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Asymmetric Syntheses of the Homalium Alkaloids (−)-(*S*,*S*)-Homaline and (−)-(*R*,*R*)-Hopromine

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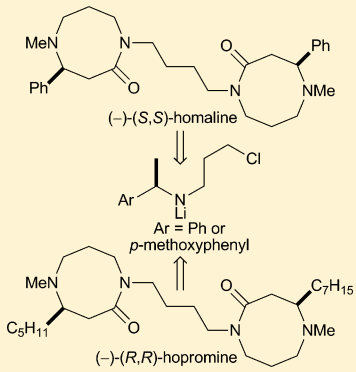
Supporting Information

ABSTRACT: The highly diastereoselective conjugate additions of the novel lithium amide reagents lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amide and lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methyl-*p*-methoxybenzyl)amide to α,β-unsaturated esters were used as the key steps in syntheses of the homalium alkaloids (−)-(*S*,*S*)-homaline and (−)-(*R*,*R*)-hopromine. The asymmetric synthesis of (−)-(*S*,*S*)-homaline was achieved in 8 steps and 18% overall yield, and the asymmetric synthesis of (−)-(*R*,*R*)-hopromine was achieved in 9 steps and 23% overall yield, from commercially available starting materials in each case. These syntheses therefore represent by far the most efficient total asymmetric syntheses of these alkaloids reported to date. A sample of the (4′*R*,4′′*S*)-epimer of hopromine was also produced using this approach, which provided the first unambiguous confirmation of its absolute configuration and therefore that of natural (−)-(*R*,*R*)-hopromine.



INTRODUCTION

The family of homalium alkaloids, comprising (−)-(*S*,*S*)-homaline **1**, (−)-(*R*,*R*)-hopromine **2**, (−)-hoprominol **3**, and (−)-hopromalinol **4**, were first isolated in the early 1970s 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] They have unique bis-eight-membered azalactam structures, and it has been postulated that they are biogenetically based on a combination of two α,β-unsaturated carboxylic acid residues combined with a spermine structural backbone.[7]

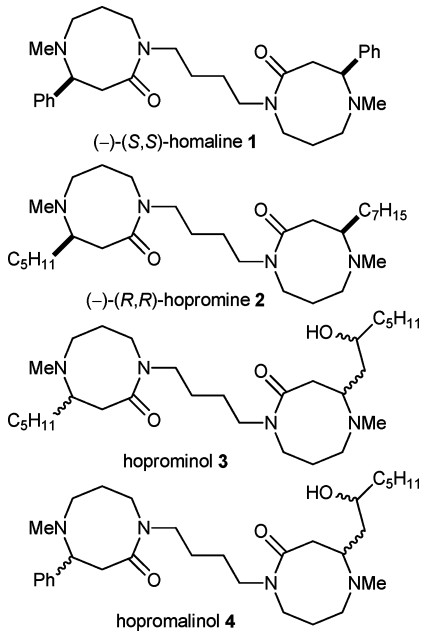


Figure 1. Homalium alkaloids **1**−**4**.

(−)-(*S*,*S*)-Homaline **1** is the only member of this family of alkaloids whose structure and relative configuration has since been unambiguously confirmed by single crystal X-ray diffraction analysis,[8] and because of the inherent symmetry within this compound it has received significantly more interest from synthetic chemists than the other homalium alkaloids. For example, in 1982 Wasserman and Berger reported the transamidation of enantiopure β-lactam precursors for their synthesis of the eight-membered azalactam units within (−)-(*S*,*S*)-homaline **1**.[9,10] In this synthesis methyl (*RS*)-3-amino-3-phenylpropanoate was resolved by recrystallization of its L-tartrate salt[11] and after a further 14 steps enantiopure (−)-(*S*,*S*)-homaline **1** was isolated in 0.07% overall yield. In 1983 Crombie et al. first reported their enantiospecific synthesis of (−)-(*S*,*S*)-homaline **1**, which proceeded via an Arndt−Eistert homologation of (*R*)-phenylglycine.[12] Ten years later they reported their full investigations within this area, which revealed that (−)-(*S*,*S*)-homaline **1** was produced in 10 steps and 1.4% overall yield from (*R*)-phenylglycine.[13] An enantiospecific synthesis of the unsymmetrical dialkylsubstituted analogue (−)-(*R*,*R*)-hopromine **2** was reported by Ensch and Hesse in 2002.[7,14] In this synthesis *N*-tosyl protected β-amino esters **5** and **6** (which were both prepared from L-aspartic acid via seven-step procedures) were treated with $Sb(OEt)_3$ to give azalactams **7** and **8** in good yield. Subsequent

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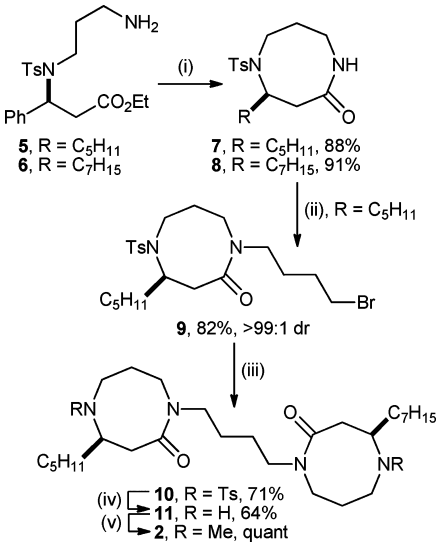
alkylation of C(4)-pentyl substituted azalactam **7** with 1,4-dibromobutane gave **9** in 82% yield, and then treatment of bromide **9** with C(4)-heptyl substituted azalactam **8** gave **10** in 71% yield. Further elaboration of **10** gave (−)-(*R*,*R*)-hopromine **2**, which was isolated in 7% overall yield (from L-aspartic acid) for this 12-step procedure (Scheme 1).

Scheme 1[a]



[a]Reagents and conditions: (i) $Sb(OEt)_3$, dry benzene, 4 Å sieves, reflux, 16 h; (ii) $Br(CH_2)_4Br$ (2.2 equiv), KOH, DMSO, rt, overnight; (iii) **8**, KOH, DMSO, 0 °C to rt, overnight; (iv) electrolysis, Me_4NCl, aq EtOH, 5 °C; (v) 37% aq CH_2O, AcOH, 0 °C, 15 min, then $NaBH_3CN$, MeOH, 0 °C to rt, 4 h.

Comparison of the specific rotation of this synthetic sample with that of the sample of (−)-hopromine **2** isolated from the natural source established the absolute (*R*,*R*)-configuration within this alkaloid.[7] However, it is noteworthy that only one of the two possible diastereoisomers was synthesized in this study, and the possibility that the epimer could also display a specific rotation of comparable magnitude should not be discounted; these data do not therefore provide unambiguous proof of the absolute configuration within (−)-hopromine **2**. The assigned absolute configuration within (−)-(*S*,*S*)-homaline **1** is, however, secure as the epimer is a meso structure. Several other methods for the synthesis of the homalium alkaloids **1**−**4** have also been investigated, although inseparable mixtures of stereoisomers were formed in each case.[15−17] As such, the relative and absolute configurations within (−)-hoprominol **3** and (−)-hopromalinol **4** are unknown.

Previous investigations from our laboratory have demonstrated that the conjugate addition of numerous enantiopure secondary lithium amides (derived from α-methylbenzylamine) to α,β-unsaturated esters represents a general and efficient protocol for the synthesis of β-amino esters and their derivatives.[18] This methodology has found many applications, including the total syntheses of natural products,[19] molecular recognition phenomena,[20] and resolution protocols,[21] and has been reviewed.[22] As part of our ongoing research program in this area we became interested in the application of this methodology for the preparation of the homalium alkaloids **1**−**4** and envisaged that the conjugate addition of functionalized lithium amides [such as *N*-(3-chloropropyl) substituted lithium amide **12**] to α,β-unsaturated esters **13**, followed by functional group interconversion of the resultant β-amino esters and cyclization (in a manner analogous to that used by Ensch and Hesse)[7] could be used to produce all the azalactam units **14** within the homalium alkaloids **1**−**4** (Figure 2). We report herein our full investigations concerning the syntheses of (−)-(*S*,*S*)-homaline **1** and (−)-(*R*,*R*)-hopromine **2**; part of this work has been communicated previously.[23]

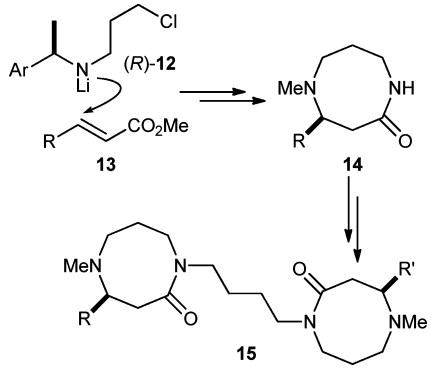


Figure 2. Conjugate addition of 3-chloropropyl substituted lithium amides **12** to α,β-unsaturated esters **13** in the asymmetric synthesis of the homalium alkaloid skeleton **15**.

RESULTS AND DISCUSSION

Asymmetric Synthesis of (−)-(*S*,*S*)-Homaline 1. Following Ensch and Hesse's $Sb(OEt)_3$ mediated cyclization strategy for the formation of the desired azalactam units, we set out to establish the structural requirements of this reaction manifold by attempting the cyclization of substrates **20**−**22** that incorporate either a primary or secondary amino substituent and either a methyl or *tert*-butyl ester. These substrates were prepared via the conjugate addition of lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amide (*R*)-**17**[24] to *tert*-butyl cinnamate **16**,[25] which gave β-amino ester **18** in 84% yield as a single diastereoisomer (>99:1 dr). The stereochemical outcome of this transformation was assigned by reference to the well established transition state mnemonic developed by us to rationalize the diastereoselectivity observed upon conjugate addition of lithium amides derived from α-methylbenzylamine.[26] Subsequent elaboration of **18** via displacement of the primary chloride functionality with NaN_3 under Finkelstein conditions (i.e., in the presence of NaI) gave **19** in 79% yield, and then Staudinger reduction of the azide moiety within **19** gave primary amine **20** in 88% yield. Similarly, displacement of the chloride functionality within **18** with allylamine (also in the presence of NaI) gave **21** in 86% yield, and transesterification of **21** upon treatment with $SOCl_2$ in MeOH produced the corresponding methyl ester **22** in 72% yield. Unfortunately, attempted formation of the azalactam scaffolds derived from either **20**, **21**, or **22** via $Sb(OEt)_3$ mediated cyclization[7,14] was in each case unsuccessful, confirming that an unhindered ester and a primary amino group are both required to achieve this transformation (Scheme 2).

The corresponding substrate containing both a primary amino substituent and a methyl ester moiety was therefore prepared via conjugate addition of lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amide (*R*)-**17**[24] to methyl cinnamate **23**, which gave β-amino ester **24** in quantitative yield as a single diastereoisomer (>99:1 dr); the stereochemical outcome

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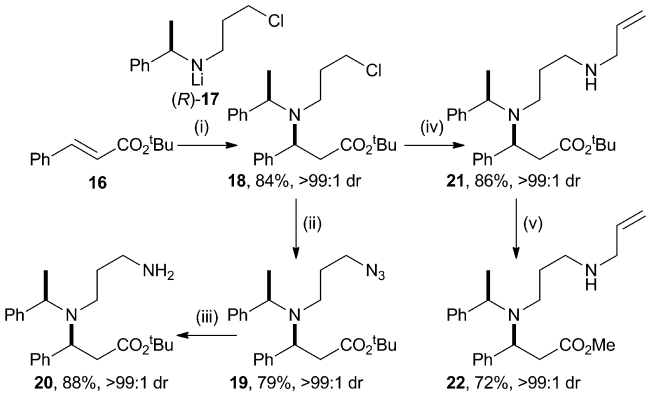
Scheme 2[a]

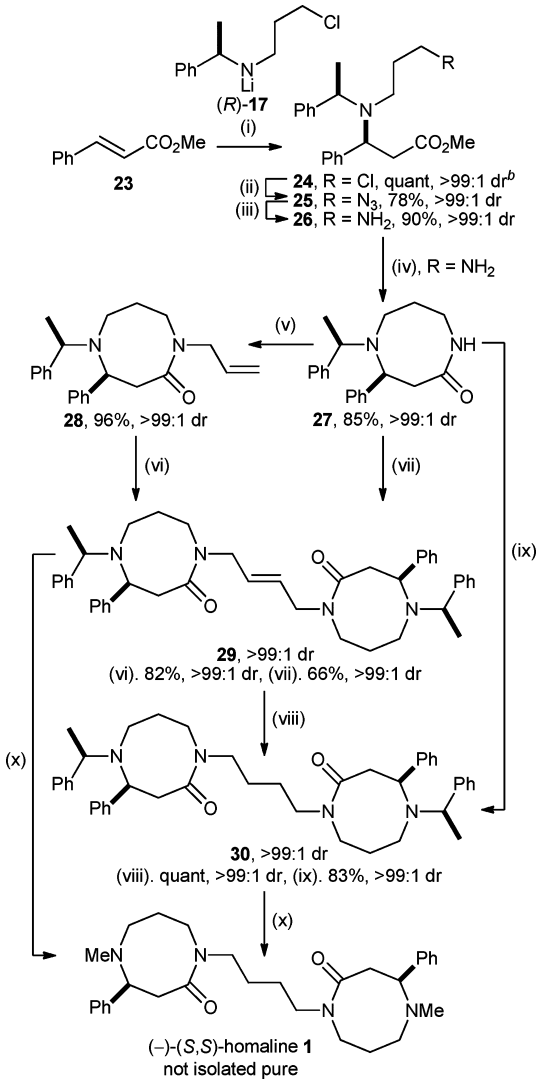


[a]Reagents and conditions: (i) (*R*)-**17**, THF, −78 °C, 2 h; (ii) NaN_3, NaI, DMSO, 50 °C, 48 h; (iii) PPh_3, THF/H_2O (v/v 7:3), 50 °C, 2 h; (iv) allylamine, NaI, 65 °C, 24 h; (v) $SOCl_2$, MeOH, reflux, 4 h.

of this transformation was initially assigned by reference to our well established transition state mnemonic[26] and was later confirmed by chemical correlation. Displacement of the primary chloride functionality within **24** with NaN_3 gave **25** in 78% yield, and then Staudinger reduction of **25** followed by $Sb(OEt)_3$ mediated cyclization[7,14] of **26** gave azalactam **27** in 77% overall yield for the two-step procedure. Upon scale-up, without purification of any intermediates, the overall yield of azalactam **27** was improved further, giving **27** in 69% overall yield from methyl cinnamate **23**. Alkylation of the N(1) atom within **27** with a range of electrophiles under different conditions proved to be somewhat problematic, consistent with the reported difficulties encountered upon attempted alkylation of similar substrates.[7,12−17] After extensive optimization it was found that reacting **27** with allyl bromide in the presence of K_2CO_3, NaOH, and triethylbenzylammonium chloride (TEBAC) in THF at 75 °C gave **28** in 96% yield. Homodimerization of **28** upon treatment with Grubbs II catalyst then gave **29** in 82% isolated yield. The configuration of the newly formed C═C double bond within **29** was established by the preparation of an authentic sample of (*E*)-**29** in 66% yield via the alkylation of azalactam **27** with *trans*-1,4-dibromobut-2-ene in the presence of K_2CO_3, KOH, and TEBAC. Attempted tandem hydrogenation/hydrogenolysis of **29** under our standard conditions for removal of *N*-α-methylbenzyl groups [i.e., H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt, 1 h][22] did not result in *N*-debenzylation and gave only **30**, which was isolated in quantitative yield. It was found that alkylation of **27** with 1,4-dibromobutane in the presence of K_2CO_3, KOH, and tetrabutylammonium chloride (TBAC) in PhMe at 160 °C in a microwave reactor gave **30** directly in 83% isolated yield. Exhaustive attempts at removal of the *N*-α-methylbenzyl groups within **30** gave inseparable mixtures of products, and procedures for *N*-debenzylation and *in situ N*-methylation of either **29** or **30** also gave inseparable mixtures of compounds, including (−)-(*S*,*S*)-homaline **1** as well as other products arising from incomplete *N*-debenzylation (Scheme 3).

An alternative protecting group strategy was therefore investigated that employed the acid-labile *N*-α-methyl-*p*-methoxybenzyl group, negating the requirement for a hydrogenolysis step. Accordingly, conjugate addition of lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methyl-*p*-methoxybenzyl)amide (*R*)-**31**[27] to methyl cinnamate **23** proceeded to full conversion to give β-amino ester **32** as a single diastereoisomer (>99:1 dr);

Scheme 3[a]



[a]Reagents and conditions: (i) (*R*)-**17**, THF, −78 °C, 2 h; (ii) NaN_3, NaI, DMSO, 50 °C, 24 h; (iii) PPh_3, THF/H_2O (v/v 7:3), 50 °C, 2 h; (iv) $Sb(OEt)_3$, PhMe, reflux, 18 h; (v) allyl bromide, K_2CO_3, NaOH, TEBAC, THF, 75 °C, 18 h; (vi) Grubbs II, CH_2Cl_2, 40 °C, 18 h; (vii) *trans*-1,4-dibromobut-2-ene, K_2CO_3, KOH, TEBAC, DMSO, rt, 72 h; (viii) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt, 1 h; (ix) 1,4-dibromobutane, K_2CO_3, KOH, TBAC, PhMe, 160 °C, microwave, 15 min; (x) H_2 (5 atm), $Pd(OH)_2/C$, MeOH/formalin/AcOH (v/v/v 1:2:3), rt, 48 h.

[b]Crude and isolated.

again, the stereochemical outcome of this transformation was initially assigned by reference to our well established transition state mnemonic,[26] and this assignment was latter confirmed by chemical correlation. Displacement of the primary chloride functionality within **32** with NaN_3 followed by Staudinger reduction of **33** and $Sb(OEt)_3$ mediated cyclization[7,14] of **34** gave azalactam **35** in 53% overall yield from methyl cinnamate **23**. Subsequent alkylation of **35** with 1,4-dibromobutane in the presence of K_2CO_3, KOH, and TBAC at 160 °C in a microwave reactor gave **36** in 67% yield, and then *N*-debenzylation was achieved upon treatment of **36** with TFA, giving **37** in 30% yield. Finally, treatment of **37** with $NaBH_3CN$ in the presence of formalin (37% formaldehyde in water with 12% MeOH

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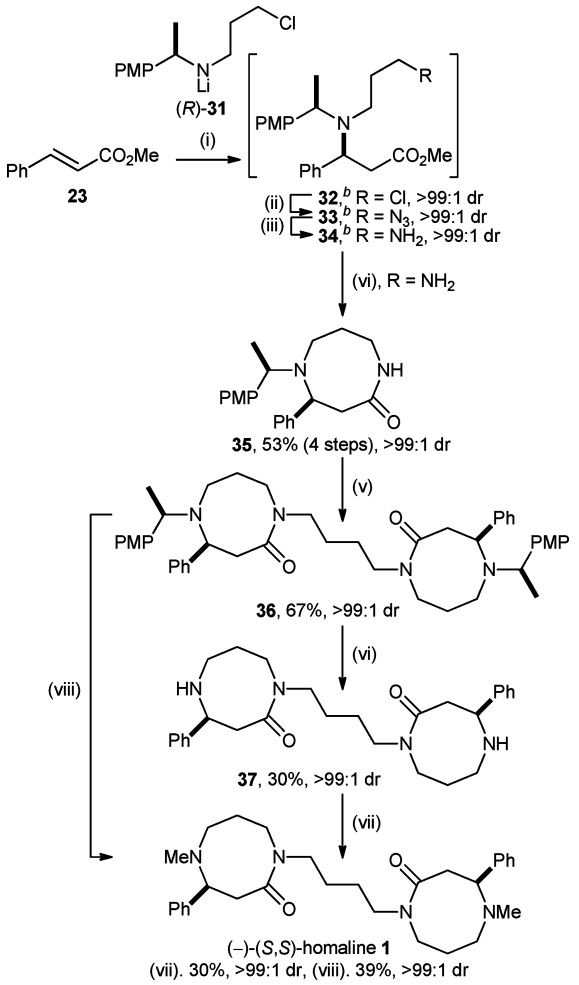
stabilizer) effected reductive *N*-methylation of both secondary amino groups within **37** to give a sample of (−)-(*S*,*S*)-homaline **1** in >99:1 dr. Attempted purification of the crude reaction mixture gave (−)-(*S*,*S*)-homaline **1** in approximately 30% yield, although it could not be separated from trace quantities of unidentified impurites.[28] However, reaction of **36** under Eschweiler−Clarke conditions (i.e., heating **36** in a mixture of formic acid and formalin at reflux) effected both *N*-debenzylation and *N*-methylation to give (−)-(*S*,*S*)-homaline **1** directly in 39% isolated yield and >99:1 dr (Scheme 4). The overall yield of this synthesis was therefore 10% in 7 steps from commercially available starting materials. The specific rotation of this sample of (−)-(*S*,*S*)-homaline **1** {$[\alpha]_D^{24}$ −29.2 (*c* 1.0 in $CHCl_3$)} was in excellent agreement with that of the sample isolated from the natural source {lit.[6] $[\alpha]_D^{20}$ −34 (*c* 1.0 in $CHCl_3$)}.

In an effort to improve the overall yield of (−)-(*S*,*S*)-homaline **1**, a further strategy was investigated in which the chiral *N*-protecting group was removed at an earlier stage in the synthesis. Attempted deprotection of either *N*-α-methylbenzyl protected azalactam **27** or *N*-α-methyl-*p*-methoxybenzyl protected azalactam **35** gave either returned starting material, poor mass return, or a complex mixture of unidentifiable products. Procedures involving attempted *in situ* *N*-methylation were also attempted in the hope that methylation of the N(5) atom would aid with isolation of the desired product; in the case of *N*-α-methyl-*p*-methoxybenzyl protected azalactam **35** this again gave a complex mixture of products. Hydrogenolysis of *N*-α-methylbenzyl protected azalactam **27** in the presence of formalin, however, gave a complex mixture of products from which only **39** and **40** were isolated in 13% and 28% yield, respectively (Scheme 5). Comparison of the specific rotation value for this sample of **39** with that of the previously reported[17] sample confirmed the absolute configuration within (*S*)-**39**, as well as the absolute configurations within **24**−**30**. The identities of both **39** and **40** were also unambiguously confirmed via single crystal X-ray diffraction analyses,[29] and the determination of a Flack *x* parameter[30] of 0.19(19) for the crystal structure of **39** allowed the absolute (*S*)-configuration within **39** to be confirmed.

It was therefore decided that *N*-debenzylation of β-amino esters **24** and **32** (i.e., the products arising from conjugate addition of lithium amides (*R*)-**17** and (*R*)-**31** to methyl cinnamate **23**) and *N*-methylation of the resultant secondary β-amino ester **41** would be investigated. Thus, hydrogenolytic removal of the *N*-α-methylbenzyl group from within β-amino ester **24** (in the presence of HCl)[31] gave **41** in 70% yield, and *N*-debenzylation of *N*-α-methyl-*p*-methoxybenzyl protected β-amino ester **32** upon treatment with TFA gave **41** in 92% yield. Subsequent reductive *N*-methylation of **41** upon treatment with $(CH_2O)_n$ and $NaBH_3CN$ gave **42** in 75% isolated yield. Displacement of the primary chloride functionality within **42** with NaN_3 gave **43**, and Staudinger reduction of **43** followed by $Sb(OEt)_3$ mediated cyclization[7,14] of **44** gave azalactam **39** in 62% yield over the three-step procedure (Scheme 6).

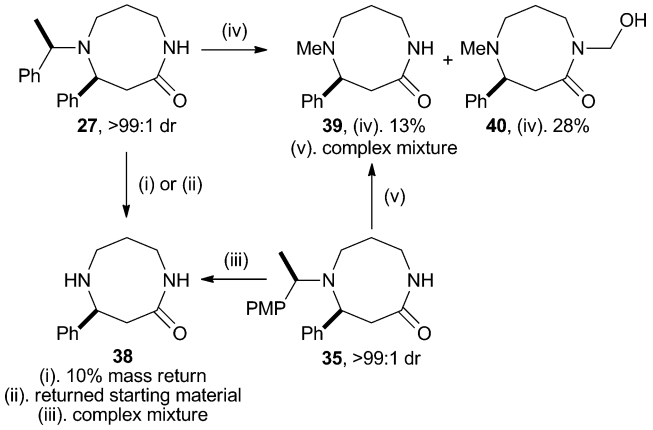
Two strategies for the homodimerization of azalactam **39** were then explored. In the first of these strategies, *N*-allylation of **39** upon treatment with allyl bromide, K_2CO_3, NaOH, and

Scheme 4[a]



[a]Reagents and conditions: (i) (*R*)-**31**, THF, −78 °C, 2 h; (ii) NaN_3, NaI, DMSO, 50 °C, 24 h; (iii) PPh_3, THF/H_2O (v/v 7:3), 50 °C, 2 h; (iv) $Sb(OEt)_3$, PhMe, reflux, 18 h; (v) 1,4-dibromobutane, K_2CO_3, KOH, TBAI, PhMe, 160 °C, microwave, 15 min; (vi) TFA, 60 °C, 2.5 h; (vii) $NaBH_3CN$, formalin, AcOH, MeOH, 0 °C to rt, 3.5 h; (viii) HCO_2H/formalin (v/v 5:6), reflux, 2.5 h. [b]Not isolated. [PMP = *p*-methoxyphenyl].

Scheme 5[a]



[a]Reagents and conditions: (i) H_2 (1 atm), $Pd(OH)_2$/C, AcOH, rt, 18 h; (ii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, rt, 24 h; (iii) TFA, 60 °C, 2.5 h; (iv) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/formalin/AcOH (v/v/v 1:2:3), rt, 72 h; (v) formalin, HCO_2H, reflux, 2.5 h. PMP = *p*-methoxyphenyl.

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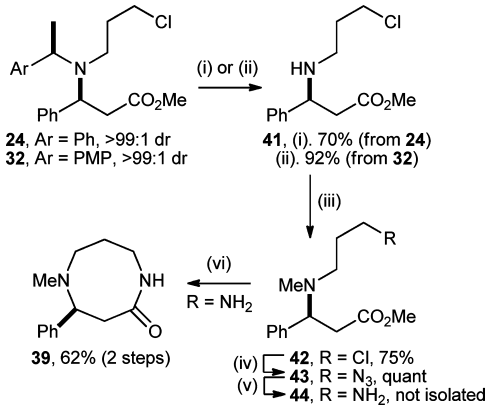
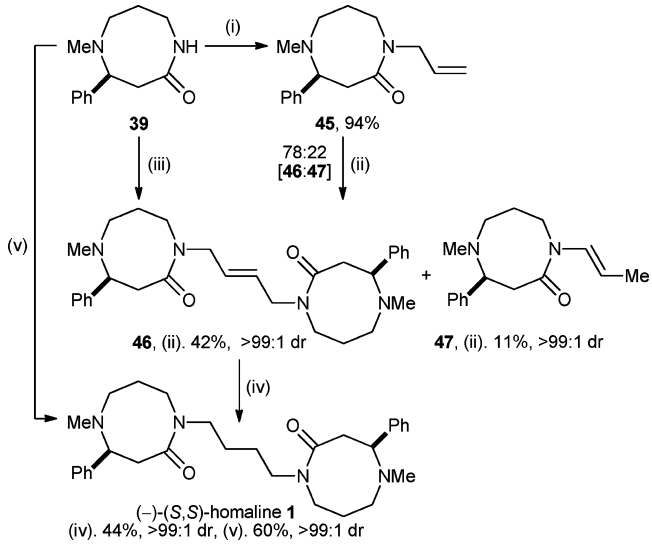
Scheme 6[a]



[a]Reagents and conditions: (i) H_2 (1 atm), $Pd(OH)_2/C$, HCl (1.0 M, aq), rt, 18 h; (ii) TFA, 60 °C, 2.5 h; (iii) $(CH_2O)_n$, $NaBH_3CN$, MeOH, rt, 18 h; (iv) NaN_3, NaI, DMSO, 50 °C, 24 h; (v) PPh_3, THF/H_2O (v/v 7:3), 50 °C, 2 h; (vi) $Sb(OEt)_3$, PhMe, reflux, 18 h. [PMP = *p*-methoxyphenyl].

Scheme 7[a]



[a]Reagents and conditions: (i) allyl bromide, K_2CO_3, NaOH, TEBAC, THF, 75 °C, 18 h; (ii) Grubbs II, CH_2Cl_2, 40 °C, 40 h; (iii) *trans*-1,4-dibromobut-2-ene, K_2CO_3, KOH, TEBAC, DMSO, rt, 96 h; (iv) H_2 (1 atm), $Pd(OH)_2/C$, EtOAc, rt, 2 h; (v) 1,4-dibromobutane, KOH, DMSO, rt, 96 h.

TEBAC gave **45** in 94% yield. Homodimerization of **45** using Grubbs II catalyst gave a complex mixture of olefinic products from which **46** and **47** were isolated in 42% and 11% yield, respectively, after purification by flash column chromatography. The configuration of the newly formed C=C double bond within **46** was established by the preparation of an authentic sample of (*E*)-**46** via the alkylation of azalactam **39** with *trans*-1,4-dibromobut-2-ene.[32] Unfortunately, resubjection of **47** to the reaction conditions did not produce **46**, and all attempts to suppress the formation of **47** failed. Hydrogenation of **46** gave a pure sample of (−)-(*S*,*S*)-homaline **1** {$[\alpha]_D^{24}$ −32.5 (*c* 1.0 in $CHCl_3$)} in 44% yield, concluding the synthesis in 10 steps and 5.3% overall yield from commercially available starting materials. In the second strategy for the conversion of azalactam **39** into (−)-(*S*,*S*)-homaline **1**, direct alkylation of **39** with 1,4-dibromobutane and KOH in DMSO was found to give (−)-(*S*,*S*)-homaline **1** {$[\alpha]_D^{21}$ −28.1 (*c* 1.0 in $CHCl_3$)} as a single diastereoisomer in 60% yield (Scheme 7). The overall yield for this synthesis of (−)-(*S*,*S*)-homaline **1** (in 8 steps from commercially available starting materials) was 18%, representing by far the most efficient synthesis of this natural product reported to date (*vide supra*). The spectroscopic data obtained for these samples of (−)-(*S*,*S*)-homaline **1** were again in excellent agreement with those for the sample isolated from the natural source,[6] and other samples obtained by total synthesis.[33]

Asymmetric Synthesis of (−)-(*R*,*R*)-Hopromine 2. We envisaged that this methodology would also be readily applicable to the asymmetric synthesis of the C(4)-alkyl substituted azalactam units within (−)-(*R*,*R*)-hopromine **2**, and then a stepwise alkylation strategy could be used to couple the differentially substituted azalactam scaffolds. Substrates **58** and **59** were therefore prepared in a similar manner as the C(4)-phenyl substituted azalactam **27**. α,β-Unsaturated esters **48** and **49** were prepared in >99:1 dr by our MeMgBr mediated Wadswoth−Emmons olefination of the corresponding aldehydes.[25,34] Conjugate addition of lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amide (*R*)-**17**[24] to either **48** or **49** gave the corresponding β-amino esters **50** and **51** as single diastereoisomers (>99:1 dr) in 81% and 73% isolated yield, respectively.[35] Transesterification of **50** and **51** upon treatment with $SOCl_2$ in MeOH gave methyl esters **52** and **53** in 80% and 61% yield, and subsequent treatment of **52** and **53** with NaN_3 (again under Finkelstein conditions) gave **54** and **55** in 94% and 87% yield, respectively. Staudinger reduction of azides **54** and **55** followed by $Sb(OEt)_3$ mediated cyclization[7,14] of **56** and **57** gave the corresponding azalactams **58** and **59** in 98% and 52% yield over the two-step procedures. Upon scale-up of this process, it was found that the overall yields of azalactams **58** and **59** could be significantly improved if the intermediate compounds **48**−**57** were used without purification; this gave **58** and **59** in 72% and 40% overall yield from the corresponding aldehydes (Scheme 8). The relative configuration within **58** was unambiguously established via single crystal X-ray diffraction analysis of the corresponding hydrochloride salt **58**·HCl,[36] with the absolute (*R*,*R*)-configuration within **58** being assigned from the known configuration of the (*R*)-α-methylbenzyl fragment. Furthermore, the determination of a Flack *x* parameter[30] of 0.03(4) for the crystal structure of **58**·HCl allowed the absolute (*R*,*R*)-configuration within **58** to be confirmed, and the absolute (*R*,*R*)-configuration within **59** was therefore assigned by analogy.

The compatibility of these substrates with *N*-α-methylbenzyl deprotection and *N*-methylation procedures was established next: hydrogenolysis of **58** and **59** in the presence of $Pd(OH)_2/C$ gave **60** and **61** in 95% and quantitative yield, respectively. Subsequent reductive methylation of the N(5) atoms within both **60** and **61** gave the corresponding *N*-methyl substituted azalactams **62** and **63** in 36% and 83% yield. The overall yield of this process was improved further by conducting a one-pot hydrogenolysis/*N*-methylation procedure, which gave **62** and **63** in quantitative and 98% yield from **58** and **59**, respectively (Scheme 9).

As C(4)-alkyl substitution was compatible with the *N*-α-methylbenzyl deprotection and *N*-methylation procedures, coupling of *N*(5)-(*R*)-α-methylbenzyl substituted azalactams **58** and **59** was attempted first. Monoalkylation of C(4)-pentyl substituted azalactam **58** with 1,4-dibromobutane (3.0 equiv) in

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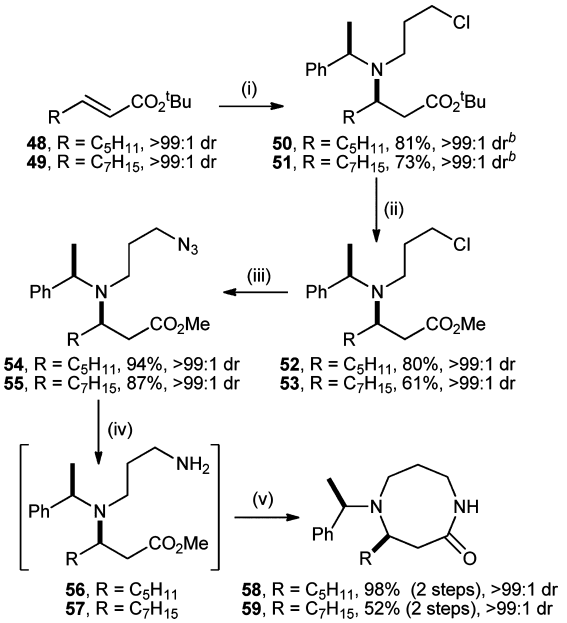
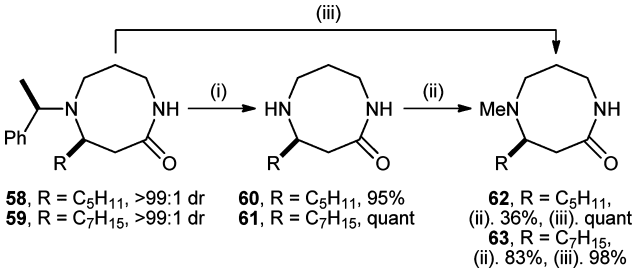
Scheme 8[a]



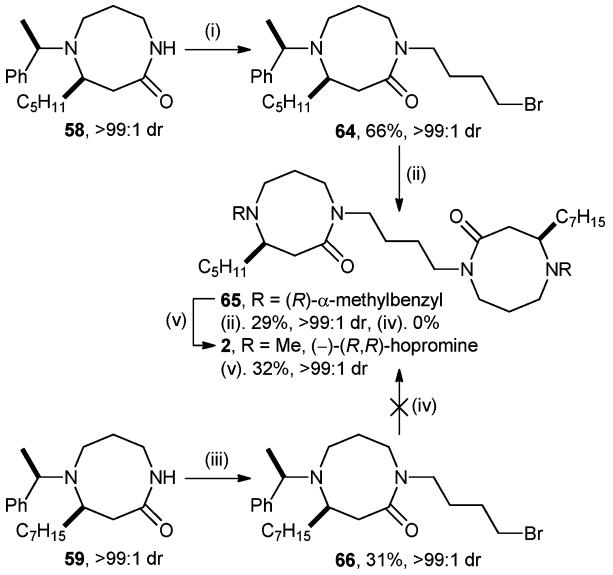
[a]Reagents and conditions: (i) (*R*)-**17**, THF, −78 °C, 2 h; (ii) $SOCl_2$, MeOH, reflux, 3 h; (iii) NaN_3, NaI, DMSO, 50 °C, 24 h; (iv) PBu_3, THF/H_2O (v/v 7:3), 50 °C, 2 h; (v) $Sb(OEt)_3$, PhMe, reflux, 18 h. [b]Crude and isolated.

Scheme 9[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; (iii) H_2 (1 atm), $Pd(OH)_2/C$, $(CH_2O)_n$, MeOH, rt, 72 h.

Scheme 10[a]



[a]Reagents and conditions: (i) 1,4-dibromobutane (3.0 equiv), K_2CO_3, KOH, TEBAC, DMSO, rt, 24 h; (ii) **59**, KOH, DMSO, rt, 96 h; (iii) 1,4-dibromobutane (3.0 equiv), KOH, K_2CO_3, TBAC, DMSO, rt, 24 h; (iv) **58**, KOH, K_2CO_3, TBAC, DMSO, rt, 24 h; (v) H_2 (1 atm), $Pd(OH)_2/C$, $(CH_2O)_n$, MeOH, rt, 72 h.

the presence of KOH in DMSO gave **64** in 66% yield, and then treatment of bromide **64** with C(4)-heptyl substituted azalactam **59** and KOH in DMSO over an extended reaction time of 96 h gave **65** in 29% yield. Subsequent tandem hydrogenolysis/*N*-methylation of **65** gave (−)-(*R*,*R*)-hopromine **2** in 32% yield and >99:1 dr (Scheme 10). The spectroscopic data obtained for this sample of (−)-(*R*,*R*)-hopromine **2** were in excellent agreement with those for the sample isolated from the natural source {$[\alpha]_D^{20}$ −12.1 (*c* 0.1 in $CHCl_3$); lit.[6] $[\alpha]_D^{20}$ −10 (*c* 3.0 in $CHCl_3$)}, and also a sample obtained by total synthesis {lit.[7] $[\alpha]_D^{20}$ −14.4 (*c* 2.1 in $CHCl_3$)}. (−)-(*R*,*R*)-Hopromine **2** was therefore produced in 9 steps and 4% overall yield from commercially available starting materials via this route. Conversely, alkylation of the C(4)-heptyl substituted azalactam **59** with 1,4-dibromobutane gave **66** in 31% isolated yield, although repeated attempts at the treatment of bromide **66** with azalactam **58** failed to give **65** (Scheme 10).

Coupling of the corresponding *N*(5)-methyl substituted azalactams **62** and **63** was found to give significantly improved overall yields of (−)-(*R*,*R*)-hopromine **2**. Monoalkylation of C(4)-pentyl substituted azalactam **62** with 1,4-dibromobutane was achieved under a range of conditions; however, it was found that treatment of **62** with 1,4-dibromobutane (3.0 equiv), KOH, K_2CO_3, and TEBAC in DMSO at rt for 24 h proved optimal, giving **67** in 66% isolated yield. Subsequent treatment of bromide **67** with C(4)-heptyl substituted azalactam **63** gave (−)-(*R*,*R*)-hopromine **2** {$[\alpha]_D^{24}$ −13.8 (*c* 1.0 in $CHCl_3$)} in 48% yield and >99:1 dr. This strategy was found to be superior to alkylation of the C(4)-heptyl substituted azalactam **63** with 1,4-dibromobutane, which gave **68** in 35% isolated yield, followed by treatment of bromide **68** with C(4)-pentyl substituted azalactam **62**, which gave (−)-(*R*,*R*)-hopromine **2** {$[\alpha]_D^{24}$ −11.2 (*c* 0.3 in $CHCl_3$)} in 7% yield and >99:1 dr (Scheme 11). Under the former, optimized set of conditions, (−)-(*R*,*R*)-hopromine **2** was produced in 9 steps and 23% overall yield from commercially available starting materials, representing the most efficient synthesis of this natural product to date.

In order to unambiguously confirm the assigned absolute (*R*,*R*)-configuration within (−)-hopromine **2** we sought to use this synthetic strategy to produce an authentic sample of the epimer **69** so that its specific rotation could also be compared with the sample of (−)-hopromine **2** isolated from the natural source. A sample of the C(4)-heptyl substituted azalactam *ent*-**63** was therefore prepared in six steps and 31% overall yield from *α*,*β*-unsaturated ester **49** under identical conditions to those used previously. Coupling of this azalactam unit with bromide **67** then produced a sample of (4′*R*,4′′*S*)-**69** in 17% isolated yield (Scheme 12). Comparison of the specific rotation value for this sample {$[\alpha]_D^{24}$ +2.3 (*c* 0.8 in $CHCl_3$)} with that of the sample of (−)-hopromine **2** isolated from the natural source {lit.[6] $[\alpha]_D^{20}$ −10 (*c* 3.0 in $CHCl_3$) unambiguously confirmed the assigned absolute (*R*,*R*)-configuration within (−)-hopromine **2**.

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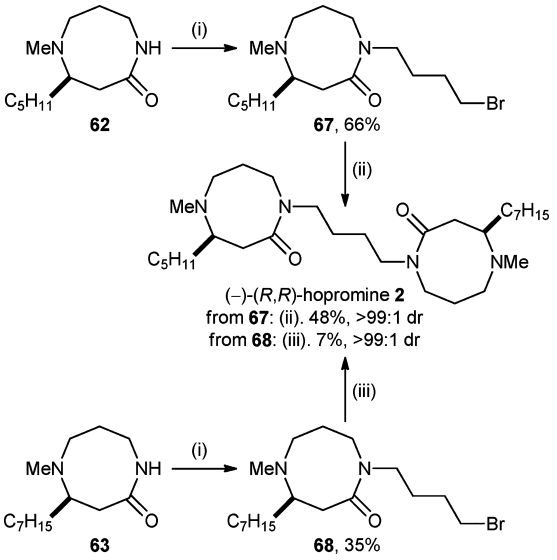
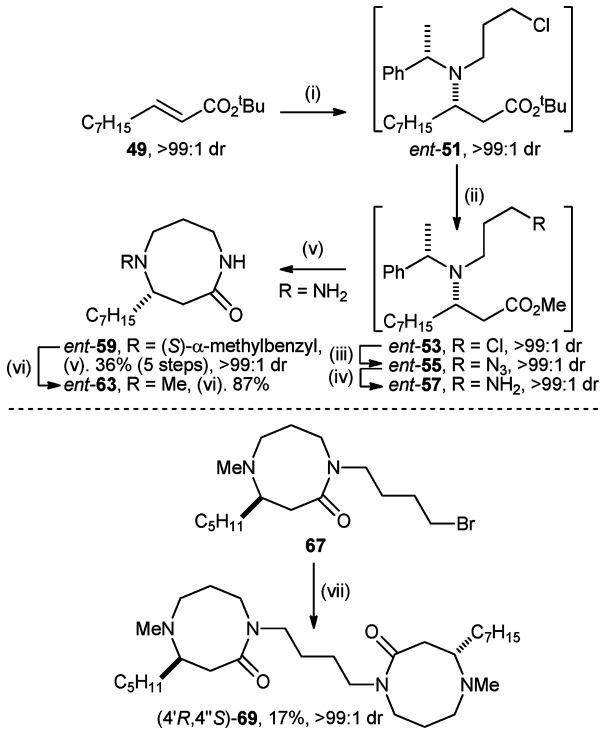
Scheme 11[a]



[a]Reagents and conditions: (i) 1,4-dibromobutane (3.0 equiv), K_2CO_3, KOH, TEBAC, DMSO, rt, 24 h; (ii) **63**, KOH, DMSO, rt, 96 h; (iii) **62**, KOH, DMSO, rt, 96 h.

Scheme 12[a]



[a]Reagents and conditions: (i) (*S*)-**17**, 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/H_2O (v/v 7:3), 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, 72 h; (vii) *ent*-**63**, K_2CO_3, KOH, TEBAC, DMSO, rt, 96 h.

CONCLUSION

The highly diastereoselective conjugate additions of the novel lithium amide reagents lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amide and lithium (*R*)-*N*-(3-chloropropyl)-*N*-(α-methyl-*p*-methoxybenzyl)amide to α,β-unsaturated esters were used as the key steps in the total asymmetric syntheses of (−)-(*S*,*S*)-homaline and (−)-(*R*,*R*)-hopromine. (−)-(*S*,*S*)-Homaline was produced in 8 steps and 18% overall yield, and (−)-(*R*,*R*)-hopromine was produced in 9 steps and 23% overall yield, from commercially available starting materials in each case. These syntheses therefore represent by far the most efficient total asymmetric syntheses of these alkaloids reported to date. A sample of the (4′*R*,4′′*S*)-epimer of hopromine was also produced using this approach, which allowed the assigned absolute configuration within (−)-(*R*,*R*)-hopromine to be unambiguously confirmed.

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.[37] BuLi was purchased as a solution in hexanes and titrated against diphenylacetic acid before use. MeMgBr was purchased as a solution in Et_2O and titrated against (*E*)-2-(2′-phenylhydrazonomethyl)phenol before use.[38] 1,4-Dibromobutane was distilled from $CaCl_2$ before use. Formalin was purchased as a 37% aq solution of formaldehyde, stabilized with 12% MeOH. All other reagents were used as supplied without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminum plates coated with 60 F_{254} silica. Plates were visualized using UV light (254 nm), 1% aq $KMnO_4$, or Dragendorff's reagent. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points are uncorrected. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g 100 mL^{-1}. IR spectra were recorded as either a thin film on NaCl plates (film) or using an ATR module (ATR), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. 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. $^1H-^1H$ COSY, $^1H-^{13}C$ HMQC, and $^1H-^{13}C$ HMBC analyses were used to establish atom connectivity. Accurate mass measurements were run on a TOF spectrometer internally calibrated with polyalanine.

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, 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 either 24 or 48 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, dried, and concentrated *in vacuo*.

General Procedure 3: Staudinger Reduction. PPh_3 or 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 and

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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, and 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 for 5 min, and then $Sb(OEt)_3$ was added. The resultant mixture was heated at reflux for 18 h and 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 24, 72, 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, 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 24 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, 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, EtOAc or 1.0 M aq HCl, as stated), and the resultant mixture was stirred under H_2 (1 atm) at rt for either 1, 2, 18, 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, dried, and concentrated *in vacuo*.

(*R*)-*N*-(3-Chloropropyl)-*N*-(α-methylbenzyl)amine. (*R*)-α-Methylbenzylamine (32.2 mL, 253 mmol) was added to a solution of 1-bromo-3-chloropropane (10.0 mL, 101 mmol) in MeCN (80 mL), and the resultant mixture was stirred for 16 h at rt. The reaction mixture was basified to pH 9 with satd aq $NaHCO_3$ and then extracted with EtOAc (3 × 100 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 3:7) gave (*R*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amine as a yellow oil (13.9 g, 70%, >99:1 er); $[\alpha]_D^{24}$ +59.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3337 (N−H); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.7, C(α)*Me*), 1.91 (2H, app quintet, *J* 6.6, C(2)H_2), 2.58 (1H, dt, *J* 11.9, 6.8, C(1)H_A), 2.68 (1H, dt, *J* 11.9, 6.6, C(1)H_B), 3.55−3.66 (2H, m, C(3)H_2), 3.78 (1H, q, *J* 6.7, C(α)*H*), 7.24−7.28 (1H, m, *Ph*), 7.31−7.37 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.5 (C(α)*Me*), 33.2 (*C*(2)), 43.2 (*C*(3)), 44.8 (*C*(1)), 58.3 (*C*(α)), 126.5, 126.9, 128.5 (*o,m,p-Ph*), 145.6 (*i-Ph*); *m/z* (ESI$^+$) 200 ([M(^{37}Cl) + H]$^+$, 19%), 198 ([M(^{35}Cl) + H]$^+$, 47%), 162 ([M − Cl]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{17}{}^{37}ClN^+$ ([M(^{37}Cl) + H]$^+$) requires 200.1015, found 200.1013; $C_{11}H_{17}{}^{35}ClN^+$ ([M(^{35}Cl) + H]$^+$) requires 198.1044, found 198.1045.

***tert*-Butyl (3*S*,α*R*)-3-[*N*-(3′-Chloropropyl)-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 18.** Following General Procedure 1, (*R*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amine (1.55 g, 7.83 mmol), BuLi (2.5 M, 3.04 mL, 7.59 mmol), and **16** (1.00 mL, 4.90 mmol) were reacted in THF (40 mL) to give **18** in >99:1 dr. Purification via flash column chromatography (gradient elution, 0% → 8% Et_2O in 30−40 °C petrol) gave **18** as a yellow oil (1.65 g, 84%, >99:1 dr); $[\alpha]_D^{20}$ −4.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1728 (C═O); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, s, C(α)*Me*), 1.35 (9H, s, C*Me*$_3$), 1.71−1.84 (2H, m, C(2′)H_2), 2.65−2.71 (3H, m, C(2)H_A, C(1′)H_2), 2.83 (1H, app dd, *J* 14.7, 6.6, C(2)H_B), 3.22−3.32 (2H, m, C(3′)H_2), 4.02 (1H, q, *J* 6.7, C(α)*H*), 4.44 (1H, dd, *J* 8.6, 6.6, C(3)*H*), 7.25−7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.7 (C(α)*Me*), 27.9 (C*Me*$_3$), 33.1 (*C*(2′)), 38.5 (*C*(2)), 43.3 (*C*(3′)), 43.9 (*C*(1′)), 57.1 (*C*(α)), 58.7 (*C*(3)), 80.3 (*C*Me$_3$), 126.8, 127.2, 127.7, 128.1, 128.2 (*o,m,p-Ph*), 141.4, 144.8 (*i-Ph*), 171.2 (*C*(1)); *m/z* (ESI$^+$) 426 ([M(^{37}Cl) + Na]$^+$, 24%), 424 ([M(^{35}Cl) + Na]$^+$, 58%), 404 ([M(^{37}Cl) + H]$^+$, 55%), 402 ([M(^{35}Cl) + H, 100%); HRMS (ESI$^+$) $C_{24}H_{33}{}^{37}ClNO_2^+$ ([M(^{37}Cl) + H]$^+$) requires 404.2165, found 404.2163; $C_{24}H_{33}{}^{35}ClNO_2^+$ ([M(^{35}Cl) + H]$^+$) requires 402.2194, found 402.2182.

***tert*-Butyl (3*S*,α*R*)-3-[*N*-(3′-Azidopropyl)-*N*-(α-methylbenzyl)-amino]-3-phenylpropanoate 19.** Following General Procedure 2, NaN_3 (129 mg, 1.99 mmol), NaI (298 mg, 1.99 mmol) and **18** (400 mg, 995 μmol, >99:1 dr) in DMSO (2 mL) were reacted for 48 h. Purification via flash column chromatography (gradient elution, 3% → 9% Et_2O in 30−40 °C petrol) gave **19** as a yellow oil (323 mg, 79%, >99:1 dr); $[\alpha]_D^{24}$ −0.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2095 (N≡N), 1728 (C═O); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.8, C(α)*Me*), 1.32 (9H, s, C*Me*$_3$), 1.48−1.62 (2H, m, C(2′)H_2), 2.58 (2H, t, *J* 7.1, C(1′)H_2), 2.64 (1H, dd, *J* 14.7, 8.5, C(2)H_A), 2.79 (1H, dd, *J* 14.7, 6.6, C(2)H_B), 2.91−3.03 (2H, m, C(3′)H_2), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.39 (1H, dd, *J* 8.5, 6.6, C(3)*H*), 7.22−7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.6 (C(α)*Me*), 27.9 (C*Me*$_3$), 29.1 (*C*(2′)), 38.4 (*C*(2)), 43.5 (*C*(1′)), 49.4 (*C*(3′)), 57.0 (*C*(α)), 59.6 (*C*(3)), 80.4 (*C*Me$_3$), 126.8, 127.2, 127.7, 128.0, 128.1, 128.2 (*o,m,p-Ph*), 141.3, 144.8 (*i-Ph*), 171.2 (*C*(1)); *m/z* (ESI$^+$) 431 ([M + Na]$^+$, 46%), 409 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{33}N_4O_2^+$ ([M + H]$^+$) requires 409.2598, found 409.2600.

***tert*-Butyl (3*S*,α*R*)-3-[*N*-(3′-Aminopropyl)-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 20.** Following General Procedure 3, **19** (270 mg, 660 μmol, >99:1 dr) and PPh_3 (192 mg, 730 μmol) in THF (1.3 mL) and H_2O (0.27 mL) were reacted. The residue was partitioned between CH_2Cl_2 (10 mL) and 2.0 M aq HCl (5 mL). The organic layer was extracted with 2.0 M aq HCl (2 × 5 mL) and the combined aqueous layers washed with CH_2Cl_2 (15 mL). The aqueous layer was then basified to pH 12 by addition of solid KOH and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **20** as a colorless oil (222 mg, 88%, >99:1 dr); $[\alpha]_D^{24}$ −3.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1725 (C═O); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.8, C(α)*Me*), 1.29 (9H, s, C*Me*$_3$), 1.48 (2H, app quintet, *J* 6.8, C(2′)H_2), 2.39−2.46 (2H, m, C(1′)H_2), 2.53 (2H, app td, *J* 6.8, 2.5, C(3′)H_2), 2.63 (1H, dd, *J* 14.6, 8.8, C(2)H_A), 2.71 (1H, dd, *J* 14.6, 6.2, C(2)H_B), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.39 (1H, dd, *J* 8.8, 6.2, C(3)*H*), 7.20−7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.4 (C(α)*Me*), 27.9 (C*Me*$_3$), 33.2 (*C*(2′)), 38.3 (*C*(2)), 39.7 (*C*(1′)), 43.4 (*C*(3′)), 56.7 (*C*(α)), 59.4 (*C*(3)), 80.3 (*C*Me$_3$), 126.7, 127.1, 127.8, 128.0, 128.1, 128.2 (*o,m,p-Ph*), 141.6, 144.8 (*i-Ph*), 171.3 (*C*(1)); *m/z* (ESI$^+$) 405 ([M + Na]$^+$, 18%), 383 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{35}N_2O_2^+$ ([M + H]$^+$) requires 383.2693, found 383.2682.

***tert*-Butyl (3*S*,α*R*)-3-{*N*-[3′-(*N*′-Allylamino)propyl]-*N*-[α-methylbenzyl]amino}-3-phenylpropanoate 21.** NaI (182 mg, 1.21 mmol) was added to a solution of **18** (163 mg, 405 μmol, >99:1 dr) in allyl amine (1.22 mL, 16.3 mmol) and the resultant mixture was heated at 65 °C for 24 h before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (25 mL) and satd aq $NaHCO_3$ (25 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed with brine (75 mL), then dried and concentrated *in vacuo*. Purification via flash

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column chromatography (eluent CH_2Cl_2/MeOH, 19:1) gave **21** as a yellow oil (147 mg, 86%, >99:1 dr); $C_{27}H_{38}N_2O_2$ requires C, 76.7; H, 9.1; N, 6.6%, found C, 76.7; H, 9.0; N, 6.7%; $[\alpha]_D^{24}$ −4.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1727 (C═O); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.8, C(*α*)*Me*), 1.27 (9H, s, C*Me*$_3$), 1.52−1.64 (2H, m, C(2′)H_2), 2.28−2.50 (3H, m, C(1′)H_2, N*H*), 2.56 (2H, app t, *J* 6.8, C(3′)H_2), 2.64−2.67 (2H, m, C(2)H_2), 3.02 (2H, d, *J* 6.0, NCH_2CH═CH_2), 3.98 (1H, q, *J* 6.8, C(*α*)*H*), 4.38 (1H, dd, *J* 8.6, 6.6, C(3)*H*), 5.06−5.14 (2H, m, CH═CH_2), 5.75−5.85 (1H, m, C*H*═CH_2), 7.20−7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.6 (C(*α*)*Me*), 28.0 (C*Me*$_3$), 29.4 (*C*(2′)), 38.0 (*C*(2)), 44.0 (*C*(3′)), 47.0 (*C*(1′)), 52.0 (NCH_2CH═CH_2), 56.8 (*C*(*α*)), 59.4 (*C*(3)), 80.3 (CMe_3), 116.4 (CH═CH_2), 126.7, 127.1, 127.7, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 135.9 (CH═CH_2), 141.7, 144.6 (*i*-*Ph*), 171.2 (*C*(1)); *m*/*z* (ESI$^+$) 423 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{39}N_2O_2^+$ ([M + H]$^+$) requires 423.3006, found 423.3008.

Methyl (3*S*,*αR*)-3-{*N*-[3′-(*N*′-Allylamino)propyl]-*N*-[*α*-methylbenzyl]amino}-3-phenylpropanoate 22. Following General Procedure 4, **21** (900 mg, 1.19 mmol, >99:1 dr) and $SOCl_2$ (0.90 mL, 12.4 mmol) in MeOH (9 mL) were reacted. Purification via flash column chromatography (gradient elution, 1% → 5% MeOH in CH_2Cl_2) gave **22** as a yellow oil (585 mg, 72%, >99:1 dr); $C_{27}H_{38}N_2O_2$ requires C, 76.7; H, 9.0; N, 6.6%, found C, 76.7; H, 9.0; N, 6.7%; $[\alpha]_D^{24}$ −1.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1739 (C═O); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.8, C(*α*)*Me*), 1.56 (2H, app quintet, *J* 7.1, C(2′)H_2), 2.28−2.39 (2H, m, C(1′)H_2), 2.56 (2H, t, *J* 7.1, C(3′)H_2), 2.70 (1H, dd, *J* 14.9, 8.6, C(2)H_A), 2.79 (1H, dd, *J* 14.9, 6.3, C(2)H_B), 3.03 (2H, app d, *J* 6.1, NCH_2CH═CH_2), 3.52 (3H, s, O*Me*), 4.00 (1H, q, *J* 6.8, C(*α*)*H*), 4.44−4.48 (1H, m, C(3)*H*), 5.03−5.12 (2H, m, CH═CH_2), 5.75−5.85 (1H, m, C*H*═CH_2), 7.18−7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.7 (C(*α*)*Me*), 29.5 (*C*(2′)), 36.8 (*C*(2)), 43.9 (*C*(3′)), 46.9 (*C*(1′)), 51.5 (O*Me*), 52.2 (NCH_2CH═CH_2), 56.7 (*C*(*α*)), 58.9 (*C*(3)), 116.0 (CH═CH_2), 126.8, 127.2, 127.7, 127.9, 128.1, 128.3 (*o*,*m*,*p*-*Ph*), 136.4 (CH═CH_2), 141.5, 144.6 (*i*-*Ph*), 172.4 (*C*(1)); *m*/*z* (ESI$^+$) 381 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{33}N_2O_2^+$ ([M + H]$^+$) requires 381.2537, found 381.2526.

Methyl (3*S*,*αR*)-3-[*N*-(3′-Chloropropyl)-*N*-(*α*-methylbenzyl)-amino]-3-phenylpropanoate 24. Following General Procedure 1, (*R*)-*N*-(3-chloropropyl)-*N*-(*α*-methylbenzyl)amine (5.00 g, 25.3 mmol), BuLi (2.2 M in hexanes, 9.8 mL, 24.5 mmol) and **23** (2.56 g, 15.8 mmol) in THF (250 mL) were reacted to give **24** as a yellow oil (5.68 g, quant, >99:1 dr); $C_{21}H_{26}ClNO_2$ requires C, 70.1; H, 7.3; N, 3.9%, found C, 70.2; H, 7.2; N, 3.8%; $[\alpha]_D^{24}$ −7.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1738 (C═O); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.8, C(*α*)*Me*), 1.69−1.81 (2H, m, C(2′)H_2), 2.67 (2H, t, *J* 6.8, C(1′)H_2), 2.71 (1H, dd, *J* 14.9, 8.2, C(2)H_A), 2.87 (1H, dd, *J* 14.9, 6.8, C(2)H_B), 3.21−3.31 (2H, m, C(3′)H_2), 3.58 (3H, s, O*Me*), 3.99 (1H, q, *J* 6.8, C(*α*)*H*), 4.45 (1H, dd, *J* 8.2, 6.8, C(3)*H*), 7.22−7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.9 (C(*α*)*Me*), 32.8 (*C*(2′)), 37.2 (*C*(2)), 43.2 (*C*(3′)), 43.8 (*C*(1′)), 51.6 (O*Me*), 57.1 (*C*(*α*)), 59.3 (*C*(3)), 126.9, 127.4, 127.7, 128.0, 128.2, 128.4 (*o*,*m*,*p*-*Ph*), 141.2, 144.7 (*i*-*Ph*), 172.3 (*C*(1)); *m*/*z* (ESI$^+$) 384 ([M(^{37}Cl) + Na], 66%), 382 ([M(^{35}Cl) + Na]$^+$, 100%), 362 ([M(^{37}Cl) + H], 44%), 360 ([M(^{35}Cl) + H]$^+$, 72%); HRMS (ESI$^+$) $C_{21}H_{27}{}^{37}ClNO_2^+$ ([M(^{37}Cl) + H]$^+$) requires 362.1695, found 362.1697; $C_{21}H_{27}{}^{35}ClNO_2^+$ ([M(^{35}Cl) + H]$^+$) requires 360.1725, found 360.1721.

Methyl (3*S*,*αR*)-3-[(*N*-3′-Azidopropyl)-*N*-(*α*-methylbenzyl)-amino]-3-phenylpropanoate 25. Following General Procedure 2, NaN_3 (1.08 g, 16.7 mmol, >99:1 dr), NaI (2.49 g, 16.7 mmol) and **24** (3.00 g, 8.36 mmol, >99:1 dr) in DMSO (15 mL) were reacted for 24 h. Purification via column chromatography (eluent 30−40 °C petrol/Et_2O, 8:2) gave **25** as a yellow oil (2.38 g, 78%, >99:1 dr); $C_{21}H_{26}N_4O_2$ requires C, 68.8; H, 7.15; N, 15.3%, found C, 68.9; H, 7.1; N, 15.2%; $[\alpha]_D^{24}$ −9.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2096 (N≡N), 1738 (C═O); δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.8, C(*α*)*Me*), 1.50−1.66 (2H, m, C(2′)H_2), 2.62 (2H, t, *J* 6.8, C(1′)H_2), 2.73 (1H, dd, *J* 14.8, 8.1, C(2)H_A), 2.90 (1H, dd, *J* 14.8, 6.8, C(2)H_B), 2.95−3.06 (2H, m, C(3′)H_2), 3.61 (3H, s, O*Me*), 4.02 (1H, q, *J* 6.8, C(*α*)*H*), 4.49 (1H, app t, *J* 7.6, C(3)*H*), 7.24−7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.8 (C(*α*)*Me*), 30.0 (*C*(2′)), 37.1 (*C*(2)), 43.5 (*C*(1′)), 49.4 (*C*(3′)), 51.6 (O*Me*), 57.0 (*C*(*α*)), 59.3 (*C*(3)), 126.9, 127.4, 127.6, 127.9, 128.2, 128.4 (*o*,*m*,*p*-*Ph*), 141.2, 144.7 (*i*-*Ph*), 172.3 (*C*(1)); *m*/*z* (ESI$^+$) 389 ([M + Na]$^+$, 100%), 367 ([M + H]$^+$, 74%); HRMS (ESI$^+$) $C_{21}H_{27}N_4O_2^+$ ([M + H]$^+$) requires 367.2129, found 367.2129.

Methyl (3*S*,*αR*)-3-[*N*-(3′-Aminopropyl)-*N*-(*α*-methylbenzyl)-amino]-3-phenylpropanoate 26. Following General Procedure 3, **25** (1.20 g, 3.24 mmol, >99:1 dr) and PPh_3 (948 mg, 3.60 mmol) in THF (6.6 mL) and H_2O (1.2 mL) were reacted. The residue was partitioned between CH_2Cl_2 (40 mL) and 2.0 M aq HCl (25 mL). The organic layer was extracted with 2.0 M aq HCl (2 × 25 mL), and the combined aqueous layers were washed with CH_2Cl_2 (50 mL). The aqueous layer was then basified to pH 12 by the addition of solid KOH and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **26** as a colorless oil (1.19 g, 90%, >99:1 dr); $[\alpha]_D^{20}$ −9.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1736 (C═O); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.8, C(*α*)*Me*), 1.52 (2H, app t, *J* 7.0, C(2′)H_2), 2.44−2.48 (2H, m, C(3′)H_2), 2.57 (2H, t, *J* 7.3, C(1′)H_2), 2.71 (1H, dd, *J* 14.9, 8.5, C(2)H_A), 2.82 (1H, dd, *J* 14.9, 6.7, C(2)H_B), 3.56 (3H, s, O*Me*), 4.02 (1H, q, *J* 6.8, C(*α*)*H*), 4.46 (1H, dd, *J* 8.5, 6.7, C(3)*H*), 7.21−7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.5 (C(*α*)*Me*), 33.4 (*C*(2′)), 37.0 (*C*(2)), 39.8 (*C*(3′)), 43.3 (*C*(1′)), 51.5 (O*Me*), 56.5 (*C*(*α*)), 58.9 (*C*(3)), 126.7, 127.2, 127.7, 127.9, 128.1, 128.3 (*o*,*m*,*p*-*Ph*), 141.6, 144.7 (*i*-*Ph*), 172.4 (*C*(1)); *m*/*z* (ESI$^+$) 363 ([M + Na]$^+$, 76%), 341 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{29}N_2O_2^+$ ([M + H]$^+$) requires 341.2224, found 341.2213.

(4*S*,*αR*)-4-Phenyl-*N*(5)-(*α*-methylbenzyl)-1,5-diazocan-2-one 27. Following General Procedure 5, **26** (1.19 g, 3.50 mmol, >99:1 dr) and $Sb(OEt)_3$ (0.72 mL, 4.18 mmol) in PhMe (350 mL) were reacted. Purification via flash column chromatography (gradient elution, 50% → 100% EtOAc in 30−40 °C petrol) gave **27** as a white solid (915 mg, 85%, >99:1 dr); mp 46−48 °C; $[\alpha]_D^{24}$ +22.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1662 (C═O); δ_H (400 MHz, $CDCl_3$) 1.00−1.07 (1H, m, C(7)H_A), 1.16−1.30 (4H, m, C(7)H_B, C(*α*)*Me*), 2.57−2.70 (2H, m, C(6)H_2), 3.04−3.16 (3H, m, C(8)H_A, C(3)H_2), 3.46−3.58 (1H, m, C(8)H_B), 3.99 (1H, q, *J* 6.8, C(*α*)*H*), 4.55 (1H, br s, C(4)*H*), 6.59 (1H, br t, *J* 7.1, N*H*), 7.18−7.44 (10H, m, *Ph*); δ_H (500 MHz, PhMe-d_8, 363 K) 0.74−0.81 (1H, m, C(7)H_A), 1.03−1.11 (1H, m, C(7)H_B), 1.18 (3H, d, *J* 6.6, C(*α*)*Me*), 2.48−2.56 (2H, m, C(3)H_A, C(6)H_A), 2.59−2.65 (1H, m, C(8)H_A), 2.79 (1H, app t, *J* 11.7, C(3)H_B), 2.92 (1H, ddd, *J* 15.8, 8.5, 2.8, C(6)H_B), 3.05−3.14 (1H, m, C(8)H_B), 3.96 (1H, q, *J* 6.6, C(*α*)*H*), 4.51 (1H, dd, *J* 11.0, 3.8, C(4)*H*), 5.94 (1H, br s, N*H*), 7.04−7.11 (2H, m, *Ph*), 7.14−7.21 (4H, m, *Ph*), 7.24−7.28 (2H, m, *Ph*), 7.30−7.34 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 33.2 (*C*(7)), 41.2 (*C*(3)), 46.8 (*C*(8)), 60.7 (*C*(*α*)), 62.8 (*C*(4)), 126.8, 127.0, 127.2, 128.0, 128.1, 128.6 (*o*,*m*,*p*-*Ph*), 143.1, *145.5* (*i*-*Ph*), 176.7 (*C*(2));[39] δ_C (125 MHz, PhMe-d_8, 363 K) 16.5 (C(*α*)*Me*), 33.8 (*C*(7)), 41.8 (*C*(6)), 41.9 (*C*(3)), 46.7 (*C*(8)), 61.2 (*C*(*α*)), 63.5 (*C*(4)), 126.9, 127.0, 127.6, 128.1, 128.4, 128.6 (*o*,*m*,*p*-*Ph*), 144.3, 146.0 (*i*-*Ph*), 175.0 (*C*(2)); *m*/*z* (ESI$^+$) 948 ([3M + Na]$^+$, 46%), 639 ([2M + Na]$^+$, 100%), 331 ([M + Na]$^+$, 82%), 309 ([M + H]$^+$, 66%); HRMS (ESI$^+$) $C_{20}H_{25}N_2O^+$ ([M + H]$^+$) requires 309.1961, found 309.1960.

(4*S*,*αR*)-*N*(1)-Allyl-4-phenyl-*N*(5)-(*α*-methylbenzyl)-1,5-diazocan-2-one 28. Allyl bromide (17 μL, 196 μmol) was added to a mixture of **27** (51 mg, 165 μmol, >99:1 dr), K_2CO_3 (28 mg, 203 μmol), NaOH (28 mg, 700 μmol), and TEBAC (5 mg, 22.0 μmol) in THF (1 mL). The resultant mixture was heated at 75 °C for 18 h, then filtered through Celite (eluent EtOAc), and concentrated *in vacuo*. Purification via column chromatography (gradient elution, 10% → 65% EtOAc in 30−40 °C petrol) gave **28** as a yellow oil (55 mg, 96%, >99:1 dr); $C_{23}H_{28}N_2O$ requires C, 79.3; H, 8.1; N, 8.0%, found C, 79.4; H, 7.9; N, 7.9%; $[\alpha]_D^{24}$ −4.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1635 (C═O); δ_H (400 MHz, $CDCl_3$) 0.92−0.99 (1H, m, C(7)H_A), 1.20−1.32 (1H, m, C(7)H_B), 1.24 (3H, d, *J* 6.6, C(*α*)*Me*), 2.52 (1H, br s, C(6)H_A), 2.67 (1H, dd, *J* 12.9, 3.8, C(3)H_A), 3.04−3.19 (3H, m, C(3)H_B, C(6)H_B, C(8)H_A), 3.49 (1H, dd, *J* 15.2, 7.1, CH_AH$_B$CH═CH_2), 3.75 (1H, app br t, *J* 13.6, C(8)H_B), 3.95 (1H, q, *J* 6.6, C(*α*)*H*), 4.52−

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4.61 (2H, m, C(4)H, $CH_AH_BCH{=}CH_2$), 5.12−5.18 (2H, m, $CH_2CH{=}CH_2$), 5.76−5.87 (1H, m, $CH_2CH{=}CH_2$), 7.17−7.31 (4H, m, *Ph*), 7.33−7.38 (4H, m, *Ph*), 7.40−7.45 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 30.3 (*C*(7)), 43.1 (*C*(3)), 46.7 (*C*(8)), 48.3 ($CH_2CH{=}CH_2$), *60.7* (*C*(*α*)), *63.5* (C(4)), 117.2 ($CH_2CH{=}CH_2$), 126.8, 127.0, 127.2, 127.9, 128.0, 128.6 (*o,m,p-Ph*), 143.4, *145.6* (*i-Ph*), 173.2 (*C*(2));[40] *m/z* (ESI$^+$) 371 ([M + Na]$^+$, 38%), 349 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{29}N_2O^+$ ([M + H]$^+$) requires 349.2274, found 349.2266.

(4′*S*,*αR*,*E*)-1,4-Di[2′-oxo-4′-phenyl-*N*(5′)-*α*-methylbenzyl-1′,5′-diazocan-*N*(1′)-yl]but-2-ene 29. *Method A*: Grubbs II catalyst (120 mg, 143 *μ*mol) was added to a degassed solution of **28** (500 mg, 1.43 *μ*mol, >99:1 dr) in CH_2Cl_2 (7 mL, EtOH stabilized), and the reaction mixture was heated at 40 °C for 18 h. The reaction mixture was then concentrated *in vacuo*. Purification via column chromatography (gradient elution, 0% → 7% MeOH in CH_2Cl_2) gave **29** as a yellow solid (394 mg, 82%, >99:1 dr); mp 64−67 °C; $[\alpha]_D^{20}$ −7.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1637 (C═O); δ_H (400 MHz, $CDCl_3$) 0.91−1.01 (2H, m, 2 × C(7′)H_A), 1.19−1.28 (2H, m, 2 × C(7′)H_B) overlapping 1.24 (6H, d, *J* 6.6, 2 × C(*α*)*Me*), 2.42−2.57 (2H, m, 2 × C(6′)H_A), 2.65 (2H, dd, *J* 12.6, 3.3, 2 × C(8′)H_A), 3.03−3.18 (6H, m, 2 × C(3′)H_A, 2 × C(6′)H_B, 2 × C(8′)H_B), 3.44 (2H, br d, *J* 12.1, C(1)H_A, C(4)H_A), 3.74 (2H, br t, *J* 11.9, 2 × C(3′)H_B), 3.95 (2H, br q, *J* 6.6, 2 × C(*α*)*H*), 4.40−4.66 (4H, m, C(1)H_B, C(4)H_B, 2 × C(4′)*H*), 5.54−5.59 (2H, m, C(2)*H*, C(3)*H*), 7.19−7.45 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 30.2 (2 × *C*(7′)), 46.9 (2 × *C*(3′)), 126.8, 127.0, 127.1, 127.9, 128.0, 128.6 (*o,m,p-Ph*), 143.3 (*i-Ph*), 172.2 (2 × *C*(2′));[41] *m/z* (ESI$^+$) 691 ([M + Na]$^+$, 95%), 669 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{44}H_{53}N_4O_2^+$ ([M + H]$^+$) requires 669.4163, found 669.4161.

Method B: Following General Procedure 6A, **27** (244 mg, 791 *μ*mol), *trans*-1,4-dibromobutane (85 mg, 397 *μ*mol), K_2CO_3 (132 mg, 955 *μ*mol), KOH (177 mg, 3.15 mmol), and TEBAC (22 mg, 98.3 *μ*mol) in DMSO (4.0 mL) were reacted for 72 h. Purification via column chromatography (gradient elution, 0% → 2% MeOH in $CHCl_3$) gave **29** as a white solid (175 mg, 66%, >99:1 dr); mp 67−69 °C; $[\alpha]_D^{20}$ −7.9 (*c* 1.0 in $CHCl_3$).

(4′*S*,*αR*)-1,4-Di[2′-oxo-4′-phenyl-*N*(5′)-*α*-methylbenzyl-1′,5′-diazocan-1′-yl]butane 30. *Method A*: 1,4-Dibromobutane (0.29 mL, 2.43 mmol) was added to a mixture of **27** (1.50 g, 4.86 mmol, >99:1 dr), K_2CO_3 (2.69 g, 19.5 mmol), KOH (1.10 g, 19.5 mmol), and TBAC (135 mg, 486 *μ*mol) in PhMe (16 mL) under N_2 and sealed in a tube. The resultant mixture was heated at 160 °C in a microwave reactor for 15 min before being cooled to rt and partitioned between H_2O (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic extracts were washed with brine (40 mL), then dried, and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 40% → 100% EtOAc in 30−40 °C petrol) gave **30** as a yellow oil (1.36 g, 83%, >99:1 dr); $[\alpha]_D^{24}$ +4.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1614 (C═O); δ_H (400 MHz, $CDCl_3$) 0.95−1.04 (2H, m, 2 × C(7′)H_A), 1.20−1.33 (8H, m, 2 × C(*α*)*Me*, 2 × C(7′)H_B), 1.53−1.59 (4H, m, C(2)H_2, C(3)H_2), 2.57−2.65 (2H, m, 2 × C(6′)H_A), 2.78−2.86 (2H, m, C(1)H_A, C(4)H_A), 3.02−3.19 (8H, m, 2 × C(3′)H_A, 2 × C(8′)H_2, 2 × C(6′)H_B), 3.80 (2H, br t, *J* 11.9, 2 × C(3′)H_B), 3.90−4.01 (4H, m, 2 × C(*α*)*H*, C(1)H_B, C(4)H_B), 4.42−4.60 (2H, m, 2 × C(4′)*H*), 7.17−7.47 (20H, m, *Ph*); δ_H (500 MHz, PhMe-d_8, 363 K) 0.74−0.80 (2H, m, 2 × C(7′)H_A), 1.13 (6H, d, *J* 6.6, 2 × C(*α*)*Me*), 1.17−1.27 (2H, m, 2 × C(7′)H_B), 1.51−1.57 (4H, m, C(2)H_2, C(3)H_2), 2.40−2.47 (2H, m, 2 × C(6′)H_A), 2.56 (2H, dd, *J* 12.6, 3.8, C(1)H_A, C(4)H_A), 2.77−2.94 (8H, m, 2 × C(3′)H_A, 2 × C(6′)H_B, 2 × C(8′)H_2), 3.45 (2H, t, *J* 13.6, 2 × C(3′)H_B), 3.89−3.98 (4H, m, 2 × C(*α*)*H*, C(1)H_B, C(4)H_B), 4.47 (2H, dd, *J* 11.0, 3.5, 2 × C(4′)*H*), 7.02−7.08 (4H, m, *Ph*), 7.15 (8H, app t, *J* 7.9, *Ph*), 7.22−7.29 (8H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.3 (*C*(2), *C*(3)), 30.5 (2 × *C*(7′)), 45.5 (*C*(1), *C*(4)), 126.7, 127.0, 127.1, 127.2, 127.9, 128.0, 128.1, 128.6, 128.7 (*o,m,p-Ph*), 173.3 (2 × *C*(2′));[42] δ_C (125 MHz, PhMe-d_8, 363 K) *16.5* (2 × C(*α*)*Me*), 26.3 (*C*(2), *C*(3)), 31.4 (2 × *C*(7′)), 43.7 (2 × *C*(3′)), 46.1 (*C*(1), *C*(4)), 46.9 (2 × *C*(8′)), 47.9 (2 × *C*(6′)), 61.2 (2 × *C*(*α*)), 64.3 (2 × *C*(4′)), 127.3, 127.4, 128.0, 128.6, 128.9, 129.1 (*o,m,p-Ph*), 145.0, 146.5 (*i-Ph*), 172.5 (2 × *C*(2′)); *m/z* (ESI$^+$) 693 ([M + Na]$^+$, 41%), 671 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{44}H_{55}N_4O_2^+$ ([M + H]$^+$) requires 671.4320, found 671.4312.

Method B: Following General Procedure 7, **29** (20 mg, 29.9 *μ*mol) and $Pd(OH)_2/C$ (10 mg) in MeOH (1.0 mL) were reacted in the presence of H_2 (5 atm) for 1 h. The residue was partitioned between CH_2Cl_2 (5 mL) and satd aq $NaHCO_3$ (5 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give **30** as a yellow oil (21 mg, quant, >99:1 dr); $[\alpha]_D^{24}$ +4.2 (*c* 1.0 in $CHCl_3$).

(*R*)-*N*-3-(Chloropropyl)-*N*-(*α*-methyl-4′-methoxybenzyl)-amine. (*R*)-*N*-*α*-Methyl-4-methoxybenzyl amine (5.00 g, 33.1 mmol) was added to a solution of 1-bromo-3-chloropropane (1.81 mL, 18.3 mmol) in MeCN (10 mL), and the resultant mixture was stirred for 16 h at rt. The reaction mixture was basified to pH 9 with satd aq $NaHCO_3$ and then extracted with EtOAc (3 × 100 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent Et_2O) gave (*R*)-*N*-3-(chloropropyl)-*N*-(*α*-methyl-4′-methoxybenzyl)amine as a yellow oil (2.90 g, 70%, >99:1 er); $C_{12}H_{18}ClNO$ requires C, 63.3; H, 8.0; N, 6.15%, found C, 63.5; H, 7.9; N, 6.1%; $[\alpha]_D^{24}$ +28.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3323 (N−H); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.7, C(*α*)*Me*), 1.89 (2H, app quintet, *J* 6.8, C(2)H_2), 2.56 (1H, dt, *J* 11.9, 6.8, C(1)H_A), 2.66 (1H, dt, *J* 11.9, 6.6, C(1)H_B), 3.54−3.65 (2H, m, C(3)H_2), 3.73 (1H, q, *J* 6.7, C(*α*)*H*), 3.80 (3H, s, O*Me*), 6.86−6.89 (2H, m, C(3′)*H*, C(5′)*H*), 7.22−7.25 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 24.4 (C(*α*)*Me*), 33.1 (*C*(2)), 43.2 (*C*(3)), 44.7 (*C*(1)), 55.2 (O*Me*), 57.6 (*C*(*α*)), 113.8 (*C*(3′), *C*(5′)), 127.5 (*C*(2′), *C*(6′)), 137.7 (*C*(1′)), 158.5 (*C*(4′)); *m/z* (ESI$^+$) 252 ([M(^{37}Cl) + Na]$^+$, 4%), 250 ([M(^{35}Cl) + Na]$^+$, 10%), 230 ([M(^{37}Cl) + H]$^+$, 40%), 228 ([M(^{35}Cl) + H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{19}{}^{37}ClNO^+$ ([M(^{37}Cl) + H]$^+$) requires 230.1120, found 230.1119; $C_{12}H_{19}{}^{35}ClNO^+$ ([M(^{35}Cl) + H]$^+$) requires 228.1150, found 228.1145.

(4*S*,*αR*)-4-Phenyl-*N*(5)-(*α*-methyl-4′-methoxybenzyl)-1,5-diazocan-2-one 35. *Step 1*: Following General Procedure 1, (*R*)-*N*-3-(chloropropyl)-*N*-(*α*-methyl-4′-methoxybenzyl)amine (3.00 g, 13.2 mmol), BuLi (2.5 M, 5.12 mL, 12.8 mmol), and **23** (1.33 g, 8.23 mmol) in THF (75 mL) were reacted to give **32** (3.37 g, >99:1 dr). Purification of an aliquot via flash column chromatography (gradient elution, 2% → 20% Et_2O in 30−40 °C petrol) gave **32** as a colorless oil; $C_{22}H_{28}ClNO_3$ requires C, 67.8; H, 7.2; N, 3.6%, found C, 67.9; H, 7.0; N, 3.3%; $[\alpha]_D^{24}$ −3.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1737 (C═O); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.8, C(*α*)*Me*), 1.69−1.85 (2H, m, C(2′)H_2), 2.68 (2H, t, *J* 7.1, C(1′)H_2), 2.73 (1H, dd, *J* 14.9, 8.2, C(2)H_A), 2.90 (1H, dd, *J* 14.9, 6.7, C(2)H_B), 3.23−3.33 (2H, m, C(3′)H_2), 3.59 (3H, s, CO_2Me), 3.81 (3H, s, ArO*Me*), 3.98 (1H, q, *J* 6.8, C(*α*)*H*), 4.48 (1H, dd, *J* 8.2, 6.7, C(3)*H*), 6.87−6.91 (2H, m, C(3′′)*H*, C(5′′)*H*), 7.27−7.32 (3H, m, C(2′′)*H*, C(6′′)*H*, *Ph*), 7.33−7.39 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.9 (C(*α*)*Me*), 32.9 (*C*(2′)), 37.1 (*C*(2)), 43.2 (*C*(3′)), 43.6 (*C*(1′)), 51.5 (CO_2Me), 55.2 (ArO*Me*), 56.4 (*C*(*α*)), 59.2 (*C*(3)), 113.5 (*C*(3′′), *C*(5′′)), 127.3 (*C*(2′′), *C*(6′′)), 128.0, 128.4, 128.7 (*o,m,p-Ph*), 136.6 (*C*(1′′)), 141.4 (*i-Ph*), 158.5 (*C*(4′′)), 172.3 (*C*(1)); *m/z* (ESI$^+$) 414 ([M(^{37}Cl) + Na]$^+$, 35%), 412 ([M(^{35}Cl) + Na]$^+$, 100%), 392 ([M(^{37}Cl) + H]$^+$, 21%), 390 ([M(^{35}Cl) + H]$^+$, 84%); HRMS (ESI$^+$) $C_{22}H_{29}{}^{37}ClNO_3^+$ ([M(^{37}Cl) + H]$^+$) requires 392.1801, found 392.1804; $C_{22}H_{29}{}^{35}ClNO_3^+$ ([M(^{35}Cl) + H]$^+$) requires 390.1830, found 390.1819.

Step 2: Following General Procedure 2, NaN_3 (1.07 g, 16.5 mmol), NaI (2.47 g, 16.5 mmol), and **32** (3.00 g, >99:1 dr) in DMSO (20 mL) were reacted for 24 h to give **33** (2.93 g, >99:1 dr). Purification of an aliquot via flash column chromatography (gradient elution, 2% → 20% Et_2O in 30−40 °C petrol) gave **33** as a yellow oil; $[\alpha]_D^{24}$ −3.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2096 (N≡N), 1738 (C═O); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.8, C(*α*)*Me*), 1.48−1.64 (2H, m, C(2′)H_2), 2.59 (2H, t, *J* 6.8, C(1′)H_2), 2.73 (1H, dd, *J* 14.9, 8.1, C(2)H_A), 2.89 (1H, dd, *J* 14.9, 6.8, C(2)H_B), 2.95−3.05 (2H, m, C(3′)H_2), 3.60 (3H, s, CO_2Me), 3.82 (3H, s, ArO*Me*), 3.97 (1H, q, *J* 6.8, C(*α*)*H*), 4.45−4.49 (1H, m, C(3)*H*), 6.87−6.90 (2H, m, C(3′′)*H*, C(5′′)*H*), 7.28−7.31 (2H, m, C(2′′)*H*, C(6′′)*H*), 7.34−7.38 (5H, m, *Ph*); δ_C

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(100 MHz, $CDCl_3$) 16.8 (C(α)*Me*), 29.0 (*C*(2′)), 37.1 (*C*(2)), 43.3 (*C*(1′)), 49.4 (*C*(3′)), 51.6 (CO_2*Me*), 55.2 (ArO*Me*), 56.3 (*C*(α)), 59.2 (*C*(3)), 113.5 (*C*(3″), *C*(5″)), 127.3 (*C*(2″), *C*(6″)), 127.9, 128.4, 128.7 (*o,m,p-Ph*), 136.6 (*C*(1″)), 141.3 (*i-Ph*), 158.4 (*C*(4″)), 172.3 (*C*(1)); *m/z* (ESI$^+$) 419 ([M + Na]$^+$, 100%), 397 ([M + H]$^+$, 94%); HRMS (ESI$^+$) $C_{22}H_{29}N_4O_3^+$ ([M + H]$^+$) requires 397.2234, found 397.2232.

Step 3: Following General Procedure 3, **33** (2.69 g, >99:1 dr) and PPh_3 (1.78 g, 6.77 mmol) in THF (10 mL) and H_2O (2.7 mL) were reacted. The residue was partitioned between CH_2Cl_2 (100 mL) and 2.0 M aq HCl (25 mL). The organic layer was extracted with 2.0 M aq HCl (2 × 25 mL), and the combined aqueous layers were washed with CH_2Cl_2 (50 mL). The aqueous layer was then basified to pH 12 by the addition of solid KOH and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **34** as a colorless oil (1.95 g, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.8, C(α)*Me*), 1.50 (2H, app quintet, *J* 6.9, C(2′)H_2), 2.46 (2H, td, *J* 6.9, 2.7, C(3′)H_2), 2.54 (2H, t, *J* 7.9, C(1′)H_2), 2.70 (1H, dd, *J* 14.9, 8.7, C(2)H_A), 2.81 (1H, dd, *J* 14.9, 6.5, C(2)H_B), 3.57 (3H, s, CO_2*Me*), 3.81 (3H, s, ArO*Me*), 3.96 (1H, q, *J* 6.8, C(α)*H*), 4.45 (1H, dd, *J* 8.7, 6.5, C(3)*H*), 6.86 (2H, d, *J* 8.5, C(3″)*H*, C(5″)*H*), 7.24−7.36 (7H, m, *Ph*, C(2″)*H*, C(6″)*H*).

Step 4: Following General Procedure 5, **34** (1.95 g, >99:1 dr) and $Sb(OEt)_3$ (1.07 mL, 6.31 mmol) in PhMe (600 mL) were reacted. Purification via flash column chromatography (eluent EtOAc) gave **35** as a colorless oil (1.31 g, 53% over 4 steps, >99:1 dr); $C_{21}H_{26}N_2O_2$ requires C, 74.5; H, 7.7; N, 8.3%, found C, 74.4; H, 7.6; N, 8.2%; $[\alpha]_D^{20}$ +21.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1663 (C═O); δ_H (400 MHz, $CDCl_3$) 0.99−1.08 (1H, m, C(7)H_A), 1.20−1.30 (1H, m, C(7)H_B) overlapping 1.21 (3H, d, *J* 6.3, C(α)*Me*), 2.51−2.66 (2H, m, C(2)H_A, C(6)H_A), 2.98−3.17 (3H, m, C(2)H_B, C(6)H_B, C(8)H_A), 3.49 (1H, app br q, *J* 9.9, C(8)H_B), 3.74 (3H, s, O*Me*), 3.93 (1H, q, *J* 6.3, C(α)*H*), 4.49 (1H, br s, C(4)*H*), 6.81 (2H, d, *J* 8.3, C(3′)*H*, C(5′)*H*), 7.02 (1H, br t, *J* 6.8, N*H*), 7.21−7.41 (7H, m, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (125 MHz, PhMe-d_8, 363 K) 16.8 (C(α)*Me*), 33.8 (*C*(7)), 41.9 (*C*(6)), 42.0 (*C*(3)), 46.6 (*C*(8)), 54.9 (O*Me*), 60.4 (*C*(α)), 63.4 (*C*(4)), 114.0 (*C*(3′), *C*(5′)), 127.0, 127.6, 128.6, 129.4 (*o,m,p-Ph*, *C*(2′), *C*(6′)), 138.0, 144.4 (*i-Ph*), 159.3 (*C*(4′)), 175.7 (*C*(2));[43] *m/z* (ESI$^+$) 699 ([2M + Na]$^+$, 100%), 361 ([M + Na]$^+$, 79%), 339 ([M + H]$^+$, 76%); HRMS (ESI$^+$) $C_{21}H_{26}N_2NaO_2^+$ ([M + Na]$^+$) requires 361.1886, found 361.1880.

(4′*S*,α*R*)-1,4-Di[2′-oxo-4′-phenyl-*N*(5′)-(α-methyl-4″-methoxybenzyl)-1′,5′-diazocan-1′-yl]butane 36. 1,4-Dibromobutane (88 μL, 739 μmol) was added to a suspension of **35** (500 mg, 1.48 mmol, >99:1 dr), K_2CO_3 (818 mg, 5.92 mmol), KOH (332 mg, 5.92 mmol), and TBAI (55 mg, 148 μmol) in PhMe (8 mL) under N_2 and sealed in a tube. The resultant mixture was heated at 160 °C in a microwave reactor for 15 min before being cooled to rt and partitioned between H_2O (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were washed with brine (20 mL), then dried, and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 70% → 100% EtOAc in 30−40 °C petrol) gave **36** as a white solid (363 mg, 67%, >99:1 dr); mp 46−49 °C; $[\alpha]_D^{24}$ +20.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1661 (C═O); δ_H (500 MHz, $CDCl_3$) 0.96−1.04 (2H, m, 2 × C(7′)H_A), 1.19 (6H, d, *J* 6.5, 2 × C(α)*Me*), 1.27−1.37 (2H, m, 2 × C(7′)H_B), 1.56 (4H, br s, C(2)H_2, C(3)H_2), 2.45 (2H, br s, 2 × C(6′)H_A), 2.78−2.86 (2H, m, C(1)H_A, C(4)H_A), 3.02 (2H, br s, 2 × C(3′)H_A), 3.06−3.17 (4H, m, 2 × C(6′)H_B, 2 × C(8′)H_A), 3.78−3.84 (8H, m, O*Me*, 2 × C(8′)H_B), 3.88 (2H, q, *J* 6.5, 2 × C(α)*H*), 3.90−3.98 (2H, m, C(1)H_B, C(4)H_B), 4.44 (2H, br s, 2 × C(4′)*H*), 6.82 (4H, d, *J* 8.8, 2 × C(3″)*H*, 2 × C(5″)*H*), 7.22−7.28 (6H, m, 2 × C(2″)*H*, 2 × C(6″)*H*, *Ph*), 7.32−7.37 (4H, m, *Ph*), 7.38−7.44 (4H, m, *Ph*);[44] δ_C (125 MHz, $CDCl_3$) 15.1 (2 × C(α)*Me*), 25.3 (*C*(2), *C*(3)), 30.6 (2 × *C*(7′)), 43.4 (2 × *C*(3′)), 45.4 (*C*(1), *C*(4)), 47.5 (2 × (*C*(8′)), 55.2 (2 × O*Me*), 59.5 (2 × *C*(α)), 63.7 (2 × *C*(4′)), 113.2 (2 × *C*(3″), 2 × (*C*(5″)), 126.9, 127.1, 128.6, 129.0 (2 × *C*(2″), 2 × *C*(6″), *o,m,p-Ph*), 137.5 (2 × *C*(1″)), 143.6 (*i-Ph*), 158.3 (2 × *C*(4″)), 170.3 (2 × *C*(1′));[45] *m/z* (ESI$^+$) 753 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{46}H_{58}N_4NaO_4^+$ ([M + Na]$^+$) requires 753.4350, found 753.4358.

(*S,S*)-1,4-Di[2′-oxo-4′-phenyl-1′,5′-diazocan-*N*(1′)-yl]butane 37. A mixture of TFA (1.00 mL) and **36** (50 mg, 78.1 μmol, >99:1 dr) was heated at 60 °C for 2.5 h, then allowed to cool to rt, and concentrated *in vacuo*. The residue was partitioned between EtOAc (5 mL) and satd aq $NaHCO_3$ (5 mL), and then the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine (10 mL), then dried, and concentrated *in vacuo*. Purification via column chromatography (gradient elution, 0% → 10% MeOH in $CHCl_3$) gave **37** as a colorless oil (11 mg, 30%, >99:1 dr);[10] $[\alpha]_D^{24}$ −32.5 (*c* 0.5 in $CHCl_3$); {lit.[10] $[\alpha]_D^{20}$ −30 (*c* 1.3 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.59−1.68 (2H, m, 2 × C(7′)H_A), 1.76−1.84 (6H, m, C(2)H_2, C(3)H_2, 2 × C(7′)H_B), 2.38 (2H, dd, *J* 12.3, 8.9, 2 × C(3′)H_A), 2.50 (2H, dd, *J* 12.3, 1.7, 2 × C(3′)H_B), 2.89−3.04 (4H, m, 2 × C(6′)H_2), 3.13−3.32 (4H, m, C(1)H_2, C(4)H_2), 3.83−3.92 (2H, m, 2 × C(8′)H_A), 3.95−4.23 (4H, m, 2 × C(4′)*H*, 2 × C(8′)H_B), 7.23−7.43 (10H, m, *Ph*).

(*S*)-*N*(1)-(Hydroxymethyl)-4-phenyl-*N*(5)-methyl-1,5-diazocan-2-one 40. $Pd(OH)_2/C$ (200 mg) was added to a degassed solution of **27** (200 mg, 648 μmol, >99:1 dr) in MeOH (3.4 mL), formalin (6.4 mL), and AcOH (10 mL), and the resultant mixture was stirred under H_2 (5 atm) for 72 h. The reaction mixture was degassed, filtered through Celite (eluent MeOH), and concentrated *in vacuo*. The residue was partitioned between EtOAc (15 mL) and satd aq $NaHCO_3$ (15 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 19:1) gave **40** as a white solid (45 mg, 28%); mp 94−97 °C; $[\alpha]_D^{24}$ −5.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3357 (O−H), 1631 (C═O); δ_H (400 MHz, $CDCl_3$) 1.67−1.75 (1H, m, C(7)H_A), 1.85−1.96 (1H, m, C(7)H_B), 2.25 (3H, s, N*Me*), 2.51−2.57 (2H, m, C(6)H_A, C(3)H_A), 2.97 (1H, ddd, *J* 15.4, 7.1, 3.3, C(6)H_B), 3.14 (1H, app t, *J* 11.9, C(3)H_B), 3.49 (1H, dt, *J* 15.4, 3.8, C(8)H_A), 3.88−4.00 (2H, m, C(4)*H*, C(8)H_B), 4.11 (1H, br s, O*H*), 4.77 (1H, d, *J* 10.3, N(1)C$H_A$$H_B$OH), 5.02 (1H, d, *J* 10.3, N(1)C$H_A$$H_B$OH), 7.23−7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 31.1 (*C*(7)), 41.5 (*C*(3)), 43.8 (N*Me*), 48.6 (*C*(8)), 51.5 (*C*(6)), 68.4 (*C*(4)), 72.9 (N(1)CH_2OH), 127.3, 127.5, 128.4 (*o,m,p-Ph*), 141.8 (*i-Ph*), 175.5 (*C*(2)); *m/z* (ESI$^+$) 271 ([M + Na]$^+$, 100%), 249 ([M + H]$^+$, 41%); HRMS (ESI$^+$) $C_{14}H_{21}N_2O_2^+$ ([M + H]$^+$) requires 249.1598, found 249.1599. Further elution gave **39** as a white solid (18 mg, 13%, >99:1 dr).

X-ray Crystal Structure Determination for 40.[29] Data were collected using graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined using CRYSTALS.[46] X-ray crystal structure data for **40** [$C_{14}H_{20}N_2O_2$]: *M* = 248.32, monoclinic, space group $P2_1$, *a* = 6.0224(3) Å, *b* = 6.8706(3) Å, *c* = 15.3642(6) Å, β = 93.565(2)°, *V* = 634.50(5) Å^3, *Z* = 2, μ = 0.088 mm^{-1}, colorless plate, crystal dimensions = 0.08 × 0.19 × 0.22 mm^3. A total of 1545 unique reflections were measured for 5 < θ < 27, and 1545 reflections were used in the refinement. The final parameters were wR_2 = 0.105 and R_1 = 0.058 [$I > -3.0\sigma(I)$].

Methyl (*S*)-3-(3′-Chloropropylamino)-3-phenylpropanoate 41. *Method A*: Following General Procedure 7, **24** (1.00 g, 2.78 mmol, >99:1 dr), and $Pd(OH)_2/C$ (500 mg) in 1.0 M aq HCl (10 mL) were reacted for 18 h. The residue was partitioned between CH_2Cl_2 (20 mL) and satd aq $NaHCO_3$ (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **41** as a yellow oil (496 mg, 70%); $[\alpha]_D^{24}$ −29.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3347 (N−H), 1735 (C═O); δ_H (400 MHz, $CDCl_3$) 1.83−1.95 (2H, m, C(2′)H_2), 2.54−2.67 (3H, m, C(1′)H_2, C(2)H_A), 2.72 (1H, dd, *J* 15.7, 8.7 C(2)H_B), 3.54−3.64 (2H, m, C(3′)H_2), 3.66 (3H, s, O*Me*), 4.09 (1H, dd, *J* 8.7, 5.3, C(3)*H*), 7.25−7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 32.7 (*C*(2′)), 42.7 (*C*(2)), 42.9 (*C*(3′)), 44.2 (*C*(1′)), 51.7 (O*Me*), 59.4 (*C*(3)), 126.9, 127.6, 128.6 (*o,m,p-Ph*), 142.3 (*i-Ph*), 172.2 (*C*(1)); *m/z* (ESI$^+$) 280 ([M(^{37}Cl) + Na]$^+$, 9%), 278 ([M(^{35}Cl)

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+ Na]$^+$, 26%), 258 ([M(^{37}Cl) + H]$^+$, 47%), 256 ([M(^{35}Cl) + H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{19}{}^{37}ClNO_2^+$ ([M(^{37}Cl) + H]$^+$) requires 258.1069, found 256.1068; $C_{13}H_{19}{}^{35}ClNO_2^+$ ([M(^{35}Cl) + H]$^+$) requires 256.1099, found 256.1096.

Method B: A mixture of **32** (958 mg, 2.66 mmol, >99:1 dr) and TFA (9.6 mL) was heated at 60 °C for 2.5 h, then allowed to cool to rt, and concentrated *in vacuo*. The residue was partitioned between EtOAc (20 mL) and satd aq $NaHCO_3$ (20 mL) and then the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (30 mL), then dried, and concentrated *in vacuo*. Purification via column chromatography (eluent, 30−40 °C petrol/Et_2O, 3:7) gave **41** as a yellow oil (581 mg, 92%); $[\alpha]_D^{24}$ −28.5 (*c* 1.0 in $CHCl_3$).

Methyl (*S*)-3-[*N*-(3′-Chloropropyl)-*N*-methylamino]-3-phenylpropanoate 42. Following General Procedure 8, **41** (675 mg, 2.64 mmol), $(CH_2O)_n$ (159 mg, 5.28 mmol), and $NaBH_3CN$ (664 mg, 10.6 mmol) in MeOH (27 mL) were reacted. Purification via flash column chromatography (gradient elution, 60% → 100% EtOAc in 30−40 °C petrol) gave **42** as a yellow oil (573 mg, 75%); $[\alpha]_D^{24}$ −5.3 (*c* 0.4 in $CHCl_3$); ν_{max} (ATR) 1737 (C═O); δ_H (400 MHz, $CDCl_3$) 1.85−1.93 (2H, m, C(2′)H_2), 2.14 (3H, s, N*Me*), 2.38−2.45 (1H, m, C(1′)H_A), 2.49−2.55 (1H, m, C(1′)H_B), 2.70 (1H, dd, *J* 14.8, 7.1, C(2)H_A), 3.00 (1H, dd, *J* 14.8, 8.3, C(2)H_B), 3.57 (2H, t, *J* 6.3, C(3′)H_2), 3.64 (3H, s, O*Me*), 4.17 (1H, app t, *J* 7.8, C(3)*H*), 7.23−7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 30.4 (*C*(2′)), 37.3 (N*Me*, *C*(2)), 42.9 (*C*(3′)), 50.7 (*C*(1′)), 51.6 (O*Me*), 64.5 (*C*(3)), 127.5, 128.1, 128.3 (*o*,*m*,*p*-*Ph*), 137.9 (*i*-*Ph*), 172.3 (*C*(1)); *m*/*z* (ESI$^+$) 294 ([M(^{37}Cl) + Na]$^+$, 11%), 292 ([M(^{35}Cl) + Na]$^+$, 31%), 272 ([M(^{37}Cl) + H]$^+$, 53%), 270 ([M(^{35}Cl) + H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{21}{}^{37}ClNO_2^+$ ([M(^{37}Cl) + H]$^+$) requires 272.1226, found 272.1227; HRMS (ESI$^+$) $C_{14}H_{21}{}^{35}ClNO_2^+$ ([M(^{35}Cl) + H]$^+$) requires 270.1255, found 270.1250.

Methyl (*S*)-3-[*N*-(3′-Azidopropyl)-*N*-methylamino]-3-phenylpropanoate 43. Following General Procedure 2, NaN_3 (1.21 g, 18.6 mmol), NaI (2.79 g, 18.6 mmol), and **42** (2.51 g, 9.31 mmol) in DMSO (40 mL) were reacted for 24 h. Purification via flash column chromatography (gradient elution, 10% → 50% Et_2O in 30−40 °C petrol) gave **43** as a yellow oil (2.57 g, quant); $[\alpha]_D^{24}$ −4.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2096 (N≡N), 1739 (C═O); δ_H (400 MHz, $CDCl_3$) 1.69−1.73 (2H, m, C(2′)H_2), 2.14 (3H, s, N*Me*), 2.30−2.36 (1H, m, C(1′)H_A), 2.41−2.48 (1H, m, C(1′)H_B), 2.70 (1H, dd, *J* 14.9, 7.2, C(2)H_A), 2.99 (1H, dd, *J* 14.9, 8.4, C(2)H_B), 3.31 (2H, t, *J* 6.8, C(3′)H_2), 3.64 (3H, s, O*Me*), 4.16 (1H, app t, *J* 7.9, C(3)*H*), 7.21−7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.7 (*C*(2′)), 37.2 (*C*(2)), 37.3 (N*Me*), 49.2 (*C*(3′)), 50.7 (*C*(1′)), 51.6 (O*Me*), 64.3 (*C*(3)), 127.5, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 137.9 (*i*-*Ph*), 172.3 (*C*(1)); *m*/*z* (ESI$^+$) 299 ([M + Na]$^+$, 49%), 277 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{21}N_4O_2^+$ ([M + H]$^+$) requires 277.1659, found 277.1654.

(*S*)-4-Phenyl-*N*(5)-methyl-1,5-diazocan-2-one 39. *Step 1*: Following General Procedure 3, **43** (2.40 g, 8.69 mmol) and PPh_3 (2.51 g, 9.55 mmol) in THF (25 mL) and H_2O (7.2 mL) were reacted to give **44** as a yellow oil (5.15 g);[4,13] δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.55−1.62 (2H, m, C(2′)H_2), 2.15 (3H, s, N*Me*), 2.29−2.35 (1H, m, C(1′)H_A), 2.39−2.46 (1H, m, C(1′)H_B), 2.67−2.72 (3H, m, C(2)H_A, C(3′)H_2), 3.00 (1H, app dd, *J* 14.9, 8.0, C(2)H_B), 3.63 (3H, s, O*Me*), 4.16 (1H, app t, *J* 7.9, C(3)*H*).

Step 2: Following General Procedure 5, **44** (5.15 g) and $Sb(OEt)_3$ (1.49 mL, 8.77 mmol) in PhMe (750 mL) were reacted. Purification via flash column chromatography (gradient elution, 0% → 10% MeOH in EtOAc) gave **39** as a white solid (1.18 g, 62% over 2 steps); mp 97−99 °C; $[\alpha]_D^{24}$ +6.7 (*c* 1.0 in $CHCl_3$); {lit.[47] for enantiomer $[\alpha]_D^{25}$ −6.2 (*c* 0.9 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.54−1.64 (1H, m, C(7)H_A), 1.67−1.78 (1H, m, C(7)H_B), 2.31 (3H, s, N*Me*), 2.46 (1H, dd, *J* 12.6, 3.8, C(3)H_A), 2.53 (1H, ddd, *J* 15.4, 6.8, 2.8, C(6)H_A), 2.99−3.04 (1H, m, C(6)H_B), 3.08 (1H, app t, *J* 12.1, C(3)H_B), 3.24−3.34 (1H, m, C(8)H_A), 3.46−3.57 (1H, m, C(8)H_B), 4.05 (1H, dd, *J* 8.3, 3.5, C(4)*H*), 5.77 (1H, br s, N*H*), 7.21−7.35 (5H, m, *Ph*).

X-ray Crystal Structure Determination for ***39***.[29] Data were collected using graphite monochromated Cu Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined using CRYSTALS.[46] X-ray crystal structure data for **39** [$C_{13}H_{18}N_2O$]: M = 218.30, monoclinic, space group $P2_1$, a = 6.0474(2) Å, b = 6.8974(2) Å, c = 13.9812(4) Å, β = 96.696(3)°, V = 579.19(3) Å^3, Z = 2, μ = 0.632 mm^{-1}, colorless plate, crystal dimensions =0.05 × 0.11 × 0.23 mm^3. A total of 6077 reflections were measured for 5 < θ < 77 and 5458 reflections were used in the refinement. The final parameters were wR_2 = 0.084 and R_1 = 0.034 [$I > -3.0\sigma(I)$].

(*S*)-*N*(1)-Allyl-4-phenyl-*N*(5)-methyl-1,5-diazocan-2-one 45. Allyl bromide (0.24 mL, 2.80 mmol) was added to a mixture of **39** (500 mg, 2.29 mmol), K_2CO_3 (380 mg, 2.75 mmol), NaOH (387 mg, 9.68 mmol), and TEBAC (69 mg, 298 μmol) in THF (14 mL). The resultant mixture was heated at 75 °C for 18 h, then filtered through Celite (eluent EtOAc) and concentrated *in vacuo*. Purification via column chromatography (gradient elution, 60% → 100% EtOAc in 30−40 °C petrol) gave **45** as a yellow oil (555 mg, 94%); $[\alpha]_D^{24}$ −31.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1633 (C═O); δ_H (400 MHz, $CDCl_3$) 1.55−1.64 (1H, m, C(7)H_A), 1.77−1.88 (1H, m, C(7)H_B), 2.28 (3H, s, N*Me*), 2.52 (1H, ddd, *J* 15.4, 7.8, 3.0, C(6)H_A), 2.58 (1H, dd, *J* 12.9, 3.3, C(3)H_A), 2.98 (1H, ddd, *J* 15.4, 7.8, 3.0, C(6)H_B), 3.19 (1H, app t, *J* 12.1, C(3)H_B), 3.33 (1H, dt, *J* 15.4, 3.8, C(8)H_A), 3.68 (1H, dd, *J* 15.2, 6.8, C$H_A$$H_B$CH═$CH_2$), 3.79−3.86 (1H, m, C(8)H_B), 4.03 (1H, dd, *J* 11.6, 3.3, C(4)*H*), 4.45 (1H, dd, *J* 15.2, 5.3, C$H_A$$H_B$CH═$CH_2$), 5.16−5.24 (2H, m, CH_2CH═CH_2), 5.79−5.89 (1H, m, CH_2C*H*═CH_2), 7.22−7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 29.6 (*C*(7)), 41.1 (*C*(3)), 43.7 (N*Me*), 47.1 (*C*(8)), 48.5 (CH_2CH═CH_2), 51.1 (*C*(6)), 68.1 (*C*(4)), 117.2 (CH_2CH═CH_2), 127.1, 127.5, 128.3 (*o*,*m*,*p*-Ph), 133.9 (CH_2CH═CH_2), 141.9 (*i*-*Ph*), 173.3 (*C*(2)); *m*/*z* (ESI$^+$) 539 ([2M + Na]$^+$, 100%), 517 ([2M + H]$^+$, 13%), 281 ([M + Na]$^+$, 96%) 259 ([M + H]$^+$, 90%); HRMS (ESI$^+$) $C_{16}H_{23}N_2O^+$ ([M + H]$^+$) requires 259.1805, found 259.1803.

(*S*,*E*)-1,4-Di[2′-oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-1′-yl]but-2-ene 46 and (*S*,*E*)-1-(Prop-1′-en-1′-yl)-4-phenyl-*N*(5)-methyl-1,5-diazocan-2-one 47. Grubbs II catalyst (75 mg, 88.6 μmol) was added to a degassed solution of **45** (229 mg, 886 μmol) in CH_2Cl_2 (3 mL, EtOH stabilized), and the resultant mixture was heated at 40 °C for 16 h. The reaction mixture was then concentrated *in vacuo* to give a 78:22 mixture of **46** and **47**. Purification via flash column chromatography (gradient elution, 0% → 10% MeOH in CH_2Cl_2) gave **47** as a brown oil (26 mg, 11%, >99:1 dr); $[\alpha]_D^{24}$ +14.4 (*c* 0.4 in $CHCl_3$); ν_{max} (ATR) 1644 (C═O); δ_H (400 MHz, $CDCl_3$) 1.75 (3H, dd, *J* 6.6, 1.5, C(3′)H_3), 1.80−1.93 (2H, m, C(7)H_2), 2.24 (3H, s, N*Me*), 2.50 (1H, ddd, *J* 15.3, 8.3, 2.8, C(6)H_A), 2.64 (1H, dd, *J* 13.1, 3.3, C(3)H_A), 2.93 (1H, ddd, *J* 15.3, 6.8, 3.3, C(6)H_B), 3.25 (1H, br t, *J* 12.1, C(3)H_B), 3.75 (1H, dt, *J* 15.4, 3.5, C(8)H_A), 3.94−4.05 (2H, m, C(4)*H*, C(8)H_B), 5.11 (1H, dq, *J* 14.7, 6.6, C(2′)*H*), 7.19−7.37 (6H, m, C(1′)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.5 (*C*(3′)), 28.6 (*C*(7)), 42.1 (*C*(3)), 43.8 (N*Me*), 44.3 (*C*(8)), 51.4 (*C*(6)), 68.9 (*C*(4)), 106.5 (*C*(2′)), 126.5, 127.5, 128.4 (*o*,*m*,*p*-*Ph*), 127.3 (*C*(1′)), 171.7 (*C*(2));[48] *m*/*z* (ESI$^+$) 539 ([2M + Na]$^+$, 100%), 517 ([2M + H]$^+$, 6%), 281 ([M + Na]$^+$, 82%) 259 ([M + H]$^+$, 71%); HRMS (ESI$^+$) $C_{16}H_{23}N_2O^+$ ([M + H]$^+$) requires 259.1805, found 259.1805. Further elution gave **46** as a brown oil (92 mg, 42%, >99:1 dr) $[\alpha]_D^{24}$ −29.2 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 1631 (C═O); δ_H (400 MHz, $CDCl_3$) 1.55−1.68 (2H, m, 2 × C(7′)H_A), 1.74−1.87 (2H, m, 2 × C(7′)H_B), 2.27 (6H, s, 2 × N*Me*), 2.46−2.59 (4H, m, 2 × C(3′)H_A, 2 × C(6′)H_A), 2.98 (2H, app ddd, *J* 15.2, 7.8, 2.8, 2 × C(6′)H_B), 3.18 (2H, app t, *J* 12.1, 2 × C(3′)H_B), 3.31 (2H, app dt, *J* 15.4, 3.5, 2 × C(8′)H_A), 3.68 (2H, dd, *J* 15.7, 3.3, C(1)H_A, C(4)H_A), 3.81 (2H, app t, *J* 13.4, 2 × C(8′)H_B), 4.01 (2H, dd, *J* 11.6, 3.0, 2 × C(4′)*H*), 4.41 (2H, app d, *J* 13.4, C(1)H_B, C(4)H_B), 5.65 (2H, t, *J* 3.3, C(2)*H*, C(3)*H*), 7.23−7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 29.6 (2 × C(7′)), 41.0 (2 × C(3′)), 43.7 (2 × N*Me*), 47.3 (2 × C(8′)), 47.4 (C(1), C(4)), 51.1 (2 × (C(6′)), 68.1 (2 × C(4′)), 127.2, 127.5, 128.3 (*o*,*m*,*p*-*Ph*), 128.5 (*C*(2), C(3)), 141.7 (*i*-*Ph*), 173.3 (2 × C(2′)); *m*/*z* (ESI$^+$) 511 ([M + Na]$^+$, 69%), 489 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{41}N_4O_2^+$ ([M + H]$^+$) requires 489.3224, found 489.3233.

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(*S*,*S*)-1,4-Di[2′-oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]butane [(−)-Homaline] 1. *Method A*: Formalin (2.71 mL) was added to a stirred mixture of **36** (50 mg, 78.1 μmol, >99:1 dr) in HCO_2H (2.28 mL), and the resultant mixture was heated at reflux for 2.5 h and then allowed to cool to rt. Next 1.0 M aq NaOH was added to the reaction mixture until pH >13 was achieved, and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification via column chromatography (gradient elution, 0% → 13% MeOH in Et_2O) gave **1** as a white solid (15 mg, 39%, >99:1 dr); mp 113−116 °C; {lit.[6] mp 132 °C (Et_2O)}; $[\alpha]_D^{24}$ −29.2 (*c* 1.0 in $CHCl_3$); {lit.[6] $[\alpha]_D^{20}$−34 (*c* 1.0 in $CHCl_3$)}; ν_{max} (film) 1630 (C═O); δ_H (400 MHz, $CDCl_3$) 1.57−1.67 (6H, m, C(2)H_2, C(3)H_2, 2 × C(7′)H_A), 1.76−1.87 (2H, m, 2 × C(7′)H_B), 2.26 (6H, s, 2 × N*Me*), 2.47−2.55 (4H, m, 2 × C(3′)H_A), 2 × C(6′)H_A), 2.93−3.08 (4H, m, C(1)H_A, C(4)H_A, 2 × C(6′)H_B), 3.16 (2H, app t, *J* 12.1, 2 × C(3′)H_B), 3.32 (2H, app dt, *J* 15.4, 3.5, 2 × C(8′)H_A), 3.77−3.90 (4H, m, C(1)H_B, C(4)H_B, 2 × C(8′)H_B), 4.00 (2H, dd, *J* 11.6, 3.0, 2 × C(4′)*H*), 7.23−7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.4 (*C*(2), *C*(3)), 29.9 (2 × *C*(7′)), 41.2 (2 × *C*(3′)), 43.7 (2 × N*Me*), 45.7 (*C*(1), *C*(4)), 47.9 (2 × *C*(8′)), 51.0 (2 × *C*(6′)), 68.1 (2 × *C*(4′)), 127.1, 127.5, 128.3 (*o*,*m*,*p*-*Ph*), 142.0 (*i*-*Ph*), 173.5 (2 × *C*(2′)); *m*/*z* (ESI$^+$) 982 ([2*M* + H]$^+$, 43%), 513 ([*M* + Na]$^+$, 100%), 491 ([*M* + H]$^+$, 96%); HRMS (ESI$^+$) $C_{30}H_{43}N_4O_2^+$ ([*M* + H]$^+$) requires 491.3381, found 491.3389.

Method B:[7] Formalin (0.81 mL) was added to a solution of **37** (25 mg, 54 μmol, >99:1 dr) in AcOH (2.5 mL) at 0 °C, and the resultant mixture was stirred for 15 min. $NaBH_3CN$ (65 mg, 1.03 mmol) in MeOH (0.43 mL) was added, and the resultant mixture was allowed to warm to rt over 3.5 h. The reaction mixture was cooled to 0 °C, 2.0 M aq HCl (2 mL) was added, and the resultant mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and satd aq Na_2CO_3 (5 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic extracts were washed with brine (10 mL), then dried, and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0% → 4% MeOH in $CHCl_3$) gave (−)-homaline **1** as a white solid (8 mg, 30%, >99:1 dr);[6] mp 115−117 °C; $[\alpha]_D^{21}$ −16.8 (*c* 0.4 in $CHCl_3$).

Method C: Following General Procedure 7, **46** (57 mg, 117 μmol, >99:1 dr) and $Pd(OH)_2/C$ in EtOAc (1 mL) were reacted for 2 h. Purification via column chromatography (gradient elution, 1% → 10% MeOH in Et_2O) gave (−)-homaline **1** as a white solid (25 mg, 44%, >99:1 dr); mp 122−124 °C; $[\alpha]_D^{24}$ −32.5 (*c* 1.0 in $CHCl_3$).

Method D: Following General Procedure 6B, **39** (100 mg, 458 μmol), 1,4-dibromobutane (28 μL, 234 μmol), and KOH (103 mg, 1.84 mmol) in DMSO (0.92 mL) were reacted for 96 h. Purification via column chromatography (gradient elution, 0% → 2.5% MeOH in CH_2Cl_2) gave (−)-homaline **1** as a white solid (67 mg, 60%, >99:1 dr); mp 115−117 °C; $[\alpha]_D^{21}$ −28.1 (*c* 1.0 in $CHCl_3$).

***tert*-Butyl (*E*)-Oct-2-enoate 48.** MeMgBr (2.5 M in Et_2O, 17.5 mL, 43.7 mmol) was added to a solution of *tert*-butyl diethylphosphonoacetate (10.7 mL, 45.7 mmol) in THF (300 mL) at rt, and the resultant mixture was stirred for 15 min. Hexanal (5 mL, 41.6 mmol) was then added, and the resulatant mixture was heated at reflux for 2.5 h. The reaction mixture was allowed to cool to rt and partitioned between satd aq NH_4Cl (100 mL) and Et_2O (100 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL), and the combined organic extracts were washed with brine (200 mL), then dried, and concentrated *in vacuo* to give **48** in >99:1 dr. Purification via flash column chromatography (eluent 30−40 °C petrol) gave **48** as a colorless oil (4.18 g, 51%, >99:1 dr);[49] δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8, C(8)H_3), 1.25−1.60 (6H, m, C(5)H_2, C(6)H_2, C(7)H_2) overlapping 1.49 (9H, s, C*Me*$_3$), 2.17 (2H, app q, *J* 7.0, C(4)H_2), 5.74 (1H, dt, *J* 15.7, 1.6, C(2)*H*), 6.87 (1H, dt, *J* 15.7, 7.0, C(3)*H*).

***tert*-Butyl (*E*)-Dec-2-enoate 49.** MeMgBr (2.5 M in Et_2O, 17.5 mL, 43.7 mmol) was added to a solution of *tert*-butyl diethylphosphonoacetate (10.7 mL, 45.7 mmol) in THF (300 mL) at rt, and the resultant mixture was stirred for 15 min. Octanal (6.5 mL, 41.6 mmol) was then added, and the resulatant mixture was heated at reflux for 2.5 h. The reaction mixture was allowed to cool to rt and partitioned between satd aq NH_4Cl (100 mL) and Et_2O (100 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL), and the combined organic extracts were washed with brine (200 mL), then dried, and concentrated *in vacuo* to give **49** in >99:1 dr. Purification via flash column chromatography (eluent 30−40 °C petrol) gave **49** as a colorless oil (3.57 g, 38%, >99:1 dr);[50] δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8, C(10)H_3), 1.22−1.48 (10H, m, C(5)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2), 1.49 (9H, s, C*Me*$_3$), 2.17 (2H, app q, *J* 7.2, C(4)H_2), 5.74 (1H, dt, *J* 15.6, 1.5, C(2)*H*), 6.87 (1H, dt, *J* 15.6, 6.8, C(3)*H*).

***tert*-Butyl (*R*,*R*)-3-[*N*-(3′-Chloropropyl)-*N*-(α-methylbenzyl)-amino]octanoate 50.** Following General Procedure 1, (*R*)-*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amine (6.67 g, 33.7 mmol), BuLi (2.5 M, 13.1 mL, 32.7 mmol), and **48** (4.18 g, 21.1 mmol) in THF (300 mL) were reacted to give **50** in >99:1 dr. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 19:1) gave **50** as a yellow oil (6.75 g, 81%, >99:1 dr); $[\alpha]_D^{24}$ −13.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1726 (C═O); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.3, C(8)H_3), 1.17−1.35 (7H, m, C(4)H_A, C(5)H_2, C(6)H_2, C(7)H_2), 1.40−1.48 (13H, m, C*Me*$_3$, C(4)H_B, C(α)*Me*), 1.85 (2H, app quintet, *J* 6.6, C(2′)H_2), 2.00 (1H, dd, *J* 14.7, 7.8, C(2)H_A), 2.06 (1H, dd, *J* 14.7, 5.3, C(2)H_B), 2.55−2.68 (2H, m, C(1′)H_2), 3.17−3.24 (1H, m, C(3)*H*), 3.50 (2H, td, *J* 6.3, 1.0, C(3′)H_2), 3.87 (1H, q, *J* 6.8, C(α)*H*), 7.19−7.25 (1H, m, *Ph*), 7.26−7.34 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(8)), 20.6 (C(α)*Me*), 22.7, 26.6, 31.9, 32.6 (*C*(4), *C*(5), *C*(6), *C*(7)), 28.0 (C*Me*$_3$), 33.1 (*C*(2′)), 38.1 (*C*(2)), 42.9 (*C*(1′)), 43.3 (*C*(3′)), 55.3 (*C*(3)), 58.7 (*C*(α)), 79.9 (C*Me*$_3$), 126.8, 127.7, 128.1 (*o*,*m*,*p*-*Ph*), 144.5 (*i*-*Ph*), 172.3 (*C*(1)); *m*/*z* (ESI$^+$) 420 ([*M*(^{37}Cl) + Na]$^+$, 67%), 418 ([*M*(^{35}Cl) + Na]$^+$, 100%), 398 ([*M*(^{37}Cl) + H]$^+$, 77%), 396 ([*M*(^{35}Cl) + H]$^+$, 72%); HRMS (ESI$^+$) $C_{23}H_{39}{}^{37}ClNO_2^+$ ([*M*(^{37}Cl) + H]$^+$) requires 398.2634, found 398.2626; HRMS (ESI$^+$) $C_{23}H_{39}{}^{35}ClNO_2^+$ ([*M*(^{35}Cl) + H]$^+$) requires 396.2664, found 396.2664.

***tert*-Butyl (*R*,*R*)-3-[*N*-(3′-Chloropropyl)-*N*-(α-methylbenzyl)-amino]decanoate 51.** Following General Procedure 1, (*R*)-*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amine (4.99 g, 25.2 mmol), BuLi (2.5 M, 9.72 mL, 24.3 mmol), and **49** (3.57 g, 15.7 mmol) in THF (230 mL) were reacted to give **51** in >99:1 dr. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 19:1) gave **51** as a yellow oil (4.85 g, 73%, >99:1 dr); $[\alpha]_D^{24}$ −13.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1727 (C═O); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.6, C(10)H_3), 1.20−1.35 (12H, m, C(4)H_2, C(5)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2), 1.40−1.44 (12H, m, C*Me*$_3$, C(α)*Me*), 1.85 (2H, app quintet, *J* 6.6, C(2′)H_2), 2.00 (1H, dd, *J* 14.6, 8.1, C(2)H_A), 2.06 (1H, dd, *J* 14.6, 5.3, C(2)H_B), 2.55−2.68 (2H, m, C(1′)H_2), 3.17−3.24 (1H, m, C(3)*H*), 3.49 (2H, app td, *J* 8.6, 1.2, C(3′)H_2), 3.87 (1H, q, *J* 7.1, C(α)*H*), 7.20−7.24 (1H, m, *Ph*), 7.26−7.34 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(10)), 20.6 (C(α)*Me*), 22.7, 27.0, 29.3, 29.6, 31.9, 32.6 (*C*(4), *C*(5), *C*(6), *C*(7), *C*(8), *C*(9)), 28.0 (C*Me*$_3$), 33.1 (*C*(2′)), 38.1 (*C*(2)), 42.9 (*C*(1′)), 43.3 (*C*(3′)), 55.3 (*C*(3)), 58.7 (*C*(α)), 79.9 (C*Me*$_3$), 126.8, 127.7, 128.1 (*o*,*m*,*p*-*Ph*), 144.5 (*i*-*Ph*), 172.2 (*C*(1)); *m*/*z* (ESI$^+$) 448 ([*M*(^{37}Cl) + Na]$^+$, 12%), 446 ([*M*(^{35}Cl) + Na]$^+$, 34%), 426 ([*M*(^{37}Cl) + H]$^+$, 91%), 424 ([*M*(^{35}Cl) + H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{43}{}^{37}ClNO_2^+$ ([*M*(^{37}Cl) + H]$^+$) requires 426.2947, found 426.2951; $C_{25}H_{43}{}^{35}ClNO_2^+$ ([*M*-(^{35}Cl) + H]$^+$) requires 424.2977, found 424.2969.

Methyl (*R*,*R*)-3-[*N*-(3′-Chloropropyl)-*N*-(α-methylbenzyl)-amino]octanoate 52. Following General Procedure 4, **50** (1.00 g, 2.53 mmol, >99:1 dr) in MeOH (7.5 mL) and $SOCl_2$ (0.25 mL, 3.45 mmol) in MeOH (7.5 mL) were reacted. Purification via flash column chromatography (gradient elution, 0% → 6% Et_2O in 30−40 °C petrol) gave **52** as a yellow oil (717 mg, 80%, >99:1 dr); $[\alpha]_D^{24}$ −12.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1737 (C═O); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.3, C(8)H_3), 1.20−1.53 (8H, m, C(4)H_2, C(5)H_2, C(6)H_2, C(7)H_2) overlapping 1.41 (3H, d, *J* 6.8, C(α)*Me*), 1.86 (2H, app quintet, *J* 6.6, C(2′)H_2), 2.10−2.19 (2H, m, C(2)H_2), 2.59−2.72 (2H, m, C(1′)H_2), 3.23 (1H, app quintet, *J* 6.6, C(3)*H*), 3.51 (2H, t, *J* 6.1, C(3′)H_2), 3.57 (3H, s, O*Me*), 3.90 (1H, q, *J* 6.8, C(α)*H*), 7.20−7.26 (1H, m, *Ph*), 7.27−7.32 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (C(8)), 20.0 (C(α)*Me*), 22.7, 26.8, 31.9, 32.8 (*C*(4), *C*(5), *C*(6), *C*(7)), 32.9 (*C*(2′)), 37.0 (*C*(2)), 42.8 (*C*(1′)), 43.3 (*C*(3′)), 51.3

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(OMe), 55.4 (C(3)), 58.3 (C(α)), 126.8, 127.7, 128.1 (o,m,p-Ph), 144.4 (i-Ph), 173.3 (C(1)); m/z (ESI+) 378 ([M(37Cl) + Na]+, 22%), 376 ([M(35Cl) + Na]+, 64%), 356 ([M(37Cl) + H]+, 59%), 354 ([M(35Cl) + H]+, 100%); HRMS (ESI+) $C_{20}H_{33}{}^{37}ClNO_2^+$ ([M(37Cl) + H]+) requires 356.2165, found 356.2173; $C_{20}H_{33}{}^{35}ClNO_2^+$ ([M-(35Cl) + H]+) requires 354.2194, found 354.2196.

Methyl (*R,R*)-3-[*N*-(3′-Chloropropyl)-*N*-(α-methylbenzyl)-amino]decanoate 53. Following General Procedure 4, **51** (1.00 g, 2.36 mmol, >99:1 dr) in MeOH (7.5 mL) and $SOCl_2$ (0.25 mL, 3.45 mmol) in MeOH (7.5 mL) were reacted. Purification via flash column chromatography (gradient elution, 0% → 6% Et_2O in 30−40 °C petrol) gave **53** as a yellow oil (550 mg, 61%, >99:1 dr); $[\alpha]_D^{24}$ −15.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1737 (C═O); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.8, C(10)H_3), 1.21−1.63 (12H, m, C(4)H_2, C(5)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2), 1.41 (3H, d, *J* 7.0, C(α)*Me*), 1.86 (2H, app quintet, *J* 6.6, C(2′)H_2), 2.09−2.19 (2H, m, C(2)H_2), 2.58−2.72 (2H, m, C(1′)H_2), 3.23 (1H, app quintet, *J* 6.8, C(3)*H*), 3.51 (2H, t, *J* 6.3, C(3′)H_2), 3.57 (3H, s, O*Me*), 3.89 (1H, q, *J* 7.0, C(α)*H*), 7.20−7.25 (1H, m, *Ph*), 7.29−7.30 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(10)), 20.0 (C(α)*Me*), 22.7, 29.2, 29.3, 29.6, 31.9, 32.8 (*C*(4), *C*(5), *C*(6), *C*(7), *C*(8), *C*(9)), 32.9 (*C*(2′)), 37.0 (*C*(2)), 42.8 (*C*(1′)), 43.3 (*C*(3′)), 51.3 (O*Me*), 55.4 (*C*(3)), 58.3 (*C*(α)), 126.8, 127.7, 128.1 (*o,m,p-Ph*), 144.4 (*i-Ph*), 173.3 (*C*(1)); *m/z* (ESI+) 406 ([M(37Cl) + Na]+, 14%), 404 ([M(35Cl) + Na]+, 37%), 384 ([M(37Cl) + H]+, 61%), 382 ([M(35Cl) + H]+, 100%); HRMS (ESI+) $C_{22}H_{37}{}^{37}ClNO_2^+$ ([M(37Cl) + H]+) requires 384.2478, found 384.2494; $C_{22}H_{37}{}^{35}ClNO_2^+$ ([M(35Cl) + H]+) requires 382.2507, found 382.2506.

Methyl (*R,R*)-3-[*N*-(3′-Azidopropyl)-*N*-(α-methylbenzyl)-amino]octanoate 54. Following General Procedure 2, NaN_3 (367 mg, 5.65 mmol, >99:1 dr), NaI (847 mg, 5.65 mmol), and **52** (1.00 g, 2.83 mmol) in DMSO (6 mL) were reacted for 24 h. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 30:1) gave **54** as a yellow oil (959 mg, 94%, >99:1 dr); $[\alpha]_D^{25}$ −22.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2096 (N≡N), 1737 (C═O); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.3, C(8)H_3), 1.20−1.55 (8H, m, C(4)H_2, C(5)H_2, C(6)H_2, C(7)H_2) overlapping 1.40 (3H, d, *J* 6.8, C(α)*Me*), 1.60−1.72 (2H, m, C(2′)H_2), 2.11−2.21 (2H, m, C(2)H_2), 2.52−2.63 (2H, m, C(1′)H_2), 3.20−3.27 (3H, m, C(3)*H*, C(3′)H_2), 3.58 (3H, s, O*Me*), 3.89 (3H, q, *J* 6.8, C(α)*H*), 7.20−7.26 (1H, m, *Ph*), 7.28−7.30 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(8)), 19.9 (C(α)*Me*), 22.7, 26.8, 31.9, 32.7 (*C*(4), *C*(5), *C*(6), *C*(7)), 29.2 (*C*(2′)), 37.0 (*C*(2)), 42.8 (*C*(1′)), 49.4 (*C*(3′)), 51.3 (O*Me*), 55.4 (*C*(3)), 58.3 (*C*(α)), 126.8, 127.7, 128.1 (*o,m,p-Ph*), 144.6 (*i-Ph*), 173.3 (*C*(1)); *m/z* (ESI+) 383 ([M + Na]+, 28%), 361 ([M + H]+, 100%); HRMS (ESI+) $C_{20}H_{33}N_4O_2^+$ ([M + H]+) requires 361.2598, found 361.2597.

Methyl (*R,R*)-3-[(3′-Azidopropyl)(α-methylbenzyl)amino]-decanoate 55. Following General Procedure 2, NaN_3 (367 mg, 5.65 mmol), NaI (847 mg, 5.65 mmol) and **53** (1.08 g, 2.83 mmol, >99:1 dr) in DMSO (6 mL) were reacted for 24 h. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 30:1) gave **55** as a yellow oil (958 mg, 87%, >99:1 dr); $C_{22}H_{36}N_4O_2$ requires C, 68.0; H, 9.3; N, 14.4%, found C, 68.1; H, 9.1; N, 14.3%; $[\alpha]_D^{24}$ −20.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2096 (N≡N), 1737 (C═O); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.1, C(10)H_3), 1.22−1.53 (12H, m, C(4)H_2, C(5)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2) overlapping 1.40 (3H, d, *J* 6.8, C(α)*Me*), 1.61−1.69 (2H, m, C(2′)H_2), 2.11−2.21 (2H, m, C(2)H_2), 2.53−2.61 (2H, m, C(1′)H_2), 3.20−3.26 (3H, m, C(3)*H*, C(3′)H_2), 3.58 (3H, s, O*Me*), 3.89 (1H, q, *J* 6.8, C(α)*H*), 7.20−7.26 (1H, m, *Ph*), 7.28−7.31 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(10)), 19.8 (C(α)*Me*), 22.7, 27.1, 29.3, 29.7, 31.9, 32.7 (*C*(4), *C*(5), *C*(6), *C*(7), *C*(8), *C*(9)), 29.2 (*C*(2′)), 37.1 (*C*(2)), 42.8 (*C*(1′)), 49.4 (*C*(3′)), 51.3 (O*Me*), 55.4 (*C*(3)), 58.3 (*C*(α)), 126.8, 127.7, 128.1 (*o,m,p-Ph*), 144.6 (*i-Ph*), 173.3 (*C*(1)); *m/z* (ESI+) 411 ([M + Na]+, 15%), 389 ([M + H]+, 100%); HRMS (ESI+) $C_{22}H_{37}N_4O_2^+$ ([M + H]+) requires 389.2911, found 389.2914.

(*R,R*)-4-Pentyl-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one 58. *Step 1*: Following General Procedure 3, **54** (100 mg, 277 μmol, >99:1 dr) and PBu_3 (74 μL, 297 μmol) in THF (1 mL) and H_2O (0.3 mL) were reacted to give **56** as a yellow oil (158 mg, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.2, C(8)H_3), 1.18−1.54 (8H, m, C(4)H_2, C(5)H_2, C(6)H_2, C(7)H_2) overlapping 1.40 (3H, d, *J* 6.9, C(α)*Me*), 1.60 (2H, app quintet, *J* 6.8, C(2′)H_2), 2.15 (2H, app dd, *J* 6.3, 2.1, C(2)H_2), 2.54 (2H, app q, *J* 7.7, C(3′)H_2), 2.66 (2H, app td, *J* 7.0, 3.8, C(1′)H_2), 3.22 (1H, app quintet, *J* 6.7, C(3)*H*), 3.56 (3H, s, O*Me*), 3.93 (1H, q, *J* 6.9, C(α)*H*), 7.19−7.25 (1H, m, *Ph*), 7.28−7.33 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(8)), 19.7 (C(α)*Me*), 22.6, 26.7, 31.9, 32.8, 33.5 (*C*(4), *C*(5), *C*(6), *C*(7), *C*(2′)), 37.0 (*C*(2)), 40.0 (*C*(1′)), 42.9 (*C*(3′)), 51.3 (*C*(3)), 55.2 (O*Me*), 57.9 (*C*(α)), 126.6, 127.7, 128.0 (*o,m,p-Ph*), 144.6 (*i-Ph*), 173.4 (*C*(1)); *m/z* (ESI+) 335 ([M + H]+, 100%); HRMS (ESI+) $C_{20}H_{35}N_2O_2^+$ ([M + H]+) requires 335.2693, found 335.2692.

Step 2: Following General Procedure 5, **56** (158 mg, >99:1 dr) and $Sb(OEt)_3$ (57 μL, 333 μmol) in PhMe (20 mL) were reacted. Purification via flash column chromatography (gradient elution, 10% → 100% EtOAc in 30−40 °C petrol) gave **58** as a colorless oil (82 mg, 98% over 2 steps, >99:1 dr); $C_{19}H_{30}N_2O$ requires C, 75.45; H, 10.0; N, 9.3%, found C, 75.55; H, 10.0; N, 9.25%; $[\alpha]_D^{24}$ +3.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1661 (C═O); δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 6.8, C(5′)H_3), 0.97−1.06 (1H, m, C(7)H_A), 1.12−1.54 (9H, m, C(7)H_B, C(1′)H_2, C(2′)H_2, C(3′)H_2, C(4′)H_2) overlapping 1.27 (3H, d, *J* 6.4, C(α)*Me*), 2.43 (2H, d, *J* 7.1, C(3)H_2), 2.46−2.55 (1H, m, C(6)H_A), 2.81 (1H, br t, *J* 12.9, C(6)H_B), 3.20 (2H, br s, C(8)H_2), 3.44 (1H, br s, C(4)*H*), 3.74 (1H, q, *J* 6.4, C(α)*H*), 6.83 (1H, br s, N*H*), 7.12−7.16 (1H, m, *Ph*), 7.22 (2H, app t, *J* 7.8, *Ph*), 7.29−7.33 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(5′)), *21.9* (C(α)*Me*), 22.6, 26.5, 28.2 (*C*(2′), *C*(3′), *C*(4′)), 32.1 (*C*(7)), 32.4 (*C*(1′)), *37.9* (*C*(3)), *42.6* (*C*(8)), *45.9* (*C*(6)), 56.5 (*C*(4)), 62.6 (*C*(α)), 126.8, 128.0 (*o,m,p-Ph*), 146.5 (*i-Ph*), 177.1 (*C*(2)); *m/z* (ESI+) 930 ([3M + Na]+, 36%), 627 ([2M + Na]+, 100%), 325 ([M + Na]+, 23%), 303 ([M + H]+, 34%); HRMS (ESI+) $C_{19}H_{31}N_2O^+$ ([M + H]+) requires 303.2431, found 303.2435.

*X-ray Crystal Structure Determination for **58**·HCl.*[36] Data were collected using graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined using CRYSTALS.[46] X-ray crystal structure data for **58**·HCl [$C_{19}H_{31}ClN_2O$]: M = 338.92, triclinic, space group $P1$, a = 7.2921(4) Å, b = 7.3234(4) Å, c = 9.7967(6) Å, α = 102.695(3)°, β = 94.987(3)°, γ = 109.832(2)°, V = 472.62(5) Å^3, Z = 1, μ = 0.209 mm^{-1}, colorless block, crystal dimensions =0.10 × 0.16 × 0.18 mm^3. A total of 3477 unique reflections were measured for 5 < θ < 27, and 3477 reflections were used in the refinement. The final parameters were wR_2 = 0.074 and R_1 = 0.032 [$I > -3.0\sigma(I)$], with Flack enantiopole = 0.03(4).[30]

(*R,R*)-4-Heptyl-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one 59. *Step 1*: Following General Procedure 3, **55** (7.66 g, 19.7 mmol, >99:1 dr) and PBu_3 (5.42 mL, 21.7 mmol) in THF (75 mL) and H_2O (22 mL) were reacted to give **57** as a yellow oil (11.2 g, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.1, C(10)H_2), 1.18−1.68 (14H, m, C(4)H_2, C(5)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2, C(2′)H_2) overlapping 1.39 (3H, d, *J* 7.2, C(α)*Me*), 2.11 (2H, app t, *J* 6.8, C(2)H_2), 2.49 (2H, app q, *J* 7.3, C(3′)H_2), 2.61 (2H, td, *J* 7.1, 1.5, C(1′)H_2), 3.18 (1H, app quintet, *J* 6.6, C(3)*H*), 3.52 (3H, s, O*Me*), 3.88 (1H, q, *J* 7.2, C(α)*H*), 7.14−7.30 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(10)), 19.6 (C(α)*Me*), 22.6, 25.8, 29.2, 29.6, 31.8, 32.8, 33.4 (*C*(4), *C*(5), *C*(6), *C*(7), *C*(8), *C*(9), *C*(2′)), 37.0 (*C*(2)), 40.0 (*C*(1′)), 42.9 (*C*(3′)), 51.3 (*C*(3)), 55.2 (O*Me*), 57.9 (*C*(α)), 126.7, 127.7, 128.0 (*o,m,p-Ph*), 144.6 (*i-Ph*), 173.4 (*C*(1)); *m/z* (ESI+) 363 ([M + H]+, 100%); HRMS (ESI+) $C_{22}H_{39}N_2O_2^+$ ([M + H]+) requires 363.3006, found 363.3006.

Step 2: Following General Procedure 5, **57** (11.2 g, >99:1 dr) and $Sb(OEt)_3$ (4.02 mL, 23.7 mmol) in PhMe (2.00 L) were reacted. Purification via flash column chromatography (gradient elution, 60% → 100% EtOAc in 30−40 °C petrol) gave **59** as a white solid (3.38 g, 52% over 2 steps, >99:1 dr); mp 47−49 °C; $[\alpha]_D^{24}$ +3.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1658 (C═O); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.1, C(7′)H_3), 0.99−1.07 (1H, m, C(7)H_A), 1.12−1.54 (13H, m, C(7)H_B, C(1′)H_2, C(2′)H_2, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2)

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overlapping 1.29 (3H, d, *J* 6.6, C(α)*Me*), 2.45 (2H, d, *J* 7.3, C(3)H_2), 2.52 (1H, dt, *J* 15.4, 3.0, C(6)H_A), 2.79−2.82 (1H, m, C(6)H_B), 3.22 (2H, br s, C(8)H_2), 3.45 (1H, br s, C(4)*H*), 3.75 (1H, q, *J* 6.6, C(α)*H*), 6.60 (1H, t, *J* 7.1, N*H*), 7.15−7.18 (1H, m, *Ph*), 7.22−7.26 (2H, m, *Ph*), 7.32−7.34 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(7′)), 21.9 (C(α)*Me*), 22.6, 26.9, 28.3, 29.3, 30.0, 31.8, 32.4 (*C*(7), *C*(1′), *C*(2′), *C*(3′), *C*(4′), *C*(5′), *C*(6′)), 37.9 (*C*(3)), *42.6* (*C*(8)), *45.9* (*C*(6)), 56.5 (*C*(4)), 62.7 (*C*(α)), 126.8, 128.0, 128.1 (*o,m,p-Ph*), 146.5 (*i-Ph*), 177.0 (*C*(2)); *m/z* (ESI$^+$) 683 ([2M + Na]$^+$, 100%), 353 ([M + Na]$^+$, 25%), 331 ([M + H]$^+$, 49%); HRMS (ESI$^+$) $C_{21}H_{35}N_2O^+$ ([M + H]$^+$) requires 331.2744, found 331.2742.

(*R*)-4-Pentyl-1,5-diazocan-2-one 60. Following General Procedure 7, **58** (200 mg, 661 μmol, >99:1 dr) and $Pd(OH)_2/C$ (100 mg) in MeOH (3 mL) were reacted for 24 h to give **60** as a colorless oil (125 mg, 95%);[16] $[\alpha]_D^{24}$ +39.3 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.75 (3H, t, *J* 6.9, C(5′)H_3), 1.11−1.27 (6H, m, C(2′)H_2, C(3′)H_2, C(4′)H_2), 1.34−1.40 (2H, m, C(1′)H_2), 1.47−1.59 (2H, m, C(7)H_2), 2.25 (1H, app d, *J* 12.3, C(3)H_A), 2.32−2.43 (2H, m, C(3)H_B, C(6)H_A), 2.79−2.85 (1H, m, C(4)*H*), 3.01 (1H, dt, *J* 14.8, 4.1, C(6)H_B), 3.10−3.17 (1H, m, C(8)H_A), 3.40−3.53 (2H, m, C(8)H_B, N(5)*H*), 7.06 (1H, br s, N(1)*H*).

(*R*)-4-Heptyl-1,5-diazocan-2-one 61. Following General Procedure 7, **59** (100 mg, 303 μmol, >99:1 dr) and $Pd(OH)_2/C$ (50 mg) in MeOH (3.0 mL) were reacted for 24 h to give **61** as a colorless oil (69 mg, quant);[16] $[\alpha]_D^{24}$ +34.7 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.83 (3H, t, *J* 6.7, C(7′)H_3), 1.16−1.35 (10H, m, C(2′)H_2, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2), 1.39−1.47 (2H, m, C(1′)H_2), 1.49−1.67 (2H, m, C(7)H_2), 2.29−2.57 (4H, m, C(3)H_2, N(5)*H*, C(6)H_A), 2.83−2.92 (1H, m, C(4)*H*), 3.08 (1H, dt, *J* 14.9, 4.0, C(6)H_B), 3.15−3.25 (1H, m, C(8)H_A), 3.50−3.61 (1H, m, C(8)H_B), 6.64 (1H, br s, N(1)*H*).

(*R*)-4-Pentyl-*N*(5)-methyl-1,5-diazocan-2-one 62. *Method A*: Following General Procedure 7, **58** (100 mg, 331 μmol, >99:1 dr), $(CH_2O)_n$ (20 mg, 666 μmol) and $Pd(OH)_2/C$ (50 mg) in MeOH (1.3 mL) were reacted for 72 h to give **62** as a colorless oil (71 mg, quant);[16] $[\alpha]_D^{24}$ −0.3 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8, C(5′)H_3), 1.26−1.41 (7H, m, C(1′)H_A, C(2′)H_2, C(3′)H_2, C(4′)H_2), 1.47−1.60 (2H, m, C(7)H_A, C(1′)H_B), 1.68−1.80 (1H, m, C(7)H_B), 2.43 (2H, d, *J* 7.2, C(3)H_2), 2.46 (3H, s, N*Me*), 2.54 (1H, app dt, *J* 15.4, 4.3, C(6)H_A), 2.90−3.04 (2H, m, C(4)*H*, C(6)H_B), 3.29−3.33 (2H, m, C(8)H_2), 5.60 (1H, br s, N*H*).

Method B: Following General Procedure 8, **60** (965 mg, 4.87 mmol), $(CH_2O)_n$ (231 mg, 7.69 mmol) and $NaBH_3CN$ (970 mg, 29.5 mmol) in MeOH (40 mL) were reacted. Purification via flash column chromatography (gradient elution, 0% → 5% MeOH in CH_2Cl_2) gave **62** as a colorless oil (373 mg, 36%); $[\alpha]_D^{24}$ −0.5 (*c* 1.0 in $CHCl_3$).

(*R*)-4-Heptyl-5-methyl-1,5-diazocan-2-one 63. *Method A*: Following General Procedure 7, **59** (109 mg, 331 μmol, >99:1 dr), $(CH_2O)_n$ (20 mg, 666 μmol), and $Pd(OH)_2/C$ (50 mg) in MeOH (1.3 mL) were reacted for 72 h to give **63** as a colorless oil (78 mg, 98%);[16] $[\alpha]_D^{24}$ −0.5 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.3,C(7′)H_3), 1.22−1.41 (11H, m, C(1′)H_A, C(2′)H_2, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2), 1.47−1.67 (2H, m, C(1′)H_B, C(7)H_A), 1.68−1.79 (1H, m, C(7)H_B), 2.42 (2H, d, *J* 7.0, C(3)H_2), 2.46 (3H, s, N*Me*), 2.54 (1H, dt, *J* 15.2, 4.1, C(6)H_A), 2.90−3.04 (2H, m, C(4)*H*, C(6)H_B), 3.28−3.34 (2H, m, C(8)H_2), 6.54 (1H, br s, N*H*).

Method B: Following General Procedure 8, **61** (989 mg, 4.37 mmol), $(CH_2O)_n$ (231 mg, 7.69 mmol) and $NaBH_3CN$ (970 mg, 29.5 mmol) in MeOH (40 mL) were reacted. Purification via flash column chromatography (gradient elution, 0% → 5% MeOH in CH_2Cl_2) gave **63** as a colorless oil (875 mg, 83%); $[\alpha]_D^{24}$ −0.4 (*c* 1.0 in $CHCl_3$).

(*R,R*)-*N*(1)-(4′-Bromobutyl)-4-pentyl-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one 64. Following General Procedure 6A, **58** (150 mg, 496 μmol, >99:1 dr), 1,4-dibromobutane (0.18 mL, 1.48 mmol), K_2CO_3 (83 mg, 600 μmol), KOH (111 mg, 1.97 mmol), and TEBAC (14 mg, 61.8 μmol) in DMSO (1.0 mL) were reacted for 24 h. Purification via flash column chromatography (gradient elution, 20% → 50% Et_2O in 30−40 °C petrol) gave **64** as a yellow oil (143 mg, 66%, >99:1 dr); $[\alpha]_D^{24}$ −16.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1636 (C═O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.81−0.91 (1H, m, C(7)H_A), 0.92 (3H, t, *J* 7.3, C(5′′)H_3), 1.11−1.20 (1H, m, C(7)H_B), 1.24−1.61 (8H, m, C(1′′)H_2, C(2′′)H_2, C(3′′)H_2, C(4′′)H_2), 1.27 (3H, d, *J* 6.5, C(α)*Me*), 1.53 (2H, app quintet, *J* 7.6, C(2′)H_2), 1.67 (2H, app quintet, *J* 7.6, C(3′)H_2), 2.34 (1H, dd, *J* 12.3, 8.8, C(3)H_A), 2.41−2.52 (2H, m, C(3)H_B, C(6)H_A), 2.57−2.67 (1H, m, C(6)H_B), 2.97−3.15 (3H, m, C(8)H_2, C(1′)H_A), 3.15 (2H, t, *J* 6.9, C(4′)H_2), 3.32−3.48 (2H, m, C(4)*H*, C(1′)H_B), 3.71 (1H, q, *J* 6.5, C(α)*H*), 7.06−7.12 (1H, m, *Ph*), 7.18 (2H, app t, *J* 7.6, *Ph*), 7.23−7.29 (2H, m, *Ph*); δ_C (125 MHz, PhMe-d_8, 363 K) 13.9 (*C*(5′′)), 21.3 (C(α)*Me*), 22.9, 26.9, 27.2, 29.3, 30.7, 32.5 (*C*(7), *C*(2′), *C*(3′), *C*(2′′), *C*(3′′), *C*(4′′)), 30.5 (*C*(1′′)), 33.0 (*C*(4′)), 39.3 (*C*(3)), 45.0 (*C*(1′), *C*(6)), 47.8 (*C*(8)), 57.5 (*C*(4)), 62.8 (*C*(α)), 127.1, 128.2 (*o,m,p-Ph*), 146.8 (*i-Ph*), 172.4 (*C*(2)); *m/z* (ESI$^+$) 461 ([M(^{81}Br) + Na]$^+$, 83%), 459 ([M(^{79}Br) + Na]$^+$, 82%), 439 ([M(^{81}Br) + H]$^+$, 100%), 437 ([M(^{79}Br) + H]$^+$, 93%); HRMS (ESI$^+$) $C_{23}H_{38}{}^{81}BrN_2O^+$ ([M(^{81}Br) + H]$^+$) requires 439.2142, found 439.2155; $C_{23}H_{38}{}^{79}BrN_2O^+$ ([M-(^{79}Br) + H]$^+$) requires 437.2162, found 437.2174.

(*R,R*)-1-(4′-Bromobutyl)-4-heptyl-5-(α-methylbenzyl)-1,5-diazocan-2-one 66. Following General Procedure 6A, **59** (233 mg, 706 μmol, >99:1 dr), 1,4-dibromobutane (0.25 mL, 2.12 mmol), K_2CO_3 (118 mg, 854 μmol), KOH (158 mg, 2.81 mmol), and TEBAC (20 mg, 88.0 μmol) in DMSO (2.0 mL) were reacted for 24 h. Purification via flash column chromatography (gradient elution, 25% → 60% Et_2O in 30−40 °C petrol) gave **66** as a yellow oil (101 mg, 31%, >99:1 dr); $[\alpha]_D^{24}$ −11.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1628 (C═O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.83−0.90 (1H, m, C(7)H_A), 0.92 (3H, t, *J* 7.3, C(7′′)H_3), 1.12−1.22 (1H, m, C(7)H_B), 1.23−1.48 (12H, m, C(1′′)H_2, C(2′′)H_2, C(3′′)H_2, C(4′′)H_2, C(5′′)H_2, C(6′′)H_2), 1.27 (3H, d, *J* 6.6, C(α)*Me*), 1.53 (2H, app quintet, *J* 7.6, C(2′)H_2), 1.66 (2H, app quintet, *J* 7.6, C(3′)H_2), 2.35 (1H, dd, *J* 12.3, 8.8, C(3)H_A), 2.43−2.52 (2H, m, C(3)H_B, C(6)H_A), 2.63 (1H, app dt, *J* 12.6, 2.5, C(6)H_B), 2.98−3.14 (2H, m, C(8)H_2, C(1′)H_A), 3.15 (2H, t, *J* 6.6, C(4′)H_2), 3.33−3.47 (2H, m, C(4)*H*, C(1′)H_B), 3.72 (1H, q, *J* 6.6, C(α)*H*), 7.07−7.12 (1H, m, *Ph*), 7.18 (2H, t, *J* 7.6, *Ph*), 7.24−7.29 (2H, m, *Ph*); δ_C (125 MHz, PhMe-d_8, 363 K) 14.0 (*C*(7′′)), 21.3 (C(α)*Me*), 22.9, 27.2, 27.3, 29.4, 29.6, 30.3, 30.5, 30.7, 32.2 (*C*(7), *C*(2′), *C*(3′), *C*(1′′), *C*(2′′), *C*(3′′), *C*(4′′), *C*(5′′), *C*(6′′)), 33.0 (*C*(4′)), 39.3 (*C*(3)), 45.0 (*C*(1′), *C*(6)), 47.8 (*C*(8)), 57.5 (*C*(4)), 62.8 (*C*(α)), 127.1, 128.3 (*o,m,p-Ph*), 146.8 (*i-Ph*), 172.3 (*C*(2)); *m/z* (ESI$^+$) 489 ([M(^{81}Br) + Na]$^+$, 40%), 487 ([M(^{79}Br) + Na]$^+$, 47%), 467 ([M(^{81}Br) + H]$^+$, 100%), 465 ([M(^{79}Br) + H]$^+$, 95%); HRMS (ESI$^+$) $C_{25}H_{42}{}^{81}BrN_2O^+$ ([M(^{81}Br) + H]$^+$) requires 467.2455, found 467.2464; $C_{25}H_{42}{}^{79}BrN_2O^+$ ([M(^{79}Br) + H]$^+$) requires 465.2475, found 465.2483.

(*R,R,R,R*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-(α-methylbenzyl)-1′,5′-diazocan-*N*(1′)-yl]-4-[2′′-oxo-4′′-heptyl-*N*(5′′)-(α′-methylbenzyl)-1′′,5′′-diazocan-*N*(1′′)-yl]butane 65. Following General Procedure 6B, **59** (91 mg, 275 μmol, >99:1 dr), **64** (109 mg, 249 μmol, >99:1 dr), and KOH (62 mg, 1.10 mmol) in DMSO (1.0 mL) were reacted for 96 h. Purification via flash column chromatography (gradient elution, 0% → 2% MeOH in CH_2Cl_2) gave **65** as a yellow oil (50 mg, 29%, >99:1 dr); $[\alpha]_D^{24}$ −23.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1630 (C═O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.89−0.98 (6H, br m, C(4′)$(CH_2)_4CH_3$, C(4′′)$(CH_2)_6CH_3$), 1.20−1.53 (30H, br m, C(7′)H_2, C(7′′)H_2, C(α)*Me*, C(α′)*Me*, C(4′)$(CH_2)_4CH_3$, C(4′′)-$(CH_2)_6CH_3$), 1.57−1.65 (4H, br m, C(2)H_2, C(3)H_2), 2.35−2.44 (2H, br m, C(3′)H_A, C(3′′)H_A), 2.46−2.58 (4H, br m, C(3′)H_B, C(3′′)H_B, C(6′)H_A, C(6′′)H_A), 2.63−2.73 (2H, br m, C(6′)H_B, C(6′′)H_B), 3.07−3.18 (2H, br m, C(8′)H_A, C(8′′)H_A), 3.24 (4H, br s, C(8′)H_B, C(8′′)H_B, C(1)H_A, C(4)H_A), 3.38 (2H, br s, C(4′)*H*, C(4′′)*H*), 3.59 (2H, br s, C(1)H_B, C(4)H_B), 3.72−3.79 (2H, br m, C(α)*H*, C(α′)*H*), 7.08−7.14 (2H, br m, *Ph*), 7.18−7.24 (4H, br m, *Ph*), 7.27−7.33 (4H, br m, *Ph*); δ_C (125 MHz, PhMe-d_8, 363 K) 13.9, 14.0 (C(4′)$(CH_2)_4CH_3$, C(4′′)$(CH_2)_6CH_3$), 21.3 (C(α)*Me*, C(α′)*Me*), 22.9, 22.9, 26.9, 27.3, 29.5, 29.5, 29.6, 30.3, 30.6, 30.6, 32.2, 32.5 (*C*(7′), *C*(7′′), C(4′)$(CH_2)_4CH_3$, C(4′′)$(CH_2)_6CH_3$), 26.2 (*C*(2), *C*(3)), 39.4 (*C*(3′), *C*(3′′)), *45.0* (*C*(6′), *C*(6′′)), 46.0 (*C*(1), *C*(4)), *47.9* (*C*(8′), *C*(8′′)), 57.5, 57.5 (*C*(4′), *C*(4′′)), 62.7 (*C*(α), *C*(α′)), 127.1, 128.3, 128.3 (*o,m,p-Ph*), 146.9 (*i-Ph*), 172.3 (*C*(2′), *C*(2′′)); *m/*

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z (ESI$^+$) 710 ([M + Na]$^+$, 100%), 688 ([M + H]$^+$, 94%); HRMS (ESI$^+$) $C_{44}H_{71}N_4O_2^+$ ([M + H]$^+$) requires 687.5572, found 687.5591.

(*R*)-*N*(1)-(4′-Bromobutyl)-4-pentyl-*N*(5)-methyl-1,5-diazocan-2-one 67. Following General Procedure 6A, **62** (423 mg, 1.99 mmol), 1,4-dibromobutane (0.71 mL, 6.00 mmol), K_2CO_3 (333 mg, 2.41 mmol), KOH (446 mg, 7.94 mmol), and TEBAC (56 mg, 248 μmol) in DMSO (6 mL) were reacted for 24 h. Purification via flash column chromatography (eluent Et_2O) gave **67** as a colorless oil (456 mg, 66%); $[\alpha]_D^{24}$ −8.1 (c 1.0 in $CHCl_3$); ν_{max} (ATR) 1634 (C═O); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J 7.0, C(5′′)H_3), 1.23−1.92 (14H, m, C(7)H_2, C(2′)H_2, C(3′)H_2, C(1′′)H_2, C(2′′)H_2, C(3′′)H_2, C(4′′)H_2), 2.42 (3H, s, N*Me*), 2.46−2.56 (3H, m, C(3)H_2, C(6)H_A), 2.83−3.00 (2H, m, C(4)*H*, C(6)H_B), 3.26−3.51 (6H, m, C(8)H_2, C(1′)H_2, C(4′)H_2); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(5′′)), 22.6, 26.5, 26.6, 28.8, 29.9, 31.9 (*C*(2′), *C*(3′), *C*(1′′), *C*(2′′), *C*(3′′), *C*(4′′)), 30.5 (*C*(7)) 33.7 (*C*(4′)), 38.4 (*C*(3)), 40.0 (N*Me*), 44.8 (*C*(8)), 47.1 (*C*(6)), 47.7 (*C*(1′)), 63.2 (*C*(4)), 173.8 (*C*(2)); m/z (ESI$^+$) 349 ([M(^{81}Br) + H]$^+$, 100%), 347 ([M(^{79}Br) + H]$^+$, 94%); HRMS (ESI$^+$) $C_{16}H_{32}{}^{81}BrN_2O^+$ ([M(^{81}Br) + H]$^+$) requires 349.1672, found 349.1678; $C_{16}H_{32}{}^{79}BrN_2O^+$ ([M(^{79}Br) + H]$^+$) requires 347.1693, found 347.1694.

(*R*)-1-(4′-Bromobutyl)-4-heptyl-5-methyl-1,5-diazocan-2-one 68. Following General Procedure 6B, **63** (165 mg, 687 μmol), 1,4-dibromobutane (0.24 mL, 2.06 mmol), and KOH (155 mg, 2.76 mmol) in DMSO (1.4 mL) were reacted for 24 h. Purification via flash column chromatography (gradient elution, 50% → 100% Et_2O in 30−40 °C petrol) gave **68** as a colorless oil (83 mg, 35%); $[\alpha]_D^{24}$ −10.4 (c 1.0 in $CHCl_3$); ν_{max} (ATR) 1631 (C═O); δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, J 6.8, C(7′′)H_3), 1.20−1.90 (18H, m, C(7)H_2, C(2′)H_2, C(3′)H_2, C(1′′)H_2, C(2′′)H_2, C(3′′)H_2, C(4′′)H_2, C(5′′)H_2, C(6′′)H_2), 2.40 (3H, s, N*Me*), 2.44−2.54 (3H, m, C(3)H_2, C(6)H_A), 2.81−2.96 (2H, m, C(4)*H*, C(6)H_B), 3.24−3.47 (6H, m, C(8)H_2, C(1′)H_2, C(4′)H_2); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(7′′)), 22.6, 26.5, 27.0, *28.7*, 29.3, 29.7, 29.9, 31.8 (*C*(2′), *C*(3′), *C*(1′′), *C*(2′′), *C*(3′′), *C*(4′′), *C*(5′′), *C*(6′′)), *30.3* (*C*(7)), 33.7 (*C*(4′)), *38.3* (*C*(3)), 40.1 (N*Me*), 44.8 (*C*(8)), 47.3 (*C*(6)), 47.6 (*C*(1′)), 63.3 (*C*(4)), 173.7 (*C*(2)); m/z (ESI$^+$) 399 ([M(^{81}Br) + Na]$^+$, 39%), 397 ([M(^{79}Br) + Na]$^+$, 44%), 377 ([M(^{81}Br) + H]$^+$, 100%), 375 ([M(^{79}Br) + H]$^+$, 89%); HRMS (ESI$^+$) $C_{18}H_{36}{}^{81}BrN_2O^+$ ([M(^{81}Br) + H]$^+$) requires 377.1985, found 377.1982, $C_{18}H_{36}{}^{79}BrN_2O^+$ ([M(^{79}Br) + H]$^+$) requires 375.2006, found 375.2002.

(*R*,*R*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2′′-oxo-4′′-heptyl-*N*(5′′)-methyl-1′′,5′′-diazocan-*N*(1′′)-yl]butane [(−)-hopromine] 2. *Method A*: Following General Procedure 7, **65** (17 mg, 24.7 μmol), $(CH_2O)_n$ (3 mg, 99.0 μmol) and Pd(OH)$_2$/C (9 mg) in MeOH (1.0 mL) were reacted for 72 h. Purification via column chromatography (gradient elution, 0% → 2.5% MeOH in $CHCl_3$) gave **2** as a colorless oil (4 mg, 32%, >99:1 dr);[6] $[\alpha]_D^{24}$ −12.1 (c 0.1 in $CHCl_3$); {lit.[6] $[\alpha]_D^{20}$ −10 (c 3 in $CHCl_3$)}; {lit.[7] $[\alpha]_D^{20}$ −14.4 (c 2.1 in $CHCl_3$)}; ν_{max} (ATR) 1635 (C═O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.91 (6H, t, J 7.25, C(4′)(CH$_2$)$_4$$CH_3$, C(4′′)(CH$_2$)$_6$$CH_3$), 1.16−1.63 (28H, m, C(2)H_2, C(3)H_2, C(7′)H_2, C(7′′)H_2, C(4′)(CH$_2$)$_4$CH$_3$, C(4′′)(CH$_2$)$_6$CH$_3$), 2.27−2.47 (12H, m, C(3′)H_2, N(5′)*Me*, C(6′)H_A, C(3′′)H_2, N(5′′)*Me*, C(6′′)H_A), 2.66−2.77 (2H, m, C(6′)H_B, C(6′′)H_B), 2.84−2.95 (2H, m, C(4′)*H*, C(4′′)*H*), 3.04−3.22 (4H, m, C(8′)H_2, C(8′′)H_2), 3.22−3.43 (4H, m, C(1)H_2, C(4)H_2); δ_C (125 MHz, PhMe-d_8, 363 K) 14.0, 14.0 (C(4′)-(CH$_2$)$_4$CH$_3$, C(4′′)(CH$_2$)$_6$CH$_3$), 22.9, 26.0, 27.0, 27.4, 29.1, 29.6, 30.0, 31.5, 31.6, 32.2, 32.3 (*C*(2), *C*(3), *C*(7′), *C*(7′′), C(4′)-(CH$_2$)$_4$CH$_3$, C(4′′)(CH$_2$)$_6$CH$_3$), 39.0 (N(5′)*Me*, N(5′′)*Me*), 39.9 (*C*(3′), *C*(3′′)), 45.8 (*C*(1), *C*(4)), 47.2 (*C*(6′), *C*(6′′)), 47.4 (*C*(8′), *C*(8′′)), 63.6 (*C*(4′), *C*(4′′)), 172.4 (*C*(2′), *C*(2′′)); m/z (ESI$^+$) 529 ([M + Na]$^+$, 100%), 507 ([M + H]$^+$, 66%); HRMS (ESI$^+$) $C_{30}H_{59}N_4O_2^+$ ([M + H]$^+$) requires 507.4633, found 507.4640.

Method B: Following General Procedure 6B, **63** (57 mg, 238 μmol), **67** (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% → 2.5% MeOH in $CHCl_3$) gave **2** as a colorless oil (53 mg, 48%, >99:1 dr); $[\alpha]_D^{24}$ −13.8 (c 1.0 in $CHCl_3$).

Method C: Following General Procedure 6B, **62** (32 mg, 149 μmol), **68** (51 mg, 136 μmol) and KOH (34 mg, 598 μmol) in DMSO (0.6 mL) were reacted for 96 h. Purification via column chromatography (gradient elution, 0% → 2.5% MeOH in $CHCl_3$) gave **2** as a colorless oil (5 mg, 7%, >99:1 dr); $[\alpha]_D^{24}$ −11.2 (c 0.3 in $CHCl_3$).

(*S*)-*N*-(3-Chloropropyl)-*N*-(α-methylbenzyl)amine. (*S*)-α-Methylbenzylamine (16.1 mL, 127 mmol) was added to a solution of 1-bromo-3-chloropropane (5.00 mL, 50.5 mmol) in MeCN (40 mL), and the resultant mixture was stirred for 16 h at rt. The reaction mixture was basified to pH 9 with satd aq $NaHCO_3$ and then extracted with EtOAc (3 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 3:7) gave (*S*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amine as a yellow oil (5.45 g, 55%, >99:1 er); $[\alpha]_D^{24}$ −57.7 (c 1.0 in $CHCl_3$).

(*S*,*S*)-4-Heptyl-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one *ent*-59. *Step 1*: Following General Procedure 1, (*S*)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amine (5.25 g, 26.6 mmol), BuLi (2.5 M, 10.2 mL, 25.6 mmol), and **49** (4.80 g, 21.2 mmol) were reacted to give *ent*-**51** as a yellow oil (5.41 g, >99:1 dr).

Step 2: Following General Procedure 4, *ent*-**51** (5.41 g, >99:1 dr) in MeOH (40 mL) and $SOCl_2$ (1.35 mL, 18.6 mmol) in MeOH (40 mL) were reacted to give *ent*-**53** as a yellow oil (4.93 g, >99:1 dr).

Step 3: Following General Procedure 2, NaN_3 (1.66 g, 25.5 mmol), NaI (3.83 g, 25.6 mmol), and *ent*-**53** (4.93 g, >99:1 dr) in DMSO (27 mL) were reacted for 24 h to give *ent*-**55** as a yellow oil (4.74 g, >99:1 dr).

Step 4: Following General Procedure 3, *ent*-**55** (4.74 g, >99:1 dr) and PBu_3 (3.50 mL, 14.0 mmol) in THF (50 mL) and H_2O (14 mL) were reacted to give *ent*-**57** as a yellow oil (7.31 g, >99:1 dr).

Step 5: Following General Procedure 5, *ent*-**57** (7.31 g, >99:1 dr) and Sb(OEt)$_3$ (2.28 mL, 13.4 mmol) in PhMe (1.10 L) were reacted. Purification via flash column chromatography (gradient elution, 60% → 100% EtOAc in 30−40 °C petrol) gave *ent*-**59** as a white solid (2.53 g, 36% over 5 steps, >99:1 dr); mp 45−47 °C; $[\alpha]_D^{24}$ −3.1 (c 1.0 in $CHCl_3$).

(*S*)-4-Heptyl-*N*(5)-methyl-1,5-diazocan-2-one *ent*-63. Following General Procedure 7, *ent*-**59** (2.50 g, 7.56 mmol, >99:1 dr), $(CH_2O)_n$ (459 mg, 15.3 mmol), and Pd(OH)$_2$/C (1.15 g) in MeOH (25 mL) were reacted for 72 h to give *ent*-**63** as a colorless oil (1.58 g, 87%);[16] $[\alpha]_D^{24}$ +0.4 (c 1.0 in $CHCl_3$).

(4′*R*,4′′*S*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2′′-oxo-4′′-heptyl-*N*(5′′)-methyl-1′′,5′′-diazocan-*N*(1′′)-yl]butane 69. Following General Procedure 6A, *ent*-**63** (30 mg, 127 μmol), **67** (40 mg, 115 μmol), KOH (26 mg, 457 μmol), K_2CO_3 (19 mg, 138 μmol), and TEBAC (3 mg, 14.3 μmol) in DMSO (0.75 mL) were reacted for 96 h. Purification via column chromatography (gradient elution, 0% → 4% MeOH in $CHCl_3$) gave **69** as a yellow oil (10 mg, 17%, >99:1 dr); $[\alpha]_D^{24}$ +2.3 (c 0.8 in $CHCl_3$); ν_{max} (ATR) 1636 (C═O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.92 (6H, br s, C(4′)(CH$_2$)$_4$$CH_3$, C(4′′)(CH$_2$)$_6$$CH_3$), 1.22−1.60 (28H, m, C(2)H_2, C(3)H_2, C(7′)H_2, C(7′′)H_2, C(4′)(CH$_2$)$_4$)CH$_3$, C(4′′)(CH$_2$)$_6$CH$_3$), 2.30−2.49 (12H, m, C(3′)H_2, N(5′)*Me*, C(6′)H_A, C(3′′)H_2, N(5′′)*Me*, C(6′′)H_A), 2.68−2.77 (2H, m, C(6′)H_B, C(6′′)H_B), 2.92 (2H, br s, C(4′)*H*, C(4′′)*H*), 3.07−3.22 (4H, m, C(8′)H_2, C(8′′)H_2), 3.24−3.32 (2H, m, C(1)H_A, C(4)H_A), 3.35−3.43 (2H, m, C(1)H_B, C(4)H_B); δ_C (125 MHz, PhMe-d_8, 363 K) 13.9, 14.0 (C(4′)(CH$_2$)$_4$$CH_3$, C(4′′)(CH$_2$)$_6$$CH_3$), 22.9, 26.0, 26.7, 27.4, 29.1, 29.6, 30.0, 30.1, 31.4, 31.5, 32.2, 32.3 (*C*(2), *C*(3), *C*(7′), *C*(7′′), C(4′)(CH$_2$)$_4$CH$_3$, C(4′′)(CH$_2$)$_6$CH$_3$), 39.0 (N(5′)*Me*, N(5′′)*Me*), 39.9 (*C*(3′), *C*(3′′)), 45.8 (*C*(1), *C*(4)), 47.2 (*C*(6′), *C*(6′′)), 47.4 (*C*(8′), *C*(8′′)), 63.7 (*C*(4′), *C*(4′′)), 172.3 (*C*(2′), *C*(2′′)); m/z (ESI$^+$) 529 ([M + Na]$^+$, 89%), 507 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{59}N_4O_2^+$ ([M + H]$^+$) requires 507.4633, found 507.4617.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H, ^{13}C NMR spectra, and crystallographic information files (for structures CCDC 880488−880490).

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Notes

The authors declare no competing financial interest.

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(28) This sample of (−)-(*S*,*S*)-homaline **1** was found to be chromatographically identical to other samples of (−)-(*S*,*S*)-homaline **1** and displayed ^{1}H and ^{13}C NMR data consistent with those of the natural product, although interestingly the value of the specific rotation for this sample {$[\alpha]_D^{21}$ −16.8 (*c* 0.4 in $CHCl_3$)} did not show close agreement with that of the sample isolated from the natural source {lit.[6] $[\alpha]_D^{20}$ −34 (*c* 1.0 in $CHCl_3$)}; it is, however, in close agreement with the value obtained by Wasserman and Berger for a sample of (−)-(*S*,*S*)-homaline **1** obtained via the same Borch methylation procedure {lit.[10] $[\alpha]_D^{24}$ −15.4 (*c* 1.0 in $CHCl_3$)}.

(29) Crystallographic data (excluding structure factors) for **39** and **40** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 880488 and 880489, respectively.

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(31) Without acid present, cleavage of the N-C(3) bond also occurred and methyl 3-phenylpropanate was the only observable product of the reaction.

(32) Approximately 37% conversion to (*E*)-**46** was observed under these conditions, and the remaining starting material could not be separated from the product so a pure sample of **46** was not isolated in this case.

(33) See: ref 9 $[\alpha]_D^{22}$−32 (*c* 0.95 in $CHCl_3$); ref 10 $[\alpha]_D^{24}$−35 (*c* 0.9 in $CHCl_3$); ref 12 $[\alpha]_D^{22}$−32 (*c* 0.95 in $CHCl_3$); ref 13 $[\alpha]_D^{22}$−32 (*c* 0.95 in $CHCl_3$).

(34) Both reactions proceeded with excellent diastereoselectivity (>99:1 dr), and following purification of the crude reaction mixtures **48** and **49** were isolated in 51% and 38% yield, respectively.

(35) Conjugate addition of (*R*)-**17** to the corresponding α,β-unsaturated methyl esters also proceeded in >99:1 dr, although in both cases the crude reaction mixtures were contaminated with several other species that could not be separated from the desired β-amino esters; it was therefore far more practical to scale-up the reactions using α,β-unsaturated *tert*-butyl esters **48** and **49** instead.

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(40) Resonances corresponding to *C*(6), *C*(2′), and C(*α*)*Me* were not observed in the 100 MHz ^{13}C NMR spectrum of **28** at rt.
(41) No other resonances were observed in the 100 MHz ^{13}C NMR spectrum of **29** at rt.
(42) No other resonances were observed in the 100 MHz ^{13}C NMR spectrum of **30** at rt.
(43) A resonance corresponding to C(1′) was not observed in the 125 MHz ^{13}C NMR spectrum of **35** at 363 K.
(44) A resonance corresponding to 2 × C(3′)H_B was not observed in the 500 MHz ^{1}H NMR spectrum of **36** at rt.
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