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Tetrahedron Letters 49 (2008) 3902–3905
Tetrahedron Letters

A convenient asymmetric synthesis of the octalactin lactone

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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 staring from (*R*)-cyclohexylideneglyceraldehyde (**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.

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 ($IC_{50} = 7.2$ μg/mL) and HCT-116 human colon tumour cell lines ($IC_{50} = 0.5$ 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 stereomers 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*)-cyclohexylideneglyceraldehyde **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 $\mathbf{A}_1$, the olefinic precursor of the core lactone **A**, led to acid $\mathbf{A}_5$ and alcohol $\mathbf{A}_3$ or $\mathbf{A}_4$ as the key building blocks. Esterification of $\mathbf{A}_5$ with $\mathbf{A}_3$, or with $\mathbf{A}_4$ under Mitsunobu conditions[5] would give the dienic ester $\mathbf{A}_2$, while its ring closing metathesis (RCM)[6a–f] to $\mathbf{A}_1$ 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, $\mathbf{A}_3$ or $\mathbf{A}_4$, and $\mathbf{A}_5$. Both these building blocks possess similar structural features, albeit with

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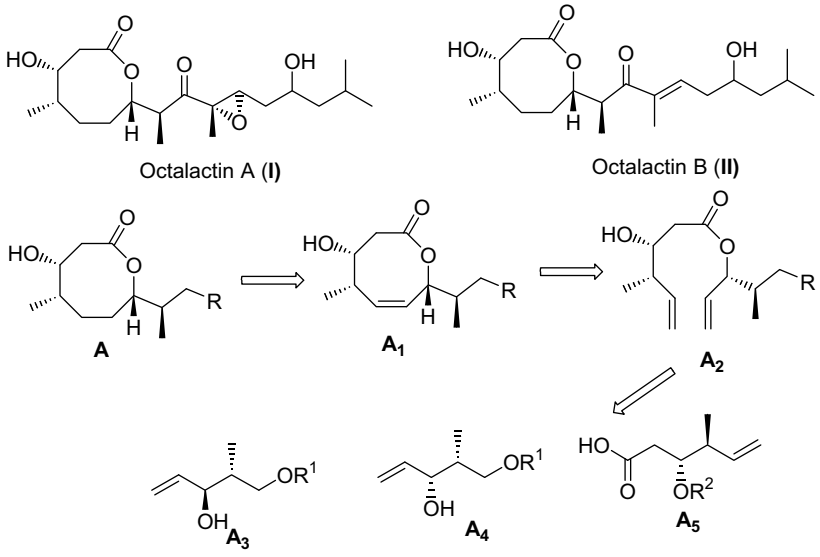
doi:10.1016/j.tetlet.2008.04.058

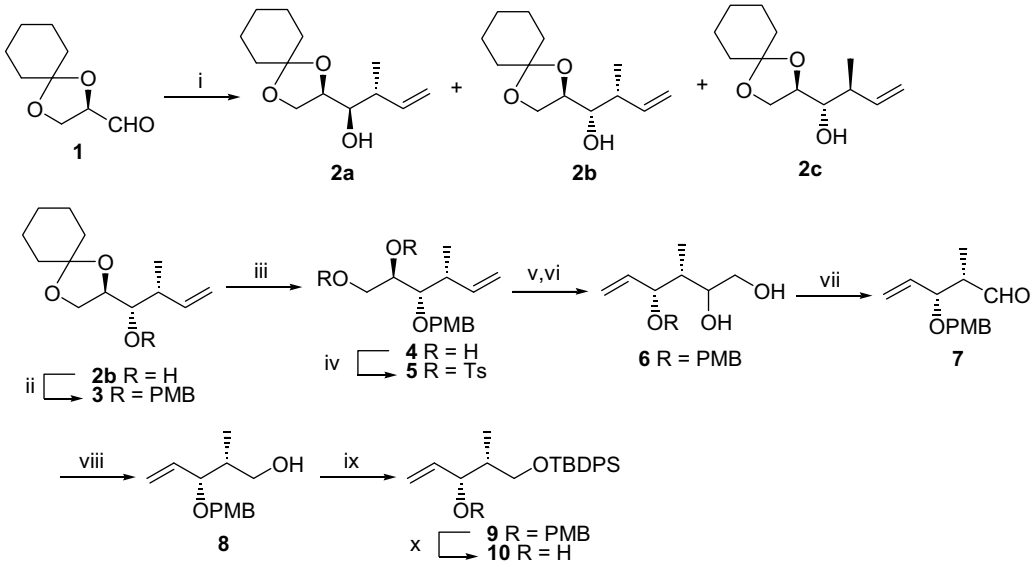


Scheme 1.

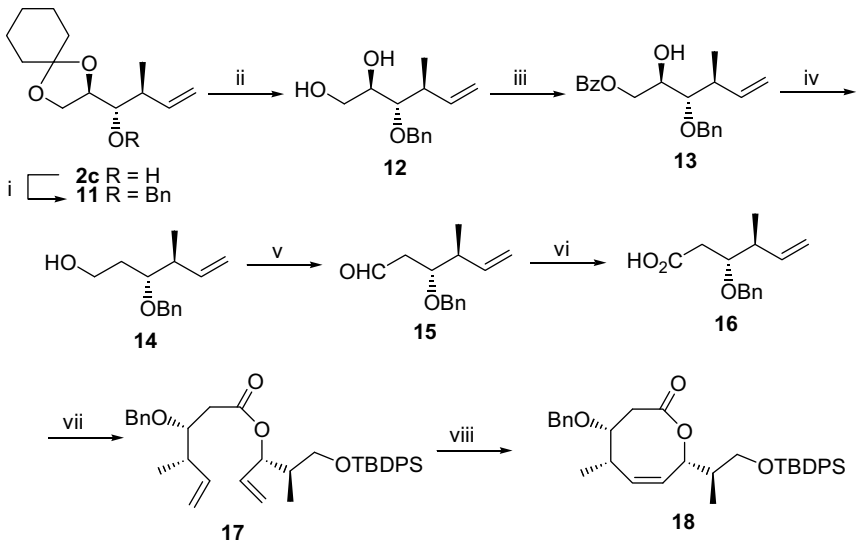
different relative configurations and variations in the functional groups.

The homoallylic alcohols **2a**–**c** that can be prepared[8a–c] easily by crotylation of aldehyde **1** (Scheme 2) appeared well suited for the synthesis of A_3–A_5. 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 reaction[9] 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/H_2O (75%); (ii) NaH/PMBCl/DMF/−10 °C (82%); (iii) $CuCl_2{\cdot}2H_2O$/MeOH/50 °C (75%); (iv) *p*-TsCl/pyridine/0 °C (80%); (v) OsO_4/NMO/*t*-BuOH-H_2O(86%); (vi) Zn/NaI/DMF/Δ (77%); (vii) $NaIO_4$/MeCN–H_2O (92%); (viii) $NaBH_4$/MeOH/0 °C (91%); (ix) TBDPSCl/triethylamine/DMAP/CH_2Cl_2 (93%); (x) DDQ/aqueous CH_2Cl_2 (88%).



Scheme 3. Reagents and conditions: (i) NaH/BnBr/THF/Δ (91%); (ii) 2% HCl/MeOH (88%); (iii) PhCOCN/triethylamine/CH_2Cl_2/0 °C (88%); (iv) MsCl/pyridine/CH_2Cl_2; LAH/ether/Δ (65%); (v) PCC/NaOAc/CH_2Cl_2 (84%); (vi) $NaClO_2$/TEMPO/MeCN-buffer pH 6.5/55 °C (71%); (vii) Ph_3P/DEAD/**10**/Et_2O–PhMe (2:1) (68%); (viii) Grubbs's II catalyst/CH_2Cl_2 (84%).

with $CuCl_2{\cdot}2H_2O$ in MeOH[10] to give diol **4**, which was ditosylated to furnish **5**. Dihydroxylation of the olefin function followed by detosylation with NaI/Zn afforded diol **6**. Cleavage of the α-diol function with $NaIO_4$ gave aldehyde **7**, which was reduced with $NaBH_4$ to give **8** in appreciable yield. This was silylated to **9**, which on DDQ-mediated deprotection gave alcohol **10**[11] (an $\mathbf{A}_4$ equivalent).

For the synthesis of the $\mathbf{A}_5$ equivalent (Scheme 3), alcohol **2c** was benzylated to give **11**, which on acidic hydrolysis furnished diol **12**. Regioselective monobenzoylation of its primary hydroxyl function proceeded smoothly to afford alcohol **13**. Mesylation followed by reduction with lithium aluminium hydride (LAH) furnished **14**. This was oxidized with pyridinium chlorochromate (PCC) to aldehyde **15**, which on oxidation with $NaClO_2$ gave the required acid **16**.

Esterification of **16** with **10** under Mitsunobu conditions afforded ester **17**. This underwent RCM reaction smoothly with Grubbs's II catalyst to furnish the target lactone **18** (Scheme 3). Besides being the advanced precursor of octalactins, the PMB (in place of Bn) derivative of **18** is reported[12] to block tubulin polymerization partially, resulting in significant antitumour activity. This might be useful for it to act as a novel mitotic spindle poison.

So far a few synthetic routes[13a–e] to compounds **I** and **II**, and several formal[14a–c] and partial syntheses[14d,e] of octalactin segments as well as other related studies[14f–k] have been reported. Most of these adopted Corey's lactonization for the ring construction, while the RCM strategy was used in only one method.[13c] However, the left and right half chiral segments of the octalactin were synthesized using innovative but circuitous routes that also require exotic and expensive reagents and often proceeded with poor diastereoselectivity.

The major novelty in our synthesis was the formulation of a crotylation protocol with adequate and optimum diastereoselectivity as required for the synthesis of the octalactin lactone. Overall, our method offers several practical advantages such as the use of an easily amenable chiral template **1**, inexpensive reagents, operational simplicity and the possibility of synthesizing all the stereomers of the octalactin lactone.

Acknowledgement

S.R. thanks the Directorate of Forensic Science (DFS), Ministry of Home Affairs, Government of India, for awarding the fellowship.

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11. All the compounds were fully characterized from their spectral, optical and microanalytical data. Representative data are included. Data for **10**: Colourless oil; $[\alpha]_D^{24}$ −6.7 (*c* 0.610, $CHCl_3$); IR (film): 3440, 1162, 915 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.85 (d, $J = 7.2$ Hz, 3H), 1.07 (s, 9H), 1.93–1.98 (m, 1H), 3.12 (br s, 1H), 3.70 (d, $J = 6.2$ Hz, 2H), 4.32–4.38 (m, 1H), 5.17–5.37 (m, 2H), 5.82–5.99 (m, 1H), 7.39 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.3, 19.1, 26.6, 67.7, 75.4, 113.4, 127.8, 129.8, 132.9, 133.0, 134.8, 135.6. Anal. Calcd for $C_{22}H_{30}O_2Si$: C, 74.53; H, 8.53. Found: C, 74.67; H, 8.35. Data for **16**: Colourless oil; $[\alpha]_D^{24}$ +4.9 (*c* 0.820, $CHCl_3$); IR (film): 3514, 1731, 912 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.04 (d, $J = 6.9$ Hz, 3H), 1.86–2.02 (m, 1H), 2.45–2.56 (m, 2H), 3.53–3.72 (m, 1H), 4.44–4.67 (m, 2H), 5.03–5.10 (m, 2H), 5.68–5.78 (m, 1H), 7.30 (s, 5H); ^{13}C NMR ($CDCl_3$, 200 MHz): δ 14.7, 39.7, 43.8, 71.5, 77.2, 115.8, 127.8, 128.6, 138.3, 140.2, 178.7. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.59; H, 7.57. Data for **18**: Colorless oil; $[\alpha]_D^{24}$ −44.2 (*c* 1.144, $CHCl_3$); IR (film): 1741 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.88 (d, $J = 6.8$ Hz, 3H), 1.07 (s, 9H), 1.18 (d, $J = 7.0$ Hz, 3H), 1.81–2.04 (m, 1H), 2.38–2.45 (m, 1H), 2.68–2.73 (m, 2H), 3.53–3.61 (m, 1H), 3.67–3.72 (m, 2H), 4.28 (d, $J = 11.2$ Hz, 1H), 4.37–4.44 (m, 1H), 4.55 (d, $J = 11.2$ Hz, 1H), 5.54–5.68 (m, 2H), 7.27–7.42 (m, 11H), 7.60–7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1, 18.7, 22.1, 24.0, 26.6, 31.2, 33.8, 38.2, 42.4, 65.7, 71.3, 77.8, 80.8, 118.4, 127.5, 128.6, 128.8, 129.5, 134.2, 135.3, 140.3, 175.2. Anal. Calcd for $C_{34}H_{42}O_4Si$: C, 75.24; H, 7.80. Found: C, 75.09; H, 7.95.
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