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Synthesis and derivatisation of *N*,*N*′-trisubstituted 1,2-diamines derived from (1*R*,2*R*)-1,2-diaminocyclohexane

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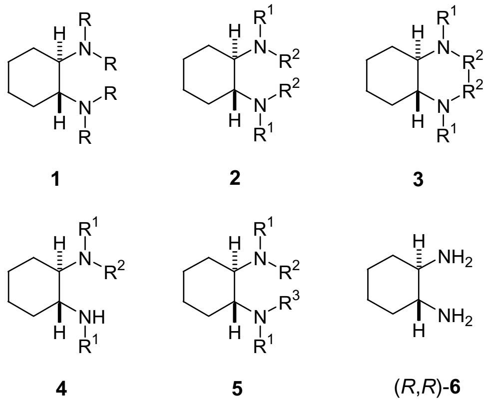
Abstract—The synthesis of *N*,*N*′-trisubstituted 1,2-diamines can be achieved by simple reduction of an aminal derived from (1*R*,2*R*)-diaminocyclohexane. We comment on the scope and limitation of this reduction and discuss its application towards the synthesis of unsymmetrical *N*,*N*′-tetrasubstituted 1,2-diamines.

1. Introduction

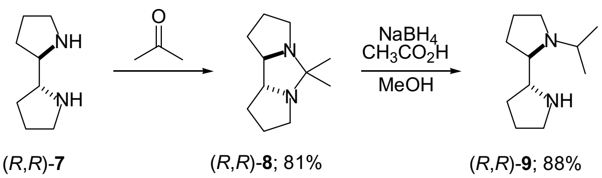
The synthesis of enantiomerically pure symmetrical[1] and unsymmetrical[2] *N*,*N*′-tetrasubstituted 1,2-diamines such as **1** and **2** are well known (Scheme 1). By comparison, the synthesis of cyclic 1,2-diamines,[3] like **3** is much less documented (Scheme 1), and reports into the synthesis of unsymmetrically trisubstituted and tetrasubstituted 1,2-diamines, such as **4** and **5**, derived from the corresponding 1,2-diamine [e.g., (*R*,*R*)-**6**] are rare (Scheme 1).[4]



Scheme 1.

Alexakis has recently reported[5] an elegant approach for the synthesis of trisubstituted 1,2-diamines involving reduction of an aminal (*R*,*R*)-**8** [derived from the enantiomerically pure 1,2-diamine (*R*,*R*)-**7**] using sodium borohydride to give the required trisubstituted 1,2-diamine (*R*,*R*)-**9** in excellent yield (Scheme 2).

We have recently become interested in the synthesis of enantiomerically pure symmetrical[6] and unsymmetrical[6,7] *N*,*N*′-tetrasubstituted 1,2-diamines [e.g., (*R*,*R*)-**10**, (*R*,*R*)-**11** and (*R*,*R*)-**12**] derived from the readily available (1*R*,2*R*)-diaminocyclohexane (*R*,*R*)-**6** (Scheme 3). We have previously focused[6,7] on the use of direct *N*-alkylation using S_N2 active electrophiles, such as methyl iodide, benzyl bromide and allyl bromide mediated by lithium hydroxide monohydrate ($LiOH·H_2O$) as a stoichiometric base to give tetrasubstituted 1,2-diamines in



Scheme 2.

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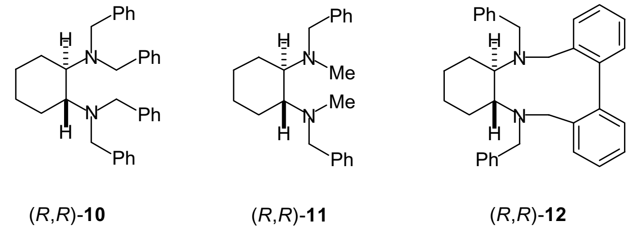
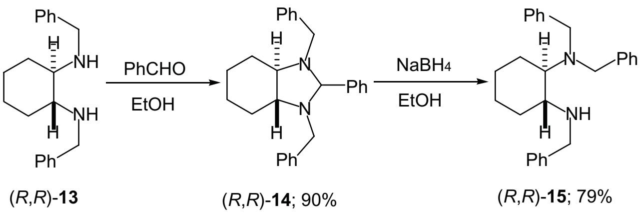


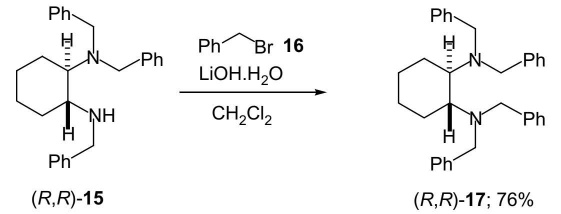
Scheme 3.

good yield. We now report an extension to our methodology for the synthesis of *N*,*N*′-trisubstituted 1,2-diamines, and we discuss their functionalisation as an efficient method for the formation of unsymmetrical *N*,*N*′-tetrasubstituted 1,2-diamines.

We initially focused our attention towards the synthesis of trisubstituted 1,2-diamine (*R*,*R*)-**15** (Scheme 4). We chose to study the simple reduction of aminal (*R*,*R*)-**14**—synthesised by condensation[8] of benzaldehyde with the *N*,*N*′-dibenzyl 1,2-diamine (*R*,*R*)-**13**[9] in 90% yield—as a potential method for constructing the trisubstituted 1,2-diamine (*R*,*R*)-**15** (Scheme 4). Simple addition of the aminal (*R*,*R*)-**14** to a stirred solution of sodium borohydride in absolute ethanol gave, after 12 h the required *N*,*N*′-tribenzyl 1,2-diamine (*R*,*R*)-**15** in 79% yield (Scheme 4).



Scheme 4.

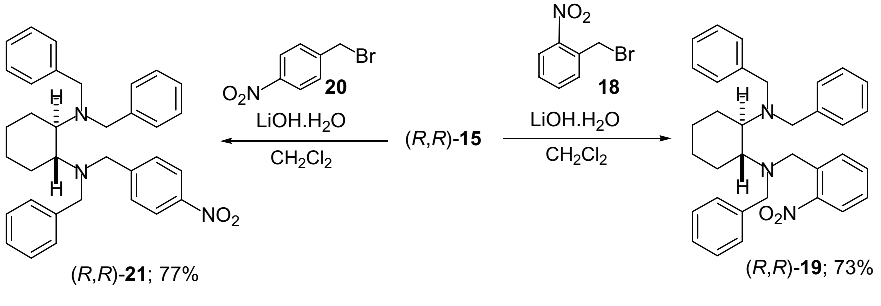


Scheme 5.

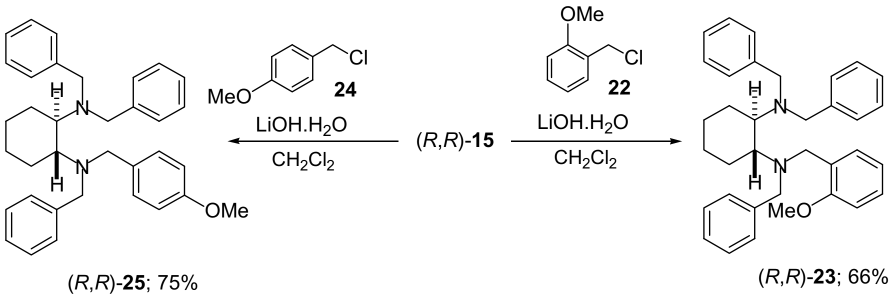
With this 1,2-diamine (*R*,*R*)-**15** in hand, we next investigated its direct *N*-alkylation using our standard reaction protocol[6] (e.g., alkylating agent and $LiOH{\cdot}H_2O$ in dichloromethane) as a method for synthesising *N*,*N*′-tetrasubstituted 1,2-diamines. We first used benzyl bromide **16** as the alkylating agent as this would lead to the known symmetrically tetrasubstituted 1,2-diamine (*R*,*R*)-**17**[6] (Scheme 5). Addition of benzyl bromide **16** to a stirred solution of trisubstituted 1,2-diamine (*R*,*R*)-**15** and $LiOH{\cdot}H_2O$ in dichloromethane gave, after 12 h, the C_2-symmetric *N*,*N*′-tetrabenzyl 1,2-diamine (*R*,*R*)-**17**[6] in good yield (Scheme 5). We next focused on the use of substituted bromides **18**, **20** and **26**, and chlorides **22** and **24**, in an attempt to synthesise unsymmetrically *N*,*N*′-tetrasubstituted 1,2-diamines (Schemes 6–8). Addition of the trisubstituted 1,2-diamine (*R*,*R*)-**15** to a stirred solution of lithium hydroxide monohydrate and bromides **18**, **20** and **26**, and chlorides **22** and **24** in dichloromethane gave, after 12 h, the tetrasubstituted 1,2-diamines (*R*,*R*)-**19**, (*R*,*R*)-**21**, (*R*,*R*)-**23**, (*R*,*R*)-**25** and (*R*,*R*)-**27** in moderate to good yield (Schemes 6–8). This protocol appears to be efficient for a wide variety of structurally related activated bromides **16**, **18**, **20** and **26** and chlorides **22** and **24**.

We next turned our attention towards the synthesis of unsymmetrically trisubstituted 1,2-diamines (*R*,*R*)-**34**–**39** by reduction of the corresponding aminals (*R*,*R*)-**28**–**33** (Scheme 9). These reductions proceed smoothly leading to the required trisubstituted 1,2-diamines (*R*,*R*)-**34**–**38** in good yield. However, for the remaining aminal (*R*,*R*)-**33**, reduction to give the related 1,2-diamine (*R*,*R*)-**39** did not occur. This may presumably be due to the electron-withdrawing nitro-substituent disfavouring formation of the intermediate (positively charged) iminium ion.

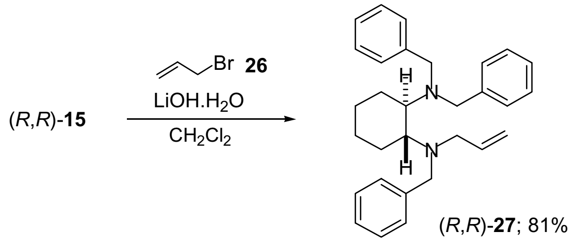
We next studied the alkylation of these unsymmetrically *N*,*N*′-trisubstituted 1,2-diamines as a method for the formation of unsymmetrically *N*,*N*′-tetrasubstituted 1,2-diamines. Addition of these trisubstituted 1,2-diamines (*R*,*R*)-**34**–**37** to a stirred solution of lithium hydroxide monohydrate and bromides **16** and **26** in dichloromethane, gave the required tetrasubstituted 1,2-diamines (*R*,*R*)-**40**, (*R*,*R*)-**42** and (*R*,*R*)-**44**, and



Scheme 6.



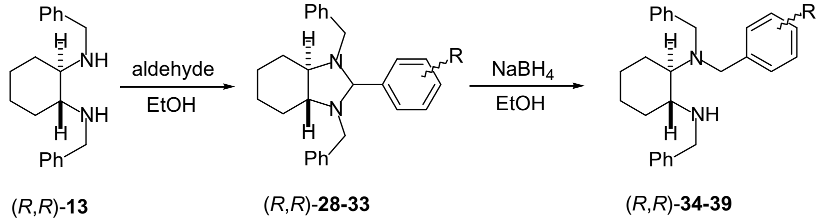
Scheme 7.

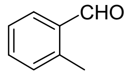
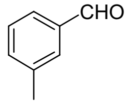
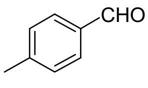
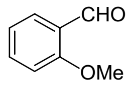
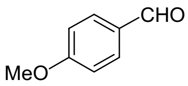
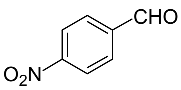


Scheme 8.

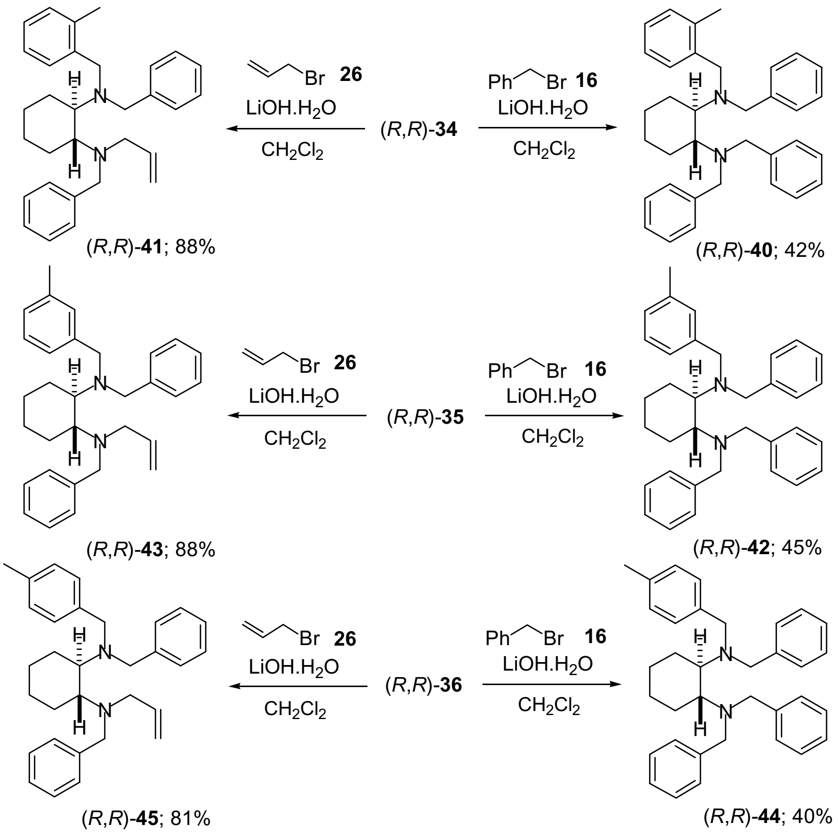
(*R*,*R*)-**41**, (*R*,*R*)-**43**, (*R*,*R*)-**45**, (*R*,*R*)-**46** and (*R*,*R*)-**47** in good yield (Schemes 10 and 11).

We next probed the structural nature of the parent *N*,*N*′-disubstituted diamine to investigate the scope and limitations of this methodology. We first studied the synthesis of trisubstituted 1,2-diamine (*R*,*R*)-**50** derived from the known *N*,*N*′-di-2-methoxybenzyl 1,2-diamine (*R*,*R*)-**48**[10] (Scheme 12). Addition of benzaldehyde to 1,2-diamine (*R*,*R*)-**48** gave the aminal (*R*,*R*)-**49** (in 76% yield) and reduction with sodium



Entry	Aldehyde	$\xrightarrow{(R,R)\text{-}\mathbf{13}}$ Aminal	$\xrightarrow[\text{EtOH}]{\text{NaBH}_4}$ Diamine
1		(*R*,*R*)-**28**; 85%	(*R*,*R*)-**34**; 56%
2		(*R*,*R*)-**29**; 85%	(*R*,*R*)-**35**; 83%
3		(*R*,*R*)-**30**; 81%	(*R*,*R*)-**36**; 87%
4		(*R*,*R*)-**31**; 75%	(*R*,*R*)-**37**; 86%
5		(*R*,*R*)-**32**; 76%	(*R*,*R*)-**38**; 83%
6		(*R*,*R*)-**33**; 91%	(*R*,*R*)-**39**; 0%

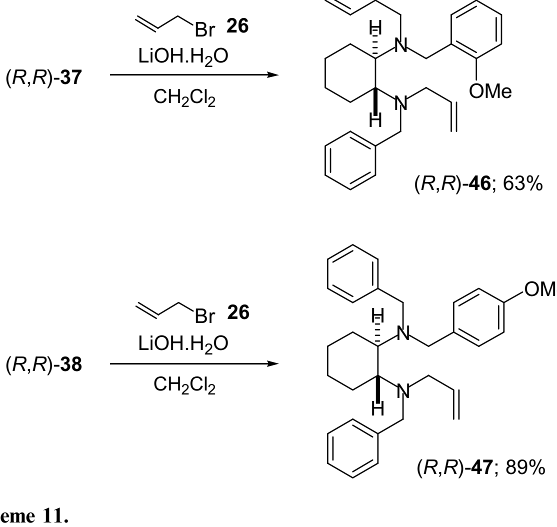
Scheme 9.



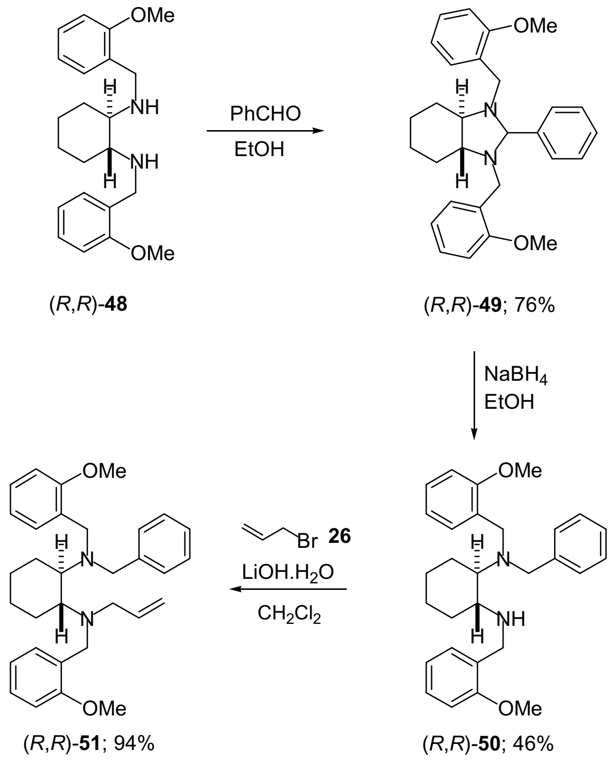
Scheme 10.

borohydride in absolute ethanol gave the required trisubstituted 1,2-diamine (*R*,*R*)-**50** in 46% yield. This was converted to the unsymmetrically *N*,*N*′-tetrasubstituted 1,2-diamine (*R*,*R*)-**51** in 94% yield by simple addition of allyl bromide **26** and lithium hydroxide monohydrate in dichloromethane (Scheme 12).

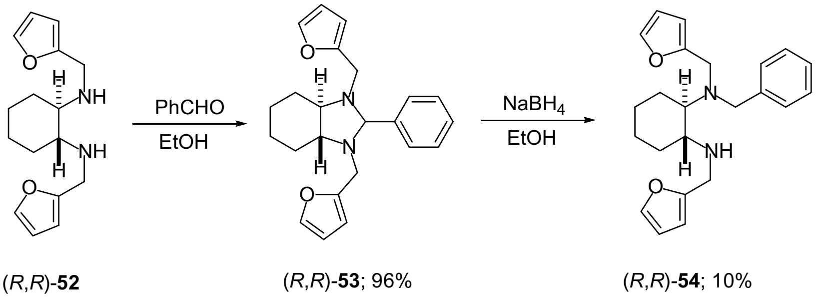
In addition, we studied the use of *N*,*N*′-difuryl 1,2-diamine (*R*,*R*)-**52** as our parent disubstituted 1,2-diamine (Scheme 13). The corresponding aminal (*R*,*R*)-**53** was efficiently synthesised in 96% yield by condensation with benzaldehyde. However, reduction using sodium



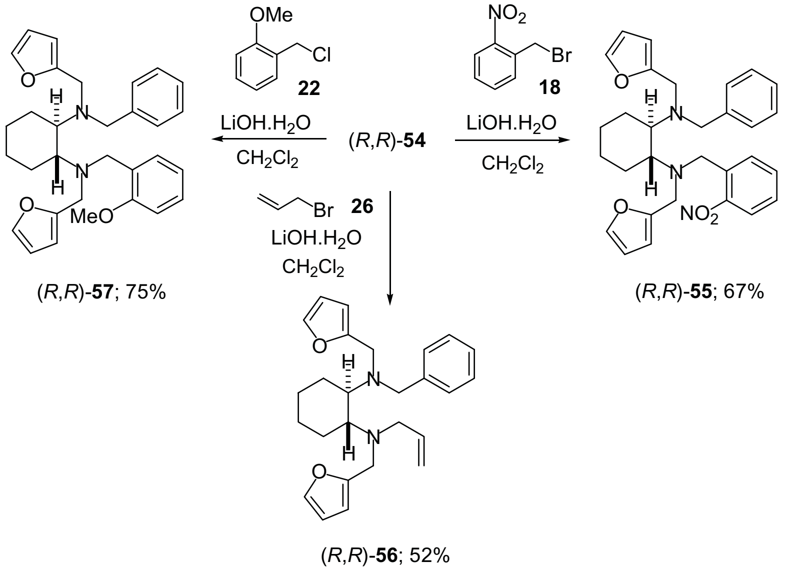
Scheme 11.



Scheme 12.



Scheme 13.



Scheme 14.

borohydride under our standard conditions proceeded slowly to give the trisubstituted 1,2-diamine (*R*,*R*)-**54** in low yield. However, this 1,2-diamine (*R*,*R*)-**54** was efficiently converted to the required unsymmetrical tetrasubstituted 1,2-diamines (*R*,*R*)-**55**–**57** by simple addition to a solution of lithium hydroxide monohydrate and bromides **18** and **26**, and chloride **22** in dichloromethane (Scheme 14).

In conclusion, we report an efficient and practical route for the synthesis of tri- and tetrasubstituted 1,2-diamines [e.g., (*R*,*R*)-**15** and (*R*,*R*)-**27**] derived from readily available *N*,*N*′-disubstituted 1,2-diamines [e.g., (*R*,*R*)-**13**]. From this study, it appears the structural nature of the substituents present in the trisubstituted 1,2-diamines (*R*,*R*)-**15**, (*R*,*R*)-**34**–**38**, (*R*,*R*)-**50** and (*R*,*R*)-**54** plays little or no role within formation of these tetrasubstituted 1,2-diamines (*R*,*R*)-**17**, (*R*,*R*)-**19**, (*R*,*R*)-**21**, (*R*,*R*)-**23**, (*R*,*R*)-**25**, (*R*,*R*)-**27**, (*R*,*R*)-**40**–**47**, (*R*,*R*)-**51** and (*R*,*R*)-**55**–**57**. However, reduction of the corresponding aminal was found to be dependent on the structural nature of the *N*,*N*′-substituents. The presence of an electron deficient group [e.g., a 4-nitrobenzyl substituent in (*R*,*R*)-**33** and a furyl ring in (*R*,*R*)-**53**] appears to disfavour formation of the intermediate iminium ion and consequently lowers the rate of reduction. These particular tri- and tetrasubstituted 1,2-diamines are valuable synthetic products as related 1,2-diamines[11] have been shown to be useful chiral mediators for a wide variety of important stereoselective transformations.[12]

2. Representative experimental procedures

2.1. (−)-2-Phenyl-1,3-dibenzyloctahydrobenzoimidazole (*R*,*R*)-14

Benzaldehyde (1.43 g, 1.37 mL, 13.5 mmol) was added to a stirred solution of *N*,*N*′-dibenzyldiaminocyclohexane (*R*,*R*)-**13** (3.96 g, 13.5 mmol) in absolute ethanol (20 mL). The resulting solution was stirred for 2 h. The reaction solvent was removed under vacuum to give the 2-phenyl-1,3-dibenzyloctahydrobenzoimidazole (*R*,*R*)-**14** (4.64 g, 90%) as a yellow oil; $[\alpha]_D^{22}$ −45.5 (*c* 1.0, $CHCl_3$); δ_H (270 MHz, $CDCl_3$): 7.20–7.00 (15H, br m, 15 × H; 3 × Ph), 4.59 (1H, s, NCHN), 3.81 (1H, d, *J* 13.8 Hz, CH_AH_BPh), 3.64 (1H, d, *J* 13.8 Hz, CH_AH_BPh), 3.53 (1H, d, *J* 14.6 Hz, CH_CH_DPh), 3.28

(1H, d, J 14.6 Hz, CH_CH_DPh), 2.79 (1H, br m, NCH), 2.47 (1H, br m, NCH), 1.73 (4H, br m, 4 × CH) and 1.21 (4H, br m, 4 × CH); δ_C (100 MHz, $CDCl_3$): 129.8, 129.0, 128.5, 128.2, 127.8, 127.5, 127.0 and 126.3 (8 × CH; 3 × Ph) 85.7 (NCN), 68.6 (NCH_2Ph), 67.5 (NCH_2Ph), 56.4 (NCH), 52.3 (NCH), 30.5 (CH_2), 29.9 (CH_2) and 24.5 (2 × CH_2).

2.2. (−)-(*R*,*R*)-*N*,*N*,*N*′-Tribenzyl-1,2-diaminocyclohexane 15

Sodium borohydride (2.27 g, 60.6 mmol) was cautiously added to a solution of aminal (*R*,*R*)-**14** (4.64 g, 12.1 mmol) in ethanol (50 mL). The resulting solution was stirred for 1 h at room temperature and reflux for a further 12 h. The solvent was removed under vacuum. The residue was dissolved in dichloromethane (20 mL). Dilute aqueous HCl (1 M, 3 mL) was added dropwise until the effervescence ceased. The organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure to give (−)-(*R*,*R*)-*N*,*N*,*N*′-tribenzyl-1,2-diaminocyclohexane **15** (3.67 g, 79%) as a yellow oil; $[\alpha]_D^{22}$ −46.2 (*c* 2.9, $CHCl_3$); ν_{max} (NaCl)/cm^{-1} 3301 (N–H), 2804, 1604, 1496, 1454, 1311 and 1026; δ_H (270 MHz, $CDCl_3$): 7.22–7.15 (15H, m, 15 × CH; 3 × Ph), 3.87 (1H, d, J 13.9 Hz, CH_AH_BPh), 3.74 (2H, d, J 13.7 Hz, 2 × CH_AH_BPh), 3.51 (1H, d, J 13.9 Hz, CH_AH_BPh), 3.40 (2H, d, J 13.7 Hz, 2 × CH_AH_BPh), 2.49 (2H, br m, 2 × NCH), 2.12 (1H, m, CH), 2.01 (1H, m, CH), 1.80 (2H, m, 2 × CH), 1.67 (1H, br s, NH) and 1.20 (4H, br m, 4 × CH); δ_C (67.5 MHz, $CDCl_3$): 141.0, 140.0, 130.0, 129.1, 128.8, 128.4, 128.2, 127.8, 127.6, 127.4, 126.9 and 126.6 (12 × C; 3 × Ph), 62.1 (CN), 57.9 (CN), 53.8 (CN), 53.6 (CN), 51.5 (CN), 31.8, 25.8, 24.7 and 22.8 (4 × CH_2).

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