

Synthesis of (–)-Swainsonine and (–)-8-*epi*-Swainsonine by the Addition of Allenylmetals to Chiral α,β -Alkoxy Sulfinylimines

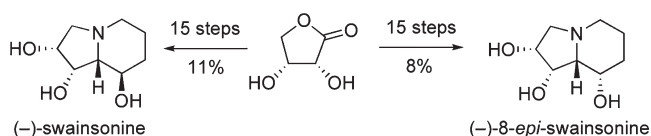
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ABSTRACT



The asymmetric synthesis of (–)-swainsonine and (–)-8-*epi*-swainsonine is reported through the addition of either the allenylzinc or the allenyl lithio cyanocuprate reagents derived from [3-(methoxymethoxy)prop-1-ynyl]trimethylsilane to enantiopure α,β -dialkoxy *N*-*tert*-butanesulfinylimines derived from D-erythronolactone.

(–)-Swainsonine (Figure 1) is a naturally occurring trihydroxylated indolizidine alkaloid found in nature in several species of flowering plants and some fungi. It was first isolated in 1973 by Broquist¹ from the fungus *Rhizoctonia leguminicola*. Since then, it has also been extracted from diverse fungi such as *Embellisia*^{2a} and *Metharhizium anisopliae* F-3622^{2b} and from other plants of the *Swainsona*^{2c} (flowering plants of western Australia), *Astragalus*, and *Oxytropis* species^{2d} (herbs and small shrubs of southwestern USA). Because they cause chronic intoxication with a variety of neurological disorders in livestock, these plants are collectively known as locoweeds. Diverse effects of intoxication including reduced appetite and consequent reduced growth in young animals and loss

of weight in adults, loss of fertility, and abortion have been extensively reported.³ All of these severe adverse effects on livestock, analogous to those of human α -mannosidosis, have been attributed to the remarkable lysosomal α -mannosidase inhibitory activities of (–)-swainsonine.⁴ Furthermore, this molecule exhibits interesting activity against some mammalian tumor cell lines⁵ and possesses immunomodulatory^{2b,6}

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and antiviral⁷ activities. (–)-Swainsonine also has potential uses as an adjuvant for anticancer drugs and other therapies in use.⁸

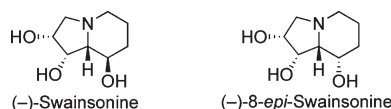
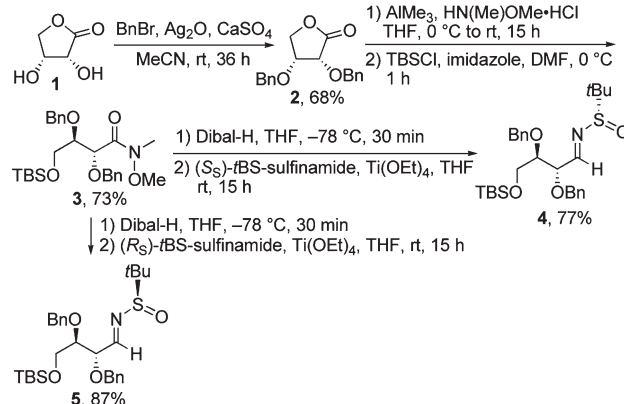


Figure 1. (–)-Swainsonine and (–)-8-*epi*-swainsonine.

Due to their interesting biological properties, (–)-swainsonine and a number of its epimers, including (–)-8-*epi*-swainsonine (Figure 1), have been the subject of frequent publications. To date, several reports on the synthesis of (–)-swainsonine and (–)-8-*epi*-swainsonine can be found

in the literature.^{9–12} In this paper, we disclose our recent efforts in this field.

Scheme 1. Synthesis of Imines **4** and **5**



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As part of our ongoing research on the preparation and use of 3-heterosubstituted allenylmetal species,¹³ we have shown that the reaction of *N*-*tert*-butanesulfinylimines with allenylmetals derived from [3-(methoxymethoxy)-prop-1-ynyl]trimethylsilane can afford either *anti*^{14a} or *syn*^{14b} acetylenic 1,2-amino ethers with high selectivities depending on the metal salt used. More recently, a stereo-selective access to *O,N,O*-stereotriads by addition of 3-(methoxymethoxy)allenylzinc bromide to *N*-*tert*-butanesulfinylimines possessing an α -alkoxy stereocenter has been developed.^{14c} The overall utility of the methodology is reflected in applications to the synthesis of several biologically active compounds.^{13,14b}

To broaden further the synthetic scope of our technology, we envisioned preparing (–)-swainsonine and (–)-8-*epi*-swainsonine starting from imines **4** and **5** having both an α - and a β -alkoxy stereocenter. These imines were readily prepared as single isomers in five steps and good yields (38% and 43%, respectively) from commercially available D-erythrone (**1**). The synthetic sequence involved condensation of (*S*)- or

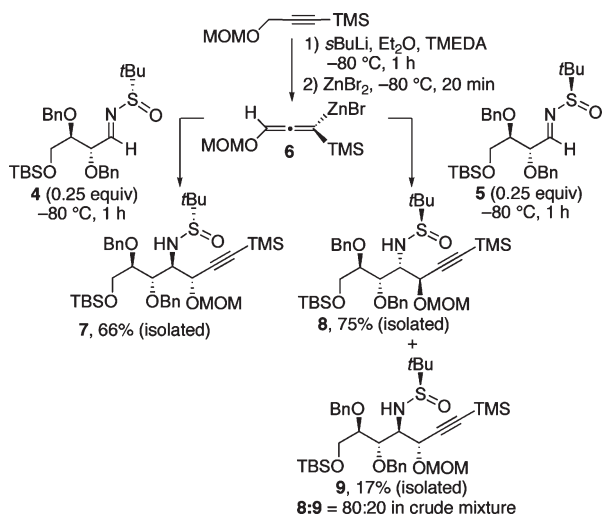
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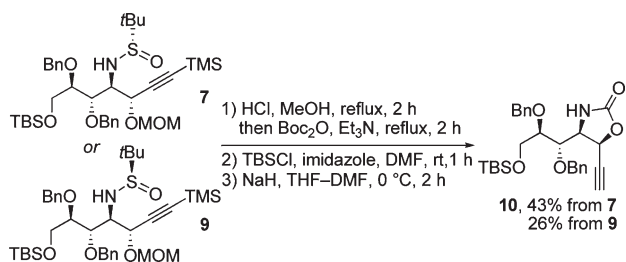
(*R*_S)-*N*-*tert*-butanesulfinamide with the aldehyde derived from **3** prepared following a described procedure¹⁵ (Scheme 1).

Scheme 2. Reaction of **4** and **5** with **6**



Having imines **4** and **5** in hand, we examined their reaction with allenylzinc **6** prepared by lithiation of [3-(methoxymethoxy)prop-1-ynyl]trimethylsilane followed by transmetalation with ZnBr_2 (Scheme 2). Under our reported conditions,^{14a,c} *i.e.* 4 equiv of **6** at -80°C in Et_2O , the reaction of **4** led exclusively to adduct **7** in 66% yield.¹⁶ Conversely, the reaction of **5** afforded a mixture of two isomeric adducts in an 80:20 ratio. Major and minor isomers were isolated in 75% and 17% yields respectively by silica gel column chromatography. The configuration of **8** was established by completion of the synthesis of (–)-swainsonine (*vide infra*). The configuration of the two newly created stereogenic centers of **7** and **9** was proven to be identical and opposite respectively to **8** following their transformation into oxazolidinone **10** (Scheme 3).

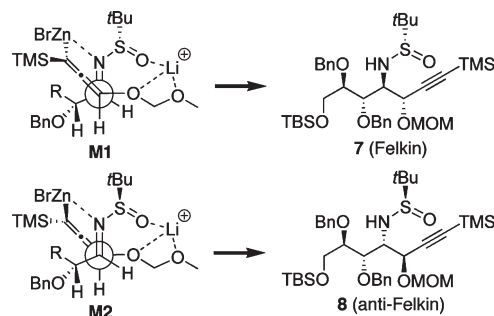
Scheme 3. Stereochemical Assignment of **7** and **9**



We explain the high stereoselectivity observed with **4** using model **M1** analogous to that postulated for the

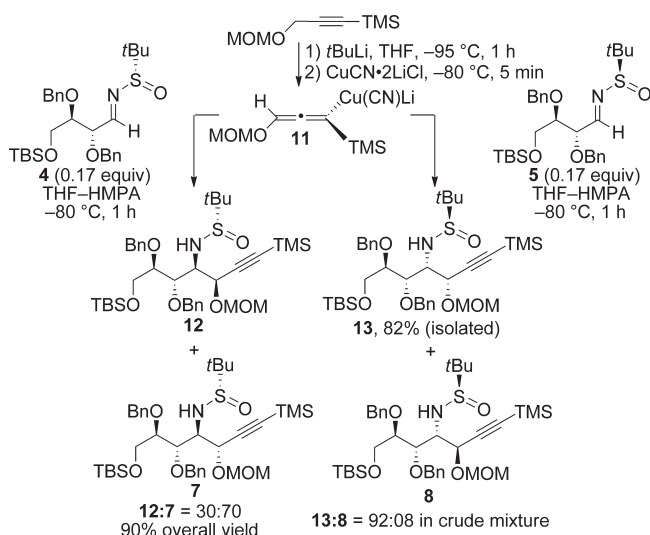
synthesis of *O,N,O*-stereotriads^{14c} (Scheme 4). In **M1**, the imine adopts its less energetic conformation¹⁷ and the lithium cation is chelated by both the oxygen atoms of the methoxymethyl ether and the sulfinyl group. The addition occurs from the face opposite to the bulky *tert*-butyl group. The high level of stereoselectivity is consistent with a cooperative effect between the sulfinyl group and the α -benzyloxy stereocenter by Felkin–Anh control. Correspondingly, we explain the selectivity observed with **5** with model **M2**. In this case an anti-Felkin approach with respect to the α -benzyloxy stereocenter is involved. Hence the lower selectivity observed is consistent with a noncooperative effect between the two stereodirecting groups of the imine.

Scheme 4. Stereoselectivity Models with **6**



We next envisaged securing adducts with a *syn* relationship between the two newly created stereocenters by carrying out an addition of allenyl(cyano)cuprate **11** prepared by lithiation of [3-(methoxymethoxy)prop-1-ynyl]trimethylsilane followed by transmetalation with $\text{CuCN} \cdot 2\text{LiCl}$ (Scheme 5).

Scheme 5. Reaction of **4** and **5** with **11**



Much to our surprise, under our reported conditions^{14b} at -80°C in THF-HMPA , the reaction with **4** afforded

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(16) Noteworthy is that the excess of allenylmetal used gave [3-(methoxymethoxy)prop-1-ynyl]trimethylsilane upon hydrolysis.

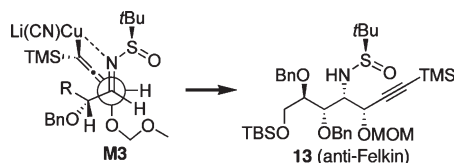
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an inseparable mixture of major **7** and minor **12** stereoisomers in 90% overall yield and a **12**:**7** ratio of 30:70.¹⁶ The *syn* stereochemistry of the two newly created stereocenters of **12** was assigned by conversion to the corresponding *trans* oxazolidinone (isomeric of **10**).¹⁸

Conversely, under the same conditions, **5** afforded a mixture of two isomers in a ratio of 92:08. In this case, the major adduct **13** could be isolated by silica gel column chromatography in 82% yield. As before, its absolute stereochemistry was established by completion of the synthesis of (–)-8-*epi*-swainsonine (*vide infra*). Noteworthy is that the minor isomer was found to be compound **8**.

While we cannot put forward a satisfying model to account for the selectivity observed with **4**, the one observed with **5** can be explained by model **M3**, similar to that postulated in previous works^{14b} (Scheme 6). This model, in which no chelation of the lithium cation occurs, affords **13** (anti-Felkin adduct) as the major isomer.

Scheme 6. Stereoselectivity Model for **13**



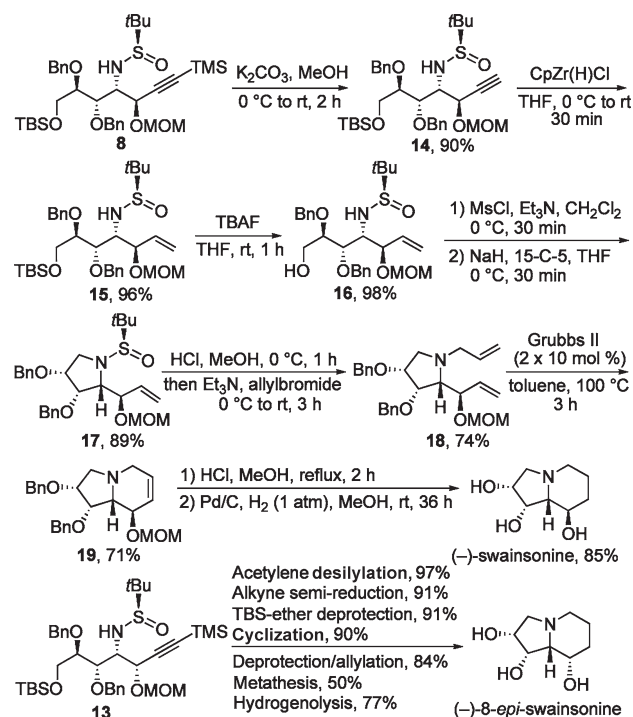
Having an efficient entry to *O,O,N,O*-stereotetrads, we undertook the preparation of (–)-swainsonine and (–)-8-*epi*-swainsonine from **8** and **13**, respectively.

First, product **8** was converted into intermediate **16** through desilylation of the acetylenic position followed by semi-reduction of the carbon–carbon triple bond with Schwartz's reagent and desilylation of the *tert*-butyldimethylsilyl ether moiety (Scheme 7).^{14b} The pyrrolizidine ring of (–)-swainsonine was constructed by mesylation of the primary hydroxyl group and subsequent treatment of the resulting mesylate with NaH. Selective acidic removal of the sulfinyl auxiliary, by treatment with methanolic HCl at 0 °C, followed by allylation of the nitrogen atom led to divinyl product **18**. Upon treatment with 2 × 10 mol % of second generation Grubbs' catalyst in toluene at 100 °C, the latter gave bicyclic intermediate **19**. Finally, (–)-swainsonine was obtained by acidic hydrolysis of the methoxymethyl ether and concomitant hydrogenolysis of the two benzyl ethers and reduction of the internal alkene. The product obtained was spectroscopically and physically in good agreement with the literature data reported^{1,2c} for (–)-swainsonine.

The same synthetic sequence was successfully applied to **13** to prepare (–)-8-*epi*-swainsonine in similar yields. The product obtained exhibits spectroscopical and physical data in good agreement with those reported (Scheme 7).^{9m}

(18) Further removal of the sulfinyl auxiliary of **12** gave a product which was found to be isomeric to that obtained from **13**. This allowed unambiguous assignment of the absolute stereochemistry of **12**.

Scheme 7. Synthesis of (–)-Swainsonine and (–)-8-*epi*-Swainsonine



In conclusion we have developed a stereoselective access to *O,O,N,O*-stereotetrads through the coupling of *N*-*tert*-butanesulfinylimines derived from D-erythronolactone with allenylmetals obtained from [3-(methoxymethoxy)prop-1-ynyl]trimethylsilane by a lithiation/transmetalation sequence. The *anti* or *syn* relationship between the two newly created stereocenters can be selected by simply choosing the appropriate solvent and metal salt for the transmetalation step. The synthetic usefulness and flexibility of the method have been demonstrated by the development of a new access to (–)-swainsonine and (–)-8-*epi*-swainsonine in 15 steps and 11% and 8% overall yield, respectively.

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Supporting Information Available. General information; experimental procedures; ¹H and ¹³C spectra for all new compounds, (–)-swainsonine, and (–)-8-*epi*-swainsonine. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Note Added after ASAP Publication. This manuscript was published ASAP on November 14, 2011. In Scheme 5, structures **4** and **5** have been switched and Compound **8** has been updated. The corrected version was reposted on November 21, 2011.