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Asymmetric Syntheses of Methyl *N*,*O*-Diacetyl-D-3-*epi*-daunosaminide and Methyl *N*,*O*-Diacetyl-D-ristosaminide

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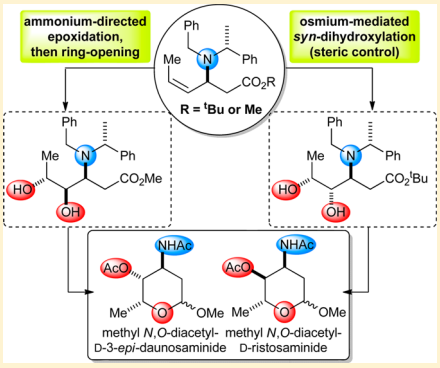
Supporting Information

ABSTRACT: Ab initio asymmetric syntheses of methyl *N*,*O*-diacetyl-D-3-*epi*-daunosaminide and methyl *N*,*O*-diacetyl-D-ristosaminide, employing diastereoselective epoxidation and dihydroxylation, respectively, of alkyl (3*S*,α*R*,*Z*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoates as the key steps, are reported. The requisite substrates were readily prepared using the conjugate additions of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to methyl and *tert*-butyl (*E*)-hexa-2-en-4-ynoates followed by diastereoselective alkyne reduction. *syn*-Dihydroxylation using OsO_4 proceeded under steric control on the 4*Re*,5*Re* face of the olefin to give the corresponding diol, which subsequently underwent lactonization. Meanwhile, epoxidation using F_3CCO_3H in conjunction with F_3CCO_2H proceeded on the opposite 4*Si*,5*Si* face of the olefin under hydrogen-bonding control from the in situ formed ammonium ion. Treatment of the intermediate epoxide with concd aq H_2SO_4 promoted highly regioselective ring-opening (distal to the in situ formed ammonium moiety) to give the corresponding diol (completing overall the formal *anti*-dihydroxylation of the olefin), which then underwent lactonization under the reaction conditions. Elaboration of these diastereoisomeric lactones through hydrogenolysis, *N*-Boc protection, reduction, methanolysis, and acetate protection gave methyl *N*,*O*-diacetyl-D-3-*epi*-daunosaminide and methyl *N*,*O*-diacetyl-D-ristosaminide.



INTRODUCTION

An amino sugar is any species resulting from the formal replacement of any of the nonglycosidic hydroxyl groups of a monosaccharide with an amino group. The amino sugar family of compounds comprises a structurally diverse array of species, and an important, specific subclass of these are the 2,3,6-trideoxy-3-aminohexoses: daunosamine **1**,[1] 3-*epi*-daunosamine **2**,[2] ristosamine **3**,[3,4] and acosamine **4**.[5] These compounds have attracted considerable interest, mainly due to their occurrence as the glycosidic fragment of a variety of naturally occurring and synthetic anthracycline antibiotics,[6] for example, naturally occurring daunorubicin **5**,[7] doxorubicin **6**,[8] and carubicin **7**[9] and the synthetic analogues idarubicin **8**[10] and epirubicin **9**[11] (Figure 1).

As a result of these potential therapeutic applications, a range of approaches to enable syntheses of the 2,3,6-trideoxy-3-aminohexoses have been developed,[12] with the majority of these commencing with carbohydrate-derived starting materials as the sources of chirality.[13] In contrast, relatively few asymmetric syntheses have been reported.[14] We have shown that (*E*)-configured β-amino-γ,δ-unsaturated esters such as **10**, which are readily derived from conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to the requisite ester of (*E*,*E*)-hexa-2,4-dienoic acid (sorbic acid), are valuable precursors for the synthesis of amino sugars through their oxidative functionalization in a diastereoselective manner.[15−17] For example, treatment of **10** with 40% aq HBF_4 followed by *m*-chloroperbenzoic acid (*m*-CPBA) gave an ∼70:30 mixture of lactones **13** and **14**. This is consistent with a completely diastereoselective (>95:5 dr), ammonium-directed epoxidation[18,19] of the 4*Si*,5*Re* face[20] of **10** to give epoxide **11**, followed by regioselective ring-opening at the C(5)-oxirane carbon atom (distal to the in situ formed ammonium moiety) to give the corresponding diol **12** (overall a formal *anti*-dihydroxylation of the olefin). Lactonization of **12** under the acidic reaction conditions upon attack of either the C(4)-hydroxyl group or the C(5)-hydroxyl group at the carbonyl group gives γ-lactone **13** or δ-lactone **14**, respectively. The mixture of lactones **13** and **14** was converted to the corresponding 2,3,6-trideoxy-3-aminohexose, viz. L-acosamine **4**, which was isolated as the corresponding *N*,*O*-diacetyl-protected methyl glycoside **15** in only seven steps and 15% overall yield from sorbic acid[15] (Scheme 1).

Herein, efficient asymmetric syntheses of methyl *N*,*O*-diacetyl-D-3-*epi*-daunosaminide and methyl *N*,*O*-diacetyl-D-ristosaminide are reported, which employ highly diastereoselective epoxidation and dihydroxylation, respectively, of (*Z*)-configured β-amino-γ,δ-unsaturated esters **16** as the key steps. From the outset of these studies, it was expected that these

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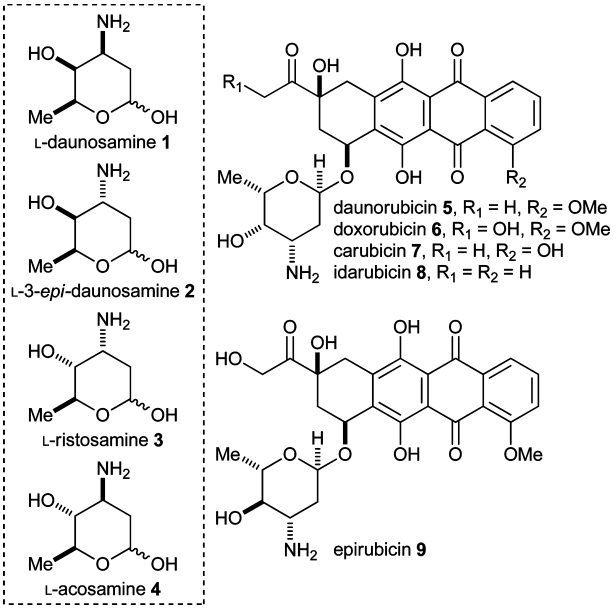


Figure 1. Structures of L-daunosamine **1**, L-3-*epi*-daunosamine **2**, L-ristosamine **3**, L-acosamine **4**, and the anthracycline antibiotics daunorubicin **5**, doxorubicin **6**, carubicin **7**, idarubicin **8**, and epirubicin **9**.

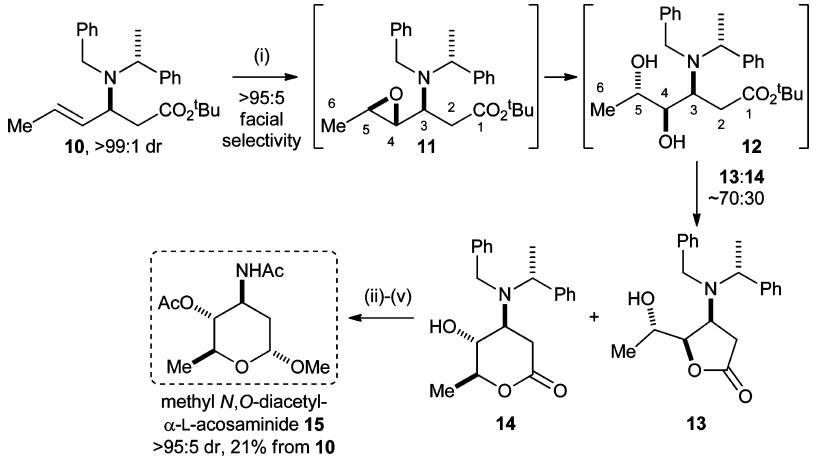
substrates would favor a conformation with the C(5)−C(6) bond parallel to the C(3)−H bond to minimize 1,3-allylic strain.[21] In this conformation, the (bulky) *N*-benzyl-*N*-(α-methylbenzyl)amino substituent is placed above one face of the olefin. Invoking this as the reactive conformation, dihydroxylation using OsO_4 under either Upjohn[22] or Donohoe[23] conditions was expected to proceed, in both cases, on the sterically more accessible 4*Re*,5*Re* face[20] of the olefin (opposite to the amino group) owing to the absence of any potential hydrogen-bond donors.[24] This would result in the formation of diol **19**. In contrast, sequential treatment with a strong Brønsted acid and a peracid (e.g., 40% aq HBF_4 and *m*-CPBA, as employed with **10**) was anticipated to result in ammonium-directed epoxidation on the opposite 4*Si*,5*Si* face[20] of the olefin. Subsequent regioselective ring-opening of the intermediate epoxide **17** was expected to occur at C(5), distal to the ammonium moiety where its destabilizing electron-withdrawing influence on the transition state is less pronounced,[25] to give the corresponding diol **18**. This transformation constitutes a formal *anti*-dihydroxylation of the olefin. Diols **18** and **19** represent precursors to the corresponding 2,3,6-trideoxy-3-amino sugars, viz. D-3-*epi*-daunosamine **2** and D-ristosamine **3**, respectively (Figure 2).

RESULTS AND DISCUSSION

A scalable synthesis of the requisite β-amino esters **25** (R = Me) and **26** (R = ^{t}Bu) was first developed. A one-pot Swern/Wittig reaction[26] of propargylic alcohol **20** using $Ph_3P{=}CHCO_2Me$ as the ylide resulted in the formation of an 80:20 mixture of enyne diastereoisomers, from which the major product (*E*)-**21** ($^3J_{2,3}$ = 15.9 Hz) was isolated in 64% yield as a single diastereoisomer (>99:1 dr). Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to (*E*)-**21** gave the corresponding β-amino ester **23** in 61% isolated yield and 93:7 dr. The absolute (3*S*,α*R*)-configuration within **23** was assigned by reference to the transition-state mnemonic developed by us to rationalize, and reliably predict, the very high levels of diastereoselectivity observed upon conjugate addition of this class of lithium amide.[27] Subsequent reduction of β-amino ester **23** upon treatment with Lindlar's catalyst[28] gave β-amino ester **25** in 95:5 dr [(*Z*):(*E*) ratio], which was isolated in 83% yield and >95:5 dr (Scheme 2). The relative configuration within **25** was unambiguously established by single crystal X-ray diffraction analysis,[29] with the absolute (3*S*,α*R*,*Z*)-configuration being assigned from the known (*R*)-configuration of the α-methylbenzyl fragment. The predicted solution-phase conformation was consistent with the observed solid-state conformation of **25**. From this solid-state analysis, the assigned absolute configuration within β-amino ester **23** was also confirmed. In a directly analogous manner, the corresponding *tert*-butyl β-amino ester (3*S*,α*R*,*Z*)-**26** was prepared from propargylic alcohol **20** in 35% overall yield and >95:5 dr (Scheme 2).

Asymmetric Synthesis of Methyl *N*,*O*-Diacetyl-D-3-*epi*-daunosaminide. Treatment of **25** with 40% aq HBF_4 followed by *m*-CPBA under our previously reported con-

Scheme 1[a]



[a]Reagents and conditions: (i) 40% aq HBF_4, *m*-CPBA, CH_2Cl_2, rt, 48 h; (ii) H_2, $Pd(OH)_2/C$, Boc_2O, EtOAc, rt, 48 h; (iii) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (iv) MeOH, HCl, rt, 48 h; (v) Ac_2O, pyridine, DMAP, rt, 30 min.

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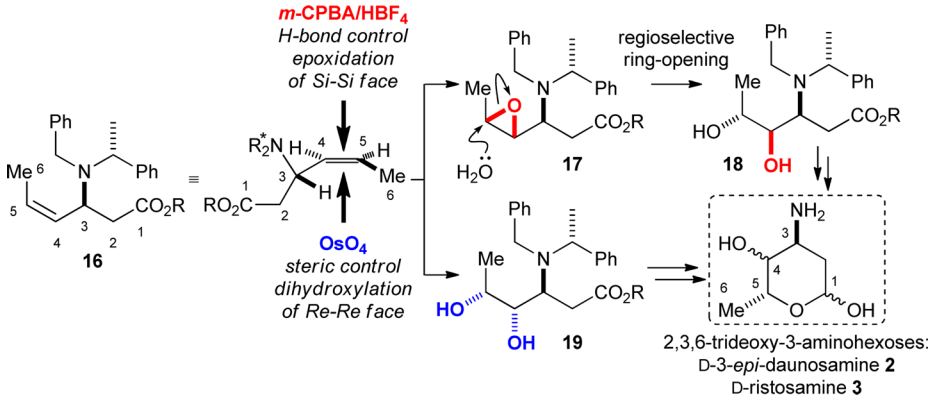
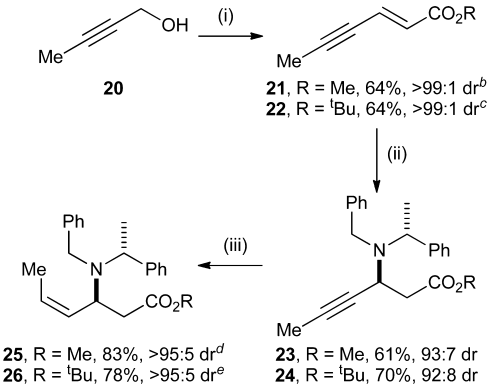


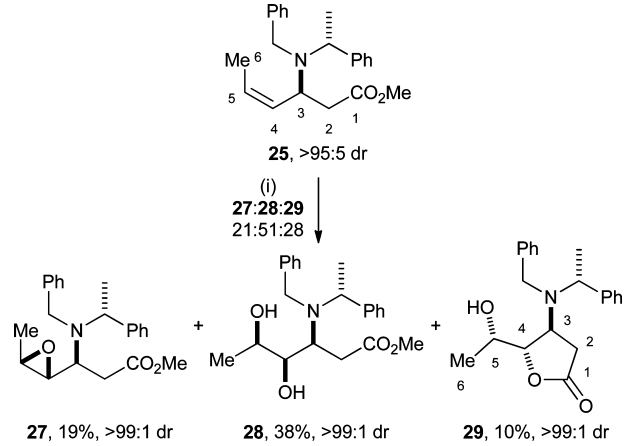
Figure 2. Proposed synthesis of the 2,3,6-trideoxy-3-aminohexoses D-3-*epi*-daunosamine **2** and D-ristosamine **3** via diastereoselective epoxidation and dihydroxylation, respectively, of β-amino esters **16**.

Scheme 2[a]



[a]Reagents and conditions: (i) $(ClCO)_2$, DMSO, Et_3N, −78 °C to rt, 1 h, then $Ph_3P{=}CHCO_2R$, rt, 18 h; (ii) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h; (iii) Pd/$CaCO_3$, quinoline, H_2 (1 atm), EtOAc, rt, 2 h. [b]Crude ratio 80:20 [(*E*):(*Z*)]. [c]Crude ratio 90:10 [(*E*):(*Z*)]. [d]Crude ratio 95:5 [(*Z*):(*E*)]. [e]Crude ratio 96:4 [(*Z*):(*E*)].

Scheme 3[a]



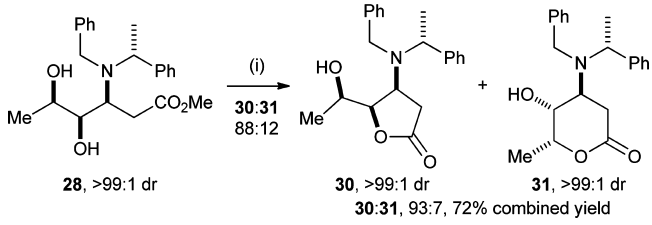
[a]Reagents and conditions: (i) 40% aq HBF_4, *m*-CPBA, CH_2Cl_2, rt, 48 h.

ditions[15] resulted in complete conversion of starting material to a complex mixture of products, of which the three major components were identified as epoxide **27**, diol **28**, and γ-lactone **29**[16] in the ratio 21:51:28, respectively. Chromatographic purification of these polar compounds proved difficult, but nonetheless samples of **27**, **28**, and **29** were isolated in 19, 38, and 10% yield, respectively, and in >95% purity (Scheme 3). The relative configuration within lactone **29** was confirmed unambiguously by single-crystal X-ray diffraction analysis,[29] with the absolute (3*S*,4*S*,5*S*,α*R*)-configuration following from the known (*R*)-configuration of the α-methylbenzyl group. The stereochemistry within diol **28** was initially tentatively assigned by comparison of its ^1H NMR spectrum with that of the known *tert*-butyl ester analogue:[17] the chemical shifts corresponding to the protons on the carbon backbone and the *N*-benzyl-*N*-α-methylbenzyl fragment of these two species were essentially identical; however the configurations within both epoxide **27** and diol **28** were subsequently assigned unambiguously by chemical correlation (vide infra).

In order to probe the origin of the products of this oxidation reaction, the behavior of epoxide **27** and diol **28** under the acidic conditions of the reaction was next studied. Treatment of diol **28** with 40% aq HBF_4 in CH_2Cl_2 resulted in the formation of an 88:12 mixture of the known γ-lactone **30**[16] as the major product and a minor product assigned as the corresponding δ-lactone **31**, which were isolated as a 93:7 mixture in 72% combined yield (Scheme 4). The presence of δ-lactone **31** was supported by ^1H and ^{13}C NMR chemical shift, $^1H{-}^1H$ ^3J coupling constant, and COSY analyses. In addition, analysis of the mixture of **30** and **31** by IR absorption spectroscopy revealed bands consistent with the presence of both a γ-lactone (ν_{max} 1773 cm^{-1}) and a δ-lactone (ν_{max} 1728 cm^{-1}). Formation of γ-lactone **30** as the major product in this reaction allowed unambiguous assignment of the stereochemistry within diol **28**.

When epoxide **27** was treated with 40% aq HBF_4 in CH_2Cl_2, a 45:51:4 mixture of γ-lactone **29**,[16] γ-lactone **30**,[16] and δ-lactone **31**, respectively, was produced. Purification and

Scheme 4[a]



[a]Reagents and conditions: (i) 40% aq HBF_4, CH_2Cl_2, rt, 48 h.

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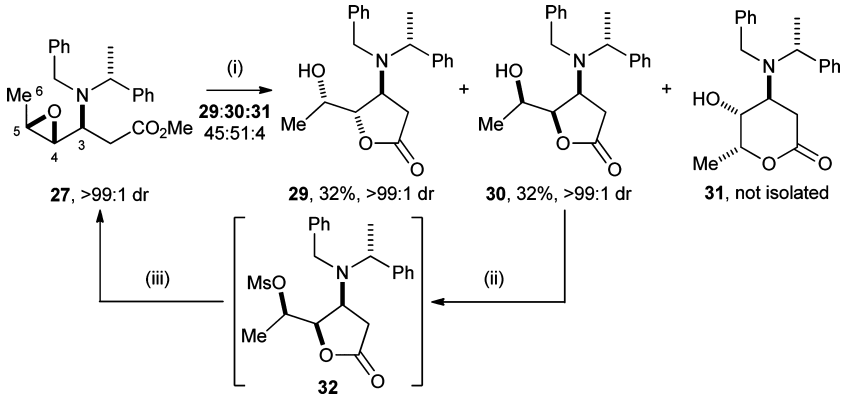
Scheme 5[a]

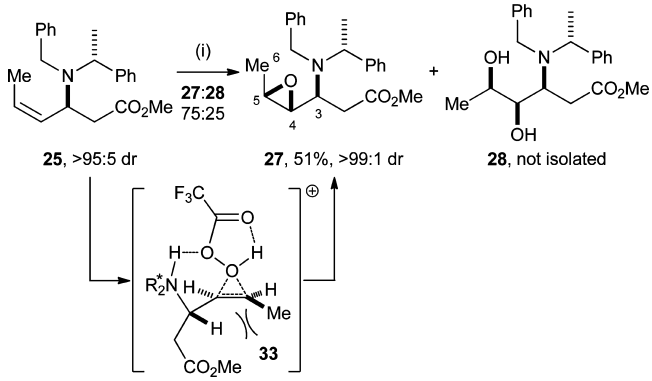


[a]Reagents and conditions: (i) 40% aq HBF_4, CH_2Cl_2, rt, 48 h; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h; (iii) K_2CO_3, MeOH, rt, 12 h.

separation via chromatography gave **29** in 32% yield and >99:1 dr, and **30**, also in 32% yield and >99:1 dr. Treatment of a sample of γ-lactone **30** with mesyl chloride (MsCl) gave the corresponding mesylate **32**, which upon treatment with K_2CO_3 in MeOH gave complete conversion to epoxide **27**, which was isolated in 26% yield and >99:1 dr, thus unambiguously establishing its stereochemistry (Scheme 5).

The production of a mixture of γ-lactones **29** and **30** upon treatment of epoxide **27** with 40% aq HBF_4 suggests two competing mechanisms for lactone formation are occurring under these conditions. S_N2-type ring-opening of epoxide **27** upon attack of H_2O at C(5), distal to the in situ formed ammonium moiety,[25,30] gives the intermediate diol **28**. Subsequent lactonization of **28** through attack of the C(4)-hydroxyl group at the ester carbonyl gives γ-lactone **30**. Alternatively, ring-opening of epoxide **27** may occur via a formal 5-*exo*-*trig*[31] cyclization by attack of the ester carbonyl group at C(4), followed by hydrolysis to give γ-lactone **29** directly. The conformational bias of **27** may serve to promote this latter pathway: the ester functionality would presumably be held in relatively close proximity to the approach trajectory necessary to effect attack at C(4). The production of γ-lactone **29** from β-amino ester **25** may therefore be attributable solely to the fate of a single intermediate epoxide **27** under the reaction conditions. However, the possibility that **29** arises from the corresponding diastereoisomeric epoxide undergoing S_N2-type ring-opening upon regioselective attack of H_2O at C(5) followed by lactonization cannot be excluded from the data available. Hence, this precludes assessment of the diastereoselectivity of epoxidation of **25** under these conditions. In order to probe the levels of diastereoselectivity in the epoxidation process, reaction of **25** under conditions which enabled isolation of the intermediate epoxide in a directly analogous system[15] was investigated. Treatment of **25** with F_3CCO_3H[32] in the presence of F_3CCO_2H gave complete conversion to a 75:25 mixture of epoxide **27** and diol **28**. The formation of **28** in this reaction can be rationalized by regioselective S_N2-type ring-opening of **27** occurring in situ upon attack of trifluoroacetate anion at C(5), followed by hydrolysis of the labile trifluoroacetate functionality upon basic aqueous workup.[33] Chromatographic purification of the crude reaction mixture allowed isolation of **27** in 51% yield and >99:1 dr, although **28** did not elute from the column in this case. From all these data it could be concluded that the epoxidation diastereoselectivity is complete (>95:5 dr in favor of reaction on the 4*Si*,5*Si* face),[20] consistent with an ammonium-directed process proceeding via transition-state model **33** (Scheme 6).

Scheme 6[a]



[a]Reagents and conditions: (i) F_3CCO_2H, F_3CCO_3H, CH_2Cl_2, 0 °C to rt, 16 h.

With an efficient method for the preparation of epoxide **27** in hand, a method to effect its regioselective ring-opening was examined. Treatment of **27** with concd aq H_2SO_4 in 1,4-dioxane resulted in the formation of a 65:35 mixture of γ-lactone **30**[16] and δ-lactone **31**, which were isolated as a 65:35 mixture in 43% combined yield. This product distribution is consistent with initial formation of diol **28** being followed by lactonization and, indeed, treatment of a sample of **28** with concd aq H_2SO_4 under identical conditions gave a 65:35 mixture of **30** and **31**, which were isolated as a 65:35 mixture in 56% combined yield. Although formed as a mixture, importantly the stereochemistries within **30** and **31** are identical and so both these lactones would converge upon the same final 2,3,6-trideoxy-3-amino sugar product (Scheme 7).

Hydrogenolysis of the 65:35 mixture of γ-lactone **30** and δ-lactone **31** in the presence of di-*tert*-butyl dicarbonate (Boc_2O) in EtOAc gave a 65:35 mixture of two species, assigned as the corresponding *N*-Boc protected lactones **34**[16] and **35**. Chromatographic purification allowed isolation of **34** in 58% yield and >99:1 dr, although **35** did not elute from the column and so was not isolated. Treatment of γ-lactone **34** with diisobutylaluminum hydride (DIBAL-H) gave a mixture of the corresponding lactols (as mixtures of anomers), which were

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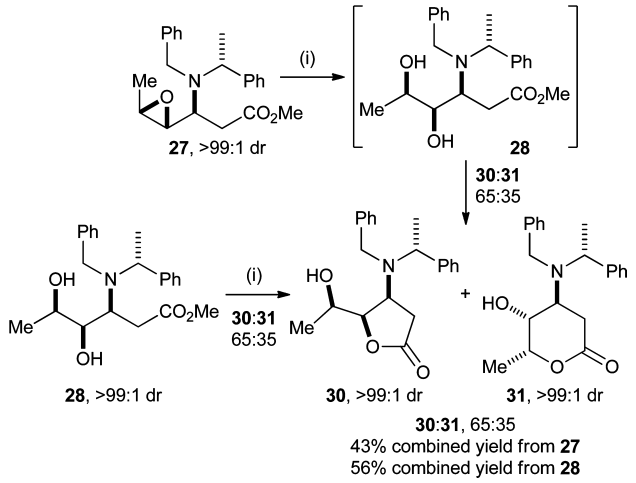
Scheme 7[a]

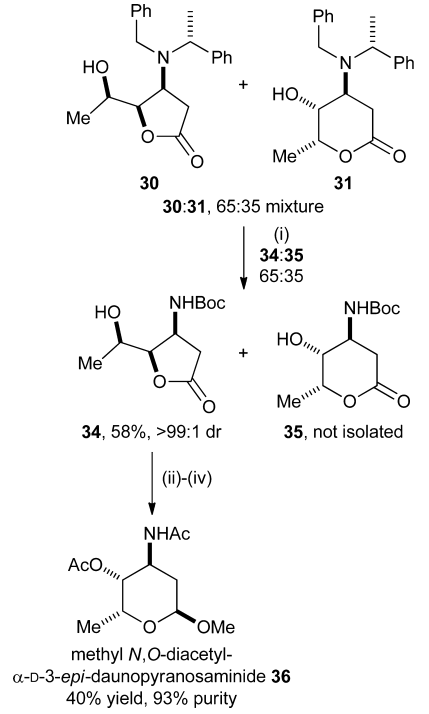


[a]Reagents and conditions: (i) concd aq H_2SO_4, 1,4-dioxane, H_2O, rt, 12 h.

treated with HCl in MeOH followed by peracetylation to give the known methyl *N,O*-diacetyl-α-D-3-*epi*-daunopyranosaminide **36**,[34] which was isolated in 40% yield and 93% purity[35] over three steps from **34**. The ^1H and ^{13}C NMR spectroscopic data for this sample of **36** were entirely consistent with those previously reported,[34] thus confirming the stereochemical assignments of all intermediates (Scheme 8).

Asymmetric Synthesis of Methyl *N,O*-Diacetyl-D-ristosaminide. Using the protocol originally reported by the Upjohn Company,[22] treatment of **26** with 0.1 equiv of OsO_4 and 4 equiv of *N*-methylmorpholine-*N*-oxide (NMO) gave an

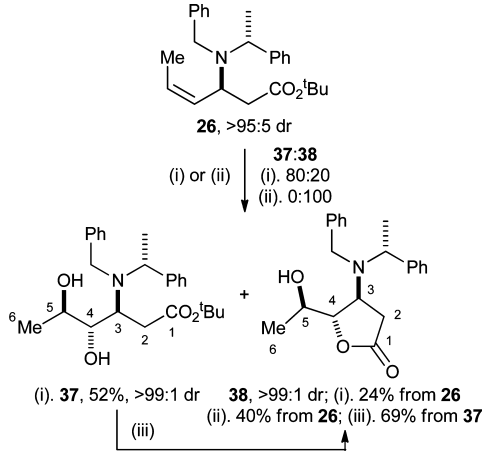
Scheme 8[a]



[a]Reagents and conditions: (i) Boc_2O, H_2, $Pd(OH)_2/C$, MeOH, rt, 48 h; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (iii) HCl, MeOH, rt, 16 h; (iv) Ac_2O, pyridine, DMAP, rt, 12 h.

80:20 mixture of two species, which were identified as diol **37** and γ-lactone **38**. Chromatography on silica gel allowed the isolation of **37** in 52% yield and >99:1 dr, and **38** in 24% yield and >99:1 dr (Scheme 9). The relative configuration within **37** was unambiguously established via single crystal X-ray diffraction analysis,[29] with the absolute (3*S*,4*S*,5*R*,α*R*)-configuration being assigned from the known absolute (*R*)-configuration of the α-methylbenzyl fragment. The isolated yield of **38** (24%) is greater than the theoretical maximum suggested by the crude product ratio, which suggests that **37** undergoes partial lactonization during chromatography to give **38**. In support of this assertion, treatment of **37** with F_3CCO_2H resulted in formation of **38** as the only product, which was isolated in 69% yield. Therefore, the absolute (3*S*,4*S*,5*R*,α*R*)-configuration within **38** was unambiguously established. From this result, the diastereofacial selectivity of the dihydroxylation reaction in favor of reaction on the 4*Re*,5*Re* face[20] can be inferred as >95:5. The procedure reported by Donohoe et al. for *syn*-dihydroxylation using OsO_4 in conjuction with *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) was also investigated,[23] and cleavage of the intermediate osmate ester using tris(hydroxymethyl)phosphine[36] gave γ-lactone **38** as the only product in 40% isolated yield after chromatography. The stereochemical outcome of the Upjohn dihydroxylation is known to be controlled by steric and/or stereoelectronic factors,[24] and in the absence of any potential hydrogen-bond donors, the Donohoe procedure[23] should also result in dihydroxylation of the sterically more accessible face of the expected solution-phase conformation of β-amino ester **26** (Scheme 9).

Scheme 9[a]



[a]Reagents and conditions: (i) OsO_4, NMO, THF, H_2O, rt, 16 h; (ii) OsO_4, TMEDA, CH_2Cl_2, −78 °C, 1 h, then $P(CH_2OH)_3$, CH_2Cl_2, Et_3N, SiO_2, rt, 48 h; (iii) F_3CCO_2H, CH_2Cl_2, rt, 12 h.

Hydrogenolysis of γ-lactone **38** in the presence of Boc_2O gave *N*-Boc-protected γ-lactone **39**[37] in 92% isolated yield and >99:1 dr (Scheme 10). The relative configuration within **39** was unambiguously confirmed by single-crystal X-ray diffraction analysis.[29] Sequential reduction of **39** with DIBAL-H, treatment with HCl in MeOH, and peracetylation resulted in equilibration to give an approximate 10:15:65:10 mixture of the α- and β-anomers of the furanose and pyranose forms of methyl *N,O*-diacetyl-D-ristopyranosaminide **40**−**43**, respectively (i.e., all possessing the same stereochemistry at all nonanomeric

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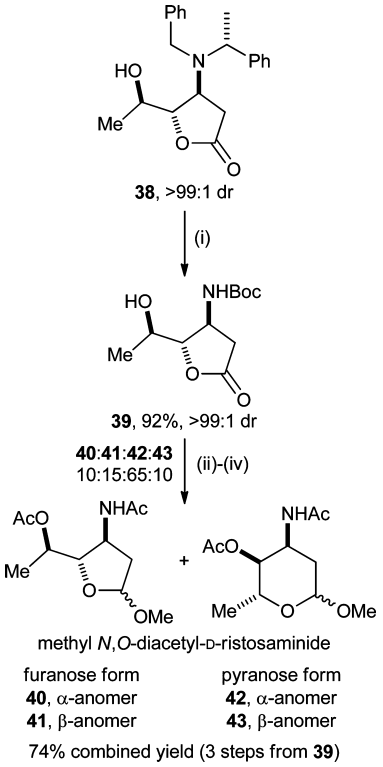
Scheme 10[a]



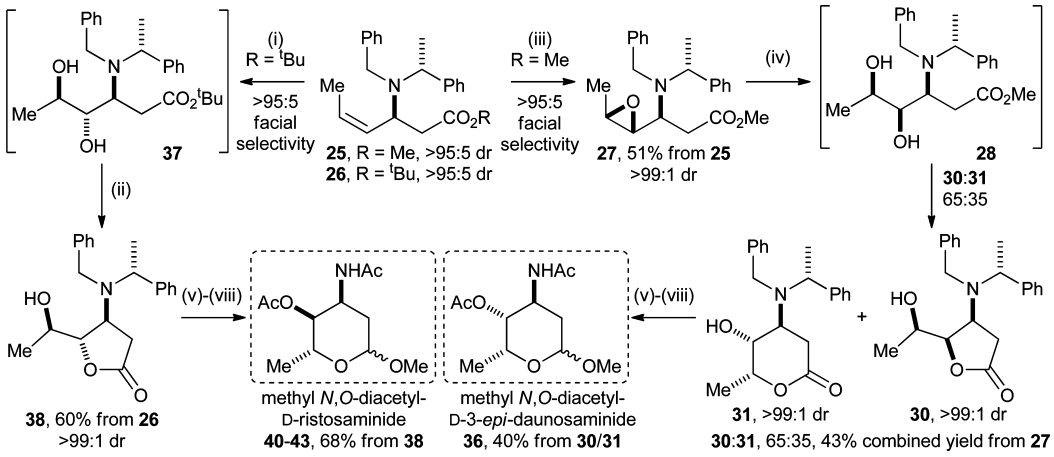
[a]Reagents and conditions: (i) Boc_2O, H_2, $Pd(OH)_2/C$, MeOH, rt, 48 h; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (iii) HCl, MeOH, rt, 16 h; (iv) Ac_2O, pyridine, DMAP, rt, 12 h.

stereocenters). In a related approach, Sibi reported the formation of a mixture of all four possible α- and β-anomers of the furanose and pyranose forms of methyl *N*-benzoyl-D-ristosamide, although the relative amount of each of these components was not quantified and their identities were not assigned.[37] However, in our study, partial separation of the mixture of **40**−**43** was achieved via chromatography, enabling the isolation of a sample of methyl *N*,*O*-diacetyl-β-D-ristofuranosaminide **41** in 15% overall yield (three steps from **39**), in >99:1 dr and 95% purity,[38] and methyl *N*,*O*-diacetyl-α-D-ristopyranosaminide **42** in 48% overall yield (three steps from **39**) and >99:1 dr, along with a 70:30 mixture of methyl *N*,*O*-diacetyl-α-D-ristofuranosaminide **40** and methyl *N*,*O*-diacetyl-β-D-ristopyranosaminide **43** in 11% combined yield (3 steps from **39**). The identities of and relative configurations within **40**−**43** were established by ^1H and ^{13}C NMR spectroscopic analyses (COSY, HSQC, HMBC, and NOE). Furthermore, the ^1H and ^{13}C NMR spectroscopic data for our sample of methyl *N*,*O*-diacetyl-α-D-ristopyranosaminide **43** were entirely consistent with those previously reported[39] (Scheme 10).

CONCLUSION

In conclusion, efficient asymmetric syntheses of methyl *N*,*O*-diacetyl-D-3-*epi*-daunosaminide and methyl *N*,*O*-diacetyl-D-ristosaminide have been developed that utilize a highly diastereoselective conjugate addition and a highly diastereoselective epoxidation or dihydroxylation, respectively, as the key steps to introduce the stereochemistry. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to α,β-unsaturated esters facilitates the preparation of alkyl (3*S*,α*R*,*Z*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoates **25** and **26**. These systems favor a solution-phase conformation with the C(5)−C(6) bond parallel to the C(3)−H bond in order to minimize 1,3-allylic strain. In this conformation, the (bulky) *N*-benzyl-*N*-(α-methylbenzyl)amino substituent is placed above one face of the olefin, which allows for its oxidative functionalization in a diastereoselective manner, under either steric control or hydrogen-bonding control. *syn*-Dihydroxylation of **26** (R = ^{t}Bu) using OsO_4 (under Upjohn or Donohoe conditions) proceeded on the least hindered 4*Re*,5*Re* face of the olefin (opposite the amino group) to give the corresponding diol **37**, which upon lactonization results in γ-lactone **38** only. Meanwhile, epoxidation of **25** (R = Me) using F_3CCO_3H in conjunction with F_3CCO_2H proceeded on the 4*Si*,5*Si* face under hydrogen-bonding control from the in situ formed ammonium ion. Subsequent regioselective ring-opening of the intermediate epoxide **27** in concd aq H_2SO_4 proceeded at the carbon atom distal to the ammonium moiety to give the corresponding diol **28** (a formal *anti*-dihydroxylation process), which lactonized under the reaction conditions to give a

Scheme 11[a]



[a]Reagents and conditions: (i) OsO_4, NMO, THF, H_2O, rt, 16 h; (ii) F_3CCO_2H, CH_2Cl_2, rt, 12 h; (iii) F_3CCO_2H, F_3CCO_3H, CH_2Cl_2, rt, 16 h; (iv) concd aq H_2SO_4, 1,4-dioxane, H_2O, rt, 12 h; (v) Boc_2O, H_2, $Pd(OH)_2/C$, MeOH, rt, 48 h; (vi) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (vii) HCl, MeOH, rt, 16 h; (viii) Ac_2O, pyridine, DMAP, rt, 12 h.

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mixture of γ-lactone **30** and δ-lactone **31** (both possessing the same stereochemistry). Elaboration of either the mixture of lactones **30** and **31**, or γ-lactone **38** via hydrogenolysis, *N*-Boc protection, reduction with DIBAL-H, methanolysis, and peracetylation gave mixtures of the α- and β-anomers of the pyranose and furanose forms of methyl *N*,*O*-diacetyl-D-3-*epi*-daunosaminide **36** and methyl *N*,*O*-diacetyl-D-ristosaminide **40**−**43**, respectively (Scheme 11). The ready availability of the enantiomeric β-amino ester starting materials [i.e., derived from conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide] renders these strategies equally applicable to the syntheses of either enantiomeric form of this important product class, and further applications of this methodology will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Details. All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame-dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[40] *m*-CPBA was supplied as a 70−77% slurry in water and titrated according to the procedure of Swern[41] immediately before use. Water was purified by an Elix UV-10 system. Organic solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over Na_2SO_4 or $MgSO_4$, as stated. Thin layer chromatography was performed on aluminum plates coated with 60 F_{254} silica. Plates were visualized using UV light (254 nm) or 1% aq $KMnO_4$. Flash column chromatography was performed on Kieselgel 60 silica on a glass column.

Melting points are uncorrected. IR spectra were recorded using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. $^1H-^1H$ COSY and $^1H-^{13}C$ HMQC analyses were used to establish atom connectivity. Accurate mass measurements were run on a MicroTOF instrument internally calibrated with polyalanine.

Methyl (*E*)-Hex-2-en-4-ynoate 21. DMSO (2.6 mL, 37.1 mmol) was added to a stirred solution of $(COCl)_2$ (2.9 mL, 34.2 mmol) in CH_2Cl_2 (224 mL) at −78 °C. After 5 min, a solution of **20** (2.00 g, 28.5 mmol) in CH_2Cl_2 (10 mL) was added. The resultant mixture was stirred at −60 °C for a further 1 h before the addition of Et_3N (7.95 mL, 57.1 mmol). The resultant mixture was allowed to warm to rt, and $Ph_3P{=}CHCO_2Me$ (9.54 g, 28.5 mmol) was added. The reaction mixture was stirred for 18 h at rt. Saturated aq Na_2CO_3 (200 mL) was then added, and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo to give an 80:20 mixture of (*E*):(*Z*) diastereoisomers. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 99:1) gave **21** as a yellow oil (2.27 g, 64%, >99:1 dr): ν_{max} (film) 2222 (C≡C), 1719 (C=O); δ_H (400 MHz, $CDCl_3$) 2.01 (3H, dd, *J* 2.4, 0.6, C(6)H_3), 3.73 (3H, s, O*Me*), 6.13 (1H, dd, *J* 15.9, 0.6 C(3)*H*), 6.74 (1H, dq, *J* 15.9, 2.4, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 4.6 (*C*(6)), 51.6 (O*Me*), 96.4 (*C*(4), *C*(5)), 126.3 (*C*(2)), 128.9 (*C*(3)), 166.5 (*C*(1)); *m*/*z* (FI^+) 124 ($[M]^+$, 100); HRMS (FI^+) $C_7H_8O_2^+$ ($[M]^+$) requires 124.0524; found 124.0523.

***tert*-Butyl (*E*)-Hex-2-en-4-ynoate 22.** DMSO (2.6 mL, 37.1 mmol) was added to a stirred solution of $(COCl)_2$ (2.9 mL, 34.2 mmol) in CH_2Cl_2 (224 mL) at −78 °C. After 5 min, a solution of **20** (2.00 g, 28.5 mmol) in CH_2Cl_2 (10 mL) was added. The resultant mixture was stirred at −60 °C for a further 1 h before the addition of Et_3N (7.95 mL, 57.1 mmol). The resultant mixture was allowed to warm to rt, and $Ph_3P{=}CHCO_2{}^tBu$ (10.7 g, 28.5 mmol) was added. The reaction mixture was stirred for 18 h at rt. Saturated aq Na_2CO_3 (200 mL) was then added, and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo to give a 90:10 mixture of (*E*):(*Z*) diastereoisomers. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 99:1) gave **22** as a yellow oil (3.00 g, 64%, >99:1 dr): ν_{max} (film) 2222 (C≡C), 1717 (C=O); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, CMe_3), 1.97 (3H, dd, *J* 2.5, 0.6, C(6)H_3), 6.02 (1H, dd, *J* 15.8, 0.6, C(3)*H*), 6.58 (1H, dq, *J* 15.8, 2.5, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 4.7 (*C*(6)), 27.9 (CMe_3), 80.7 (CMe_3), 95.4 (*C*(4), *C*(5)), 124.9 (*C*(2)), 131.3 (*C*(3)), 165.4 (*C*(1)); *m*/*z* (ESI^+) 167 ($[M + H]^+$, 100); HRMS (ESI^+) $C_{10}H_{15}O_2^+$ ($[M + H]^+$) requires 167.1067; found 167.1068.

Methyl (3*S*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]hex-4-ynoate 23. *n*-BuLi (2.50 M in hexanes, 11.9 mL, 24.5 mmol) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (5.99 g, 28.4 mmol) in THF (30 mL) at −78 °C. After the solution was stirred for 30 min, a solution of **21** (2.20 g, 17.9 mmol) in THF (10 mL) at −78 °C was added dropwise via cannula. The reaction mixture was allowed to stir for a further 2 h before addition of satd aq NH_4Cl (10 mL). The resultant mixture was allowed to warm to rt and then extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed sequentially with 10% aq citric acid (30 mL) and satd aq $NaHCO_3$ (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 19:1) gave **23** as a colorless oil (3.62 g, 61%, 93:7 dr): $[\alpha]_D^{20}$ −136.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2233 (C≡C), 1731 (C=O); δ_H (500 MHz, $CDCl_3$) 1.51 (3H, d, *J* 6.9, C(α)*Me*), 1.89 (3H, d, *J* 2.4, C(6)H_3), 2.48 (1H, dd, *J* 14.6, 6.6, C(2)H_A), 2.59 (1H, dd, *J* 14.6, 8.5, C(2)H_B), 3.47 (3H, s, O*Me*), 3.74 (1H, d, *J* 14.3, NCH_A), 3.88 (1H, d, *J* 14.3, NCH_B), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.00 (1H, ddq, *J* 8.6, 6.6, 2.2, C(3)*H*), 7.18−7.41 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 3.6 (*C*(6)), 13.4 (C(α)*Me*), 41.0 (*C*(2)), 46.6 (*C*(3)), 51.4 (NCH_2), 51.5 (O*Me*), 57.2 (*C*(α)), 77.2, 81.1 (*C*(4), *C*(5)), 126.7, 126.8 (*p*-*Ph*), 127.9, 128.0, 128.2, 128.9 (*o*,*m*-*Ph*), 140.4, 143.9 (*i*-*Ph*), 170.9 (*C*(1)); *m*/*z* (ESI^+) 336 ($[M + H]^+$, 100); HRMS (ESI^+) $C_{22}H_{26}NO_2^+$ ($[M + H]^+$) requires 336.1958, found 336.1953.

***tert*-Butyl (3*S*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-hex-4-ynoate 24.** *n*-BuLi (2.50 M in hexanes, 0.75 mL, 1.86 mmol) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (406 mg, 1.93 mmol) in THF (4.0 mL) at −78 °C. After the solution was stirred for 30 min, a solution of **22** (200 mg, 1.20 mmol) in THF (2 mL) at −78 °C was added dropwise via cannula. The reaction mixture was allowed to stir for a further 2 h before addition of satd aq NH_4Cl (3 mL). The resultant mixture was allowed to warm to rt and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed sequentially with 10% aq citric acid (10 mL) and satd aq $NaHCO_3$ (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 19:1) gave **24** as a colorless oil (318 mg, 70%, 92:8 dr): $[\alpha]_D^{20}$ −66.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2230 (C≡C), 1727 (C=O); δ_H (500 MHz, $CDCl_3$) 1.40 (9H, s, CMe_3), 1.50 (3H, d, *J* 6.9, C(α)*Me*), 1.87 (3H, d, *J* 2.2, C(6)H_3), 2.37−2.42 (2H, m, C(2)H_2), 3.71 (1H, d, *J* 14.5, NCH_A), 3.83 (1H, d, *J* 14.5, NCH_B), 3.96 (1H, q, *J* 6.9, C(α)*H*), 4.00−4.03 (1H, m, C(3)*H*), 7.17−7.37 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 3.6 (*C*(6)), 14.8 (C(α)*Me*), 28.0 (CMe_3), 42.2 (*C*(2)), 47.3 (*C*(3)), 51.6 (NCH_2), 57.9 (*C*(α)), 78.1 (CMe_3), 80.2, 80.7 (*C*(4), *C*(5)), 126.6, 126.7 (*p*-*Ph*), 127.8, 127.9, 128.0, 128.6 (*o*,*m*-*Ph*), 140.9, 144.2 (*i*-*Ph*), 170.1 (*C*(1)); *m*/*z* (ESI^+) 378 ($[M + H]^+$, 100); HRMS (ESI^+) $C_{25}H_{32}NO_2^+$ ($[M + H]^+$) requires 378.2428, found 378.2429.

Methyl (3*S*,α*R*,*Z*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-hex-4-enoate 25. A mixture of **23** (2.60g, 7.75 mmol), Pd/$CaCO_3$ (5 wt % Pd, 780 mg, 30% w/w of substrate) and quinoline (27 μL, 6.08 mmol) in degassed EtOAc (15 mL) was stirred under H_2 (1 atm) at rt for 2 h. The reaction mixture was then filtered through a short plug of Celite (eluent EtOAc) and concentrated in vacuo to give a 95:5 mixture of (*Z*):(*E*) diastereoisomers. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 19:1) gave **25** as a white solid (2.17 mg, 83%, >95:5 dr); mp 43−46 °C; $[\alpha]_D^{20}$ +24.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1740 (C=O); δ_H (500 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.8, C(α)*Me*), 1.58 (3H, d, *J* 5.5, C(6)H_3), 2.24 (1H, dd, *J* 13.9, 7.7, C(2)H_A), 2.58 (1H, *J* 13.9, 5.3, C(2)H_B), 3.49

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(3H, s, OMe), 3.70 (1H, d, *J* 14.8, NCH_A), 3.88 (1H, d, *J* 14.8, NCH_B), 4.00 (1H, q, *J* 6.8, C(α)*H*), 4.09 (1H, dt, *J* 8.9, 7.3, C(3)*H*), 5.54−5.64 (2H, m, C(4)*H*, C(5)*H*), 7.19−7.39 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.4 (*C*(6)), 14.8 (C(α)*Me*), 39.6 (*C*(2)), 50.2 (NCH_2), 51.3 (O*Me*), 51.5 (*C*(3)), 56.3 (*C*(α)), 126.0, 126.6, 127.8, 127.9, 128.1, 128.4, 130.3 (*o,m,p-Ph*, *C*(4), *C*(5)), 141.2, 144.3 (*i-Ph*), 171.9 (*C*(1)); *m/z* (ESI$^+$) 338 ([M + Na]$^+$, 100); HRMS (ESI$^+$) $C_{22}H_{28}NO_2^+$ ([M + H]$^+$) requires 338.2115, found 338.2112.

***tert*-Butyl (3*S*,α*R*,*Z*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-hex-4-enoate 26.** A mixture of **24** (130 mg, 0.34 mmol), Pd/$CaCO_3$ (5 wt % Pd, 26 mg, 20% w/w of substrate), and quinoline (27 μL, 0.07 mmol) in degassed EtOAc (5 mL) was stirred under H_2 (1 atm) at rt for 1 h 20 min. The reaction mixture was then filtered through a short plug of Celite (eluent EtOAc) and concentrated in vacuo to give a 96:4 mixture of (*Z*):(*E*) diastereoisomers. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/Et_2O, 19:1) gave **26** as a colorless oil (102 mg, 78%, >95:5 dr): $[\alpha]_D^{20}$ −24.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1784 (C═O); δ_H (500 MHz, $CDCl_3$) 1.36 (9H, s, CMe_3), 1.38 (3H, d, *J* 6.6, C(α)*Me*), 1.56 (3H, d, *J* 5.0, C(6)H_3), 2.18 (1H, dd, *J* 13.6, 9.1, C(2)H_A), 2.50 (1H, *J* 13.6, 5.2, C(2)H_B), 3.70 (1H, d, *J* 14.8, NCH_A), 3.80 (1H, d, *J* 14.8, NCH_B), 4.01−4.09 (2H, m, C(α)*H*, C(3)*H*), 5.52−5.61 (2H, m, C(4)*H*, C(5)*H*), 7.15−7.42 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.6 (*C*(6)), 16.4 (C(α)*Me*), 28.0 (CMe_3), 40.6 (*C*(2)), 50.5 (NCH_2), 52.0 (*C*(3)), 57.1 (*C*(α)), 80.0 (CMe_3), 126.2, 126.5, 126.9, 127.8, 127.9, 128.0, 128.2, 130.5 (*o,m,p-Ph*, *C*(4), *C*(5)), 141.7, 144.6 (*i-Ph*), 171.0 (*C*(1)); *m/z* (ESI$^+$) 402 ([M + Na]$^+$, 100); HRMS (ESI$^+$) $C_{25}H_{33}NaNO_2^+$ ([M + Na]$^+$) requires 402.2404, found 402.2405.

Methyl (3*S*,4*R*,5*S*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)-amino]-4,5-epoxyhexanoate 27. $(F_3CCO)_2O$ (0.33 mL, 2.37 mmol) was added to a stirred solution of urea hydrogen peroxide (836 mg, 8.89 mmol) and CH_2Cl_2 (3 mL) at 0 °C, and the resultant solution was stirred for 30 min at 0 °C. A solution of **25** (200 mg, 0.52 mmol) and F_3CCO_2H (0.12 mL, 1.48 mmol) in CH_2Cl_2 (3 mL) was then added, and the resultant mixture was stirred for 16 h at rt. The reaction mixture was then cooled to 0 °C, and satd aq Na_2SO_3 (~3 mL) was added until starch iodide paper indicated no remaining oxidant. The resultant mixture was then diluted with CH_2Cl_2 (10 mL) and washed with 2.0 M aq NaOH (2 × 10 mL). The combined aqueous washings were extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a 75:25 mixture of **27** and **28**, respectively. Purification via flash column chromatography (eluent PhMe/EtOAc, 4:1) gave **27** as a colorless oil (107 mg, 51%, >99:1 dr): $[\alpha]_D^{20}$ +8.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3062, 3028, 2973, 2251 (C−H), 1737 (C═O); δ_H (500 MHz, $CDCl_3$) 1.18 (3H, d, *J* 5.4, C(6)H_3), 1.49 (3H, d, *J* 6.6, C(α)*Me*), 2.24 (1H, dd, *J* 14.0, 6.5, C(2)H_A), 2.51 (1H, dd, *J* 14.0, 7.6, C(2)H_B), 3.04−3.12 (2H, m, C(4)*H*, C(5)*H*), 3.14−3.19 (1H, m, C(3)*H*), 3.50 (3H, s, O*Me*), 3.86 (1H, d, *J* 14.2, NCH_A), 3.95 (1H, d, *J* 14.2, NCH_B), 4.09 (1H, q, *J* 6.9, C(α)*H*), 7.21−7.41 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.4 (*C*(6)), 16.8 (C(α)*Me*), 36.5 (*C*(2)), 50.4 (NCH_2), 51.5 (O*Me*), 52.8 (*C*(3)), 53.0 (*C*(5)), 56.4 (*C*(4)), 57.0 (*C*(α)), 126.7, 126.8 (*p-Ph*), 127.9, 128.0, 128.1, 128.7 (*o,m-Ph*), 140.7, 144.0 (*i-Ph*), 171.4 (*C*(1)); *m/z* (ESI$^+$) 354 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{22}H_{28}NO_3^+$ ([M + H]$^+$) requires 354.2064, found 354.2062.

Methyl (3*S*,4*R*,5*S*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)-amino]-4,5-epoxyhexanoate 27, Methyl (3*S*,4*R*,5*R*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-4,5-dihydroxyhexanoate 28, and (3*S*,4*S*,5*S*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-hydroxy-4-hexanolactone 29. HBF_4 (40% aq, 0.23 mL, 1.48 mmol) was added to a stirred solution of **25** (100 mg, 0.29 mmol) in CH_2Cl_2 (0.9 mL), and the resultant solution was stirred at rt for 5 min. Then *m*-CPBA (75%, 272 mg, 1.19 mmol) was added, and stirring was continued for 48 h at rt. The reaction mixture was then diluted with CH_2Cl_2 (3 mL) and washed sequentially with satd aq Na_2SO_3 (2 × 5 mL) and satd aq $NaHCO_3$ (10 mL). The combined aqueous washings were extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a 21:51:28 mixture of **27**, **28** and **29**, respectively. Purification via flash column chromatography (eluent PhMe/EtOAc, 4:1) gave **27** as a colorless oil (18 mg, 19%, >99:1 dr). Further elution gave **29** as white solid (9 mg, 10%, >99:1 dr):[16] mp 129−134 °C (lit.[16] mp 132−136 °C); $[\alpha]_D^{20}$ +112.6 (*c* 1.0 in $CHCl_3$) [lit.[16] $[\alpha]_D^{26}$ +101.2 (*c* 1.6 in $CHCl_3$)]; δ_H (500 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.6, C(6)H_3), 1.42 (3H, d, *J* 7.0, C(α)*Me*), 2.02 (1H, dd, *J* 18.6, 9.1, C(2)H_A), 2.11 (1H, dd, *J* 18.6, 7.3, C(2)H_B), 3.66 (1H, d, *J* 14.8, NCH_A), 3.74 (1H, d, *J* 14.8, NCH_B), 3.83 (1H, q, *J* 7.0, C(α)*H*), 4.01−4.05 (2H, m, C(3)*H*, C(5)*H*), 4.12 (1H, dd, *J* 6.0, 2.8, C(4)*H*), 7.27−7.43 (10H, m, *Ph*). Further elution gave **28** as colorless oil (37 mg, 38%, >99:1 dr): $[\alpha]_D^{20}$ +36.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3428 (O−H), 3062, 3029, 2973, 2933, 2848 (C−H), 1730 (C═O); δ_H (500 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.6, C(6)H_3), 1.47 (3H, d, *J* 7.1, C(α)*Me*), 1.80 (1H, dd, *J* 16.9, 1.7, C(2)H_A), 2.14 (1H, dd, *J* 16.9, 9.0, C(2)H_B), 3.26 (1H, d, *J* 7.6, C(4)*H*), 3.54 (1H, d, *J* 13.9, NCH_A), 3.62 (3H, s, O*Me*), 3.70−3.78 (2H, m, C(3)*H*, C(5)*H*), 3.86 (1H, d, *J* 13.9, NCH_B), 3.92 (1H, q, *J* 7.1, C(α)*H*), 7.27−7.43 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 19.6 (C(α)*Me*), 20.2 (*C*(6)), 32.0 (*C*(2)), 51.4 (NCH_2), 51.8 (O*Me*), 54.1 (*C*(3)), 56.9 (*C*(α)), 66.6 (*C*(5)), 74.4 (*C*(4)), 127.4, 127.7 (*p-Ph*), 128.1, 128.4, 128.7, 128.8 (*o,m-Ph*), 138.7, 139.7 (*i-Ph*), 173.3 (*C*(1)); *m/z* (ESI$^+$) 372 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{22}H_{30}NO_4$ ([M + H]$^+$) requires 372.2169, found 372.2165.

(3*S*,4*S*,5*S*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-hydroxy-4-hexanolactone 29 and (3*S*,4*R*,5*R*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-hydroxy-4-hexanolactone 30. HBF_4 (40% aq, 44 μL, 0.28 mmol) was added to a stirred solution of **27** (20 mg, 0.06 mmol) in CH_2Cl_2 (0.1 mL), and the resultant solution was stirred at rt for 48 h. Saturated aq $NaHCO_3$ (0.5 mL) was added, and the resultant mixture was extracted with EtOAc (3 × 1 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a 45:55 mixture of **29** and **30**, respectively. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 3:1) gave **29** as a white solid (6 mg, 32%, >99:1 dr).[16] Further elution gave **30** as a white solid (6 mg, 32%, >99:1 dr):[16] mp 133−135 °C (lit.[16] mp 132−136 °C); $[\alpha]_D^{25}$ +75.8 (*c* 1.0 in $CHCl_3$) [lit.[16] $[\alpha]_D^{26}$ +101.2 (*c* 1.6 in $CHCl_3$)]; δ_H (500 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.1, C(6)H_3), 1.47 (3H, d, *J* 7.1, C(α)*Me*), 1.98 (1H, dd, *J* 17.8, 6.5, C(2)H_A), 2.16 (1H, dd, *J* 17.8, 8.4 C(2)H_B), 3.77 (2H, app s, NCH_2), 3.95 (1H, q, *J* 7.1, C(α)*H*), 4.05 (1H, dt, *J* 8.4, 6.6, C(3)*H*), 4.35 (1H, dd, *J* 6.6, 5.8, C(4)*H*), 4.40 (1H, app quintet, *J* 5.8, C(5)*H*), 7.15−7.41 (10H, m, *Ph*).

(3*S*,4*R*,5*R*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-hydroxy-4-hexanolactone 30 and (3*S*,4*R*,5*R*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-4-hydroxy-5-hexanolactone 31. *Method A.* H_2SO_4 (concd aq, 37 μL, 0.71 mmol) and H_2O (2 drops) were added to a stirred solution of **27** (50 mg, 0.14 mmol) in 1,4-dioxane (0.5 mL). The reaction mixture was stirred at rt for 16 h and then concentrated in vacuo. Saturated aq $NaHCO_3$ (1 mL) was added to the residue, and the resultant mixture was extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a 65:35 mixture of **30** and **31**, respectively. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 4:1) gave a 65:35 mixture of **30** and **31** as a colorless oil (21 mg, 43% combined yield).[16] Data for mixture: ν_{max} (film) 3419 (O−H), 3061, 3028, 2975, 2930, 2850 (C−H), 1773 (C═O, *γ-lactone*), 1728 (C═O, *δ-lactone*); *m/z* (ESI$^+$) 340 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{21}H_{26}NO_3^+$ ([M + H]$^+$) requires 340.1907, found 340.1912. Data for **31**: δ_H (500 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.7, C(6)H_3), 1.44 (3H, d, *J* 6.4, (C(α)*Me*), 2.14 (1H, dd, *J* 17.0, 6.3, C(2)H_A), 2.25 (1H, dd, *J* 17.0, 10.8, C(2)H_B), 3.36 (1H, ddd, *J* 10.8, 7.8, 6.3, C(3)*H*), 3.70 (1H, d, *J* 14.5, NCH_A), 3.79 (1H, d, *J* 14.5, NCH_B), 3.84 (1H, dd, *J* 7.8, 4.4, C(4)*H*), 3.90−3.92 (1H, m, C(α)*H*), 4.54 (1H, dq, *J* 6.7, 4.4, C(5)*H*), 7.15−7.41 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.5 (*C*(6)), 21.4 (C(α)*Me*), 30.9 (*C*(2)), 50.3 (NCH_2), 54.7 (*C*(3)), 57.8 (*C*(α)), 68.2 (*C*(4)), 75.7 (*C*(5)), 127.4, 127.5 (*p-Ph*), 128.1, 128.2, 128.8, 129.0 (*o,m-Ph*), 137.8, 141.7 (*i-Ph*), 170.7 (*C*(1)).

Method B. HBF_4 (40% aq, 63 μL, 0.40 mmol) was added to a stirred solution of **28** (30 mg, 0.08 mmol) in CH_2Cl_2 (0.2 mL), and the resultant solution was stirred at rt for 48 h. Saturated aq $NaHCO_3$

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(0.5 mL) was added, and the resultant mixture was extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give an 88:12 mixture of **30** and **31**, respectively. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 4:1) gave a 93:7 mixture of **30** and **31** as a colorless oil (22 mg, 72% combined yield).

Method C. H_2SO_4 (concd aq, 14 μL, 0.27 mmol) and H_2O (1 drop) were added to a stirred solution of **28** (20 mg, 0.05 mmol) in 1,4-dioxane (0.1 mL). The reaction mixture was stirred at rt for 16 h and then concentrated in vacuo. Satd aq $NaHCO_3$ (1 mL) was added to the residue and the resultant mixture was extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a 65:35 mixture of **30** and **31**, respectively. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 4:1) gave a 65:35 mixture of **30** and **31** as a colorless oil (10 mg, 56% combined yield).

(3*S*,4*R*,5*R*,α*R*)-4-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-(methanesulfonyloxy)-4-hexanolactone 32. MsCl (33 μL, 0.42 mmol) was added dropwise to a stirred solution of **30** (90 mg, 0.42 mmol) and Et_3N (74 μL, 0.53 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The resultant solution was stirred at rt for 1 h, washed with satd aq $CuSO_4$ (5 mL), dried ($MgSO_4$), and concentrated in vacuo to give **32** as a yellow oil (110 mg). Purification of an aliquot via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave an analytical sample (>95% purity): $[\alpha]_D^{20}$ +117.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3029, 2975, 2938 (C−H), 1786 (C═O); δ_H (500 MHz, $CDCl_3$) 1.45 (3H, d, *J* 7.2, C(α)*Me*), 1.71−1.74 (1H, m, C(2)H_A), 1.74 (3H, d, *J* 6.3, C(6)H_3), 2.21 (1H, dd, *J* 18.4, 8.0, C(2)H_B), 2.97 (3H, s, SO_2Me), 3.70 (1H, d, *J* 14.5, NCH_A), 3.82 (1H, d, *J* 14.5, NCH_B), 3.89 (1H, q, *J* 7.2, C(α)*H*), 4.07−4.10 (1H, m, C(3)*H*), 4.41 (1H, dd, *J* 8.9, 6.3, C(4)*H*), 5.17 (1H, dq, *J* 8.9, 6.3, C(5)*H*), 7.19−7.45 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.2 (*C*(6)), 18.4 (C(α)*Me*), 32.2 (*C*(2)), 38.6 (SO_2Me), 51.8 (NCH_2), 53.9 (*C*(3)), 56.7 (*C*(α)), 77.8 (*C*(5)), 84.6 (*C*(4)), 127.7, 127.8, 128.0, 128.7, 128.8, 129.1 (*o*,*m*,*p*-*Ph*), 137.7, 139.2 (*i*-*Ph*), 175.1 (*C*(1)); *m*/*z* (ESI$^+$) 418 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{22}H_{27}NNaO_5S^+$ ([M + Na]$^+$) requires 440.1502, found 440.1492.

K_2CO_3 (182 mg, 1.32 mmol) was added to a solution of **32** (90 mg, 0.22 mmol) in MeOH (2 mL). The reaction mixture was stirred at rt for 16 h and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 95:5) gave **27** as oil colorless oil (24 mg, 26% from **30**, >99:1 dr).

(3*S*,4*R*,5*R*)-3-(*N*-*tert*-Butoxycarbonylamino)-5-hydroxy-4-hexanolactone 34. Boc_2O (92 mg, 0.42 mmol) and $Pd(OH)_2$/C (50% w/w of substrate, 65 mg) were added sequentially to a solution of a 65:35 mixture of **30** and **31** (130 mg, 0.38 mmol) in MeOH (2 mL). The resultant suspension was placed under H_2 (1 atm) and stirred vigorously at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH) and concentrated in vacuo to give a 65:35 mixture of **34** and **35**, respectively. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 1:1) gave **34** as a white solid (54 mg, 58%, >99:1 dr):[16] mp 156−161 °C (lit.[16] mp 159−162 °C); $[\alpha]_D^{20}$ −39.2 (*c* 1.0 in $CHCl_3$) [lit.[16] $[\alpha]_D^{25}$ −52.5 (*c* 2.1 in $CHCl_3$)]; δ_H (500 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.6, C(6)H_3), 1.45 (9H, s, CMe_3), 2.59 (1H, dd, *J* 17.8, 8.2, C(2)H_A), 2.82 (1H, dd, *J* 17.8, 9.4, C(2)H_B), 4.08−4.12 (1H, m, C(5)*H*), 4.45 (1H, d, *J* 7.5, C(4)*H*), 4.76 (1H, app quintet, *J* 8.5, C(3)*H*), 5.47 (1H, d, *J* 8.2, N*H*).

Methyl *N*,*O*-Diacetyl-D-3-*epi*-α-daunopyranosaminide 36. DIBAL-H (1.0 M in CH_2Cl_2, 0.5 mL, 0.5 mmol) was added dropwise via syringe (over 1 min) to a stirred solution of **34** (35 mg, 0.14 mmol) in CH_2Cl_2 (3 mL) at −78 °C. The resultant mixture was stirred for 30 min at −78 °C. MeOH (∼0.5 mL) was then added dropwise until effervescence ceased. Saturated aq Rochelle salt (10 drops) was then added, and the resultant suspension was stirred at rt for 16 h before being filtered through Celite (eluent MeOH) and concentrated in vacuo. The residue was dissolved in anhydrous MeOH (0.2 mL), and HCl (1.25 M in MeOH, 0.4 mL) was added. The resultant solution was stirred at rt for 48 h before being concentrated in vacuo. The residue was dissolved in pyridine (0.3 mL), Ac_2O (0.3 mL) and DMAP (1 mg) were added, and the resultant solution was stirred at rt for 12 h. The reaction mixture was then diluted with CH_2Cl_2 (2 mL), EtOAc (2 mL), and satd aq $CuSO_4$ (2 mL). The resultant solution was extracted with EtOAc (3 × 2 mL), and the combined organic extracts were washed with satd aq $NaHCO_3$ (2 × 2 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification via flash column chromatography (eluent PhMe/^{i}PrOH, 4:1) gave **36** as a colorless oil (10 mg, 40% from **34**, 93% purity):[34,35] ν_{max} (film) 3407 (N−H), 2973, 2941, 2857, 2831 (C−H), 1739 (C═O, *ester*), 1693 (C═O, *amide*); δ_H (500 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.5, C(6)H_3), 1.62 (1H, dd, *J* 14.5, 0.9, C(2)H_A), 1.99 (3H, s, CO*Me*), 2.13 (3H, s, CO*Me*), 2.15−2.20 (1H, m, C(2)H_B), 3.41 (3H, s, O*Me*), 4.10 (1H, q, *J* 6.5, C(5)*H*), 4.15 (1H, ddt, *J* 7.2, 5.0, 2.4, C(3)*H*), 4.80−4.82 (2H, m, C(1)*H*, C(4)*H*), 6.82 (1H, br d, *J* 6.9, N*H*); δ_C (125 MHz, $CDCl_3$) 16.7 (*C*(6)), 20.9, 23.5 (CO*Me*), 28.3 (*C*(2)), 44.5 (*C*(3)), 55.3 (O*Me*), 61.3 (*C*(5)), 69.1 (*C*(4)), 98.6 (*C*(1)), 169.0, 169.8 (*C*OMe); *m*/*z* (ESI$^+$) 268 ([M + Na]$^+$, 100); HRMS (ESI$^+$) $C_{11}H_{19}NNaO_5^+$ ([M + Na]$^+$) requires 268.1155, found 268.1158.

Data for minor (7%) component:[35] δ_H (500 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.6, C(6)H_3), 1.95 (1H, d, *J* 13.6 C(2)H_A), 2.05−2.09 (1H, m, C(2)H_B), 2.10 (3H, s, CO*Me*), 2.17 (3H, s, CO*Me*), 3.38 (3H, s, O*Me*), 3.95−3.97 (1H, m, C(5)*H*), 4.20−4.23 (1H, m, C(3)*H*), 5.02−5.04 (1H, m, C(4)*H*), 5.41 (1H, d, *J* 3.5, C(1)*H*), 6.47 (1H, br d, *J* 10.1, N*H*); δ_C (125 MHz, $CDCl_3$) 16.8 (*C*(6)), 21.4, 23.7 (CO*Me*), 30.8 (*C*(2)), 44.4 (*C*(3)), 55.0 (O*Me*), 60.0 (*C*(5)), 69.2 (*C*(4)), 99.1 (*C*(1)), 168.9, 170.5 (*C*OMe).

***tert*-Butyl (3*S*,4*S*,5*R*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)-amino]-4,5-dihydroxyhexanoate 37 and (3*S*,4*S*,5*R*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-hydroxy-4-hexanolactone 38.** *Donohoe Oxidation.* OsO_4 (147 mg, 0.58 mmol) was added to a stirred solution of **26** (200 mg, 0.53 mmol) and TMEDA (111 μL, 0.74 mmol) in CH_2Cl_2 (8 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and then allowed to warm to rt over a further 15 min before being concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL), the resultant solution was stirred, and $P(CH_2OH)_3$ (6.56 g, 52.6 mmol) and Et_3N (1.47 mL, 10.6 mmol) were added sequentially. After the mixture was stirred for 5 min, excess silica gel (∼5 g) was added, and stirring was continued at rt for a further 48 h. The resultant suspension was concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 1:1) gave **38** as a colorless oil (72 mg, 40% from **26**, >99:1 dr): $[\alpha]_D^{20}$ +109.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3422 (O−H), 1777 (C═O); δ_H (500 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.6, C(6)H_3), 1.44 (3H, d, *J* 7.3, C(α)*Me*), 1.95−2.01 (1H, m, C(2)H_A), 2.04−2.09 (1H, m, C(2)H_B), 2.47 (1H, br s, O*H*), 3.65 (1H, d, *J* 14.5, NCH_A), 3.75 (1H, d, *J* 14.5, NCH_B), 3.83 (1H, q, *J* 7.3, C(α)*H*), 4.01−4.05 (1H, m, C(3)*H*), 4.05−4.10 (1H, m, C(5)*H*), 4.23 (1H, dd, *J* 4.7, 3.5, C(4)*H*), 7.23−7.45 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.3 (*C*(6)), 19.2 (C(α)*Me*), 30.1 (*C*(2)), 50.4 (NCH_2), 53.4 (*C*(3)), 57.8 (*C*(α)), 68.4 (*C*(5)), 87.2 (*C*(4)), 127.3, 127.7 (*p*-*Ph*), 127.7, 127.9, 128.5, 128.6 (*o*,*m*-*Ph*), 139.3, 140.8 (*i*-*Ph*), 176.6 (*C*(1)); *m*/*z* (ESI$^+$) 362 ([M + Na]$^+$, 100); HRMS (ESI$^+$) $C_{21}H_{25}NNaO_3^+$ ([M + Na]$^+$) requires 362.1727, found 362.1727.

Upjohn Oxidation. OsO_4 (13 mg, 0.03 mmol) was added to a stirred solution of **26** (200 mg, 0.58 mmol) in THF (4 mL) and H_2O (1 mL), followed by a solution of NMO (246 mg, 2.10 mmol) in H_2O (0.5 mL). The reaction mixture was stirred at rt for 12 h. Saturated aq Na_2SO_3 (2 mL) was then added, and the resultant mixture was allowed to stir at rt for a further 1 h. The mixture was then extracted with EtOAc (3 × 5 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give 80:20 mixture of **37** and **38**, respectively. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 4:1) gave **37** as a yellow oil that crystallized upon standing (113 mg, 52%, >99:1 dr): mp 80−82 °C; $[\alpha]_D^{20}$ +53.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3452 (O−H), 1740 (C═O); δ_H (500 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.3, C(6)H_3), 1.41 (9H, s, CMe_3), 1.48 (3H, d, *J* 6.3, C(α)*Me*), 1.79 (1H, dd, *J* 16.7, 1.3,

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C(2)H_A), 2.21 (1H, dd, *J* 16.7, 9.5, C(2)H_B), 2.24 (1H, d, *J* 8.5, C(4)O*H*), 3.37−3.45 (1H, m, C(4)*H*), 3.52 (1H, d, *J* 13.9, NCH_A), 3.69 (1H, td, *J* 9.5, 1.3, C(3)*H*), 3.85−3.90 (3H, m, C(5)*H*, C(*α*)*H*, NCH_B), 5.44 (1H, br s, C(5)O*H*), 7.25−7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.3 (*C*(6)), 19.6 (C(*α*)*Me*), 28.0 (CMe_3), 34.5 (*C*(2)), 51.9 (NCH_2), 56.9 (*C*(3)), 57.3 (*C*(*α*)), 72.4 (*C*(5)), 75.9 (*C*(4)), 81.0 (*C*Me_3), 127.4, 127.6 (*p-Ph*), 128.1, 128.5, 128.8, 129.0 (*o,m-Ph*), 138.7, 140.3 (*i-Ph*), 173.7 (*C*(1)); *m/z* (ESI$^+$) 436 ([M + Na]$^+$, 60); HRMS (ESI$^+$) $C_{25}H_{36}NO_4^+$ ([M + H]$^+$) requires 414.2639, found 414.2632. Further elution gave **38** as a colorless oil (43 mg, 24%, >99:1 dr).

Lactonization of ***37***. F_3CCO_2H (0.5 mL) was added to a stirred solution of **37** (100 mg, 0.24 mmol) in CH_2Cl_2 (2.5 mL) at rt. The resultant solution was stirred for 12 h at rt before being neutralized (to pH 7) by the dropwise addition of satd aq $NaHCO_3$ (∼2 mL). The resultant mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 1:1) gave **38** as a colorless oil (57 mg, 69%, >99:1 dr).

(3*S*,4*S*,5*R*)-3-(*N*-*tert*-Butoxycarbonylamino)-5-dihydroxy-4-hexanolactone 39. Boc_2O (141 mg, 0.65 mmol) and $Pd(OH)_2/C$ (50% w/w of substrate, 100 mg) were added sequentially to a solution of **38** (200 mg, 0.59 mmol) in MeOH (3 mL). The resultant suspension was placed under H_2 (5 atm) and stirred vigorously at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH) and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 1:1) gave **39** as a white solid (132 mg, 92%, >99:1 dr):[37] mp 104−107 °C (lit.[37] 108−110 °C); $[\alpha]_D^{20}$ −24.4 (*c* 1.0 in $CHCl_3$) [lit.[37] $[\alpha]_D^{25}$ −24.5 (*c* 0.4 in CH_2Cl_2)]; δ_H (500 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.3, C(6)H_3), 1.46 (9H, s, CMe_3), 2.46 (1H, dd, *J* 18.2, 5.7, C(2)H_A), 2.75 (1H, br s, O*H*), 3.02 (1H, dd, *J* 18.2, 9.0, C(2)H_B), 3.98−4.02 (1H, br m, C(5)*H*), 4.10−4.16 (1H, m, C(4)*H*), 4.35−4.42 (1H, m, C(3)*H*), 4.87 (1H, d, *J* 5.4, N*H*).

Methyl *N,O*-Diacetyl-D-ristofuranosaminide 40−43. DIBAL-H (1.0 M in CH_2Cl_2, 1.42 mL, 1.42 mmol) was added dropwise via syringe (over 1 min) to a stirred solution of **39** (100 mg, 0.41 mmol) in CH_2Cl_2 (6 mL) at −78 °C. The resultant mixture was stirred for 30 min at −78 °C. MeOH (∼1 mL) was then added dropwise until effervescence ceased. Saturated aq Rochelle salt (20 drops) was then added, and the resultant suspension was stirred at rt for 16 h before being filtered through Celite (eluent MeOH) and concentrated in vacuo. The residue was dissolved in anhydrous MeOH (1 mL), and HCl (1.25 M in MeOH, 1 mL) was added. The resultant solution was stirred at rt for 48 h before being concentrated in vacuo. The residue was dissolved in pyridine (0.5 mL), Ac_2O (0.5 mL) and DMAP (1 mg) were added, and the resultant solution was stirred at rt for 12 h. The reaction mixture was then diluted with CH_2Cl_2 (3 mL), EtOAc (3 mL) and satd aq $CuSO_4$ (5 mL). The resultant solution was extracted with EtOAc (3 × 2 mL), and the combined organic extracts were washed with satd aq $NaHCO_3$ (2 × 3 mL), dried (Na_2SO_4), and concentrated in vacuo to give a 10:15:65:10 mixture of **40**, **41**, **42**, and **43** respectively. Purification via flash column chromatography (eluent PhMe/^{i}PrOH, 4:1) gave **methyl *N,O*-diacetyl-*α*-D-ristopyranosaminide 42** as a colorless oil (30 mg, 48% from **39**, >99:1 dr):[4,34f,39] $[\alpha]_D^{20}$ +173.9 (*c* 1.0 in $CHCl_3$) [lit.[4] for enantiomer $[\alpha]_D^{21}$ −134 (*c* 0.5 in $CHCl_3$); lit.[34f] for enantiomer $[\alpha]_D^{25}$ −130.4 (*c* 0.49 in $CHCl_3$); lit.[39a] for enantiomer $[\alpha]_D^{25}$ −130.8 (*c* 0.5 in $CHCl_3$); lit.[39b] $[\alpha]_D^{20}$ +134.5 (*c* 0.92 in $CHCl_3$); lit.[39c] for enantiomer $[\alpha]_D^{20}$ −130.1 (*c* 1.2 in $CHCl_3$); lit.[39d] for enantiomer $[\alpha]_D^{25}$ −132 (*c* 0.62 in $CHCl_3$); lit.[39e] for enantiomer $[\alpha]_D^{20}$ −126 (*c* 1.27 in $CHCl_3$); lit.[39f,g] $[\alpha]_D^{23}$ +127.6 (*c* 0.3 in $CHCl_3$); lit.[39h] for enantiomer $[\alpha]_D^{23}$ −141 (*c* 0.35 in $CHCl_3$); lit.[39i] for enantiomer $[\alpha]_D^{25}$ −134 (*c* 2.0 in $CHCl_3$); lit.[39j] for enantiomer $[\alpha]_D^{26}$ −136 (*c* 0.02 in $CHCl_3$)]; ν_{max} (film) 3413 (N−H), 2937, 2872, 2833 (C−H), 1737 (C═O, *ester*), 1655 (C═O, *amide*); δ_H (500 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.3, C(6)H_3), 1.83 (1H, ddd, *J* 14.7, 2.8, 1.1, C(2)H_A), 1.97 (3H, s, CO*Me*), 1.98 (3H, s, CO*Me*), 2.03 (1H, dt, *J* 14.7, 4.2, C(2)H_B), 3.39 (3H, s, O*Me*), 3.91 (1H, dq, *J* 10.1, 6.3, C(5)*H*), 4.51 (1H, dd, *J* 10.1, 3.8, C(4)*H*), 4.57 (1H, qd, *J* 8.0, 4.1, C(3)*H*), 4.72 (1H, d, *J* 3.2, C(1)*H*), 6.79 (1H, br d, *J* 8.5, N*H*); δ_C (125 MHz, $CDCl_3$) 17.4 (*C*(6)), 20.8, 23.6 (CO*Me*), 33.1 (*C*(2)), 43.5 (*C*(3)), 55.2 (O*Me*), 61.6 (*C*(5)), 72.9 (*C*(4)), 98.2 (*C*(1)), 169.6, 170.2 (COMe); *m/z* (ESI$^+$) 268 ([M + Na]$^+$, 100); HRMS (ESI$^+$) $C_{11}H_{19}NNaO_5^+$ ([M + Na]$^+$) requires 268.1155, found 268.1159. Further elution gave **methyl *N,O*-diacetyl-*β*-D-ristofuranosaminide 41** as a colorless oil (10 mg, 15% from **39**, 95% purity);[38] $[\alpha]_D^{20}$ +37.8 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 3283 (N−H), 2938, 2857, 2827 (C−H), 1736 (C═O, *ester*), 1672 (C═O, *amide*); δ_H (500 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.5, C(6)H_3), 1.78 (1H, app d, *J* 13.4, C(2)H_A), 1.97 (3H, s, CO*Me*), 2.06 (3H, s CO*Me*), 2.11−2.16 (1H, m, C(2)H_B), 3.38 (3H, s, O*Me*), 3.83 (1H, dd, *J* 4.1, 2.5, C(4)*H*), 4.59−4.63 (1H, m, C(3)*H*), 4.99 (1H, qd, *J* 6.5, 4.1, C(5)*H*), 5.07 (1H, d, *J* 4.4, C(1)*H*), 6.24 (1H, br d, *J* 8.8, N*H*); δ_C (125 MHz, $CDCl_3$) 16.2 (*C*(6)), 21.3, 23.5 (CO*Me*), 39.0 (*C*(2)), 48.6 (*C*(3)), 54.8 (O*Me*), 70.3 (*C*(5)), 88.3 (*C*(4)), 105.3 (*C*(1)), 168.7, 170.4 (*C*OMe); *m/z* (ESI$^+$) 268 ([M + Na]$^+$, 100); HRMS (ESI$^+$) $C_{11}H_{19}NNaO_5^+$ ([M + Na]$^+$) requires 268.1155, found 268.1157. Further elution gave a 70:30 mixture of **methyl *N,O*-diacetyl-*α*-D-ristofuranosaminide 40 and methyl *N,O*-diacetyl-*β*-D-ristopyranosaminide 43** as a colorless oil (7 mg, 11% from 39). Data for mixture: ν_{max} (film) 3286 (N−H), 2937 (C−H), 1735 (C═O, *ester*), 1653 (C═O, *amide*); *m/z* (ESI$^+$) 268 ([M + Na]$^+$, 100); HRMS (ESI$^+$) $C_{11}H_{19}NNaO_5^+$ ([M + Na]$^+$) requires 268.1155; found 268.1154. Data for **40**: δ_H (500 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.6, C(6)H_3), 1.88−1.94 (1H, m, C(2)H_A), 1.98 (3H, s, CO*Me*), 2.07 (3H, s, CO*Me*), 2.35 (1H, d, *J* 13.3, 7.3, 1.4, C(2)H_B), 3.35 (3H, s, O*Me*), 3.79 (1H, t, *J* 5.5, C(4)*H*), 4.58 (1H, dd, *J* 7.9, 6.0, C(3)*H*), 5.00 (1H, dd, *J* 6.6, 5.5, C(5)*H*), 5.04 (1H, dd, *J* 5.7, 1.4, C(1)*H*), 5.55 (1H, br d, *J* 5.4, N*H*); δ_C (125 MHz, $CDCl_3$) 15.8 (*C*(6)), 21.3, 23.4 (CO*Me*), 39.7 (*C*(2)), 50.5 (*C*(3)), 55.2 (O*Me*), 71.0 (*C*(5)), 86.1 (*C*(4)), 105.0 (*C*(1)), 169.5, 170.6 (COMe). Data for **43**:[34b] δ_H (500 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.9, C(6)H_3), 1.85−1.87 (1H, m, C(2)H_A), 2.00 (3H, s, CO*Me*), 2.02−2.05 (1H, m, C(2)H_B), 2.10 (3H, s, CO*Me*), 3.44 (3H, s, O*Me*), 3.91−3.96 (1H, m, C(5)*H*), 4.63−4.69 (2H, m, C(1)*H*, C(3)*H*), 4.73−4.75 (1H, m, C(4)*H*), 6.41 (1H, d, *J* 4.7, N*H*); δ_C (125 MHz, $CDCl_3$) 18.8 (*C*(6)), 21.1, 23.5 (CO*Me*), 33.1 (*C*(2)), 42.1 (*C*(3)), 55.8 (O*Me*), 70.5 (*C*(5)), 73.0 (*C*(4)), 99.2 (*C*(1)), 169.0, 170.2 (COMe).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra and crystallographic information files (for structures CCDC 953270−953273). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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