SYNTHESIS OF NOVEL 3-AMINOBENZ[*c,d*]INDOl-2(1*H*)-ONES *via* TANDEM ADDITION-REARRANGEMENT ARYNE PATHWAY

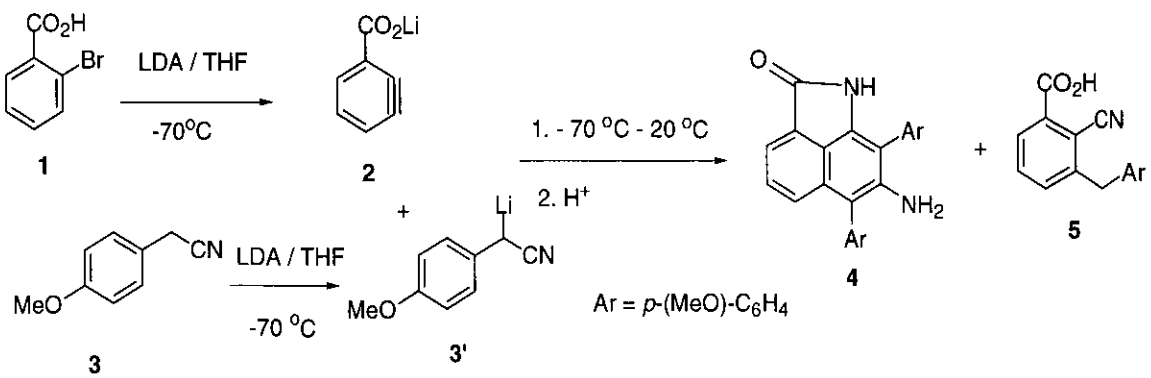
Anlai Wang, Hongming Zhang and Ed Biehl*

Department of Chemistry, Southern Methodist University,

Dallas, Texas 75275 U. S. A.

Abstract - The reaction of *p*-methoxyphenylacetonitrile (**3**) with 2-bromobenzoic acid (**1**) and LDA gave 7-amino-6,8-bis-(4'-methoxyphenyl)benz[*c,d*]indol-2(1*H*)- one (**4**) and 2-cyano-3-(4-methoxyphenyl)methyl benzoic acid (**5**). However, treatment of **3** with 2-bromo-4-methylbenzoic acid (**12**) and LiTMP yielded 5-pentyl-7-amino-6,8-bis (4'-methoxyphenyl)benz[*c,d*]indol-2(1*H*-one (**13**). The structure of **4** was established by single-crystal X-Ray diffractometry.

During the course of our studies[1] on the role of charged substituents on the orientation to and the reactivity of arynes, we carried out the reaction of 2-bromobenzoic acid (**1**) with 4-methoxyphenylaceto-nitrile (**3**) in the presence of LDA and THF. The experimental procedure involved generating benzyne-3-carboxylate (**2**) by the successive addition of LDA and α-lithio-4-methoxyphenylacetonitrile (**3'**), prepared *in situ* by the reaction of LDA and **3** at -70 °C. The resulting solution developed a red color upon addition of **3'** and increased in intensity as the solution was stirred at -70 °C for 30 min then allowed to warm to room temperature. The usual work up gave 7-amino-6,8-bis-(4-methoxyphenyl)benz[*c,d*]indol-



2(1*H*)-one (**4**) in 35% yield as well as the rearranged 2-cyano-3-(4-methoxyphenyl)methyl benzoic acid (**5**) in 53% . The structure of **4** was confirmed by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, HRMS, and single crystal X-Ray diffractometry. For example, the ^{1}H NMR spectrum of **4** showed singlet signals at δ 3.88 and 3.89 ($OC\underline{H}_3$), 4.35 ($N\underline{H}_2$), 9.30 ($CON\underline{H}$), and characteristic splitting patterns of the adjacent hydrogen atoms of the *p*-methoxy substituted aromatic rings at C-6 and C-8 (δ 7.44 [d, J = 8.5 Hz, 2H] and δ 7.05 [d, J = 8.5 Hz, 2 H]; and δ 7.38 [d, J = 8.5 Hz, 2 H] and δ 7.06 [d, J = 8.5 Hz, 2 H]) and the three adjacent hydrogen atoms in the aromatic ring containing the carbonyl group (δ 7.45 [d, J = 2.1 Hz, 1 H]; δ 7.56 [t, J = 2.1 Hz 1 H]; δ 7.66 [d, J = 2.1 Hz 1 H]). Furthermore, the ^{13}C NMR spectrum exhibited the requisite number of aromatic carbon signals (19) including one at δ 170 (C=O), and the observed HRMS molecular ion (m/z 396.1440) was in agreement with the calculated value of m/z 396.1474. The ORTEP[2] drawing of **4** obtained from the X-Ray single crystal analysis is shown in the Figure, and the bond lengths and bond angles are listed in Table 1. The Figure clearly shows the linkage of the amide group to the 1- and 8-positions of the naphthalene ring.

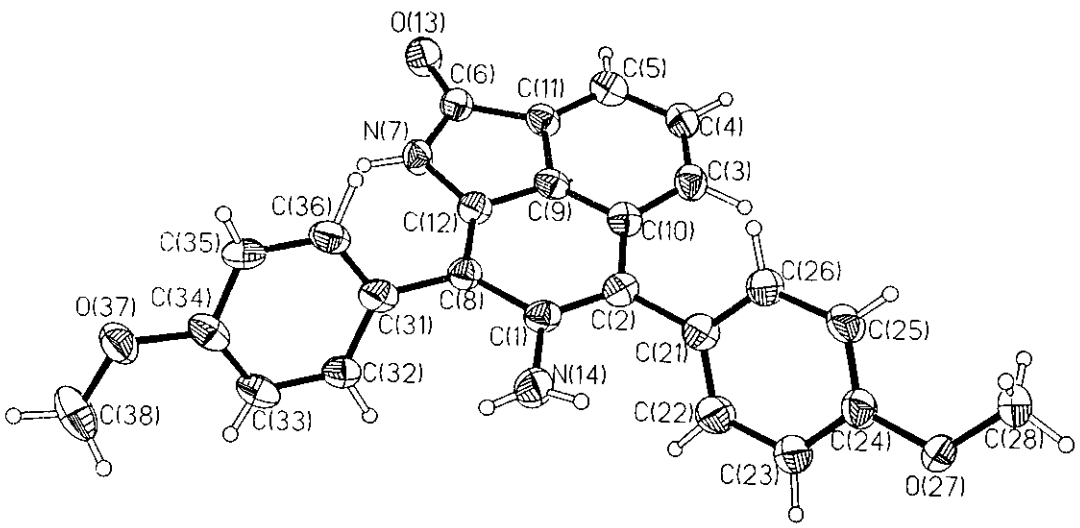


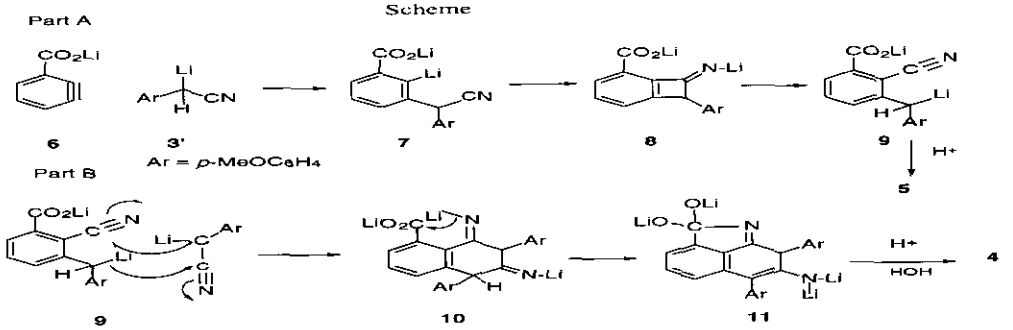
Figure ORTEP Drawing of **4**

A possible 2-part mechanism to account for the formation of **4** is shown in the following Scheme. Part A consists of the tandem addition-rearrangement pathway[3] in which benzyne-3-carboxylate (**6**), generated

Table 1. Bond lengths (Å) and bond angles (°)

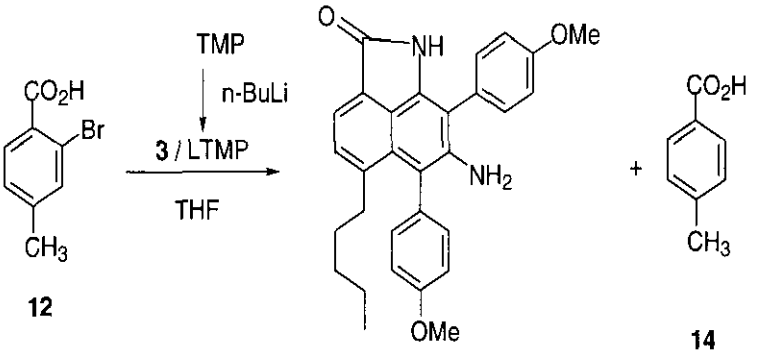
C(1)-C(2)	1.383(8)	C(1)-C(8)	1.465(8)
C(1)-N-14)	1.372(8)	C(2)-C(10)	1.442(8)
C(2)-C(21)	1.496(8)	C(3)-C(4)	1.366(10)
C(3)-C(10)	1.404(8)	C(4)-C(5)	1.411(9)
C(5)-C(11)	1.375(9)	C(6)-N(7)	1.376(8)
C(6)-C(11)	1.486(8)	C(9)-C(10)	1.226(7)
C(7)-C(12)	1.404(7)	C(8)-C(12)	1.363(8)
C(8)-C(31)	1.487(8)	C(9)-C(10)	1.380(8)
C(9)-C(11)	1.403(8)	C(9)-C(12)	1.403(7)
C(21)-C(22)	1.370(11)	C(21)-C(26)	1.390(9)
C(22)-C(23)	1.400(10)	C(23)-C(24)	1.372(9)
C(24)-C(25)	1.384(11)	C(24)-C(27)	1.383(7)
C(25)-C(26)	1.380(9)	C(27)-C(28)	1.417(8)
C(31)-C(32)	1.403(9)	C(31)-C(36)	1.385(11)
C(32)-C(33)	1.385(9)	C(33)-C(34)	1.381(12)
C(34)-C(35)	1.396(10))	C(34)-C(37)	1.390(7)
C(35)-C(36)	1.390(9)	C(37)-C(38)	1.425(9)
C(2)-C(1)-C(8)	122.8(5)	C(2)-C(1)-N(14)	121.3(5)
C(8)-C(1)-N(14)	115.9(5)	C(1)-C(2)-C(10)	119.5(5)
C(2)-C(1)-C(8)	122.8(5)	C(2)-C(1)-N(14)	121.3(5)
C(4)-C(3)-C(21)	122.3(6)	C(3)-C(4)-C(5)	122.7(6)
C(4)-C(5)-C(11)	116.8(6)	N(7)-C(6)-C(11)	106.1(5)
N(7)-C(6)-O(13)	124.9(5)	C(11)-C6)-O(13)	129.0(5)
C(6)-N(7)-C(12)	110.7(5)	C(1)-C(8)-C(12)	116.4(5)
C(1)-C(8)-C(31)	123.3(5)	C(12)-C(8)-C(31)	120.1(5)
C(10)-C(9)-C(11)	126.3(5)	C(10)-C(9)-C(12)	124.4(5)
C(11)-C(9)-C(12)	109.2(5)	C(2)-C(10)-C(3)	130.1(5)
C(2)-C(10)-C(9)	116.6(5)	C(3)-C(10)-C(9)	113.3(5)
C(5)-C(11)-C(6)	135.0(6)	C(5)-C(11)-C(9)	118.5(5)
C(6)-C(11)-C(9)	106.4(5)	N(7)-C(12)-C(8)	131.8(5)
N(7)-C(12)-C(9)	107.5(5)	C(8)-C(12)-C(9)	120.6(5)
C(2)-C(21)-C(22)	122.6(6)	C(2)-C(21)-C(26)	120.0(6)
C(22)-C(23)-C(26)	117.4(6)	C(21)-C(22)-C(23)	121.5(6)
C(22)-C(23)-C(24)	119.3(8)	C(23)-C(24)-C(25)	120.6(6)
C(23)-C(24)-O(27)	115.7(7))	C(25)-C(24)-O(27)	123.6(6)
C(24)-C(25)-C(26)	118.6(6)	C(21)-C(26)-C(25)	122.4(7)
C(24)-C(27)-C(28)	117.9(6)	C(8)-C(31)-C(32)	121.3(6)
C(8)-C(31)-C(36)	120.4(6)	C(32)-C(31)-C(36)	118.2(6)
C(31)-C(32)-C(33)	120.8(7)	C(32)-C(33)-C(34)	119.5(7)
C(33)-C(34)-C(35)	121.2(6)	C(33)-C(34)-O(37)	125.1(6)
C(35)-C)36)-O(37)	113.7(7)	C(34)-C(35)-C(36)	118.1(7)
C(31)-C(36)-C(35)	122.1(7)	C(34)-O(37)-C(38)	116.3(6)

Scheme



from the reaction of **1** and LDA, reacts with α-lithio-4-methoxyphenylacetonitrile (**3'**) to give adduct (**7**). The orientation of **3'** to the 1-position of aryne (**6**) is presumably due to unfavorable electrostatic interactions between the carboxylate group and **3'** which is consistent with that observed in the addition of alkanenitrile anions to benzyne-3-carboxylate under sodium amide mediated aryne reactions in liquid ammonia.[1] Adduct (**7**) then rearranges to the 2-cyano-3-α-lithiobenzyl intermediate (**9**) *via* the cyclobutanimium ion (**8**). Proton quench of **9** thus affords rearranged nitrile (**5**). The preference of adduct (**7**) to proceed along the rearrangement pathway rather than the usual aryne arylation pathway reflects the electron-releasing nature of the carboxylate group,[4] which increases the nucleophilicity at the lithiated ring cyclization site.[5] In Part B, intermediate (**9**) then reacts with another molecule of **3'** to give the tetrahydronaphthalene (**10**) which further cyclizes to the tricyclic diolate cyclic amide (**11**). Neutralization of **11** then affords **4**. The two-step conversion of **9** to **11** may well be a concerted one-step process in which nitrile anion addition and amide formation occur simultaneously.

We subsequently found that similar treatment of 2-bromo-4-methylbenzoic acid (**12**) and **3** with lithium tetramethylpiperidide (LTMP) and a 0.5 molar excess of BuLi in THF gave 7-amino-6,8-bis-(4-methoxyphenyl) -5-n-pentylbenz[*c,d*]indol-2(1*H*)-one (**13**) in 32% yield and p-toluic acid (**14**). The ^{1}H NMR and



^{13}C NMR spectra of **13** were consistent with proposed structure. The elaboration of 5-methyl to 5-n-pentyl presumably could be due to an S_N2 reaction involving the 5-methide carbanion with butyl bromide. LTMP is known to deprotonate methyl aromatics under aryne-forming conditions.[6] Furthermore, since the acidity of the 5-methyl group can be further enhanced by the delocalization of negative charge into an amide function, the deprotonation probably occurred some time after the formation of the napthalene ring. Butyl

bromide is most likely formed by the well-documented halogen metal exchange between the excess n-BuLi and the 3-bromo acid **12**.[7] In support of this conclusion, p-toluic acid (**14**) was recovered in *ca.* 26% yield. This one-step arynic synthesis is particularly significant in that several natural occurring materials contain, at least in part, the benz[*c,d*]indol-2(1*H*)-one basic skeleton, e.g. ergot[8] and aristolactam,[9,10] alkaloids, and several of these compounds have been found to have potentially significant biological active properties such as inhibitors of thymidylate synthase,[11,12] cardiovascular agents,[12] selective serotonin uptake inhibitors,[13] and antihypertensive agents.[14] Furthermore, the methodology delivers an amino group to the 7-position which is difficult to do by other synthetic methods.

EXPERIMENTAL

Melting points were taken on an electrochemical apparatus and are uncorrected. IR spectra were obtained from a FTIR spectrometer and the ^{1}H and ^{13}C NMR spectra were recorded on a 200 or 400 MHz spectrometer; chemical shifts were related to TMS as internal standard. HRMS analyses were performed by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR0954). THF was distilled from Na/benzophenone prior to use. n-BuLi was purchased from Aldrich Chemical Company as a solution in hexane. The glassware was heated at 125 °C in an oven overnight prior to use. All benzyne reactions were done under an atmosphere of dry O_2-free N_2.

General Procedure for Arynic Reactions. In a flame-dried flask flushed with nitrogen, fresh LDA (15 mmol) prepared by adding n-butyllithium (15 mmol, 2.5 M in hexane) to a solution of diisopropylamine (1.5 g, 15 mmol) or LTMP was prepared by adding tetramethylpiperidine (2.8 g, 20 mmol)) in THF (30 mL) at -70 °C. After stirring for 10 min, 2-bromobenzoic acid (1.0 g, 5 mmol) or 2-bromo-4-methylbenzoic acid (1.1 g, 5 mmol) in THF (30 mL) was added dropwise over 20 min and the stirring was continued for 10 min at -70 °C. 4-Methoxyphenylacetonitrile (740 mg, 5 mmol) was then added during which time the solution developed a deep red color. The resulting solution was stirred an additional 30 min, then was allowed to warm to rt , stirred overnight, then quenched with 30 mL of sat. NH_4Cl. The THF was evaporated under reduced pressure, and the remaining residue was extracted with methylene chloride (3 X 20 mL). The combined exacts were washed with 10 % HCl (1 X 20 mL), brine (2 X 20 mL), dried (Na_2SO_4), and concentrated (rotary evaporator) to provide crude solid material. The mixture was subjected to flash column chromatography (silica gel) using a mixture of hexane/acetone (6:4) as the eluent to give the benz[*c,d*]indoles (**4**) and (**13**), respectively, which were further recrystallized from

EtOAc. Nitrile (**5**) was also isolated from ther LDA reaction. The mp, elemental analyses and NMR spectral data of **4**, **5**, and **13** follow.

7-Amino-6,8-bis-(4-methoxyphenyl)benz[*c,d*]indol-2(1*H*)-one (4): colorless solid, mp 223-225 °C; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3 H), 3.89 (s, 3 H), 4.35 (s, 2 H), 7.05 (d, *J* = 8.5 Hz, 2 H), 7.06 (d, *J* = 8.5 Hz, 2 H), 7.38 (d, *J* = 8.5 Hz, 2 H), 7.44 (d, *J* = 8.5 Hz, 2 H), 7.45 (d, *J* = 2.1 Hz, 1 H); δ 7.56 (t, *J* = 2.1 Hz, 1 H); δ 7.66 (d, *J* = 2.1 Hz, 1 H), 9.30 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 55.6, 55.7, 111.2, 113.4, 113.5, 115.4, 115.6, 119.4, 126.9, 127.5, 128.6, 129.3, 129.5, 120.7, 132.2, 133.0, 144.4, 146.6, 160.0, 160.6, 170.4. HRMS: Calcd for $C_{25}H_{20}N_2O_3$: 396.1474. Found: 396.1440. *Anal.* Calcd for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.08; N, 7.07. Found: C, 75.88, H, 5.14; N, 7.15.

2-Cyano-3-(4-methoxyphenyl)methylbenzoic Acid (5): mp 295-297 °C, ^{1}H NMR (DMSO-d_6) δ3.70 (s, 3 H), 4.10 (s, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 7.17 (d, *J* = 8.6, 2 H), 7.37 (d, *J* = 7.2 Hz, 1 H), 7.48 (t, *J* = 7.2 Hz, 1 H), 7.80 (t, *J* = 7.2 Hz, 1 H),; ^{13}C NMR (DMSO-d_6) δ 31.2, 56.4, 112.3, 115.3, 119.3, 129.0, 129.4, 131.0, 131.6, 132.8, 144.9, 146.9, 159.2, 170.2; IR 3412 (OH). *Anal.* Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.85; H, 4.97; N, 5.17.

7-Amino-6,8-bis-(4-methoxyphenyl)-5-pentylbenz[*c,d*]indol-2(1*H*)-one (13): colorless solid, mp 233-235 °C; ^{1}H NMR ($CDCl_3$) δ 0.81 (t, *J* = 7.2 Hz, 3 H), 0.89 (m, 2 H), 1.57 (m, 2 H), 1.31 (m, 2 H), 2.29 (t, *J* = 8.1 Hz, 2 H), 3.74 (s, 2 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 7.04 (d, *J* = 8.5 Hz, 2 H), 7.06 (d, *J* = 8.5 Hz, 2 H), 7.26 (s, 1 H), 7.32-7.36 (m, 3 H), 7.43 (d, *J* = 8.4 Hz, 1 H); δ 9.30 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 14.9, 23.4, 32.8, 33.3, 35.4, 56.3, 56.3, 112.9, 113.4, 115.7, 115.9, 119.4, 121.4, 125.9, 126.4, 128.4, 129.3, 131.9, 132.1, 133.1, 136.0, 144.3, 146.2, 160.2, 160.9, 170.5. HRMS: Calcd for $C_{30}H_{30}N_2O_3$: 466.2256. Found: 466. 2261. *Anal.* Calcd for $C_{30}H_{30}N_2O_3$: C, 77.23; H, 6.48; N, 6.00. Found: C, 77.18, H, 6.52; N, 5.89.

Crystal Data and Data Collecting and Processing: A colorless cubic shaped crystal (0.35 x 0.25 x 0.25 mm) of **4** was mounted on a Nicolet R3m/V diffractometer unit cell parameters by least-squares fit of 25 reflections in the range $15<2q<23^0$. **a** = 12.034(1) Å, **b** = 13.143(1) Å, **c** = 12.769(1) Å, *B* =

101.08 (1)°. Space group $P2_1/c$ (hkl, h+k odd; h01, l odd) was confirmed by satisfactory refinement. Graphite monochromated Mo-Kα ($\lambda = 0.71073$), $\theta - 2\theta$ scan type, scan speed scan speed 3.0-15 deg min^{-1}, 3639 measured reflections, 1914 independent reflections in the range $3<2\theta<50°$, hkl range h -21-->19, k 0-->20, l 0--9, 1914 observed reflections with $F \geq 6.0\sigma(F)$. Three standard reflections measured after every 197 reflections showed crystal and electronic stability. Lorentz-polarization, absorption correction based on psi-scans, and no extinction correction was applied.

Structure Analysis and Refinement. Direct methods. Full-matrix least-squares refinement with all nonhydro-gen atoms anistropic. Hydrogen atom in calculated positions and riding model with fixed isotropic parameters. Find R = 0.0778 and wR = 0.114, $w = [s^2(F)] = 0.0022\ F^2]^{-1}$, $Sw(|Fol-1|\ Fcl)^2$ minimized. SHELXTL-Plus 88[15] on a Microvax II was used. Final positional parameters and thermal parameters and their estimated standard deviations are available upon request.

ACKNOWLEDGMENTS

This work was sponsored in part by the Welch Foundation, Houston, Tx, and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

REFERENCES

1. E. R. Biehl and H. Li, *J. Org. Chem.*, 1965, **31**, 602.
2. C. K. Johnson, ORTEP (1965), Report ORNL-3794, Oak Ridge National Laboratory, Tennessee.
3. P. D. Pansegrau, W. F. Rieker, and A. I. Meyers, *J. Am. Chem. Soc.*, 1988, **110**, 611.
4. The reported σ_m and σ_p for the carboxylate group range from -0.30 to 0.02 and -0.25 to 0.00, respectively, which are similar to those reported for the methyl group. O. Exner, 'Correlation Analysis in Chemistry,' N. B. Chapman and J. Shorter, Editors; Plenum Press, 1988, NY; Ch. 10, pp. 439-540.
5. E. R. Biehl and S. P. Khanapure, *Acc. Chem. Res.*, 1989, **22**, 275.
6. E. J. Corey, M. D. Azimioara, and A. K. Fischer, *Tetrahedron Lett.*, 1997, **38**, 6625.
7. R. G. Jones and H. Gilman, 'Organic Reactions', Vol. 6, ed. by R. Adams, Wiley, NY, p. 339.
8. I. Ninomiya and T. Kiguchi, 'The Alkaloids,' Vol. 38, ed. by A. Brossi, Academic Press, 1990, p. 1.
9. M. Shamma and J. L Moniot, 'Isoquinolines Alkaloid Research 1972-1977', Plenum Press, 1978.
10. Z.-L. Chang and D.-Y. Zhu, 'The Alkaloids,' Vol. 31, ed. A. Brossi, Academic Press, 1987, p. 29.
11. M. D. Varney, C. L. Palmer, J. G. Deal, S. Webber, K. M. Welsh, C. A. Bartlett, C. A. Morse, W. W. Smith, and C. A. Janson, *J. Med. Chem.*, 1995, **38**, 1892.

12. A. S. Tomcufcik, W. E. Meyer, and N. H. Eudy, Eur. Patent, Appl. EP 446,603 (14/3/90). *Chem. Abstr.* 115, P2779810a, 1991.
13. J. L. Mallerson, C. Gueremy, S. Mignani, J. F. Peyronel, A. Pierre, and O. Piot, *J. Med. Chem.*, 1993, **36**, 2242.
14. H. Newman, M. L. Sassiver, and A. S. Tomcufcik, U. S. Patent, US 5,229,441 (20/7/93). *Chem. Abstr.*, 118, P270998t, 1993.
15. G. M. Sheldrick, SHELX 76, 'Programs for Crystal Structure Determination,' University of Cambridge, England, 1976.

Received, 16th September, 1997