# Stereodivergent Approaches to the Synthesis of Isoxazolidine Analogues of α-Amino Acid Nucleosides. Total Synthesis of Isoxazolidinyl Deoxypolyoxin C and Uracil Polyoxin C†

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*Received February 26, 2000*

The synthesis of new nucleoside analogues is currently of high interest. We report here full details of a study leading to the synthesis of novel isoxazolidinyl analogues of α-amino acid nucleosides. Three different synthetic approaches starting from L-serine have been evaluated for the construction of the isoxazolidine ring. These approaches consisted of Michael addition of *N*-benzylhydroxylamine to α,β-unsaturated esters, nucleophilic addition of silyl ketene acetals to nitrones and 1,3-dipolar cycloaddition of nitrones with vinyl acetate. Both Michael addition and nucleophilic addition of enolates could be carried out with stereocontrol at the newly formed stereogenic carbon. The stereocontrol observed in these reactions arises from the protecting group arrangement in the L-serine-derived substrates. Thus, whereas compounds having a diprotected nitrogen led to syn adducts, compounds having a monoprotected nitrogen gave rise to anti adducts. On the other hand, substrates having either a diprotected or monoprotected nitrogen atom led to anti adducts through the cycloaddition route. So, by choosing the appropriate route, isoxazolidinyl analogues having either syn or anti configuration with respect to the glycine unit can be prepared in enantiomerically pure form. The stereoselective synthesis of isoxazolidinyl analogues of deoxypolyoxin C and uracil polyoxin C in both D and L enantiomeric forms using these techniques has been achieved in good yields.

## Introduction

The polyoxins are a class of pyrimidine nucleoside peptide antibiotics that were first isolated and characterized by Isono and co-workers from culture broths of *Streptomyces cacaoi* var *asoensis* over 30 years ago.[1] Interest in polyoxins and closely related compounds such as nikkomycins was prompted by their activity as potent inhibitors of chitin synthase, the enzyme which catalyzes the final step in the biosynthesis of chitin, one of the major structural components of the cell wall of most fungi.[2] Thus, polyoxins display significant activity against phytopathogenic fungi as well as *Candida albicans*, a fungal pathogen which affects immunocompromised humans. In addition polyoxins are ineffective against other microorganisms, plants, or animals.[3]

This characteristic activity profile has served as the impetus for a number of efforts directed toward the total synthesis of several members of the polyoxin and nikkomycins families. Reports from this[4] and other[5] laboratories have described total synthesis of polyoxin J, and very recently Akita and co-workers have reported an elegant convergent approach to both polyoxins J and L.[6] Several synthetic approaches to nikkomycin B have also been described.[7] All of these syntheses are based on the previous construction of the 1-(5-amino-5-deoxy-β-D-allofuranuronosyl)pyrimidine unit, the nucleoside skeleton common to most of the members of the polyoxin and nikkomycin families. For this reason, considerable synthetic effort has been directed toward the synthesis of polyoxin C, deoxypolyoxin C, and uracil polyoxin C.[8]

Due to the differences found in the biological activities of polyoxins and nikkomycins when measured against the enzyme (chitin synthase) and *Candida albicans* in culture[9] it is of high interest to prepare new analogues which could be more effective as anticandidal agents. In this regard some attention has also been paid to the synthesis of structural analogues of polyoxins and nikkomycins. Rosenthal and Cliff[10] reported the synthesis of a protected branched analogue of thymine polyoxin C (deoxypolyoxin C). Several analogues of polyoxins having alkylamino[11] and *N*-methyl[9b] groups have been prepared. Naider and

† The manuscript is dedicated to Prof. K. Isono for his contribution to the field of nucleoside antibiotics.

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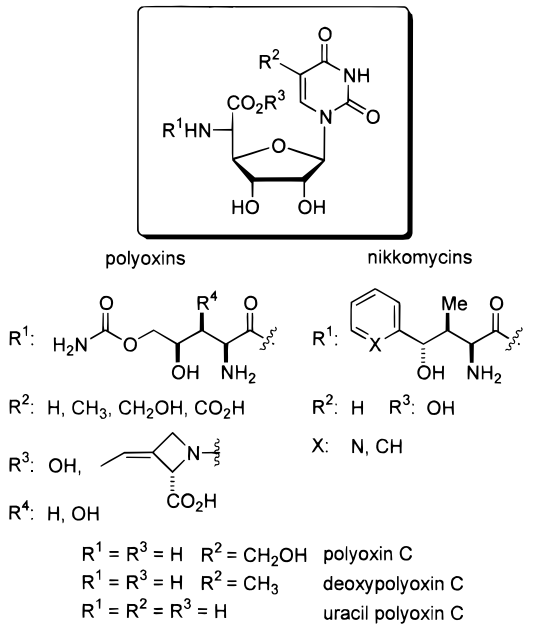
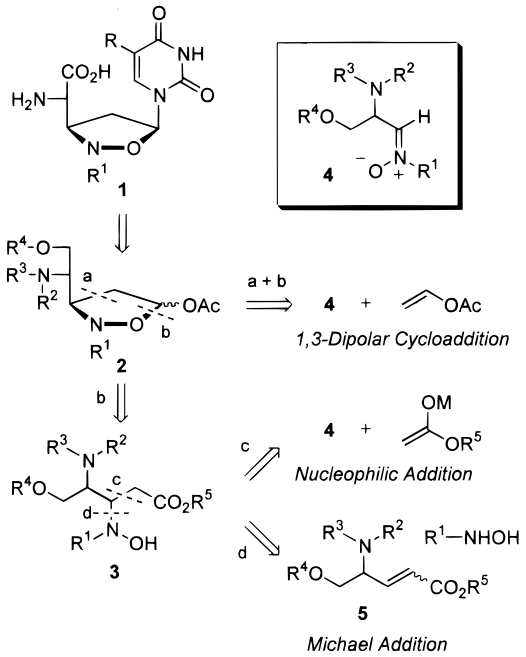
10.1021/jo0002689 CCC: $19.00 
Published on Web 08/08/2000




co-workers[9a] have synthesized and biologically evaluated peptidyl analogues of both polyoxins and nikkomycins. More recently, carbocyclic analogues of both nikkomycins[12] and polyoxins[13] have also been prepared. Baltas and Gorrichon have recently reported the synthesis of a thymidine 2-deoxypolyoxin C analogue.[14]

Despite this synthetic activity[15] there are no reports concerning structural modifications consisting of replacing the furanose ring by a different heterocyclic ring, a well-established alternative in the field of nucleoside chemistry.[16] In our laboratory is an ongoing program aimed at demonstrating the versatility of chiral nitrones and hydroxylamines as building blocks for the efficient

**Scheme 1**




construction of biologically interesting nitrogenated compounds.[17] In particular, we are interested in the synthesis of isoxazolidinyl nucleosides, a class of nucleoside analogues in which the furanose ring has been replaced by an isoxazolidine ring. These compound have attracted considerable interest in the last years.[18] Recently, we reported the synthesis of isoxazolidinyl thymidine via the nucleophilic addition of an enolate to a nitrone derived from D-glyceraldehyde.[19] Our experience in the synthesis of polyoxins[4,8d] suggested that isoxazolidinyl analogues of such compounds could be synthesized by applying our nitrone-based methodology. Our goal has been to design isoxazolidinyl analogues of deoxypolyoxin C and uracil polyoxin C.

**Retrosynthetic Analysis.** Several conceived approaches to isoxazolidine amino acid nucleosides **1** are retrosynthetically depicted in Scheme 1. Disconnection of the isoxazolidine ring and of the base moiety and appropriate functional group interconversion lead from the targeted **1** to intermediate **2**. This compound could arise from a regioselective 1,3-dipolar cycloaddition between suitable protected serine-derived nitrone **4** and vinyl acetate (disconnection a+b, *1,3-dipolar cycloaddi-*

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(16) For representative examples, see: (oxothiolanyl) (a) Caputo, R.; Guaragna, A.; Palumbo, G.; Pedatella, S. *Eur. J. Org. Chem.* **1999**, 1455−1458. (b) Perry, C. M.; Faulds, D. *Drugs* **1997**, *53*, 657−680. (dioxolanyl) (c) Lin, J.-S.; Kira, T.; Gullen, E.; Choi, Y.; Qu, F.; Chu, C. K.; Cheng, Y.-C. *J. Med. Chem.* **1999**, *42*, 2212−2217. (d) Mellor, B. J.; Murray, P. E.; Thomas, E. J. *Tetrahedron* **1998**, *54*, 243−256. (isoxazolidinyl) (e) Xiang, Y.; Gi, H.-J.; Niu, D.; Schinazi, R. F.; Zhao, K. *J. Org. Chem.* **1997**, *62*, 7430−7434. (thiofuranosyl) (f) Hong, J. J.; Gao, M.-Y.; Chu, C. K. *Tetrahedron Lett.* **1999**, *40*, 231−234. (g) Yamada, K.; Sakata, S.; Yoshimura, Y. *J. Org. Chem.* **1998**, *63*, 6891−6899. (thiazolidinyl) (h) Rassu, G.; Zanardi, F.; Cornia, M.; Casiraghi, G. *Nucleosides Nucleotides* **1996**, *15*, 1113−1120. (pyrrolidinyl (aza)) (i) Yokoyama, M.; Momotake, A. *Synthesis* **1999**, 1541−1554.

(17) For recent accounts, see: (a) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442−454. (b) Merino, P.; Tejero, T. *Molecules* **1999**, *4*, 165−175. (c) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. In *Recent Research Developments in Synthetic Organic Chemistry*; Pandalai, S. G., Ed.; Transworld Research Network: Trivandum, India, 1998; Vol. 1, pp 109−121.

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(19) Merino, P.; Franco, S.; Garces, N.; Merchan, F. L.; Tejero, T. *Chem. Commun.* **1998**, 493−494.

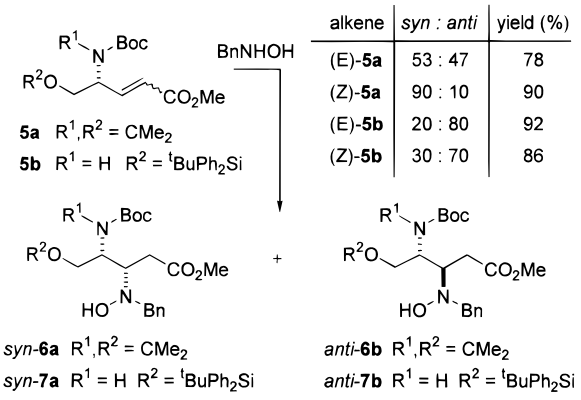
*tion approach*). The isoxazolidine ring could also be generated by cyclization (disconnection b). Thus compound **2** can be traced back to **3**. If the $\beta$-hydroxyamino ester **3** could be prepared by the nucleophilic addition of a ketene acetal to nitrone **4** (disconnection c), then there exists the possibility to control the configuration at the 3-position of the isoxazolidine ring (*nucleophilic addition approach*).[20] Alternatively, **2** could be obtained from a Michael addition of a hydroxylamine to alkene **5** (disconnection d), easily accessible from serine in both *E* and *Z* forms (*Michael addition approach*). This Michael addition approach has been successfully applied by other authors to the synthesis of 3-substituted isoxazolidin-5-ones[21] and in one case extended to the preparation of isoxazolidinyl nucleosides.[22]

The synthetic approaches we devised takes advantage of the Garner's methodology for the synthesis of complex α-amino acids, which is based on the use of the isoxazolidine ring as a synthetic equivalent of the glycine unit.[8g,23] in this approach we envisaged that serine-derived nitrones **4** would be very convenient starting materials for the construction of the isoxazolidine ring of the target molecules.[24]

## Results and Discussion

**Construction of the Isoxazolidine Ring. I. First Approach. Michael Addition of *N*-Benzylhydroxylamine.** Alkenes **5a** and **5b** were synthesized in both *Z* and *E* forms from the corresponding α-amino aldehydes following the general guidelines from Mann and coworkers[25] (Still's reagent[26] for (*Z*)-alkenes and Horner−Wadsworth−Emmons reaction under protic conditions for (*E*)-alkenes). The Michael addition was carried out with *N*-benzylhydroxylamine generated in situ from the hydrochloride and triethylamine.[27] Preliminary work[28] showed that good levels of selectivity are reached, with an opposite stereochemical sense, in additions to α-amino-diprotected alkenes **5a** and α-amino-monoprotected alkenes **5b** at ambient temperature using anhydrous $Et_2O$ as a solvent (Scheme 2).[29] In the Michael addition of *N*-benzylhydroxylamine to L-serine-derived alkenes there is thus a substantial degree of substrate control of asymmetric induction. It is notable that whereas the (*Z*)-isomer of **5a** displayed better selectivity than the corresponding (*E*)-isomer, the opposite effect was observed with **5b** for which better selectivity was achieved with the (*E*)-isomer. Both sense[30] (syn) and degree of the selectivity observed for (*E*)- and (*Z*)-isomers of **5a** are in good agreement with other Michael additions reported in the literature.[26] A model to account for the considerable difference in syn selectivity of (*Z*)-**5a** compared to (*E*)-**5a** has been proposed.[31]

**Scheme 2**




| alkene | *syn* : *anti* | yield (%) |
|---|---|---|
| (E)-**5a** | 53 : 47 | 78 |
| (Z)-**5a** | 90 : 10 | 90 |
| (E)-**5b** | 20 : 80 | 92 |
| (Z)-**5b** | 30 : 70 | 86 |

On the other hand, the anti selectivity observed with **5b** is more in agreement with the selectivity observed for Michael additions to $\gamma$-alkoxy-α,$\beta$-unsaturated esters.[32] Nevertheless, the obvious differences between an alkoxy and a (*tert*-butoxycarbonylamino) group require that the mechanism of the addition must await further studies. In contrast to previous reports[21,25] $\beta$-(hydroxyamino) esters **6** and **7** were obtained preferentially and only small amounts (5−10%) of the corresponding isoxazolidin-5-ones were detected in the reaction mixture.[33] Because chromatographic separations of diastereomeric mixtures of **6** and **7** were rather tedious, cyclization was carried out directly with the crude reaction mixtures, thus obtaining the corresponding isoxazolidin-5-ones. For analytical purposes pure samples of major adducts **6a** and **7b** could be separated by preparative, centrifugally accelerated, radial, thin-layer chromatography (PCAR-TLC).[34]

(20) We have amply demonstrated that nucleophilic additions to nitrones derived from serine can be stereocontrolled by the appropriate choice of the protecting groups in the nitrone. See: (a) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1998**, *63*, 5627−5630. (b) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 629−646. (c) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron Lett.* **1997**, *38*, 1813−1816.

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(26) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.

(27) For previous studies on Michael additions of alkyl hydroxylamines to α,$\beta$-unsaturated carbonyl compounds, see: (a) Ishikawa, T.; Nagai, K.; Kudoh, T.; Saito, S. *Synlett.* **1998**, 1291−1293. (b) Baldwin, S. W.; Aube, J. *Tetrahedron Lett.* **1987**, *28*, 179−182. (c) Langlois, N.; Calvez, O.; Radom, M.-O. *Tetrahedron Lett.* **1997**, *38*, 8037−8040. (d) Lubineau, A.; Auge, J. *Tetrahedron Lett.* **1992**, *33*, 8073−8074. (e) Chan, P. W. H.; Cottrell, I. F.; Moloney, M. G. *Tetrahedron Lett.* **1997**, *38*, 5891−5894. (f) Cardillo, G.; Casolari, S.; Gentilucci, L.; Tomasini, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1848−1941. See also ref 22 and references therein.

(28) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3945−3949.

(29) Although it has been reported that Michael additions of *N*-benzylhydroxylamine are favored by the presence of water (see ref 25d), we have not observed such an effect.

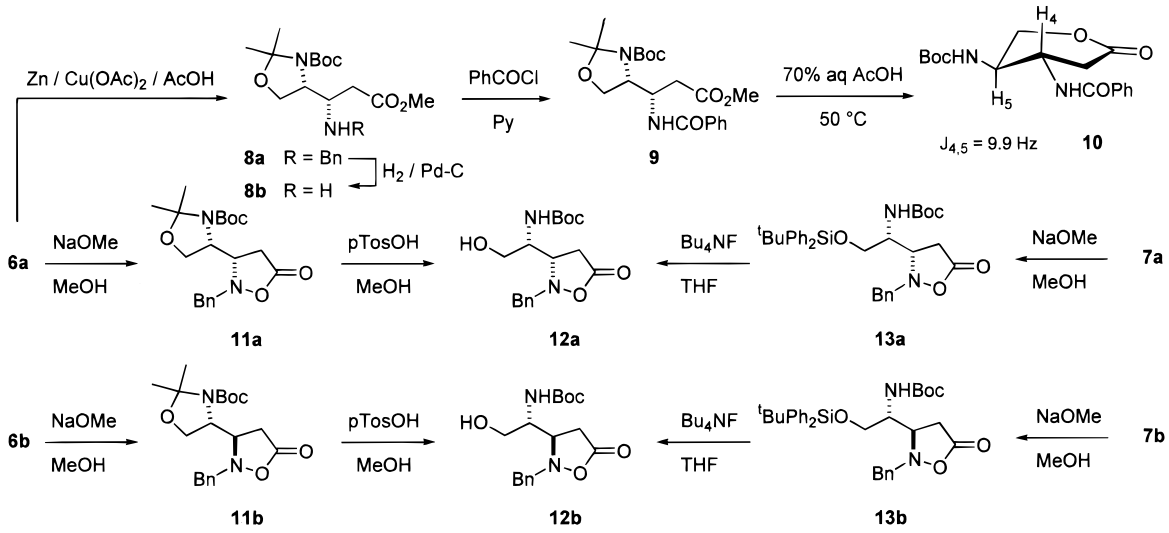
(30) In this work we use the syn/anti nomenclature according to Masamune convention. See: Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557−558. Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521−5523.

(31) Raghavan, S.; Ishida, M.; Shinozaki, H.; Nakanishi, K.; Ohfune, Y. *Tetrahedron Lett.* **1993**, *34*, 5765−5768.

(32) For a discussion on the selectivity of Micahel addition to $\gamma$-alkoxy and $\gamma$-amino-α,$\beta$-unsaturated esters, see: Hanessian, S.; Sumi, K. *Synthesis* **1991**, 1083−1089.

(33) From a preparative standpoint the obtention of mixtures of open-chain and cyclized products was inconsequential since treatment of the reaction mixture with NaOMe in MeOH afforded the desired isoxazolidin-5-ones which are easily purified by flash chromatography (see Scheme 3).

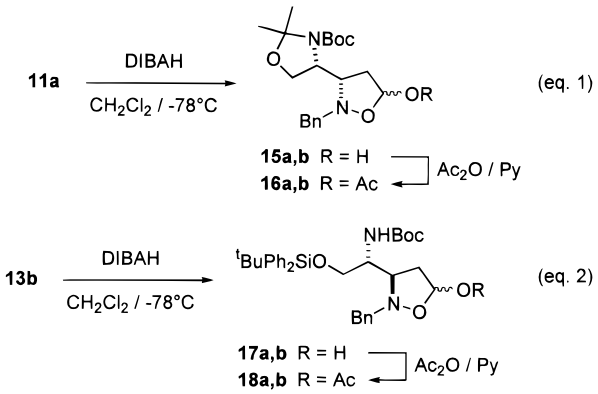
**Scheme 3**




To establish the relative configuration in **6a**, this $\beta$-(hydroxyamino) ester was transformed into the corresponding cyclic six-membered lactone **10** by a reaction sequence involving the reduction in two steps of the benzylhydroxyamino moiety, benzoylation of the resulting primary amine **8b** and lactonization (Scheme 3). The configuration of **10** was established by NMR spectroscopy (see Supporting Information). The configuration of the newly created stereogenic centers in **7a** and **7b** was not determined; however, the four $\beta$-(hydroxyamino) esters **6** and **7** were immediately cyclized with NaOMe in MeOH to give the corresponding isoxazolidin-5-one **11**−**13** (Scheme 3). Deprotection (p-TosOH, MeOH) of **11a**, obtained from major adduct **6a**, afforded **12a**, which was also prepared from **13a**, the isoxazolidin-5-one obtained from minor adduct **7a**. Similarly, desilylation ($Bu_4NF$, THF) of **13b**, obtained from the major adduct **7b** gave **12b** which was alternatively prepared from **11b**. Since the absolute configuration of **6a** had been secured as described above, the transformations illustrated in Scheme 3 not only proved the stereodivergency of the Michael addition to alkenes **5** but also the configuration of hydroxylamines **7a** and **7b**.

Compounds **11a** and **13b** were subjected directly to reduction with DIBAH in $CH_2Cl_2$ at −78 °C (eqs 1 and 2). The resulting 5-hydroxy isoxazolidines were isolated and characterized as the corresponding acetyl derivatives **16** and **18**. These compounds were obtained as *anomeric* mixtures from which single stereoisomers could be separated by PCAR-TLC[34] in the case of compounds **18**. The cis/trans stereochemistry of **18a** and **18b** were determined by NOE experiments. Unfortunately, compounds **16** were unseparable and we could not determine the configuration of each diastereomer spectrally, and the mixture was therefore used for the next step.[35]

**II. Second Approach. Nucleophilic Addition of Enolates.** Pursuing a different strategy to the formation




of $\beta$-(hydroxyamino) esters, consideration was given to the nucleophilic addition of enolates to nitrones, a strategy which had been successfully applied in our laboratory to the stereoselective synthesis of isoxazolidinyl thymidine.[19] On the basis of our previous experience with L-serine-derived nitrones,[20] we chose nitrones **4a** and **4b** as suitable starting compounds.[36]

Subjection of nitrones **4a** and **4b** to several metal enolates of methyl acetate under a range of conditions (bases NaHMDS, LHMDS, KHMDS, LDA, BuLi; solvents THF, $Et_2O$, THF/HMPA at <50 °C) led only to reisolation of starting material. It thus appeared that the nitrone group was simply too sterically hindered to react with alkaline metal enolates of methyl acetate. Reaction at higher temperatures led only to complex mixtures from which no products could be isolated. Attempts of activating the nitrone group by the action of Lewis acids ($Et_2AlCl$, $ZnBr_2$, $MgBr_2$) also led to recovery of starting material, perhaps due to the formation of less reactive enolates after transmetalation with the Lewis acids.[37]

Kita and co-workers[38] have introduced silyl ketene acetals for the stereoselective enolate additions of α-alkoxy nitrones. More recently, Greene and co-workers[39] have

(34) (a) Desai, H. K.; Joshi, B. S.; Panu, A. M.; Pelletier, S. W. *J. Chromatogr.* **1985**, *322*, 223−227. (b) Hostettmann, K.; Hostettmann-Kaldas, M.; Sticher, O. *J. Chromatogr.* **1980**, *202*, 154−156. (c) Ferrari, M.; Verotta, L. *J. Chromatogr.* **1988**, *437*, 328−332. (d) Heimbel, A.; Bosold, F. *Angew. Chem.* **1990**, *102*, A298−A299.

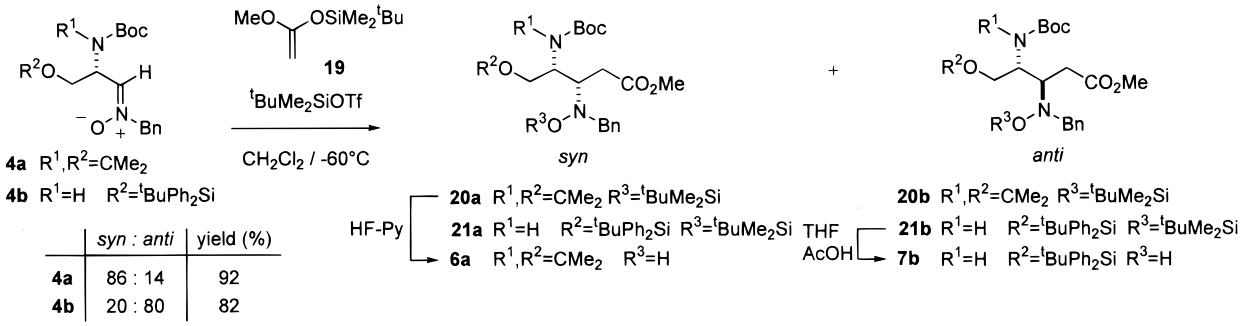
(35) Purification of cis and trans isomers of **16** and **18** have only analytical purposes. From a synthetic standpoint such a separation is not necessary since those compounds will be used for introducing the base through *N*-glycosylation.

(36) Nitrones **4a** ($R^1$ = Bn; $R^2$ = Boc; $R^3$, $R^4$ = $CMe_2$) and **4b** ($R^1$ = Bn; $R^2$ = Boc; $R^3$ = H.; $R^4$ = $^t$BuPh$_2$Si) can be easily prepared (6 steps) from serine in 57.7 and 51.2% overall yields, respectively. See ref 20b.

(37) This fact had been observed in the reaction of α-alkoxy nitrones with sodium enolates in the presence of $Et_2AlCl$. See ref 19.

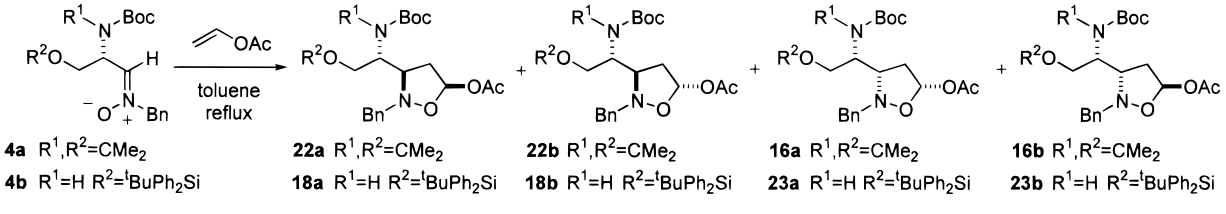
(38) (a) Kita, Y.; Itoh, F.; Tamura, O.; Ke, Y. Y.; Tamura, Y. *Tetrahedron Lett.* **1987**, *28*, 1431−1434. (b) Kita, Y.; Tamura, O.; Itoh, F.; Kishino, H.; Miki, T.; Kohno, M.; Tamura, Y. *Chem. Commun.* **1988**, 761−763.

**Scheme 4**




| | *syn* : *anti* | yield (%) |
|---|---|---|
| **4a** | 86 : 14 | 92 |
| **4b** | 20 : 80 | 82 |

**Scheme 5**




| | **22a** : **22b** : **16a** : **16b** | yield (%) |
|---|---|---|
| **4a** | 50 20 21 9 | 93 |

| | **18a** : **18b** : **23a** : **23b** | yield (%) |
|---|---|---|
| **4b** | 70 17 13 0 | 89 |

used a similar reaction for a stereocontrolled synthesis of phenylisoserines and Murahashi and co-workers[40] for the stereoselective synthesis of $\beta$-amino acids. When nitrone **4a** was treated with *O*-(*tert*-butyldimethylsilyl)-*O*-methyl ketene acetal **19** under modified Kita's conditions (TBSOTf (1.0 equiv), $CH_2Cl_2$, −60 °C for 2 h) an excellent yield (92%) of $\beta$-(siloxyamino) esters **20** was obtained (Scheme 4). A good syn diastereoselectivity was observed for the reaction (syn:anti = 86:14), consistent with other nucleophilic additions to nitrone **4a**.[20,41] Encouraged by the success of the silyl ketene acetal nucleophilic addition to **4a**, we decided to investigate whether substrate control might also be used in that reaction. Gratifyingly, the addition to nitrone **4b** provided anti-**21b** (Scheme 4) in good yield (82%) and selectivity (syn:anti = 20:80) thus proving again the tunable selectivity of differentially protected L-serine-derived nitrones.

The configuration of major adducts **20a** and **21b** was readily assigned by their conversion to the previously prepared $\beta$-(hydroxyamino) esters **6a** and **7b**, respectively. Desilylation of **20a** was achieved in virtually quantitative yield by using hydrogen fluoride−pyridine (HF−Py) complex at 0 °C for 1 h and **6a** was obtained. Chemoselective deprotection of the *tert*-butyldimethylsiloxy group proved to be problematic. Treatment with stoichiometric amounts of $Bu_4NF$ in THF led to mixtures of compounds, and HF−Py afforded a completely desilylated compound in a very low yield. Finally, selective desilylation was achieved by using a 1:3:1 mixture of THF:AcOH:$H_2O$ as described.[42] However, at best, only modest yields could be achieved, and other methods of selectively cleaving the TBS protecting group fared no better. Thus, although a straightforward preparation of **6a** (precursor of key intermediates **16**) can also be achieved, access to epimeric **7b**, and so **18**, is rather limited by this approach.

**III. Third Approach. 1,3-Dipolar Cycloaddition.** Although the Michael and nucleophilic additions described in the preceding paragraphs permitted an access to both syn and anti isomers in a stereodivergent fashion, the purpose of improving the preparation of key intermediates **16** and **18** led us to consider the 1,3-dipolar cycloaddition approach. Examination of the literature[43] suggested that cycloaddition of nitrones **4** with vinyl acetate could form the isoxazolidine ring directly with the necessary acetyl group in the 5-position for further introducing the base moiety. Reaction of the nitrone **4a** with vinyl acetate was carried out in refluxing toluene and gave rise to 5-acetoxy isoxazolidines **16a,b** and **22a,b** (Scheme 6). $^1$H NMR analysis of the crude mixture allowed the determination of the amount of four stereoisomers present in the original reaction mixture. The crude residue was purified by PCAR-TLC[34] and cycloadducts **22a** and **22b** could be obtained in pure form. Additionally, an unseparable 70:30 mixture of **16a** and **16b** was also obtained.

Similarly, cycloaddition of **4b** with vinyl acetate afforded a mixture of three cycloadducts (Scheme 5). In this case each cycloadduct could be obtained in pure form from the crude residue. For synthetic purposes it is possible to use the mixture of cis/trans isomers **18** and **22** for the next *N*-glycosylation step.

(39) Jost, S.; Gimbert, Y.; Greene, A. E. *J. Org. Chem.* **1997**, *62*, 6672−6677.

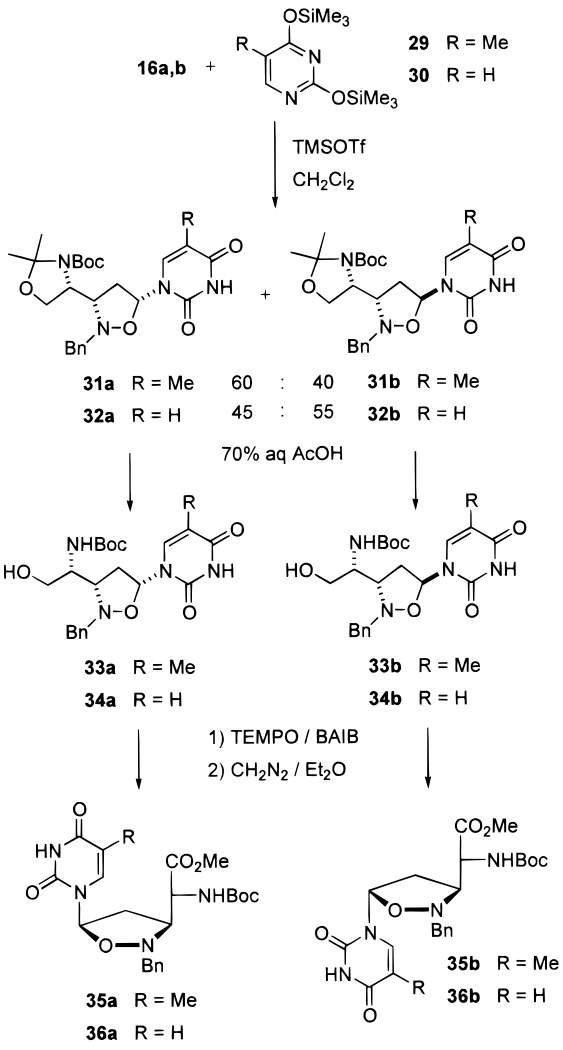
(40) Ohtake, H.; Imada, Y.; Murahashi, S.-I. *J. Org. Chem.* **1999**, *64*, 3790−3791.

(41) (a) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1996**, *61*, 9028−9032. (b) Shade, W.; Reissig, H.-U. *Synlett* **1999**, 632−634. (c) Denis, J.-N.; Tchertchian, S.; Tomassini, A.; Vallee, Y. *Tetrahedron Lett.* **1997**, *38*, 5503−5506.

(42) Kocienski, P. *Protecting Groups*; Georg Thieme Verlag: New York, 1994; p 33.

(43) For 1,3-dipolar cycloadditions of nitrones with vinyl acetate, see: (a) DeShong, P.; Dicken, M.; Staib, R. R., Freyer, A. J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *47*, 4397−4403. (b) DeShong, P.; Dicken, C. M.; Leginus, J. M.; Whittle, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 5598−5602. (c) Chiacchio, U.; Gumina, G.; Rescifina, A.; Romeo, R.; Uccella, N.; Casuscelli, F.; Piperno, A.; Romeo, G. *Tetrahedron* **1996**, *52*, 8889−8898. (d) Chiacchio, U.; Corsaro, A.; Gumina, G.; Rescifina, A.; Iannazzo, D.; Piperno, A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **1999**, *64*, 9322−9327.

**Scheme 6**

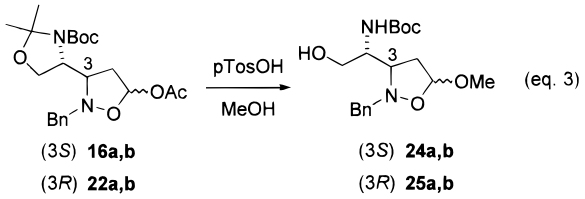



The diastereofacial selectivity with respect to the α-chirality of nitrones **4** was anti in both cases (syn/anti = 30:70 for **4a**; syn/anti = 13:87 for **4b**), and the preference for the cis isomers coming from an exo attack is in agreement with precedents found in the literature.[43] The syn/anti assignment of the new compounds **22** and **23** were indirectly determined by comparison of the corresponding diastereomers **16** and **18** with the same compounds previously obtained via the Michael addition approach (see above). The cis/trans relative configuration was determined by NOE experiments on pure compounds. Further confirmation of structures for compounds **22** follow from their conversion into common derivatives also obtained from compounds **18** (see below).

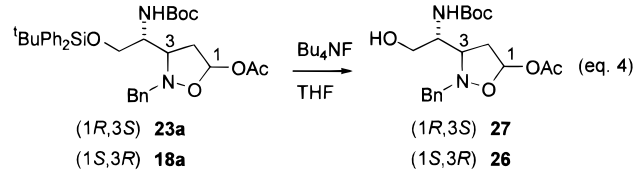
In contrast to Michael and nucleophilic addition approaches, the 1,3-dipolar cycloaddition approach did not allow stereocontrol to obtain both syn and anti adducts. Therefore, this approach relied less upon an alternative synthetic approach to syn and anti 5-acetoxy isoxazolidines and more upon the accessibility of the compounds **22** having an anti configuration. The crucial role of these compounds in which the α-amino group is diprotected is discussed in the following paragraphs.

**IV. Synthesis of Isoxazolidinyl α-Amino Acids and Nucleosides.** Having constructed the isoxazolidine ring in a stereodivergent fashion and with the adequate functionality at C-5 for further elaborations, the remaining transformations necessary were unmasking of the carboxylic acid functionality (deprotection and primary hydroxyl group oxidation) and introduction of the base moiety.

Unfortunately, we could not find practical reaction conditions for chemoselective hydrolysis of the isopropylidene group in **16** and **22** without affecting the acetyl group, and after trying various acetonide-deprotection conditions[44] including AcOH (aq), HCl (aq), and Dowex 50W−H, we found that when compounds **16** and **22** were treated with catalytic pTosOH in MeOH, mixtures of methyl derivatives **24** and **25** were obtained respectively[45] (eq 3). The major problem was the instability of the C-5




acetoxy group to the acidic conditions necessary for the cleavage of the isopropylidene group. This was in marked contrast to the stability to acidic conditions of the anomeric acetoxy group of ribosyl α-amino acids.[4a] On the other hand, desilylation of **18a** and **23** with $Bu_4NF$ in THF gave the *O*-acetyl derivatives **26** and **27**, respectively in good yields (eq 4). Alternatively, the treatment



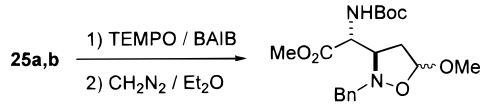

of **18a** with 10% HCl in MeOH afforded the same mixture of compounds **25** that had been obtained from **22**. This experiment further confirmed the previously assigned anti configuration to compounds **22**.

Our initial plan was to carry out the oxidation of the primary hydroxyl group in compounds **26** and **27** to create common precursors to the targeted compounds. However, the oxidation step proved to be more challenging than anticipated. Under the various conditions examined (PDC−DMF,[46] $NaClO_2$−$H_2O_2$,[47] $Ca(OCl)_2$−AcOH−MeOH,[48] $RuCl_3$−KOH,[49] TEMPO−$^t$BuOCl−NaOH,[50] TEMPO−BAIB,[51] Swern oxidation[52] and then oxidation of the resulting aldehyde[53]) the hydrolysis of the acetyl

(44) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed; John Wiley & Sons, New York, 1999; pp 207−215.
(45) Identical results were obtained when other acids (PPTS, CSA) were used.
(46) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399−402.
(47) (a) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567−569. (b) Ho, T.-L.; Hall, T. W. *Synth. Commun.* **1975**, *5*, 309−313.
(48) (a) McDonald, C. E.; Nice, L. E.; Shaw, A. W.; Nestor, N. B. *Tetrahedron Lett.* **1993**, *34*, 2741−2744. (b) Kabalka, G. W.; Chatla, N.; Wadgaonkar, P. P.; Deshpande, S. M. *Synth. Commun.* **1990**, *20*, 1617−1623.
(49) (a) Varma, R. S.; Hogan, M. E. *Tetrahedron Lett.* **1992**, *33*, 7719−7720. (b) Singh, A. K.; Varma, R. S. *Tetrahedron Lett.* **1992**, *33*, 2307−2310.
(50) Melvin, F.; McNeill, A.; Henderson, P. J. F.; Herbert, R. B. *Tetrahedron Lett.* **1999**, *40*, 1201−1202.
(51) Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293−295.
(52) Tidwell, T. T. In *Handbook of Reagents for Organic Synthesis. Oxidizing and Reducing Agents*; Burke, S. D., Danheiser, R. L., Eds.; John Wiley & Sons: Chichester, 1999; pp 154−157 and references therein.

group predominated affording complex mixtures and the desired isoxazolidinyl α-amino acids could not be obtained.

Alternatively, with 1,2-amino alcohols **24** and **25** in hand, albeit in a yield reduced by unwanted acetyl hydrolysis, the *critical* oxidation and glycosylation steps could be attempted. Oxidation of the 60:40 anomeric mixture of **25a** and **25b** with TEMPO−BAIB[51] afforded, after esterification with diazomethane, a 60:40 mixture of isoxazolidinyl α-amino acids **28a** and **28b** in 71% yield (eq 5). The conditions chosen for glycosylation were those




(eq. 5)

**28a,b**

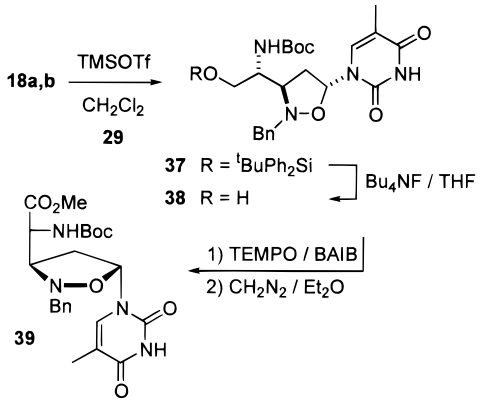
developed by Zhao and co-workers[22] ($CH_2Cl_2$-TMSOTf-silylated base) which had been used with notable success in our earlier synthesis of isoxazolidinyl thymidine.[19] However, under those conditions the starting compounds **28** were recovered almost quantitatively. Under other glycosylation reactions carried out with a variety of Lewis acids, such as $SnCl_4$, $BF_3Et_2O$, $SnCl_4$ or $TiCl_4$, complex mixtures from which no products could be identified, were obtained. From these disappointing results, we concluded that it was essential to introduce the base moiety prior to the oxidation of the primary hydroxyl group.

Subjection of **16** to silylated thymine and uracil[54] under the Vorbrüggen conditions[55] (TMSOTf, $CH_3CN$) afforded nucleosides **31** and **32** in 82 and 80% yields, respectively (Scheme 6). Glycosylation with the thymine derivative **29** gave a 60:40 mixture of **31a** and **31b**; similarly, glycosylation to give the uracil nucleoside afforded a 45:55 mixture of the corresponding isomers **32a** and **32b**. The anomeric mixtures were separated by column chromatography and the cis/trans configurations of nucleosides **31a**, **31b**, **32a**, and **32b** were confirmed by NOE experiments.

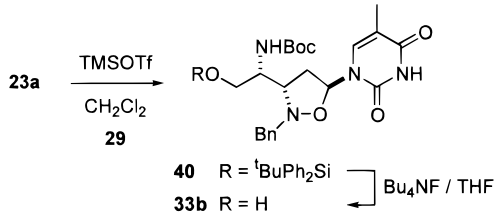
The obtained pure isoxazolidinyl nucleosides **31a,b** and **32a,b** were treated with 70% aqueous AcOH to give deprotected compounds **33**−**34**. Oxidation of the primary hydroxyl group to carboxylic acid was achieved by using TEMPO in the presence of BAIB[51] in a 1:1 $CH_3CN-H_2O$ mixture as a solvent. The crude carboxylic acids were isolated and characterized as the corresponding methyl esters.[56] This completed the synthesis of targeted isoxazolidinyl nucleoside α-amino acids. Compounds **35a** (31.8% overall yield for 4 steps starting from **16**) and **36a** (20.9% overall yield for 4 steps starting from **16**) could be considered structural analogues of deoxypolyoxin C and uracil polyoxin C, respectively.[57]

Next, our synthetic efforts were focused on the elaboration of anti compounds **18**. Unexpectedly, *N*-glycosylation of the mixture **18** as indicated above (silylated thymine, TMSOTf) afforded trans nucleoside **37** as the only detectable stereoisomer (Scheme 7). As anticipated, the same result was obtained by reacting either the cis or the trans isomer of **18**. Also, several model studies employing a wide range of reaction conditions including various Lewis acids, invariably produced a preponderance of the trans isomer. Compound **37** was deprotected ($Bu_4NF$, THF), and the resulting primary alcohol **38** was oxidized with TEMPO−BAIB[51] to afford, after esterification with diazomethane, the α-amino acid nucleoside **39** in 76% yield.

**Scheme 7**




Examined next was the glycosidation of minor syn adduct **23a** (eq 6). Reaction of **23a** with silylated thymine afforded the trans isomer **40** exclusively. This result was




(eq. 6)

in accord with that of Scheme 7 and indicated that it is no dependent on the relative stereochemistry with the α-amino group but that the α-(*tert*-butoxycarbonylamino) group plays a major role in dictating the selectivity of the glycosylation reaction. Confirmation of the trans stereochemistry of compounds **37** and **40** was achieved

(53) For NaOCl−TEMPO, see: (a) Davis, N. J.; Flitsch, S. L. *Tetrahedron Lett.* **1993**, *34*, 1181−1184. (b) Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970−2972. (c) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, O. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564−2566. For $KMnO_4$−$^t$BuOH−$NaH_2PO_4$, see: (d) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537−4540. For $^t$BuOCl−MeOH−$Na_2CO_3$, see: (e) Milovanovic, J. N.; Vasojevic, M.; Gojkovic, S. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1231−1233.

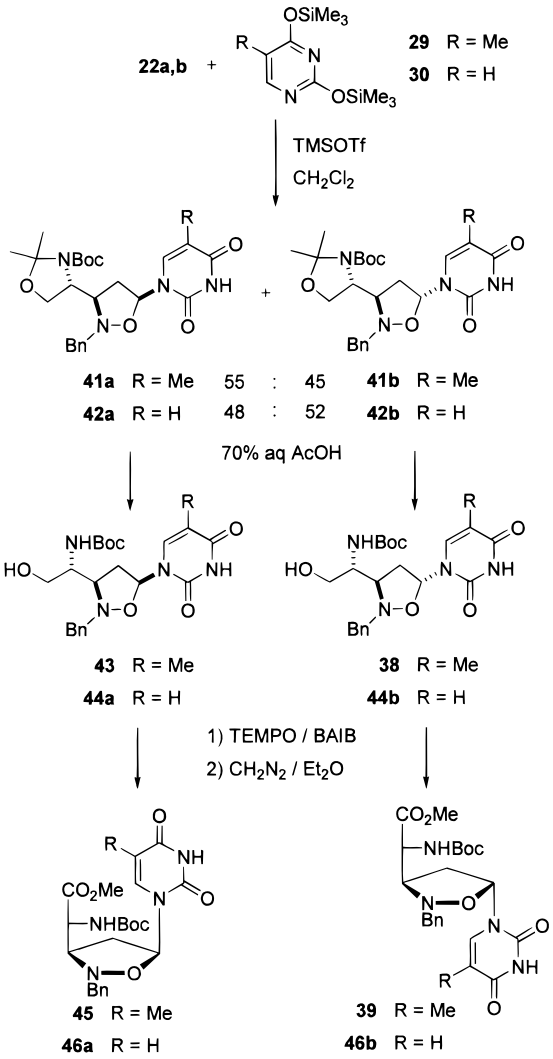
(54) Nishimura, T.; Iwai, I. *Chem. Pharm. Bull.* **1961**, *12*, 352−356.

(55) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234−1255.

(56) In our preliminary communication[24] we described the oxidation of **33a** in a 2-step protocol (Swern oxidation and then $NaClO_2$), to an isoxazolidine analogue of thymine polyoxin C that was originally thought to have L-configuration at the amino acid unit. However, we realize that something was wrong in our preliminary work when a different compound (authentic **35a**) was obtained in the oxidation of **33a** with TEMPO−BAIB. After preparing all of the possible stereoisomers of one enantiomeric series (compounds **35a**, **35b**, **39**, and **45**), we discovered that the compound we had previosuly assigned as being **35a** was in fact its epimer *ent*-**45**. The configuration of **33a** is well-established since this compound was prepared from adducts **16a,b** obtained by the three synthetic approaches described in this paper. In all cases, compound **33a** showed the same physical and spectroscopic properties, including an optical rotation value of $[\alpha]_D^{20}$ −11.7 (*c* 0.89, $CHCl_3$). Evidently, the transformation of **33a** into the α-amino ester occurs with epimerization, thus implying that the 2-step oxidation protocol, consisting of Swern reaction and then treatment with $NaClO_2$, employed for the oxidation of amino alcohols is unreliable.

(57) The overall yields, starting from commercial L-serine, for compound **35a** were 11.0% via Michael addition route and 9.5% via nucleophilic addition route. For compound **36a** the overall yields, also starting from commercial L-serine, were 7.2% via Michael addition route and 6.2% via nucleophilic addition route.

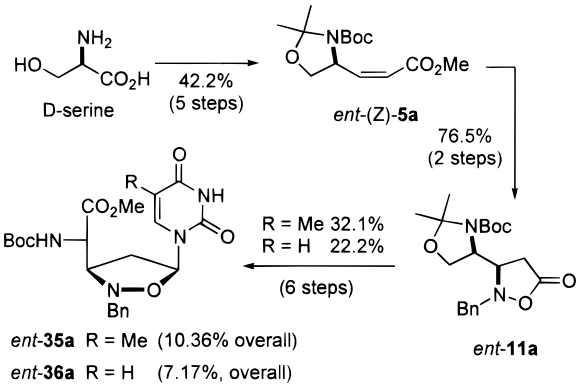
**Scheme 8**




by NOE experiments. In addition, nucleoside **40** was transformed into **33b**, which had been prepared from **31b**.

From the above results, we finally arrived at the conclusion that diprotection at the α-nitrogen atom was crucial for preparing cis isoxazolidinyl nucleosides. To produce the corresponding diastereoisomers having a cis configuration at the isoxazolidine ring and an anti configuration with respect to the α-nitrogen, we required compounds **22** obtained via the 1,3-dipolar cycloaddition approach. Thus, *N*-glycosylation of compounds **22** (either in pure form or as a mixture) with silylated thymine gave a 55:45 ratio of nucleosides cis-**41a** and trans-**41b** (estimated by integration of H−C-1 in the $^1$H NMR spectrum) in a yield of 82% (Scheme 8). This mixture was easily separated by column chromatography. Removal of the isopropylidene group of **41a** and **41b** by treatment with 70% aq AcOH proceeded in 90−92% yield to give amino alcohol nucleosides **43** and **38**. Further conversion to the corresponding α-amino acid nucleosides **45** and **39** was achieved by oxidation with TEMPO−BAIB.[51] Compounds **45** and **39** were thus obtained in 82 and 80% yields, respectively. Following an identical protocol uracil derivatives **46a** and **46b** were also synthesized. The overall yields (4 steps) for the thymine derivatives **45** and **39** were 33.9 and 26.6%, respectively starting from **22a**. For uracil derivatives **46a** and **46b** the corresponding overall yields (4 steps from **22a**) were 29.3 and 26.7%, respectively.[58]

**Scheme 9**




After carrying out the study described above, we executed all of the necessary steps in the enantiomeric D-series beginning with commercially available D-serine in order to prepare both isoxazolidinyl deoxypolyoxin C and isoxazolidinyl uracil polyoxin C. For this purpose, isoxazolidin-5-one *ent*-**11a** ($[\alpha]_D$ +122.5 (*c* 0.92, $CHCl_3$)) was prepared in 76.5% yield via the Michael addition approach (Scheme 9). By the methodology previously described compound *ent*-**11a** was converted into the target compounds. Thus, *ent*-**35a** ($[\alpha]_D$ +7.1 (*c* 0.60, $CHCl_3$)) and *ent*-**36a** ($[\alpha]_D$ +5.7 (*c* 1.11, $CHCl_3$)) were synthesized in 13 steps from D-serine in overall yields of 10.36 and 7.17%, respectively.

## Conclusions

We have reported the first stereoselective synthesis of isoxazolidinyl nucleosides **35** and **36** which are analogues of deoxypolyoxin C and uracil polyoxin C. The earlier part of the research featured the efficient construction of the isoxazolidine ring by employing the three synthetic approaches studied. The Michael addition approach proved highly successful in providing the key isoxazolidin-5-ones with stereocontrol. Similarly, the nucleophilic addition of silyl ketene acetals also took place with stereocontrol as a function of the protecting group arrangement in the starting α-amino nitrones. Although without stereocontrol, the 1,3-cycloaddition approach provided a direct entry to 5-acetoxy isoxazolidines with good anti selectivity with respect to the α-amino group. Many challenges arose and were overcome during the course of our investigations. The release of the glycine unit required the previous introduction of the base moiety due to the extreme lability of the acetoxy group at the 5-position of the isoxazolidine ring. Obtaining cis nucleoside analogues required to the presence of a diprotected α-amino group. Finally, an adequate choice of the synthetic route (Michael addition or nucleophilic addition for syn compounds and 1,3-dipolar cycloaddition for anti compounds) led to the preparation of isoxazolidinyl analogues of deoxypolyoxin C and uracil polyoxin C in both enantiomeric forms.

The methods developed for our syntheses should be applicable for the preparation of a variety of other complex nucleoside analogues and open the way for the

(58) The overall yields, starting from commercial L-serine and via 1,3-dipolar cycloaddition route, for cis compounds **45** and **46a** were 10.6% and 9.2%, respectively.

design and synthesis of polyoxins and nikkomycins libraries for biological studies.

## Experimental Section

**General.** The reaction flasks and other glass equipment were heated in an oven at 130 °C overnight and assembled in a stream of Ar. Syringes were assembled and fitted with needles while hot and cooled in a stream of Ar. Special techniques were used in handling moisture- and air-sensitive materials as described.[59] All solvents were dried by the usual methods.[60] All reactions were monitored by TLC on silica gel 60 F254; the position of the spots were detected with 254 nm UV light or by spraying with one of the following staining systems: 50% methanolic sulfuric acid, 5% ethanolic phosphomolybdic acid, and iodine. Preparative column chromatography was performed on columns of silica gel (60−240 mesh) and with solvents that were distilled prior to use. Preparative centrifugally accelerated radial thin-layer chromatography (PCAR-TLC) was performed with rotors (1 or 2 mm layer thickness) coated with silica gel type 7749, TLC grade, with binder and fluorescence indicator and the eluting solvents were delivered by the pump at a flow rate of 0.5−1.5 mL $min^{-1}$. Melting points were uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded at 300 and 75.5 MHz, respectively, and at 55 °C in $CDCl_3$ unless otherwise noted. Chemical shifts are reported in ppm ($\delta$) relative to $CHCl_3$ ($\delta$ 7.26) in $CDCl_3$. Optical rotations were taken at 25 °C.

**Materials.** α,β-Unsaturated esters **5** were prepared as described in ref 26. *N*-Benzyl nitrones **4** were prepared as described in ref 20b. *O*-(*tert*-Butyldimethylsilyl)-*O*-methyl ketene acetal **19** was prepared as described in ref 61. Bis-(trimethylsilyl)thymine and bis(trimethylsilyl)uracil were prepared as described in ref 54.

**General Procedure for Michael Addition of *N*-Benzylhydroxylamine.** To a solution of alkene **5** (2 mmol) in anhydrous THF (15 mL) at ambient temperature were added sequentially benzylhydroxylamine hydrochloride (0.4 g, 2.5 mmol) and triethylamine (0.253 g, 2.5 mmol). The reaction mixture was stirred at ambient temperature for 12 h at which time the reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The diastereoselectivity (ds %) was determined on the residue by $^1H$ NMR analysis. The crude product was purified by PCAR-TLC (2-mm layer thickness).

**Methyl (3*S*,4*R*)-3-(*N*-Benzylhydroxyamino)-4-(*tert*-butoxycarbonylamino)-5-hydroxy-4,5-*N*,*O*-isopropylidenepentanoate (6a).** The starting material (*Z*)-**5a** (0.571 g, 2 mmol) gave, after chromatographic purification (hexane/ethyl acetate, 80:20) **6a** (0.662 g, 81%) as an oil: $[\alpha]_D$ −83.6 (*c* 0.55, $CHCl_3$); $^1H$ NMR $\delta$ 1.46 (s, 3H), 1.51 (bs, 12H), 2.15−2.26 (m, 1H), 3.02−3.38 (m, 2H), 3.73 (s, 3H), 3.77−3.85 (m, 2H), 3.92−3.99 (m, 2H), 4.09 (dd, 1H, $J$ = 5.2, 9.3 Hz), 6.92 (bs, 1H), 7.09−7.40 (m, 5H); $^{13}C$ NMR $\delta$ 24.6, 27.2, 28.4, 30.9, 51.7, 59.6, 60.4, 63.6, 65.2, 80.9, 93.8, 126.7, 127.9, 128.7, 138.6, 154.3, 173.4. Anal. Calcd for $C_{21}H_{32}N_2O_6$: C, 61.75; H, 7.90; N, 6.86. Found: C, 61.55; H, 8.16; N, 6.92.

**Methyl (3*R*,4*R*)-3-(*N*-Benzylhydroxyamino)-4-(*tert*-butoxycarbonylamino)-5-hydroxy-4,5-*N*,*O*-isopropylidenepentanoate (6b).** The starting material (*E*)-**5a** (0.571 g, 2 mmol) gave, after chromatographic purification (hexane/ethyl acetate, 80:20), **6b** (0.302 g, 37%) as an oil: $[\alpha]_D$ −10.3 (*c* 1.80, $CHCl_3$); $^1H$ NMR (25 °C) $\delta$ 1.41 (bs, 9H), 1.49 (s, 6H), 2.39−2.64 (m, 1H), 2.94 (dd, 1H, $J$ = 3.7, 15.8 Hz), 3.61 (dt, 1H, $J$ = 5.5, 6.0 Hz), 3.67 (s, 3H), 3.77 (d, 1H, $J$ = 13.2 Hz), 3.85 (dd, 1H, $J$ = 6.0, 9.1 Hz), 3.93 (d, 1H, $J$ = 13.2 Hz), 3.99−4.21 (m, 2H), 5.32 (bs, 1H), 7.16−7.37 (m, 5H); $^{13}C$ NMR (25 °C) $\delta$ 23.8, 25.9, 28.3, 29.3, 51.5, 59.6, 61.7, 64.6 (2C), 80.0, 94.7, 127.1, 128.2, 129.2, 137.9, 152.4, 173.2. Anal. Calcd for $C_{21}H_{32}N_2O_6$: C, 61.75; H, 7.90; N, 6.86. Found: C, 61.62; H, 7.83; N, 6.67.

**Methyl (3*S*,4*R*)-3-(*N*-Benzylhydroxyamino)-4-(*tert*-butoxycarbonylamino)-5-(*tert*-butyldiphenylsiloxy)pentanoate (7a).** The starting material (*Z*)-**5b** (0.967 g, 2 mmol) gave, after chromatographic purification (hexane/ethyl acetate, 80:20), **7a** (0.314 g, 26%) as an oil: $[\alpha]_D$ −16.0 (*c* 0.50, $CHCl_3$); $^1H$ NMR (25 °C) $\delta$ 1.02 (s, 9H), 1.44 (s, 9H), 2.32 (dd, 1H, $J$ = 4.7, 17.2 Hz), 2.87 (dd, 1H, $J$ = 4.9, 17.2 Hz), 3.36 (m, 1H), 3.63 (s, 3h), 3.76 (m, 1H), 3.82 (d, 1H, $J$ = 13.7 Hz), 3.84 (m, 2H), 3.97 (d, 1H, $J$ = 13.7 Hz), 4.90 (d, 1H, $J$ = 9.2 Hz), 6.01 (bs, 1H, ex. $D_2O$), 7.25−7.43 (m, 11H), 7.58−7.72 (m, 4H); $^{13}C$ NMR (25 °C) $\delta$ 19.2, 26.9, 28.4, 30.1, 51.6, 54.5, 62.2, 63.5, 65.6, 79.6, 127.7 (2C), 127.8, 128.0, 128.6, 129.8 (2C), 133.1, 133.2, 135.5, 135.6, 138.4, 154.8, 173.0. Anal. Calcd for $C_{34}H_{46}N_2O_6Si$: C, 67.30; H, 7.64; N, 4.62. Found: C, 67.18; H, 7.42; N, 4.48.

**Methyl (3*R*,4*R*)-3-(*N*-Benzylhydroxyamino)-4-(*tert*-butoxycarbonylamino)-5-(*tert*-butyldiphenylsiloxy)pentanoate (7b).** The starting material (*E*)-**5b** (0.967 g, 2 mmol) gave, after chromatographic purification (hexane/ethyl acetate, 80:20), **7b** (0.898 g, 74%) as an oil: $[\alpha]_D$ +10.6 (*c* 0.39, $CHCl_3$); $^1H$ NMR (25 °C) $\delta$ 1.02 (s, 9H), 1.42 (s, 9H), 2.58 (dd, 1H, $J$ = 7.0, 16.5 Hz), 2.89 (dd, 1H, $J$ = 4.4, 16.5 Hz), 3.57 (dt, 1H, $J$ = 4.5, 7.5 Hz), 3.69 (s, 3H), 3.75 (d, 1H, $J$ = 13.5 Hz), 3.77 (dd, 1H, $J$ = 3.6, 9.6 Hz), 3.88 (d, 1H, $J$ = 13.5 Hz), 3.87−4.01 (m, 2H), 4.88 (bs, 2H), 7.19−7.44 (m, 11H), 7.56−7.70 (m, 4H); $^{13}C$ NMR (25 °C) $\delta$ 19.3, 26.9, 28.4, 29.9, 51.8, 53.8, 61.2, 63.0, 63.4, 79.4, 127.7, 127.8, 127.9, 128.2, 128.6, 129.0, 129.8, 133.1 (2C), 135.5, 135.6, 138.0, 155.9, 174.1. Anal. Calcd for $C_{34}H_{46}N_2O_6Si$: C, 67.30; H, 7.64; N, 4.62. Found: C, 67.46; H, 7.51; N, 4.46.

**Methyl (3*S*,4*R*)-3-Benzamido-4-(*tert*-butoxycarbonylamino)-5-hydroxy-4,5-*N*,*O*-isopropylidenepentanoate (9).** To a solution of copper(II) acetate (22.5 mg, 0.15 mmol) in acetic acid (2 mL) was added Zn dust (0.5 g, 7.65 mmol), and the mixture was stirred at ambient temperature for 15 min under argon atmosphere. A solution of **6a** (0.613 g, 1.5 mmol) in acetic acid (2 mL) and water (0.7 mL) was added, and the resulting mixture was heated at 70 °C for 1 h. After cooling to 20 °C the disodium salt of EDTA (1.5 g) was added, and the solution was made alkaline (pH = 10) by the addition of 3 M NaOH. The solution was extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous EDTA and with brine. The organic layer was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue containing essentially pure secondary amine **8a** [$^1H$ NMR (25 °C) $\delta$ 1.45 (s, 9H), 1.48 (bs, 6H), 1.62 (bs, 1H, ex. $D_2O$), 2.28 (dd, 1H, $J$ = 9.5, 15.5 Hz), 2.64 (dd, 1H, $J$ = 3.5, 15.5 Hz), 3.51 (dt, 1H, $J$ = 3.5, 9.5 Hz), 3.63 (s, 3H), 3.86 (dd, 1H, $J$ = 6.7, 9.6 Hz), 3.95 (dd, 1H, $J$ = 1.6, 9.6 Hz), 4.12 (ddd, 1H, $J$ = 1.6, 3.5, 6.7 Hz), 7.20−7.40 (m, 5H); $^{13}C$ NMR (25 °C) $\delta$ 28.4, 28.5, 29.6, 35.2, 51.4, 52.3, 56.1, 58.6, 63.8, 80.2, 94.6, 126.6, 127.9, 128.2, 140.7, 153.8, 173.0] was taken up in methanol (15 mL) and treated with Pd−C (20 mg), and the resulting suspension was stirred under hydrogen at 50 psi for 4 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue containing crude amine **8b** was dissolved in dichloromethane (15 mL) and treated with benzoyl chloride (0.562 g, 4 mmol) and pyridine (0.474 g, 6 mmol). The resulting mixture was allowed to stirr for 16 h, at which time it was poured into saturated aqueous $CuSO_4$ (15 mL). After 5 min of vigorous stirring, the layers were separated, and the organic layer was sequentially washed with saturated aqueous $CuSO_4$, water, and brine. The solution was dried ($MgSO_4$) and concentrated under reduced pressure to give a colorless oil which was subjected to purification by column chromatography on silica gel (hexane/ethyl acetate, 60:40), to afford the benzamide **9** (0.463 g, 76%) as an oil: $[\alpha]_D$ +27.3 (*c* 0.53, $CHCl_3$); $^1H$ NMR (25 °C) $\delta$ 1.38 (s, 9H), 1.50 (s, 3H), 1.55 (s, 3H), 2.55 (dd, 1H, $J$ = 5.0, 15.5 Hz), 2.86 (dd, 1H, $J$ = 4.9, 15.5 Hz), 3.66 (s, 3H), 3.90 (bd, 1H, $J$ = 9.5 Hz), 3.97 (dd, 1H, $J$ = 5.3, 9.5 Hz), 4.38 (dd, 1H, $J$ = 5.0, 9.1 Hz), 4.69 (m, 1H), 7.30−7.46 (m, 3H), 7.65 (bs, 1H), 7.78−7.85 (m, 2H); $^{13}C$ NMR (25 °C) $\delta$ 24.1, 27.2,

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28.2, 36.5, 50.2, 51.6, 58.6, 65.4, 81.0, 94.3, 127.1, 128.3, 131.2, 134.4, 154.8, 166.6, 171.4. Anal. Calcd for $C_{21}H_{30}N_2O_6$: C, 62.05; H, 7.44; N, 6.89. Found: C, 62.24; H, 7.23; N, 7.00.

**(4*S*,5*R*)-4-Benzamido-5-(*tert*-butoxycarbonylamino)-tetrahydropyran-2-one (10).** Compound **9** (0.203 g, 0.5 mmol) was dissolved in 70% aqueous acetic acid, and the resulting mixture was heated at 60 °C for 2 h. After cooling to ambient temperature the reaction mixture was diluted with saturated aqueous bicarbonate (25 mL) and ethyl acetate (25 mL), and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue which after purification by PCAR-TLC (hexane/ethyl acetate, 60:40; 1-mm layer thickness) afforded 109 mg (65%) of **10** as a white foam: $[\alpha]_D$ −33.3 (*c* 0.13, $CHCl_3$); $^1$H NMR (25 °C) $\delta$ 1.35 (s, 9H), 2.62 (dd, 1H, $J$ = 6.5, 17.6 Hz), 3.23 (dd, 1H, $J$ = 10.0, 17.6 Hz), 4.05 (dd, 1H, $J$ = 9.7, 11.5 Hz), 4.06 (ddd, 1H, $J$ = 5.3, 7.4, 9.7 Hz), 4.40 (dddd, 1H, $J$ = 6.5, 7.2, 9.9, 10.0 Hz), 4.50 (dd, 1H, $J$ = 5.3, 11.5 Hz), 4.91 (d, 1H, $J$ = 7.2 Hz), 6.73 (d, 1H, $J$ = 7.4 Hz), 7.31−7.39 (m, 3H), 7.72−7.80 (m, 2H); $^{13}$C NMR (25 °C) $\delta$ 28.1, 35.9, 48.8, 49.6, 68.4, 81.0, 127.1, 128.6, 132.1, 133.1, 156.4, 167.9, 168.3. Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63; N, 8.38. Found: C, 60.88; H, 6.47; N, 8.51. Compound **10** was misrepresented as the antipode in our previous communication.[24] Coupling constant calculation for this compound was aided by simulation techniques. For detailed assignments aided by homodecoupling 2D experiments, see Supporting Information.

**General Procedure for Cyclization of *β*-(Hydroxyamino) Esters.** To a solution of the corresponding *β*-(hydroxyamino) ester (1.5 mmol) in methanol (15 mL) was added sodium methoxide (97.2 mg, 1.8 mmol) at ambient temperature. After 2 h of stirring, the reaction mixture was diluted with aqueous $NH_4Cl$ (20 mL) and ethyl acetate (20 mL). The organic layer was separated, washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue which was purified by column chromatography on silica gel.

**(3*S*)-2-Benzyl-3-[(4*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonylamino)-1,3-oxazolidin-4-yl]isoxazolidin-5-one (11a).** The starting material **6a** (0.613 g, 1.5 mmol) gave, after chromatographic purification (hexane/ethyl acetate, 80:20), **11a** (0.536 g, 95%) as an oil: $[\alpha]_D$ −128.7 (*c* 1.40, $CHCl_3$); $^1$H NMR $\delta$ 1.44 (s, 3H), 1.47 (s, 9H), 1.51 (s, 3H), 2.62 (dd, 1H, $J$ = 17.9, 8.2 Hz), 2.93 (dd, 1H, $J$ = 17.9, 9.6 Hz), 3.87−4.01 (m, 3H), 4.08−4.22 (m, 3H), 7.24−7.39 (m, 5H); $^{13}$C NMR $\delta$ 23.5, 26.6, 28.3, 31.7, 56.9, 63.1, 63.3, 65.0, 80.8, 94.4, 127.9, 128.5, 129.0, 135.0, 152.2, 173.3. Anal. Calcd for $C_{20}H_{28}N_2O_5$: C, 63.81; H, 7.50; N, 7.44. Found: C, 63.88; H, 7.43; N, 7.31.

**(3*R*)-2-Benzyl-3-[(4*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonylamino)-1,3-oxazolidin-4-yl]isoxazolidin-5-one (11b).** The starting material **6b** (0.613 g, 1.5 mmol) gave, after chromatographic purification (hexane/ethyl acetate, 80:20), **11b** (0.525 g, 93%) as an oil: $[\alpha]_D$ −13.7 (*c* 0.63, $CHCl_3$); $^1$H NMR $\delta$ 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), 3.73−3.85 (m, 1H), 3.90 (dd, 1H, $J$ = 5.4, 9.2 Hz), 3.99−4.10 (m, 1H), 4.17 (s, 2H), 7.29−7.41 (m, 5H); $^{13}$C NMR $\delta$ 23.4, 23.5, 28.2, 30.4, 58.5, 63.3, 64.1, 65.4, 81.1, 94.5, 128.2, 128.9, 129.5, 134.4, 152.6, 175.7. Anal. Calcd for $C_{20}H_{28}N_2O_5$: C, 63.81; H, 7.50; N, 7.44. Found: C, 63.98; H, 7.39; N, 7.62.

**(3*S*)-2-Benzyl-3-[(1*R*)-1-(*tert*-butoxycarbonylamino)-2-(*tert*-butyldiphenylsiloxy)ethyl]isoxazolidin-5-one (13a).** The starting material **7a** (0.910 g, 1.5 mmol) gave, after chromatographic purification (hexane/ethyl acetate, 80:20), **13a** (0.819 g, 95%) as an oil: $[\alpha]_D$ −41.6 (*c* 1.55, $CHCl_3$); $^1$H NMR $\delta$ 1.07 (s, 9H), 1.41 (s, 9H), 2.59−2.70 (m, 2H), 3.63 (dd, 1H, $J$ = 7.5, 10.2 Hz), 3.72 (dd, 1H, $J$ = 5.2, 10.2 Hz), 3.77−3.93 (m, 2H), 4.05 (d, 1H, $J$ = 13.8 Hz), 4.13 (d, 1H, $J$ = 13.8 Hz), 4.65 (d, 1H, $J$ = 9.4 Hz), 7.22−7.48 (m, 11H), 7.58−7.65 (m, 4H); $^{13}$C NMR $\delta$ 19.2, 27.0, 28.3, 31.6, 54.9, 61.7, 63.1, 64.2, 80.0, 127.8, 127.9, 128.2, 128.7 (2C), 129.6, 129.9, 130.0, 132.9, 133.1, 134.7, 135.6, 155.7, 175.2. Anal. Calcd for $C_{33}H_{42}N_2O_5Si$: C, 68.96; H, 7.37; N 4.87. Found: C, 68.82; H, 7.10; N, 4.75.

**(3*R*)-2-Benzyl-3-[(1*R*)-1-(*tert*-butoxycarbonylamino)-2-(*tert*-butyldiphenylsiloxy)ethyl]isoxazolidin-5-one (13b).** The starting material **7b** (0.910 g, 1.5 mmol) gave, after chromatographic purification (hexane/ethyl acetate, 80:20), **13b** (0.820 g, 95%) as an oil: $[\alpha]_D$ +27.9 (*c* 0.35, $CHCl_3$); $^1$H NMR $\delta$ 1.08 (s, 9H), 1.41 (s, 9H), 2.58 (dd, 1H, $J$ = 8.2, 17.8 Hz), 2.67 (dd, 1H, $J$ = 5.6, 17.8 Hz), 3.55−3.85 (m, 3H), 3.90 (dd, 1H, $J$ = 9.7, 3.3 Hz), 4.01 (d, 1H, $J$ = 13.9 Hz), 4.17 (d, 1H, $J$ = 13.9 Hz), 4.71 (d, 1H, $J$ = 8.6 Hz), 7.22−7.71 (m, 15H); $^{13}$C NMR $\delta$ 19.3, 27.1, 28.3, 31.3, 53.2, 63.1, 63.3, 64.0, 80.0, 127.9, 128.0, 128.6 (2C), 129.5, 130.0 (2C), 132.9, 133.0, 134.8, 135.5, 135.6, 155.4, 175.0. Anal. Calcd for $C_{33}H_{42}N_2O_5Si$: C, 68.96; H, 7.37; N, 4.87. Found: C, 69.15; H, 7.21; N, 4.96.

**(3*S*)-2-Benzyl-3-[(1*R*)-1-(*tert*-butoxycarbonylamino)-2-hydroxyethyl]-isoxazolidin-5-one (12a). (a) From 11a.** To a solution of **11a** (0.264 g, 0.7 mmol) in methanol (20 mL) was added *p*-toluensulfonic acid monohydrate (5.4 mg, 29 $\mu$mol), and the resulting mixture was heated at 50 °C for 4 h. The reaction mixture was treated with saturated aqueous $NaHCO_3$ (30 mL) and extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), and the solvent was distilled under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate, 50:50) to give 170 mg (72%) of **12a** as an oil: $[\alpha]_D$ −64.2 (*c* 0.50, $CHCl_3$); $^1$H NMR $\delta$ 1.41 (s, 9H), 2.08 (bs, 1H), 2.67 (dd, 1H, $J$ = 3.5, 18.0 Hz), 2.80 (dd, 1H, $J$ = 8.9, 18.0 Hz), 3.44 (m, 2H), 3.68 (ddd, 1H, $J$ = 4.2, 6.7, 13.8 Hz), 3.81 (td, 1H, $J$ = 3.5, 8.9 Hz), 4.08 (d, 1H, $J$ = 13.0 Hz), 4.24 (d, 1H, $J$ = 13.0 Hz), 4.95 (d, 1H, $J$ = 8.7 Hz), 7.29−7.40 (m, 5H); $^{13}$C NMR $\delta$ 28.2, 30.5, 54.2, 62.1, 62.6, 63.9, 80.3, 128.5, 128.8, 129.7, 134.1, 156.1, 175.4. Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C,60.86; H, 7.31; N, 8.02.

**(b) From 13a.** Compound **13a** (0.402 g, 0.7 mmol) was dissolved in THF (15 mL) and treated with $Bu_4NF$ (0.8 mmol, 0.8 mL of a 1.0 M solution in THF) at ambient temperature. After 2 h saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the crude product by column chromatography (hexane/ethyl acetate 50:50) gave **12a** (0.217 g, 92%). The physical and spectroscopic properties of this compound were identical to those of the same product obtained from **11a**.

**(3*R*)-2-Benzyl-3-[(1*R*)-1-(*tert*-butoxycarbonylamino)-2-hydroxyethyl]isoxazolidin-5-one (12b). (a) From 11b.** The method described above to convert **11a** to **12a** was applied to **11b** (0.264 g, 0.7 mmol) to give, after column chromatography (hexane/ethyl acetate, 80:20), **12b** (0.165 g, 70%) as an oil: $[\alpha]_D$ +8.0 (*c* 0.40, $CHCl_3$); $^1$H NMR (25 °C) $\delta$ 1.41 (s, 9H), 2.32 (t, 1H, $J$ = 7.5 Hz), 2.67 (dd, 1H, $J$ = 4.5, 18.0 Hz), 2.78 (dd, 1H, $J$ = 8.1, 18.0 Hz), 3.59−3.69 (m, 3H), 3.79−3.89 (m, 1H), 4.12 (d, 1H, $J$ = 13.2 Hz), 4.23 (d, 1H, $J$ = 13.2 Hz), 4.91 (bs, 1H), 7.29−7.38 (m, 5H); $^{13}$C NMR (25 °C) $\delta$ 28.2, 31.0, 53.4, 61.9, 63.3, 63.5, 80.2, 128.5, 128.8, 129.7, 134.3, 155.6, 175.0. Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.65; H, 7.23; N, 8.16.

**(b) From 13b.** The method described above to convert **13a** to **12a** was applied to **13b** (0.402 g, 0.7 mmol) to give, after purification, **12b** (0.212 g, 90%). The physical and spectroscopic properties of this compound were identical to those of the same product obtained from **11b**.

**General Procedure for Reduction of Isoxazolidin-5-ones.** To a solution of the corresponding isoxazolidin-5-one (1.5 mmol) in anhydrous dichloromethane (15 mL) at −80 °C was added DIBAH (1.65 mmol, 1.1 mL of a 1.5 M solution in toluene). The reaction was stirred at −80 °C for 2 h, quenched with methanol (0.5 mL), and allowed to warm to ambient temperature. The mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL) and dichloromethane (10 mL), and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give crude 5-hydroxy isoxazolidines as anomeric mixtures. The obtained residue was dissolved in dichloromethane (5 mL) and treated sequentially with pyridine

(0.474 g, 6 mmol) and acetic anhydride (0.612 g, 6 mmol). The resulting mixture was stirred at ambient temperature for 12 h, at which time it was diluted with dichloromethane (10 mL) and poured into saturated aqueous $CuSO_4$ (15 mL). After 5 min of vigorous stirring, the layers were separated and the organic layer was sequentially washed with saturated aqueous $CuSO_4$, water, and brine. The solution was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by PCAR-TLC (2-mm layer thickness).

**(3*S*,5*R*)- and (3*S*,5*S*)-5-Acetoxy-2-benzyl-3-[(4*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonylamino)-1,3-oxazolidin-4-yl]isoxazolidine (16a) and (16b).** The starting material **11a** (0.565 g, 1.5 mmol) gave, after chromatographic purification (hexane/ethyl acetate, 70:30), a 70:30 anomeric mixture of **16a** and **16b** (0.492 g, 78%) as an oil (separation of this mixture could not be achieved): $^1$H NMR (25 °C) $\delta$ (mixture of anomers) 1.47 (s, 6.3H), 1.48 (s, 2.7H), 1.52 (s, 3H), 1.57 (s, 3H), 2.03 (s, 0.9H), 2.05 (s, 2.1H), 2.36 (dd, 0.7H, $J$ = 6.9, 13.5 Hz), 2.49 (ddd, 0.3H, $J$ = 2.0, 7.6, 14.0 Hz), 2.55−2.64 (m, 1H), 3.50 (dt, 0.7H, $J$ = 2.5, 10.0 Hz), 3.83−3.92 (m, 1.3H), 4.00−4.35 (m, 4H), 6.27 (dd, 0.3H, $J$ = 2.0, 6.4 Hz), 6.35 (d, 0.7H, $J$ = 5.0 Hz), 7.30−7.46 (m, 5H).

Anal. (anomeric mixture) Calcd for $C_{22}H_{32}N_2O_6$: C, 62.84; H, 7.67; N, 6.66. Found: C, 62.71; H, 7.80; N, 6.49.

**(3*R*,5*S*) and (3*R*,5*R*)-2-Benzyl-3-[(1*R*)-1-(*tert*-butoxycarbonylamino)-2-(*tert*-butyldiphenylsiloxy)ethyl]isoxazolidine (18a) and (18b).** The starting material **13b** (0.862 g, 1.5 mmol) gave, after chromatographic purification (hexane/ethyl acetate, 80:20) a 62:38 anomeric mixture of **18a** and **18b** (0.743 g, 80%) as an oil. Purification of that mixture by PCAR-TLC (hexane/ethyl acetate, 85:15) afforded the pure isomers. For **18a**: 0.464 g, 50%; oil; $[\alpha]_D$ +53.1 (*c* 0.65, $CHCl_3$); $^1$H NMR $\delta$ 1.09 (s, 9H), 1.42 (s, 9H), 2.02 (s, 3H), 2.27 (ddd, 1H, $J$ = 1.2, 3.8, 14.0 Hz), 2.36 (ddd, 1H, $J$ = 5.4, 8.9, 14.0 Hz), 3.39 (dt, 1H, $J$ = 3.8, 8.4 Hz), 3.73 (dd, 1H, $J$ = 4.2, 10.2 Hz), 3.90 (m, 1H), 3.92 (d, 1H, $J$ = 14.0 Hz), 4.01 (dd, 1H, $J$ = 3.6, 10.2 Hz), 4.07 (d, 1H, $J$ = 14.0 Hz), 4.81 (d, 1H, $J$ = 8.7 Hz), 6.33 (dd, 1H, $J$ = 1.2, 5.4 Hz), 7.17−7.45 (m,11H), 7.56−7.68 (m, 4H); $^{13}$C NMR $\delta$ 19.3, 21.2, 27.1, 28.4, 37.3, 53.3, 62.6, 63.0, 63.9, 79.3, 96.6, 127.4, 127.8, 128.2, 128.6 (2C), 129.0, 129.3, 129.8, 133.2, 135.5, 135.6, 136.4, 155.4, 170.1. Anal. Calcd for $C_{35}H_{46}N_2O_6Si$: C, 67.93; H, 7.49; N, 4.53. Found: C, 67.80; H, 7.32; N, 4.74. For **18b**: 0.279 g, 30%; oil; $[\alpha]_D$ −19.0 (*c* 0.11, $CHCl_3$); $^1$H NMR $\delta$ 1.06 (s, 9H), 1.42 (s, 9H), 2.05 (s, 3H), 2.55 (ddd, 1H, $J$ = 2.5, 7.5, 13.8 Hz), 2.63 (dt, 1H, $J$ = 5.4, 13.8 Hz), 3.53 (td, 1H, $J$ = 5.4, 7.5 Hz), 3.62 (m, 1H), 3.74 (dd, 1H, $J$ = 4.0, 10.4 Hz), 3.89 (dd, 1H, $J$ = 4.2, 10.4 Hz), 3.95 (d, 1H, $J$ = 13.3 Hz), 4.24 (d, 1H, $J$ = 13.3 Hz), 4.65 (d, 1H, $J$ = 9.4 Hz), 6.39 (dd, 1H, $J$ = 2.0, 5.9 Hz), 7.15−7.44 (m, 11H), 7.51−7.66 (m, 4H); $^{13}$C NMR $\delta$ = 19.3, 21.2, 27.0, 28.3, 38.4, 54.3, 63.7, 64.1, 64.5, 79.5, 99.1,127.4, 127.8, 128.3, 128.8, 129.0, 129.1, 129.8 (2C), 133.2, 135.6 (2C), 137.2, 155.5, 169.5. Anal. Calcd for $C_{35}H_{46}N_2O_6Si$: C, 67.93; H, 7.49; N, 4.53. Found: C, 68.16; H, 7.57; N, 4.80

**General Procedure for Nucleophilic Addition of 19 to Nitrones 4.** A cooled (−80 °C) and stirred solution of the corresponding nitrone (1 mmol) in anhydrous THF (10 mL) was treated sequentially with a solution of *O*-(*tert*-butyldimethylsilyl)-*O*-methyl ketene acetal **19** (0.282 g, 1.5 mmol) in THF (10 mL) and *tert*-butyldimethylsilyl triflate (0.396 g, 1.5 mmol). During the addition, the temperature of the reaction mixture was not allowed to raise above −70 °C. The mixture was stirred for 2 h, quenched with saturated $NH_4Cl$ (10 mL), stirred again at ambient temperature for 10 min, and diluted with diethyl ether (20 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The diastereoselectivity (ds %) was determined on the residue by $^1$H NMR analysis. The crude product was purified by PCAR-TLC (2-mm layer thickness).

**Methyl (3*S*,4*R*)- and (3*R*,4*R*)-3-(*N*-Benzyl-*tert*-butyldimethylsiloxyamino)-4-(*tert*-butoxycarbonylamino)-5-hydroxy-4,5-*N*,*O*-isopropylidenepentanoate (20a) and (20b).** The starting material **4a** (0.334 g, 1 mmol) gave, after chromatographic purification (hexane/ethyl acetate, 80:20), pure isomers **20a** and **20b**. For **20a**: 0.413 g, 79%; oil; $[\alpha]_D$ −35.6 (*c* 0.55, $CHCl_3$); $^1$H NMR $\delta$ 0.03 (s, 3H), 0.15 (s, 3H), 0.89 (s, 9H), 1.43 (s, 9H), 1.45 (s, 3H), 1.54 (s, 3H), 2.56 (dd, 1H, $J$ = 3.0, 15.5 Hz), 2.73 (dd, 1H, $J$ = 9.3, 15.5 Hz), 3.49 (s, 3H), 3.66 (m, 1H), 3.94 (d, 1H, $J$ = 13.3 Hz), 3.98 (dd, 1H, $J$ = 6.9, 9.9 Hz), 4.12 (d, 1H, $J$ = 9.6 Hz), 4.27 (d, 1H, $J$ = 13.3 Hz), 4.38−4.53 (m, 1H), 7.17−7.28 (m, 3H), 7.30−7.43 (m, 2H); $^{13}$C NMR $\delta$ −4.7, −4.3, 17.8, 23.6, 26.3, 27.2, 28.4, 32.0, 51.2, 56.3, 62.6, 65.8, 65.9, 80.4, 93.3, 127.2, 127.9, 130.0, 137.6, 152.6, 172.7. Anal. Calcd for $C_{27}H_{46}N_2O_6Si$: C, 62.04; H, 8.87; N, 5.36. Found: C, 62.27; H, 8.64; N, 5.10. For **20b**: 68 mg, 13%; oil; $[\alpha]_D$ −16.8 (*c* 1.00, $CHCl_3$); $^1$H NMR $\delta$ −0.20 (s, 3H), 0.02 (s, 3H), 0.85 (s, 9H), 1.42 (s, 3H), 1.46 (s, 3H), 1.47 (s, 9H), 2.70 (dd, 1H, $J$ = 6.5, 15.9 Hz), 2.98 (dd, 1H, $J$ = 4.4, 15.9 Hz), 3.46 (m, 1H), 3.63 (s, 3H), 3.74 (dd, 1H, $J$ = 5.0, 8.5 Hz), 3.76 (d, 1H, $J$ = 13.0 Hz), 3.88 (d, 1H, $J$ = 13.0 Hz), 3.95−4.26 (m, 2H), 7.20−7.33 (m, 5H); $^{13}$C NMR $\delta$ −4.5 (2C), 17.8, 24.0, 26.1, 27.0, 28.5, 29.9, 51.2, 58.9, 60.4, 65.0, 66.2, 80.3, 94.5, 127.5, 128.2, 130.2, 137.2, 153.2, 173.7. Anal. Calcd for $C_{27}H_{46}N_2O_6Si$: C, 62.04; H, 8.87; N, 5.36. Found: C, 62.18; H, 8.59; N, 5.46.

**Methyl (3*S*,4*R*)- and (3*R*,4*R*)-3-(*N*-Benzyl-*tert*-butyldimethylsiloxyamino)-4-(*tert*-butoxycarbonylamino)-5-(*tert*-butyldiphenylsiloxy)pentanoate (21a) and (21b).** The starting material **4b** (0.533 g, 1 mmol) gave, after chromatographic purification (hexane/ethyl acetate, 90:10), pure isomers **21a** and **21b**. For **21a:** 0.115 g, 16%; oil; $[\alpha]_D$ +12.9 (*c* 0.15, $CHCl_3$); $^1$H NMR $\delta$ −0.20 (s, 3H), −0.18 (s, 3H), 0.80 (s, 9H), 1.02 (s, 9H), 1.43 (s, 9H), 2.53 (dd, 1H, $J$ = 5.1, 15.6 Hz), 2.75 (dd, 1H, $J$ = 6.1, 15.6 Hz), 3.38 (m, 1H), 3.60 (d, 1H, $J$ = 12.8 Hz), 3.63 (s, 3H), 3.76 (m, 1H), 3.84 (d, 1H, $J$ = 12.8 Hz), 3.90 (m, 2H), 5.40 (bs, 1H), 7.10−7.19 (m, 5H), 7.31−7.42 (m, 6H), 7.58−7.64 (m, 4H); $^{13}$C NMR (25 °C) $\delta$ −5.2, −4.1, 17.5, 19.4, 27.2 (2C), 26.4, 27.9, 52.3, 54.5, 60.7, 63.8, 64.6, 79.9, 127.6 (2C), 127.7, 127.8, 128.2, 128.5, 129.2, 129.6, 134.1, 135.4, 135.7, 137.6, 155.6, 173.8. Anal. Calcd for $C_{40}H_{60}N_2O_6Si_2$: C, 66.63; H, 7.37; N, 4.87. Found: C, 66.80; H, 7.53; N, 4.99. For **21b**: 0.476 g, 66%; oil; $[\alpha]_D$ −8.5 (*c* 0.22, $CHCl_3$); $^1$H NMR $\delta$ −0.32 (s, 3H), −0.06 (s, 3H), 0.78 (s, 9H), 1.02 (s, 9H), 1.44 (s, 9H), 2.49 (dd, 1H, $J$ = 8.3, 16.0 Hz), 2.96 (dd, 1H, $J$ = 3.6, 16.0 Hz), 3.47 (m, 1H), 3.61 (m, 1H), 3.64 (d, 1H, $J$ = 13.1 Hz), 3.67 (s, 3H), 3.85 (d, 1H, $J$ = 13.1 Hz), 3.92 (m, 2H), 4.55 (bs, 1H), 7.11−7.20 (m, 5H), 7.30−7.42 (m, 6H), 7.58−7.66 (m, 4H); $^{13}$C NMR (25 °C) $\delta$ −4.9, −3.8, 17.6, 19.8, 27.1, 27.2, 26.6, 28.6, 50.1, 55.6, 61.9, 64.7, 64.8, 80.1, 127.5, 127.6, 127.8 (2C), 128.2, 128.5, 129.0, 129.7, 134.2, 135.5 (2C), 138.0, 154.7, 174.1. Anal. Calcd for $C_{40}H_{60}N_2O_6Si_2$: C, 66.63; H, 7.37; N, 4.87. Found: C, 66.80; H, 7.53; N, 4.99.

**Desilylation of 20a.** To a cooled (0 °C) solution of **20a** (0.183 g, 0.35 mmol) in THF (10 mL) was added hydrogen fluoride−pyridine complex (0.5 g). After 1 h of stirring at 0 °C, the reaction mixture was diluted with saturated aqueuous $NaHCO_3$ (10 mL) and ethyl acetate (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel (hexane/ethyl acetate, 80:20) afforded **6a** (0.126 g, 88%). The physical and spectroscopic properties of this compound were identical to those of the product obtained from **5a**.

**Desilylation of 21b.** Compound **21b** (0.231 g, 0.32 mmol) was dissolved in a 3:1:1 mixture of THF−AcOH−$H_2O$ (15 mL), and the resulting solution was stirred at ambient temperature for 8 h. The mixture was neutralized with saturated aqueous $NaHCO_3$ (aproximately 25 mL) and diluted with ethyl acetate (20 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel (hexane/ethyl acetate, 90:10) afforded **7b** (85 mg, 44%). The physical and spectroscopic properties of this compound were identical to those of the product obtained from **5b**.

**General Procedure 1,3-Dipolar Cycloaddition of Nitrones with Vinyl Acetate.** To a solution of the corresponding nitrone (1 mmol) in toluene was added vinyl acetate (4.3 g, 50 mmol), and the resulting solution was heated under reflux for 4 h at which time the mixture was cooled to ambient temperature and concentrated under reduced pressure. The diastereomeric ratio (dr) was determined on the residue by $^1$H NMR analysis. The crude material was purified by PCAR-TLC (2 mm layer thickness).

**Cycloaddition Reaction of 4a.** The starting material **4a** (0.334 g, 1 mmol) gave, after chromatographic purification (hexane/ethyl acetate, 80:20), pure isomers **22a** (0.198 g, 47%) and **22b** (80 mg, 19%) and an unseparable 70:30 mixture of compounds **16a** and **16b** (0.118 g, 28%). The spectroscopic properties of this mixture were similar to those of the mixture obtained from **11a**, although with a different isomeric ratio.

**(3*R*,5*S*)-5-Acetoxy-2-benzyl-3-[(4*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonylamino)-1,3-oxazolidin-4-yl]isoxazolidine (22a):** oil; $[\alpha]_D$ +37.6 (*c* 0.85, $CHCl_3$); $^1$H NMR $\delta$ 1.47 (s, 9H), 1.48 (s, 3H), 1.51 (s, 3H), 2.05 (s, 3H), 2.40 (ddd, 1H, $J$ = 1.6, 4.2, 13.8 Hz), 2.47 (ddd, 1H, $J$ = 5.3, 8.7, 13.8 Hz), 3.45 (ddd, 1H, $J$ = 4.5, 6.5, 8.7 Hz), 3.90 (dd, 1H, $J$ = 6.0, 9.0 Hz), 3.96 (d, 1H, $J$ = 13.9 Hz), 4.10 (d, 1H, $J$ = 13.9 Hz), 4.14−4.28 (m, 2H), 6.36 (dd, 1H, $J$ = 1.6, 5.3 Hz), 7.22−7.40 (m, 5H); $^{13}$C NMR $\delta$ 21.2, 24.1, 27.3, 28.4, 38.3, 59.4, 63.5, 63.7, 64.9, 80.3, 94.3, 97.0, 127.5, 128.3, 129.4, 136.5, 152.9, 170.1. Anal. Calcd for $C_{22}H_{32}N_2O_6$: C, 62.84; H, 7.67; N, 6.66. Found: C, 62.63; H, 7.53; N, 6.48.

**(3*R*,5*R*)-5-Acetoxy-2-benzyl-[(4*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonylamino)-1,3-oxazolidin-4-yl]isoxazolidine (22b):** oil; $[\alpha]_D$ = −81.6 (*c* 0.40, $CHCl_3$); $^1$H NMR $\delta$ 1.49 (s, 12H), 1.51 (s, 3H), 2.06 (s, 3H), 2.54 (ddd, 1H, $J$ = 2.7, 7.8, 13.9 Hz), 2.73 (ddd, 1H, $J$ = 4.3, 6.0, 13.9 Hz), 3.52−3.62 (m, 1H), 3.77−3.86 (m, 2H), 3.89−3.96 (m, 1H), 3.97 (d, 1H, $J$ = 13.1 Hz), 4.28 (d, 1H, $J$ = 13.1 Hz), 6.46 (dd, 1H, $J$ = 2.7, 6.0 Hz), 7.22−7.41 (m, 5H); $^{13}$C NMR $\delta$ 21.3, 27.3, 27.4, 28.4, 37.9, 56.4, 59.1, 64.1, 65.5, 80.5, 94.3, 99.6, 127.6, 128.4, 129.2, 137.1, 153.0, 169.7. Anal. Calcd for $C_{22}H_{32}N_2O_6$: C, 62.84; H, 7.67; N, 6.66. Found: C, 2.91; H, 7.49; N, 6.85.

**Cycloaddition of 4b.** The starting material **4b** (0.533 g, 1 mmol) gave, after chromatographic purification (hexane/ethyl acetate, 90:10), pure isomers **18a** (0.384 g, 62%), **18b** (93 mg, 15%), and **23a** (74 mg, 12%). The physical and spectroscopic properties of compounds **18a,b** were identical to those of the same products obtained from **13b**.

**(3*S*,5*R*)-2-Benzyl-3-[(1*R*)-1-(*tert*-butoxycarbonylamino)-2-(*tert*-butyldiphenylsiloxy)ethyl]isoxazolidine (23a):** oil; $[\alpha]_D$ −51.6 (*c* 0.12, $CHCl_3$); $^1$H NMR $\delta$ 1.05 (s, 9H), 1.40 (s, 9H), 1.99 (s, 3H), 2.22 (ddd, 1H, $J$ = 1.0, 4.7, 13.9 Hz), 2.68 (ddd, 1H, $J$ = 6.1, 10.1, 13.9 Hz), 3.56 (td, 1H, $J$ = 4.5, 10.1 Hz), 3.63 (dd, 1H, $J$ = 7.3, 9.9 Hz), 3.78 (dd, 1H, $J$ = 4.9, 10.1 Hz), 3.86 (m, 1H), 3.94 (d, 1H, $J$ = 14.3 Hz), 4.08 (d, 1H, $J$ = 14.3 Hz), 4.98 (d, 1H, $J$ = 7.5 Hz), 6.31 (d, 1H, $J$ = 5.6 Hz), 7.20−7.42 (m, 11H), 7.55−7.66 (m, 4H); $^{13}$C NMR $\delta$ 19.2, 21.1, 26.9, 28.4, 39.2, 53.5, 62.0, 63.0, 63.7, 79.2, 95.8, 127.3, 127.8 (2C), 128.2 (2C), 129.0, 129.8 (2C), 133.2, 135.5 (2C), 136.9, 155.5, 170.0. Anal. Calcd for $C_{35}H_{46}N_2O_6Si$: C, 67.93; H, 7.49; N, 4.53. Found: C, 67.79; H, 7.38; N, 4.29.

**Methyl (2*R*)-2-(*tert*-Butoxycarbonylamino)-2-[(3*R*,5*R*)-2-benzyl-5-methoxyisoxazolidin-3-yl]acetate (28a) and (2*R*)-2-(*tert*-butoxycarbonylamino)-2-[(3*R*,5*S*)-2-benzyl-5-methoxyisoxazolidin-3-yl]acetate (28b).** To a solution of an anomeric mixture of **25a** and **25b** (0.176 g, 0.5 mmol) in a 1:1 mixture of acetonitrile−water (5 mL) were added (2,2,6,6-tetramethyl-1-piperidinyloxy)-(16 mg, 0.1 mmol) and bis-[(acetoxy)iodo]benzene (0.355 g, 1.1 mmol). The reaction mixture was stirred at ambient temperature for 4 h and then filtered through a pad of Celite. The solid was washed with ethyl acetate, and the filtrate was diluted with brine (10 mL) and ethyl acetate (10 mL). The organic layer was separated, washed with brine (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Purification of the residue by PCAR-TLC (hexane/ethyl acetate, 70:30; 1-mm layer thickness) afforded a 60:40 anomeric mixture of **28a** and **28b** (0.135 g, 71%) as an oil: $^1$H NMR (25 °C) $\delta$ (mixture of anomers) 1.37 (s, 5.4H), 1.44 (s, 3.6H), 2.28 (ddd, 0.6H, $J$ = 1.1, 4.3, 13.8 Hz), 2.36 (ddd, 0.6H, $J$ = 5.8, 10.0, 13.8 Hz), 2.54 (ddd, 0.4H, $J$ = 2.2, 8.3, 13.8 Hz), 2.75 (ddd, 0.4H, $J$ = 4.1, 6.0, 13.8 Hz), 3.32 (s, 1.8H), 3.36 (s, 1.2H), 3.38 (ddd, 0.6H, $J$ = 4.3, 5.8, 10.0 Hz), 3.59 (ddd, 0.4H, $J$ = 3.6, 4.1, 8.3 Hz), 3.70 (s, 1.2H), 3.72 (s, 1.8 H), 3.98 (d, 0.6H, $J$ = 13.8 Hz), 4.05 (d, 0.4H, $J$ = 13.1 Hz), 4.12 (dd, 0.4H, $J$ = 3.6, 9.4 Hz), 4.14 (d, 0.6H, $J$ = 13.8 Hz), 4.26 (t, 0.6H, $J$ = 5.8 Hz), 4.32 (d, 0.4H, $J$ = 13.1 Hz), 4.99 (dd, 0.6H, $J$ = 1.1, 5.8 Hz), 5.04 (dd, 0.4H, $J$ = 2.2, 6.0 Hz), 5.11 (bd, 0.4H, $J$ = 9.4 Hz), 5.75 (bd, 0.6H, $J$ = 5.8 Hz), 7.22−7.44 (m, 5H). Anal. (anomeric mixture) Calcd for $C_{19}H_{28}N_2O_6$: C, 59.98; H, 7.42; N, 7.36. Found: C, 59.82; H, 7.60; N, 7.48.

**General Procedure for the *N*-Glycosylation of 5-Acetoxyisoxazolidines.** To a solution of the corresponding anomeric mixture of 5-(acetoxy)isoxazolidines (0.5 mmol) in dry $CH_3CN$ (10 mL) were added the silylated base (thymine or uracil) (2 mmol) and trimethylsilyl triflate (0.38 mL, 2 mmol). The resulting mixture was stirred at ambient temperature for 12 h at which time the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL) and ethyl acetate (15 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The cis/trans ratio was determined on the residue by $^1$H NMR analysis. The crude product was purified by PCAR-TLC (2-mm layer thickness).

**1-{(3*S*,5*R*)-2-Benzyl-3-[(4*R*)-3-(*tert*-butoxycarbonylamino)-2,2-dimethyl-1,3-oxazolidin-4-yl]isoxazolidin-5-yl}-thymine (31a) and 1-{(3*S*,5*S*)-2-Benzyl-3-[(4*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonylamino)-1,3-oxazolidin-4-yl]isoxazolidin-5-yl}thymine (31b).** The starting material, an anomeric mixture of **16a** and **16b** (0.210 g, 0.5 mmol) and bis(trimethylsilyl)thymine (0.540 g, 2 mmol) gave, after chromatographic purification (toluene/ethyl acetate, 70:30) **31a** and **31b**. For **31a**: 0.119 g, 49%; white solid; mp 54−55 °C; $[\alpha]_D$ −64.8 (*c* 0.45, $CHCl_3$); $^1$H NMR (25 °C) $\delta$ 1.44 (s, 3H), 1.48 (s, 9H), 1.53 (s, 3H), 1.77 (d, 3H, $J$ = 1.0 Hz), 2.42 (ddd, 1H, $J$ = 3.5, 9.2, 13.8 Hz), 2.90 (td, 1H, $J$ = 7.6, 13.8 Hz), 3.47−3.60 (m, 1H), 3.88 (d, 1H, $J$ = 14.0 Hz), 3.89−3.97 (m, 2H), 3.98−4.23 (m, 2H), 5.95 (bs, 1H), 7.26−7.36 (m, 6H), 8.79 (bs, 1H); $^{13}$C NMR $\delta$ 12.3, 23.5, 26.9, 28.4, 40.0, 56.3, 61.2, 63.6, 65.8, 80.8, 83.2, 94.6, 109.9, 127.8, 128.5, 128.7 (2C), 135.5, 136.8, 150.4, 163.8. Anal. Calcd for $C_{25}H_{34}N_4O_6$: C, 61.71; H, 7.04; N, 11.51. Found: C, 61.89; H, 6.90; N, 11.81. For **31b**: 80 mg, 33%; white solid; mp 70−72 °C; $[\alpha]_D$ −95.4 (*c* 0.33, $CHCl_3$); $^1$H NMR $\delta$ 1.45 (s, 3H), 1.49 (s, 9H), 1.54 (s, 3H), 1.84 (bs, 3H), 2.18−2.36 (m, 1H), 2.94 (td, 1H, $J$ = 7.6, 13.9 Hz), 3.70−3.84 (m, 1H), 3.93 (dd, 1H, $J$ = 6.3, 9.6 Hz), 3.97−4.24 (m, 4H), 6.07 (dd, 1H, $J$ = 4.5, 7.6 Hz), 7.09 (bs, 1H), 7.24−7.38 (m, 5H), 8.48 (bs, 1H); $^{13}$C NMR (25 °C) $\delta$ 12.3, 23.5, 26.8, 28.4, 36.95, 56.4, 60.4, 63.9 (2C), 80.7, 83.2, 94.2, 110.8, 127.7, 128.4, 128.8 (2C), 135.5, 136.4, 150.1, 163.3. Anal. Calcd for $C_{25}H_{34}N_4O_6$: C, 61.71; H, 7.04; N, 11.51. Found: C, 61.92; H, 7.18; N, 11.33.

**1-{(3*S*,5*R*)-2-Benzyl-3-[(4*R*)-3-(*tert*-butoxycarbonylamino)-2,2-dimethyl-1,3-oxazolidin-4-yl]isoxazolidin-5-yl}-uracil (32a) and 1-{(3*S*,5*S*)-2-Benzyl-3-[(4*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonylamino)-1,3-oxazolidin-4-yl]isoxazolidin-5-yl}uracil (32b).** The starting materials, an anomeric mixture of **16a** and **16b** (0.210 g, 0.5 mmol) and bis(trimethylsilyl)uracil (0.513 g, 2 mmol) gave, after chromatographic purification (toluene/ethyl acetate, 70:30), pure isomers **32a** and **32b**. For **32a**: 85 mg, 36%; oil; $[\alpha]_D$ −68.8 (*c* 0.50, $CHCl_3$); $^1$H NMR $\delta$ 1.44 (s, 3H), 1.49 (s, 9H), 1.50 (s, 3H), 2.36−2.53 (m, 1H), 2.94 (td, 1H, $J$ = 7.7, 14.3 Hz), 3.41−3.69 (m, 1H), 3.84−3.97 (m, 3H), 4.03−4.31 (m, 2H), 5.56 (d, 1H, $J$ = 8.1 Hz), 5.93−6.05 (m, 1H), 7.27−7.38 (m, 5H), 7.49 (d, 1H, $J$ = 8.1 Hz), 8.06 (bs, 1H); $^{13}$C NMR $\delta$ 24.0, 26.6, 28.4, 40.1, 56.1, 61.4, 63.5, 65.6, 80.8, 83.3, 94.3, 101.6, 127.8, 128.5, 128.7, 136.4, 139.5, 150.0, 156.1, 162.6. Anal. Calcd for $C_{24}H_{32}N_4O_6$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.77; H, 6.78; N, 12.02. For **32b**: 0.104 g, 44%; oil; $[\alpha]_D$ −68.3 (*c* 0.90, $CHCl_3$); $^1$H NMR $\delta$ 1.45 (s, 3H), 1.48 (s, 9H), 1.53 (s, 3H), 2.16−2.38 (m, 1H), 2.97 (td, 1H, $J$ = 7.9, 13.9 Hz), 3.64−3.82 (m,

1H), 3.92 (dd, 1H, $J$ = 6.1, 9.9 Hz), 4.01−4.23 (m, 4H), 5.64 (d, 1H, $J$ = 7.8 Hz), 6.07 (dd, 1H, $J$ = 3.4, 7.1 Hz), 7.25−7.40 (m, 6H), 8.31 (bs, 1H); $^{13}$C NMR $\delta$ 23.7, 26.8, 28.4, 37.1, 56.4, 60.6, 63.7, 65.2, 80.8, 83.4, 94.2, 102.4, 127.7, 128.4, 128.7, 136.2, 139.6, 149.9, 156.0, 162.5. Anal. Calcd for $C_{24}H_{32}N_4O_6$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.92; H, 6.96; N, 11.76.

**1-{(3*R*,5*R*)-2-Benzyl-3-[(1*R*)-1-(*tert*-butoxycarbonylamino)-2-(*tert*-butyldiphenylsiloxy)ethyl]isoxazolidin-5-yl}uracil (37).** The starting materials, an anomeric mixture of **18a** and **18b** (0.124 g, 0.2 mmol) and bis(trimethylsilyl)thymine (0.203 g, 0.75 mmol), gave after chromatographic purification (toluene/ethyl acetate, 70:30) **37** (0.105 g, 77%) as an oil: $[\alpha]_D$ +16.6 (*c* 0.32, $CHCl_3$); $^1$H NMR $\delta$ 1.07 (s, 9H), 1.46 (s, 9H), 1.80 (bs, 3H), 2.40 (ddd, 1H, $J$ = 5.4, 7.3, 13.8 Hz), 2.80 (ddd, 1H, $J$ = 7.0, 8.0, 13.8 Hz), 3.50 (q, 1H, $J$ = 6.4 Hz), 3.72 (dd, 1H, $J$ = 4.5, 9.8 Hz), 3.89−3.99 (m, 2H), 4.02 (d, 1H, $J$ = 14.1 Hz), 4.18 (d, 1H, $J$ = 14.1 Hz), 4.79 (d, 1H, $J$ = 8.5 Hz), 5.95 (dd, 1H, $J$ = 5.4, 7.0 Hz), 7.04 (bs, 1H), 7.25−7.45 (m, 11H), 7.57−7.66 (m, 4H), 8.15 (bs, 1H); $^{13}$C NMR $\delta$ 12.3, 19.3, 27.0, 28.4, 37.1, 51.8, 60.5, 64.1, 64.6, 80.0, 85.5, 110.3, 127.7 (2C), 127.9, 128.4, 129.1, 130.0 (2C), 133.0, 134.8, 135.6 (2C), 135.8, 136.4, 150.0, 155.6, 163.3. Anal. Calcd for $C_{38}H_{48}N_4O_6Si$: C, 66.64; H, 7.06; N, 8.18. Found: C, 66.38; H, 7.19; N, 8.34.

**1-{(3*R*,5*S*)-2-Benzyl-3-[(4*R*)-3-(*tert*-butoxycarbonylamino)-2,2-dimethyl-1,3-oxazolidin-4-yl]isoxazolidin-5-yl}thymine (41a) and 1-{(3*R*,5*R*)-2-Benzyl-3-[(4*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonylamino)-1,3-oxazolidin-4-yl]isoxazolidin-5-yl}thymine (41b).** The starting materials, an anomeric mixture of **22a** and **22b** (0.210 g, 0.5 mmol) and bis(trimethylsilyl)thymine (0.540 g, 2 mmol), gave, after chromatographic purification (cyclohexane/ethyl acetate, 50:50), pure **41a** and **41b**. For **41a**: 0.109 g, 45%; sticky foam; $[\alpha]_D$ −18.8 (*c* 0.85, $CHCl_3$); $^1$H NMR $\delta$ 1.47 (s, 9H), 1.50 (s, 3H), 1.55 (s, 3H), 1.80 (s, 3H), 2.19−2.39 (m, 1H), 2.94 (td, 1H, $J$ = 7.7, 13.4 Hz), 3.36 (dt, 1H, $J$ = 4.3, 7.8 Hz), 3.80 (d, 1H, $J$ = 13.5 Hz), 3.84−3.93 (m, 1H), 3.97 (dd, 1H, $J$ = 6.5, 9.0 Hz), 4.16−4.24 (m, 1H), 4.37 (d, 1H, $J$ = 13.5 Hz), 6.02 (bs, 1H), 7.16−7.54 (m, 6H), 8.52 (bs, 1H); $^{13}$C NMR $\delta$ 12.3, 23.9, 27.04, 28.3, 39.1, 57.2, 61.7, 65.0, 66.9, 80.9, 83.1, 94.8, 109.8, 127.7, 128.4, 129.08, 136.51, 137.0, 150.5, 153.7, 164.1. Anal. Calcd for $C_{25}H_{34}N_4O_6$: C, 61.71; H, 7.04; N, 11.51. Found: C, 61.79; H, 6.87; N, 11.42. For **41b**: 90 mg, 37%; oil; $[\alpha]_D$ −10.5 (*c* 0.60, $CHCl_3$); $^1$H NMR $\delta$ 1.50 (bs, 12H), 1.52 (s, 3H), 1.78 (s, 3H), 2.54 (td, 1H, $J$ = 7.0, 13.6 Hz), 2.79−3.08 (m, 1H), 3.52 (dt, 1H, $J$ = 3.2, 7.5 Hz), 3.86−3.93 (m, 2H), 4.09 (dd, 1H, $J$ = 7.1, 14.2 Hz), 4.10 (s, 2H), 6.00 (t, 1H, $J$ = 6.5 Hz), 7.13 (d, 1H, $J$ = 1.2 Hz), 7.26−7.40 (m, 5H), 8.77 (bs, 1H); $^{13}$C NMR $\delta$ 12.3, 23.8, 27.5, 28.4, 37.5, 57.8, 62.1, 66.0, 66.4, 81.0, 87.3, 94.5, 110.2, 127.9, 128.6, 128.9, 135.9, 136.4, 150.1, 154.2, 163.7. Anal. Calcd for $C_{25}H_{34}N_4O_6$: C, 61.71; H, 7.04; N, 11.51. Found: C, 61.52; H, 6.79; N, 11.36.

**1-{(3*R*,5*S*)-2-Benzyl-3-[(4*R*)-3-(*tert*-butoxycarbonylamino)-2,2-dimethyl-1,3-oxazolidin-4-yl]isoxazolidin-5-yl}uracil (42a) and 1-{(3*R*,5*R*)-2-Benzyl-3-[(4*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonylamino)-1,3-oxazolidin-4-yl]isoxazolidin-5-yl}uracil (42b).** The starting materials, an anomeric mixture of **22a** and **22b** (0.210 g, 0.5 mmol) and bis(trimethylsilyl)uracil (0.513 g, 2 mmol), gave, after chromatographic purification (cyclohexane/ethyl acetate, 50:50), pure **42a** and **42b**. For **42a**: 89 mg, 38%; oil; $[\alpha]_D$ −35.9 (*c* 1.40, $CHCl_3$); $^1$H NMR $\delta$ 1.46 (s, 3H), 1.47 (s, 12H), 2.28−2.44 (m, 1H), 2.94 (td, 1H, $J$ = 8.5, 13.8 Hz), 3.27−3.40 (m, 1H), 3.33 (dt, 1H, $J$ = 4.6, 7.8 Hz), 3.82 (d, 1H, $J$ = 13.5 Hz), 3.97 (dd, 1H, $J$ = 6.5, 9.2 Hz), 4.13−4.21 (m, 1H), 4.37 (d, 1H, $J$ = 13.5 Hz), 5.55 (d, 1H, $J$ = 8.2 Hz), 5.99−6.09 (m, 1H), 7.26−7.47 (m, 5H), 7.63 (d, 1H, $J$ = 8.2 Hz), 8.29 (bs, 1H); $^{13}$C NMR $\delta$ 23.8, 27.0, 28.3, 39.1, 57.2, 62.1, 64.9, 67.0, 80.9, 83.6, 94.8, 101.4, 127.7, 128.3, 129.1, 136.7, 140.3, 150.3, 156.4, 162.9. Anal. Calcd for $C_{24}H_{32}N_4O_6$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.88; H, 7.00; N, 11.74. Fpr **42b**: 0.100 g, 42%; oil; $[\alpha]_D$ −4.8 (*c* 0.60, $CHCl_3$); $^1$H NMR $\delta$ 1.48 (s, 3H), 1.50 (s, 9H), 1.51 (s, 3H), 2.52 (ddd, 1H, $J$ = 6.3, 7.0, 13.8 Hz), 2.87−3.02 (m, 1H), 3.49 (dt, 1H, $J$ = 3.3, 7.6 Hz), 3.83 (dd, 1H, $J$ = 1.4, 9.0 Hz), 3.90 (dd, 1H, $J$ = 5.3, 9.0 Hz), 4.06−4.14 (m, 1H), 4.07 (d, 1H, $J$ = 13.3 Hz), 4.13 (d, 1H, $J$ = 13.3 Hz), 5.59 (d, 1H, $J$ = 8.1 Hz), 6.03 (t, 1H, $J$ = 6.4 Hz), 7.26−7.36 (m, 5H), 7.38 (d, 1H, $J$ = 8.1 Hz), 8.07 (bs, 1H); $^{13}$C NMR $\delta$ 23.9, 27.5, 28.4, 37.6, 57.7, 62.3, 65.9, 66.4, 81.1, 87.6, 94.5, 101.8, 128.0, 128.6, 128.9, 136.2, 139.9, 149.8, 156.6, 162.5. Anal. Calcd for $C_{24}H_{32}N_4O_6$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.28; H, 6.96; N, 12.13.

**1-{(3*S*,5*R*)-2-Benzyl-3-[(1*R*)-1-(*tert*-butoxycarbonylamino)-2-hydroxyethyl]isoxazolidin-5-yl}thymine (33a).** The method described above to convert **9** to **10** was applied to **31a** (88 mg, 0.18 mmol) to give, after column chromatography (ethyl acetate), **33a** (72 mg, 90%) as a white solid: mp 157−159 °C; $[\alpha]_D$ −11.7 (*c* 0.89, $CHCl_3$); $^1$H NMR $\delta$ 1.41 (s, 9H), 1.78 (d, 3H, $J$ = 1.1 Hz), 2.35 (ddd, 1H, $J$ = 4.2, 7.4, 13.9 Hz), 2.57 (bs, 1H), 2.99 (ddd, 1H, $J$ = 7.1, 9.0, 13.9 Hz), 3.43 (ddd, 1H, $J$ = 4.5, 7.4, 9.0 Hz), 3.60 (dd, 1H, $J$ = 5.9, 11.0 Hz), 3.68 (dd, 1H, $J$ = 4.8, 11.0 Hz), 3.75−3.86 (m, 1H), 3.93 (d, 1H, $J$ = 13.7 Hz), 4.23 (d, 1H, $J$ = 13.7 Hz), 5.12 (d, 1H, $J$ = 9.0 Hz), 6.00 (dd, 1H, $J$ = 4.2, 7.1 Hz), 7.26 (q, 1H, $J$ = 1.1 Hz), 7.27−7.39 (m, 5H), 8.89 (bs, 1H); $^{13}$C NMR $\delta$ 12.3, 28.4, 40.4, 53.3, 62.5, 63.1, 64.9, 80.3, 83.6, 110.2, 127.9, 128.6, 129.2, 135.6, 136.7, 150.6, 156.0, 163.8. Anal. Calcd for $C_{22}H_{30}N_4O_6$: C, 59.18; H, 6.77; N, 12.55. Found: C, 59.37; H, 6.90; N, 12.73.

**1-{(3*S*,5*S*)-2-Benzyl-3-[(1*R*)-1-(*tert*-butoxycarbonylamino)-2-hydroxyethyl]isoxazolidin-5-yl}thymine (33b).** The method described above to convert **9** to **10** was applied to **31b** (73 mg, 0.15 mmol) to give, after column chromatography (ethyl acetate), **33b** (55 mg, 82%) as an oil: $[\alpha]_D$ −45.0 (*c* 1.26, $CHCl_3$); $^1$H NMR $\delta$ 1.44 (s, 9H), 1.82 (d, 3H, $J$ = 1.1 Hz), 2.61 (ddd, 1H, $J$ = 5.8, 8.2, 13.9 Hz), 2.63 (bs, 1H), 2.86 (ddd, 1H, $J$ = 4.4, 7.2, 13.9 Hz), 3.54−3.83 (m, 4H), 4.10 (d, 1H, $J$ = 13.6 Hz), 4.16 (d, 1H, $J$ = 13.6 Hz), 5.15 (d, 1H, $J$ = 8.7 Hz), 5.97 (dd, 1H, $J$ = 5.8, 7.0 Hz), 7.10 (q, 1H, $J$ = 1.1 Hz), 7.25−7.38 (m, 5H), 8.66 (bs, 1H); $^{13}$C NMR $\delta$ 12.2, 28.3, 38.0, 53.5, 62.3, 63.1, 64.5, 80.2, 86.5, 110.6, 128.0, 128.5, 129.0, 135.4, 135.9, 150.1, 156.0, 163.4. Anal. Calcd for $C_{22}H_{30}N_4O_6$: C, 59.18; H, 6.77; N, 12.55. Found: C, 59.02; H, 6.91; N, 12.66.

**1-{(3*S*,5*R*)-2-Benzyl-3-[(1R)-1-(*tert*-butoxycarbonylamino)-2-hydroxyethyl]isoxazolidin-5-yl}uracil (34a).** The method described above to convert **9** to **10** was applied to **32a** (85 mg, 0.18 mmol) to give, after column chromatography (ethyl acetate), **34a** (69 mg, 88%) as an oil: $[\alpha]_D$ −16.2 (*c* 0.65, $CHCl_3$); $^1$H NMR $\delta$ 1.40 (s, 9H), 2.37 (ddd, 1H, $J$ = 4.0, 7.3, 14.0 Hz), 2.96 (bs, 1H, ex. $D_2O$), 3.01 (ddd, 1H, $J$ = 7.2, 9.0, 14.0 Hz), 3.41 (dt, 1H, $J$ = 4.3, 8.2 Hz), 3.59 (dd, 1H, $J$ = 5.9, 10.7 Hz), 3.68 (dd, 1H, $J$ = 4.3, 10.7 Hz), 3.74−3.85 (m, 1H), 3.92 (d, 1H, $J$ = 13.8 Hz), 4.22 (d, 1H, $J$ = 13.8 Hz), 5.25 (bs, 1H), 5.56 (d, 1H, $J$ = 8.2 Hz), 6.01 (dd, 1H, $J$ = 4.0, 7.2 Hz), 7.25−7.38 (m, 5H), 7.47 (d, 1H, $J$ = 8.2 Hz), 9.53 (bs, 1H); $^{13}$C NMR $\delta$ 28.3, 40.3, 53.0, 62.5, 62.7, 65.0, 80.2, 83.7, 101.7, 127.8, 128.5, 129.1, 136.4, 139.8, 150.5, 155.9, 163.6. Anal. Calcd for $C_{21}H_{28}N_4O_6$: C, 58.32; H, 6.53; N, 12.96. Found: C, 58.49; H, 6.22; N, 13.15.

**1-{(3*S*,5*S*)-2-Benzyl-3-[(1*R*)-1-(*tert*-butoxycarbonylamino)-2-hydroxyethyl]isoxazolidin-5-yl}uracil (34b).** The method described above to convert **9** to **10** was applied to **32b** (66 mg, 0.14 mmol) to give, after column chromatography (ethyl acetate), **34b** (50 mg, 83%) as an oil: $[\alpha]_D$ −40.8 (*c* 0.42, $CHCl_3$); $^1$H NMR $\delta$ 1.41 (s, 9H), 2.58 (ddd, 1H, $J$ = 5.4, 8.1, 13.7 Hz), 2.86 (ddd, 1H, $J$ = 5.0, 7.0, 13.7 Hz), 3.19 (bs, 1H, ex. $D_2O$), 3.52−3.70 (m, 3H), 3.77 (dt, 1H, $J$ = 4.3, 9.2 Hz), 4.07 (d, 1H, $J$ = 13.5 Hz), 4.13 (d, 1H, $J$ = 13.5 Hz), 5.32 (d, 1H, $J$ = 8.6 Hz), 5.62 (d, 1H, $J$ = 8.1 Hz), 5.96 (dd, 1H, $J$ = 5.4, 7.0 Hz), 7.24−7.33 (m, 5H), 7.35 (d, 1H, $J$ = 8.1 Hz), 9.71 (bs, 1H); $^{13}$C NMR $\delta$ 28.3, 38.1, 53.4, 62.2, 62.9, 64.3, 80.1, 86.4, 102.1, 127.9, 128.6, 129.0, 136.1, 139.8, 150.3, 156.1, 163.5. Anal. Calcd for $C_{21}H_{28}N_4O_6$: C, 58.32; H, 6.53; N, 12.96. Found: C, 58.44; H, 6.49; N, 12.88.

**1-{(3*R*,5*R*)-2-Benzyl-3-[(1*R*)-1-(*tert*-butoxycarbonylamino)-2-hydroxyethyl]isoxazolidin-5-yl}thymine (38). From 37.** The method described above to convert **13a** to **12a** was applied to **31a** (88 mg, 0.18 mmol) to give, after column chromatography (chloroform/methanol, 95:5), **38** (74 mg, 92%) as a white solid: mp 100−102 °C; $[\alpha]_D$ +23.0 (*c* 0.36, MeOH); $^1$H NMR $\delta$ 1.46 (s, 9H), 1.84 (s, 3H), 2.53 (ddd, 1H, $J$ = 5.7,

7.9, 13.9 Hz), 2.60 (bs, 1H), 2.80 (ddd, 1H, $J$ = 5.9, 7.1, 13.9 Hz), 3.53 (td, 1H, $J$ = 5.5, 7.9 Hz), 3.66 (dd, 1H, $J$ = 3.8, 11.1 Hz), 3.72−3.81 (m, 1H), 3.87 (dd, 1H, $J$ = 3.6, 11.1 Hz), 4.11 (d, 1H, $J$ = 13.6 Hz), 4.22 (d, 1H, $J$ = 13.6 Hz), 5.20 (d, 1H, $J$ = 7.6 Hz), 6.03 (dd, 1H, $J$ = 5.7, 7.1 Hz), 7.09 (q, 1H, $J$ = 1.2 Hz), 7.28−7.39 (m, 5H), 8.74 (bs, 1H); $^{13}$C NMR $\delta$ 12.3, 28.4, 36.9, 58.1, 61.4, 62.9, 65.1, 80.3, 85.5, 110.8, 128.0, 128.6, 129.2, 135.6, 135.9, 150.2, 156.1, 163.4. Anal. Calcd for $C_{22}H_{30}N_4O_6$: C, 59.18; H, 6.77; N, 12.55. Found: C, 58.96; H, 6.59; N, 12.60. **From 41b.** The method described above to convert **9** to **10** was applied to **41b** (73 mg, 0.15 mmol) to give, after column chromatography (ethyl acetate), **38** (60 mg, 90%). The physical and spectroscopic properties of this compounds were identical to those of the same product obtained from **37**.

**1-{(3*R*,5*S*)-2-Benzyl-3-[(1R)-1-(*tert*-butoxycarbonylamino)-2-hydroxyethyl]isoxazolidin-5-yl}thymine (43).** The method described above to convert **9** to **10** was applied to **41a** (78 mg, 0.16 mmol) to give, after column chromatography (chloroform/methanol, 95:5), **43** (66 mg, 92%) as an oil: $[\alpha]_D$ −10.7 (*c* 0.45, $CHCl_3$); $^1$H NMR $\delta$ 1.45 (s, 9H), 1.78 (s, 3H), 2.29 (ddd, 1H, $J$ = 3.6, 7.8, 14.1 Hz), 2.45 (bs, 1H), 2.93 (td, 1H, $J$ = 7.8, 14.1 Hz), 3.19 (dt, 1H, $J$ = 4.5, 8.0 Hz), 3.67 (dd, 1H, $J$ = 4.5, 11.3 Hz), 3.74 (dd, 1H, $J$ = 4.2, 11.3 Hz), 3.84 (d, 1H, $J$ = 13.3 Hz), 3.96 (dt, 1H, $J$ = 4.3, 8.7 Hz), 4.38 (d, 1H, $J$ = 13.3 Hz), 5.42 (bs, 1H), 6.00 (dd, 1H, $J$ = 3.6, 7.5 Hz), 7.28−7.46 (m, 6H), 8.73 (bs, 1H); $^{13}$C NMR $\delta$ 12.2, 28.4, 38.2, 58.1, 63.4, 64.7, 66.5, 80.3, 83.5, 110.3, 127.8, 128.4, 129.3, 135.9, 136.7, 150.7, 156.1, 163.6. Anal. Calcd for $C_{22}H_{30}N_4O_6$: C, 59.18; H, 6.77; N, 12.55. Found: C, 59.07; H, 6.58; N, 12.42.

**1-{(3*R*,5*S*)-2-Benzyl-3-[(1*R*)-1-(*tert*-butoxycarbonylamino)-2-hydroxyethyl]isoxazolidin-5-yl}uracil (44a).** The method described above to convert **9** to **10** was applied to **42a** (85 mg, 0.18 mmol) to give, after column chromatography (hexane/ethyl acetate, 10:90), **44a** (70 mg, 90%) as an oil: $[\alpha]_D$ = −23.9 (*c* 0.80, $CHCl_3$); $^1$H NMR $\delta$ 1.42 (s, 9H), 2.34 (ddd, 1H, $J$ = 3.3, 7.6, 14.3 Hz), 2.55 (bs, 1H), 2.91 (ddd, 1H, $J$ = 7.6, 8.5, 14.3 Hz), 3.17 (ddd, 1H, $J$ = 4.6, 7.6, 8.5 Hz), 3.62−3.73 (m, 2H), 3.83 (d, 1H, $J$ = 13.5 Hz), 3.91 (dt, 1H, $J$ = 4.4, 8.7 Hz), 4.35 (d, 1H, $J$ = 13.5 Hz), 5.35 (bd, 1H, $J$ = 8.2 Hz), 5.53 (d, 1H, $J$ = 8.1 Hz), 6.00 (dd, 1H, $J$ = 3.3, 7.5 Hz), 7.25−7.41 (m, 5H), 7.52 (d, 1H, $J$ = 8.1 Hz), 8.96 (bs, 1H); $^{13}$C NMR $\delta$ 28.4, 38.8, 51.3, 61.0, 63.2, 66.4, 80.0, 83.7, 101.5, 127.8, 128.3, 129.3, 136.4, 140.2, 150.5, 156.0, 163.3. Anal. Calcd for $C_{21}H_{28}N_4O_6$: C, 58.32; H, 6.53; N, 12.96. Found: C, 58.11; H, 6.41; N, 13.25.

**1-{(3*R*,5*R*)-2-Benzyl-3-[(1*R*)-1-(*tert*-butoxycarbonylamino)-2-hydroxyethyl]isoxazolidin-5-yl}uracil (44b).** The method described above to convert **9** to **10** was applied to **42b** (57 mg, 0.12 mmol) to give, after column chromatography (hexane/ethyl acetate, 10:90), **44b** (45 mg, 86%) as an oil: $[\alpha]_D$ +19.2 (*c* 0.32, $CHCl_3$); $^1$H NMR $\delta$ 1.42 (s, 9H), 2.49 (ddd, 1H, $J$ = 5.3, 7.8, 13.5 Hz), 2.81 (ddd, 1H, $J$ = 5.3, 7.0, 13.5 Hz), 2.90 (bs, 1H), 3.46 (td, 1H, $J$ = 5.3, 7.5 Hz), 3.61 (dd, 1H, $J$ = 5.5, 12.4 Hz), 3.72−3.82 (m, 2H), 4.08 (d, 1H, $J$ = 13.5 Hz), 4.18 (d, 1H, $J$ = 13.5 Hz), 5.28 (d, 1H, $J$ = 7.6 Hz), 5.62 (d, 1H, $J$ = 8.1 Hz), 5.99 (dd, 1H, $J$ = 5.3, 7.0 Hz), 7.24−7.35 (m, 6H), 9.40 (bs, 1H); $^{13}$C NMR $\delta$ 28.3, 37.0, 52.2, 61.3, 62.8, 64.9, 80.1, 85.6, 102.2, 127.9, 128.5, 129.1, 136.0, 139.8, 150.2, 156.0, 163.2. Anal. Calcd for $C_{21}H_{28}N_4O_6$: C, 58.32; H, 6.53; N, 12.96. Found: C, 58.46; H, 6.73; N, 13.18.

**Methyl (2*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[(3*S*,5*R*)-2-benzyl-4-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)isoxazolidin-3-yl]glycinate (35a).** The method described above to convert **25** to **28** was applied to **33a** (89 mg, 0.2 mmol) to give, after column chromatography (hexane/ethyl acetate, 80:20), **35a** (68 mg, 72%) as an oil: $[\alpha]_D$ −6.2 (*c* 0.40, $CHCl_3$); $^1$H NMR $\delta$ 1.43 (s, 9H), 1.81 (d, 3H, $J$ = 1.2 Hz), 2.45 (ddd, 1H, $J$ = 3.6, 7.1, 14.1 Hz), 3.06 (ddd, 1H, $J$ = 7.1, 9.3, 14.1 Hz), 3.65 (ddd, 1H, $J$ = 3.1, 7.1, 9.3 Hz), 3.72 (s, 3H), 3.88 (d, 1H, $J$ = 13.7 Hz), 4.03 (d, 1H, $J$ = 13.7 Hz), 4.53 (bd, 1H, $J$ = 9.1 Hz), 5.18 (d, 1H, $J$ = 9.1 Hz), 5.99 (dd, 1H, $J$ = 3.6, 7.1 Hz), 7.22 (q, 1H, $J$ = 1.2 Hz), 7.29−7.42 (m, 5H), 8.02 (bs, 1H); $^{13}$C NMR $\delta$ 12.3, 28.2, 40.5, 52.5, 54.3, 61.8, 65.0, 80.9, 83.2, 110.0, 128.0, 128.6, 129.1, 135.5, 136.2, 150.1, 155.6, 163.3, 170.8. Anal. Calcd for $C_{23}H_{30}N_4O_7$: C, 58.22; H, 6.37; N, 11.81. Found: C, 58.45; H, 6.23; N, 11.90.

**Methyl (2*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[(3*S*,5*S*)-2-benzyl-4-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)isoxazolidin-3-yl]glycinate (35b).** The method described above to convert **25** to **28** was applied to **33b** (63 mg, 0.14 mmol) to give, after column chromatography (hexane/ethyl acetate, 80:20), **35b** (51 mg, 76%) as an oil: $[\alpha]_D$ −30.6 (*c* 0.3, $CHCl_3$); $^1$H NMR $\delta$ 1.48 (s, 9H), 1.83 (d, 3H, $J$ = 1.2 Hz), 2.61 (ddd, 1H, $J$ = 5.6, 8.5, 14.0 Hz), 2.91 (ddd, 1H, $J$ = 4.0, 7.3, 14.0 Hz), 3.68 (s, 3H), 3.92−4.00 (m, 1H), 4.06 (s, 2H), 4.49 (bd, 1H, $J$ = 8.5 Hz), 5.36 (bd, 1H, $J$ = 8.5 Hz), 5.94 (dd, 1H, $J$ = 5.6, 7.3 Hz), 7.04 (q, 1H, $J$ = 1.2 Hz), 7.28−7.39 (m, 5H), 7.96 (bs, 1H); $^{13}$C NMR $\delta$ 12.5, 28.3, 38.6, 52.6, 55.3, 61.4, 64.5, 80.8, 85.5, 110.6, 128.0, 128.6, 129.1, 135.4, 135.7, 149.8, 155.9, 163.2, 170.8. Anal. Calcd for $C_{23}H_{30}N_4O_7$: C, 58.22; H, 6.37; N, 11.81. Found: C, 58.04; H, 6.19; N, 11.62.

**Methyl (2*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[(3*S*,5*R*)-2-benzyl-4-(3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl)isoxazolidin-3-yl]glycinate (36a).** The method described above to convert **25** to **28** was applied to **34a** (43 mg, 0.1 mmol) to give, after column chromatography (hexane/ethyl acetate, 80:20), **36a** (30 mg, 66%) as an oil: $[\alpha]_D$ −4.5 (*c* =1.90, $CHCl_3$); $^1$H NMR $\delta$ 1.39 (s, 9H), 2.40 (ddd, 1H, $J$ = 3.3, 6.6, 14.2 Hz), 3.08 (ddd, 1H, $J$ = 7.2, 9.5, 14.2 Hz), 3.57−3.68 (m, 1H), 3.69 (s, 3H), 3.85 (d, 1H, $J$ = 13.7 Hz), 3.97 (d, 1H, $J$ = 13.7 Hz), 4.53 (dd, 1H, $J$ = 2.0, 9.5 Hz), 5.26 (d, 1H, $J$ = 9.5 Hz), 5.57 (d, 1H, $J$ = 8.1 Hz), 5.99 (dd, 1H, $J$ = 3.3, 7.2 Hz), 7.26−7.40 (m, 6H), 9.23 (bs, 1H); $^{13}$C NMR $\delta$ 28.2, 40.4, 52.7, 54.0, 62.0, 65.0, 80.9, 83.5, 101.6, 128.1, 128.6, 129.1, 135.9, 139.6, 150.4, 155.5, 163.3, 170.7. Anal. Calcd for $C_{22}H_{28}N_4O_7$: C, 57.38; H, 6.13; N, 12.17. Found: C, 57.18; H, 6.38; N, 12.03.

**Methyl (2*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[(3*S*,5*S*)-2-benzyl-4-(3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl)isoxazolidin-3-yl]glycinate (36b).** The method described above to convert **25** to **28** was applied to **34b** (43 mg, 0.1 mmol) to give, after column chromatography (hexane/ethyl acetate, 80:20), **36b** (33 mg, 72%) as an oil: $[\alpha]_D$ −61.4 (*c* 0.50, $CHCl_3$); $^1$H NMR $\delta$ 1.47 (s, 9H), 2.63 (ddd, 1H, $J$ = 5.5, 8.4, 14.0 Hz), 2.94 (ddd, 1H, $J$ = 4.3, 7.2, 14.0 Hz), 3.63 (s, 3H), 3.89−3.97 (m, 1H), 4.01 (d, 1H, $J$ = 13.4 Hz), 4.09 (d, 1H, $J$ = 13.4 Hz), 4.48 (bd, 1H, $J$ = 8.2 Hz), 5.39 (d, 1H, $J$ = 9.5 Hz), 5.63 (d, 1H, $J$ = 8.2 Hz), 5.94 (dd, 1H, $J$ = 5.5, 7.2 Hz), 7.26−7.38 (m, 6H), 8.73 (bs, 1H); $^{13}$C NMR $\delta$ 28.2, 38.6, 52.4, 55.4, 61.7, 64.6, 80.7, 86.0, 102.2, 128.0, 128.5, 129.0, 135.7, 139.6, 149.9, 155.8, 162.7, 170.6. Anal. Calcd for $C_{22}H_{28}N_4O_7$: C, 57.38; H, 6.13; N, 12.17. Found: C, 57.47; H, 6.29; N, 12.32.

**Methyl (2*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[(3*R*,5*R*)-2-benzyl-4-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)isoxazolidin-3-yl]glycinate (39).** The method described above to convert **25** to **28** was applied to **38** (45 mg, 0.1 mmol) to give, after column chromatography (hexane/ethyl acetate, 50:50), **39** (36 mg, 76%) as a foam: $[\alpha]_D$ −3.5 (*c* 0.4, $CHCl_3$); $^1$H NMR (25 °C) $\delta$ 1.46 (s, 9H), 1.80 (d, 3H, $J$ = 1.1 Hz), 2.43 (ddd, 1H, $J$ = 4.8, 8.4, 13.8 Hz), 2.95 (ddd, 1H, $J$ = 5.2, 7.5, 13.8 Hz), 3.66−3.75 (m, 1H), 3.79 (s, 3H), 4.09 (d, 1H, $J$ = 13.8 Hz), 4.30 (d, 1H, $J$ = 13.8 Hz), 4.52−4.60 (m, 1H), 5.40 (d, 1H, $J$ = 7.7 Hz), 5.97 (dd, 1H, $J$ = 4.8, 7.5 Hz), 7.03 (q, 1H, $J$ = 1.1 Hz), 7.27−7.39 (m, 5H), 8.41 (bs, 1H); $^{13}$C NMR (25 °C) $\delta$ 12.5, 28.3, 38.4, 52.9, 53.8, 59.4, 64.9, 80.6, 83.7, 110.7, 127.9, 128.4, 129.2, 135.5, 136.0, 150.2, 155.0, 163.6, 170.7. Anal. Calcd for $C_{23}H_{30}N_4O_7$: C, 58.22; H, 6.37; N, 11.81. Found: C, 58.13; H, 6.02; N, 12.04.

**Methyl (2*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[(3*R*,5*S*)-2-benzyl-4-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)isoxazolidin-3-yl]glycinate (45).** The method described above to convert **25** to **28** was applied to **43** (45 mg, 0.1 mmol) to give, after column chromatography (hexane/ethyl acetate, 50:50), **45** (39 mg, 82%) as an oil: $[\alpha]_D$ −37.6 (*c* 0.30, $CHCl_3$); $^1$H NMR (25 °C) $\delta$ 1.47 (s, 9H), 1.74 (d, 3H, $J$ = 1.0 Hz), 2.34 (ddd, 1H, $J$ = 2.7, 8.8, 12.5 Hz), 2.91 (td, 1H, $J$ = 8.0, 13.0 Hz), 3.39 (dt, 1H, $J$ = 2.6, 8.8 Hz), 3.74 (d, 1H, $J$ = 13.2 Hz), 3.76 (s, 3H), 4.52 (d, 1H, $J$ = 13.2 Hz), 4.74 (dd, 1H, $J$ = 2.3, 7.4 Hz), 5.46 (d, 1H, 7.4 Hz), 5.87 (dd, 1H, $J$ = 2.7, 7.5 Hz), 7.20 (pseudo d, 1H, $J$ = 1.0 Hz), 7.28−7.45 (m, 5H), 8.30 (bs,

1H); $^{13}$C NMR (25 °C) $\delta$ 12.4, 28.3, 39.7, 52.1, 52.9, 60.5, 66.7, 80.6, 82.7, 109.5, 127.8, 128.3, 129.2, 136.0, 136.6, 150.4, 155.2, 163.8, 170.2. Anal. Calcd for $C_{23}H_{30}N_4O_7$: C, 58.22; H, 6.37; N, 11.81. Found: C, 58.49; H, 6.56; N, 11.65.

**Methyl (2*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[(3*R*,5*S*)-2-benzyl-4-(3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl)isoxazolidin-3-yl]glycinate (46a).** The method described above to convert **25** to **28** was applied to **44a** (43 mg, 0.1 mmol) to give, after column chromatography (hexane/ethyl acetate, 40:60), **46a** (36 mg, 78%) as an oil: $[\alpha]_D$ −29.9 (*c* 1.2, $CHCl_3$); $^1$H NMR $\delta$ 1.45 (s, 9H), 2.26−2.41 (m, 1H), 2.89 (td, 1H, $J$ = 8.7, 13.6 Hz), 3.37 (dt, 1H, $J$ = 3.0, 8.5 Hz), 3.75 (s, 3H), 3.76 (d, 1H, $J$ = 13.4 Hz), 4.46 (d, 1H, $J$ = 13.4 Hz), 4.68 (bs, 1H), 5.35 (d, 1H, $J$ = 6.8 Hz), 5.47 (d, 1H, $J$ = 8.1 Hz), 5.92 (dd, 1H, $J$ = 3.0, 7.6 Hz), 7.25−7.40 (m, 5H), 7.42 (d, 1H, $J$ = 8.1 Hz), 8.33 (bs, 1H); $^{13}$C NMR $\delta$ 28.3, 39.6, 52.4, 52.8, 60.8, 66.7, 80.6, 82.9, 101.2, 127.8, 128.3, 129.3, 136.2, 140.1, 150.2, 162.8, 170.1. Anal. Calcd for $C_{22}H_{28}N_4O_7$: C, 57.38; H, 6.13; N, 12.17. Found: C, 57.51; H, 5.92; N, 12.34.

**Methyl (2*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[(3*R*,5*R*)-2-benzyl-4-(3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl)isoxazolidin-3-yl]glycinate (46b).** The method described above to convert **25** to **28** was applied to **44b** (43 mg, 0.1 mmol) to give, after column chromatography (hexane/ethyl acetate, 40:60), **46b** (37 mg, 81%) as an oil: $[\alpha]_D$ −2.9 (*c* 0.75, $CHCl_3$); $^1$H NMR $\delta$ 1.43 (s, 9H), 2.40 (ddd, 1H, $J$ = 4.2, 8.0, 13.5 Hz), 2.96 (td, 1H, $J$ = 7.4, 13.5 Hz), 3.58−3.69 (m, 1H), 3.77 (s, 3H), 4.05 (d, 1H, $J$ = 13.5 Hz), 4.29 (d, 1H, $J$ = 13.5 Hz), 4.58 (dd, 1H, $J$ = 2.5, 7.2 Hz), 5.46 (d, 1H, $J$ = 8.0 Hz), 5.61 (d, 1H, $J$ = 8.2 Hz), 5.94 (dd, 1H, $J$ = 4.2, 7.2 Hz), 7.24−7.36 (m, 6H), 9.02 (bs, 1H); $^{13}$C NMR $\delta$ 28.3, 38.4, 52.9, 53.7, 59.8, 64.8, 80.6, 84.1, 102.2, 127.9, 128.5, 129.1, 135.8, 139.7, 150.1, 155.0, 163.0, 170.6. Anal. Calcd for $C_{22}H_{28}N_4O_7$: C, 57.38; H, 6.13; N, 12.17. Found: C, 57.04; H, 6.37; N, 12.52.

**Acknowledgment.** We are grateful to the Direccion General de Enseñanza Superior e Investigacion Cientifico-Tecnica (PB97-1014, MEC, Madrid, Spain) and Diputación General de Aragon (Project PO79/99-C) for financial support.

**Supporting Information Available:** Details on the determination of the configuration of **6a** and **10**, experimental details for the preparation of **24a**, **24b**, **25a**, **25b**, **26**, **27**, and **40** and characterization data of this compounds, and diagnostic NOE data for compounds **18a**, **18b**, **22a**, **22b**, **31a**, **31b**, **32a**, **32b**, **41a**, **41b**, **42a**, **42b**, **37**, and **40**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0002689