Notes

Microbial Transformations. 8. First Example of a Highly Enantioselective Microbiological Hydroxylation Process

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The use of bioconversion processes for preparation of optically active building blocks has received more and more attention owing to the importance of asymmetric synthesis.[1] Two general approaches are possible: first, enantioselective transformation of one of the two enantiomers of a racemic mixture; second, stereospecific transformation of a prochiral substrate, leading predominantly, or exclusively, to one enantiomer of the desired product. Thus enantioselective hydrolysis of various functions like amides[2] or esters,[3] as well as asymmetric reduction of prochiral carbonyl functions by microorganisms[4] or enzymes,[5] has been widely used. Surprisingly, processes leading to hydroxylation of unactivated carbon atoms have been very rarely described in this respect. Whereas some bioconversions involving stereospecific hydroxylations of prochiral substrates have been observed,[6] it appears that hydroxylation processes leading to enantiomer differentiation are very rare.[7] To our knowledge, no such process leading to high enantioselectivity has been previously described.

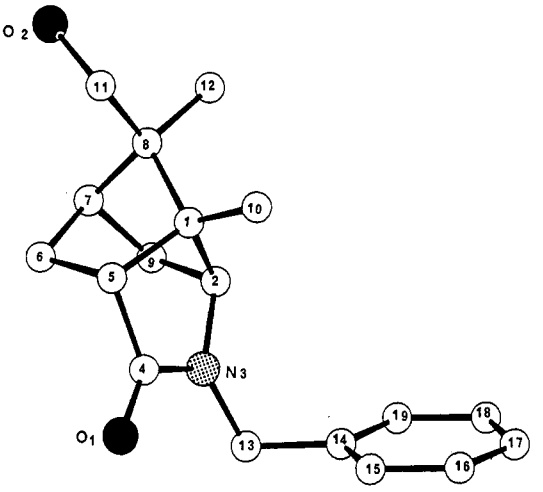

Figure 1. X-ray crystal structure of compound 2.

We report here the first example of such a process.

Results and Discussion

In the course of our work related to microbial hydroxylation of various polycyclic amides,[8] we noticed that bornyl amides could lead to partially enantioselective differentiation. We were interested in determining whether the enantioselectivity could be enhanced by using structurally blocked substrates like azabrendane derivatives 1 and 3. These rigid models were particularly attractive for two reasons. First, these substrates can be regarded as bornyl amide derivatives, "rigidified" by the introduction of an additional methylene bridge. Second, the bulk of the carbon skeleton appears to be completely located on one side of the plane of the amide moiety, thus leading to a very important spatial difference between the two enantiomers of the substrate. Because of this fact, we presumed that a different positioning of each of the enantiomers of these models into the active site of the hydroxylating enzyme could lead, as far as the regioselectivity of the hydroxylation process is concerned, to differentiation between the two enantiomers. X-ray crystallography of a cytochrome P-450 camphor complex[9] has shown that two factors influence the regioselectivity of the hydroxylation reaction: first, the attachment of the substrate to the

(1) For reviews, see, for instance: (a) Whitesides, M.; Wong, C. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 617. (b) *Enzymes as Catalysts in Organic Synthesis*; Schneider, M. P., Ed.; NATO ASI Series; D. Reidel: Dordrecht, 1986. (c) *Biocatalysts in Organic Synthesis*; Tramper, J., Van der Plas, H. C., Linko, P., Ed.; Elsevier: Amsterdam, 1985. (d) *Enzymes in Organic Synthesis*; Ciba Foundation Symposium 111; Pitman: London, 1985.

(2) (a) Fuganti, P.; Grasselli, P.; Seneci, P. F.; Servi, S.; Casati, P. *Tetrahedron Lett.* **1986**, *27*, 2061. Vriesema, B. K.; Ten Hoeve, W.; Wynberg, H.; Kellogg, R. M.; Boester, W. H. J.; Meijer, E. M.; Schoemaker, H. E. *Tetrahedron Lett.* **1986**, *27*, 2045. (c) Keller, J. W.; Hamilton, B. J. *Tetrahedron Lett.* **1986**, *27*, 1249.

(3) (a) Kitazume, T.; Sato, T.; Kobayashi, T.; Lin, J. T. *J. Org. Chem.* **1986**, *51*, 1003. (b) Gu, Q. M.; Reddy, D. R.; Sih, C. J. *Tetrahedron Lett.* **1986**, *27*, 5203. (c) Akita, H.; Matsukkura, H.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 5241. (d) Sweers, H. M.; Wong, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 6421. (e) Zaks, A.; Klibanov, A. M. *J. Am. Chem. Soc.* **1986**, *108*, 2762. (f) Han, C. Q.; Ditullio, D.; Wang, Y. F.; Sih, C. J. *J. Org. Chem.* **1986**, *51*, 1253. (g) Glanzer, B. I.; Faber, K.; Griengl, H. *Tetrahedron Lett.* **1986**, *27*, 4293. (h) Ramaswamy, S.; Hui, R. A. H. F.; Jones, J. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1545. (i) Chen, S. T.; Wang, K. T.; Wong, C. H. *J. Chem. Soc., Chem. Commun.* **1986**, 1514.

(4) (a) Nakamura, K.; Higaki, M.; Ushio, K.; Oka, S.; Ohno, A. *Tetrahedron Lett.* **1985**, *26*, 4213. (b) Itoh, T.; Yonekawa, Y.; Sato, T.; Fujisawa, T. *Tetrahedron Lett.* **1986**, *27*, 5405. (c) Kozikowski, A. P.; Mugrage, B. B.; Li, C. S.; Felder, L. *Tetrahedron Lett.* **1986**, *27*, 1986. (d) Stibor, I. *Synthesis* **1986**, 640. (e) Utaka, M.; Konishi, S.; Takeda, A. *Tetrahedron Lett.* **1986**, *27*, 4737. (f) Deshong, P.; Lin, M. T.; Perez, J. J. *Tetrahedron Lett.* **1986**, *27*, 2091. (g) Tsuboi, S.; Nishiyama, E.; Utaka, M.; Takeda, A. *Tetrahedron Lett.* **1986**, *27*, 1915. (h) Fronza, G.; Fuganti, C.; Grasselli, P.; Servi, S. *Tetrahedron Lett.* **1986**, *27*, 4363.

(5) (a) Lee, L. J.; Whitesides, G. M. *J. Org. Chem.* **1986**, *51*, 25. (b) Dutler, H.; Van der Baan, J. L.; Hochuli, E.; Kis, Z.; Taylor, K. E.; Prelog, V. *Eur. J. Biochem.* **1977**, *75*, 423. (c) Grunwald, J.; Wirz, B.; Scollar, M. P.; Klibanov, A. M. *J. Am. Chem. Soc.* **1976**, *108*, 6732.

(6) (a) Goodhue, C. T.; Schaeffer, J. R. *Biotechnol. Bioeng.* **1971**, *13*, 203. (b) Ishii, H.; Hayashi, M.; Niwaguchi, T.; Nakahara, Y. *Chem. Pharm. Bull.* **1979**, *27*, 1570. (c) Branca, Q.; Fischli, A. *Helv. Chim. Acta* **1977**, *60*, 925. (d) Caspi, E.; Piper, J.; Shapiro, S. *J. Chem. Soc., Chem. Commun.* **1981**, 76. (e) Timori, T.; Shibasaki, M. *Tetrahedron Lett.* **1985**, *26*, 1523. (f) Yamazaki, Y.; Maeda, H. *Tetrahedron Lett.* **1985**, *26*, 4775.

(7) (a) "In theory, the generation of optically active materials by enzymatic resolution is possible. A literature search did not reveal a corresponding example." Fischli, A. *Modern Synthetic Methods*; Otto Salle Verlag: 1980; p 296. See, however: (b) Fonken, G. S.; Herr, M. E.; Murray, H. C.; Reineke, L. M. *J. Org. Chem.* **1968**, *33*, 3207. (c) Archelas, A.; Furstoss, R.; Waegell, B. *Tetrahedron* **1984**, *40*, 355. (d) See also ref 8.

(8) Fourneron, J. D.; Archelas, A.; Vigne, B.; Furstoss, R. *Tetrahedron* **1987**, *43*, 2273.

(9) Poulos, T. L.; Finzel, B. C.; Gunsalus, I. C.; Wagner, G. C.; Kraut, J. *J. Biol. Chem.* **1985**, *260*, 16122.

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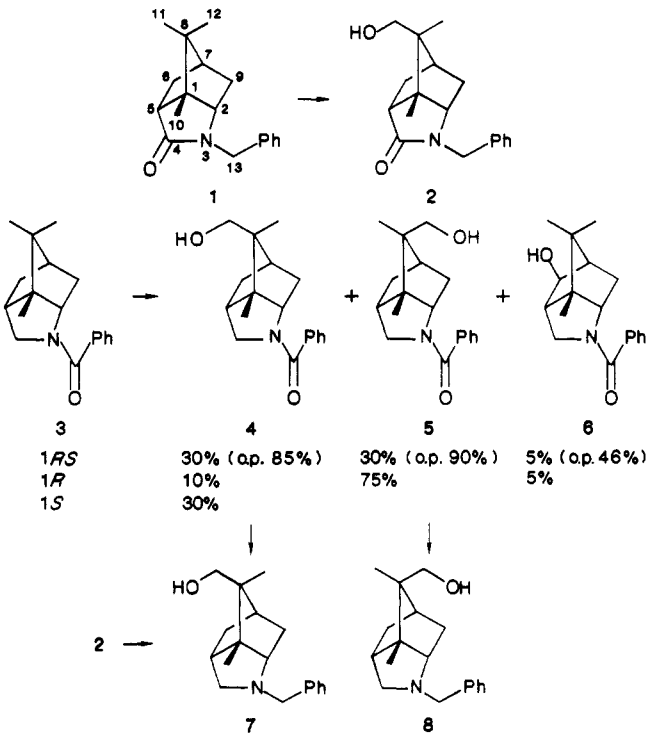
Scheme I



enzymatic site by means of a hydrogen bond, and second, the positioning of the carbon skeleton into the site, taking into account steric interactions due to the internal shape of the hydrophobic part of the active site.

Compounds **1** and **3** can be easily prepared, by using conventional methods, starting from either racemic or optically active α-pinene.[10] When submitted to a 48-h-old culture of the fungus *Beauveria sulfurescens* (ATCC 7159), racemic **1** afforded **2** as a single product (63% overall yield) resulting from hydroxylation of one of the C-11 or C-12 carbon atom, as shown by ^1H and ^{13}C NMR spectroscopy. The observed optical rotation of this product is $[\alpha]^{20}_D$ −3.6° (*c* 1.67, $CHCl_3$). When the procedure was conducted on optically active 1*R*-(+)-**1** or 1*S*-(−)-**1** (prepared respectively from (+)- and (−)-α-pinene), the same product was obtained in similar yield, thus leading to 1*R*-(+)-**2**, $[\alpha]^{20}_D$ +44° (*c* 1.45, $CHCl_3$), and 1*S*-(−)-**2**, $[\alpha]^{20}_D$ −45° (*c* 1.33, $CHCl_3$). It appears that in this case the observed enantioselectivity of the process is very poor. As far as the exact structure of **2** is concerned, no unambiguous determination has been possible on the basis of either ^1H or ^{13}C NMR spectroscopy. Therefore an X-ray structure determination has been carried out. The structure, shown in Figure 1, leads to the conclusion that hydroxylation occurred at carbon C-11.

Thus, the test of our hypothesis concerning the possible influence of the substrate positioning into the enzymatic active site then relied on the results we would obtain after hydroxylation of the racemic mixture of amide **3**. When submitted to a culture of the same fungus, racemic **3** led to a mixture of three products, as shown in Scheme I. These are obtained in an overall yield of 65% based on starting material (respective yields are indicated in Scheme I). Interestingly enough, each of these products appeared to be optically active.

Control experiments, conducted by starting from respectively 1*R*-(−)-**3** and 1*S*-(+)-**3** (obtained from optically active α-pinene), led to the results shown in Scheme I. It thus appears that, in this case, we had obtained a very highly enantioselective hydroxylation process. Indeed, the optical purities of amides **4** and **5** can be determined, on the basis of their optical rotations, as being respectively 85% and 90%. Interestingly, this enantioselectivity may be attributed to the fact that each of the enantiomers of **3** is *hydroxylated on a different carbon atom*, i.e., the regioselectivity of the process is governed by the absolute configuration of the substrate. Thus, 1*R*-(−)-**3** is primarily hydroxylated at C-12, whereas for 1*S*-(+)-**3**, hydroxylation occurs at C-11. In fact, only the minor product **6** (5%) still results from hydroxylation of each one of the enantiomers on the same carbon atom.

As in the case of amido alcohol **2**, it has been impossible to determine unambiguously, on the basis of ^1H and/or ^{13}C NMR spectroscopy, which one of the methyl groups had been functionalized to lead to compounds **4** and **5**. Whereas it was obvious from the spectroscopic analysis of **4** and **5** that each of these compounds resulted from hydroxylation at one of the geminal methyl groups, no indication on the exact location of the hydroxyl group could be obtained. Therefore, the structures of these products have been established by using chemical correlations with amido alcohol **2**. Thus, lithium aluminum hydride (LAH) reduction of **2** leads to amino alcohol **7**, which proved to be identical with the product obtained by reduction of compound **4**. On the other hand, reduction of **5** afforded amino alcohol **8**, which is different from **7**.

These results firmly establish, for the first time, that a microbial hydroxylation process, conducted on a racemic mixture, may lead to highly enantiospecific differentiation, owing to different regioselectivities induced by the substrate chirality. The microbial approach to new chiral synthons, using such hydroxylation processes, may be a valuable tool in this respect. Work is in progress in our laboratory in order to explore these possibilities.

Experimental Section

General Procedures. The strain used in the present work is *Beauveria sulfurescens* ATCC 7159, originally purchased as *Sporotrichum sulfurescens*. The culture conditions used have been described previously (see, for instance, reference 7c). The ^1H and ^{13}C NMR spectra have been realized on a Bruker AM 200 apparatus using $CDCl_3$ as solvent. Chemical shifts (δ) are given in parts per million relative to TMS as internal standard. IR spectra were recorded on a Beckman Acculab 4 spectrometer using chloroform as solvent. Elemental analyses of C, H, N were performed by the Service Central d'Analyse du CNRS (Vernaison, France). Melting points have been measured on a Büchi 510 apparatus and are not corrected. GC analyses have been performed by using a 25-m capillary column coated with OV 17. HPLC analyses have been achieved by using a 5-μm silica gel column (10 × 0.4 cm) (Merck); the preparative operations have been conducted with a column (25 × 0.9 cm) filled with 7-μm Merck silica gel.

Biohydroxylation of *N*-Benzyl-1,8,8-trimethyl-3-azabrendan-4-one (1). This product was obtained from 480 mg of racemic **1**[10] (200 mg/L of culture). After continuous extraction of the filtered culture with CH_2Cl_2 overnight, the organic phase was washed with NaOH (3 N) and dried over $MgSO_4$. The product was purified by "flash" chromatography (silica gel 60H from Merck and solvent mixtures ranging from 1:0 hexane–ether to 100% ether) and then by preparative HPLC (10% EtOH–hexane eluant), leading to 320 mg (63%) of **2**: mp 111–112 °C; IR (cm^{-1}) 3450, 1680; ^1H NMR 0.96 (s, 6 H, CH_3), 1.15 (d, 1 H), 1.50 (d, 1 H), 1.86 (m, 1 H), 2.16–2.27 (m, 3 H, H_5, H_7), 2.62 (s large, 1 H, OH), 3.16 (d, 1 H, H_2), 3.42 (d, 1 H, H_{11}), 3.58 (d, 1 H, H_{11}), 3.93 (d, 1 H, H_{13}), 4.82 (d, 1 H, H_{13}), and 7.26 (m, 5 H, ar); ^{13}C NMR 55.8 (C_1), 64.9 (C_2), 178.7 (C_4), 49.2 (C_5), 32.6 (C_6), 43.3 (C_7), 52.8 (C_8), 34.6 (C_9), 12.2 (C_{10}), 65.9 (C_{11}), 14.5 (C_{12}), 45.7 (C_{13}), 127.6, 128.4, 128.7, 137.0 (ar). Exact mass calcd for $C_{18}H_{23}NO_2$

(10) Furst, G. T.; Wachsman, M. A.; Pieroni, J.; White, J. G.; Moriconi, E. J. *Tetrahedron* **1973**, *29*, 1675.

285.1728, found 285.1719. Anal. Calcd: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.55; H, 8.07; N, 4.85.

Biohydroxylation of *N*-Benzoyl-1,8,8-trimethyl-3-azabrendane (3). Starting from 960 mg of 1*RS*-3[10] (300 mg/L of culture), one obtains, after HPLC purification (10% EtOH–hexane eluant), 186 mg of starting material, 45 mg of **6** (5%), 310 mg of **4** (30%), and 310 mg of **5** (30%).

***N*-Benzoyl-11-hydroxy-1,8,8-trimethyl-3-azabrendane (4):** mp 124–125 °C; IR (cm^{-1}) 3400, 1600; ^1H NMR 0.84–1.06 (m, 6 H, CH_3) (main peaks at 0.84 and 0.90),[11] 1.10–1.40 (m, 2 H), 2.00–2.50 (m, 5 H), 3.20–4.40 (m, 5 H), 7.40 (m, 5 H); ^{13}C NMR 57.3 (55.4) (C_1),[12] 67.1 (64.7) (C_2), 52.4 (54.7) (C_4), 41.2 (43.1) (C_5), 37.1 (36.7) (C_6), 39.8 (40.1) (C_7), 53.7 (C_8), 40.0 (38.6) (C_9), 12.1 (12.4) (C_{10}), 66.1 (66.4) (C_{11}), 15.8 (C_{12}), 169.9 (C_{13}), 127.1 (126.9), 128.3, 129.7, 137.4 (ar). Exact mass calcd for $C_{18}H_{23}NO_2$ 285.1728, found 285.1719. Anal. Calcd: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.65; H, 8.18; N, 4.86.

***N*-Benzoyl-12-hydroxy-1,8,8-trimethyl-3-azabrendane (5):** mp 126–127 °C; IR (cm^{-1}) 3400, 1600; ^1H NMR 0.85–1.08 (m, 6 H, CH_3) (main peaks at 0.85 and 1.05),[11] 1.14–2.50 (m, 7 H), 3.18–4.22 (m, 5 H), 7.40 (m, 5 H); ^{13}C NMR 57.3 (55.3) (C_1),[12] 66.2 (63.8) (C_2), 51.3 (53.7) (C_4), 41.9 (43.8) (C_5), 37.7 (37.2) (C_6), 40.0 (40.1) (C_7), 53.9 (C_8), 39.3 (38.0) (C_9), 12.0 (12.2) (C_{10}), 15.3 (15.2) (C_{11}), 66.6 (C_{12}), 169.9 (C_{13}), 127.1 (126.9), 128.3, 129.7, 137.4 (ar). Exact mass calcd for $C_{18}H_{23}NO_2$ 285.1728, found 285.1730. Anal. Calcd: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.50; H, 8.03; N, 4.87.

***N*-Benzoyl-6-*exo*-hydroxy-1,8,8-trimethyl-3-azabrendane (6):** IR (cm^{-1}) 3400, 1600; ^1H NMR 0.76–1.25 (m, 11 H) (main peaks at 0.76, 0.87, and 1.15),[11] 1.74 (m, 1 H), 2.01–2.38 (m, 2 H), 2.8 (m, 1 H, OH), 3.25–4.20 (m, 3 H), 7.40 (m, 5 H, ar); ^{13}C NMR 58.2 (56.2) (C_1),[12] 65.3 (62.8) (C_2), 50.5 (52.8) (C_4), 51.1 (51.5) (C_5), 84.1 (83.9) (C_6), 53.2 (54.8) (C_7), 48.4 (C_8), 36.6 (35.0) (C_9), 11.2 (11.4) (C_{10}), 21.8 (C_{11}*),[13] 21.4 (21.3) (C_{12}*), 169.9 (C_{13}), 127.2 (126.9), 128.3, 129.8, 137.3 (ar). Exact mass calcd for $C_{18}H_{23}NO_2$ 285.1728, found 285.1719.

***N*-Benzyl-11-hydroxy-1,8,8-trimethyl-3-azabrendane (7).** A solution of **2** (100 mg, 0.35 mmol) in 6 mL of dry THF and $LiAlH_4$ (200 mg, 5.3 mmol) was heated under reflux for 18 h. After cooling, sequential addition of water (0.2 mL), 10% aqueous NaOH (0.6 mL), and water (0.2 mL), and filtration (THF wash), the filtrate was dried ($MgSO_4$) and concentrated in vacuo, affording 90 mg of crude **7** as a yellow oil. Purification by bulb-to-bulb distillation in a Kugelrohr apparatus at 220 °C (0.1 mm) gave 80 mg (84%) of **7**: IR (cm^{-1}) 3620 and 1030; ^1H NMR (CCl_4) 0.94 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 1.04–2.26 (m, 7 H), 2.40 (d, 1 H, H_4), 2.99 (d, 1 H, H_2), 3.16 (dd, 1 H, H_4), 3.30 (d, 1 H, H_{13}), 3.54 (d, 1 H, H_{13}), 3.70 (d, 1 H, H_{11}), 3.81 (d, 1 H, H_{11}), 7.21 (m, 5 H, ar); ^{13}C NMR 57.0 (C_1**),[13] 69.5 (C_2), 59.8 (C_4*), 43.5 (C_5#),[13] 32.6 (C_6), 39.6 (C_7#), 53.4 (C_8**), 38.9 (C_9), 13.2 (C_{10}), 67.0 (C_{11}), 16.0 (C_{12}), 58.4 (C_{13}*), 126.6, 128.2, 128.3, 141.0 (ar). Anal. Calcd for $C_{18}H_{25}NO$: C, 79.72; H, 9.29; N, 5.17. Found: C, 79.58; H, 9.37; N, 4.87. Reduction of **4** (70 mg, 0.24 mmol) with lithium aluminum hydride in THF by the procedure described above afforded 50 mg (75%) of **7** after Kugelrohr distillation. The spectral characteristics of the product are identical with those reported for the hydroxy amino compound from **2**.

***N*-Benzyl-12-hydroxy-1,8,8-trimethyl-3-azabrendane (8).** This product was obtained by LAH–THF reduction of 70 mg of **5** using the procedure described for **7**, which afforded 50 mg (75%) of an oily product **8**: IR (cm^{-1}) 3620 and 1000; ^1H NMR (CCl_4) 0.94 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 1.04–2.18 (m, 7 H), 2.41 (d, 1 H, H_4), 2.97 (d, 1 H, H_2), 3.09 (dd, 1 H, H_4), 3.27 (d, 1 H, H_{13}), 3.43 (d, 1 H, H_{13}), 3.72 (d, 1 H, H_{12}), 3.83 (d, 1 H, H_{12}), 7.21 (m, 5 H, ar); ^{13}C NMR 57.0 (C_1*), 68.6 (C_2), 58.5 (C_4), 44.3 (C_5#), 32.5 (C_6), 39.6 (C_7#), 54.0 (C_8*), 39.3 (C_9), 13.2 (C_{10}), 15.4 (C_{11}), 67.7 (C_{12}), 58.5 (C_{13}), 126.5, 128.1, 128.2, 141.0 (ar). Anal. Calcd for $C_{18}H_{25}NO$: C, 79.72; H, 9.29; N, 5.17. Found: C, 78.83; H, 9.26; N, 5.27.

X-ray Analysis of *N*-Benzyl-11-hydroxy-1,8,8-trimethyl-3-azabrendan-4-one (2). Crystal data: $C_{18}H_{23}NO_2$, M_r 285.37; orthorhombic; a = 18.738 (8) Å, b = 11.561 (5) Å, and c = 7.090 (4) Å; space group $P2_12_12_1$; Z = 4, ρ_{calcd} = 1.234 g cm^{-3}; λ = 1.5418 Å.

A crystal of dimensions 0.5 × 0.16 × 0.16 mm was mounted on a four-circle diffractometer, Philips PW1100, using graphite-monochromated Cu Kα radiation. From a total of 1670 measured independent reflections, 1317 with $I > 3\sigma(I)$ were considered observed. Lorentz and polarization corrections were applied. The structure was solved by direct methods using a local program[14] and refined by a large blocks least-squares method.[15] The refinement converged at R and R_w values of 0.049 and 0.047 respectively:

$$R = \sum||F_o| - |F_c||/\sum|F_o|$$

$$R_w = \{\sum w(|F_o| - |F_c|)^2/\sum wF_o^2\}^{1/2}$$

$$w = 1/\sigma^2(F_o) + 0.010\,657F_o^2$$

All hydrogen atoms were found on difference Fourier syntheses, and their atomic coordinates and isotropic thermal parameters were refined. Maximum residuals were 0.10 e $Å^{-3}$.

Atomic coordinates of non-hydrogen atoms and hydrogen atoms (Tables 1 and 2), anisotropic thermal parameters (Table 3), bond lengths (Table 4), and angles (Table 5) are available as supplementary material. Structure factors are available from the crystallographer authors.

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Registry No. **1**, 113132-67-5; **2**, 113132-68-6; **3**, 105512-51-4; **4**, 105512-52-5; **5**, 105562-05-8; **6**, 105512-53-6; **7**, 113132-69-7; **8**, 113215-78-4.

Supplementary Material Available: Tables of atomic coordinates, anisotropic thermal parameters, bond lengths, and angles (3 pages). Ordering information is given on any current masthead page.

(11) Because of the existence of two rotamers of the amide moiety, the signals of several ^1H groups are doubled. We indicate here the chemical shifts related to the more abundant rotamer.

(12) Owing to the existence of two rotamers of the amide moiety, several carbon atoms do lead to two NMR signals. We indicate here the chemical shift of the major rotamers; the one corresponding to the same carbon atom in the minor isomer is indicated in parentheses.

(13) The assignments of the carbon atoms marked by the same signs are interchangeable.

(14) Riche, C. 7th European Crystallographic Meeting, Jerusalem, 1982; Abstract 25.

(15) Sheldrick, G. 1976 SHELX76. A program for crystal structure determination, University of Cambridge, England.

Monobromination of Deactivated Active Rings Using Bromine, Mercuric Oxide, and Strong Acid

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Electrophilic substitution of aromatic hydrocarbons by bromine is a well-known organic reaction.[1] Recently, the reagents such as NBS in DMF,[2] bromine and thallium(III) acetate,[3] and $CuBr_2$,[4] have been successfully used for the

(1) Fuson, R. C. *Reactions of Organic Compounds*; Wiley: New York, 1962; pp 58–65, 98–102. Norman, R. O. C.; Taylor, R. *Electrophilic Substitution in Benzenoid Compounds*; Elsevier: New York, 1965; pp 130–132. Braendin, H. P.; McBee, E. T. *Friedel–Crafts and Related Reactions*; Wiley: New York, 1964; Vol. III, Chapter 46. Djerassi, C. *Chem. Rev.* **1948**, *48*, 271.

(2) Mitchell, R. H.; Lai, Y. H.; Williams, R. V. *J. Org. Chem.* **1979**, *44*, 4733.

(3) McKillop, A.; Bromley, D.; Taylor, E. C. *J. Org. Chem.* **1972**, *37*, 88.

(4) Mosnaim, D.; Nonhebel, D. C. *Tetrahedron* **1969**, *25*, 1591.

0022-3263/88/1953-1799$01.50/0