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# Total Synthesis of Cruciferane *via* Epoxidation/Tandem Cyclization Sequence

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**The total synthesis of alkaloid cruciferane is obtained in three steps with overall yield 60.3 %. Key step involves *in situ* epoxidation of indole followed by tandem cyclisation *via* epoxide ring opening to furnish the 3-hydroxypyrroloindoline skeleton. This methodology gave step economical and protecting group free total synthesis of cruciferane.**

Nitrogen based alkaloids always being a major constituent of nature.[1] Among them, particularly indole based natural products come with a broad skeleton diversity, which might be one of the reason for their wide bioactivity spectrum.[2,3] Thus, indole natural products are always being a fascinated target to the synthetic chemists.[3] Quinazolinone is another class of heterocycles which shows vital biological properties like, anti-inflammatory, diuretic, anticancer, anticonvulsant and anti-hypertensive.[4] The examples for the indoloquinazolinone based natural product are scarce.[5] In 2012, Shi group isolated 17 new alkaloids from the root of the *Isatis indigotica* plant, among them cruciferane is the first racemic natural product which contains a pyrrolo[2,3-*b*]indolo[5,5*a*,6-*b,a*]quinazoline skeleton (Figure 1).[6] *Isatis indigotica* Fortune is a biennial plant in the Cruciferae family also known as Chinese woad. The dried root of *Isatis indigotica* is used ethnomedically to treat erysipelas, influenza, carbuncles, epidermic hepatitis and encephalitis B and as an antipyretic. A large number of compounds have been isolated from this plant which include indigotin, indrubin, isatin, isatan A, isatan B, trytanthrin, purin, isaindigotidione, organic acids and many amino acids.[7] As a part of our ongoing research on indoloquinazolinone based natural products and also due to the biological importance, we have chosen cruciferane as the target molecule.[8] So far, two reports are available those demonstrate the total synthesis of Cruciferane.[9] The first report was from Nair et al. in 2013, where they synthesized the alkaloids using condensation followed by aldol reaction.[9a] The next report also came in the same year by Argade group, where they synthesized the cruciferane using benzyne cyclisation.[9b]

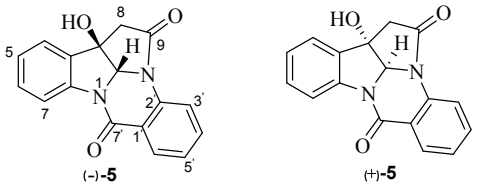


**Figure 1. Structure of naturally occurring Cruciferane alkaloids**

Later, Ji reported the formal synthesis of this alkaloid.[10] However, these syntheses were carried out with same intermediate core tryptanthrin, which was prepared from either complicated starting materials or expensive reagents.

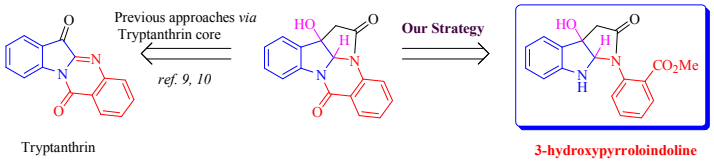


**Figure 2. Strategies for synthesis of Cruciferane**

Thus our initial objective was to simplify the route with easy and inexpensive starting materials. Thus, we planned our synthesis for this alkaloid from the 3-hyroxypyrroloindoline intermediate (fig. 2) which was not used so far. There are some noteworthy reports for construction of 3-hydroxypyrroloindoline, such as iodine (III)-mediated intramolecular annulation,[11] selenocyclization/ oxidative deselenation sequence,[12] photosensitized oxygenation,[13] and metal catalyzed radical cyclisation.[14] Another well-known approach was

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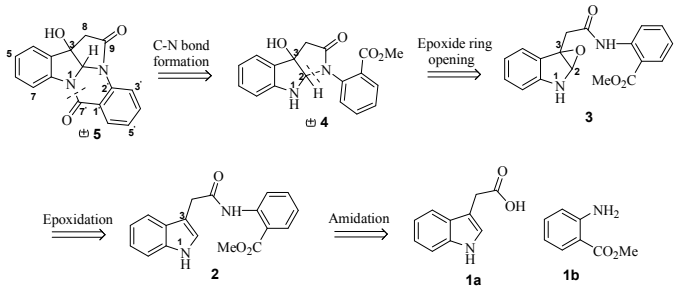
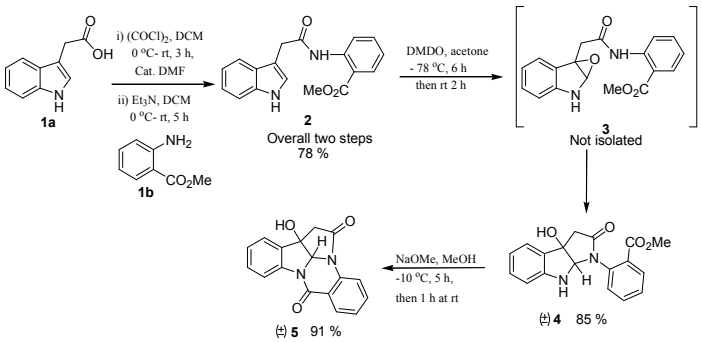
epoxidation of indole as the key step with dioxirane, but most of the cases it needs an array of protecting groups or complicated reaction conditions.[15] Thus, we intended to synthesize the molecule devoid of any protecting group and simplified the conditions which will led to a step economy[16] total synthesis of cruciferane. Thus, in this paper, we wish to report a three step total synthesis of racemic cruciferane *via* epoxidation/ tandem cyclization strategy.

The retrosynthetic approach is depicted in scheme 1. We envisioned the late stage C-N bond formation of 3-hydroxypyrroloindoline skeleton (**4**) would lead to the cruciferane. 3-hydroxypyrroloindoline skeleton (**4**) could be elaborated from the intermediate, contains an epoxide at C2-C3 (see transition structure **3**) of the indole core. This key intermediate (**3**) could stem from the epoxidation on the C2-C3 bond of corresponding 3-substituted indole (**2**), which would be prepared in one pot procedure from corresponding indole acid and amino ester.




**Scheme 1. Retrosynthetic representation of Cruciferane**

As we envisioned the retrosynthetic approach, we started our venture by synthesis of starting materials. Thus, we synthesized the methyl anthranilate (**1b**) from anthranilic acid following the literature procedure[17] and another starting material indole 3-acetic acid (**1a**) was obtained from commercial source. Next, we focused on the C-N bond formation between **1a** and methyl anthranilate. We have chosen the most conventional and simple method for the synthesis of compound **2**, via acid chloride formation followed by base mediated amidation in one pot sequence. Thus we transformed indole 3-acetic acid to its corresponding acid chloride with oxalyl chloride . Without further purification of the acid chloride, it was used for subsequent amidation reaction to a solution of methyl anthranilate and triethylamine (base) in dry DCM at 0 $^{o}$C. The successive reactions gave the amidation product (**2**) in 78 % yield (Scheme 2). With compound **2** in hand, we next focused on the epoxidation step, which was supposed to be the key reaction step in the total synthesis. As we envisaged, because of its chemoselective nature particularly on indole C2-C3, the reaction with dimethyldioxirane (DMDO) might be one of the convenient methods to synthesis the 3-hydroxypyrroloindoline core. Literature (*vide supra*) showed DMDO method was applied mostly to tryptophan derivatives. The derivative (**2**) contains an adjacent carbonyl group (C9) to the nucleophilic nitrogen, and an aromatic ester as substitution which made it little different from other conventional tryptophan derivatives. The DMDO solution in acetone was first prepared from the reported procedure by Taber *et al.*[18] which was added dropwise to the compound **2** in dry acetone at -78 $^{o}$C and stirred at the same temperature for 6 h, then stirred at rt for additional 2 h.




**Scheme 2: Synthesis of racemic Cruciferane**

Though, after 1 h of reaction TLC shows formation of some complex mixtures, this might be due to the intermediate epoxide. After completion of reaction (checked by TLC) it showed a polar intense spot. This *in situ* epoxidation followed by tandem cyclisation gave the step economy for this total synthesis. Next, we sought for a condition to form the C-N bond between N1-C7' of compound **4**. We found that freshly prepared NaOMe (base)/ MeOH (solvent) at -10 $^{o}$C for 5 h and then at rt for 1 h gave the cyclised product in 91 % yield. This C-N formation led to our final target molecule racemic cruciferane. Thus, we have completed the total synthesis for racemic cruciferane via three graceful steps with an overall yield of 60.31 %. The spectral data and HRMS data is consistent with the data of isolated natural product as well as the synthetic product.

In summary, we have developed a new step economical and protecting group free strategy to synthesize racemic cruiferane in three steps. The main features of this total synthesis are easily available and preparable starting materials, devoid of any protecting groups, mild conditions, with a good overall yield.

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## Notes and references

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1. a) M. Ishikura, T. Abe, T. Choshi and S. Hibino, *Nat. Prod. Rep*., 2013, **30**, 694−752. b) B. S. Bharate, S. D. Sawant, P. P. Singh and R. A. Vishwakarma, *Chem. Rev.,* 2013, **113**, 6761−6815. c) M. Iranshahy, R. J. Quinn, and M. Iranshahi, *RSC Adv.,* 2014, **4**, 15900–15913. d) D. Skropeta and L. Wei,

RSC Advances Accepted Manuscript

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*Nat. Prod. Rep*., 2014, **31**, 999-1025. d) T. R. Welcha and R. M. Williams, *Nat. Prod. Rep*., 2014, **31**, 1376-1404. and references therein.

2. a) Y-Y. Low, F-J. Hong, K-H. Lim, N. F. Thomas and T-S. Kam, *J. Nat. Prod.,* 2014, **77**, 327−338. b) M. M. F. Queiroz, E. F. Queiroz, M. L. Zeraik, S. N. Ebrahimi, L. Marcourt, M. Cuendet, I. C. Gamboa, M. Hamburger, V. D. S. Bolzani and J. -L. Wolfender, *J. Nat. Prod.,* 2014, **77**, 650−656.
3. a) S. Rizzo and H. Waldmann, *Chem. Rev.,* 2014, **114**, 4621−4639. b) A. E. Goetz, A. L. Silberstein, M. A. Corsello and N. K Garg, *J. Am. Chem. Soc.,* 2014, **136**, 3036−3039. c) B. R. Rosen, E. W. Werner, A. G. O'Brien and P. S. Baran, *J. Am. Chem. Soc*., 2014, **136**, 5571−5574. d) S. Lancianesi, A. Palmieri and M. Petrini, *Chem. Rev.,* 2014, **114**, 7108- 7149 and references therein.
4. a) S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2006, **62**, 9787-9826. b) M. Sharma, K. Chauhan, R. Shivahare, P. Vishwakarma, M. K. Suthar, A. Sharma, S. Gupta, J. K. Saxena, J. Lal, P. Chandra, B. Kumar and P. M. S. Chauhan, *J. Med. Chem.,* 2013, **56**, 4374−4392. c) I. Khan, A. Ibrar, N. Abbas and A. Saeed, *Eur. J. Med. Chem.,* 2014, **76***,* 193-244.
5. a) J. Teng and X. W. Yang, *Heterocycles,* 2006, **68**, 1691-1698. b) J. D. Wansi, E. N. Happi, J. L. D. Bavoua, K. P. Devkota, and N. Sewald, *Planta Med*., 2012, **78**, 71-75.
6. M. Chen, L. Gan, S. Lin, X. Wang, L. Li, Y. Li, C. Zhu, Y. Wang, B. Jiang, J. Jiang, Y. Yang and J. Shi, *J. Nat. Prod.,* 2012, **75**, 1167-1176.
7. a) X. Wu and G. Qin, *Tetrahedron,* 1997*,* **53**, 13323-13328. b) Y. -L. Ho and Y.-S. Chang, *Phytomedicine,* 2002, **9**, 419–424. c) P. Zou, Y. Hong and H. L. Koh, *J. Pharm. Biomed. Anal.,* 2005, **38**, 514–520. d) J. F. Liu, Z. Y. Jiang, R. R. Wang, Y. T. Zheng, J. J. Chen, X. M. Zhang and Y. B. Ma, *Org. Lett.,* 2007, **9**, 4127-4129.
8. a) S. K. Ghosh and R. Nagarajan, *RSC Adv.,* 2014, **4**, 20136-20144. b) M. Viji and R. Nagarajan, *J. Chem. Sci.*, **2014**, 126, 1075-1080.
9. a) D. Gahtory, M. Chouhan, R. Sharma and V. A. Nair, *Org. Lett.,* 2013, **15**, 3942-3945. b) S. D. Vaidya and N. P. Argade, *Org. Lett.* 2013, **15**, 4006-4009**.**
10. Z. -J. Cai, S. -Y. Wang and S. –J. Ji, *Org. Lett.,* 2013, **15**, 5226- 5229.
11. a) D. Tu, L. Ma, X. Tong, X. Deng and C. Xia, *Org. Lett.,* 2012, **14**, 4830−4833. b) D. Kajiyama, T. Saitoh, S. Yamaguchi and S. Nishiyama, *Synthesis,* 2012, **44**, 1667−1671.
12. a) K. M. Depew, S. P. Marsden, D. Zatorska, A. Zatorski, W. G. Bornmann and S. J. Danishefsky, *J. Am. Chem. Soc.,* 1999, **121**, 11953−11963. b) D. Crich and X. Huang, *J. Org. Chem.,* 1999, **64**, 7218−7223. c) S. V. Ley, E. Cleatora and P. R. Hewitt, *Org. Biomol. Chem.,* 2003, **1,** 3492−3494.
13. a) U. Anthoni, C. Christophersen, P. H. Nielsen, M. W. Christoffersen and D. Sorensen, *Acta Chem. Scand.* 1998, **52**, 958−960. (b) A. Sakai, H. Tani, T. Aoyama and T. Shioiri, *Synlett,* 1998, **3**, 257−258. (c) Y. Fukui and M. Somei, *Heterocycles,* 2001, **55**, 2055−2057.
14. X. Deng, K. Liang, X. Tong, M. Ding, D. Li and C. Xia, *Org. Lett.* 2014, **16**. 3276- 3279.
15. a) J. M. Schkeryantz, J. C. G. Woo, P. Siliphaivanh, K. M. Depew and S. J. Danishefsky, *J. Am. Chem. Soc.,* 1999, **121**, 11964−11975. b) Q. –L. Peng, S. -P. Luo, X. –E. Xia, L. –X. Liu and P. –Q. Huang, *Chem. Commun.,* 2014, **50**, 1986-1988. c) C. –P. Xu, S. -P. Luo, A. -E. Wanga and P. -Q. Huang, *Org. Biomol. Chem.*, 2014, **12**, 2859–2863.
16. a) P. A. Wender, M. P. Croatt and B. Witulski, *Tetrahedron*, 2006, **62**, 7505–7511. b) P. A. Wender, V. A. Verma, T. J. Paxton and T. H. Pillow, *Acc. Chem. Res.,* 2008, **41**, 40–49.
17. S. Hinsberger, K. Hüsecken, M. Groh, M. Negri, J. Haupenthal and R. W. Hartmann, *J. Med. Chem.,* 2013, **56**, 8332−8338.
18. D. F. Taber, P. W. DeMatteo and R. A. Hassan, *Org. Synth.,* 2013, **90**, 350-357.

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