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Synthesis of isoxazolidin-5-ones via stereocontrolled Michael additions of benzylhydroxylamine to L-serine derived α,β-unsaturated esters

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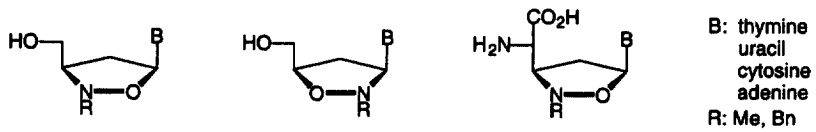
Abstract

The synthesis of optically active isoxazolidin-5-ones from α,β-unsaturated esters is reported. The key features of this synthetic sequence include the stereocontrolled Michael addition of benzylhydroxylamine to alkenes **7** and **8** and the intramolecular cyclization to the target compounds

Nitrogen containing nucleoside analogs and, in particular, isoxazolidinyl nucleosides such as **1** and **2**, have attracted considerable interest in recent years due to their potential antiviral capabilities.[1,2] In a preceding paper we described the synthesis of isoxazolidinyl thymidine **1a** in enantiomerically pure form by the nucleophilic addition of an ester enolate to a readily available D-glyceraldehyde derived nitrone.[3] As a continuation of our interest in new isoxazolidinyl nucleosides we were intrigued by more complex compounds, e.g. **3**, which bear analogous structural relationship to amino acid nucleosides. By an extension of our nitrone-based methodology we also reported the synthesis of an isoxazolidine nucleoside analog of thymine polyoxin C.[4] Given the importance of new complex nucleoside analogs, of both D- and L-series, in biology [5–10] the development of new strategies for their synthesis is of great interest.



1 **2** **3**

A retrosynthetic analysis for the isoxazolidinyl nucleosides **1** and **3** (type $C_3O^cN^d$ according to the notation method recently proposed by Zhao and co-workers for cyclic nucleoside analogs[1]) based on nucleoside chemistry is outlined in Scheme 1. This strategy shows that isoxazolidin-5-ones **4** are obvious precursors. In this context, the synthetic versatility of those compounds has recently been pointed out.[11,12]

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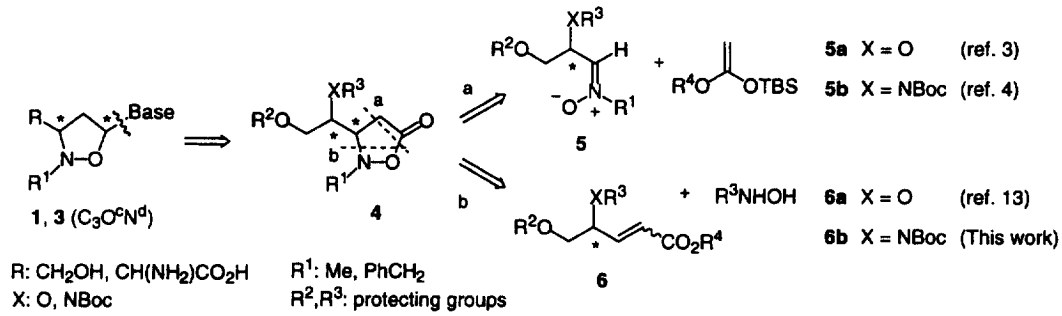
The cyclic system would need to be formed, presumably in situ, from an intramolecular cyclization of the corresponding β-(hydroxyamino)ester, so that two key starting materials (nitrones **5** and alkenes **6**) can be considered, depending on the disconnection approach contemplated.



Scheme 1.

In our previous work the nitrone-approach (disconnection **a**) was used for constructing the key intermediate **4** (X=O, NBoc).[3,4] The other approach (disconnection **b**) was applied by Zhao and co-workers[13] for the synthesis of β-D-isoxazolidinyl nucleosides **1** (X=O).

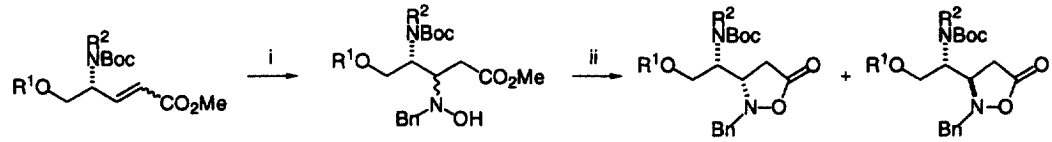
Herein we report the stereocontrolled synthesis of isoxazolidin-5-ones **4** (X=NBoc) by a Michael addition of benzylhydroxylamine (Scheme 1, disconnection **b**) to differentially protected α,β-unsaturated esters derived from L-serine.

These alkenes **7** and **8** were regioselectively prepared from the corresponding α-amino aldehydes in a straightforward manner.[14] *E*-alkenes were synthesized by a Wittig–Horner reaction [$(C_2H_5O)_2POCH_2CO_2Me$] under protic conditions and *Z*-isomers† were obtained by condensation of the aldehydes with Still's reagent [$(CF_3CH_2O)_2POCH_2CO_2Me$].[15] The Michael additions were performed by adding sequentially benzylhydroxylamine hydrochloride (1.2 equiv.) and triethylamine (1.2 equiv.). Control experiments revealed that the reaction did not take place at low temperatures (−30 to −80°C), so all the reactions were carried out at ambient temperature.

In all cases examined, the resulting β-(hydroxyamino)esters **9** and **10** were isolated as mixtures of diastereomers (Scheme 2) and because we were unable to purify these mixtures by column chromatography, they were used directly in cyclization reactions. Attempts to cyclize **9** and **10** using zinc(II) chloride as described[13] were unsuccessful, the starting material being recovered in all cases. Gratifyingly, reaction of β-(hydroxyamino)esters **9** and **10** with sodium methoxide in methanol was found to give isoxazolidin-5-ones **11** and **12**, respectively, in good yields. The diastereoselectivity of the addition was determined by ^{1}H NMR on isolated mixtures of diastereomers of compounds **11**, **12**. The *syn/anti* ratios obtained with the various alkenes employed are given in Table 1. The corresponding diastereomers **11a,b** and **12a,b**

† Data for (*E*)-**7**: $[\alpha]_D^{20}=-64.8$ (*c* 0.75, $CHCl_3$); oil. (*Z*)-**7**: $[\alpha]_D^{20}=+21.8$ (*c* 0.28, $CHCl_3$); mp 50–51°C. (*E*)-**8**: $[\alpha]_D^{20}=+13.0$ (*c* 0.68, $CHCl_3$); oil. (*Z*)-**8**: $[\alpha]_D^{20}=+0.5$ (*c* 0.84, $CHCl_3$); oil.

were separable by flash chromatography,‡ with the only exception of **12a** which was contaminated with c.a. 8% of the stereoisomer **12b**, judged by the integration of the ^{1}H NMR spectrum.



7 R^1, R^2 = CMe_2 **9a,b** R^1, R^2 = CMe_2 **11a,b** R^1, R^2 = CMe_2

8 R^1 = ^{t}BuPh$_2$Si, R^2 = H **10a,b** R^1 = ^{t}BuPh$_2$Si, R^2 = H **12a,b** R^1 = ^{t}BuPh$_2$Si, R^2 = H

a and **b** series refer to *syn* and *anti* compounds, respectively

Reagents and conditions: i, BnNHOH • HCl, Et_3N, r.t. ii, MeONa, MeOH, r.t.

Scheme 2.

The stereostructure of the adducts is strongly correlated with both the protecting group arrangement at the 1,2-aminoalcohol unit of the alkene and the configuration of the double bond. In particular, with the *Z*-ester (*Z*)-**7**, the *syn* isomer **11a** was obtained (Table 1, entries 1 and 2), whereas the *E*-ester (*E*)-**7** gave a 1:1 mixture of the *syn* and *anti* adducts (Table 1, entries 3 and 4). The diastereoselectivity of the Michael addition was reversed when the α-amino group was monoprotected, and for the open-chain compounds **8** the *anti* isomer **12b** was obtained as the major adduct. For compounds **8**, the selectivity was improved when the configuration of the double bond changed from *Z* to *E* (Table 1, entries 5–9). In general, the use of diethyl ether as a solvent resulted in a slight increase of the diastereoselectivity. Thus the choice of the

Table 1
Stereocontrolled Michael addition of benzylhydroxylamine to alkenes **7** and **8**[a]

entry	alkene	solvent	isoxazolidinone[b]	*syn*:*anti*[c]	yield (%)[d]
1	(Z)-**7**	Et_2O	**11**	**90:10**	90
2	(Z)-**7**	THF	**11**	81:19	72
3	(E)-**7**	Et_2O	**11**	53:47	78
4	(E)-**7**	THF	**11**	52:48	90
5	(Z)-**8**	Et_2O	**12**	30:70	86
6	(Z)-**8**	THF	**12**	45:55	80
7	(E)-**8**	Et_2O	**12**	**20:80**	92
8	(E)-**8**	THF	**12**	21:79	90
9	(E)-**8**	CH_2Cl_2	**12**	40:60	76

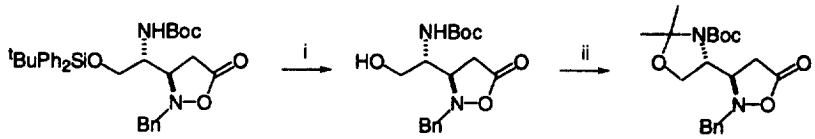
[a] All reactions were performed at ambient temperature. [b] **a** and **b** series refer to *syn* and *anti* compounds, respectively. [c] measured from the intensities of NMR signals. [d] determined on isolated mixture.

‡ Data for **11a**: $[\alpha]_D^{20}=-128.0$ (*c* 1.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 3H), 1.47 (s, 9H), 1.51 (s, 3H), 2.62 (dd, 1H, *J*=8.2, 17.9 Hz), 2.93 (dd, 1H, *J*=9.6, 17.9 Hz), 3.87–4.01 (m, 3H), 4.08–4.22 (m, 3H), 7.24–7.39 (m, 5H). **11b**: $[\alpha]_D^{20}=-13.7$ (*c* 0.63, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 1.50 (s, 3H), 1.52 (s, 3H), 2.68 (dd, 1H, *J*=8.3, 17.9 Hz), 2.78 (dd, 1H, *J*=3.8, 17.9 Hz), 3.52–3.69 (m, 1H), 3.80 (m, 1H), 3.90 (dd, 1H, *J*=5.4, 9.2 Hz), 4.00 (m, 1H), 4.17 (s, 2H), 7.29–7.41 (m, 5H). **12a**: ^{1}H NMR ($CDCl_3$) δ (selected signals) 1.05 (s, 9H), 1.39 (s, 9H), 2.58 (dd, 1H, *J*=5.3, 17.9 Hz), 2.67 (dd, 1H, *J*=8.1, 17.9 Hz), 3.65 (dt, 1H, *J*=5.3, 7.6 Hz), 3.70 (dd, 1H, *J*=4.9, 9.9 Hz), 3.83 (m, 1H), 3.93 (dd, 1H, *J*=5.1, 9.9 Hz), 4.02 (d, 1H, *J*=13.8 Hz), 4.08 (d, 1H, *J*=13.8 Hz), 4.59 (bd, 1H, *J*=9.5 Hz), 7.30 (bs, 5H), 7.35–7.49 (m, 6H), 7.60–7.72 (m, 4H). **12b**: $[\alpha]_D^{20}=+27.9$ (*c* 0.35, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H), 1.41 (s, 9H), 2.57 (dd, 1H, *J*=8.3, 17.8 Hz), 2.65 (dd, 1H, *J*=5.6, 17.8 Hz), 3.61 (dt, 1H, *J*=5.6, 8.0 Hz), 3.74 (dd, 1H, *J*=4.2, 10.0 Hz), 3.80 (m, 1H), 3.91 (dd, 1H, *J*=3.3, 10.0 Hz), 4.00 (d, 1H, *J*=13.9 Hz), 4.12 (d, 1H, *J*=13.9 Hz), 4.70 (bd, 1H, *J*=8.8 Hz), 7.29 (bs, 5H), 7.32–7.45 (m, 6H), 7.57–7.63 (m, 4H).

protecting group is crucial for the stereochemical outcome of the reaction. In fact, the sense and level of the diastereoselectivity is surprisingly similar to those exhibited by L-serine derived nitrones **5** bearing the same protecting groups at the 1,2-aminoalcohol subunit.[16,17] These results reveal the importance of having either a ring substituent, fixed firmly due to the five-membered structure of the 1,3-oxazolidine, or a bulky open chain in α-position of the reactive centre.[18]

Configuration of the isoxazolidin-5-ones **11** and **12** was assigned by chemical correlation with known structures. The absolute configuration of compounds **11** was determined by comparing the physical (optical rotation) and spectroscopic (^{1}H and ^{13}C NMR) properties of **11a** with those reported in our previous communication.[4]

In addition, the reversal of the stereochemistry was ascertained by preparing **13** (Scheme 3) from **12b** (major isomer in addition to **8**; Table 1, entries 5–9) by treatment with pyridine–hydrogen fluoride complex at 0°C. Further acetalization (DMP, acetone) of **13** gave **11b** which was shown to be identical to the minor diastereomer obtained in addition to alkenes **7** (Table 1, entries 1–4).



Reagents and conditions: i, HF, pyridine, 0°C, 1 h. ii, DMP, BF_3Et_2O, acetone, r.t., 2 h

Scheme 3.

In summary, L-serine derived alkenes **7** and **8** add *N*-benzylhydroxylamine in good chemical yield and with remarkable stereocontrol. Since they can be easily prepared from L-serine as the only chiral source, both *syn* and *anti* isoxazolidin-5-ones **11** and **12** are accessible as homochiral building blocks in a stereodivergent way. A synthetic application of these compounds, consisting of preparing isoxazolidinyl thymine polyoxin C was outlined in a previous report from our laboratory.[4] Further application of this technology to the synthesis of various α-amino acid nucleoside analogs is now in progress and will be reported in due course.

Acknowledgements

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