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Asymmetric Synthesis of *anti*-1,2-Amino Alcohols via the Borono-Mannich Reaction: A Formal Synthesis of (−)-Swainsonine

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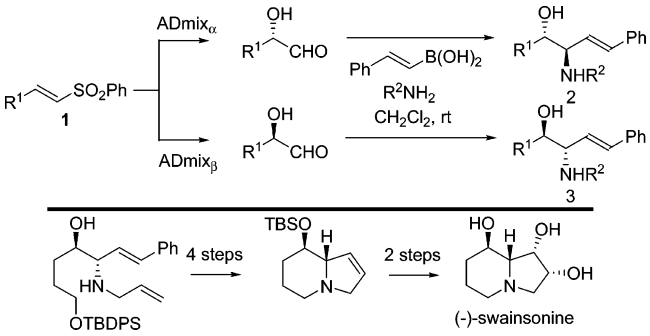
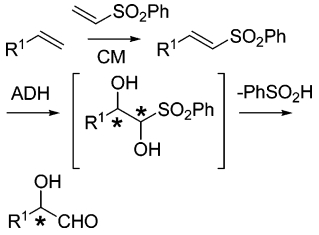


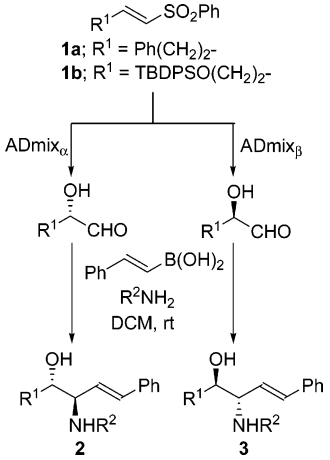
Chiral α-hydroxy aldehydes generated in situ by the ADH reaction of vinyl sulfones undergo a borono-Mannich reaction with *β*-styrenyl boronic acid and primary amines to give *anti*-1,2-amino alcohols in high enantiomeric purities (83−95% ee). This new method allows much more rapid access to these valuable 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 generally derived from carbohydrates which limited the generality of this reaction because 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,[3] as further demonstrated here by a short, formal synthesis of the important natural product (−)-swainsonine.[4]

SCHEME 1



SCHEME 2



The (*E*)-vinyl sulfones **1a**,**b** were readily prepared from their corresponding terminal alkenes either via cross metathesis with phenyl vinyl sulfone (*E*:*Z* = >99:<1)[5] (Scheme 1) or by iodosulfonation followed by elimination of HI (*E*:*Z* = 98:2; see Supporting Information).[6] Treatment of vinyl sulfone **1a** with either ADmix$_\alpha$ or ADmix$_\beta$, under the conditions described by Evans,[2] gave, after extraction into EtOAc and evaporation, material that showed no characteristic downfield aldehyde ^{1}H NMR resonances, more consistent with a mixture of acetal-like structures. This material was then treated with *β*-styrenyl boronic acid (1.00 molar equiv relative to **1a**) and allylamine (1.06 molar equiv relative to **1a**) in CH_2Cl_2 (DCM) at room temperature for 40 h to give the *anti*-1,2-amino alcohol dienes **2a** (R^2 = allyl) and **3a** (R^2 = allyl), respectively (Scheme 2 and 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

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TABLE 1. Synthesis of 2 and 3 (Scheme 2)

entry	vinyl sulfone	AD mix	amine R^2	overall yield (%) from **1**[a]	ee (%)[b]
1	**1a**	α	allyl	44	91
2	**1a**	*β*	allyl	51	94
3	**1a**	α	PMB	46	91
4	**1a**	*β*	PMB	43	95
5	**1b**	α	allyl	35	83
6	**1b**	*β*	allyl	38	93

[a] Yield of **2** or **3** after purification by column chromatography. [b] Determined by ^{19}F NMR spectroscopy on the corresponding Mosher ester.

of these products were high, 91 and 94%, respectively, as determined by ^{19}F NMR spectroscopic analysis of their corresponding Mosher esters (see Supporting Information). When these reactions were repeated using 4-methoxybenzylamine ($PMBNH_2$), the *anti*-1,2-amino alcohol dienes **2a** (R^2 = PMB) and **3a** (R^2 = PMB) were isolated as single diastereomers in 46 and 43% overall yields and had enantiomeric purities of 91 and 95%, respectively (Scheme 2 and Table 1, entries 3 and 4).

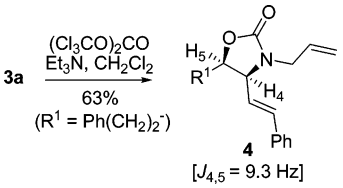
When this sequence of reactions was performed starting with vinyl sulfone **1a** and using the secondary amine, morpholine, and the aromatic amine, 4-methoxyaniline ($PMPNH_2$), the overall yields were disappointing. The morpholine-derived *anti*-1,2-amino alcohol product was obtained as a single diastereomer in only 12% yield (ee not determined), while none of the adduct **2a** (R^2 = PMP) could be isolated.

Treatment of the TBDPS-protected vinyl sulfone **1b** with either $ADmix_\alpha$ or $ADmix_\beta$ followed by treatment of the crude oxidation product with *β*-styrenyl boronic acid and allylamine gave the *anti*-1,2-amino alcohol dienes **2b** (R^2 = allyl) and **3b** (R^2 = allyl), respectively (Scheme 2 and 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, were significantly different, with enantiomeric excesses determined as 83 and 93%, respectively.

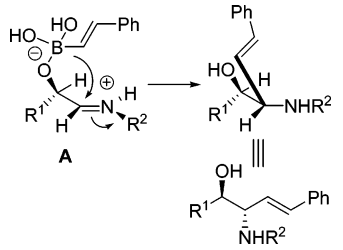
While, in general, the overall yields of **2** and **3** were only modest, the overall brevity of their synthesis (total of three steps) compares more than favorably with previously published methods for these *anti*-1,2-amino alcohol dienes (R^2 = allyl) that involve the ring opening of vinyl epoxides with allylamine, where the former substrates requires six synthetic steps from commercially available starting materials.[3a,7,8] Furthermore, these yields are based on 1.0 equiv of **1** and 1.0 equiv of *β*-styrenyl boronic acid.[9] These modest yields most likely reflect the instability of the α-hydroxy aldehyde or their acetal-like intermediates; however, the high enantiomeric excesses of the product 1,2-amino alcohols indicate that racemization of these intermediates is not a major problem.

To verify the relative stereochemistry of **3a** (R^2 = allyl), it was converted to the oxazolidinone **4** (Scheme 3) by treatment with triphosgene under basic conditions. The 9.3 Hz vicinal coupling constant, $J_{4,5}$, in the ^1H NMR spectrum of **4** was consistent with the 4,5-*cis* relative stereochemistry.[3g,7]

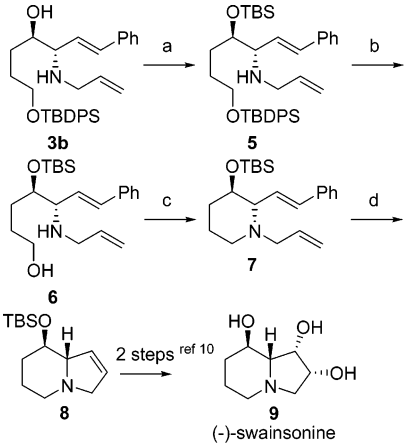
SCHEME 3



SCHEME 4



SCHEME 5[a]



[a] Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2.5 h, 70%; (b) KOH, MeOH, reflux, 7 h, 60%; (c) Ph_3P, CBr_4, Et_3N, CH_2Cl_2, 0 °C, 2 h, 71%; (d) Ti(O*i*-Pr)$_4$, Grubbs II catalyst, CH_2Cl_2, reflux, 2.5 h, 80%.

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** (R^2 = allyl) was converted in four steps to the known indolizidine **8**[10,11] as shown in Scheme 5. Protection of the secondary hydroxyl of **3b** (R^2 = allyl) as its TBS ether and then deprotection of the primary TBDPS ether under basic conditions[11] gave the amino alcohol **6**. Cyclization of this compound by intramolecular N-alkylation (Ph_3P, CBr_4, Et_3N)[3g,13] gave the piperidine derivative **7** in 71% yield (Scheme 3). The ring-closing metathesis of **7**, employing Ti(O*i*-Pr)$_4$ as a

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(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.

(9) Often organo-catalyzed Mannich reactions require an excess amount of the aldehyde or ketone donor. See: Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719−724 and references cited therein.

(10) Buschmann, N.; Rückert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325−4329.

(11) Mukai, C.; Sugimoto, Y.-i.; Miyazawa, K.; Yamaguchi, S.; Hanaoka, M. *J. Org. Chem.* **1998**, *63*, 6281−6287.

(12) Hatakeyama, S.; Irie, H.; Shintani, T.; Noguchi, Y.; Yamada, H.; Nishizawa, M. *Tetrahedron* **1994**, *50*, 13369−13376.

Lewis acid to protect the amino group in situ by complexation,[14] provided the silica gel sensitive indolizidine **8** ($[\alpha]^{26}_D$ −72°, *c* 0.65, benzene) in 80% yield after purification on basic alumina. This compound has been prepared previously in >99% ee ($[\alpha]^{20}_D$ −91.73°, *c* 0.955, benzene)[10,15] and in racemic form and converted to (−)-[9] and (±)-swainsonine,[12] 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 favorably with earlier syntheses of **9** that typically involve 10 or more steps.[4]

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.

Experimental Section

((*E*)-5-(Phenylsulfonyl)pent-4-enyloxy)(*tert*-butyl)diphenylsilane (1b). To an argon-flushed 50 mL round-bottom flask containing phenyl vinyl sulfone (0.204 g, 1.213 mmol) were added *tert*-butyl(pent-4-enyloxy)diphenylsilane (0.202 g, 0.622 mmol) and distilled CH_2Cl_2 (15 mL). The content of the round-bottom flask was then transferred via syringe to a argon-flushed 100 mL two-neck round-bottom flask containing a solution of Grubbs II catalyst (0.028 g, 0.033 mmol, 5.33 mol %) in CH_2Cl_2 (5 mL). The reaction mixture was stirred under argon and heated at reflux for 18 h and then concentrated in vacuo to give a brown oil. Flash column chromatography (increasing polarity from 1:10:2 to 1:5:2 Et_2O:pet. sp.:CH_2Cl_2 as eluent) gave the title compound (0.263 g, 0.565 mmol, 90.8%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.90−7.35 (15H, m), 7.00 (1H, dt, *J* = 6.3, 15.0 Hz), 6.30 (1H, d, *J* = 15.1 Hz), 3.65 (2H, t, *J* = 6.3 Hz), 2.36 (2H, q, *J* = 7.8 Hz), 1.69 (2H, quint., *J* = 6.8 Hz), 1.03 (9H, s). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 146.7, 140.6, 135.4, 133.5, 133.1, 129.6, 129.5, 129.1, 127.6, 127.5, 62.5, 30.3, 27.9, 26.8, 19.1. MS (ES+) *m*/*z* 465 ($[M + 1]^+$), HRMS found 465.1916, calcd for $C_{27}H_{33}O_3SSi$ 465.1920 ($[M + 1]^+$).

(3*S*,4*R*,*E*)-3-(Allylamino)-7-(*tert*-butyldiphenylsilyloxy)-1-phenylhept-1-en-4-ol (3b). To a round-bottom flask containing an solution of AD-mix-*β* (5.3 g) and $MeSO_2NH_2$ (0.16 g, 1.68 mmol) in water (9 mL) was added a solution of vinyl sulfone **1b** (0.406 g, 0.874 mmol) in *t*-BuOH (9 mL). Additional AD-mix-*β* (1.6 g) and $MeSO_2NH_2$ (0.040 g, 0.420 mmol) were added after 6 h, and the reaction mixture was stirred at room temperature for a total of 24 h and then diluted with water, followed by extraction with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford a brown oil. A solution of the crude product in dry DCM (5 mL) was purged with nitrogen, and then allylamine (0.07 mL, 0.053 g, 0.927 mmol) and (*E*)-2-phenylvinylboronic acid (0.125 g, 0.847 mmol) were added. The reaction mixture was stirred at room temperature for 40 h. The reaction mixture was partitioned between 5% aqueous NaOH (20 mL) and EtOAc (20 mL). The organic layer was washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo to give a brown oil. Flash column chromatography (increasing polarity 2−4% MeOH in DCM as eluent) afforded the *β*-amino alcohol **3b** (0.164 g, 38%, over two steps). $[\alpha]^{24}_D$ +7.5° (*c* 1.08, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 7.66−7.62 (4H, m), 7.42−7.26 (11H, m), 6.50 (1H, d, *J* = 15.4 Hz), 6.14 (1H, dd, *J* = 8.8, 15.4 Hz), 5.91 (1H, ddt, *J* = 5.9, 10.3, 17.0 Hz), 5.20 (1H, d, *J* = 17.0 Hz), 5.12 (1H, d, *J* = 10.3 Hz), 3.75 (1H, dt, *J* = 3.8, 8.5 Hz), 3.67 (2H, t, *J* = 5.9 Hz), 3.39−3.15 (3H, m), 2.40 (2H, br s), 1.88−1.4 (4H, m), 1.01 (9H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 136.3, 135.5, 133.8, 129.5, 128.5, 127.6, 127.2, 126.4, 116.3, 72.4, 64.7, 63.9, 49.5, 29.9, 29.0, 29.8, 19.1. MS (ES+) *m*/*z* 500 ($[M + 1]^+$), HRMS (ES+) found 500.2987, calcd for $C_{32}H_{42}NO_2Si$ 500.2985 ($[M + 1]^+$). The enantiomeric purity of this compound was determined to be 93% from ^{19}F NMR analysis of its Mosher ester (see Supporting Information).

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Supporting Information Available: Full experimental details, characterization data, and NMR assignments 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. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) We attribute the difference in the specific rotation of **8** and the literature value[10] to the relative small scale of our reactions and the sensitive nature of the product.