Cyclodehydration of N- and C-Substituted β-Amino Alcohols to the Corresponding Aziridines with Diethoxytriphenylphosphorane

Jeffery W. Kelly, Nita L. Eskew, and Slayton A. Evans, Jr.*

The William Rand Kenan, Jr., Laboratories of Chemistry, The University of North Carolina, Chapel Hill, North Carolina 27514

Received February 25, 1985

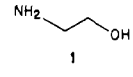
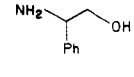
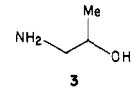
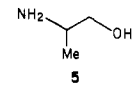
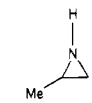
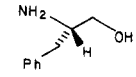
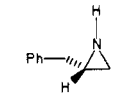
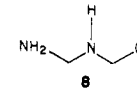
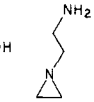
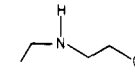
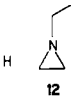
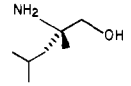
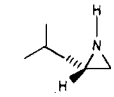
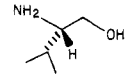
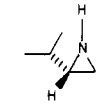
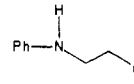
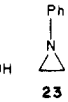
The growing importance of functionalized aziridines in organic synthesis[1] and their presence in numerous biomolecules[2] suggest that a general synthetic procedure leading to C- and N-substituted aziridines under essentially *neutral* conditions would be attractive. The availability of such a procedure coupled with readily accessible, enantiomerically homogeneous β-amino alcohols from optically pure α-amino acids[3] would also serve to extend the utility of chiral aziridines as useful synthetic building blocks.[4]

Recent research efforts have focused on development of single-step, stereoselective/stereospecific conversions of suitable precursors (e.g., 1,2-amino alcohols,[5] 1,2-azido alcohols,[6] epoxides,[7] etc.) to aziridines utilizing a variety of "organophosphorus reagents". Exploration of the synthetic potential of diethoxytriphenylphosphorane (DTPP) as a versatile cyclodehydrating reagent for 1,2-amino alcohols has been virtually nonexistent despite Denney's early report[8] that DTPP initiates cyclodehydration of ethanolamine (**1**) and 2-amino-2-phenylethanol to aziridine (**2**) and 2-phenylaziridine, respectively. The results of our recent work detailing the scope of DTPP in diol cyclodehydrations[9] strongly suggest that DTPP should be uniquely applicable for effecting cyclodehydrations of 1,2-amino alcohols.

Results and Discussion

Generally, *N*-alkyl and *N*-aryl β-amino alcohols afford excellent yields (90–95%) of the corresponding N-substituted aziridines when allowed to react with an equivalent of DTPP[9,10] [60 °C, 24–48 h (Table I)] in anhydrous toluene solvent. Similarly, *C*-alkyl β-amino alcohols are smoothly converted to the corresponding aziridines [1–24 h, 60 °C, toluene; 85–90% (Table I)].

Table I. Aziridines from DTPP-Promoted Cyclodehydrations of Various 1,2-Diamino Alcohols

amino alcohol	aziridine	yield, %	^{13}C NMR data[b]
 1	 2	90 (81)[c]	17.9 (C2, C3)[d]
		85[c]	
 3	 4	85	25.2 (C2), 25.7 (C3), 19.1 (CH_3)[d]
 5	 4	90	
 (S)-6	 (S)-7[e]	85	30.9 (C2), 24.5 (C3), 40.3 (C4)
 8	 9	50	26.7 (C2, C3), 64.8 (C4), 42.7 (C5)
 13	 12	90	26.8 (C2, C3), 56.1 (NCH_2CH_3), 14.5 (NCH_2CH_3)
 18	 19[f]	90	38.2 (C2), 23.0 (C3)* 27.7 (C4)*, 28.8 (C5)*, 24.9 (C6), 22.5 (C7)*[g]
 20	 21[f]	90	36.9 (C2), 23.8 (C3), 32.7 (C4), 20.4 (C5), 19.8 (C6)[d]
 22	 23	90	27.17 (C2, C3)[h]

[a] Confirmation of structure and identity of the components of the reaction was accomplished by comparison of GLC retention times and ^{13}C NMR data with authentic samples when available and by comparison with published NMR spectra. [b] All ^{13}C NMR data (Bruker WM-250) were collected on samples dissolved in C_6D_6/toluene (1:1 v/v) at ambient temperature with tetramethylsilane (Me_4Si) as internal reference. [c] See ref 8. [d] Mison, P.; Chaabouni, R.; Diab, Y.; Martino, R.; Lopex, A.; Lattes, A.; Wehrli, F. W.; Wirthlin, T. *Org. Magn. Reson.* **1976**, *8*, 79–89. [e] See ref 12. [f] Rubinstein, H.; Feibush, B.; Gil-Av, E. *J. Chem. Soc., Perkin Trans. 2* **1973**, 2094–2097. [g] The ^{13}C NMR resonances marked with an asterisk may be interchangeable. [h] Nash, C. P.; Maciel, G. E. *J. Phys. Chem.* **1964**, *68*, 832.

Methyl substitution at the carbinol carbon (C_1) compared to methyl substitution at the amino carbon (C_2) (e.g., **3** vs. **5**) causes a slight diminution in the yield of 2-methylaziridine (**4**). This finding is, of course, consistent with the lower reactivity in intramolecular S_N2 displacements at secondary centers compared to that at primary ones.

Cyclodehydration of optically active 2-substituted β-amino alcohols with DTPP occurs with the expected retention of configuration at the amino carbon (C_2). For example, enantiomerically homogeneous (*S*)-(+)-2-

(1) (a) Duggan, M. E.; Karanewsky, D. S. *Tetrahedron Lett.* **1983**, *24*, 2935–2938. (b) Laurent, A.; Mison, P.; Nafti, A.; Cheikh, R. B.; Chaabouni, R. *J. Chem. Res.* **1984**, 354–355. (c) Tsuge, O.; Kaneonasa, S.; Suga, H.; Matsuda, K. *Heterocycles* **1984**, *22*, 1955–1958.

(2) See for example: Tomasz, M.; Jung, M.; Verdine, G.; Nakanishi, K. *J. Am. Chem. Soc.* **1984**, *106*, 7367–7370.

(3) Poindexter, G. S.; Meyers, A. I. *Tetrahedron Lett.* **1977**, 3527–3528 and references cited therein.

(4) Laurent, A. *Bull. Soc. Chim. Belg.* **1983**, *92*, 797–810.

(5) (a) Okada, I.; Ichimura, K.; Sudo, R. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1185. (b) Pommelet, J. C.; Chuche, J. *Tetrahedron Lett.* **1974**, 3897–3898. (c) Pommelet, J. C.; Chuche, J. *Can. J. Chem.* **1976**, *54*, 1571. (d) Manisse, N.; Chuche, J. *J. Am. Chem. Soc.* **1977**, *99*, 1272–1273. (e) Appel, R.; Kleinstuck, R. *Chem. Ber.* **1974**, *107*, 5.

(6) (a) Weitzberg, M.; Aizenshtat, Z.; Jerushalmy, P.; Blum. J. *J. Org. Chem.* **1980**, *45*, 4252. (b) Blum, J.; Ben-Shoshan, S. *J. Heterocycl. Chem.* **1983**, *20*, 1461–1464. (c) Willert, A.; Mueller, E. P.; Peringer, P. *Helv. Chem. Acta* **1983**, *66*, 2467–2480. (d) Shfelzer, S.; Weitzberg, M.; Jeries, J.; Sheradsky, T.; Aizenshtat, Z.; Blum, J. *J. Heterocycl. Chem.* **1984**, *21*, 1–3. (e) Poechlauer, P.; Muller, E. P.; Peringer, P. *Helv. Chim. Acta* **1984**, *67*, 1238–1247.

(7) (a) Appel, R.; Halstenberg, H. *Chem. Ber.* **1976**, *109*, 814–818. (b) Shahak, I.; Ittah, Y.; Blum, J. *Tetrahedron Lett.* **1976**, 4003–4004.

(8) Denney, D. B.; Powell, R. L.; Taft, A.; Twitchell, D. *Phosphorus* **1971**, *1*, 151.

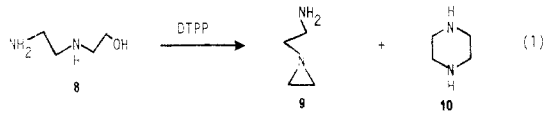
(9) Robinson, P. L.; Barry, C. N.; Kelly, J. W.; Evans, S. A., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 5210–5219.

(10) Chang, B. C.; Conrad, W. E.; Denney, D. B.; Denney, D. Z.; Edelman, R.; Powell, R. L.; White, D. W. *J. Am. Chem. Soc.* **1971**, *93*, 4004.

0022-3263/86/1951-0095$01.50/0

amino-1-propanol [(+)-5][11] and (S)-(−)-2-amino-3-phenyl-1-ethanol [(−)-6],[12] from borane reduction [BH_3 THF, 25 °C, 24 h][3,13] of L-alanine and L-phenylalanine, respectively, undergo cyclodehydration (85%) with 1 equiv of DTPP to afford enantiomerically pure (S)-(+)-2-methylaziridine [(+)-4][14] and (S)-(−)-2-benzylaziridine [(S)-7],[12,15] respectively.

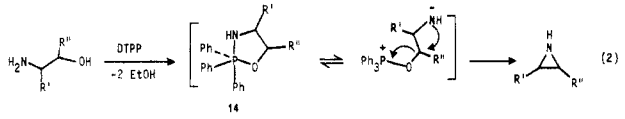
The low chemoselectivity[16] exhibited by DTPP in the cyclodehydration of 2-[(2-aminoethyl)amino]ethanol (8) is interesting. Diamine 8 is converted into an equimolar mixture of N-(ethylamino)aziridine (9; 50%) and piperazine (10; 50%) with DTPP. Apparently, the free energy considerations controlling cyclization to three- and six-membered rings are (surprisingly)[17] identical (eq 1). An



(1)

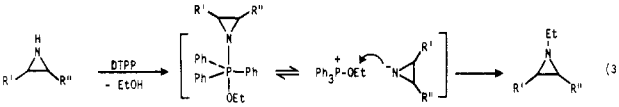
independent experiment has shown that aziridine 9 is stable under the reaction conditions for 2 weeks, thus verifying that 10 comes directly from the cyclodehydration process and not via thermal isomerization of 9 to 10.

Interestingly, 1-amino-2-propanol monohydrate ($3 \cdot H_2O$) is converted to 2-methylaziridine (85% by ^{13}C NMR) utilizing 2 equiv of DTPP, one of which is rapidly hydrolyzed by the water of hydration. If 3 equiv of DTPP are employed to cyclodehydrate $3 \cdot H_2O$, 1-ethyl-2-methylaziridine (11)[18] is formed by ethylation of the aziridinyl nitrogen in 4 by DTPP.[19] The ^{13}C NMR spectrum of 11 is completely superimposable on the spectrum derived from separate treatment of 4 with 1 equiv of DTPP. Similarly, 1 equiv of DTPP smoothly converts 1 to the parent aziridine 2 (90%) and the use of 2 equiv of DTPP gives N-ethylaziridine (12; 99%) directly. The ^{13}C NMR spectrum of 12 by this route is identical with that obtained from treatment of N-ethylamino ethanol (13) with 1 equiv of DTPP. While it is clear that formation of N-ethylaziridines from 1,2-amino alcohols in excess DTPP occurs by initial cyclodehydration following by N-ethylation, a further comment may be useful. Formation of the aziridine is undoubtedly controlled by rapid phosphoranylation of the 1,2-amino alcohol to afford the intermediate 1,3,2-oxazaphospholane 14,[7a] the driving force being related to favorable formation of the cyclic structure (eq 2). The process is largely irreversible such that N-



(2)

ethylation of the 1,2-amino alcohol is not competitive. Finally, the reactions between aziridines and DTPP appear to require initial phosphoranylation of the aziridinyl nitrogen subsequent to N-ethylation rather than direct ethylation. DTPP does not react with tertiary aziridines [e.g., N-ethylaziridine (12)], suggesting that proton exchange between N–H and ethoxide is required for phosphoranylation and ultimately alkylation (eq 3).



(3)

The ethylation potential of DTPP seems to be quite general. For example, benzylamine (15) can be ethylated with 1 equiv of DTPP at 60 °C affording N-ethylbenzylamine (16; 63%)[20] and N,N-diethylbenzylamine (17; 20%).[21] However, at −30 °C, the selectivity for 16 over 17 increases to 98:2 by ^{13}C NMR analysis.

In summary, the ease of DTPP preparation, its efficiency in the cyclodehydration of 1,2-amino alcohols, and the ready removal of byproducts (CH_3CH_2OH, Ph_3PO) allowing for near quantitative isolation of the aziridine make DTPP an attractive addition to the storehouse of useful synthetic methodology.

Experimental Section[22]

Diethoxytriphenylphosphorane[9,10] is easily prepared by combining equimolar quantities of diethyl peroxide (investigators should always exercise caution when working with peroxides)[23] with triphenylphosphine in anhydrous toluene solvent *while stirring at 0 °C under a nitrogen atmosphere*. This mixture is then heated at 65 °C for 48 h to form DTPP; the final composition of the mixture as well as the concentration of DTPP can be conveniently determined by ^{31}P NMR analysis. DTPP is easily transferred in an anhydrous environment by syringe and is stable indefinitely below 70 °C in toluene solution. More specifically, the concentration of DTPP in toluene solution is determined from the initial amount of triphenylphosphine, the total volume of toluene, and the composition measured by an inverse gated decoupled ^{31}P NMR spectrum: $Ph_3P(OEt)_2$, δ −55.0; Ph_3P, δ −5.6; Ph_3PO, δ 24–26 (relative to external 85% H_3PO_4 reference).

The following synthesis of N-ethylaziridine (12) is representative of the overall synthetic procedure: 1.1 mL (10.4 mmol) of anhydrous 2-(ethylamino)ethanol (13) is added to 10.4 mL of 1.0 M DTPP under a nitrogen atmosphere. After the mixture was heated (60 °C for 48 h), the yield of aziridine 12 (90%) was ascertained by ^{13}C NMR and GLC analyses and isolation of 12 was accomplished by fractional distillation (bp 50–53 °C). The aziridines are generally stored over sodium hydroxide pellets.

The amino alcohols employed here are commercially available and the optically active ones were prepared by borane reduction of the precursor α-amino acid. All of the aziridines have been

(11) Minoura, Y.; Takebayashi, M.; Price, C. C. *J. Am. Chem. Soc.* **1959**, *81*, 4689.
(12) Bates, G. S.; Varelas, M. A. *Can. J. Chem.* **1980**, *58*, 2562–2566.
(13) Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* **1973**, *38*, 2786–2792.
(14) Yahiro, N. *Chem. Lett.* **1982**, 1479–1480.
(15) The preparation of 2-benzylaziridine (85%) by this method is particularly significant in light of the report by Okada et al.[5a] where attempted cyclodehydration of 6 with Ph_3PBr_2/2 Et_3N in CH_3CN solvent gave only 1,4-dibenzylpiperazine.
(16) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887–4902.
(17) Stirling, C. J. M. *J. Chem. Educ.* **1973**, *50*, 844. See also: DeTar, D. F.; Brooks, W., Jr. *J. Org. Chem.* **1978**, *43*, 2245–2248.
(18) 11: ^{13}C NMR [C_6D_6/toluene (1:1 v/v)] δ 34.3 (C2), 34.2 (C3), 18.35 (C4), 55.3 (NCH_2CH_3), 14.5 (NCH_2CH_3).
(19) It is relevant that pentamethoxyphosphorane, $P(OMe)_5$, also methylates a variety of heteroatoms having X–H bonds where X = N, S, and O. See: Denney, D. B.; Melis, R.; Pendse, A. D. *J. Org. Chem.* **1978**, *43*, 4672.
(20) 16: ^{13}C NMR [C_6D_6/toluene (1:1 v/v)] δ 53.9 ($PhCH_2N$), 43.7 (NCH_2CH_3), 15.3 (NCH_2CH_3). Only the aliphatic carbons are reported here.
(21) 17: ^{13}C NMR [C_6D_6/toluene (1:1 v/v)] δ 58.0 ($PhCH_2N$), 47.0 [$N(CH_2CH_3)_2$], 12.1 [$N(CH_2CH_3)_2$)]. Only the aliphatic carbons are reported here.
(22) Proton and carbon magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on the Bruker WM-250 NMR Spectrometer. Chemical shifts of samples as 5–15 wt % deuteriobenzene/toluene (1:3 v/v) solutions are presented in parts per million (δ) downfield from internal tetramethylsilane (Me_4Si). ^{31}P NMR spectra were recorded on the Bruker WM-250 and the ^{31}P NMR shifts are referenced to external 85% H_3PO_4. Gas chromatographic analyses were obtained on the Hewlet-Packard Model 5754B research gas chromatograph, using a stainless-steel column [0.125 in. (i.d.) × 10 ft packed with 20% Carbowax 20 M on Chromosorb W-HP-AW-DMCS, 100–200 mesh]. Thin-layer chromatography (TLC) on plastic coated with silica gel (Baker-Flex) was used for confirmation of sample homogeneity and iodine vapor was used for visualization. Melting points were obtained with a Mel-Temp melting point apparatus with an open capillary tube and are uncorrected.
(23) (a) Magelli, O. L.; Sheppard, C. S. In "Organic Peroxides"; Swern, D., Ed.; Wiley-Interscience: New York, 1972; Chapter 1, Vol. 1, pp 1–104. (b) Shanley, E. S. In "Organic Peroxides"; Swern, D., Ed.; Wiley-Interscience: New York, 1972; Chapter 5, Vol. III, pp 341–364.

previously synthesized and their physical properties reported (for references, see Table I).

Acknowledgment. We are grateful for the American Chemical Society Organic Divisional Fellowship to J.W.K. sponsored by the Rohm & Haas Co. We also express our appreciation to Philip L. Robinson for useful discussions and the Department of Energy (DE-AS05-80-ER10641), the National Research Council's Senior Postdoctoral Fellowship Program, and the Fulbright Research Scholar's Program (to S.A.E.) for support of this research.

Friedel-Crafts Acylation of Methyl Ester of Phenylacetic Acid: A Reinvestigation

Fulvio Uggeri,* Claudio Giordano, and Adriano Brambilla

Zambon Chimica S.p.A., Via Cimabue 26, 20032 Cormando (MI), Italy

Rita Annunziata*

Dipartimento di Chimica Organica e Industriale, Via G. Golgi 19, 20123 Milano, Italy

Received April 1, 1985

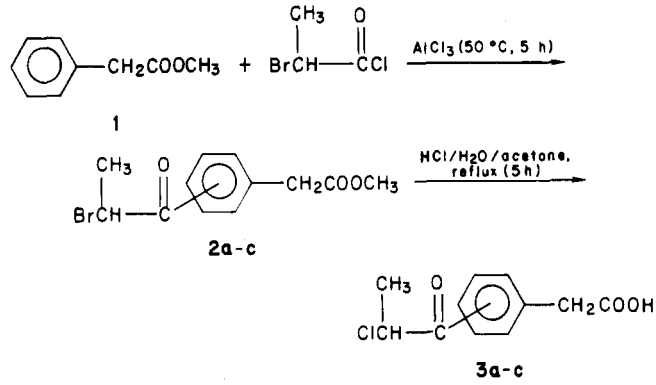
The Friedel–Crafts acylation of phenylacetic acid derivatives has been a conflicting matter, as far as positional selectivity is concerned.[1,2]

In 1966 Morgan[3] reported conclusive results on the Friedel–Crafts acylation of alkyl esters of phenylacetic acid with several acyl halides: a mixture of alkyl esters of acylphenylacetic acid (isomers ratio ortho/meta/para = (4–6)/(38–49)/(44–58)) was obtained, thus showing the lack of positional selectivity of the reaction.

Recently,[4,5] it has been reported that the methyl ester of phenylacetic acid is acylated with 2-bromopropionyl chloride, in the presence of aluminum chloride, to give the *p*-acyl isomer in 86% yield.

These results were of particular interest for two main reasons: (i) The unusual high para selectivity certainly should have had mechanistic involvements concerning the relationships among structure, reactivity, and selectivity in the Friedel–Crafts acylation. On the other hand the above result[4,5] was in agreement with the behavior of other electrophiles in aromatic electrophilic substitution of esters of phenylacetic acid. As a matter of fact, in the chloromethylation of ethyl ester of phenylacetic acid the para position is 10 times more reactive than the meta position[6] and in the not very selective nitration, the para position is 5 times more reactive than the meta position.[7] The $-CH_2COOR$ group appears to be, on the whole, activating[7] (the partial rate factors of both, meta and para position, are >1) though the reported substituent constants[8] σ_I = +0.19 and σ_R^+ = −0.08 are not fully consistent with the above conclusion.

Scheme I



(ii) The (α-bromopropionyl)arenes are important intermediates on the synthesis of α-arylpropionic acids,[9] which are well known as antiinflammatory drugs.[10]

Our interest in the synthesis of α-arylalkanoic acids from α-haloalkyl aryl ketones[9] and the unexpected and very promising result[4,5] prompted us to revisit the reaction between methyl ester of phenylacetic acid (1) and 2-bromopropionyl chloride in the presence of aluminum chloride in 1,1,2,2-tetrachloroethane. The reaction was carried out according to the given procedure: distillation of reaction crude gave an oil (bp 145–147 °C (0.2 mmHg)) in the described amount.

GC, ^1H NMR, and GC–MS analyses performed on the reaction crude as well as on the distilled fraction showed the presence of three isomeric acyl derivatives **2a–c** in the ratio 6:46:48, respectively (see Scheme I).

It is worth noting that the isomeric ratio does not change during the reaction course.

Moreover, when mixtures of **2a–c**, with diverse compositions, were treated under the reaction conditions described for the acylation of the methyl ester of phenylacetic acid (1), the starting products were recovered almost quantitatively and the isomeric ratio was found to be unchanged (see Experimental Section).

These results show unequivocally that the isomer distribution observed in the preparation of **2a–c** is determined by the kinetics of the reaction.

Hydrolysis, according to the procedure described by the authors,[5] of the isomer mixture gave the corresponding acids **3a–c** in unchanged ratio with respect to that of starting esters **2a–c**.

The GC–mass spectroscopy of **2a**, **2b**, and **2c** showed (see Experimental Section) the molecular ion M^+ *m/e* 284/286 as expected for isomeric methyl esters of (2-bromopropionyl)phenylacetic acid. Moreover, the fragmentation of **2b** and **2c** is identical whereas **2a** showed fragments *m/e* 174 and 146 related to typical cyclic structures of this ortho-substituted system.

Methyl esters **2b** and **2c** were separated as pure compounds, by preparative GC, respectively (see Experimental Section). The attribution of the para structure, by ^1H and ^{13}C NMR, to **2c** and **3c** (see Experimental Section) was straightforward on the basis of the analysis of the signal multiplicity of aromatic protons (AA′BB′ system) and on

(1) Papa, D.; Schwenk, E.; Klingshig, A. *J. Am. Chem. Soc.* **1946**, *68*, 2133.
(2) Bergmann, E. D.; Blum, J. *J. Org. Chem.* **1950**, *24*, 549.
(3) Morgan, E. D. *Tetrahedron* **1967**, *23*, 1735.
(4) Tjoeng, F. S.; Heavner, G. A. *Tetrahedron Lett.* **1982**, *23*, 4439.
(5) Tjoeng, F. S.; Heavner, G. A. *J. Org. Chem.* **1983**, *48*, 355.
(6) Nogarov, I. N.; Semenovskii, A. V. *Izv. Akad. Nauk SSSR* **1957**, 100.
(7) Knowles, J. R.; Norman, R. O. C. *J. Chem. Soc.* **1961**, 2938.
(8) Charton, M. In "Physical Organic Chemistry"; R. W. Toft, Ed.; Wiley–New York, **1981**; Vol. 13, pp 145, 211.
(9) Giordano, C.; Castaldi, G.; Uggeri, F. *Angew. Chem.* **1984**, *96*, 403; *Angew Chem., Int. Ed. Engl.* **1984**, *23*, 413.
(10) Lednicer, D. and Metscher, L. A. "The Organic Chemistry of Drugs Synthesis"; Wiley: New York **1977**; Chapter 6. Shen, T. Y. *Angew. Chem.* **1972**, *84*, 512; *Angew Chem.; Int. Ed. Engl.* **1972**, 6, 460, Ferreira, S. H.; Vane, J. R. "Antiinflammatory Drugs"; Springer-Verlag: New York, **1979**; p 321; *Scrip.* **1980**, 497, 10.

0022-3263/86/1951-0097$01.50/0