JOC The Journal of Organic Chemistry

Article

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Stereospecific Cyclization Strategies for α,ε-Dihydroxy-β-amino Esters: Asymmetric Syntheses of Imino and Amino Sugars

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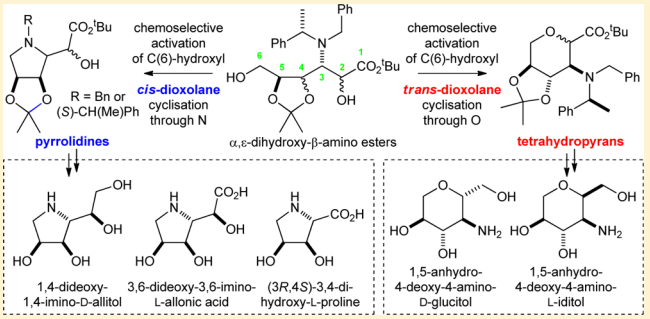
Supporting Information

ABSTRACT: A range of biologically significant imino and amino sugars [1,4-dideoxy-1,4-imino-D-allitol, 3,6-dideoxy-3,6-imino-L-allonic acid, (3*R*,4*S*)-3,4-dihydroxy-L-proline, 1,5-anhydro-4-deoxy-4-amino-D-glucitol, and 1,5-anhydro-4-deoxy-4-amino-L-iditol] has been prepared via stereospecific cyclization of α,ε-dihydroxy-β-amino esters. These substrates are readily prepared via conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to enantiopure α,β-unsaturated esters (β-substituted with *cis*- and *trans*-dioxolane units) coupled with in situ enolate oxidation with camphorsulfonyloxaziridine (CSO). Activation of the ε-hydroxyl group allowed cyclization to either the corresponding pyrrolidine or the tetrahydropyran scaffold, with the course of the cyclization process being dictated by the relative configuration of the dioxolane unit. When the α,ε-dihydroxy-β-amino ester bears a *cis*-dioxolane unit, cyclization occurs upon attack of the β-amino substituent to give the corresponding pyrrolidine after in situ *N*-debenzylation. In contrast, when the α,ε-dihydroxy-β-amino ester bears a *trans*-dioxolane unit, cyclization occurs upon attack of the α-hydroxyl substituent to give the corresponding tetrahydropyran.



INTRODUCTION

Carbohydrates are ubiquitous in cellular recognition events, growth, differentiation, and death, and have been implicated in the progression of several diseases, including cancer. Molecules able to mimic carbohydrates therefore have potential as therapeutic agents, and a vast amount of research has been directed toward the identification and evaluation of the biological properties of such species.[1] Perhaps one of the flagship compounds of this class is the iminosugar[2,3] 1,5-dideoxy-1,5-imino-D-glucitol (1-deoxynojirimycin), which was originally prepared by synthesis,[4] but subsequently isolated from mulberry leaves,[5] and found to be a potent glucosidase inhibitor. Development of this core structure has led to the discovery and approval by the FDA of miglitol (Glyset)[6] and subsequently miglustat (Zavesca)[7] as therapeutics for the treatment of type II diabetes and type I Gaucher's disease, respectively. These potential therapeutic applications have incited significant interest in carbohydrate mimetics based upon a range of heterocyclic scaffolds, for example, pyrrolidines such as 1,4-dideoxy-1,4-imino-D-arabinitol (DAB) and indolizidines such as swainsonine[2,3,8−11] (Figure 1).

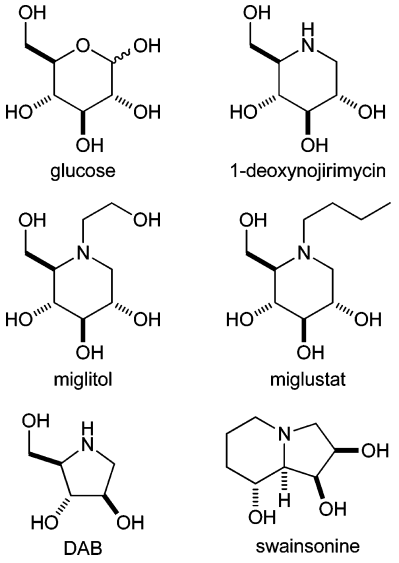


Figure 1. Structures of glucose, 1-deoxynojirimycin, miglitol, miglustat, DAB, and swainsonine.

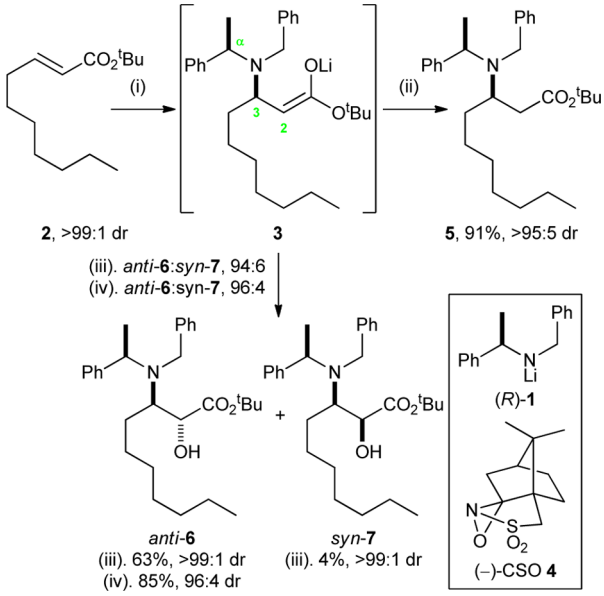
Extensive studies from within our laboratory have developed the asymmetric conjugate addition of secondary lithium amides derived from α-methylbenzylamine as a powerful and versatile synthetic route to β-amino esters and their derivatives, with very high and predictable levels of diastereoselectivity.[12] Thus, for example, conjugate addition of (*R*)-**1** to α,β-unsaturated ester **2** followed by protonation of the intermediate lithium β-amino (*Z*)-enolate **3** gave β-amino ester **5** in 91% yield and

Received: August 7, 2014
Published: September 9, 2014

   dx.doi.org/10.1021/jo5018298 | J. Org. Chem. 2014, 79, 9686−9698

>95:5 dr.[13] The conjugate addition reaction can be combined with in situ enolate oxidation (rather than protonation) using enantiopure camphorsulfonyloxaziridine **4** (CSO) to give access to the corresponding *anti*-α-hydroxy-β-amino esters (i.e., a process to achieve diastereoselective aminohydroxylation of the olefin).[12] The stereochemical outcome of the oxidation process is generally dictated by the stereochemical information present within the enolate substrate [induction by the stereocenters at C(3) and/or C(α)] rather than reagent control, and hence the use of either enantiomer of CSO **4** gives comparable diastereoselectivity. Thus, for example, in our synthesis of a fragment of microginin,[13] treatment of α,β-unsaturated ester **2** with (*R*)-**1** then (+)-CSO **4** gave the corresponding α-hydroxy-β-amino esters *anti*-**6** and *syn*-**7** in 94:6 dr, with isolated yields of 63% and 4%, respectively, while use of (−)-CSO **4** gave *anti*-**6** and *syn*-**7** in 96:4 dr and 85% combined isolated yield[13] (Scheme 1). These results are also consistent with the poor enantioselectivities observed in the hydroxylation of achiral ester enolates with CSO **4**.[14]

Scheme 1[a]



[a]Reagents and conditions: (i) (*R*)-**1**, THF, −78 °C; (ii) NH_4Cl (satd, aq), −78 °C to rt, 15 min; (iii) (+)-CSO **4**, −78 °C to rt, 12 h; (iv) (−)-CSO **4**, −78 °C to rt, 12 h.

As part of an ongoing research program aimed at the development of asymmetric syntheses of imino and amino sugars, we have recently examined the conjugate addition of the antipodes of lithium amide **1** to enantiopure α,β-unsaturated esters (4*S*,5*S*,*E*)-**8**[15] and (4*R*,5*S*,*E*)-**9**[16] (β-substituted with *trans*- and *cis*-dioxolane units, respectively). We determined that the combinations of (*S*)-**1**/(4*S*,5*S*,*E*)-**8** and (*S*)-**1**/(4*R*,5*S*,*E*)-**9** are the doubly diastereoselective "matched" reaction pairings, and proceed in >99:1 dr in both cases to give, after protonation of the intermediate enolates, the corresponding β-amino esters.[15,16] We anticipated that these highly diastereoselective conjugate addition reactions could be coupled with our enolate oxidation protocol (using CSO **4**)[12,17] to give the corresponding α-hydroxy-β-amino esters **10** as key intermediates en route to a range of imino and amino sugars. The presence of several heteroatoms within α-hydroxy-β-amino esters **10** was expected to render them ideal precursors to either pyrrolidine or tetrahydropyran scaffolds via *O*-desilylation and activation of the resultant ε-hydroxyl group, followed by cyclization of **11**. It was predicted that the course of the cyclization would be directed by the relative configuration of the dioxolane unit. When **11** bears a *cis*-dioxolane unit, cyclization may proceed through attack of the C(3)-amino group (leading to the corresponding pyrrolidine after in situ *N*-debenzylation),[18] or through attack of the C(2)-hydroxyl group (leading to the corresponding tetrahydropyran). It was anticipated, however, that the former of these two processes would be favored kinetically to give *cis*-fused-[3.3.0]-bicycle **12**, not only due to the expected superior nucleophilicity of the C(3)-amino group as compared to the C(2)-hydroxyl group, but also due to the formation of a five-membered versus a six-membered ring.[19,20] Elaboration of **12** would then lead to a range of imino sugars **14**. In contrast, when **11** bears a *trans*-dioxolane unit, it was expected that cyclization would occur upon attack of the C(2)-hydroxyl substituent to give the corresponding *trans*-fused-[4.3.0]-bicycle **13**, as the alternative cyclization pathway through the C(3)-amino group would involve the concomitant formation of an unfavorable *trans*-fused-[3.3.0]-bicycle. Sequential ester reduction, hydrogenolysis, and acetal hydrolysis would then supply amino sugars **15** (Figure 2).

RESULTS AND DISCUSSION

Attempted aminohydroxylation of (4*S*,5*S*,*E*)-**8**[15] using lithium amide (*S*)-**1** and (−)-CSO **4** gave rise to a complex mixture of products, along with returned (4*S*,5*S*,*E*)-**8**. However, conjugate addition of (*S*)-**1** to (4*S*,5*S*,*E*)-8 and quenching with (+)-CSO **4** gave complete conversion to a single diastereoisomer of α-hydroxy-β-amino ester **16**, which was isolated in 66% yield. The relative configuration within **16** was later established unambiguously by single-crystal X-ray diffraction analysis of a derivative (vide infra), and hence the absolute (2*S*,3*R*,4*S*,5*S*,α*S*)-configuration within **16** was assigned from the known absolute configurations of the C(4)- and C(5)-stereogenic centers (derived from diethyl L-tartrate) and the (*S*)-α-methylbenzyl stereocenter (Scheme 2).

Attempted aminohydroxylation of (4*R*,5*S*,*E*)-**9**[16] via conjugate addition of lithium amide (*S*)-**1** and in situ enolate oxidation with (+)-CSO **4** gave capricious results: several runs of this reaction resulted either in returned (4*R*,5*S*,*E*)-**9** or in the formation of β-amino ester **17**[16] (the product of enolate protonation rather than oxidation) as the major product. The complexity of the ^{1}H NMR spectra of the crude reaction mixtures precluded accurate determinations of the product distributions and diastereoselectivities, although chromatographic purification facilitated the isolation of the desired α-hydroxy-β-amino ester **18** in a maximum of 34% isolated yield (and >99:1 dr). In contrast, conjugate addition of (*S*)-**1** to (4*R*,5*S*,*E*)-**9** and quenching with (−)-CSO **4** gave α-hydroxy-β-amino ester **18** as the major product, which was isolated in 60% yield and >99:1 dr (Scheme 3). As with **16**, the relative configuration within **18** was subsequently established unambiguously by single-crystal X-ray diffraction analysis of a derivative (vide infra), allowing the absolute (2*S*,3*R*,4*R*,5*S*,α*S*)-configuration of **18** to be assigned from the known absolute configurations of the C(4)- and C(5)-stereogenic centers (derived from D-ribose) and the (*S*)-α-methylbenzyl stereogenic center. In both of these examples, the relative *anti*-configuration of the C(2)- and C(3)-stereogenic centers is consistent with the well-established stereochemical outcome of

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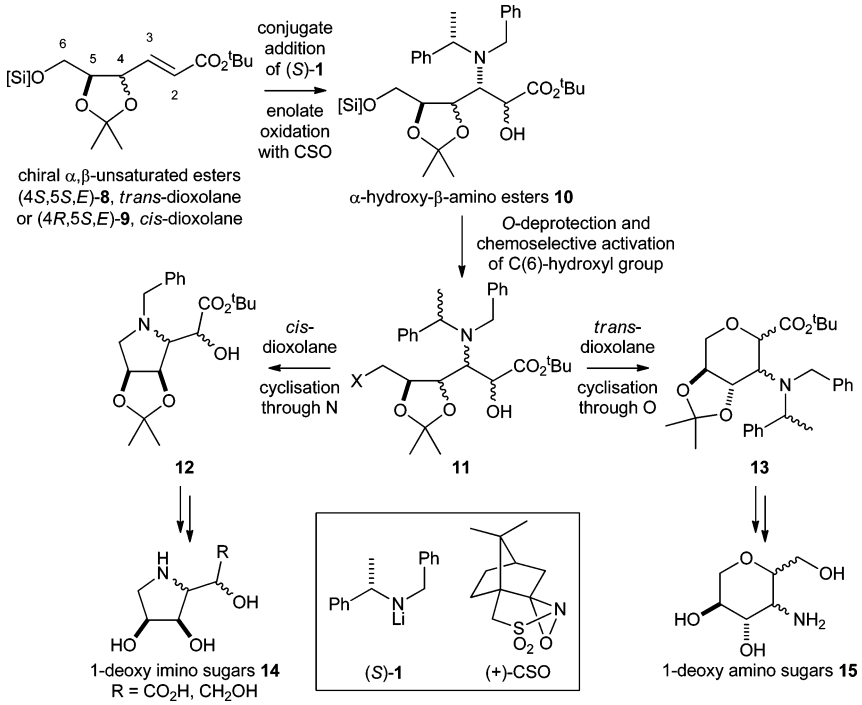
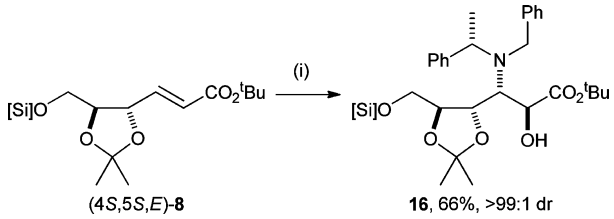


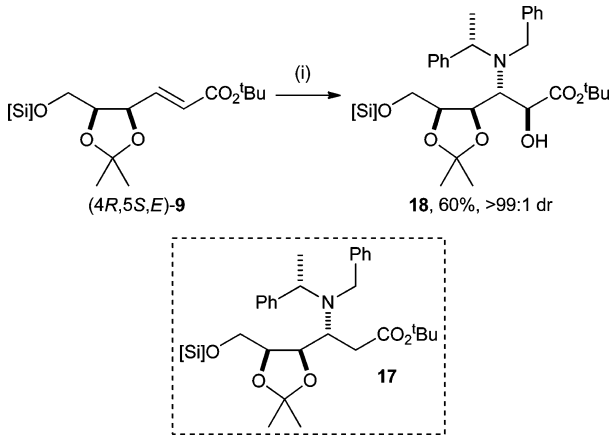
Figure 2. Proposed synthetic route from α-hydroxy-β-amino esters **10** to imino sugars **14** and amino sugars **15**.

Scheme 2[a]



[a]Reagents and conditions: (i) (*S*)-**1**, THF, −78 °C, 2 h, then (+)-CSO **4**, −78 °C to rt, 12 h. [Si] = *tert*-butyldimethylsilyl.

Scheme 3[a]



[a]Reagents and conditions: (i) (*S*)-**1**, THF, −78 °C, 2 h, then (−)-CSO **4**, −78 °C to rt, 12 h. [Si] = *tert*-butyldimethylsilyl.

this aminohydroxylation process when applied to achiral α,β-unsaturated esters.[12] The unusually high levels of enantiorecognition with the antipodes of CSO **4** are, however, noteworthy: we have previously observed such pronounced recognition in only one other case, upon aminohydroxylation of *tert*-butyl 4-phenylbutanoate (an achiral substrate) during a synthesis of allophenylnorstatine.[21] In the cases of **8** and **9**, it may be that the presence of the C(4)- and C(5)-stereogenic centers [in addition to those at C(3)/C(α)] is also significant in determining the overall efficacies of these processes.[22]

To increase the structural diversity of the range of α-hydroxy-β-amino esters available for elaboration to imino and amino sugar derivatives, the preparation of the corresponding C(2)-epimers of **16** and **18** was explored. Using our previously established procedure to effect inversion of configuration of the C(2)-stereogenic center of similar substrates,[23] oxidation of **16** to the corresponding ketone **19** and subsequent reduction using $NaBH_4$ gave a 15:85 mixture of **16** and **20**, from which **20** was isolated in 66% yield as a single diastereoisomer (Scheme 4). An analogous procedure applied to α-hydroxy-β-amino ester **18** gave complete conversion to the corresponding ketone **21**. Subsequent reduction with $NaBH_4$ proceeded in a completely diastereoselective manner, albeit to give return of **18** only: no trace of the desired *syn*-α-hydroxy-β-amino ester **22** was evident in the ^1H NMR spectrum of the crude reaction mixture. Taken together, these results suggest that the C(4)-stereogenic center has the controlling influence (Scheme 5).

Attention was now focused upon cyclization of α-hydroxy-β-amino ester **18** (β-substituted with a *cis*-dioxolane unit) to the corresponding pyrrolidine scaffold, using a strategy of *O*-desilylation followed by chemoselective activation of the resultant diol at the primary, C(6)-hydroxyl group, with ensuing cyclization and in situ *N*-debenzylation.[18] Desilylation of α-hydroxy-β-amino ester **18** with TBAF gave diol **23** in 85% isolated yield as a single diastereoisomer. Initial studies to effect cyclization of **23** centered on conversion of the C(6)-hydroxyl group to the corresponding mesylate. However, treatment of **23** with MsCl at low temperature resulted in the formation of **27**, which was isolated in 34% yield. This presumably arises from initial formation of **24** (X = OMs) followed by attack of

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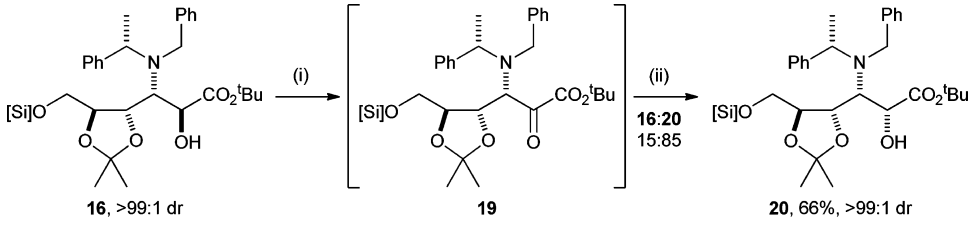
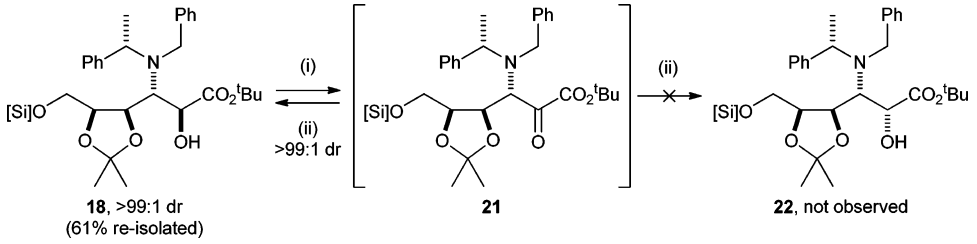
Scheme 4[a]



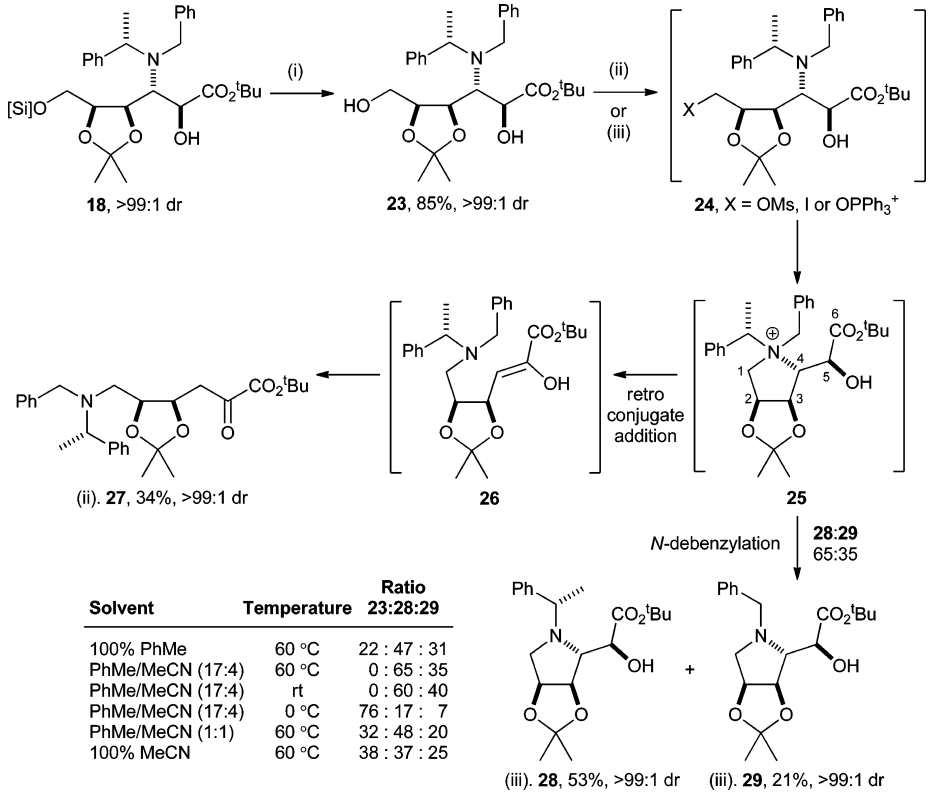
[a]Reagents and conditions: (i) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, 35 min, then Et_3N, −78 °C to rt, 30 min; (ii) $NaBH_4$, MeOH, −20 °C, 2 h. [Si] = *tert*-butyldimethylsilyl.

Scheme 5[a]



[a]Reagents and conditions: (i) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, 35 min, then Et_3N, −78 °C to rt, 30 min; (ii) $NaBH_4$, MeOH, −20 °C, 2 h. [Si] = *tert*-butyldimethylsilyl.

Scheme 6[a]



Solvent	Temperature	Ratio 23:28:29
100% PhMe	60 °C	22 : 47 : 31
PhMe/MeCN (17:4)	60 °C	0 : 65 : 35
PhMe/MeCN (17:4)	rt	0 : 60 : 40
PhMe/MeCN (17:4)	0 °C	76 : 17 : 7
PhMe/MeCN (1:1)	60 °C	32 : 48 : 20
100% MeCN	60 °C	38 : 37 : 25

[a]Reagents and conditions: (i) TBAF, THF, rt, 16 h; (ii) MsCl, Et_3N, DMAP, CH_2Cl_2, −10 °C, 6 h; (iii) I_2, imidazole, PPh_3, PhMe, MeCN, 60 °C, 1 h. [Si] = *tert*-butyldimethylsilyl.

the tertiary C(3)-amino group to give the intermediate ammonium species **25** (of unknown diastereoisomeric ratio at the nitrogen atom), as anticipated, with subsequent retro-conjugate addition (rather than the desired *N*-debenzylation) resulting in the formation of **27**. An alternative procedure to promote cyclization was therefore investigated, and treatment of **23** under Appel conditions[24] gave a 65:35 mixture of *N*-*α*-methylbenzyl protected pyrrolidine **28** and *N*-benzyl protected pyrrolidine **29**.[25] Chromatography facilitated isolation of **28** in 53% yield and **29** in 21% yield. This product distribution is

dx.doi.org/10.1021/jo5018298 | J. Org. Chem. 2014, 79, 9686−9698

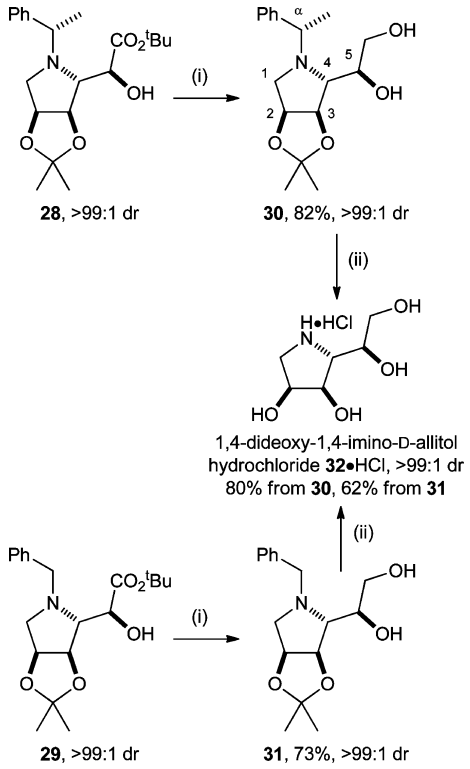
consistent with formation of **25** being followed by either loss of the *N*-benzyl group to give *N*-α-methylbenzyl protected pyrrolidine **28** or loss of the *N*-α-methylbenzyl group to give *N*-benzyl protected pyrrolidine **29**. The surprising preferential loss of the *N*-benzyl group from ammonium **25** is in contrast to our previously reported cyclization of a related β-amino-ζ-iodo ester, which proceeds with exclusive loss of the α-methylbenzyl group to give the corresponding piperidine scaffold.[18] To probe the origin of the change of selectivity in the present case, Appel reaction of **23** was examined using solvent combinations of varying polarity (ranging from 100% PhMe to 100% MeCN), and at a range of temperatures. It is apparent from the results of these reactions that both the conversion and the ratio of **28** to **29** are dependent on both variables. Although no firm mechanistic conclusions can be drawn from these data, one potential rationale for these product distributions is that the ratio of **28** to **29** corresponds to the diastereoisomeric ratio (*N*-epimers) of the intermediate ammonium ion **25** and that in each case the *N*-substituent in the more sterically encumbered environment is lost rapidly in an S_N1-type process. Nonetheless, pyrrolidines **28** and **29** represent valuable building blocks because after *N*-debenzylation they would converge on the same intermediate en route to imino sugar scaffolds (Scheme 6).

Pyrrolidines **28** and **29** were next elaborated to 1,4-dideoxy-1,4-imino-D-allitol **32**.[26] Thus, reduction of the ester functionality within **28** gave **30**, with subsequent hydrogenolysis of **30** in the presence of aqueous HCl effecting concomitant *N*-debenzylation and acetal hydrolysis to give **32**, which was isolated as its hydrochloride salt **32**·HCl after chromatographic purification, in >99:1 dr and 66% yield over the two steps. An analogous sequence of reactions applied to **29** gave initially the known *N*-benzyl pyrrolidine **31**,[26] which upon hydrogenolysis gave **32**·HCl in >99:1 dr and 45% yield over the two steps (Scheme 7). In both cases, the samples of **32**·HCl displayed spectroscopic properties that were entirely consistent with those previously reported.[26] The relative configuration within diol **30** was unambiguously established by single-crystal X-ray diffraction analysis,[27] with the absolute (2*S*,3*R*,4*R*,5*S*,α*S*)-configuration (1,4-dideoxy-1,4-iminohexitol numbering) being assigned by reference to the known absolute configurations of the C(2)- and C(3)-stereogenic centers (derived from D-ribose) and the (*S*)-α-methylbenzyl stereocenter. This analysis therefore also established unambiguously the relative (and hence absolute) configurations of α-hydroxy-β-amino esters **18** and **23**, and pyrrolidines **28** and **29**.

The conversions of pyrrolidines **28** and **29** to 3,6-dideoxy-3,6-imino-L-allonic acid[28] and (3*R*,4*S*)-dihydroxy-L-proline[26,29] were also explored. *N*-Debenzylation of pyrrolidines **28** and **29** converged on pyrrolidine **33** in 87% and quantitative yield, respectively, and in >99:1 dr in each case. Hydrolysis of **33** via treatment with 2 M aqueous HCl at 100 °C effected global deprotection; 3,6-dideoxy-3,6-imino-L-allonic acid **34** was subsequently isolated in 94% yield and >99:1 dr after purification by ion-exchange chromatography, and displayed spectroscopic properties that were entirely consistent with those reported previously[28] (Scheme 8).

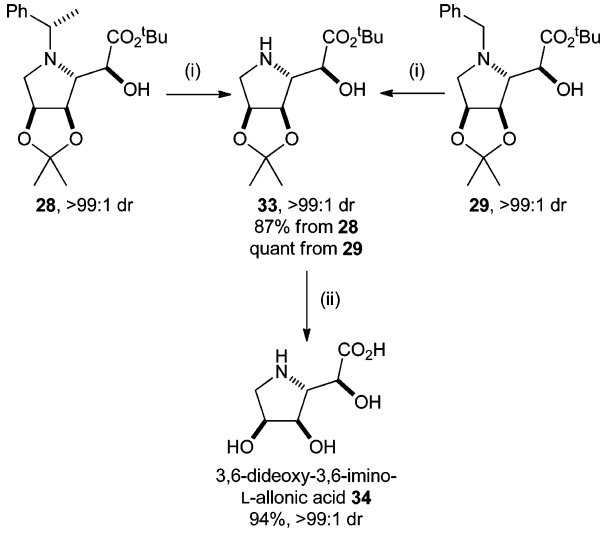
Meanwhile, hydrogenolysis of pyrrolidine **30** (derived from **28**) in the presence of Boc_2O gave *N*-Boc protected pyrrolidine **35** in 98% yield and >99:1 dr, while subjection of pyrrolidine **31** (derived from **29**) to identical conditions gave **35** in 96% yield and >99:1 dr (Scheme 9).

Scheme 7[a]



[a]Reagents and conditions: (i) $LiAlH_4$, THF, −78 °C to rt, 16 h; (ii) H_2, $Pd(OH)_2/C$, MeOH, HCl (3 M, aq), rt, 18 h.

Scheme 8[a]



[a]Reagents and conditions: (i) H_2, $Pd(OH)_2/C$, MeOH, rt, 12 h; (ii) HCl (2 M, aq), reflux, 8 h, then DOWEX 50WX8-200.

Following the procedure described by Fleet et al.,[26] cleavage of the 1,2-diol functionality within **35** using $NaIO_4$ gave aldehyde **36**, which was immediately subjected to oxidation with $NaClO_2$[30−32] to give carboxylic acid **37**. Global hydrolysis of **37** using 2 M aqueous HCl followed by purification via ion-exchange chromatography gave (3*R*,4*S*)-3,4-dihydroxy-L-proline **38** in 42% yield and >99:1 dr over the three steps. This sample of **38** was found to have spectroscopic properties that

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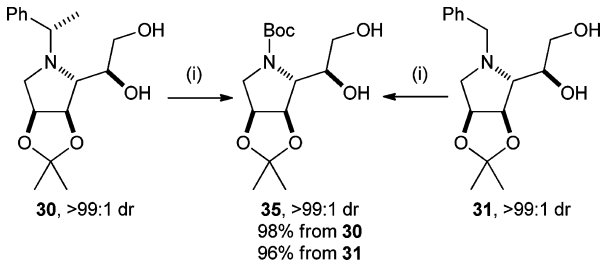
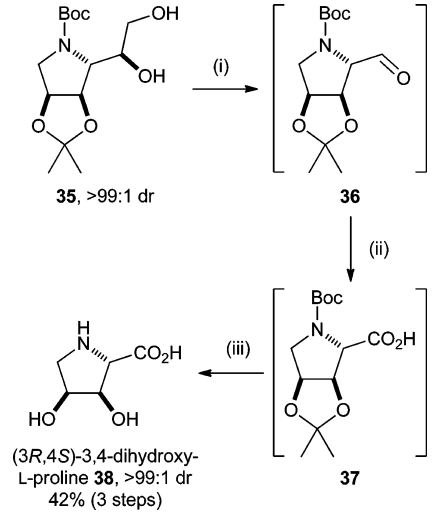
Scheme 9[a]



[a]Reagents and conditions: (i) Boc_2O, H_2, Pd/C, MeOH, rt, 18 h.

Scheme 10[a]



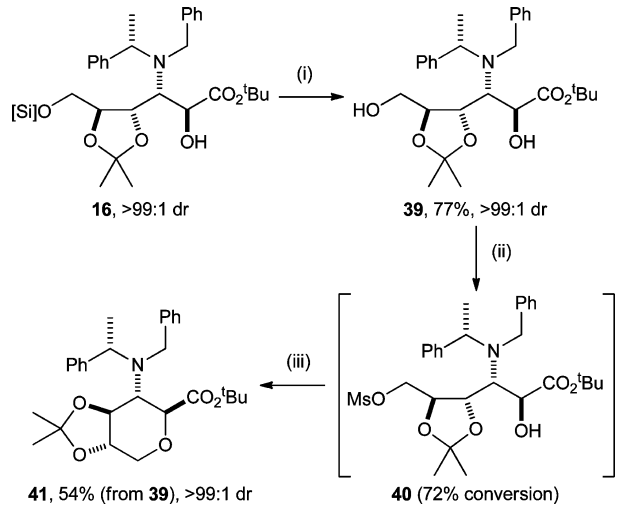
[a]Reagents and conditions: (i) $NaIO_4$, EtOH, H_2O, rt, 15 min; (ii) $NaClO_2$, KH_2PO_4, cyclohexene, ^{t}BuOH, H_2O, rt, 18 h; (iii) HCl (2 M, aq), reflux, 8 h, then DOWEX 50WX8-200.

were entirely consistent with those reported previously[26] (Scheme 10).

Having demonstrated the synthetic utility of pyrrolidines **28** and **29** (derived from *α*-hydroxy-*β*-amino ester **18**), the potential of *α*-hydroxy-*β*-amino esters **16** and **20** to undergo cyclization (promoted by *O*-desilylation followed by chemoselective activation of the resultant diol at the primary, C(6)-hydroxyl group) was next investigated. Initial *O*-desilylation of *α*-hydroxy-*β*-amino ester **16** upon treatment with TBAF gave diol **39** in 77% isolated yield as a single diastereoisomer. The relative configuration within **39** was unambiguously established by single-crystal X-ray diffraction analysis,[27] with the absolute (2*S*,3*R*,4*S*,5*S*,*αS*)-configuration being assigned from the known configuration of the (*S*)-*α*-methylbenzyl stereocenter and the C(4) and C(5)-stereocenters (derived from diethyl L-tartrate). This analysis also established the relative (and hence absolute) configurations within *α*-hydroxy-*β*-amino esters **16** and **20**. Development of an efficient chemoselective mono-C(6)-mesylation strategy to promote cyclization of **39** was initially pursued, and, in the event, treatment with 2.5 equiv of MsCl in pyridine at rt proved optimal, giving 72% conversion to the desired mesylate **40**. Treatment of the crude reaction mixture with NaH in THF then gave the desired tetrahydropyran **41**, which was isolated in 54% yield and >99:1 dr over the two steps (Scheme 11).

This optimized sequence of transformations was next applied to *α*-hydroxy-*β*-amino ester **20**. *O*-Desilylation of **20** upon

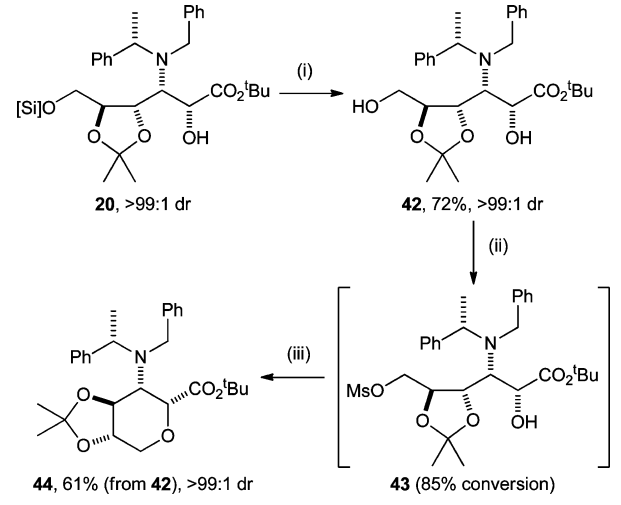
Scheme 11[a]



[a]Reagents and conditions: (i) TBAF, THF, rt, 16 h; (ii) MsCl, pyridine, rt, 18 h; (iii) NaH, THF, rt, 16 h. [Si] = *tert*-butyldimethylsilyl.

treatment with TBAF gave diol **42** in 72% isolated yield as a single diastereoisomer. Treatment of **42** with MsCl (2.5 equiv) in pyridine gave 85% conversion to mesylate **43**, which upon treatment with NaH in THF underwent cyclization to give the substituted tetrahydropyran **44**. Chromatography facilitated the isolation of **44** in 61% yield and >99:1 dr over the two steps (Scheme 12).

Scheme 12[a]



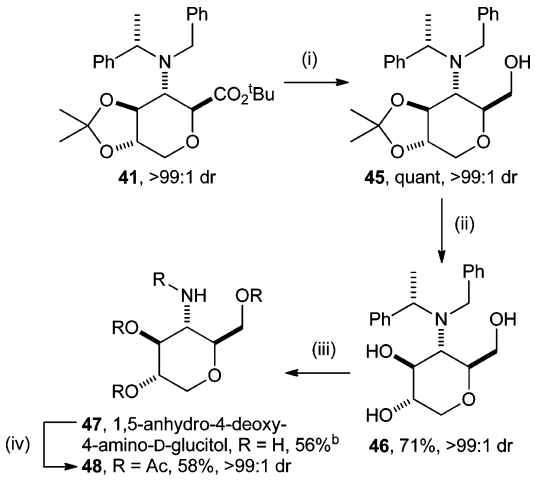
[a]Reagents and conditions: (i) TBAF, THF, rt, 16 h; (ii) MsCl, pyridine, rt, 18 h; (iii) NaH, THF, rt, 16 h. [Si] = *tert*-butyldimethylsilyl.

With tetrahydropyrans **41** and **44** in hand, their utility for the synthesis of the corresponding 1,5-anhydro-4-deoxy-4-amino-hexitols could be studied. Reduction of the ester functionality within tetrahydropyran **41** was achieved upon treatment with $LiAlH_4$ to give **45**, and was followed by sequential acetal hydrolysis and hydrogenolytic *N*-debenzylation to give 1,5-anhydro-4-deoxy-4-amino-D-glucitol **47**, which was isolated as its hydrochloride salt **47**·HCl in 40% yield over the three steps. Treatment with Ac_2O in pyridine gave the *N*,*O*,*O*,*O*-

dx.doi.org/10.1021/jo5018298 | J. Org. Chem. 2014, 79, 9686−9698

tetraacetate derivative **48** in 58% yield (Scheme 13). The relative configurations within both **47**·HCl and **48** were

Scheme 13[a]



[a]Reagents and conditions: (i) $LiAlH_4$, THF, −78 °C to rt, 16 h; (ii) HCl (3 M, aq), MeOH, 50 °C, 3 h; (iii) H_2, $Pd(OH)_2$/C, MeOH, rt, 18 h; (iv) Ac_2O, DMAP, pyridine, rt, 24 h. [b]Isolated as the corresponding HCl salt (in >99:1 dr).

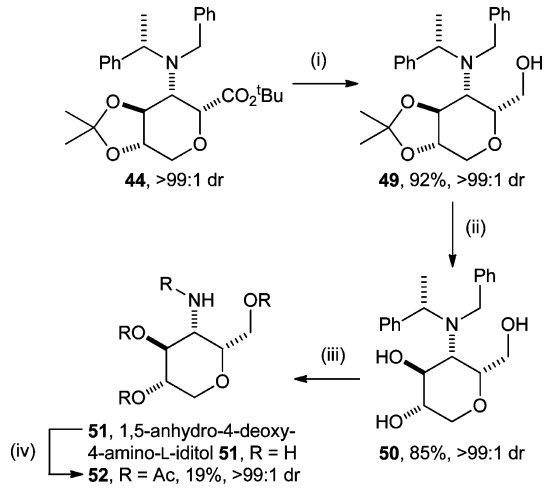
unambiguously confirmed by single-crystal X-ray diffraction analyses,[27] with their absolute configurations being assigned from the known absolute configurations of the C(2)- and C(3)-stereocenters (derived from diethyl L-tartrate). In addition, ^{1}H NMR ^3J coupling constant analyses of **46**, **47**·HCl, and **48** suggested that a chair conformation with an "all equatorial" arrangement of substituents is adopted in solution in all cases, as would be expected.

Finally, via a directly analogous set of transformations, sequential ester reduction, acetal hydrolysis, and hydrogenolysis of tetrahydropyran **44** gave 1,5-anhydro-4-deoxy-4-amino-L-iditol **51**, which was isolated as the *N*,*O*,*O*,*O*-tetraacetate derivative **52** in 15% yield over the four steps (Scheme 14). The assigned relative configurations within both **50** and **52** were supported by ^{1}H NMR ^3J coupling constant analyses.

CONCLUSION

A range of enantiopure α,ε-dihydroxy-β-amino esters (containing four contiguous stereogenic centers) has been prepared using the conjugate addition reactions of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to enantiopure α,β-unsaturated esters (β-substituted with *cis*- and *trans*-dioxolane units) coupled with in situ enolate oxidation with camphorsulfonyloxaziridine as the key step. Activation of the ε-hydroxyl group resulted in cyclization to either the corresponding pyrrolidine or the tetrahydropyran scaffold, with the chemoselectivity of the cyclization process being determined by the relative configuration of the dioxolane unit. When the α,ε-dihydroxy-β-amino ester bears a *cis*-dioxolane unit, cyclization occurs upon attack of the β-amino substituent to give the corresponding pyrrolidine after in situ *N*-debenzylation. In contrast, when the α,ε-dihydroxy-β-amino ester bears a *trans*-dioxolane unit, cyclization occurs upon attack of the α-hydroxyl substituent to give the corresponding tetrahydropyran. The potential for diversification of these pyrrolidines and tetrahydropyrans to a number of biologically significant imino and amino sugars is demonstrated by the preparation of 1,4-dideoxy-1,4-imino-D-allitol, 3,6-dideoxy-3,6-imino-L-allonic acid, (3*R*,4*S*)-3,4-dihydroxy-L-proline, 1,5-anhydro-4-deoxy-4-amino-D-glucitol, and 1,5-anhydro-4-deoxy-4-amino-L-iditol.

Scheme 14[a]



[a]Reagents and conditions: (i) $LiAlH_4$, THF, −78 °C to rt, 16 h; (ii) HCl (3 M, aq), MeOH, 50 °C, 3 h; (iii) H_2, $Pd(OH)_2$/C, MeOH, rt, 18 h; (iv) Ac_2O, DMAP, pyridine, rt, 24 h.

EXPERIMENTAL SECTION

General Experimental Details. Reactions involving moisture-sensitive reagents were carried out under a nitrogen 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.[33] Organic layers were dried over $MgSO_4$. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points are uncorrected. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded as a thin film on NaCl plates (film), as a KBr disc (KBr), or using an ATR module (ATR), as stated. 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. ^{1}H−^{1}H COSY and ^{1}H−^{13}C HMQC analyses were used to establish atom connectivity. Accurate mass measurements were run on a MicroTOF instrument internally calibrated with polyalanine.

X-ray Crystal Structure Determination.[27] Data were collected using either graphite monochromated Mo Kα radiation (for **30**, **39**, and **47**·HCl) or graphite monochromated Cu Kα radiation (for **48**) using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined using CRYSTALS.[34]

***tert*-Butyl (2*S*,3*R*,4*S*,5*S*,α*S*)-2,4,5,6-Tetrahydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-6-*O*-*tert*-butyldimethylsilylhexanoate 16.** BuLi (2.5 M in hexanes, 4.16 mL, 10.4 mmol) was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (2.27 g, 10.7 mmol) in THF (130 mL) at −78 °C, and stirring was continued for 30 min. A solution of **8** (2.50 g, 6.71 mmol) in THF (130 mL) was then added via cannula, and the reaction mixture was stirred for 2 h. (+)-CSO **4** (2.46 g, 10.7 mmol) was then added, and the reaction mixture was allowed to warm to rt over 12 h. The mixture was quenched with satd aqueous NH_4Cl (10 mL) and then concentrated in vacuo. The resultant residue was dissolved in Et_2O (200 mL) and then washed sequentially with 10% aqueous citric acid (200 mL), satd aqueous $NaHCO_3$ (200 mL), and brine (200 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 10:1)

dx.doi.org/10.1021/jo5018298 | J. Org. Chem. 2014, 79, 9686−9698

gave **16** as a colorless oil (2.63 g, 66%, >99:1 dr); $[\alpha]_D^{25}$ +3.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3512 (O−H), 1728 (C═O); δ_H (400 MHz, $CDCl_3$) 0.06 (3H, s, *Me*SiMe), 0.09 (3H, s, *Me*SiMe), 0.90 (9H, s, SiMe_3), 1.29 (3H, s, *Me*CMe), 1.31 (3H, d, *J* 7.1, C(*α*)*Me*), 1.32 (3H, s, *Me*CMe), 1.50 (9H, s, CMe_3), 3.33 (1H, d, *J* 9.2, O*H*), 3.42 (1H, dd, *J* 11.6, 3.4, C(6)H_A), 3.44−3.47 (1H, m, C(3)*H*), 3.74 (1H, dd, *J* 11.6, 3.8, C(6)H_B), 3.82−3.88 (1H, m, C(2)*H*) overlapping 3.85 (1H, d, *J* 15.2, NCH_AH_BPh), 3.99 (1H, q, *J* 7.1, C(*α*)*H*), 4.14 (1H, dd, *J* 8.2, 3.1, C(4)*H*), 4.44−4.49 (1H, m, C(5)*H*), 4.79 (1H, d, *J* 15.2, NCH_AH_BPh), 7.22−7.39 (8H, m, *Ph*), 7.49−7.54 (2H, m, *Ph*); δ_C (100 MHz, $CHCl_3$) −5.6, −5.4 (SiMe_2), 18.4 (SiCMe$_3$), 20.1 (C(*α*)*Me*), 25.9 (SiCMe_3), 26.5, 26.9 (CMe_2), 27.9 (OCMe_3), 53.8 (NCH_2Ph), 56.3 (*C*(3)), 58.2 (*C*(*α*)), 62.4 (*C*(6)), 72.8 (*C*(2)), 77.8 (*C*(4)), 78.0 (*C*(5)), 81.8 (OCMe$_3$), 108.7 (CMe_2), 126.2, 127.0 (*p*-*Ph*), 127.9, 128.0, 128.1 (*o*,*m*-*Ph*), 141.8, 142.0 (*i*-*Ph*), 172.9 (*C*(1)); *m*/*z* (ESI$^+$) 600 ([M + H]$^+$, 100%), 544 ([M − C_4H_7]$^+$, 20%); HRMS (ESI$^+$) $C_{34}H_{54}NO_6Si^+$ ([M + H]$^+$) requires 600.3720; found 600.3734.

***tert*-Butyl (2*S*,3*R*,4*R*,5*S*,*αS*)-2,4,5,6-Tetrahydroxy-3-[*N*-benzyl-*N*-(*α*-methylbenzyl)amino]-4,5-*O*-isopropylidene-6-*O*-*tert*-butyldimethylsilylhexanoate 18.** BuLi (2.5 M in hexanes, 5.82 mL, 14.6 mmol) was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-(*α*-methylbenzyl)amine (3.18 g, 15.0 mmol) in THF (140 mL) at −78 °C, and stirring was continued for 30 min. A solution of **9** (3.50 g, 9.39 mmol) in THF (140 mL) was then added via cannula, and the reaction mixture was stirred for 2 h. (−)-CSO **4** (4.31 g, 18.8 mmol) was then added, and the reaction mixture was allowed to warm to rt over 12 h. The mixture was quenched with satd aqueous NH_4Cl (10 mL) and then concentrated in vacuo. The resultant residue was dissolved in Et_2O (200 mL) and then washed sequentially with 10% aqueous citric acid (200 mL), satd aqueous $NaHCO_3$ (200 mL), and brine (200 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 10:1) gave **18** as a pale yellow oil (3.39 g, 60%, >99:1 dr); $[\alpha]_D^{25}$ −4.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3491 (O−H), 3085, 3063, 3029, 2928, 2855 (C−H), 1736 (C═O); δ_H (400 MHz, $CDCl_3$) 0.15 (6H, s, SiMe_2), 1.01 (9H, s, SiCMe_3), 1.26 (3H, s, *Me*CMe), 1.38 (3H, s, *Me*CMe), 1.44 (3H, d, *J* 6.9, C(*α*)*Me*), 1.54 (9H, s, CMe_3), 3.13 (1H, d, *J* 7.1, O*H*), 3.52 (1H, dd, *J* 10.4, 8.9, C(6)H_A), 3.73−3.78 (2H, m, C(3)*H*, C(6)H_B), 3.79 (1H, d, *J* 16.2, NCH_AH_BPh), 4.08 (1H, q, *J* 6.9, C(*α*)*H*), 4.13 (1H, d, *J* 7.1, C(2)*H*), 4.23 (1H, ddd, *J* 8.9, 5.7, 2.8, C(5)*H*), 4.42 (1H, dd, *J* 10.0, 5.7, C(4)*H*), 4.50 (1H, d, *J* 16.2, NCH_AH_BPh), 7.23−7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) −5.1 (SiMe_2), 18.4 (SiCMe$_3$), 20.2 (C(*α*)*Me*), 25.4 (*Me*CMe), 25.9 (SiCMe_3), 28.0 (CMe_3), 28.1 (*Me*CMe), 50.8 (NCH_2Ph), 57.7 (*C*(3)), 59.8 (*C*(*α*)), 62.8 (*C*(6)), 70.4 (*C*(2)), 73.9 (*C*(4)), 77.9 (*C*(5)), 81.7 (CMe$_3$), 107.2 (CMe_2), 126.4, 127.4 (*p*-*Ph*), 127.5, 128.0, 128.2, 128.4 (*o*,*m*-*Ph*), 141.8, 142.0 (*i*-*Ph*), 172.7 (*C*(1)); *m*/*z* (ESI$^+$) 600 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{53}NNaO_6Si^+$ ([M + Na]$^+$) requires 622.3534; found 622.3535.

***tert*-Butyl (2*R*,3*R*,4*S*,5*S*,*αS*)-2,4,5,6-Tetrahydroxy-3-[*N*-benzyl-*N*-(*α*-methylbenzyl)amino]-4,5-*O*-isopropylidene-6-*O*-*tert*-butyldimethylsilylhexanoate 20.** DMSO (0.47 mL, 6.67 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (56 *μ*L, 0.67 mmol) in CH_2Cl_2 (2.5 mL) at −78 °C, and the resultant mixture was stirred for 5 min. A solution of **16** (200 mg, 0.33 mmol) in CH_2Cl_2 (2.5 mL) was then added via cannula, and the reaction mixture was stirred at −78 °C for 30 min. Et_3N (0.19 mL, 1.33 mmol) was added, and stirring was continued for a further 10 min. The reaction mixture was then allowed to warm to rt over 20 min. H_2O (20 mL) was added, and the resultant mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried and concentrated in vacuo to give **19** as a yellow oil (192 mg); δ_H (400 MHz, $CDCl_3$) 0.14 (6H, s, SiMe_2), 0.97 (9H, s, SiCMe_3), 1.14 (3H, s, *Me*CMe), 1.36 (3H, s, *Me*CMe), 1.42 (3H, d, *J* 6.8, C(*α*)*Me*), 1.50 (9H, s, OCMe_3), 3.79 (1H, dd, *J* 11.4, 8.2, C(6)H_A), 3.94−4.04 (2H, m, C(5)*H*, C(6)H_B) overlapping 3.97 (1H, q, *J* 6.8, C(*α*)*H*), 4.19 (1H, d, *J* 16.5, NCH_AH_BPh), 4.28 (1H, dd, *J* 9.0, 6.1, C(4)*H*), 4.46 (1H, d, *J* 16.5, NCH_AH_BPh), 4.92 (1H, d, *J* 9.0, C(3)*H*), 7.24−7.34 (10H, m, *Ph*); *m*/*z* (ESI$^+$) 598 ([M + H]$^+$, 100%). Crude **19** (192 mg) was dissolved in MeOH (4 mL), and the resultant solution was cooled to −20 °C. $NaBH_4$ (13 mg, 0.33 mmol) was added portionwise, and stirring was continued at −20 °C for 2 h. The reaction mixture was then allowed to warm to rt and concentrated in vacuo. The residue was partitioned between H_2O (10 mL) and Et_2O (10 mL), and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried and concentrated in vacuo to give a 15:85 mixture of **16** and **20**. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 20:1) gave **20** as a pale yellow oil (132 mg, 66%, >99:1 dr); $[\alpha]_D^{25}$ −11.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3496 (O−H), 3085, 3062, 3028, 2981, 2955, 2932, 2885, 2857 (C−H), 1724 (C═O); δ_H (400 MHz, $CDCl_3$) 0.08 (3H, s, *Me*SiMe), 0.09 (3H, s, *Me*SiMe), 0.92 (9H, s, SiCMe_3), 1.36 (3H, s, *Me*CMe), 1.37 (3H, s, *Me*CMe), 1.42 (3H, d, *J* 7.0, C(*α*)*Me*), 1.47 (9H, s, CMe_3), 2.72 (1H, d, *J* 6.8, O*H*), 3.36 (1H, t, *J* 5.2, C(3)*H*), 3.52 (1H, dd, *J* 11.4, 3.5, C(6)H_A), 3.77 (1H, dd, *J* 11.4, 4.0, C(6)H_B), 4.05 (1H, d, *J* 15.0, NCH_AH_BPh), 4.05−4.09 (1H, m, C(2)*H*), 4.21−4.27 (1H, m, C(5)*H*), 4.30 (1H, q, *J* 7.0, C(*α*)*H*), 4.32−4.38 (1H, m, C(4)*H*) overlapping 4.35 (1H, d, *J* 15.0, NCH_AH_BPh), 7.18−7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) −5.5, −5.3 (SiMe_2), 18.5 (SiCMe$_3$), 20.1 (C(*α*)*Me*), 26.0 (SiCMe_3), 26.3, 27.1 (CMe_2), 27.9 (CMe_3), 53.1 (NCH_2Ph), 59.9 (*C*(*α*)), 60.2 (*C*(3)), 63.2 (*C*(6)), 72.3 (*C*(2)), 77.2 (*C*(4)), 79.0 (*C*(5)), 82.4 (CMe$_3$), 108.2 (CMe_2), 126.3, 126.9 (*p*-*Ph*), 128.1, 128.6 (*o*,*m*-*Ph*), 142.0, 144.0 (*i*-*Ph*), 173.1 (*C*(1)); *m*/*z* (ESI$^+$) 600 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{54}NO_6Si^+$ ([M + H]$^+$) requires 600.3715; found 600.3716.

***tert*-Butyl (2*S*,3*R*,4*R*,5*S*,*αS*)-2,4,5,6-Tetrahydroxy-3-[*N*-benzyl-*N*-(*α*-methylbenzyl)amino]-4,5-*O*-isopropylidenehexanoate 23.** TBAF (1.0 M in THF, 9.75 mL, 9.75 mmol) was added dropwise to a stirred solution of **18** (1.17 g, 1.95 mmol) in THF (15 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with Et_2O (30 mL) and washed with H_2O (20 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 5:1) gave **23** as a white solid (807 mg, 85%, >99:1 dr); mp 83−89 °C; $[\alpha]_D^{25}$ +5.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3490 (O−H), 3085, 3062, 3029, 2980, 2935 (C−H), 1730 (C═O); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, s, *Me*CMe), 1.35 (3H, s, *Me*CMe), 1.42 (3H, d, *J* 6.8, C(*α*)*Me*), 1.51 (9H, s, CMe_3), 2.66 (1H, d, *J* 5.3, C(6)O*H*), 3.21 (1H, d, *J* 6.1, C(2)O*H*), 3.37−3.44 (1H, m, C(6)H_A), 3.46−3.54 (1H, m, C(6)H_B), 3.73−3.76 (1H, m, C(3)*H*), 3.78 (1H, d, *J* 13.1, NCH_AH_BPh), 4.02 (1H, q, *J* 6.8, C(*α*)*H*), 4.12 (1H, d, *J* 6.1, C(2)*H*), 4.16−4.22 (1H, m, C(5)*H*), 4.46−4.52 (1H, m, C(4)*H*) overlapping 4.48 (1H, d, *J* 13.1, NCH_AH_BPh), 7.22−7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.4 (C(*α*)*Me*), 25.2 (*Me*CMe), 27.9 (CMe_3), 28.0 (*Me*CMe), 51.2 (NCH_2Ph), 57.3 (*C*(3)), 60.0 (*C*(*α*)), 60.9 (*C*(6)), 69.7 (*C*(2)), 73.8 (*C*(4)), 77.1 (*C*(5)), 82.0 (CMe$_3$), 107.4 (CMe_2), 126.5, 127.4 (*p*-*Ph*), 127.5, 128.0, 128.2, 128.4 (*o*,*m*-*Ph*), 141.3, 141.7 (*i*-*Ph*), 172.7 (*C*(1)); *m*/*z* (ESI$^+$) 486 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{40}NO_6^+$ ([M + H]$^+$) requires 486.2850; found 486.2839.

***tert*-Butyl (4*R*,5*S*,*αS*)-2-Keto-4,5-dihydroxy-4,5-*O*-isopropylidene-6-[*N*-benzyl-*N*-(*α*-methylbenzyl)amino]hexanoate 27.** MsCl (40 *μ*L, 0.52 mmol) was added dropwise to a stirred solution of **23** (50 mg, 0.10 mmol), Et_3N (0.14 mL, 1.0 mmol), and DMAP (5 mg, cat.) in CH_2Cl_2 (2 mL) at −10 °C, and the resultant mixture was stirred at −10 °C for 6 h. H_2O (1 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed sequentially with 10% aq $CuSO_4$ (10 mL), H_2O (10 mL), and satd aq $NaHCO_3$ (10 mL). The organic layer was then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 10:1) gave **27** as a pale yellow oil (16 mg, 34%, >99:1 dr); $[\alpha]_D^{25}$ +13.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3085, 3062, 3029, 2982, 2934, 2837 (C−H), 1721 (C═O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, s, *Me*CMe), 1.37 (3H, s, *Me*CMe), 1.41 (3H, d, *J* 6.9, C(*α*)*Me*), 1.55 (9H, s, CMe_3), 1.97 (1H, dd, *J* 16.1, 3.5, C(3)H_A), 2.55 (1H, dd, *J* 13.4, 6.9, C(6)H_A), 2.74 (1H, dd, *J* 16.1, 10.1, C(3)H_B), 2.75 (1H, dd, *J* 13.4, 5.5, C(6)H_B), 3.56 (1H, d, *J* 13.7, NCH_AH_BPh), 3.74 (1H, d, *J* 13.7, NCH_AH_BPh), 4.03 (1H, q, *J* 6.9, C(*α*)*H*), 4.27 (1H, app dt, *J* 6.9, 5.5, C(5)*H*), 4.49 (1H,

dx.doi.org/10.1021/jo5018298 | *J. Org. Chem.* 2014, 79, 9686−9698

ddd, *J* 10.1, 5.5, 3.5, C(4)*H*), 7.19–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.4 (C(*α*)*Me*), 25.7, 28.2 (*CMe*$_2$), 27.8 (*CMe*$_3$), 39.3 (*C*(3)), 48.4 (*C*(6)), 55.1 (NCH_2Ph), 57.8 (*C*(*α*)), 73.5 (*C*(4)), 75.8 (*C*(5)), 83.7 (*CMe*$_3$), 108.2 (*CMe*$_2$), 126.9, 127.0 (*p-Ph*), 128.1, 128.3, 128.8 (*o,m-Ph*), 140.0, 143.2 (*i-Ph*), 160.1 (*C*(1)), 193.4 (*C*(2)); *m/z* (ESI^+) 468 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{38}NO_5^+$ ($[M + H]^+$) requires 468.2744; found 468.2728.

***tert*-Butyl (*αS*)-*N*-*α*-Methylbenzyl-3,6-dideoxy-3,6-imino-4,5-*O*-isopropylidene-L-allonate 28 and *tert*-Butyl *N*-Benzyl-3,6-dideoxy-3,6-imino-4,5-*O*-isopropylidene-L-allonate 29.** PPh_3 (65 mg, 0.25 mmol) and imidazole (21 mg, 0.31 mmol) were added to a solution of **23** (100 mg, 0.21 mmol) in PhMe and MeCN (v/v 17:4, 2.1 mL). I_2 (63 mg, 0.25 mmol) was then added, and the mixture was heated at 60 °C for 1 h. The reaction mixture was then allowed to cool to rt, diluted with H_2O (5 mL), then washed sequentially with satd aqueous $Na_2S_2O_3$ (10 mL), H_2O (10 mL), and brine (10 mL), dried, and concentrated in vacuo to give a 65:35 mixture of **28** and **29**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **28** as a pale yellow oil (41 mg, 53%, >99:1 dr); $[\alpha]_D^{25}$ −8.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3437 (O–H), 2978, 2934, 2849 (C–H), 1717 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, *Me*CMe), 1.37 (9H, s, C*Me*$_3$), 1.42 (1H, d, *J* 6.6, C(*α*)*Me*), 1.50 (3H, s, *Me*CMe), 2.97 (1H, dd, *J* 10.1, 2.2, C(6)H_A), 2.99 (1H, br s, O*H*), 3.21 (1H, dd, *J* 10.1, 6.0, C(6)H_B), 3.28–3.30 (1H, m, C(3)*H*), 3.96 (1H, q, *J* 6.6, C(*α*)*H*), 4.31 (1H, s, C(2)*H*), 4.43 (1H, dd, *J* 6.0, 1.3, C(4)*H*), 4.68 (1H, td, *J* 6.0, 2.2, C(5)*H*), 7.20–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.9 (C(*α*)*Me*), 25.4, 27.1 (*CMe*$_2$), 27.8 (*CMe*$_3$), 55.8 (*C*(6)), 58.6 (*C*(*α*)), 67.5 (*C*(3)), 69.5 (*C*(2)), 79.6 (*C*(5)), 81.0 (*C*(4)), 82.7 (*CMe*$_3$), 111.3 (*CMe*$_2$), 126.9 (*p-Ph*), 127.4, 128.3 (*o,m-Ph*), 143.3 (*i-Ph*), 173.0 (*C*(1)); *m/z* (ESI^+) 378 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{32}NO_5^+$ ($[M + H]^+$) requires 378.2275; found 378.2270. Further elution gave **29** as a pale yellow oil (16 mg, 21%, >99:1 dr); $[\alpha]_D^{25}$ −32.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3460 (O–H), 3063, 3028, 2980, 2934, 2850 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, *Me*CMe), 1.50 (9H, s, C*Me*$_3$), 1.51 (3H, s, *Me*CMe), 2.63 (1H, dd, *J* 10.1, 3.0, C(6)H_A), 3.22 (1H, dd, *J* 10.1, 4.9, C(6)H_B), 3.26 (2H, br s, C(3)*H*, O*H*), 3.67 (1H, d, *J* 13.2, NCH_AH_BPh), 4.03 (1H, d, *J* 13.2, NCH_AH_BPh), 4.35 (1H, d, *J* 2.5, C(2)*H*), 4.56–4.62 (2H, m, C(4)*H*, C(5)*H*), 7.24–7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.1, 27.3 (*CMe*$_2$), 28.0 (*CMe*$_3$), 57.1 (NCH_2Ph), 58.8 (*C*(6)), 69.3 (*C*(2)), 70.7 (*C*(3)), 78.5 (*C*(4)), 80.5 (*C*(5)), 82.9 (*CMe*$_3$), 112.4 (*CMe*$_2$), 127.2 (*p-Ph*), 128.4, 128.8 (*o,m-Ph*), 138.0 (*i-Ph*), 172.0 (*C*(1)); *m/z* (ESI^+) 364 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{30}NO_5^+$ ($[M + H]^+$) requires 364.2118; found 364.2111.

(*αS*)-*N*-*α*-Methylbenzyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-allitol 30. $LiAlH_4$ (1.0 M in THF, 0.69 mL, 0.69 mmol) was added dropwise to a stirred solution of **28** (127 mg, 0.34 mmol) in THF (10 mL) at −78 °C, and the resultant mixture was allowed to warm to rt over 16 h. 1 M aqueous NaOH (1 mL) and EtOAc (2 mL) were then added, and the resultant suspension was stirred at rt for 1 h. The mixture was then filtered through a pad of Celite (eluent EtOAc), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent Et_2O) gave **30** as a white solid (85 mg, 82%, >99:1 dr); mp 103–107 °C; $[\alpha]_D^{25}$ −36.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3329 (O–H), 2922, 2888, 2851, 2836 (C–H); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, *Me*CMe), 1.45 (3H, s, *Me*CMe), 1.47 (3H, d, *J* 6.8, C(*α*)*Me*), 2.83 (1H, dd, *J* 12.0, 2.3, C(1)H_A), 3.08 (1H, dd, *J* 12.0, 5.3, C(1)H_B), 3.09–3.13 (1H, m, C(4)*H*), 3.38 (2H, br s, O*H*), 3.71 (1H, dd, *J* 10.9, 6.1, C(6)H_A), 3.76 (1H, dd, *J* 10.9, 5.8, C(6)H_B), 3.81 (1H, q, *J* 5.8, C(5)*H*), 4.21 (1H, q, *J* 6.8, C(*α*)*H*), 4.59–4.64 (1H, m, C(2)*H*), 4.73 (1H, dd, *J* 6.3, 1.3, C(3)*H*), 7.21–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.4 (C(*α*)*Me*), 24.5, 26.9 (*CMe*$_2$), 53.9 (*C*(1)), 59.0 (*C*(*α*)), 65.5 (*C*(6)), 67.8 (*C*(5)), 68.7 (*C*(4)), 79.4 (*C*(2)), 81.7 (*C*(3)), 112.0 (*CMe*$_2$), 127.3 (*p-Ph*), 127.8, 128.4 (*o,m-Ph*), 141.8 (*i-Ph*); *m/z* (ESI^+) 308 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{26}NO_4^+$ ($[M + H]^+$) requires 308.1856; found 308.1856.

***N*-Benzyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-allitol 31.** $LiAlH_4$ (1.0 M in THF, 0.36 mL, 0.36 mmol) was added dropwise to a stirred solution of **29** (66 mg, 0.18 mmol) in THF (10 mL) at −78 °C, and the resultant mixture was allowed to warm to rt over 16 h. 1 M aqueous NaOH (1 mL) and EtOAc (2 mL) were then added, and the resultant suspension was stirred at rt for 1 h. The mixture was then filtered through a pad of Celite (eluent EtOAc), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent Et_2O) gave **31** as pale yellow solid[35] (39 mg, 73%, >99:1 dr);[26] mp 46–52 °C;[35] $[\alpha]_D^{25}$ −42.1 (*c* 1.0 in $CHCl_3$); {lit.[26] $[\alpha]_D^{20}$ −48.2 (*c* 2.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.53 (3H, s, *Me*CMe), 2.63 (1H, dd, *J* 10.9, 4.2, C(1)H_A), 2.83 (1H, t, *J* 4.2, C(4)*H*), 3.24 (1H, dd, *J* 10.9, 6.3, C(1)H_B), 3.51 (1H, d, *J* 12.9, NCH_AH_BPh), 3.71 (1H, dd, *J* 11.4, 5.3, C(6)H_A), 3.82 (1H, dd, *J* 11.4, 6.1, C(6)H_B), 3.92 (1H, td, *J* 5.6, 4.2, C(5)*H*), 4.07 (1H, d, *J* 12.9, NCH_AH_BPh), 4.59 (1H, td, *J* 6.3, 4.3, C(2)*H*), 4.71 (1H, dd, *J* 6.3, 4.2, C(3)*H*), 7.26–7.37 (5H, m, *Ph*).

1,4-Dideoxy-1,4-imino-D-allitol Hydrochloride 32·HCl. From **30**: $Pd(OH)_2/C$ (47 mg, 50% w/w of substrate) was added to a solution of **30** (94 mg, 0.31 mmol) and 3 M aqueous HCl (1 mL) in MeOH (5 mL) at rt. The resultant solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) at rt for 18 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 2:1) gave **32**·HCl as a hygroscopic white solid (49 mg, 80%, >99:1 dr);[26,36] $[\alpha]_D^{25}$ +24.4 (*c* 1.0 in H_2O); {lit.[26] +29.4 (*c* 0.53 in H_2O)}; δ_H (400 MHz, D_2O) 3.20 (1H, dd, *J* 12.6, 2.1, C(1)H_A), 3.31 (1H, dd, *J* 12.6, 3.8, C(1)H_B), 3.50 (1H, dd, *J* 8.0, 3.6, C(4)*H*), 3.60 (1H, dd, *J* 11.8, 6.5, C(6)H_A), 3.64 (1H, dd, *J* 11.8, 4.6, C(6)H_B), 3.96–4.00 (1H, m, C(5)*H*), 4.21–4.26 (1H, m, C(2)*H*), 4.28 (1H, dd, *J* 8.0, 4.3, C(3)*H*).

From **31**: $Pd(OH)_2/C$ (18 mg, 50% w/w of substrate) was added to a solution of **31** (36 mg, 0.12 mmol) and 3 M aqueous HCl (1 mL) in MeOH (5 mL) at rt. The resultant solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) at rt for 18 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 2:1) gave **32**·HCl as a white solid (15 mg, 62%, >99:1 dr).

***tert*-Butyl 3,6-Dideoxy-3,6-imino-4,5-*O*-isopropylidene-L-allonate 33.** From **28**: $Pd(OH)_2/C$ (50% w/w of substrate, 27 mg) was added to a stirred solution of **28** (54 mg, 0.14 mmol) in MeOH (1 mL) at rt. The resultant solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 12 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent EtOAc) gave **33** as a white solid (34 mg, 87%, >99:1 dr); mp 130–135 °C; $[\alpha]_D^{25}$ +21.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3293 (N–H), 3074, 2980, 2938 (C–H), 1736 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, s, *Me*CMe), 1.44 (3H, s, *Me*CMe), 1.48 (9H, s, C*Me*$_3$), 2.97 (1H, d, *J* 13.0, C(5′)H_A), 3.06 (2H, br s, N*H*, O*H*), 3.12 (1H, dd, *J* 13.0, 4.4, C(5′)H_B), 3.44 (1H, d, *J* 2.8, C(2′)*H*), 4.11 (1H, d, *J* 4.0, C(2)*H*), 4.60 (1H, d, *J* 5.8, C(3′)*H*), 4.66–4.69 (1H, m, C(4′)*H*); δ_C (100 MHz, $CDCl_3$) 24.1, 26.5 (*CMe*$_2$), 27.9 (*CMe*$_3$), 53.4 (*C*(5′)), 67.8 (*C*(2′)), 72.5 (*C*(2)), 82.1 (*C*(3′)), 82.5 (*C*(4′)), 83.0 (*CMe*$_3$), 111.3 (*CMe*$_2$), 172.5 (*C*(1)); *m/z* (ESI^+) 274 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{24}NO_5^+$ ($[M + H]^+$) requires 274.1649; found 274.1653.

From **29**: $Pd(OH)_2/C$ (50% w/w of substrate, 25 mg) was added to a stirred solution of **29** (49 mg, 0.13 mmol) in MeOH (1 mL) at rt. The resultant solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 12 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent EtOAc) gave **33** as a white solid (36 mg, quant, >99:1 dr).

3,6-Dideoxy-3,6-imino-L-allonic Acid 34. A solution of **33** (74 mg, 0.27 mmol) in 2 M aq HCl (2.8 mL) was heated at reflux for 8 h. The reaction mixture was allowed to cool to rt and was then concentrated in vacuo. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1 M aq NH_4OH) gave **34** as a white

dx.doi.org/10.1021/jo5018298 | J. Org. Chem. 2014, 79, 9686–9698

solid (45 mg, 94%, >99:1 dr);[28] mp 238−243 °C (dec); {lit.[28] mp ~250 °C (dec)}; $[\alpha]_D^{25}$ +42.7 (*c* 1.0 in 1.0 M aq HCl); {lit.[28] for enantiomer}; $[\alpha]_D^{20}$ −12.7 (*c* 0.9 in H_2O); δ_H (500 MHz, D_2O) 3.26 (1H, dd, *J* 12.6, 2.5, C(6)H_A), 3.39 (1H, dd, *J* 12.6, 4.1, C(6)H_B), 3.76 (1H, dd, *J* 6.9, 3.8, C(3)*H*), 4.24−4.31 (3H, m, C(2)*H*, C(4)*H*, C(5)*H*).

***N*-*tert*-Butoxycarbonyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-allitol 35.** From **30**: Pd/C (50% w/w of substrate, 51 mg) was added to a stirred solution of **30** (102 mg, 0.33 mmol) and Boc_2O (80 mg, 0.37 mmol) in MeOH (3 mL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH), and the filtrate was concentrated in vacuo to give **35** as a white solid (99 mg, 98%, >99:1 dr);[26] mp 66−69 °C; {lit.[26] 73−74 °C}; $[\alpha]_D^{25}$−24.2 (*c* 1.0 in $CHCl_3$); {lit.[26] $[\alpha]_D^{25}$ −33.5 (*c* 0.17 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) [major rotamer][37] 1.27 (3H, s, *Me*CMe), 1.39 (3H, s, *Me*CMe), 1.41 (9H, s, CMe_3), 3.28 (1H, dd, *J* 13.0, 4.7, C(1)H_A), 3.32−3.41 (1H, m, C(5)*H*), 3.52−3.62 (2H, m, C(6)H_2), 3.80 (1H, d, *J* 13.0, C(1)H_B), 3.98 (1H, d, *J* 8.6, C(4)*H*), 4.65−4.71 (1H, m, C(2)*H*), 4.77−4.83 (1H, m, C(3)*H*).

From **31**: Pd/C (50% w/w of substrate, 48 mg) was added to a stirred solution of **31** (95 mg, 0.32 mmol), and Boc_2O (78 mg, 0.36 mmol) in MeOH (3 mL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH), and the filtrate was concentrated in vacuo to give **35** as a white solid (94 mg, 96%, >99:1 dr).

(3*R*,4*S*)-3,4-Dihydroxy-L-proline 38. Step 1: $NaIO_4$ (356 mg, 1.66 mmol) was added to a solution of **35** (187 mg, 0.62 mmol) in EtOH/H_2O (v/v 5:2, 9.2 mL) at rt, and the resultant suspension was stirred at rt for 15 min. The reaction mixture was then filtered through a short plug of Celite (eluent EtOH), and the filtrate was concentrated in vacuo. The residue was dissolved in Et_2O (10 mL) and then filtered through a short plug of Celite (eluent Et_2O), and the filtrate was concentrated in vacuo to give **36** (180 mg).

Step 2: Cyclohexene (0.60 mL) was added to a solution of crude **36** (180 mg) in ^{t}BuOH (9 mL) at rt. A solution of $NaClO_2$ (557 mg, 6.20 mmol) and KH_2PO_4 (839 mg, 6.20 mmol) in H_2O (6 mL) was then added dropwise at rt. The resultant mixture was stirred at rt for 18 h and then concentrated in vacuo. The residue was partitioned between EtOAc (50 mL) and H_2O (50 mL), and the aqueous layer was then extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried and concentrated in vacuo to give **37** (130 mg).

Step 3: A solution of crude **37** (130 mg) in 2 M aq HCl (4.5 mL) was heated at reflux for 8 h. The reaction mixture was allowed to cool to rt and was then concentrated in vacuo. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1 M aq NH_4OH) gave **38** as a white solid (38 mg, 42% over three steps, >99:1 dr);[26] mp 240−250 °C (dec); lit.[26] mp 240−250 °C (dec); $[\alpha]_D^{25}$ +5.8 (*c* 1.0 in H_2O); {lit.[26] $[\alpha]_D^{25}$ +7.5 (*c* 0.16 in H_2O)}; δ_H (400 MHz, D_2O) 3.20 (1H, dd, *J* 12.3, 4.2, C(5)H_A), 3.44 (1H, dd, *J* 12.3, 4.8, C(5)H_B), 3.87 (1H, d, *J* 4.8, C(2)*H*), 4.21−4.28 (2H, m, C(3)*H*, C(4)*H*).

***tert*-Butyl (2*S*,3*R*,4*S*,5*S*,α*S*)-2,4,5,6-Tetrahydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidenehexanoate 39.** TBAF (1.0 M in THF, 16.4 mL, 16.4 mmol) was added dropwise to a stirred solution of **16** (1.97 g, 3.28 mmol) in THF (19.7 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with Et_2O (30 mL) and washed with H_2O (20 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 1:1) gave **39** as a white solid (1.22 g, 77%, >99:1 dr); mp 93−94 °C; $[\alpha]_D^{25}$ +10.2 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 3521, 3486, 3471, (O−H), 1732 (C═O); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, s, *Me*CMe), 1.30 (3H, d, *J* 7.2, C(α)*Me*), 1.34 (3H, s, *Me*CMe), 1.49 (9H, s, CMe_3), 1.67 (1H, dd, *J* 7.9, 5.1, C(6)O*H*), 3.20 (1H, d, *J* 8.2, C(2)O*H*), 3.32 (1H, ddd, *J* 12.0, 7.9, 4.1, C(6)H_A), 3.40−3.43 (1H, m, C(3)*H*), 3.64 (1H, ddd, *J* 12.0, 5.1, 3.8, C(6)H_B), 3.83 (1H, d, *J* 15.5, NC$H_A$$H_B$Ph), 3.97−4.06 (3H, m, C(2)*H*, C(4)*H*, C(α)*H*), 4.34−4.40 (1H, m, C(5)*H*), 4.78 (1H, d, *J* 15.5, NC$H_A$$H_B$Ph), 7.20−7.40 (8H, m, *Ph*), 7.48−7.54 (2H, m, *Ph*); δ_C (100 MHz, $CHCl_3$) 20.4 (C(α)*Me*), 26.6, 26.9 (CMe_2), 27.9 (CMe_3), 53.8 (NCH_2Ph), 57.0 (C(3)), 58.9 (C(α)), 61.4 (C(6)), 72.3 (C(2)), 77.6 (C(4)), 77.9 (C(5)), 82.6 (CMe_3), 109.0 (CMe_2), 126.3, 127.2 (*p*-*Ph*), 127.9, 128.1, 128.2 (*o*,*m*-*Ph*), 142.2, 142.4 (*i*-*Ph*), 173.3 (C(1)); *m*/*z* (ESI$^-$) 484 ([M − H]$^-$, 25%), 410 ([M − $C_4H_{11}O$]$^-$, 100%); HRMS (ESI$^-$) $C_{28}H_{38}NO_6^-$ requires 484.2699; found 484.2700.

***tert*-Butyl (α*S*)-2,6-Anhydro-3-deoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-L-gulonate 41.** Step 1: MsCl (0.12 mL, 1.54 mmol) was added dropwise to a stirred solution of **39** (300 mg, 0.62 mmol) in pyridine (15 mL), and the resultant mixture was stirred at rt for 18 h. The reaction mixture was diluted with Et_2O (50 mL) and washed sequentially with H_2O (2 × 50 mL), 1 M aqueous HCl (50 mL), and satd aqueous $NaHCO_3$ (50 mL). The organic layer was then dried and concentrated in vacuo to give a 28:72 mixture of **39** and **40** (208 mg). Data for **40**: δ_H (400 MHz, $CDCl_3$) 1.31 (3H, s, *Me*CMe), 1.34 (3H, d, *J* 7.2, C(α)*Me*), 1.36 (3H, s, *Me*CMe), 1.50 (9H, s, CMe_3), 3.01 (3H, s, SO_2Me), 3.12 (1H, d, *J* 6.8, O*H*), 3.51 (1H, dd, *J* 3.8, 1.7, C(3)*H*), 3.85 (1H, d, *J* 15.7, NC$H_A$$H_B$Ph), 3.92−3.97 (2H, m, C(2)*H*, C(6)H_A), 4.01 (1H, dd, *J* 8.1, 3.8, C(4)*H*), 4.04 (1H, q, *J* 7.2, C(α)*H*), 4.27 (1H, dd, *J* 11.4, 2.8, C(6)H_B), 4.55 (1H, ddd, *J* 8.1, 5.1, 2.8, C(5)*H*), 4.71 (1H, d, *J* 15.7, NC$H_A$$H_B$Ph), 7.23−7.40 (8H, m, *Ph*), 7.47−7.52 (2H, m, *Ph*).

Step 2: NaH (60% dispersion in mineral oil, 15 mg, 0.36 mmol) was added to a stirred solution of the crude 28:72 mixture of **39** and **40** (208 mg) in THF (30 mL) at rt, and the resultant suspension was stirred at rt for 16 h. The reaction mixture was diluted with H_2O (30 mL), and the aqueous layer was separated and extracted with Et_2O (3 × 30 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 3:1) gave **41** as a pale yellow oil (155 mg, 54% from **39**, >99:1 dr); $[\alpha]_D^{25}$ +24.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1739 (C═O); δ_H (400 MHz, $CHCl_3$) 1.45 (3H, s, *Me*CMe), 1.49 (3H, s, *Me*CMe), 1.53 (9H, s, CMe_3), 1.56 (3H, d, *J* 6.8, C(α)*Me*), 3.28 (1H, app t, *J* 10.0, C(6)H_A), 3.42−3.62 (4H, m, C(2)*H*, C(3)*H*, C(4)*H*, C(5)*H*), 3.78 (1H, d, *J* 14.3, NC$H_A$$H_B$Ph), 3.95 (1H, d, *J* 14.3, NC$H_A$$H_B$Ph), 4.13−4.20 (2H, m, C(6)H_B, C(α)*H*), 7.20−7.45 (10H, m, *Ph*); δ_C (100 MHz, $CHCl_3$) 18.8 (C(α)*Me*), 26.6, 26.7 (CMe_2), 27.9 (CMe_3), 50.8 (NCH_2Ph), 59.3 (C(α)), 61.7 (C(3)), 68.3 (C(6)), 74.8 (C(5)), 79.4, 79.6 (C(2), C(4)), 81.7 (CMe_3), 110.1 (CMe_2), 126.6, 126.8 (*p*-*Ph*), 127.8, 128.0, 128.9 (*o*,*m*-*Ph*), 140.6, 144.2 (*i*-*Ph*), 168.5 (C(1)); *m*/*z* (ESI$^+$) 468 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{38}NO_5^+$ ([M + H]$^+$) requires 468.2750; found 468.2746.

***tert*-Butyl (2*R*,3*R*,4*S*,5*S*,α*S*)-2,4,5,6-Tetrahydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidenehexanoate 42.** TBAF (1.0 M in THF, 3.63 mL, 3.63 mmol) was added dropwise to a stirred solution of **20** (435 mg, 0.72 mmol) in THF (6 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with Et_2O (20 mL) and washed with H_2O (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 1:1) gave **42** as a pale yellow oil (253 mg, 72%, >99:1 dr); $[\alpha]_D^{25}$ −11.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3453 (O−H), 3085, 3062, 3038, 2982, 2934 (C−H), 1723 (C═O); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, s, *Me*CMe), 1.39 (3H, s, *Me*CMe), 1.42 (3H, d, *J* 7.0, C(α)*Me*), 1.48 (9H, s, CMe_3), 2.42 (1H, br s, C(6)O*H*), 3.02 (1H, br s, C(2)O*H*), 3.34 (1H, t, *J* 5.6, C(3)*H*), 3.44 (1H, dd, *J* 12.1, 4.3, C(6)H_A), 3.68 (1H, dd, *J* 12.1, 3.5, C(6)H_B), 4.06 (1H, d, *J* 14.9, NC$H_A$$H_B$Ph), 4.15 (1H, d, *J* 5.6, C(2)*H*), 4.19−4.24 (1H, m, C(5)*H*), 4.31 (1H, dd, *J* 8.3, 5.6, C(4)*H*), 4.36 (1H, d, *J* 14.9, NC$H_A$$H_B$Ph), 4.42 (1H, q, *J* 7.0, C(α)*H*), 7.18−7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.4 (C(α)*Me*), 26.4, 27.0 (CMe_2), 27.8 (CMe_3), 52.8 (NCH_2Ph), 60.2 (C(3)), 60.5 (C(α)), 62.3 (C(6)), 72.6 (C(2)), 76.9 (C(4)), 78.9 (C(5)), 82.8 (CMe_3), 108.3 (CMe_2), 126.2, 126.8 (*p*-*Ph*), 128.0, 128.5 (*o*,*m*-*Ph*), 142.0, 144.3 (*i*-*Ph*), 172.8 (C(1)); *m*/*z* (ESI$^+$) 486 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{40}NO_6^+$ ([M + H]$^+$) requires 486.2850; found 486.2849.

dx.doi.org/10.1021/jo5018298 | J. Org. Chem. 2014, 79, 9686−9698

***tert*-Butyl (αS)-2,6-Anhydro-3-deoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-L-idonate 44.** Step 1: MsCl (99 μL, 1.3 mmol) was added dropwise to a stirred solution of **42** (247 mg, 0.51 mmol) in pyridine (12.5 mL), and the resultant mixture was stirred at rt for 18 h. The reaction mixture was diluted with Et_2O (30 mL) and washed sequentially with H_2O (2 × 30 mL), 1 M aqueous HCl (30 mL), and satd aqueous $NaHCO_3$ (30 mL). The organic layer was then dried and concentrated in vacuo to give an 15:85 mixture of **42** and **43** (260 mg). Data for **43**: δ_H (400 MHz, $CDCl_3$) 1.31 (3H, s, *Me*CMe), 1.36 (3H, s, *Me*CMe), 1.46 (3H, d, *J* 6.3, C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 2.68 (1H, d, *J* 6.4, O*H*), 3.00 (3H, s, SO_2*Me*), 3.27 (1H, t, *J* 5.3, C(3)*H*), 3.86 (1H, dd, *J* 11.4, 5.3, C(6)H_A), 4.02 (1H, d, *J* 14.9, NCH_AH_BPh), 4.10 (1H, dd, *J* 6.4, 5.3, C(2)*H*), 4.21 (1H, dd, *J* 8.4, 5.3, C(4)*H*), 4.28 (1H, dd, *J* 11.4, 2.6, C(6)H_B), 4.36 (1H, d, *J* 14.9, NCH_AH_BPh), 4.36–4.42 (2H, m, C(5)*H*, C(α)*H*), 7.19–7.39 (10H, m, *Ph*).

Step 2: NaH (60% dispersion in mineral oil, 18 mg, 0.44 mmol) was added to a stirred solution of the crude 15:85 mixture of **42** and **43** (260 mg) in THF (35 mL) at rt, and the resultant suspension was stirred at rt for 16 h. The reaction mixture was diluted with H_2O (30 mL), and the aqueous layer was separated and extracted with Et_2O (3 × 30 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **44** as a colorless oil (144 mg, 61% from **42**, >99:1 dr); $[\alpha]_D^{25}$ −52.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3087, 3062, 3029, 2981, 2934, 2900 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.6, C(α)*Me*), 1.50 (3H, s, *Me*CMe), 1.52 (3H, s, *Me*CMe), 1.53 (9H, s, C*Me*$_3$), 3.13 (1H, dd, *J* 11.4, 6.7, C(3)*H*), 3.32 (1H, ddd, *J* 13.4, 8.6, 4.8, C(5)*H*), 3.67 (1H, d, *J* 6.7, C(2)*H*), 3.94–4.09 (2H, m, C(6)H_A, C(α)*H*) overlapping 3.98 (1H, d, *J* 13.6, NCH_AH_BPh), 4.06 (1H, app t, *J* 10.2, C(6)H_B), 4.23 (1H, d, *J* 13.6, NCH_AH_BPh), 4.33 (1H, dd, *J* 11.4, 8.6, C(4)*H*), 7.22–7.57 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.1 (C(α)*Me*), 26.6, 26.9 (CMe_2), 28.1 (CMe_3), 51.4 (NCH_2Ph), 54.5 (C(α)), 58.5 (C(3)), 65.3 (C(6)), 74.8 (C(4)), 75.6 (C(5)), 77.5 (C(2)), 81.8 (CMe_3), 109.4 (CMe_2), 126.8 (*p*-*Ph*), 127.9, 128.2, 128.8 (*o*,*m*-*Ph*), 140.1, 143.3 (*i*-*Ph*), 169.8 (C(1)); *m*/*z* (ESI$^+$) 468 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{37}NNaO_5^+$ ([M + Na]$^+$) requires 490.2564; found 490.2555.

(αS)-1,5-Anhydro-2,3-*O*-isopropylidene-4-deoxy-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-D-glucitol 45. $LiAlH_4$ (1.0 M in THF, 0.66 mL, 0.66 mmol) was added dropwise to a stirred solution of **41** (155 mg, 0.33 mmol) in THF (10 mL) at −78 °C, and the resultant mixture was allowed to warm to rt over 16 h. 1 M aqueous NaOH (1 mL) and EtOAc (2 mL) were then added, and the suspension was stirred at rt for 1 h. The reaction mixture was filtered through a pad of Celite (eluent EtOAc), and the filtrate was concentrated in vacuo to give **45** as a pale yellow oil (132 mg, quant, >99:1 dr); $[\alpha]_D^{25}$ +57.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3454 (O–H), 3061, 3028, 2983, 2918, 2877, 2850 (C–H); δ_H (400 MHz, $CDCl_3$) 1.53 (3H, s, *Me*CMe), 1.53 (3H, d, *J* 6.8, C(α)*Me*), 1.54 (3H, s, *Me*CMe), 1.95 (1H, br s, O*H*), 2.93 (1H, dd, *J* 10.6, 9.1, C(4)*H*), 3.20–3.27 (1H, m, C(5)*H*), 3.28 (1H, dd, *J* 11.3, 5.8, C(6)H_A), 3.33–3.45 (2H, m, C(1)H_A, C(2)*H*), 3.56 (1H, dd, *J* 11.3, 3.2, C(6)H_B), 3.67 (1H, dd, *J* 10.6, 8.2, C(3)*H*), 3.87 (1H, d, *J* 13.1, NCH_AH_BPh), 3.94 (1H, d, *J* 13.1, NCH_AH_BPh), 4.07 (1H, q, *J* 6.8, C(α)*H*), 4.12 (1H, dd, *J* 8.8, 3.3, C(1)H_B), 7.23–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.7 (C(α)*Me*), 26.6, 26.8 (CMe_2), 51.6 (NCH_2Ph), 56.2 (C(α)), 58.1 (C(4)), 63.3 (C(6)), 67.9 (C(1)), 75.3 (C(2)), 78.5 (C(5)), 79.7 (C(3)), 110.0 (CMe_2), 127.0, 127.2 (*p*-*Ph*), 128.0, 128.2, 128.4, 129.2 (*o*,*m*-*Ph*), 139.8, 143.7 (*i*-*Ph*); *m*/*z* (ESI$^+$) 398 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{32}NO_4^+$ ([M + H]$^+$) requires 398.2326; found 398.2308.

(αS)-1,5-Anhydro-4-deoxy-4-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-D-glucitol 46. 3 M aqueous HCl (1 mL) was added dropwise to a stirred solution of **45** (100 mg, 0.25 mmol) in MeOH (5 mL) at rt, and the resultant solution was then heated at 50 °C for 3 h. The reaction mixture was allowed to cool to rt and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL), and the resultant solution was washed with 2 M aqueous NaOH (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were dried and concentrated in vacuo to give **46** as a pale yellow oil (64 mg, 71%, >99:1 dr); $[\alpha]_D^{25}$ −4.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3417 (O–H), 3085, 3062, 3028, 2968, 2922, 2852 (C–H); δ_H (400 MHz, $CDCl_3$) 1.52 (3H, br s, C(α)*Me*), 2.75 (1H, t, *J* 9.2, C(4)*H*), 2.91 (1H, br s, O*H*), 3.07 (1H, t, *J* 10.5, C(1)H_A), 3.16–3.27 (1H, m, C(5)*H*), 3.28–3.39 (1H, m, C(6)H_A), 3.48 (1H, ddd, *J* 10.5, 8.8, 5.3, C(2)*H*), 3.53–3.60 (1H, m, C(6)H_B), 3.61–3.71 (1H, m, C(3)*H*), 3.80 (1H, d, *J* 14.4, NCH_AH_BPh), 3.87 (1H, dd, *J* 11.1, 5.3, C(1)H_B), 4.09–4.19 (2H, m, NCH_AH_BPh, C(α)*H*), 7.22–7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.6 (C(α)*Me*), 50.7 (NCH_2Ph), 59.9 (C(4)), 63.1 (C(6)), 69.0 (C(1)), 71.7 (C(2)), 74.6 (C(3)), 79.0 (C(5)), 127.2, 127.4 (*p*-*Ph*), 127.6, 128.5, 128.7 (*o*,*m*-*Ph*), 144.3 (*i*-*Ph*);[38] *m*/*z* (ESI$^+$) 358 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{28}NO_4^+$ ([M + H]$^+$) requires 358.2013; found 358.2008.

1,5-Anhydro-4-deoxy-4-amino-D-glucitol Hydrochloride 47·HCl. Pd(OH)$_2$/C (50% w/w of substrate, 43 mg) was added to a stirred solution of **46** (85 mg, 0.24 mmol) in MeOH (3 mL) at rt. The solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH), and the filtrate was concentrated in vacuo. Purification via recrystallization (CH_2Cl_2/MeOH, v:v 3:1) gave **47**·HCl as a pale yellow solid (27 mg, 56%, >99:1 dr); $[\alpha]_D^{25}$ −3.2 (*c* 1.0 in MeOH); ν_{max} (film) 3359, 3275 (N–H, O–H), 3134, 3086, 2936, 2870 (C–H); δ_H (400 MHz, MeOH-d_4) 3.06 (1H, t, *J* 9.9, C(4)*H*), 3.22 (1H, dd, *J* 11.1, 10.1, C(1)H_A), 3.45–3.56 (3H, m, C(2)*H*, C(3)*H*, C(5)*H*), 3.74 (1H, dd, *J* 11.7, 4.8, C(6)H_A), 3.78 (1H, dd, *J* 11.7, 4.6, C(6)H_B), 3.96 (1H, dd, *J* 11.1, 5.1, C(1)H_B); δ_C (100 MHz, MeOH-d_4) 55.5 (C(4)), 63.2 (C(6)), 71.1 (C(1)), 71.6 (C(2)), 75.7, 77.9 (C(3), C(5)); *m*/*z* (ESI$^+$) 186 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_6H_{13}NNaO_4^+$ ([M + Na]$^+$) requires 186.0737; found 186.0746.

***N*,*O*,*O*,*O*-Tetraacetyl-1,5-anhydro-4-deoxy-4-amino-D-glucitol 48.** Ac_2O (60 μL, 0.64 mmol) and DMAP (5 mg, catalytic) were added to a solution of **47**·HCl (26 mg, 0.13 mmol) in pyridine (1 mL) at rt, and the resultant solution was stirred at rt for 24 h. The reaction mixture was then diluted with CH_2Cl_2 (3 mL), EtOAc (3 mL), and satd aqueous $CuSO_4$ (3 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic extracts were washed with satd aqueous $NaHCO_3$ (2 × 3 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 20:1) gave **48** as a white solid (25 mg, 58%, >99:1 dr); mp 182–188 °C; $[\alpha]_D^{25}$ +46.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3306 (N–H), 2949, 2864 (C–H), 1731, 1659 (C=O); δ_H (500 MHz, $CDCl_3$) 1.95 (3H, s, CO*Me*), 2.04 (3H, s, CO*Me*), 2.07 (3H, s, CO*Me*), 2.10 (3H, s, CO*Me*), 3.25 (1H, dd, *J* 11.1, 9.7, C(1)H_A), 3.49 (1H, ddd, *J* 10.4, 6.2, 2.1, C(5)*H*), 4.06–4.13 (1H, m, C(4)*H*), 4.13 (1H, dd, *J* 12.5, 6.2, C(6)H_A), 4.18 (1H, dd, *J* 11.1, 5.3, C(1)H_B), 4.24 (1H, dd, *J* 12.5, 2.1, C(6)H_B), 5.00 (1H, td, *J* 9.7, 5.3, C(2)*H*), 5.05 (1H, t, *J* 9.7, C(3)*H*), 5.63 (1H, d, *J* 9.1, N*H*); δ_C (125 MHz, $CDCl_3$) 20.7, 20.9, 23.2 (CO*Me*), 50.6 (C(4)), 63.4 (C(6)), 66.8 (C(1)), 68.9 (C(2)), 73.6 (C(3)), 78.1 (C(5)), 169.7, 170.2, 171.1, 171.6 (COMe); *m*/*z* (ESI$^+$) 354 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{21}NNaO_8^+$ ([M + Na]$^+$) requires 354.1159; found 354.1156.

(αS)-1,5-Anhydro-2,3-*O*-isopropylidene-4-deoxy-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-L-iditol 49. $LiAlH_4$ (1.0 M in THF, 0.62 mL, 0.62 mmol) was added dropwise to a stirred solution of **44** (144 mg, 0.33 mmol) in THF (10 mL) at −78 °C, and the resultant mixture was allowed to warm to rt over 16 h. 1 M aqueous NaOH (1 mL) and EtOAc (2 mL) were then added, and the suspension was stirred for 1 h at rt. The reaction mixture was filtered through a pad of Celite (eluent EtOAc), and the filtrate was concentrated in vacuo to give **49** as a pale yellow oil (113 mg, 92%, >99:1 dr); $[\alpha]_D^{25}$ +17.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3443 (O–H), 3086, 3062, 3029, 2983, 2934, 2890 (C–H); δ_H (400 MHz, $CDCl_3$) 1.43 (3H, d, *J* 6.8, C(α)*Me*), 1.46 (3H, s, *Me*CMe), 1.50 (3H, s, *Me*CMe), 2.37 (1H, br s, O*H*), 3.22 (1H, dd, *J* 11.0, 6.4, C(4)*H*), 3.44–3.52 (2H, m, C(2)*H*, C(5)*H*), 3.60 (1H, t, *J* 10.2, C(6)H_A), 3.76 (1H, dd, *J* 11.0, 8.7, C(3)*H*), 3.82–3.89 (1H, m, C(1)H_A), 3.92–4.02 (2H, m, C(6)H_B, C(α)*H*) overlapping 3.95 (1H, dd, *J* 9.9, 4.8, C(1)H_B) and 3.97 (1H, d, *J* 14.4, NCH_AH_BPh), 4.01 (1H, d, *J* 14.4, NCH_AH_BPh), 7.22–7.42

dx.doi.org/10.1021/jo5018298 | J. Org. Chem. 2014, 79, 9686–9698

(10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.2 (C(α)*Me*), 26.6, 26.9 (CMe_2), 52.1 (NCH_2Ph), 55.4 (C(α)), 58.5 (*C*(4)), 59.0 (*C*(1)), 63.7 (*C*(6)), 75.4, 76.0, 78.1 (*C*(2), *C*(3), *C*(5)), 110.0 (CMe_2), 126.9, 127.1 (*p-Ph*), 128.0, 128.1, 128.5, 128.6 (*o,m-Ph*), 139.8, 143.0 (*i-Ph*); *m/z* (ESI$^+$) 398 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{32}NO_4^+$ ([M + H]$^+$) requires 398.2326; found 398.2334.

(αS)-1,5-Anhydro-4-deoxy-4-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-L-iditol 50. 3 M aqueous HCl (1 mL) was added dropwise to a stirred solution of **49** (113 mg, 0.28 mmol) in MeOH (5 mL) at rt, and the resultant solution was then heated at 50 °C for 3 h. The reaction mixture was allowed to cool to rt and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL), and the resultant solution was washed with 2 M aqueous NaOH (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were dried and concentrated in vacuo to give **50** as a white solid (86 mg, 85%, >99:1 dr); mp 62−64 °C; $[\alpha]_D^{25}$ −31.4 (*c* 1.0 in MeOH); ν_{max} (film) 3381 (O−H), 2927 (C−H); δ_H (400 MHz, MeOH-d_4) 1.38 (3H, d, *J* 6.8, C(α)*Me*), 2.90 (1H, dd, *J* 10.1, 6.1, C(4)*H*), 3.11 (1H, ddd, *J* 10.1, 6.1, 2.8, C(5)*H*), 3.40−3.49 (2H, m, C(1)H_A, C(2)*H*), 3.52−3.61 (1H, m, C(1)H_B), 3.73−3.81 (2H, m, C(3)*H*, C(6)H_A), 3.90 (1H, q, *J* 6.8, C(α)*H*), 3.98 (1H, dd, *J* 11.9, 10.1, C(6)H_B), 4.03 (1H, d, *J* 14.1, NCH_AH_BPh), 4.17 (1H, d, *J* 14.1, NCH_AH_BPh), 7.15−7.59 (10H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 13.2 (C(α)*Me*), 53.2 (NCH_2Ph), 56.6 (*C*(α)), 58.6 (*C*(6)), 59.5 (*C*(4)), 64.9 (*C*(1)), 72.4 (*C*(3)), 73.7 (*C*(2)), 80.6 (*C*(5)), 127.9, 128.2 (*p-Ph*), 129.1, 129.4, 129.6, 129.9 (*o,m-Ph*), 142.3, 145.3 (*i-Ph*); *m/z* (ESI$^+$) 358 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{28}NO_4^+$ ([M + H]$^+$) requires 358.2013; found 358.2006.

***N,O,O,O*-Tetraacetyl-1,5-anhydro-4-deoxy-4-amino-L-iditol 52.** $Pd(OH)_2$/C (50% w/w of substrate, 43 mg) was added to a stirred solution of **50** (86 mg, 0.24 mmol) in MeOH (3 mL) at rt. The solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH), and the filtrate was concentrated in vacuo. The residue was dissolved in pyridine (0.5 mL), and Ac_2O (82 μL, 1.4 mmol) and DMAP (5 mg, catalytic) were added sequentially. The resultant solution was stirred at rt for 24 h. The reaction mixture was diluted with CH_2Cl_2 (3 mL), EtOAc (3 mL), and satd aqueous $CuSO_4$ (3 mL) and was then extracted with EtOAc (3 × 5 mL). The combined organic extracts were then washed with satd aqueous $NaHCO_3$ (2 × 5 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 20:1) gave **52** as a white solid (15 mg, 19%, >99:1 dr); mp 129−132 °C; $[\alpha]_D^{25}$ +22.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3271 (N−H), 3046, 2962, 2925 (C−H), 1734, 1633 (C═O); δ_H (500 MHz, $CDCl_3$) 2.03 (3H, s, COM*e*), 2.09 (3H, s, COM*e*), 2.14 (3H, s, COM*e*), 2.16 (3H, s, COM*e*), 3.87 (1H, dd, *J* 13.6, 1.6, C(1)H_A), 4.00−4.05 (2H, m, C(1)H_B, C(5)*H*), 4.11 (1H, dd, *J* 12.0, 4.4, C(6)H_A), 4.14 (1H, dd, *J* 12.0, 7.7, C(6)H_B), 4.23−4.27 (1H, m, C(4)*H*), 4.76−4.79 (1H, m, C(2)*H*), 4.89−4.91 (1H, m, C(3)*H*), 6.20 (1H, d, *J* 10.1, N*H*); δ_C (125 MHz, $CDCl_3$) 20.9, 21.1, 23.3 (COM*e*), 46.0 (*C*(4)), 63.5 (*C*(6)), 66.8 (*C*(1)), 67.1 (*C*(2)), 67.3 (*C*(3)), 73.2 (*C*(5)), 168.6, 168.7, 169.3, 170.7 (COMe); *m/z* (ESI$^+$) 354 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{21}NNaO_8^+$ ([M + Na]$^+$) requires 354.1159; found 354.1153.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra, and crystallographic information files (for structures CCDC 1017540−1017543). 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.

■ REFERENCES

(1) Sears, P.; Wong, C. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2301.
(2) Nash, R. J.; Kato, A.; Yu, C.-Y.; Fleet, G. W. J. *Future Med. Chem.* **2011**, *3*, 1513.
(3) Horne, G.; Wilson, F. X. *Prog. Med. Chem.* **2011**, *50*, 135.
(4) Inouye, S.; Tsurouka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *24*, 2125.
(5) Yagi, M.; Kouno, T.; Aoyagi, Y. *Nippon Nogeikagaka Kaishi* **1976**, *50*, 571.
(6) Scott, L. J.; Spencer, C. M. *Drugs* **2000**, *59*, 521.
(7) Butters, T. D. *Curr. Opin. Chem. Biol.* **2007**, *11*, 412.
(8) Stocker, B. L.; Dangerfield, E. M.; Win-Mason, A. L.; Haslett, G. W.; Timer, M. S. M. *Eur. J. Org. Chem.* **2010**, 1615.
(9) Watson, A. A.; Fleet, G. W. J. F.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.
(10) Asano, N. *Cell. Mol. Life Sci.* **2009**, *66*, 1479.
(11) Winchester, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 645.
(12) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2012**, *23*, 1111.
(13) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1995**, *6*, 165.
(14) Davies, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919.
(15) Davies, S. G.; Durbin, M. J.; Goddard, E. C.; Kelly, P. M.; Kurosawa, W.; Lee, J. A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2009**, *7*, 761.
(16) Davies, S. G.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2014**, *25*, 534.
(17) For an example of the application of this protocol to chiral α,β-unsaturated esters, see: Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; Waul, M. A. *Tetrahedron* **2014**, *40*, 7106.
(18) We have previously reported a similar cyclization/debenzylation process in the syntheses of piperidine and quinolizidine alkaloids, see: (a) Davies, S. G.; Hughes, D. G.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Synlett* **2010**, 567. (b) Davies, S. G.; Fletcher, A. M.; Hughes, D. G.; Lee, J. A.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Tetrahedron* **2011**, *67*, 9975. (c) Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Houlsby, I. T. T.; Roberts, P. M.; Schofield, T. M.; Thomson, J. E. *Chem. Commun.* **2014**, *50*, 8309.
(19) For discussions concerning the kinetics of ring-closure, see: (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95. (b) Casadei, M. A.; Galli, C.; Mandolini, L. *J. Am. Chem. Soc.* **1984**, *106*, 1051.
(20) For a directly analogous cyclization process (5-ring through N vs 6-ring through O), see: (a) da Cruz, F. P.; Horne, G.; Fleet, G. W. J. F. *Tetrahedron Lett.* **2008**, *49*, 6812. For closely related cyclization processes (5-ring through O vs 6-ring through O), see: (b) Barrett, A. G. M.; Broughton, H. B.; Attwood, S. V.; Gunatilaka, A. A. L. *J. Org. Chem.* **1986**, *51*, 495. (c) Radha Krishna, P.; Lavanya, B.; Ilangovan, A.; Sharma, G. V. M. *Tetrahedron: Asymmetry* **2000**, *11*, 4463.
(21) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J.; Ichihara, O. *Tetrahedron* **1994**, *50*, 3975.
(22) Attempted aminohydroxylation of either (4*S*,5*S*,*E*)-**8** or (4*R*,5*S*,*E*)-**9** using conjugate addition of lithium amide (*R*)-**1** and in situ oxidation with either enantiomer of CSO **4** resulted in a complex mixture of products in all cases.
(23) Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Hao, L.; Lv, L.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2014**, *70*, 3491 and references cited therein.
(24) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801.
(25) Although not isolated, benzyl iodide and α-methylbenzyl iodide were also tentatively assigned as being present in the ^{1}H NMR spectrum of the crude reaction mixture.
(26) Fleet, G. W. J.; Son, J. C. *Tetrahedron* **1988**, *44*, 2637.
(27) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as

supplementary publication numbers CCDC 1017540 (**30**), 1017541 (**39**), 1017542 (**47**·HCl), and 1017543 (**48**).
(28) Lundt, I.; Madsen, R. *Synthesis* **1993**, 714.
(29) Syntheses of all four of the possible diastereoisomers of the 3,4-dihydroxyprolines have been reported; for example, see: (a) Huang, Y.; Dalton, D. R.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 372. (b) Schumacher, K. K.; Jiang, J.; Joullié, M. M. *Tetrahedron: Asymmetry* **1998**, *9*, 47.
(30) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888.
(31) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175.
(32) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
(33) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
(34) Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
(35) Previously reported as "a pale yellow oil" (see ref 26).
(36) It was not possible to determine a melting point for this compound under aerial conditions due to its hygroscopic nature.
(37) The ^{1}H NMR resonances for the minor rotamer were indistinguishable due to significant peak overlap.
(38) No resonance corresponding to C(α) was observed in the ^{13}C NMR spectrum of **46**.