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PII: S0040-4039(18)30728-7
DOI: https://doi.org/10.1016/j.tetlet.2018.05.090
Reference: TETL 50037

To appear in: *Tetrahedron Letters*

Received Date: 29 March 2018
Revised Date: 24 May 2018
Accepted Date: 30 May 2018

Please cite this article as: Madala, N., Rao Ghanta, V., Vinnakota, S., Mendu, N., Ingle, A.B., Ethiraj, K., Sharma, V., Total Synthesis of Carpatamides A–D, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.05.090

Tetrahedron Letters
journal homepage: www.elsevier.com

Total Synthesis of Carpatamides A–D

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Wittig olefination
Cross metathesis
Carpatamides
NSCLC
Cytotoxicity

ABSTRACT

A synthetic strategy was developed for the synthesis of the common core structure of Carpatamides A–D. The total synthesis of Carpatamides A and C was completed in 6 steps and of Carpatamides B and D in 7 steps, by employing the Wittig olefination, olefin cross metathesis and acid amine coupling reactions as key steps.

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1. Introduction

Non-small-cell lung cancer (NSCLC) is the most prevalent form of lung cancer.[1] It is also relatively insensitive to chemotherapy, compared to small cell lung cancer.[2] In order to identify compounds with selective activity against NSCLC, MacMillan and co-workers screened several natural product fractions against a panel of comprehensively annotated NSCLC cell lines. As a part of these studies, they isolated Carpatamides A–C (**1–3**, Fig. 1) from marine derived *Streptomyces sp*. (strain SNE-011).[3] Carpatamide A and C showed cytotoxicity against the NSCLC cell lines HCC366, A549, and HCC44 with IC_{50} values ranging from 2.2 to 8.4 μM. Another compound of same family Carpatamide D (**4**) was isolated from the marine derived *Streptomyces* strain SNE-011.[4]

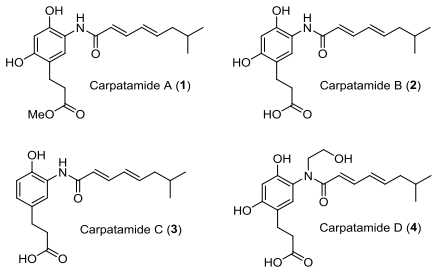
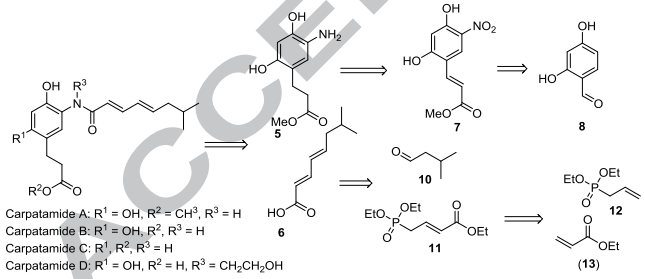


Figure 1. Carpatamides A–D

These compounds possess a novel amide structure consisting of an amino-phenyl propionic acid core and an unsaturated fatty acid side-chain, which was previously observed only in manumycin derivatives from *Streptomyces parvulus*.[5,6]

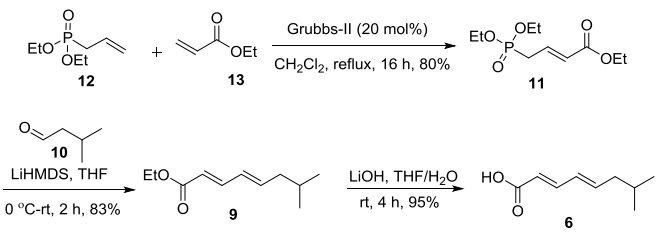
Herein, we report the first total synthesis of Carpatamides A–D (**1-4**). We envisioned their synthesis from amine **5** and acid **6** by amide coupling and further functional group manipulation. Amine **5** can be obtained from aldehyde **8** by nitration and Wittig olefination to give compound **7** followed by reduction. Acid **6** could be synthesized in 3 steps by the cross metathesis of olefins **12** and **13** to give compound **11** followed by Horner-Wadsworth-Emmons olefination and hydrolysis (Scheme 1).



Scheme 1. Synthetic strategy and retrosynthesis

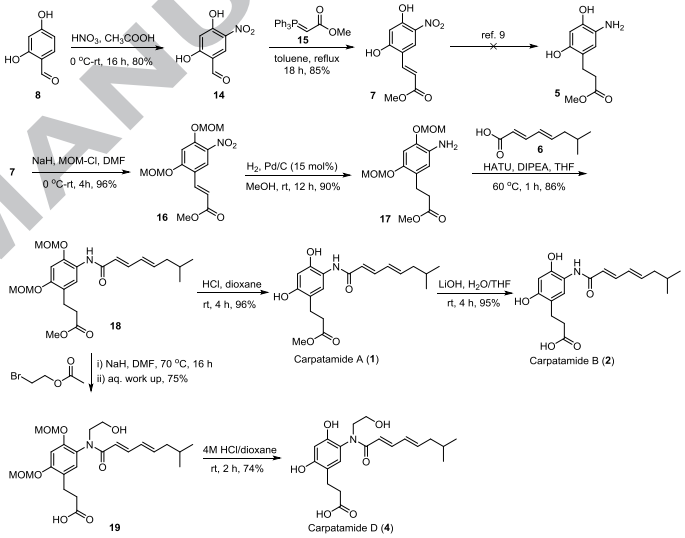
2. Results and Discussion

The synthesis commenced with the preparation of acid **6**. The cross metathesis of allyl phosphonate **12** with ethyl acrylate **13** gave olefin **11**[7] in good yield. Subsequent Horner-Wadsworth-Emmons olefination with 3-methylbutanal (**10**) gave diene ester **9**.[8] The hydrolysis of ester **9** then gave the required acid **6** in 63% overall yield from compound **13** (Scheme 2).



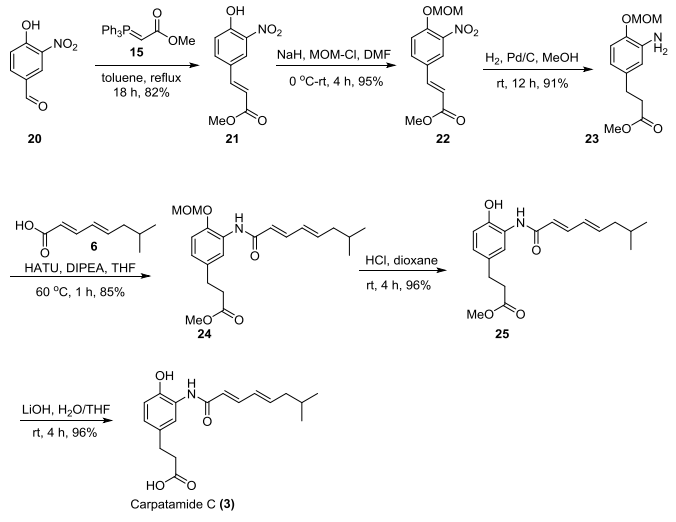
Scheme 2. Synthesis of acid **6**

The synthesis of amine **5**, started from commercially available aldehyde **8**. The regioselective nitration of **8** followed by Wittig olefination with ylide **15** produced α,β-unsaturated ester **7**. The reduction of **7** to **5** using different reaction conditions resulted complex reaction mixtures.[9] Crude LCMS indicated *in-situ* isomerization of the double bond and cyclisation with the adjacent hydroxyl to give coumarin derivatives with different oxidation states. The phenolic hydroxyl group was therefore protected as a MOM ether to give compound **16**, which upon hydrogenation gave amine **17** in good yield. Amine **17** was coupled with acid **6** to give the key intermediate **18**. MOM deprotection of compound **18** resulted in the formation of Carpatamide A (**1**), and subsequent hydrolysis afforded Carpatamide B (**2**). The alkylation of compound **18** with 2-bromoethyl acetate and aqueous work-up produced acid **19**, which was subjected to MOM deprotection by treatment with 4M HCl in 1,4-dioxane to give Carpatamide D (**4**, Scheme 3).



Scheme 3. Synthesis of Carpatamides A, B and D

The synthesis of Carpatamide C (**3**) started with 4-hydroxy-3-nitrobenzaldehyde (**20**) as shown in Scheme 4. The Wittig olefination of aldehyde **20** with ylide **15** gave unsaturated ester **21**, which was protected as the MOM ether and nitro reduction gave the desired amine **23**. The coupling amine **23** with acid **6** produced amide **24**, which upon MOM deprotection and ester hydrolysis gave Carpatamide C (**3**). The ^{1}H and ^{13}C NMR of all synthesized Carpatamides A–D (**1-4**) were in agreement with the isolated compounds by MacMillan and co-workers.[1,2]



Scheme 4. Synthesis of Carpatamide C

3. Conclusion

In conclusion, we have developed a synthetic strategy for Carpatamides A–D employing Wittig olefination, olefin cross metathesis and acid amine coupling reactions as the key steps.

Acknowledgments

The authors are thankful to GVK Biosciences Private Limited for financial support and facilities for accomplishing this research. Help from the analytical department for all spectroscopic analysis is highly appreciated. We are thankful to Dr. Sudhir Kumar Singh (President, Discovery and Development Services, GVK Bioscinces) for his immense support and motivation. We are also thankful to JNTU, Hyderabad.

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9. The reduction was attempted with i) H_2, Pd/C (10 mol%), EtOH ii) H_2, $Pd(OH)_2$ (10 mol%), EtOH, iii) Fe/NH_4Cl, EtOH then H_2, Pd/C (10 mol%), EtOH.

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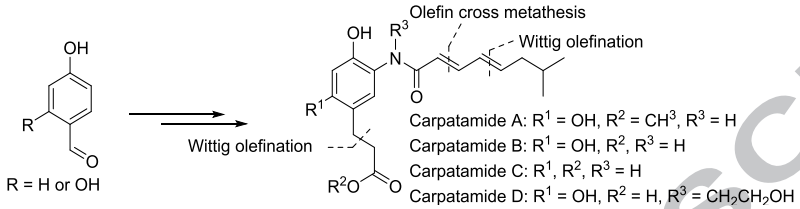

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Synthetic strategy developed for common core structure of Carpatamides A–D
Total synthesis of Carpatamides A-D is reported
Spectroscopic data of synthesized compounds is in agreement with reported compounds