A short stereoselective synthesis of (+)-(6R,2′S)-cryptocaryalactone via ring-closing metathesis

Palakodety Radha Krishna*,1, Krishnarao Lopinti1 and K. L. N. Reddy2

Abstract
A short stereoselective synthesis of (+)-(6R,2′S)-cryptocaryalactone was successfully completed. Key steps included the application of Carreira’s asymmetric alkynylation reaction to form a propargylic alcohol and subsequently lactone formation using the powerful ring-closing metathesis reaction.

Introduction
Natural products play an important role in the development of drugs and mankind has always taken advantage of nature as pharmacy: approximately 40% of the drugs that have been approved over the last years are either natural products or derivatives and analogs thereof [1-3]. Indeed, 5,6-dihydropyran-2-ones of both natural and non-natural origin have been found to be cytotoxic. In addition to many other relevant pharmacological properties [4-7], they inhibit HIV protease [8,9], induce apoptosis [10-15], and have even proved to be antileukemic [16]. At least some of these pharmacological effects may be related to the presence of the conjugated double bond, which acts as a Michael acceptor [17-23].

One of the sub-classes of these 5,6-dihydro-2H-pyran-2-one compounds is the styryl lactones which possess a styryl moiety side chain. The styryl moiety of goniothalamin has been shown to be of importance for its cytotoxic effect on different cancer cells as well as its antimicrobial, larvicidal activity and anti-inflammatory activity [24]. The styryl-pyrene skeleton is often found in natural products from Equisetaceae and also from the primitive angiosperm families, such as Lauraceae, Piperaceae, Ranunculaceae and Zingiberaceae.

Cryptocaryalactone 1 [25,26], kurzilactone (2) [27], goniothalamin (3) [28], (+)-obolactone (4) [29] and (+)-cryptofoline
Figure 1: Some natural products containing styryl lactones.

(5) [30] (Figure 1) are some of the naturally occurring styryl lactones. (+)-(6R,2′S)-Cryptocaryalactone (1) first featured in the phytochemical literature when its isolation from Cryptocarya bourdilloni GAMB (Lauraceae) was reported in 1972 by Govindachari [31,32]. Its absolute stereochemistry was established by H. H. Meyer through stereoselective synthesis [25]. Recently Yadav et al. have synthesized (6R,2′S)-cryptocaryalactone and its epimer using stereoselective reduction of δ-hydroxy-β-keto ester [33]. All other possible isomers of cryptocaryalactone were also isolated from C. bourdilloni, C. moschata and C. myrtifolia and their absolute configuration was established [34]. These cryptocaryalactones are natural germination inhibitors with no effect on corn [35]. We were interested in synthesizing natural products containing 5,6-dihydro-2H-pyran-2-one moiety [36,37], and herein we describe a short and efficient synthesis of cryptocaryalactone 1.

Results and Discussion

Retrosynthetic analysis

Retrosynthetic analysis (Figure 2) reveals that compound 1 could be synthesized from bis-olefin 6 by a ring-closing metathesis reaction, while the bis-olefin itself could be realised from the acryloylation of the corresponding homoallylic alcohol which in turn can be synthesized from 7. Chiral propargyl alcohol 7 was obtained by the Carreira asymmetric alknylation reaction of the corresponding aldehyde, which was synthesized from the corresponding primary alcohol that was obtained from a regioselective ring-opening reaction of 2,3-epoxy alcohol 8.

The known 2,3-epoxy alcohol 8 was synthesized from the corresponding dienyl alcohol by the well-established Sharpless asymmetric epoxidation conditions in >94% ee as described in
Scheme 1: Synthesis of chiral propargyl secondary hydroxyl group.

Table 1: Asymmetric alkylation with phenylacetylene.

| Reagents                  | Solvent     | Temperature | de  |
|---------------------------|-------------|-------------|-----|
| n-BuLi                    | THF         | −78 °C      | 28% |
| LDA                       | THF         | −78 °C      | 56% |
| LDA/HMPA                  | THF         | −78 °C      | 78% |
| Zn(OTf)₂, Et₃N, (−)-N-methylphedrine | toluene, 25 °C | 94% |

*The diastereoselectivity was determined by NMR studies.

Confirmation of absolute configuration

The structure of compound 7 was confirmed by ¹H NMR and ¹³C spectral analysis (Scheme 2). The absolute stereochemistry was assigned based on Rychnovsky’s analogy [42-44].

According to literature precedent, the relative configuration of a secondary 1,3-diol can be assigned from the chemical shift of acetonide carbon atoms in ¹³C NMR spectrum. So, upon deprotection of 7, diol 12 was obtained in good chemical yield (84%) and was further protected with 2,2-DMP, in presence of catalytic amount of PTSA, to furnish compound 13. The analytical data of acetone 13 confirmed the anti configuration of the 1,3-diol. Since the first hydroxyl center was obtained through an unambiguous method, the stereochemistry of the newly created hydroxyl functionality could be confirmed as that depicted in Scheme 2.

The propargylic alcohol 7 was chemoselectively reduced with LiAlH₄ in THF at 0 °C to give cinnamyl alcohol derivative 14 (87%, Scheme 3). Alcohol 14 was protected as its acetate under conventional reaction conditions. The PMB (p-methoxybenzyl protecting group) in compound 15 was selectively removed with DDQ in CH₂Cl₂/H₂O (19:1) to afford homoallylic alcohol 16 (89%) without promoting the migration of the acetyl group. Finally, 16 was acrylated with acryloyl chloride/Et₃N/CH₂Cl₂/0 °C to furnish the required bis-olefin 6 in 82% yield. Ring-closing metathesis of bis-olefin 6 with Grubbs’ 1st generation catalyst (1; 10 mol%) [45] gave the required (+)-(6R,2’S)-cryptocaryalactone (1) as a solid in 58% yield (m.p. 122–125 °C/lit. 126–127 °C and [α]D = +20.1 (c = 0.20)/lit. +19.0 (c = 0.67)) [25]. All the spectral data matched with the literature values.
Conclusion

In conclusion, a short stereoselective total synthesis of 1 has been accomplished by a convergent strategy wherein a chiral 2,3-epoxy alcohol was the starting material and Sharpless asymmetric epoxidation and Carreira asymmetric alkynylation were used as key steps for generating unambiguous assigned stereocenters. More importantly, the Grubbs’ ring-closing metathesis protocol was applied to construct the final 5,6-dihydropyrene ring of cryptocaryalactone. The advantage of this synthetic methodology is that one can in principle synthesize the other three diastereomers of cryptocaryalactone by altering the Sharpless epoxidation and Carreira’s conditions.

Supporting Information

Supporting Information File 1
Experimental Data
[http://beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-14-S1.doc]

Acknowledgments

One of the authors (K.L.) thanks the CSIR, New Delhi, for financial support in the form of a fellowship.
License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the Beilstein Journal of Organic Chemistry terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.5.14