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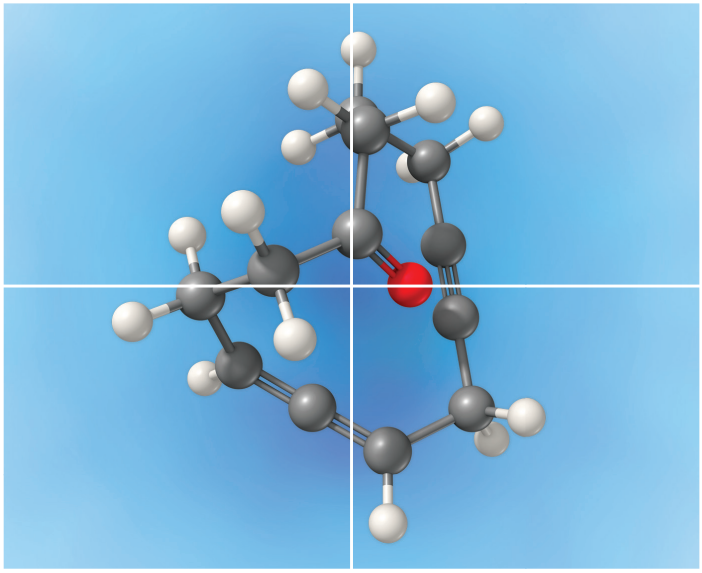

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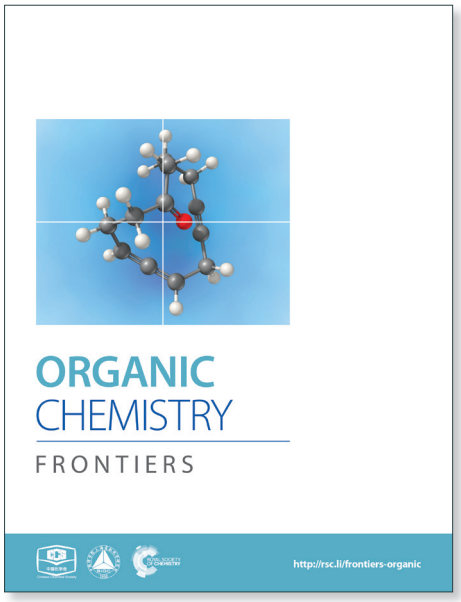

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ARTICLE TYPE

Concise Asymmetric Total Synthesis of Bruceolline J

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We have developed a concise biomimetic and asymmetric approach involving Sharpless asymmetric dihydroxylation and *Lewis* acid catalysed cyclopenta[*b*]annulation as key steps to synthesize (+)-bruceolline J, and a racemic approach employing an intramolecular rhodium carbenoid C-H insertion and highly regioselective *gem*-dimethylation reactions as key steps to synthesize bruceolline D, E along with (±)-bruceolline J.

Bruceollines are a small group of natural products containing highly oxygenated cyclopent[*b*]indole moiety.[1] In 1994, Ohmoto and co-workers have reported isolation of bruceollines D-F (**1**-**3**) (Figure 1), from the root wood of *Brucea mollis* Wall. var. *tonkinensis* Lecomte.[2] Recently, in 2011 Yu and co-workers isolated bruceolline J (**4**) along with several other bruceollines fr-

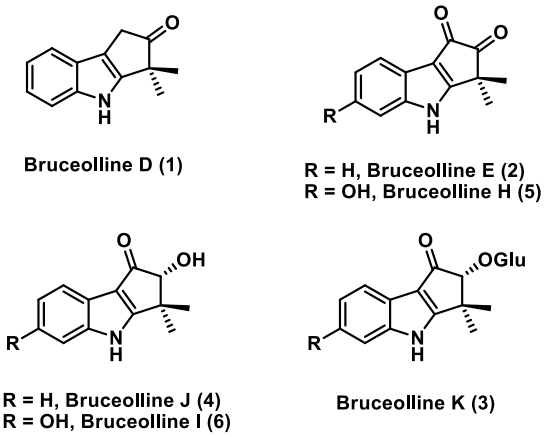
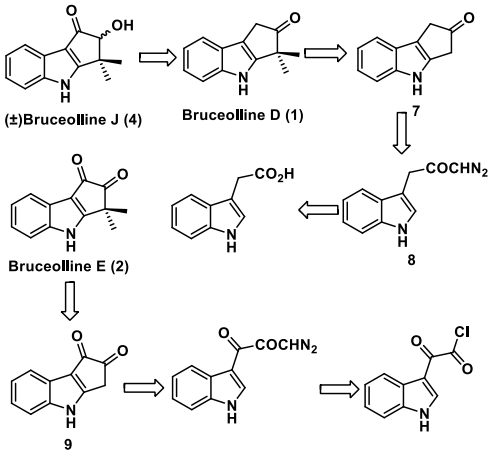


Figure 1. The structures of bruceolline family of natural products

-om an ethanol extract of the stems of *Brucea mollis*.[3] The genus *B. mollis* are found in southern china and traditionally used as remedy for malaria and other parasitic diseases. Despite their potential medicinal utility, bruceollines have attracted much less attention from synthetic community.

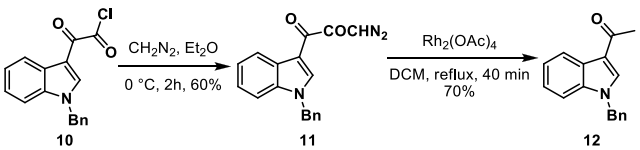
So far only one synthesis of bruceolline E (**2**) and J (**4**) has been reported in literature by Gribble and co-workers.[4,5] Recently the same group also reported a concise asymmetric synthesis of bruceolline J using superstoichiometric amount (3 equiv) of (+) and (-)-DIPCl for the asymmetric induction. Herein we report racemic as well as asymmetric syntheses of bruceolline-J using two different strategies and synthesis of related natural products.

We planned the racemic total synthesis of bruceolline J (**4**), D (**1**) and E (**2**) using intramolecular rhodium carbenoid C–H insertion and highly regioselective alkylation as the key steps. It was envisaged that bruceolline E (**2**) and J (**4**) could be obtained from bruceolline D (**1**) by functional group manipulations. Bruceolline D (**1**) in turn could be obtained from ketone **7** by regioselective *gem*-dimethylation. The ketone **7** could be accessed by intramolecular rhodium carbenoid C-H insertion reaction of diazoketone **8** which in turn could be easily synthesized from indole acetic acid. On the other hand, bruceolline E (**2**) was thought to be obtained from diketone **9** by *gem*-dimethylation. The diketone **9** could be generated by C-H insertion reaction of corresponding diazoketone made from indole glyoxyl chloride (Scheme 1).



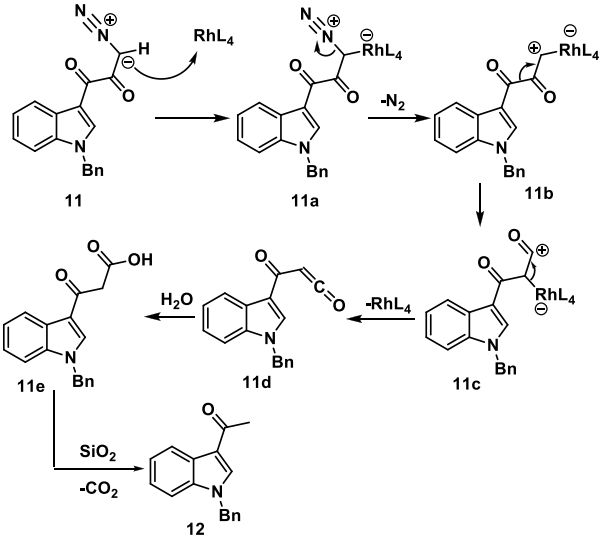
Scheme 1. Retrosynthetic analysis of Bruceolline D, E and J

To begin with, we adopted the second strategy as it is more direct route and would result in short synthesis of bruceolline E (**2**). The synthesis commenced with the treatment of Indolyl glyoxyl chloride **10** (prepared from N-benzyl indole and oxalyl chloride) [6] with diazomethane to generate diazoketone **11**. To our surprise, exposure of the diazoketone **11** to a catalytic amount of $Rh(OAc)_4$ under CH_2Cl_2 reflux condition generated the acetyl indole **12** in 70% yield instead of diketone **9** (Scheme 2). Even the usage of more reactive catalyst $Rh(OCOCF_3)_4$ also afforded compound **12**. Mechanism for the formation of acetyl indole is proposed in Scheme 3.



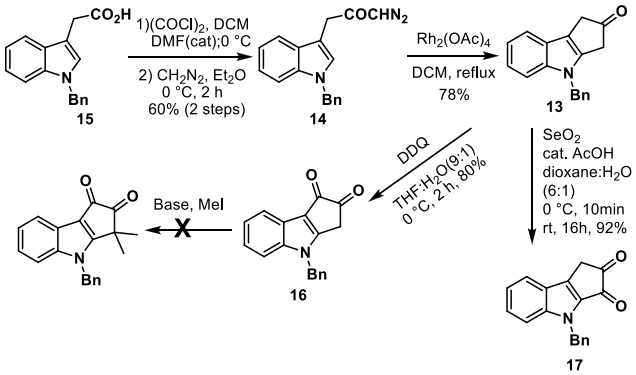
Scheme 2. Attempts towards the synthesis of bruceolline E

In the first step, reaction of rhodium acetate with diazoketone **11** generates rhodium carbenoid **11b**. The wolff rearrangement of rhodium carbenoid **11b** generates the ketene **11d**. Once **11d** is formed, reaction with water (during silica gel column purification) rapidly generates 3-acetyl indole **12** and carbon dioxide.



Scheme 3. Mechanism showing the formation of 3-aetyl indole (12) from diazoketone (11)

Next, we turned our attention towards the synthesis of ketone **13** from diazoketone **14**. Thus N-benzyl indole acetic acid **15** on reaction with oxalyl chloride followed by treatment with diazomethane afforded diazoketone **14** in moderate yield. Exposure of diazoketone **14** to a catalytic amount of rhodium (II) acetate in CH_2Cl_2 under reflux condition afforded the ketone **13** in 78% yield. In an effort to synthesize diketone **16**, ketone **13** was treated with SeO_2 in dioxane: H_2O (6:1) for 16 hours.[7] Unfortunately, it furnished the undesired regioisomer **17** in 92% yield (Scheme 4). Structure of **17** was unambiguously confirmed by the single crystal X-ray analysis (Figure 2).



Scheme 4. Synthesis of ketone 13

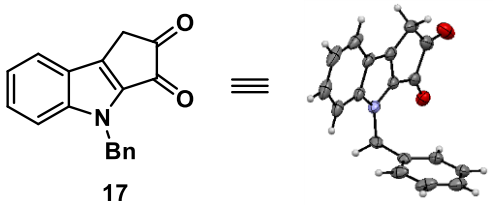
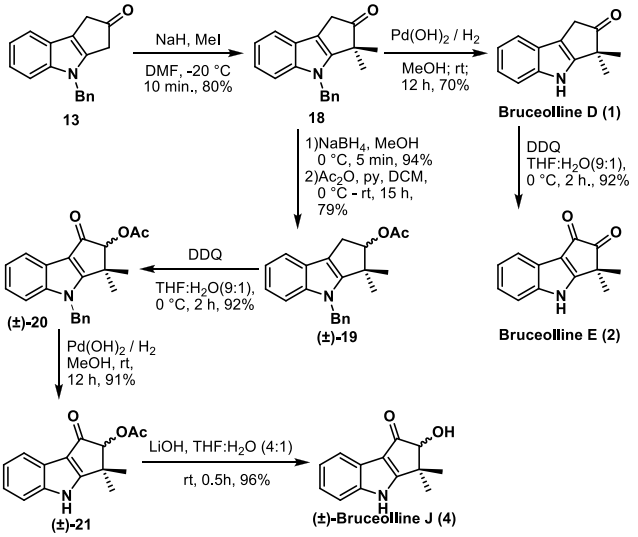


Figure 2. X-ray crystal structure of compound 17

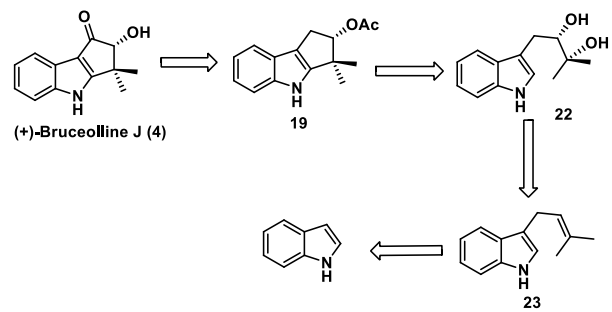
Benzylic oxidation of ketone **13** on treatment with DDQ[9] in THF: H_2O (9:1) afforded the required diketone **16** in 80% yield. However *gem*-dimethylation of diketone **16** to generate bruceolline E (**2**) under various basic conditions such as LDA, NaH, *t*-BuOK, NaOMe encountered a deadlock as the diketone **16** decomposed under these reaction conditions. But, to our delight, treatment of ketone **13** with NaH and MeI furnished the **18** in highly regioselective manner with 80% yield. The nucleophilic C-3 position of indole might be making the enolate formation at other side of the ketone **13** less favourable, resulting in the excellent regioselective gem-dimethylation. Hydrogenolysis of *N*-benzyl group using $H_2/Pd(OH)_2$ afforded the natural product bruceolline D (**1**) in 70% yield. A simple benzylic oxidation of bruceolline D (**1**) assisted by DDQ furnished bruceolline E (**2**) in 92% yield.



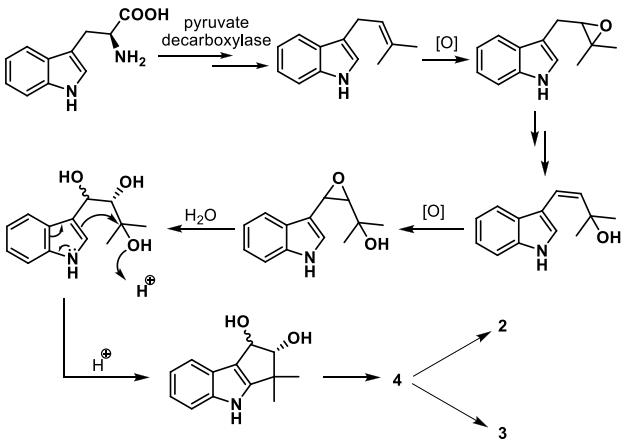
Scheme 5. Total synthesis of bruceolline D (1), E (2) and J (4)

Next we targeted the synthesis of **(±)**-bruceolline J (**4**) from the common intermediate **18**. Reduction of ketone group of compound **18** and acetylation of the resulted hydroxyl group gave rise to **(±)-19.** A successive benzylic oxidation using DDQ, debenzylation[10] using $H_2/Pd(OH)_2$ followed by acetate hydrolysis under basic conditions afforded the natural product **(±)**-bruceolline J (**4**) in 96% yield (Scheme 5).

Our task then was a concise catalytic asymmetric synthesis of **(+)**-bruceolline J. It was contemplated that **(+)**-bruceolline J (**4**) could be obtained from cyclopenta[b]indole **19** by benzylic oxidation (Scheme 6). Inspired by the biosynthetic pathway of bruceolline alkaloids (Scheme 7)[3], it was envisaged that compound **19** could be accessed from diol **22** by *Lewis* acid catalysed cyclopentannulation reaction. The chiral diol **22** could be prepared by Sharpless asymmetric dihydroxylation of compound **23**, which in turn could be obtained by prenylation of indole.

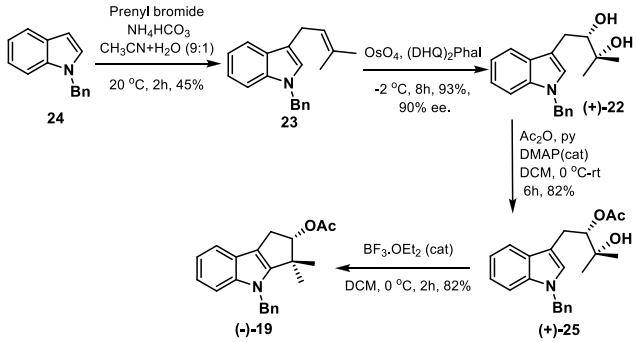


Scheme 6. Retrosynthetic analysis of bruceolline J



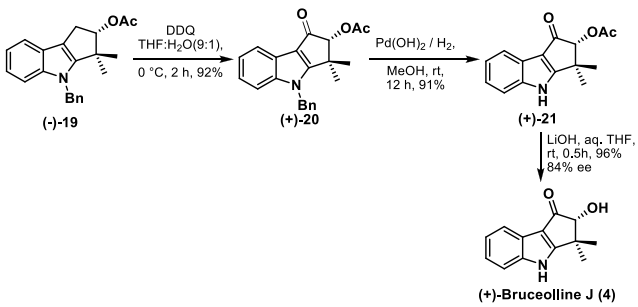
Scheme 7. Plausible biosynthetic pathway

Thus, treatment of N-benzyl protected indole **24** with prenylbromide in prescence of base[11] furnished compound **23** which was then subjected to sharpless asymmetric dihydroxylation protocol[12] to get diol **(+)-22** with 93% yield and 90% ee. Selective acetylation of secondary alcohol followed by $BF_3.OEt_2$ catalysed cyclopentannulation allowed a rapid construction of the cyclopentane ring to afford cyclopenta-[*b*]-indole **(-)-19** in good yield which represented key intermediate of the scheme (Scheme 8).



Scheme 8. Synthesis of the key intermediate 19

Benzylic oxidation of the compound **(-)-19** using DDQ in THF:H_2O (9:1) afforded ketone **(+)-20** in good yield which was then employed in debenzylation[13] using palladium hydroxide to give **(+)-21** in 91% yield. Base mediated hydrolysis of acetyl group of **(+)-21** furnished the natural product, **(+)**-bruceolline J (**4**), in excellent yield with 84% ee (Scheme 9). The ^{1}**H**, ^{13}**C** spectroscopic data, optical rotations of (+)-bruceolline J (**4**) are identical with that of the natural (+)-bruceolline.



Scheme 9. Synthesis of (+)-Bruceollines J from (-)-19

In conclusion, we have reported a successful integration of two divergent synthetic strategies that allow the efficient total syntheses of racemic as well as chiral bruceolline J and bruceollines D, E. Asymmetric synthesis of bruceoilline J was accomplished by using Sharpless asymmetric dihydroxylation and *Lewis* acid catalysed cyclopentannulation as key steps. Racemic approach constitutes a common route for the synthesis of bruceolline D, E and J in 4, 5 and 8 steps respectively in very good overall yield using an intramolecular rhodium carbenoid C-H insertion and highly regioselective methylation reactions as key steps. The racemic and asymmetric approaches also give a ready access to other natural products such as bruceollines H **(5)**, I **(6)** and K **(3)** for further biological studies.

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Notes and references

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Electronic Supplementary Information (ESI)available: Figures giving ^{1}H and ^{13}C NMR spectra for all compounds and a CIF file giving crystallographic data for compound **17.** See DOI: 10.1039/b000000x/

1 Gribble, G. W. *Pure Appl. Chem.* **2003**, *75*, 1417.
2 Ouyang, Y.; Koike, K.; Ohmoto, T. *Phytochemistry* **1994**, *36*, 1543.
3 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.
4 Jordan, J. A.; Gribble, G. W.; Badenock, J. C. *Tetrahedran Lett.* **2011,** *52*, 6772.
5 Lopchuk, J. M.; Green, I. L.; Badenock, J. C.; Gribble, G. W. *Org. Lett*., **2013**, *15*, 4485.
6 Guinchard, X.; Vallee, Y.; Denis, J. N. *Org. Lett.*, **2007**, *9*, 3761.
7 Mehta, G.; Shinde, H. M. *Tetrahedran Lett.* **2003,** *44*, 7049.
8 CCDC 1004473 (**17**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
9 Nicolaou, K.C.; Chen, D. Y. K.; Huang, X.; Ling, T.; Bella, M.; Snyder, S. A. *J. Am. Chem. Soc.*, **2004**, *126*, 12888.
10 Fekner, T.; Gallucci, J.; Chan, M. K. *Org. Lett*., **2003**, *5*, 4795.
11 Westermaier, M.; Mayr, H. *Org. Lett*., **2006**, *8*, 4791.
12 Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X. L. *J. Org. Chem.*,**1992**, *57*, 2768.
13 Fujiwara, T.; Sasaki, M.; Omata, K.; Kebuto, C.; Kabuto, K.; Takeuchi, Y. *Tetrahedron: Asymmetry*, **2004**, *15*, 555.