Iodo-cyclizations: Novel Strategy for the Total Syntheses of Polyrhacitide A and *epi*-Cryptocaryolone

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Highly stereoselective total syntheses of polyrhacitide A and *epi*-cryptocaryolone have been achieved in 11 steps with high overall yield of 24% and 28%, respectively, following a recently developed strategy for the construction of *trans*-2,6-disubstituted-3,4-dihydropyrans. In this report, the versatility of iodo-cyclization for the total syntheses of polyrhacitide A and *epi*-cryptocaryolone is demonstrated.

In 2008, Jiang and Kouno reported the isolation of two aliphatic polyketides known as polyrhacitide A (1) and polyrhacitide B (2) (Figure 1) from the Chinese ant species *Polyrhachis lamellidens*.¹ This unit was also recently found to be present as a constituent in the molecules obtained from the tree extracts Cryptocarya species.² The structural features of these aliphatic polyketides are comprised of a

The structure of polyrhacitides A (1) and B (2) have been determined on the basis of extensive NMR investigations, whereas the absolute configuration was ascertained by applying acetonide and Mosher's MTPA ester methods.¹ Biological activity of the polyrhacitides has not been extensively studied presumably due to the limited supply

extensively studied presumably due to the limited supply from natural sources. However, the Chinese medicinal ant *P. lamellidens* has been used traditionally as a folk medicine for the treatment of rheumatoid arthritis and hepatitis in China. This role in folk medicine has been substantiated by the recent finding that extracts of *P. lamellidens* exhibit significant analgesic and anti-inflammatory effects.⁴ Another two similar molecules cryptocaryolone (**3**) and cryptocaryolone diacetate (**4**) were isolated from the bark of a South African plant, *Cryptocarya latifolia*.^{3c} Further

bicyclic lactone unit that is unusual in ants, although

related compounds occur in plants of various families.³

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Figure 1. Structures of polyrhacitide A (1), polyrhacitide B (2), cryptocaryolone (3), and cryptocaryolone diacetate (4).

investigation showed that they have significant biological activities and medicinal properties, ranging from the treatment of headaches and morning sickness to that of cancer, pulmonary disease, and various bacterial and fungal infections.⁵ The absolute and relative configurations of cryptocaryolone (3) and cryptocaryolone diacetate (4) was established by its first total synthesis.^{7a} The distinctive biological activities and fascinating architectures have stimulated synthetic efforts directed toward their total synthesis.^{6,7} In all previous reports, intramolecular Michael addition reaction⁸ was the only route for the synthesis of the bicyclic lactone core. To overcome these constraints, new synthetic strategies are well desired, and this prompted us to develop a concise, stereoselective synthetic pathway via an advanced intermediate from which both polyrhacitide A (1) and epicryptocaryolone (3a) could be obtained.

In recent years, the use of molecular iodine in organic synthesis has received considerable attention as an inexpensive, nontoxic, readily available mild Lewis acid catalyst for various organic synthesis and transformations.⁹ Recently, we have reported a highly stereoselective synthesis of *trans*-2,6-disubstituted dihydropyran using molecular iodine as a cheap and eco-friendly Lewis acid catalyst.¹⁰ As part of our ongoing research on iodo-cyclization reactions and its applications toward complex natural product

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Scheme 1. Retrosynthetic analysis of Polyrhacitide A (1) and *epi*-Cryptocaryolone (3a)



synthesis, herein, we report a successful syntheses of polyrhacitide A (1) and *epi*-cryptocaryolone (3a) in a highly stereoselective and concise manner.

From a retrosynthetic perspective, we envisioned that the most challenging bicyclic lactone would be constructed from the acid **5** via iodo-lactonization that in turn would arise from the terminal epoxide **6** (Scheme 1). The epoxide could be prepared from iodo-derivative **7**, which serves as an advanced common intermediate for the syntheses of **1** and **3a**. Iodo-carbonate intermediate **7** could be obtained from a known intermediate **8** which in turn could be prepared following a recently reported protocol from our lab.

The synthesis commenced from the known chiral epoxide 9 which was converted to a trans-2,6-disubstituted dihydropyran ring system 8 via recently reported highly stereoselective iodine catalyzed allylation methodology.¹⁰ The homoallyl alcohol 10 was obtained by treating epoxide 9 with vinylmagnesium bromide in the presence of a catalytic amount of CuI at -20 °C in 85% yield (Scheme 2). In order to achieve the synthesis of α,β -unsaturated aldehyde 11, a cross-metathesis (CM) between homoallyl alcohol 10 and acrolein (6.0 equiv) was carried out using a Hoveyda-Grubbs catalyst (10 mol %) in CH₂Cl₂ at room temperature for 2 h afforded δ -hydroxy α,β -unsaturated aldehyde 11 in 85% yield. Treatment of 11 with 10 mol % molecular iodine in THF at room temperature furnished the trans-2,6-disubstituted-3,4-dihydropyran 8 in 91% yield. Next, following Jin's one-step dihydroxylation-oxidation protocol,¹¹ terminal olefin was selectively oxidized to aldehyde **12** in 84% yield. The resultant aldehyde was subjected to a Maruoka asymmetric allylation¹² reaction using (R)-BINOL to furnish the homoallyl alcohol 13 as a single isomer. It was then treated with di-tert-butyl

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Scheme 2. Synthesis of Iodo-carbonate 7



dicarbonate in the presence of DMAP to form homoallylic *tert*-butyl carbonate **14** in 89% yield.¹³ The next stereogenic center of the polyol system with the desired stereochemistry was achieved via a Bartlett–Smith iodo-carbonate cyclization reaction.^{14,15} Treatment of compound **14** with *N*-iodo succinimide in CH₃CN at 0 °C produced the desired iodo-carbonate derivative **7** in good yield (92%) as the only product. It is worthy of mention here that the iodo-carbonate **7** can be synthesized in a sizable amount, was unstable on long-standing, and quickly purified by flash column chromatography.

The iodo-carbonate 7 was treated with K_2CO_3 in MeOH which rapidly underwent hydrolysis and *in situ* facile epoxidation to furnish the 1,3-*syn*-epoxy alcohol **6** in 94% yield (Scheme 3).¹⁴ Treatment of epoxide **6** with hexylmagnesium bromide in the presence of a catalytic amount of CuI¹⁶ at 0 °C afforded 1,3-*syn* diol **15** which was subsequently protected as its acetonide with 2,2-DMP to obtain **16** in 96% yield.¹⁷ The PMB group was selectively deprotected using DDQ under standard conditions to give the primary alcohol **17** in 98% yield. The primary alcohol **17** was converted to acid by following a two-step sequence of an oxidation process; first alcohol was converted to aldehyde by Dess-Martin periodinane¹⁷ followed by Scheme 3. Synthesis of Polyrhacitide A (1)



Pinnick oxidation¹⁸ to form acid **5a** in 83% yield over two steps. Our next task was the third iodo-cyclization which went smoothly with molecular iodine in the presence of KI in aqueous NaHCO₃ solution¹⁹ to furnish the desired iodo-lactone **18** as a single diastereomeric product in 81% yield. The iodo group was knocked down using tri-*n*butyltinhydride²⁰ in refluxing toluene in the presence of catalytic AIBN to obtain **19** in 95% yield. Finally, the 1,3-acetonide group was deprotected with CSA in MeOH to afford polyrhacitide A (**1**) in excellent yield. The integrity of synthetic polyrhacitide A (**1**) was assigned by comparison with its spectral (¹H and ¹³C NMR) and analytical data { $[\alpha]_D^{25}$ +8.0 (*c* 1.2, MeOH); lit.¹ $[\alpha]_D^{25}$ +8.3 (*c* 0.6, MeOH)} which were in good agreement with the reported values for natural product.^{1,6}

To accomplish the second target molecule *epi*-cryptocaryolone (**3a**), we initiated our synthesis from the advanced iodocarbonate derivative **7**. It was reduced to **20** via deiodination using tri-*n*-butyltin hydride and a catalytic amount of AIBN in refluxing toluene (Scheme 4). The carbonate derivative **20** was hydrolyzed to *syn*-1,3-diol **21** by KOH in the MeOH/H₂O system in quantitative yield and subsequently treated with 2,2-DMP in the presence of catalytic CSA to achieve acetonide protected **22** in 95% yield. Following the same sequence of reactions and

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Scheme 4. Synthesis of *epi*-Cryptocaryolone (3a)



conditions as followed in Scheme 3, *epi*-cryptocaryolone (**3a**) was furnished in good overall yield. The spectral

(¹H and ¹³C NMR) and analytical data { $[\alpha]_D^{25}$ +18.6 (*c* 1.0, CHCl₃); lit.^{7b} $[\alpha]_D^{20}$ -20 (*c* 0.04, CHCl₃)} were in good agreement with the reported values for natural product.

In conclusion, we have demonstrated an efficient, highly diastereoselective, and concise approach to accomplish both polyrhacitide A and *epi*-cryptocaryolone from a known intermediate 7 in 11 steps and 24% and 28% of overall yield, respectively. We have utilized cheap, environmentally benign molecular iodine for different iodo-cyclizations as key steps to construct the 2,6-*trans*-tetrahydropyran ring, 1,3-*syn*-diol, and bicyclic lactone in a highly stereoselective manner. In addition, following the above protocol other molecules of the series can readily be achievable in sizable amounts from an advanced common intermediate 7 for further biological studies which are in progress in our laboratory and will be reported in due course.

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Supporting Information Available. Experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.