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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 7527–7529

Asymmetric synthesis of all the stereoisomers of tarchonanthuslactone

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Received 11 July 2005; revised 25 August 2005; accepted 31 August 2005
Available online 15 September 2005

Abstract—We describe herein an efficient synthesis of all the four stereoisomers of tarchonanthuslactone from (*R*)-3-hydroxy butanoate, easily prepared from L-threonine. The approach involves the use of a β,γ-unsaturated δ-lactone as an intermediate, obtained via a Kulinkovich reaction followed by a ring-closing metathesis strategy.

6-Substituted 5,6-dihydro-2*H*-pyran-2-one is an important structural subunit in many biologically important natural products.[1] The α,β-unsaturated δ-lactone functionality is presumed to be responsible for biological activities, such as plant growth inhibition, antifeedent, antifungal, antibacterial, and antitumoral properties. This is mainly due to its ability to act as a Michael acceptor, enabling it to bind to a target enzyme. One of these natural products is tarchonanthuslactone **1a**, which was isolated by Bohlmann in 1979 from the leaves of a tree *Tarchonanthus trilobus*.[2] Nakata et al. were able to assign the absolute configuration of this molecule by carrying out the first asymmetric synthesis.[3] A few years ago, Hsu et al. showed that **1a** lowered the plasma glucose level in diabetic rats.[4] This important biological activity gave an indication that tarchonanthuslactone **1a** or its analogs have potential to be used in human beings, thus making it the target of several total syntheses.[3,5a–f] The complexity in the synthesis of this natural product is due to the inherent instability of a hydroxy lactone **2**, an obvious precursor, as it forms bicyclic lactone **3** under basic conditions (Fig. 1). Most of the published approaches were aimed at the synthesis of only the natural isomer **1a**, and to the best of our knowledge, there is no flexible method reported to synthesize all the four stereoisomers of tarchonanthuslactone. As a part of our continuing interest in the asymmetric synthesis of natural products having δ-lactone rings,[6] we were interested in the synthesis of all stereoisomers of this natural product. In this letter, we delineate our efforts on their total synthesis from L-threonine.

The synthesis of tarchonanthuslactone **1a** commenced from (*R*)-3-hydroxybutanoate **7**, which was easily synthesized from L-threonine using the literature procedure.[7] The hydroxyl group of **7** was protected as a TBS ether. Using Kulinkovich methodology[8] reaction of **8** with excess ethylmagnesium bromide in the presence of Ti(O*i*-Pr)$_4$ at room temperature produced substituted cyclopropanol **9** in excellent yield (Scheme 1). The cyclopropanol **9**, when treated with NBS, gave a 1:1 mixture of α,β-unsaturated ketone **10** and a β-bromoketone. However, with a slight modification to the reported procedure[9] by adding triethylamine as a base, the desired ketone **10** could be obtained in quantitative yield (Scheme 1). The α,β-unsaturated ketone **10** was subjected to the Luche protocol[10] to obtain an allyl alcohol **6** with a predominance of *syn* selectivity (*syn*:*anti* ratio = 86:14; inseparable mixture). Various attempts[11] to improve the 1,3-diastereoselectivity[12] failed. The alcohol **6** (*syn* major) was coupled[13] with vinylacetic acid (VAA) to give the metathesis precursor **5a** as an inseparable mixture of *syn* (major) and *anti* (minor) isomers, which was subjected to a RCM[14] reaction using the first generation Grubbs catalyst **I**. Although the isolated yield of the desired cyclized products was poor (40%), both the diastereomers (**4a** and **4c**) could be easily separated by silica gel column chromatography. The yield in the above RCM reaction was improved to 90% using the second generation Grubbs catalyst **II** (Scheme 1).

Keywords: Tarchonanthuslactone; Asymmetric synthesis; Kulinkovich reaction; RCM.
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doi:10.1016/j.tetlet.2005.08.164

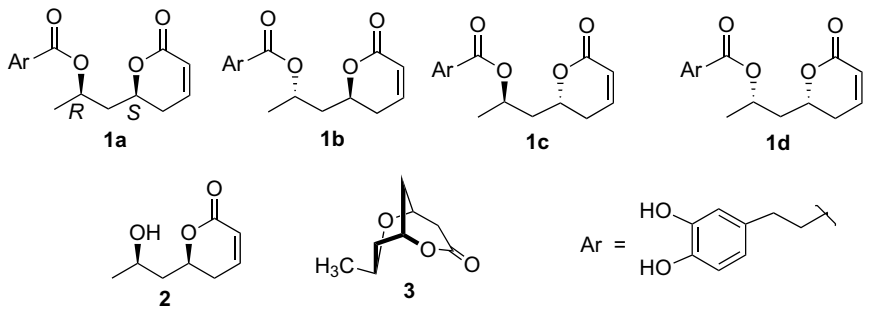
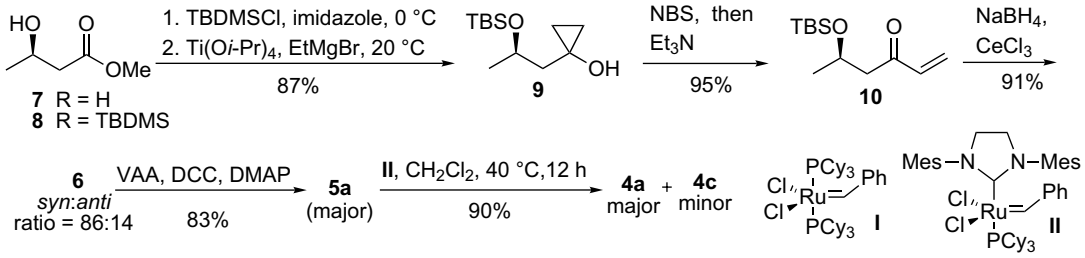


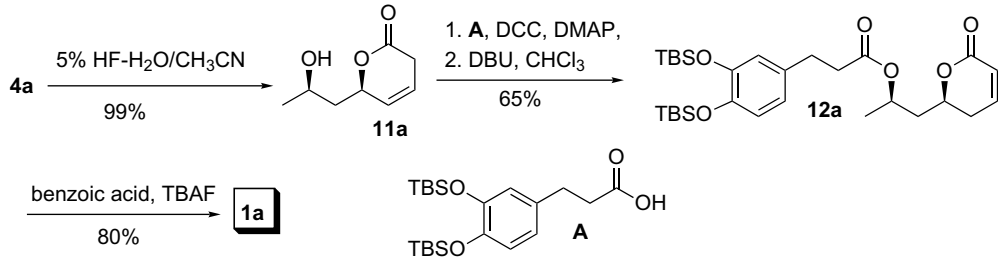
Figure 1.



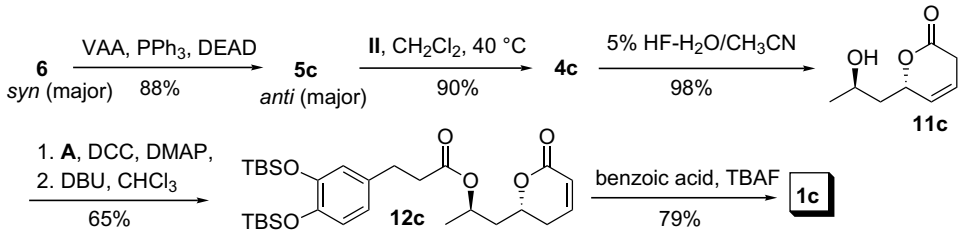
Scheme 1.

Having pure **4a** in hand, the synthesis of the natural isomer **1a** could be accomplished in just a few steps. The TBS group was removed with 5% HF–H_2O/CH_3CN to furnish a corresponding alcohol **11a**, coupling of which with an acid **A**[5c] using DCC followed by treatment of the crude product with DBU afforded the desired product **12a**. Finally, the synthesis of the natural isomer **1a** was accomplished by desilylation using TBAF in the presence of benzoic acid[5c] (Scheme 2). Using the same sequence of reactions, **1c** was synthesized from **11c**, which in turn was prepared from **4c**, the minor product (Scheme 1). In order to synthesize **4c** in good yield, the common intermediate **6** (*syn*, major) was subjected to Mitsunobu conditions[15a] to deliver the *anti* isomer **5c** as a major product, which was then exposed to the second generation Grubbs catalyst **II** to furnish the cyclized products (**4c** and **4a**). As above, these could be easily separated, and thus **4c** was obtained in good yield (Scheme 3).

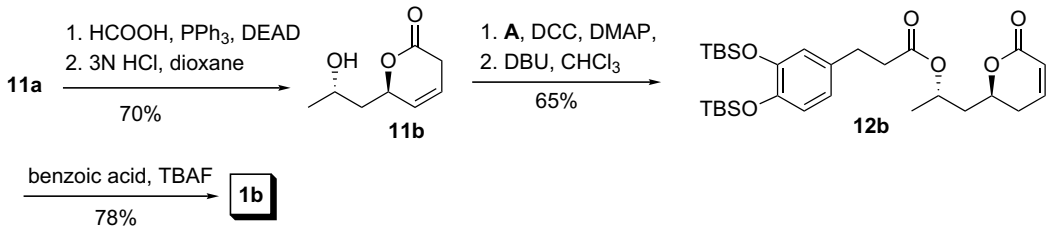
Once the routes to **1a** and **1c** were successfully established, it was planned that the other two stereoisomers could be synthesized by inverting the stereochemistry of the hydroxyl group in **11a** and **11c**. However, Mitsunobu



Scheme 2. Synthesis of natural stereoisomer **1a**.



Scheme 3. Synthesis of **1c**.



Scheme 4. Synthesis of **1b**.

inversion[15a] with the acid **A** gave only 5–10% yields of the products. An alternative strategy was conceived, where formic acid was to be used to invert the hydroxyl groups in **11a** and **11c**.[15b] Reaction of the alcohol **11a** with formic acid under Mitsunobu condition followed by in situ hydrolysis of the formate ester provided inverted alcohol **11b** easily. Once **11b** was in hand, it was transformed into the final target **1b** using a similar sequence of reactions (Scheme 4). Similarly, the synthesis of **1d** was completed from **11c**.

In conclusion, we have accomplished the asymmetric synthesis of all the four stereoisomers of tarchonanthuslactone **1a**–**d** from a common intermediate **6**, which was readily prepared from (*R*)-3-hydroxy butanoate **7**. The approach involved the use of β,γ-unsaturated lactone obtained via a Kulinkovich reaction followed by a ring closing metathesis (RCM). The overall yield of the natural product **1a** by our method is 26%, which is higher than the literature methods.

Acknowledgements

We thank CSIR for a research Grant to V.K.S. and research fellowships to S.B. and S.S.

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