ORGANIC LETTERS

2006
Vol. 8, No. 1
151−153

An Enantioselective Total Synthesis of (+)-Ricciocarpin A

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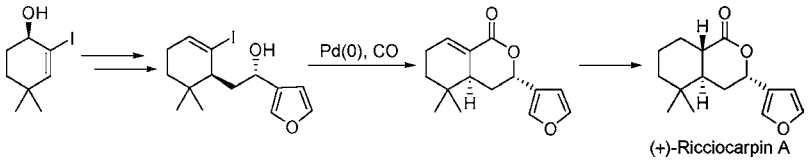
Received October 31, 2005

ABSTRACT

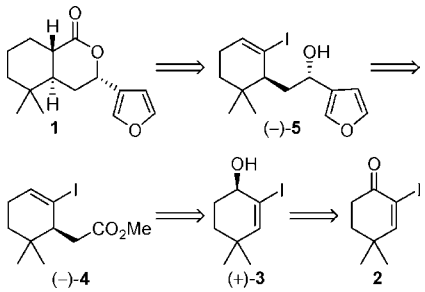


Starting from 4,4-dimethyl-2-cyclohexenone, an efficient total synthesis of ricciocarpin A (1) in natural form has been accomplished.

(+)-Ricciocarpin A (**1**), a furanosesquiterpene lactone, was first isolated from an axenic culture of the European liverwort *Ricciocarpos natans* about 15 years ago.[1] It bears a δ-lactone functionality appended with a 3-furyl group and displays high molluscicidal activity against the water snail *Biomphalaria glabrata*, one of the vectors of schistosomiasis.[2] Owing to these interesting structural and biological features, ricciocarpin A (**1**) has attracted considerable efforts toward its synthesis over the past decade, cumulating in the successful implementation of several elegant approaches[3−8] including two asymmetric versions disclosed recently.[7,8] Herein we wish to report a concise total synthesis of this compound in natural form using a fundamentally different strategy.

As schemetically illustrated in Scheme 1, our synthetic design makes use of the known catalytic asymmetric reduction of 4,4-dimethyl-2-iodo-2-cyclohexenone (**2** → **3**)[9] in conjunction with an ortho ester rearrangement reaction[10] (**3** → **4**) to set the absolute stereochemistry required for the target natural product. The latter process is also expected to facilitate the incorporation of a two-carbon side chain properly functionalized for the introduction of a 3-furyl group

Scheme 1



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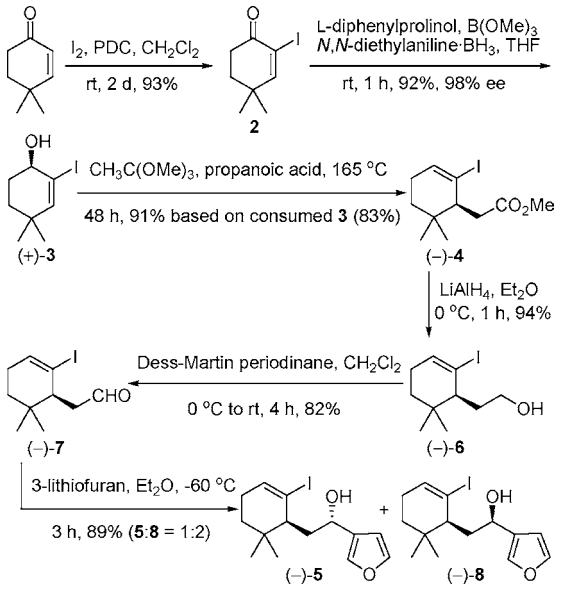
10.1021/ol052638r CCC: $33.50
Published on Web 12/03/2005

(**4** → **5**) and the subsequent lactone ring formation via a carbonyl insertion reaction en route to **1**.

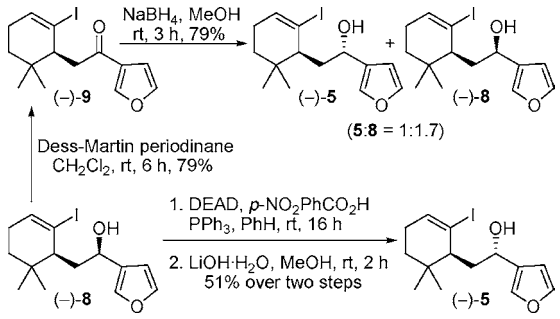
In practice, iodo enone **2**, readily accessible from 4,4-dimethyl-2-cyclohexenone[11] (Scheme 2), was subjected to

Scheme 2



asymmetric reduction according to the procedure developed by Knochel and Soorukram[9b] to give the corresponding iodo alcohol **3** in high optical purity (98% ee).[12] This alcohol was treated with trimethyl ortho ester at 165 °C in the presence of a small amount of propanoic acid. Apart from the somewhat slow reaction rate (83% conversion after 48 h), most likely due to the involvement of a neopentyl trigonal center, the ortho ester rearrangement proceeded cleanly to furnish the desired iodo ester (−)-**4** in good yield (91% based on consumed starting material) with no observable optical scrambling.[12] To install the furan moiety, iodo ester (−)-**4** was first reduced with lithium aluminum hydride to give the corresponding alcohol (−)-**6**. This was followed by Dess−Martin periodinane[13] oxidation to provide aldehyde (−)-**7** in 77% yield over two steps. Aldehyde (−)-**7** was subjected to treatment with 3-lithiofuran, prepared in situ from 3-bromofuran and *n*-butyllithium.[14] Although the addition reaction occurred readily, to our disappointment, regardless of the conditions applied, the desired alcohol (−)-**5**[15] was formed as the minor product in deference to its epimer (−)-**8**. The best results were obtained when the addition reaction was carried out in ether at −60 °C for 3 h. Under these conditions, alcohols (−)-**5** and (−)-**8** were obtained in a 1:2 ratio in a combined yield of 89%. Two other reagents, 3-furylmagnesium bromide[16] and 3-furyltitanium triisopropoxide,[17] were also examined in an attempt to improve the stereoselectivity. These reagents, however, were shown to be inferior in terms of both yield and product ratio. To circumvent the stereochemical problem, alcohol **8** with the incorrect stereochemistry was oxidized to the corresponding ketone **9** with Dess−Martin periodinane (Scheme 3). It was hoped that this

Scheme 3



compound could be selectively reduced, resulting in the preferential formation of the desired epimer (−)-**5**. The reduction was attempted with a number of reducing agents, including sodium borohydride, lithium aluminum hydride, diisobutylaluminum hydride, and lithium aluminum tri-*tert*-butoxy hydride. Unfortunately, all of these reagents were found to be ineffective; in all cases studied, the undesired epimer (−)-**8** was generated predominantly. Even in the best case involving sodium borohydride, the amount obtained for the desired alcohol (−)-**5** was merely 60% of that of (−)-**8**. In an alternate approach to rectify the stereochemistry, alcohol (−)-**8** was treated with diethyl azodicarboxylate, triphenylphosphine, and *p*-nitrobenzoic acid in benzene, and the resulting ester was hydrolyzed with lithium hydroxide in methanol. This Mitsunobu inversion approach proved to be more satisfactory; the desired alcohol (−)-**5** was formed in 51% yield over two steps. Thus, with the assistance of the latter process, alcohol (−)-**5** could be obtained in a total yield of 60% from aldehyde (−)-**7**.

To complete the synthesis of ricciocarpin A (**1**) from (−)-**5**, it remains to introduce the lactone ring and to reduce the cyclohexene double bond. The former was carried out by treatment of alcohol (−)-**5** with a catalytic amount of palladium acetate (0.06 equiv) and triphenylphosphine (0.12 equiv) in methanol and *N*,*N*′-dimethylpropyleneurea in the presence of triethylamine at 55 °C under an atmosphere of carbon monoxide for 24 h[18] (Scheme 4). The intramolecular carbonyl insertion occurred smoothly to give an 89% yield of (+)-lactone **10**, which on reduction with sodium boro-

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(15) The stereochemical assignment of this compound follows from its transformation to the natural product **1**.

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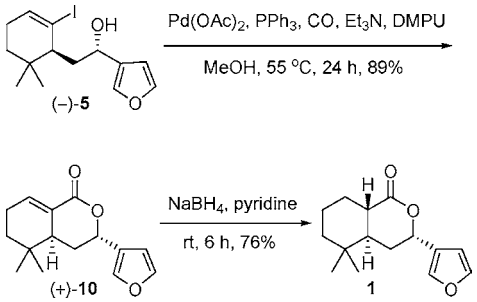
Scheme 4



hydride in pyridine[19] resulted in the formation of (+)-ricciocarpin A (**1**) in 76% yield. The spectral data (^{1}H NMR, ^{13}C NMR, IR, and HRMS) and specific rotation of the synthetic material were found to be in good agreement with those reported for the natural product.[1−8] Thus, a short (10 steps including Mitsunobu inversion) and rather efficient (24% overall yield) total synthesis of ricciocarpin A (**1**) in natural form with high optical purity (98% ee) has been accomplished based on a novel synthetic approach.

Acknowledgment. We are grateful to the National Science Council of the Republic of China for financial support.

Supporting Information Available: Experimental procedures and spectral characterizations for compounds **1** and **4**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052638R

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