Modified nucleosides from nitrones: a new and efficient stereoselective approach to isoxazolidinyl thymidine derivatives

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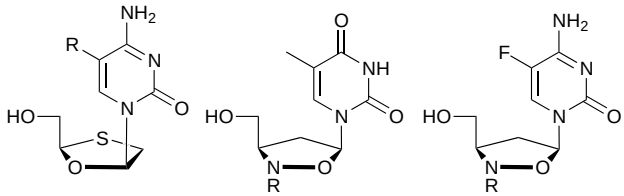
The addition of the sodium enolate of methyl acetate to the *N*-benzyl nitrone 4 derived from D-glyceraldehyde affords the 3-substituted isoxazolidin-5-one 6a with a high degree of *syn* selectivity and in quantitative chemical yield; its further elaboration leads to the preparation of the important isoxazolidine nucleoside analogue 2a in enantiomerically pure form.

Nucleoside analogues have aroused a considerable amount of attention because of their biological activity.[1,2] In particular, modified nucleosides, such as lamivudine **1a** and its 5-fluoro derivative **1b** show potent specific, competitive anti-HIV activities.[3] Also, nucleosides **2** and **3** containing an isoxazolidine moiety have been described to have promising



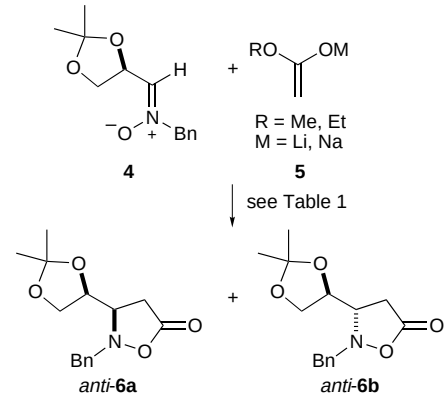
1a R = H **2a** R = Me **3a** R = Me
b R = F **b** R = Bn **b** R = Bn

therapeutic utility in the development of anti-AIDS agents.[4] As a consequence, syntheses of isoxazolidinyl nucleosides of type **2** and **3** have been recently reported.[5,6]

Recent investigations in this laboratory have revealed that chiral α-alkoxy and α-amino nitrones serve as versatile chiral building blocks in the preparation of several naturally occurring nitrogen-containing compounds.[7] Here we present a successful implementation of this strategy directed to the stereoselective synthesis of isoxazolidinyl nucleosides **2**.

The key step of our approach consists of the stepwise addition of an ester enolate to a chiral nitrone in order to construct the isoxazolidine ring. It had been described by Trombini and co-workers that both ketone silyl enol ethers and vinylketene acetals add to nitrones in the presence of trimethylsilyl triflate.[8] Kita and co-workers reported that α-alkoxy nitrones undergo nucleophilic additions with ketene silyl acetals to give the corresponding β-(siloxyamino) esters in good yields and stereoselectivity.[9] With this background in mind we felt that the ready availability of the enantiomerically pure nitrone derived from 1,2-di-*O*-isopropylidene-D-glyceraldehyde[10] and the well-precedented stereodirecting effect of the dioxolane group[7] made **4** an ideal starting material. The addition of nitrone **4** to 1.5 equiv. of the lithium enolate of methyl acetate (LDA and methyl acetate) afforded a 75:25 mixture of diastereomeric isoxazolidinones **6** in 60% isolated yield (Scheme 1).‡

The β-(hydroxyamino) ester was not observed in the crude product and only compounds **6**, coming from an intramolecular cyclization, were obtained. The stereochemistry of the obtained isoxazolidines **6** was ascertained by an X-ray crystallographic analysis of a single crystal of the major diastereomer *syn*-**6a**.§



Scheme 1

The stereochemical outcome of the reaction is in accord with Kita's results[9] and our own previous data concerning the nucleophilic additions to α-alkoxy nitrones.[11] Efforts to improve both the diastereoselectivity and the chemical yield by variation of the counterion and the solvent, plus attempts of stereocontrol of the reaction by addition of a Lewis acid, are summarised in Table 1.

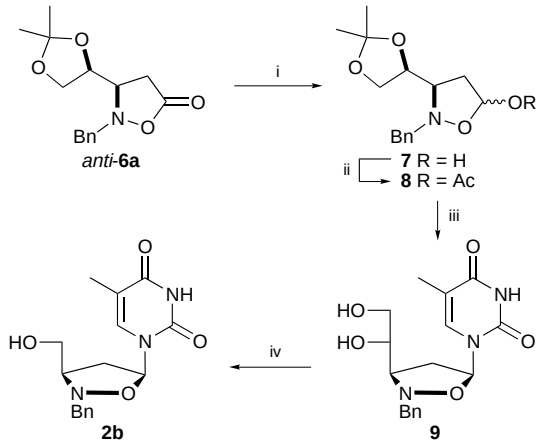
In all cases, sodium enolates afforded the *syn* adduct **6a** as the only product of the reaction (ds ⩾ 95%) in excellent chemical yield (Table 1, compare entries 1–4 with 5, 6 and 9), the solvent only having a slight influence on the chemical yield of the process. Guided by our previous results[11] on nucleophilic additions to **4** we next carried out the reaction in the presence of 1.0 equiv. of diethylaluminium chloride (Table 1, entries 7, 8 and 10). Unfortunately, the chemical yield was rather low (20–25%) in all cases, substantial amounts of starting nitrone being recovered. This behaviour suggests that the Lewis acid used as a pre-complexing agent of the nitrone eliminates the sodium enolate from the reaction mixture by forming the corresponding aluminium enolate, which is unable to react with **4**.

Thus, metal exchange should proceed rapidly at the expense of nucleophilic addition, which proceeds in only 20–25%

Table 1 Stereoselective addition of enolates to nitrone **4**

Entry	R	Base (solvent)	**6a**:**6b**	Yield[b] (%)
1	Me	LDA (THF)	75:25	60
2	Me	LDA (Et_2O)	70:30	54
3	Me	LiHMDS (THF)	86:14	68
4	Me	LiHMDS (Et_2O)	60:40	70
5	Me	NaHMDS (THF)	⩾95:5	100
6	Me	NaHMDS (Et_2O)	⩾95:5	95
7	Me	NaHMDS (THF)[a]	34:66	25
8	Me	NaHMDS (Et_2O)[a]	30:70	22
9	Et	NaHMDS (THF)	⩾95:5	93
10	Et	NaHMDS (Et_2O)[a]	32:68	20

[a] 1.0 equiv. of Et_2AlCl was used. [b] Isolated yield of the crude mixture of diastereomers.



Scheme 2 *Reagents and conditions*: i, DIBAL-H, −80 °C, CH_2Cl_2, 2 h, 80%; ii, Ac_2O, Py, 0 °C, 1 h, 82%; iii, 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine, TMSOTf, CH_2Cl_2, room temp., 2 h, 63%; iv, $NaIO_4$ (aq.), SiO_2, CH_2Cl_2, room temp., 20 min, then $NaBH_4$, MeOH, 0 °C, 90 min, 89%

yield.¶ The lower reactivity of aluminium enolates has been described in nucleophilic additions to imines.[12] A further confirmation of that hypothesis emerged from the fact that an identical result was obtained when nitrone **4** was made to react with the aluminium enolate of methyl acetate prepared *in situ* from methyl acetate and diethylaluminium chloride as described.[13] Nevertheless, despite these adverse results concerning the chemical yield, a reversal of the diastereofacial selectivity was observed (Table 1, entries 7, 8 and 10) and the *anti* isomer **6b** could be fully characterized‡ and used in further transformations.

Treatment of *syn*-**6a** with DIBAL-H in CH_2Cl_2 at −80 °C afforded lactols **7** as a 60 : 40 mixture of anomers. The first order 300 MHz ^{1}H NMR spectrum of the mixture provided unequivocal information on their structures.‖ Acetylation of **7** as described[6] afforded only unreacted starting material when stoichiometric amounts of reagents were used; on the other hand, an excess reagents led to deprotection of the acetonide moiety. If, however, compounds **7** were treated at 0 °C with Ac_2O and pyridine a 76 : 24 mixture of anomeric acetates **8** was formed in 82% combined yield, with the α anomer predominating. Coupling of **8** with 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine[14] using the glycosylation methodology developed by Vörbruggen[15] afforded the N^1-nucleoside **9** as a 22 : 78 mixture of α/β anomers‖ in which the acetonide moiety had been hydrolysed (Scheme 2). The major β isomer (depicted in Scheme 2) was easily separated by column chromatography (100% EtOAc, R_f α-isomer = 0.13, R_f β-isomer = 0.23, visualized with UV at 254 nm). Finally, oxidative cleavage ($NaIO_4$) of the diol unit followed by *in situ* reduction with $NaBH_4$ generated the desired isoxazolidine nucleoside **2b** in good overall yield as summarised in Scheme 2.

As expected from these results, nitrone **4** behaved as an excellent precursor to other related isoxazolidinyl nucleosides, and thus further studies on its reactivity are underway.

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Notes and References

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‡ All new compounds exhibited consistent spectral (^{1}H and ^{13}C NMR, IR) and analytical data. Optical rotations: 20 ± 2 °C (*c* 1, $CHCl_3$). *Selected data* for **6a**: mp 60–62 °C, $[\alpha]_D$ + 122.6. For **6b**: mp 75–77 °C, $[\alpha]_D$ −9.7. For **9**: mp 182–183 °C, $[\alpha]_D$ −12.2 (*c* 0.34, MeOH). For **2b**: sticky foam, $[\alpha]_D$ +6.1 (*c* 0.80, MeOH); δ_H ($CDCl_3$) 1.70 (br s, 1 H, OH), 1.77 (d, 3 H, *J* 1.2, CH_3), 2.29 (ddd, 1 H, *J* 3.6, 8.5, 13.7, H_{2a}), 2.99 (dt, 1 H, *J* 7.4, 13.7, H_{2b}), 3.15 (ddt, 1 H, *J* 3.6, 5.2, 8.6, H_3), 3.68 (dd, 1 H, *J* 5.0, 11.7, H_{4a}), 3.79 (dd, 1 H, *J* 3.3, 11.7, H_{4b}), 3.92 (d, 1 H, *J* 13.9, CH_2Ph), 4.32 (d, 1 H, *J* 13.9, CH_2Ph), 4.32 (d, 1 H, *J* 13.9, CH_2Ph), 5.986 (dd, 1 H, *J* 3.6, 7.4, H_1), 7.23–7.50 (m, 6 H, ArH + CH), 8.47 (br s, 1 H, NH).

§ *Crystal data* for **6a**: $C_{15}H_{19}NO_4$, monoclinic, space group $P2_1$, a = 6.011(1), b = 8.039(1), c = 15.598 (2) Å, β = 92.680 (10)°, V = 752.9(2) Å^3, Z = 2, D_c = 1.223 g cm^{-3}, μ = 0.089 mm^{-1}. Of the 1452 unique measured reflections, 1182 with $I \geqslant 2\sigma(I)$ were used in the refinement. R(on F^2) = 3.83, R_w = 9.07. The data were collected on a Siemens P4 diffractometer with graphite monochromated Mo-Kα radiation ω–2θ scan technique (2.61 ⩽ θ ⩽ 23.99). The structure was solved by direct methods using the SHELXS-86 package.[16] All other calculations were accomplished by SHELXL-93.[17] CCDC 182/729.

¶ Similar results were observed with other Lewis acids such as $ZnCl_2$, $ZnBr_2$ or $MgBr_2$. In all cases the yield dropped considerably.

‖ The anomeric configurations were confirmed by ^{1}H NMR (300 MHz) and NOE experiments.

1 D. M. Huryn and M. Okabe, *Chem. Rev.*, 1992, **92**, 1745.
2 M. Kassou and S. Castillon, *J. Org. Chem.*, 1997, **62**, 3696; R. R. Talekar and R. H. Wightman, *Tetrahedron*, 1997, **53**, 3831 and references cited therein.
3 H. Jin, M. A. Siddiqui, C. A. Evans, H. L. A. Tse, T. S. Mansour, M. D. Goodyear, P. Ravenscroft and C. D. Beels, *J. Org. Chem.*, 1995, **60**, 262 and references cited therein.
4 J. M. J. Tronchet, M. Iznaden, F. Barbalatrey, H. Dhimane, A. Ricca, J. Balzarini and E. Declercq, *Eur. J. Med. Chem.*, 1992, **27**, 555; J. M. J. Tronchet, M. Iznaden, F. Barbalatrey, I. Komaromi, N. Dolatshami and G. Berbardinelli, *Nucleosides Nucleotides*, 1995, **14**, 1737.
5 U. Chiacchio, G. Gumina, A. Rescifina, R. Romero, N. Uccella, F. Casuscelli, A. Piperno and G. Romeo, *Tetrahedron*, 1996, **52**, 8889; G. Sindona, C. Siciliano, G. Giglio, A. Napoli, A. Leggio, A. Liguori and A. Procopio, *Synth. Commun.*, 1997, **26**, 4211.
6 Y. Xiang, Y. Gong and K. Zhao, *Tetrahedron Lett.*, 1996, **37**, 4877. During the refereeing process of this manuscript a similar approach based on the diastereoselective Michael addition of hydroxylamine to unsaturated esters has been reported by the same authors. See Y. Xiang, H.-J. Gi, D. Niu, R. F. Schinazi and K. Zhao, *J. Org. Chem.*, 1997, **62**, 7430.
7 P. Merino, A. Lanaspa, F. L. Merchan and T. Tejero, *Tetrahedron Lett.*, 1997, **38**, 1813; P. Merino, A. Lanaspa, F. L. Merchan and T. Tejero, *J. Org. Chem.*, 1996, **61**, 9028; A. Dondoni, F. Junquera, F. L. Merchan, P. Merino and T. Tejero, *J. Chem. Soc., Chem. Commun.*, 1995, 2127.
8 D. D. Dhavale and C. Trombini, *J. Chem. Soc., Chem. Commun.*, 1992, 1268; C. Camiletti, D. D. Dhavale, F. Donati and C. Trombini, *Tetrahedron Lett.*, 1995, **36**, 7293.
9 Y. Kita, F. Itoh, O. Tamura, Y. Y. Ke and Y. Tamura, *Tetrahedron Lett.*, 1987, **28**, 1431; Y. Kita, O. Tamura, F. Itoh, H. Kishino, T. Miki, M. Kohno and Y. Tamura, *J. Chem. Soc., Chem. Commun.*, 1988, 761.
10 P. Merino, S. Franco, F. L. Merchan and T. Tejero, *Tetrahedron: Asymmetry*, 1997, **8**, 3489.
11 P. Merino, E. Castillo, F. L. Merchan and T. Tejero, *Tetrahedron: Asymmetry*, 1997, **8**, 1725; P. Merino, S. Anoro, E. Castillo, F. L. Merchan and T. Tejero, *Tetrahedron: Asymmetry*, 1996, **7**, 1887.
12 T. Fujisawa, Y. Koorijama and M. Shimizu, *Tetrahedron Lett.*, 1996, **37**, 3881.
13 T.-J. Sturm, A. E. Marolewski, E. S. Rezenka and S. K. Taylor, *J. Org. Chem.*, 1989, **54**, 2039.
14 T. Niahimura and T. Iwai, *Chem. Pharm. Bull.*, 1964, **12**, 352.
15 H. Vorbruggen, K. Krolikiewicz and B. Bennua, *Chem. Ber.*, 1981, **114**, 1234.
16 G. M. Sheldrick, *Acta Crystallogr.*, 1990, **A46**, 467.
17 G. M. Sheldrick, SHELXL-93, *Program for the Refinement of Crystal Structures*, University of Gottingen, Germany, 1993.

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