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Concise Asymmetric Total Synthesis of Bruceolline J

Dattatraya H. Dethe* and Vijay Kumar B

We have developed a concise biomimetic and asymmetric approach involving Sharpless asymmetric dihydroxylation and Lewis acid catalysed cycloental[b]annulation as key steps to synthesize (+)-bruceolline J, and a racemic approach employing an intramolecular rhodium carbendoid 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 cycloental[b]indole moieties. In 1994, Ohmoto and co-workers have reported isolation of bruceollines D-F (1-3) (Figure 1), from the root wood of *Brueca mollis* Wall. var. *tonkinensis* Lecomte. Recently, in 2011 Yu and co-workers isolated bruceolline J (4) along with several other bruceollines from an ethanol extract of the stems of *Brueca mollis*. The genus *B. mollis* are found in southern China and traditionally used as a 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. 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 carbendoid 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. Brueolline D (1) in turn could be obtained from ketone 7 by regioselective gem-dimethylation. The ketone 7 could be accessed by intramolecular rhodium carbendoid 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 glyoxylic chloride (Scheme 1).

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 Indoyl glyoxylic chloride 10 (prepared from N-benzyl indole and oxalyl chloride) with diazomethane to generate diazoketone 11. To our surprise, exposure of the diazoketone 11 to a catalytic amount of Rh(OAc)₃ under CH₂Cl₂ reflux condition generated the acetyl indole 12 in 70% yield instead of diketone 9 (Scheme 2). Even the usage of more reactive catalyst Rh(OOCF₃)₃ also afforded compound 12. Mechanism for the formation of acetyl indole is proposed in Scheme 3.

![Scheme 1. Retrosynthetic analysis of Bruceolline D, E and J](image1.png)

![Scheme 2. Attempts towards the synthesis of bruceolline E](image2.png)
Scheme 3. Mechanism showing the formation of 3-acetyl 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 CH₂Cl₂ under reflux condition afforded the keto 13 in 78% yield. In an effort to synthesize diketone 16, ketone 13 was treated with SeO₂ in dioxane: H₂O (6:1) for 16 hours. 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 DDQ⁹ in THF: H₂O (9:1) afforded the required diketone 16 in 80% yield. However gem-dimethylation of diketone 16 in 80% yield. However gem-dimethylation of diketone 16 in 80% yield. However gem-dimethylation of diketone 16 in 80% yield. However gem-dimethylation of diketone 16 in 80% yield. However gem-dimethylation of diketone 16 in 80% yield. However gem-dimethylation of diketone 16 in 80% yield. However gem-dimethylation of diketone 16 in 80% yield. However gem-dimethylation of diketone 16 in 80% yield. However gem-dimethylation of diketone 16 in 80% yield. However gem-dimethylation of diketone 16 in 80% yield. However gem-dimethylation of diketone 16 in 80% yield.

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 using H₂/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), 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 5. Total synthesis of bruceolline D (1), E (2) and J (4)

Scheme 6. Retrosynthetic analysis of bruceolline J

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 Mel 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 H₂/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.
Thus, treatment of N-benzyl protected indole 24 with prenyl bromide in presence of base\textsuperscript{11} furnished compound 23 which was then subjected to Sharpless asymmetric dihydroxylation protocol\textsuperscript{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](image)

Benzylc oxidation of the compound (+)-19 using DDQ in THF:H\(_2\)O (9:1) afforded ketone (+)-20 in good yield which was then employed in debenzylation\textsuperscript{13} using palladium hydroxide to give (+)-21 in 91% yield. Base mediated hydrolysis of acetyl group of (+)-21 furnished the natural product, (+)-brucellolone J (4), in excellent yield with 84% ee (Scheme 9). The \(^1\)H, \(^13\)C spectroscopic data, optical rotations of (+)-brucellolone J (4) are identical with that of the natural (+)-brucellolone.

![Scheme 9. Synthesis of (+)-Brucellolones J from (-)-19](image)

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 brucellone J and brucellolines D, E. Asymmetric synthesis of brucellolone 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 brucellone 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 brucellolines H (5), I (6) and K (3) for further biological studies.

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**Notes and references**

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](http://www.ccdc.cam.ac.uk/data_request/cif).