A NEW ROUTE TOWARDS 8-OXOPROTOBERBERINES[1]

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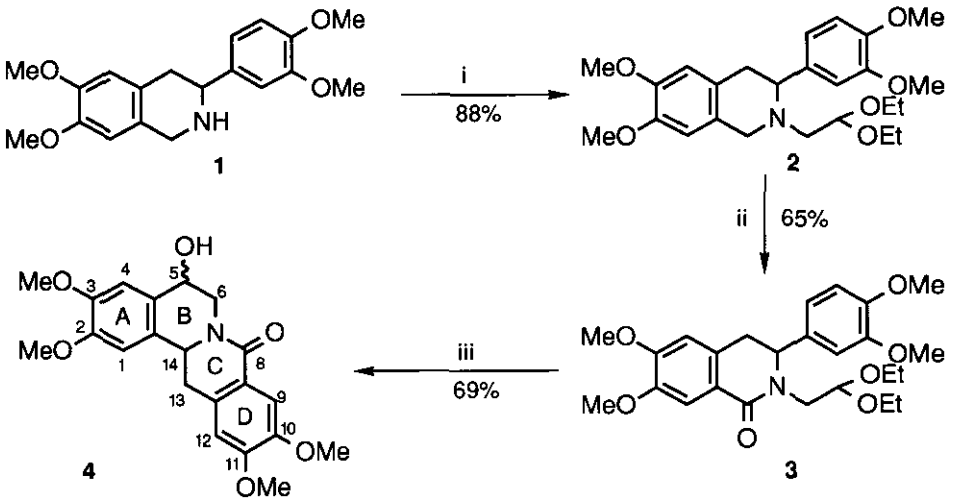
Abstract—A new and short route for the preparation of 5-hydroxy-8-oxoprotoberberines and their conformational analysis are reported.

Although 8-oxoprotoberberines 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 protoberberines and derivatives[3] and because of their biological activity.[4] Only one[5] of the several ways for the preparation of the 8-oxoprotoberberine system[6] has used 3-arylisoquinoline 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-arylisoquinolines.[7] Thus we report a new and short route for the synthesis of 5-hydroxy-8-oxoprotoberberines as outlined below.

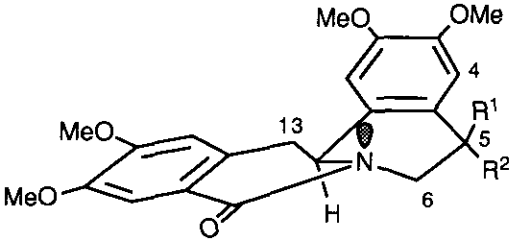


Reagents: i) KOH/$BrCH_2CH(OEt)_2$, DMSO, 4 h, 80°C; ii) $KMnO_4/MgSO_4$, acetone:water 2:1, 20 min, room temperature.; iii) 3M HCl, 4 h, room temperature

For the alkylation of isoquinoline (**1**)[8] we used bromoacetaldehyde diethyl acetal with the KOH/DMSO[9] system. Standard permanganate oxidation[10] 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, ^{1}H and ^{13}C nmr and ms). In the ^{1}H 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 R^1=H, R^2=OH
b R^1=OH, R^2=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 PF_{254} using uv light (λ 254 nm) and Dragendorff's reagent[13] as developing agents; column chromatography[14] 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, CH_2Cl_2-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 (Na_2SO_4) 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)); $\delta_H(CDCl_3)$ 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, CH_3O), 3.89 (3H, s, CH_3O), 3.86 (6H, s, 2 × CH_3O), 2.95 (2H, m, H-4), 2.01 (1H, b s, exchanges with D_2O, NH); δ_C ($CDCl_3$) 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 × CH_3O), 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 Rose[9] 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, CH_2Cl_2-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 (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (CH_2Cl_2-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(CH_2Cl_2-EtOAc 8.8:1.2) 0.35, υ_{max}(KBr/cm^{-1}) 1270 (OCH_2); $\delta_H(CDCl_3)$ 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, CH_3O), 3.86 (3H, s, CH_3O), 3.84 (3H, s, CH_3O), 3.65 (6H, m, H-1, H-3, 2 × CH_3-CH_2), 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, NCH_2), 2.36 (1H, dd, J_{AX} 5.1, J_{AB} 13.5, NCH_2), 1.20 (3H, t, *J* 7.0, CH_3-CH_2), 1.15 (3H, t, *J* 6.9, CH_3-CH_2); δ_C ($CDCl_3$) 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 × CH_3-CH_2), 61.32 (C-1), 55.89 (CH_3O), 55.87 (CH_3O), 55.82 (CH_3O), 55.74 (CH_3O), 55.19 (NCH_2), 35.95 (C-4), 15.28 (2 × CH_3-CH_2); 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 $C_{25}H_{35}NO_6$: 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] Potasium 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 (CH_2Cl_2-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 (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (CH_2Cl_2-MeOH 9.5:0.5) gave the isoquinolone (**3**) (1.01 g, 65%) as an oil, R_f(CH_2Cl_2-AcOEt 8.8:1.2) 0.40 and R_f(CH_2Cl_2-MeOH 9.5:0.5) 0.20, and υ_{max}(KBr/cm^{-1}) 1270 (OCH_2); δ_H($CDCl_3$) 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, NCH_2), 3.93 (3H, s, CH_3O), 3.84 (3H, s, CH_3O), 3.80 (3H, s, CH_3O), 3.74 (3H, s, CH_3O), 3.61 (5H, m, H-4ax, 2 × CH_3-CH_2), 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, NCH_2), 1.26 (3H, t, *J* 7.0, CH_3-CH_2), 1.22 (3H, t, *J* 6.9, CH_3-CH_2); δ_C ($CDCl_3$) 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 (CH_3-CH_2), 63.09 (CH_3-CH_2), 60.51 (C-3), 55.95 (CH_3O), 55.83 (CH_3O), 55.71 (CH_3O), 55.69 (CH_3O), 49.60 (NCH_2), 35.20 (C-4), 15.48 (CH_3-CH_2), 15.36 (CH_3-CH_2); 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 $C_{25}H_{33}NO_7$: C, 65.34; H, 7.24; N, 3.05. Found: C, 65.15; H, 7.38; N, 2.87.

(5R,14R*)-5-Hydroxy*-2,3,10,11-*tetramethoxy-8(H)-5,6,13,14-tetrahydroprotoberberin*-8-*one* **4a** and *(5R*,14S*)-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, SiO_2, CH_2Cl_2-EtOAc, 1:1). The mixture was extracted with dichloromethane (5 × 15 ml) and the extract was stirred at room temperature with NH_4OH (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 (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (CH_2Cl_2-EtOAc 1:1) gave the protoberberinone (**4a**) (0.20 g, 33%) as a solid, mp 210-212 °C (MeOH), R_f(CH_2Cl_2-EtOAc 1:1) 0.20, υ_{max}(KBr/cm^{-1}) 3400, 1635; δ_H($CDCl_3$) 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 × CH_3O), 3.93 (3H, s, CH_3O), 3.92 (3H, s, CH_3O), 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, $CDCl_3$) 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 (CH_3O), 56.11 (CH_3O), 56.06 (CH_3O), 55.96 (CH_3O), 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 $C_{21}H_{23}NO_6$: 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(CH_2Cl_2-EtOAc 1:1) 0.15, υ_{max}(KBr/cm^{-1}) 3450, 1630 ; δ_H($CDCl_3$) 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_{AX} 2.1, J_{AB} 13.7, H-6), 4.81 (2H, m, H-5, H-14), 3.92 (6H, s, 2 × CH_3O), 3.91 (6H, s, 2 × CH_3O), 3.16 (1H, dd, J_{AX} 4.2, J_{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 $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.52; H, 6.01; N, 3.38.

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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 tetrahydroisoquinolinmethylphtalimides: 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.

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