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Synthesis of (−)-Sedinine by Allene Cyclization and Iminium Ion Chemistry

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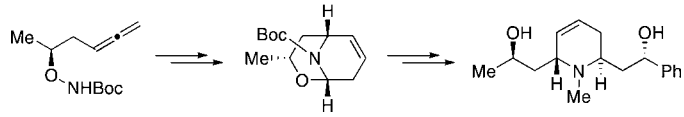
ABSTRACT



A synthesis of the *sedum* alkaloid sedinine has been achieved employing silver(I)-catalyzed allenic hydroxylamine cyclization and ring-closing metathesis to form a bicyclic *N,O*-acetal. Ring opening of this acetal with a silyl enol ether under Lewis acidic conditions is exclusively *trans* selective, leading to the natural product after reduction. On the other hand, conversion of the bicyclic *N,O*-acetal to a semicyclic *N,O*-acetal results in no stereoselectivity during such a reaction. The contrasting results can be rationalized by consideration of the conformation of the iminium ions.

The *sedum* alkaloids have held the interest of synthetic chemists over many decades.[1−3] In addition to some interesting biological activity, they offer a range of targets for the application of synthetic methodology. The *sedum* alkaloids may be considered to be either "one-armed", having a 2′-hydroxyalkyl substituent at the 2-position of a piperidine, or "two-armed", having an additional oxygenated substituent at the 6-position. Sedinine **1** is a "two-armed" *sedum* alkaloid with the two substituents *trans* to each other. Sedinine also possesses a double bond within the heterocycle. It was originally reported by Franck,[4] and the structure was revised by Hootelé on the basis of X-ray analysis of both the alkaloid and its hydrochloride.[5]

Retrosynthetically, the *sedum* alkaloids may be considered to be 1,3-amino alcohols. Recently, we reported syntheses of sedamine **2**[2a] and porantheridine **3**[6] (Figure 1) employing silver(I)-catalyzed allenic hydroxylamine cyclization.[7] We now wish to report the use of this chemistry, as well as ring-closing metathesis and iminium ion trapping,[8] for the synthesis of sedinine.

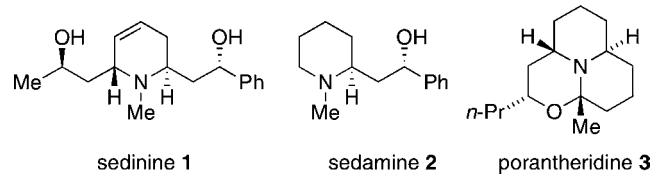


Figure 1. Sedinine, sedamine, and porantheridine.

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(3) For reviews on the synthesis of piperidines, see: Cossy, J. *Chem. Rec.* **2005**, *5*, 70. Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953.

(4) Franck, B. *Chem. Ber.* **1958**, *91*, 2803. Franck, B. *Chem. Ber.* **1959**, *92*, 1001. Franck, B. *Chem. Ber.* **1960**, *93*, 2360.

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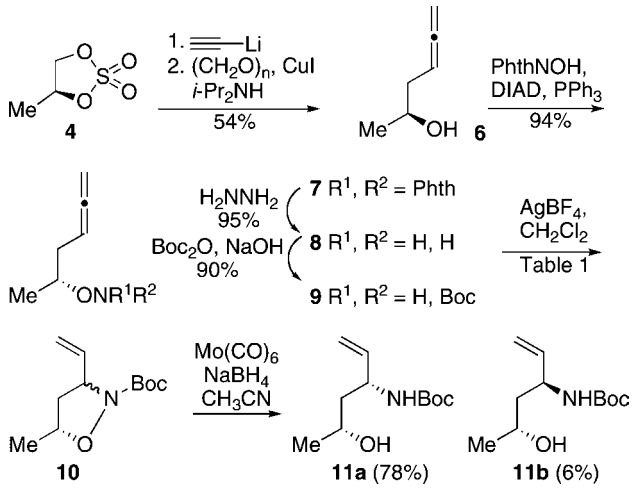
The desired allenic hydroxylamine was prepared by the previously reported method (Scheme 1).[2a,6] Ring opening

Scheme 1. Allene Cyclization



of the cyclic sulfate **4** derived from (*S*)-propylene glycol with lithium acetylide gave (*S*)-pent-4-yn-1-ol **5**.[9] The alkyne was homologated to the corresponding allene **6** following the Searles−Crabbé procedure.[10] Neither of these alcohols were rigorously purified due to their volatility. In each case, the principle impurity was residual reaction solvent (THF or 1,4-dioxane) which did not interfere with the subsequent reaction. After Mitsunobu reaction with *N*-hydroxyphthalimide,[11] the (*R*)-hydroxylamine **7** derivative was obtained chemically pure and with excellent enantioselectivity (>98% ee by chiral HPLC). Deprotection of the nitrogen atom and reprotection gave the allenic hydroxylamine substrate **9** for cyclization. Treatment of this allene with silver(I) tetrafluoroborate in dichloromethane at room temperature gave the desired isoxazolidine **10** as an inseparable mixture of diastereoisomers. A significant dependence of the diastereoselectivity on catalyst loading was observed (Table 1).[12] Fortunately, the diastereoselectivity increased as the catalyst loading was decreased. The optimum loading was found to be 10 mol %. At loadings below this, both the dr and the yield dropped.

Table 1. $AgBF_4$-Catalyzed Cyclization of Allene **9**

entry	$AgBF_4$ loading	isolated yield (%)	*cis*:*trans* ratio[a]
1	100	96	4.5:1
2	80	95	5.5:1
3	60	97	6.5:1
4	50	99	6.0:1
5	40	95	9.0:1
6	20	86	10.0:1
7	10	90	13.0:1
8	8	63	8.0:1
9	5	40	4.0:1

[a] Determined by ^{1}H NMR.

The isoxazolidine **10**, as a mixture of isomers, was converted to the amino alcohol derivative **11** by cleavage of the N−O bond with molybdenum hexacarbonyl and sodium borohydride.[13] At this point, the two diastereoisomers could be separated by column chromatography. Although the major isomer **11a** was an oil, the minor isomer **11b** proved to be crystalline. X-ray analysis (Figure 2) demonstrated that it was, as expected from our earlier work,[2a] the *anti*-isomer.[14]

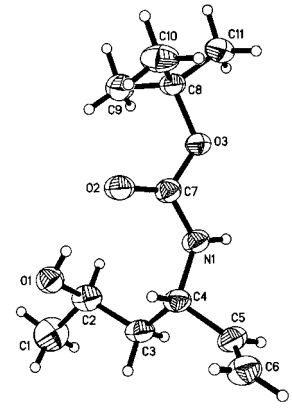


Figure 2. X-ray structure of amino alcohol derivative **11b**.

It was intended to employ the vinyl group generated by the allene cyclization in a metathesis reaction to form the alkene present in the piperidine ring of sedinine. To obtain the required *cis*-geometry, a ring-closing metathesis, rather than a cross metathesis, was required. We therefore decided to attach the second alkene partner via formation of an *N*,*O*-acetal, so that we would also have an iminium ion precursor without having to resort to redox chemistry.[15]

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(6) Bates, R. W.; Lu, Y. *J. Org. Chem.* **2009**, *74*, 9460.

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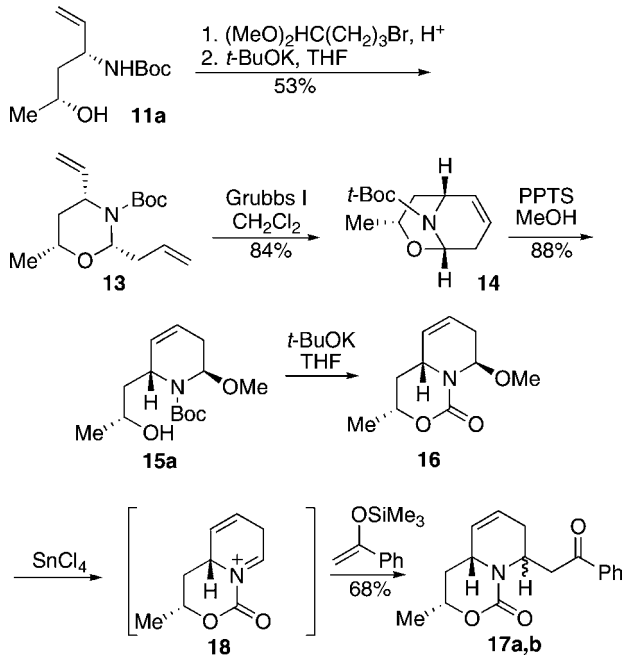
(14) Details have been deposited with the Cambridge Crystallographic Database, CCDC 784128, and may be obtained at http://www.ccdc.cam.ac.uk.

Treatment of amino alcohol derivative **11a** with the dimethyl acetal of 4-bromobutanal in toluene at 100 °C in the presence of polymer-supported PPTS,[16] followed by elimination of HBr with potassium *t*-butoxide, gave the desired bicyclic *N*,*O*-acetal **13** as a 6:1 mixture of isomers (Scheme 2). The two isomers were separable, and the major

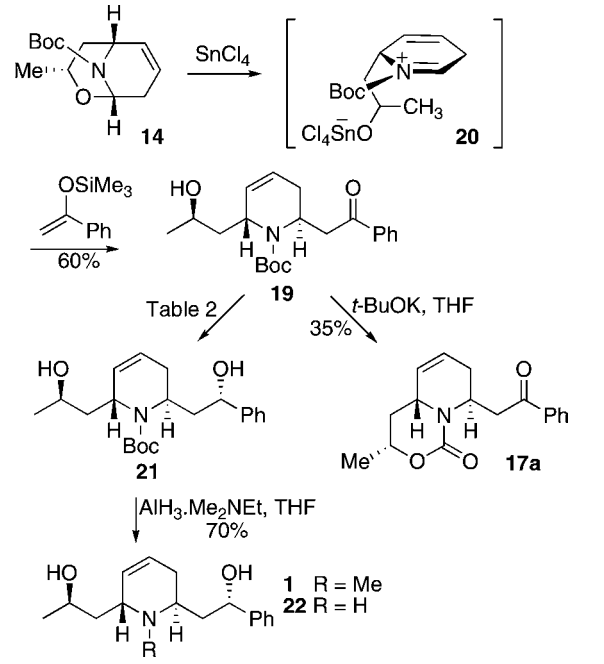
Scheme 2. Unstereoselective Iminium Ion Chemistry



isomer **13** was obtained in 53% yield from amino alcohol **11a**. For this acetal to be a competent RCM substrate, it is, of course, necessary for the two alkene moieties to be in proximity.[17] The stereochemistry of the newly formed stereogenic center of the acetal could not, however, be determined, as the problem of rotamers complicated the ^{1}H NMR spectrum. Upon the basis of our previous work with *N*,*O*-acetals,[11a] and drawing on earlier reports on piperidines,[18] including that of Martin,[19] we expected that the vinyl and allyl substituents would both be *cis* and pseudoaxial and, hence, in proximity. It was, therefore, gratifying to find that treatment of *N*,*O*-acetal **13** with Grubbs' first-generation catalyst yielded the desired bicyclic acetal **14** in 84% yield. From our recent work on porantheridine,[6] and also from the work of Lhommet,[20] it may be expected that treatment of this bicyclic *N*,*O*-acetal **14** with a nucleophile under Lewis acidic conditions would yield the *cis* isomer under stereoelectronic control, rather than the required *trans* isomer.[21] We, therefore, employed the same strategy as in our porantheridine synthesis,[6] converting the cyclic *N*,*O*-acetal **14** to a semicyclic *N*,*O*-acetal **15a**,[22] and converting the acyclic carbamate to a cyclic carbamate **16**. In the case of porantheridine **3**, treatment of such an *N*,*O*-acetal with a Lewis acid and allyl trimethylsilane gave exclusively the *trans* isomer. In the present case, treatment of **16** with tin(IV) chloride[23] and the trimethylsilyl enol ether of acetophenone[24] yielded the desired ketone **17** as a 1:1 diastereoisomeric mixture. This dramatic change of outcome is attributed to the presence of the ring alkene. The iminium ion (or dihydropyridinium ion) intermediate **18** is substantially planar, with no stereoelectronic or steric bias favoring either face.

Treatment of the bicyclic *N*,*O*-acetal **14** under the same conditions, however, led to ketone **19** as a single isomer (Scheme 3). As the ^{1}H NMR spectrum showed the typical line

Scheme 3. Stereoselective Iminium Ion Chemistry and Sedinine Synthesis



broadening of such piperidine Boc derivatives, it was converted to the corresponding cyclic carbamate **17a** which proved to be crystalline. X-ray analysis (Figure 3) showed the *trans* disposition of the two piperidine substituents,[25] in complete contrast to the result in the porantheridine case. This is again attributed to the presence of the ring alkene. The resulting flattening of the ring of the iminium ion intermediate **20** ensures that neither

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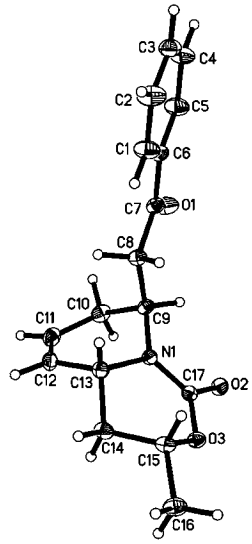
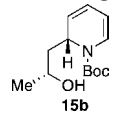


Figure 3. X-ray structure of piperidine **17a**.

of the two transition states is chairlike, hence, again, the absence of any stereoelectronic bias. However, the oxypropyl substituent is compelled to adopt a pseudoaxial position to avoid the 1,2-interaction with the *N*-Boc group, thus shielding one face of the iminium ion and compelling the enol ether to approach from the opposite face. This results in the remarkably high selectivity in favor of the *trans* isomer. This *trans* selectivity is in contrast to the results of Craig[26] and Shipman[27] who found *cis*-selective additions to dihydropyridinium ions. In those cases, however, the alkene had an α,β-relationship to the iminium ion. In our case, with a β,γ-relationship, the iminium ion conformation must be quite different.

With the *trans* adduct in hand, the synthesis was completed by reduction of the keto group. Diastereoselective reduction of side-chain ketones in *sedum* alkaloid syntheses has been reported.[1] While all reagents tried gave the desired diastereoisomer **21** as the major product, in our hands, the best diastereoselectivity on reduction of the ketone group of **19** by substrate control was obtained using DIBAL (Table 2).[28,2g] A much lower dr was obtained using K-selectride[29]

(22) If the reaction is carried out at room temperature, a byproduct identified as dihydropyridine **15b** is also obtained. Formation of this byproduct was suppressed by maintaining a temperature of 0 to −10°C.



15b

(23) In contrast, use of TMSOTf, $BF_3{\cdot}OEt_2$, or $SnCl_2$ resulted in decomposition; starting material was largely recovered when Cp_2TiCl_2 or $Yb(OTf)_3$ was used. Use of $TiCl_4$ gave a slightly lower yield and some formation of dihydropyridine **15b**.

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Table 2. Reduction of Ketone **19**

entry	reagent and conditions	yield (%)	dr
1	DIBAL-H, CH_2Cl_2, −78 °C	99	4.5:1
2	$LiAl(Ot\text{-}Bu)_3H$, THF, −78 °C	99	1.1:1
3	K-selectride, THF, 0 °C	80	1.5:1
4	Red-Al, CH_2Cl_2, −78 °C	60	2.7:1
5	$BH_3{\cdot}SMe_2$, (*R*)-Me-CBS, THF −10 to 0 °C	92	>99:1

or lithium tri(*t*-butoxy)aluminum hydride.[30] On the other hand, use of the B-methyl (*R*)-CBS catalyst[31] with borane dimethyl sulfide gave alcohol **21** as a single diastereoisomer within the limits of detection.

Finally, reduction of the Boc group to an *N*-methyl group to give sedinine **1** was found to proceed best using alane[32] as its commercially available dimethylethylamine complex. Heating piperidine **21** with this reagent in THF at reflux gave sedinine **1** in 70% yield, accompanied by a small amount of des-methyl sedinine **22** (15%). Reduction of piperidine **21** with lithium aluminum hydride or Red-Al gave lower yields of sedinine **1** (40% and 50%, respectively). The ^1H and ^{13}C NMR spectroscopic data of the synthetic sedinine **1** were in good agreement with those reported by Hootelé.[33] In addition, the optical rotation recorded for our synthetic sample, $[\alpha]_D^{20} = -97$ ($c = 0.57$, MeOH) was also in good agreement with that reported by Hootelé, $[\alpha]_D^{20} = -98$ ($c = 1.9$, MeOH), as was the melting point of 118−120 °C, compared to the reported value of 120−121 °C.[5a]

In conclusion, we have completed a stereoselective synthesis of sedinine, one of the more complex *sedum* alkaloids. All of the stereocenters can be derived from the readily available starting material (*S*)-propylene glycol. The excellent stereoselectivity in the addition to the iminium ion shows that inclusion of an alkene in the ring is an additional strategy for switching from *cis* to *trans* addition.

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Supporting Information Available: Experimental procedures for (*S*)-propylene glycol, compounds **1**, **4**−**17**, **19**, **21**, and **22**; ^1H and ^{13}C NMR spectra for compounds **1**, **6**−**17**, **19**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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