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Absolute Configuration Assignment by Asymmetric Syntheses of the Homalium Alkaloids (−)-(*R*,*R*,*R*)-Hoprominol and (−)-(4′*S*,4″*R*,2‴*R*)-Hopromalinol

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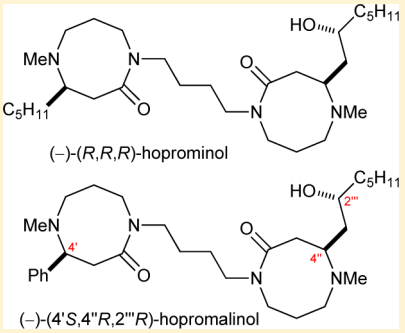
Supporting Information

ABSTRACT: The conjugate addition of lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amide to α,β-unsaturated esters was used as the key step in the syntheses of all possible diastereoisomers of the homalium alkaloids hoprominol and hopromalinol. Comparison of the specific rotation data for these synthetic samples with those of samples isolated from the natural source enabled the absolute configurations within these alkaloids to be confidently assigned for the first time as (−)-(*R*,*R*,*R*)-hoprominol and (−)-(4′*S*,4″*R*,2‴*R*)-hopromalinol. The asymmetric syntheses of (−)-(*R*,*R*,*R*)-hoprominol (in 10 steps and 4.0% overall yield) and (−)-(4′*S*,4″*R*,2‴*R*)-hopromalinol (in 10 steps and 9.3% overall yield), from commercially available starting materials in each case, therefore represent the first total asymmetric syntheses of these alkaloids to be reported.



INTRODUCTION

(−)-(*S*,*S*)-Homaline **1**, (−)-(*R*,*R*)-hopromine **2**, (−)-hoprominol **3**, and (−)-hopromalinol **4** constitute the family of homalium alkaloids. All four alkaloids were isolated from the leaves of an African *Homalium* species and *Homalium pronyense* Guillaum (a member of the Flacourtiacae family) found in the forests of New Caledonia (Figure 1).[1−6] The unique bis-eight-membered lactam structure[7] of these compounds has led to various synthetic investigations, although to date only the simpler (−)-(*S*,*S*)-homaline **1** and (−)-(*R*,*R*)-hopromine **2** have been synthesized in stereoisomerically pure form.[8−15] Several other methods for the synthesis of the homalium alkaloids have also been investigated, although inseparable mixtures of stereoisomers were formed in each case.[16−18] Despite being isolated over 40 years ago, (−)-hoprominol **3** and (−)-hopromalinol **4** are yet to acquiesce to total synthesis, and so the relative and absolute configurations within these two alkaloids are yet to be established.

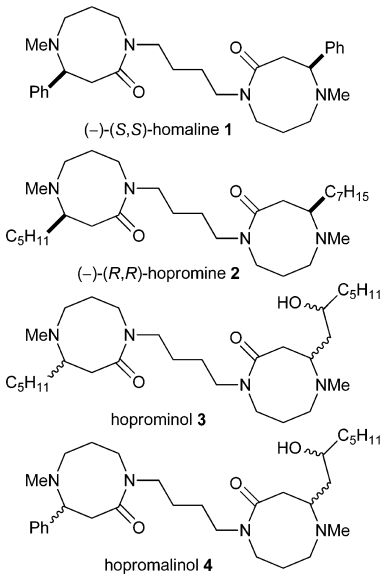


Figure 1. The homalium alkaloids **1**−**4**.

As part of our ongoing research program concerning the conjugate additions of chiral lithium amides to α,β-unsaturated esters,[19−21] we have recently reported total asymmetric syntheses of (−)-(*S*,*S*)-homaline **1** and (−)-(*R*,*R*)-hopromine **2**.[14,15] For example, our strategy for the synthesis of the unsymmetrical alkaloid (−)-(*R*,*R*)-hopromine **2** involved the preparation of the monomeric 8-membered azalactam units **16** and **17**, followed by their sequential alkylation with 1,4-dibromobutane. Azalactams **16** and **17** were prepared via conjugate addition of lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amide (*R*)-**7**[22] to α,β-unsaturated esters **5** and **6**,[23] transesterification of the resultant β-amino esters **8** and **9**, treatment of **10** and **11** with NaN_3 (under Finkelstein[24] conditions), Staudinger reduction of azides **12** and **13**, followed by $Sb(OEt)_3$-mediated cyclization,[12,13] which gave the corresponding azalactams **14** and **15** in 60% and 20% overall yield

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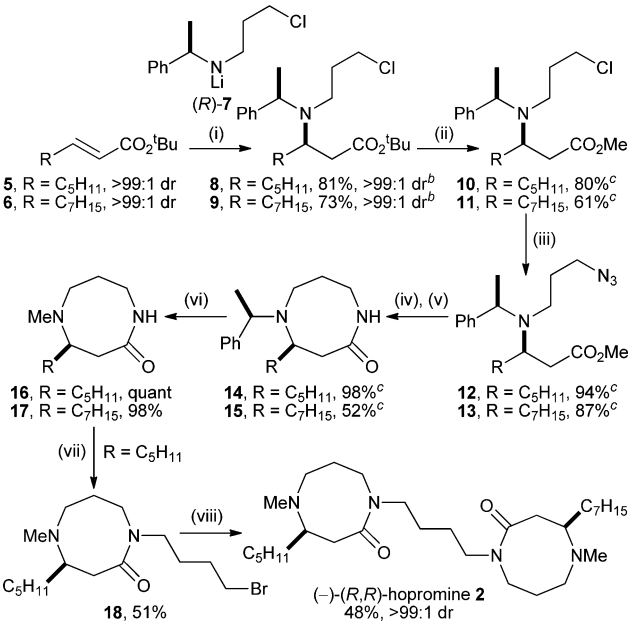
for the five-step procedure. Upon scale-up of this process, it was found that the overall yields of azalactams **14** and **15** could be significantly improved if the intermediate compounds **8**–**13** were used without purification: this gave **14** and **15** in 72% and 40% overall yield, respectively. Tandem hydrogenolysis/*N*-methylation of **14** and **15** gave the corresponding *N*(5)-methyl-substituted azalactams **16** and **17** in quantitative and 98% yield. Subsequent monoalkylation of azalactam **16** with 1,4-dibromobutane (3.0 equiv) in the presence of triethylbenzylammonium chloride (TEBAC) proved optimal, giving **18** in 51% isolated yield, and finally treatment of bromide **18** with azalactam **17** gave (−)-(*R*,*R*)-hopromine **2** in 48% yield and >99:1 dr (Scheme 1).

Scheme 1[a]



[a]Reagents and conditions: (i) (*R*)-7, THF, −78 °C, 2 h; (ii) $SOCl_2$, MeOH, reflux, 3 h; (iii) NaN_3, NaI, DMSO, 50 °C, 24 h; (iv) PBu_3, THF, rt, 30 min then H_2O, 50 °C, 2 h; (v) $Sb(OEt)_3$, PhMe, reflux, 18 h; (vi) H_2 (1 atm), $Pd(OH)_2/C$, $(CH_2O)_n$, MeOH, rt, 3 days; (vii) 1,4-dibromobutane (3.0 equiv), KOH, K_2CO_3, TEBAC, DMSO, rt, 24 h; (viii) **17**, KOH, DMSO, rt, 96 h. [b]Crude and isolated. [c]Isolated as a single diastereoisomer (>99:1 dr).

We envisaged that a similar strategy could be used for the preparation of the more elaborate alkaloids (−)-hoprominol **3** and (−)-hopromalinol **4**, and the results of these investigations, which culminated in the assignment of the absolute configurations within both (−)-hoprominol **3** and (−)-hopromalinol **4**, are reported herein.

RESULTS AND DISCUSSION

At the onset of this project, the relative and absolute configurations within (−)-hoprominol **3** and (−)-hopromalinol **4** had yet to be established, and as the structures of both (−)-hoprominol **3** and (−)-hopromalinol **4** contain three stereogenic centers, there were eight possible stereoisomers to consider for each alkaloid. However, given the homochirality between (−)-homaline **1** and (−)-hopromine **2** (i.e., both substituents within **1** and **2** are pointing upward as drawn in Figure 1), we predicted that (−)-hoprominol **3** and (−)-hopromalinol **4** would also be homochiral with respect to the other alkaloids in this family, and possess (4′*R*,4″*R*)- and (4′*S*,4″*R*)-configurations, respectively, as shown for **19** and **20**. This assumption was also advocated by Ensch and Hesse[13] who reported a synthesis of the protected "hoprominol derivative" (*R*,*R*,*R*)-**25** and speculated that "all the members of the homalium family share the same three-dimensional orientation of the residues at their corresponding stereogenic centers of the lactam rings", although **25** was not deprotected and correlated with the natural product as part of their investigations. As only very limited characterization data have previously been reported for both (−)-hoprominol **3** and (−)-hopromalinol **4**,[6] we envisaged that it would be necessary to prepare authentic samples of all four possible diastereoisomers of each alkaloid so that the magnitudes of their specific rotations could be compared to the reported data for the samples of (−)-hoprominol **3** and (−)-hopromalinol **4** isolated from the natural source. A versatile synthetic strategy enabling the rapid synthesis of all possible stereochemical permutations of 4-(2′-hydroxyheptyl) or 4-(2′-benzyloxyheptyl)-substituted azalactams **21** was therefore devised: it was envisaged that conjugate addition of lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amide (*R*)-7 to a racemic δ-benzyloxy-α,β-unsaturated ester **24** would proceed under the dominant stereocontrol of the lithium amide reagent[25] to give a mixture of C(3)-epimeric β-amino ester conjugate addition products **23**. Separation of these compounds, followed by functional group manipulation and $Sb(OEt)_3$-mediated cyclization[12,13] of **22** (using our established protocols),[14,15] would then provide access to the corresponding azalactams **21**; the antipodes would then be accessed via an analogous approach starting with the conjugate addition of lithium (*S*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amide (*S*)-7 to α,β-unsaturated ester **24** (Figure 2).

Synthesis of the 2-Hydroxyheptyl-Substituted Azalactam Units. Racemic samples of the requisite C(5)-benzyloxy-substituted α,β-unsaturated esters (*RS*)-**29** and (*RS*)-**30** were prepared via initial treatment of hexanal **26** with allylmagnesium bromide, which gave homoallylic alcohol

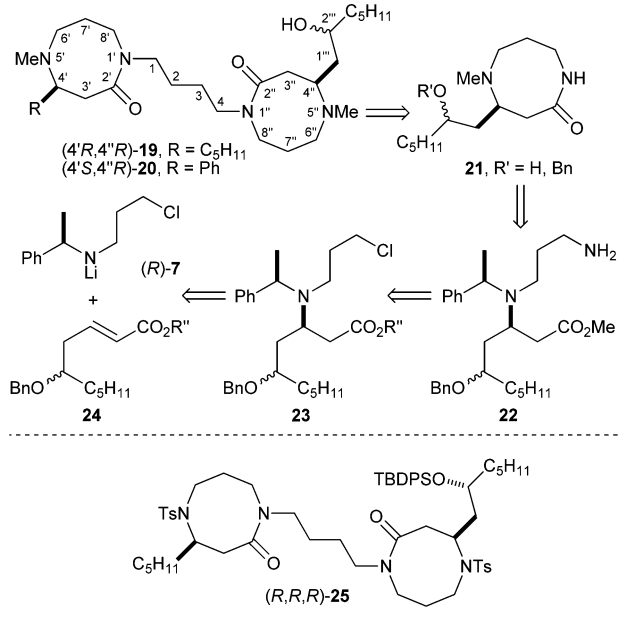


Figure 2. Synthetic strategy to access the stereoisomers of hoprominol **3** and hopromalinol **4**.

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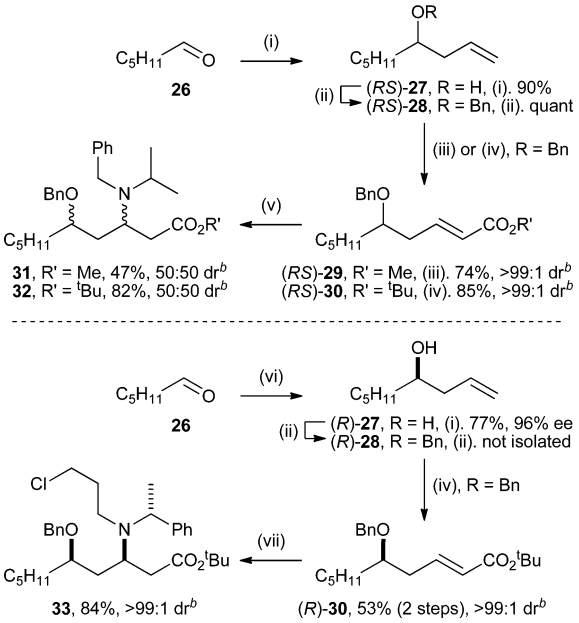
(*RS*)-**27** in 90% isolated yield; subsequent protection of the hydroxyl group within (*RS*)-**27** upon treatment with NaH and BnBr gave (*RS*)-**28** in quantitative yield, then cross metathesis of (*RS*)-**28** with either methyl acrylate or *tert*-butyl acrylate gave (*RS*)-**29** and (*RS*)-**30** in 74% and 85% yield, respectively. When investigating doubly diastereoselective[26] conjugate additions of lithium amide reagents to chiral α,β-unsaturated esters, we have previously found that it is prudent to follow a strategy of first investigating the levels of substrate control offered by the chiral α,β-unsaturated ester upon conjugate addition of an achiral lithium amide (such as lithium *N*-isopropyl-*N*-benzylamide),[27] prior to attempting the conjugate addition reactions of chiral secondary lithium amides derived from α-methylbenzylamine. In both cases, conjugate addition of lithium *N*-isopropyl-*N*-benzylamide to racemic α,β-unsaturated esters (*RS*)-**29** and (*RS*)-**30** gave essentially 50:50 mixtures[28] of the corresponding diastereoisomeric products, which could not be separated and were therefore isolated in 47% and 82% combined yield, respectively, and 50:50 dr in each case. These reaction outcomes established that there is effectively no substrate control upon the conjugate addition of achiral lithium amide reagent lithium *N*-isopropyl-*N*-benzylamide to **29** and **30**, and suggested that any diastereoisomeric excess arising from conjugate addition of chiral lithium amide (*R*)-**7** to α,β-unsaturated esters **29** and **30** will be due to reagent control alone. An enantiopure sample of α,β-unsaturated ester (*R*)-**30** was prepared by Brown allylation of hexanal **26** in the presence of (−)-*B*-chlorodiisopinocampheylborane [(−)-Ipc$_2$BCl], which gave homoallylic alcohol (*R*)-**27**[29] in 77% yield and 96% ee.[30] The absolute configuration within (*R*)-**27** was assigned by comparison of the specific rotation of this sample with that of a sample of known configuration reported in the literature {$[\alpha]^{24}_D$ +9.0 (*c* 1.0 in $CHCl_3$); lit.[31] $[\alpha]^{25}_D$ +8.9 (*c* 1.1 in $CHCl_3$)}. *O*-Benzyl protection of (*R*)-**27**, followed by cross metathesis of (*R*)-**28** with *tert*-butyl acrylate, gave (*R*)-**30** in 53% yield [from (*R*)-**27**]. Subsequent conjugate addition of lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amide (*R*)-**7**[22] to enantiopure α,β-unsaturated ester (*R*)-**30** gave **33** as a single diastereoisomer (>99:1 dr), which was isolated in 84% yield after purification (Scheme 2). Given the usually very high reagent control and predictable sense of diastereoselectivity observed upon conjugate addition of secondary lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters,[21] and the extremely low substrate control observed upon conjugate addition of lithium *N*-isopropyl-*N*-benzylamide to (*RS*)-**30**, the (*R*)-configuration of the newly formed C(3)-stereogenic center within **33** was confidently assigned by reference to our well-established transition state mnemonic.[32]

A sample of the C(5)-epimeric β-amino ester **34** was then accessed upon conjugate addition of lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amide (*R*)-**7**[22] to racemic α,β-unsaturated ester (*RS*)-**30**, which gave a 50:50 mixture of **33** and **34**; after chromatographic purification of the crude reaction mixture, **33** and **34** were isolated as single diastereoisomers (>99:1 dr) in 41% and 46% yield, respectively. The absolute configuration within **34** was assigned by analogy to the established configuration within **33**, given very high reagent control and predictable sense of diastereoselectivity observed upon conjugate addition of secondary lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters,[21] and the extremely low substrate control observed upon conjugate addition of lithium *N*-isopropyl-*N*-benzylamide to (*RS*)-**30**. Subsequent conversion of β-amino esters **33** and **34** into the corresponding azalactams **41** and **42** was then achieved in 54% and 47% overall yield[33] using our established four-step sequence of reactions for azalactam formation: sequential transesterification, displacement of the chloride functionality with NaN_3, Staudinger reduction of the resultant azide, and $Sb(OEt)_3$-mediated lactamization (Scheme 3).

Scheme 2[a]



[a] Reagents and conditions: (i) allylmagnesium bromide, THF, rt, 1 h; (ii) NaH, THF, rt, 1 h, then BnBr, rt, 18 h; (iii) Grubbs II, methyl acrylate, CH_2Cl_2, 40 °C, 24 h; (iv) Grubbs II, *tert*-butyl acrylate, CH_2Cl_2, 40 °C, 24 h; (v) lithium *N*-isopropyl-*N*-benzylamide, THF, −78 °C, 2 h; (vi) (−)-Ipc$_2$BCl, allylmagnesium bromide, Et_2O, −78 °C, 1 h; (vii) (*R*)-**7**, THF, −78 °C, 2 h. [b]Crude and isolated.

Deprotection of 4-(2′-benzyloxyheptyl)-substituted azalactams **41** and **42** via hydrogenolysis gave **43** and **44** in 63% and 81% yield, respectively, and then *N*-methylation of these substrates upon treatment with $(CH_2O)_n$ and $NaBH_3CN$ gave **45** and **46** in 45% and 40% isolated yield (Scheme 4). Attempted tandem hydrogenolysis/*N*-methylation of **41** produced an 85:15 mixture of **45** and **47**, which were isolated in 29% and 14% yield, respectively, after chromatographic purification. Upon changing the solvent used for this reaction from MeOH to AcOH, it was possible to completely suppress the formation of **47**, giving **45** as the sole reaction product in 90% isolated yield. Treatment of the epimeric compound **42** under identical conditions gave **46** in quantitative yield (Scheme 5).

The enantiomeric azalactams *ent*-**45** and *ent*-**46** were prepared via an analogous sequence of reactions: conjugate addition of lithium (*S*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amide (*S*)-**7**[34] to racemic α,β-unsaturated ester (*RS*)-**30** gave a 50:50 mixture of diastereoisomeric conjugate addition products *ent*-**33** and *ent*-**34**, which were isolated as single diastereoisomers (>99:1 dr) in 36% and 40% yield, respectively. Subsequent conversion of β-amino esters *ent*-**33** and *ent*-**34** into the corresponding azalactams *ent*-**41** and *ent*-**42** was then achieved in 60% and 69% overall yield using our standard four-step sequence of reactions for azalactam formation. Finally, tandem hydrogenolysis/*N*-methylation of

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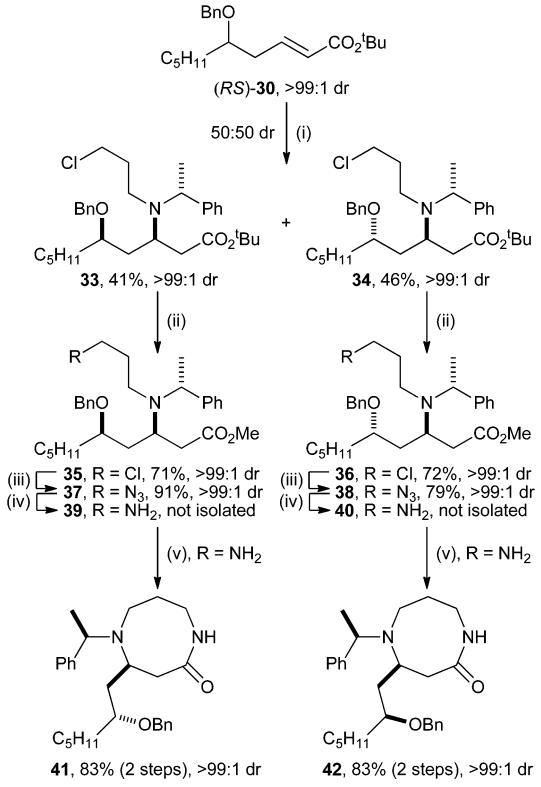
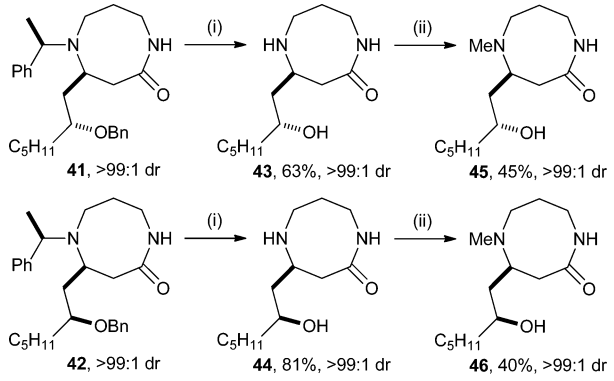
Scheme 3[a]



[a]Reagents and conditions: (i) (*R*)-**7**, THF, −78 °C, 2 h; (ii) $SOCl_2$, MeOH, reflux, 4 h; (iii) NaN_3, NaI, DMSO, 50 °C, 24 h; (iv) PBu_3, THF, rt, 30 min, then H_2O, 50 °C, 2 h; (v) $Sb(OEt)_3$, PhMe, reflux, 18 h.

Scheme 4[a]

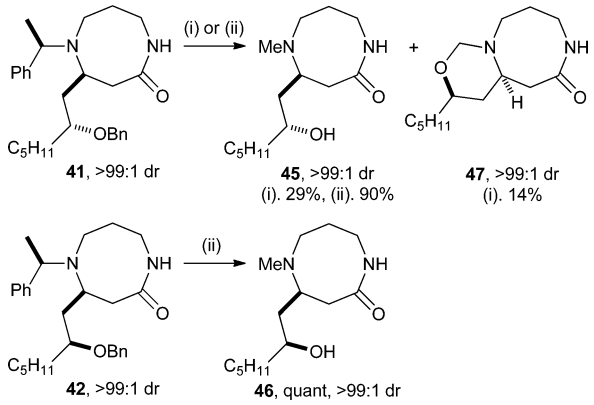


[a]Reagents and conditions: (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 24 h; (ii) $NaBH_3CN$, $(CH_2O)_n$, MeOH, rt, 18 h.

both *ent*-**41** and *ent*-**42** gave samples of *ent*-**45** and *ent*-**46** in quantitative and 85% yield, respectively (Scheme 6).

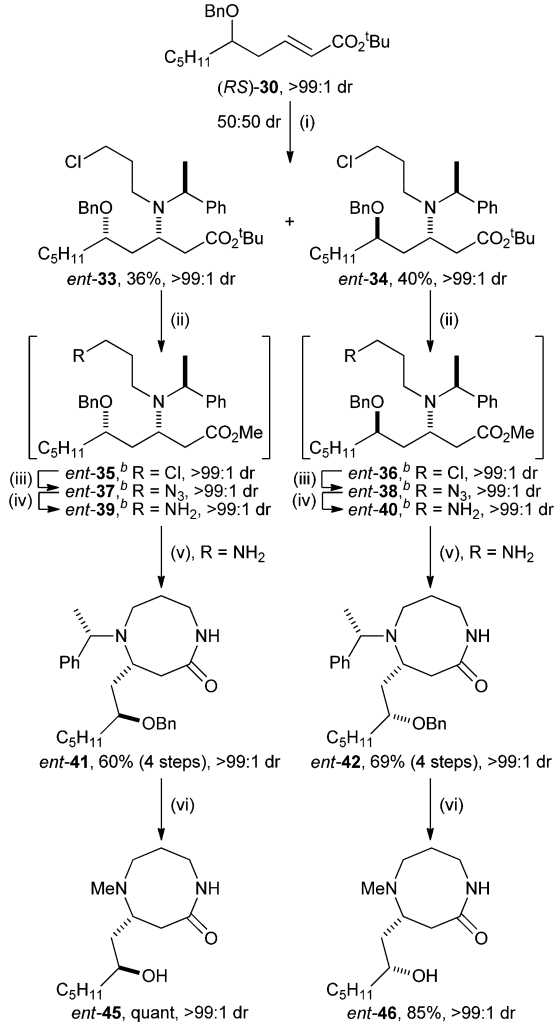
Asymmetric Synthesis of (−)-Hoprominol. Reaction of the known bromide **18** [an intermediate in our synthesis of (−)-(*R*,*R*)-hopromine **2**][15] with 4-(2′-benzyloxyheptyl)-substituted azalactam **42** gave **48** in 21% isolated yield. Tandem hydrogenolysis/*N*-methylation of **48** gave (4′*R*,4″*R*,2‴*S*)-**49** {$[\alpha]^{24}_D$ −18.4 (*c* 1.0 in $CHCl_3$)} in 38% yield after purification. However, treatment of bromide **18** with the corresponding 4-(2′-hydroxyheptyl)-substituted azalactam **46** was found to proceed with superior yield, giving (4′*R*,4″*R*,2‴*S*)-**49** {$[\alpha]^{24}_D$ −18.4 (*c* 1.0 in $CHCl_3$)} directly in 26% isolated yield. This

Scheme 5[a]



[a]Reagents and conditions: (i) H_2 (1 atm), $Pd(OH)_2/C$, $(CH_2O)_n$, MeOH, rt, 72 h; (ii) H_2 (1 atm), $Pd(OH)_2/C$, $(CH_2O)_n$, AcOH, rt, 24 h.

Scheme 6[a]



[a]Reagents and conditions: (i) (*S*)-**7**, THF, −78 °C, 2 h; (ii) $SOCl_2$, MeOH, reflux, 4 h; (iii) NaN_3, NaI, DMSO, 50 °C, 24 h; (iv) PBu_3, THF, rt, 30 min, then H_2O, 50 °C, 2 h; (v) $Sb(OEt)_3$, PhMe, reflux, 18 h; (vi) H_2 (1 atm), $Pd(OH)_2/C$, $(CH_2O)_n$, AcOH, rt, 24 h. [b]Not isolated.

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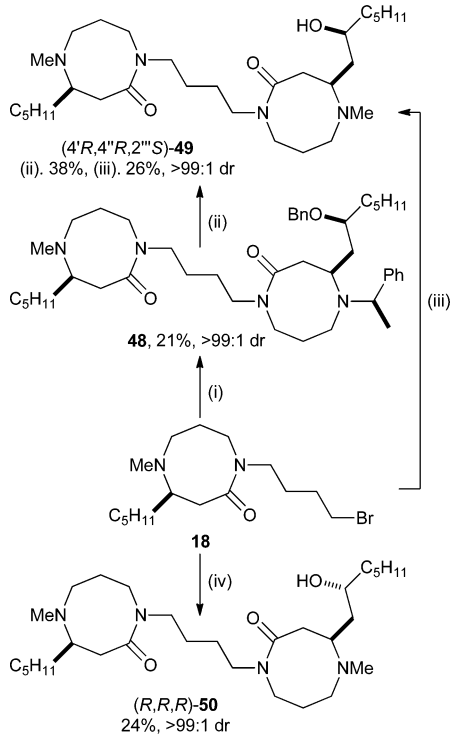
procedure was therefore repeated using the epimeric 2-hydroxyheptyl-substituted azalactam **45**, which gave (*R*,*R*,*R*)-**50** {$[\alpha]^{24}_{D}$ −17.5 (*c* 1.0 in $CHCl_3$)} in 24% isolated yield (Scheme 7).

Scheme 7[a]



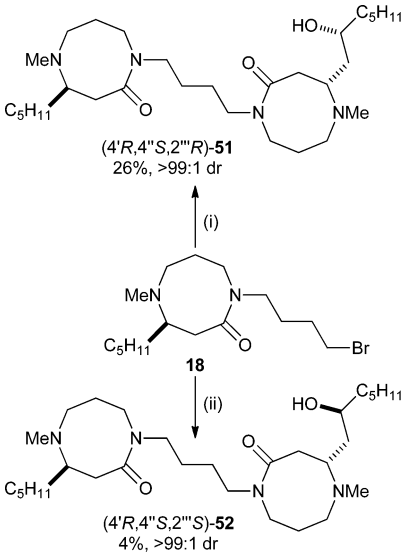
[a]Reagents and conditions: (i) **42**, KOH, DMSO, rt, 96 h; (ii) H_2 (1 atm), $Pd(OH)_2/C$, $(CH_2O)_n$, AcOH, rt, 24 h; (iii) **46**, KOH, K_2CO_3, TEBAC, DMSO, rt, 48 h; (iv) **45**, KOH, K_2CO_3, TEBAC, DMSO, rt, 48 h.

The same strategy was then followed for the synthesis of the remaining diastereoisomers of (−)-hoprominol via alkylation of azalactams *ent*-**45** and *ent*-**46** with bromide **18**. Reaction of bromide **18** with 4-(2′-hyrdoxyheptyl)-substituted azalactam *ent*-**46** gave (4′*R*,4″*S*,2‴*R*)-**51** {$[\alpha]^{24}_{D}$ −2.4 (*c* 1.0 in $CHCl_3$)} in 26% yield and >99:1 dr after chromatographic purification, and treatment of **18** with the epimeric 4-(2′-hydroxyheptyl)-substituted azalactam *ent*-**45** gave (4′*R*,4″*S*,2‴*S*)-**52** {$[\alpha]^{24}_{D}$ +5.8 (*c* 1.0 in $CHCl_3$)} in 4% isolated yield and >99:1 dr (Scheme 8).

Asymmetric Synthesis of (−)-Hopromalinol. Alkylation of 4-phenyl-substituted azalactam **53** [an intermediate in our synthesis of (−)-(*R*,*R*)-homaline **1**][14,15] with 3.0 equiv of 1,4-dibromobutane gave **54** in 59% yield. Subsequent treatment of bromide **54** with 4-(2′-hydroxyheptyl)-substituted azalactam **46** gave (4′*S*,4″*R*,2‴*S*)-**55** {$[\alpha]^{24}_{D}$ −9.3 (*c* 1.0 in $CHCl_3$)} in 36% isolated yield, and analogous alkylation of **54** with the epimeric 2-hydroxyheptyl-substituted azalactam **45** gave (4′*S*,4″*R*,2‴*R*)-**56** {$[\alpha]^{24}_{D}$ −16.8 (*c* 1.0 in $CHCl_3$)} in 56% isolated yield (Scheme 9).

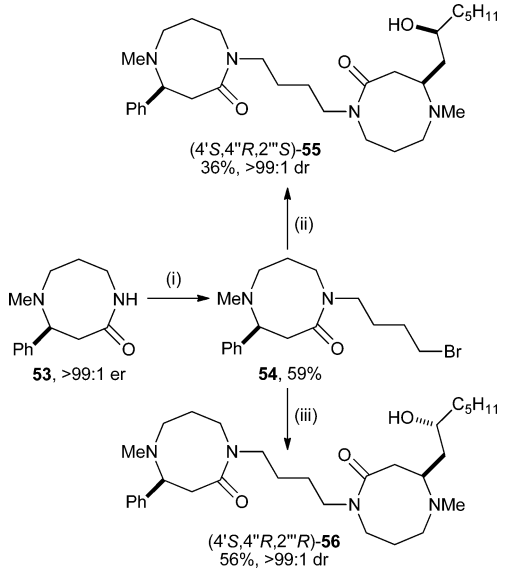
Similarly, alkylation of bromide **54** with 4-(2′-hydroxyheptyl)-substituted azalactam *ent*-**46** gave (4′*S*,4″*S*,2‴*R*)-**57** {$[\alpha]^{24}_{D}$ −7.1 (*c* 1.0 in $CHCl_3$)} in >99:1 dr and 22% isolated yield, and alkylation of **54** with the epimeric 4-(2′-hydroxyheptyl)-substituted azalactam *ent*-**45** gave (*S*,*S*,*S*)-**58** {$[\alpha]^{24}_{D}$ +2.1 (*c* 1.0 in $CHCl_3$)} in 59% isolated yield and >99:1 dr (Scheme 10).

Scheme 8[a]



[a]Reagents and conditions: (i) *ent*-**46**, KOH, K_2CO_3, TEBAC, DMSO, rt, 60 h; (ii) *ent*-**45**, KOH, K_2CO_3, TEBAC, DMSO, rt, 60 h.

Scheme 9[a]



[a]Reagents and conditions: (i) 1,4-dibromobutane (3.0 equiv), KOH, DMSO, rt, 18 h; (ii) **46**, KOH, K_2CO_3, TEBAC, DMSO, rt, 48 h; (iii) **45**, KOH, K_2CO_3, TEBAC, DMSO, rt, 48 h.

Comparison with Literature Data. Unfortunately, only very limited NMR data for both (−)-hoprominol and (−)-hopromalinol are available in the literature,[6] and, despite exhaustive enquiries, we have been unable to acquire authentic samples of either of these alkaloids, or more extensive characterization data. The specific rotations for our synthetic samples of the possible diastereoisomers of (−)-hoprominol and (−)-hopromalinol were therefore compared to the originally reported values: considering the four diastereoisomers of hopromalinol (i.e., the authentic synthetic samples of **55**−**58**), the (4′*S*,4″*R*,2‴*R*)-stereoisomer **56** {$[\alpha]^{24}_{D}$ −16.8 (*c* 1.0 in $CHCl_3$)} is the only one of these possibilities that

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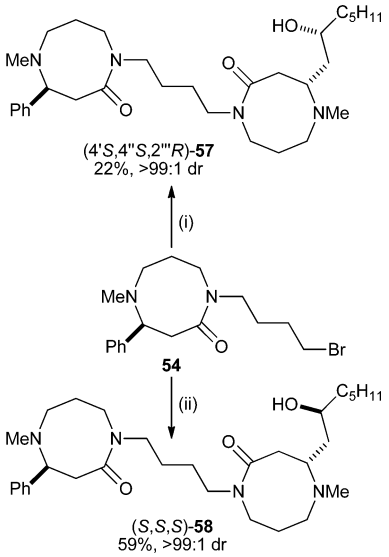
Scheme 10[a]



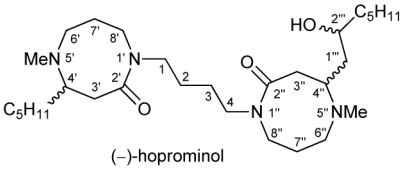
[a]Reagents and conditions: (i) *ent*-**46**, KOH, K_2CO_3, TEBAC, DMSO, rt, 60 h; (ii) *ent*-**45**, KOH, K_2CO_3, TEBAC, DMSO, rt, 60 h.

shows good agreement between its specific rotation value and that reported for the natural product {lit.[6] $[\alpha]^{20}_D$ −17 (*c* 2.5 in $CHCl_3$)}, in terms of both sign and magnitude; the other three diastereoisomers **55**, **57**, and **58** all have specific rotations that are far too small to be consistent with either antipode of the natural product. This analysis has therefore enabled the absolute (4′*S*,4″*R*,2‴*R*)-configuration within (−)-hopromalinol **56** to be unambiguously assigned. For hoprominol, however, there are two possible stereoisomers, epimeric at the C(2‴) position, (4′*R*,4″*R*,2‴*S*)-**49** {$[\alpha]^{24}_D$ −18.4 (*c* 1.0 in $CHCl_3$)} and (*R*,*R*,*R*)-**50** {$[\alpha]^{24}_D$ −17.5 (*c* 1.0 in $CHCl_3$)}, which have comparable specific rotation values (both sign and magnitude) with that of the sample isolated from the natural source {lit.[6] $[\alpha]^{20}_D$ −19 (*c* 2.0 in $CHCl_3$)}; the other two diastereoisomers **51** and **52** have specific rotations that are far too small to be consistent with either antipode of the natural product. This confirms that all four homalium alkaloids are homochiral with respect to the configurations of the azalactam rings, and it is only the configuration of the C(2‴) position within hoprominol that cannot be unambiguously assigned given the comparable specific rotation values observed for the C(2‴)-epimers **49** and **50**. However, given the homochirality observed between all four homalium alkaloids with respect to the configurations of the azalactam rings, it seems reasonable that the configurations at the C(2‴) positions within both (−)-hoprominol and (−)-hopromalinol are identical. On the basis of this analysis, we have therefore confidently assigned the absolute (*R*,*R*,*R*)-configuration to (−)-hoprominol **50** (Figure 3).

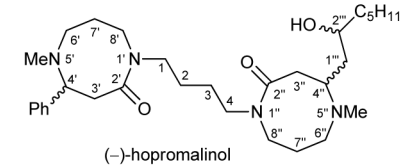
This study represents the first reported total asymmetric syntheses of these alkaloids: (−)-(*R*,*R*,*R*)-hoprominol **50** was produced in 10 steps and 4.0% overall yield, and (−)-(4′*S*,4″*R*,2‴*R*)-hopromalinol **56** was produced in 10 steps and 9.3% overall yield, from commercially available starting materials in each case.

CONCLUSION

The conjugate addition of lithium (*R*)- or (*S*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amide to an α,β-unsaturated ester was used as the key step in the syntheses of all possible diastereoisomers of the homalium alkaloids hoprominol and hopromalinol. Comparison of the specific rotation data for



	absolute configuration C(4')	C(4'')	C(2''')	specific rotation [α]D24 (c 1.0 in CHCl3)
49	*R*	*R*	*S*	−18.4
50	*R*	*R*	*R*	−17.5
51	*R*	*S*	*R*	−2.4
52	*R*	*S*	*S*	+5.8



	absolute configuration C(4')	C(4'')	C(2''')	specific rotation [α]D24 (c 1.0 in CHCl3)
55	*S*	*R*	*S*	−9.3
56	*S*	*R*	*R*	−16.8
57	*S*	*S*	*R*	−7.1
58	*S*	*S*	*S*	+2.1

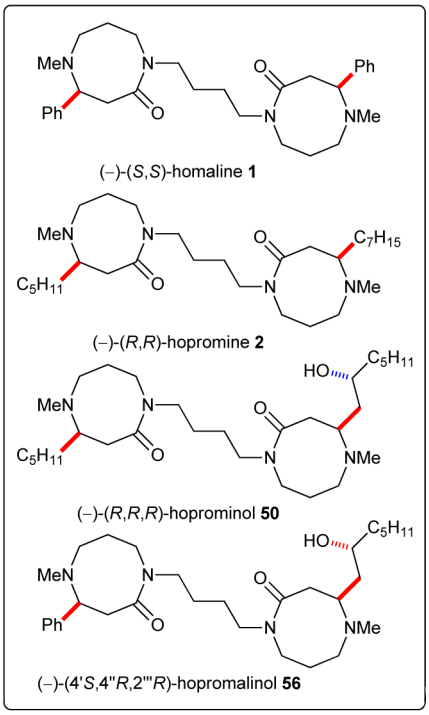


Figure 3. Comparison of specific rotation data for the synthetic samples of all possible diastereoisomers of (−)-hoprominol and (−)-hopromalinol [red = configuration unambiguously secured; blue = proposed configuration].

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these synthetic samples with those of samples isolated from the natural source enabled the absolute configurations within these alkaloids to be confidently assigned for the first time as (−)-(*R*,*R*,*R*)-hopromine and (−)-(4′*S*,4″*R*,2‴*R*)-hopromalinol. The asymmetric syntheses of (−)-(*R*,*R*,*R*)-hopromine (in 10 steps and 4.0% overall yield) and (−)-(4′*S*,4″*R*,2‴*R*)-hopromalinol (in 10 steps and 9.3% overall yield), from commercially available starting materials in each case, represent the first total asymmetric syntheses of these alkaloids to be reported.

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 vacuum before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[35] BuLi was purchased as a solution in hexanes, and titrated against diphenylacetic acid before use. Allylmagnesium bromide was purchased as a solution in Et_2O, and titrated against (*E*)-2-(2′-phenylhydrazonomethyl)phenol before use.[36] 1,4-Dibromobutane was distilled from $CaCl_2$ before use. All other reagents were used as supplied without prior purification. Organic layers were dried over $MgSO_4$ unless otherwise stated. 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 are in g/100 mL. IR spectra were recorded on 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. Resonances in the ^{13}C NMR spectra, which are broad, have their corresponding chemical shifts italicized in the list of assignments. ^{1}H−^{1}H COSY, ^{1}H−^{13}C HMQC, and ^{1}H−^{13}C HMBC analyses were used to establish atom connectivity. Accurate mass measurements were run on a TOF spectrometer internally calibrated with polyalanine.

General Procedure 1: Lithium Amide Conjugate Addition. BuLi was added to a solution of the requisite amine in THF at −78 °C, and the resultant mixture was stirred at −78 °C for 15 min. A solution of the requisite α,β-unsaturated ester in THF at −78 °C was then added via cannula, and the resultant mixture was stirred at −78 °C for 2 h. Saturated aq NH_4Cl was then added, and the reaction mixture was allowed to warm to rt and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and 10% aq citric acid, and the aqueous layer was extracted with two portions of CH_2Cl_2. The combined organic extracts were washed with satd aq $NaHCO_3$ and brine, then dried and concentrated in vacuo.

General Procedure 2: NaN_3 Displacement. NaN_3 and NaI were added to a stirred solution of the requisite amine in DMSO, and the resultant mixture was heated at 50 °C for 24 h. The reaction mixture was then allowed to cool to rt and partitioned between Et_2O and H_2O. The aqueous layer was extracted with two portions of Et_2O, and the combined organic extracts were washed sequentially with two portions of H_2O and brine, then dried and concentrated in vacuo.

General Procedure 3: Staudinger Reduction. PBu_3 was added to a solution of the requisite amine in THF, and the resultant mixture was stirred at rt for 30 min. H_2O was then added, and the reaction mixture was heated at 50 °C for 2 h before being allowed to cool to rt and concentrated in vacuo.

General Procedure 4: Transesterification. $SOCl_2$ was added to MeOH at 0 °C, and the resultant mixture was stirred for 1 min, then allowed to warm to rt. A solution of the requisite *tert*-butyl ester in MeOH was then added, and the resultant mixture was heated at reflux for 4 h. The reaction mixture was then allowed to cool to rt and concentrated in vacuo. The residue was partitioned between satd aq $NaHCO_3$ and CH_2Cl_2, the aqueous layer was extracted with two portions of CH_2Cl_2, then the combined organic extracts were dried and concentrated in vacuo.

General Procedure 5: $Sb(OEt)_3$-Mediated Macrolactamization. A solution of the requisite amine in PhMe was added to a two-necked round-bottomed flask fitted with an open pressure equalizing dropping funnel part filled with activated 4 Å molecular sieves and a condenser attached to the top of the dropping funnel. A glass stopper was placed in the second neck, and the solution was heated at reflux so that the PhMe vapor condensed above the level of the molecular sieves for a period of 2 h. The resultant solution was allowed to cool to rt over 5 min, then $Sb(OEt)_3$ was added. The resultant mixture was heated at reflux for 18 h then allowed to cool to rt. Saturated aq NH_4Cl was then added, and the reaction mixture was stirred at rt for 15 min before being filtered through Celite (eluent EtOAc). The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried and concentrated in vacuo.

General Procedure 6: *N*-Alkylation of Amide. *Method A.* Powdered KOH, K_2CO_3, and TEBAC were added to a solution of the requisite amide and alkyl bromide in DMSO, and the resultant mixture was stirred at rt for either 48 or 60 h (as stated). The reaction mixture was then partitioned between H_2O and $CHCl_3$, and the aqueous layer was extracted with two portions of $CHCl_3$. The combined organic extracts were sequentially washed with two portions of H_2O and brine, then dried and concentrated in vacuo.

Method B. Powdered KOH was added to a solution of the requisite amide and alkyl bromide in DMSO, and the resultant mixture was stirred at rt for either 18 or 96 h (as stated). The reaction mixture was then partitioned between H_2O and $CHCl_3$, and the aqueous layer was extracted with two portions of $CHCl_3$. The combined organic extracts were sequentially washed with two portions of H_2O and brine, then dried and concentrated in vacuo.

General Procedure 7: Hydrogenolysis. $Pd(OH)_2/C$ (20% w/w) was added to a solution of the requisite substrate [in some cases with $(CH_2O)_n$ also added, if specified] in degassed solvent (either MeOH or AcOH, as stated), and the resultant mixture was stirred at rt under H_2 (1 atm) for either 24 or 72 h (as stated). The reaction mixture was then degassed, filtered through Celite (eluent EtOAc then MeOH), and concentrated in vacuo.

General Procedure 8: Reductive *N*-Methylation. $NaBH_3CN$ was added to a stirred solution of the requisite amine and $(CH_2O)_n$ in MeOH, and the resultant mixture was stirred at rt for 18 h before being concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and H_2O, the aqueous layer was extracted with two portions of CH_2Cl_2, and the combined organic extracts were washed with brine, then dried and concentrated in vacuo.

(*RS*)-Non-1-en-4-ol 27. Allylmagnesium bromide (1.0 M, 50 mL, 50 mmol) was added to a stirred solution of **26** (5.70 mL, 4.75 mmol) in THF (125 mL) at 0 °C. The resultant mixture was allowed to warm to rt over 1 h. Saturated aq NH_4Cl (50 mL) was then added, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (100 mL), then dried and concentrated in vacuo to give (*RS*)-**27** as a colorless oil (6.02 g, 90%);[37] δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.1, C(9)H_3), 1.26−1.52 (8H, m, C(5)H_2, C(6)H_2, C(7)H_2, C(8)H_2), 2.14 (1H, dt, *J* 14.0, 7.9, C(3)H_A), 2.29−2.35 (1H, m, C(3)H_B), 3.62−3.69 (1H, m, C(4)*H*), 5.12−5.18 (2H, m, C(1)H_2), 5.79−5.89 (1H, m, C(2)*H*).

(*R*)-Non-1-en-4-ol 27. Allylmagnesium bromide (1.0 M, 11 mL, 11.0 mmol) was added to a stirred solution of (−)-Ipc_2BCl (4.24 g, 13.2 mmol) in Et_2O (60 mL) at −78 °C, and the resultant mixture was warmed to 0 °C over 1 h. The stirring was ceased, and the mother liquor was carefully transferred to another flask via cannula such that the white precipitate remained. The resultant solution was cooled to −78 °C, and a solution of **26** (1.08 mL, 8.79 mmol) in Et_2O (30 mL) was added. The resultant solution was stirred at −78 °C for 1 h, then phosphate pH 7 buffer (60 mL), MeOH (60 mL), and 30% aq H_2O_2 (30 mL) were added sequentially, and the resultant mixture was allowed to warm to rt. The reaction mixture was then stirred at rt for 30 min and poured into satd aq $NaHCO_3$ (100 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL), and the combined

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organic extracts were washed with satd aq $Na_2S_2O_3$ (100 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 2% → 10% Et_2O in 30−40 °C petrol) gave (*R*)-**27** as a colorless oil (959 mg, 77%, 96% ee); $[\alpha]^{24}_D$ +9.0 (*c* 1.0 in $CHCl_3$); {lit.[31] $[\alpha]^{25}_D$ +8.9 (*c* 1.1 in $CHCl_3$)}.

(*RS*)-4-(Benzyloxy)non-1-ene 28. NaH (60% dispersion in mineral oil, 1.55 g, 38.7 mmol) was added to a solution of (*RS*)-**27** (5.00 g, 35.2 mmol) in THF (100 mL) at rt, and the resultant mixture was stirred for 1 h. BnBr (4.39 mL, 36.9 mmol) was added, and the resultant mixture was stirred at rt for 18 h. H_2O (50 mL) was then cautiously added, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic extracts were then dried and concentrated in vacuo to give (*RS*)-**28** as a colorless oil (8.16 g, quant);[38] δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.2, C(9)H_3), 1.21−1.57 (8H, m, C(5)H_2, C(6)H_2, C(7)H_2, C(8)H_2), 2.30−2.36 (2H, m, C(3)H_2), 3.44 (1H, app quintet, *J* 5.8, C(4)*H*), 4.50 (1H, d, *J* 11.6, OC$H_A$$H_B$Ph), 4.57 (1H, d, *J* 11.6, OC$H_A$$H_B$Ph), 5.05−5.12 (2H, m, C(1)H_2), 5.81−5.92 (1H, m, C(2)*H*), 7.26−7.37 (5H, m, *Ph*).

Methyl (*RS*,*E*)-5-(Benzyloxy)dec-2-enoate 29. Grubbs II catalyst (92 mg, 108 μmol) and methyl acrylate (0.48 mL, 3.28 mmol) were added to a degassed solution of (*RS*)-**28** (500 mg, 2.15 mmol) in CH_2Cl_2 (6 mL, EtOH stabilized), and the resultant mixture was heated at 40 °C for 24 h, then allowed to cool to rt and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0% → 10% Et_2O in 30−40 °C petrol) gave (*RS*,*E*)-**29** as a colorless oil (461 mg, 74%, >99:1 dr); ν_{max} (ATR) 1724 (C═O), 1658 (C═C); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.1, C(10)H_3), 1.23−1.65 (8H, m, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2), 2.46 (2H, app t, *J* 6.6, C(4)H_2), 3.53 (1H, app quintet, *J* 5.8, C(5)*H*), 3.74 (3H, s, O*Me*), 4.51 (1H, d, *J* 11.6, OC$H_A$$H_B$Ph), 4.56 (1H, d, *J* 11.6, OC$H_A$$H_B$Ph), 5.90 (1H, d, *J* 15.6, C(2)*H*), 7.02 (1H, dt, *J* 15.6, 7.6, C(3)*H*), 7.26−7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(10)), 22.6, 25.0, 31.8, 34.0 (*C*(6), *C*(7), *C*(8), *C*(9)), 36.8 (*C*(4)), 51.4 (O*Me*), 71.1 (OCH_2Ph), 77.7 (*C*(5)), 123.0 (*C*(2)), 127.6, 127.8, 128.4 (*o*,*m*,*p*-*Ph*), 138.5 (*i*-*Ph*), 145.9 (*C*(3)), 166.8 (*C*(1)); *m*/*z* (ESI$^+$) 313 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{26}NaO_3^+$ ([M + Na]$^+$) requires 313.1774; found 313.1764.

***tert*-Butyl (*RS*,*E*) 5-(Benzyloxy)dec-2-enoate 30.** Grubbs II catalyst (121 mg, 143 μmol) and *tert*-butyl acrylate (4.87 mL, 33.2 mmol) were added to a degassed solution of (*RS*)-**28** (3.37 g, 14.5 mmol) in CH_2Cl_2 (33 mL, EtOH stabilized), and the resultant mixture was heated at 40 °C for 24 h, then allowed to cool to rt and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0% → 5% Et_2O in 30−40 °C petrol) gave (*RS*,*E*)-**30** as a colorless oil (4.10 g, 85%, >99:1 dr); $C_{21}H_{32}O_3$ requires C, 75.9%; H, 9.7%; found C%, 75.9; H, 9.6%; ν_{max} (ATR) 1713 (C═O), 1653 (C═C); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(10)H_3), 1.22−1.60 (8H, m, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2), 1.50 (9H, s, CMe_3), 2.41−2.46 (2H, m, C(4)H_2), 3.51 (1H, app quintet, *J* 5.6, C(5)*H*), 4.50 (1H, d, *J* 11.5, OC$H_A$$H_B$Ph), 4.56 (1H, d, *J* 11.5, OC$H_A$$H_B$Ph), 5.81 (1H, dt, *J* 15.6, 1.3, C(2)*H*), 6.90 (1H, dt, *J* 15.6, 7.3, C(3)*H*), 7.26−7.41 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(10)), 22.6, 25.0, 31.8, 34.0 (C(6), C(7), C(8), C(9)), 28.2 (*C*Me_3), 36.7 (*C*(4)), 71.1 (OCH_2Ph), 77.9 (*C*(5)), 80.1 (*C*Me_3), 125.1 (*C*(2)), 127.6, 127.8, 128.3 (*o*,*m*,*p*-*Ph*), 138.6 (*i*-*Ph*), 144.2 (*C*(3)), 165.8 (*C*(1)); *m*/*z* (ESI$^+$) 687 ([2M + Na]$^+$, 23%), 355 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{32}NaO_3^+$ ([M + Na]$^+$) requires 355.2244; found 355.2246.

***tert*-Butyl (*R*,*E*)-5-(Benzyloxy)dec-2-enoate 30.** *Step 1.* NaH (60% dispersion in mineral oil, 155 mg, 3.87 mmol) was added to a solution of (*R*)-**27** (500 mg, 3.52 mmol) in THF (5 mL) at rt, and the resultant mixture was stirred at rt for 1 h. BnBr (0.44 mL, 3.69 mmol) was then added, and the resultant mixture was stirred at rt for 18 h. H_2O (5 mL) was cautiously added, and the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic extracts were then dried and concentrated in vacuo to give (*R*)-**28** as a colorless oil (707 mg).

Step 2. Grubbs II catalyst (22 mg, 25.9 μmol) and *tert*-butyl acrylate (0.89 mL, 6.08 mmol) were added to a degassed solution of (*R*)-**28** (615 mg, 2.65 mmol) in CH_2Cl_2 (6 mL, EtOH stabilized), and the resultant mixture was heated at 40 °C for 24 h. The reaction mixture was then concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0% → 5% Et_2O in 30−40 °C petrol) gave (*R*,*E*)-**30** as a colorless oil (539 mg, 53% over two steps, >99:1 dr); $[\alpha]^{20}_D$ +10.9 (*c* 1.0 in $CHCl_3$).

Methyl (*RS*,*RS*)- and (*RS*,*SR*)-3-(*N*-Isopropyl-*N*-benzylamino)-5-(benzyloxy)decanoate 31. Following general procedure 1, *N*-isopropyl-*N*-benzylamine (0.34 mL, 2.06 mmol), BuLi (2.4 M, 0.83 mL, 2.00 mmol), and (*RS*,*E*)-**29** (375 mg, 1.29 mmol, >99:1 dr) in THF (10 mL) were reacted to give **31** in 50:50 dr. Purification via flash column chromatography (gradient elution, 2% → 10% Et_2O in 30−40 °C petrol) gave **31** as a colorless oil (266 mg, 47%, 50:50 dr);[39] ν_{max} (ATR) 1737 (C═O); δ_H (400 MHz, $CDCl_3$) 0.97 (6H, t, *J* 7.3, 2 × C(10)H_3), 1.09−1.14 (12H, m, 2 × CHMe_2), 1.25−1.68 (18H, m, C(4)H_A, C(4)H_A, 2 × C(6)H_2, 2 × C(7)H_2, 2 × C(8)H_2, 2 × C(9)H_2), 1.77 (1H, ddd, *J* 14.2, 7.3, 3.5, C(4)H_B), 2.01 (1H, app dt, *J* 13.9, 6.3, C(4)H_B), 2.40 (1H, dd, *J* 13.9, 6.8, C(2)H_A), 2.46 (1H, dd, *J* 13.8, 7.6, C(2)H_A), 2.63 (1H, dd, *J* 13.9, 7.1, C(2)H_B), 2.71 (1H, dd, *J* 13.8, 6.1, C(2)H_B), 3.05 (2H, app d, *J* 6.1, 2 × NC*H*Me_2), 3.45−3.76 (8H, m, 2 × C(3)*H*, 2 × C(5)*H*, 2 × NCH_2Ph), 3.69 (3H, s, O*Me*), 3.69 (3H, s, O*Me*), 4.32 (1H, d, *J* 11.3, OC$H_A$$H_B$Ph), 4.52 (1H, d, *J* 11.6, OC$H_A$$H_B$Ph), 4.53 (1H, d, *J* 11.3, OC$H_A$$H_B$Ph), 4.57 (1H, d, *J* 11.6, OC$H_A$$H_B$Ph), 7.22−7.42 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (2 × C(10)), 20.0, 20.6, 20.7, 21.2 (2 × NCH*Me*$_2$), 22.7, 22.8, 24.8, 24.9, 32.1, 32.2, 33.7, 33.9 (2 × *C*(6), 2 × *C*(7), 2 × C(8), 2 × C(9)), 37.4, 38.7 (2 × *C*(2)), 38.1 (2 × *C*(4)), 47.5, 48.2 (2 × NCHMe$_2$), 49.1, 49.3 (2 × NCH_2Ph), 51.3, 51.4 (O*Me*), 51.4, 52.1 (2 × C(3)), 70.3, 71.0 (2 × OCH_2Ph), 76.9, 77.2 (2 × *C*(5)), 126.6, 126.7, 127.3, 127.4, 127.6, 127.8, 128.1, 128.1, 128.2, 128.3, 128.5, 128.7 (*o*,*m*,*p*-*Ph*), 139.0, 139.2, 141.3, 141.5 (*i*-*Ph*), 173.1, 173.2 (2 × *C*(1)); *m*/*z* (ESI$^+$) 902 ([2M + Na]$^+$, 71%), 462 ([M + Na]$^+$, 100%), 440 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{42}NO_3^+$ ([M + H]$^+$) requires 440.3159; found 440.3166.

***tert*-Butyl (*RS*,*RS*) and (*RS*,*SR*)-3-(*N*-Isopropyl-*N*-benzylamino)-5-(benzyloxy)decanoate 32.** Following general procedure 1, *N*-isopropyl-*N*-benzylamine (0.30 mL, 1.77 mmol), BuLi (2.5 M, 0.69 mL, 1.72 mmol), and (*RS*,*E*)-**30** (369 mg, 1.11 mmol) in THF (5 mL) were reacted to give **32** in 50:50 dr. Purification via flash column chromatography (gradient elution, 1% → 9% Et_2O in 30−40 °C petrol) gave **32** as a colorless oil (411 mg, 82%, 50:50 dr);[40] ν_{max} (ATR) 1723 (C═O); δ_H (400 MHz, $CDCl_3$) 0.95−1.00 (6H, m, 2 × C(10)H_3), 1.11 (3H, app d, *J* 3.0, NCHMe_A), 1.12 (3H, app d, *J* 3.0, NCHMe_B), 1.15 (6H, app t, *J* 6.7, NCHMe_2), 1.23−1.66 (18H, m, 2 × C(4)H_A, 2 × C(6)H_2, 2 × C(7)H_2, 2 × C(8)H_2, 2 × C(9)H_2), 1.50 (9H, s, CMe_3), 1.54 (9H, s, CMe_3), 1.73 (1H, ddd, *J* 14.4, 8.3, 3.5, C(4)H_B), 2.02 (1H, ddd, *J* 13.9, 8.1, 5.3, C(4)H_B), 2.24−2.32 (2H, m, C(2)H_2), 2.66 (2H, app td, *J* 13.6, 5.6, C(2)H_2), 2.99−3.14 (2H, m, 2 × NC*H*Me$_2$), 3.35−3.43 (1H, m, C(3)*H*), 3.50−3.58 (2H, m, C(3)*H*, C(5)*H*), 3.61 (1H, d, *J* 14.2, NC$H_A$$H_B$Ph), 3.63−3.70 (1H, m, C(5)*H*), 3.64 (1H, d, *J* 14.2, NC$H_A$$H_B$Ph), 3.77 (2H, app d, *J* 14.2, 2 × NC$H_A$$H_B$Ph), 4.27 (1H, d, *J* 11.1, OC$H_A$$H_B$Ph), 4.50 (1H, d, *J* 11.1, OC$H_A$$H_B$Ph), 4.54 (1H, d, *J* 11.5, OC$H_A$$H_B$Ph), 4.58 (1H, d, *J* 11.5, OC$H_A$$H_B$Ph), 7.22−7.47 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1, 14.1 (2 × C(10)), 19.5, 19.8, 21.7, 21.8 (2 × NCH*Me*$_2$), 22.7, 22.8, 24.8, 24.9, 32.1, 32.2, 33.7, 33.9 (2 × *C*(6), 2 × *C*(7), 2 × *C*(8), 2 × C(9)), 28.1, 28.2 (2 × C*Me*$_3$), 37.4, 38.3 (2 × *C*(4)), 39.2, 39.9 (2 × *C*(2)), 47.5, 48.3 (2 × NCHMe$_2$), 49.1, 49.3 (2 × NCH_2Ph), 51.5, 52.1 (2 × *C*(3)), 70.3, 71.0 (2 × OCH_2Ph), 76.9, 77.1 (2 × *C*(5)), 80.1, 80.1 (2 × CMe_3), 128.6, 127.1, 127.4, 127.6, 127.8, 128.1, 128.1, 128.1, 128.3, 128.7, 128.9 (*o*,*m*,*p*-*Ph*), 139.2, 139.4, 141.4, 141.7 (*i*-*Ph*), 172.1, 172.3 (2 × *C*(1)); *m*/*z* (ESI$^+$) 986 ([2M + Na]$^+$, 75%), 504 ([M + Na]$^+$, 100%), 482 ([M + H]$^+$, 78%); HRMS (ESI$^+$) $C_{31}H_{48}NO_3^+$ ([M + H]$^+$) requires 482.3629; found 482.3614.

***tert*-Butyl (*R*,*R*,*R*)-3-[*N*-(3′-Chloropropyl)-*N*-(α-methylbenzyl)amino]-5-(benzyloxy)decanoate 33 and *tert*-Butyl (3*R*,5*S*,α*R*)-3-[*N*-(3′-Chloropropyl)-*N*-(α-methylbenzyl)-amino]-5-(benzyloxy)decanoate 34.** *Method A.* Following general procedure 1, (*R*)-*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amine[15] (6.60 g, 33.4 mmol), BuLi (2.5 M, 12.9 mL, 32.4 mmol), and (*RS*,*E*)-**30** (6.95 g, 20.9 mmol, >99:1 dr) in THF (190 mL) were reacted to give a 50:50 mixture of **33** and **34**. Purification via flash

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column chromatography (gradient elution, 5% → 6.25% Et_2O in 30–40 °C petrol) gave **34** as a colorless oil (5.11 g, 46%, >99:1 dr); $C_{32}H_{48}ClNO_3$ requires C, 72.5%; H, 9.1%; N, 2.6%; found C, 72.4%; H, 9.2%; N, 2.65%; $[\alpha]^{24}_D$ −11.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1718 (C═O); δ_H (500 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.3, C(10)H_3), 1.25–1.46 (6H, m, C(7)H_2, C(8)H_2, C(9)H_2), 1.38 (9H, s, CMe_3), 1.40 (3H, d, *J* 6.9, C(α)*Me*), 1.54–1.62 (4H, m, C(4)H_2, C(6)H_2), 1.85 (2H, app quintet, *J* 6.3, C(2′)H_2), 2.03–2.06 (2H, m, C(2)H_2), 2.56–2.68 (2H, m, C(1′)H_2), 3.44–3.55 (3H, m, C(3)*H*, C(3′)H_2), 3.56–3.61 (1H, m, C(5)*H*), 3.88 (1H, q, *J* 6.9, C(α)*H*), 4.31 (1H, d, *J* 11.2, OC$H_A$$H_B$Ph), 4.52 (1H, d, *J* 11.2, OC$H_A$$H_B$Ph), 7.18–7.35 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.1 (*C*(10)), 20.4 (C(α)*Me*), 22.7, 24.5, 32.2 (*C*(7), *C*(8), *C*(9)), 28.0 (C*Me*$_3$), 32.9 (*C*(2′)), 33.5, 37.5 (*C*(4), *C*(6)), 38.6 (*C*(2)), 42.8 (*C*(1′)), 43.2 (*C*(3′)), 52.8 (*C*(3)), 58.5 (*C*(α)), 69.8 (OCH_2Ph), 76.6 (*C*(5)), 80.0 (CMe_3), 126.9, 127.1, 127.5, 127.9, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 139.2, 144.0 (*i*-*Ph*), 172.0 (*C*(1)); *m*/*z* (ESI$^+$) 554 ([M(^{37}Cl) + Na]$^+$, 11%), 552 ([M(^{35}Cl) + Na]$^+$, 26%), 532 ([M(^{37}Cl) + H]$^+$, 97%), 530 ([M(^{35}Cl) + H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{49}{}^{37}ClNO_3{}^+$ ([M(^{37}Cl) + H]$^+$) requires 532.3366; found 532.3392; $C_{32}H_{49}{}^{35}ClNO_3{}^+$ ([M(^{35}Cl) + H]$^+$) requires 530.3395; found 530.3400. Further elution gave **33** as a colorless oil (4.57 g, 41%, >99:1 dr); $C_{32}H_{48}ClNO_3$ requires C, 72.5%; H, 9.1%; N, 2.6%; found C, 72.45%; H, 9.1%; N, 2.5%; $[\alpha]^{24}_D$ −16.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1724 (C═O); δ_H (500 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.3, C(10)H_3), 1.20–1.47 (9H, m, C(4)H_A, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2), 1.40 (3H, d, *J* 6.8, C(α)*Me*), 1.42 (9H, s, CMe_3), 1.71–1.80 (1H, m, C(2′)H_A), 1.82–1.91 (2H, m, C(4)H_B, C(2′)H_B), 2.09 (1H, dd, *J* 14.5, 7.3, C(2)H_A), 2.19 (1H, dd, *J* 14.5, 6.3, C(2)H_B), 2.57–2.69 (2H, m, C(1′)H_2), 3.37–3.50 (4H, m, C(3)*H*, C(5)*H*, C(3′)H_2), 3.85 (1H, q, *J* 6.8, C(α)*H*), 4.53 (2H, app s, OCH_2Ph), 7.20–7.25 (1H, m, *Ph*), 7.26–7.32 (5H, m, *Ph*), 7.32–7.40 (4H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.1 (*C*(10)), 19.6 (C(α)*Me*), 21.7, 23.8, 31.1, 32.7 (*C*(6), *C*(7), *C*(8), *C*(9)), 27.1 (C*Me*$_3$), 32.3 (*C*(2′)), 35.8 (*C*(4)), 37.1 (*C*(2)), 42.4, 42.4 (*C*(1′), *C*(3′)), 51.8 (*C*(3)), 57.9 (*C*(α)), 69.9 (OCH_2Ph), 75.7 (*C*(5)), 79.1 (CMe_3), 125.9, 126.4, 126.8, 126.8, 127.1, 127.3 (*o*,*m*,*p*-*Ph*), 137.9, 143.8 (*i*-*Ph*), 170.8 (*C*(1)); *m*/*z* (ESI$^+$) 554 ([M(^{37}Cl) + Na]$^+$, 36%), 552 ([M(^{35}Cl) + Na]$^+$, 94%), 532 ([M(^{37}Cl) + H]$^+$, 100%), 530 ([M(^{35}Cl) + H]$^+$, 93%); HRMS (ESI$^+$) $C_{32}H_{49}{}^{37}ClNO_3{}^+$ ([M(^{37}Cl) + H]$^+$) requires 532.3366; found 532.3389; $C_{32}H_{49}{}^{35}ClNO_3{}^+$ ([M-(^{35}Cl) + H]$^+$) requires 530.3395; found 530.3399.

Method B. Following general procedure 1, (*R*)-*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amine[15] (190 mg, 962 μmol), BuLi (2.3 M, 0.41 mL, 931 μmol), and (*R*,*E*)-**30** (200 mg, 602 μmol) in THF (5 mL) were reacted to give **33** in >99:1 dr. Purification via flash column chromatography (gradient elution, 2% → 10% Et_2O in 30–40 °C petrol) gave **33** as a colorless oil (267 mg, 84%, >99:1 dr).

***tert*-Butyl (*S*,*S*,*S*)-3-[*N*-(3′-Chloropropyl)-*N*-(α-methylbenzyl)-amino]-5-(benzyloxy)decanoate *ent*-33 and *tert*-Butyl (3*S*,5*R*,α*S*)-3-[*N*-(3′-Chloropropyl)-*N*-(α-methylbenzyl)amino]-5-(benzyloxy)decanoate *ent*-34.** Following general procedure 1, (*S*)-*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amine[15] (5.44 g, 27.6 mmol), BuLi (2.1 M, 12.6 mL, 26.5 mmol), and (*RS*,*E*)-**30** (6.91 g, 20.8 mmol, >99:1 dr) were reacted in THF (190 mL) to give a 50:50 mixture of *ent*-**33** and *ent*-**34**. Purification via flash column chromatography (gradient elution, 5% → 6.25% Et_2O in 30–40 °C petrol) gave *ent*-**34** as a yellow oil (4.36 g, 40%, >99:1 dr); $[\alpha]^{24}_D$ +13.3 (*c* 1.0 in $CHCl_3$). Further elution gave *ent*-**33** as a yellow oil (3.94 g, 36%, >99:1 dr); $[\alpha]^{24}_D$ +16.7 (*c* 1.0 in $CHCl_3$).

Methyl (*R*,*R*,*R*)-3-[*N*-(3′-Chloropropyl)-*N*-(α-methylbenzyl)-amino]-5-(benzyloxy)decanoate 35. Following general procedure 4, **33** (3.45 g, 10.8 mmol, >99:1 dr) and $SOCl_2$ (0.79 mL, 10.8 mmol) in MeOH (50 mL) were reacted. Purification via flash column chromatography (gradient elution, 0% → 6% Et_2O in 30–40 °C petrol) gave **35** as a yellow oil (2.25 g, 71%, >99:1 dr); $C_{29}H_{42}ClNO_3$ requires C, 71.4%; H, 8.7%; N, 2.9%; found C, 71.3%; H, 8.6%; N, 2.7%; $[\alpha]^{24}_D$ −30.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1735 (C═O); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.3, C(10)H_3), 1.26–1.59 (9H, m, C(4)H_A, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2), 1.41 (3H, d, *J* 6.8, C(α)*Me*), 1.75–1.83 (1H, m, C(2′)H_A), 1.85–1.96 (2H, m, C(4)H_B, C(2′)H_B), 2.22 (1H, dd, *J* 14.4, 6.3, C(2)H_A), 2.29 (1H, dd, *J* 14.4, 7.3, C(2)H_B), 2.63–2.75 (2H, m, C(1′)H_2), 3.41–3.47 (1H, m, C(5)*H*), 3.51 (2H, app t, *J* 6.3, C(3)*H*, C(3′)H_2), 3.54 (3H, s, O*Me*), 3.90 (1H, q, *J* 6.8, C(α)*H*), 4.49 (1H, d, *J* 11.5, OC$H_A$$H_B$Ph), 4.59 (1H, d, *J* 11.5, OC$H_A$$H_B$Ph), 7.21–7.26 (1H, m, *Ph*), 7.26–7.33 (5H, m, *Ph*), 7.34–7.40 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(10)), 19.0 (C(α)*Me*), 22.7, 24.7, 32.1, 33.7 (*C*(6), *C*(7), *C*(8), *C*(9)), 33.0 (*C*(2′)), 37.3 (*C*(4)), 37.4 (*C*(2)), 43.1 (*C*(1′)), 43.3 (*C*(3′)), 51.4 (O*Me*), 52.3 (*C*(3)), 58.4 (*C*(α)), 71.0 (OCH_2Ph), 76.7 (*C*(5)), 126.8, 127.5, 127.8, 127.8, 128.1, 128.3 (*o*,*m*,*p*-*Ph*), 144.7, 138.9 (*i*-*Ph*), 172.9 (*C*(1)); *m*/*z* (ESI$^+$) 512 ([M(^{37}Cl) + Na]$^+$, 34%), 510 ([M(^{35}Cl) + Na]$^+$, 81%), 490 ([M(^{37}Cl) + H]$^+$, 44%), 488 ([M(^{35}Cl) + H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{43}{}^{37}ClNO_3{}^+$ ([M(^{37}Cl) + H]$^+$) requires 490.2896; found 490.2905; $C_{29}H_{43}{}^{35}ClNO_3{}^+$ ([M(^{35}Cl) + H]$^+$) requires 488.2926; found 488.2921.

Methyl (3*R*,5*S*,α*R*)-3-[*N*-(3′-Chloropropyl)-*N*-(α-methylbenzyl)amino]-5-(benzyloxy)decanoate 36. Following general procedure 4, **34** (5.93 g, 11.2 mmol, >99:1 dr) and $SOCl_2$ (1.36 mL, 18.6 mmol) in MeOH (90 mL) were reacted. Purification via flash column chromatography (gradient elution, 0% → 6% Et_2O in 30–40 °C petrol) gave **36** as a colorless oil (3.91 g, 72%, >99:1 dr); $C_{29}H_{42}ClNO_3$ requires C, 71.4%; H, 8.7%; N, 2.9%; found C, 71.4%; H, 8.7%; N, 2.8%; $[\alpha]^{24}_D$ −11.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1733 (C═O); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.1, C(10)H_3), 1.29–1.45 (6H, m, C(7)H_2, C(8)H_2, C(9)H_2), 1.42 (3H, d, *J* 6.9, C(α)*Me*), 1.52–1.74 (4H, m, C(4)H_2, C(6)H_2), 1.84–1.93 (2H, m, C(2′)H_2), 2.17 (1H, dd, *J* 14.5, 6.1, C(2)H_A), 2.24 (1H, dd, *J* 14.5, 7.8, C(2)H_B), 2.61–2.75 (2H, m, C(1′)H_2), 3.47–3.63 (4H, m, C(3)*H*, C(5)*H*, C(3′)H_2), 3.57 (3H, s, O*Me*), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.36 (1H, d, *J* 11.5, OC$H_A$$H_B$Ph), 4.56 (1H, d, *J* 11.5, OC$H_A$$H_B$Ph), 7.20–7.26 (1H, m, *Ph*), 7.26–7.33 (5H, m, *Ph*), 7.34–7.40 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(10)), 19.9 (C(α)*Me*), 22.7, 24.7, 32.2 (*C*(7), *C*(8), *C*(9)), 32.9 (*C*(2′)), 33.7, 37.8 (*C*(4), *C*(6)), 37.5 (*C*(2)), 42.8 (*C*(3′)), 43.2 (*C*(1′)), 51.4 (O*Me*), 52.8 (*C*(3)), 58.3 (*C*(α)), 69.8 (OCH_2Ph), 76.9 (*C*(5)), 127.0, 127.3, 127.5, 127.8, 128.2, 128.3 (*o*,*m*,*p*-*Ph*), 139.1, 144.0 (*i*-*Ph*), 173.0 (*C*(1)); *m*/*z* (FI$^+$) 489 ([M(^{37}Cl)]$^+$, 32%), 487 ([M(^{35}Cl)]$^+$, 100%); HRMS (FI$^+$) $C_{29}H_{42}{}^{37}ClNO_3{}^+$ ([M(^{37}Cl)]$^+$) requires 489.2818; found 489.2833; $C_{29}H_{42}{}^{35}ClNO_3{}^+$ ([M(^{35}Cl)]$^+$) requires 487.2848; found 487.2867.

Methyl (*R*,*R*,*R*)-3-[*N*-(3′-Azidopropyl)-*N*-(α-methylbenzyl)-amino]-5-(benzyloxy)decanoate 37. Following general procedure 2, NaN_3 (557 mg, 8.56 mmol), NaI (1.28 g, 8.56 mmol), and **35** (2.09 g, 4.28 mmol, >99:1 dr) in DMSO (8 mL) were reacted. Purification via flash column chromatography (gradient elution, 0% → 6% Et_2O in 30–40 °C petrol) gave **37** as a yellow oil (1.93 g, 91%, >99:1 dr); $C_{29}H_{42}N_4O_3$ requires C, 70.4%; H, 8.6%; N, 11.3%; found C, 70.5%; H, 8.4%; N, 11.3%; $[\alpha]^{24}_D$ −33.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2095 (N≡N), 1737 (C═O); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.3, C(10)H_3), 1.26–1.62 (10H, m, C(4)H_A, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2, C(2′)H_A), 1.41 (3H, d, *J* 6.8, C(α)*Me*), 1.64–1.73 (1H, m, C(2′)H_B), 1.84–1.91 (1H, m, C(4)H_B), 2.23 (1H, dd, *J* 14.4, 6.3, C(2)H_A), 2.29 (1H, dd, *J* 14.4, 7.6, C(2)H_B), 2.54–2.66 (2H, m, C(1′)H_2), 3.23 (2H, t, *J* 6.6, C(3′)H_2), 3.39–3.46 (1H, m, C(5)*H*), 3.52–3.59 (1H, m, C(3)*H*), 3.55 (3H, s, O*Me*), 3.90 (1H, q, *J* 6.8, C(α)*H*), 4.48 (1H, d, *J* 11.4, OC$H_A$$H_B$Ph), 4.60 (1H, d, *J* 11.4, OC$H_A$$H_B$Ph), 7.21–7.26 (1H, m, *Ph*), 7.27–7.33 (5H, m, *Ph*), 7.34–7.40 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(10)), 18.9 (C(α)*Me*), 22.7, 24.7, 32.1, 33.7 (*C*(6), *C*(7), *C*(8), *C*(9)), 29.2 (*C*(2′)), 37.1 (*C*(4)), 37.5 (*C*(2)), 43.0 (*C*(1′)), 49.4 (*C*(3′)), 51.4 (O*Me*), 52.2 (*C*(3)), 58.3 (*C*(α)), 71.0 (OCH_2Ph), 76.7 (*C*(5)), 126.8, 127.5, 127.8, 127.9, 128.1, 128.3 (*o*,*m*,*p*-*Ph*), 138.9, 144.8 (*i*-*Ph*), 172.9 (*C*(1)); *m*/*z* (ESI$^+$) 517 ([M + Na]$^+$, 100%), 495 ([M + H]$^+$, 97%); HRMS (ESI$^+$) $C_{29}H_{43}N_4O_3{}^+$ ([M + H]$^+$) requires 495.3330; found 495.3326.

Methyl (3*R*,5*S*,α*R*)-3-[*N*-(3′-Azidopropyl)-*N*-(α-methylbenzyl)amino]-5-(benzyloxy)decanoate 38. Following general procedure 2, NaN_3 (783 mg, 12.0 mmol), NaI (1.80 g, 12.0 mmol), and **36** (2.94 g, 6.02 mmol, >99:1 dr) in DMSO (10 mL) were reacted. Purification via flash column chromatography (gradient elution, 0% → 6% Et_2O in 30–40 °C petrol) gave **38** as a yellow

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oil (2.36 g, 79%, >99:1 dr); $[\alpha]^{24}_{D}$ −9.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2095 (N≡N), 1736 (C═O); δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 6.8, C(10)H_3), 1.27−1.43 (6H, m, C(7)H_2, C(8)H_2, C(9)H_2), 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.50−1.75 (6H, m, C(4)H_2, C(6)H_2, C(2′)H_2), 2.19 (1H, dd, *J* 14.5, 6.3, C(2)H_A), 2.25 (1H, dd, *J* 14.5, 7.3, C(2)H_B), 2.58 (2H, t, *J* 7.6, C(1′)H_2), 3.23 (2H, t, *J* 6.6, C(3′)H_2), 3.50−3.59 (2H, m, C(3)*H*, C(5)*H*), 3.56 (3H, s, O*Me*), 3.90 (1H, q, *J* 6.8, C(α)*H*), 4.34 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.53 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 7.19−7.25 (1H, m, *Ph*), 7.25−7.31 (5H, m, *Ph*), 7.32−7.38 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(10)), 19.7 (C(α)*Me*), 22.7, 24.7, 29.2, 32.1, 33.7, 37.6 (*C*(4), *C*(6), *C*(7), *C*(8), *C*(9), *C*(2′)), 37.7 (*C*(2)), 42.9 (*C*(1′)), 49.4 (*C*(3′)), 51.4 (O*Me*), 53.0 (*C*(3)), 58.3 (*C*(α)), 69.9 (OCH_2Ph), 77.0 (*C*(5)), 127.0, 127.3, 127.5, 127.8, 128.2, 128.3 (*o,m,p-Ph*), 139.0, 144.1 (*i-Ph*), 173.0 (*C*(1)); *m/z* (ESI$^+$) 517 ([M + Na]$^+$, 100%), 495 ([M + H]$^+$, 95%); HRMS (ESI$^+$) $C_{29}H_{43}N_4O_3^+$ ([M + H]$^+$) requires 495.3330; found 495.3331.

(*R,R,R*)-4-[2′-(Benzyloxy)heptyl]-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one 41. *Step 1.* Following general procedure 3, **37** (2.45 g, 4.95 mmol, >99:1 dr) and PBu_3 (1.32 mL, 5.28 mmol) in THF (15 mL) and H_2O (1.7 mL) were reacted to give **39** as a yellow oil (3.48 g, >99:1 dr); δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.17 (1H, dd, *J* 14.3, 6.7, C(2)H_A), 2.25 (1H, dd, *J* 14.3, 7.2, C(2)H_B), 2.48−2.65 (4H, m, C(1′)H_2, C(3′)H_2), 3.35−3.50 (2H, m, C(3)*H*, C(5)*H*), 3.52 (3H, s, O*Me*), 3.91 (1H, q, *J* 6.8, C(α)*H*), 4.45 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.55 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 7.17−7.37 (10H, m, *Ph*).

Step 2. Following general procedure 5, **39** (3.48 g, >99:1 dr) and $Sb(OEt)_3$ (0.87 mL, 5.12 mmol) in PhMe (450 mL) were reacted. Purification via flash column chromatography (eluent EtOAc) gave **41** as a yellow oil (1.80 g, 83% over two steps, >99:1 dr); $[\alpha]^{24}_{D}$ −16.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1661 (C═O); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.0, C(7′)H_3), 1.06−1.16 (1H, br m, C(7)H_A), 1.24−1.45 (7H, m, C(7)H_B, C(4′)H_2, C(5′)H_2, C(6′)H_2), 1.37 (3H, d, *J* 6.6, C(α)*Me*), 1.49−1.59 (1H, m, C(1′)H_A), 1.62−1.76 (3H, m, C(1′)H_B, C(3′)H_2), 2.33 (1H, br s, C(3)H_A), 2.49 (1H, dd, *J* 12.4, 4.3, C(3)H_B), 2.52−2.60 (1H, m, C(6)H_A), 2.77 (1H, br t, *J* 13.1, C(6)H_B), 3.12−3.23 (1H, br m, C(8)H_A), 3.39 (1H, br s, C(8)H_B), 3.49−3.58 (1H, m, C(2′)*H*), 3.69−3.83 (2H, m, C(4)*H*, C(α)*H*), 4.44 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.62 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 5.51 (1H, br s, N*H*), 7.19−7.24 (1H, m, *Ph*), 7.25−7.30 (4H, m, *Ph*), 7.31−7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*(7′)), 22.7 (C(α)*Me*), 24.7, 32.4 (*C*(4′), *C*(5′), *C*(6′)), 32.2 (*C*(7)), 33.5 (*C*(3′)), 34.4 (*C*(1′)), 38.3 (*C*(3)), 41.7 (*C*(8)), 45.0 (*C*(6)), 52.4 (*C*(4)), 62.6 (*C*(α)), 71.1 (OCH_2Ph), 76.7 (*C*(2′)), 126.8, 127.4, 127.8, 128.0, 128.1, 128.3 (*o,m,p-Ph*), 138.9, *146.2* (*i-Ph*), 176.7 (*C*(2));[41] δ_H (500 MHz, PhMe-d_8, 363 K) 0.78−0.85 (1H, m, C(7)H_A), 0.94 (3H, t, *J* 6.6, C(7′)H_3), 1.10−1.19 (1H, m, C(7)H_B), 1.30−1.84 (10H, m, C(1′)H_2, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2), 1.34 (3H, d, *J* 6.6, C(α)*Me*), 2.25 (1H, dd, *J* 12.5, 7.6, C(3)H_A), 2.41 (1H, dd, *J* 12.5, 4.1, C(3)H_B), 2.46 (1H, app dt, *J* 15.5, 3.2, C(6)H_A), 2.65 (1H, app dt, *J* 12.6, 2.8, C(6)H_B), 2.69−2.76 (1H, m, C(8)H_A), 3.07−3.16 (1H, m, C(8)H_B), 3.55−3.62 (1H, m, C(2′)*H*), 3.70−3.79 (2H, m, C(4)*H*, C(α)*H*), 4.36 (1H, d, *J* 11.7, OCH_AH$_B$Ph), 4.53 (1H, d, *J* 11.7, OCH$_A$$H_B$Ph), 5.72 (1H, br s, N*H*), 7.05−7.13 (2H, m, *Ph*), 7.16 (2H, app t, *J* 7.6, *Ph*), 7.20 (2H, t, *J* 7.3, *Ph*), 7.29 (4H, app dd, *J* 14.5, 7.3, *Ph*); δ_C (125 MHz, PhMe-d_8, 363 K) 14.0 (*C*(7′)), 20.6 (C(α)*Me*), 22.9, 25.0, 33.2, 34.6, 34.9 (*C*(1′), *C*(3′), *C*(4′), *C*(5′), *C*(6′)), 32.5 (*C*(7)), 38.5 (*C*(3)), 41.2 (*C*(8)), 44.3 (*C*(6)), 53.1 (C(4)), 63.1 (*C*(α)), 71.4 (OCH_2Ph), 77.4 (*C*(2′)), 126.9, 127.4, 128.0, 128.2, 128.4, 128.4 (*o,m,p*-Ph), 139.9, 146.6 (*i-Ph*), 174.9 (*C*(2)); *m/z* (ESI$^+$) 896 ([2M + Na]$^+$, 97%), 459 ([M + Na]$^+$, 100%), 437 ([M + H]$^+$, 91%); HRMS (ESI$^+$) $C_{28}H_{41}N_2O_2^+$ ([M + H]$^+$) requires 437.3163; found 437.3159.

(*S,S,S*)-4-[2′-(Benzyloxy)heptyl]-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one *ent*-41. *Step 1.* Following general procedure 4, *ent*-**33** (3.69 g, 6.96 mmol, >99:1 dr) and $SOCl_2$ (0.91 mL, 12.5 mmol) in MeOH (60 mL) were reacted to give *ent*-**35** as a yellow oil (3.61 g, >99:1 dr).

Step 2. Following general procedure 2, NaN_3 (1.16 g, 17.9 mmol), NaI (2.68 g, 17.9 mmol), and *ent*-**35** (3.61 g, >99:1 dr) in DMSO (10 mL) were reacted to give *ent*-**37** as a yellow oil (3.18 g, >99:1 dr).

Step 3. Following general procedure 3, *ent*-**37** (3.18 g, >99:1 dr) and PBu_3 (1.77 mL, 7.09 mmol) in THF (30 mL) and H_2O (8.0 mL) were reacted to give *ent*-**39** as a yellow oil (3.05 g, >99:1 dr).

Step 4. Following general procedure 5, *ent*-**39** (3.05 g, >99:1 dr) and $Sb(OEt)_3$ (1.31 mL, 7.71 mmol) in PhMe (550 mL) were reacted. Purification via flash column chromatography (eluent EtOAc) gave *ent*-**41** as a yellow oil (1.81 g, 60% over four steps, >99:1 dr); $[\alpha]^{24}_{D}$ −2.7 (*c* 1.0 in $CHCl_3$).

(4*R*,2′*S*,α*R*)-4-[2′-(Benzyloxy)heptyl]-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one 42. *Step 1.* Following general procedure 3, **38** (2.55 g, 5.16 mmol, >99:1 dr) and PBu_3 (1.32 mL, 5.28 mmol) in THF (15 mL) and H_2O (1.7 mL) were reacted to give **40** as a yellow oil (3.54 g, >99:1 dr); δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.13−2.24 (2H, m, C(2)H_2), 2.52 (2H, td, *J* 7.3, 2.4, C(3′)H_2), 2.59−2.67 (2H, m, C(1′)H_2), 3.47−3.58 (2H, m, C(3)*H*, C(5)*H*), 3.54 (3H, s, O*Me*), 3.92 (1H, q, *J* 6.8, C(α)*H*), 4.32 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.51 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 7.16−7.36 (10H, m, *Ph*).

Step 2. Following general procedure 5, **40** (3.54 g, >99:1 dr) and $Sb(OEt)_3$ (0.87 mL, 5.12 mmol) in PhMe (450 mL) were reacted. Purification via flash column chromatography (eluent EtOAc) gave **42** as a yellow oil (1.86 g, 83% over two steps, >99:1 dr); $C_{28}H_{40}N_2O_2$ requires C, 77.0%; H, 9.2%; N, 6.4%; found C, 76.9%; H, 9.2%; N, 6.4%; $[\alpha]^{24}_{D}$ +2.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1658 (C═O); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.8, C(7′)H_3), 1.02−1.12 (1H, m, C(7)H_A), 1.19−1.63 (12H, m, C(7)H_B, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2, C(α)*Me*), 1.63−1.72 (1H, m, C(1′)H_A), 1.85 (1H, br s, C(1′)H_B), 2.50−2.61 (3H, m, C(3)H_2, C(6)H_A), 2.81−2.90 (1H, m, C(6)H_B), 3.17−3.32 (2H, m, C(8)H_2), 3.46 (1H, app quintet, *J* 5.8, C(2′)*H*), 3.54−3.64 (1H, m, C(4)*H*), 3.74 (1H, q, *J* 6.5, C(α)*H*), 4.50 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.55 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 5.55−5.66 (1H, m, N*H*), 7.19−7.24 (1H, m, *Ph*), 7.25−7.30 (4H, m, *Ph*), 7.31−7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*(7′)), 21.9 (C(α)*Me*), 22.7, 24.8, 32.0, 34.0 (*C*(3′), *C*(4′), *C*(5′), *C*(6′)), 32.4 (*C*(7)), 33.2 (*C*(1′)), 38.8 (*C*(3)), 42.5 (*C*(8)), 45.6 (*C*(6)), 54.2 (*C*(4)), 62.5 (*C*(α)), 70.5 (OCH_2Ph), 77.5 (*C*(2′)), 126.9, 127.4, 127.9, 128.0, 128.1, 128.3 (*o,m,p-Ph*), 138.9, 146.2 (*i-Ph*), 176.9 (*C*(2)); *m/z* (ESI$^+$) 896 ([2M + Na]$^+$, 100%), 874 ([2M + H]$^+$, 18%), 459 ([M + Na]$^+$, 96%), 437 ([M + H]$^+$, 94%); HRMS (ESI$^+$) $C_{28}H_{41}N_2O_2^+$ ([M + H]$^+$) requires 437.3163; found 437.3175.

(4*S*,2′*R*,α*S*)-4-[2′-(Benzyloxy)heptyl]-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one *ent*-42. *Step 1.* Following general procedure 4, *ent*-**34** (4.36 g, 8.22 mmol, >99:1 dr) and $SOCl_2$ (1.05 mL, 14.5 mmol) in MeOH (70 mL) were reacted to give *ent*-**36** sas a yellow oil (4.20 g, >99:1 dr).

Step 2. Following general procedure 2, NaN_3 (1.16 g, 17.9 mmol), NaI (2.68 g, 17.9 mmol), and *ent*-**36** (4.20 g, >99:1 dr) in DMSO (10 mL) were reacted to give *ent*-**38** as a yellow oil (3.66 g, >99:1 dr).

Step 3. Following general procedure 3, *ent*-**38** (3.66 g, >99:1 dr) and PBu_3 (2.03 mL, 8.13 mmol) in THF (30 mL) and H_2O (8.0 mL) were reacted to give *ent*-**40** as a yellow oil (3.46 g, >99:1 dr).

Step 4. Following general procedure 5, *ent*-**40** (3.46 g, >99:1 dr) and $Sb(OEt)_3$ (1.50 mL, 8.77 mmol) in PhMe (650 mL) were reacted. Purification via flash column chromatography (eluent EtOAc) gave *ent*-**42** as a yellow oil (2.48 g, 69% over four steps, >99:1 dr); $[\alpha]^{24}_{D}$ +16.0 (*c* 1.0 in $CHCl_3$).

(*R,R*)-4-(2′-Hydroxyheptyl)-1,5-diazocan-2-one 43. Following general procedure 7, **41** (140 mg, 321 μmol, >99:1 dr) and $Pd(OH)_2$/C (70 mg) in MeOH (2.1 mL) were reacted for 24 h to give **43** as a white solid (49 mg, 63%, >99:1 dr); mp 84−86 °C; $[\alpha]^{24}_{D}$ +7.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3289 (N−H, O−H), 1651 (C═O); δ_H (400 MHz, $CDCl_3$) 0.84 (3H, t, *J* 7.3, C(7′)H_3), 1.18−1.55 (12H, m, C(1′)H_2, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2), 1.61−1.74 (2H, m, C(7)H_2), 2.36 (1H, dd, *J* 12.5, 2.7, C(3)H_A), 2.53 (1H, dd, *J* 12.5, 9.7, C(3)H_B), 2.63−2.71 (1H, m, C(6)H_A), 3.06 (1H, dt, *J* 10.4, 4.4, C(6)H_B), 3.21−3.31 (2H, m, C(4)*H*, C(8)H_A), 3.40−3.50 (1H, m, C(8)H_B), 3.59−3.99 (3H, br m, C(2′)*H*, N(5)*H*, O*H*), 6.88 (1H, br s, N(1)*H*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(7′)), 22.6, 25.0, 31.8, 38.0 (*C*(3′),

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C(4′), C(5′), C(6′)), 33.9 (C(7)), 40.9 (C(3)), 41.0 (C(8)), 41.4 (C(1′)), 42.8 (C(6)), 58.9 (C(4)), 72.4 (C(2′)), 175.9 (C(2)); *m*/*z* (ESI$^+$) 507 ([2M + Na]$^+$, 100%), 485 ([2M + H]$^+$, 93%), 265 ([M + Na]$^+$, 51%), 243 ([M + H]$^+$, 97%); HRMS (ESI$^+$) $C_{13}H_{27}N_2O_2^+$ ([M + H]$^+$) requires 243.2067; found 243.2071.

(4*R*,2′*S*)-4-(2′-Hydroxyheptyl)-1,5-diazocan-2-one 44. Following general procedure 7, **42** (160 mg, 366 μmol, >99:1 dr) and Pd(OH)$_2$/C (80 mg) in MeOH (2 mL) were reacted for 24 h to give **44** as a colorless oil (72 mg, 81%, >99:1 dr); $[\alpha]^{24}_D$ +13.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3298 (N−H, O−H), 1649 (C═O); δ_H (400 MHz, $CDCl_3$) 0.83 (3H, t, *J* 6.8, C(7′)H_3), 1.16−1.77 (12H, m, C(7)H_2, C(1′)H_2, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2), 2.37 (1H, app d, *J* 12.1, C(3)H_A), 2.51−2.63 (2H, m, C(3)H_B, C(6)H_A), 3.03−3.12 (1H, m, C(6)H_B), 3.20−3.30 (1H, m, C(8)H_A), 3.30−3.39 (1H, m, C(4)*H*), 3.41−3.54 (1H, m, C(8)H_B), 3.69−3.77 (1H, m, C(2′)*H*), 4.06 (2H, br s, N(5)*H*, O*H*), 6.86 (1H, br s, N(1)*H*); δ_C (100 MHz, $CDCl_3$) 14.0 (C(7′)), 22.6, 25.5, 31.8, 33.2, 37.5 (C(7), C(3′), C(4′), C(5′), C(6′)), 39.6 (C(3)), 40.4 (C(8)), 41.8 (C(1′)), 43.1 (C(6)), 55.7 (C(4)), 68.7 (C(2′)), 176.4 (C(2)); *m*/*z* (ESI$^+$) 750 ([3M + Na]$^+$, 10%), 727 ([3M + H]$^+$, 4%), 507 ([2M + Na]$^+$, 100%), 265 ([M + Na]$^+$, 24%), 243 ([M + H]$^+$, 22%); HRMS (ESI$^+$) $C_{13}H_{27}N_2O_2^+$ ([M + H]$^+$) requires 243.2067; found 243.2066.

(*R*,*R*)-4-(2′-Hydroxyheptyl)-*N*(5)-methyl-1,5-diazocan-2-one 45. *Method A.* Following general procedure 8, **43** (97 mg, 400 μmol, >99:1 dr), $(CH_2O)_n$ (24 mg, 799 μmol), and $NaBH_3CN$ (101 mg, 1.61 mmol) in MeOH (4 mL) were reacted. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 19:1) gave **45** as a colorless oil (46 mg, 45%, >99:1 dr); $[\alpha]^{24}_D$ −1.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3291 (O−H), 1657 (C═O); δ_H (400 MHz, $CDCl_3$) 0.79 (3H, t, *J* 6.5, C(7′)H_3), 1.12−1.40 (9H, m, C(1′)H_A, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2), 1.43−2.57 (2H, m, C(7)H_A, C(1′)H_B), 1.88−1.99 (1H, m, C(7)H_B), 2.20−2.43 (2H, m, C(3)H_2), 2.45 (3H, s, N*Me*), 2.72 (1H, app br d, *J* 15.4, C(6)H_A), 2.97 (1H, app br t, *J* 12.4, C(6)H_B), 3.17−3.34 (3H, m, C(4)*H*, C(8)H_2), 3.68 (1H, br s, C(2′)*H*), 7.18 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 14.0 (C(7′)), 22.6, 25.0, 29.6, 31.8, 37.9 (C(7), C(1′), C(3′), C(4′), C(5′), C(6′)), 36.7 (C(3)), 39.0 (N*Me*), 41.9 (C(8)), 45.4 (C(6)), 63.4 (C(4)), 72.5 (C(2′)), 176.5 (C(2));[42] *m*/*z* (ESI$^+$) 535 ([2M + Na]$^+$, 25%), 279 ([M + Na]$^+$, 59%), 257 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{29}N_2O_2^+$ ([M + H]$^+$) requires 257.2224; found 257.2219.

Method B. Following general procedure 7, **41** (150 mg, 344 μmol, >99:1 dr), $(CH_2O)_n$ (21 mg, 699 μmol), and Pd(OH)$_2$/C (75 mg) in MeOH (2.0 mL) were reacted for 72 h. Purification via flash column chromatography (gradient elution, 1% → 8% MeOH in CH_2Cl_2) gave **47** as a colorless oil (12 mg, 14%, >99:1 dr); $[\alpha]^{24}_D$ −26.7 (*c* 0.6 in $CHCl_3$); ν_{max} (ATR) 1663 (C═O); δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.3, CH_3), 1.23−1.55 (10H, m, C(4)H_2, C(3)$CH_2CH_2CH_2CH_2$), 1.59−1.66 (1H, m, C(9)H_A), 1.69−1.78 (1H, m, C(9)H_B), 2.27 (1H, br s, C(5)H_A), 2.59 (1H, br t, *J* 10.7, C(5)H_B), 2.85 (2H, br s, C(10)H_2), 3.21−3.47 (4H, m, C(3)*H*, C(4a)*H*, C(8)H_2), 4.23 (1H, br d, *J* 9.2, C(1)H_A), 4.46 (1H, d, *J* 9.2, C(1)H_B), 5.98 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$) 14.0 (CH_3), 22.6, 24.7, 31.8, 33.2 (C(3)$CH_2CH_2CH_2CH_2$), 33.7 (C(9)), 36.2 (C(4)), 38.7 (C(5)), 42.8 (C(8)), 47.4 (C(10)), 58.6 (C(4a)), 77.0 (C(3)), 87.7 (C(1)), 175.3 (C(6)); *m*/*z* (ESI$^+$) 531 ([2M + Na]$^+$, 88%), 509 ([2M + H]$^+$, 54%), 277 ([M + Na]$^+$, 100%), 255 ([M + H]$^+$, 86%); HRMS (ESI$^+$) $C_{14}H_{27}N_2O_2^+$ ([M + H]$^+$) requires 255.2067; found 255.2068. Further elution gave **45** as a colorless oil (26 mg, 29%, >99:1 dr).

Method C. Following general procedure 7, **41** (750 mg, 1.72 mmol, >99:1 dr), $(CH_2O)_n$ (98 mg, 3.26 mmol), and Pd(OH)$_2$/C (375 mg) in AcOH (11.3 mL) were reacted for 24 h. The residue was partitioned between $CHCl_3$ (10 mL) and satd aq $NaHCO_3$ (10 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 10 mL), and the combined organic extracts were then dried (Na_2SO_4) and concentrated in vacuo to give **45** as a colorless oil (395 mg, 90%, >99:1 dr).

(*S*,*S*)-4-(2′-Hydroxyheptyl)-*N*(5)-methyl-1,5-diazocan-2-one *ent*-45. Following general procedure 7, *ent*-**41** (1.75 g, 4.01 mmol, >99:1 dr), $(CH_2O)_n$ (229 mg, 7.63 mmol), and Pd(OH)$_2$/C (875 mg) in AcOH (25 mL) were reacted for 24 h. The residue was partitioned between $CHCl_3$ (30 mL) and satd aq $NaHCO_3$ (30 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 30 mL), and the combined organic extracts were then dried (Na_2SO_4) and concentrated in vacuo to give *ent*-**45** as a colorless oil (1.03 g, quant, >99:1 dr); $[\alpha]^{24}_D$ +1.1 (*c* 1.0 in $CHCl_3$).

(4*R*,2′*S*)-4-(2′-Hydroxyheptyl)-*N*(5)-methyl-1,5-diazocan-2-one 46. *Method A.* Following general procedure 8, **44** (70 mg, 289 μmol, >99:1 dr), $(CH_2O)_n$ (17 mg, 578 μmol), and $NaBH_3CN$ (73 mg, 1.16 mmol) in MeOH (3 mL) were reacted. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 19:1) gave **46** as a colorless oil (30 mg, 40%, >99:1 dr); $[\alpha]^{24}_D$ −1.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3293 (O−H), 1654 (C═O); δ_H (400 MHz, $CDCl_3$) 0.79 (3H, t, *J* 6.6, C(7′)H_3), 1.15−1.50 (10H, m, C(7)H_A, C(1′)H_A, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2), 1.70−1.85 (2H, m, C(7)H_B, C(1′)H_B), 2.40 (5H, app s, C(3)H_2, N*Me*), 2.57 (1H, br dt, *J* 15.4, 3.5, C(6)H_A), 2.85 (1H, app br t, *J* 12.1, C(6)H_B), 3.16−3.28 (3H, m, C(4)*H*, C(8)H_2), 3.57 (1H, br s, C(2′)*H*), 3.89 (1H, br s, O*H*), 7.05 (1H, br t, *J* 6.6, N*H*); δ_C (100 MHz, $CDCl_3$) 14.0 (C(7′)), 22.6, 25.6, 30.4, 31.9, 36.9, 37.7 (C(7), C(1′), C(3′), C(4′), C(5′), C(6′)), 37.2 (C(3)), 40.1 (N*Me*), 41.6 (C(8)), 45.7 (C(6)), 60.0 (C(4)), 70.0 (C(2′)), 177.1 (C(2)); *m*/*z* (ESI$^+$) 535 ([2M + Na]$^+$, 44%), 279 ([M + Na]$^+$, 65%), 257 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{29}N_2O_2^+$ ([M + H]$^+$) requires 257.2224; found 257.2220.

Method B. Following general procedure 7, **42** (154 mg, 353 μmol, >99:1 dr), $(CH_2O)_n$ (20 mg, 666 μmol), and Pd(OH)$_2$/C (77 mg) in AcOH (2.3 mL) were reacted for 24 h. The residue was partitioned between $CHCl_3$ (10 mL) and satd aq $NaHCO_3$ (10 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 10 mL), and the combined organic extracts were then dried (Na_2SO_4) and concentrated in vacuo to give **46** as a colorless oil (90 mg, quant, >99:1 dr).

(4*S*,2′*R*)-4-(2′-Hydroxyheptyl)-*N*(5)-methyl-1,5-diazocan-2-one *ent*-46. Following general procedure 7, *ent*-**42** (50 mg, 115 μmol, >99:1 dr), $(CH_2O)_n$ (7 mg, 233 μmol), and Pd(OH)$_2$/C (25 mg) in AcOH (0.75 mL) were reacted for 24 h. The residue was partitioned between $CHCl_3$ (4 mL) and satd aq $NaHCO_3$ (4 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 44 mL), and the combined organic extracts were then dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 1% → 5% MeOH in $CHCl_3$) gave *ent*-**46** as a colorless oil (25 mg, 85%, >99:1 dr); $[\alpha]^{24}_D$ +1.3 (*c* 1.0 in $CHCl_3$).

(4′*R*,4″*R*,2‴*S*,α*R*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-{2″-oxo-4″-[2‴-(benzyloxy)heptyl]-*N*(5″)-(α-methylbenzyl)-1″,5″-diazocan-*N*(1′)-yl}butane 48. Following general procedure 6B, **42** (104 mg, 238 μmol, >99:1 dr), **18**[15] (75 mg, 216 μmol), and KOH (48 mg, 864 μmol) in DMSO (0.5 mL) were reacted for 96 h. Purification via column chromatography (gradient elution, 0% → 3% MeOH in $CHCl_3$) gave **48** as a colorless oil (32 mg, 21%, >99:1 dr); $[\alpha]^{24}_D$ −16.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1632 (C═O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.85−1.01 (7H, m, C(4′)$(CH_2)_4CH_3$, C(7″)H_A, C(7‴)H_3), 1.18−1.69 (27H, m, C(2)H_2, C(3)H_2, C(7′)H_A, C(4′)$(CH_2)_4$, C(7″)H_B, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2, C(α)*Me*), 1.98 (1H, br s, C(7′)H_B), 2.33 (3H, s, N*Me*), 2.34−2.48 (4H, m, C(3′)H_2, C(6′)H_A, C(3″)H_A), 2.53 (1H, br dt, *J* 15.1, 2.5, C(6″)H_A), 2.58−2.77 (3H, m, C(6′)H_B, C(3″)H_B, C(6″)H_B), 2.86−2.93 (1H, m, C(4′)*H*), 3.02−3.21 (3H, m, $NCH_AH_B(CH_2)_2CH_2$), 3.22−3.33 (3H, m, $NCH_AH_B(CH_2)_2CH_2$, C(8′)H_A, C(8″)H_A), 3.35−3.45 (1H, m, C(8″)H_B), 3.45−3.60 (3H, m, C(8′)H_B, C(4″)*H*, C(2‴)*H*), 3.75 (1H, q, *J* 6.3, C(α)*H*), 4.56 (2H, s, OCH_2Ph), 6.98−7.03 (1H, m, *Ph*), 7.06−7.13 (2H, m, *Ph*), 7.15−7.23 (4H, m, *Ph*), 7.25−7.30 (2H, m, *Ph*), 7.39−7.45 (1H, m, *Ph*); δ_C (125 MHz, PhMe-d_8, 363 K) 14.0 (C(4′)$(CH_2)_4CH_3$, C(7‴)), 21.3 (C(α)*Me*), 22.9, 25.2, 26.1, 27.0, 29.1, 31.5, 32.3, 32.4, 34.4 (C(2), C(3), C(4′)$(CH_2)_4$, C(1‴), C(3‴), C(4‴), C(5‴), C(6‴)), 30.5 (C(7″)), 34.6 (C(7′)), 39.0 (C(3″)), 39.9 (N*Me*), 40.4 (C(3′)), 44.7 (C(6″)), 45.8, 47.4, 47.7 (C(1), C(4), C(8′)), 45.8 (C(8″)), 47.2 (C(6′)), 54.9 (C(4″)), 62.6 (C(α)), 63.6 (C(4′)), 70.8 (OCH_2Ph), 77.9 (C(2‴)), 127.1, 127.3, 128.1, 128.3, 129.0 (*o*,*m*,*p*-*Ph*), 140.2, 146.6 (*i*-*Ph*), 172.3 (C(2′), C(2″)); *m*/*z* (ESI$^+$) 726 ([M + Na]$^+$, 100%), 704 ([M + H]$^+$, 56%); HRMS (ESI$^+$) $C_{44}H_{71}N_4O_3^+$ ([M + H]$^+$) requires 703.5521; found 703.5537.

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(4′*R*,4″*R*,2‴*S*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-(2‴-hydroxyheptyl)-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl]butane 49. *Method A.* Following general procedure 6A, **46** (39 mg, 152 μmol, >99:1 dr), **18**[15] (48 mg, 138 μmol), KOH (34 mg, 609 μmol), K_2CO_3 (26 mg, 185 μmol), and TEBAC (4 mg, 19.0 μmol) in DMSO (0.75 mL) were reacted for 48 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in $CHCl_3$) gave **49** as a colorless oil (19 mg, 26%, >99:1 dr); $[\alpha]^{24}_D$ −18.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3399 (O−H), 1626 (C═O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.88−0.97 (6H, m, C(7‴)H_3, C(4′)$(CH_2)_4CH_3$), 1.21−1.63 (26H, m, C(2)H_2, C(3)H_2, C(7′)H_2, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2, C(4′)$(CH_2)_4$), 2.31 (3H, s, N*Me*), 2.32−2.47 (4H, m, C(3′)H_2, C(6′)H_A, C(6″)H_A), 2.33 (3H, s, N*Me*), 2.51−2.58 (2H, m, C(3″)H_2), 2.64 (1H, app ddd, *J* 15.5, 11.0, 2.8, C(6″)H_B), 2.72 (1H, app ddd, *J* 14.8, 10.1, 3.5, C(6′)H_B), 2.87−2.96 (1H, m, C(4′)*H*), 3.01 (1H, dt, *J* 15.5, 4.7, C(8″)H_A), 3.07−3.43 (8H, m, C(1)H_2, C(4)H_2, C(8′)H_2, C(4″)*H*, C(8″)H_B), 3.61−3.69 (1H, m, C(2‴)*H*); δ_C (125 MHz, PhMe-d_8, 363 K) 14.2, 14.2 (*C*(7‴), C(4′)$(CH_2)_4CH_3$), 23.1, 23.2, 26.1, 26.1, 26.2, 27.2, 29.1, 29.4, 30.3, 32.5, 32.7, 38.3, 38.7 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), *C*(6‴), C(4′)$(CH_2)_4$), 39.2, 39.5 (*C*(3′), *C*(3″)), 40.2 (N*Me*), 40.8 (N*Me*), 46.0, 46.0, 46.3, 47.2, 47.5, 47.7 (*C*(1), *C*(4), *C*(6′), *C*(6″), *C*(8′), *C*(8″)), 61.9 (*C*(4″)), 63.9 (*C*(4′)), 70.2 (*C*(2‴)), 172.7, 173.2 (*C*(2′), *C*(2″)); *m*/*z* (ESI$^+$) 545 ([M + Na]$^+$, 100%), 523 ([M + H]$^+$, 95%); HRMS (ESI$^+$) $C_{30}H_{59}N_4O_3^+$ ([M + H]$^+$) requires 523.4582; found 523.4577.

Method B. Following general procedure 7, **48** (25 mg, 35.6 μmol, >99:1 dr), $(CH_2O)_n$ (2 mg, 66.6 μmol), and Pd(OH)$_2$/C (13 mg) in AcOH (1.0 mL) were reacted for 24 h. The residue was partitioned between $CHCl_3$ (5 mL) and satd aq $NaHCO_3$ (5 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 5 mL), and the combined organic extracts were then dried (Na_2SO_4) and concentrated in vacuo. Purification via column chromatography (gradient elution, 0% → 3% MeOH in $CHCl_3$) gave **49** as a colorless oil (7 mg, 38%, >99:1 dr).

(*R*,*R*,*R*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-(2‴-hydroxyheptyl)-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl]butane [(−)-hoprominol] 50. Following general procedure 6A, **45** (39 mg, 152 μmol, >99:1 dr), **18**[15] (48 mg, 138 μmol), KOH (34 mg, 609 μmol), K_2CO_3 (26 mg, 185 μmol), and TEBAC (4 mg, 19.0 μmol) in DMSO (0.75 mL) were reacted for 48 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in $CHCl_3$) gave **50** as a colorless oil (17 mg, 24%, >99:1 dr); $[\alpha]^{24}_D$ −17.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3390 (O−H), 1626 (C═O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.88−0.99 (6H, m, C(7‴)H_3, C(4′)$(CH_2)_4CH_3$), 1.15−1.63 (26H, m, C(2)H_2, C(3)H_2, C(7′)H_2, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2, C(4′)$(CH_2)_4$), 2.26 (3H, s, N*Me*), 2.31−2.46 (6H, m, C(3′)H_2, C(6′)H_A, C(3″)H_2, C(6″)H_A), 2.33 (3H, s, N*Me*), 2.72 (2H, app ddd, *J* 15.1, 10.4, 3.2, C(6′)H_B, C(6″)H_B), 2.87−2.95 (1H, m, C(4′)*H*), 2.98−3.42 (9H, m, C(1)H_2, C(4)H_2, C(8′)H_2, C(4″)*H*, C(8″)H_2), 3.72−3.79 (1H, m, C(2‴)*H*); δ_C (125 MHz, PhMe-d_8, 363 K) 14.2, 14.2 (*C*(7‴), C(4′)$(CH_2)_4CH_3$), 23.1, 23.2, 25.8, 26.1, 26.3, 27.2, 28.3, 29.4, 30.3, 31.7, 32.5, 32.7, 38.6 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), *C*(6‴), C(4′)$(CH_2)_4$), 38.8, 39.2 (*C*(3′), *C*(3″)), 39.4 (N*Me*), 40.2 (N*Me*), 46.0, 46.1, 46.2, 47.5, 47.5, 47.7 (*C*(1), *C*(4), *C*(6′), *C*(6″), *C*(8′), *C*(8″)), 63.1 (*C*(4″)), 63.9 (*C*(4′)), 71.9 (*C*(2‴)), 172.3, 172.7 (*C*(2′), *C*(2″)); *m*/*z* (ESI$^+$) 545 ([M + Na]$^+$, 100%), 523 ([M + H]$^+$, 98%); HRMS (ESI$^+$) $C_{30}H_{59}N_4O_3^+$ ([M + H]$^+$) requires 523.4582; found 523.4577.

(4′*R*,4″*S*,2‴*R*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-(2‴′-hydroxyheptyl)-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl]butane 51. Following general procedure 6A, *ent*-**46** (74 mg, 289 μmol, >99:1 dr), **18**[15] (91 mg, 262 μmol), KOH (65 mg, 1.15 mmol), K_2CO_3 (48 mg, 349 μmol), and TEBAC (8 mg, 35.9 μmol) in DMSO (1.4 mL) were reacted for 60 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in $CHCl_3$) gave **51** as a colorless oil (36 mg, 26%, >99:1 dr); $[\alpha]^{24}_D$ −2.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3391 (O−H), 1625 (C═O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.89−0.95 (6H, m, C(7‴)H_3, C(4′)$(CH_2)_4CH_3$), 1.23−1.73 (26H, m, C(2)H_2, C(3)H_2, C(7′)H_2, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2, C(4′)$(CH_2)_4$), 2.30 (3H, s, N*Me*), 2.32−2.46 (4H, m, C(3′)H_2, C(6′)H_A, C(6″)H_A), 2.33 (3H, s, N*Me*), 2.52−2.57 (2H, m, C(3″)H_2), 2.63 (1H, ddd, *J* 14.8, 11.0, 3.2, C(6″)H_B), 2.72 (1H, ddd, *J* 13.9, 10.1, 2.8, C(6′)H_B), 2.88−2.93 (1H, m, C(4′)*H*), 3.00 (1H, app dt, *J* 15.1, 4.7, C(8″)H_A), 3.05−3.42 (8H, m, C(1)H_2, C(4)H_2, C(8′)H_2, C(4″)*H*, C(8″)H_B), 3.61−3.67 (1H, m, C(2‴)*H*); δ_C (125 MHz, PhMe-d_8, 363 K) 14.2, 14.2 (*C*(7‴), C(4′)$(CH_2)_4CH_3$), 23.1, 23.2, 26.1, 26.1, 26.2, 27.2, 29.1, 29.4, 31.7, 32.5, 32.7, 38.3, 38.7 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), *C*(6‴), C(4′)$(CH_2)_4$), 39.2, 39.5 (*C*(3′), *C*(3″)), 40.2 (N*Me*), 40.8 (N*Me*), 45.9, 46.0, 46.2, 47.1, 47.5, 47.7 (*C*(1), *C*(4), *C*(6′), *C*(6″), *C*(8′), *C*(8″)), 61.9 (*C*(4″)), 63.9 (*C*(4′)), 70.3 (*C*(2‴)), 172.7, 173.2 (*C*(2′), *C*(2″)); *m*/*z* (ESI$^+$) 545 ([M + Na]$^+$, 58%), 523 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{59}N_4O_3^+$ ([M + H]$^+$) requires 523.4582; found 523.4574.

(4′*R*,4″*S*,2‴*S*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-(2‴-hydroxyheptyl)-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl}butane 52. Following general procedure 6A, *ent*-**45** (142 mg, 554 μmol, >99:1 dr), **18** (175 mg, 504 μmol), KOH (125 mg, 2.23 mmol), K_2CO_3 (92 mg, 664 μmol), and TEBAC (15 mg, 66 μmol) were reacted in DMSO (2.9 mL) for 60 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in $CHCl_3$) and further purification via supercritical fluid chiral HPLC (eluent MeOH/CO_2/diethanolamine, 49.9:50:0.1) gave **52** as a colorless oil (11 mg, 4%, >99:1 dr); $[\alpha]^{24}_D$ +5.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3405 (O−H), 1622 (C═O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.88−1.01 (6H, m, C(7‴)H_3, C(4′)$(CH_2)_4CH_3$), 1.14−1.68 (26H, m, C(2)H_2, C(3)H_2, C(7′)H_2, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2, C(4′)$(CH_2)_4$), 2.26 (3H, s, N*Me*), 2.28−2.50 (6H, m, C(3′)H_2, C(6′)H_A, C(3″)H_2, C(6″)H_A), 2.34 (3H, s, N*Me*), 2.72 (2H, app t, *J* 12.5, C(6′)H_B, C(6″)H_B), 2.91 (1H, br s, C(4′)*H*), 2.99−3.44 (9H, m, C(1)H_2, C(4)H_2, C(8′)H_2, C(4″)*H*, C(8″)H_2), 3.76 (1H, br s, C(2‴)*H*), 3.95 (1H, br s, O*H*); δ_C (125 MHz, PhMe-d_8, 363 K) 14.2, 14.2 (*C*(7′), *C*(7″)), 23.1, 23.2, 25.8, 26.1, 26.3, 27.3, 28.3, 29.4, 31.7, 32.5, 32.7, 38.6, 38.7 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), *C*(6‴), C(4′)$(CH_2)_4$), 38.8, 39.3 (*C*(3′), *C*(3″)), 39.3 (N*Me*), 40.2 (N*Me*), 46.0, 46.1, 46.2, 47.4, 47.5, 47.7 (*C*(1), *C*(4), *C*(6′), *C*(6″), *C*(8′), *C*(8″)), 63.1 (*C*(4″)), 63.9 (*C*(4′)), 71.9 (*C*(2‴)), 172.3, 172.7 (*C*(2′), *C*(2″)); *m*/*z* (ESI$^+$) 545 ([M + Na]$^+$, 62%), 523 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{59}N_4O_3^+$ ([M + H]$^+$) requires 523.4582; found 523.4588.

(*S*)-*N*(1)-(4′-Bromobutyl)-4-phenyl-*N*(5)-methyl-1,5-diazocan-2-one 54. Following general procedure 6B, **53**[15] (150 mg, 687 μmol, >99:1 er), 1,4-dibromobutane (0.24 mL, 2.01 mmol), and KOH (155 mg, 2.76 mmol) in DMSO (1.4 mL) were reacted for 18 h. Purification via column chromatography (gradient elution, 50% → 100% Et_2O in 30−40 °C petrol) gave **54** as a yellow oil (143 mg, 59%); $[\alpha]^{24}_D$ −15.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1635 (C═O); δ_H (400 MHz, $CDCl_3$) 1.57−1.95 (6H, m, C(7)H_2, C(2′)H_2, C(3′)H_2), 2.27 (3H, s, N*Me*), 2.45−2.56 (2H, m, C(3)H_A, C(6)H_A), 2.99 (1H, ddd, *J* 15.4, 7.8, 3.0, C(6)H_B), 3.11−3.20 (2H, m, C(3)H_B, C(1′)H_A), 3.30 (1H, app dt, *J* 15.4, 3.5, C(8′)H_A), 3.41−3.51 (2H, m, C(4′)H_2), 3.68−3.75 (1H, m, C(1′)H_B), 3.85 (1H, app br t, *J* 13.5, C(8)H_B), 4.00 (1H, dd, *J* 11.6, 3.3, C(4)*H*), 7.22−7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.7 (*C*(7)), 29.9 (*C*(3′)), 30.0 (*C*(2′)), 33.7 (*C*(4′)), 41.1 (*C*(3)), 43.8 (N*Me*), 45.3 (*C*(1′)), 48.1 (*C*(8)), 50.9 (*C*(6)), 67.9 (*C*(4)), 127.2, 127.5, 128.3 (*o*,*m*,*p*-*Ph*), 141.7 (*i*-*Ph*), 173.5 (*C*(2)); *m*/*z* (ESI$^+$) 377 ([M(^{81}Br) + Na]$^+$, 96%), 375 ([M(^{79}Br) + Na]$^+$, 95%), 355 ([M(^{81}Br) + H]$^+$, 100%), 353 ([M(^{79}Br) + H]$^+$, 94%); HRMS (ESI$^+$) $C_{17}H_{26}{}^{81}BrN_2O^+$ ([M(^{81}Br) + H]$^+$) requires 355.1203; found 355.1202; $C_{17}H_{26}{}^{79}BrN_2O^+$ ([M(^{79}Br) + H]$^+$) requires 353.1223; found 353.1219.

(4′*S*,4″*R*,2‴*S*)-1-[2′-Oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-(2‴-hydroxyheptyl)-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl]butane 55. Following general procedure 6A, **46** (39 mg, 152 μmol), **54** (49 mg, 138 μmol, >99:1 dr), KOH (34 mg, 609 μmol), K_2CO_3 (26 mg, 185 μmol), and TEBAC (4 mg, 19.0 μmol) in DMSO (0.75 mL) were reacted for 48 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in $CHCl_3$) gave **55** as a colorless oil (26 mg, 36%, >99:1 dr); $[\alpha]^{24}_D$ −9.3

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(*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3401 (O−H), 1625 (C═O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.89−0.97 (3H, m, C(7‴)H_3), 1.26−1.73 (18H, m, C(2)H_2, C(3)H_2, C(7′)H_2, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2), 2.18 (3H, s, N(5′)*Me*), 2.30 (3H, s, N(5″)*Me*), 2.31−2.44 (2H, m, C(3″)H_A, C(6″)H_A), 2.51−2.67 (4H, m, C(3′)H_A, C(6′)H_2, C(3″)H_B), 2.72 (1H, ddd, *J* 15.5, 7.6, 2.8, C(6″)H_B), 2.91 (1H, app t, *J* 11.4, C(3′)H_B), 2.96−3.12 (4H, m, C(1)H_A, C(8′)H_A, C(4″)*H*, C(8″)H_A), 3.19−3.33 (2H, m, C(4)H_A, C(8′)H_B), 3.34−3.41 (1H, m, C(4)H_B), 3.50 (1H, br t, *J* 12.9, C(8″)H_B), 3.62−3.70 (2H, m, C(1)H_B, C(2‴)*H*), 3.99 (1H, dd, *J* 11.4, 3.2, C(4′)*H*), 7.05−7.09 (1H, m, *Ph*), 7.14−7.20 (4H, m, *Ph*); δ_C (125 MHz, PhMe-d_8, 363 K) 14.2 (*C*(7‴)), 23.2, 26.0, 26.1, 26.4, 29.0, 30.3, 30.6, 32.6, 38.3 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), *C*(6‴)), 38.7 (*C*(3″)), 39.5 (N(5″)*Me*), 42.0 (*C*(3′)), 43.4 (N(5′)*Me*), 46.0 (*C*(4)), 46.4 (*C*(1), *C*(6″)), 47.1 (*C*(8′)), 48.1 (*C*(8″)), 51.5 (*C*(6′)), 62.0 (*C*(4″)), 68.8 (*C*(4′)), 70.2 (*C*(2‴)), 128.0, 128.4, 128.6 (*o*,*m*,*p*-*Ph*), 143.5 (*i*-*Ph*), 172.7 (*C*(2″)), 173.2 (*C*(2′)); *m*/*z* (ESI$^+$) 551 ([M + Na]$^+$, 100%), 529 ([M + H]$^+$, 92%); HRMS (ESI$^+$) $C_{31}H_{52}N_4NaO_3^+$ ([M + Na]$^+$) requires 551.3932; found 551.3918.

(4′*S*,4″*R*,2‴*R*)-1-[2′-Oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-(2‴-hydroxyheptyl)-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl]butane [(−)-Hopromalinol] 56. Following general procedure 6A, **45** (39 mg, 152 μmol, >99:1 dr), **54** (49 mg, 138 μmol), KOH (34 mg, 609 μmol), K_2CO_3 (26 mg, 185 μmol), and TEBAC (4 mg, 19.0 μmol) in DMSO (0.75 mL) were reacted for 48 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in $CHCl_3$) gave **56** as a colorless oil (41 mg, 56%, >99:1 dr); $[\alpha]^{24}_D$ −16.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3385 (O−H), 1623 (C═O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.90 (3H, br s, C(7‴)H_3), 1.11−1.19 (1H, m, C(7′)H_A), 1.20−1.61 (16H, m, C(2)H_2, C(3)H_2, C(7′)H_B, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2), 2.15 (3H, s, N(5′)*Me*), 2.24 (3H, s, N(5″)*Me*), 2.28−2.41 (4H, m, C(6′)H_A, C(3″)H_2, C(6″)H_A), 2.51 (1H, dd, *J* 12.6, 2.6, C(3′)H_A), 2.64−2.75 (3H, m, C(6′)H_B, C(6″)H_B, O*H*), 2.87 (1H, app t, *J* 12.0, C(3′)H_B), 2.93−3.04 (3H, m, C(1)H_A, C(8′)H_A, C(8″)H_A), 3.05−3.20 (3H, m, C(4)H_A, C(4″)*H*, C(8′)H_B), 3.34−3.43 (1H, m, C(4)H_B), 3.46 (1H, app t, *J* 13.4, C(8″)H_B), 3.62−3.76 (2H, m, C(1)H_B, C(2‴)*H*), 3.96 (1H, dd, *J* 11.4, 2.5, C(4′)*H*), 7.02−7.08 (1H, m, *Ph*), 7.10−7.17 (4H, m, *Ph*); δ_C (125 MHz, PhMe-d_8, 363 K) 14.2 (*C*(7‴)), 23.2, 25.8, 26.0, 26.3, 28.3, 30.3, 30.6, 32.7, 38.8 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), *C*(6‴)), 38.6 (*C*(3″)), 39.4 (N(5″)*Me*), 42.0 (*C*(3′)), 43.4 (N(5′)*Me*), 46.1 (*C*(4)), 46.3, 46.3 (*C*(1), *C*(6″)), 47.6 (*C*(8′)), 48.0 (*C*(8″)), 51.5 (*C*(6′)), 63.0 (*C*(4″)), 68.8 (*C*(4′)), 71.9 (*C*(2‴)), 127.3, 128.0, 128.6 (*o*,*m*,*p*-*Ph*), 143.6 (*i*-*Ph*), 172.4 (*C*(2″)), 172.7 (*C*(2′)); *m*/*z* (ESI$^+$) 551 ([M + Na]$^+$, 89%), 529 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{53}N_4O_3^+$ ([M + H]$^+$) requires 529.4112; found 529.4120.

(4′*S*,4″*S*,2‴*R*)-1-[2′-Oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-(2‴-hydroxyheptyl)-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl}butane 57. Following general procedure 6A, *ent*-**46** (74 mg, 289 μmol, >99:1 dr), **54** (93 mg, 262 μmol), KOH (65 mg, 1.15 mmol), K_2CO_3 (48 mg, 349 μmol), and TEBAC (8 mg, 35.9 μmol) in DMSO (1.4 mL) were reacted for 60 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in $CHCl_3$) gave **57** as a white solid (31 mg, 22%, >99:1 dr); mp 120−122 °C; $[\alpha]^{24}_D$ −7.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3401 (O−H), 1623 (C═O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.89 (3H, br s, C(7‴)H_3), 1.19−1.71 (18H, m, C(2)H_2, C(3)H_2, C(7′)H_2, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2), 2.15 (3H, s, N(5′)*Me*), 2.28 (3H, s, N(5″)*Me*), 2.29−2.41 (2H, m, C(3″)H_A, C(6″)H_A), 2.46−2.73 (5H, m, C(3′)H_A, C(6′)H_2, C(3″)H_B, C(6″)H_B), 2.88 (1H, app t, *J* 12.0, C(3′)H_B), 2.93−3.03 (3H, m, C(1)H_A, C(8′)H_A, C(8″)H_A), 3.04−3.17 (2H, m, C(4)H_A, C(4″)*H*), 3.21−3.30 (1H, m, C(8′)H_B), 3.36−3.54 (2H, m, C(4)H_B, C(8″)H_B), 3.59−3.71 (2H, m, C(1)H_B, C(2‴)*H*), 3.96 (1H, d, *J* 10.1, C(4′)*H*), 7.01−7.08 (1H, m, *Ph*), 7.10−7.18 (4H, m, *Ph*); δ_C (125 MHz, PhMe-d_8, 363 K) 14.2 (*C*(7‴)), 23.2, 26.0, 26.1, 26.3, 29.0, 30.3, 30.6, 32.6, 38.2 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), *C*(6‴)), 38.5 (*C*(3″)), 39.5 (N(5″)*Me*), 42.0 (*C*(3′)), 43.4 (N(5′)*Me*), 45.9 (*C*(4)), 46.3 (*C*(1), *C*(6″)), 47.1 (*C*(8′)), 48.0 (*C*(8″)), 51.5 (*C*(6′)), 62.0 (*C*(4″)), 68.8 (*C*(4′)), 70.2 (*C*(2‴)), 127.3, 128.0, 128.6 (*o*,*m*,*p*-*Ph*), 143.5 (*i*-*Ph*), 172.7 (*C*(2″)), 173.2 (*C*(2′)); *m*/*z* (ESI$^+$) 551 ([M + Na]$^+$, 100%), 529 ([M + H]$^+$, 88%); *m*/*z* (ESI$^+$) 551 ([M + Na]$^+$, 100%), 529 ([M + H]$^+$, 96%); HRMS (ESI$^+$) $C_{31}H_{53}N_4O_3^+$ ([M + H]$^+$) requires 529.4112; found 529.4099.

(*S*,*S*,*S*)-1-[2′-Oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-(2‴-hydroxyheptyl)-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl}butane 58. Following general procedure 6A, *ent*-**45** (74 mg, 289 μmol, >99:1 dr), **54** (93 mg, 262 μmol), KOH (65 mg, 1.15 mmol), K_2CO_3 (48 mg, 349 μmol), and TEBAC (8 mg, 35.9 μmol) in DMSO (1.4 mL) were reacted for 60 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in $CHCl_3$) gave **58** as a white solid (82 mg, 59%, >99:1 dr); mp 110−115 °C; $[\alpha]^{24}_D$ +2.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3409 (O−H), 1625 (C═O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.93 (3H, br t, *J* 6.9, C(7‴)H_3), 1.19−1.25 (1H, m, C(7′)H_A), 1.26−1.66 (17H, m, C(2)H_2, C(3)H_2, C(7′)H_B, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2), 2.19 (3H, s, N(5′)*Me*), 2.29 (3H, s, N(5″)*Me*), 2.33−2.50 (4H, m, C(6′)H_A, C(6″)H_A, C(3″)H_2), 2.54 (1H, dd, *J* 12.6, 3.2, C(3′)H_A), 2.70−2.77 (2H, m, C(6′)H_B, C(6″)H_B), 2.92 (1H, br t, *J* 12.3, C(3′)H_B), 2.97−3.10 (3H, m, C(1)H_A, C(8′)H_A, C(8″)H_A), 3.12−3.38 (4H, m, C(4)H_2, C(8′)H_B, C(4″)*H*), 3.51 (1H, app br t, *J* 12.9, C(8″)H_B), 3.64−3.71 (1H, m, C(1)H_B), 3.77 (1H, br s, C(2‴)*H*), 3.99 (1H, dd, *J* 11.0, 3.2, C(4′)*H*), 7.06−7.12 (1H, m, *Ph*), 7.14−7.21 (4H, m, *Ph*); δ_C (125 MHz, PhMe-d_8, 363 K) 14.2 (C(7‴)), 23.2, 25.8, 26.0, 26.3, 28.3, 30.3, 30.6, 32.7, 38.8 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), *C*(6‴)), 38.5 (*C*(3″)), 39.6 (N(5″)*Me*), 42.0 (*C*(3′)), 43.4 (N(5′)*Me*), 46.1 (*C*(4)), 46.3 (*C*(1)), 46.4 (*C*(6″)), 47.5 (*C*(8′)), 48.0 (*C*(8″)), 51.5 (*C*(6′)), 62.9 (*C*(4″)), 68.8 (*C*(4′)), 71.6 (*C*(2‴)), 127.3, 128.0, 128.6 (*o*,*m*,*p*-*Ph*), 143.5 (*i*-*Ph*), 172.4 (*C*(2″)), 172.7 (*C*(2′)); *m*/*z* (ESI$^+$) 551 ([M + Na]$^+$, 100%), 529 ([M + H]$^+$, 88%); HRMS (ESI$^+$) $C_{31}H_{52}N_4NaO_3^+$ ([M + Na]$^+$) requires 551.3932; found 551.3918.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H, ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(34) Enantiopure (*S*)-α-methylbenzylamine (99% ee) is commercially available. Alkylation of (*S*)-α-methylbenzylamine upon treatment with 1-bromo-3-chloropropane gave (*S*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amine in 55% yield; subsequent deprotonation with BuLi in THF generated a yellow solution of lithium (*S*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amide (*S*)-**7**.
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(40) Because of substantial peak overlap, it was not possible to unambiguously assign the ^{1}H and ^{13}C NMR spectra for the diastereoisomers of **32**.
(41) A resonance corresponding to one of either *C*(4′), *C*(5′), or *C*(6′) was not observed in the 100 MHz ^{13}C NMR spectrum of **41** at room temperature.
(42) A resonance corresponding to one of either *C*(7), *C*(1′), *C*(3′), *C*(4′), *C*(5′), or *C*(6′) was not observed in the 100 MHz ^{13}C NMR spectrum of **45** at room temperature.