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# First asymmetric synthesis of a $C_2$-symmetric 2-*endo*,6-*endo*-disubstituted bispidine

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**Abstract**—The enantioselective synthesis of a $C_2$-symmetric 2-*endo*,6-*endo*-disubstituted bispidine (3,7-diazabicyclo[3.3.1]nonane) has been accomplished for the first time. The key step was a Michael addition of the protected β-amino ester methyl (*R*)-3-{*N*-benzyl-*N*-[(*S*)-1-phenylethyl]amino}-3-phenylpropionate to its α-methylene derivative delivering an *anti*,*anti*-configured α,α′-methylene-bridged bis(β-amino ester) as the major diastereomer. Deprotection, reduction and cyclisation furnished (1*R*,2*R*,5*R*,6*R*)-2,6-diphenyl-3,7-bis((*S*)-1-phenylethyl)-3,7-diazabicyclo[3.3.1]nonane in six steps and 15% overall yield.


## 1. Introduction

Chiral bispidines (3,7-diazabicyclo[3.3.1]nonanes) have found manifold applications in asymmetric synthesis.[1–3] The most prominent member of this class, the commercially available lupine alkaloid (−)-sparteine (−)-**1** (Fig. 1),[4] is unrivalled as a chiral ligand for organolithium bases in enantioselective deprotonations,[1,5] carbolithiations[6] and *ortho*-metallations.[7] It has also successfully been applied in enantioselective allylic substitutions,[8] additions to imines[9] and the ring opening of *meso*-anhydrides.[10] Recent developments disclose the use of (−)-**1** as a ligand in $Cu^{I}$-mediated dynamic kinetic resolutions of racemic 1,1′-biaryl-2,2′-diols[11] and in $Pd^{II}$-catalysed oxidative kinetic resolutions of secondary alcohols.[12] The lack of an easily accessible source for (+)-sparteine (+)-**1**[13] is compensated by the synthetic diamine (+)-**2**,[14,15] which is devoid of the axially annelated ring of **1**, but offers a comparably high potential in asymmetric synthesis as (−)-**1** does. Further simplification of the structure as in the *N*,*N*′-dimethyl-2-*endo*-methylbispidine (−)-**3** resulted in a significantly reduced capability to transfer chirality.[16]

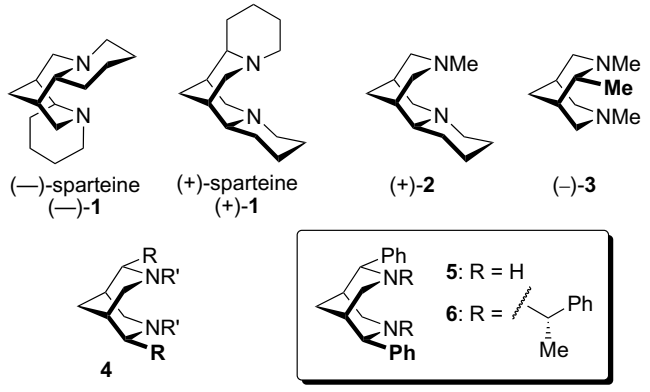


**Figure 1.** Chiral $C_1$-symmetric bispidines and the $C_2$-symmetric target diamines **5** and **6**.

The stereoselective synthesis of bispidines possessing a chirally modified backbone is still a challenging endeavour. Four different approaches have been developed: Aubé et al. prepared (+)-sparteine (+)-**1** from enantiomerically pure (*S*,*S*)-norbornan-2,5-dione by two successive ring enlargement reactions,[17,18] whereas Michael addition of an (*R*)-homopipecolic ester to its oppositely configured α-methylene derivative was used as the key step in O'Brien's synthesis of (−)-sparteine (−)-**1**.[19] Diamine (+)-**2** is derived from (−)-cytisine, a natural product[14,20] that is also accessible by total synthesis.[21,22] Finally, Kozlowski's diamine (−)-**3** was prepared in enantiomerically pure form by resolution of racemic **3**, which was obtained from an achiral bispidine precursor by α-deprotonation and methylation.[16] An approach to the $C_2$-symmetric bispidines of the general formula **4**, however, is still missing,[23] even though such

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diamines might possess high potential in the asymmetric transformations mentioned above or as the chiral backbone of Lewis acids. Herein we report our studies towards the enantioselective synthesis of the $C_2$-symmetric 2-*endo*,6-*endo*-diphenylbispidine **5**; its N,N′-diprotected derivative **6** was prepared in six steps and 15% overall yield from known compounds using a Michael addition as the key step.

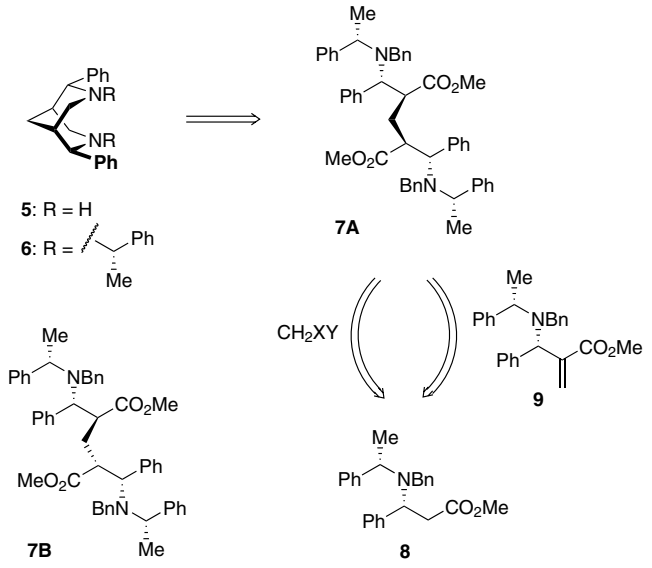
## 2. Results and discussion

### 2.1. Retrosynthesis and stereochemical considerations

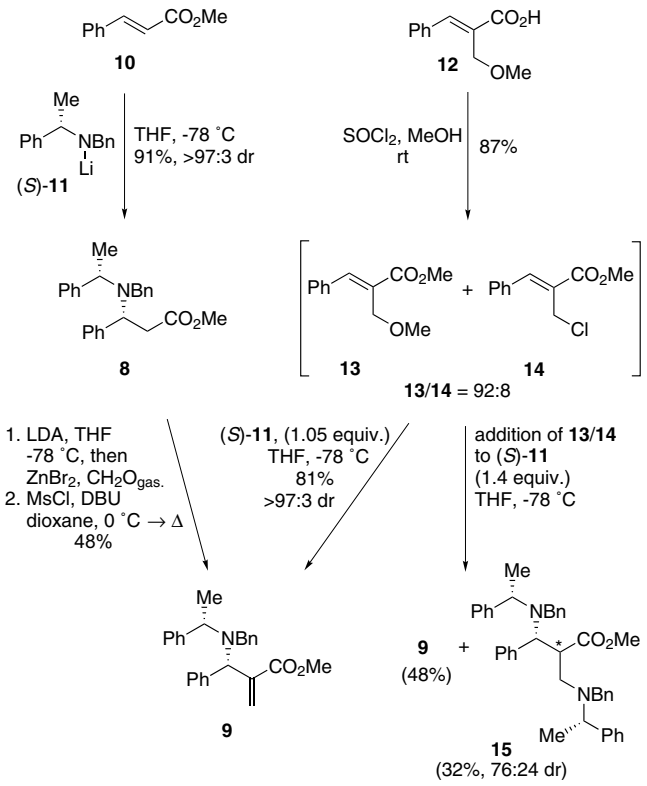
Our retrosynthetic analysis of bispidines **5** and **6** is shown in Scheme 1. The key intermediate is the *anti*,*anti*-configured α,α′-methylene-bridged bis(β-amino ester) **7A**, which should be convertible into **6** and, subsequently, into **5** by a deprotection, cyclisation and reduction sequence.[24] For the preparation of **7A**, we intended to evaluate two chemically related, but stereochemically different routes, both starting from the readily available β-amino ester **8**:[25,26] (a) the direct junction of two molecules of **8** by a bridging α-alkylation using a bifunctional $CH_2XY$-unit and (b) the Michael addition of **8** to the acrylic ester derivative **9**. It is well known that the α-alkylations of the enolate of **8** and of the related β-amino esters occur highly *anti*-diastereoselectively.[27] Therefore, approach (a), which comprises of two such α-alkylations, should predominately deliver the desired *anti*,*anti*-configured isomer **7A**. By contrast, the addition of the enolate of **8** to the acrylate **9** generates a new enolate at the former Michael system, which can be protonated upon work up. If this protonation proceeds, like the α-alkylation, *anti*-selectively, the alignment of the substituents will be *syn* thus giving rise to the formation of the unwanted *anti*,*syn*-diastereomer **7B**. Such an *anti*,*syn*-connection was successfully applied in the synthesis of (−)-sparteine (−)-**1** by O'Brien.[19] In order to obtain the desired *anti*,*anti*-diastereomer **7A**, an epimerisation of **7B** is required or conditions for a preferred *syn*-protonation have to be developed.

### 2.2. Synthesis of the starting materials

Enantiomerically pure β-amino ester **8** is available on large scale from methyl cinnamate **10** and lithium *N*-benzyl-(*S*)-phenylethylamide (*S*)-**11** according to a procedure developed by Davies (Scheme 2).[25–28] The synthesis of the Michael acceptor **9** was accomplished by two different routes: treatment of the zinc enolate of **8** with gaseous formaldehyde introduced a hydroxymethyl substituent at the α-position. Mesylation of the OH-group and subsequent elimination induced by DBU (1,3-diazabicyclo[5.4.0]undecane) gave **9** in 48% yield. An alternative approach to **9** was established from the cinnamic acid derivative **12**, which is readily accessible from benzaldehyde and methyl acrylate.[29] Esterification of **12** with thionyl chloride in methanol afforded a 92:8 mixture of the α-methoxymethyl-substituted cinnamate **13**[30] and its chloro derivative **14**[31] (87% yield). Slow addition of a stoichiometric amount of (*S*)-**11** to this mixture gave **9** in high 81% yield and with excellent stereocontrol (>97:3 dr). The newly formed double bond was not attacked under these conditions. However, an addition to this double bond was observed if an excess of (*S*)-**11** was used or if the addition order was reversed. For example, the addition of esters **13**/**14** to 1.4 equiv of (*S*)-**11** gave 48% of **9** and 32% of **15** (76:24 dr). The latter preparation of **9** from **12** is superior to that from **8**, since it provides a higher overall yield (70% vs 48%) and avoids the labour-intensive hydroxymethylation procedure of **8**.




**Scheme 1.** Retrosynthetic analysis of the bispidines **5** and **6**.

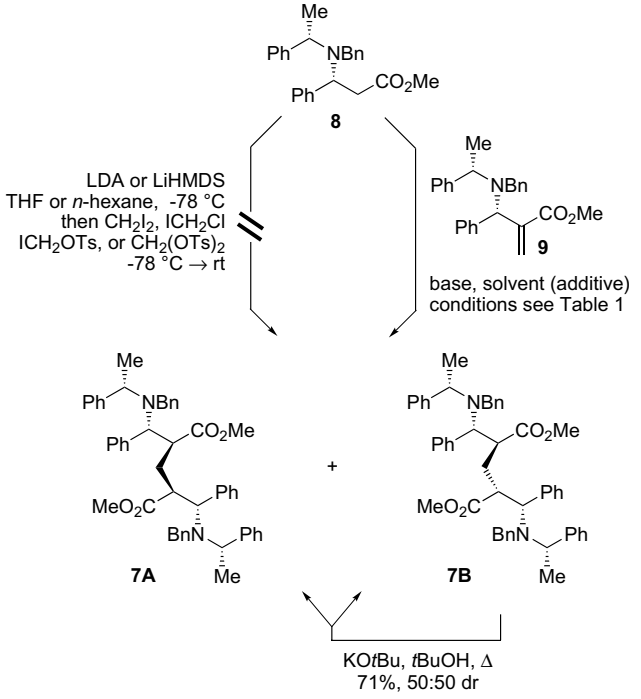



**Scheme 2.** Synthesis of the β-amino esters **8** and **9**.

### 2.3. Preparation of the 2-*endo*,6-*endo*-diphenylbispidine 6

The direct junction of two molecules of **8** by a methylene bridge was attempted (Scheme 3). Deprotonation of **8** with LDA in THF and treatment with a bifunctional C1-unit such as $CH_2I_2$, $ICH_2Cl$, $ICH_2OTs$ or $CH_2(OTs)_2$ at −78 °C resulted in no reaction.[32] At higher temperatures, decomposition occurred, probably due to carbene formation. Despite extensive variations of the reaction conditions, no traces of the desired coupling product **7A** or of its diastereomer **7B** were detected.

The alternative approach, the Michael addition of lithiated **8** to acrylic ester derivative **9** (Scheme 3 and Table 1), was expected to predominately give the *anti*,*syn*-diastereomer **7B** (see discussion, Section 2.1). Indeed, a 29:71 mixture of **7A**:**7B** was obtained with LDA in THF at −30 °C to rt and work up with aqueous $NH_4Cl$ at rt (entry 1). Chromatographic purification afforded **7B** in 24% yield and **7A** in 10% yield. LiHMDS as the base gave an almost identical result (entry 2). The addition of HMPA (1.3 equiv) to the enolate of **8** further enhanced the diastereoselectivity towards the undesired isomer **7B** (16:84 dr), albeit at low conversion (<50%, entry 3).




**Scheme 3.** Studies on the preparation of **7A** from **8**.

A dramatic change in the diastereofacial discrimination was observed in *n*-hexane as the solvent. With either LDA or LiHMDS, the desired *anti*,*anti*-isomer **7A** was obtained as the major product (71:29 dr, entries 4 and 5). Since the formation of a suspension was observed over the course of the reaction, a possible explanation for this reversal in diastereoselectivity might be the occurrence of aggregates, in which the formal *syn*-protonation leading to **7A** is favoured for steric or stereoelectronic reasons. A thermodynamically driven epimerisation process, that is **7B**→**7A**, can be excluded. Samples taken at low conversions and at prolonged reaction times did not reveal any change in the dr. All attempts to further increase the diastereomeric ratio, for example, by protonation with solid $NH_4Cl$ at −78 °C or with the bulky proton source BHT (2,6-di-*tert*-butyl-4-methylphenol) at 0 °C, failed (entry 4). The addition of $LiClO_4$ (2.0 equiv) to the lithium enolate of **8** had no effect; the lithium ion as the counter ion, however, is crucial: deprotonation of **8** with NaHMDS or KHMDS in *n*-hexane again gave the undesired *anti*,*syn*-diastereomer **7B** as the main isomer (entries 6 and 7). Optimum conditions with respect to the yield were found with 2.5 equiv of LDA and of the Michael acceptor **9** delivering the *anti*,*anti*-diastereomer **7A** in good 52% yield and **7B** in 21% yield after chromatography.

**Table 1.** Optimisation of the Michael addition of **8** to **9**[a]

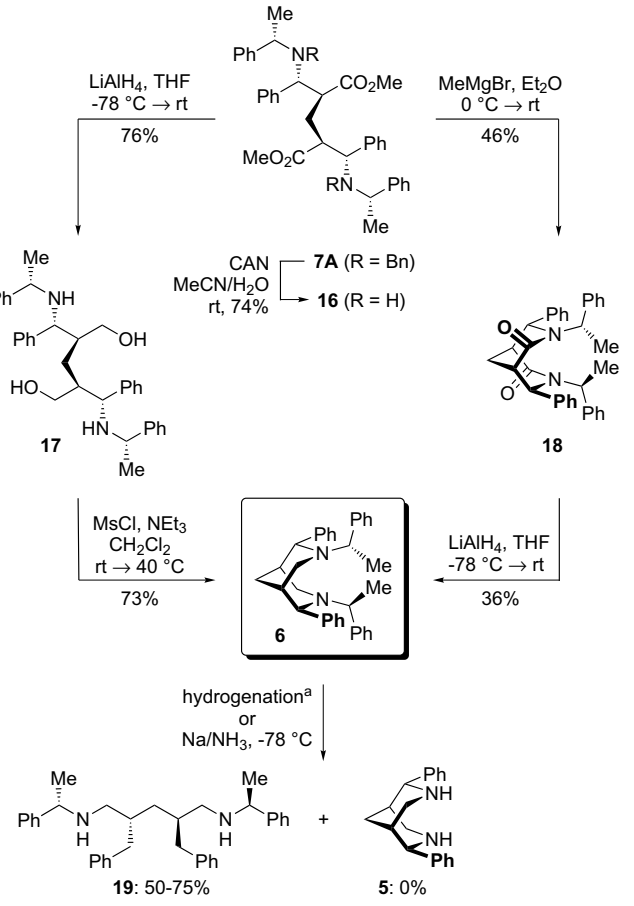
| Entry | Base | Solvent | **7A**:**7B**[b] | **7A**[c] (%) | **7B**[c] (%) |
|---|---|---|---|---|---|
| 1 | LDA | THF | 29:71 | 10 | 24 |
| 2 | LiHMDS | THF | 28:72 | 10 | 25 |
| 3 | LiHMDS[d] | THF | 16:84 | —[e] | —[e] |
| 4 | LDA[f] | *n*-Hexane | 71:29 | 25 | 11 |
| 5 | LiHMDS | *n*-Hexane | 71:29 | 37 | 15 |
| 6 | NaHMDS | *n*-Hexane | 35:65 | —[e] | —[e] |
| 7 | KHMDS | *n*-Hexane | 26:74 | —[e] | —[e] |
| **8** | **LDA**[g] | ***n*-Hexane** | **70:30** | **52** | **21** |

[a] Unless otherwise noted, the following procedure was used: deprotonation of **8** with base (1.25 equiv) at −30 °C, addition of **9** (1.25 equiv), warming to rt overnight, and protonation with satd aq $NH_4Cl$ at rt.
[b] Calculated from the $^1H$ NMR spectra of the crude reaction mixtures.
[c] Isolated yields of the diastereomerically pure compounds.
[d] Addition of HMPA (1.3 equiv) after deprotonation.
[e] Not isolated due to low conversion (<50%).
[f] The addition of $LiClO_4$ (2.0 equiv) had no effect; protonation with $NH_4Cl$ at −78 °C or with BHT (2,6-di-*tert*-butyl-4-methylphenol) at 0 °C resulted in lower diastereomeric ratios.
[g] 2.5 equiv of LDA and **9** used.

Finally, it should be noted that the unwanted *anti*,*syn*-product **7B** is not lost; it can be successively recycled by epimerisation with KO*t*-Bu in refluxing *t*-BuOH to give a 50:50 mixture of **7A** and **7B** (71% yield).

Further construction of the bispidine skeleton was straightforward (Scheme 4): oxidative debenzylation of **7A** with CAN (ceric ammonium nitrate) in aqueous acetonitrile afforded the secondary diamine **16** (74% yield),[33] which was reduced with $LiAlH_4$ to give diol **17** (76% yield). Mesylation of the two hydroxy groups resulted in a spontaneous cyclisation delivering the $C_2$-symmetric bispidine **6** in 73% yield. The alternative cyclisation–reduction sequence via dilactam **18** was less successful giving **6** in low 17% yield (vs 56% yield via **17**).

Finally, removal of the chiral protecting groups at the nitrogen atoms was investigated. Even though two different types of benzylic C–N bonds, two *endo*- and two *exo*-cyclic ones, are present in **6**, we anticipated the latter ones to be preferentially attacked by hydrogenolysis due to the sensibility of these reactions to steric hindrance.[34] However, a selective cleavage of the *endo*-cyclic C–N bonds occurred




**Scheme 4.** Transformation of **7A** into the bispidine **6** and the attempted deprotection of **6** to give **5**. Reagents: $H_2$, Pd/C, MeOH; $H_2$, Pd/C, EtOH/6 N HCl; $H_2$, $Pd(OH)_2$/C, MeOH/AcOH; $H_2$, $PtO_2$, EtOH; $NH_4HCO_2$, Pd/C, MeOH, Δ.

under all conditions screened thus affording acyclic diamine **19** in 50–75% yield. The same result was observed in the attempted reductive removal of the *N*-phenylethyl groups of **6** with sodium in liquid ammonia. Cleavage of the chiral auxiliary in an earlier stage of the synthesis, that is in **16**, **17** or **18**, failed, as well. Inseparable product mixtures were obtained.

## 3. Conclusions

The enantioselective synthesis of the $C_2$-symmetric 2-*endo*,6-*endo*-diphenyl-substituted bispidine **6** was achieved in six steps and 15% overall yield starting from β-amino ester **8** and the cinnamic acid **12**. The key step was the Michael addition of **8** to its α-methylene derivative **9**, which was prepared from **12**. The desired *anti*,*anti*-configured α,α′-methylene-bridged bis(β-amino ester) **7A** was obtained as the major diastereomer with LDA in *n*-hexane as the solvent; the *anti*,*syn*-isomer **7B** was preferentially formed in THF. Debenzylation, reduction and cyclisation delivered the N,N′-diprotected bispidine **6**. Attempted hydrogenolytic or reductive removal of the chiral protecting groups caused a cleavage of the bispidine core giving acyclic diamine **19**. Further work in this area will focus on the preparation of target molecule **5** by using a different protection strategy, on the enantioselective syntheses of derivatives with other substituents in 2-*endo*- and 6-*endo*-position, and on the application of these bispidines in asymmetric synthesis.

## 4. Experimental

Optical rotations (10 cm cell) were measured on a Jasco P-1020 polarimeter. All NMR spectra were acquired at 20 °C on a Bruker AV 400 instrument using $CDCl_3$ as the internal reference. IR spectra were recorded on a Jasco FT-IR-410 spectrometer. High resolution mass spectra were measured on a Bruker Daltonics micrOTOF focus. Column chromatography was carried out on silica gel (63–200 mesh). Microanalyses were performed at the Institute of Inorganic Chemistry, University of Würzburg. Anhydrous solvents were prepared using standard procedures. The β-amino ester **8** (>97 ee, >95% de) was synthesised according to Ref. 25 and *N*-benzyl-(*S*)-phenylamine (>97% ee) according to Ref. 35. All reactions with anhydrous solvents were performed under an argon atmosphere. The diastereomeric ratios of **7** and **9** were determined by $^1$H NMR of the crude reaction mixtures.

### 4.1. Methyl (*E*)-2-methoxymethyl cinnamate 13 and methyl (*E*)-2-chloromethyl cinnamate 14

Thionyl chloride (17 mL, 27.7 g, 233 mmol) was slowly added to a solution of **12** (15.0 g, 78.0 mmol) in anhydrous methanol (50 mL). After 15 h at rt, the reaction mixture was carefully neutralised with 3 M NaOH (160 mL) and extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure yielded a 92:8 mixture of the known methyl cinnamates **13**[29] and **14**[31] (15.3 g, 74.0 mmol, 95%) as a colourless oil.

### 4.2. Methyl 2-{(*S*)-[*N*-benzyl-*N*-((*S*)-1-phenylethyl)amino]phenylmethyl}acrylate 9

**4.2.1. From β-amino ester 8.** A solution of LDA, prepared from *i*-$Pr_2NH$ (14.2 mL, 10.2 g, 101 mmol) and *n*-BuLi (1.6 M in hexanes, 60.3 mL, 96.4 mmol) in anhydrous THF (100 mL) at −30 °C to 0 °C, was slowly added at −78 °C to a solution of **8** (24.0 g, 64.3 mmol) in anhydrous THF (500 mL). After 1 h, anhydrous $ZnBr_2$ (21.7 g, 96.4 mmol) was added and stirring was continued for 30 min. In a second flask, attached via a short glass bridge, paraformaldehyde (29.0 g, 965 mmol) was heated to ca. 180 °C (heatgun) and the resulting monomeric formaldehyde transported in an argon stream over the vigorously stirred reaction mixture. After 1 h at −78 °C, satd aq $NH_4Cl$ (300 mL) was added and the reaction mixture extracted with EtOAc (2 × 300 mL). The combined organic layers were washed with brine (300 mL), dried over $MgSO_4$ and the solvent removed in vacuo. The crude product was purified by column chromatography (silica gel, *n*-pentane–$Et_2O$ 2:1) to give the α-hydroxymethyl derivative of **8** (14.7 g, 36.3 mmol, 56%) as a colourless oil.

The product (10.1 g, 25 mmol) was dissolved in dioxane (250 mL) and cooled to 0 °C. MsCl (2.36 mL, 3.44 g, 30.0 mmol) and DBU (1,3-diazabicyclo[5.4.0]undecane, 12.0 mL, 12.2 g, 80.0 mmol) were added slowly. The reaction mixture was stirred for 20 min at 0 °C, 1 h at rt, and 16 h at 60 °C. Satd aq $NH_4Cl$ (1 L) was added and the reaction mixture extracted with $Et_2O$ (2 × 1 L). The combined organic layers were washed with brine (250 mL), dried over $MgSO_4$ and evaporated. Column chromatography (silica gel, *n*-pentane–$Et_2O$ 40:1→10:1) delivered **9** (8.20 g, 21.3 mmol, 85%) as a colourless oil. $[\alpha]_D^{21} = +88.7$ (*c* 0.13, $CHCl_3$). IR (film): *v* 3084, 3060, 3027, 2970, 2949, 2844, 1721, 1493, 1452, 1283, 1135, 749, 699 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.20 (3H, d, $J = 7.0$ Hz, CHC*H*$_3$), 3.57 (3H, s, $OCH_3$), 3.82 (1H, d, $J = 15.2$ Hz, C*H*HPh), 3.87 (1H, d, $J = 15.0$ Hz, C*H*HPh), 4.16 (1H, q, $J = 7.0$ Hz, C*H*MePh), 5.04 (1H, s, NCHPh), 5.93 (1H, s, 3-H), 6.28 (1H, s, 3-H′), 7.10–7.40 (15H, m, ArH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 16.9 (CH*C*H$_3$), 51.3 ($CH_2$Ph), 51.6 ($OCH_3$), 57.6 (CHMePh), 63.8 (NCHPh), 126.2 (C-3), 126.7, 127.1, 127.8, 127.9, 128.0, 128.1, 129.2, 140.2 (ArH), 141.9 (C-2), 142.0, 143.4 (ArC), 167.5 (C=O). HRMS (ESI, +): calcd for $C_{26}H_{27}NO_2$+Na: 408.1934, found: 408.1938. Anal. Calcd for $C_{26}H_{27}NO_2$ (385.49): C, 81.01; H, 7.06; N, 3.63. Found: C, 80.84; H, 7.07; N, 3.56.

**4.2.2. From the methyl cinnamates 13 and 14.** Amide (*S*)-**11** was prepared by deprotonation of *N*-benzyl-(*S*)-phenylethylamine (10.8 g, 50.9 mmol) with *n*-BuLi (1.6 M in hexanes, 30.6 mL, 48.9 mmol) in anhydrous THF (80 mL) at −78 °C for 30 min. The resulting pink solution was added over a period of 2 h to a 92:8 mixture of **13** and **14** (10.0 g, 48.5 mmol) in anhydrous THF (80 mL). After 1 h at −78 °C, the reaction mixture was quenched with satd aq $NH_4Cl$ (150 mL) and extracted with $Et_2O$–$CH_2Cl_2$ (1:1, 2 × 150 mL). The combined organic layers were washed with brine (200 mL) and dried over $MgSO_4$. Removal of the solvent in vacuo and column chromatographic purification (silica gel, *n*-pentane–$Et_2O$ 40:1→10:1) gave **9** (15.1 g, 39.2 mmol, 81%, >97:3 dr) as a colourless oil.

### 4.3. Methyl (*R*)-3-[*N*-benzyl-*N*-((*S*)-1-phenylethyl)amino]-2-{[*N*-benzyl-*N*-((*S*)-1-phenylethyl)amino]methyl}-3-phenylpropionate 15

A 92:8 mixture of **13** and **14** (4.55 g, 22.0 mmol) in anhydrous THF (10 mL) was added at −78 °C to a pink solution of (*S*)-**11**, prepared by deprotonation of *N*-benzyl-(*S*)-phenylethylamine (6.52 g, 30.9 mmol) with *n*-BuLi (1.6 M in hexanes, 18.6 mL, 29.8 mmol) in anhydrous THF (70 mL) at −78 °C for 30 min. The reaction was stirred for 1 h at −78 °C, quenched with satd aq $NH_4Cl$ (90 mL) and extracted with $Et_2O$–$CH_2Cl_2$ (1:1, 2 × 90 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and evaporated. Column chromatography (silica gel, *n*-pentane–$Et_2O$ 40:1→10:1) delivered in the order of elution **9** (4.04 g, 10.5 mmol, 48%) as a colourless oil and the diastereomers of **15** (faster eluting diastereomer: 3.10 g, 5.19 mmol, 24%; slower eluting diastereomer: 989 mg, 1.66 mmol, 8%) as colourless solids. Faster eluting diastereomer of **15**: mp 53 °C. $[\alpha]_D^{22} = -102.2$ (*c* 0.14, $CHCl_3$). IR (KBr): *v* 3084, 3060, 3026, 2967, 2930, 2848, 1736, 1494, 1451, 1372, 1262, 748, 698 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.80 (3H, d, $J = 7.0$ Hz, CHC*H*$_3$), 1.18 (3H, d, $J = 7.0$ Hz, CHC*H*$_3$), 1.85 (1H, dd, $J = 13.3$, 3.5 Hz, CHC*H*H), 2.67 (1H, dd, $J = 13.3$, 11.5 Hz, CHC*H*H), 3.16 (1H, d, $J = 13.8$ Hz, C*H*HPh), 3.26 (1H, td, $J = 11.6$, 3.5 Hz, 2-H), 3.38 (1H, d, $J = 13.9$ Hz, C*H*HPh), 3.51 (1H, d, $J = 14.5$ Hz, C*H*HPh), 3.56 (3H, s, $OCH_3$), 3.72 (1H, q, $J = 7.0$ Hz, CHMePh), 3.82 (1H, d, $J = 11.6$ Hz, 3-H), 4.04 (2H, m, CHMePh, C*H*HPh), 6.92 (2H, m, ArH), 7.11–7.38 (23H, m, ArH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 14.1 (CH*C*H$_3$), 14.7 (CH*C*H$_3$), 49.9 (C-2), 50.4 ($CH_2$Ph), 51.1 (OMe), 52.2 (CH*C*H$_2$), 54.7 ($CH_2$Ph), 55.1 (CHMePh), 58.4 (CHMePh), 61.6 (C-3), 126.3, 126.6, 126.76, 126.77, 127.3, 127.7, 127.8, 127.97, 128.02, 128.04, 128.15, 128.23, 128.8, 128.9, 129.1, 138.8, 139.8, 140.3, 142.1, 144.1 (ArC), 174.3 (C=O). HRMS (ESI, +): calcd for $C_{41}H_{44}N_2O_2$+Na: 619.3295, found: 619.3305. Slower eluting diastereomer of **15**: mp 50 °C. $[\alpha]_D^{22} = +25.9$ (*c* 0.10, $CHCl_3$). IR (KBr): *v* 3085, 3060, 3027, 2967, 2935, 2841, 1736, 1494, 1451, 1224, 1029, 749, 699 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.88 (3H, d, $J = 6.8$ Hz, CHC*H*$_3$), 1.24 (3H, d, $J = 6.8$ Hz, CHC*H*$_3$), 2.29 (1H, t, $J = 12.6$ Hz, CHC*H*H), 2.97 (3H, s, $OCH_3$), 3.08 (1H, dd, $J = 12.9$, 3.9 Hz, CHC*H*H), 3.24 (1H, d, $J = 13.4$ Hz, C*H*HPh), 3.45 (1H, td, $J = 11.3$, 3.9 Hz, 2-H), 3.59 (1H, d, $J = 13.8$ Hz, C*H*HPh), 3.67 (1H, d, $J = 13.4$ Hz, C*H*HPh), 3.78 (1H, d, $J = 11.0$ Hz, 3-H), 3.88 (1H, q, $J = 6.8$ Hz, CHMePh), 3.98 (1H, d, $J = 13.8$ Hz, C*H*HPh), 4.17 (1H, q, $J = 6.8$ Hz, CHMePh), 7.10–7.43 (25H, m, ArH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 10.0 (CH*C*H$_3$), 14.7 (CH*C*H$_3$), 48.3 (C-2), 50.7 (CH*C*H$_2$, $CH_2$Ph), 50.9 (OMe), 54.1 ($CH_2$Ph), 55.5 (CHMePh), 55.8 (CHMePh), 61.9 (C-3), 126.3, 126.6, 126.7, 127.0, 127.2, 127.6, 127.8, 127.88, 127.90, 128.1, 128.2, 128.4, 129.08, 129.10, 129.2, 138.7, 140.0, 140.1, 143.4, 144.7 (ArC), 173.3 (C=O). HRMS (ESI, +): calcd for $C_{41}H_{44}N_2O_2$+Na: 619.3295, found: 619.3312. Anal. Calcd for $C_{41}H_{44}N_2O_2$ (596.82): C, 82.51; H, 7.43; N, 4.69. Found: C, 82.13; H, 7.64; N, 4.42.

### 4.4. Dimethyl (2*S*,4*S*)-2,4-bis{(*R*)-[*N*-benzyl-*N*-((*S*)-1-phenylethyl)amino]phenylmethyl}glutarate 7A and dimethyl (2*S*,4*R*)-2,4-bis{(*R*)-[*N*-benzyl-*N*-((*S*)-1-phenylethyl)amino]phenylmethyl}glutarate 7B

A solution of LDA, prepared from *i*-$Pr_2NH$ (4.39 mL, 3.15 g, 31.2 mmol) and *n*-BuLi (1.6 M in hexanes, 18.6 mL, 29.8 mmol) in anhydrous *n*-hexane (100 mL) at −30 °C to 0 °C, was added at −30 °C to a solution of **8** (4.44 g, 11.9 mmol) in anhydrous *n*-hexane (120 mL). After 30 min, a solution of **9** (11.5 g, 29.8 mmol) in anhydrous *n*-hexane (300 mL) was slowly added and the reaction was warmed to rt overnight giving a white suspension. Satd aq $NH_4Cl$ (350 mL) was added and the reaction mixture extracted with $Et_2O$ (2 × 700 mL). The combined organic layers were washed with brine (350 mL), dried over $MgSO_4$ and evaporated. Column chromatography (silica gel, *n*-pentane–$Et_2O$ 10:1→5:1) delivered in the order of elution **7A** (4.69 g, 6.18 mmol, 52%) and **7B** (1.91 g, 2.52 mmol, 21%) as colourless solids. Compound **7A**: mp 59 °C. $[\alpha]_D^{21} = +9.8$ (*c* 0.13, $CHCl_3$). IR (KBr): *v* 3085, 3060,

3027, 2947, 2849, 1737, 1494, 1452, 1162, 762, 699 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.82 (6H, d, $J = 6.8$ Hz, $2 \times CHCH_3$), 1.03 (2H, dd, $J = 8.3$, 5.9 Hz, 3-H, 3-H′), 3.04 (2H, m, 2-H, 4-H), 3.45 (2H, d, $J = 14.2$ Hz, $2 \times CHHPh$), 3.47 (6H, s, $2 \times OCH_3$), 3.76 (2H, d, $J = 11.4$ Hz, $2 \times NCHPh$), 3.89 (2H, d, $J = 14.2$ Hz, $2 \times CHHPh$), 4.07 (2H, q, $J = 6.8$ Hz, $2 \times CHMePh$), 6.94–6.99 (4H, m, ArH), 7.12–7.31 (26H, m, ArH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 15.4 ($CHCH_3$), 30.8 (C-3), 47.2 (C-2/C-4), 50.5 ($CH_2Ph$), 51.2 (OMe), 55.7 (CHMePh), 63.4 (NCHPh), 126.3, 126.6, 127.4, 127.70, 127.74, 128.0, 128.2, 128.9, 129.0, 137.5, 139.8, 144.4 (ArC), 174.0 (C=O). HRMS (ESI, +): calcd for $C_{51}H_{54}N_2O_4$+H: 759.4156, found: 759.4158. Anal. Calcd for $C_{51}H_{54}N_2O_4$ (758.99): C, 80.71; H, 7.17; N, 3.69. Found: C, 80.69; H, 7.31; N, 3.39. Compound **7B**: mp 136 °C. $[\alpha]_D^{21} = +29.9$ ($c$ 0.14, $CHCl_3$). IR (KBr): $\nu$ 3085, 3060, 3027, 2970, 2854, 1728, 1494, 1450, 1122, 749, 700 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.82 (3H, d, $J = 7.0$ Hz, $CHCH_3$), 0.86 (3H, d, $J = 7.0$ Hz, $CHCH_3$), 1.33 (1H, m, 3-H), 1.91 (1H, dt, $J = 14.0$, 3.0 Hz, 3-H), 2.79 (1H, td, $J = 10.5$, 2.5 Hz, 2-H or 4-H), 3.06 (3H, s, $OCH_3$), 3.14 (1H, td, $J = 11.0$, 3.8 Hz, 2-H or 4-H), 3.40 (3H, s, $OCH_3$), 3.44 (1H, d, $J = 13.9$ Hz, $CHHPh$), 3.57 (1H, d, $J = 10.9$ Hz, NCHPh), 3.58 (1H, d, $J = 13.9$ Hz, $CHHPh$), 3.70 (1H, d, $J = 13.9$ Hz, $CHHPh$), 3.88 (1H, q, $J = 7.0$ Hz, CHMePh), 3.93 (1H, d, $J = 11.4$ Hz, NCHPh), 4.11 (2H, m, CHMePh, $CHHPh$), 6.85–6.91 (2H, m, ArH), 7.02–7.11 (4H, m, ArH), 7.14–7.38 (21H, m, ArH), 7.43–7.51 (3H, m, ArH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 14.2 ($CHCH_3$), 15.6 ($CHCH_3$), 31.0 (C-3), 48.3 (C-2 or C-4), 48.5 (C-2 or C-4), 50.7 ($CH_2Ph$), 50.9 (OMe), 51.0 (OMe), 51.1 ($CH_2Ph$), 55.5 (CHMePh), 56.8 (CHMePh), 63.7 (NCHPh), 64.3 (NCHPh), 126.4, 126.7, 127.2, 127.60, 127.63, 127.7, 127.8, 128.0, 128.15, 128.17, 128.3, 128.4, 128.5, 128.7, 129.0, 129.4, 129.5, 138.1, 138.8, 139.8, 144.4 (ArC), 174.0 (C=O), 174.2 (C=O). HRMS (ESI, +): calcd for $C_{51}H_{54}N_2O_4$+Na: 781.3976, found: 781.3978.

Modifications of this procedure (see Table 1) were performed on a 200–500 μmol scale.

### 4.5. Epimerisation of 7B

Compound **7B** (500 mg, 659 μmol) was dissolved in warm *t*-BuOH (25 mL) after which KO*t*-Bu (37.0 mg, 330 μmol) was added. After reflux for 72 h, the reaction was quenched with satd aq $NH_4Cl$ (100 mL) and extracted with EtOAc ($2 \times 100$ mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure to give a 50:50 mixture of **7A** and **7B**. Column chromatography (silica gel, *n*-pentane–$Et_2O$ 10:1→5:1) delivered **7A** (155 mg, 204 μmol, 31%) and **7B** (148 mg, 195 μmol, 30%) as colourless solids.

### 4.6. Dimethyl (2*S*,4*S*)-2,4-bis[(*R*)-phenyl-((*S*)-1-phenylethylamino)methyl]glutarate 16

CAN [$Ce(NH_4)_2(NO_3)_6$, 6.26 g, 11.4 mmol] was added to a solution of **7A** (1.70 g, 2.24 mmol) in acetonitrile/water (5:1, 42 mL). After 7 h at rt, satd aq $NaHCO_3$ (340 mL) was added. The white solid formed, was removed by suction and washed with $Et_2O$ (200 mL). The filtrate was extracted with $Et_2O$ ($2 \times 400$ mL) and the combined organic layers were washed with brine (250 mL) and dried over $MgSO_4$. Evaporation of the solvent and purification by column chromatography (silica gel, *n*-pentane–EtOAc 10:1) gave **16** (954 mg, 1.65 mmol, 74%) as a yellowish foamy solid. Mp 39 °C. $[\alpha]_D^{19} = -40.3$ ($c$ 0.18, $CHCl_3$). IR (KBr): $\nu$ 3448, 3319, 3083, 3060, 3026, 2968, 2949, 1738, 1452, 1262, 1162, 766, 700 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.17 (6H, d, $J = 6.3$ Hz, $2 \times CHCH_3$), 1.41 (2H, dd, $J = 8.6$, 6.2 Hz, 3-H, 3-H′), 2.56 (2H, m, 2-H, 4-H), 3.44 (2H, q, $J = 6.3$ Hz, $2 \times CHMePh$), 3.67 (6H, s, $2 \times OCH_3$), 3.69 (2H, d, $J = 9.7$ Hz, $2 \times NCHPh$), 7.01–7.06 (4H, m, ArH), 7.07–7.11 (4H, m, ArH), 7.14–7.22 (6H, m, ArH), 7.25–7.32 (6H, m, ArH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 22.0 ($CHCH_3$), 29.7 (C-3), 51.36 (C-2/C-4), 51.39 (OMe), 54.3 (CHMePh), 62.1 (NCHPh), 126.5, 126.8, 127.2, 127.4, 128.2, 128.5, 141.1, 146.3 (ArC), 174.5 (C=O). HRMS (ESI, +): calcd for $C_{37}H_{42}N_2O_4$+H: 579.3217, found: 579.3211.

### 4.7. (2*S*,4*S*)-2,4-Bis[(*R*)-phenyl-((*S*)-1-phenylethylamino)methyl]pentane-1,5-diol 17

$LiAlH_4$ (1.0 M in THF, 2.58 mL, 2.58 mmol) was added at −78 °C to a solution of **16** (750 mg, 1.29 mmol) in anhydrous THF (40 mL). After 30 min, the reaction was warmed to rt and stirred for 16 h. The reaction mixture was quenched with satd aq $NH_4Cl$ (120 mL) and extracted with EtOAc ($2 \times 350$ mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$ and evaporated to give **17** (515 mg, 985 μmol, 76%) as a slightly yellowish solid. Mp 102 °C. $[\alpha]_D^{21} = -125.5$ ($c$ 0.06, $CHCl_3$). IR (KBr): $\nu$ 3422, 2926, 2854, 1602, 1452, 1082, 768, 700 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.37 (2H, dd, $J = 7.4$, 5.2 Hz, 3-H, 3-H′), 1.29 (6H, d, $J = 6.4$ Hz, $2 \times CHCH_3$), 1.80 (2H, m, 2-H/4-H), 3.23 (2H, dd, $J = 11.2$, 9.1 Hz, 1-H/5-H), 3.32 (2H, d, $J = 10.2$ Hz, $2 \times NCHPh$), 3.41 (2H, q, $J = 6.4$ Hz, $2 \times CHMePh$), 3.61 (2H, dd, $J = 11.2$, 2.8 Hz, 1-H′/5-H′), 6.91–7.01 (6H, m, ArH), 7.07–7.31 (14H, m, ArH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 21.0 ($CHCH_3$), 28.2 (C-3), 43.4 (C-2/C-4), 54.7 (CHMePh), 67.1 (NCHPh), 67.6 (C-1/C-5), 126.4, 127.0, 127.3, 127.6, 128.5, 128.8, 141.9, 144.9 (ArC). HRMS (ESI, +): calcd for $C_{35}H_{42}N_2O_2$+H: 523.3319, found: 523.3323.

### 4.8. (1*S*,4*R*,5*S*,8*R*)-4,8-Diphenyl-3,7-bis((*S*)-1-phenylethyl)-3,7-diazabicyclo[3.3.1]nonane-2,6-dione 18

MeMgBr (3.0 M in THF, 2.40 mL, 8.00 mmol) was slowly added at 0 °C to a solution of **16** (580 mg, 1.00 mmol) in anhydrous $Et_2O$ (60 mL). The reaction was stirred for 30 min at 0 °C and for 18 h at rt. Satd aq $NH_4Cl$ (100 mL) was added and the reaction mixture extracted with $Et_2O$ ($2 \times 200$ mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. Column chromatography (silica gel, *n*-pentane–$Et_2O$ 2:1) delivered **18** (239 mg, 491 μmol, 46%) as a colourless solid. Mp 66 °C. $[\alpha]_D^{21} = +15.7$ ($c$ 0.10, $CHCl_3$). IR (KBr): $\nu$ 3063,

3030, 2926, 2855, 1740, 1456, 1381, 1219, 768, 699 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.24 (6H, d, $J = 7.2$ Hz, $2 \times CHCH_3$), 1.97 (2H, t, $J = 7.9$ Hz, 9-H, 9-H′), 2.93 (2H, dt, $J = 7.9$, 2.1 Hz, 1-H/5-H), 3.89 (2H, d, $J = 2.2$ Hz, 4-H/8-H), 4.95 (2H, q, $J = 7.2$ Hz, $2 \times CHMePh$), 7.04–7.08 (4H, m, ArH), 7.09–7.16 (10H, m, ArH), 7.24–7.28 (6H, m, ArH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 18.5 ($CHCH_3$), 27.2 (C-9), 51.9 (CHMePh), 57.6 (C-1/C-5), 60.4 (C-4/C-8), 126.3, 127.0, 127.6, 128.0, 128.4, 128.5, 138.6, 139.7 (ArC), 169.3 (C=O). HRMS (ESI, +): calcd for $C_{35}H_{34}N_2O_2$+Na: 537.2513, found: 537.2516.

### 4.9. (1*R*,2*R*,5*R*,6*R*)-2,6-Diphenyl-3,7-bis((*S*)-1-phenylethyl)-3,7-diazabicyclo[3.3.1]nonane 6

**4.9.1. From diol 17.** $Et_3N$ (268 μL, 193.2 mg, 1.91 mmol) and MsCl (89.2 μL, 132 mg, 1.15 mmol) were slowly added at 0 °C to a solution of **17** (200 mg, 382 μmol) in anhydrous $CH_2Cl_2$ (20 mL). The reaction was stirred for 2 h at rt and refluxed for 22 h. The reaction was quenched with satd aq $NH_4Cl$ (40 mL) and extracted with EtOAc ($3 \times 90$ mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and the solvent removed in vacuo to give **6** (136 mg, 280 μmol, 73%) as a yellowish solid. Mp 88 °C. $[\alpha]_D^{21} = -5.5$ (*c* 0.10, $CHCl_3$). IR (KBr): *v* 2926, 2854, 1656, 1450, 1368, 1261, 1075, 692 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.18 (6H, d, $J = 6.6$ Hz, $2 \times CHCH_3$), 1.66 (2H, t, $J = 7.2$ Hz, 9-H, 9-H′), 2.23 (2H, sext, $J = 7.6$ Hz, 1-H/5-H), 2.49 (2H, dd, $J = 8.6$, 6.7 Hz, 4-H/8-H), 3.27 (2H, q, $J = 6.6$ Hz, CHMePh), 3.40 (2H, d, $J = 7.8$ Hz, 2-H/6-H), 3.49 (2H, t, $J = 6.9$ Hz, 4-H′/8-H′), 6.87–6.95 (10H, m, ArH), 6.95–7.09 (10H, m, ArH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 20.3 ($CHCH_3$), 37.3 (C-9), 38.6 (C-1/C-5), 56.9 (C-4/C-8), 68.7 (CHMePh), 75.5 (C-2/C-6), 126.4, 126.7, 127.3, 127.39, 127.41, 127.9, 142.3, 142.4 (ArC). HRMS (ESI, +): calcd for $C_{35}H_{38}N_2$+H: 487.3108, found: 487.3110.

**4.9.2. From the bispidine dilactam 18.** Dilactam **18** (106 mg, 205 μmol) was dissolved in anhydrous THF (2 mL) and cooled to −78 °C. $LiAlH_4$ (1.0 M in THF, 410 μl, 410 μmol) was added. After 1 h at −78 °C and 2 h at rt, the reaction was quenched with satd aq $NH_4Cl$ (20 mL) and extracted with EtOAc ($2 \times 30$ mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$. Removal of the solvent under a reduced pressure and column chromatography (silica gel, *n*-pentane–EtOAc 1:1) yielded **6** (35.9 mg, 73.7 μmol, 36%) as a yellowish solid.

### 4.10. (2*R*,4*R*)-2,4-Dibenzyl-*N*,*N*′-bis((*S*)-1-phenylethyl)-pentane-1,5-diamine 19

**4.10.1. Hydrogenation of 6.** A solution of **6** (30.0 mg, 61.6 μmol) in anhydrous EtOH (10 mL) was hydrogenated over $PtO_2$ (5 mg) under 4 bar $H_2$ pressure for 6 h at 65 °C. The mixture was filtered through a pad of Celite and washed with $CH_2Cl_2$ (60 mL). Removal of the solvent in vacuo and column chromatography (silica gel, *n*-pentane–$Et_2O$ 1:1) delivered **19** (22.7 mg, 46.2 μmol, 75%) as a yellowish oil. $[\alpha]_D^{22} = +26.9$ (*c* 0.10, $CHCl_3$). IR (KBr): *v* 3433, 3026, 2924, 2852, 1640, 1494, 1452, 1123, 1030, 759, 699, 460, 423, 411 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.17 (2H, t, $J = 6.7$ Hz, 3-H, 3-H′), 1.22 (6H, d, $J = 6.6$ Hz, $2 \times CHCH_3$), 1.71 (2H, m, 2-H/4-H), 2.16 (2H, dd, $J = 12.0$, 6.6 Hz, 1-H/5-H), 2.29 (2H, dd, $J = 12.0$, 4.3 Hz, 1-H′/5-H′), 2.39 (2H, dd, $J = 13.5$, 7.1 Hz, $2 \times CHHPh$), 2.67 (2H, dd, $J = 13.5$, 7.0 Hz, $2 \times CHHPh$), 3.56 (2H, q, $J = 6.6$ Hz, $2 \times CHMePh$), 7.04–7.10 (4H, m, ArH), 7.12–7.32 (16H, m, ArH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 24.3 ($CHCH_3$), 35.1 (C-3), 37.8 (C-2/C-4), 39.8 ($CH_2Ph$), 50.7 (C-1/C-5), 58.2 (CHMePh), 125.7, 126.6, 126.7, 128.2, 128.3, 129.1, 141.2, 146.0 (ArC). MS (ESI, +): *m*/*z* 491 [100, M+H]$^+$, 387 (29), 266 (17). HRMS (ESI, +): calcd for $C_{35}H_{42}N_2$+H: 491.3426, found: 491.3431.

Hydrogenation of **6** with $H_2$ (3 bar) and Pd/C (10 wt %) in MeOH at 40 °C, with $H_2$ (1 bar) and Pd/C (10 wt %) in EtOH/6 N HCl at 65 °C, with $H_2$ (1 bar) and $Pd(OH)_2$/C (10 wt %) in MeOH/AcOH (2:1) at rt, and with $NH_4HCO_2$ and Pd/C (10 wt %) in MeOH at 60 °C delivered **19** in 50–75% yield.

**4.10.2. Birch reduction of 6.** A solution of **6** (30.0 mg, 61.6 mmol) in anhydrous THF (1 mL) was added at −78 °C to liquid ammonia (20 mL). Sodium ($2 \times 14$ mg, 1.22 mmol) was then added in two portions. The reaction mixture was warmed to rt overnight, quenched with satd aq $NH_4Cl$ (20 mL), and extracted with $CH_2Cl_2$ ($2 \times 30$ mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and evaporated. Column chromatography (silica gel, *n*-pentane–$Et_2O$ 1:1) delivered **19** (14.5 mg, 29.6 μmol, 48%) as a yellowish oil.

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