

A convenient asymmetric synthesis of the octalactin lactone

Anubha Sharma^a, Sunita Gamre^a, Siddharth Roy^b, Dibakar Goswami^a,
Angshuman Chattopadhyay^{a,b}, Subrata Chattopadhyay^{a,*}

^a Bio-Organic Division, bNAA Unit, Central Forensic Science Laboratory, Bhabha Atomic Research Centre, Mumbai 400 085, India

^b NAA Unit, Central Forensic Science Laboratory, Bhabha Atomic Research Centre, Mumbai 400 085, India

Received 9 February 2008; revised 8 April 2008; accepted 10 April 2008

Available online 12 April 2008

Abstract

A facile asymmetric synthesis of the octalactin lactone was developed starting from (*R*)-cyclohexylidene-glyceraldehyde (**1**). The key step of the synthesis is an In-mediated diastereoselective crotylation of **1** in water, which furnished the building blocks with the required stereochemistry under operationally simple conditions. Their conversion to the appropriate intermediates, invertive esterification and a ring closing metathesis reaction furnished the target compound.

© 2008 Elsevier Ltd. All rights reserved.

Keywords: Asymmetric synthesis; Chiral pool; Crotylation; Octalactin

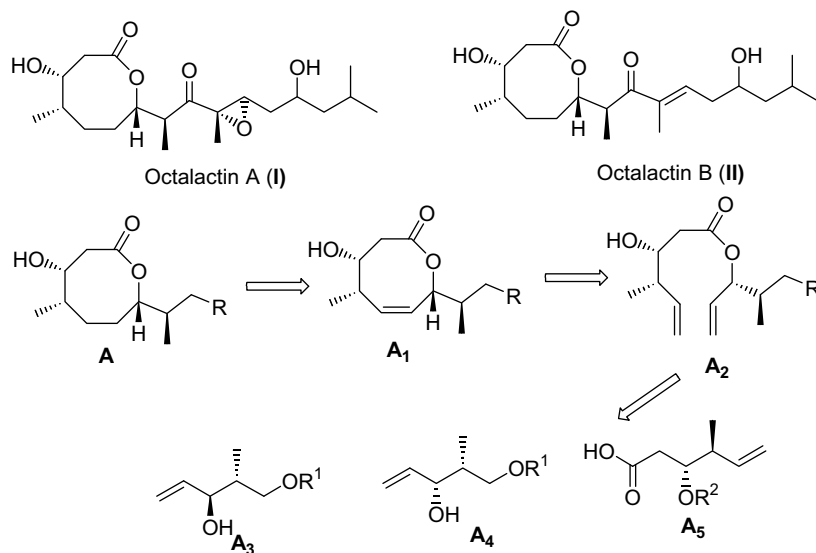
The medium-size natural lactones, octalactins A and B (**I** and **II**), are polyketide metabolites derived from a marine *Streptomyces* sp. found living on the surface of gorgonian coral.¹ Compound **I**, in particular, is noted for its potent *in vitro* cytotoxicity towards B-16-F-10 murine melanoma (IC₅₀ = 7.2 µg/mL) and HCT-116 human colon tumour cell lines (IC₅₀ = 0.5 µg/mL), and has emerged as a highly promising new anti-cancer agent. Compound **II** on the other hand is inactive, indicating that the bioactivity is linked to the ability for covalent adduct formation at the epoxy site of **I**. The combination of their unusual structures, the challenge associated with the synthesis and the therapeutic potential of **I** makes octalactins attractive synthetic targets. Given that the compounds cannot be produced by fermentation, the availability of their stereoisomers would be useful in establishing the unknown mode of their biological action. The major challenges of the synthesis lie in the construction of the 8-membered ring system as well as the structural moiety possessing the adjacent asymmetric centres, bearing a hydroxyl group and

methyl branching. Similar chiral building blocks are common structural elements of other bioactive macrolides (e.g., tylosin and leucomycins) of interest in pharmacy and veterinary science.²

Despite the impressive progress,^{3a} the development of simple and efficient strategies remains a challenging area in asymmetric synthesis.^{3b,c} To this end, we have recently endeavoured in formulating reliable routes utilizing inexpensive and readily available materials leading to the asymmetric syntheses^{4a-f} of a diverse array of natural compounds using easily accessible (*R*)-cyclohexylidene-glyceraldehyde **1** as a chiral template. This Letter reports an efficient asymmetric synthesis of the core unit of octalactin lactone starting from **1**.

Retrosynthetic disconnection (Scheme 1) of **A**₁, the olefinic precursor of the core lactone **A**, led to acid **A**₅ and alcohol **A**₃ or **A**₄ as the key building blocks. Esterification of **A**₅ with **A**₃, or with **A**₄ under Mitsunobu conditions⁵ would give the dienic ester **A**₂, while its ring closing metathesis (RCM)^{6a-f} to **A**₁ can be used to accomplish the difficult task^{7a-c} of constructing the eight-membered ring. Based on this plan, the primary task of the synthesis was to prepare the building blocks, **A**₃ or **A**₄, and **A**₅. Both these building blocks possess similar structural features, albeit with

* Corresponding author. Tel.: +91 22 25593703; fax: +91 22 25505151.
E-mail address: schatt@barc.gov.in (S. Chattopadhyay).



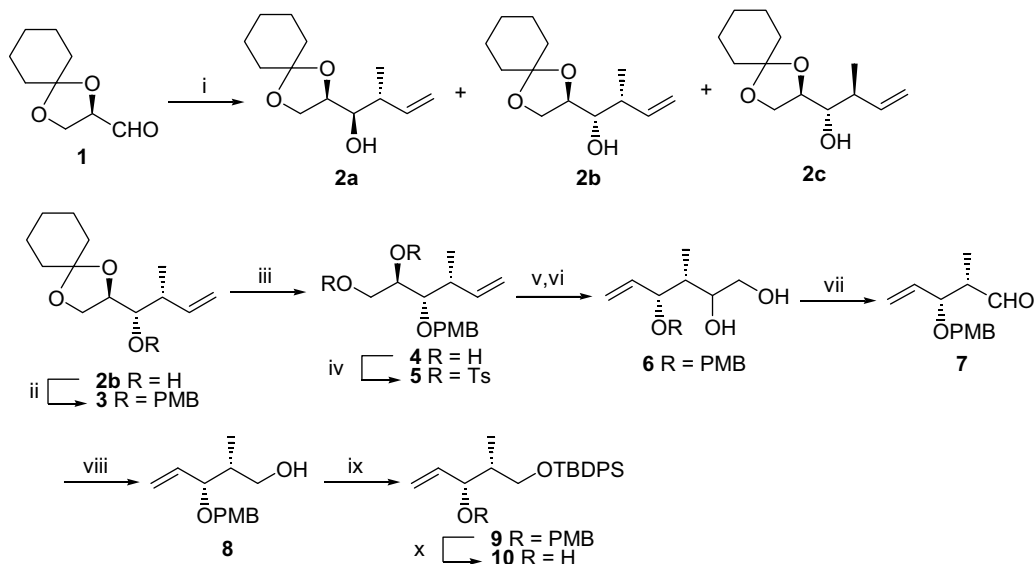
Scheme 1.

different relative configurations and variations in the functional groups.

The homoallylic alcohols **2a–c** that can be prepared^{18a–c} easily by crotylation of aldehyde **1** (Scheme 2) appeared well suited for the synthesis of **A₃–A₅**. Earlier, we reported^{8b,c} that the Zn-mediated reaction of crotyl bromide with aldehyde **1** proceeds with moderate stereoselectivity to furnish the diastereomeric homoallylic alcohols **2a–c** in the ratio 2.4:33.1:64.5. Given that the synthesis required **2c**, and **2a** or **2b** in equal ratio, the Zn-mediated crotylation protocol was unsuitable, as it did not afford **2a** or **2b** in appreciable amounts. Consequently, the initial task for

the synthesis was to develop a method for crotylation of **1** to afford **2c** and **2b/2a** selectively, in almost equal yields.

In our approach, the In (2.0 equiv)-mediated reaction⁹ between **1** and commercially available crotyl bromide (1.2 equiv) in water produced alcohols **2b** and **2c** in almost 1:1 ratio in 75% combined yield. The products were separated conveniently by column chromatography without further derivatization. With both **2b** and **2c** in hand, we proceeded to the synthesis of the octalactin core as follows (Schemes 2 and 3). Alcohol **2b** was converted to PMB derivative **3** by reaction with PMB chloride in the presence of NaH as the base. The acetal group of **3** was hydrolyzed



Scheme 2. Reagents and conditions: (i) Crotyl bromide/In/H₂O (75%); (ii) NaH/PMBCl/DMF/−10 °C (82%); (iii) CuCl₂·2H₂O/MeOH/50 °C (75%); (iv) *p*-TsCl/pyridine/0 °C (80%); (v) OsO₄/NMO/*t*-BuOH-H₂O (86%); (vi) Zn/NaI/DMF/Δ (77%); (vii) NaIO₄/MeCN-H₂O (92%); (viii) NaBH₄/MeOH/0 °C (91%); (ix) TBDPSCl/triethylamine/DMAP/CH₂Cl₂ (93%); (x) DDQ/aqueous CH₂Cl₂ (88%).

Download English Version:

<https://daneshyari.com/en/article/5284349>

Download Persian Version:

<https://daneshyari.com/article/5284349>

[Daneshyari.com](https://daneshyari.com)