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TOTAL SYNTHESIS OF ACOSAMINE AND DAUNOSAMINE UTILIZING A DIASTEREOSELECTIVE INTRAMOLECULAR [3+2] CYCLOADDITION

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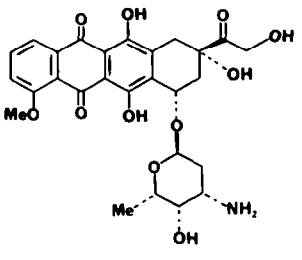
Abstract—A total synthesis of daunosamine (**3**) and acosamine (**4**) has been accomplished via a diastereoselective intramolecular nitrone–olefin cyclization. In the key step the chiral nitrone **12a** cyclized to give two isoxazolidines **13a** and **14a** in an 82:18 ratio. Further elaboration of **13a** led to daunosamine and acosamine. The effects of olefin substitution on the diastereoselectivity of the cycloaddition was also examined.

The 1,3-dipolar cycloaddition of a nitrone with an olefin is an extremely powerful, yet mild means of producing carbon–carbon bonds as well as carbon–oxygen and carbon–nitrogen bonds, and is particularly well suited to the construction of nitrogen containing substances.[1,2] The synthetic worth of this reaction is, however, to a large degree determined by the extent to which regio- and stereochemical control can be achieved. We now wish to report the details of our investigation on the application of the [3+2] nitrone–olefin cycloaddition reaction to the synthesis of 1-acosamine and 1-daunosamine.[3]

The 2,3,6-trideoxy-3-amino-hexoses constitute an important class of sugars, perhaps best known for their presence in anthracycline antibiotics such as adriamycin (**1**) and aclacinomycin (**2**). Indeed, the antitumor activity of these antibiotics has stimulated much research into new methodologies for the preparation of the sugars, their analogs, anthracycline analogs and their respective coupling.[4] Daunosamine (**3**) is found in adriamycin which is presently used clinically in antitumor therapy, while the N-methylated derivative, rhodosamine, is found in the aclaxinomycins. A therapeutically important modification in adriamycin is the replacement of daunosamine for its C-4 epimer, acosamine (**4**), a change which is reported to reduce the relative cardiotoxicity of adriamycin. At the time, this work was initiated, most approaches to these important sugars depended on the relay synthesis from other carbohydrates.[5,6] Our goal was to generate **3** and **4** by total synthesis.

An analysis of the synthetic problem is outlined in Scheme 1. The 1,3-disposed amino-alcohol function in acosamine (**5**, open form shown) was envisioned as being derived from isoxazolidine **6**, the formation of which would require a regio-, diastereo- and enantioselective cycloaddition of nitrone **7** to the *trans*-enol of propionaldehyde in the manner shown. The regiochemical aspect demanded immediate attention since it is well known that for enol ethers and esters the regiochemical preference is for the nitrone oxygen to add to the carbon already bearing the oxygen substituent.[7,8] Twenty-five years ago, Le Bel observed that simple nitrones cyclized preferentially to *cis* fused [3.3.0] bicyclooctane systems and not the bridged [3.2.2] bicycloheptane systems when the nitrone and olefin moieties are linked by a three-carbon chain.[9] If the constraints of the intramolecular process were sufficient to overwhelm the usual regiochemical preference of the nitrone–enol ester cycloaddition, then the intramolecular variation, nitrone **8**, would be a viable solution. Finally from the precedent of Belzecki



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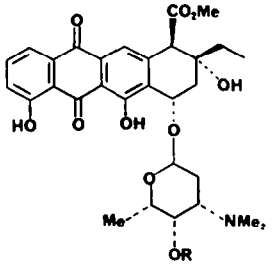
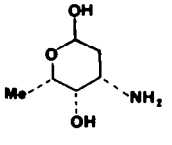


2 R = 2-deoxy-fucose-cinerulose A



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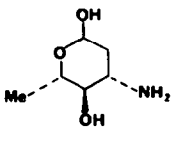

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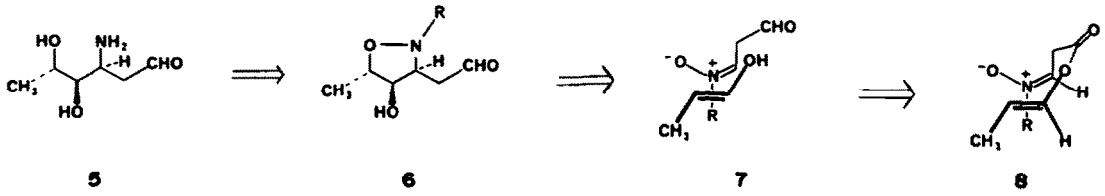


Scheme 1.

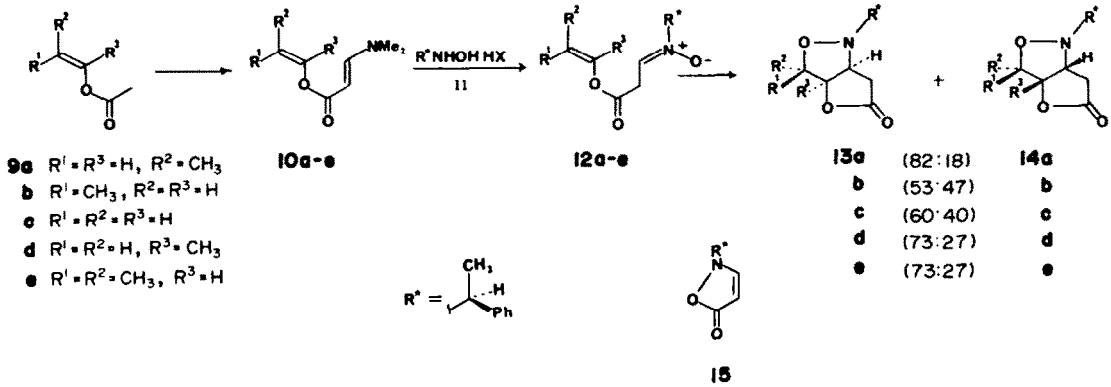
and Panfil[10] and Vasella[11] it seemed reasonable to expect that some measure of enantioselection could be achieved with a chiral substituent on nitrogen.

Typically, nitrones may be obtained by condensation of an aldehyde with a mono-N-substituted hydroxylamine.[1] In this case, it was found that β-dimethyl-amino-acrylate esters were convenient aldehyde equivalents, easily obtained by the general procedure of Bredereck *et al.*[12] Heating *trans*-propenyl acetate (**9a**)[13] with an excess of bis-dimethylamino-t-butoxymethane cleanly produced the desired acrylate derivative **10a** in 90% yield (Scheme 2). Similarly prepared were esters **10b–e** from their corresponding enol acetates.

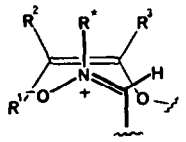
The stage was now set to examine the cycloaddition reaction. On exposure to the oxalate salt (*S*)-(−)-N-hydroxy-α-methylbenzenemethanamine (**11**)[14] in refluxing xylene the β-dimethylamino acrylate-*trans*-propenyl ester **10a** underwent the exchange reaction with loss of dimethylamine oxalate and isomerization to form nitrone **12a** which cyclized to an 82 : 18 mixture of diastereomers (Scheme 2).[15] The NMR spectra indicated both to be of the desired bicyclo[3.3.0]octane series, the stereochemistry of which was deduced from the rather large (*ca* 1 ppm) upfield shift of the methylene protons α to the carbonyl in the major isomer relative to the minor isomer. Consideration of the preferred rotamers for each possibility led to the assignment of **13a** for the major isomer, where the phenyl group would be in proximity to the methylene protons, and **14a** to the minor isomer, where the benzylic methyl group would be closer to the methylene protons. An unambiguous confirmation was secured by both an X-ray crystallographic analysis and by conversion of the major isomer to known compounds (*vide infra*). Thus, in a single step, the [3 + 2] cycloaddition has created three new chiral centers, each bearing the necessary functionality and proper relative and absolute stereochemistry for acosamine. Significantly, the crucial reversal of the usual regiochemical preference for nitrone to enol ester cycloaddition had been achieved.[16]

The effects of olefin substitution on the cycloaddition were examined using enol ester derivatives **9b–e** (Scheme 2). Under similar conditions as above, the *cis*-monosubstituted ester **9b** and the unsubstituted enol ester **9c** underwent the nitrone formation and cycloaddition in good overall yield (81 and 90%, respectively) but with low diastereoselectivity (53 : 47, **13b/14b** and 60 : 40, **13c/14c**, respectively) No *cis–trans* isomerization of the enol double bond for **9a** or **9b** was observed. The isopropenyl acetate derivative **9d** produced a 73 : 27 mixture of **13d** and **14d** in 30% yield. Unfortunately **9d**, to a major extent, is transformed to the by-product **15** prior to cycloaddition. Attempts to suppress this unwanted reaction have not yet been successful.[17] The disubstituted enol ester **9e** gave a 73 : 27 mixture of **13e** and **14e** in 65% yield. Taken together these results implicate some of the controlling elements for the diastereoselection.

Assuming that the cycloaddition proceeds via the *Z* nitrone, then the transition state would be represented by **16**, in which the proton on the nitrone carbon and R^3 end up in a *cis* relationship. The degree of diastereoselection would seem to depend on the extent of interaction between R^2 or R^3 and the nitrogen substituent R* as well as the manner in which the rotamers of R* best accommodate this interaction during the cycloaddition. The olefinic substituent R^1 should have little direct influence on this process. From the above results, the selection was smallest for the examples where R^2 and R^3 are hydrogen (i.e. **9b** and **c**)



Scheme 2.

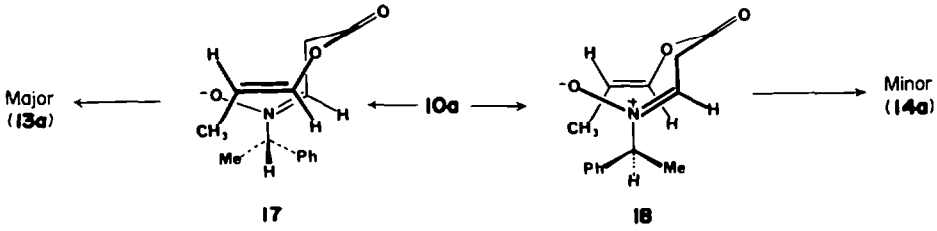


16

increasing to 73 : 27–82 : 18 for R^2 or R^3 = methyl as in **9a,d,e**.

While the details of the diastereoselection remain unknown, a working model is given in Scheme 3. By Dreiding models, these rotamers appear to have the least amount of interaction between the incoming olefin and the α-methylbenzyl group and are similar to their respective orientations in the cycloadducts.[18,19] Cycloaddition via **17** is the preferred route leading to the major isomer (**13a**) and via the less favored **18** gives the minor cycloadduct (**14a**). Applying this same model daunosamine required an additional inversion of the C-4 hydroxyl group. Two approaches were examined, the first as a route to l-daunosamine and the second as a more practical route to l-acosamine.

The first approach began with cleavage of the N—O bond in **13a** using zinc in acetic acid to give **19a** which was converted to the corresponding N-carbomethoxy derivative **19b** with methylchloroformate (Scheme 4). Dibal reduction produced lactol **20** which underwent the furanose to pyranose rearrangement to **21a** and its anomer (*ca* 4 : 1) with acidic methanol in 89% yield. For analytical purposes, **21a** only was carried on in the synthesis. The α-methylbenzyl group was removed by sodium in liquid ammonia to give **21b**. The C-4 hydroxyl inversion was accomplished by heating the mesylate **21c** in aqueous dimethylformamide to give **22a**.[21] Hydrolysis of the N-carbomethoxy group with aqueous barium hydroxide gave 1-α-methyl-daunosaminide **22b** which was identical with authentic

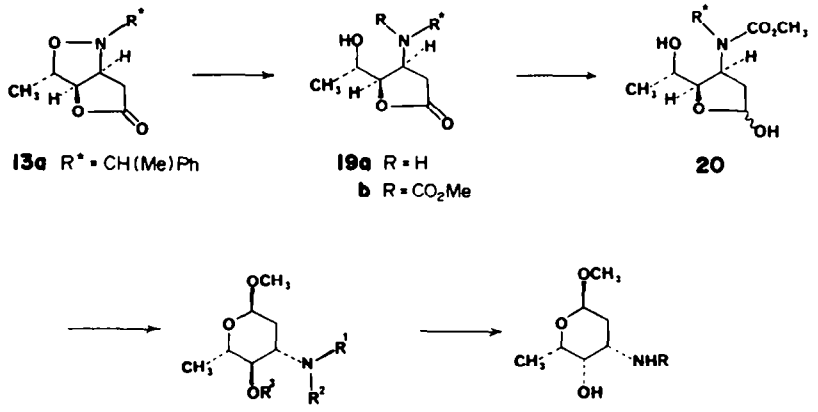


Scheme 3.

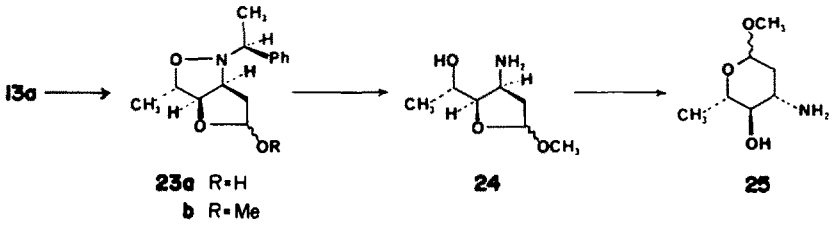
(i.e. rotamer **17** preferred to **18**) to intermolecular situations also consistently reproduces the direction of diastereoselection for the intermolecular examples (*exo* and *endo* modes) observed by Belzecki and Panfil.[10]

The final conversion of cycloadduct **13a** to 1-acosamine required three basic operations: (1) cleavage of the isoxazolidine N—O bond; (2) reduction of the lactone carbonyl to an aldehyde level; (3) removal of the benzyl group on nitrogen. The conversion to 1-material[22] by NMR, mass spec., TLC and mixed m.p. The conversion of **22b** to l-daunosamine (**3**) has been described previously.[6] A similar hydrolysis of **21b** provided 1-α-methyl-acosaminide (**21d**) which was identical with authentic material[22] by NMR, mass spec., TLC and mixed m.p. The conversion of **21d** to 1-acosamine (**4**) has likewise been carried out previously.[6]

The ordering of operations was changed in the second route to acosamine from **13a**. First the lactone



Scheme 4.



Scheme 5.

was reduced to lactols **23a** (*ca* 2:1 mixture) with diisobutylaluminum hydride and then converted to acetals **23b** (*ca* 3:1 anomeric mixture) with methanol and an acidic ion exchange resin (Scheme 5). Scission of both the N—O and N—benzyl bonds was accomplished by hydrogenolysis over Pd/C in methanol to **24** which could be rearranged to a mixture of pyranose anomers **25** under acidic conditions. This anomeric mixture is inconsequential for the hydrolysis to acosamine (**4**) and in principle, hydrolysis directly from **24** to **4** is feasible. For the purpose of identification, however, the anomeric mixture **25** was converted to the corresponding N-trifluoroacetyl derivatives, the major one of which was found to be **21e** by comparison to authentic material.[22,23] The minor N-trifluoroacetyl anomer was reconverted to a mixture of anomers with acidic methanol.

In summary, an intramolecular version of a [3+2] nitrone–olefin cycloaddition has reversed the usual regiochemical preference for a nitrone to add to an enol ester. With a chiral substituent on the nitrogen cycloadducts are formed with varying degrees of diastereoselection, the extent of which was dependent on the olefin substitution pattern. One of these richly functionalized cycloadducts was elaborated to immediate precursors of 1-acosamine and 1-daunosamine in only a few steps. The synthetic utility of the other cycloadducts is presently under investigation.

EXPERIMENTAL

General methods. M.ps were obtained on a Thomas–Hoover m.p. apparatus and are uncorrected. IR spectra were obtained on a Digilab Model FTS-15E spectrometer. The ^{1}H-NMR spectra were obtained on a Varian XL200 (200 mHz) spectrometer as solns in $CDCl_3$ unless indicated otherwise. Chemical shifts are reported in ppm downfield from internal TMS and apparent splittings are given in hertz. Mass spectral data were obtained on a Varian MAT CH-5 mass spectrometer. Preparative liquid chromatography was carried out at medium pressure on home built LC systems employing 40–60 μm silica gel packed commercially available empty glass columns.

Preparation of (S)-(−)-N-hydroxy-α-methylbenzenemethanamine oxalate (**11**)[5]

A mixture of 200 g $MgSO_4$ anhyd, 600 ml CH_2Cl_2, 96.3 g (0.79 mol) of (*S*)-(−)-α-methylbenzylamine and 110 ml (0.90 mol) of *p*-anisaldehyde was stirred under argon at room temp overnight. The mixture was then filtered through a pad of $MgSO_4$ washing with 1.4 l CH_2Cl_2. The filtrate was transferred to a flask equipped with a mechanical stirrer and under an argon atmosphere cooled to 0°. Then 208 g (*ca* 1.02 mol) of 85% *m*-chloroperbenzoic acid slurried in 400 ml CH_2Cl_2 was added. The temp rose to 17° then declined. Stirring was continued for 1.5 hr at which time the cooling bath was removed and stirring continued for 2.5 hr. The mixture was filtered, the solid washed with 500 ml CH_2Cl_2 and the filtrate washed successively with 600 ml 0.5 M Na_2SO_3, 800 ml of 0.5 M K_2CO_3, 200 ml H_2O and dried over Na_2SO_4. Removal of solvents by rotary evaporator (water not exceeding 30°) gave a 221 g residue (oxaziridine) which was dissolved in 1 l of absolute EtOH, cooled to 0° under argon, and treated with 75.5 g (1.09 mol) hydroxylamine hydrochloride. The mixture was stirred overnight during which time the cooling bath was allowed to warm to room temp. 1.5 l of $CHCl_3$ was added to precipitate excess hydroxylamine hydrochloride. After 2 hr the mixture was filtered and the solvents removed under reduced pressure. The residue was taken up in 500 ml H_2O and washed 2 × 500 ml Et_2O. The aqueous phase was treated with 500 ml sat $NaHCO_3$ and extracted 5 × 500 ml Et_2O. The combined extracts were dried over Na_2SO_4 and filtered into a flask containing 94 g (1.04 mol) of anhyd oxalic acid dissolved in 600 ml Et_2O. The precipitated oxalate salt was recrystallized from EtOH–MeOH to give 123.6 g (69%) of oxalate **11**, m.p. 177–180° (dec.), $[\alpha]_D^{25} = -2.6$ (c 1.02, CH_3OH). Mother liquors could be reworked to give another 7 g (3.8%).

Preparation of trans-3-(dimethylamino)-propenic acid, trans-propenyl ester **10a**

A soln of 20 g (0.2 mol) of *trans*-propenylacetate, **9a**,[13] and 101 g (0.6 mol) of bis(dimethylamino)-t-butoxymethane[12] was heated at 50° overnight (16.5 hr). The excess reagent was removed by vacuum distillation (0.7 mmHg, oil bath 50°). The residue was chromatographed rapidly on silica gel eluting with hexane–EtOc (3:2) to give 28.2 g (91%) of product **10a** which was used in the next step with no further purification. For an analytical sample, a portion of this material was sublimed (40–50°/0.2 mmHg) to remove a yellow color, then recrystallized from pentane. M.p. 48.5°. (Found: C, 62.14; H, 8.21; N, 9.08. Calc for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03%), IR ($CHCl_3$) 1692, 1677, 1617 cm^{-1}, NMR δ 1.62 (dd, J = 1, 7 Hz, 3H), 2.91 (s, 6H), 4.50 (d, J = 13 Hz, 1H), 5.28 (dq, J = 12, 7 Hz, 1H), 7.14 (dq, J = 12, 1H), 7.47 (d, J = 13 Hz, 1H), UV (dioxane) 285 (34,400).

Trans-3-(dimethylamino)-2-propenic acid, *cis*-propenyl ester **10b** was obtained from *cis*-propenyl acetate **9b**.[13] NMR (100 mHz) δ 1.60 (dd, J = 2, 6 Hz, 3H), 2.89 (s, 6H), 4.48 (d, J = 13 Hz, 1H), 4.71 (dq, J = 6, 6 Hz, 1H), 7.03 (dq, J = 6, 2 Hz, 1H), 7.45 (d, J = 13 Hz, 1H).

Trans-3-(dimethylamino)-2-propenic acid, ethenyl ester **10c** was prepared from **9c**. NMR (200 mHz) δ 2.95 (s, 3H), 4.35 (d, J = 6 Hz, 1H), 4.44 (d, J = 13 Hz, 1H), 4.75 (d, J = 14 Hz, 1H), 7.38 (dd, J = 6, 14 Hz, 1H), 7.55 (d, J = 3 Hz, 1H).

Trans-3-(dimethylamino)-2-propenic acid, isopropenyl ester **10d** was prepared from **9d**. NMR (200 mHz) δ 1.86 (s, 3H), 2.83 (s, 6H), 4.45 (d, J = 13 Hz, 1H), 4.56 (m, 2H), 7.40 (d, J = 13 Hz, 1H).

Trans-3-(dimethylamino)-2-propenic acid, isobutenyl ester **10e** was prepared from **9e**. NMR (200 mHz) δ 1.64 (s, 3H), 1.69 (s, 3H), 2.86 (s, 3H), 4.49 (d, J = 13 Hz, 1H), 6.87 (s, 1H), 7.45 (d, J = 13 Hz, 1H).

Cycloaddition of nitrones **12a–e** *to isoxazolidines* **13a–e** *and* **14a–e**

On *ca* 1 g scale, a mixture of enol ester, 1.3 equiv oxalate **11** and dry xylene were heated (oil bath *ca* 150°) under argon for 1–2 hr, cooled, filtered and purified whereas for larger scale it

was advantageous to add the oxalate portionwise, an example of each is given for the enol ester **10a**.

A mixture of 1.57 g (6.9 mmol) **11**, 0.776 g (5.0 mmol) **10a** and 65 ml of dry xylene was heated under argon at 150° for 50 min, cooled and filtered, washing the solid with CH_2Cl_2. Concentration of the filtrate *in vacuo* gave a solid residue which on recrystallization from Et_2O gave 0.475 g of **13a**. The mother liquors were chromatographed on silica gel eluting with ether–toluene (10 : 1) to give a combined total of 0.721 g (58%) of **13a**,[24] m.p. 138–138.5° (ether); $[\alpha]_D^{25} = 17.2°$ (c 0.69, $CHCl_3$). (Found: C, 68.28; H, 6.80; N, 5.60. Calc for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66%), IR ($CHCl_3$) 1782 cm^{-1}, NMR (100 mHz) δ 1.37 (d, J = 7 Hz, 3H), 1.52 (d, J = 7 Hz, 3H), 1.69 (AB, J_{gem} = 18 Hz, J_{vic} = 2 Hz, 1H), 1.98 (AB, J_{gem} = 18 Hz, J_{vic} = 8 Hz, 1H), 3.44 (dt, J = 2, 8 Hz, 1H), 3.69 (q, J = 7 Hz, 1H), 4.02 (dq, J = 5, 7 Hz, 1H), 4.52 (dd, J = 5, 8 Hz, 1H), 7.24 (s, 5H); and 0.164 g (13%) of **14a**,[24] m.p. 133–133.5° (ether), $[\alpha]_D^{25} = -54.3°$ (c 0.83, $CHCl_3$). (Found: C, 67.87; H, 6.78; N, 5.54. Calc for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66%), IR ($CHCl_3$) 1785 cm^{-1}, NMR (100 mHz) δ 1.28 (d, J = 7 Hz, 3H), 1.40 (d, J = 7 Hz, 3H), 2.60 (d, J = 6 Hz, 2H), 3.52 (dt, J = 7, 6 Hz, 1H), 3.85 (q, J = 7 Hz, 1H), 3.99 (dq, J = 4.7 Hz, 1H), 4.56 (dd, J = 4, 7 Hz, 1H), 7.25 (s, 5H).

Large scale cycloaddition: In a 3 l, 3-necked flask fitted with reflux condenser and mechanical stirrer was placed 1.5 l of dry xylenes and 37.25 g (0.24 mol) of **10a**. The mixture was heated to reflux under argon, then in eight portions (*ca* 9.4 g each slurried with 100 ml of xylenes) a total of 75.22 g (0.33 mol) of oxalate **11** was added at 10 min intervals, and the mixture refluxed for an additional 75 min. The cooled mixture was filtered, concentrated, crystallized from ether and mother liquors chromatographed on silica gel (applied in CH_2Cl_2) eluting with hexane–EtOAc (4 : 1) to give 29.4 g (50%) **13a** and 6.3 g (11%) of **14a**.

Isoxazolidines **13b** *and* **14b** *from* **10b** *and* **11**

The reaction was run in refluxing toluene for 1 hr, chromatographed on silica gel eluting with hexane–CH_2Cl_2–EtOAc (2 : 2 : 1) to give **13b** (43%) and **14b** (38%). **13b**, m.p. 113–113.5° (Et_2O), $[\alpha]_D^{25} = 10.3°$ (c 0.62, $CHCl_3$). (Found: C, 68.18; H, 6.89; N, 5.63. Calc for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66%), IR ($CHCl_3$) 1781 cm^{-1}, NMR (200 mHz) δ 1.32 (d, J = 6.5 Hz, 3H), 1.41 (d, J = 6Hz, 3H), 2.58 (dd, J = 8, 19 Hz, 1H), 2.62 (dd, J = 5.5, 19 Hz, 1H), 3.86 (q, J = 6 Hz, 1H), 3.95 (ddd, J = 5.5, 7, 8 Hz, 1H), 4.28 (dq, J = 4, 6.5 Hz, 1H), 5.10 (dd, J = 4, 7 Hz, 1H), 7.24 (s, 5H).

14b,[24] m.p. 137–137.5° (ether), $[\alpha]_D^{25} = -46.7°$ (c 0.61, $CHCl_3$). (Found: C, 68.07; H, 7.03; N, 5.44. Calc for $C_{14}H_{17}NO_3$: C, 68,00; H, 6.93; N, 5.66%), IR ($CHCl_3$) 1787 cm^{-1}, NMR (100 mHz) δ 1.18 (d, J = 7 Hz, 3H), 1.41 (d, J = 7 Hz, 3H), 2.48 (dd, J = 9, 19, 1H), 2.90 (dd, J = 4, 19 Hz, 1H), 3.87 (q, J = 7 Hz, 1H), 4.05 (ddd, J = 4, 7, 9 Hz, 1H), 4.12 (dq, J = 4, 7 Hz, 1H), 5.05 (dd, J = 4, 7 Hz, 1H), 7.23 (s, 5H).

Isoxazolidines **13c** *and* **14c** *from* **10c** *and* **11**

The reaction was run in refluxing toluene for 1.5 hr, chromatographed on silica eluting with ether to give **13c** (54%) and **14c** (36%). **13c**, m.p. 92–93° (ether–hexane), $[\alpha]_D^{25} = 45.8°$ (c 0.52, $CHCl_3$). (Found: C, 66.84; H, 6.45; N, 5.93. Calc for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00%), NMR (200 mHz) δ 1.41 (d, J = 7 Hz, 3H), 2.39 (d, J = 4, 20 Hz, 1H), 2.51 (d, J = 8, 20 Hz, 1H), 3.76 (q, J = 7 Hz, 1H), 3.82 (m, 1H), 4.04 (dd, J = 2, 10 Hz, 1H), 4.18 (dd, J = 5, 10 Hz, 1H), 5.27 (ddd, J = 2, 5, 7 Hz, 1H), 7.25 (s, 5H).

14c, m.p. 100–101° (ether–hexane), $[\alpha]_D^{25} = -63.6°$ (c 0.52, $CHCl_3$). (Found: C, 66.75; H, 6.62; N, 5.91. Calc for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00%), NMR (200 mHz), δ 1.43 (d, J = 7 Hz, 3H), 2.62 (brdd, J = 8, 19 Hz, 1H), 2.80 (dd, J = 4, 19 Hz), 3.81 (m, 2H), 3.85 (q, J = 7 Hz, 1H), 4.06 (dd, J = 6, 10 Hz, 1H), 5.23 (m, 1H), 7.30 (s, 5H). At 55° the brd at 2.62 became sharper.

Isoxazolidines **13d** *and* **14d** *from* **10d** *and* **11**

The reaction was run in refluxing xylene for 2 hr, chromatographed on silica gel eluting with hexane–EtOAc (1 : 1) to give **13d** (22%) and **14d** (8%). **13d**,[24] m.p. 65.5° (ether–pentane), $[\alpha]_D^{25} = 36.9°$ (c 0.77, $CHCl_3$). (Found: C, 68.05; H, 7.07; N, 5.60. Calc for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66%), IR ($CHCl_3$) 1763 cm^{-1}, NMR (100 mHz) δ 1.46 (d, J = 6 Hz, 3H), 1.56 (s, 3H), 2.28 (dd, J = 4, 19 Hz, 1H), 2.51 (dd, J = 8, 19 Hz, 1H), 3.30 (dd, J = 4, 8 Hz, 1H), 3.83 (q, J = 6 Hz, 1H), 3.95 (AB, J = 12 Hz, 2H), 7.29 (s, 5H).

14d, m.p. 70.5–71° (ether–pentane), $[\alpha]_D^{25} = -70.4°$ (c 1.01, $CHCl_3$). (Found: C, 68.20; H, 6.74; N, 5.78. Calc for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66%), IR ($CHCl_3$) 1768 cm^{-1}, NMR (100 mHz) δ 1.41 (d, J = 7 Hz, 3H), 1.53 (s, 3H), 2.59 (dd, J = 7, 19 Hz, 1H), 2.82 (dd, J = 4, 19 Hz, 1H), 3.30 (dd, J = 4, 7 Hz, 1H), 3.85 (m, 3H), 7.29 (s, 3H).

15, IR ($CHCl_3$) 1730 cm^{-1}, NMR δ 1.70 (d, J = 7 Hz, 3H), 4.84 (q, J = 7 Hz, 1H), d 5.08 (d, J = 4 Hz, 1H), s 7.30 (s, 5H), 7.68 (d, J = 4 Hz, 1H).

Isoxazolidines **13e** *and* **14e** *from* **10e** *and* **11**

The reaction was run in xylenes for 2 hr, chromatographed on silica gel eluting with hexane–EtOAc (4 : 1) to give **13e** (48%) and **14e** (17%). **13e**,[24] m.p. 117–118° (ether), $[\alpha]_D^{25} = 4.5°$ (c 0.97, $CHCl_3$). (Found: C, 69.10; H, 7.27; N, 5.26. Calc for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36%), IR ($CHCl_3$) 1783 cm^{-1}, NMR (100 mHz) δ 1.30 (s, 3H), 1.38 (s, 3H), 1.47 (d, J = 7 Hz, 3H), 1.90 (dd, J = 4, 19 Hz, 1H), 2.03 (dd, J = 7, 19 Hz, 1H), 3.67 (ddd, J = 4, 7, 7 Hz, 1H), 3.75 (q, J = 7 Hz, 1H), 4.58 (d, J = 7 Hz, 1H), 7.30 (s, 5H).

14e, m.p. 106–107° (ether) $[\alpha]_D^{25} = -64.6°$ (c 1.12, $CHCl_3$). (Found: C, 69.09; H, 7.61; N, 5.31. Calc for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36%), IR ($CHCl_3$) 1781 cm^{-1}, NMR (200 mHz) δ 1.26 (s, 3H), 1.33 (s, 3H), 1.40 (d, J = 6 Hz, 3H), 2.41 (dd, J = 8, 18 Hz, 1H), 2.76 (dd, J = 3, 18 Hz, 1H), 3.69 (ddd, J = 3, 8, 8 Hz, 1H), 3.81 (q, J = 6 Hz), 4.68 (d, J = 8 Hz, 1H), 7.30 (s, 5H).

Preparation of lactone **19a** *from* **13a**

A soln of 0.939 g (4 mmol) **13a**, 120 ml HOAc–H_2O (1 : 1) and 3.73 g Zn dust were stirred under an argon atmosphere at room temp for 22.5 hr. The mixture was filtered washing the solid with water then EtOAc and concentrated *in vacuo*. The residue was taken up with 400 ml EtOAc and 60 ml 2 N K_2CO_3, washed 1 × 60 ml 2 N K_2CO_3 and dried over Na_2SO_4. The crude product was chromatographed on silica gel eluting with EtOAc to give 0.891 g (89%) of **19a**, m.p. 58–60° (ether), $[\alpha]_D^{25} = -17.1°$ (c 0.90, CH_3OH). (Found: C, 67.58; H, 7.69; N, 5.88. Calc for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62%), IR ($CHCl_3$) 1780 cm^{-}, NMR (100 mHz) δ 1.33 (d, J = 6 Hz, 3H), 1.38 (d, J = 6 Hz, 3H), 2.29 (dd, J = 7, 19 Hz, 1H), 2.49 (dd, J = 8, 19 Hz, 1H), 3.6–4.2 (m, 4H), 7.30 (s, 5H).

Preparation of **19b**

To a soln of 10.0 g (40 mmol) **19a** in 400 ml of THF was added (with cooling), 800 ml 2 N Na_2CO_3 and 160 ml of methylchloroformate. The mixture was stirred for 5 hr then extracted 4 × 500 ml of EtOAc. The combined extracts were washed with water then dried over Na_2SO_4. The crude product was chromatographed on silica gel eluting with EtOAc to give 9.82 g of product which after crystallization from ether gave 6.94 g (54%) of **19b**, m.p. 124.5° (ether), $[\alpha]_D^{25} = -82.1$ (c 1.03, $CHCl_3$). (Found: C, 62.58; H, 6.58; N, 4.52. Calc for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56%), IR ($CHCl_3$) 1783, 1703 cm^{-1}, NMR (200 mHz) δ 1.14 (d, J = 7 Hz, 3H), 1.56 (d, J = 7 Hz, 3H), 2.52 (brd, J = 18 Hz, 1H), 2.95 (dd, J = 9, 18 Hz, 1H), 3.61 (m, 1H), 3.76 (s, 3H), 3.88 (dd, J = 9, 9 Hz, 1H), 4.07 (brt, J = 9 Hz, 1H), 5.50 (m, 1H), 7.33 (s, 5H). At 55°, the brd at 2.52 sharpened, and the m at 5.50 became a broad quartet (coupled to Me doublet at 1.56 brq, J = 7 Hz, 1H).

Preparation of **21a** *from* **19b**

Diisobutylaluminum hydride (33 ml, *ca* 50 mmol) in toluene (25%) was added to a mixture of 3.07 g (10 mmol) of **19b** in 300 ml of dry THF under an argon atmosphere and at −78°. After 5 hr the reaction was quenched by addition of methanol. 150 ml of sat Na_2SO_4 soln was added followed by brine to break-

up an emulsion. The mixture was extracted 3 × 500 ml CH_2Cl_2. The combined extracts were washed with water then dried over Na_2SO_4. The crude product (**20**, 3.35 g) was stirred with 5.75 g of Amberlite CG 120 (200–400 mesh, H^+ form) and 500 ml of MeOH. The mixture was filtered and concentrated *in vacuo*, chromatographed on silica gel [hexane–EtOAc (1:1)] to give 2.88 g (89%) of **21a** and its anomer as a 4:1 mixture. **21a** was isolated by mplc [hexane–EtOAc (3:1)], $[\alpha]_D^{25} = -106.1°$ (c 0.90, $CHCl_3$). (Found: C, 63.26; H, 7.94; N, 4.31. Calc for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33%), IR ($CHCl_3$) 3570, 1693 cm^{-1}, NMR (100 mHz) δ 1.09 (d, J = 6 Hz, 3H), 1.50 (d, J = 7 Hz, 3H), 1.76 (brd, J = 14 Hz, 1H), 2.36 (brd, J = 14 Hz, 1H), 3.23 (s, 3H), 3.2–3.6 (m, 3H), 3.61 (s, 3H), 4.63 (d, J = 3 Hz, 1H), 5.28 (m, 1H), 7.29 (m, 5H).

Preparation of **21b**

Ca 10 ml of NH_3 was distilled from Na into a soln of 0.277 g (4 mmol) **21a** and 3 ml of dry THF at −78°, then *ca* 0.1 g (4 mmol) Na metal added and mixture stirred 3 hr. The reaction was quenched by addition of solid NH_4Cl and the ammonia evaporated under a stream of argon. The residue was taken up in 20 ml sat $NaHCO_3$, extracted 3 × 50 ml CH_2Cl_2 and the combined extracts dried over anhyd Na_2SO_4. The crude product (0.171 g) was recrystallized from ether to give 0.142 g (75%) of **21b**, m.p. 142.5–143° (ether), $[\alpha]_D^{25} = -162.6°$ (c 0.71, $CHCl_3$). (Found: C, 49.26; H, 7.83; N, 6.22. Calc for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39%), IR ($CHCl_3$) 3440, 1706 cm^{-1}, NMR (100 mHz) δ 1.26 (d, J = 6 Hz, 3H), 1.59 (dt, 3, 13 Hz, 1H), 2.08 (dd, J = 4, 13 Hz, 1H), 3.04 (m, 1H), 3.37 (s, 3H), 3.4–4.1 (m, 3H), 3.72 (s, 3H), 4.76 (d, J = 3 Hz, 1H), 5.04 (m, 1H).

Preparation of **21c**

To a soln of 0.3 g (1.37 mmol) of **21b** in 30 ml of dry pyridine under argon at 0° was added 0.6 ml (*ca* 7.8 mmol) of methanesulfonyl chloride. After 2.5 hr ice was added, the mixture was stirred 5 min, treated with 20 ml sat $NaHCO_3$ and extracted 3 × 100 ml CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered and concentrated, *in vacuo* to give 0.3635 g of crude product. Recrystallization from ether gave 0.28 g (69%) of **21c**, m.p. 141–142°, $[\alpha]_D^{25} = -109.5°$ (c 0.97, $CHCl_3$). (Found: C, 40.66; H, 6.46; N, 4.58. Calc for $C_{10}H_{19}NO_7S$: C, 40.40; H, 6.44; N, 4.71%), IR ($CHCl_3$) 3430, 1725 cm^{-1}, NMR (100 mHz) δ 1.31 (d, J = 6 Hz, 3H), 1.71 (m, 1H), 2.18 (dd, J = 4, 13 Hz, 1H), 3.02 (s, 3H), 3.31 (s, 3H), 3.65 (s, 3H), 3.7–4.3 (m, 3H), 4.68 (d, J = 3 Hz, 1H), 5.12 (m, 1H).

Preparation of **21d**

A mixture of 0.02 g (0.091 mmol) of **21b**, 10 ml H_2O, 5 ml MeOH, and 0.063 g $Ba(OH)_2 \cdot 8H_2O$ were refluxed under argon for 5 hr, then an additional 0.12 g $Ba(OH)_2 \cdot 8H_2O$ was added. After 24 hr the cooled mixture was treated with CO_2, filtered and concentrated *in vacuo*. The residue was taken up in H_2O and passed through AG-1-X4 (OH^- form) ion exchange resin and concentrated *in vacuo*. The residue was sublimed under vacuum to give 0.008 g (54%)[25] of **21d**, m.p. 129.5–130.5° (lit.[26] m.p. 132–133°), which did not depress on mixture with authentic material. $[\alpha]_D^{25} = -140.4°$ (c 0.23, CH_3OH) (lit.[26] $[\alpha]_D^{25} = -145.1°$ (c 0.61, CH_3OH)). In addition, the sample was identical to authentic material[25] by NMR and mass spec.

Preparation of **22a**

A mixture of 0.1189 g (0.4 mmol) of **21c**, 0.32 g of anhyd NaOAc, and 40 ml DMF–H_2O (65:35) was heated under argon at 105° for 42.5 hr. The mixture was concentrated *in vacuo*, treated with 20 ml sat $NaHCO_3$ and extracted 3 × 60 ml of CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered, concentrated *in vacuo* and the residue (0.081 g) chromatographed on silica gel eluting with EtOAc to give 0.044 g (50%)[25] of **22a**, m.p. 90–90.5° (ether–pentane), $[\alpha]_D^{25} = -166.7°$ (c 0.40, $CHCl_3$). (Found: C, 49.33; H, 7.80; N, 6.45. Calc for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39%), IR ($CHCl_3$) 3580, 3445, 1722 cm^{-1}, NMR (100 mHz) δ 1.21 (d, J = 6.5 Hz, 3H), 1.68 (dt, J = 4, 14 Hz), 1.88 (dd, J = 4, 14 Hz, 1H), 3.31 (s, 3H), 3.56 (m, 1H), 3.64 (s, 3H), 3.95 (q, J = 6.5 Hz, 1H), 3.98 (m, 1H), 4.72 (d, J = 3 Hz, 1H), 5.15 (brm, 1H).

Preparation of **22b**

A mixture of 0.0151 g (0.069 mmol) **22a**, 0.1 g $Ba(OH)_2 \cdot 8H_2O$, 10 ml of H_2O and 5 ml of MeOH were heated at 110° for 12 hr then room temp 8 hr. The solvents were removed *in vacuo*, the residue taken up in MeOH, filtered and concentrated *in vacuo*. This residue was boiled 2 × 40 ml of Et_2O, the extracts concentrated, and the residue (0.129 g) passed through AG-1-X4 (OH^- form) ion exchange resin with H_2O. After evaporation of solvent, the residue was sublimed at *ca* 60° (0.05 mmHg) to give 0.0051 g (46%)[25] of **22b**, which was identical with authentic material[22] by mixed m.p., NMR, mass spec and TLC.

Preparation of lactol **23a** *from* **3a**

Diisobutylaluminum hydride (24 ml, *ca* 3 mmol, 25% in toluene) was added to a mixture of 3.711 g (15 mmol) of **13a**, in 120 ml of dry THF at −78° over 10 min. The mixture was stirred 3 hr then quenched by addition of 12 ml of MeOH. The cooling bath was removed and after 15 min, 400 ml of EtOAc was added and stirring continued from 30 min. The mixture was filtered through Celite and concentrated *in vacuo* to give 4.07 g of crude product. Silica gel chromatography [hexane–EtOAc (1:1)] gave 3.67 g (98%) of **23a** as a 2:1 anomeric mixture, m.p. 106–108° (ether). (Found: C, 67.22; H, 7.55; N, 5.93. Calc for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.69; N, 5.62%), NMR (100 mHz) δ 1.31 (d, J = 7 Hz, 3H), 1.50 (d, J = 7 Hz, 3H), 1.3–1.8 (m, 2H), 3.20 (m, 1H), 3.63 (m, 1H), 3.72 (q, J = 7 Hz, 1H), 3.97 (dq, J = 5, 7 Hz, 1H), 4.48 (dd, J = 5, 8 Hz, 1H), 5.05–5.3 (m, 0.33H), 5.54 (m, 0.67H), 7.31 (s, 5H).

Preparation of **23b**

A mixture of 7.36 g (30 mmol) of crude **23a** used directly as crude material from a scaled-up experiment, 415 ml MeOH, 8.35 g of Amberlite CG 120 (200–400 mesh, H^+ form) and 2.5 g of 3 Å molecular sieves was stirred overnight then filtered through Celite. The filter cake was stirred for 2 hr with 500 ml MeOH and 15 ml of Et_3N, then filtered and combined filtrates concentrated *in vacuo* to give 6.28 g (88%) of crude product. Chromatography on silica gel eluting with hexane–EtOAc (1:1) gave 6.34 g (82%) of **23b** as a 3:1 mixtures of anomers. The analytical sample was Kugelrohr distilled (105°, 0.05 mmHg), $[\alpha]_D^{25} = -51.5°$ (c 1.27, $CHCl_3$). (Found: C, 68.48; H, 7.89; N, 5.21. Calc for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32%), NMR (100 mHz) distinguishing resonances δ 1.49 (d, J = 6 Hz, Me_{major}) 1.53 (d, J = 6 Hz, Me_{minor}), 3.22 (s, Me_{major}), 3.30 (s, Me_{minor}), 4.92 (dd, J = 2, 4 Hz, CH_{minor}), 5.00 (dd, J = 2, 5 Hz, CH_{major}).

Preparation of **24**

A mixture of 10.58 g (40 mmol) of **23b** (3:1 anomeric mixture) was hydrogenated at 50 psi over 4.0 g of 5% Pd/C in 930 ml MeOH for *ca* 46 hr. Filtration and concentration *in vacuo* gave 6.065 g of crude product as an anomeric mixture. Recrystallization from ether gave **24** as a single anomer, m.p. 59–62°, $[\alpha]^{25} = -120.8°$ (c 0.998, CH_3OH), NMR (100 mHz) δ 1.29 (d, J = 6 Hz, 3H), 1.84 (ddd, J = 4.5, 5.5, 13.5 Hz, 1H), 2.20 (ddd, J = 3, 7, 13.5 Hz, 1H), 2.75 (s, 3H), 3.29 (s, 3H), 3.5–4.0 (m, 3H), d 5.05 (dd, J = 3, 5.5 Hz, 1H), ^{13}C-NMR (25.2 mHz) δ 20.9 (CH_3), 43.3 (CH_2), 51.8 (CH), 54.8 (CH_3), 66.3 (CH), 82.8 (CH), 103.7 (CH).

Preparation of **25** *and* **21e**

A mixture of 4.524 g (28 mmol) of **24**, 2.57 g of Amberlite CG 120 (200–400 mesh, H^+ form), 1.5 g of 3 Å molecular sieves and 250 ml MeOH was stirred for 20 hr then 10 ml of Et_3N added. After an additional 1 hr the mixture was filtered and concentrated *in vacuo*. The residue was treated again with 5.14 g Amberlite CG 120 (200–400 mesh, H^+ form) and 250 ml of MeOH for 65 hr. 15 ml of Et_3N was added and after 1.5 hr the mixture was filtered through Celite. The filter cake was stirred 1 hr with 200 ml MeOH and 5 ml of Et_3N then filtered. The

combined filtrates were concentrated *in vacuo* to give 4.056 g of crude **25** from which 2.189 g of **25** could be crystallized from ether as a 2:1 mixture of anomers (by NMR, comparison to authentic material[22]). The mother liquors consisted of a mixture of **24** and **25**. For identification and anomer separation, 0.20 g (1.2 mmol) of **25** obtained above in 4 ml of Et_2O was treated with 0.8 ml of trifluoroacetic anhydride at 0°. After 15 min, the ice bath was removed and stirring under an argon atmosphere continued for 3 hr. Solvent and excess reagent were removed *in vacuo*. The residue was stirred 20 hr with 6 ml MeOH, then evaporated to dryness *in vacuo*. The crude product (0.344 g) was sublimed at 135° (0.092 mmHg) to give 0.279 g (93%) of **21e** and its β-anomer as a *ca* 2:1 mixture. The anomers were separated by silica gel chromatography eluting with hexane–EtOAc (2:1). **21e** gave m.p. 192–193.5°, no depression on mixture with authentic material,[22,23] $[\alpha]_D^{25} = -122°$ (c 0.56, $CHCl_3$), $[\alpha]_D^{25} = -109°$ (c 0.50, CH_3OH) and was identical by NMR to authentic material.[22,23] The β-anomer of **21e** could be reconverted to an α/β anomeric mixture by stirring it in methanol with Amberlite CG 120 (200–400 mesh, H^+ form) as above.

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[14] T. Polonski and A. Chimiak, *Tetrahedron Lett.* 2453 (1974). We are indebted to Professor Chimiak for providing us with a detailed experimental procedure for the preparation of the chiral hydroxylamine prior to its appearance in print [T. Polonski and A. Chimiak, *Bull. Acad. Pol. Sci. Ser. Sci. Chim.* **27**, 459 (1979)]. For convenience, we modified the procedure slightly and include it in the experimental section. The method of Polonski and Chimiak is superior to and safer than the procedure of G. Zinner, *Arch. Pharm.* **296**, 420 (1963).

[15] While this work was in progress, the isomerization of N-hydroxy-N-phenyl-β-aminoacrylate to a nitrone was described. R. A. Reamer, M. Sletzinger and I. Shinkai, *Tetrahedron Lett.* **21**, 3447 (1980). The resulting nitrone, however, suffered rather facile dimerization.

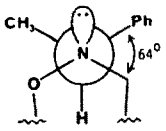
[16] This example is the only case, to our knowledge, where this regiochemical preference for simple enol ethers or esters has been reversed. In a previous intramolecular example reported by Oppolzer[8] the regio-preference was still 2:1 in the usual direction and may be suggestive of an additional electronic component from the ester carbonyl in **12**. Furan, a very special enol ether type, undergoes the initial nitrone cycloaddition in the reversed sense to a monoadduct which then behaves as a typical enol ether to undergo a second nitrone addition in the usual regiochemical sense. L. Fisera, J. Kováč, J. Poliačikova and J. Leško, *Montash. Chemie* **111**, 909 (1980) and references therein.

[17] The unwanted reaction of **9d** → **15** is apparently an acid catalyzed reaction which is further aggravated by the use of more polar solvents. Omission of an acid catalyst slows down the exchange reaction considerably and the lifetime of **9b** is consequently extended. Alternate routes to the nitrone **12d** are being evaluated.

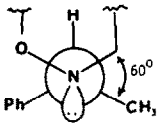
[18] We emphasize that this is an empirical model which attempts to rationalize the trends of diastereoselection here and in Belzecki and Panfil's[10] case. An estimation of the relative stabilities of **17** and **18** based on the assumption that for eclipsing interactions the nitrone oxygen is analogous to an aldehydic oxygen and the nitrone carbon is similar to a

substituted propene (for a review covering rotation about sp^2–sp^3 carbon–carbon bonds see G. J. Karabatsos and D. J. Fenoglio, *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger), Vol. 5, pp. 167–203. Wiley-Interscience, New York (1970) suggests that **17** would be lower energy then **18**. Ideally theoretical calculations should provide further insight into transition state stabilizations or destabilizations, from orbital interactions, steric effects, bond strains, etc. to account for the experimental results.[20]

[19] From the X-ray data for the major diastereomer (**13a**) the Ph—C—N—C angle is 64° (cf. **i**) and in the minor cycloadduct (**14a**) the CH_3—C—N—C angle is 60° (cf. **ii**).



i



ii

[20] In examining a system where the chiral substituent on the nitrogen is part of a furanose ring, Vasella[11] has suggested that favorable orbital interactions would arise when the carbon–oxygen bond is orthogonal to the nitrone in the transition state. The importance of such a rotamer in the present system is uncertain.

[21] For a similar inversion process see: J. P. Marsh, C. W. Mosher, E. M. Acton and L. Goodman, *J. Chem. Soc. Chem. Commun.* 973 (1967).

[22] Authentic methyl - 3 - amino - 2,3,6 - trideoxy - α - L - lyxo - hexopyranoside (**22a**) and methyl - 3 - amino - 2,3,6 - trideoxy - α - L - arabino - hexopyranoside (**21d**) were prepared by Dr G. Grethe.[6i,j]

[23] We thank F. Arcamone for providing an authentic sample of methyl - 2,3,6 - trideoxy - 3 - trifluoroacetamido - α - L - arabinohexopyranoside (**21e**).

[24] The structure was confirmed by an X-ray crystallographic analysis. We thank Dr J. Blount and his staff for making this determination.

[25] These conditions were not optimized.

[26] S. K. Gupta, *Carbohydr. Res.* **37**, 38 (1974).