

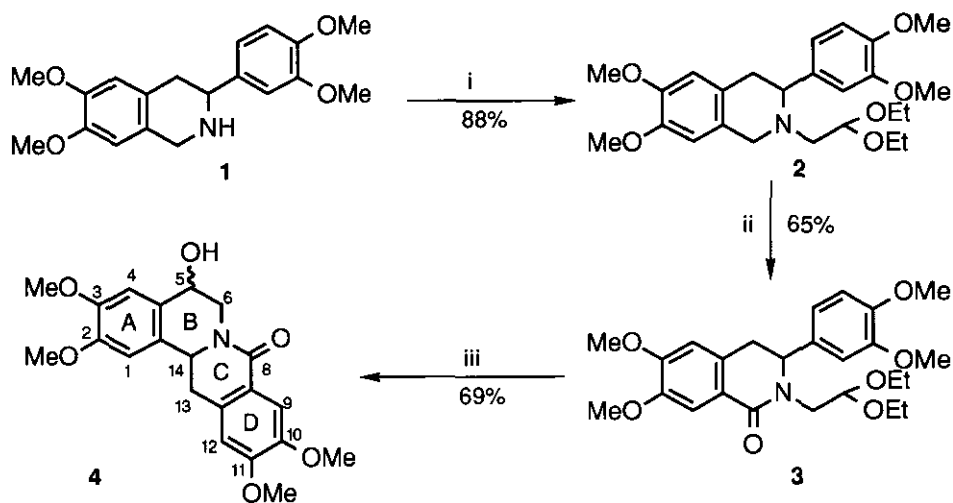
A NEW ROUTE TOWARDS 8-OXOPROTOBERBERINES¹

Teresa Vicente, Eduardo Martínez de Marigorta, Esther Domínguez,* Luisa Carrillo, and Dolores Badía

Department of Organic Chemistry, Faculty of Sciences, University of Basque Country, P.O. Box 644, 48080 Bilbao, Spain

Abstract—A new and short route for the preparation of 5-hydroxy-8-oxoprotuberberines and their conformational analysis are reported.

Although 8-oxoprotuberberines are not very common in nature,² this type of compounds have focused a considerable interest because they are useful intermediates for the synthesis of protuberberines and derivatives³ and because of their biological activity.⁴ Only one⁵ of the several ways for the preparation of the 8-oxoprotuberberine system⁶ has used 3-arylisquinoline derivatives as starting material. Therefore we decided to explore a new way towards the synthesis of those compounds making use of our experience on the chemistry of 3-arylisquinolines.⁷ Thus we report a new and short route for the synthesis of 5-hydroxy-8-oxoprotuberberines as outlined below.

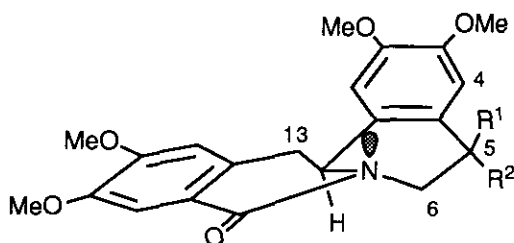


Reagents: i) KOH/BrCH₂CH(OEt)₂, DMSO, 4 h, 80°C; ii) KMnO₄/MgSO₄, acetone:water 2:1, 20 min, room temperature.; iii) 3M HCl, 4 h, room temperature

For the alkylation of isoquinoline (1)⁸ we used bromoacetaldehyde diethyl acetal with the KOH/DMSO⁹ system. Standard permanganate oxidation¹⁰ of the acetal containing substrate (2) gave the amide (3). The latter derivative was cyclized in acidic medium to produce two epimeric 5-hydroxy-8-oxoprotoberberines (1:1 ratio) in a 39% overall yield from the readily available 3-arylisoquinoline (1).

Both isomers could be separated and fully characterized (ir, ¹H and ¹³C nmr and ms). In the ¹H nmr spectra one of the methylenic protons at C-6 clearly appeared at a lower field than the other (2-3 ppm) thus showing its location in the same plane of the neighbouring carbonyl group.¹¹

The coupling constants between H-6eq/H-5 (4.9 Hz) and H-6ax/H-5 (10.3 Hz) for one of the isomers are coherent with a pseudoaxial location for H-5, therefore the hydroxy group must be in the pseudoequatorial position, as in **4a**.



4 a R¹=H, R²=OH
b R¹=OH, R²=H

We were unable to measure analogue coupling constants for the other isomer but the high field chemical shift corresponding to the aromatic proton H-4 relative to **4a** suggests that the hydroxy group must be much more far away from H-4 than is in **4a**, then being pseudoaxial as proposed for **4b**. Furthermore, the ir spectrum in solution for the latter derivative showed that the OH band absorption did not depend on the concentration, so we propose that there is an intramolecular hydrogen bond between the hydroxy group at C-5 and the non-bonding occupied orbital on the nitrogen atom. Taking into account a *trans* B/C ring fusion, that bond is only possible for a compound like **4b** having the hydroxy group in pseudoaxial position.

EXPERIMENTAL

Solvents were either purified according to methods described by Perrin *et al.*,¹² or used as received from the manufacturers, depending on their purity. Thin layer chromatography (tlc) was performed on plates coated to a thickness of 0.2 mm with Merck Kieselgel 60 PF₂₅₄ using uv light (λ 254 nm) and Dragendorff's reagent¹³ as developing agents; column chromatography¹⁴ was carried out using Merck Kieselgel 60 (230-400 mesh ASTM). Evaporation of solvents under reduced pressure were performed with a Heidolph VV 60 rotatory evaporator.

Melting points were measured in a Büchi apparatus and they are uncorrected. Infrared spectra were recorded on a Perkin-Elmer R-1430 infrared spectrophotometer. Nmr spectra were recorded on a Bruker ACE-250 (250 MHz for ^1H and 62.83 MHz for ^{13}C). Chemical shifts (δ) were measured in ppm relative to tetramethylsilane (δ 0.00) or chloroform (δ 7.26 for ^1H or 77.00 for ^{13}C) as internal standards. Mass spectra were recorded on a Hewlett-Packard 5930A spectrometer. Combustion analyses were performed with a Perkin-Elmer 2400 CHN apparatus.

6,7-Dimethoxy-3-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline 1. The method used was based on that of Dyke.^{8a} A mixture of bis-1,2-(3,4-dimethoxyphenyl)ethylamine^{8a} (12.00 g, 6.30 mmol) and HCl (100 ml of 1 mol l⁻¹ solution in water) was stirred at 50 °C under argon until the solid had dissolved. Formaldehyde (2.5 ml of a 38% solution in water) was added and stirring was continued until no starting material was left (tlc, CH₂Cl₂-MeOH, 9.5:0.5). The mixture was washed with ether (5 × 10 ml), the aqueous layer was basified with NaOH (40% solution in water) and extracted with dichloromethane (4 × 20 ml). The organic extracts of dichloromethane were dried (Na₂SO₄) and evaporated to a solid which was crystallized (MeOH) to give the isoquinoline (**1**) (1.86 g, 90%) as needles, mp 104-105 °C (MeOH) (lit.,^{8a} 97-98 °C (EtOH)); δ_{H} (CDCl₃) 7.03 (1H, s, H-2'), 6.96 (1H, d, *J* 8.3, H-6'), 6.86 (1H, d, *J* 8.1, H-5'), 6.58, 6.60 (2H, 2s, H-5, H-8), 4.12 (1H, d, *J* 15.2, H-1), 4.08 (1H, d, *J* 15.2, H-1), 3.94 (1H, m, H-3), 3.90 (3H, s, CH₃O), 3.89 (3H, s, CH₃O), 3.86 (6H, s, 2 × CH₃O), 2.95 (2H, m, H-4), 2.01 (1H, b s, exchanges with D₂O, NH); δ_{C} (CDCl₃) 149.03, 148.16, 147.46, 147.30 (C-6, C-7, C-3' and/or C-4'), 136.88, 126.59, (C-4a, C-8a and/or C-1'), 118.58, 111.58, 110.94, 109.52, 109.01, (C-5, C-8, C-2', C-5' and/or C-6'), 58.37 (C-3), 55.87 (4 × CH₃O), 48.84 (C-1), 37.20 (C-4).

N-(2,2-Diethoxyethyl)-6,7-dimethoxy-3-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline 2. The method of Johnstone and Rose⁹ was used. Isoquinoline (**1**) (1.75 g, 5.3 mmol) and bromoacetaldehyde diethyl acetal (4.1 ml, 5.24 g, 26.6 mmol) were added to a stirred solution of freshly grounded KOH (1.21 g, 21.3 mmol) in 10 ml of DMSO. The mixture was heated at 80 °C for 4 h (tlc, CH₂Cl₂-MeOH, 9.7:0.3), water added (20 ml) and the solution was extracted with dichloromethane (5 × 15 ml). The combined organic extracts were washed with water (5 × 15 ml), dried (Na₂SO₄) and concentrated under reduced pressure. Purification by column chromatography (CH₂Cl₂-EtOAc 8.8:1.2) followed by crystallization (MeOH) gave the isoquinoline (**2**) (2.08 g, 88%) as white needles, mp 93-95 °C, *R*_f(CH₂Cl₂-EtOAc 8.8:1.2) 0.35, ν_{max} (KBr/cm⁻¹) 1270 (OCH₂); δ_{H} (CDCl₃) 6.97 (1H, d, *J* 1.7, H-2'), 6.87 (1H, dd, *J*_O 8.2, *J*_m 1.7, H-6'), 6.80 (1H, d, *J* 8.2, H-5'), 6.57 (1H, s, H-5 or H-8), 6.56 (1H, s, H-5 or H-8), 4.61 (1H, t, *J* 5.1, CH(OEt)₂), 4.12 (1H, d, *J* 15.3, H-1), 3.88 (3H, s, CH₃O), 3.86 (3H, s, CH₃O), 3.84 (3H, s, CH₃O), 3.65 (6H, m, H-1, H-3, 2 × CH₃-CH₂), 3.04 (1H, dd, *J*_{BX} 8.9, *J*_{AB} 16.4, H-4ax), 2.93 (1H, dd, *J*_{AX} 5.0, *J*_{AB} 16.3, H-4ec), 2.73 (1H, dd, *J*_{BX} 5.3, *J*_{AB} 13.5, NCH₂), 2.36 (1H, dd, *J*_{AX} 5.1, *J*_{AB} 13.5, NCH₂), 1.20 (3H, t, *J* 7.0, CH₃-CH₂), 1.15 (3H, t, *J* 6.9, CH₃-CH₂); δ_{C} (CDCl₃) 148.98, 148.10, 147.52, 147.30, (C-6, C-7, C-3' and/or C-4'), 135.15, 126.46, 126.05, (C-4a, C-8a and/or C-1'), 120.14, 110.84, 110.75, 110.68, 109.15, (C-5, C-8, C-2', C-5' and/or C-6'), 102.25 (CH(OEt)₂), 63.67 (C-3), 62.24, 62.21 (2 × CH₃-CH₂), 61.32 (C-1), 55.89 (CH₃O), 55.87 (CH₃O), 55.82 (CH₃O), 55.74 (CH₃O), 55.19 (NCH₂), 35.95 (C-4), 15.28 (2 × CH₃-CH₂); *m/z* 445 (3%, M⁺), 343(14%), 342(16%), 314(21%), 313(100%), 287(7%), 282(15%), 175(9%), 164(16%), 151(11%), 103(7%). *Anal. Calcd* for C₂₅H₃₅NO₆: C, 67.39; H, 7.92; N, 3.14. Found: C, 67.50; H, 7.81; N, 2.96.

N-(2,2-Diethoxyethyl)-6,7-dimethoxy-3-(3,4-dimethoxyphenyl)-3,4-dihydro-1(2H)-isoquinolinone **3**. This was prepared using the method of Iida.¹⁰ Potassium permanganate (0.99 g, 5.9 mmol) was added to a stirred solution of the isoquinoline **2** (1.50 g 3.4 mmol) and magnesium sulfate (0.75 g 5.9 mmol) in a 2:1 acetone:water mixture (125 ml) at room temperature. After 20 min tlc (CH₂Cl₂-MeOH 9.7:0.3) showed no starting material, the brown solid was filtered, the filtrate was evaporated under reduced pressure and the residue was extracted with dichloromethane (5 × 30 ml) The organic extracts were combined, dried (Na₂SO₄) and concentrated under reduced pressure. Purification by column chromatography (CH₂Cl₂-MeOH 9.5:0.5) gave the isoquinolone (**3**) (1.01 g, 65%) as an oil, *R*_f(CH₂Cl₂-AcOEt 8.8:1.2) 0.40 and *R*_f(CH₂Cl₂-MeOH 9.5:0.5) 0.20, and ν_{\max} (KBr/cm⁻¹) 1270 (OCH₂); δ_{H} (CDCl₃) 7.64 (1H, s, H-8), 6.70 (1H, d, *J* 8.8, H-2'), 6.58 (2H, m, H-5', H-6'), 6.48 (1H, s, H-5), 4.99 (1H, m, H-3), 4.81 (1H, dd, *J*_{AX} 7.9, *J*_{BX} 2.9, CH(OEt)₂), 4.29 (1H, dd, *J*_{BX} 2.9, *J*_{AB} 13.7, NCH₂), 3.93 (3H, s, CH₃O), 3.84 (3H, s, CH₃O), 3.80 (3H, s, CH₃O), 3.74 (3H, s, CH₃O), 3.61 (5H, m, H-4ax, 2 × CH₃-CH₂), 2.90 (1H, dd, *J*_{AX} 1.5, *J*_{AB} 15.7, H-4eq), 2.74 (1H, dd, *J*_{AX} 8.0, *J*_{AB} 13.7, NCH₂), 1.26 (3H, t, *J* 7.0, CH₃-CH₂), 1.22 (3H, t, *J* 6.9, CH₃-CH₂); δ_{C} (CDCl₃) 162.72 (C-1), 151.97, 148.82, 148.28, 147.90 (C-6, C-7, C-3' and/or C-4'), 132.70, 128.91, 121.66 (C-4a, C-8a and/or C-1'), 118.55, 110.87, 109.93, 109.73, 109.58 (C-5, C-8, C-2', C-5' and/or C-6'), 101.67 (CH(OEt)₂), 64.42 (CH₃-CH₂), 63.09 (CH₃-CH₂), 60.51 (C-3), 55.95 (CH₃O), 55.83 (CH₃O), 55.71 (CH₃O), 55.69 (CH₃O), 49.60 (NCH₂), 35.20 (C-4), 15.48 (CH₃-CH₂), 15.36 (CH₃-CH₂); *m/z* 459(3%, M⁺), 414(7%), 344(6%), 343(26%), 328(5%), 327(14%), 178(6%), 151(31%), 150(8%), 104(6%), 103(100%). *Anal. Calcd* for C₂₅H₃₃NO₇: C, 65.34; H, 7.24; N, 3.05. Found: C, 65.15; H, 7.38; N, 2.87.

(5*R**,14*R**)-5-Hydroxy-2,3,10,11-tetramethoxy-8(*H*)-5,6,13,14-tetrahydroprotoberberin-8-one **4a** and (5*R**,14*S**)-5-hydroxy-2,3,10,11-tetramethoxy-8(*H*)-5,6,13,14-tetrahydroprotoberberin-8-one **4b**. HCl (30 ml of 3 mol solution in water) was added to the isoquinolinone **3** (0.75 g, 1.63 mmol) and the suspension was stirred at room temperature for 4 h (tlc, SiO₂, CH₂Cl₂-EtOAc, 1:1). The mixture was extracted with dichloromethane (5 × 15 ml) and the extract was stirred at room temperature with NH₄OH (50 ml of a 10% solution in water) for 3 h at room temperature. The aqueous layer was extracted again with dichloromethane (5 × 15 ml), the organic extracts were combined, dried (Na₂SO₄) and concentrated under reduced pressure. Column chromatography (CH₂Cl₂-EtOAc 1:1) gave the protoberberinone (**4a**) (0.20 g, 33%) as a solid, mp 210-212 °C (MeOH), *R*_f(CH₂Cl₂-EtOAc 1:1) 0.20, ν_{\max} (KBr/cm⁻¹) 3400, 1635; δ_{H} (CDCl₃) 7.63 (1H, s, H-9), 7.25 (1H, s, H-4), 6.72 (1H, s, H-12), 6.71 (1H, s, H-1), 5.15 (1H, dd, *J*_{BX} 4.9, *J*_{AB} 12.1, H-6eq), 4.89 (2H, m, H-5, H-14), 2.79 (1H, dd, *J*_{AX} 10.3, *J*_{AB} 12.0, H-6ax), 3.95 (6H, s, 2 × CH₃O), 3.93 (3H, s, CH₃O), 3.92 (3H, s, CH₃O), 3.17 (1H, dd, *J*_{AX} 3.8, *J*_{AB} 15.7, H-13eq), 2.93 (1H, m, H-13ax); δ_{C} (62.83 MHz, CDCl₃) 164.71 (C-8), 152.11, 148.69, 148.43, 148.28 (C-2, C-3, C-10 and/or C-11), 131.13, 130.94, 127.38, 121.28 (C-4a, C-8a, C-12a and/or C-14a), 110.73, 109.20, 108.03, 107.95 (C-1, C-4 C-9 and/or C-12), 66.04 (C-5), 56.16 (CH₃O), 56.11 (CH₃O), 56.06 (CH₃O), 55.96 (CH₃O), 55.43 (C-14), 45.68 (C-6), 37.38 (C-13); *m/z* 385(23%, M⁺), 368(15%), 366(14%), 352(11%), 342(11%), 206(10%), 205(23%), 179(17%), 178(90%), 151(18%), 150(100%), 135(15%), 107(13%), 91(14%), 79(10%), 77(20%). *Anal. Calcd* for C₂₁H₂₃NO₆: C,

65.44; H, 6.02; N, 3.63. Found: C, 65.26; H, 5.91; N, 3.45.; and the protoberberinone (**4b**) (0.22 g, 36%) as a solid, mp 217-219 °C (MeOH), $R_f(\text{CH}_2\text{Cl}_2\text{-EtOAc } 1:1)$ 0.15, $\nu_{\text{max}}(\text{KBr}/\text{cm}^{-1})$ 3450, 1630; $\delta_{\text{H}}(\text{CDCl}_3)$ 7.57 (1H, s, H-9), 6.92 (1H, s, H-4), 6.71 (1H, s, H-12), 6.65 (1H, s, H-1), 5.09 (1H, dd, $J_{\text{AX}} 2.1$, $J_{\text{AB}} 13.7$, H-6), 4.81 (2H, m, H-5, H-14), 3.92 (6H, s, $2 \times \text{CH}_3\text{O}$), 3.91 (6H, s, $2 \times \text{CH}_3\text{O}$), 3.16 (1H, dd, $J_{\text{AX}} 4.2$, $J_{\text{AB}} 15.6$, H-13eq), 3.03 (2H, m, H-6, H-13ax); δ_{C} (62.83 MHz, CDCl_3) 166.00 (C-1), 151.97, 149.55, 148.33, 148.06 (C-2, C-3, C-10 and/or C-11), 131.02, 128.13, 128.00, 121.33 (C-4a, C-8a, C-12a and/or C-14a), 112.01, 110.63, 109.01, 108.24 (C-1, C-4, C-9 and/or C-12), 66.30 (C-5), 56.11 (CH_3O), 56.07 (CH_3O), 55.98 (CH_3O), 55.94 (CH_3O), 55.12 (C-14), 45.44 (C-6), 37.53 (C-13); m/z 385(30%, M^+), 368(20%), 367(62%), 366(14%), 352(11%), 342(18%), 179(17%), 178(85%), 151(16%), 150(100%), 135(15%), 107(12%), 92(12%), 77(13%). *Anal. Calcd* for $\text{C}_{21}\text{H}_{23}\text{NO}_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.52; H, 6.01; N, 3.38.

ACKNOWLEDGMENTS

We thank the Spanish Ministry of Education and Science and the Basque Government for fellowships to E. M. de M. and T. V. respectively. Financial support of the University of Basque Country (Proyect UPV 170.310-E125/91) is gratefully acknowledged.

REFERENCES

1. A preliminary report has been produced for "7th European Symposium on Organic Chemistry" Namur (Belgium), 1991, Com. 13-TUES-A, p. 118.
2. C. W. W. Beeher and W. J. Kelleher, 'Alkaloids: Chemical and Biological Perspectives', Vol. 6, ed. by S. W. Pelletier, Wiley-Interscience, New York, 1988; pp. 297-337; P. M. M. Pinho, M.M. M. Pinto, A. Kijjoa, K. Pharadai, J. G. Díaz, and W. Herz, *Phytochemistry*, 1992, **31**, 1403; J.-S. Zhang and Z.-L. Chen, *Planta Med.*, 1991, **57**, 457.
3. M. Cushman, P. Chinnasamy, D. A. Patrick, A. T. McKenzie, and P. H. Toma, *J. Org. Chem.*, 1990, **55**, 5995; C. R. Dorn, F. J. Koszyk, and G. R. Lenz, *J. Org. Chem.*, 1984, **49**, 2642; V. I. Ognyanov, M. A. Haimova, and N. M. Mollov, *Heterocycles*, 1982, **19**, 1069; G. Manikumar, and M. Shamma, *J. Org. Chem.*, 1981, **46**, 386; M. Cushman and F. W. Dekow, *Tetrahedron*, 1978, **34**, 1435.
4. C. Weimar, S. v. Angerer, and W. Wiegrebe, *Arch. Pharm. (Wienheim)*, 1991, **324**, 509; S. v. Angerer, G. Brandl, A. Mannschreck, C. Weimar, and W. Wiegrebe, *Anti-Cancer Drug Design*, 1992, **7**, 351.
5. R. Beugelmans and M. Bois-Choussy, *Tetrahedron*, 1992, **48**, 8285.

6. Photochemical cyclization of tetrahydroisoquinolinemethylphthalimides: L. R. Bryant, J. D. Coyle, J. F. Challiner, and E. J. Haws, *Tetrahedron Lett.*, 1984, **25**, 1087; photoinduced cyclization of enamides: G. R. Lenz, *J. Org. Chem.*, 1974, **39**, 2839; G. R. Lenz, *J. Org. Chem.*, 1974, **39**, 2846; I. Ninomiya, T. Naito, and H. Takasugi, *J. Chem. Soc., Perkin Trans. I*, 1975, 1720; I. Ninomiya, T. Naito, and H. Takasugi, *J. Chem. Soc., Perkin Trans. I*, 1975, 1791; T. Kametani, N. Takagi, M. Toyota, T. Honda, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. I*, 1981, 2830; A. L. Campbell and G. R. Lenz, *Synthesis*, 1987, 421; C. Weimar, S. v. Angerer, and W. Wiegrebe, *Arch. Pharm. (Wienheim)*, 1991, **324**, 907; condensation of imines with homophthalic anhydrides: M. A. Haimova, V. I. Ognyanov, and N. M. Mollov, *Synthesis*, 1980, 845; P. Chinnasamy, K. Iwasa, S. v. Angerer, C. Weimar, and W. Wiegrebe, *Arch. Pharm. (Wienheim)*, 1987, **320**, 790; other methods: D. W. Brown, S. F. Dyke, M. Sainsbury, and G. Hardy, *J. Chem. Soc. (C)*, 1971, 3219; T. Shono, H. Hamaguchi, M. Sasaki, S. Fujita, and K. Nagami, *J. Org. Chem.*, 1983, **48**, 1621; Marsden, R.; MacLean, D. B. *Tetrahedron Lett.*, 1983, **24**, 2063; L. S. Trifonov and A. S. Orahovats, *Tetrahedron Lett.*, 1985, **26**, 3159; C. Lamas, C. Saá, L. Castedo, and D. Domínguez, *Tetrahedron Lett.*, 1992, **33**, 5653; R. Yamaguchi, A. Otsuji, K. Utimoto, and S. Kozima *Bull. Chem. Soc. Jpn.*, 1992, **65**, 298.
7. See for example: E. Domínguez and E. Lete, *Heterocycles*, 1983, **20**, 1247; E. Domínguez and E. Lete, *An. Quim.* 1984, **80C**, 13; D. Badía, E. Domínguez, C. Iriondo, and E. Martínez de Marigorta, *Heterocycles*, 1986, **24**, 1867; E. Domínguez, E. Lete, D. Badía, M. J. Villa, L. Castedo, and D. Domínguez, *Tetrahedron*, 1987, **43**, 1943; E. Domínguez, D. Badía, L. Castedo, and D. Domínguez, *Tetrahedron*, 1988, **44**, 203.
8. S. F. Dyke, D. W. Brown, M. Sainsbury, and G. Hardy, *Tetrahedron*, 1971, **27**, 3495.
9. R. A. W. Johnstone and M. E. Rose, *Tetrahedron*, 1979, **35**, 2169.
10. H. Iida, K. Fukuhara, I. Murayama, M. Machiba, and Kikuchi, *J. Org. Chem.*, 1986, **51**, 4701.
11. G. R. Lenz, *J. Org. Chem.* 1974, **39**, 2846; G. E. Hawkes, P. D. Palasz, J. H. P. Utley, and J. D. Hardstone, *J. Chem. Research (S)*, 1983, 208.
12. D. D. Perrin, and W. L. F. Armarego, 'Purification of Laboratory Chemicals,' 3rd edition, Pergamon Press, Oxford, 1988.
13. K. G. Krebs, D. Heusser, and H. Wimmer, 'Thin-Layer Chromatography,' ed. by E. Stahl, Springer-Verlag, Berlin, 1969; p. 854.
14. W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

Received, 15th March, 1993