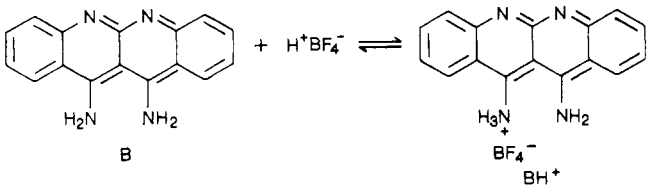
H). MS (EI, rel intensity): 443 ($M^+ + 1$, 4.5), 442 (M^+, 4.7), 377 (12.3), 376 (24.9), 276 (14.7), 275 (32.4), 261 (34.2), 260 (57.1), 259 (11.2), 209 (11.5), 195 (22.6), 194 (100.0), 119 (35.9), 108 (12.7) *m/e*. Anal. Calcd for $C_{26}H_{18}N_8$: C, 70.58; H, 4.07; N, 25.34. Found: C, 69.70; H, 4.14; N, 24.84.

Method 2. To 150 mg of **3** (0.5 mmol) in 5 mL of acetone was added 100 mg of sodium azide (1.54 mmol) in 2.5 mL of water at 0 °C while stirring. The resulting mixture was stirred at 0 °C for 1 h. Then 10 mL of cold water was added and a white solid was collected by filtration.[9] The solid was dissolved in 10 mL of dimethoxyethane and dried with $MgSO_4$. After filtration, 150 mg of aniline was added to the solution and the mixture was heated to 60–70 °C for 1 h. The solvent was then removed under vacuum and the residue was washed with benzene and methanol to afford 152 mg (yield 69%) of a white-grey product, identical by ^1H NMR and IR with the product obtained by method 1.

Measurements of pK_a.[5] Observation of the equilibrium protonation was made spectrophotometrically at 411.0 nm where 1 (or B below) absorbs strongly. Upon titrating with tetrafluoroboric acid, the absorbance decreased. In 80% (v/v) DMSO–H_2O at 20 °C with 10^{-4} mol/L B, the absorbance at 411.0 nm was measured in the presence of various concentrations of tetrafluoroboric acid in the range 2×10^{-5} to 7×10^{-5} mol/L. The equilibrium constants for the above reaction can be expressed as and can thus be obtained from the measured absorbance at



$$K_b = [BH^+]/[B][H^+]$$
$$K_a = [B][H^+]/[BH^+]$$

each hydrogen ion concentration. The average pK_a value is 3.3 ± 0.2. Since the difference in λ_{max} of the conjugate acid and base forms of 9-aminoacridine and 1,8-diaminonaphthalene were too small to give an accurate value for their pK_a's by direct titration, we used *p*-nitrophenol as an indicator in a spectrophotometric titration. Thus, *p*-nitrophenol (1×10^{-4} M) was titrated with 2 $\times 10^{-4}$ M 9-aminoacridine while monitoring the strong 321-nm absorption of the nitrophenol was monitored. The equilibrium constant was

$$K = \frac{[B_1^-][B_2H^+]}{[B_1H][B_2]} = \frac{K_{B_2}}{K_{B_1}}$$

where K_{B_1} is the dissociation constant of *p*-nitrophenol (determined previously) and K_{B_2} is the dissociation constant of the conjugate acid of the base whose K_a is unknown; finally,

$$pK_a = -\log K_{B_2}$$

Acknowledgment. We are indebted to the National Science Foundation for support of this work; Grant DMR 86-01206.

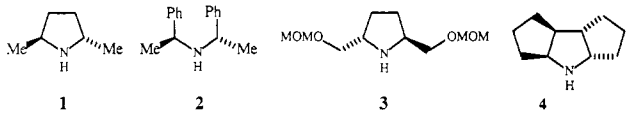
(*R,R*)-1,3-Dibenzylisoindoline: A New C_2-Symmetric Secondary Amine, by Stereoselective and Regioselective α,α'-Dialkylation of Isoindoline, and an Improved Procedure for the Preparation of Isoindoline

Robert E. Gawley,* Sanjay R. Chemburkar, Arthur L. Smith, and Tarakeshwar V. Anklekar

Department of Chemistry, University of Miami, Coral Gables, Florida 33124

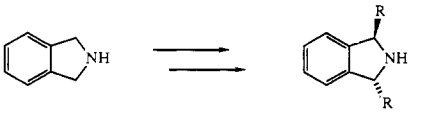
Received August 3, 1988

The advantages inherent in C_2 symmetry for asymmetric processes were first enunciated by Kagan in 1972, in the context of chiral phosphine design for asymmetric hydrogenation.[1] In 1977, Whitesell published the resolution of *trans*-2,5-dimethylpyrrolidine, **1**,[2] a C_2-symmetric amine which has seen some use in asymmetric processes[2,3] and has also been synthesized from alanine.[4] An amine with similar symmetry, **2**, was prepared much earlier by Overberger[5] and has been used as an enantioselective deprotonating agent[3a,6] and proton source.[7] Katsuki has used a MOM-protected *trans*-2,5-bis(hydroxymethyl)-pyrrolidine, **3**, as chiral auxiliary in a number of asymmetric processes.[8] In the accompanying paper, Whitesell reports the synthesis and resolution of a new C_2-symmetric pyrrolidine, **4**, which appears comparable to **1** in its effectiveness as a chiral auxiliary.[9]



1 2 3 4

Compounds **1–4** are prepared either by resolution or from a natural product, but structural analogues are unavailable. We now report the synthesis of the first member of a new class of secondary amines, prepared by sequential asymmetric alkylation[10] of isoindoline.[11] This alkylation sequence offers the potential advantage of structural variation in the electrophile, and either enantiomer is available, depending on the configuration of the chiral auxiliary.

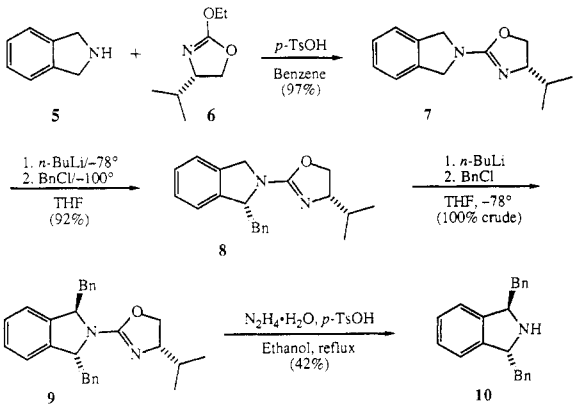


In 1986, we reported a method for the asymmetric α-alkylation of heterocycles using an oxazoline chiral auxiliary.[10] The successful α,α'-dimethylation of piperidine[10] suggested the possible use of the method in the design of C_2-symmetric homochiral secondary amines. However, significant problems were encountered in extending the alkylation to other electrophiles in the piperidine system,[12] and so we chose to first apply the concept to a better behaved benzylic system.[13,14]

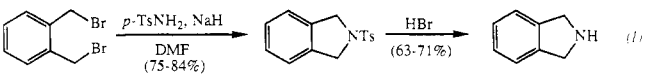
(1) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429–6433.
(2) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1977**, *42*, 1663–1664.
(3) (a) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755–756. (b) Schlessinger, R.; Iwanowicz, E. J.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 3070–3073. (c) Schlessinger, R.; Tata, J. R.; Springer, J. P. *Ibid.* **1987**, *52*, 708–710.
(4) Schlessinger, R.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083–2086.
(5) Overberger, C. G.; Marullo, N. P.; Hiskey, R. G. *J. Am. Chem. Soc.* **1961**, *83*, 1374–1378. For a correction of the absolute configuration indicated in this paper, see ref 7a.
(6) Marshall, J. A.; Lebreton, J. *J. Am. Chem. Soc.* **1988**, *110*, 2925–2931.
(7) (a) Hogeveen, H.; Zwart, L. *Tetrahedron Lett.* **1982**, *23*, 105–108. (b) Eleveld, M. B.; Hogeveen, H. *Ibid.* **1986**, *27*, 631–634.
(8) For a leading reference to the use of **3** in asymmetric synthesis, see: Ikegami, S.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3403–3406. For the synthesis of **3**, see: Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Ibid.* **1984**, *25*, 857–860.
(9) Whitesell, J. K.; Minton, M. A.; Chen, K.-M. *J. Org. Chem.*, following paper in this issue.
(10) Gawley, R. E.; Hart, G.; Goicoechea-Pappas, M.; Smith, A. L. *J. Org. Chem.* **1986**, *51*, 3076–3078.
(11) (a) Bornstein, J.; Shields, J. E.; Boisselle, A. P. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 406–408. (b) Bornstein, J.; Shields, J. E. *Ibid.* pp 1064–1066.
(12) Gawley, R. E.; Hart, G. C.; Bartolotti, L. J. *J. Org. Chem.*, in press.
(13) For a detailed study of the asymmetric alkylation of benzylic and allylic systems, see: Rein, K. R.; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, G. A.; Gawley, R. E. *J. Am. Chem. Soc.*, submitted.

0022-3263/88/1953-5381$01.50/0 © 1988 American Chemical Society

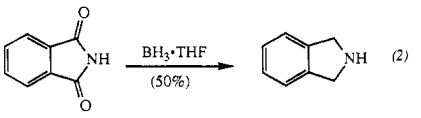
Sequential Asymmetric Alkylation of Isoindoline. Isoindoline, **5**,[11] was condensed with ethoxyoxazoline **6** to afford isoindolyloxazoline **7** in 87% yield. Asymmetric alkylation with benzyl chloride afforded a 13/1 mixture of **8** and its diastereomer.[15] Although careful column chromatography allowed separation of the two diastereomers, this step is not necessary. Alkylation of **8** (as a mixture of diastereomers) occurred regioselectively at the methylene position to give a mixture of three diastereomers in 86/7.5/6.5 ratio.[16] The major diastereomer, **9** may be isolated by careful column chromatography[17] or by trituration and recrystallization. The trans relationship of the two benzyl groups is readily apparent from the 400-MHz ^1H and 100-MHz ^{13}C NMR spectra. For the trans isomer **9**, the symmetry-related atoms in the isoindoline fragment are homotopic, whereas the same groups are diastereotopic in the *cis*-1,3-dibenzyl isomer. All the pertinent groups are isochronous in the isomer we have assigned the trans stereochemistry, although the signals assigned to the benzylic methylenes are significantly broadened at room temperature due to conformational restrictions. Hydrazinolysis affords the enantiomerically pure secondary amine **10** in 42% yield after chromatography. Studies on the use of **10** and related compounds in asymmetric processes are in progress and will be reported in due course.



Improved Procedure for the Preparation of Isoindoline. Although isoindoline is available by detosylation of *N*-tosylisoindoline,[11a] which in turn is available by alkylation of *o*-xylylene dibromide with *p*-toluenesulfonamide (eq 1),[11b] this procedure is not very attractive. Specifically, the procedure is cumbersome, and the starting material, *o*-xylylene dibromide, is a powerful and persistent lachrymator. Considerable care must be exercised in handling it, and all the glassware it contacts must be soaked in concentrated KOH to remove any trace of the noxious material.[18]



Our interest in asymmetric alkylations of isoindoline such as described above prompted us to investigate alternative methods of preparation. Phthalimide is attractive as a starting material because of its low price; the reduction of phthalimide to isoindoline with lithium aluminum hydride in a Soxhlet extractor was reported in 1948,[19] but we have been unable to duplicate that procedure. After considerable experimentation, we can now report a procedure that consistently affords ~50% yields in the reduction of phthalimide to isoindoline with borane–THF (eq 2).[20] This reaction proceeds in yields that are comparable to those of the two combined *Organic Syntheses* preparations, but is a "one pot" procedure and avoids the use of *o*-xylylene dibromide.



Experimental Section

1,3-Dihydroisoindole (Isoindoline) (5). *Caution: Due to the evolution of hydrogen, this procedure should be carried out in a well-ventilated hood.* An oven-dried, 500-mL, three-neck flask was equipped with a magnetic stirrer, reflux condenser, addition funnel, nitrogen inlet, and a gas vent, was flushed with nitrogen, and then was charged with a suspension of 11 g of phthalimide (75 mmol) in 18 mL of THF (dried from sodium benzophenone). To this suspension at room temperature was added dropwise, over a 25-min period, 200 mL of a 1 M solution of BH_3–THF (Aldrich). During this addition, hydrogen is evolved and should be vented to the back of the hood. After the addition, the reaction mixture, which looked like orange juice, was refluxed for 14 h. After cooling to 0 °C, the reaction mixture was quenched by dropwise addition of 18.5 mL of methanol over a 30-min period (there may be considerable foaming at this point). After stirring for 20 min at room temperature, 21 mL of 6 M HCl was added, and the mixture was refluxed for 1 h. The solution was then cooled to 0 °C and slowly basified (to pH >10) with 47 mL of 6 M NaOH. The layers were separated, and the aqueous layer was extracted with ether. The organic layers were combined and dried over NaOH pellets. After condensation of the organic phase in vacuo, vacuum distillation afforded isoindoline as a colorless, liquid: bp 48 °C/0.08 mm (lit.[11a] bp 55–56 °C/2 mm);[21] yield 4.3 g (50%). Isoindoline darkens upon exposure to air, but may be stored under nitrogen in a freezer.[11a] This procedure may be scaled up to double or triple the scale described here with no loss in yield.

***N*-[(*S*)-4,5-Dihydro-4-(1-methylethyl)-2-oxazolyl]-1,3-dihydroisoindole (7).** A solution of 0.568 g of isoindoline, **5** (4.77 mmol), 0.03 g of *p*-toluenesulfonic acid, and 0.750 g of ethoxyoxazoline **6** (4.77 mmol)[12] in 10 mL of benzene was refluxed for 1–3 h (reaction monitored by TLC). After cooling, the reaction mixture was washed sequentially with bicarbonate and brine, dried with $MgSO_4$, and condensed to yield 0.978 g of **7** (97%). Recrystallization from hexane afforded white crystals; mp 117–117.5 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 0.87 (3 H, d, J = 6.6), 0.97 (3 H, d, J = 6.6), 1.50–1.95 (1 H, m), 4.71 (4 H, s), 7.18–7.28 (4 H, m); ^{13}C NMR (20 MHz) δ 158.8, 136.8, 126.6, 121.9, 70.5, 70.2, 52.8, 32.9, 18.4, 17.2. Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88. Found: C, 72.90; H, 7.91.

(*R*)-1-Benzyl-*N*-[(*S*)-4,5-dihydro-4-(1-methylethyl)-2-oxazolyl]-1,3-dihydroisoindole (8). To a stirring solution of 2.0 g of **7** (8.7 mmol) in 100 mL of dry THF at −78 °C was added 6.0 mL of a 1.6 M solution of *n*-butyllithium (9.6 mmol) in hexane. The reaction mixture was stirred for 20 min at −78 °C and then cooled to −100 °C (liquid nitrogen–90% methanol slush bath). After being stirred for 10 min at −100 °C, the reaction mixture was quenched with 1.1 mL of benzyl chloride. The layers were separated, and the aqueous phase was extracted with ethyl

(14) This work is taken in part from the Ph.D. Dissertation of S. R. Chemburkar, University of Miami, 1987, and was presented at the Southeastern Regional Meeting of the American Chemical Society, Orlando, FL, Nov 6, 1987; Abstract 384.

(15) The diastereomer ratio was determined by capillary gas chromatography. The absolute configuration was assigned by analogy to numerous other examples; see ref 13.

(16) Alkylation of pure **8** (single diastereomer) affords **9** in 89% de.

(17) Hunt, B. J.; Rigby, W. *Chem. Ind. (London)* **1967**, 1868–1869.

(18) For a description of the precautions necessary in handling *o*-xylylene dibromide, see: Stephenson, E. F. M. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, pp 984–986.

(19) Uffer, A.; Schlittler, E. *Helv. Chim. Acta* **1948**, *31*, 1397–1400.

(20) For the reduction of amides with borane–THF, see: Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912–916.

(21) We speculate that the discrepancy in boiling point pressure is due to a misplaced decimal in ref 11a.

acetate or chloroform. The combined organic layers were washed with brine, dried with $MgSO_4$, and condensed. Capillary GC analysis (50-m DB-5 column) of various runs indicated 80–90% diastereomeric excess. Vacuum distillation from CaH_2 affords 2.55 g (92%) of 8, which was used directly in the next step: ^1H NMR (60 MHz, $CDCl_3$) δ 0.91 (3 H, d, J = 5), 1.0 (3 H, d, J = 5), 1.5–2.15 (1 H, m), 3.24 (2 H, d, br d), 3.82–4.36 (3 H, m), 4.5 (2 H, s), 5.20–5.45 (1 H, m), 6.85–7.2 (9 H, m); ^{13}C NMR (20 MHz) δ 158.9, 140.1, 137.1, 129.9, 127.7, 127.3, 126.7, 126.4, 122.9, 122.2, 70.9, 70.4, 65.0, 53.1, 40.35, 33.6, 18.8, 18.0.

(*R*,*R*)-1,3-Dibenzyl-*N*-[(*S*)-4,5-dihydro-4-(1-methylethyl)-2-oxazolyl]-1,3-dihydroisoindole (9). The procedure is the same as described for the preparation of 8 (crude yield 100%). The major diastereomer may be isolated by trituration and recrystallization from hexanes or by careful column chromatography, eluting with 20% ethyl acetate in hexane:[17] white crystals, mp 107 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (3 H, d, J = 7.2), 1.10 (3 H, d, J = 7.2), 1.8 (1 H, m), 3.26 (2 H, br d) and 3.32 (2 H, br d) (these signals are assigned to the benzylic methylenes—see the carbon assignments below), 4.0 (1 H, dd), 4.2 (1 H, dd), 4.4 (1 H, t), 5.0 (2 H, br d), 6.8 (2 H, m), 6.9 (2 H, m), 7.1 (10 H, br d); ^{13}C NMR (100 MHz) δ 157.9, 139.7, 137.2, 129.9, 127.7, 126.9, 126.0, 122.7, 70.9, 70.7, 64.7, 40 (v br; at 20 MHz, this line is somewhat sharper; it is assigned to the benzylic methylenes), 34.1, 19.1, 18.7. Anal. Calcd for $C_{28}H_{30}N_2O$: C, 81.91; H, 7.37. Found: C, 81.82; H, 7.41.

(*R*,*R*)-1,3-Dibenzyl-1,3-dihydroisoindole (10). A solution of 0.164 g of 9, 0.08 g of *p*-toluenesulfonic acid, and 3 mL of hydrazine hydrate in 15 mL of 95% ethanol was refluxed for 70 h (reaction monitored by GC), then cooled, and condensed. The residue was extracted with chloroform, washed with dilute NaOH and brine, dried with $MgSO_4$, and condensed. The product was purified by radial chromatography, eluting with 20% ethyl acetate in hexane (the plate was first deactivated with 10% triethylamine in hexane and then rinsed with hexane): yield, 0.05 g, 42%; $[\alpha]_D$ –5.4°, c = 2.15 (EtOH); ^1H NMR (60 MHz, $CDCl_3$) δ 2.81–2.99 (4 H, m), 4.55–4.78 (2 H, t, br d), 7.0–7.3 (14 H, m).

Acknowledgment. We are grateful to Professor James Whitesell for graciously agreeing to delay publication of his work so that our paper could appear simultaneously. The 400-MHz NMR instrument used in this work was funded by the NIH, 1 S10 RR 03351.

Communications

A New C_2 Chiral Secondary Amine

Summary: The synthesis and application to asymmetric induction of the novel chiral tricyclic amine **2** are described.

Sir: In 1977 we reported on the preparation of enantiomerically resolved *trans*-2,5-dimethylpyrrolidine (**1**) and the intervention of this amine in enamine alkylation to form 2-alkylcyclohexanones with high levels of asymmetric induction.[1] The design feature of a pseudo C_2 symmetry axis[2] in this material, while conceived independently, follows directly from the seminal contribution of Kagan[3] and represented the first C_2 amine as well as the first monodentate, C_2 chiral auxiliary used in asymmetric induction.[4] While we[5] and others[6] have found applications for this amine in asymmetric induction schemes, its use has been severely hampered by the lack of practical routes for its synthesis, notwithstanding contributions from others.[7,8] Further, recovery of the amine **1** as well as routine manipulations are made difficult due to its low boiling point (102 °C). Recently we were motivated to overcome the practical difficulties associated with **1** by a need for a C_2 amine for incorporation into organic materials for nonlinear optical applications.[9] We report here the practical preparation of the tricyclic amine **2** (bp 97 °C (12.5 mmHg)) (Figure 1) in enantiomerically resolved form[10,11] as well as its application to asymmetric induction in the innovative sequence described by Schlessinger.[6] It should be noted that **2** is unique among C_2-symmetric, secondary amines in that the large thermodynamic preference for the cis ring fusion in bicyclo[3.3.0]octane systems[12] will effectively prevent epimerization α to nitrogen, even in processes that involve deprotonation at this position.[13]

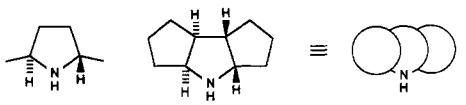


Figure 1.

Synthesis of racemic **2**[14,15] was accomplished in three operational steps, commencing with the radical-induced,

(1) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1977**, *42*, 1663.
(2) Strictly speaking, the pyramidal nitrogen breaks the C_2 symmetry of this and related amines.
(3) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.
(4) Important contributions to this area have followed from many groups. A review of this area is in preparation by one of us (J.K.W) for *Chem. Rev.*
(5) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755.
(6) Schlessinger, R.; Tata, J. R.; Springer, J. P. *J. Org. Chem.* **1987**, *52*, 708. Schlessinger, R. H.; Iwanowicz, E. J.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 3070.
(7) Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1981**, *46*, 3920. Harding, K. E.; Marman, T. H. *J. Org. Chem.* **1984**, *49*, 2838.
(8) Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083.
(9) Chemla, D. S., Zyss, J., Eds. *Non-Linear Optical Properties of Organic Molecules and Crystals*; Academic: New York, 1987; Vols. 1 and 2. Williams, D. J., Ed. *Non-Linear Optical Properties of Organic and Polymeric Materials*; ACS Symposium Series 233; American Chemical Society: Washington, DC, 1983.
(10) The term homochiral has recently come into vogue to describe optically active materials. We prefer not to use this term as its use implies an absolute level of enantiomeric purity that is not experimentally verifiable.
(11) We have found the three-ring, abbreviated notation for **2** illustrated in Figure 1 to be quite convenient. In addition, we have coined the nickname "tricyclamine" for **2**.
(12) Dale, J. *Stereochemistry and Conformational Analysis*; Verlag Chemie: New York, 1978.
(13) For an alternate C_2 amine, see: Gawley, R. E.; Chemburkar, S. R.; Smith, A. L.; Anklekar, T. V. *J. Org. Chem.*, preceding paper in this issue.
(14) Both the anti, tricyclic amine **2** and the syn (or meso) amine **7** are new compounds. Indeed, only two previous reports on tricyclic compounds with this dicyclopentapyrrole framework have appeared. See: Posvic, H.; Dombro, R.; Ito, H.; Telinski, T. *J. Org. Chem.* **1974**, *39*, 2575. Hegedus, L. S.; Hoden, M. S. *J. Org. Chem.* **1985**, *50*, 3920.
(15) Spectral data (^{13}C and ^1H NMR) consistent with the structure of all new compounds *and* with purities greater than 95% were obtained.

0022-3263/88/1953-5383$01.50/0 © 1988 American Chemical Society