Asymmetric synthesis of anti-1,2-amino alcohols via the Borono-Mannich reaction: a formal synthesis of (-)-swainsonine

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Publication Details
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Keywords
Asymmetric, synthesis, anti, amino, alcohols, via, Borono, Mannich, reaction, formal, synthesis, swainsonine, CMMB

Disciplines
Life Sciences | Physical Sciences and Mathematics | Social and Behavioral Sciences

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This journal article is available at Research Online: http://ro.uow.edu.au/scipapers/1191
Asymmetric Synthesis of *Anti*-1,2-Amino Alcohols via the Borono-Mannich Reaction: A Formal Synthesis of (−)-Swainsonine

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Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT

Abstract: Chiral α-hydroxy-aldehydes generated in situ by the ADH reaction of vinyl sulfones undergo a borono-Mannich reaction with β-styrenyl boronic acid and primary amines to give *anti*-1,2-amino alcohols in high enantiomeric purities (ee 83-95%). This new method allows much more rapid access to these valuable chiral building blocks that has been used in a short formal synthesis (10 synthetic steps from 4-penten-1-ol) of (−)-swainsonine.

In 1998, Petasis reported the synthesis of *anti*-1,2-amino alcohols from a borono-Mannich reaction of aryl or vinyl boronic acids, with primary or secondary amines and chiral α-hydroxy-aldehydes.1 The latter were derived from carbohydrates which limited the generality of this reaction as enantiomerically enriched chiral α-hydroxy-aldehydes were not generally available. A more recent paper by Evans,2 however, showed that these valuable substrates could be prepared in situ from the Sharpless asymmetric dihydroxylation (ADH) reaction of vinyl sulfones (Scheme 1). We report here that chiral α-hydroxy-aldehydes generated in situ by this method
undergo the borono-Mannich reaction with β-styrenyl boronic acid and primary amines to give anti-1,2-amino alcohols in high enantiomeric purities. This new method allows much more rapid access to these valuable chiral building blocks. More specifically, the derived anti-1,2-amino alcohol diene products, obtained using allylamine, are valuable precursors for alkaloid synthesis, as further demonstrated here by a short, formal synthesis of the important natural product (-)-swainsonine.

**Scheme 1**

Results and Discussion

The (E)-vinyl sulfones 1a,b were readily prepared from their corresponding terminal alkenes via either cross metathesis with phenyl vinyl sulfone ((E) : (Z) = 99 : <1)), or by iodosulfonation followed by elimination of HI ((E) : (Z) = 98 : 2, see Supporting Information).

Treatment of vinyl sulfone 1a with either ADmixα or ADmixβ, under the conditions described by Evans, gave, after extraction into EtOAc and evaporation, material that showed no characteristic, downfield aldehyde 1H NMR resonances, more consistent with a mixture of acetal-like structures. This material was then treated with β-styrenyl boronic acid (1.00 mol equiv. relative to 1a) and allylamine (1.06 mol equiv. relative to 1a) in CH2Cl2 at rt for 40 h to give the anti-1,2-amino alcohol dienes 2a (R2 = allyl) and 3a (R2 = allyl), respectively (Scheme 2, Table 1, entries 1 and 2). These compounds were isolated as single diastereomers in 44 and 51% overall yields for the two step sequence, respectively, from 1a. The isomeric syn-1,2-amino alcohol dienes could not be detected. The enantiomeric purities of these products was high, 91% and 94%, respectively, as determined by 19F NMR spectroscopic analysis of their corresponding Mosher esters (see Supporting Information).

When this sequence of reactions was performed starting with vinyl sulfone 1a and using the secondary amine, morpholine and the aromatic amine, 4-methoxylaniline (PMPNH2), the overall yields were disappointing. The morpholine derived anti-1,2-amino alcohol product was obtained as a single diastereomer in only 12% yield (ee not determined), while none of the adduct 2a (R2 = PMP) could be isolated.

**Scheme 2**

![Scheme 2](image)

**Table 1. Synthesis of 2 and 3 (Scheme 2).**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Vinyl sulfone</th>
<th>AD mix</th>
<th>Amine R2</th>
<th>Overall yield (%) from 1a</th>
<th>Ee (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>α</td>
<td>allyl</td>
<td>44</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>β</td>
<td>allyl</td>
<td>51</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>α</td>
<td>PMB</td>
<td>46</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>β</td>
<td>PMB</td>
<td>43</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>α</td>
<td>allyl</td>
<td>35</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>1b</td>
<td>β</td>
<td>allyl</td>
<td>38</td>
<td>93</td>
</tr>
</tbody>
</table>

*Yield of 2 or 3 after purification by column chromatography. bDetermined by 19F NMR spectroscopy on the corresponding Mosher ester.*

Treatment of the TBDPS protected vinyl sulfone 1b with either ADmixα or ADmixβ, followed by treatment of the crude oxidation product with β-styrenyl boronic acid and allylamine gave the anti-1,2-amino alcohol dienes 2b (R2 = allyl) and 3b (R2 = allyl), respectively (Scheme 2, Table 1, entries 5 and 6) in overall yields of 35 and 38%, respectively, for the two step sequence. The enantiomeric purities of these products however was...
significantly different, with ee’s determined as 83% and 93%, respectively.

While in general the overall yields of 2 and 3 were only modest, the overall brevity of their synthesis (total of 3 steps) compares more than favourably with previously published methods for these anti-1,2-amino alcohol dienes (R = allyl) that involve the ring opening of vinyl epoxides with allylamine, where the former substrates requires six synthetic steps from commercially available starting materials. Furthermore, these yields are based on 1.0 equiv of 1 and 1.0 equiv of β-styrenyl boronic acid. These modest yields most likely reflect the instability of the α-hydroxy-aldehyde or their acetal-like intermediates, however the high ee’s of the product 1,2-amino alcohols indicates that racemization of these intermediates is not a major problem.

To verify the relative stereochemistry of 3a (R2 = allyl) it was converted to the oxazolidinone 4 (Scheme 3) by treatment with triphosgene under basic conditions. The 9.3 Hz vicinal coupling constant, J4,5, in the 1H NMR spectrum of 4 was consistent with the 4,5-cis relative stereochemistry. 

While the exact mechanism of the borono-Mannich reaction is not known, we speculate that these reactions occur via the boronate complex intermediate A (Scheme 4) in which the iminium ion adopts the reactive conformation shown to minimize 1,3-allylic strain.

To demonstrate the utility of these substrates further, the anti-1,2-amino alcohol diene 3b (R2 = allyl) was converted in four steps to the known indolizidine 8 as shown in Scheme 5. Protection of the secondary hydroxyl of 3b (R2 = allyl) as its TBS ether and then deprotection of the primary TBDDS ether under basic conditions gave the amino alcohol 6. Cyclization of this compound by intramolecular N-alkylation (Ph3P, CBr4, Et3N) gave the piperidine derivative 7 in 71% yield (Scheme 3). The ring-closing metathesis of 7, employing Ti(OI-Pr)4 as a Lewis acid to protect the amino group in situ by complexation, provided the silica gel sensitive indolizidine 8 ([α]20D -72, c 0.65, benzene) in 80% yield after purification on basic alumina. This compound has been prepared previously, in >99% ee ([α]20D -91.73, c 0.955, benzene) and in racemic form and converted to (-)9 and (+)-swainsonine, respectively. Thus our synthesis of 8 represents a formal asymmetric synthesis of (-)-swainsonine 9 in 10 steps from commercially available 4-penten-1-ol. This number of steps compares more than favourably with earlier syntheses of 9 that typically involve 10 or more steps.

\[ \text{Scheme 3} \]

\[ \text{Scheme 4} \]

\[ \text{Scheme 5} \]

Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH2Cl2, 0 °C, 2.5 h, 70%. (b) KOH, MeOH, reflux, 7 h, 60%. (c) Ph3P, CBr4, Et3N, CH2Cl2, 0 °C, 2 h, 71%. (d) Ti(OI-Pr)4, Grubbs’ II cat., CH2Cl2, reflux, 2.5 h, 80%.

In conclusion, chiral α-hydroxy-aldehydes generated in situ by the ADH reaction of vinyl sulfones undergo the borono-Mannich reaction with β-styrenyl boronic acid and primary amines to give anti-1,2-amino alcohols in high enantiomeric purities (83-95%). This new method allows a much more rapid access to these valuable chiral building blocks that have been used in a formal synthesis of (-)-swainsonine in 10 synthetic steps.
Acknowledgment We thank the Australian Research Council and the University of Wollongong for financial support.

Supporting Information Available Full experimental details and characterization data for all compounds. Copies of the $^1$H and $^{13}$C NMR spectra of 1a,b, 2a,b, 3a,b, 4-8 and copies of the $^1$H and $^{19}$F NMR spectra of the Mosher esters of 2a,b and 3a,b in CDCl$_3$ solution.

References

(8) An alternative and direct synthesis of anti-1,2-amino alcohols, from the addition of chiral imino-allylboranes to aldehydes, has also been reported. These products in principle, could also be converted to similar anti-1,2-amino alcohol dienes, see: Barrett, A. G. M.; Seefeld, M. A.; Williams, D. J. J. Chem. Soc. Chem. Commun. 1994, 1053-1054.
(15) We attribute the difference in the specific rotation of 8 and the literature value$^8$ to the relative small scale of our reactions and the sensitive nature of the product.