Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 3945–3949

TETRAHEDRON: *ASYMMETRY*

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

Pedro Merino,* Santiago Franco, Francisco L. Merchan and Tomas Tejero

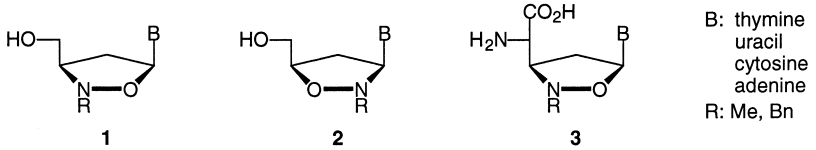
Departamento de Química Orgánica, ICMA, Facultad de Ciencias, Universidad de Zaragoza, E-50009 Aragon, Spain

Received 24 September 1998; accepted 12 October 1998

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.

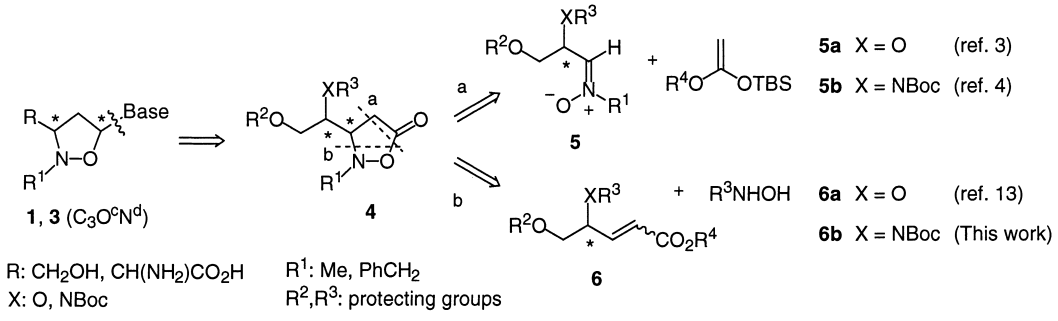


A retrosynthetic analysis for the isoxazolidinyl nucleosides **1** and **3** (type $C_3O^cN^d$ according to the notation method recently proposed by Zhao and co-workers for cyclic nucleoside analogs[1]) based on nucleoside chemistry is outlined in Scheme 1. This strategy shows that isoxazolidin-5-ones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

* Corresponding author. Fax: +34 976 761194; e-mail: pmerino@posta.unizar.es

0957-4166/98/$ - see front matter
PII: S0957-4166(98)00412-1

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).

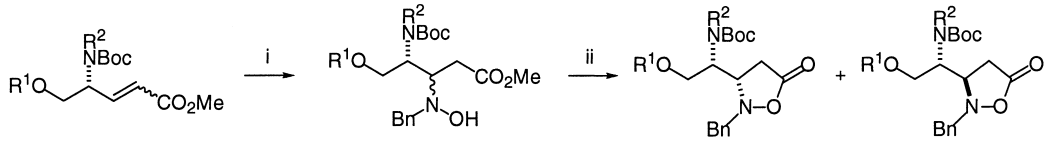
Herein we report the stereocontrolled synthesis of isoxazolidin-5-ones **4** (X=NBoc) by a Michael addition of benzylhydroxylamine (Scheme 1, disconnection **b**) to differentially protected α,β-unsaturated esters derived from L-serine.

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

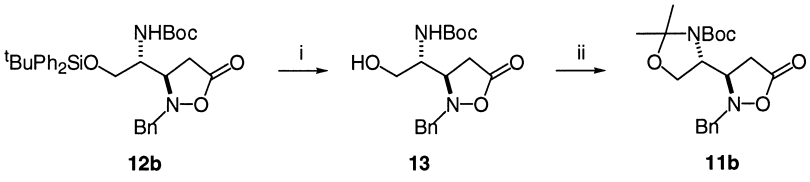
[a] All reactions were performed at ambient temperature. [b] **a** and **b** series refer to *syn* and *anti* compounds, respectively. [c] measured from the intensities of NMR signals. [d] determined on isolated mixture.

‡ 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).



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

The authors gratefully acknowledge the financial support by the Direccion General de Enseñanza Superior (Project PB97-1014, MEC, Madrid, Spain).

References

1. For a review see: Pan, S.; Amankulor, N. M.; Zhao, K. *Tetrahedron* **1998**, *54*, 6587–6604.
2. Adams, D. R.; Boyd, A. S. F.; Ferguson, R.; Grierson, D. S; Monneret, C. *Nucleosides & Nucleotides* **1998**, *17*, 1053–1075.
3. Merino, P.; Franco, S.; Garces, N.; Merchan, F. L.; Tejero, T. *Chem. Commun*. **1998**, 493–494.
4. Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron Lett*. **1998**, *39*, 6411–6414.
5. Perigaud, C.; Gosselin, G.; Inbach, J.-L. *Nucleosides & Nucleotides* **1992**, *11*, 903–945.
6. Huryn, D. M.; Okabe, M. *Chem. Rev*. **1995**, *95*, 1745–1768.
7. Matteucci, M. *Perspectives in Drug Discovery and Design* **1996**, *4*, 1–16.
8. Nair, V.; Jahnke, T. S. *Antimicr. Agent Chemother*. **1995**, *39*, 1017–1029.
9. Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229–9272.
10. Knapp, S. *Chem. Rev*. **1995**, *95*, 1859–1876.

11. Li, P.; Gi, H.-J.; Sun, L.; Zhao, K. *J. Org. Chem*. **1998**, *63*, 366–369.
12. Niu, D.; Zhao, H.; Doshi, A.; Zhao, K. *Synlett* **1998**, 979–980.
13. Xiang, Y.; Gi, H.-J.; Niu, D.; Schinazi, R. F.; Zhao, K. *J. Org. Chem*. **1997**, *62*, 7430–7434.
14. Jako, I.; Uiber, P.; Mann, A.; Taddei, M.; Wermuth, C.-G. *Tetrahedron Lett*. **1990**, *31*, 1011–1014.
15. Still, C. W.; Gennari, C. *Tetrahedron Lett*. **1983**, *24*, 4405–4408.
16. Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *J. Org. Chem*. **1998**, *63*, 5627–5630.
17. Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron Lett*. **1997**, *38*, 1813–1816.
18. For a detailed discussion on this topic concerning L-serine derived nitrones see: Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 629–646.