JOC The Journal of Organic Chemistry

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Asymmetric Syntheses of (−)-ADMJ and (+)-ADANJ: 2-Deoxy-2-amino Analogues of (−)-1-Deoxymannojirimycin and (+)-1-Deoxyallonojirimycin

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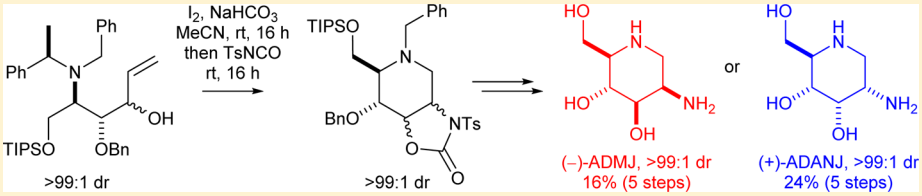
Supporting Information



ABSTRACT: The asymmetric syntheses of (−)-ADMJ and (+)-ADANJ, the 2-deoxy-2-amino analogues of (−)-1-deoxymannojirimycin and (+)-1-deoxyallonojirimycin, are described herein. Methodology for the ring-closing iodoamination of bishomoallylic amines followed by in situ ring-expansion (via intramolecular ring-opening of the corresponding aziridinium intermediates with a tethered carbamate moiety) to give oxazolidin-2-ones was initially optimized on a model system. Subsequent application of this methodology to two enantiopure bishomoallylic amines (which were produced via aminohydroxylation of an α,β-unsaturated ester, partial reduction, and reaction of the corresponding aldehyde with vinylmagnesium bromide) also proceeded with concomitant *N*-debenzylation to afford the corresponding diastereoisomerically pure (>99:1 dr) oxazolidin-2-ones. Subsequent deprotection of these enantiopure templates gave (−)-ADMJ and (+)-ADANJ as single diastereoisomers in 16% and 24% overall yield, respectively.

INTRODUCTION

The isosteric replacement of oxygen with nitrogen in compounds displaying useful biological activity is a useful strategy in the search for potential therapeutic agents. Aminosugars are defined as monosaccharides having one hydroxyl group replaced by an amino group[1] (although glycosylamines, where such replacement occurs at the C(1) position, are excluded from this category), and iminosugars are defined as monosaccharides in which the endocyclic oxygen atom has been replaced by a nitrogen atom.[2] Aminosugars and iminosugars have been a crucial area of recent research with regard to the isosteric replacement of oxygen with nitrogen as naturally occurring deoxyaminosugars and deoxyiminosugars which exhibit useful biological activity are already known. For example, glucose **1**, glucosamine **2** (i.e., 2-deoxy-2-aminoglucose), and nojirimycin **3** (i.e., 5-deoxy-5-aminoglucose) are illustrative of the isosteric replacement of oxygen with nitrogen: glucosamine **2** has been shown to bring about symptomatic relief of osteoarthritis,[3] and nojirimycin **3** displays antimicrobial activity against several drug-resistant strains of bacteria.[4] The formal replacement of oxygen with nitrogen in compounds already containing at least one amino group furnishes polyamines with further biological applications. For instance, platinum complexes of 3-deoxy-3-aminoglucosamine **4** have been investigated as potential treatments for cancers which offer reduced side effects compared to treatments using cisplatin and carboplatin.[5] (+)-ADMDP **7**, the synthetic 1-deoxy-1-amino analogue of (+)-DMDP **6**, and *N*(1)-substituted derivatives have been reported to display significantly enhanced selectivity and potency toward the inhibition of glucosidases than the parent iminosugar **6**.[6] Furthermore, 2-deoxy-2-acetamidonojirimycin **8** (i.e., the *N*-acetyl derivative of 2-deoxy-2-aminonojirimycin **5**) has been investigated as a potent inhibitor of *N*-acetylglucosaminidases,[7] and 1,2-dideoxy-2-acetamidonojirimycin **9** has been shown to be one of the most powerful reversible inhibitors of hexosaminidases[8] reported to date (Figure 1). However, relatively few syntheses of deoxyamino analogues of naturally occurring iminosugars have been documented in the literature, with most being derived from carbohydrate precursors.[9]

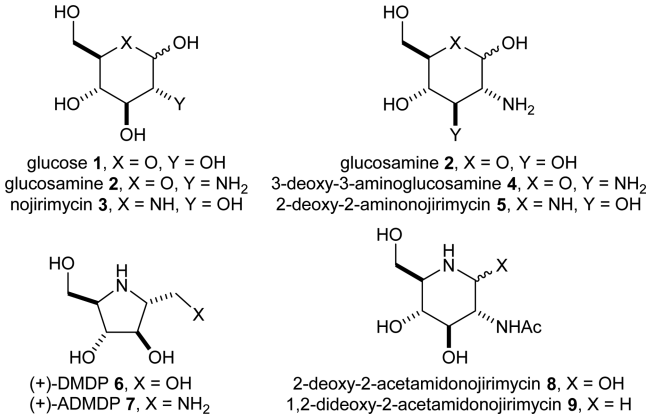


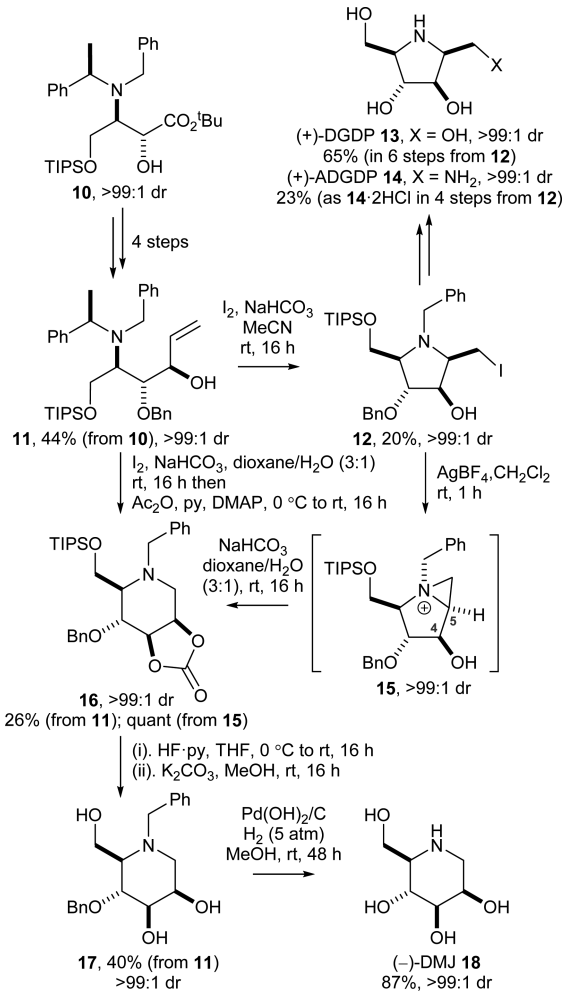
Figure 1. Structures of several representative aminosugars and iminosugars and their deoxyamino analogues.

Received: May 11, 2016
Published: June 29, 2016

DOI: 10.1021/acs.joc.6b01107
J. Org. Chem. 2016, 81, 6481−6495

As part of our ongoing research program concerning the asymmetric syntheses of enantiopure pyrrolidines,[10] piperidines,[11] and related natural products,[12] we recently reported the ring-closing iodoamination of enantiopure bishomoallylic amine **11**, which proceeds with concomitant *N*-debenzylation, to give iodomethyl pyrrolidine **12**. Bishomoallylic amine **11** was prepared in four steps from enantiopure α-hydroxy-β-amino ester **10**, which in turn was prepared from the corresponding α,β-unsaturated ester using our asymmetric aminohydroxylation protocol.[13] Treatment of bishomoallylic amine **11** with I_2 and $NaHCO_3$ in MeCN gave iodomethyl pyrrolidine **12**, which was then elaborated to 2,5-dideoxy-2,5-imino-D-glucitol [(+)-DGDP] **13** in 6 steps and 65% overall yield, and the 1-deoxy-1-amino analogue 1,2,5-trideoxy-1-amino-2,5-imino-D-glucitol [(+)-ADGDP] **14**, which was isolated as the corresponding dihydrochloride salt **14**·2HCl, in 23% yield and 99:1 dr.[14] Alternatively, iodomethyl pyrrolidine **12** was converted into carbonate **16** in quantitative yield following intramolecular ring-opening of aziridinium intermediate **15** at the C(5) position by a carbonate group tethered to the C(4) position.[15] However, under optimized conditions the triol derivative **17** was obtained in 40% overall yield (from **11**) following sequential ring-closing iodoamination, desilylation of **16**, and methanolysis of the carbonate functionality. Subsequent hydrogenolysis of **17** then gave (−)-1-deoxymannojirimycin [(−)-DMJ] **18** in 87% yield and >99:1 dr (Scheme 1).

Scheme 1



Herein, we describe the extension of this ring-expansion methodology for introduction of other substituents around the piperidine scaffold, specifically targeting the 2-deoxy-2-amino analogues of (−)-1-deoxymannojirimycin [(−)-DMJ] **18** and (+)-1-deoxyallonojirimycin [(+)-DANJ] **24**. This methodology was initially explored in a model system, where bishomoallylic amine **19** was first subjected to the ring-closing iodoamination protocol in the presence of CO_2 (for the formation of cyclic carbonate **21**); then alternative "X=C=Y" electrophiles (e.g., X, Y = O, NR, S, etc.) were examined for the formation of **23**. The application of this strategy to enantiopure bishomoallylic amine **11** and its epimer then culminated in the total asymmetric syntheses of (−)-ADMJ **25** and (+)-ADANJ **26**, the 2-deoxy-2-amino analogues of (−)-DMJ **18** and (+)-DANJ **24**, respectively (Figure 2).

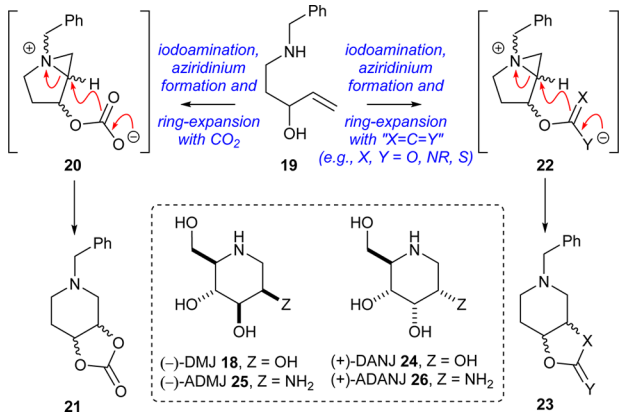


Figure 2. Synthetic strategy toward (−)-ADMJ **25** and (+)-ADANJ **26**, the 2-deoxy-2-amino analogues of (−)-DMJ **18** and (+)-DANJ **24**.

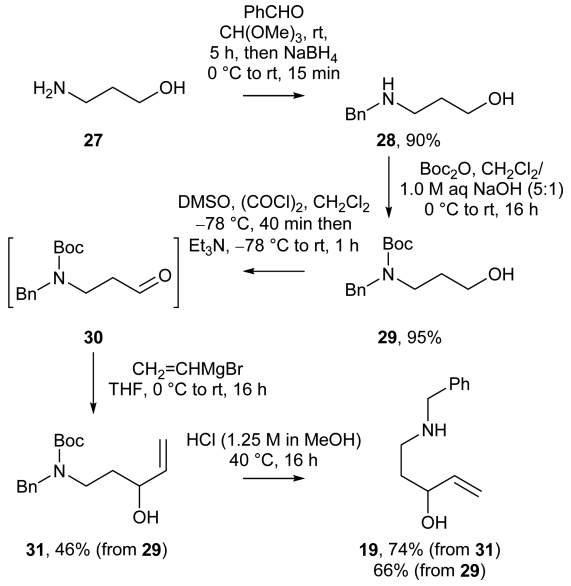
RESULTS AND DISCUSSION

The model bishomoallylic amine substrate **19** was prepared via monobenzylation of amino alcohol **27** upon treatment with benzaldehyde and $CH(OMe)_3$ followed by $NaBH_4$, which gave *N*-benzyl-substituted amino alcohol **28** in 90% yield.[16] Subsequent reaction of **28** with Boc_2O in a mixture of CH_2Cl_2 and 1.0 M aq NaOH (5:1) at 0 °C delivered *N*-Boc-*N*-benzyl-protected amino alcohol **29** in 95% yield.[17] Oxidation of the primary hydroxyl moiety within **29** under Swern conditions followed by direct treatment of the crude reaction mixture of aldehyde **30** with vinylmagnesium bromide gave *N*-Boc-protected bishomoallylic amine **31** in 46% yield over two steps (from **29**). Subjection of **31** to 1.25 M HCl in MeOH at 40 °C effected *N*-Boc deprotection, and *N*-benzyl-substituted bishomoallylic amine **19** was then isolated in 74% yield. Repetition of this procedure while omitting the purification of **31** reproducibly led to the production of **19** in 66% isolated yield over three steps (from **29**) on multigram scales (Scheme 2).

Ring-closing iodoamination/ring-expansion of **19** using the conditions that were previously[15] optimized for the conversion of bishomoallylic amine **11** into the corresponding carbonate **16** resulted in the formation of cyclic carbonate **32**. Although **32** was observed as the major compound in the ^1H NMR spectrum of the crude reaction mixture, it was isolated in only 36% yield after flash column chromatography.[18] Methanolysis of an analytically pure sample of **32** upon treatment with K_2CO_3 and MeOH gave diol **33** in quantitative yield. Analysis of the ^1H NMR ^3J coupling constants within **33** proved difficult due to the peaks in the ^1H NMR spectrum of **33** (recorded at rt

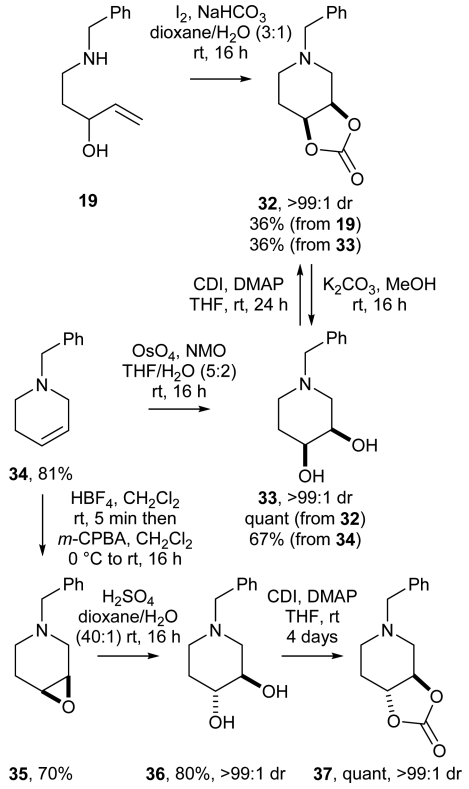
DOI: 10.1021/acs.joc.6b01107
J. Org. Chem. 2016, 81, 6481−6495

Scheme 2



in $CDCl_3$) being broad.[19] Thus, the relative configurations within diol **33** and the carbonate precursor **32** were established via chemical correlation. It was anticipated that tetrahydropyridine **34** would be the ideal common precursor for the syntheses of authentic samples of both *cis*-diol **33**[20] and *trans*-diol **36**[21] (and the corresponding carbonates *cis*-**32** and *trans*-**37**). The preparation of **34** was achieved via the reduction of *N*-benzylpyridinium bromide following a literature procedure:[22] treatment of pyridine with BnCl at 140 °C followed by reduction of *N*-benzylpyridinium bromide with $NaBH_4$ gave tetrahydropyridine **34**[22] in 81% yield. Stereospecific *cis*-dihydroxylation[23] of **34** upon treatment with OsO_4 and NMO (i.e., under Upjohn conditions[24]) in a mixture of THF/H_2O (5:1) gave *cis*-diol **33**, which was isolated in 67% yield after purification via flash column chromatography. Alternatively, epoxidation of the corresponding ammonium salt of **34** (to prevent *N*-oxidation) using HBF_4 and *m*-CPBA in CH_2Cl_2 produced epoxide **35**,[23] which underwent reaction with H_2SO_4 in dioxane/H_2O (40:1) to give *trans*-diol **36** in 56% overall yield (from **34**). Authentic samples of *cis*-carbonate **32** and *trans*-carbonate **37** were then synthesized from *cis*-diol **33** and *trans*-diol **36**, respectively: treatment of *cis*-diol **33** with CDI and DMAP in THF promoted full conversion to *cis*-carbonate **32**, which was observed as the sole product of the reaction in the ^{1}H NMR spectrum of the crude reaction mixture and was subsequently isolated in 36% yield after purification via flash column chromatography. The preparation of *trans*-carbonate **37** using similar conditions required 4 days to reach completion, and **37** was characterized as the sole product of the reaction, as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Attempted purification of *trans*-**37** by flash column chromatography led to its degradation; therefore, ^{1}H and ^{13}C NMR spectroscopic analyses were recorded using the crude reaction mixture. Comparison of the ^{1}H NMR spectra of these authentic samples of *cis*-carbonate **32** and *trans*-carbonate **37** (and *cis*-diol **33** and *trans*-diol **36**) with the ^{1}H NMR spectrum of the ring-closing iodoamination/ring-expansion product **32** derived from bishomoallylic amine **19** established the relative configurations within both **32** and **33** and also confirmed the absence of the alternative diastereoisomeric products **36** and **37** from the reaction of **19** under the ring-closing iodoamination conditions (Scheme 3).

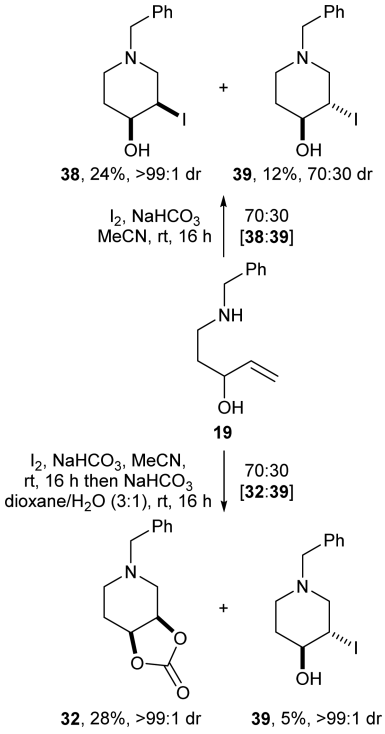
Scheme 3



Having established that the conditions developed for the trapping of CO_2 could be applied in the one-pot ring-closing iodoamination/ring-expansion of the model bishomoallylic substrate **19**, a study into the mechanism of reaction was next initiated. Iodoamination of **19** upon treatment with 3.0 equiv of I_2 and 3.0 equiv of $NaHCO_3$ in MeCN resulted in the formation of a 70:30 mixture of iodopiperidines **38** and **39**, respectively. Although the crude reaction mixture was obtained in quantitative mass return, the purification of **38** and **39** by flash column chromatography proved difficult and only **38** could be isolated as a pure sample in 24% yield, and an enriched sample of **39** (70:30 dr) was collected in 12% yield (Scheme 4). The relative configuration of **38** was established unambiguously by single-crystal X-ray diffraction analysis.[25] ^{1}H and ^{13}C NMR spectroscopic analyses, including a ^{1}H–^{13}C HMBC study, supported the assigned connectivity within **39**. The chemical shifts of the carbons directly bonded to iodine in the ^{13}C NMR spectra of both **38** (δ_C = 39.9 ppm) and **39** (δ_C = 38.4 ppm) were diagnostic of the iodine being supported by a *C*H carbon (i.e., a piperidine scaffold) as opposed to a *C*H$_2$ carbon (i.e., a pyrrolidine scaffold).[26] The ^{1}H NMR ^3J coupling constant analyses of these samples of **38** and **39** were also consistent with their assigned relative configurations. In contrast to the sharp peaks displayed in the ^{1}H NMR spectrum of **39** (recorded at rt in $CDCl_3$), the peaks observed in the ^{1}H NMR spectrum of **38** (recorded at rt in $CDCl_3$) were extremely broad[27] and only a limited number of correlations could be distinguished in the ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, and ^{1}H–^{13}C HMBC NMR spectra. The ^{1}H and ^{13}C NMR spectra of **38** were therefore recorded at 363 K in PhMe-d_8. In this case the peaks in the ^{1}H and ^{13}C NMR spectra were resolved, and characteristic correlations were also observed in the corresponding 2D NMR spectra; these data were all consistent with the structure of **38**. The formation of iodopiperidines **38** and **39**

DOI: 10.1021/acs.joc.6b01107
J. Org. Chem. 2016, 81, 6481–6495

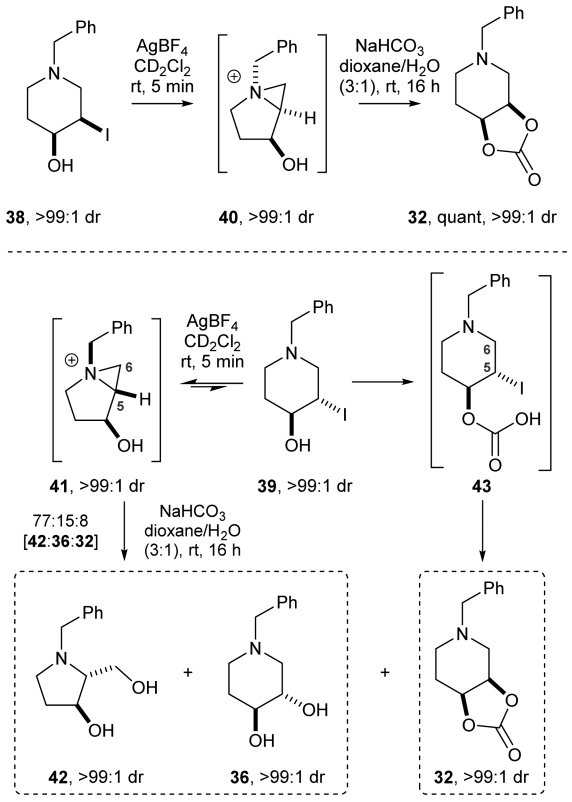
Scheme 4



in the iodoamination of **19** is in direct contrast with the formation of iodomethyl pyrrolidine **12** when bishomoallylic amine **11** was subjected to the same conditions.[15] This reaction outcome could be rationalized by either 5-exo cyclization of the corresponding iodonium species followed by rearrangement (presumably via the intermediacy of the corresponding aziridinium species) or 6-endo cyclization. Repetition of the iodoamination of **19** followed by direct treatment of the 70:30 crude reaction mixture of **38** and **39** with $NaHCO_3$ in a mixture of dioxane/H_2O (3:1) afforded a 70:30 mixture of carbonate **32** and iodopiperidine **39**. Subsequent purification by flash column chromatography led to the isolation of **32** in 28% yield and **39** in 5% yield as single diastereoisomers (>99:1 dr) in each case (Scheme 4). The isolation of iodopiperidine **39** following this stepwise process was in contrast with the sole isolation of carbonate **32** when performing the corresponding one-pot transformation (vide supra) and provided some insight into the reaction mechanism: in this case, carbonate **32** seemed to derive from **38**, while **39** is apparently inert under the conditions for carbonate formation.

With diastereoisomerically pure (>99:1 dr) samples of iodopiperidines *cis*-**38** and *trans*-**39** in hand, it was now possible to separately investigate the trapping of CO_2 from $NaHCO_3$ by each diastereoisomer. Treatment of **38** with $AgBF_4$ in CD_2Cl_2 delivered the corresponding aziridinium **40**, which could not be isolated due to degradation. Aziridinium **40** was subsequently subjected to the trapping conditions (i.e., $NaHCO_3$ in a 3:1 mixture of dioxane/H_2O was added to the NMR sample) to give carbonate **32** in quantitative yield as a single diastereoisomer (>99:1 dr). Direct treatment of **38** with $NaHCO_3$ in a mixture of dioxane/H_2O (3:1) promoted the formation of carbonate **32**, which was obtained in quantitative yield and >99:1 dr, thereby supporting the intermediacy of aziridinium **40** in the conversion of iodopiperidine **38** to carbonate **32**. In contrast, **39** was converted into the corresponding aziridinium **41** (upon treatment of **39** with $AgBF_4$ in CD_2Cl_2) and subjected to the same trapping conditions, which gave a 77:15:8 mixture of pyrrolidine **42**, piperidine **36**, and carbonate **32**, respectively. Presumably, intermolecular ring-opening of **41** by H_2O gave pyrrolidine **42** [i.e., ring-opening at C(6)] and piperidine **36** [i.e., ring-opening at C(5) with inversion of configuration]. The formation of carbonate **32** in this case was rationalized by the trapping of CO_2 by *trans*-iodopiperidine **39** and subsequent S_N2-type substitution of the C(5)-iodide within **43** (Scheme 5). Direct treatment of **39**

Scheme 5

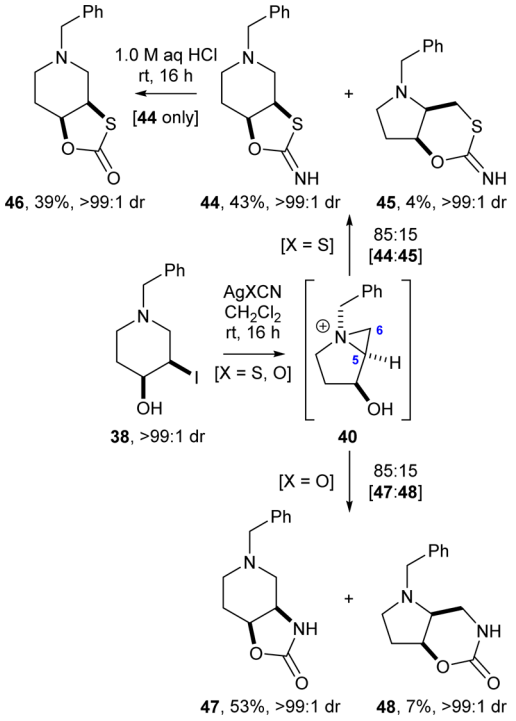


with $NaHCO_3$ in a mixture of dioxane/H_2O (3:1) resulted in the formation of a complex mixture of products.

Having demonstrated that aziridinium **40** successfully underwent ring-expansion via the trapping of CO_2 to give carbonate **32**, our attention next turned to examine the trapping of sulfur- and nitrogen-containing "X=C=Y" electrophiles. It was envisaged that the trapping of either isothiocyanates (RNCS) or isocyanates (RNCO) by aziridinium **40** would result in the subsequent intramolecular ring-opening at the C(5) position by the more nucleophilic sulfur or nitrogen atom, respectively, to give the corresponding oxathiolan-2-one (after hydrolysis of the oxathiolan-2-imine intermediate) or oxazolidin-2-one. Prior to investigating the trapping of isothiocyanates and isocyanates, it was anticipated that the synthesis of authentic samples of oxathiolan-2-one **46** and oxazolidin-2-one **47** could be achieved by the intermolecular ring-opening of aziridinium **40** at the C(5) position by either the thiocyanate anion (NCS^-) or the cyanate anion (OCN^-), respectively, followed by cyclization. Thus, **38** was treated with AgSCN, which resulted in the formation of an 85:15 regioisomeric mixture of bicyclic derivatives **44** and **45**, from which **44** was isolated in 43% yield and >99:1 dr and **45** was isolated in 4% yield and >99:1 dr (Scheme 6). The atomic connectivities within **44** and **45** were assigned by ^1H and ^{13}C NMR spectroscopic analyses, including $^1H-^{13}C$

DOI: 10.1021/acs.joc.6b01107
J. Org. Chem. 2016, 81, 6481−6495

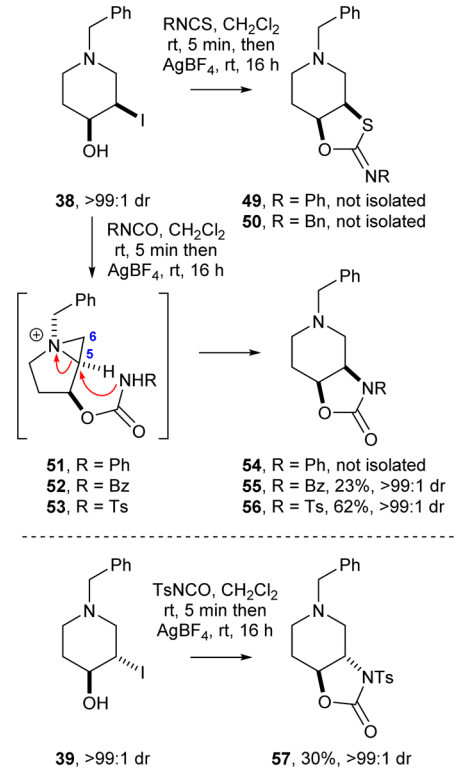
Scheme 6



HMBC studies. In addition, characteristic C═N absorbances at 1639 cm^{-1} in the IR spectra of both **44** and **45**, along with diagnostic chemical shifts for the SCN carbons (δ_C = ~169 ppm) in the ^{13}C NMR spectra of both **44** and **45**, confirmed the presence of a carbonimidothioate moiety. Hydrolysis of **44** upon treatment with 1.0 M aq HCl delivered oxathiolan-2-one **46** in 39% yield and >99:1 dr. The IR spectrum of **46** displayed a diagnostic C═O absorbance at 1732 cm^{-1}, which along with the diagnostic chemical shift at δ_C = 172.5 ppm for the SCO carbon observed in the ^{13}C NMR spectrum of **46** fully supported the assigned structure of **46**. Analogous reaction of **38** with AgOCN afforded an 85:15 regioisomeric mixture of bicyclic derivatives **47** and **48**, from which **47** was isolated in 53% yield and >99:1 dr and **48** was isolated in 7% yield and >99:1 dr (Scheme 6). The atomic connectivities within **47** and **48** were again assigned following ^1H and ^{13}C NMR spectroscopic analyses, including $^1H-^{13}C$ HMBC studies. In addition, the presence of diagnostic C═O absorbances at 1749 cm^{-1} in the IR spectrum of **47** and at 1756 cm^{-1} in the IR spectrum of **48** were entirely consistent with the presence of a carbamate functionality. In both cases, ring-opening of aziridinium **40** by thiocyanate or cyanate anions at the C(5) position (with inversion of configuration) was responsible for the formation of the major regioisomers **44** and **47**, while ring-opening of **40** at the C(6) position was responsible for the formation of the minor regioisomers **45** and **48**.

The trapping of either isothiocyanates (RNCS) or isocyanates (RNCO) was investigated next. Treatment of **38** with $AgBF_4$ in CH_2Cl_2 (to convert **38** to the corresponding aziridinium **40**) followed by the addition of PhNCS gave a complex mixture of products. Alternatively, reaction of **38** with either PhNCS or BzNCS followed by $AgBF_4$ also resulted in the formation of complex mixtures of products, failing to give oxathiolan-2-imines **49** or **50** (or the corresponding oxathiolan-2-ones) in all attempts. In light of these results, the trapping of isothiocyanates was abandoned and attention was next turned to the trapping of isocyanates. While treatment of **38** with PhNCO followed by the addition of $AgBF_4$ did not provide oxazolidin-2-one **54**, submission of **38** to the same reaction conditions with BzNCO resulted in the formation of oxazolidin-2-one **55**, which was observed as the major product in the ^1H NMR spectrum of the crude reaction mixture. In this case, purification by flash column chromatography gave **55** in 23% yield as a single diastereoisomer (>99:1 dr). Similarly, treatment of **38** with *p*-toluenesulfonyl isocyanate (TsNCO) followed by the addition of $AgBF_4$ produced oxazolidin-2-one **56**, which was observed as the sole product upon inspection of the ^1H NMR spectrum of the crude reaction mixture and obtained in 62% yield and >99:1 dr after purification by flash column chromatography.[28] The relative configuration of **56** was unambiguously established by single-crystal X-ray diffraction analysis.[25] The relative configuration of **55** was assigned by analogy [on the basis that the ring-opening of aziridinium **52** proceeds with inversion of configuration at the C(5) position], and this assignment was supported via ^1H NMR ^3J coupling constant correlation with both **47** and **56**. Subjecting **39** to TsNCO in CH_2Cl_2 followed by the addition of $AgBF_4$ led to the isolation of the epimeric oxazolidin-2-one **57** in 30% yield and >99:1 dr (Scheme 7).[29]

Scheme 7

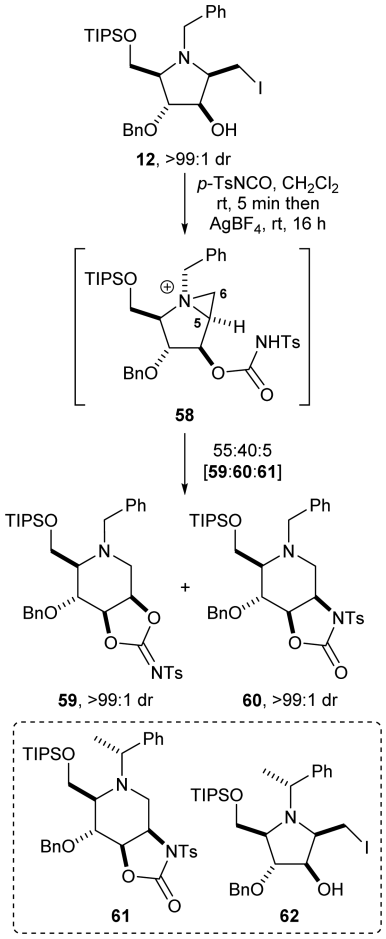


It was interesting to note that the formation of **57** from the formal trapping of TsNCO by **39** was in direct contrast with the unsuccessful formation of *trans*-carbonate **37** from **39**. While the conversion of **38** to **49** or **50** was unsuccessful, the trapping of TsNCO led to the isolation of oxazolidin-2-one **56** in good yield as a single regioisomer, and it was envisaged that this methodology could be employed in the syntheses of (−)-ADMJ **25** and (+)-ADANJ **26**, the 2-deoxy-2-amino analogues of (−)-DMJ **18** and (+)-DANJ **24**.

Treatment of a freshly prepared sample of iodomethylpyrrolidine **12** with TsNCO in CH_2Cl_2 for 5 min followed by the addition of $AgBF_4$ produced a 55:40:5 mixture of dioxolan-2-imine

DOI: 10.1021/acs.joc.6b01107
J. Org. Chem. 2016, 81, 6481−6495

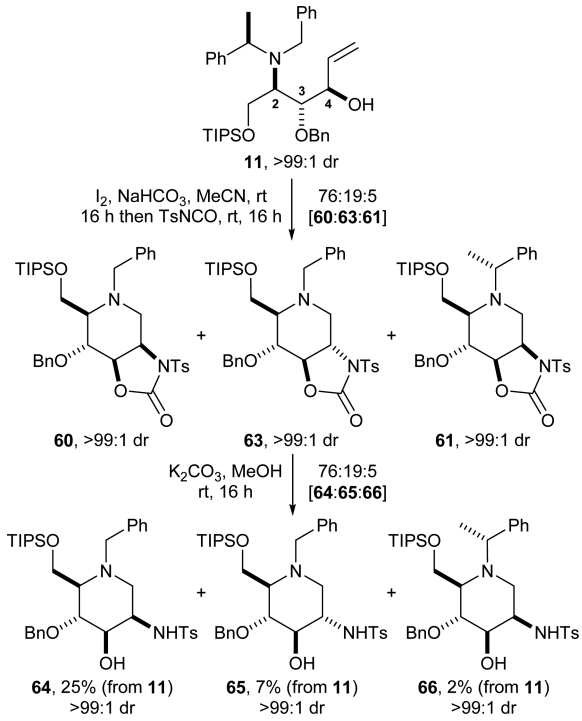
Scheme 8



59 and carbamates **60** and **61**, respectively, in quantitative mass return (Scheme 8). This outcome is consistent with the formation of aziridinium ion **58** followed by tethered ring-opening at the C(5) position through either the carbamate oxygen atom (to give dioxolan-2-imine **59**) or the carbamate nitrogen atom (to give cyclic carbamate **60**). Carbamate **61** is presumably derived from a trace amount of the corresponding *N*(1)-*α*-methylbenzyl-substituted pyrrolidine **62** present in the sample of **12**.[30] The IR spectrum of the crude reaction mixture displayed a diagnostic C═N absorbance at 1640 cm^{-1}, supporting the assigned identity of **59**, and upon attempted purification of the crude reaction mixture by flash column chromatography carbonate **16** (which presumably resulted from hydrolysis of **59**) was recovered in 48% yield. A 90:10 mixture of carbamates **60** and **61** was also isolated, and the IR spectrum of this mixture displayed a diagnostic C═O absorbance at 1788 cm^{-1}. The relative configuration of **60** (and **61**) was initially assigned by analogy to the stereochemical outcome observed upon reaction of the model substrate **39** under these conditions and was later confirmed via ^{1}H NMR ^3J coupling constant analyses of several derivatives.

Further reaction optimization revealed that treatment of bishomoallylic amine **11** with I_2 and $NaHCO_3$ in MeCN followed by the addition of 4.5 equiv of TsNCO to the reaction mixture after 16 h (i.e., omitting the addition of $AgBF_4$) gave a 76:19:5 mixture of **60**, **63**, and **61**, respectively, in addition to *N*-(*α*-methylbenzyl)acetamide (which resulted from loss of the *N*-*α*-methylbenzyl group in a Ritter-type process).[15] Purification by flash column chromatography resulted in the isolation of a 76:19:5 mixture of **60**, **63**, and **61**, respectively. Repetition of the reaction followed by direct methanolysis of the crude reaction mixture upon treatment with K_2CO_3 and MeOH gave a 76:19:5 mixture of **64**, **65**, and **66**, respectively. Purification of the crude reaction mixture by flash column chromatography gave **64** in 25% yield (from **11**), **65** in 7% yield (from **11**), and **66** in 2% yield (from **11**) as single diastereoisomers (>99:1 dr) in each case (Scheme 9). The relative

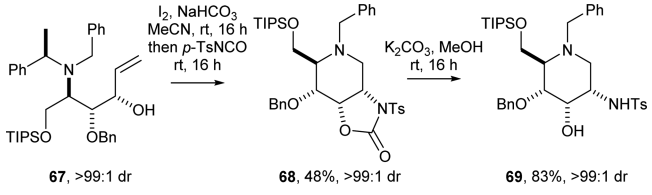
Scheme 9



configurations of piperidines **64**–**66** (and therefore also those of the synthetic precursors **60**, **61**, and **63**) were established by ^{1}H NMR ^3J coupling constant analyses, and the absolute configurations of these compounds were assigned from the known absolute configurations at the C(2), C(3), C(4), and C(*α*) stereogenic centers within the precursor bishomoallylic amine **11**.

One-pot ring-closing iodoamination/ring-expansion of the epimeric bishomoallylic amine **67**[15] upon treatment with I_2 and $NaHCO_3$ followed by the addition of TsNCO after 16 h resulted in the formation of carbamate **68** and *N*-(*α*-methylbenzyl)-acetamide. Purification of the crude reaction mixture by flash column chromatography gave **68** in 48% yield and >99:1 dr. Subsequent treatment of **68** with K_2CO_3 and MeOH led to the isolation of piperidine **69** in 83% yield and >99:1 dr (Scheme 10). The relative configuration of **69** was unambiguously established by single-crystal X-ray diffraction analysis.[25]

Scheme 10



DOI: 10.1021/acs.joc.6b01107
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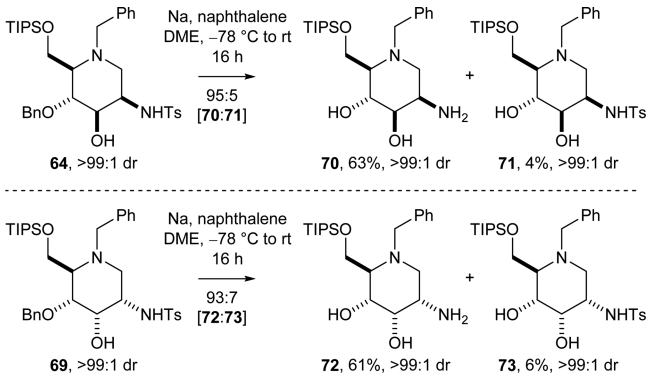
Furthermore, the determination of a Flack x parameter[31] of −0.004(9) for the crystal structure of **69** allowed the assigned absolute (2*R*,3*R*,4*S*,5*S*)-configuration of **69** to be confirmed. This analysis also unambiguously established the absolute configuration of the carbamate precursor **68**.

With piperidines **64** and **69** in hand, it was now possible to commence investigations into the deprotection of the *N*-tosyl moiety. Following a literature procedure,[32] treatment of **69** with Na and naphthalene in THF at −10 °C for 3 h proceeded with concomitant *O*-benzyl deprotection to give a 40:60 mixture of **72** and **73**, respectively. Purification of the crude reaction mixture by flash column chromatography gave **72** in 40% yield and **73** in 60% yield in >99:1 dr in both cases. Reaction optimization revealed that treatment of **69** with Na and naphthalene in THF at rt for 16 h gave a 93:7 mixture of **72** and **73**, respectively. Purification of this mixture via flash column chromatography led to the isolation of **72** in 61% yield and >99:1 dr and **73** in 6% yield and >99:1 dr. Submission of **64** to these optimized reaction conditions resulted in the formation of a 95:5 mixture of **70** and **71**, from which **70** was isolated in 63% yield and >99:1 dr and **71** was isolated in 4% yield and 99:1 dr (Scheme 11).

Scheme 11

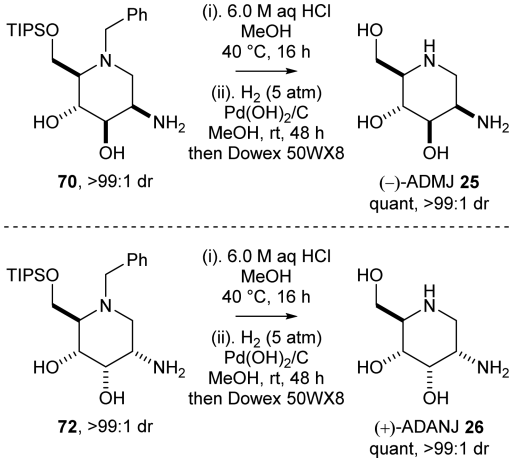


Treatment of **70** with 6.0 M aq HCl in MeOH at 40 °C effected *O*-TIPS deprotection, and subsequent hydrogenolysis upon treatment with Pearlman's catalyst under H_2 (5 atm) followed by purification of this sample by ion exchange chromatography on Dowex 50WX8 (H^+ form) resin afforded (−)-ADMJ **25** in quantitative yield and >99:1 dr. Identical treatment of **72** gave (+)-ADANJ **26** in quantitative yield and >99:1 dr (Scheme 12). While there was no precedent in the literature for the synthesis or identification of (+)-ADANJ **26**, the specific rotation and ^1H and ^{13}C NMR spectra of this sample of (−)-ADMJ **25** {$[\alpha]_D^{20}$ −11.5 (*c* 0.3 in H_2O)} were in very good agreement with the data previously reported for a synthetic sample of (−)-ADMJ **25** by Le Merrer et al.[9b] {$[\alpha]_D$ −14 (*c* 0.4 in H_2O)}.

CONCLUSION

In conclusion, the methodology for the ring-closing iodoamination of bishomoallylic amines followed by in situ ring-expansion (via intramolecular ring-opening of the corresponding aziridinium intermediates with a tethered carbamate moiety) to give oxazolidin-2-ones was initially optimized on a model system. Subsequent application of this methodology to two enantiopure bishomoallylic amines (which were produced via aminohydroxylation of an α,β-unsaturated ester, partial reduction,

Scheme 12



and reaction of the resultant aldehyde with vinylmagnesium bromide) also proceeded with concomitant *N*-debenzylation to afford the corresponding diastereoisomerically pure (>99:1 dr) oxazolidin-2-ones. Subsequent deprotection of these enantiopure templates gave (−)-ADMJ and (+)-ADANJ, the 2-deoxy-2-amino analogues of (−)-1-deoxymannojirimycin and (+)-1-deoxyallonojirimycin, as single diastereoisomers (>99:1 dr) in 16% and 24% overall yield, respectively.

EXPERIMENTAL SECTION

General Experimental Details. All reactions involving organometallic or other 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] BuLi was purchased as a solution in hexanes and titrated against diphenylacetic acid before use. All other reagents were used as supplied without prior purification. Organic layers were dried over Na_2SO_4. Thin layer chromatography was performed on aluminum plates coated with 60 F_{254} silica. Plates were visualized using UV light (254 nm), 1% aq $KMnO_4$, or Dragendorff's reagent. 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 using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. $^1H-^1H$ COSY, $^1H-^{13}C$ HMQC, and $^1H-^{13}C$ HMBC analyses were used to establish atom connectivity. Accurate mass measurements were run on a TOF spectrometer internally calibrated with polyalanine.

X-ray Crystal Structure Determination.[25] Data were collected using either graphite-monochromated Mo/Kα radiation (for **39**) or graphite-monochromated Cu/Kα radiation (for **56** and **69**) 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]

3-(*N*-Benzylamino)propan-1-ol 28. 3-Aminopropan-1-ol **27** (5.00 g, 66.6 mmol) was added to a stirred solution of PhCHO (6.77 mL, 66.6 mmol) and $CH(OMe)_3$ (10.9 mL, 99.8 mmol), and the resultant mixture was stirred at rt for 5 h. The reaction mixture was then cooled to 0 °C, and $NaBH_4$ (2.52 g, 66.6 mmol) was added portionwise. The reaction mixture was then concentrated in vacuo, and the residue was partitioned between H_2O (200 mL) and EtOAc (200 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were then dried and concentrated in vacuo to give **28** as a colorless oil (9.95 g, 90%);[16] δ_H (400 MHz,

DOI: 10.1021/acs.joc.6b01107
J. Org. Chem. 2016, 81, 6481−6495

$CDCl_3$) 1.76 (2H, app quintet, *J* 5.5, C(2)H_2), 2.93 (2H, t, *J* 5.5, C(3)H_2), 3.16 (2H, br s, O*H*, N*H*), 3.82 (2H, s, NCH_2Ph), 3.84 (2H, t, *J* 5.5, C(1)H_2), 7.26−7.38 (5H, m, *Ph*).

3-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]propan-1-ol 29. $(Boc)_2O$ (6.60 g, 30.3 mmol) was added to a stirred solution of **28** (5.00 g, 30.3 mmol) in CH_2Cl_2/1.0 M aq NaOH (5:1, 90 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was washed with H_2O (100 mL), dried, and concentrated in vacuo to give **29** as a colorless oil (7.66 g, 95%);[17,35] δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, CMe_3), 1.65 (2H, app br s, C(2)H_2), 2.75 (1H, br s, O*H*), 3.40 (2H, app br s, C(3)H_2), 3.57−3.61 (2H, m, C(1)H_2), 4.41 (2H, br s, NCH_2Ph), 7.23−7.38 (5H, m, *Ph*).

5-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]pent-1-en-3-ol 31. *Step 1*. DMSO (0.24 mL, 3.3 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.12 mL, 1.4 mmol) in CH_2Cl_2 (15 mL) at −78 °C. After 20 min, a solution of **29** (200 mg, 0.75 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added dropwise via cannula. After a further 20 min, Et_3N (0.63 mL, 4.5 mmol) was added and the resultant mixture was stirred at −78 °C for 30 min before being allowed to warm to rt over 30 min. The reaction mixture was then concentrated in vacuo, and the residue was partitioned between H_2O (30 mL) and Et_2O (30 mL). The aqueous layer was extracted with Et_2O (2 × 15 mL), and the combined organic extracts were then dried and concentrated in vacuo to give **30** as a yellow oil (204 mg); δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, CMe_3), 2.60−2.72 (2H, m, C(2)H_2), 3.39−3.56 (2H, m, C(3)H_2), 4.40−4.47 (2H, m, NCH_2Ph), 7.25−7.37 (5H, m, *Ph*), 9.75 (1H, s, C(1)*H*).

Step 2. Vinylmagnesium bromide (1.0 M in THF, 2.25 mL, 2.25 mmol) was added dropwise to a stirred solution of the residue of **30** (204 mg) in THF (5 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C, and H_2O (1 mL) was added dropwise. The resultant mixture was concentrated in vacuo, and the residue was partitioned between H_2O (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL), and the combined organic extracts were washed with brine (10 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 2:1) gave **31** as a yellow oil (100 mg, 46% from **29**); ν_{max} (ATR) 3428 (O−H), 2976, 2932 (C−H), 1692, 1670 (C═O), 1477, 1454, 1417 (C═C); δ_H (400 MHz, $CDCl_3$) 1.44−1.60 (10H, m, CMe_3, C(4)H_A), 1.68−1.76 (1H, m, C(4)H_B), 3.06−3.10 (1H, m, C(5)H_A), 3.72−3.76 (1H, m, C(5)H_B), 4.01 (1H, br s, O*H*), 4.06−4.10 (1H, m, C(3)*H*), 4.26−4.31 (1H, m, NC$H_A$$H_B$Ph), 4.53 (1H, d, *J* 15.6, NC$H_A$$H_B$Ph), 5.08 (1H, d, *J* 10.4, C(1)H_A), 5.23 (1H, d, *J* 17.2, C(1)H_B), 5.85 (1H, ddd, *J* 17.2, 10.4, 5.2, C(2)*H*), 7.21−7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.4 (CMe_3), 35.2 (*C*(4)), 42.7 (*C*(5)), 50.6 (NCH_2Ph), 68.7 (*C*(3)), 80.5 (CMe_3), 113.8 (*C*(1)), 127.3 (*p-Ph*), 128.5, 128.6 (*o,m-Ph*), 138.1 (*i-Ph*), 140.4 (*C*(2)), 156.8 (NCO); *m/z* (ESI$^+$) 292 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{26}NO_3^+$ ([M + H]$^+$) requires 292.1907; found 292.1908.

5-(*N*-Benzylamino)pent-1-en-3-ol 19. *Method A (from **31**)*. A solution of **31** (50 mg, 0.17 mmol) in HCl (1.25 M in MeOH, 2 mL) was heated at 40 °C for 16 h before being allowed to cool to rt and concentrated in vacuo. The residue was then partitioned between 2.0 M aq KOH (10 mL) and $CHCl_3$/^{i}PrOH (3:1, 10 mL). The aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1, 2 × 5 mL), and the combined organic extracts were then dried over Na_2SO_4 and concentrated in vacuo to give **19** as a yellow oil (24 mg, 74%); ν_{max} (ATR) 3298 (N−H, O−H), 2924, 2850 (C−H), 1495, 1454 (C═C); δ_H (400 MHz, $CDCl_3$) 1.60−1.70 (1H, m, C(4)H_A), 1.76−1.84 (1H, m, C(4)H_B), 2.86 (1H, ddd, *J* 12.3, 9.1, 3.5, C(5)H_A), 3.01 (1H, ddd, *J* 12.3, 6.4, 3.5, C(5)H_B), 3.65 (1H, br s, O*H*), 3.80 (1H, d, *J* 13.0, NC$H_A$$H_B$Ph), 3.84 (1H, d, *J* 13.0, NC$H_A$$H_B$Ph), 4.32−4.39 (1H, m, C(3)*H*), 5.08 (1H, app dt, *J* 10.5, 1.5, C(1)H_A), 5.27 (1H, app dt, *J* 17.0, 1.5, C(1)H_B), 5.85 (1H, ddd, *J* 17.0, 10.5, 5.2, C(2)*H*), 7.25−7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 34.4 (*C*(4)), 47.1 (*C*(5)), 53.4 (NCH_2Ph), 73.5 (*C*(3)), 113.9 (*C*(1)), 127.5 (*p-Ph*), 128.4, 128.6 (*o,m-Ph*), 138.2 (*i-Ph*), 140.7 (*C*(2)); *m/z* (ESI$^+$) 192 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{18}NO^+$ ([M + H]$^+$) requires 192.1383; found 192.1387.

*Method B (from **29**)*. *Step 1*: DMSO (5.90 mL, 83.0 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (2.92 mL, 34.0 mmol) in CH_2Cl_2 (400 mL) at −78 °C. After 20 min, a solution of **29** (5.00 g, 18.9 mmol) in CH_2Cl_2 (400 mL) at −78 °C was added dropwise via cannula. After a further 20 min, Et_3N (15.8 mL, 114 mmol) was added and the resultant mixture was stirred at −78 °C for 30 min before being allowed to warm to rt over 30 min. The reaction mixture was then concentrated in vacuo, and the residue was partitioned between H_2O (500 mL) and Et_2O (500 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL), and the combined organic extracts were then dried and concentrated in vacuo to give **30** as a yellow oil (5.26 g).

*Method B (from **29**)*. *Step 2*: Vinylmagnesium bromide (1.0 M in THF, 56.7 mL, 56.7 mmol) was added dropwise to a stirred solution of the residue of **30** (5.26 g) in THF (400 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C, and H_2O (20 mL) was added dropwise. The resultant mixture was concentrated in vacuo, and the residue was partitioned between H_2O (400 mL) and EtOAc (400 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with brine (400 mL), dried, and concentrated in vacuo to give **31** as a yellow oil (5.59 g).

*Method B (from **29**)*. *Step 3*: The residue of **31** (5.59 g) was dissolved in HCl (1.25 M in MeOH, 50 mL), and the resultant mixture was heated at 40 °C for 16 h before being allowed to cool to rt and concentrated in vacuo. The residue was partitioned between 2.0 M aq KOH (50 mL) and $CHCl_3$/^{i}PrOH (3:1, 50 mL). The aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1, 2 × 20 mL), and the combined organic extracts were then dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 48:1) gave **19** as a yellow oil (2.40 g, 66% from **29**).

(*RS,SR*)-*N*(1)-Benzyl-3,4-dihydroxy-3,4-*O*-carbonylpiperidine 32. *Method A (from **19**)*. I_2 (1.20 g, 4.71 mmol) and $NaHCO_3$ (396 mg, 4.71 mmol) were added to a stirred solution of **19** (300 mg, 1.57 mmol) in dioxane/H_2O (3:1, 4 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL), washed with satd aq $Na_2S_2O_3$ (15 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 2:1) gave **32** as a yellow oil (130 mg, 36%, >99:1 dr); ν_{max} (ATR) 2925 (C−H), 1799 (C═O); δ_H (400 MHz, $CDCl_3$) 1.98−2.07 (1H, m, C(5)H_A), 2.17 (1H, app dq, *J* 15.1, 4.2, C(5)H_B), 2.42−2.56 (3H, m, C(2)H_A, C(6)H_2), 2.94 (1H, ddd, *J* 12.5, 5.4, 1.4, C(2)H_B), 3.56 (1H, d, *J* 13.1, NC$H_A$$H_B$Ph), 3.58 (1H, d, *J* 13.1, NC$H_A$$H_B$Ph), 4.69 (1H, app q, *J* 6.4, C(3)*H*), 4.73−4.78 (1H, m, C(4)*H*), 7.25−7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.4 (*C*(5)), 47.3 (*C*(6)), 53.3 (*C*(2)), 62.2 (NCH_2Ph), 73.7 (*C*(3)), 74.1 (*C*(4)), 127.4 (*p-Ph*), 128.4, 128.8 (*o,m-Ph*), 137.2 (*i-Ph*), 155.0 (CO); *m/z* (ESI$^+$) 234 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{15}NNaO_3^+$ ([M + Na]$^+$) requires 256.0944; found 256.0950.

*Method B (from **33**)*. CDI (59 mg, 0.36 mmol) and DMAP (6 mg, 0.05 mmol) were added to a stirred solution of **33** (50 mg, 0.24 mmol, >99:1 dr) in THF (2 mL), and the resultant mixture was allowed to stir at rt for 24 h. Saturated aq NH_4Cl (0.5 mL) was added, and the reaction mixture was extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 2:1) gave **32** as a yellow oil (20 mg, 36%, >99:1 dr).

*Method C (from **38**)*. $AgBF_4$ (18 mg, 95 μmol) was added to **38** (25 mg, 78 μmol, >99:1 dr) in CD_2Cl_2, and the reaction mixture was shaken at rt for 5 min. The reaction mixture was then poured into a stirred solution of $NaHCO_3$ (20 mg, 0.23 mmol) in dioxane/H_2O (3:1, 4 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (10 mL), and the organic layer was washed with satd aq $NaHCO_3$ (10 mL), dried, and concentrated in vacuo to give **32** as a yellow oil (20 mg, quant, >99:1 dr).

(*RS,SR*)-*N*(1)-Benzyl-3,4-dihydroxypiperidine 33. *Method A (from **32**)*. K_2CO_3 (116 mg, 0.84 mmol) was added to a stirred solution of **32** (65 mg, 0.28 mmol, >99:1 dr) in MeOH (4 mL) at rt, and the resultant mixture was allowed to stir at rt for 16 h before being

DOI: 10.1021/acs.joc.6b01107
J. Org. Chem. 2016, 81, 6481−6495

concentrated in vacuo. The residue was then partitioned between H_2O (5 mL) and $CHCl_3$/^{i}PrOH (3:1, 5 mL), and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1, 2 × 5 mL). The combined organic extracts were then dried and concentrated in vacuo to give **33** as a yellow oil (60 mg, quant, >99:1 dr);[20] ν_{max} (ATR) 3377 (O−H), 2812, 2926 (C−H); δ_H (400 MHz, CD_2Cl_2) 1.63−1.72 (1H, m, C(5)H_A), 1.73−1.78 (1H, m, C(5)H_B), 2.04−2.11 (1H, m, C(6)H_A), 2.26 (1H, app d, *J* 10.6, C(2)H_A), 2.65−2.72 (1H, m, C(6)H_B), 2.80 (1H, app br s, C(2)H_B), 3.50 (1H, d, *J* 13.2, NC$H_A$$H_B$Ph), 3.53 (2H, m, NC$H_A$$H_B$Ph, C(4)*H*), 3.69−3.71 (1H, m, C(3)*H*), 7.23−7.33 (5H, m, *Ph*); δ_C (100 MHz, CD_2Cl_2) 30.5 (*C*(5)), 50.9 (*C*(6)), 57.5 (*C*(2)), 62.6 (NCH_2Ph), 69.3 (*C*(3)), 69.8 (*C*(4)), 127.7 (*p-Ph*), 128.8, 129.5 (*o,m-Ph*), 138.8 (*i-Ph*); *m/z* (ESI$^+$) 208 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{18}NO_2^+$ ([M + H]$^+$) requires 208.1332; found 208.1331.

Method B (from ***34****).*[23] OsO_4 (37 mg, 0.14 mmol) was added to a stirred solution of **34** (500 mg, 2.89 mmol) in THF (20 mL) and H_2O (5 mL), followed by a solution of NMO (1.22 g, 10.4 mmol) in H_2O (2.5 mL). The reaction mixture was stirred at rt for 16 h. Saturated aq Na_2SO_3 (1 mL) was then added, and the resultant mixture was allowed to stir at rt for 1 h. The reaction mixture was then extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (CH_2Cl_2/MeOH, 24:1) gave **33** as a yellow oil (399 mg, 67%, >99:1 dr).

***N*(1)-Benzyl-1,2,3,6-tetrahydropyridine 34.** A mixture of pyridine (10.2 mL, 126 mmol) and BnCl (17.5 mL, 152 mmol) was stirred at 140 °C for 1 h, before being allowed to cool to rt. The red resin was dissolved in EtOH (350 mL). Since the resin was barely soluble in EtOH, this dissolution was best performed by repeated addition of portions (∼50 mL) of EtOH to the resin, equilibrating the mixture with ultrasonication and decanting the liquid phase. $NaBH_4$ (10.5 g, 277 mmol) was then added portionwise to the ethanolic solution at 0 °C, and the resultant mixture was allowed to stir at rt for 16 h. H_2O (150 mL) was added, and the organic layer was decanted off from the resultant colorless solid. The solid residue (2 × 50 mL) and the aqueous layer (3 × 10 mL) were both extracted with Et_2O, and the combined organic extracts were then dried and concentrated in vacuo to give **34** as a yellow oil (17.6 g, 81%);[22] δ_H (400 MHz, $CDCl_3$) 2.18−2.24 (2H, m, C(3)H_2), 2.60 (2H, t, *J* 5.7, C(2)H_2), 3.01 (2H, m, C(6)H_2), 3.62 (2H, s, NCH_2Ph), 5.66−5.74 (1H, m, C(4)*H*), 5.76−5.82 (1H, m, C(5)*H*), 7.26−7.43 (5H, m, *Ph*).

***(RS,SR)*-*N*(1)-Benzyl-3,4-epoxypiperidine 35.** HBF_4 (40% aq, 4.53 mL, 28.9 mmol) was added to a stirred solution of **34** (1.00 g, 5.78 mmol) in CH_2Cl_2 (30 mL), and the resultant mixture was allowed to stir at rt for 5 min. *m*-CPBA (62%, 2.41 g, 8.67 mmol) was then added, and the reaction mixture was stirred at rt for 16 h. Saturated aq Na_2SO_3 (1 mL) was then added until starch-iodide paper indicated that no oxidant remained. The organic layer was washed with $NaHCO_3$ (3 × 10 mL), and the combined aqueous layers were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 3:2) gave **35** as a yellow oil (77 mg, 70%);[36] δ_H (400 MHz, $CDCl_3$) 1.95−2.09 (2H, m, C(5)H_2), 2.21 (1H, ddd, *J* 11.5, 9.2, 4.3, C(6)H_A), 2.32−2.38 (1H, m, C(6)H_B), 2.69 (1H, d, *J* 13.4, C(2)H_A), 3.04 (1H, ddd, *J* 13.4, 4.3, 1.1, C(2)H_B), 3.22−3.27 (2H, m, C(3)*H*, C(4)*H*), 3.46 (1H, d, *J* 13.6, NC$H_A$$H_B$Ph), 3.48 (1H, d, *J* 13.6, NC$H_A$$H_B$Ph), 7.24−7.36 (5H, m, *Ph*).

***(RS,RS)*-*N*(1)-Benzyl-3,4-dihydroxypiperidine 36.** Concentrated H_2SO_4 (1.4 mL) and a few drops of H_2O were added to a stirred solution of **35** (1.00 g, 5.28 mmol) in 1,4-dioxane (20 mL), and the resultant mixture was stirred at rt for 16 h and then concentrated in vacuo. $NaHCO_3$ (5 mL) was added to the residue, and the reaction mixture was extracted with $CHCl_3$/^{i}PrOH (3:1, 3 × 10 mL). The combined organic extracts were washed with 2.0 M aq KOH (15 mL), dried, and concentrated in vacuo to give **36** as a yellow oil (874 mg, 80%, >99:1 dr);[21] δ_H (400 MHz, $CDCl_3$) 1.57−1.67 (1H, m, C(5)H_A), 1.91−2.00 (1H, m, C(5)H_B), 2.05 (1H, app t, *J* 9.8, C(2)H_A), 2.15 (1H, app td, *J* 11.0, 2.7, C(6)H_A), 2.25 (2H, br s, O*H*), 2.72−2.80 (1H, m, C(6)H_B), 2.95 (1H, dd, *J* 11.0, 2.7, C(2)H_B), 3.44−3.51 (1H, m, C(4)*H*), 3.52−3.60 (3H, m, C(3)*H*, NCH_2Ph), 7.25−7.35 (5H, m, *Ph*).

***(RS,RS)*-*N*(1)-Benzyl-3,4-dihydroxy-3,4-*O*-carbonylpiperidine 37.** CDI (156 mg, 0.96 mmol) and DMAP (12 mg, 98 μmol) were added to a stirred solution of **36** (100 mg, 0.48 mmol, >99:1 dr) in THF (4 mL), and the resultant mixture was allowed to stir at rt for 4 days. NH_4Cl (1 mL) was added, and the reaction mixture was extracted with EtOAc (2 × 10 mL). The combined organic extracts were then washed with brine (10 mL), dried, and concentrated in vacuo to give **37** as a yellow oil (129 mg, >99:1 dr);[37] ν_{max} (ATR) 2925 (C−H), 1815 (C═O); δ_H (400 MHz, $CDCl_3$) 1.91−2.02 (1H, m, C(5)H_A), 2.25−2.40 (3H, m, C(2)H_A, C(5)H_B, C(6)H_A), 2.92−2.97 (1H, m, C(6)H_B), 3.27 (1H, dd, *J* 12.5, 4.7, C(2)H_B), 3.63 (2H, s, NCH_2Ph), 5.08−5.15 (1H, m, C(4)*H*), 5.30 (1H, td, *J* 9.3, 4.7, C(3)*H*), 7.27−7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 29.1 (*C*(5)), 50.1 (*C*(6)), 54.4 (*C*(2)), 61.8 (NCH_2Ph), 74.5 (*C*(3)), 76.5 (*C*(4)), 128.5, 128.8, 130.9 (*o,m,p-Ph*), 137.1 (*i-Ph*), 147.9 (*CO*); *m/z* (ESI$^+$) 208 ([(M−CO)+3H]$^+$, 100%); HRMS (TOF MS EI$^+$) $C_{13}H_{15}NO_3^+$ (M$^+$) requires 233.1052; found 233.1052.

***(RS,SR)*-*N*(1)-Benzyl-3-iodopiperidin-4-ol 38.** I_2 (398 mg, 1.57 mmol) and $NaHCO_3$ (132 mg, 1.57 mmol) were added to a stirred solution of **19** (100 mg, 0.52 mmol) in MeCN (4 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL) and washed with satd aq $Na_2S_2O_3$ (15 mL); then the organic layer was dried and concentrated in vacuo to give a 70:30 mixture of **38** and **39**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 2:1) gave **38** as a brown solid (40 mg, 24%, >99:1 dr); mp 103−105 °C; ν_{max} (ATR) 3350 (O−H), 2945 (C−H); δ_H (400 MHz, $CDCl_3$) 1.93−2.00 (1H, m, C(5)H_A), 2.08 (1H, app br s, C(5)H_B), 2.51 (1H, app br s, C(6)H_A), 2.60−2.78 (2H, m, C(2)H_A, C(6)H_B), 2.92 (1H, app t, *J* 10.0, C(2)H_B), 3.53 (1H, d, *J* 13.2, NC$H_A$$H_B$Ph), 3.61 (1H, d, *J* 13.2, NC$H_A$$H_B$Ph), 4.57 (1H, dt, *J* 8.5, 3.2, C(3)*H*), 7.24−7.36 (5H, m, *Ph*);[38] δ_H (400 MHz, PhMe-d_8, 363 K) 1.50−1.59 (1H, m, C(5)H_A), 1.66−1.73 (1H, m, C(5)H_B), 2.14−2.21 (1H, m, C(6)H_A), 2.41−2.48 (2H, m, C(2)H_A, C(6)H_B), 2.78 (1H, dd, *J* 11.7, 8.8, C(2)H_B), 3.07 (1H, app br s, C(4)*H*), 3.22 (1H, d, *J* 13.2, NC$H_A$$H_B$Ph), 3.31 (1H, d, *J* 13.2, NC$H_A$$H_B$Ph), 4.20 (1H, dt, *J* 8.8, 3.0, C(3)*H*), 7.00−7.24 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 31.9 (*C*(5)), 39.9 (*C*(3)), 48.3 (*C*(6)), 57.4 (*C*(2)), 62.1 (NCH_2Ph), 68.7 (*C*(4)), 127.3, 128.4, 129.0 (*o,m,p-Ph*), 137.7 (*i-Ph*);[39] δ_C (100 MHz, PhMe-d_8, 363 K) 32.0 (*C*(5)), 39.7 (*C*(3)), 48.0 (*C*(6)), 57.7 (*C*(2)), 61.8 (NCH_2Ph), 68.4 (*C*(4)), 124.4, 124.6, 124.8 (*o,m,p-Ph*), 137.1 (*i-Ph*); *m/z* (ESI$^+$) 318 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{17}INO^+$ ([M + H]$^+$) requires 318.0349; found 318.0349. Further elution gave a 30:70 mixture of **38** and **39**, respectively, as a yellow oil (19 mg, 12%). Data for mixture: ν_{max} (ATR) 3350 (O−H), 2945 (C−H); *m/z* (ESI$^+$) 318 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{17}INO^+$ ([M + H]$^+$) requires 318.0349; found 318.0347. Data for **39**: δ_H (400 MHz, $CDCl_3$) 1.71 (1H, dtd, *J* 12.6, 10.8, 4.3, C(5)H_A), 2.05 (1H, ddt, *J* 12.6, 4.3, 2.7, C(5)H_B), 2.21 (1H, app td, *J* 12.6, 2.7, C(6)H_A), 2.56 (1H, t, *J* 11.5, C(2)H_A), 2.93−2.99 (1H, m, C(6)H_B), 3.28 (1H, app dq, *J* 11.5, 2.2, C(2)H_B), 3.56 (2H, app d, *J* 1.7, NCH_2Ph), 3.64 (1H, app td, *J* 10.8, 4.3, C(4)*H*), 4.11 (1H, ddd, *J* 11.5, 9.8, 4.3, C(3)*H*), 7.25−7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 33.3 (*C*(5)), 38.4 (*C*(3)), 51.5 (*C*(6)), 61.4 (*C*(2)), 61.4 (NCH_2Ph), 75.2 (*C*(4)), 127.3 (*p-Ph*), 128.4, 128.9 (*o,m-Ph*), 137.8 (*i-Ph*).

***(RS,RS)*-*N*(1)-Benzyl-3-iodopiperidin-4-ol 39.** *Step 1.* I_2 (752 mg, 2.31 mmol) and $NaHCO_3$ (586 mg, 2.31 mmol) were added to a stirred solution of **19** (147 mg, 0.77 mmol) in MeCN (4 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL) and washed with satd aq $Na_2S_2O_3$ (15 mL); then the organic layer was dried and concentrated in vacuo to give a 70:30 mixture of **38** and **39**, respectively, as a yellow oil (205 mg).

Step 2. $NaHCO_3$ (586 mg, 2.31 mmol) was added to a stirred solution of the residue of **38** and **39** (70:30, 205 mg) in dioxane/H_2O (3:1, 4 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL), and the organic layer was washed with satd aq $NaHCO_3$ (15 mL), dried, and concentrated in vacuo to give a 70:30 mixture of **32** and **39**, respectively.

DOI: 10.1021/acs.joc.6b01107
J. Org. Chem. 2016, 81, 6481−6495

Purification via flash column chromatography (eluent 30−40 °C petrol/acetone, 5:1) gave **39** as a yellow oil (13 mg, 5%, >99:1 dr). Further elution gave **32** as a yellow oil (51 mg, 28%).

(1*RS*,4*SR*,5*SR*)-*N*(1)-Benzyl-4-hydroxy-1-azabicyclo[3.1.0]-hexanium Tetrafluoroborate 40. $AgBF_4$ (18 mg, 95 μmol) was added to a solution of **38** (25 mg, 78 μmol, >99:1 dr) in CD_2Cl_2, and the reaction mixture was shaken at rt for 5 min to give **40** (>99:1 dr); δ_H (400 MHz, CD_2Cl_2) 1.66−1.77 (1H, m, C(3)H_A), 2.42−2.47 (1H, m, C(3)H_B), 3.15 (1H, dd, *J* 7.7, 4.1, C(6)H_A), 3.18−3.22 (1H, m, C(6)H_B), 3.58 (1H, app d, *J* 12.6, C(2)H_A), 3.63 (1H, app d, *J* 12.6, C(2)H_B), 3.96 (1H, app dt, *J* 7.7, 5.5, C(5)*H*), 4.35 (1H, d, *J* 13.4, NC$H_A$$H_B$Ph), 4.58 (1H, d, *J* 13.4, NC$H_A$$H_B$Ph), 5.12 (1H, app td, *J* 8.2, 5.0, C(4)*H*), 7.19−7.52 (5H, m, *Ph*); δ_C (100 MHz, CD_2Cl_2) 28.6 (*C*(3)), 36.4 (*C*(6)), 52.0 (*C*(5)), 54.8 (*C*(2)), 62.6 (NCH_2Ph), 68.7 (*C*(4)), 130.3 (*p-Ph*), 128.9, 131.2 (*o,m-Ph*), 134.0 (*i-Ph*).

(1*RS*,4*RS*,5*SR*)-*N*(1)-Benzyl-4-hydroxy-1-azabicyclo[3.1.0]-hexanium Tetrafluoroborate 41. $AgBF_4$ (18 mg, 95 μmol) was added to a solution of **39** (25 mg, 78 μmol, >99:1 dr) in CD_2Cl_2, and the reaction mixture was shaken at rt for 5 min to give **41** (>99:1 dr); δ_H (400 MHz, CD_2Cl_2) 1.99−2.08 (1H, m, C(3)H_A), 2.17 (1H, app dd, *J* 15.3, 7.9, C(3)H_B), 2.83 (1H, dd, *J* 6.1, 4.9, C(6)H_A), 3.23 (1H, dd, *J* 8.1, 4.9, C(6)H_B), 3.49−3.57 (1H, m, C(2)H_A), 3.62−3.70 (1H, m, C(2)H_B), 3.92 (1H, app t, *J* 7.1, C(5)*H*), 4.48 (1H, d, *J* 13.4, NC$H_A$$H_B$Ph), 4.61 (1H, d, *J* 13.4, NC$H_A$$H_B$Ph), 4.70 (1H, app d, *J* 4.9, C(4)*H*), 7.25−7.51 (5H, m, *Ph*); δ_C (100 MHz, CD_2Cl_2) 30.8 (*C*(3)), 38.1 (*C*(6)), 53.7 (*C*(2)), 57.8 (*C*(5)), 62.4 (NCH_2Ph), 70.4 (*C*(4)), 128.9, 129.5, 130.2 (*o,m,p-Ph*), 131.2 (*i-Ph*).

(*RS*,*SR*)-*N*(1)-Benzyl-2-hydroxymethyl-3-hydroxypyrrolidine 42. $AgBF_4$ (18 mg, 95 μmol) was added to a solution of **39** (25 mg, 78 μmol, >99:1 dr) in CD_2Cl_2, and the reaction mixture was shaken at rt for 5 min. The reaction mixture was then poured into a stirred solution of $NaHCO_3$ (20 mg, 0.23 mmol) in dioxane/H_2O (3:1, 4 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (10 mL), and the organic layer was washed with satd aq $NaHCO_3$ (10 mL), dried, and concentrated in vacuo to give a 77:15:8 mixture of **42**, **36**, and **32**, respectively (6 mg). Data for **42**:[40] δ_H (400 MHz, $CDCl_3$) 1.71 (1H, ddt, *J* 13.4, 6.8, 1.9, C(4)H_A), 1.93−2.01 (1H, m, C(4)H_B), 2.61−2.66 (2H, m, C(2)*H*, C(5)H_A), 2.96−3.01 (1H, m, C(5)H_B), 3.53 (1H, d, *J* 12.9, NC$H_A$$H_B$Ph), 3.62−3.65 (2H, m, C(2)CH_2), 3.96 (1H, d, *J* 12.9, NC$H_A$$H_B$Ph), 4.34 (1H, app dt, *J* 6.8, 2.8, C(3)*H*), 7.25−7.40 (5H, m, *Ph*).

(*RS*,*SR*)-*N*(1)-Benzyl-3-mercapto-4-hydroxy-3,4-*S*,*O*-iminopiperidine 44 and (*RS*,*SR*)-(5-*N*-Benzyl)hexahydro-[1,3]oxathiino-[5,6-*b*]pyrrol-2-imine 45. AgSCN (44 mg, 0.26 mmol) was added to a stirred solution of **38** (70 mg, 0.22 mmol, >99:1 dr) in CH_2Cl_2 (4 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was filtrated through Celite (eluent CH_2Cl_2), and the resultant solution was washed with 2.0 M aq KOH (20 mL) and brine (20 mL), dried, and concentrated in vacuo to give a 85:15 mixture of **44** and **45**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 1:4) gave **45** as a yellow oil (4 mg, 4%, >99:1 dr); ν_{max} (ATR) 3437 (N−H), 1639 (C═N); δ_H (400 MHz, $CDCl_3$) 1.70−1.78 (1H, m, C(7)H_A), 2.19−2.31 (2H, m, C(6)H_A, C(7)H_B), 2.91 (1H, q, *J* 6.0, C(4a)*H*), 3.02−3.07 (1H, m, C(6)H_B), 3.24−3.27 (2H, m, C(4)H_2), 3.42 (1H, d, *J* 13.1, NC$H_A$$H_B$Ph), 3.97 (1H, d, *J* 13.1, NC$H_A$$H_B$Ph), 4.42−4.46 (1H, m, C(7a)*H*), 7.28−7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 33.4 (*C*(7)), 33.7 (*C*(4)), 51.3 (*C*(6)), 58.7 (NCH_2Ph), 66.2 (*C*(4a)), 72.4 (*C*(7a)), 113.6 (*C*(2)), 127.4, 128.5, 128.8 (*o,m,p-Ph*), 137.9 (*i-Ph*), 169.3 (SCN); *m*/*z* (ESI^+) 249 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{17}N_2OS^+$ ($[M + H]^+$) requires 249.1056; found 249.1054. Further elution gave **44** as a yellow oil (40 mg, 43%, >99:1 dr); ν_{max} (ATR) 3300 (N−H), 1639 (C═N); δ_H (400 MHz, $CDCl_3$) 1.94−2.02 (1H, m, C(5)H_A), 2.18−2.33 (3H, m, C(2)H_A, C(5)H_B, C(6)H_A), 2.67−2.73 (1H, m, C(6)H_B), 3.00 (1H, ddd, *J* 11.9, 5.8, 1.7, C(2)H_B), 3.50 (1H, d, *J* 13.1, NC$H_A$$H_B$Ph), 3.57 (1H, d, *J* 13.1, NC$H_A$$H_B$Ph), 3.67 (1H, ddd, *J* 10.8, 5.8, 4.1, C(3)*H*), 4.64−4.67 (1H, m, C(4)*H*), 7.26−7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9 (*C*(5)), 47.1 (*C*(3)), 47.5 (*C*(6)), 56.4 (*C*(2)), 62.5 (NCH_2Ph), 80.3 (*C*(4)), 127.3, 128.3, 129.0 (*o,m,p-Ph*), 137.6 (*i-Ph*), 169.1 (SCN); *m*/*z* (ESI^+) 249 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{17}N_2OS^+$ ($[M + H]^+$) requires 249.1056; found 249.1054.

(*RS*,*SR*)-*N*(1)-Benzyl-3-mercapto-4-hydroxy-3,4-*S*,*O*-carbonylpiperidine 46. A solution of **44** (33 mg, 0.13 mmol) in 1.0 M aq HCl (4 mL) was stirred at rt for 16 h before being concentrated in vacuo. The reaction mixture was then partitioned between H_2O (10 mL) and $CHCl_3$/^{i}PrOH (3:1, 10 mL). The aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1, 4 × 5 mL), and the combined organic extracts were washed with 2.0 M aq KOH, dried, and concentrated in vacuo to give **46** as a yellow oil (13 mg, 39%, >99:1 dr);[41] ν_{max} (ATR) 1732 (C═O); δ_H (400 MHz, $CDCl_3$) 1.96−2.06 (1H, m, C(5)H_A), 2.27−2.35 (3H, m, C(2)H_A, C(5)H_B, C(6)H_A), 2.68−2.73 (1H, m, C(6)H_B), 3.05 (1H, ddd, *J* 12.0, 5.7, 1.8, C(2)H_B), 3.51 (1H, d, *J* 13.1, NC$H_A$$H_B$Ph), 3.58 (1H, d, *J* 13.1, NC$H_A$$H_B$Ph), 3.78 (1H, ddd, *J* 10.6, 5.7, 4.4, C(3)*H*), 4.69−4.73 (1H, m, C(4)*H*), 7.27−7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.7 (*C*(5)), 46.5 (*C*(3)), 47.5 (*C*(6)), 56.7 (*C*(2)), 62.5 (NCH_2Ph), 78.6 (*C*(4)), 127.4 (*p-Ph*), 128.4, 128.9 (*o,m-Ph*), 137.5 (*i-Ph*), 172.5 (SCO); *m*/*z* (ESI^+) 250 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{16}NO_2S^+$ ($[M + H]^+$) requires 250.0896; found 250.0894.

(*RS*,*SR*)-*N*(1)-Benzyl-3-amino-4-hydroxy-3,4-*N*,*O*-carbonylpiperidine 47 and (*RS*,*RS*)-(5-*N*-Benzyl)hexahydropyrrolo[2,3-*e*][1,3]oxazin-2(3*H*)-one 48. AgOCN (50 mg, 0.33 mmol) was added to a stirred solution of **38** (88 mg, 0.28 mmol, >99:1 dr) in CH_2Cl_2 (4 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was filtrated through Celite (eluent CH_2Cl_2), and the resultant solution was washed with 2.0 M aq KOH (20 mL) and brine (20 mL), dried, and concentrated in vacuo to give an 85:15 mixture of **47** and **48**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc/Et_3N, 80:19:1) gave **47** as a yellow oil (34 mg, 53%, >99:1 dr); ν_{max} (ATR) 1749 (C═O); δ_H (400 MHz, $CDCl_3$) 2.00 (1H, ddd, *J* 15.5, 10.5, 5.2, C(5)H_A), 2.12−2.20 (2H, m, C(2)H_A, C(5)H_B), 2.37 (1H, td, *J* 10.5, 3.5, C(6)H_A), 2.58−2.64 (1H, m, C(6)H_B), 2.88 (1H, ddd, *J* 11.3, 5.8, 1.6, C(2)H_B), 3.50 (1H, d, *J* 13.2, NC$H_A$$H_B$Ph), 3.56 (1H, d, *J* 13.2, NC$H_A$$H_B$Ph), 3.77 (1H, dt, *J* 8.2, 5.8, C(3)*H*), 4.64 (1H, ddd, *J* 5.8, 4.7, 3.5, C(4)*H*), 5.41 (1H, br s, N*H*), 7.26−7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.9 (*C*(5)), 48.1 (*C*(6)), 51.1 (*C*(3)), 55.7 (*C*(2)), 62.4 (NCH_2Ph), 74.3 (*C*(4)), 127.3 (*p-Ph*), 128.4, 128.9 (*o,m-Ph*), 137.7 (*i-Ph*), 159.9 (NCO); *m*/*z* (ESI^+) 233 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{17}N_2O_2^+$ ($[M + H]^+$) requires 233.1285; found 233.1282. Further elution gave **48** as a yellow oil (5 mg, 7%, >99:1 dr); ν_{max} (ATR) 1756 (C═O); δ_H (400 MHz, $CDCl_3$) 2.00−2.09 (1H, m, C(7)H_A), 2.15−2.24 (1H, m, C(7)H_B), 2.30−2.37 (1H, m, C(6)H_A), 2.83−2.87 (1H, m, C(4a)*H*), 3.17 (1H, dd, *J* 8.5, 3.8, C(6)H_B), 3.25 (1H, ddd, *J* 12.7, 3.8, 3.2, C(4)H_A), 3.35 (1H, ddd, *J* 12.7, 5.3, 1.4, C(4)H_B), 3.52 (1H, d, *J* 13.4, NC$H_A$$H_B$Ph), 3.88 (1H, d, *J* 13.4, NC$H_A$$H_B$Ph), 4.82−4.88 (1H, m, C(7a)*H*), 5.44 (1H, br s, N*H*), 7.25−7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 31.4 (*C*(7)), 40.4 (*C*(4)), 51.5 (*C*(6)), 57.9 (NCH_2Ph), 59.9 (*C*(4a)), 80.7 (*C*(7a)), 127.3, 128.4, 128.4 (*o,m,p-Ph*), 138.4 (*i-Ph*), 154.4 (*C*(2)); *m*/*z* (ESI^+) 233 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{17}N_2O_2^+$ ($[M + H]^+$) requires 233.1285; found 233.1282.

(*RS*,*SR*)-*N*(1)-Benzyl-3-(*N*-benzoylamino)-4-hydroxy-3,4-*N*,*O*-carbonylpiperidine 55. BzNCO (10 μL, 78 μmol) was added dropwise to a stirred solution of **38** (25 mg, 78 μmol, >99:1 dr) in CH_2Cl_2 (2 mL) at rt, and the resultant mixture was stirred at rt for 5 min. $AgBF_4$ (18 mg, 94 μmol) was then added in one portion, and the reaction mixture was stirred at rt for 16 h before being filtrated through Celite (eluent CH_2Cl_2). The resultant solution was washed with 2.0 M aq KOH (10 mL) and brine (10 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 2:1) gave **55** as a yellow oil (6 mg, 23%, >99:1 dr); ν_{max} (ATR) 1786, 1680 (C═O); δ_H (400 MHz, $CDCl_3$) 2.04−2.11 (1H, m, C(5)H_A), 2.21 (1H, dq, *J* 15.1, 3.3, C(5)H_B), 2.33−2.41 (2H, m, C(2)H_A, C(6)H_A), 2.64 (1H, m, C(6)H_B), 3.50 (1H, d, *J* 13.1, NC$H_A$$H_B$Ph), 3.51−3.53 (1H, m, C(2)H_B), 3.66 (1H, d, *J* 13.1, NC$H_A$$H_B$Ph), 4.59 (1H, dt, *J* 8.2, 5.9, C(3)*H*), 4.73−4.77 (1H, m, C(4)*H*), 7.26−7.34 (5H, m, *Ph*), 7.42−7.45 (2H, m, *Ph*), 7.54−7.57 (1H, m, *Ph*), 7.63−7.65 (2H, m, *Ph*);

DOI: 10.1021/acs.joc.6b01107
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δ_C (100 MHz, $CDCl_3$) 26.8 (*C*(5)), 47.2 (*C*(6)), 53.7 (*C*(2)), 54.7 (*C*(3)), 62.4 (NCH_2Ph), 72.8 (*C*(4)), 127.3 (*p-Ph*), 127.9, 128.4, 128.9, 129.0 (*o,m-Ph*), 132.4 (*p-Ph*), 132.9, 137.6 (*i-Ph*), 153.3 (NCO), 169.6 (NCOPh); *m/z* (ESI^+) 337 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{21}N_2O_3^+$ ($[M + H]^+$) requires 337.1547; found 337.1537.

(*RS,SR*)-*N*(1)-Benzyl-3-(*N*-tosylamino)-4-hydroxy-3,4-*N,O*-carbonylpiperidine 56. *Method A (from 38).* TsNCO (22 μL, 145 μmol) was added dropwise to a stirred solution of **38** (46 mg, 145 μmol, >99:1 dr) in CH_2Cl_2 (2 mL) at rt, and the resultant mixture was stirred at rt for 5 min. $AgBF_4$ (37 mg, 188 μmol) was then added in one portion, and the reaction mixture was stirred at rt for 16 h and filtrated through Celite (eluent CH_2Cl_2). The resultant solution was washed with 2.0 M aq KOH (20 mL) and brine (20 mL), dried, and concentrated in vacuo to give **56** as a yellow solid (35 mg, 62%, >99:1 dr); mp 111−113 °C; ν_{max} (ATR) 1782 (C═O); δ_H (400 MHz, $CDCl_3$) 1.90−2.00 (1H, m, C(5)H_A), 2.05−2.18 (3H, m, C(2)H_A, C(5)H_B C(6)H_A), 2.47 (3H, s, Ar*Me*), 2.56−2.65 (1H, m, C(6)H_B), 3.31 (1H, ddd, *J* 11.6, 6.3, 1.8, C(2)H_B), 3.47 (1H, d, *J* 13.5, NCH_AH_BPh), 3.50 (1H, d, *J* 13.5, NCH_AH_BPh), 4.51 (1H, dt, *J* 9.1, 6.3, C(3)*H*), 4.60−4.64 (1H, m, C(4)*H*), 7.21−7.38 (7H, m, *Ar*, *Ph*), 7.92 (2H, d, *J* 8.4, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.7 (Ar*Me*), 26.5 (*C*(5)), 46.8 (*C*(6)), 54.5 (*C*(2)), 56.3 (*C*(3)), 62.4 (NCH_2Ph), 73.3 (*C*(4)), 127.5 (*p-Ph*), 128.4, 128.5, 128.9, 129.7 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 135.4 (*C*(1′)), 137.1 (*i-Ph*), 145.5 (*C*(4′)), 151.9 (NCO) *m/z* (ESI^+) 387 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{23}N_2O_4S^+$ ($[M + H]^+$) requires 387.1373; found 387.1373.

Method B (from 47). Step 1: AgOCN (28 mg, 0.19 mmol) was added to a stirred solution of **38** (50 mg, 0.16 mmol, >99:1 dr) in CH_2Cl_2 (2 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was filtrated through Celite (eluent CH_2Cl_2), and the resultant solution was washed with 2.0 M aq KOH (15 mL) and brine (15 mL), dried, and concentrated in vacuo to give an 85:15 mixture of **47** and **48**, respectively, as a yellow oil (33 mg).

Method B (from 47). Step 2: A solution of the residue of **47** and **48** (85:15, 33 mg) in THF (1 mL) and TsCl (39 mg, 0.20 mmol) was added to a stirred slurry of NaH (60% dispersion in mineral oil, 13 mg, 0.31 mmol) in THF/DMF (1:1, 2 mL) at 0 °C. The resultant mixture was allowed to warm to rt over 16 h. Saturated aq NH_4Cl (1 mL) was then added at −78 °C, and the reaction mixture was allowed to warm to rt. The resultant mixture was partitioned between H_2O (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL), and the combined organic extracts were then washed with satd aq $NaHCO_3$ (5 mL), dried, and concentrated in vacuo to give **56** as a yellow oil (40 mg, >99:1 dr).

(*RS,RS*)-*N*(1)-Benzyl-3-(*N*-tosylamino)-4-hydroxy-3,4-*N,O*-carbonylpiperidine 57. TsNCO (22 μL, 148 μmol) was added dropwise to a stirred solution of **39** (47 mg, 148 μmol, >99:1 dr) in CH_2Cl_2 (2 mL) at rt, and the resultant mixture was stirred at rt for 5 min. $AgBF_4$ (37 mg, 188 μmol) was then added in one portion, and the reaction mixture was stirred at rt for 16 h and then filtrated through Celite (eluent CH_2Cl_2). The resultant solution was washed with 2.0 M aq KOH (20 mL) and brine (20 mL), dried, and concentrated in vacuo to give **57** as a yellow oil (17 mg, 30%, >99:1 dr); ν_{max} (ATR) 1797 (C═O); δ_H (400 MHz, $CDCl_3$) 1.72 (1H, qd, *J* 11.5, 4.5, C(5)H_A), 1.96−2.02 (1H, m, C(5)H_B), 2.15 (1H, td, *J* 11.5, 2.6, C(6)H_A), 2.40 (3H, s, Ar*Me*), 2.47 (1H, t, *J* 11.5, C(2)H_A), 2.90−2.92 (1H, m, C(6)H_B), 3.48−3.57 (2H, m, C(3)*H*, NCH_AH_BPh), 3.68−3.75 (2H, m, C(2)H_B, NCH_AH_BPh), 3.82 (1H, td, *J* 11.5, 4.5, C(4)*H*), 7.10−7.32 (7H, m, *Ar*, *Ph*), 7.81 (2H, d, *J* 8.2, *Ar*); δ_C (100 MHz, $CDCl_3$) 22.7 (Ar*Me*), 27.9 (*C*(5)), 49.7 (*C*(6)), 55.4 (*C*(2)), 61.7 (NCH_2Ph), 62.4 (*C*(3)), 80.8 (*C*(4)), 126.2 (*p-Ph*), 127.5 (*C*(1′)), 128.4, 128.6, 129.9, 132.9 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 137.3 (*i-Ph*), 145.8 *C*(4′), 153.1 (NCO); *m/z* (ESI^+) 387 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{23}N_2O_4S^+$ ($[M + H]^+$) requires 387.1373; found 387.1374.

(*R,R,R,R*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(*N*-tosylamino)-4,5-*O,N*-carbonylpiperidine 60. *p*-TsNCO (6 μL, 39 μmol) was added dropwise to a stirred solution of **12** (20 mg, 32.8 μmol, >99:1 dr) in CH_2Cl_2 (2 mL) at rt, and the resultant mixture was stirred at rt for 5 min. $AgBF_4$ (6 mg, 32.8 μmol) was added in one portion, and the reaction mixture was stirred at rt for 16 h and then filtrated through Celite (eluent CH_2Cl_2). The resultant solution was washed with 2.0 M aq KOH (10 mL) and brine (10 mL), dried, and concentrated in vacuo to give a 55:40:5 mixture of **59**, **60**, and **61**, respectively, as a brown oil (35 mg). Data for **59**: ν_{max} (ATR) 1640 (C═N); δ_H (400 MHz, $CDCl_3$) 0.98−1.14 (21H, m, Si(C*HMe*$_2$)$_3$), 2.41 (3H, s, Ar*Me*), 2.86−2.94 (3H, m, C(2)*H*, C(6)H_2), 3.41 (1H, d, *J* 14.2, NCH_AH_BPh), 3.77−3.83 (1H, m, C(2)CH_AH_B), 3.90 (1H, dd, *J* 10.4, 4.1, C(2)CH_AH_B), 4.03 (1H, d, *J* 14.2, NCH_AH_BPh), 4.35−4.37 (1H, m, C(3)*H*), 4.49 (1H, d, *J* 11.8, OCH_AH_BPh), 4.72 (1H, d, *J* 11.8, OCH_AH_BPh), 4.93−4.95 (2H, m, C(4)*H*, C(5)*H*), 7.25−7.38 (12H, m, *Ar*, *Ph*), 7.89 (2H, d, *J* 8.5, *Ar*); *m/z* (ESI^+) 679 ($[M + H]^+$, 100%). Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 5:1) gave a 90:10 mixture of **60** and **61**, respectively, as a yellow oil (10 mg). Data for mixture: ν_{max} (ATR) 1788 (C═O). Data for **60**: δ_H (400 MHz, $CDCl_3$) 1.00−1.11 (21H, m, Si(C*HMe*$_2$)$_3$), 2.38 (3H, s, Ar*Me*), 2.94 (1H, app dd, *J* 9.5, 4.4, C(2)*H*), 3.06 (1H, dd, *J* 13.2, 2.2, C(6)H_A), 3.12 (1H, dd, *J* 13.2, 3.2, C(6)H_B), 3.50 (1H, app t, *J* 9.8, C(2)CH_AH_B), 3.57 (1H, d, *J* 14.3, NCH_AH_BPh), 3.69 (1H, dd, *J* 10.1, 4.4, C(2)CH_AH_B), 3.75 (1H, d, *J* 14.3, NCH_AH_BPh), 4.19 (1H, dd, *J* 3.9, 1.2, C(3)*H*), 4.46 (1H, d, *J* 11.7, OCH_AH_BPh), 4.59 (1H, app dt, *J* 8.8, 3.2, C(5)*H*), 4.65−4.70 (2H, m, C(4)*H*, OCH_AH_BPh), 7.12 (2H, dd, *J* 7.5, 1.8, *Ar*), 7.23−7.36 (10H, m, *Ph*), 7.87 (2H, d, *J* 7.5, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.8 (Si(CHMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 21.6 (Ar*Me*), 50.4 (*C*(6)), 55.9 (*C*(5)), 60.6 (NCH_2Ph), 62.7 (C(2)CH_2), 64.8 (*C*(2)), 71.8 (OCH_2Ph), 72.5 (*C*(3)), 72.9 (*C*(4)), 127.1, 127.9 (*p-Ph*), 127.6, 128.2, 128.3, 128.4, 128.5, 129.7 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 135.3 (*C*(1′)), 137.6, 137.9 (*i-Ph*), 145.3 (*C*(4′)), 151.8 (NCO); *m/z* (ESI^+) 679 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{37}H_{51}N_2O_6SSi^+$ ($[M + H]^+$) requires 679.3232; found 679.3218. Data for **61**: δ_H (400 MHz, $CDCl_3$) 0.99−1.09 (21H, m, Si(C*HMe*$_2$)$_3$), 1.40 (3H, d, *J* 6.8, C(*α*)*Me*), 2.43 (3H, s, Ar*Me*), 2.89 (1H, dd, *J* 13.4, 4.1, C(6)H_A), 3.15−3.19 (1H, m, C(2)*H*), 3.21 (1H, dd, *J* 13.4, 3.8, C(6)H_B), 3.64−3.67 (1H, m, C(2)CH_AH_B), 3.83 (1H, dd, *J* 10.1, 4.1, C(2)CH_AH_B), 4.03 (1H, q, *J* 6.8, C(*α*)*H*), 4.17−4.19 (1H, m, C(3)*H*), 4.45−4.49 (1H, m, C(5)*H*), 4.56−4.58 (1H, m, OCH_AH_BPh), 4.58−4.60 (1H, m, C(4)*H*), 4.69−4.71 (1H, m, OCH_AH_BPh), 7.11−7.13 (2H, m, *Ar*), 7.23−7.36 (10H, m, *Ph*), 7.86−7.88 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 9.5 (C(*α*)*Me*), 11.5 (Si(C*H*Me$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 21.6 (Ar*Me*), 44.1 (*C*(6)), 55.3 (*C*(5)), 58.6 (*C*(*α*)), 60.8 (*C*(2)), 62.9 (C(2)CH_2), 72.2 (OCH_2Ph), 73.1 (*C*(3)), 73.7 (*C*(4)), 127.0, 127.3 (*p-Ph*), 127.6, 128.1, 128.3, 128.4, 128.5, 129.8 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 135.1 (*C*(1′)), 137.6, 143.1 (*i-Ph*), 145.3 (*C*(4′)), 151.9 (NCO); *m/z* (ESI^+) 693 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{38}H_{53}N_2O_6SSi^+$ ($[M + H]^+$) requires 693.3388; found 693.3375. Further elution gave **16** as a colorless oil (8 mg, 48%, >99:1 dr);[15] $[\alpha]_D^{20}$ −32.6 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.02−1.15 (21H, m, Si(C*HMe*$_2$)$_3$), 2.83 (1H, dd, *J* 13.7, 1.0, C(6)H_A), 2.90 (1H, dd, *J* 13.7, 2.0, C(6)H_B), 2.98 (1H, app dd, *J* 9.2, 4.5, C(2)*H*), 3.43 (1H, d, *J* 14.2, NCH_AH_BPh), 3.71 (1H, app t, *J* 9.2, C(2)CH_AH_B), 3.91 (1H, dd, *J* 10.1, 4.5, C(2)CH_AH_B), 4.06 (1H, d, *J* 14.2, NCH_AH_BPh), 4.30 (1H, app d, *J* 3.6, C(3)*H*), 4.52 (1H, d, *J* 11.6, OCH_AH_BPh), 4.70−4.78 (2H, m, C(5)*H*, OCH_AH_BPh), 4.79−4.84 (1H, dd, *J* 8.3, 3.6, C(4)*H*), 7.23−7.40 (10H, m, *Ph*).

(*R,R,R,R*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(*N*-tosylamino)piperidine 64, (2*R*,3*R*,4*R*,5*S*)-*N*(1)-benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(*N*-tosylamino)piperidine 65, and (*R,R,R,R,R*)-*N*(1)-(*α*-methylbenzyl)-2-[(triisopropylsilyloxy)-methyl]-3-benzyloxy-4-hydroxy-5-(*N*-tosylamino)piperidine 66. *Step 1*. I_2 (363 mg, 1.43 mmol) and $NaHCO_3$ (120 mg, 1.43 mmol) were added to a stirred solution of **11**[15] (280 mg, 0.48 mmol, >99:1 dr) in MeCN (4 mL) at rt, and the resultant mixture was stirred at rt for 16 h. TsNCO (0.33 mL, 2.16 mmol) was added dropwise, and the reaction mixture was allowed to stir at rt for 16 h. The reaction mixture was diluted with Et_2O (20 mL), washed with satd aq $Na_2S_2O_3$ (20 mL), dried, and concentrated in vacuo to give a 76:19:5 mixture of **60**, **63**, and **61**, respectively (300 mg).

DOI: 10.1021/acs.joc.6b01107
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Step 2. K_2CO_3 (267 mg, 1.93 mmol) was added to a stirred solution of the residue of **60**, **63**, and **61** (57:14:4:25, 300 mg) in MeOH (5 mL) at rt, and the resultant mixture was allowed to stir at rt for 16 h. The resultant mixture was concentrated in vacuo, and the residue was partitioned between H_2O (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were then dried and concentrated in vacuo to give a 76:19:5 mixture of **64**, **65**, and **66**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/acetone, 9:1) gave **66** as a colorless oil (6 mg, 2% from **11**, >99:1 dr); $[\alpha]_D^{20}$ +5.0 (*c* 0.06 in $CHCl_3$); ν_{max} (ATR) 3532, 3276 (O−H, N−H), 2942, 2865 (C−H), 1160, 1092 (S═O); δ_H (400 MHz, $CDCl_3$) 1.03−1.12 (21H, m, Si(C*H*Me$_2$)$_3$), 1.22 (3H, d, *J* 6.8, C(α)*Me*), 1.96 (1H, dd, *J* 12.3, 4.3, C(6)H_A), 2.16 (1H, dd, *J* 12.3, 1.6, C(6)H_B), 2.37 (3H, s, Ar*Me*), 2.59 (1H, ddd, *J* 8.8, 4.5, 1.3, C(2)*H*), 2.97 (1H, d, *J* 8.8, O*H*), 3.03−3.07 (1H, m, C(5)*H*), 3.31 (1H, app t, *J* 8.8, C(3)*H*), 3.54 (1H, app td, *J* 8.8, 3.9, C(4)*H*), 3.99 (1H, dd, *J* 11.0, 4.5, C(2)CH_AH$_B$), 4.16 (1H, dd, *J* 11.0, 1.3, C(2)CH$_A$H$_B$), 4.60 (1H, d, *J* 11.0, OCH_AH$_B$Ph), 4.65 (1H, q, *J* 6.8, C(α)*H*), 5.07−5.13 (2H, m, OCH$_A$H$_B$Ph, N*H*), 6.97−6.99 (2H, m, *Ar*), 7.02−7.05 (2H, m, *Ar*), 7.27−7.43 (8H, m, *Ph*), 7.48−7.51 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.6 (C(α)*Me*), 11.9 (Si(CHMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 21.5 (Ar*Me*), 46.1 (*C*(6)), 52.4 (*C*(5)), 54.8 (*C*(α)), 63.3 (C(2)CH_2), 64.6 (*C*(2)), 74.7 (OCH$_2$Ph), 75.1 (*C*(4)), 78.9 (*C*(3)), 127.6, 127.6 (*p-Ph*), 127.1, 127.9, 128.1, 128.3, 128.7, 129.6 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 135.7 (*C*(1′)), 138.6 (*i-Ph*), 143.2 (*C*(4′)), 144.2 (*i-Ph*); *m/z* (ESI$^+$) 667 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{37}H_{55}N_2O_5SSi^+$ ([M + H]$^+$) requires 667.3595; found 667.3571. Further elution gave **64** as a colorless oil(78 mg, 25% from **11**, >99:1 dr); $[\alpha]_D^{20}$ −16.2 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3532, 3276 (O−H, N−H), 2942, 2891 (C−H), 1160, 1091 (S═O); δ_H (400 MHz, $CDCl_3$) 1.02−1.13 (21H, m, Si(C*H*Me$_2$)$_3$), 2.08 (1H, dd, *J* 12.3, 2.4, C(6)H_A), 2.32 (1H, dd, *J* 12.3, 5.3, C(6)H_B), 2.36 (3H, s, Ar*Me*), 2.37−2.41 (1H, m, C(2)*H*), 3.12−3.16 (2H, m, O*H*, NCH_AH$_B$Ph), 3.27−3.32 (1H, m, C(5)*H*), 3.39 (1H, app t, *J* 8.0, C(3)*H*), 3.57 (1H, app td, *J* 8.0, 3.9, C(4)*H*), 3.88 (1H, dd, *J* 11.0, 4.4, C(2)CH_AH$_B$), 4.15 (1H, dd, *J* 11.0, 1.9, C(2)CH$_A$H$_B$), 4.39 (1H, d, *J* 13.2, NCH_AH$_B$Ph), 4.57 (1H, d, *J* 11.2, OCH_AH$_B$Ph), 4.97 (1H, d, *J* 11.2, OCH$_A$H$_B$Ph), 5.22 (1H, d, *J* 8.4, N*H*), 7.05 (2H, d, *J* 8.0, *Ar*), 7.26−7.42 (12H, m, *Ar*, *Ph*); δ_H (400 MHz, MeOH-d_4) 0.96−1.02 (21H, m, Si(C*H*Me$_2$)$_3$), 2.16 (1H, dd, *J* 12.5, 4.3, C(6)H_A), 2.35 (3H, s, Ar*Me*), 2.67 (1H, dd, *J* 12.5, 9.5, C(6)H_B), 2.75−2.78 (1H, m, C(2)*H*), 3.44−3.49 (1H, m, C(5)*H*), 3.60 (1H, d, *J* 13.7, NCH_AH$_B$Ph), 3.64 (1H, app t, *J* 4.0, C(3)*H*), 3.75 (1H, app t, *J* 4.0, C(4)*H*), 3.92 (1H, dd, *J* 10.1, 6.0, C(2)CH_AH$_B$), 3.99 (1H, dd, *J* 10.1, 5.8, C(2)CH$_A$H$_B$), 4.02 (1H, d, *J* 13.7, NCH$_A$H$_B$Ph), 4.47 (1H, d, *J* 12.0, OCH_AH$_B$Ph), 4.58 (1H, d, *J* 12.0, OCH$_A$H$_B$Ph), 7.12 (2H, d, *J* 8.0, *Ar*), 7.18−7.32 (10H, m, *Ph*), 7.62 (2H, d, *J* 8.0, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(CHMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 21.5 (Ar*Me*), 51.8 (*C*(6)), 52.0 (*C*(5)), 57.2 (NCH$_2$Ph), 63.0 (C(2)CH_2), 65.9 (*C*(2)), 73.6 (*C*(4)), 74.2 (OCH$_2$Ph), 78.7 (*C*(3)), 127.3, 127.6 (*p-Ph*), 127.0, 127.9, 128.3, 128.6, 129.1, 129.6 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 136.3 (*C*(1′)), 138.4, 139.3 (*i-Ph*), 143.2 (*C*(4′)); δ_C (100 MHz, MeOH-d_4) 13.3 (Si(CHMe$_2$)$_3$), 18.7 (Si(CH*Me*$_2$)$_3$), 21.6 (Ar*Me*), 51.3 (*C*(6)), 51.8 (*C*(5)), 60.6 (NCH$_2$Ph), 63.3 (C(2)CH_2), 64.1 (*C*(2)), 73.0 (*C*(4)), 73.3 (OCH$_2$Ph), 79.0 (*C*(3)), 127.8, 128.6 (*p-Ph*), 128.0, 128.9, 129.2, 129.4, 130.1, 130.1 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 140.4, 141.4 (*i-Ph*), 141.7 (*C*(4′)), 144.3 (*C*(1′)); *m/z* (ESI$^+$) 653 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{53}N_2O_5SSi^+$ ([M + H]$^+$) requires 653.3439; found 653.3411. Further elution gave **65** as a colorless oil (22 mg, 7% from **11**, >99:1 dr); $[\alpha]_D^{20}$ −5.6 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3532, 3276 (O−H, N−H), 2926, 2865 (C−H), 1094, 1158 (S═O); δ_H (400 MHz, $CDCl_3$) 1.01−1.08 (21H, m, Si(C*H*Me$_2$)$_3$), 2.12 (1H, dd, *J* 12.1, 6.6, C(6)H_A), 2.39 (3H, s, Ar*Me*), 2.70 (1H, app q, *J* 4.0, C(2)*H*), 3.04 (1H, dd, *J* 12.1, 3.5, C(6)H_B), 3.25−3.30 (1H, m, C(5)*H*), 3.43−3.56 (4H, m, C(3)*H*, C(4)*H*, NCH_AH$_B$Ph, O*H*), 3.76 (1H, dd, *J* 11.0, 4.0, C(2)CH_AH$_B$), 4.01 (1H, d, *J* 13.7, NCH$_A$H$_B$Ph), 4.16 (1H, dd, *J* 11.0, 3.2, C(2)CH$_A$H$_B$), 4.56 (1H, d, *J* 11.5, OCH_AH$_B$Ph), 4.66 (1H, d, *J* 11.5, OCH$_A$H$_B$Ph), 5.35 (1H, d, *J* 8.2, N*H*), 7.13−7.15 (2H, m, *Ar*), 7.25−7.38 (10H, m, *Ph*), 7.54−7.58 (2H, m, *Ar*); δ_H (400 MHz, MeOH-d_4) 0.95−1.02 (21H, m, Si(C*H*Me$_2$)$_3$), 1.71 (1H, app t, *J* 11.2, C(6)H_A), 2.30 (1H, app dd, *J* 9.8, 5.2, C(2)*H*), 2.45 (1H, dd, *J* 11.2, 4.5, C(6)H_B), 2.81 (1H, app dd, *J* 9.8, 4.5, C(5)*H*), 3.07 (1H, d, *J* 13.6, NCH_AH$_B$Ph), 3.20 (1H, app t, *J* 9.8, C(3)*H*), 3.39 (1H, app t, *J* 9.8, C(4)*H*), 3.85 (1H, dd, *J* 11.2, 5.2, C(2)CH_AH$_B$), 4.17 (1H, app d, *J* 9.8, C(2)CH$_A$H$_B$), 4.38 (1H, d, *J* 13.6, NCH$_A$H$_B$Ph), 4.58 (1H, d, *J* 12.0, OCH_AH$_B$Ph), 5.08 (1H, d, *J* 12.0, OCH$_A$H$_B$Ph), 7.00 (2H, d, *J* 8.0, *Ar*), 7.18−7.37 (10H, m, *Ph*), 7.50 (2H, d, *J* 8.0, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.8 (Si(CHMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 21.5 (Ar*Me*), 50.9 (*C*(6)), 53.9 (*C*(5)), 57.5 (NCH$_2$Ph), 61.9 (C(2)CH_2), 63.0 (*C*(2)), 71.7 (*C*(4)), 73.1 (OCH$_2$Ph), 79.5 (*C*(3)), 127.0, 127.8 (*p-Ph*), 126.9, 127.7, 128.3, 128.5, 128.5, 129.6 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 137.7 (*C*(1′)), 138.0, 138.7 (*i-Ph*), 143.1 (*C*(4′)); δ_C (100 MHz, MeOH-d_4) 13.3 (Si(CHMe$_2$)$_3$), 18.7 (Si(CH*Me*$_2$)$_3$), 21.6 (Ar*Me*), 57.0 (*C*(5)), 57.9 (*C*(6)), 59.0 (NCH$_2$Ph), 65.2 (C(2)CH_2), 69.8 (*C*(2)), 75.7 (OCH$_2$Ph), 81.4 (*C*(3)), 81.8 (*C*(4)), 127.8, 128.6 (*p-Ph*), 128.0, 128.9, 129.2, 129.4, 130.1, 130.1 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 140.4, 141.4 (*i-Ph*), 141.7 (*C*(4′)), 144.3 (*C*(1′)); *m/z* (ESI$^+$) 653 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{53}N_2O_5SSi^+$ ([M + H]$^+$) requires 653.3439; found 653.3413.

(2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(*N*-tosylamino)-4,5-*O*,*N*-carbonylpiperidine 68. I_2 (129 mg, 0.51 mmol) and $NaHCO_3$ (43 mg, 0.51 mmol) were added to a stirred solution of **67**[15] (100 mg, 0.17 mmol, >99:1 dr) in MeCN (2 mL) at rt, and the resultant mixture was stirred at rt for 16 h. TsNCO (0.12 mL, 0.77 mmol) was added dropwise, and the reaction mixture was allowed to stir at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL), washed with satd aq $Na_2S_2O_3$ (15 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 9:1) gave **68** as a yellow oil (56 mg, 48%, >99:1 dr); $[\alpha]_D^{20}$ +14.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2942, 2865 (C−H), 1785 (C═O), 1173, 1100 (S═O); δ_H (400 MHz, $CDCl_3$) 1.02−1.11 (21H, m, Si(C*H*Me$_2$)$_3$), 2.36 (3H, s, Ar*Me*), 2.94 (1H, app quintet, *J* 3.2, C(2)*H*), 3.10 (1H, dd, *J* 12.0, 7.1, C(6)H_A), 3.43 (1H, dd, *J* 12.0, 6.0, C(6)H_B), 3.60−3.66 (2H, m, NCH_AH$_B$Ph, C(2)CH_AH$_B$), 3.70−3.73 (2H, m, NCH$_A$H$_B$Ph, C(2)CH$_A$H$_B$), 4.12 (1H, app t, *J* 3.2, C(3)*H*), 4.51 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.54−4.58 (2H, m, C(5)*H*, OCH$_A$H$_B$Ph), 4.84 (1H, dd, *J* 9.1, 3.2, C(4)*H*), 7.16−7.20 (6H, m, *Ar*, *Ph*), 7.25−7.33 (6H, m, *Ph*), 7.87 (2H, dd, *J* 8.4, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.8 (Si(CHMe$_2$)$_3$), 18.1 (Si(CH*Me*$_2$)$_3$), 21.6 (Ar*Me*), 50.6 (*C*(6)), 55.6 (*C*(5)), 58.8 (NCH$_2$Ph), 61.4 (*C*(2)), 61.8 (C(2)CH_2), 72.0 (*C*(4)), 72.5 (OCH$_2$Ph), 74.5 (*C*(3)), 127.3, 127.6 (*p-Ph*), 127.6, 128.1, 128.3, 128.3, 128.4, 129.6 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 135.2 (*C*(1′)), 137.5, 137.9 (*i-Ph*), 145.1 (*C*(4′)), 152.5 (NCO); *m/z* (ESI$^+$) 679 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{37}H_{51}N_2O_6SSi^+$ ([M + H]$^+$) requires 679.3232; found 679.3219.

(2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(*N*-tosylamino)piperidine 69. K_2CO_3 (175 mg, 1.26 mmol) was added to a stirred solution of **68** (85 mg, 0.12 mmol, >99:1 dr) in MeOH (4 mL) at rt, and the resultant mixture was allowed to stir at rt for 16 h. The reaction mixture was then concentrated in vacuo, and the residue was partitioned between H_2O (15 mL) and EtOAc (15 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were then dried and concentrated in vacuo to give **69** as a white solid (68 mg, 83%, >99:1 dr); mp 88−90 °C; $[\alpha]_D^{20}$ +6.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3532, 3276 (O−H, N−H), 2942, 2865 (C−H), 1169, 1160, 1091 (S═O); δ_H (400 MHz, $CDCl_3$) 0.99−1.09 (21H, m, Si(C*H*Me$_2$)$_3$), 2.27 (1H, dd, *J* 12.0, 5.8, C(6)H_A), 2.36 (3H, s, Ar*Me*), 2.60 (1H, d, *J* 7.6, O*H*), 2.62 (1H, dd, *J* 12.0, 2.8, C(6)H_B), 2.89−2.92 (1H, m, C(2)*H*), 3.51−3.57 (2H, m, C(5)*H*, NCH_AH$_B$Ph), 3.67 (1H, app t, *J* 4.0, C(3)*H*), 3.80−3.86 (2H, m, NCH$_A$H$_B$Ph, C(2)CH_AH$_B$), 3.87−3.91 (2H, m, C(2)CH$_A$H$_B$, C(4)*H*), 4.46 (1H, d, *J* 11.5, OCH_AH$_B$Ph), 4.51 (1H, d, *J* 11.5, OCH$_A$H$_B$Ph), 5.63 (1H, d, *J* 9.9, N*H*), 7.10 (2H, d, *J* 8.0, *Ar*), 7.24−7.39 (10H, m, *Ph*), 7.53 (2H, d, *J* 8.0, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.8 (Si(CHMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 21.5 (Ar*Me*), 50.2 (*C*(6)), 53.0 (*C*(5)), 57.6 (NCH$_2$Ph), 59.5 (C(2)CH_2), 60.4 (*C*(2)), 66.2 (*C*(4)),

DOI: 10.1021/acs.joc.6b01107
J. Org. Chem. 2016, 81, 6481−6495

72.0 (OCH_2Ph), 77.6 (*C*(3)), 127.1, 128.0 (*p-Ph*), 126.6, 127.7, 128.3, 128.5, 128.6, 129.5 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 137.6 (*i-Ph*), 138.5 (*C*(1′)), 139.0 (*i-Ph*), 142.8 (*C*(4′)); *m/z* (ESI^+) 653 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{36}H_{53}N_2O_5SSi^+$ ($[M + H]^+$) requires 653.3439; found 653.3436.

(*R,R,R,R*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3,4-dihydroxy-5-aminopiperidine 70 and (*R,R,R,R*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3,4-dihydroxy-5-(*N*-tosylamino)-piperidine 71. Naphthalene (346 mg, 2.70 mmol) was dissolved in DME (3 mL), then Na (46 mg, 2.02 mmol) was added under nitrogen, and the resultant green solution was stirred at rt for 2 h. A solution of **64** (60 mg, 92 μmol, >99:1 dr) in DME (3 mL) was added via cannula at −78 °C;then the resultant mixture was allowed to warm gradually to rt and stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C, and H_2O (1 mL) was added. The reaction mixture was then allowed to warm to rt, and Et_2O (15 mL) was added. The organic layer was washed with satd aq NH_4Cl (15 mL) and brine (15 mL) before being dried and concentrated in vacuo to give a 95:5 mixture of **70** and **71**, respectively. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH/NH_4OH, 95:4:1) gave **71** as a colorless oil (2 mg, 4%, >99:1 dr); $[\alpha]_D^{20}$ −44.0 (*c* 0.2 in $CHCl_3$); ν_{max} (ATR) 3322 (O−H, N−H), 2940, 2865 (C−H), 1160, 1094, 1070 (S═O); δ_H (400 MHz, MeOH-d_4) 1.08−1.15 (21H, m, Si(C*H*Me$_2$)$_3$), 1.96 (1H, dd, *J* 12.0, 1.9, C(6)H_A), 2.21 (1H, dd, *J* 12.0, 4.6, C(6)H_B), 2.32−2.36 (1H, m, C(2)*H*), 2.34 (3H, s, Ar*Me*), 3.18 (1H, d, *J* 13.4, NCH_AH_BPh), 3.37−3.40 (2H, m, C(4)*H*, C(5)*H*), 3.52−3.55 (1H, m, C(3)*H*), 4.10 (1H, dd, *J* 11.0, 4.7, C(2)CH_AH_B), 4.19 (1H, dd, *J* 11.0, 2.7, C(2)CH_AH_B), 4.23 (1H, d, *J* 13.4, NCH_AH_BPh), 7.09 (2H, d, *J* 8.0, *Ar*), 7.24−7.40 (7H, m, *Ar*, *Ph*); δ_C (100 MHz, MeOH-d_4) 13.3 (Si(CHMe$_2$)$_3$), 18.7 (Si(CH*Me*$_2$)$_3$), 21.6 (Ar*Me*), 52.2 (*C*(6)), 53.6 (*C*(5)), 58.8 (NCH_2Ph), 63.0 (C(2)CH_2), 69.4 (*C*(2)), 70.9 (*C*(3)), 74.7 (*C*(4)), 128.3 (*p-Ph*), 128.0, 129.7, 130.1, 130.8 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 139.1 (*C*(1′)), 141.0 (*i-Ph*), 144.5 (*C*(4′)); *m/z* (ESI^+) 563 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{47}N_2O_5SSi^+$ ($[M + H]^+$) requires 563.2969; found 563.2954. Further elution gave **70** as a colorless oil (23 mg, 63%, >99:1 dr); $[\alpha]_D^{20}$ −28.4 (*c* 0.5 in MeOH); ν_{max} (ATR) 3360 (O−H, N−H), 2942, 2865 (C−H); δ_H (400 MHz, MeOH-d_4) 1.10−1.17 (21H, m, Si(C*H*Me$_2$)$_3$), 2.19−2.24 (2H, m, C(6)H_A, C(2)*H*), 2.77 (1H, dd, *J* 12.0, 3.6, C(6)H_B), 2.79−2.83 (1H, m, C(5)*H*), 3.17 (1H, d, *J* 13.4, NCH_AH_BPh), 3.41 (1H, dd, *J* 8.9, 4.0, C(4)*H*), 3.53 (1H, app t, *J* 8.9, C(3)*H*), 4.11 (1H, dd, *J* 11.0, 4.3, C(2)CH_AH_B), 4.28 (1H, dd, *J* 11.0, 2.1, C(2)CH_AH_B), 4.47 (1H, d, *J* 13.4, NCH_AH_BPh), 7.20−7.36 (5H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 13.4 (Si(CHMe$_2$)$_3$), 18.7 (Si(CH*Me*$_2$)$_3$), 51.6 (*C*(5)), 55.1 (*C*(6)), 58.7 (NCH_2Ph), 63.4 (C(2)CH_2), 70.2 (*C*(3)), 70.3 (*C*(2)), 76.7 (*C*(4)), 128.1 (*p-Ph*), 129.5, 130.1 (*o,m-Ph*), 141.2 (*i-Ph*); *m/z* (ESI^+) 409 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{41}N_2O_3Si^+$ ($[M + H]^+$) requires 409.2881; found 409.2872.

(2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3,4-dihydroxy-5-aminopiperidine 72 and (2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3,4-dihydroxy-5-(*N*-tosylamino)piperidine 73. Naphthalene (461 mg, 3.60 mmol) was dissolved in DME (3 mL), then Na (62 mg, 2.70 mmol) was added under nitrogen, and the resultant green solution was stirred at rt for 2 h. A solution of **69** (79 mg, 0.12 mmol, >99:1 dr) in DME (3 mL) was added via cannula at −78 °C, and the resultant mixture was allowed to warm gradually to rt and stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C, and H_2O (1 mL) was added. The reaction mixture was then allowed to warm to rt, and Et_2O (15 mL) was added. The organic layer was washed with satd aq NH_4Cl (15 mL) and brine (15 mL) before being dried and concentrated in vacuo. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH/NH_4OH, 95:4:1) gave **73** as a colorless oil (4 mg, 6%, >99:1 dr); $[\alpha]_D^{20}$ −7.1 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3463 (O−H, N−H), 2942, 2866 (C−H), 1159, 1092, 1058 (S═O); δ_H (400 MHz, $CDCl_3$) 0.99−1.12 (21H, m, Si(C*H*Me$_2$)$_3$), 2.35 (1H, dd, *J* 11.2, 10.2, C(6)H_A), 2.39 (3H, s, Ar*Me*), 2.58 (1H, dd, *J* 11.2, 4.5, C(6)H_B), 2.69 (1H, app td, *J* 7.8, 4.3, C(2)*H*), 2.73 (1H, br s, O*H*), 3.40 (1H, d, *J* 14.0, NCH_AH_BPh), 3.45−3.51 (1H, m, C(5)*H*), 3.68−3.77 (4H, m, NCH_AH_BPh, C(2)CH_AH_B, C(3)*H*, C(4)*H*), 4.15 (1H, dd, *J* 9.9, 4.3, C(2)CH_AH_B), 4.49 (1H, br s, O*H*), 5.27 (1H, br s, N*H*), 7.16 (2H, d, *J* 8.0, *Ar*), 7.20−7.22 (2H, m, *Ph*), 7.25−7.33 (3H, m, *Ph*), 7.62 (2H, d, *J* 8.0, *Ar*); δ_H (400 MHz, MeOH-d_4) 1.05−1.12 (21H, m, Si(C*H*Me$_2$)$_3$), 2.11 (1H, app t, *J* 11.0, C(6)H_A), 2.16−2.19 (1H, m, C(6)H_B), 2.37 (3H, s, Ar*Me*), 2.45−2.50 (1H, m, C(2)*H*), 3.13 (1H, d, *J* 13.7, NCH_AH_BPh), 3.25 (1H, ddd, *J* 11.0, 4.7, 2.7, C(5)*H*), 3.42 (1H, dd, *J* 9.5, 3.1, C(3)*H*), 3.78 (1H, app t, *J* 3.1, C(4)*H*), 3.96 (1H, dd, *J* 11.0, 4.7, C(2)CH_AH_B), 4.23 (1H, dd, *J* 11.0, 2.1, C(2)CH_AH_B), 4.31 (1H, d, *J* 13.7, NCH_AH_BPh), 7.13−7.25 (7H, m, *Ar*, *Ph*), 7.53−7.58 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.6 (Si(CHMe$_2$)$_3$), 17.6 (Si(CH*Me*$_2$)$_3$), 21.6 (Ar*Me*), 51.2 (*C*(6)), 51.6 (*C*(5)), 57.7 (NCH_2Ph), 60.3 (*C*(2)), 66.0 (C(2)CH_2), 68.6 (*C*(3)), 73.6 (*C*(4)), 127.1 (*p-Ph*), 126.7, 128.1, 128.4, 129.7 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 138.2 (*C*(1′)), 138.8 (*i-Ph*), 143.2 (*C*(4′)); δ_C (100 MHz, MeOH-d_4) 13.3 (Si(CHMe$_2$)$_3$), 18.7 (Si(CH*Me*$_2$)$_3$), 21.7 (Ar*Me*), 50.9 (*C*(6)), 53.7 (*C*(5)), 58.6 (NCH_2Ph), 64.3 (C(2)CH_2), 64.5 (*C*(2)), 70.3 (*C*(3)), 72.1 (*C*(4)), 128.0 (*p-Ph*), 127.8, 129.4, 130.0, 130.8 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 140.2 (*C*(1′)), 140.6 (*i-Ph*), 144.4 (*C*(4′)); *m/z* (ESI^+) 563 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{47}N_2O_5SSi^+$ ($[M + H]^+$) requires 563.2969; found 563.2955. Further elution gave **72** as a colorless oil (30 mg, 61%, >99:1 dr); $[\alpha]_D^{20}$ −14.7 (*c* 0.3 in MeOH); ν_{max} (ATR) 3337 (O−H, N−H), 2942, 2866 (C−H); δ_H (400 MHz, MeOH-d_4) 1.09−1.14 (21H, m, Si(C*H*Me$_2$)$_3$), 2.53 (1H, dd, *J* 11.9, 7.5, C(6)H_A), 2.83−2.89 (2H, m, C(2)*H*, C(6)H_B), 3.12−3.15 (1H, m, C(5)*H*), 3.59 (1H, d, *J* 13.4, NCH_AH_BPh), 3.81−3.83 (1H, m, C(3)*H*), 3.97 (1H, app t, *J* 3.2, C(4)*H*), 4.03 (1H, dd, *J* 10.9, 4.6, C(2)CH_AH_B), 4.13−4.19 (2H, m, C(2)CH_AH_B, NCH_AH_BPh), 7.21−7.25 (1H, m, *Ph*), 7.29−7.33 (2H, m, *Ph*), 7.38−7.39 (2H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 13.3 (Si(CHMe$_2$)$_3$), 18.7 (Si(CH*Me*$_2$)$_3$), 50.3 (*C*(6)), 52.1 (*C*(5)), 59.0 (NCH_2Ph), 62.2 (C(2)CH_2), 65.1 (*C*(2)), 68.6 (*C*(4)), 70.9 (*C*(3)), 128.4 (*p-Ph*), 129.6, 130.1 (*o,m-Ph*), 140.5 (*i-Ph*); *m/z* (ESI^+) 409 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{41}N_2O_3Si^+$ ($[M + H]^+$) requires 409.2881; found 409.2874.

(*R,R,R,R*)-2-Amino-1,2,5-trideoxy-1,5-imino-D-mannose [(−)-2-amino-1-deoxymannojirimycin (ADMJ)] 25. *Step 1.* A solution of **70** (30 mg) in 6.0 M aq HCl (1 mL) and MeOH (1 mL) was stirred at 40 °C for 16 h before being concentrated in vacuo to give (*R,R,R,R*)-*N*(1)-benzyl-2-hydroxymethyl-3,4-dihydroxy-5-amino-piperidine hydrochloride as a yellow oil (20 mg); $[\alpha]_D^{20}$ +31.8 (*c* 1.0 in MeOH); ν_{max} (ATR) 3350 (O−H, N−H), 2942, 2865 (C−H); δ_H (400 MHz, MeOH-d_4) 3.51−3.58 (2H, m, C(2)*H*, C(6)H_A), 3.65−3.76 (2H, m, C(2)CH_AH_B, C(6)H_B), 4.00−4.08 (1H, m, C(4)*H*), 4.09−4.14 (2H, m, C(2)CH_AH_B, C(3)*H*), 4.25−4.39 (1H, m, C(5)*H*), 4.54−4.68 (1H, m, NCH_AH_BPh), 5.00−5.09 (1H, m, NCH_AH_BPh), 7.45−7.53 (3H, m, *Ph*), 7.61−7.71 (2H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 44.6 (*C*(5)), 45.3 (*C*(6)), 57.9 (C(2)CH_2), 60.9 (NCH_2Ph), 64.7 (*C*(2)), 67.6 (*C*(3)), 69.0 (*C*(4)), 130.5, 131.3 (*o,m-Ph*), 132.7 (*p-Ph*), 132.8 (*i-Ph*); *m/z* (ESI^+) 253 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{21}N_2O_3^+$ ($[M + H]^+$) requires 253.1547; found 253.1545.

Step 2. $Pd(OH)_2$/C (10 mg) was added to a stirred solution of the residue of (*R,R,R,R*)-*N*(1)-benzyl-2-hydroxymethyl-3,4-dihydroxy-5-aminopiperidine hydrochloride (20 mg) in degassed MeOH (2 mL), and the resultant suspension was stirred at rt for 48 h under an atmosphere of H_2 (5 atm). HCl (1.0 M in Et_2O, 1 mL) was then added, and the resultant suspension was stirred for a further 5 min before being filtrated through Celite (eluent MeOH) and concentrated in vacuo. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100−200 mesh, eluent 1.0 M aq NH_4OH) gave **25** as a white solid (12 mg, quant, >99:1 dr);[9b] mp >250 °C; $[\alpha]_D^{20}$ −11.5 (*c* 0.3 in H_2O); {lit.[9b] $[\alpha]_D^{20}$ −14 (*c* 0.4 in H_2O)}; ν_{max} (ATR) 3360 (O−H, N−H); δ_H (400 MHz, D_2O) 2.50 (1H, ddd, *J* 9.7, 5.8, 3.0, C(5)*H*), 2.84 (1H, dd, *J* 14.0, 2.4, C(1)H_A), 3.00 (1H, dd, *J* 14.0, 2.4, C(1)H_B), 3.29−3.33 (1H, m, C(2)*H*), 3.44 (1H, t, *J* 9.7, C(4)*H*), 3.63−3.68 (2H, m, C(3)*H*, C(6)H_A), 3.77 (1H, dd, *J* 11.7, 3.0, C(6)H_B); δ_C (100 MHz, D_2O) 46.4 (*C*(1)), 51.2 (*C*(2)), 60.9 (*C*(5)), 60.9 (C(6)), 68.0 (*C*(4)), 73.1 (*C*(3)); *m/z* (ESI^+) 163 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_6H_{15}N_2O_3^+$ ($[M + H]^+$) requires 163.1077; found 163.1078.

DOI: 10.1021/acs.joc.6b01107
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(2*S*,3*S*,4*R*,5*R*)-2-Amino-1,2,5-trideoxy-1,5-imino-D-allose [(+)-2-Amino-1-deoxyallonojirimycin (ADANJ)] 26. *Step 1.* A solution of **72** (30 mg) in 6.0 M aq HCl (1 mL) and MeOH (1 mL) was stirred at 40 °C for 16 h before being concentrated in vacuo to give (2*R*,3*R*,4*S*,5*S*)-*N*(1)-benzyl-2-hydroxymethyl-3,4-dihydroxy-5-aminopiperidine hydrochloride as a yellow oil (19 mg); $[\alpha]_D^{20}$ −16.8 (*c* 0.2 in MeOH); ν_{max} (ATR) 3360 (O−H, N−H), 2942, 2865 (C−H); δ_H (400 MHz, MeOH-d_4) 3.20 (1H, dd, *J* 11.7, 4.3, C(6)H_A), 3.25−3.30 (1H, m, C(6)H_B), 3.41−3.46 (1H, m, C(2)*H*), 3.62−3.66 (1H, m, C(5)*H*), 3.96 (1H, app d, *J* 9.8, C(3)*H*), 4.16−4.18 (1H, m, C(4)*H*), 4.23−4.26 (2H, m, C(2)CH_2), 4.32 (1H, d, *J* 11.8, NC$H_A$$H_B$Ph), 4.86 (1H, d, *J* 11.8, NC$H_A$$H_B$Ph), 7.50−7.66 (5H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 46.7 (*C*(6)), 48.0 (*C*(5)), 54.9 (C(2)CH_2), 58.7 (NCH_2Ph), 63.8 (*C*(2)), 66.5 (*C*(3)), 67.7 (*C*(4)), 130.7, 131.7, 133.0 (*o*,*m*,*p*-*Ph*), 133.5 (*i*-*Ph*); *m*/*z* (ESI$^+$) 253 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{21}N_2O_3^+$ ([M + H]$^+$) requires 253.1547; found 253.1540.

Step 2. Pd(OH)$_2$/C (10 mg) was added to a stirred solution of the residue of (2*R*,3*R*,4*S*,5*S*)-*N*(1)-benzyl-2-hydroxymethyl-3,4-dihydroxy-5-aminopiperidine hydrochloride (19 mg) in degassed MeOH (2 mL), and the resultant suspension was stirred at rt for 48 h under an atmosphere of H_2 (5 atm). HCl (1.0 M in Et_2O, 1 mL) was then added, and the resultant suspension was stirred for a further 5 min before being filtrated through Celite (eluent MeOH) and concentrated in vacuo. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100−200 mesh, eluent 1.0 M aq NH_4OH) gave **26** as a white solid (12 mg, quant from **72**, >99:1 dr); mp > 250 °C; $[\alpha]_D^{20}$ +16.3 (*c* 0.3 in H_2O); ν_{max} (ATR) 3360 (O−H, N−H); δ_H (400 MHz, D_2O) 2.52 (1H, app t, *J* 11.8, C(1)H_A), 2.69 (1H, ddd, *J* 10.4, 5.8, 2.8, C(5)*H*), 2.76 (1H, dd, *J* 12.3, 4.8, C(1)H_B), 2.79−2.85 (1H, m, C(2)*H*), 3.42 (1H, dd, *J* 10.4, 2.8, C(4)*H*), 3.59 (1H, dd, *J* 11.7, 5.8, C(6)H_A), 3.76 (1H, dd, *J* 11.7, 2.8, C(6)H_B), 3.93−3.95 (1H, m, C(3)*H*); δ_C (100 MHz, D_2O) 44.6 (*C*(1)), 50.1 (*C*(2)), 54.5 (*C*(5)), 61.5 (*C*(6)), 69.1 (*C*(4)), 71.4 (*C*(3)); *m*/*z* (ESI$^+$) 163 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_6H_{15}N_2O_3^+$ ([M + H]$^+$) requires 163.1077; found 163.1076.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01107.

^{1}H and ^{13}C NMR spectra (PDF)

Crystallographic information file (for structures CCDC 1479041−1479043) (CIF)

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Notes

The authors declare no competing financial interest.

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(19) The ^{1}H NMR spectrum of **33** was also recorded in CH_2Cl_2 at low temperature (208 K); however, even though two conformers of **33** were observed in this spectrum, the ^{1}H NMR ^3J coupling constants of these two conformers could not be resolved due to insufficient dispersion of peaks.

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(25) Crystallographic data (excluding structure factors) for the structures of **38**, **56**, and **69** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1479041, 1479042, and 1479043, respectively.

(26) The ^{13}C NMR chemical shift for CH_2I carbons in pyrrolidines are typically lower (δ_C = 1.5−12 ppm) than the ^{13}C NMR chemical shift for CHI carbons in piperidines (δ_C = 20−40 ppm), for example, see: Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2009**, *20*, 758.

(27) The C(4)*H* proton was not observed in the ^{1}H NMR spectrum of **39** in $CDCl_3$ at rt.

(28) The atomic connectivities within **55** and **56** were initially assigned by ^{1}H and ^{13}C NMR spectroscopic analyses, and the IR spectra of **55** and **56** also displayed diagnostic absorbances at ∼1780 cm^{-1} for the C═O of the carbamate moiety.

(29) The assigned bicyclic system within **57** was entirely consistent with both ^{1}H and ^{13}C NMR spectroscopic analyses of **57**, and the IR

DOI: 10.1021/acs.joc.6b01107
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spectrum of **57** displayed a diagnostic C═O absorbance at 1797 cm^{-1} for the carbamate moiety.
(30) An impurity that was tentatively assigned as *N*(1)-*α*-methylbenzyl-substituted pyrrolidine **62** was observed in the ^1H NMR spectrum of this sample of **12** [δ_H = 1.5 ppm (3H, d, C(*α*)*Me*) and δ_H = 4.12 ppm (1H, q, C(*α*)*H*)].
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(37) Compound **37** was found to decompose upon attempted purification via flash column chromatography. The crude reaction mixture was therefore characterized as a 50:50 mixture of **37** and DMAP.
(38) A peak corresponding to C(4)*H* was not observed in the ^1H NMR spectrum of **38** in $CDCl_3$ at rt.
(39) The peaks in the ^{13}C NMR spectrum of **38** corresponding to *C*(3) and *C*(6) at 39.9 and 48.3 ppm, respectively, were extremely broad.
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DOI: 10.1021/acs.joc.6b01107
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