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<td>Bates, Roderick W.; Aslam, Nur Filza Bte Mohamed; Tang, Chi H.; Simon, Oliver</td>
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<td><strong>Date</strong></td>
<td>2014</td>
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A Synthesis of 5-Hydroxyseadamine using Hydroformylation

Roderick W. Bates, a Nur Filza bte Mohamed Aslam, a, b Chi H. Tang, a Oliver Simon b

a) Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371

b) Novartis Institute for Tropical Diseases, 10 Biopolis Road, #05-01 Chromos, Singapore 138670

E-mail: roderick@ntu.edu.sg

Abstract: A synthesis of 5-hydroxyseadamine, a sedum alkaloid, has been completed using N,O-heterocycle chemistry to establish the aminoalcohol structure, hydroformylation to form the piperidine ring and diastereoselective dihydroxylation to introduce the 5-hydroxy group.

We have recently shown that the combination of tandem hydroformylation-condensation of N-tosyl homoallylic amines, followed by diastereoselective dihydroxylation, provides an efficient route to the synthesis of 3-hydroxypiperidines. This strategy was employed for the synthesis of pseudoconhydrine 1 and azimic acid 2. We have earlier shown that cyclofunctionalisation of O-homoallyl and allenyl hydroxylamine derivatives stereoselectively provides isoxazolidines, which are useful intermediates for the synthesis of 1,3-aminoalcohols and their derivatives, such as monomorine, porantheridine and the sedum alkaloids, sedamine and sedinine.
We speculated that we could combine both of these methods in the synthesis of 5-hydroxysedamine 3. Originally isolated from *Sedum acre*, this alkaloid is both a *sedum* alkaloid, therefore containing a 1,3-aminoalcohol moiety, and a 3-hydroxypiperidine. The use of hydroformylation to construct the piperidine ring would require the synthesis of an allyl isoxazolidine. We have recently shown that these compounds are readily available by Sakurai reaction of the corresponding 3-methoxyisoxazolidines. This reaction favours formation of the trans-isomer, corresponding to the anti-aminoalcohol. As 5-hydroxysedamine possesses syn stereochemistry, an inversion of the alcohol group must be included in the synthetic pathway.

The homoallylic alcohol 4 was converted to the *N*-tosyl hydroxylamine 7 through a Mitsunobu reaction with *N*-hydroxyphthalimide, dephthaloylation and reprotection. While our previous studies of the Sakurai reaction used carbamate protecting groups on nitrogen, we selected a tosyl group due to its greater robustness, the higher possibility of obtaining crystalline intermediates and to avoid issues with rotamer formation. Ozonolysis of hydroxylamine 7 in acidic methanol, followed by a dimethyl sulfide work up, gave 3-methoxyisoxazolidine 8 as an inconsequential mixture of stereoisomers. Tosic acid monohydrate was used as the acid as amberlyst-15, which we used previously, did not result in complete conversion to the methoxy compound. Treatment of 3-methoxyisoxazolidine 8 with allyl trimethylsilane in the presence of
boron trifluoride at -78°C with slow warming to room temperature gave the allyl isoxazolidine 9 as an 8:1 mixture of stereoisomers. Pleasingly, this ratio is distinctly better than obtained with carbamate protecting groups (3:1 – 4:1). The major isomer proved to be crystalline and was confirmed to be the trans isomer by X-Ray crystallography.\textsuperscript{11} Cleavage of the N-O bond was achieved in the usual way with molybdenum hexacarbonyl in wet acetonitrile\textsuperscript{12} to give the protected amino alcohol 10a, which would be the intended hydroformylation substrate.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{allyl_isoxazolidine_9}
\caption{The X-Ray structure of allyl isoxazolidine 9}
\end{figure}

Hydroformylation of amino alcohol 10a derivatives can, in principle, give rise to four products (Table 1). Ene-sulfonamide 11a is the desired product. \textit{N,O}-Hemiaminal 12 is the precursor by dehydration of ene-sulfonamide 11a. Bicyclic \textit{N,O}-aminal 13 can arise by cyclisation of the benzylic alcohol group onto the ene-sulfonamide 11a.\textsuperscript{13} The structure of bicyclic \textit{N,O}-aminal 13 was also confirmed by X-Ray crystallography. The pyrrolidines 14, the products of branched hydroformylation, can exist as a mixture of stereoisomers.
As expected, when triphenylphosphite was used as the ligand, appreciable amounts of the branched isomers 14 were formed causing difficulties with purification. In addition, as we noted previously, increasing the amount of this ligand caused an increase in the formation of the desired ene-sulfonamide 11a at the expense of the \( N,O \)-hemiaminal 12. At the highest phosphite loading employed, some of the bicyclic \( N,O \)-aminal 13 was also isolated. When BIPHEPHOS was employed as the ligand, as expected, formation of the branched products 14 was not observed. A somewhat higher yield of the desired ene-sulfonamide 11a could be obtained in THF. This was accompanied by some formation of the bicyclic \( N,O \)-aminal 13. We did experience some variability in yield and product distribution depending on the batch of BIPHEPHOS employed. The reaction in toluene proved lower yielding, but more reproducible.

**Table 1. Hydroformylation of alkene 10a**

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand (L)</th>
<th>L:Rh ratio</th>
<th>solvent</th>
<th>yields, %</th>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>11a 12 13 14</td>
</tr>
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**Fig. 2.** The X-Ray structure of bicyclic \( N,O \)-aminal 13.
Some of the undesired products could be converted to the desired ene-sulfonamide. Thus, treatment of the bicyclic \(N,O\)-aminal 13 with acetic anhydride in the presence of amberlyst-15 gave acetate 11c. It is notable that amberlyst-15 proved effective for this ring opening while a series of Lewis acids proved less so. Acetate 11c could be converted to ene-sulfonamide 11a by treatment with methanolic potassium carbonate. \(N,O\)-Hemiaminal 12 could be converted to the desired ene-sulfonamide 11a by resubjecting this material to the hydroformylation conditions.

The rather complex results of hydroformylation of substrate 10a stand in contrast to our previous experience. It is apparent that the hydroxy group in the amino alcohol substrate introduces significant complication and is capable of interfering with the usual smooth running of the hydroformylation reaction. Accordingly, a cleaner hydroformylation was achieved when the original substrate 10a was protected as its triethylsilyl ether 10b. With this substrate, hydroformylation proved less complex (Table 2), however, to ensure that dehydration went to completion, a higher temperature (85°C) was required. Protected ene-sulfonamide 11b was formed in
excellent yield under these conditions. Deprotection then gave the ene-sulfonamide 11a.

Table 2. Hydroformylation of alkene

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand (L)</th>
<th>Rh:L ratio</th>
<th>Temp. °C</th>
<th>solvent</th>
<th>yields, %</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>des</td>
</tr>
<tr>
<td>1</td>
<td>BIPHEPHOS</td>
<td>1:1</td>
<td>65</td>
<td>toluene</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>BIPHEPHOS</td>
<td>1:1</td>
<td>85</td>
<td>toluene</td>
<td>90</td>
</tr>
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</table>

all reactions used Rh$_2$(OAc)$_4$ as the source of rhodium and were run for 22 hours at 65°C under 60 psi of 1:1 CO/H$_2$.

The ene-sulfonamide 11a represents the opportunity to carry out the necessary inversion of the alcohol to give the syn-stereochemistry. Disappointingly, a Mitsunobu reaction with acetic acid gave a substantial amount of the eliminated product 15b (30% yield), alongside the desired acetate (37%) and recovered starting material (16%). The formation of this alkene may be attributed to the steric hindrance around the reaction site.

\[ \text{15b} \]

It is known that the balance of reactivity will be tipped in favour of substitution if a more acidic partner is employed.\textsuperscript{15} Gratifyingly, the use of chloroacetic acid\textsuperscript{16} (pK$_a$ = 2.86) with toluene as the solvent gave an improved yield, 82%, of the desired substitution product 15a. Dihydroxylation gave the diols 16 as an inseparable 4.6:1
mixture of stereoisomers and, based on our previous work, it was assumed that the
\textit{cis}-isomer was the major product. This was subsequently confirmed by completion of
the synthesis. Acetylation then allowed selective removal of the $\alpha$-acetoxy group
under Kursanov-Parnes conditions.$^{17}$ Diester 18 could be obtained as a single
diastereoisomer after careful column chromatography. Removal of all of the acyl
groups and desosylation then gave des-methyl 5-hydroxysedamine 20. This compound
was then methylated to give 5-hydroxysedamine 1 using the Eschweiler-Clarke
reaction: reductive amination using the combination of formaldehyde and formic acid.
It was notable that this reaction was much more effective using para-formaldehyde
rather than formalin as the source of formaldehyde. We attribute this to the higher
concentration of formaldehyde being generated in the absence of water, as it will not
be lost due to hydrate formation. The spectroscopic and chiroptical data for our
synthetic material was in excellent agreement with that reported. The completion of
the synthesis illustrates how this chemistry can be employed to synthesise more
complex alkaloids.

$^8$ Ibebeke-Bomangwa, W.; Hootelé, C. \textit{Tetrahedron} \textbf{1987}, 43, 935. For previous
syntheses of this alkaloid, see Plehiers, M.; Hootelé, C. \textit{Tetrahedron Lett.} \textbf{1993}, 34,
$^{11}$ CCDC
31, 3351; (b) Zhang, D.; Süling, C.; Miller, M. J. \textit{J. Org. Chem.} \textbf{1998}, 63, 885; (c)
Such compounds can be useful intermediates in their own right: see sedinine ref

We were unable to protect the alcohol as a TBS ether using TBS chloride, presumably due to steric hindrance, and considered the TMS ether as potentially too labile. As Kocienski has pointed out, the “ratio of pleasure to pain is quite favourable with TES ethers”. Protecting Groups, Kocienski, P. J., Thieme, p. 195.

