Synthesis and Characterisation of Macrocyclic Diamino Chiral Crown Ethers

Waldo H. Correa* and Janet L. Scott

Centre for Green Chemistry, Monash University, P.O. Box 23, Victoria, 3800, Australia. Tel: (+61) 3 9905 4102, Fax: (+61) 3 9905 4597.

* Author to whom correspondence should be addressed: e-mail: waldo.correa@sci.monash.edu.au

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Abstract: A benign and efficient synthesis of chiral macrocyclic ‘aza-crown’ ethers of varying ring size is reported. The synthesis involves a Schiff base condensation of ether linked dialdehydes of varying chain length and (1R,2R)-(–)-1,2-diaminocyclohexane under mild conditions to yield the macrocycles, which are subsequently reduced to yield the diamino analogues.

Keywords: Chiral diamino macrocycles, ether linked dialdehydes

Introduction

In 1998 Kaupp reported the facile solvent-free condensation of aryl amines and benzaldehyde derivatives to produce azo-methines [1]. This is an advantageous and facile route as it negates the generation of excessive waste whilst proceeding more efficiently than corresponding solution phase methodologies. This approach has subsequently been extended to corresponding amine derivatives such as the tetrahydroquinazolines [2]. More recently, we have adopted an analogous, simple procedure that allows for the efficient generation of some macrocycles derived from the reduction of
Schiff bases formed using enantiomerically pure diamine precursors. We now report the synthesis of a number of novel, chiral, macrocycles not previously described or tested for this application.

Results and Discussion

Dialdehydes 1 are condensed with enantiomerically pure trans-cyclohexanediamine to form the Schiff base 2 followed by reduction with sodium borohydride to afford the aza crown analogues 3 (Scheme 1). The synthesis of dialdehyde ether linkers 1 has been reported previously [3,4] and involves the conversion of glycols to di-bromo ethers followed by a Williamson etherification of salicylaldehyde to yield the desired precursors. We were able, through some minor modifications and application of novel microwave technology, to improve upon the overall efficiency of this preliminary process.

Compounds 2a and 2b could be synthesised in the absence of solvent by simply grinding the reactants together at room temperature, however, this neat approach was not as effective for 2c and 2d, as dialdehydes 1c and 1d are oils at room temperature. In these instances Schiff base formation was achieved in ethanolic solutions, the product separating as an oil. Reaction times and yields for both steps are included in Table 1.

![Scheme 1](image)

Table 1: Reaction Times and Yields of Schiff Base and Diamino Macrocycles.

| Compound | Time (mins) | Yield (%) | Compound | Time (h) | Yield (%) |
|----------|-------------|-----------|----------|----------|-----------|
| 2a       | 25          | 89        | 3a       | 4        | 80        |
| 2b       | 20          | 95        | 3b       | 4.5      | 91        |
| 2c       | 30          | 95        | 3c       | 5        | 92        |
| 2d       | 30          | 95        | 3d       | 5        | 91        |

1a : n = 0  
1b : n = 1  
1c : n = 2  
1d : n = 3  
2a : n = 0  
2b : n = 1  
2c : n = 2  
2d : n = 3  
3a : n = 0  
3b : n = 1  
3c : n = 2  
3d : n = 3
In most cases the reduced macrocyclic products 3 were isolated as oils. Subsequent purification involved the precipitation of hydrochloride salts by reaction with excess hydrochloride in ether. The $^1$H- and $^{13}$C-NMR spectra of the respective Schiff bases 2 and diamino products 3 were consistent with the assigned structures in all cases. There was no spectroscopic evidence for the presence of any imine protons once the reduction had been performed. This reduction step needed to be conducted under relatively forcing conditions, utilising a vast excess of reducing agent and at elevated temperature, as the macrocycles 2 were poorly soluble in ethanol.

All of the macrocycles synthesised are optically active. The absence of peaks at higher m/z values than that expected for the corresponding parent ion (LH$^+$) in the electrospray ionisation mass spectra attest to exclusive formation of 1:1 condensation products. The Schiff base infrared spectra confirms the presence of the imine C=N stretch with a sharp band in the region 1630-1640 cm$^{-1}$. These bands are absent in the reduced product. The HCl salts are all hygroscopic, and in the case of 3a and 3d, there was microanalytical as well as spectral evidence for the formation of 1:1 hydrates. In addition, the salts appear to complex common solvents, which are subsequently difficult to remove, even under vacuum at elevated temperature. The presence of solvates, was inferred from the existence of corresponding signals in $^1$H-NMR and infrared spectra. Repeated attempts to crystallise the macrocycles resulted in oils or glasses, though the HCl salts are afforded as finely divided white solids.

Conclusions

We have developed a facile and high yielding route for the formation of a novel class of chiral diamino macrocyclic compounds incorporating ether chains.

Acknowledgements

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Experimental

General

All reagents were of 98 % purity or greater and used as obtained from the supplier unless noted otherwise. Grinding experiments were performed with porcelain mortar and pestles, which were rinsed with acetone and dried prior to use. All melting points were determined on an Electrochemical digital melting point apparatus. $^1$H-NMR and $^{13}$C-NMR spectra were recorded on either a Varian Mercury 300 MHz or Bruker DRX400MHz. spectrometers. Chemical shifts were referenced relative to CDCl$_3$ or CD$_3$OD. Electrospray Mass Spectroscopy (ESI) was carried out on a Micromass Platform II API QMS Electrospray Mass Spectrometer with cone voltage at 35 V, using acetone as the mobile phase. Analyses were conducted both in positive (ESI$^+$) and negative (ESI$^-$) mode. Infrared spectroscopy was
carried out on a Perkin Elmer FTIR-1600 with samples were prepared as KBr discs. Specific rotations were measured on a Hewlett Packard Polar 3005 polarimeter. Microanalyses were conducted on the HCl salts of the reduced macrocycles.

**General Procedure for the Synthesis of Diamino Macroycles**

An equimolar quantity of the relevant dialdehyde 1 together with (1R,2R)-(−)-1,2-diamino-cyclohexane was ground using a mortar and pestle at room temperature for approximately 5 minutes. The resultant powder was washed with cold ethanol; in the case of 2c and 2d the corresponding dialdehyde precursors are oils at room temperature and, consequently, the condensation was carried out in absolute ethanol at room temperature. After 20-30 min the oily products began to separate from solution; after 4.5 h the supernatant was decanted yielding the desired Schiff base. The larger macrocyclic products are all pale yellow oils, (only 2a is a solid), and were purified by washing with hot ethanol. The respective Schiff bases were combined with 10 mol equiv. of NaBH₄ in absolute ethanol. The reaction mixture was heated under reflux for 4-5 h, cooled and quenched with distilled water. Solvent was removed in vacuo and the product extracted into dichloromethane. The organic layer was washed twice with brine, dried with MgSO₄ and concentrated to afford the products as pale yellow oils. Spectroscopic data is given for the free base. The dihydrochloride salts were obtained by dissolving the oils in dichloromethane and adding an excess HCl in ether. White or pale yellow gummy solids formed instantly which were triturated and washed with hexane and filtered off.

1,12-Diaza-3,4;9,10-dibenzo-13,14-cyclohexo-5,8-dioxacyclobutadecane (2a). Isolated as a yellow solid (89%); m.p. 124-126 °C; ¹H-NMR (CDCl₃) δ: 1.41 (bs, 2H, 2 x CH), 1.74-1.98 (bm, 6H, 2 x CH & 2 x CH₂), 3.36 (bs, 2H, 2 x -C-CH-N=), 3.85-3.90 (m, 2H, 2 x Ar-CH), 4.05-4.11 (m, 2H, 2 x Ar-CH), 6.77-6.89 (2d, 4H, Ar-CH), 7.26 (m, 2H, Ar-CH), 7.83 (d, 2H, Ar-CH), 8.52 (s, 2H, -N=CH); ¹³C-NMR (CDCl₃) δ: 24.5, 32.9, 66.7 (-C-NH=), 73.7 (-C-O-C), 112.1 (Ar-C), 120.1 (Ar-C), 125.4 (Ar-C), 127.5 (Ar-C), 131.3 (Ar-C), 157.0 (Ar-C), 157.7 (-NH=C-); IR (cm⁻¹): 3080 (aromatic C-H stretch), 2928 and 2855 (C-H methylene stretch), 1634 (C=N stretch), 1599, 1486 and 1450 (C-C aromatic ring stretch), 1238 (aryl-O-CH₂ stretch), 1051 (in plane C-H bend), 735 (out of plane C-H bend), 428 (out of plane C-C bend); ESI-MS for C₂₂H₂₄N₂O₂ (MH⁺): Calc 349.2; Found 349.2; [α]₂⁰° = -30.0 (c = 0.012, CH₂Cl₂).

1,15-Diaza-3,4;12,13-dibenzo-16,17-cyclohexo-5,8,11-trioxacyclohexaundecane (2b). Isolated as a pale yellow gum (95%); ¹H-NMR (CDCl₃) δ: 1.44 (bs, 2H, 2 x CH), 1.80 (bs, 6H, 2 x CH & 2 x CH₂), 3.39 (bs, 2H, 2 x -C-CH-N=), 3.74 (t, 4H, -CH₂-O-CH₂), 3.90-4.00 (m, 2H, 2 x Ar-O-CH), 4.02-4.15 (m, 2H, 2 x Ar-O-CH), 6.80 (d, 2H, Ar-CH), 6.86 (t, 2H, Ar-CH) 7.24 (2t, 2H, Ar-CH), 7.82 (2d, 2H, Ar-CH), 8.61 (s, 2H, -N=CH-); ¹³C-NMR (CDCl₃) δ: 21.2, 34.1, 68.4 (-C-NH=), 69.6 (-C-O-C), 71.2 (Ar-C-O), 112.4 (Ar-C), 120.7 (Ar-C), 125.8 (Ar-C), 128.0 (Ar-C) 131.1 (Ar-C), 157.1 (Ar-C), 157.9 (-NH=C-); IR (cm⁻¹): 3080 (aromatic C-H stretch), 2928 and 2855 (C-H methylene stretch), 1634
(C=N stretch), 1601, 1491 and 1450 (C \( \equiv \) C aromatic ring stretch), 1243 (aryl-O-CH\(_2\) stretch), 1055 (in plane C-H bend), 751 (out of plane C-H bend); ESI-MS for C\(_{24}\)H\(_{28}\)N\(_2\)O\(_3\) (MH\(^+\)): Calc. 393.2; Found 393.1; \( [\alpha]_{D}^{16} = -28.1 \) (c = 0.005, CH\(_2\)Cl\(_2\)).

**1,18-Diaza-3,4;15,16-dibenzo-19,20-cyclohexo-5,8,11,14-tetraoxacyclododecane (2c).** Isolated as a viscous yellow oil (95%); \(^1\)H-NMR (CDCl\(_3\)) \( \delta \): 1.46 (bs, 2H, 2 x CH), 1.82 (bs, 6H, 2 x CH & 2 x CH\(_2\)), 3.4 (bs, 2H, 2 x -C-CH-N=), 3.70 (s, 4H, -O-CH\(_2\)-CH\(_2\)-O-), 3.75 (t, 4H, 2 x Ar-O-CH\(_2\)-CH\(_2\)-O-), 3.88-4.00 (m, 2H, 2 x Ar-O-CH), 4.02-4.13 (m, 2H, 2 x Ar-O-CH), 6.77 (d, 2H, Ar-CH), 6.86 (t, 2H, Ar-CH) 7.22 (2t, 2H, Ar-CH), 7.81 (2d, 2H, Ar-CH), 8.61 (s, 2H, -N=CH-); \(^{13}\)C-NMR (CDCl\(_3\)) \( \delta \): 24.5, 32.9, 67.8 (-C-NH=), 69.5 (Ar-O-C-CH\(_2\)-O-), 70.8 (Ar-O-C-CH\(_2\)-O-), 73.9 (Ar-O-C-), 112.1 (Ar-C), 120.9 (Ar-C), 125.2 (Ar-C), 127.8 (Ar-C) 131.0 (Ar-C), 156.9 (Ar-C-), 158.0 (-NH=C-); IR (cm\(^{-1}\)):
3080 (aromatic C-H stretch), 2926 and 2855 (C-H methylene stretch), 1635 (C=N stretch), 1600, 1488 and 1450 (C \( \equiv \) C aromatic ring stretch), 1247 (aryl-O-CH\(_2\) stretch), 1056 (in plane C-H bend), 754 (out of plane C-H bend), 428 (out of plane ring C \( \equiv \) C bend); ESI-MS for C\(_{26}\)H\(_{32}\)N\(_2\)O\(_4\) (MH\(^+\)): Calc. 437.2; Found 437.3; \( [\alpha]_{D}^{1.25} = -35.2 \) (c = 0.010, CH\(_2\)Cl\(_2\)).

**1,21-Diaza-3,4;18,19-dibenzo-22,23-cyclohexo-5,8,11,14,17-pentaoxacyclodecatridecane (2d).** A viscous yellow oil (95%); \(^1\)H-NMR (CDCl\(_3\)) \( \delta \): 1.48 (bt, 2H, 2 x CH), 1.83 (bs, 6H, 2 x CH & 2 x CH\(_2\)), 3.41 (bs, 2H, 2 x -C-CH-N=), 3.68 (s, 8H, -O-CH\(_2\)-CH\(_2\)-O-CH\(_2\)-CH\(_2\)-O-) 3.74 (t, 4H, 2 x Ar-O-CH\(_2\)-CH\(_2\)-O-), 3.90-4.00 (m, 2H, 2 x Ar-O-CH), 4.02-4.12 (m, 2H, 2 x Ar-O-CH), 6.77 (d, 2H, Ar-CH), 6.86 (t, 2H, Ar-CH) 7.23 (2t, 2H, Ar-CH), 7.80 (2d, 2H, Ar-CH), 8.60 (s, 2H, -N=CH-); \(^{13}\)C-NMR (CDCl\(_3\)) \( \delta \): 24.4, 32.9, 67.8 (-C-NH=), 69.4 (Ar-O-C-CH\(_2\)-O-), 70.6 (Ar-O-C-CH\(_2\)-O-), 70.7 (Ar-O-C-CH\(_2\)-O-), 73.8 (Ar-O-C), 112.1 (Ar-C), 120.7 (Ar-C), 125.2 (Ar-C), 127.3 (Ar-C) 131.2 (Ar-C), 157.0 (Ar-C-), 157.8 (-NH=C-); IR (cm\(^{-1}\)):
3080 (aromatic C-H stretch), 2929 and 2855 (C-H methylene stretch), 1653 (C=N stretch), 1600, 1488 and 1450 (C \( \equiv \) C aromatic ring stretch), 1247 (aryl-O-CH\(_2\) stretch), 1056 (in plane C-H bend), 754 (out of plane C-H bend), 428 (out of plane ring C \( \equiv \) C bend); ESI-MS for C\(_{28}\)H\(_{36}\)N\(_2\)O\(_4\) (MH\(^+\)): Calc. 481.3; Found 481.5; \( [\alpha]_{D}^{1.25} = -52.5 \) (c = 0.012, CH\(_2\)Cl\(_2\)).

**1,12-Diamino-3,4;9,10-dibenzo-13,14-cyclohexo-5,8-dioxacyclobutadecane (3a).** Isolated as an orange oil (80%); \(^1\)H-NMR (CDCl\(_3\)) \( \delta \): 0.93 (bt, 2H, 2 x CH), 1.14 (bt, 2H, 2 x CH), 1.64 (bd, 2H, 2 x CH), 2.00 (bd, 2H, 2 x CH), 2.13 (bd, 2H, 2 x -CH-N-), 3.58 (d, 2H, \( J = 13.2 \) Hz, 2 x -NH-CH\(_2\)-Ar-), 3.81 (d, 2H, \( J = 13.5 \) Hz, -NH-CH\(_2\)-CH\(_2\)-Ar-), 5.58 (s, 4H, -O-CH\(_2\)-CH\(_2\)-O-), 6.92 (bt, 2H, Ar-CH), 7.02-7.20 (m, 4H, Ar-CH), 7.25 (bd, 2H, Ar-CH); \(^{13}\)C-NMR (CDCl\(_3\)) \( \delta \): 24.9, 31.3, 45.6 (-NH-C-), 60.8 (-C-NH-), 90.6 (-O-C-O-), 111.8 (Ar-C), 122.1 (Ar-C), 127.8 (Ar-C), 129.5 (Ar-C) 130.1 (Ar-C), 154.7 (Ar-C); IR (cm\(^{-1}\)):
3080 (aromatic C-H stretch), 2926 and 2855 (C-H methylene stretch), 1634 (C=N stretch), 1599, 1486 and 1450 (C \( \equiv \) N aromatic ring stretch), 1238 (aryl-O-CH\(_2\) stretch), 1051 (in plane C-H bend), 735 (out of plane C-H bend), 428 (out of plane ring C \( \equiv \) C bend); ESI-MS for
C_{22}H_{28}N_{2}O_{2} (MH\textsuperscript{+}): Calcd 353.2; Found 353.4; Anal. Calc. for C_{22}H_{28}N_{2}O_{2} 2HCl·H_{2}O: C, 59.6; H, 7.3; N, 6.3. Found: C, 59.4; H, 7.1; N, 6.1; [\alpha]_{D}^{25} = -48.1 (c = 0.018, CH_{3}OH).

1,15-Diamino-3,4;12,13-dibenzo-16,17-cyclohexo-5,8,11-trioxacyclohexaundecane (3b). Isolated as a pale orange oil (91%); \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \delta: 1.09 (bs, 4H, -CH\textsubscript{2}-CH\textsubscript{2}-), 1.62 (bs, 2H, 2 x CH), 2.07 (d, 2H, 2 x CH), 2.19 (bs, 2H, 2 x -CH-NH-), 2.78 (bs, 2H, NH), 3.60 (d, 2H, J = 13.5 Hz, 2 x -NH-CH\textsubscript{-}), 3.67 (t, 4H, -CH\textsubscript{2}-O-CH\textsubscript{2}-), 3.92 (d, 2H, J = 13.2 Hz, 2 x -NH-CH\textsubscript{-}), 3.96 (t, 4H, 2 x Ar-O-CH\textsubscript{2}-), 6.76 (d, 2H, Ar-CH), 6.87 (t, 2H, Ar-CH), 7.25-7.38 (m, 4H, Ar-CH); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}) \delta: 24.6, 31.2, 45.9 (-NH-C-), 60.7 (-C-NH-), 67.5 (-C-O-C-), 69.8 (Ar-O-C-), 111.3 (Ar-C), 120.7 (Ar-C), 127.9 (Ar-C), 129.2 (Ar-C) 129.6 (Ar-C), 156.7 (Ar-C); IR (cm\textsuperscript{-1}): 3080 (aromatic C-H stretch), 2920 and 2850 (C-H methylene stretch), 1603, 1497 and 1458 (C=C aromatic ring stretch), 1248 (aryl-O-C ring stretch), 1052 (in plane C-H bend), 750 (out of plane C-H bend); ESI-MS for C_{24}H_{32}N_{2}O_{3} (MH\textsuperscript{+}): Calcd 397.2; Found 397.3; Anal. Calc. for C_{24}H_{32}N_{2}O_{3}·2HCl·2H_{2}O: C, 57.0; H, 7.6, N, 5.5. Found: C, 56.8; H, 7.6; N, 5.2; [\alpha]_{D}^{25} = -51.2 (c = 0.012, CH\textsubscript{3}OH).

1,18-Diamino-3,4;15,16-dibenzo-19,20-cyclohexo-5,8,11,14-tetraoxacyclooctadodecane (3c). Isolated as a pale yellow oil (92%); \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \delta: 1.03 (bs, 2H, 2 x CH), 1.21 (bt, 2H, 2 x CH) 1.68 (bd, 2H, 2 x CH), 2.11-2.21 (m, 4H, 2 x CH & 2 x –C\textsubscript{H}-NH-), 3.65 (d, 2H, J = 13.5 Hz, 2 x -NH-CH\textsubscript{-}), 3.61 (s, 4H, -O-CH\textsubscript{2}-CH\textsubscript{2}-O-), 3.67 (t, 4H, 2 x Ar-O-CH\textsubscript{2}-CH\textsubscript{2}-O-), 3.70 (s, 4H, -O-CH\textsubscript{2}-CH\textsubscript{2}-O-), 3.79 (t, 4H, 2 x Ar-O-CH\textsubscript{2}-CH\textsubscript{2}-O-), 3.89 (d, 2H, J = 13.5 Hz, 2 x -NH-CH\textsubscript{-}), 4.02 (t, 4H, 2 x Ar-O-CH\textsubscript{2}-CH\textsubscript{2}-O-) 6.77 (d, 2H, Ar-CH), 6.87 (t, 2H, Ar-CH), 7.13-7.25 (m, 4H, Ar-CH); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}) \delta: 25.0, 31.3, 45.9 (-NH-C-), 60.7 (-C-NH-), 67.5 (Ar-O-C-), 69.7 (-O-C-C-O-), 70.8 (Ar-O-C), 111.2 (Ar-C), 120.5 (Ar-C), 127.7 (Ar-C), 129.4 (Ar-C) 129.5 (Ar-C), 156.7 (Ar-C); IR (cm\textsuperscript{-1}): 3080 (aromatic C-H stretch), 2936 and 2860 (C-H methylene stretch), 1603, 1497 and 1458 (C=C aromatic ring stretch), 1248 (aryl-O-C ring stretch), 1052 (in plane C-H bend), 754 (out of plane C-H bend); ESI-MS for C_{26}H_{36}N_{2}O_{4} (MH\textsuperscript{+}): Calcd 441.3; Found 441.5; Anal. Calc. for C_{26}H_{36}N_{2}O_{4} 2HCl·H_{2}O: C, 57.0; H, 7.6, N, 5.5. Found: C, 56.8; H, 7.6; N, 5.2; [\alpha]_{D}^{25} = -51.2 (c = 0.012, CH\textsubscript{3}OH).

1,21-Diamino-3,4;12,13-dibenzo-18,19-cyclohexo-5,8,11,14,17-pentaoxacyclodecatridecane (3d). A pale yellow oil (91%); \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \delta: 1.00-1.26 (m, 4H, -CH\textsubscript{2}-CH\textsubscript{2}-), 1.68 (bd, 2H, 2 x CH), 2.10 (d, 2H, 2 x CH), 2.23 (bs, 2H, 2 x -CH-NH-), 2.33 (bs, 2H, NH), 3.60 (bs, 8H, -O-CH\textsubscript{2}-CH\textsubscript{2}-O-CH\textsubscript{2}-CH\textsubscript{2}-O-), 3.61 (d, 2H, J = 13.5 Hz, 2 x NH-CH\textsubscript{-}), 3.69 (t, 4H, 2 x Ar-O-CH\textsubscript{2}-CH\textsubscript{2}-O-) 3.92 (d, 2H, J = 13.5 Hz, 2 x -NH-CH\textsubscript{-}), 4.01 (t, 4H, 2 x Ar-O-CH\textsubscript{2}-CH\textsubscript{2}-O-) 6.77 (d, 2H, Ar-CH), 6.88 (t, 2H, Ar-CH), 7.17-7.25 (m, 4H, Ar-CH); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}) \delta: 24.9, 31.1, 45.9 (-NH-C-), 60.5 (-C-NH-), 67.3 (Ar-O-C-O-C), 69.5 (-O-C-C-O-C-C-O-), 70.5 (Ar-O-C-), 70.6 (Ar-O-C-), 111.1 (Ar-C), 120.4 (Ar-C), 127.7 (Ar-C), 129.0 (Ar-C) 129.5 (Ar-C), 156.6 (Ar-C); IR (cm\textsuperscript{-1}): 3080 (aromatic C-H stretch), 2936 and 2860 (C-H methylene stretch), 1602, 1492 and 1458 (C=C aromatic ring stretch), 1259 (aryl-O-C ring stretch), 1052 (in plane C-H bend), 754 (out of plane C-H bend), 438 (out of plane ring C=C
bend); ESI-MS for C\textsubscript{28}H\textsubscript{40}N\textsubscript{2}O\textsubscript{5} (MH\textsuperscript{+}): Calc. 485.3; Found 485.5; Anal. Calc. for C\textsubscript{28}H\textsubscript{40}N\textsubscript{2}O\textsubscript{5} 2HCl·H\textsubscript{2}O: C, 58.4; H, 7.7; N, 4.9. Found: C, 58.7; H, 8.0; N, 4.8; [\alpha]\textsubscript{D}\textsuperscript{23.8} = -25.7 (c = 0.019, CH\textsubscript{3}OH).

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*Sample Availability:* Available from the authors.

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