Tetrahedron Letters 55 (2014) 1398–1401

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective total synthesis of (+)-boronolide, (+)-anamarine, 8-*epi*-spicegerolide

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ARTICLE INFO

Article history:
Received 24 October 2013
Revised 14 December 2013
Accepted 17 December 2013
Available online 21 December 2013

Keywords:
α,β-Unsaturated lactones
Natural products
D-Xylose
Brown's allylation
Ring-closing metathesis

ABSTRACT

A stereoselective total synthesis of the naturally occurring cytotoxic lactones (+)-boronolide, (+)-anamarine, and 8-*epi*-spicigerolide is described. D-Xylose has been used as a chiral source to construct the four contiguous oxygenated stereogenic centers of target molecules. The diastereoselective allylation was performed using Brown's protocol and the lactone moiety was prepared by ring closing metathesis.

α,β-Unsaturated lactone moiety is frequently found in several natural products which display a broad spectrum of biological activities such as anticancer, antibacterial, and/or antifungal behavior.[1a,b] The inherent biological activity of these pyranone containing natural products is presumably due to the presence of a Michael acceptor in their skeleton which enables them to bind with a target enzyme.[1c] Examples of such molecules include (+)-boronolide (**1**), (+)-anamrine (**2**), and spicigerolide (**3**) (Fig. 1). Of these, (+)-boronolide (**1**) was isolated from the bark and branches of *Tetradenia fruiticosa*[2] and also from the leaves of *Tetradenia barbera*,[3] whereas the anamarine and spicegerolide were isolated from the flowers and leaves of an unclassified *Peruvian hyptis* species.[4]

The relative stereochemistry of these compounds was established by X-ray studies[5,4a] and their absolute stereochemistry was confirmed by chemical degradation.[3,4b] Numerous synthetic approaches have been reported for the synthesis of these natural products.[6]

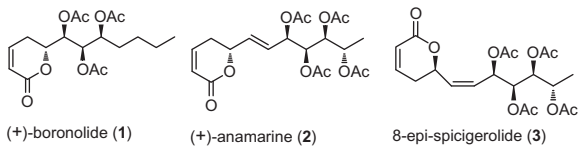

Figure 1. Pyranone containing natural products.

In most cases, the Sharpless asymmetric dihydroxylation,[6a–d] asymmetric aldol reaction,[6e,f] or the chiron approach[6g–o] has been employed to construct the four contiguous oxygenated stereogenic centers, while the six-membered α,β-unsaturated-δ-lactone ring was constructed through ring-closing olefin metathesis (RCM).[6b–f,h,j,o–r] Despite the numerous approaches reported, the development of a simple and modular approach involving readily accessible chiral precursors with well defined stereochemistry would provide an easy access to these natural products.

Following our interest in the total synthesis of biologically active natural products,[7] we herein report a simple and convenient approach for the total synthesis of (+)-boronolide, (+)-anamarine and 8-epi-spicigerolide. As per our strategy, the construction of four contiguous oxygenated stereocenters of lactones (**1**), (**2**), and (**3**) was achieved from D-xylose as the configuration of hydroxyl groups of the side chain coincides with D-xylose. The key reactions involved in this approach are the diastereoselective allylation and ring closing metathesis. As shown in retrosynthetic analysis, the total synthesis of (**1**), (**2**), and (**3**) could be accomplished from the corresponding lactones (**4**), (**5**), and (**6**) which in turn could be prepared by the ring-closing metathesis of acrylyl esters derived from compounds (**7**), (**8**), and (**9**) respectively. The key intermediates (**7**), (**8**), and (**9**) could easily be prepared by diastereoselective allylation of aldehydes, which are derived from a common intermediate **10** which in turn could be prepared from D-xylose (Scheme 1).

According to our approach, the synthesis of (**1**), (**2**), and (**3**) began from D-xylose which was converted into D-xylofuranoside **10** in three steps.[8] Thus treatment of D-xylose with allyl alcohol in

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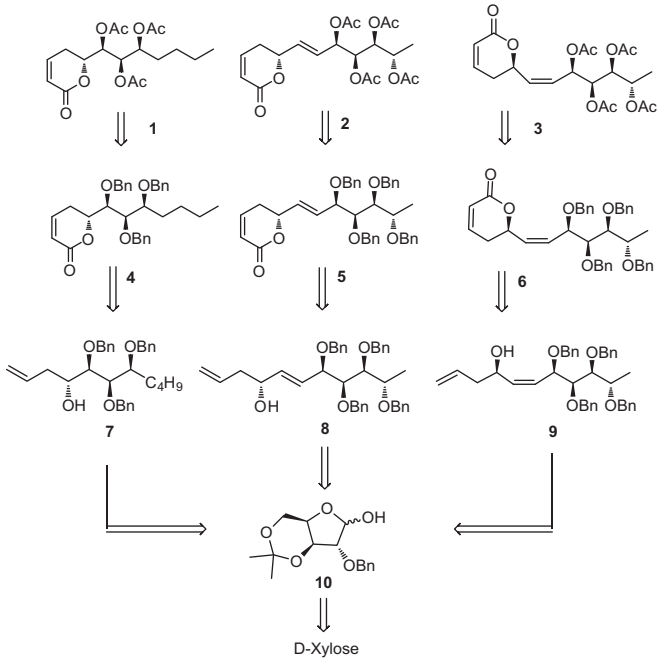
http://dx.doi.org/10.1016/j.tetlet.2013.12.061



Scheme 1. Retrosynthetic analysis of (+)-boronolide (**1**), (+)-anamarine (**2**) and 8-*epi*-spicigerolide (**3**).

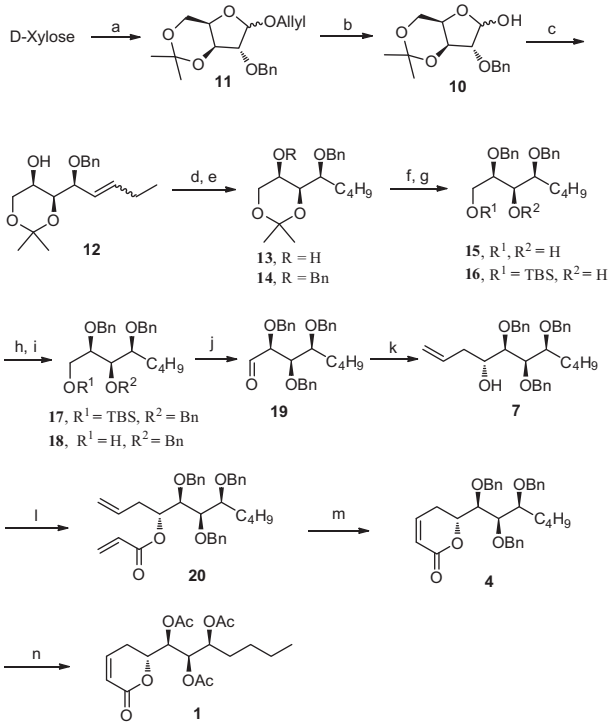
the presence of pyridinium-*p*-toluenesulfonate gave the *O*-allyl-D-xylofuranoside. Protection of C-3 and C-5 hydroxyl groups as isopropylidene acetal followed by protection of C-2 hydroxy group as a benzyl ether afforded the fully protected *O*-allylglycoside **11**. Removal of the allyl group from **11** gave the hemi-acetal **10** in 40% yield using Gigg and Warren conditions **10**. Thus obtained hemiacetal **10** was used as a common intermediate for subsequent steps.

During the synthesis of (+)-boronolide (**1**), the hemi-acetal **10** was treated with propyltriphenylphosphonium bromide[10] (prepared from *n*-propyl bromide and triphenylphosphine) in the presence of NaHMDS in dry THF at −20 °C to afford the olefin **12** as a 9:1 mixture of *Z*- and *E*-isomers. Reduction of the olefinic mixture **12** in the presence of 10% Pd/C gave the saturated compound **13.** Protection of the hydroxyl group of **13** with benzyl bromide in the presence of NaH in DMF afforded the benzyl ether **14** in 85% yield. Removal of the isopropylidene group with *p*-TsOH in MeOH at 0 °C gave diol **15** in which the primary hydroxyl group was protected as its TBDMS ether and the secondary alcohol was protected as its benzyl ether to give **16** in 85% yield. Deprotection of the silyl ether **16** with TBAF in THF at 0 °C gave the primary alcohol **18** in 78% yield. Swern oxidation of the alcohol **18**[11] gave the aldehyde **19** in quantitative yields without any epimerization at α-stereogenic center. Since the allylation of **19** with achiral reagents[12] affords the poor results, we turned our attention to chiral allylating agents.

Asymmetric allylation of the aldehyde **19** under Keck's conditions[13] gave the homoallylic alcohol **7** with low diastereoselectivity (8:2). Therefore, Brown's protocol[14] was adopted for asymmetric allylation. Accordingly, Brown's allylating reagent (allylBIpc2) was prepared from allylmagnesium bromide and (+)-DIPCl (diisopinocampheylboron chloride), which was then treated with **19** in anhydrous ether at −80 °C to furnish the desired homoallylic alcohol **7** in 82% yield with high diastereoselectivity (9:1). Esterification of **7** with acrylyl chloride afforded the acrylyl ester **20**, which was easily separated from its diastereomer by simple silica gel column chromatography. Ring-closing metathesis (RCM) of the acrylate **20** with Grubbs first generation catalyst[15] in DCM at room temperature afforded the α,β-unsaturated lactone **4** in 85% yield. Removal of the benzyl groups using 1 M solution of $TiCl_4$ in DCM at 0 °C for 4 h gave the trihydroxy lactone which was then peracetylated with acetic anhydride in the presence of pyridine to furnish the target (+)-boronolide (**1**) in 53% yield. The spectral data of the synthetic boronolide (**1**) was identical with the data reported for the natural product (Scheme 2).[1,18]

After successful synthesis of (+)-boronolide (**1**), we next attempted the synthesis of **2** and **3** from the intermediate **10**. Thus treatment of hemi-acetal **10** with MeLi (1.6 M in ether) in anhydrous ether at −20 °C afforded the diol as a separable diastereomeric mixture (9:1) favoring **21** as a major product in 82% yield via a chelation controlled mode. Protection of the hydroxy groups of **21** using benzyl bromide in the presence of NaH furnished the benzyl ether **22** in 90% yield. Removal of the isopropylidene group of **22** using *p*-TSA in methanol gave the diol **23** in 80% yield. Protection of the primary alcohol of **23** using TBSCl gave the TBDMS ether **24** in 90% yield. The secondary OH of **24** was then protected as its benzyl ether **25** in 85% yield using benzyl bromide in the presence of NaH in DMF. Desilylation of **25** using TBAF in THF gave the alcohol **26** in 78% yield which was then oxidized under Swern conditions to give the key intermediate **27** to the synthesis of **2** and **3** (Scheme 3).

Wittig olefination of **27** with triethyl phosphonoacetate[16] gave the (*E*)-α,β-unsaturated ester **28a** as a sole product in 93% yield. Reduction of the ester **28a** using DIBAL-H in dry DCM at −78 °C afforded the corresponding aldehyde which was subsequently subjected to enantioselective allylation using allylBIpc2, which was prepared in situ from allylmagnesium bromide and (+)-DIPCl



Scheme 2. Synthesis of (+)-boronolide (1). Reagents and conditions: (a) Ref. 9; (b) (i) *t*-BuOK, DMSO (ii) $Hg(OAc)_2$, THF/H_2O; (c) *n*-$PrPPh_3Br$, NaHMDS, THF, −20 °C to rt, 5 h, 75%; (d) (i) H_2, Pd/C, $NaHCO_3$, MeOH, rt, 2 h, 86%; (e) NaH, BnBr, DMF, 0 °C, 6 h, 85%; (f) *p*-TSA, MeOH, 0 °C, 3 h, 80%; (g) TBSCl, imidazole, DCM, 0 °C to rt, 1 h, 90%; (h) NaH, BnBr, DMF, 0 °C to rt, 3 h, 85%; (i) TBAF, THF, 0 °C to rt, 2 h, 78%; (j) Dess–Martin periodinane, CH_2Cl_2, 0 °C to rt, 2 h, 80%; (k) $AllylBIpc_2$ [prepared from allylmagnesium bromide and (+)-DIPCl], Et_2O, −80 °C (82%, 9:1 diastereomeric mixture); (l) Acrylyl chloride, Et_3N, DMAP, DCM, 0 °C to rt, 3h, 85%; (m) Grubb's first generation catalyst, DCM, rt, 6h, 85%; (n) i) $TiCl_4$ (1M in DCM), DCM, 0 °C to rt, 4h; ii) Ac_2O, Pyridine, DMAP, 0 °C to rt (overall 2 steps 53%).