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Synthesis of isomeric corniculatolides

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ABSTRACT

Synthesis of three natural macrolides 11-*O*-methylcorniculatolide A, 11-*O*-methylisocorniculatolide A and isocorniculatolide A is reported using a simple, straight forward and high-yielding route. The present synthesis confirms the assigned molecular structures and provides an access to sufficient quantities of the natural products for the biological evaluation. In addition, we have determined the anti-TB potential of the three natural compounds using Alamar-Blue assay ($H_{37}Rv$) and found no significant inhibitory activity at 100 μg/ml. Excellent yields, short sequence and useful SAR information are the highlights of the present work.

Very recently, five isomeric macrolides of combretastatin D-2 congeners called 11-*O*-methylcorniculatolide A (**1**), corniculatolide A (**2**), 11-*O*-methylisocorniculatolide A (**3**), isocorniculatolide A (**4**) and 12-hydroxy-11-*O*-methylcorniculatolide A (**5**) were isolated from the bark of a mangrove *Aegiceras corniculatum* by Gowri's research group from India.[1] This particular mangrove has been used traditionally to treat various inflammatory and metabolic disorders and possesses a range of interesting biological properties.[2] Out of the five isolated natural products, only corniculatolide A (**2**) was the previously known compound.[3] The structures of these new compounds were established using extensive NMR experiments and X-ray crystal structure analysis of one of the natural products. The related compounds of interesting diarylheptanoid structure coupled with interesting biological properties[4] have already been the target of several synthetic groups.[5,6] Majority of the groups focused their research using this class of compounds towards developing anti-cancer agents. Unlike many others, the novel macrocyclic compounds **1–5** attracted our attention because of their close structural resemblance with one of the potent antituberculosis lead compound called engelhardione/pterocarine, **6**.[7,8] The compound **6** is reported to have MIC of 0.2 μg/ml when screened against *Mycobacterium tuberculosis* ($H_{37}Rv$).[7] Based on the structural similarity, the title compounds **1–5** are expected to show antitubercular activity (Fig. 1). As part of our research group activity towards finding novel chemotypes for antituberculosis drug discovery,[9] we have initiated the proposed work. Our plan is to synthesize the target macrolide compounds in sufficient quantities using efficient routes for biological screening, in particular, antituberculosis assay. The present effort may provide a way forward for a drug discovery program[10] using this chemotype. In addition, the total syntheses further confirm the assigned structures by Gowri's group and the results are disclosed here in this Letter.

We have planned the synthesis of the target molecules **1–5** by relying on two key steps (i) diarylether formation[11] and (ii) macrolactonization[12] starting from readily available building blocks (Fig. 2).

The planned synthesis began with the first key step diarylether formation between the readily accessible partners, compound **7**[5b] and *para*-fluorocinnamaldehyde **8**. The reaction between **7** and **8** using Cs_2CO_3 in DMSO (at 120 °C for 8 h) was very clean and resulted in a high yield of the desired compound **9**. Next, we subjected compound **9** to hydrogenation using 10% Pd/C under hydrogen balloon pressure to remove both the unwanted double bonds in molecule **9**. We were pleased to find saturated alcohol **10** in very high yield during the hydrogenation step which is the result of further reduction of intermediate saturated aldehyde.[13] The acyclic compound **11** obtained from **10** through hydrolysis was subjected to the second key step macrolactonization. After a few attempts, we found that Mitsunobu[12] conditions (PPh_3, DIAD, 0.0025 M final concentration of solution in toluene, rt) produced the desired macrocycle 11-*O*-methylcorniculatolide A (**1**) in 65% isolated yield (Scheme 1). We did not isolate dimers or oligomers

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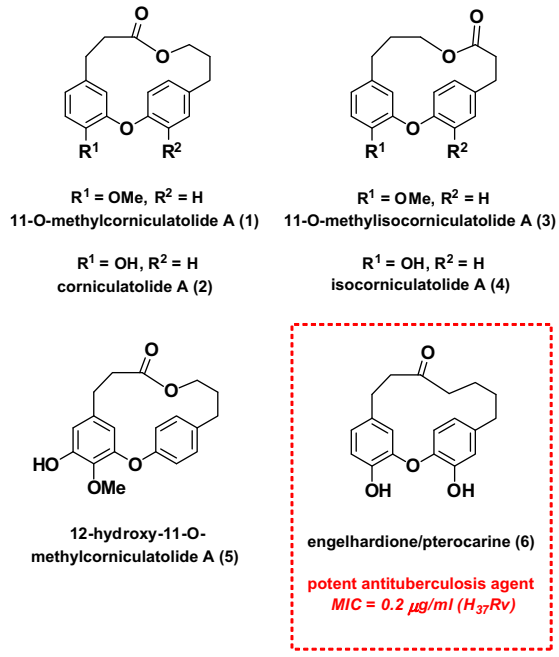


Figure 1. Structures of isomeric corniculatolides and engelhardione.

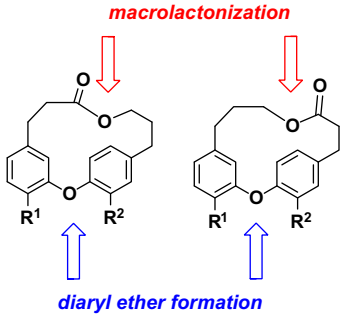
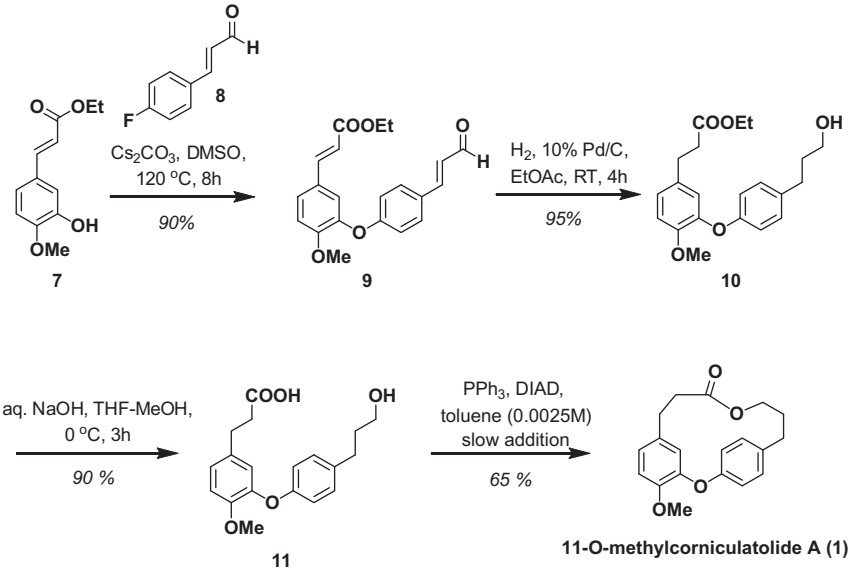


Figure 2. Key steps in planned synthesis.

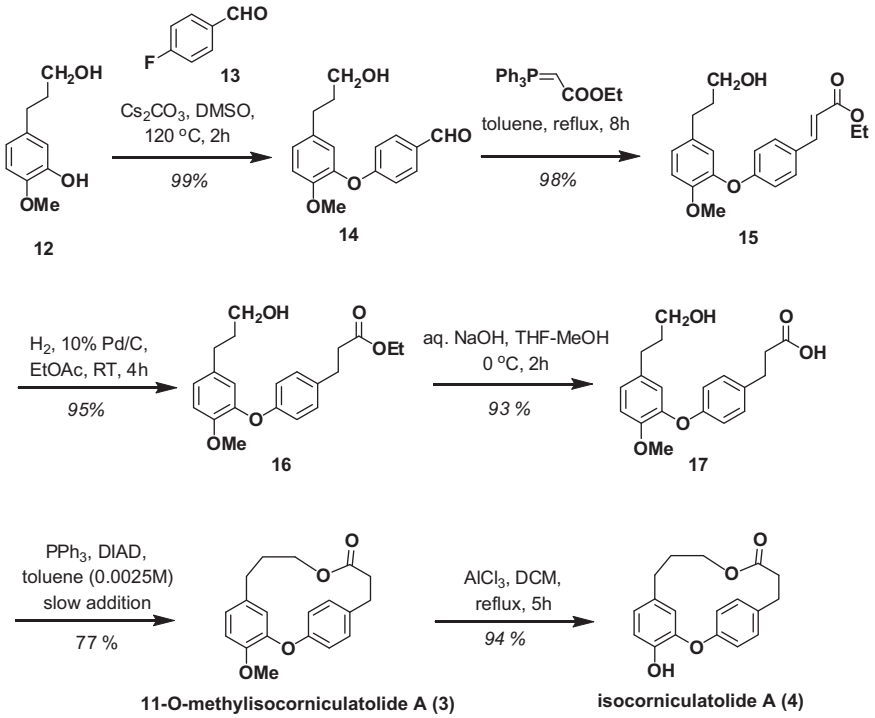
from this reaction. We believe that the addition of acyclic precursor **11** to a solution of Ph_3P and DIAD over a period of ~24 h is important.[14] The spectral data (^1H NMR and ^{13}C NMR) of synthetic compound **1** and those of natural compound **1** are identical.[1,15]

Having seen the success with the synthesis of 11-*O*-methylcorniculatolide A (**1**), we attempted the synthesis of isomeric isocorniculatolides **3** and **4**. The compound diarylether **14** was prepared from the alcohol **12**[5d] by reacting with *para*-fluorobenzaldehyde **13** in the presence of Cs_2CO_3 in DMSO. It is important to note that phenolic OH is more reactive than aliphatic OH which can be explained by the difference in nucleophilicity between the groups. Horner-Wittig reaction on aldehyde **14** produced the α,β-unsaturated ester **15** which was further transformed to saturated ester **16** using 10% Pd/C under the hydrogen atmosphere. Horner-Wittig reaction on aldehyde **14** also produced small amounts of corresponding Z-isomer of **15**. As it is not relevant for the present purpose, we reduced the mixture to furnish **16** as a single compound. Ester hydrolysis in compound **16** using aq NaOH in THF–MeOH mixture produced the acyclic precursor **17** in 93% yield. The macrocyclization under similar conditions of compound **1** synthesis (PPh_3, DIAD, 0.0025 M final concentration),[14] natural product 11-*O*-methylisocorniculatolide A (**3**) was prepared in high yield. Finally, compound **3** was transformed to third natural product isocorniculatolide A (**4**) through demethylation using $AlCl_3$ in DCM under reflux conditions. The spectral data of both the natural products **3** and **4** were compared with those of reported data and they are found to be identical.[1,15] Thus, we have synthesized 11-*O*-methylcorniculatolide A (**1**), 11-*O*-methylisocorniculatolide A (**3**), and isocorniculatolide A (**4**) using a high yielding route and further confirmed the assigned structures based on spectral data (Scheme 2).

All the three synthesized natural products 11-*O*-methylcorniculatolide A (**1**), 11-*O*-methylisocorniculatolide A (**3**) and isocorniculatolide A (**4**) were tested for antitubercular activity through inhibition of growth of the virulent strain of *Mycobacterium tuberculosis* $H_{37}Rv$ using Alamar-Blue assay method. To our surprise, the results show that none of the compounds are significantly active up to 100 μg/ml. This suggests the presence of additional substituent (like OH) on the second aromatic ring and/or absence of oxygen atom in the ring (in the form of lactone) of pterocarine chemotype are/is important for the antitubercular activity.[16] One of the



Scheme 1. Synthesis of 11-*O*-methylcorniculatolide A.



Scheme 2. Synthesis of 11-*O*-methylisocorniculatolide A and isocorniculatolide A.

reviewers pointed out that compounds of this type have the potential to exist as atropisomers.[17] We agree with the reviewer and it may not be appropriate to compare the activities with natural pterocarine as our method cannot produce the single atropisomers.

In short, we have achieved the synthesis of three out of four recently isolated isomeric corniculatolide natural products using a simple and efficient synthetic route. The present route can be used for the synthesis of most of the related compounds of this family and their analogues towards generating interesting chemotypes for drug discovery programs. Also, the route is capable of producing gram-scale materials which may be useful in further biological profiling. Although, in the present case we did not see significant inhibitory activity (even at 100 μg/ml) in our antituberculosis assay, it provides useful SAR information on this scaffold for medicinal chemists. We are yet to explore other biological screenings like anti-cancer, anti-inflammatory and other anti-bacterial assays.

Acknowledgements

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR data comparison tables of the natural products with that of synthetic samples, and copies of NMR spectra for all the new compounds)associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.010.

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14. Detailed procedure for macrolactonization is available in Supplementary data.
15. See Supplementary data for the spectra and data comparison tables.
16. We have contacted Prof. Dianqing Sun for the verifiifcation of pterocarine's anti-TB activity as they have synthesized the molecule in their lab. We were informed that engelhardione/pterocarine showed only marginal antitubercular activity in their assays. Sun, D. et al., Unpublished results.
17. While this manuscript was under review, in recent publication, it was shown that compounds of pterocarine (**6**) and related compounds are resolvable using chiral HPLC. This further supports reviewer's suggestion. See, refs (a) Salih, M. Q.; Beaudry, C. M. *Org. Lett.* **2012**, *14*, 4026; (b) Costantino, V.; Fattorusso, E.; Mangoni, A.; Perinu, C.; Teta, R.; Panza, E.; Ianaro, A. *J. Org. Chem.* **2012**, *77*, 6377.