A protecting-group-free synthesis of arbusculone, andirolactone, pinnatolide, ipomolactone, cyclocapitelline and isocyclocapitelline

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PII: S0040-4039(18)31231-0
DOI: https://doi.org/10.1016/j.tetlet.2018.10.024
Reference: TETL 50334

To appear in: *Tetrahedron Letters*

Received Date: 1 September 2018
Revised Date: 12 October 2018
Accepted Date: 13 October 2018

Please cite this article as: Gajula, S., Madhu, M., Chintakrinda, S.K., Yadav, J.S., Mohapatra, D.K., A protecting-group-free synthesis of arbusculone, andirolactone, pinnatolide, ipomolactone, cyclocapitelline and isocyclocapitelline, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.10.024

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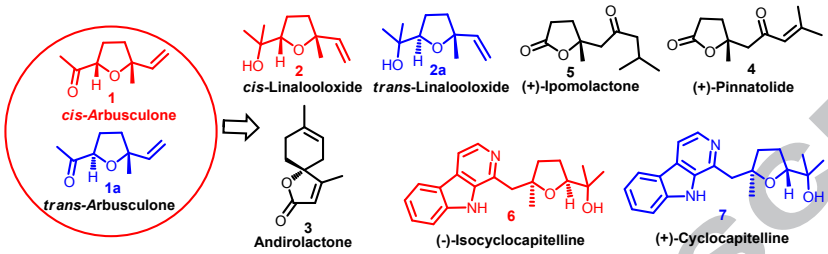

Tetrahedron Letters
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Natural products
Epoxidation reaction
Wittig reaction,
Pinnick oxidation,
Pictet-Spengler reaction.

ABSTRACT

A general approach for a collective synthesis of natural products containing substituted THF ring is described. In this paper, Arbusculone, a small molecule natural product accomplished using a short route, is used as the key intermediate to achieve the total synthesis of Andirolactone, Pinnatolide, Ipomolactone, Cyclocapitelline, Isocyclocapitelline and their two isomers in less than ten steps. The present effort highlights protecting-group-free total syntheses and the shortest route to access these natural products from commercially available cheap starting materials.

Nature has gifted us countless numbers of natural products with complex and fascinating structures with interesting biological properties. [1] Among them, THF-containing natural products belong to one relatively small but interesting category of natural products exhibiting an array of important bioactivities. [2] Due to their intriguing biological activities and potential candidates as pharmaceuticals, THF-containing natural products have been the target of a large number of research groups. [3] Among them, *cis*- and *trans*-Arbusculone were isolated for the first time from the essential oil of A. *herba-alba* growing wild in Tunsia. [4] Similarly, Andirolactone, a spirocyclic butenolide natural terpenoid isolated in 1987 from tar wood of the *Cedrus* libanottea, which is a needle leaf tree that grows in Southern Turkey and Libanon. [5] Other related natural products like Pinnatolide and Ipomolactone are isolated from *A. pinnata* in 1991 by Bohman et al. [6] Cyclocapitelline and Isocyclocapitelline are isolated from rubiaceae family and are available in minute quantities from natural sources. [7] Because of the interesting structural features and potent biological activities of these natural products, many groups [8] have reported different synthetic approaches for these natural products. As the biological activity of THF-containing natural products rely on its stereochemistry, considerable efforts have been expended on the stereoselective synthesis of tetrahydrofuran ring systems. [9] Current synthetic strategies mostly rely on lengthy synthetic routes to access THF rings and on chiral building blocks with a number of protecting group and functional group manipulations.

In continuation of our interest in the synthesis of THF and substituted THF containing natural products, [10] we report

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herein, a scalable and protecting-group-free stereoselective syntheses of a series of THF-containing natural products starting from a key intermediate *cis*-Arbusculone and *trans*-Arbusculone, both are natural products itself. According to the retrosynthetic analysis for the synthesis of natural products depicted in Figure 1, we hypothesized that *cis*-Arbusculone (**1**) could be an ideal

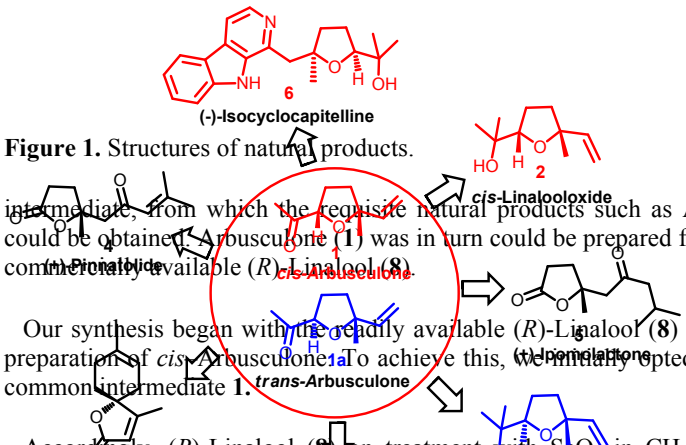
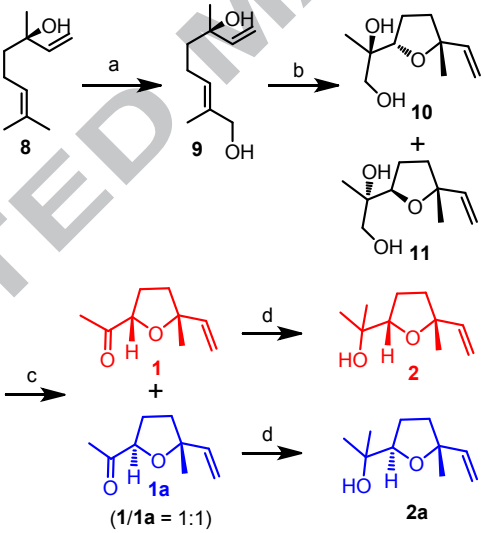


Figure 1. Structures of natural products.

intermediate, from which the requisite natural products such as Andirolactone, Pinnatolide, Ipomolactone, and Isocycloca- pitelline could be obtained. Arbusculone (**1**) was in turn could be prepared from key allylic alcohol building block which could be obtained from commercially available (*R*)-Linalool (**8**).

Our synthesis began with the readily available (*R*)-Linalool (**8**) as the starting material. The major challenge in our synthesis is the preparation of *cis*-Arbusculone. To achieve this, we initially opted for Sharpless asymmetric epoxidation reaction for the synthesis of common intermediate **1.**

Accordingly, (*R*)-Linalool (**8**) on treatment with SeO_2 in CH_2Cl_2 followed by reduction of the resultant aldehyde with $NaBH_4$ furnished allyl alcohol **9** in 68% yield over two steps. The asymmetric epoxidation of allyl alcohol **9** under Sharpless asymmetric epoxidation reaction conditions was not successful and it might be due to the presence of free tertiary alcohol in compound **9** and in our hands only 40% starting material consumed at −20 °C over a period of 7 days to obtain **10** and **11** as a mixture in 4:1 ratio. As per our knowledge, till now asymmetric Sharpless epoxidation on this substrate is not reported and as we were looking for the synthesis of *cis*-Arbusculone (**1**) and *trans*-Arbusculone (**1a**), alternatively, we carried out the epoxidation using *m*-CPBA which furnished compound **10** and **11** with almost 1:1 ratio in 89% combined

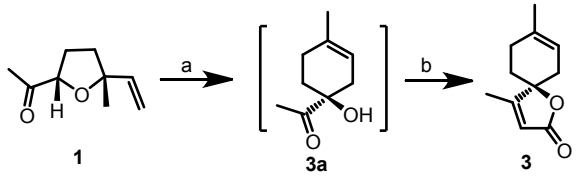


Scheme 1. Synthesis of key intermediate arbusculone (**1**/**1a**). Reagents and conditions: a) SeO_2, CH_2Cl_2, 0 °C to rt, 6 h, $NaBH_4$, 68%; b) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 2 h, 89%; c) $NaIO_4$ on silica, CH_2Cl_2, 0 °C, 2 h, 87%; d) MeMgBr, Et_2O, 0 °C, 30 min, 85% (**2**) and 84% (**2a**).

yield. Both the isomers were separated and treated with sodium metaperiodate to afford a mixture of *cis*- and *trans*-THF rings **1** and **1a** from **10** and **11**, respectively. These THFs were easily separated by silica gel column chromatography and the stereochemistry was assigned by key NOE correlations (see Supporting Information).

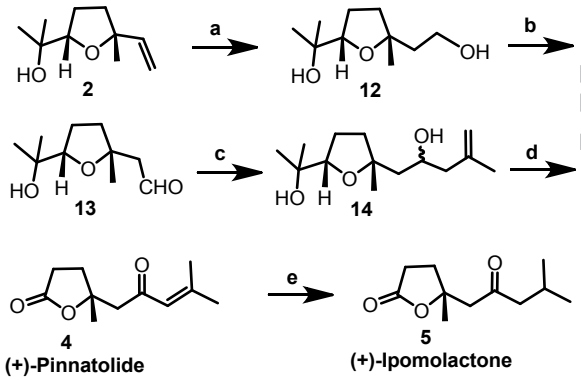
After successful synthesis of *cis*-Arbusculone (**1**), we focused our attention on the total synthesis of other four related natural products and their isomers. Toward this effort, the Arbusculone (**1**) in the present synthesis is suitable for the generation of other related natural products, as it possesses functionalities with orthogonal reactivities. Accordingly, treatment of compound **1** with methyl magnesium bromide in diethyl ether at 0 °C afforded the required alcohol compound **2** in 85% yield. For the synthesis of alcohol compound **2a**, compound **1a** was treated with methyl magnesium bromide, under same reaction conditions as reported for the preparation compound **2** (Scheme 1), to afford **2a** in 84% yield.

Towards the synthesis of Andirolactone (**3**), we identified compound **3a** as an ideal late-stage intermediate because it enabled the incorporation of the tertiary alcohol functionality retaining the double bond geometry of vinyl group through a 2,3-Wittig rearrangement. [11] The in situ formation of ketone **3a** under *cis*-Wittig reaction conditions furnished Andirolactone (**3**) in 44% yield over two steps. The spectral data of Andirolactone (**3**) matched with those reported for the natural and synthetic material. [8d] This approach highlights a protecting group free total synthesis and the shortest route to access Andirolactone (**3**).



Scheme 2. Synthesis of (−)-Andirolactone **3**. Reagents and conditions: a) *t*-BuOK, *t*-BuOH, 12 h; b) Ethyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]propanoate, *n*-BuLi, THF, 1 h, 44%, over two steps.

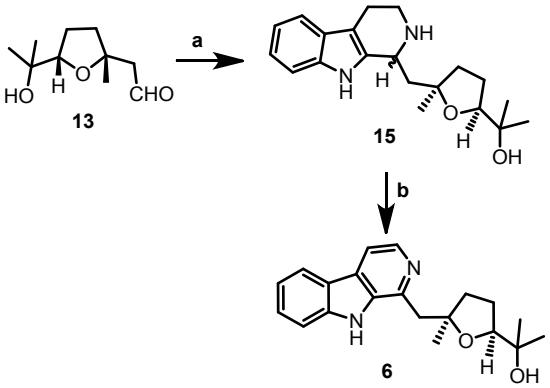
Attention was next focussed on the total synthesis of (+)-Pinnatolide and (+)-Ipomolactone. To the best of our knowledge, Pinnatolide (**5**) was prepared by Lutz *et al* using seven steps. [8g] However, we developed it in a sequence of six steps. Accordingly, hydroboration of compound **2** followed by Dess-Martin periodinane (DMP) oxidation of the resulting primary alcohol furnished the requisite aldehyde fragment **13** in 83% yield. Aldehyde **13** was subjected to Grignard reaction to give the diastereomeric mixture (1:1) of alcohols **14** in 80% yield.



Scheme 3. Synthesis of (+)-Pinnatolide (**4**) and (+)-Ipomolactone (**5**). Reagents and conditions: a) BH_3.DMS, THF, 0 °C to rt, 6 h, 81%; b) DMP, CH_2Cl_2, 0 °C to rt, 12 h, 83%; c) C_4H_7MgBr, 0 °C to rt, 1 h, THF, 80%; d) PCC, CH_2Cl_2, reflux, 12 h, 60%; e) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, 6 h, 88%.

PCC oxidation [12] of secondary alcohol **14** in refluxing CH_2Cl_2 followed by isomerization of terminal double bond to internal double bond furnished directly the (+)-Pinnatolide (**4**). Finally, *α,β*-unsaturation in compound **4** was hydrogenated using $NiCl_2$ and sodium borohydride to form (+)-Ipomolactone (**5**) in 88% yield. It is noteworthy to mention that the significance of (+)-Pinnatolide (**4**) to determine the absolute stereochemistry on C4 carbon of (+)-Ipomolactone (**5**) was identified by converting Pinnatolide to Ipomolactone.

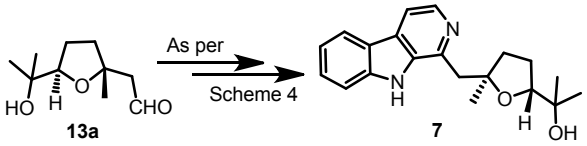
Having prepared gram quantities of the key intermediate and completed the asymmetric synthesis of two natural products, we diverted our attention for the synthesis of two more natural products (−)-Isocyclocapitelline and (+)-Cyclocapitelline. Our approach for the synthesis of (−)-Isocyclocapitelline and (+)-Cyclocapitalline is significantly shorter than the previous stereoselective routes. [8l] Hartung *et al* reported the syntheses of *cis*- and *trans*-β-carbolines, which are lower homologues of alkaloids (–)-Isocyclocapitelline and (+)-cyclocapitelline. The key step in their synthesis is the Vanadium-catalyzed oxidation of (*R*)-Linalool (**8**) in which epoxidation took place on both the double bonds, leading to low yield of the required product. Pleasingly, our protocol involves *m*-CPBA-mediated oxidation which furnished epoxidation exclusively on allylic double bond resulting in the formation of *cis* and *trans*-THF in equal ratios with good yield. Accordingly, the synthesis commenced from



Scheme 4. Synthesis of (−)-Isocyclocapitelline **6.** Reagents and conditions: a) Tryptamine, TFA, CH_2Cl_2, −78 °C, 3 h; b) Pd/C, Xylenes, reflux, 8 h, 75%, Over two-steps.

aldehyde **13** and was subjected to a Pictet-Spengler [13] reaction with tryptamine under TFA-catalyzed conditions followed by dehydrogenation using Pd/C in xylene under reflux conditions to afford (−)-Isocyclocapitelline (**6**) in 75% yield over two steps.

Following the same sequence of reactions and conditions as reported in Scheme 4, (+)-Cyclocapitelline (**7**) was furnished in 73% yield over two steps starting from aldehyde **13a** (Scheme 5).



Scheme 5. Synthesis of (+)-Cyclocapitelline **7**.

In summary, the present protocol highlights protecting-group-free total syntheses and the shortest route to access synthesis of five natural products and two isomers starting from Arbusculone as an ideal intermediate. The key steps involved are Wittig reaction, Pinnick oxidation, 2,3-Wittig rearrangement and Pictet-Spengler reaction. The present approach demonstrated wide applicability in the synthesis of various natural products containing THF motif and analogues required for biological activity. Further application of this method towards the total syntheses of other related complex natural products is in progress.

Acknowledgments

The authors thank Council of Scientific and Industrial Research (CSIR), New Delhi, India, for financial support as part of the XII Five Year plan programme under the title ORIGIN (CSC-0108; manuscript communication number IICT/Pubs/ 2018/297). G.S. M.M. and C.H.S.K. thank the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for financial assistance in the form of fellowship.

Supporting Information

Supplementary data associated with this article can be found, in the online version, at http://dx.doi/xxxxxx.

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Highlights

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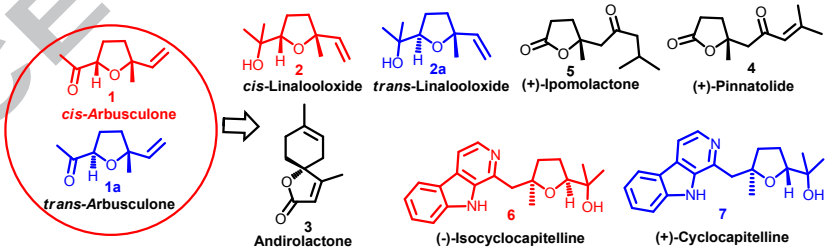

1. Protecting-group-free total synthesis.
2. Shortest route for the natural products.
3. 2,3-Wittig rearrangement for Andirolactone synthesis in one step.
4. Application of Pictet-Spengler reaction.