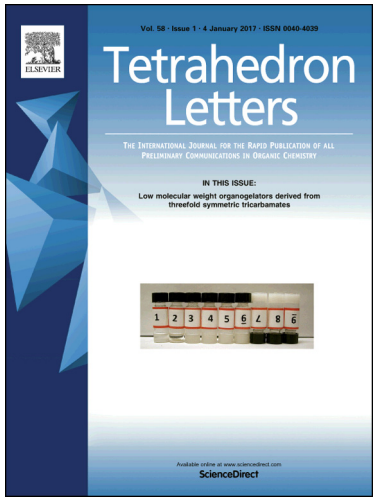


An efficient and concise synthesis of Indiacen A and Indiacen B

Kishore Kumar Anantoju, Baquer Syed Mohd, Thirumala Chary Maringanti

PII: S0040-4039(17)30290-3
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.03.002
Reference: TETL 48703

To appear in: *Tetrahedron Letters*

Received Date: 3 January 2017
Revised Date: 24 February 2017
Accepted Date: 1 March 2017

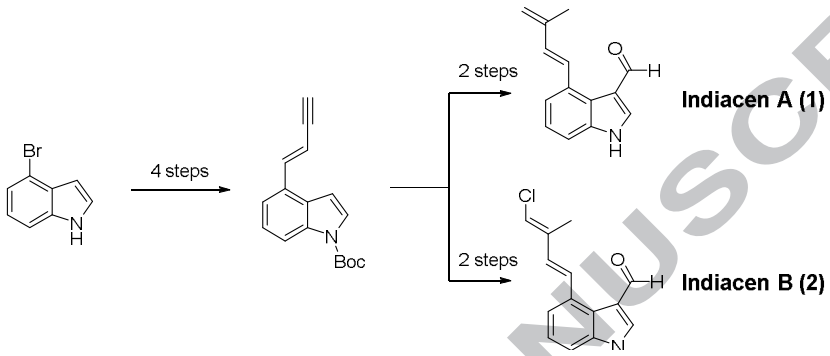
Please cite this article as: Anantoju, K.K., Mohd, B.S., Maringanti, T.C., An efficient and concise synthesis of Indiacen A and Indiacen B, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.03.002

Graphical Abstract

An efficient and concise synthesis of Indiacen A and Indiacen B

Kishore Kumar Anantoju [a,b], Baquer Syed Mohd. [a]*, Thirumala Chary Maringanti [b]

Leave this area blank for abstract info.



++

Tetrahedron Letters
journal homepage: www.elsevier.com

An efficient and concise synthesis of Indiacen A and Indiacen B

Kishore Kumar Anantoju [a], Baquer Syed Mohd [a,*], Thirumala Chary Maringanti [b]

[a]Department of Medicinal Chemistry, GVK Biosciences Pvt. Ltd., Survey Nos: 125 (part) & 126, IDA, Mallapur, Hyderabad 500076, India.
[b]Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad, 500 085, India.

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Total Synthesis
Natural Product
Antimicrobial
Carboalumination
Formylation

ABSTRACT

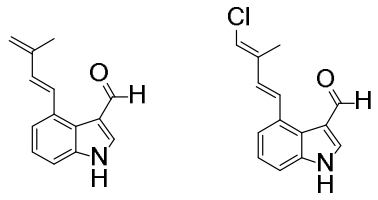
A novel total synthesis of antimicrobial prenyl indoles, Indiacen A and its chloro analogue Indiacen B has been accomplished by using Horner-Wadsworth-Emmons olefination for terminal conjugated enynes, carboalumination, chlorination and Vilsmeier-Haack formylation as the key transformations.

Introduction

Indiacen A and B (Figure 1),[1] prenyl indoles are the first reported secondary metabolites isolated from the bacterium *Sandaracinus amylolyticus* belonging to a new species of myxobacteria.[2] These secondary metabolites Indiacen A and its chloro analogue Indiacen B have been reported to present antimicrobial activity. These were found to be active against Gram-positive and Gram-negative bacteria as well as the fungus Mucor hiemalis. Indiacen A (**1**) is a 3-formylindole derivative bearing an isoprene like diene side chain and Indiacen B (**2**) is a 3-formylindole derivative bearing a dienyl chloride side chain. Lindel, T and co-workers have reported the first total synthesis of Indiacen B,[3] but the synthesis of Indiacen A has not been reported so far.

In our ongoing interest in the synthesis of biologically active compounds, the structural uniqueness and similarity in the structure prompted us to undertake the total synthesis of these compounds. We describe herein a first total synthesis of Indiacen A and an efficient, novel route to its chloro analogue Indiacen B. The synthesis features carboalumination, chlorination and Vilsmeier-Haack formylation as the key transformations.

Retrosynthetic analysis (scheme 1) revealed 4-formyl indole derivative as the suitable starting material, which upon Wittig Horner-Wadsworth Emmons reaction with the phosphonate **6** would install the desired ene-yne. Subsequent carboalumination-chlorination followed by formylation would give the desired Indiacen analogues.



Indiacen A (1) **Indiacen B (2)**

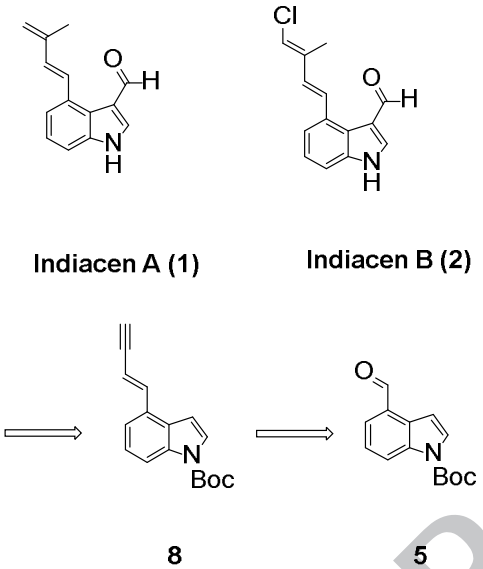
Figure 1: Structure of Indiacen A and Indiacen B

Results and Discussion

Our synthetic efforts (scheme 2) commenced with 4-bromo-1*H*-indole **3** as a commercially available, suitable starting material. *N*-Boc-indole-4-carboxaldehyde **5** was prepared from **3** following the protocol as reported in the literature.[4] Treatment of **5** with freshly prepared diethyl (3-trimethylsilyl-2-propynyl) phosphonate **6**[5] gave the silylated conjugated enyne **7** as exclusively *E*-isomer in 72% yield. Removal of the silyl group

* Corresponding author. Tel.: +91 040 6748 3456; fax: +91 40 6748 3400; e-mail: baquer@gvkbio.com

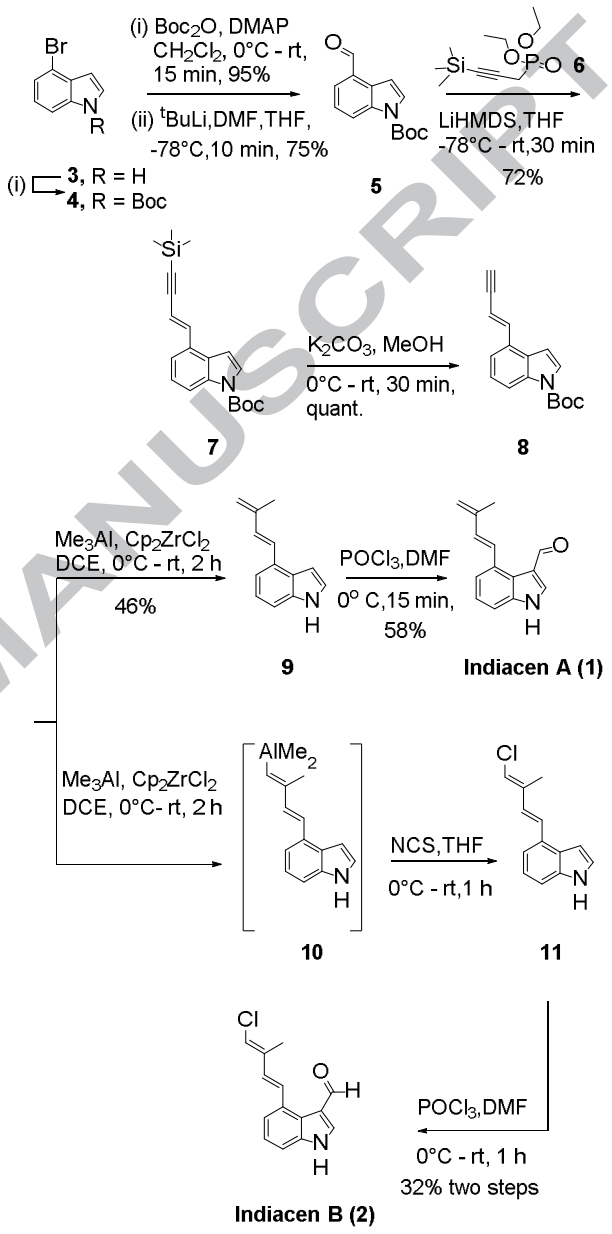
with K_2CO_3 in methanol gave the terminal conjugated enyne **8** in quantitative yield. The enyne **8** was then employed as a common intermediate for the preparation of Indiacen A (**1**) and B (**2**). Carboalumination[6] of the (*E*)-enyne **8** with trimethylaluminium in the presence of zirconocene dichloride (Cp_2ZrCl_2) followed by aqueous work up gave the diene **9** in 46% yield with the concomitant cleavage of the Boc group. The compound **9** was found to be unstable at rt and thus it was immediately formylated under Vilsmeier-Haack conditions[8] to afford Indiacen **A** in 58 % yield as a white solid. The spectral data[9] was found to be well in agreement with the data reported[1] for the natural product.



Scheme 1: Retrosynthetic strategy of Indiacen A and Indiacen B

Our next endeavor was the installation of dienyl chloride side chain as in Indiacen B (**2**) from the enyne **8**. Following a similar literature report for the preparation of the dienyl iodide[6,7] derivatives, the enyne **8** was similarly treated with trimethyl aluminium in the presence of zirconocene dichloride to give the dienyl alane **10** which upon chlorination with *N*-chlorosuccinimide (NCS) gave the desired dienyl chloride **11** as the major product (scheme 2) along with a minor amount of the 3-chlorinated indole derivative**.** To our knowledge this transformation has not been reported previously. Attempts to purify the dienyl chloride **11** over silica gel proved futile as it resulted in the decomposition of the product. Completion of the synthesis then required formylation. The mixture of products was used as such for the formylation step in anticipation to purify it in the final stage. Subsequent formylation under Vilsmeier-Haack conditions successfully delivered Indiacen **B** as a white solid in 32 % yield over two steps. The geometry of the double bond was ascertained as *E*-isomer after the formylation step by nOe experiment of 1HNMR spectroscopy. The spectral data of the prepared compound was found consistent with those of the reported values.[10] Thus, we have accomplished the synthesis of Indiacen A (**1**) and its chloro analogue Indiacen B (**2**).

In summary, a first total synthesis of Indiacen A (**1**) and a novel route to its chloro analogue Indiacen B (**2**) has been accomplished in a divergent way starting from commercially available starting materials. In this approach, the terminal enyne **8** was employed as a key intermediate while using carboalumination, chlorination and formylation as the key transformations. In addition, chlorination of the terminal enyne to give the desired dienyl chloride was achieved.



Scheme 2: Synthesis of Indiacen A and Indiacen B

Acknowledgments

The authors are thankful GVK Biosciences Pvt. Ltd. for the financial support and for the laboratory facilities. The assistance from the analytical department is greatly acknowledged.

References and notes

1. Steinmetz, H.; Mohr, K. I.; Zander, W.; Jansen R.; Gerth, K.; and Müller, R. *J. Nat. Prod*. **2012**, *75*, 1803.
2. Weissman, K. J.; Müller, R. Bioorganic & Medicinal Chemistry, **2009,** 17, 2121.

3. Marsch, N.; Jones, P. G.; and Lindel, T. *Beilstein J. Org. Chem.* **2015,** *11,* 1700.
4. Moyer, M. P; Shiurba, J. F.; Rapoport, H. *J. Org. Chem*, **1986**, *51*, 5106
5. Gibson, A.W.; Humphrey, G. R.; Kennedy, D. J.; Wright, S. H. B. *Synthesis*, **1991**, 414
6. (a) Negishi, E.; Van Horn, D. E; Yoshida, T.; *J. Am. Chem. Soc*., **1985**, *107*, 6639 (b) Baker R. and Brimble, A. M. *Tetrahedron. Lett*., **1986**, *27*, 3311
7. Tohdo, K., Hamada Y., Shioiri T., *Tetrahedron. Lett*., **1992**, *33*, 2031; Vaz, B; Alvarez, R; de Lera, A. R. *J. Org. Chem.* 2002, 67, 5040.
8. Lauchli R.; Shea, K. *J. Org. Lett*., **2006,** *8,* 5287
9. **Indiacen A (1)**: IR (KBr) 3496, 3183, 2918, 1642, 1402, 1293, 1139, 975, 852, 746 cm^{-1}. δ_H (400 MHz, acetone-d_6) 2.14 (s, 3H, CH_3), 5.03-5.16 (m, 2H, CH_2), 6.97 (d, *J*=16.14 Hz, 1H, CH), 7.25-7.31 (m, 1H, CH), 7.45 (d, *J*=7.82 Hz, 1H, CH), 7.60 (d, *J*=7.82 Hz, 1H, CH), 8.28 (s, 1H, CH), 8.49 (d, *J*=16.14 Hz, 1H, CH), 9.92 (s, 1H, CHO), 11.33 (br s, 1H, NH); δ_C (100 MHz, acetone-d_6) 19.3, 112.2, 116.4, 119.1, 121.7, 124.0, 124.9, 131.6, 132.1, 133.0, 140.0, 142.6, 144.5, 184.3. HRMS (ESI) calcd for $C_{14}H_{14}NO$ [M+H] 212.1075, found 212.1079. mp 159-162 ^oC
10. **Indiacen B (2)**: IR (KBr) 3727, 3167, 2921, 1636, 1404, 1368, 1145, 975, 795, 746, 642 cm^{-1}. δH (400 MHz, acetone-d_6) δ 2.21 (s, 3H, CH_3), 6.47 (s, 1H, CH), 6.97 (d, *J*=16.14 Hz, 1H, CH), 7.24-7.33 (m, 1H, CH), 7.47 (d, *J*=7.82 Hz, 1H, CH), 7.59 (d, *J*=7.34 Hz, 1H, CH), 8.31 (s, 1H, CH), 8.63 (d, *J*=16.14 Hz, 1H, CH), 9.91 (s, 1H, CHO), 11.36 (br s, 1H, NH); δ_C (100 MHz, acetone-d_6) δ 13.3, 112.4, 118.9, 119.3, 121.6, 124.0, 124.9, 128.7, 131.6, 132.5, 139.5, 140.0, 143.0, 184.4. HRMS (ESI) calcd for $C_{14}H_{13}NOCl$ [M+H] 246.0686, found 246.0699. mp 132-135 ^oC

Highlights:

- A novel synthesis of antimicrobial metabolites Indiacen A and Indiacen B is achieved.
- An indole derivative with terminal enyne group was employed as a common intermediate.
- The key reactions are olefination, carbo-alumination and chlorination.