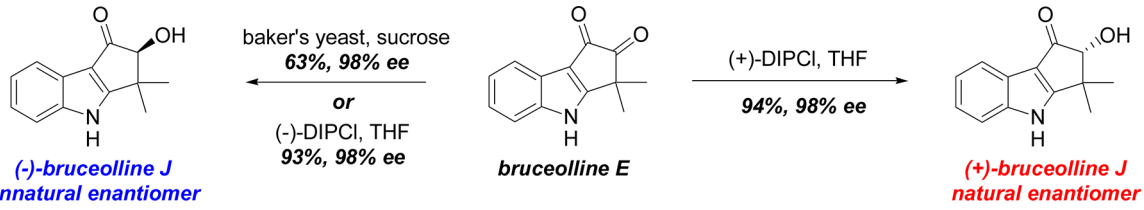
(14) (a) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275–6278. (b) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611–614. (c) West, S. P.; Bisai, A.; Lim, A. D.; Narayan, R. R.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 11187–11194.

(15) Brown, H. C.; Pai, G. G.; Jadhav, P. K. *J. Am. Chem. Soc.* **1984**, *106*, 1531–1533. Although reductions with Alpine Borane are known to run more efficiently neat or at high concentrations, the poor solubility of **6** required lower concentrations than desired.

Table 1. Enantioselective Reduction of Bruceolline E to Bruceolline J



entry	reductant	solvent	temp (C)	time	yield (%)	enantiomer	ee (%)[a,b]
1	*(R)*-CBS (cat.) with BH_3-DMS	THF	-25	1 h	92	+	18
2	*(S)*-CBS (cat.) with BH_3-DMS	THF	-25	1 h	88	–	28
3	*(S)*-CBS (stoich.) with BH_3-DMS	THF	-25	30 min	98	–	4
4	*(R)*-CBS (stoich.) with catecholborane	Toluene	-78	12 h	trace	N/A	nd
5	*(S)*-Alpine Borane	THF	room temp	10 days	no rxn	N/A	nd
6	**Baker's yeast with sucrose**	**H_2O**	**room temp**	**14 days**	**63 (91)[c]**	**–**	**98**
7	(–)-DIPCl (1.0 equiv)	THF	room temp	36 h	54	–	71
8	(–)-DIPCl (6.0 equiv)	THF	room temp	5 min	48	–	91
9	(–)-DIPCl (3.0 equiv)	THF	0	1 h	97	–	93
10	**(–)-DIPCl (3.0 equiv)**	**THF**	**-42**	**1 h**	**93**	**–**	**98**
11	(+)-DIPCl (3.0 equiv)	THF	0	1 h	93	+	85
12	(+)-DIPCl (3.0 equiv)	THF	-78	1 h	no rxn	N/A	nd
13	**(+)-DIPCl (3.0 equiv)**	**THF**	**-42**	**5 min**	**94**	**+**	**98**

[a] Enantiomeric excess (ee) was determined by HPLC (Chiralpak OD-H, 85% hexanes: 15% isopropanol). [b] nd = not determined. [c] Based on recovered starting material (brsm).

entry 7) and, after optimization, gave natural (+)-**9** in an excellent 94% yield and 98% ee. Assignment of the absolute stereochemistry was done by comparison of the CD spectrum of the synthetic material to that of the natural product.[1e,17] Similar results were obtained for the unnatural enantiomer. The reduction of bruceolline E (**6**) was also investigated by subjecting **6** to baker's yeast suspended in a solution of sucrose and water.[18] After 14 days (−)-**9**, the unnatural enantiomer, was obtained in 63% yield (91% brsm) and 98% ee.

In conclusion, we have developed a short, protecting group-free total synthesis of bruceollines D, E, and J. Both the natural and unnatural enantiomers of bruceolline J have been synthesized for the first time in excellent yields and enantioselectivities (94%, 98% ee and 93%, 98% ee, respectively). The concise nature of the synthetic route should allow for substantial analog development and biological testing in the future.

Acknowledgment. J.M.L. acknowledges support from a Department of Education GAANN fellowship. G.W.G. acknowledges support by the Donors of the Petroleum Research Fund (PRF), administered by the American Chemical Society, and by Wyeth.

Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(16) (a) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Org. Chem.* **1986**, *51*, 3396–3398. (b) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539–1546. (c) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1994**, *66*, 201–212. (d) Ramachandran, P. V.; Pitre, S.; Brown, H. C. *J. Org. Chem.* **2002**, *67*, 5315–5319.

(17) The absolute stereochemistry of the natural product (**9**) was assigned by comparison of a DFT-calculated CD spectra to the experimentally generated CD spectra (ref 1e). The CD spectrum of synthetically prepared (+)-**9** matched that found from the natural product.

(18) (a) Chenevert, R.; Thiboutot, S. *Chem. Lett.* **1988**, 1191–1192. (b) Inoue, T.; Hosomi, K.; Araki, M.; Nishide, K.; Node, M. *Tetrahedron: Asymmetry* **1995**, *6*, 31–34.