Synthesis of (5R,10S,11R)-(+)-10,11-Dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imin-11-ol: A Hydroxylated Metabolite of MK-0801

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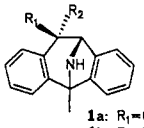
Two approaches to the synthesis of the MK-0801 metabolite, (5R,10S,11R)-(+)-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imin-11-ol (**1a**), from dibenzosuberenone (**2**) are presented. Selective ring opening of an aziridine with acetyl bromide and inversion of the stereochemistry provide **1a**. Alternatively, formation of an oxazolidinone ring at the 10,11-position of the suberenone via a bromohydrin (**9**) is followed by acid-catalyzed cyclization of the oxazolidinone–carbinol **12** to provide **1a**. A practical resolution for obtaining the active 5R,10S,11R-(+) enantiomer is described.

Introduction

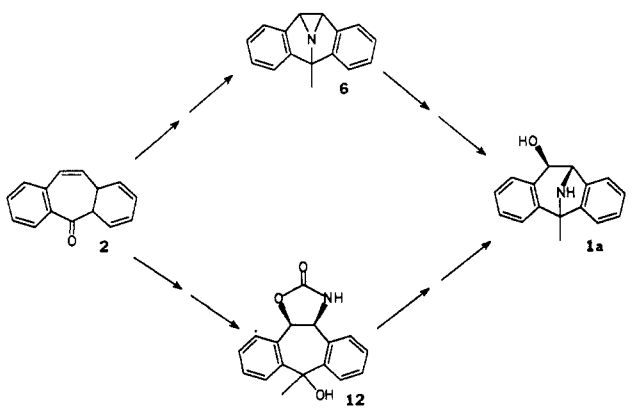
The dibenzo[a,d]cycloheptenimine MK-0801 (**1c**)[1,2] has been the focus of much attention because of its potent CNS activity as a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist.[3] Excitatory amino acids (e.g., glutamate and aspartate) are believed to be responsible for neuronal death that occurs as a result of seizures, cerebral ischemia, or an excess of the NMDA receptors in the brain. This has led to the recent study of MK-0801 as an anticonvulsant or a neuroprotective agent in the event of stroke, heart attack, and degenerative neurological disorders.[4] Studies of the biochemistry of MK-0801 have led to the isolation of a key metabolite: the 11-*exo*-hydroxy derivative **1a**.[5] The structure of this metabolite was subsequently confirmed by synthesis.[6] In order to provide sufficient material for pharmacological evaluation, more practical (i.e., higher yielding and chromatographically free) approaches to **1a** were required. Subsequent studies resulted in two alternate approaches, which are well suited to the preparation of **1a** in hundred-gram quantities.



1a: R_1=OH, R_2=H
1b: R_1=H, R_2=OH
1c: R_1, R_2=H

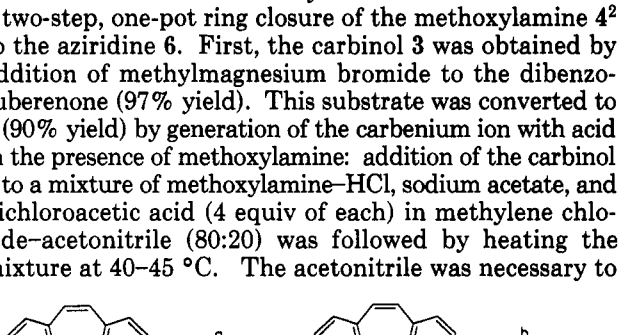
Both approaches began with commercially available dibenzosuberenone (**2**), also used in the synthesis of MK-0801 (Scheme I).[1,2] The key intermediate in the first approach was the aziridine **6**. The hydroxyl group was introduced late in the synthesis by selective opening of the aziridine ring. In the second route the hydroxyl group was added early in the synthesis by bromohydrin formation. The nitrogen was then introduced by acylation with an isocyanate and ring closure to the oxazolidinone **11**. Acid-catalyzed cyclization provided the cycloheptenimine ring system.

Scheme I



Results and Discussion

Aziridine Route. The key to the aziridine route was a two-step, one-pot ring closure of the methoxylamine **4**[2] to the aziridine **6**. First, the carbinol **3** was obtained by addition of methylmagnesium bromide to the dibenzosuberenone (97% yield). This substrate was converted to **4** (90% yield) by generation of the carbenium ion with acid in the presence of methoxylamine: addition of the carbinol **3** to a mixture of methoxylamine–HCl, sodium acetate, and dichloroacetic acid (4 equiv of each) in methylene chloride–acetonitrile (80:20) was followed by heating the mixture at 40–45 °C. The acetonitrile was necessary to



(a) MeMgBr/THF/20–25 °C; (b) $MeONH_2$·HCl/NaO_2CH_3/Cl_2CHCO_2H/CH_2Cl_2–CH_3CN/45 °C; (c) NaH/THF/DMSO/45 °C; then, 60–65 °C

(1) Christy, M. E.; Anderson, P. S.; Britcher, S. F.; Colton, C. D.; Evans, B. E.; Remy, D. C.; Engelhardt, E. L. *J. Org. Chem.* **1979**, *44*, 3117.
(2) Rothauser-Lamanec, T.; Bender, D. R.; DeMarco, A. M.; Karady, S.; Reamer, R. A.; Weinstock, L. M. *J. Org. Chem.* **1988**, *53*, 1768. The sequence 1 to 5 was originally reported in this reference. Our procedure provides an improved yield.
(3) Wong, E. H. F.; Kemp, J. A.; Priestley, T.; Knight, A. R.; Woodruff, G. N.; Iversen, L. L. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 7104.
(4) (a) Dagani, R. *Chem. Eng. News* **1986**, *64*, 23. (b) Barnes, D. M. *Science (Washington, D.C.)* **1987**, *235*, 632. (c) Kingman, S. *New Scientist* **1987**, *114*(1558), 34.
(5) Howard B. Hucker (MSDRL), unpublished results.
(6) (a) For the original syntheses of 11-*exo*-hydroxy-MK-0801 and the C-2, -7, -8, -10, (11-endo), -12, and -13 hydroxylated analogues of MK-0801, see: Britcher, S. F.; Lyle, T. A.; Thompson, W. J.; Varga, S. L. European Patent 0 264 183, 1988. Thompson, W. J.; Anderson, P. S.; Britcher, S. F.; Lyle, T. A.; Thies, J. E.; Magill, C. A.; Varga, S. L.; Schwering, J. E.; Lyle, P. A.; Christy, M. E.; Evans, B. E.; Colton, C. D.; Holloway, M. K.; Springer, J. P.; Hirshfield, J. M.; Ball, R. G.; Amato, J. S.; Larsen, R. D.; Wong, E. H. F.; Kemp, J. A.; Tricklebank, M. D.; Singh, L.; Oles, R.; Priestly, T.; Marshall, G. R.; Knight, A. R.; Middlemiss, D. N.; Woodruff, G. N.; Iversen, L. L. *J. Med. Chem.*, in press. For other approaches to hydroxylated analogues of 10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5,10-imines, see: (b) Karady, S.; Corley, E. G.; Abramson, N. L.; Weinstock, L. M. *Tetrahedron Lett.* **1989**, *30*, 2191. (c) Dygos, J. H. *J. Heterocycl. Chem.* **1976**, *13*, 1355.

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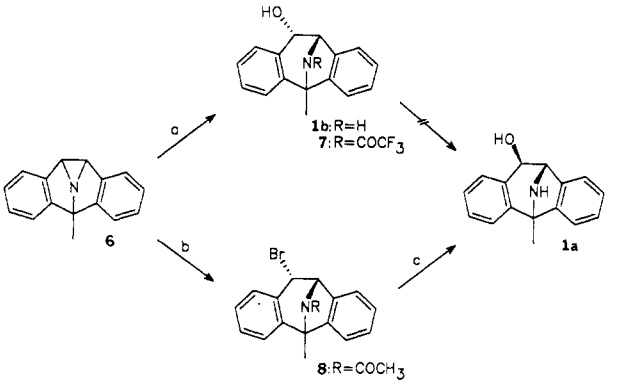
facilitate stirring. Ring closure to *N*-methoxy-MK-0801 (**5**) can be carried out with potassium *tert*-butoxide[2] in refluxing THF. Carbanion displacement of the methoxyl group of an *N*-methoxylamine is an effective approach to the formation of an aziridine ring.[7] While potassium *tert*-butoxide was not basic enough to effect ring closure to the aziridine, *n*-butyllithium in THF first gave ring closure to *N*-methoxy-MK-0801 (−78 °C) followed by closure to the aziridine (−20 °C). Unfortunately, a major byproduct, 11-butyl-MK-0801, was obtained by opening of the aziridine with butyllithium. A mild, high-yielding procedure using sodium hydride in THF–DMSO (2:1) produced the aziridine free of byproducts in 87% yield.[8] This provided the first synthesis of an unsubstituted dibenzoazasemibullvalene. Haire[9] has previously reported the preparation of a 5-alkoxydibenzoazasemibullvalene.

Ring opening of the aziridine with acid did not give selective cis addition. The acid-catalyzed ring opening of an aziridine with a secondary carbon atom can occur by both S_N1 and/or S_N2 processes.[7] Depending on the substitution pattern and reaction conditions, the nucleophile adds via either a concerted process or a carbenium ion intermediate. The former is expected to give all-trans addition, whereas the latter can provide a mixture of the cis and trans isomers, as well as rearranged products. Both processes were observed with **6**. The *endo*-hydroxy derivative **1b** was cleanly obtained in 96% yield by addition of trifluoroacetic acid to a THF solution of the aziridine (trans addition).[10] Reaction of the aziridine with 5% aqueous sulfuric acid[11] provided a 6:1 mixture of the trans/cis isomers and unidentified anthracene byproducts, through a mechanism similar to that shown in ref 15. By adding THF (9 parts THF) the selectivity of the ring opening was increased (95:5 trans/cis). THF suppressed the formation of the carbenium ion, providing better selectivity. The cis addition was completely avoided by replacing aqueous sulfuric acid with trifluoroacetic acid in THF.

Since the trans ring opening of the aziridine was the more selective reaction, inversion at the 11-position was studied. The hydroxy group of **1b** did not invert under hydrolysis conditions in the presence of sulfuric acid. The *N*-trifluoroacetamide **7** of **1b** was prepared in 72% yield by addition of trifluoroacetic anhydride to the aziridine in tetrahydrofuran followed by cleavage of the trifluoroacetate ester with aqueous ammonium hydroxide. Attempted inversion of the hydroxy group using the Mitsunobu reaction[12] failed. The 11-*endo*-bromo-*N*-acetyl derivative **8** was prepared in 92–95% yield by treatment of the aziridine with acetyl bromide in methylene chloride.[13] The bromine atom was not easily displaced under nucleophilic conditions. Potassium acetate and cesium acetate in DMF at 100 °C were not effective for inversion of the center.[14] Addition of silver nitrate (1.2 equiv) to **8** in aqueous THF gave a 55–58% yield of 11-*exo*-hydroxy-MK-0801 (**1a**) after hydrolysis of the amide group (acetic acid–aqueous sulfuric acid). The major byproduct of this solvolysis reaction was the highly fluorescent 9-methylanthracene (mp 76–77 °C)[15] formed by rearrangement of the aryl group and decarbonylation.



(a) CF_3CO_2H/THF/25 °C; (b) CH_3COBr/CH_2Cl_2/3–7 °C; (c) i, $AgNO_3$/THF–H_2O/40 °C; ii, $CH_3CO_2H/H_2O/H_2SO_4$, 90–100 °C

Oxazolidinone Route. Recently, acyl isocyanates have been reported to be effective reagents for the preparation of *cis*-1,2-amino alcohols via oxazolidin-2-one intermediates.[16] Knapp[16a] has developed a method for converting bromohydrins to the *cis*-1,2-amino alcohols with benzoyl isocyanate. Thus, dibenzosuberenone (**2**) was converted to the bromohydrin **9** in 95% yield by using 1.5 equiv of *N*-bromosuccinimide in 9:1 water–acetone at 40–50 °C.[17] Typical conditions for preparing a bromohydrin (NBS in an aqueous ethereal solvent mixture) provided near

(7) For the preparation and reactions of the aziridine ring, see: (a) Dermer, O. C.; Ham, G. E. *Ethyleneimine and Other Aziridines; Chemistry and Applications*; Academic Press: New York, 1969. (b) Deyrup, J. A. In *Small Ring Heterocycles; Vol. 1; Aziridines, azirines, thiiranes, thiirenes*; Hassner, A., Ed.; Wiley: New York, 1983; pp 1–214. (c) After submission of this work, an analogous aziridine of the dibenzocyclooctadiene series was reported: Leeson, P. D.; James, K.; Baker, R. *J. Chem. Soc., Chem. Commun.* **1989**, 433.

(8) It is interesting to note that ring closure to *N*-methoxy-MK-0801 or to the aziridine did not occur with NaH in THF.

(9) (a) Haire, M. J. *J. Org. Chem.* **1980**, *45*, 1310. (b) Haire, M. J., U.S. Patent 4,123,546; Oct. 31, 1978.

(10) Alternatively, **1b** has been obtained by treatment of **6** with acetic acid/sodium acetate followed by saponification of the 11-*endo*-acetate (65% overall yield); see ref 6a.

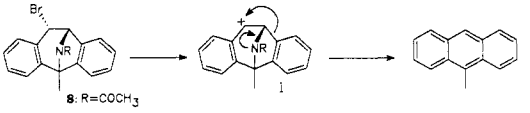
(11) Nelson, W. L.; Sherwood, B. E. *J. Org. Chem.* **1974**, *39*, 66.

(12) For a discussion of the Mitsunobu reaction, see: Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487 and references therein.

(13) The 11-chloro-*N*-benzoyl analogue was similarly prepared by addition of benzoyl chloride to **6**. The substrate was unreactive with silver nitrate. In addition, heating of this substrate in acetone did not give displacement of the halide by the amide oxygen to provide the *exo*-hydroxy compound (cf. ref 11).

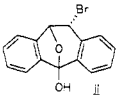
(14) In the original synthesis of 11-*exo*-hydroxy-MK-0801 (ref 6a) the *O*-methylsulfonyl-*N*-*tert*-butylcarbamate derivative of **1b** was converted to a 3:2 mixture of the *endo*/*exo*-acetoxy derivatives with tetrabutylammonium acetate. The acetate isomers were hydrolyzed to the isomers of 11-hydroxy-MK-0801 **1a** and **1b** and separated by HPLC.

(15) The formation of the anthracene ring system is believed to occur via the carbenium intermediate i. Rearrangement is followed by decarbonylation in the case of **8**:

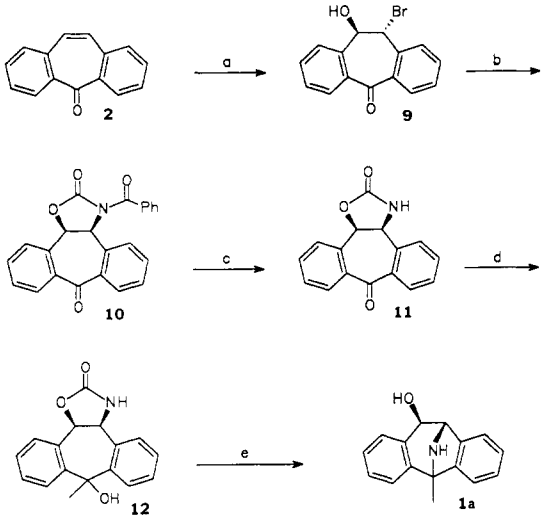


(16) (a) Knapp, S.; Kukkola, P. J.; Sharma, S.; Pietranico, S. *Tetrahedron Lett.* **1987**, *28*, 5399. (b) McCombie, S. W.; Nagabhushan, T. L. *Tetrahedron Lett.* **1987**, *28*, 5395. (c) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792.

(17) The bromohydrin exists as an equilibrium mixture of the open bromohydrin **9** and the ring-closed hemiketal ii (~94:6) by ^1H and ^{13}C NMR analysis (see Experimental Section for data). The presence of a peak at 104.7 ppm (ketal carbon) in the ^{13}C NMR and the two sets of doublets at δ 5.77 and 5.55 (J = 6.01 Hz) provide strong evidence for the structure ii.



quantitative conversion to the *trans*-dibromide.



(a) NBS/acetone–H_2O/40 °C; (b) benzoyl isocyanate/THF/room temperature; then, NaH/45–50 °C; (c) LiOH·H_2O/THF–H_2O; (d) MeLi/THF; (e) MeOH/H_2SO_4/reflux; then, 6 N aqueous HCl/reflux

Bromohydrin **9** was quantitatively converted to the *N*-benzoyloxazolidinone **10** in one pot by treatment with benzoyl isocyanate in THF to form the benzoylcarbamate intermediate. The ring closure was brought about by addition of sodium hydride and heating the mixture at 40–45 °C for 1 h. The *N*-benzoyloxazolidinone **10** was isolated as a solid in 88% yield. The benzoyl group was removed by selective saponification with lithium hydroxide to provide the oxazolidinone **11** in 80% yield. Addition of methyllithium in THF gave the carbinol **12** in 84% yield. The overall synthesis of this key intermediate was straightforward and each intermediate was isolated easily as a crystalline solid.

The key cyclization to the dibenzo[*a*,*d*]cyclohepten-5,10-imine ring system could not be carried out on the oxazolidinone directly. Attempts at acid-catalyzed ring closure with azeotropic removal of water failed to provide any product. The intramolecular cyclization of amides with a benzhydryl alcohol moiety to form the corresponding lactams was studied by Mao and Hauser.[18] The optimal conditions were reported to be refluxing acetic acid–sulfuric acid. The carbamate **12** did not cyclize under these conditions. Apparently, the cyclization of the oxazolidinone was unfavorable due to ring strain. The oxazolidinone was converted to the methyl carbamate in situ [refluxing methanol–sulfuric acid (20:1)] to overcome this problem. The intermediate was not isolated but cyclizes directly to form a mixture of acylated products and **1a**.[19] The acylated intermediates were hydrolyzed without isolation by addition of 6 N aqueous hydrochloric acid to the reaction mixture. 11-*exo*-Hydroxy-MK-0801 (**1a**) was isolated in 67% yield.

Resolution of (5*R*,10*S*,11*R*)-(+)-11-*exo*-Hydroxy-MK-0801 (1a). The active enantiomer of **1a** is the 5*R*,10*S*,11*R*-(+) isomer.[6a] Racemic material was resolved as the di-*p*-toluoyl-D-tartaric acid salt. Interestingly, the salt was a 2:3 mixture of the amino alcohol–diacid. Therefore, the salt was formed by addition of 150 mol % of the diacid to the amine in acetonitrile. The salt crystallized as a 97:3 mixture of diastereomers in 96% yield of theory. The mixture of diastereomeric salts was slurried in refluxing acetonitrile and the isolated salt was broken to provide an overall 65% yield of >99% (+) enantiomer. The enantiomeric ratio of **1a** was determined by conversion to the bis-benzoyl derivative and assay on a chiral Pirkle L-phenylglycine covalent column.

(18) Mao, C. L.; Hauser, C. R. *J. Org. Chem.* **1970**, *35*, 3704.

(19) A similar approach to **1a** has been previously carried out by cyclization of the corresponding *tert*-butylcarbamate obtained by using the Sharpless oxamination reaction; see ref 6a.

Summary

Two straightforward syntheses of the 10-amino-11-hydroxy substitution pattern of the dibenzocycloheptene system have been presented. The first reported synthesis of an unsubstituted dibenzoazasemibullvalene, the aziridine **6**, will make a variety of analogues of the dibenzo[*a*,*d*]cycloheptenimine system available. Both the endo and exo derivatives can be prepared by selective trans-opening of the aziridine ring; the exo product can then be obtained by inversion. The application of Knapp's procedure to the synthesis of 10,11-amino alcohol substituted dibenzosuberenones has also been demonstrated. The synthesis was culminated by the development of an effective cyclization procedure to form the dibenzo[*a*,*d*]-cyclohepten-5,10-imine ring system from a 10-carbamoyldibenzosuberenone, further expanding the available entries into this medicinally important class of compounds. A resolution procedure and chiral assay of the resolved product have been demonstrated.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AM-250 instrument (^{1}H NMR at 250 MHz, ^{13}C NMR at 63 MHz). Analytical high-performance liquid chromatography (HPLC) was carried out by using a Beckman Model 110B pump with Model 421A gradient controller, LDC SpectroMonitor 3000 variable wavelength detector, and the following columns: 4.6 mm × 25 cm Zorbax C-8 (DuPont), 4.6 mm × 25 cm Zorbax Phenyl (DuPont), 4.6 × 150 mm MICROSORB C-8 (Rainin). The chiral assay was carried out with an Altex Model 110A pump, LDC SpectroMonitor III variable wavelength detector, and a Pirkle L-phenylglycine covalent column (Regis). Retention times (t_R) are in minutes. Reactions were carried out under an atmosphere of N_2. As necessary, CH_2Cl_2, THF, CH_3CN, DMSO, DMF, and methanol were dried over molecular sieves.

5-Methyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol (3). An improved procedure to prevent acid-catalyzed elimination to the exo-methylene byproduct[2] follows. Under a nitrogen atmosphere a 3.0 M solution of methylmagnesium bromide in ethyl ether (474 mL, 1.42 mol) was added to THF (500 mL). The dibenzo[*a*,*d*]-cycloheptene **2** (200 g, 0.97 mol) in THF (400 mL) was added at 20–25 °C over 1.5 h. The reaction was aged at room temperature for 1 h and quenched by adding the mixture to an aqueous solution (1000 mL) of glacial acetic acid (111 mL, 1.94 mol) and sodium acetate (160 g, 1.94 mol) at 10–15 °C. The reaction mixture was rinsed with THF (400 mL). The layers were separated and the organic layer was washed with brine (500 mL). The solution of the carbinol **3** was concentrated to 400 mL and cyclohexane was added to bring the volume to 1600 mL, whereupon the carbinol crystallized from solution. The procedure was repeated two more times. The cyclohexane solution was cooled at 10 °C for 1 h and the solid was filtered: 187 g, 87% yield, (cyclohexane), mp 114–15 °C (lit.[2] mp 113.5–115 °C). A second crop was collected to bring the total yield to 97%.

***N*-Methoxy-5-methyl-5*H*-dibenzo[*a*,*d*]cycloheptene-5-amine (4).** A mixture of methoxylamine hydrochloride (37.6 g, 0.45 mmol) and anhydrous sodium acetate (36.8 g, 0.45 mmol) was suspended in a solution of acetonitrile (60 mL) and methylene chloride (150 mL). Dichloroacetic acid (37 mL, 0.45 mmol) was added neat at room temperature over 5–10 min. The exotherm heated the mixture to 30–40 °C. The mixture was heated at 43–45 °C for 30 min. The slurry was then cooled to room temperature and the carbinol **3** (25 g, 0.112 mmol) in methylene chloride (125 mL) and acetonitrile (10 mL) was added to the milky mixture

over 45 min at 20–25 °C. The mixture was then heated at 45 °C for 2–3 h. **Caution! Extreme care should be exercised during this reaction to avoid the loss of methylene chloride. A large exotherm above the reflux temperature was observed at Merck in the hazard evaluation of this class of reactions (see ref 2).** Once the carbinol (t_R 8.4 min) had been converted to the methoxylamine (t_R 6.5 min) by HPLC analysis (MICROSORB C-8, 4.6 × 150 mm; 50:50:0.1 CH_3CN–H_2O–CF_3CO_2H; 1.5 mL/min; 230 nm) the mixture was cooled to 10–15 °C and 15% aqueous ammonium hydroxide (250 mL) was added at <20 °C. The organic phase was separated and washed with brine (100 mL). The methylene chloride solution was filtered and concentrated to 100 mL. Hexanes (200 mL) was added, whereupon the solid began to crystallize. The mixture was concentrated to 100 mL again and diluted with hexanes (100 mL). Concentration to 100 mL was carried out once more and the resultant slurry was diluted with hexanes (150 mL). The mixture was cooled at −15 °C for 2 h. The methoxylamine **4** as a white solid was filtered, washed with cold hexanes (−15 °C, 200 mL), and vacuum dried (25.8 g, 91% yield). A sample was recrystallized from hexanes: sealed tube mp 125–27 °C, softens at 114 °C (lit.[2] mp 118.5–126.0 °C).

8b,8c-Dihydro-4b-methyl-4b*H*-azirino[2,1,3-*cd*]dibenzo-[*a*,*f*]pyrrolizine (6). Sodium hydride (4.77 g as an 80% oil dispersion, 0.159 mol) was suspended in tetrahydrofuran (50 mL) and dimethyl sulfoxide (50 mL) was added slowly at room temperature. **Caution! Mixtures of sodium hydride and DMSO have been reported to be explosive.**[20] The mixture was stirred at room temperature for 1 h under a nitrogen atmosphere. The methoxylamine **4** (10.0 g, 39.8 mmol) in tetrahydrofuran (70 mL) was added slowly to the slurry. The mixture was stirred at room temperature for 1.5 h. The mixture was then heated at 45 °C for 2.5 h. The conversion of the methoxylamine **4** (t_R 6.9 min) to *N*-methoxy-MK-0801 (**5**) (syn and anti isomer;[2] t_R 6.33 min and 5.84 min, respectively) was observed by HPLC: Zorbax C-8; 70:30:0.1 MeCN/H_2O/H_3PO_4; 1.2 mL/min; 210 nm. The reaction mixture was then heated at 60–65 °C for 13–18 h or until the ring closure of the aziridine (t_R 13.50 min) was complete. Water (50 mL) was added carefully to quench the excess sodium hydride over 45 min, keeping the temperature of the mixture <10 °C. The mixture was concentrated to 125 mL under reduced pressure at 30 °C to remove the volatiles. The aqueous DMSO mixture was partitioned between water (200 mL) and ethyl ether (200 mL). The layers were separated and the aqueous phase was washed with ethyl ether (50 mL). The combined organic layers were washed with water (3 × 50 mL). The solution was passed through silica gel (25 g) and the silica gel was rinsed with ethyl ether (180 mL). The combined eluents were concentrated to approximately 90 mL. The aziridine began to crystallize from solution. Hexanes (90 mL) was added. The slurry was concentrated to 90 mL again and hexanes (90 mL) was added. After the slurry was concentrated to 90 mL once more, the mixture was cooled to −15 °C for at least 2 h. The solid was filtered, washed with cold hexanes (−15 °C), and vacuum dried: 6.7 g, 77% yield. A second crop was obtained by concentrating the filtrate to 15 mL to provide 0.85 g of the aziridine as a light-yellow solid (87% overall yield). An analytical sample was recrystallized from hexanes: mp 107–109 °C; ^1H NMR ($CDCl_3$) δ 7.4–7.0 (m, 8 H), 4.05 (s, 2 H), 1.95 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.5, 133.9, 127.5, 127.2, 124.3, 119.0, 80.0, 56.0, 21.3. Anal. Calcd for $C_{16}H_{13}N$: C, 87.62; H, 5.99; N, 6.39. Found: C, 87.23; H, 6.16; N, 6.34.

(5α,10α,11β)-10,11-Dihydro-5-methyl-5*H*-dibenzo[*a*,*d*]-cyclohepten-5,10-imin-11-ol (1b). The aziridine **6** (0.5 g, 2.28 mmol) was dissolved in tetrahydrofuran (9 mL). Trifluoroacetic acid (1 mL) was added at 25 °C over 5 min. After 22 h the reaction was complete by HPLC analysis: aziridine (t_R 3.9 min); amino alcohol (t_R 2.1 min); MICROSORB C-8, 4.6 × 150 mm; 50:50:0.1 CH_3CN–H_2O–CF_3CO_2H; 1.5 mL/min; 230 nm. The reaction solution was cooled in an ice bath and was treated with concentrated ammonium hydroxide (5 mL) at <10 °C. The mixture was concentrated to 5 mL under vacuum. The product was extracted into methylene chloride (2 × 10 mL). More concentrated ammonium hydroxide (5 mL) was added and the aqueous solution was washed with methylene chloride (10 mL). The combined organic layers were washed with water (5 mL). The solution was concentrated to 10 mL and hexanes (20 mL) was added; the procedure was repeated twice. The amino alcohol crystallized during the process. The mixture was chilled at −15 °C for 2 h. The solid was filtered, washed with hexanes, and vacuum dried to provide 0.519 g (96%) of the *trans*-amino alcohol **1b** as an off-white solid. An analytical sample was prepared by decolorization (Darco G-60) and recrystallization from acetonitrile: mp 187–188.5 °C; ^1H NMR ($CDCl_3$) δ 7.41–7.35 (m, 2 H), 7.25–7.1 (m, 6 H), 5.14 (d, J = 6.01 Hz, 1 H), 4.65 (d, J = 6.01 Hz, 1 H), 3.1–2.4 (br s, 2 H), 1.88 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.2, 143.9, 140.3, 135.9, 129.4, 127.71, 127.67, 127.2, 126.7, 124.5, 120.8, 119.4, 67.8, 65.0, 63.8, 19.9. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.97; H, 6.38; N, 5.90. Found: C, 80.87; H, 6.52; N, 5.91.

(5α,10α,11β)-12-Acetyl-11-bromo-10,11-dihydro-5-methyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (8). The aziridine **6** (3.0 g, 13.7 mmol) was dissolved in methylene chloride (60 mL) and the solution was cooled in an ice bath. Acetyl bromide (1.22 mL, 16.44 mmol) was added dropwise at 3–7 °C over 10 min via syringe. After 12 h the aziridine (t_R 8.1 min) had completely reacted to afford the bromide (t_R 3.58 min) by HPLC analysis (Zorbax C-8; 55:45:0.1 MeCN/H_2O/H_3PO_4; 1.5 mL/min; 210 nm. The solution was treated with saturated aqueous sodium bicarbonate (25 mL) and the mixture was stirred at room temperature for 30 min. The layers were separated, and the organic phase was washed with water (25 mL) and decolorized (Darco G-60, 60 mg). The volatiles were evaporated, providing the crude product, which crystallized upon addition of cyclohexane (30 mL). The mixture was heated to reflux for a few minutes and then stirred at room temperature for 1 h. The mixture was cooled in an ice bath (the cyclohexane does not freeze) for 1 h. The product was filtered, washed with cold cyclohexane, and suction dried. The bromide was obtained as an off-white solid (4.44 g, 95%). An analytical sample was prepared by recrystallization from ethanol: mp 161–162 °C; ^1H NMR (DMSO-d_6) δ 7.52 (m, 1 H), 7.35 (m, 2 H), 7.4–7.2 (m, 5 H), 6.22 (d, J = 5.55 Hz, 1 H), 5.66 (d, J = 5.55 Hz, 1 H), 2.25 (s, 3 H), 2.20 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 169.0, 150.0, 144.6, 135.6, 132.4, 132.2, 128.1, 127.7, 126.4, 125.6, 121.9, 118.7, 66.0, 64.2, 48.7, 22.0, 18.9. Anal. Calcd for $C_{18}H_{16}NOBr$: C, 63.16; H, 4.72; N, 4.09. Found: C, 62.98; H, 4.66; N, 4.10.

(5α,10α,11β)-10,11-Dihydro-12-(trifluoroacetyl)-5-methyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imin-11-ol (7). The aziridine **6** (0.5 g, 2.28 mmol) was dissolved in tetrahydrofuran (9 mL) and the solution was cooled in an ice bath. Trifluoroacetic anhydride (1 mL) was added dropwise over 20 min at <10 °C. The solution was stirred at room temperature for 20 h. The solution was cooled in an ice bath and concentrated ammonium hydroxide (10 mL) was added at <15 °C. The mixture was stirred in the ice bath for 15 min and at room temperature for 1 h. The mixture was concentrated to 7 mL and water (10 mL) was added. The product was extracted with methylene chloride (3 × 10 mL). The combined organic layers were washed with water (10 mL) and decolorized (Darco G-60, 70 mg). The filtered solution was concentrated to dryness. The residue was taken up in ether and passed through a silica gel plug (10 g). The eluent was evaporated and the residue was triturated with hexanes and ethyl ether (5:1, 6 mL). The solid was filtered and washed with cold hexanes (0.547 g, 72% yield). An analytical sample was prepared by chromatography (ethyl acetate–hexanes, silica gel) and recrystallization of the sample from ethyl acetate–hexanes: mp 123–125 °C; ^1H NMR ($CDCl_3$) δ 7.5–7.14 (m, 8 H), 5.1 (d, J = 6.01 Hz, 1 H), (dd, J = 6.01, 11.1 Hz, 1 H), 2.39 (s, 3 H), 1.8 (d, J = 11.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 149.5, 141.6, 134.5, 133.6, 129.7, 128.9, 128.7, 128.1, 127.9, 124.5, 121.4, 119.4, 118.6, 114.0, 69.3, 67.8, (64.40, 64.36), 18.0. Anal. Calcd for $C_{18}H_{14}NO_2F_3$: C, 64.85; H, 4.24; N, 4.2. Found: C, 64.71; H, 4.24; N, 4.19.

(5α,10α,11α)-10,11-Dihydro-5-methyl-5*H*-dibenzo[*a*,*d*]-cyclohepten-5,10-imin-11-ol (1a). The *N*-acetyl-11-bromo-5,10-iminodibenzocycloheptene **8** (2.0 g, 5.8 mmol) was dissolved in a mixture of tetrahydrofuran–water (1:1, 40 mL) and the reaction mixture was purged with nitrogen. Silver nitrate (1.19 g, 7.0 mmol) was added and the mixture was stirred overnight at room temperature. The reaction was not complete by HPLC: Zorbax C-8; 55:45:0.1 MeCN/H_2O/H_3PO_4; 1.5 mL/min, 210 nm). The mixture was heated at 40 °C until all the starting material

(20) French, F. A. *Chem. Eng. News* **1966**, *44*, 48.

(t_R 3.6 min) was gone. The reaction mixture was filtered and the salts were washed with tetrahydrofuran (35 mL). The volatiles were removed under vacuum, leaving an aqueous slurry of the intermediates. A mixture of water–acetic acid–concentrated sulfuric acid (5, 5, and 0.25 mL, respectively) was added. The reaction mixture was heated at 90 °C until all the *N*-acetyl-11-hydroxy compound (t_R 7.9 min) had been converted to the 11-*exo*-hydroxy-5,10-iminodibenzocycloheptene **1a** (t_R 5.9 min). The volatiles were removed by evaporation under vacuum and the residue was partitioned between water (40 mL) and toluene (40 mL). The mixture was filtered and the layers were separated. The aqueous layer was washed with toluene (10 mL). The combined toluene layers were washed with 10% acetic acid in water (10 mL). The combined aqueous layers were made basic with concentrated ammonium hydroxide (10 mL). The product precipitated and the slurry was stirred at room temperature for 1 h. The solid was filtered, washed with water, and suction dried: 0.813 g, 58%. An analytical sample was prepared by recrystallization from acetonitrile: mp 212–217 °C; ^{1}H NMR ($CDCl_3$) δ 7.40–7.00 (m, 8 H), 4.59 (d, J = 1.85 Hz, 1 H), 4.45 (d, J = 1.85 Hz, 1 H), 3.5–2.5 (br s, 2 H), 1.93 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 153.7, 144.8, 142.4, 134.8, 131.2, 127.7, 127.2, 126.5, 123.0, 120.8, 119.3, 69.6, 66.0, 64.8, 19.5. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.97; H, 6.38; N, 5.90. Found: C, 81.05; H, 6.59; N, 5.96.

***trans*-10-Bromo-10,11-dihydro-11-hydroxy-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (9).** Acetone (360 mL) was diluted to 400 mL with water. Dibenzosuberenone (40 g, 0.194 mol) was suspended in the solution and *N*-bromosuccinimide (51.8 g, 0.291 mol) was added portionwise at room temperature. The reaction mixture was heated at 45 °C under a nitrogen atmosphere for 18 h or until all the dibenzosuberenone (t_R 9.1 min) had been converted to the bromohydrin **9** (t_R 4.35 min) by HPLC analysis: MICROSORB C-8; 4.6 × 150 mm; 50:50:0.1 CH_3CN–H_2O–CF_3CO_2H; 1.5 mL/min; 230 nm. The yellow slurry was cooled to room temperature and then aged at ice-bath temperatures for 2 h. The solid was filtered, washed with water (600 mL), and vacuum dried. The crude bromohydrin (58 g, theoretical yield) was found to be contaminated with starting material and *trans*-10,11-dibromodibenzosuberenone (t_R 12.8 min). Weight-percent assay by HPLC using a standard analytical sample of the bromohydrin showed the product to be 95% pure (95% yield). The material was used in the next reaction without further purification since the byproducts were easily removed at this stage. An analytical sample of the bromohydrin was prepared by recrystallization from ethyl acetate–cyclohexane: mp 157–158 °C [lit.[21] mp 149 °C]; ^{1}H NMR ($CDCl_3$) δ 8.0 (m, 1 H), 7.8 (m, 1 H), 7.6–7.37 (m, 6 H), 5.6 (d, J = 6.01 Hz, 1 H), 5.22 (unresolved dd, 1 H), 2.75 (d, J = 4.62 Hz, 1 H); ^{1}H NMR (signals due to hemiketal ii[17] with relative ratios of H) δ 7.34–7.2 (m, 6 H), 5.77 (d, J = 6.01 Hz, 1 H), 5.55 (d, J = 6.01 Hz, 1 H), 3.99 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 228.9 138.4, 137.8, 137.5, 135.7, 132.8, 132.2, 132.1, 130.7, 130.1, 129.2, 129.1, 76.6, 52.3; ^{13}C NMR (signals due to hemiketal ii) δ 146.9, 137.2, 131.3, 129.3, 128.5, 128.0, 127.9, 125.7, 120.7, 118.9, 104.7, 80.1, 45.9. Anal. Calcd for $C_{15}H_{11}O_2Br$: C, 59.42; H, 3.66. Found: C, 59.26; H, 3.62.

3-Benzoyl-3a,12b-dihydro-2*H*-dibenzo[3,4:6,7]cyclohept[1,2-*d*]oxazole-2,8(3*H*)-dione (10). The bromohydrin **9** (44.2 g, 0.146 mol) was dissolved in tetrahydrofuran (880 mL), and benzoyl isocyanate (24.3 g, 0.163 mol) in tetrahydrofuran (100 mL) was added as a stream over a few minutes. The mixture was stirred for 2 h at room temperature or until all the bromohydrin **9** (t_R 4.5 min) had been converted to the carbamate intermediate (t_R 8.8 min) by HPLC assay: Zorbax C-8; 55:45:0.1 CH_3CN/H_2O/H_3PO_4; 1.5 mL/min; 210 nm. Sodium hydride (1.0 g) as an 80% oil dispersion was added, and the mixture was slowly heated to 40 °C. The remainder of the sodium hydride (4.26 g; 0.175 mol total) was added portionwise over 1 h. This was to allow the controlled release of hydrogen upon heating of the reaction mixture. The carbamate was converted to the oxazolidinone **10** (t_R 7.4 min) in 3.5 h at 45–50 °C. The mixture was cooled to 15 °C and the excess sodium hydride was quenched with an aqueous mixture (200 mL) of acetic acid (7.9 mL) and sodium acetate (12.0 g). The layers were separated and the organic phase was washed with brine (100 mL) and decolorized with Darco G-60. The filtercake was washed with tetrahydrofuran (200 mL). The filtrate was concentrated to 250 mL and cyclohexane (250 mL) was added. The resultant slurry of the white solid was cooled to 5 °C for 30 min. The solid was filtered, washed with cold tetrahydrofuran–cyclohexane (1:1, 300 mL), and vacuum dried. The oxazolidinone **10** (46.7 g, 88% yield) was obtained as a white solid that showed no contamination by dibenzosuberenone or *trans*-10,11-dibromodibenzosuberenone (HPLC). The solid, however, turned pink over time from impurities carried over from the bromohydrin. An analytical sample was prepared by treatment with Darco G-60 and recrystallization from acetonitrile: mp 243–245 °C; ^{1}H NMR (DMSO-d_6) δ 7.78–7.50 (m, 8 H), 7.5–7.48 (m, 5 H), 6.4 (d, J = 7.86 Hz, 1 H), (d, J = 7.86 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 197.5, 168.4, 152.2, 140.4, 138.9, 133.0, 132.8, 132.63, 132.58, 132.3, 131.7, 131.3, 130.6, 130.4, 129.5, 128.8, 128.1, 127.9, 127.1, 78.5, 61.2. Anal. Calcd for $C_{23}H_{15}NO_4$: C, 74.78; H, 4.10; N, 3.79. Found: C, 74.78; H, 4.10; N, 3.79.

3a,12b-Dihydro-2*H*-dibenzo[3,4:6,7]cyclohept[1,2-*d*]oxazole-2,8(3*H*)-dione (11). The *N*-benzoyloxazolidinone **10** (45.81 g, 124 mmol) was suspended in tetrahydrofuran–water (70:30; 600 mL) at room temperature. Lithium hydroxide monohydrate (41.96 g, 149 mmol) was added and the mixture was stirred for 1.5 h. The mixture was quenched into saturated ammonium chloride (400 mL). The layers were separated and the aqueous phase was washed with ethyl acetate (150 mL). The organic layers were combined, washed with brine, and concentrated to 200 mL. Cyclohexane (200 mL) was added. The resultant solid was filtered, washed with ethyl acetate–cyclohexane (1:1), and vacuum dried at 40 °C. The oxazolidinone **11** (26.3 g) was obtained in 80% yield. An analytical sample was prepared by recrystallization from acetonitrile: mp 228–229 °C; ^{1}H NMR (DMSO-d_6) δ 8.45 (s, 1 H), 7.7–7.4 (m, 8 H), 6.04 (d, J = 7.4 Hz, 1 H), 5.43 (d, J = 7.4 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 197.2, 157.2, 140.3, 139.7, 134.5, 132.2, 132.0, 131.8, 130.9, 130.0, 129.1, 128.1, 127.7, 79.9, 59.0. Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.19; N, 5.28. Found: C, 72.23; H, 4.24; N, 5.42.

3,3a,8,12b-Tetrahydro-8-hydroxy-8-methyl-2*H*-dibenzo[3,4:6,7]cyclohept[1,2-*d*]oxazol-2-one (12). The ketone **11** (25.2 g, 95 mmol) was suspended in tetrahydrofuran (500 mL) and the mixture was cooled to −15 °C. Methyllithium as a 1.4 M solution in ethyl ether (190 mL, 266 mmol) was added over 20 min and the reaction temperature was maintained at −5 to −2 °C. The mixture was stirred at −2 to 0 °C until the all the ketone had been consumed. The reaction was quenched by the addition of 600 mL of an aqueous solution of ammonium chloride (34 g). The mixture was acidified with acetic acid to pH 6. The layers were separated and the aqueous layer was washed with ethyl acetate. The organic phases were combined, washed with brine, and dried (sodium sulfate). The filtered solution was concentrated to 50 mL, and ethyl acetate (50 mL) and cyclohexane (200 mL) were added separately and sequentially. The solid was filtered, washed with ethyl acetate–cyclohexane (1:3), and vacuum dried at 40 °C. The carbinol **12** (22.4 g, 84%) was obtained as a white solid. An analytical sample was recrystallized from acetonitrile: mp 227–228 °C; ^{1}H NMR (DMSO-d_6) δ 8.77 (s, 1 H), 7.80 (m, 2 H), 7.5–7.16 (m, 6 H), 6.33 (d, J = 9.25 Hz, 1 H), 6.1 (s, 1 H), 5.75 (d, J = 9.25 Hz, 1 H), 1.93 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 156.8, 146.1, 145.6, 132.4, 131.0, 127.2, 127.0, 126.9, 126.8, 126.7, 125.7, 123.8, 123.3, 76.4, 72.1, 54.8, 27.7. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.57; H, 5.39; N, 4.98. Found: C, 72.70; H, 5.43; N, 5.07.

(5α,10α,11α)-10,11-Dihydro-5-methyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imin-11-ol (1a). The oxazolidinone **12** (1.0 g, 3.55 mmol) was suspended in a mixture of methanol (20 mL) and concentrated sulfuric acid (1 mL). This mixture was heated at reflux for 14–24 h until the oxazolidinone (t_R 3.2 min) had been completely converted to a mixture of acylated products (t_R 5.65 and 5.97 min) and an anthracene derivative (t_R 28 min) as shown by HPLC analysis: Zorbax C-8; 50:50:0.1 CH_3CN/H_2O/CF_3CO_2H; 1.5 mL/min; 230 nm. The yellow solution was cooled to room temperature and a mixture of water (10 mL) and 12 N aqueous hydrochloric acid (10 mL) was added. This mixture was heated at reflux for 12–24 h. All the acylated intermediates had been hydrolyzed to the 11-hydroxy-MK-0801 product (t_R 3.4 min). The reaction mixture was concentrated to 20 mL and 5% aqueous acetic acid (20 mL) was added. The mixture was again concen-

(21) Hoffman, F. W. *Chem. Abstr.* **1966**, *65*, 15927h.

trated to 20 mL. Toluene (20 mL) and 5% aqueous acetic acid (20 mL) were added to the concentrate. The phases were well mixed and then separated. The toluene layer was washed with 5% aqueous acetic acid (20 mL). The combined aqueous layers were washed with toluene (10 mL). The aqueous layer was filtered and the insolubles were redissolved by washing the filter with 5% aqueous acetic acid (40 mL). The combined filtrates were concentrated to 40 mL to remove dissolved toluene. The product as the acetate salt crystallized from solution. Water (50 mL) and acetic acid (8.5 mL) were added to the concentrate and the mixture was heated at 45 °C to redissolve the solids. The clear solution was cooled to 20 °C and concentrated ammonium hydroxide (25 mL) was added with stirring at <25 °C. The product precipitated out of solution as a white solid. The slurry was cooled at 5 °C for 1 h. The solid was filtered, washed with water (25 mL), and suction dried: 0.688 g as a crude product (83 wt % by HPLC). The crude solid (500 mg) was suspended in acetonitrile (5 mL) and the mixture was heated at reflux for 45 min. The slurry was cooled to room temperature and then was chilled in an ice bath for 30 min. The solid was filtered, washed with cold acetonitrile (3 mL), and suction dried: 410 mg, 67% overall yield: mp 214-215.5 °C. The ^{1}H NMR spectrum agreed with the spectra of **1a** from the aziridine route.

(5*R*,10*S*,11*R*)-(+)-10,11-Dihydro-5-methyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imin-11-ol (1a). The hydroxylated derivative of MK-0801 was resolved by heating a slurry of **1a** (85.6 g, 0.361 mol) in acetonitrile (856 mL) to reflux. Di-*p*-toluoyl-D-tartaric acid monohydrate (218.9 g, 0.541 mol) in acetonitrile (856 mL) was added, whereupon the amine dissolved. The mixture was allowed to cool to room temperature and the amine–acid salt began to crystallize. A mixture of acetonitrile-ethyl acetate (1:1, 430 mL) was added at room temperature. The resultant slurry was stirred at room temperature for 18 h. The solid was filtered, washed with acetonitrile (1 L), and suction dried (97:3 ratio of (+)/(-) enantiomers, 96% yield of theory). The filtercake (161.7 g) was slurried in acetonitrile (2100 mL) and the slurry was heated at 70–75 °C for 2 h. The mixture was then cooled to room temperature. After a few hours the solid was filtered, washed with acetonitrile (1 L), and vacuum dried (100 g, 65% yield of 27 wt % amine). The salt was partitioned between water (1 L) and isopropyl acetate (500 mL). Concentrated ammonium hydroxide (50 mL) was added until the aqueous phase was basic. Additional isopropyl acetate (500 mL) did not dissolve the crystallized solid. Therefore, the solid was filtered and the two phases of the filtrate were separated. The aqueous layer was washed with isopropyl acetate (500 mL). The combined isopropyl acetate layers were evaporated to dryness under vacuum. The isolated solid was combined with the filtered solid. This mixture was dissolved in 5% aqueous acetic acid (750 mL). The insolubles were filtered and washed with 5% aqueous acetic acid (100 mL). The combined filtrates were made basic with stirring by addition of concentrated ammonium hydroxide (80 mL). The resultant slurry was stirred at room temperature for 30 min. The solid was filtered and washed with water and vacuum dried (25.6 g, 31% yield): mp 217–219 °C; $[\alpha]_D$ +109° (c = 1, methanol) as the maleate salt (prepared from 2-propanol–water, 9:1). Chiral HPLC assay (bis-benzoyl derivative; Pirkle L-phenylglycine covalent; 80:10:1 hexanes/CH_2Cl_2/2-propanol; 1.5 mL/min, 230 nm) gave a >99:1 ratio of the 5*R*,10*S*,11*R*-(+) enantiomer (t_R 8.0 min) to the 5*S*,10*R*,11*S*-(-) enantiomer (t_R 6.1 min). The absolute configuration of (+)-**1a** was established by comparison to the final product **1a** obtained in an alternative synthesis.[5]

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New Solid-Phase Catalysts for Asymmetric Synthesis: Cross-Linked Polymers Containing a Chiral Shiff Base–Zinc Complex

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A cross-linked polystyrene resin containing chiral primary amino alcohol moieties bound through the ether linkage to some of its *p*-methylene-substituted aromatic rings is a useful regenerable chiral auxiliary in the enantioselective catalytic alkylation of aldehydes. The primary amino groups of the chiral amino alcohols react with the aldehydes to form Schiff bases, which catalyze the addition of dialkylzinc to aldehydes leading to optically active secondary alcohols having enantiomeric purity of up to 99%. A series of polymeric amino alcohols were synthesized by two methods involving either attachment of a chiral moiety as a side chain onto a reactive cross-linked polystyrene, or the terpolymerization of a chiral monomer with styrene and a cross-linking agent. New cross-linking agents affording more flexibility to the chiral catalysts were used in the preparation of the chiral polymers and found to provide excellent performance. An interesting extension of the method is its adaptation to a continuous-flow system where diethylzinc and aldehyde are supplied continuously to a column filled with the chiral polymeric catalyst. Large amounts of chiral products and high turnovers may be obtained by this method.

Introduction

Polymers containing main-chain or pendant chirality are finding a number of interesting applications in organic chemistry. While most early work in the application of chiral polymers for asymmetric processes was directed toward materials useful in the chromatographic separation of enantiomers,[1] several reports of the use of polymers as chiral auxiliaries in asymmetric syntheses have appeared. These include polymeric phase-transfer catalysts[2] or chiral polymers used in asymmetric addition[3] or alkylation[4] re-

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