

1,3-Dipolar Cycloaddition Reactions of 1-(4-Phenylphenacyl)-1,10-phenanthroline N-Ylide with Activated Alkynes and Alkenes

F. Dumitrascu ^{1,*}, M. R. Caira ², C. Draghici ¹, M. T. Caproiu ¹ and A. Badoiu ¹

¹ Centre of Organic Chemistry "C. D. Nenitzescu", Romanian Academy, Spl. Independentei 202B, Bucharest 060023, Romania

² Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa

* Author to whom correspondence should be addressed; fdumitra@cco.ro

Received: 8 October 2004; in revised form: 4 November 2004/ Accepted: 10 November 2004 /

Published: 28 February 2005

Abstract: The 3+2 cycloaddition reaction of 1-(4-phenylphenacyl)-1,10-phenanthroline ylide **4** with activated alkynes gave pyrrolo[1,2-a][1,10]phenanthrolines **6a-d**. The "one pot" synthesis of **6a,b,d** from **4**, activated alkenes, Et₃N and tetrakis-pyridine cobalt (II) dichromate (TPCD) is described. The helical chirality of pyrrolophenanthrolines **6b-d** was put in evidence by NMR spectroscopy.

Keywords: N-ylides, 1,3-dipolar cycloaddition, pyrrolophenanthrolines, helical chirality.

Introduction

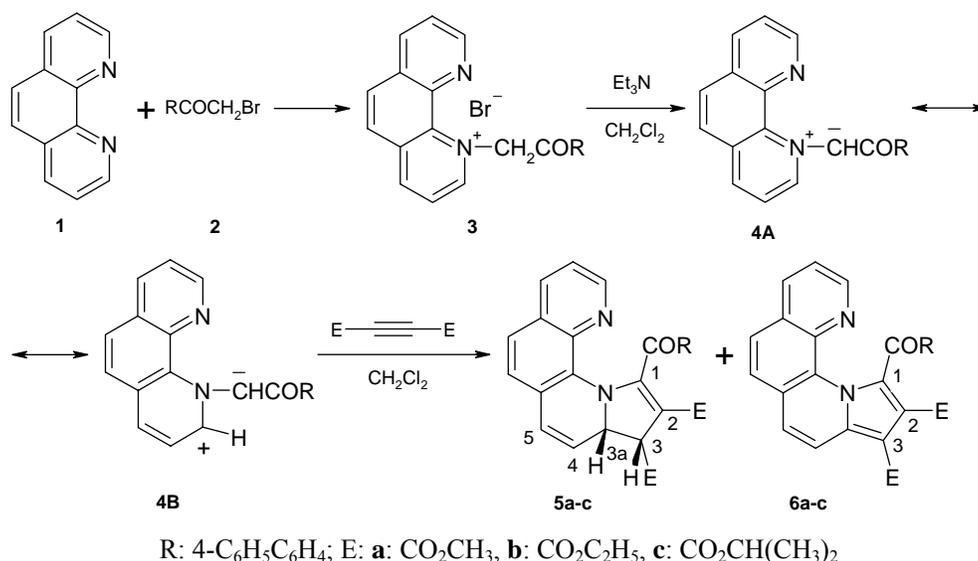
The synthesis of pyrrolo[1,2-a][1,10]phenanthroline by 1,3-dipolar cycloaddition of 1,10-phenanthroline N-ylides and acetylenic dipolarophiles was recently described. [1-4] Owing to the angular condensation, it was expected that the skeleton of this heterocyclic system might deviate from planarity, conferring helicity on the molecule. Here we describe the reaction of 1-(4-phenylphenacyl)-1,10-phenanthroline N-yliide (**4**) with activated alkynes and alkenes giving new pyrrolo[1,2-a][1,10]phenanthrolines **6a-d**. The 1,3-dipolar cycloaddition of 1,10-phenanthroline N-ylides to activated alkenes is described in detail for the first time.

Results and Discussion

1-(4-Phenylphenacyl)-1,10-phenanthroline bromide (**3**) was obtained by refluxing 1,10-phenanthroline monohydrate (**1**) and 2-bromo-4'-phenylacetophenone (**2**) in acetone. The structure of the cycloimmonium bromide was assigned by elemental analysis and NMR spectroscopy. In the ^1H -NMR spectrum of salt **3**, recorded in DMSO-d_6 , the methylenic hydrogens appeared as a broad singlet. This is due to non-planarity of the phenanthroline, as we reported recently [5].

The 1,10-phenanthroline *N*-ylide **4**, being unstable, was generated *in situ* by deprotonation of the cycloimmonium salt **3** with triethylamine. The ylide **4** can react as 1,3-dipole with acetylenic dipolarophiles. Treatment of the ylide **4** with dimethyl, diethyl or diisopropyl acetylenedicarboxylates in dichloromethane at room temperature gave a mixture of *cis*-3,3a-dihydro pyrrolophenanthrolines **5a-c**, along with variable amounts of pyrrolophenanthrolines **6a-c**. [1-3] Refluxing the above mixture in ethanol leads to the pyrrolophenanthrolines **6a-c** in yields of over 60% (Scheme 1).

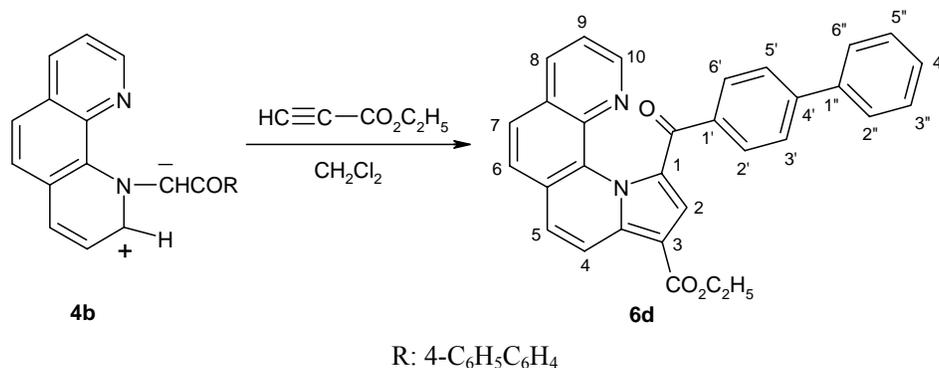
Scheme 1



The structure of the dihydroderivatives **5** was assigned by ^1H - and ^{13}C -NMR spectroscopy. The H-3 atom ($\delta = 4.59$ ppm) appeared as a doublet with coupling constant $J = 13.8$ Hz, whereas H-3a ($\delta = 5.41$ ppm) gave a double triplet with coupling constants of 13.8, 2.6 and 2.1 Hz, the last two values corresponding to the coupling with H-4 and H-5 hydrogens. In turn, the H-4 and H-5 atoms gave two double doublets at $\delta = 6.41$ ppm, $J = 2.6$ and 9.7 Hz and at $\delta = 5.94$ ppm, $J = 2.1$ and 9.7 Hz, respectively. The large value of the vicinal coupling constant between H-3 and H-3a ($J = 13.8$ Hz) indicated *cis* configuration, in agreement with similar values in pyrrolic moieties [6,7].

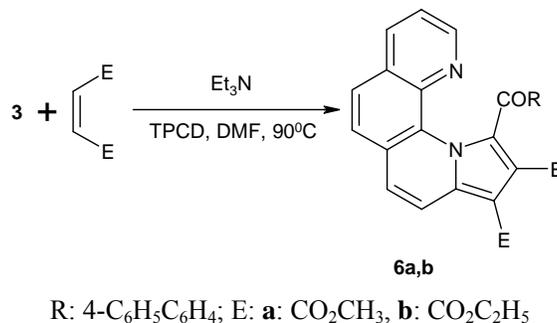
The 1,3-dipolar cycloaddition between ylide **4** and unsymmetrical alkyne ethyl propiolate is regiospecific and the pyrrolophenanthroline derivative **6d** is obtained (Scheme 2).

Scheme 2



The pyrrolophenanthrolines **6a,b** were also obtained by synthesis from salt **3**, methyl or ethyl maleate, triethylamine and tetrakis-pyridine cobalt (II) dichromate [Py₄Co(HCrO₄)₂, TPCD] in DMF, at 80-90°C (Scheme 3). Similarly, the compound **6d** was obtained from bromide **3**, triethylamine, ethyl acrylate and TPCD. This method was described previously in the case of other heteroaromatic *N*-ylides [8-10].

Scheme 3



The structures of the pyrrolophenanthrolines **6a-d** were assigned by elemental analysis and NMR spectroscopy. In the ¹H-NMR spectrum of compound **6b**, recorded in CDCl₃, the methylenic hydrogens of the ester group appeared as two ABX₃ patterns multiplets. A similar observation was made for compound **6d**. At room temperature, the same ABX₃ pattern multiplets for the methylenic hydrogens was observed [11]. In the case of the compound **6c**, the methyl groups in each isopropyl radical were found to be non-equivalent in the ¹H-NMR spectrum as well as in the ¹³C-NMR spectrum.

The behaviour can be explained by non-coplanarity between pyrrolic and pyridinic moieties, which imparts helical chirality to the molecules of **6b-d**, at room temperature.[12] This behaviour renders the molecular framework chiral, explaining thereby the non-equivalence of the diastereotopic methylene and methyl (in the isopropyl group) hydrogens in the ¹H-NMR spectra. This hypothesis was confirmed by X-ray analysis of the compound **6d** [11].

Conclusions

The new pyrrolo [1,2-*a*][1,10]phenanthrolines **6a-d** were obtained by 1,3-dipolar cycloaddition between *N*-ylide **4** and activated alkynes. A new approach to 1,3-dipolar cycloaddition to 1,10-

phenanthroline *N*-ylides is described, namely the "one pot" reaction with activated alkenes, in the presence of a versatile mild oxidant (TPCD).

Experimental

General

Melting points were determined on a Boëtius hot plate and are uncorrected. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^1H and 75 MHz for ^{13}C .

1-(4-Phenylphenacyl)-1,10-phenanthroline bromide (3)

1,10-Phenanthroline hydrate (4 g, 20 mmol) and 2'-bromo-4-phenylacetophenone (5.5 g, 20 mmol) were refluxed in acetone (80 mL) for 24 hrs. The precipitate formed was filtered by suction and washed with acetone (50 mL). Yield 75%, m.p. 227-230 °C (from ethanol); Anal. Calcd. For $\text{C}_{26}\text{H}_{19}\text{BrN}_2\text{O}$: C 68.58; H 4.21; Br 17.55; N 6.15. Found C 68.91, H 4.53, Br 17.93; N 6.42; $^1\text{H-NMR}$ (DMSO- d_6 , δ , ppm, *J*, Hz): 7.36 (bs, 2H, CH_2); 7.48-7.51 (m, 1H, H-4''); 7.54-7.59 (m, 2H, H-3'', H-5''); 7.85-7.88 (m, 2H, H-2'', H-6''); 7.91 (dd, 1H, 8.2, 4.3, H-8); 8.04 (d, 2H, 8.5, H-3', H-5'); 8.28 (d, 2H, 8.5, H-2', H-6'); 8.48 and 8.51 (2d, 2H, 8.9, H-5, H-6); 8.53 (dd, 1H, 4.3, 1.8, H-9); 8.64 (dd, 1H, 8.2, 5.9, H-3); 8.78 (dd, 1H, 8.2, 1.8, H-7); 9.62 (dd, 1H, 8.2, 1.4, H-4); 9.71 (dd, 1H, 5.9, 1.4, H-2); $^{13}\text{C-NMR}$ (DMSO- d_6 , δ , ppm): 69.6 (CH_2); 124.8 (C-3); 125.5 (C-8); 127.0 (C-6); 127.1 (C-2'', C-6''); 127.4 (C-3', C-5'); 128.7 (C-4''); 128.9 (C-2', C-6'); 129.2 (C-3'', C-5''); 130.7 (C-5); 131.5 (C-4a); 132.0 (C-6a); 133.1 (C-1'); 136.3 (C-10b); 138.0 (C-7); 138.4 (C-10a); 138.6 (C-1''); 145.3 (C-4'); 148.1 (C-4); 148.9 (C-9); 152.1 (C-2); 190.2 (COAr).

Diesters of 1-(4-phenylbenzoyl)-pyrrolo[1,2-a][1,10]phenanthroline-2,3-dicarboxylate (6a-c): *General procedure:*

Phenanthroline salt **3** (2.3 g, 5 mmol) was suspended in dichloromethane (25 mL) and then dimethyl (diethyl or diisopropyl) acetylenedicarboxylate (5.5 mmol) was added. Under vigorous stirring, triethylamine (0.7 mL, 5 mmol, dissolved in 5 mL of methylene chloride) was added dropwise. After 20 min the reaction mixture was washed twice with water (50 mL) and the solvent evaporated. The residue was refluxed in ethanol for an hour and the precipitate was isolated by filtration.

Dimethyl 1-(4-phenylbenzoyl)-pyrrolo[1,2-a][1,10]phenanthroline-2,3-dicarboxylate (6a). Yellow crystals (from DMF). Yield 60%, m.p. 286-7°C; Anal. Calcd. for $\text{C}_{32}\text{H}_{22}\text{N}_2\text{O}_5$: C 74.70, H 4.31, N 5.44. Found C 75.02, H 4.62, N 5.71; $^1\text{H-NMR}$ (CDCl_3 +TFA, δ , ppm, *J*, Hz): 3.68, 3.96 (2s, 6H, CH_3); 7.38-7.42 (m, 1H, H-4''); 7.43-7.47 (m, 2H, H-3'', H-5''); 7.50-7.55 (m, 2H, H-2'', H-6''); 7.51 (d, 2H, 8.3, H-3', H-5'); 7.62 (d, 2H, 8.3, H-2', H-6'); 7.96 (d, 1H, 9.5, H-5); 8.22 (dd, 1H, 8.2, 6.3, H-9); 8.29, 8.38 (2d, 2H, 8.9, H-6, H-7); 8.58 (d, 1H, 9.5, H-4); 9.15 (dd, 1H, 8.1, 1, H-8); 9.42 (dd, 1H, 6.3, 1, H-10); $^{13}\text{C-NMR}$ (CDCl_3 +TFA, δ , ppm): 52.7, 53.6 (2 CH_3); 96.5 (C-3); 117.7, 119.2, 122.5, 126.4,

126.9, 128.5, 130.5 (C-1, C-2, C-3a, C-5a, C-7a, C-11a, C-11b); 124.3 (C-5); 124.6 (C-9); 124.7 (C-4); 125.9 (C-7); 126.1 (C-3', C-5'); 127.0 (C-2'', C-6''); 127.8 (C-2', C-6'); 128.4 (C-4''); 129.0 (C-3'', C-5''); 130.2 (C-6); 139.0, 139.4 (C-1', C-1''); 144.4 (C-4'); 144.5 (C-10); 147.1 (C-8); 164.0 (2-CO₂Me); 166.3 (3-CO₂Me); 184.2 (COAr).

Diethyl 1-(4-phenylbenzoyl)-pyrrolo[1,2-a][1,10]phenanthroline-2,3-dicarboxylate (6b). Yellow crystals (from nitromethane). Yield 84%, m.p. 228–31°C. Anal. Calcd. for C₃₄H₂₆N₂O₅: C 75.26, H 4.83, N 5.16. Found C 75.55, H 5.09, N 5.38; ¹H-NMR (CDCl₃, δ, ppm, J, Hz): 1.07 (t, 3H, 7.1, 2-CH₂CH₃); 1.38 (t, 3H, 7.1, 3-CH₂CH₃); 3.77, 3.80 (2q, 1H, 10.2, 7.1, 2-CH_AH_BCH₃); 3.92, 3.95 (2q, 1H, 10.4, 7.1, 2-CH_AH_BCH₃); 4.13–4.47 (m, 2H, 3-CH₂CH₃); 7.32 (dd, 1H, 8.1, 4.3, H-9); 7.41–7.44 (m, 1H, 7.4, H-4''); 7.47–7.52 (m, 2H, 7.4, H-3'', H-5''); 7.68 (d, 1H, 9.2, H-5); 7.69–7.71 (m, 1H, 7.4, H-2'', H-6''); 7.75 (d, 2H, 8.4, H-3', H-5'); 7.78 and 7.84 (2d, 2H, 8.6, H-6, H-7); 8.08 (dd, 1H, 4.3, 1.7, H-10); 8.15 (dd, 1H, 8.1, 1.7, H-8); 8.23 (d, 2H, 8.4, H-2', H-6'); 8.56 (d, 1H, 9.2, H-4); ¹³C-NMR (CDCl₃, δ, ppm): 13.7, 14.3 (2 CH₃); 60.2, 61.6 (2 CH₂); 104.1 (C-3); 120.3 (C-4); 122.5 (C-9); 125.3 (C-7); 125.7, 125.9, 127.7, 129.0, 130.8, 137.3, 137.4 (C-1, C-2, C-3a, C-5a, C-7a, C-11a, C-11b); 126.0 (C-5); 126.6 (C-3', C-5'); 126.7 (C-6); 127.3 (C-2'', C-6''); 128.2 (C-4''); 129.0 (C-3'', C-5''); 130.6 (C-2', C-6'); 136.0 (C-8); 136.8 (C-1'); 140.1 (C-1''); 144.8 (C-4'); 145.8 (C-10); 163.6 (2-CO₂Et); 165.6 (3-CO₂Et); 184.1 (COAr).

Diisopropyl 1-(4-phenylbenzoyl)-pyrrolo[1,2-a][1,10]phenanthroline-2,3-dicarboxylate (6c). Yellow crystals (from acetonitrile). Yield 80%, m.p. 193–5°C. Anal. Calcd. for C₃₆H₃₀N₂O₅: C 75.77, H 5.30, N 4.91. Found C 76.1, H 5.58, N 5.07; ¹H-NMR (CDCl₃, δ, ppm, J, Hz): 0.90, 1.12 (2d, 6H, 6.3, 2-CH(CH₃)₂); 1.37, 1.40 (2d, 6H, 6.3, 3-CH(CH₃)₂); 4.78 (sep, 1H, 6.3, 2-CH(CH₃)₂); 5.32 (sep, 1H, 6.3, 3-CH(CH₃)₂); 7.32 (dd, 1H, 8.2, 4.3, H-9); 7.41–7.43 (m, 1H, 7.3, H-4''); 7.47–7.52 (m, 2H, 7.3, H-3'', H-5''); 7.68 (d, 1H, 9.2, H-5); 7.69–7.72 (m, 2H, 7.3, H-2'', H-6''); 7.75 (d, 2H, 8.2, H-3', H-5'); 7.79, 7.86 (2d, 2H, 8.5, H-6, H-7); 8.01 (dd, 1H, 4.3, 1.7, H-10); 8.15 (dd, 1H, 8.2, 1.7, H-8); 8.26 (d, 2H, 8.2, H-2', H-6'); 8.59 (d, 1H, 9.2, H-4); ¹³C-NMR (CDCl₃, δ, ppm): 20.9, 21.5, 22.0, 22.1 (4 CH₃); 67.8, 69.6 (2CH); 104.1 (C-3); 120.4 (C-4); 122.4 (C-9); 125.1 (C-7); 125.6 (C-5); 125.6, 125.8, 127.6, 129.1, 130.8, 137.2, 137.4 (C-1, C-2, C-3a, C-5a, C-7a, C-11a, C-11b); 126.7 (C-6); 126.8 (C-3', C-5'); 127.0 (C-2'', C-6''); 128.0 (C-4''); 128.9 (C-3'', C-5''); 130.8 (C-2', C-6'); 135.9 (C-8); 136.7 (C-1'); 140.2 (C-1''); 144.9 (C-4'); 145.6 (C-10); 163.1 (2-CO₂iPr); 165.2 (3-CO₂iPr); 183.8 (COAr).

Ethyl 1-(4-phenylbenzoyl)-pyrrolo[1,2-a][1,10]phenanthroline-3-carboxylate (6d)

Phenanthroline salt **3** (2.3 g, 5 mmol) was suspended in dichloromethane (25 mL) and then of ethyl propiolate (0.6 mL, 6 mmol) were added. Under vigorous stirring triethylamine (0.75 mL, 5 mmol, dissolved in 5 mL of methylene chloride) were added dropwise. After 20 min the reaction mixture was washed with water (50 mL) and the solvent evaporated. The residue was purified by column chromatography on neutral Al₂O₃ using CH₂Cl₂ as eluent. The product was recrystallized from an acetonitrile and ethanol mixture (2:1) to give yellow crystals. Yield 37%, m.p. 234–6°C. Anal. Calcd. for C₃₁H₂₂N₂O₃: C 79.13, H 4.71, N 5.95. Found C 79.41, H 5.02, N 6.24; ¹H-NMR (CDCl₃, δ, ppm, J, Hz): 1.44 (t, 3H, 7.1, CH₃); 4.38–4.50 (m, 2H, CH₂); 7.36 (dd, 1H, 8.2, 4.2, H-9); 7.41–7.47 (m,

¹H, H-4"); 7.49-7.56 (m, 2H, H-3", H-5"); 7.65 (s, 1H, H-2); 7.71 (d, 1H, 9.3, H-5); 7.73-7.78 (m, 3H, H-6/H-7, H-2", H-6"); 7.82 (d, 2H, 8.5, H-3', H-5'); 7.87 (d, 1H, 8.6, H-6/H-7); 8.14 (dd, 1H, 8.2, 1.8, H-8); 8.28 (dd, 1H, 4.2, 1.8, H-10); 8.34 (d, 2H, 8.5, H-2', H-6'); 8.60 (d, 1H, 9.3, H-4); ¹³C-NMR (CDCl₃, δ, ppm): 14.5 (CH₃); 60.0 (CH₂); 106.2 (C-3); 120.0 (C-4); 121.6 (C-2); 122.3 (C-9); 124.9, 126.5 (C-6, C-7); 125.4, 127.7, 129.6, 132.7, 136.5, 138.1 (C-1, C-3a, C-5a, C-7a, C-11a, C-11b); 125.6 (C-5); 126.9 (C-3', C-5'); 127.3 (C-2", C-6"); 128.0 (C-4"); 128.9 (C-3", C-5"); 130.7 (C-2', C-6'); 135.7 (C-8); 138.7, 140.2, 145.0 (C-1', C-4', C-1"); 146.0 (C-10); 164.6 (CO₂Et); 184.7 (COAr).

General procedure for "one pot" synthesis of pyrrolophenanthrolines **6a,b,d**

A solution of salt **3** (5 mmol), alkene (15 mmol) (dimethyl-, diethylmaleate or ethyl acrylate), triethylamine (6 mmol) and TPCD (5 mmol) in DMF (30 mL) was stirred at 80-90°C for 6 hrs. It was then cooled to the room temperature and a 5% aqueous HCl solution (100 mL) was added. The precipitate was filtered and purified by recrystallization from a suitable solvent. The pyrrolophenanthrolines **6a,b,d** were obtained in 32-61% yields.

References and Notes

1. Dumitrascu, F.; Mitan, C. I.; Draghici, C.; Caproiu, M. T.; Raileanu, D. *Tetrahedron Lett.* **2001**, 8379.
2. Dumitrascu, F.; Mitan, C. I.; Draghici, C.; Caproiu, M. T. *Rev. Roum. Chim.* **2002**, *47*, 881; [*Chem. Abstr.* **2004**, *140*, 111296e].
3. Dumitrascu, F.; Mitan, C. I.; Draghici, C.; Caproiu, M. T.; Raileanu, D. *Rev. Chim.* **2002**, *53*, 787; [*Chem. Abstr.* **2003**, *138*, 368790m].
4. Ramona, D.; Rotaru, A.; Drochioiu, G.; Druta, I. *J. Heterocycl. Chem.* **2003**, *40*, 283.
5. Dumitrascu, F.; Caira, M. R.; Draghici, C.; Caproiu, M. T.; Badoiu, A. *J. Chem. Crystallogr.*, **2004**, in press.
6. Kutsuma, T.; Sekine, Y.; Fujiyama, K.; Kobayashi, Y. *Chem. Pharm. Bull.* **1972**, *20*, 2701-2706.
7. Frolich, J.; Krohnke, F. *Chem. Ber.* **1971**, *104*, 1621-1628.
8. Wei, X.; Hu, Y.; Li, T.; Hu, H. *J. Chem. Soc. Perkin Trans I* **1993**, 2487.
9. Zhou, J.; Hu, Y.; Hu, H. *J. Heterocycl. Chem.* **2000**, *37*, 1165.
10. Wang, B.; Hu, J.; Zhang, X.; Hu, Y.; Hu, H. *J. Heterocycl. Chem.* **2000**, *37*, 1533.
11. Dumitrascu, F.; Caira, M. R.; Draghici, C.; Caproiu, M. T.; Barbu, L.; Badoiu, A. submitted to *J. Chem. Crystallogr.* **2004**.
12. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, **1994**; pp. 1163-1166.

Sample Availability: Available from the authors.