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Synthesis of *N*,*N*′-disubstituted cyclic 1,2-diamines derived from (1*R*,2*R*)-1,2-diaminocyclohexane

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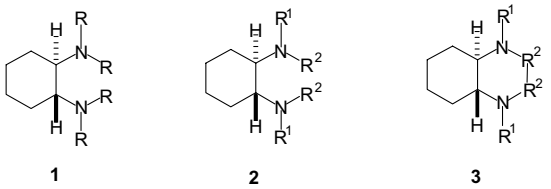
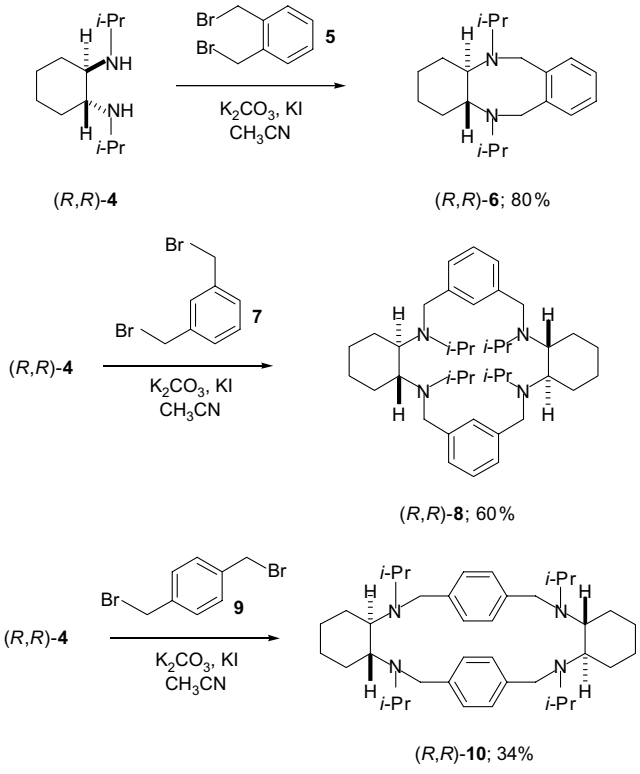
Abstract—The synthesis of *N*,*N*′-unsymmetrically tetrasubstituted cyclic 1,2-diamines derived from (1*R*,2*R*)-diaminocyclohexane is reported. We comment on the structural nature of these cyclic 1,2-diamines and discuss their characteristic features.

The synthesis of enantiomerically pure symmetrically[1] and unsymmetrically[2] *N*,*N*′-tetrasubstituted 1,2-diamines like **1** and **2** are well documented (Scheme 1). These diamines have been synthesised by either direct alkylation[3] or reductive amination[2,4] of the parent 1,2-diamine.[5] Whereas, reports into the synthesis of *N*,*N*′-tetrasubstituted cyclic 1,2-diamines like **3** are less common (Scheme 1).[6] Periasamy[7] has recently reported an efficient route for the synthesis of a variety of substituted cyclic diamines (*R*,*R*)-**6**, (*R*,*R*)-**8** and (*R*,*R*)-**10** using a series of structurally related dibenzylbromides **5**, **7** and **9**, and di*iso*propyldiamine (*R*,*R*)-**4** (Scheme 2). These different cyclisation pathways appear to be predictable and clearly allow efficient access to 8-membered ring diamines, and 18- and 20-membered ring cyclic tetraamines in moderate to good yield (Scheme 2).



Scheme 1.



Scheme 2.

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We have recently become interested[8] in the synthesis of symmetically and unsymmetrically *N*,*N*′-tetrasubstituted

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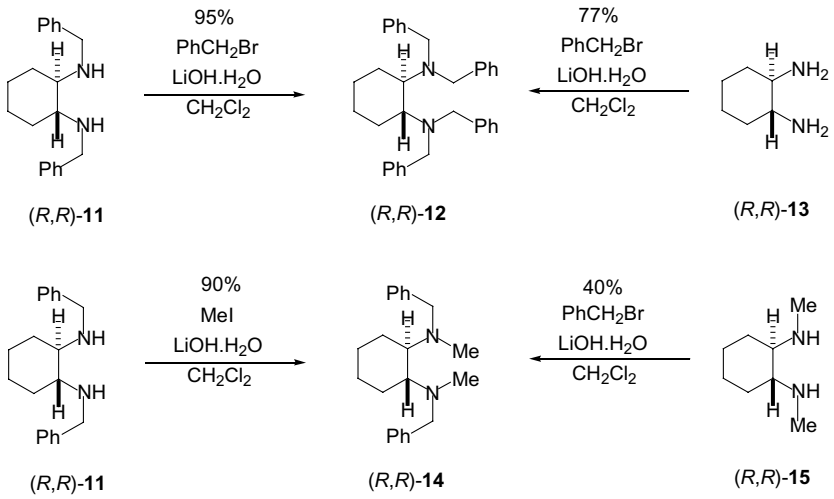


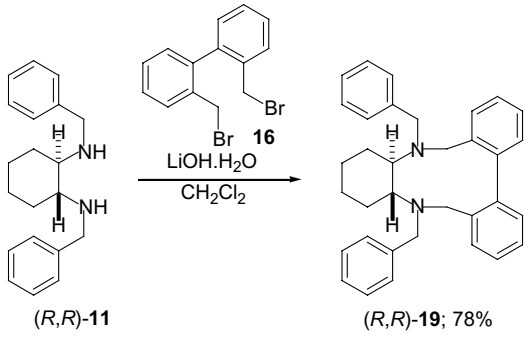
Scheme 3.

diamines like (*R*,*R*)-**12** and (*R*,*R*)-**14** by sequential alkylation of the corresponding parent diamines (*R*,*R*)-**11**,[9] (*R*,*R*)-**13** and (*R*,*R*)-**15** using benzyl bromide and methyl iodide as alkylating agents mediated by lithium hydroxide monohydrate ($LiOH{\cdot}H_2O$) as the base (Scheme 3).

Prompted by Periasamy's report,[7] we now disclose an extension of our methodology towards the synthesis of nine and 10-membered *N*,*N*′-tetrasubstituted cyclic 1,2-diamines derived from (1*R*,2*R*)-diaminocyclohexane **13** using a variety of multi-benzylating agents, including dibromide **16**, dichloride **17** and tetrabromide **18** (Scheme 4).

We first probed the dibenzylation of the dibenzyldiamine (*R*,*R*)-**11** using a 1,6-dibromide **16** due to its similarity to the corresponding double benzylation using 2 equiv of benzyl bromide (Schemes 3 and 5). Addition of the 1,6-dibromide **16** to a stirred solution of dibenzyldiamine (*R*,*R*)-**11**[9] and lithium hydroxide monohydrate in dichloromethane gave, after stirring for 12 h, the cyclic 1,2-diamine (*R*,*R*)-**19** as a single product in excellent yield (Scheme 5).

Formation of a single homologue (*R*,*R*)-**19** was confirmed by mass spectrometry and its structural nature was determined by single crystal X-ray diffraction (Fig. 1).[10] It is particularly interesting to note, the conformational arrangement of each benzyl substitutent present within this 1,2-diamine; one benzyl group is positioned pseudo-axial and the other benzyl substituent is positioned pseudo-equatorial with respect to the adjacent 1,2-diaminocyclohexane ring. These benzylic positions are evidently not equivalent and consequently this diamine (*R*,*R*)-**19** is non-C_2-symmetric in its crystal phase. The remaining biphenyl substituent was positioned similarly, with one benzylic position oriented pseudo-axial and the remaining benzylic position oriented pseudo-equatorial. This conformational arrangement induces axial chirality within the biaryl framework. The conformational preference of this cyclic diamine (*R*,*R*)-**19** was found to be surprisingly similar to that of related non-cyclic tetrabenzylsubstituted 1,2-diamines.[8,10]



Scheme 5.

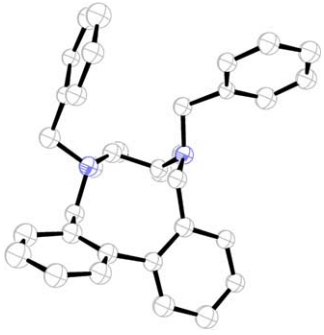
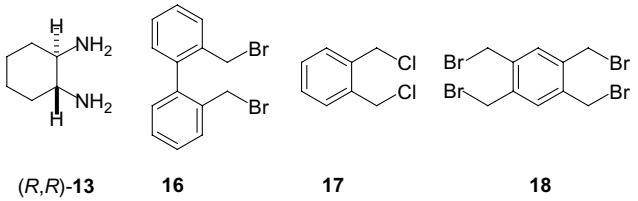
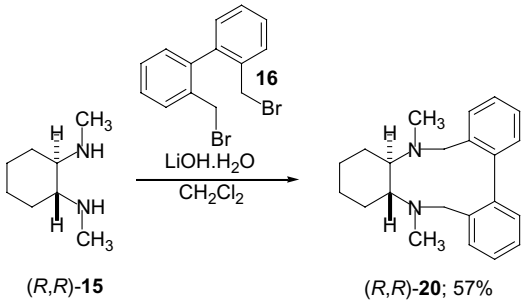


Figure 1. ORTEP diagram of diamine (*R*,*R*)-**19**.



Scheme 4.



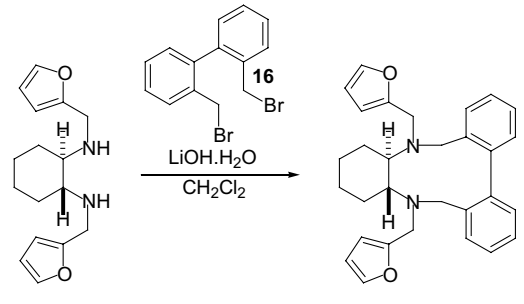
(*R*,*R*)-**15** (*R*,*R*)-**20**; 57%

Scheme 6.

We next turned our attention to probing the efficiency of this ring forming reaction by screening a variety of structurally related disubstituted diamines (*R*,*R*)-**15**,[11] (*R*,*R*)-**21**,[12] (*R*,*R*)-**23**,[13] (*R*,*R*)-**25**, (*R*,*R*)-**27** and (*R*,*R*)-**29** (Schemes 6–8). Addition of the 1,6-dibromide **16** to a stirred solution of diamines (*R*,*R*)-**15**, (*R*,*R*)-**21**, (*R*,*R*)-**23**, (*R*,*R*)-**25**, (*R*,*R*)-**27** and (*R*,*R*)-**29** and lithium hydroxide monohydrate in dichloromethane gave, after stirring for 12 h, the required cyclic 1,2-diamines (*R*,*R*)-**20**, (*R*,*R*)-**22**, (*R*,*R*)-**24**, (*R*,*R*)-**26**, (*R*,*R*)-**28** and (*R*,*R*)-**30**, respectively, in moderate to good yield (Schemes 6–8). It appears that the structural nature of these 1,2-diamines plays little or no role within these ring-forming processes.

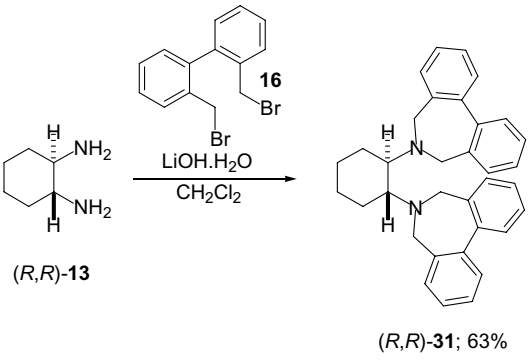
However, it was found that a secondary diamine was necessary for cyclic 1,2-diamine formation, as a primary diamine [e.g., (*R*,*R*)-**13**] was shown to form efficiently the corresponding C_2-symmetric tetrasubstituted diamine (*R*,*R*)-**31** in good yield (Scheme 9).

We next chose to investigate the use of a related 1,4-dichloride **17** in an attempt to synthesise structurally



(*R*,*R*)-**29** (*R*,*R*)-**30**; 40%

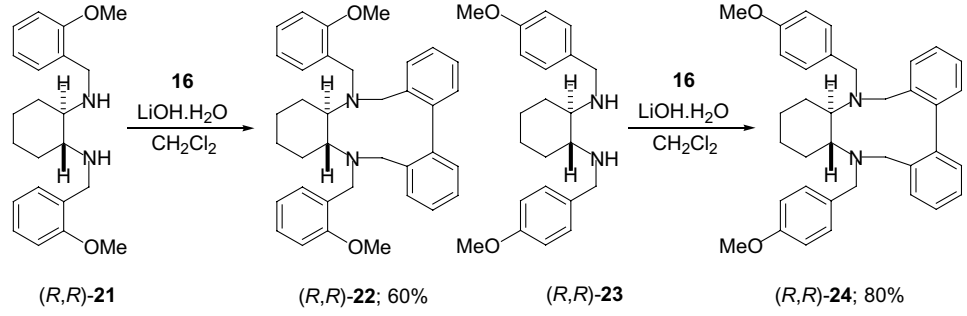
Scheme 8.



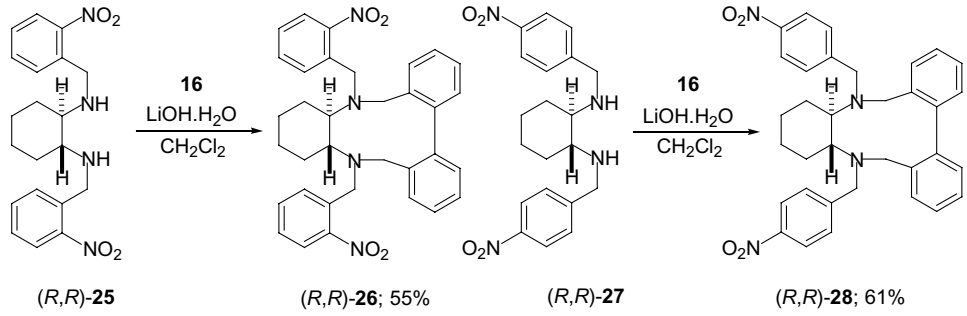
(*R*,*R*)-**13** (*R*,*R*)-**31**; 63%

Scheme 9.

unusual 8-membered ring 1,2-diamines (Schemes 10 and 11). Addition of 1,4-dichloride **17** to a stirred solution of disubstituted diamines (*R*,*R*)-**11**,[9] (*R*,*R*)-**15**,[11] (*R*,*R*)-**21**,[12] (*R*,*R*)-**23**,[13] (*R*,*R*)-**25**, (*R*,*R*)-**27** and (*R*,*R*)-**29** and lithium hydroxide monohydrate in dichloromethane under our standard reaction conditions, gave

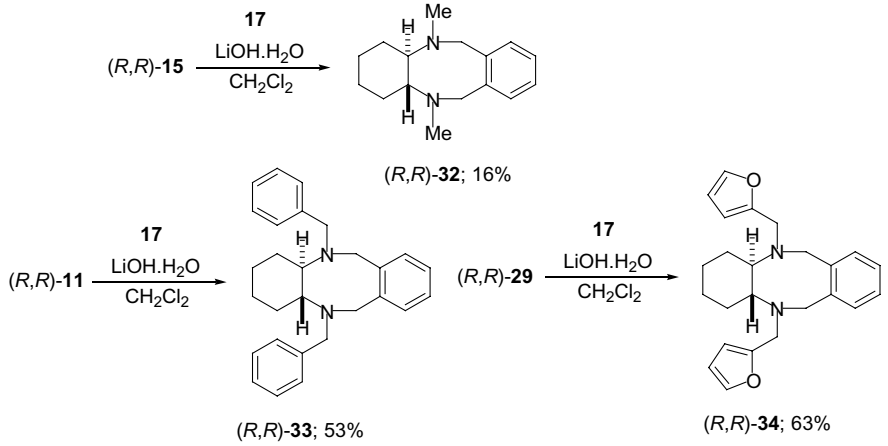


(*R*,*R*)-**21** (*R*,*R*)-**22**; 60% (*R*,*R*)-**23** (*R*,*R*)-**24**; 80%

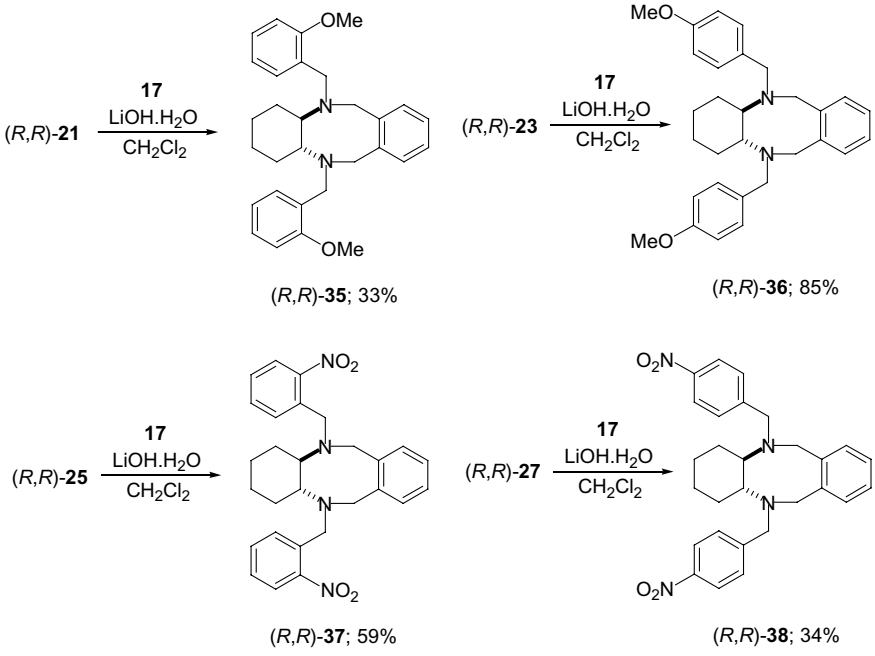


(*R*,*R*)-**25** (*R*,*R*)-**26**; 55% (*R*,*R*)-**27** (*R*,*R*)-**28**; 61%

Scheme 7.



Scheme 10.



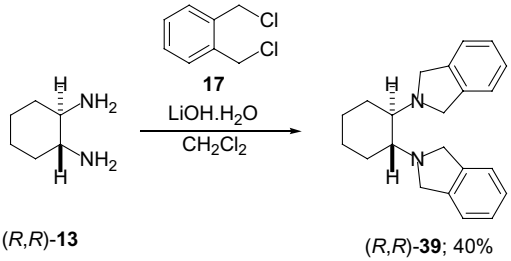
Scheme 11.

the required cyclic 1,2-diamines (*R*,*R*)-**32**–**38** in moderate to good yield (Schemes 10 and 11).

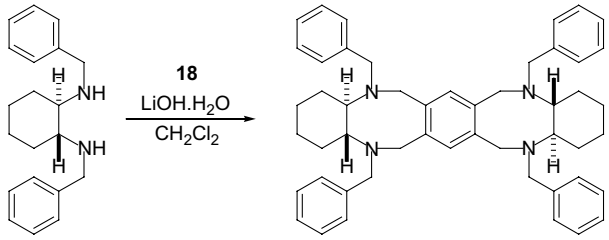
We have shown that ring formation is efficient for a range of structurally diverse disubstituted diamines (*R*,*R*)-**11**, (*R*,*R*)-**15**, (*R*,*R*)-**29** and found independently in line with Periasamy's findings[7] that no higher homologues were formed (determined by mass spectrometry). The use of a secondary diamine was also paramount for 8-membered ring formation as cyclisation to form the corresponding symmetrically substituted diamine (*R*,*R*)-**39** was evidently preferred for the corresponding primary diamine (*R*,*R*)-**13** (Scheme 12).[8,14]

However, addition of 1,2,4,5-tetrakis(bromomethyl)-benzene bromide **18** to a stirred solution of dibenzyl diamine (*R*,*R*)-**11** in dichloromethane under our standard reaction conditions, gave the unusual cyclic tetraamine (*R*,*R*,*R*,*R*)-**40** in good yield (Scheme 13). Formation of this tetraamine **40** as the sole product was confirmed by mass spectrometry and NMR spectroscopy.

In conclusion, we report an efficient and practical route for the synthesis of disubstituted cyclic 1,2-diamines (*R*,*R*)-**19**, (*R*,*R*)-**20**, (*R*,*R*)-**22**, (*R*,*R*)-**24**, (*R*,*R*)-**26**,



Scheme 12.



Scheme 13.

(*R*,*R*)-**28**, (*R*,*R*)-**30** and (*R*,*R*)-**32**–**38** derived from the corresponding disubstituted diamines (*R*,*R*)-**11**, (*R*,*R*)-**15**, (*R*,*R*)-**21**, (*R*,*R*)-**23**, (*R*,*R*)-**25**, (*R*,*R*)-**27** and (*R*,*R*)-**29**, and dibromide **16** and dichloride **17**. Intramolecular cyclisation to form these cyclic 1,2-diamines is evidently more preferred than intermolecular cyclisation to form related tetraamine homologues. However, cyclic tetraamines like (*R*,*R*,*R*,*R*)-**40** can be efficiently synthesised by use of a suitable alkylating agent, 1,2,4,5-tetrakis(bromomethyl)benzene bromide **18**. The use of a secondary diamine is paramount for formation of cyclic 1,2-diamines as primary diamines [e.g., (*R*,*R*)-**13**] prefer to cyclise to form the corresponding symmetrically substituted diamines (*R*,*R*)-**31** and (*R*,*R*)-**39** in good yield. Previous reports into the synthesis of cyclic amines and imines derived from (1*R*,2*R*) diaminocyclohexane have utilised related alkylations[15] and condensation processes involving aldehydes[16] and dialdehydes.[17]

Representative experimental procedure: (+)-*N*,*N*′-Dibenzyl-(7*R*,8*R*)-dicyclohexano-5,6,7,8,9,10-hexahydro-6,9-diaza-dibenzo[*a*,*c*]cyclodecene **19**: 2,2′-Bis(bromomethyl)-1,1′-diphenyl **16** (0.60 g, 1.76 mmol) was added to a stirred solution of (−)-(*R*,*R*)-*N*,*N*′-dibenzyldiaminocyclohexane **11** (0.20 g, 1.76 mmol) in dichloromethane (10 mL) at room temperature. Two portions of lithium hydroxide monohydrate (75 mg, 1.76 mmol) were added after four and 8 h. The resulting solution was stirred for 12 h. Water (10 mL) was added and the resulting layers separated. The aqueous layer was washed with dichloromethane (2 × 30 mL), and the combined organic extracts were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography, initially eluting with light petroleum (40–60 °C)/diethyl ether (9:1), then light petroleum (40–60 °C)/diethyl ether (1:1) to give (+)-*N*,*N*′-dibenzyl-(7*R*,8*R*)-dicyclohexano-5,6,7,8,9,10-hexahydro-6,9-diaza-dibenzo[*a*,*c*]cyclodecene **19** (0.64 g, 78 %) as a small white needles; R_f [(light petroleum (40–60 °C)/diethyl ether) 9:1] = 0.38; $[\alpha]_D^{22}$ +112.2 (*c* 0.9, $CHCl_3$); ν_{max} (film)/cm^{-1} 3055, 2927, 2854, 1596 and 1504; δ_H (270 MHz, $CDCl_3$) 7.58 (1H, d, *J* 7.2, 1 × CH; biaryl), 7.34 (4 H, br s, 4 × CH; biaryl), 7.27 (4H, br m, 4 × CH; Ph), 7.19 (2H, br s, 2 × CH; biaryl), 7.13 (6H, br m, 6 × CH; Ph), 7.03 (1H, br d, *J* 7.2, 2 × CH; biaryl), 4.46 (1H, d, *J* 12.9, 1 × CH_AH$_B$biaryl), 4.31 (1H, d, *J* 12.9, 1 × CH_AH$_B$biaryl), 3.68 (2H, dd, *J* 13.1 and 6.7, 2 CH_AH$_B$Ar), 3.37 (2H, dd, *J* 8.9 and 5.7, 2 × CH_AH$_B$Ar), 3.18 (1H, d, *J* 12.8 Hz, 1 × CH$_A$$H_B$-Ar), 2.71 (2H, br m, 2 × CHN), 2.55 (1H, d, *J* 14.8 Hz, 1 × CH$_A$$H_B$biaryl), 2.08 (1H, br m, 1 × CH), 1.71 (3H, br m, 3 × CH) and 0.99 (4H, br m, 4 × CH); δ_C (100 MHz, $CDCl_3$) 142.3, 142.2, 141.8, 140.2, 139.2, 136.6, 131.8, 130.7, 128.9, 127.9, 127.8, 127.4, 127.0, 126.9, 126.7, 126.1, 60.0, 54.8, 54.4, 53.4, 50.8, 50.4, 32.3, 26.1, 25.3 and 22.6. (Found M+H$^+$, 473.2951 $C_{34}H_{37}N_2$ requires M+H$^+$ 473.2957.)

Acknowledgements

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