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A Synthesis of 5-Hydroxysedamine using Hydroformylation

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Abstract: A synthesis of 5-hydroxysedamine, 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**¹ and azimic acid **2**.² We have earlier shown that cyclofunctionalisation of *O*-homoallyl and allenyl hydroxylamine derivatives stereoselectively provides isoxazolidines,³ which are useful intermediates for the synthesis of 1,3-aminoalcohols and their derivatives, such as monomarine,⁴ porantheridine⁵ and the *sedum* alkaloids, sedamine⁶ and sedinine.⁷

We speculated that we could combine both of these methods in the synthesis of 5-hydroxysedamine **3**.⁸ 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.⁹ 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 reaction¹⁰ 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.¹¹ Cleavage of the N-O bond was achieved in the usual way with molybdenum hexacarbonyl in wet acetonitrile¹² to give the protected amino alcohol **10a**, which would be the intended hydroformylation substrate.

Fig. 1. The X-Ray structure of allyl isoxazolidine **9**

Hydroformylation of amino alcohol **10a** derivatives can, in principle, give rise to four products (Table 1). Ene-sulfonamide **11a** is the desired product. *N,O*-Hemiaminal **12** is the precursor by dehydration of ene-sulfonamide **11a**. Bicyclic *N,O*-aminal **13** can arise by cyclisation of the benzylic alcohol group onto the ene-sulfonamide **11a**.¹³ The structure of bicyclic *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.

Fig. 2. The X-Ray structure of bicyclic *N,O*-aminal **13**.

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**^a

entry	ligand (L)	L:Rh ratio	solvent	yields, %			
				11a	12	13	14

1	P(OPh) ₃	3:1	THF	2	35	0	29
2	P(OPh) ₃	10:1	THF	19	27	0	18
3	P(OPh) ₃	20:1	THF	48	0	18	23
4	BIPHEPHOS	1:1	THF	75	0	12	0
5	BIPHEPHOS	1:1	toluene	45	0	20	0

a: all reactions used Rh₂(OAc)₄ as the source of rhodium and were run for 22 hours at 65°C under 60 psi of 1:1 CO/H₂.

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**.¹⁴ 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

entry	ligand (L)	Rh:L ratio	Temp. °C	solvent	yields, %		
					des	-OH	br
1	BIPHEPHOS	1:1	65	toluene	30	58	0
2	BIPHEPHOS	1:1	85	toluene	90	0	0

all reactions used $\text{Rh}_2(\text{OAc})_4$ as the source of rhodium and were run for 22 hours at 65°C under 60 psi of 1:1 CO/H₂.

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.

It is known that the balance of reactivity will be tipped in favour of substitution if a more acidic partner is employed.¹⁵ Gratifyingly, the use of chloroacetic acid¹⁶ ($\text{pK}_a = 2.86$) 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 *cis*-isomer was the major product. This was subsequently confirmed by completion of the synthesis. Acetylation then allowed selective removal of the α -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 detosylation 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.

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¹³ Such compounds can be useful intermediates in their own right: see sedinine ref

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