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A short stereoselective synthesis of (+)-boronolide☆

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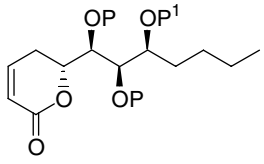
Abstract—A short and stereoselective synthesis of (+)-boronolide via oxidative functionalization of an olefin using a pendant sulfinyl group is described. Diastereoselective allylation was performed using Keck's protocol and the lactone moiety was prepared by ring closing metathesis.

(+)-Boronolide **1** was isolated from the bark and branches of *Tetradenia fruiticosa*[1] and from the leaves of *Tetradenia barbera*.[2] The partially deacetylated **2** and the totally deacetylated derivative **3** were isolated from *Tetradenia riparia*.[3] The extracts from the roots and the leaves of these trees have been used as folk medicine in Madagascar and in southern Africa as an emetic and in the treatment of malaria.[4] Boronolide has an α,β-unsaturated δ-lactone moiety and a polyhydroxylated side chain. This structural feature is characteristic of the natural products possessing a wide range of biological activity,[5] making them attractive targets for total syntheses. The relative stereochemistry of boronolide was established by X-ray studies,[6] and the absolute stereochemistry was confirmed by chemical degradation.[2]



1, P = P^1 = C(O)CH$_3$
2, P = H, P^1 = C(O)CH$_3$
3, P = P^1 = H

Earlier reported syntheses of boronolide have relied on chiral pool starting materials,[7] aldol reaction[8] and Sharpless dihydroxylation[9] to construct the contiguous oxygenated stereocentres. Our synthetic plan relied on the oxidative functionalization of an olefin via the participation of an intramolecular sulfinyl moiety.[10] The synthesis commenced with the condensation of (*S*)-methyl *p*-tolyl sulfoxide **4**,[11] and *trans*-ethyl hept-2-enoate **5** following Solladie's protocol[12] to yield β-keto sulfoxide **6** (60%, $[\alpha]_D^{25}$ −158 (*c* 1, $CHCl_3$)). Diastereoselective reduction[13] using DIBAL-H/$ZnCl_2$ afforded allyl alcohol **7** (>95% de, 84%, $[\alpha]_D^{25}$ −126 (*c* 1, $CHCl_3$)).[14] The treatment of **7** with freshly recrystallized *N*-bromosuccinimide (NBS) afforded regioisomeric bromodiols **8** and **9**, resulting from 5-exo- and 6-endo-nucleophilic attack, respectively, as an inseparable mixture in a 7:3 ratio (75%). In efforts to secure a single regioisomer, the *t*-butyldimethylsilyl ether **10**, obtained from **7** (94%, $[\alpha]_D^{25}$ −62 (*c* 1, $CHCl_3$)), was reacted with NBS. However, in this instance too, the reaction failed to proceed regioselectively and an inseparable mixture of bromohydrins **11** and **12** (72%, 3:1 ratio, respectively) were isolated (Scheme 1).[15]

The inseparable mixture of **11** and **12** was converted to an epoxide **13** (89%, $[\alpha]_D^{25}$ +119 (*c* 1, $CHCl_3$)), by treatment with the anhydrous potassium carbonate, proving beyond doubt that they were regioisomers. Also deprotection of the silyl group in **11** and **12** afforded a product mixture whose ^{1}H NMR spectra matched that of the mixture of **8** and **9**, thus proving that the facial selectivity of addition across the double bond was the same for both allyl alcohol **7** and silyl ether **10**. Having been unable to secure a single isomer in the NBS reaction, attempts were made to separate **8** and **9** by derivatizing them suitably. The acetonides **14** (61%, $[\alpha]_D^{25}$ +156 (*c* 1, $CHCl_3$)) and **15** (28%, $[\alpha]_D^{25}$ +167 (*c* 1, $CHCl_3$)) proved

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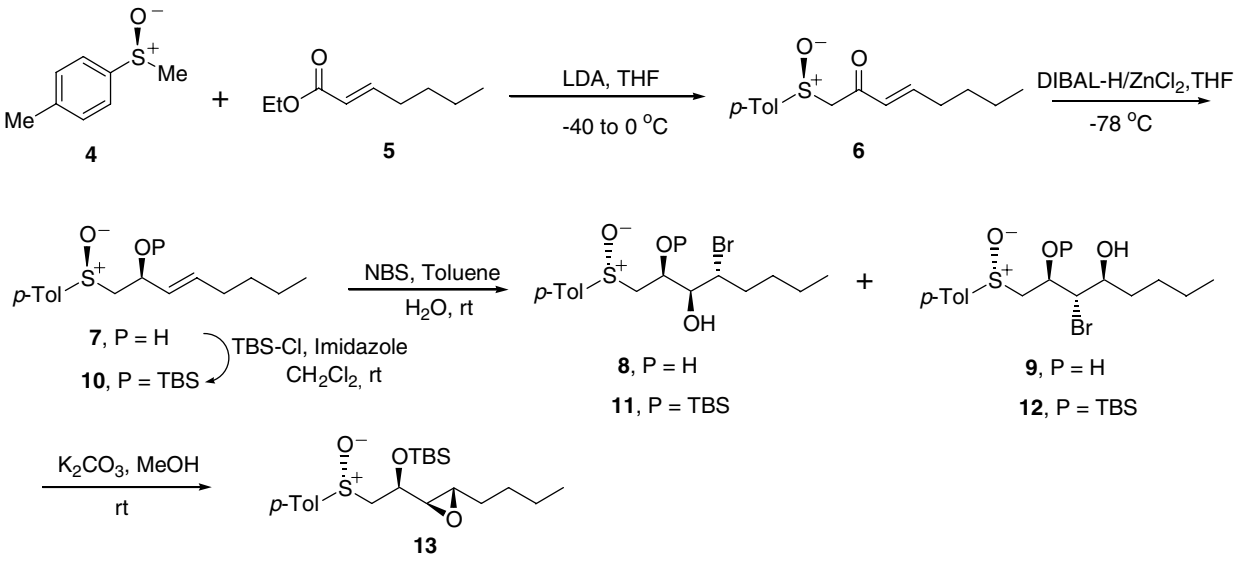
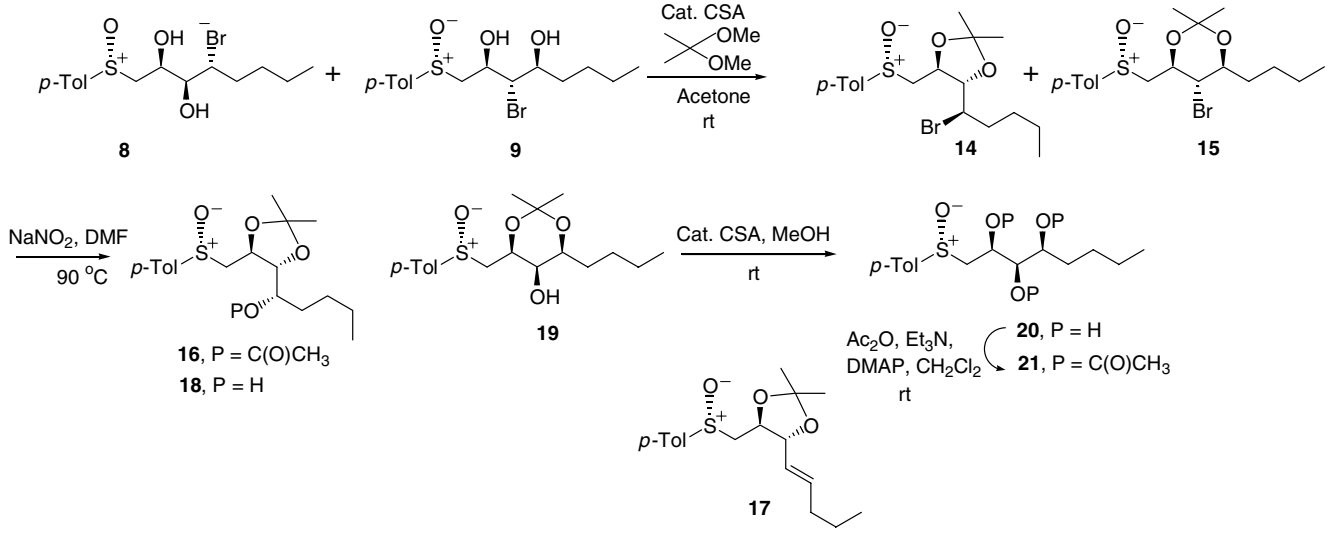


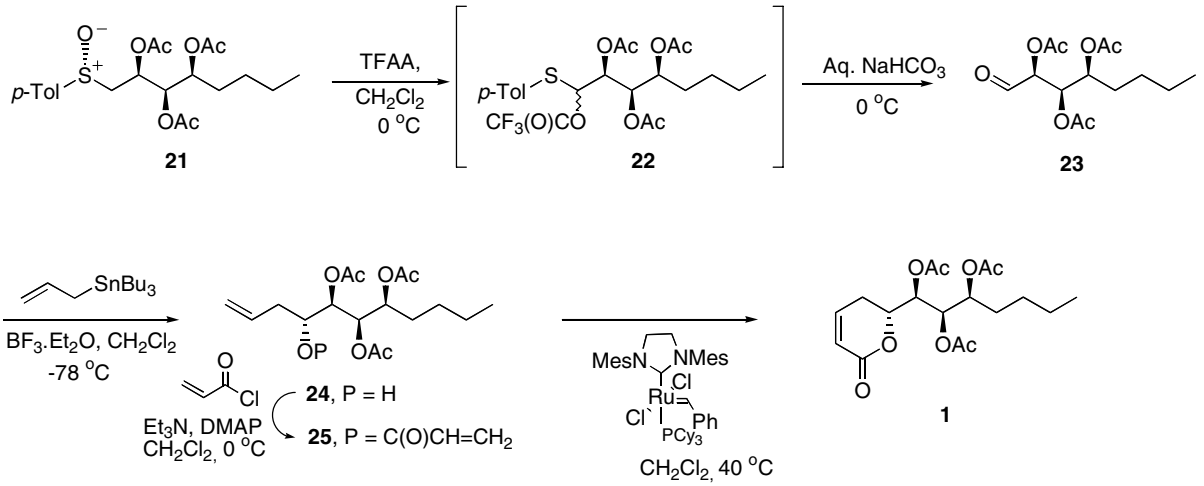
Scheme 1.

separable.[14] Nucleophilic displacement of the bromide in **14** and **15**, by an oxygen nucleophile would afford a product with three contiguous chiral centres as present in the target. The attempted displacement of the bromide in **14** with anhydrous potassium acetate in DMF, yielded none of the expected acetate **16**, but the eliminated product **17** (79%, Scheme 2).

With sodium nitrite[16] as the reagent, **14** reacted cleanly to afford alcohol **18** (68%, $[\alpha]_D^{25}$ +149 (*c* 1, $CHCl_3$)). In a similar fashion acetonide **15** afforded alcohol **19** (86%, $[\alpha]_D^{25}$ +147 (*c* 1, $CHCl_3$)). Deprotection of the acetonides followed by acetylation of the resulting triol **20** (87%, $[\alpha]_{D_{25}}^{25}$ +198 (*c* 1, $CHCl_3$))[14] furnished triacetate **21** (96% $[\alpha]_D^{25}$ +86 (*c* 1, $CHCl_3$)).[14] Thus bromodiols **8** and **9** converged to give the same triacetate **21**. Two steps (acetonide formation and deprotection) could be saved if the mixture of **8** and **9** could be directly subjected to a reaction with a suitable oxygen nucleophile. Attempted reaction of the mixture of bromohydrins with sodium nitrite however afforded a mixture of products. Having secured the triacetate, it remained to unravel the aldehyde moiety by a Pummerer reaction and subject it to diastereoselective allylation followed by acrylate ester formation to set the stage for ring closing metathesis. Activation of the sulfinyl group in **21** with TFAA[17] in the presence of 2,6-lutidine followed by hydrolysis of intermediate **22** with aqueous saturated sodium bicarbonate furnished aldehyde **23** (65%), which proved unstable to column chromatography and hence used in the next step without further purification. The aldehyde was a key intermediate in the synthetic route of Carda et al.[7d] The reagent controlled asymmetric allylation using Keck et al. protocol[18] furnished a complex mixture of products. Among various methods, allylation using allyltributyltin/$BF_3{\cdot}Et_2O$[19] proved



Scheme 2.



Scheme 3.

satisfactory[20] and the desired product **24** and its epimer (not depicted) was obtained as an inseparable mixture of diastereomers (76%, 9:1 by NMR). The mixture of alcohols was subjected to a treatment with acryloyl chloride in the presence of triethyl amine to afford **25** and its epimer that could be separated by column chromatography (79%, $[\alpha]_D^{25}$ +2 (*c* 0.5, $CHCl_3$)). Compound **25** on ring closing metathesis reaction using Grubbs' second generation catalyst afforded boronolide **1** (70%, Scheme 3). The spectroscopic data of **1** (^1H NMR, ^{13}C NMR, IR) were in agreement with literature data.[2]

In summary, a short and stereoselective synthesis of (+)-boronolide has been achieved utilizing our oxidative functionalization strategy.

Acknowledgements

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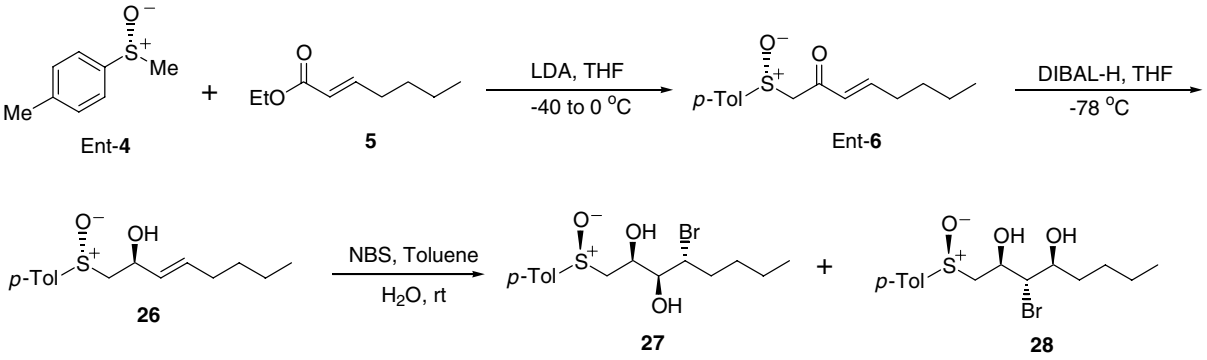
14. *Selected data*. Compound **7**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, $J = 8.3$ Hz, 2H), 7.30 (d, $J = 8.3$ Hz, 2H), 5.78–5.67 (m, 1H), 5.43 (dd, $J = 15.8$, 6.8 Hz, 1H), 4.62–4.52 (m, 1H), 4.02 (br s, 1H), 3.03 (dd, $J = 12.8$, 8.3 Hz, 1H), 2.72 (dd, $J = 12.8$, 3.7 Hz, 1H), 2.42 (s, 3H), 2.01 (q, $J = 6.7$ Hz, 2H), 1.38–1.24 (m, 4H), 0.88 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 21.2, 21.9, 30.8, 31.6, 63.3, 68.9, 123.9, 129.81, 129.88, 133.3, 140.2, 141.6. Compound **8**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, $J = 8.2$ Hz, 2H), 7.35 (d, $J = 8.2$ Hz, 2H), 4.74 (dd, $J = 9.8$, 1.6 Hz, 1H), 4.11–4.03 (m, 2H), 3.38 (d, $J = 9.0$ Hz, 1H, –OH), 3.29 (dd, $J = 13.9$, 9.8 Hz, 1H), 2.69 (dd, $J = 13.9$, 2.4 Hz, 1H), 2.43 (s, 3H), 2.19–2.05 (m, 1H), 1.81–1.67 (m, 1H), 1.61–1.49 (m, 1H), 1.44–1.21 (m, 3H), 0.89 (t, $J = 7.3$ Hz, 3H). Compound **9**: ^1H NMR

(400 MHz, $CDCl_3$) δ 7.54 (d, $J = 8.2$ Hz, 2H), 7.33 (d, $J = 8.2$ Hz, 2H), 4.82 (dd, $J = 8.2$, 4.0 Hz, 1H), 4.54–4.45 (m, 1H), 3.91–3.80 (m, 1H), 3.60 (d, $J = 9.0$ Hz, 1H, –OH), 3.22 (dd, $J = 13.9$, 2.4 Hz, 1H), 2.91 (dd, $J = 13.9$, 3.3 Hz, 1H), 2.47 (s, 3H), 2.19–2.05 (m, 1H), 1.81–1.67 (m, 1H), 1.61–1.49 (m, 1H), 1.44–1.21 (m, 3H), 0.91 (t, $J = 7.3$ Hz, 3H). Compound **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, $J = 7.5$ Hz, 2H), 7.30 (d, $J = 7.5$ Hz, 2H), 4.50–4.44 (m, 1H), 3.91–3.79 (m, 2H), 3.34 (dd, $J = 12.8$, 2.2 Hz, 1H), 2.79 (dd, $J = 12.8$, 10.5 Hz, 1H), 2.42 (s, 3H), 1.78–1.64 (m, 1H), 1.62–1.50 (m, 1H), 1.49–1.22 (m, 4H), 1.44 (s, 6H), 0.93 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 21.1, 21.6, 26.9, 27.2, 28.5, 34.5, 55.9, 63.6, 75.1, 82.7, 110.1, 123.6, 129.7, 141.2. Compound **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, $J = 7.6$ Hz, 2H), 7.31 (d, $J = 7.6$ Hz, 2H), 4.45 (td, $J = 10.5$, 1.9 Hz, 1H), 3.89 (td, $J = 10.5$, 2.8 Hz, 1H), 3.38–3.29 (m, 2H), 2.61 (dd, $J = 13.4$, 10.5 Hz, 1H), 2.42 (s, 3H), 1.59 (s, 3H), 1.48–1.40 (m, 2H), 1.44 (s, 3H), 1.37–1.25 (m, 4H), 0.91 (t, $J = 6.7$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 19.3, 21.3, 22.3, 26.7, 29.3, 32.9, 51.9, 62.9, 69.0, 73.8, 99.9, 123.9, 129.9, 141.4, 141.6. Compound **20**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.54 (d, $J = 7.8$ Hz, 2H), 7.36 (d, $J = 7.8$ Hz, 2H), 4.77 (d, $J = 3.1$ Hz, 1H, –OH), 4.31 (dd, $J = 10.1$, 2.3 Hz, 1H), 3.81–3.68 (m, 1H), 3.34 (dd, $J = 14.0$, 10.1 Hz, 1H), 3.25–3.01 (m, 3H, CH–OH, 2 –OH), 2.72 (dd, $J = 14.0$, 2.3 Hz, 1H), 2.44 (s, 3H), 1.62–1.44 (m, 2H), 1.40–1.18 (m, 4H), 0.88 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 21.3, 22.6, 27.8, 33.4, 61.0, 68.5, 72.8, 75.0, 124.8, 130.1, 139.6, 141.7. Compound **21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, $J = 8.1$ Hz, 2H), 7.32 (d, $J = 8.1$ Hz, 2H), 5.51–5.45 (m, 1H), 5.11 (t, $J = 5.7$ Hz, 1H), 5.03–4.97 (m, 1H), 2.92 (dd, $J = 13.1$, 3.2 Hz, 1H), 2.83 (dd, $J = 13.1$, 9.0 Hz, 1H), 2.43 (s, 3H), 2.1 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.54–1.45 (m, 2H), 1.34–1.17 (m, 4H), 0.88 (t, $J = 6.5$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 20.5, 20.6, 20.8, 21.3, 22.2, 26.9, 30.2, 59.2, 66.4, 71.1, 73.5, 124.0, 130.1, 140.3, 141.9, 169.5, 169.3, 170.2.

15. The intramolecular functionalization was attempted on alcohol **26** an isomer of **7**, elaborated from (*R*)-methyl *p*-tolyl sulfoxide. Disappointingly, a regioisomeric mixture of products **27** and **28** (70%, 3:1 ratio, respectively) was obtained upon reaction with NBS.



The sulfones obtained by treatment of **27** and **28** with *m*-CPBA were found to be identical to the sulfones obtained from **8** and **9**.

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20. The conditions reported by Carda et al. using allyl bromide and indium powder was also found to proceed cleanly to afford the product as reported.