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

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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]

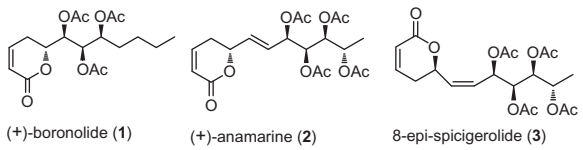

Figure 1. Pyranone containing natural products.

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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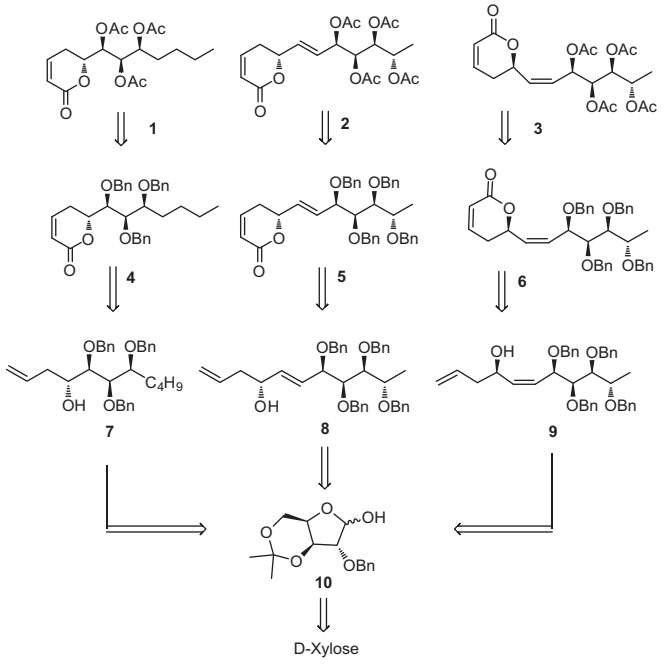


Scheme 1. Retrosynthetic analysis of (+)-boronolide (**1**), (+)-anamarine (**2**) and 8-*epi*-spicigerolide (**3**).

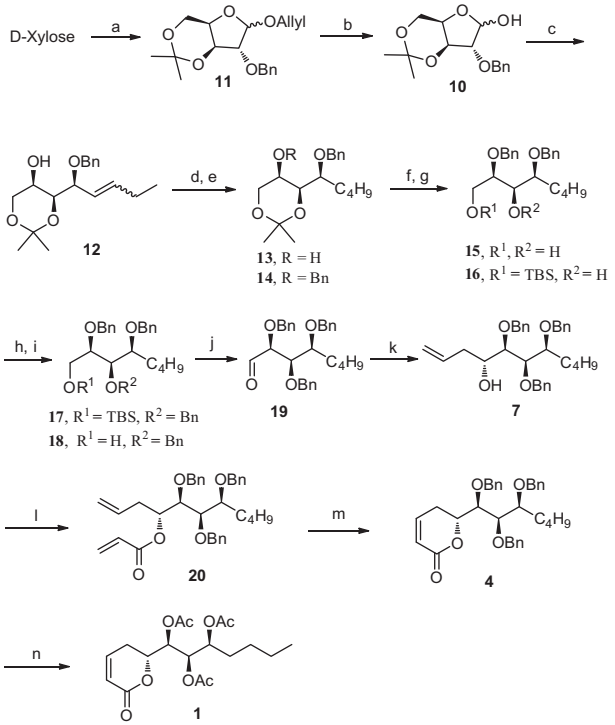
the presence of pyridinium-*p*-toluenesulfonate gave the *O*-allyl-D-xylofuranoside. Protection of C-3 and C-5 hydroxyl groups as isopropylidene acetal followed by protection of C-2 hydroxy group as a benzyl ether afforded the fully protected *O*-allylglycoside **11**. Removal of the allyl group from **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.

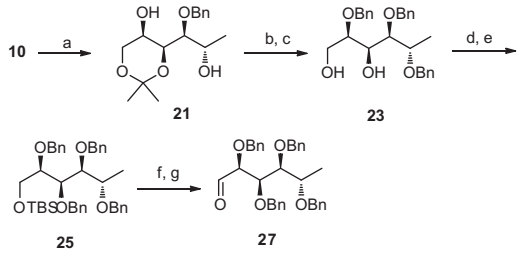
Asymmetric allylation of the aldehyde **19** under Keck's conditions[13] gave the homoallylic alcohol **7** with low diastereoselectivity (8:2). Therefore, Brown's protocol[14] was adopted for asymmetric allylation. Accordingly, Brown's allylating reagent (allylBIpc2) was prepared from allylmagnesium 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



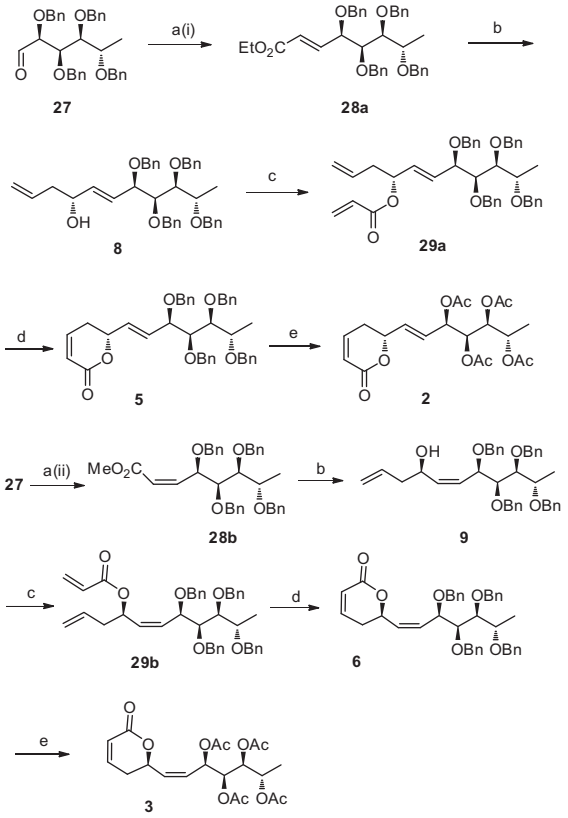
Scheme 2. Synthesis of (+)-boronolide (1). Reagents and conditions: (a) Ref. 9; (b) (i) *t*-BuOK, DMSO (ii) $Hg(OAc)_2$, THF/H_2O; (c) *n*-$PrPPh_3Br$, NaHMDS, THF, −20 °C to rt, 5 h, 75%; (d) (i) H_2, Pd/C, $NaHCO_3$, MeOH, rt, 2 h, 86%; (e) NaH, BnBr, DMF, 0 °C, 6 h, 85%; (f) *p*-TSA, MeOH, 0 °C, 3 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%).



Scheme 3. Synthesis of common intermediate **27.** Reagents and conditions: (a) MeLi (1.6 M), Et_2O, −20 °C, 4 h, 82%; (b) NaH, BnBr, DMF, 0 °C, 6 h, 90%; (c) *p*-TSA, MeOH, 0 °C, 3 h, 80%; (d) TBSCl, imidazole, DCM, 0 °C to rt, 1 h, 90%; (e) NaH, BnBr, DMF, 0 °C to rt, 3 h, 85%; (f) TBAF, THF, 0 °C to rt, 2 h, 78%; (g) DMSO, $(COCl)_2$, DCM, −78 °C, Et_3N, 3 h, 80%.

(diisopinocampheylboron chloride), in anhydrous ether at −80 °C to furnish the desired homoallylic alcohol **8** (92% de) in 82% overall yield over two steps. Esterification of **8** with acrylyl chloride afforded the acryloyl ester **29a** which was then subjected to RCM reaction using Grubbs first generation catalyst to afford the perbenzylated lactone **5** in 85% yield. Eventually, the debenzylation of **5** with $TiCl_4$ followed by peracetylation with Ac_2O furnished the anamarine (**2**) in 62% overall yield over two steps (Scheme 4).[18]

Similarly, Still-Gennari olefination[17] of **27** with bis(2,2,2-trifluoromethyl)(methoxycarbonylmethyl) phosphonate gave the *cis*-olefinic ester **28b** in 84% yield. Reduction of the ester **28b** with



Scheme 4. Synthesis of anamarine (**2**) and 8-epi-spicegerolide (**3**). Reagents and conditions: (a) (i) PPh_3CHCO_2Et, benzene, rt, 2 h, 93%; (ii) NaH/THF, 0 °C, $(CF_3CH_2O)_2P(O)CH_2COOCH_3$, 30 min, then, −78 °C, THF, 30–45 min, 84%; (b) (i) DIBAL-H, CH_2Cl_2, −78 °C to rt, 0.5 h, 80%; (ii) AllylBIpc$_2$ [prepared from allylmagnesium bromide and (+)-DIP-Cl], Et_2O, −80 °C (82%, 92:8 diastereomeric mixture); (c) Acrylyl chloride, Et_3N, DMAP, DCM, 0 °C to rt, 3 h, 85%; (d) Grubbs first generation catalyst, DCM, rt, 6 h, 85%; (e) (i) $TiCl_4$ (1 M in dichloromethane), DCM, 0 °C to rt, 6 h; (ii) Ac_2O, Et_3N, DMAP, DCM, 0 °C to rt (overall 2 steps 62%).

DIBAL-H (1 M in toluene) in dry DCM at −78 °C afforded the aldehyde which was then subjected to allylation with allylBIpc$_2$, prepared from allylmagnesium bromide and (+)-DIPCl (diisopinocampheylboron chloride), in anhydrous ether at −80 °C to furnish the homoallylic alcohol **9** (92% de) in 82% overall yield over two steps. Esterification of the alcohol **9** with acryloyl chloride gave the acryloyl ester **29b,** which was subsequently subjected to RCM reaction using Grubb's first generation catalyst to afford the perbenzylated lactone **6** in 85% yield. Finally the debenzylation of **6** with $TiCl_4$ followed by peracetylation with Ac_2O afforded the 8-epi-spicegerolide **3** in 62% overall yield over two steps.[18]

In summary, we have developed a modular approach for the enantioselective synthesis of (+)-boronolide (**1**) and (+)-anamarine (**2**) and 8-*epi*-spicigerolide (**3**) starting from D-xylose. The notable features of this synthetic strategy are highly diasteroselective Brown's allylation and ring closing metathesis to construct α,β-unsaturated lactone functionality.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.061.

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18. *Spectral data for selected compounds:*
*Boronolide (**1**):* $[\alpha]_D^{25}$ +14 (*c* 0.5, $CHCl_3$); IR (neat): υ_{max} 2927, 1744, 1219 cm; ^1H NMR (500 MHz, $CDCl_3$): δ 6.89 (ddd, *J* = 9.8, 6.2, 2.4 Hz, 1H), 6.06 (ddd, *J* = 9.8, 2.7, 0.7 Hz, 1H), 5.34–5.39 (m, 2H), 5.04 (dt, *J* = 6.2, 5.7 Hz, 1H), 4.55 (ddd, *J* = 12.0, 5.7, 4.0 Hz, 1H), 2.48 (dddd, *J* = 18.2, 12.0, 2.6, 2.6 Hz, 1H), 2.28 (dddd, *J* = 18.3, 10.1, 6.1, 0.9 Hz, 1H), 2.09 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.52 (q, *J* = 7.1 Hz, 2H), 1.17–1.30 (m, 4 H), 0.83 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 169.8, 169.5, 162.3, 144.1, 121.3, 75.1, 71.5, 70.6, 70.4, 30.1, 26.9, 25.2, 22.3, 20.8, 20.6, 20.5, 13.7; HRMS (ESI) calcd for $C_{18}H_{26}O_8Na$, [M+Na] 393.1629, found: 393.1626.
*Anamarine (**2**):* $[\alpha]_D^{25}$ +15 (*c* 0.5, $CHCl_3$); IR (neat): υ_{max} 2935, 1745, 1223, 1028 cm; ^1H NMR (300 MHz, $CDCl_3$): δ 6.88 (ddd, *J* = 1.5, 2.2, 6.7 Hz, 1H), 6.05 (ddd, *J* = 2.2, 3.7, 9.8 Hz, 1H), 5.83 (m, 2H), 5.39–5.29 (m, Hz, 2H), 5.18 (m, 1H), 5.03–4.88 (m, 2H), 2.45 (m, 2H), 2.07 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.17 (d, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 169.86, 169.83, 169.76, 163.5, 144.5, 133.0, 125.5, 121.5, 75.8, 71.9, 71.6, 70.4, 67.3, 29.1, 21.0, 20.91, 20.86, 20.6, 15.8; HRMS (ESI) calcd for $C_{20}H_{26}O_{10}Na$ [M+Na] 449.1424, found: 449.1422.
*8-epi-Spicegerolide (**3**):* $[\alpha]_D^{25}$ +34 (*c* 0.9, $CHCl_3$); IR (neat): υ_{max} 2925, 1735, 1457, 1372 cm; ^1H NMR (500 MHz, $CDCl_3$): δ 6.89 (dt, *J* = 9.6, 6.4, 2.2 Hz, 1H), 6.1–6.03 (m, 1H), 5.89–5.82 (m, 1H), 5.42 (dd, *J* = 6.7, 2.8 Hz, 1H), 5.30–5.26 (m, 1H), 5.23–5.19 (m, 1H), 5.05–4.90 (m, 2H), 2.51–2.39 (m, 2H), 2.13 (s, 6H), 2.07 (s, 3H), 2.03 (s, 3H), 1.23 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 170.1, 169.9, 169.9, 163.5, 144.8, 132.7, 128.6, 121.4, 73.7, 70.9, 69.2, 66.9, 66.2, 21.0, 20.9, 20.8, 20.7, 14.4; HRMS (ESI) calcd for $C_{20}H_{26}O_{10}Na$, [M+Na] 449.1418, found: 449.1415.