[a,d]cycloheptene (2), mp 178–180 °C, was prepared by reacting 5H-dibenzo[a,d]cycloheptene with I_2 and silver benzoate in anhydrous benzene, followed by hydrolysis with ethanolic KOH and crystallization from $CHCl_3$, as reported elsewhere.[28] *cis*-10,11-Dihydro-10,11-dihydroxy-5H-dibenzo[a,d]cycloheptene, mp 180–181 °C (from EtOH), was obtained from 5H-dibenzo[a,d]-cycloheptene and OsO_4, as reported elsewhere.[28] *p*-Methoxybenzoyl chloride (Aldrich, 99%) was distilled before use (bp 123–125 °C/25 mm). (*S*)-(+)-α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride, bp 54 °C/1 mm, was prepared from the *R*-(+) acid and thionyl chloride.[22] Solvents were reagent grade.

Enzymatic Hydrolysis of 10,11-Dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptene (1). A solution of epoxide 1 (50 mg, 0.24 mmol) in acetonitrile (1 mL) was added to 10 mL of microsomal preparation containing 40 mg protein/mL, obtained from male New Zealand white rabbits as previously reported,[19] preheated at 37 °C, and the mixture was incubated with shaking. After 12 h a fresh microsomal preparation (10 mL) was added, and the incubation continued for 12 more hours. The reaction was then stopped by addition of NaCl and the mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were reduced to an exactly known volume by evaporation in vacuo, a proper amount of a stock solution of 9-formylanthracene in EtOAc was added to a sample as an internal standard, and the amount of *trans*-10,11-dihydro-10,11-dihydroxy-5H-dibenzo[a,d]cycloheptene (2) was determined by HPLC (conditions a) in order to evaluate the extent of hydrolysis of the substrate. This was typically around 25%. The remaining part of the extract was evaporated in vacuo and chromatographed on a column of silica gel (40 g) with 7:3 hexane/EtOAc as the eluant. Eluted fractions (5 mL) were analyzed by HPLC (conditions a). The fractions containing the *trans*-diol 2 were combined and evaporated to give 10 mg of pure (HPLC) 2: mp 147–150 °C; $[\alpha]^{20}_D$ −69° (*c* = 0.55, MeOH). This product had IR and NMR spectra identical with those of synthetic (±)-2. Samples of (−)-2 with $[\alpha]^{20}_D$ ranging between −67 and −71° were obtained in several enzymatic hydrolyses of 1 under the above described conditions.

Enzymatic Hydrolysis of *cis*-Stilbene Oxide. A solution of *cis*-stilbene oxide (50 mg) in EtOH (1 mL) was added to 5 mL of microsomal preparation and 5 mL of 50 mM Tris·HCl buffer, pH 7.4, preheated at 37 °C, and the mixture was incubated for 4 h and extracted with EtOAc (3 × 10 mL). Evaporation of the extracts gave a residue containing only diol 6 (HPLC, conditions a), which, after purification by column chromatography over silica gel, had $[\alpha]^{20}_D$ +80° (*c* = 0.9, EtOH).

Determination of the Enantiomeric Excess of Diol 2. A sample of diol 2 (6 mg, 0.026 mmol), $[\alpha]^{20}_D$ −71°, was dissolved in pyridine (2 mL) containing 3 mg (0.025 mmol) of *p*-(dimethylamino)pyridine and treated with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (67 mg, 0.26 mmol). After 5 days at room temperature, the mixture was diluted with H_2O, acidified with 10% HCl, and extracted with EtOAc. The extract was washed with saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated in vacuo, and the residue was analyzed by HPLC (conditions b). Two peaks with relative retention times of 1 and 1.3, corresponding to the diastereomeric bis(MTPA esters) 3, were detected in a ratio of 24 ± 1:76 ± 1. When racemic 2 was used as starting material, the two diastereomeric bis(MTPA esters) were present in a ratio of (50 ± 1):(50 ± 1).

Determination of the Absolute Configuration of (−)-2 via Its Bis(*p*-methoxybenzoate) (4). *p*-Methoxybenzoyl chloride (92 mg, 0.53 mmol) was added to a solution of 15 mg (0.066 mmol) of (−)-2, $[\alpha]^{20}_D$ −68°, in pyridine (1.5 mL) containing 3 mg (0.025 mmol) of *p*-(dimethylamino)pyridine. After 7 days at room temperature the reaction mixture was diluted with H_2O and extracted with AcOEt. The organic phase was washed with 10% aqueous HCl and saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated in vacuo. The crude residue was crystallized from EtOH to give 8 mg of the pure bis(*p*-methoxybenzoate) 4, mp 140–141 °C. NMR ($CDCl_3$): δ 3.83 (s, 6 H, OCH_3), 4.33 (s, 2 H, CH_2), 6.90 and 8.06 (AA'BB' system, 8 H, aromatic protons ortho and meta to the methoxy groups), 7.00 (s, 2 H, CHO), 7.30 (m, 8 H, dibenzocycloheptene aromatic protons). IR (Nujol): 1690 cm^{-1} (C=O); UV λ_{max} (CH_3CN) 257 nm (32 200). CD (CH_3CN): $\Delta\epsilon_{267}$ = +13.2, $\Delta\epsilon_{249}$ = −13.4.

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Registry No. 1, 118319-30-5; 2, 118354-09-9; 4, 118319-31-6; 5, 1689-71-0; 6, 52340-78-0; MEH, 9048-63-9; 5H-dibenzo[a,d]-cycloheptene, 256-81-5.

(28) Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F.; Catalano, D. *Tetrahedron* **1988**, *44*, 4863–4870.

Hypochlorite-Induced Oxidative Decarboxylation of Trisubstituted Acetic Acids

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Hypohalite-induced oxidative decarboxylation of α-hydroxycarboxylic acids (1) is well documented,[1] and it is significant that reaction rates are dependent on pH, which may undergo substantial changes induced by consecutive reactions during oxidations.[2]

$$\underset{1}{RR'C(OH)CO_2H} \rightarrow RR'C{=}O + CO_2$$

R, R' = Ar, alkyl, or H

Initial attack upon compound 1 by the oxidant is plausible at either the alcohol or carboxyl function. Primary and secondary alcohols readily are oxidized by hypochlorite,[3] and certain tertiary alkyl hypohalites are decomposed by heat and/or light to produce ketones.[4] Alternately, hypohalites are known to effect oxidative decarboxylation of both benzoylformic acid (2, to benzoic acid)[1c,5] and phenylacetic acid (3, to benzaldehyde),[5] which lack the alcohol function.

$$\underset{2}{PhC(O)CO_2H} \qquad \underset{3}{PhCH_2CO_2H}$$

It has been suggested that α-keto acid 2 might react as an α-hydroxy compound through intermediate formation of the hydrate.[1c] Furthermore, compound 3 conceivably might be oxidized to the corresponding α-hydroxy acid under the reaction conditions used (100 °C for 8 h).[5]

In order to explore reactivity of hypochlorite at the carboxyl function in systems that could not develop α-hydroxy functionality, we have studied the interactions of trisubstituted acetic acids 4 with aqueous hypochlorite. Results obtained not only demonstrated that the α-hydroxy function is not requisite for oxidative decarboxylation but also revealed a hitherto unrecognized, hypo-

(1) (a) Nwauka, S. O.; Keehn, P. M. *Tetrahedron Lett.* **1982**, 3135. (b) Carlsen, P. H. J. *Acta Chem. Scand.* **1984**, *B38*, 343. (c) Aukett, P.; Barker, R. L. *J. Chem. Soc., Perkin Trans. 2* **1973**, 965 and references cited therein.

(2) (a) Pink, J. M.; Stewart, R. *Can. J. Chem.* **1971**, *49*, 649. (b) Gupta, P.; Grover, K. C. *J. Indian Chem. Soc.* **1973**, *50*, 397. (c) Gilliotte, B. J.; Sanders, C. L.; Wall, L. K.; Landolt, R. G. *J. Org. Chem.* **1986**, *51*, 3233.

(3) (a) Nwauka, S. O.; Keehn, P. M. *Tetrahedron Lett.* **1982**, 35 and references cited therein. (b) Lee, G. A.; Friedman, H. H. *Isr. J. Chem.* **1985**, *26*, 229 (phase transfer catalyzed reactions).

(4) (a) Greene, F. D. *J. Am. Chem. Soc.* **1959**, *81*, 2688. (b) Walsh, E. J.; Witmer, L.; McNeil, M.; Wilcko, T.; Orwig, B. *Tetrahedron Lett.* **1968**, 77.

(5) Kaberia, F.; Vickery, B. *J. Chem. Soc., Chem. Commun.* **1978**, 459.

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Table I. Reactions of Trisubstituted Acetic Acids with Hypochlorite at pH 8–9

reactant:	Ph_3CCO_2H (4a)		Ph_2CMeCO_2H (4b)		$PhCMe_2CO_2H$ (4c)
products:	5a	6a	6a	6b	6b
yield,[a] %	2–5	80–84	7–14	25–26[d]	trace[e]
yield,[b] %	13–20	13–16			
yield,[c] %	24–42	24–30			

[a] Catalyst employed, 24-h reaction. [b] No catalyst, 24-h reaction. [c] No catalyst, 2–4-day reaction. [d] Half-life of **6b** is 24 h under these conditions. [e] One to four day reaction, no benzoic acid detected.

chlorite-induced reaction of tertiary alcohols produced as reaction intermediates.

$$\underset{\mathbf{4}}{PhCQZCO_2H} \rightarrow \underset{\mathbf{5}}{PhCQZOH} + \underset{\mathbf{6}}{PhC(O)Z}$$

a, Q = Z = Ph; **b**, Q = Ph, Z = Me; **c**, Q = Z = Me

Under ambient conditions, triphenylacetic acid (**4a**) reacted with hypochlorite at a modest rate that was increased substantially by phase-transfer catalysis (Table I). Reactions with and without catalyst were conducted in a biphasic system consisting of stirred dichloromethane and hypochlorite layers. In the absence of catalyst, the reaction proceeded slowly but steadily at pH 8–9 to yield a mixture of triphenylmethanol (**5a**) and benzophenone (**6a**); above pH 11, reaction was barely perceptible, even after several days.

Through phase-transfer catalysis, reaction of compound **4a** at pH 8–9 proceeded smoothly to the ketone product in a significantly shorter period. Furthermore, the reaction scope was extended to include 2,2-diphenylpropanoic acid (**4b**), which, with catalyst and at pH 8–9, yielded a mixture of benzophenone (**6a**) and acetophenone (**6b**). Compounds **4a** and **4b** were unreactive above pH 11 in the presence of catalyst. Even at pH 8–9 in the presence of catalyst, 2-methyl-2-phenylpropanoic acid (**4c**) was relatively inert and produced only a trace of acetophenone.

Triphenylmethanol (**5a**) is a likely intermediate in the formation of benzophenone from triphenylacetic acid. Extraction of this neutral, nonpolar substance into the organic phase, away from oxidant, would account for preservation of the alcohol when a phase-transfer catalyst was not employed. Thus, the susceptibility of tertiary alcohols to biphasic reaction with hypochlorite in the presence of a phase-transfer catalyst was investigated.

Under these conditions, alcohols **5a–c** reacted smoothly to give the expected aromatic ketones **6a** and **6b**. (Acetone would not have been detected from **5c** under the conditions used.) In those reactions producing acetophenone, considerable variability was observed in yields of this haloform reaction susceptible compound. Indeed, benzoic acid was a major product of the phase transfer catalyzed reactions of alcohols **5b** and **5c** with hypochlorite at pH 8–9.

Similar to α-hydroxy acids **1**[2] and the trisubstituted acids **4a** and **4b**, benzoylformic acid (**2**) and diphenylacetic acid (**7**) exhibited enhanced oxidative decarboxylation reactivity with hypochlorite at pH 9 vs 11. The facility of pH 8–9 reactions of carboxylic acid substrates compared to the relatively inert character of these substances at higher alkalinity indicates that the active agent in oxidative decarboxylations likely is HOCl ($pK' = 7.5$).[6,7] Furthermore, the commonality of pH sensitivity points perhaps to a general reaction mechanism for oxidative decarboxylations wherein the initial attack of oxidant occurs at the carboxyl function.

Although significant carbon dioxide was produced in reactions of alcohols **5a** and **5b** with hypochlorite, no organic byproducts have been characterized that account for the loss of aryl or alkyl groups in ketone-forming reactions of tertiary alcohols with hypochlorite. These reactions may proceed by free-radical processes similar to those described by Greene et al.,[4a] by intramolecular aryl/alkyl shifts and hydrolysis, as projected for oxidations of **5a** by chromic acid or permanganate,[8] or by initial destructive attack by oxidant upon the group that is lost.[9]

Experimental Section

All reagents were obtained from commercial suppliers; sodium hypochlorite solutions were derived from Clorox (5.25%, approximately 0.8 M). Hypochlorite concentrations for the benzoylformic acid kinetic studies were established by iodometric titration using a Sargent Model IV coulometer. Liquid chromatographic (LC) analyses were performed by using a Perkin-Elmer LC-10 chromatograph fitted with a C18 reversed-phase column and a variable-wavelength UV detector, and quantitative estimates were made by using 1,4-dichlorobenzene as an internal standard. Identities of alcohol and ketone reaction products were confirmed by using a Tracor 540 gas chromatograph (GC) with a flame-ionization detector and a 6-ft OV 101 column. Infrared analysis was conducted by using a Perkin-Elmer 1420 spectrophotometer. Except where indicated, all reactions were conducted at ambient temperatures.

Oxidation of Trisubstituted Acetic Acids 4a–c. For the reactions of carboxylic acids in Table I, 7.0×10^{-4} mol of organic substrates, the internal standard, and, when employed, 0.2 g of tetra-*n*-butylammonium hydrogen sulfate (TBAHS) were dissolved in 25–50 mL of dichloromethane and mixed by magnetic stirring with a supernatant layer of 40–80 mL ($3.28–6.4 \times 10^{-2}$ mol) of aqueous hypochlorite. The pH of the aqueous layer, monitored by pH meter, was set and maintained at desired levels by addition of dilute HCl or NaOH. Product levels were determined by LC.

Oxidation of Benzoylformic Acid (2). Kinetic studies of the rate of hypochlorite consumption were conducted by mixing equal volumes of substrate and standardized hypochlorite solutions at equal initial reactant concentrations of 3.3×10^{-3} M in the presence of 0.150 M KNO_3 (to level ionic strength effects). Reactions were conducted in a constant-temperature bath at 35.0 ± 0.1 °C, and the pH was monitored by pH meter and maintained at desired levels throughout reactions. Aliquots withdrawn at timed intervals were treated with excess acidic KI solutions, and the I_2 generated was analyzed by coulometry to determine residual hypochlorite levels. After compensation for blanks, the reactions were found to follow second-order kinetics, with rate constants of 50–62 L/(mol min) at pH 9 and 13–14 L/(mol min) at pH 11. Half-lives were approximately 5 min at pH 9 and 20–30 min at pH 11.

Oxidation of Diphenylacetic Acid (7). When the procedure described for the compounds in Table I was used, LC analysis showed that approximately 50% yields of benzophenone were produced in 24-h biphasic reactions of compound **7** at pH 8–9, without catalyst. Only traces of product were detected in hypochlorite solutions maintained at pH >10.5 for the same time period.

Oxidation of Triphenylmethanol (5a). The substrate (2.5 g, 0.0096 mol) and 0.40 g of TBAHS were dissolved in 50 mL of dichloromethane. A 350-mL portion of 0.8 M hypochlorite (0.28 mol) was adjusted to pH 10, and the two layers were stirred magnetically for 5 h. During the last 4 h, the pH, which tended to drop, was maintained between 8.3 and 9.1 by addition of dilute NaOH. LC analysis indicated >90% consumption of starting

(6) Sugam, R.; Helz, G. R. *Environ. Sci. Technol.* **1976**, 385.

(7) Phase-transfer catalysts may extract hypochlorite more efficiently at pH 9–10 than at lower or higher levels (Abramovici, A.; Neuman, R.; Sasson, Y. *J. Mol. Catal.* **1985**, *29*, 291), but the present work shows enhanced reactivity at pH 9 even in the absence of catalyst.

(8) Banoo, F.; Stewart, R. *Can. J. Chem.* **1969**, *47*, 3199. Stewart, R.; Banoo, F. *Ibid.* **1969**, *47*, 3207.

(9) Under certain conditions, hypochlorite can make a direct attack upon aromatic ring systems: Landolt, R. G.; Davis, G. M.; Reilly, M. T.; Reinhold, D. S. *Chem. Ind. (London)* **1980**, 292.

material, and GC analysis confirmed significant benzophenone production. The dichloromethane layer, after washing with water, evaporation, and crystallization from petroleum ether (bp 60–80 °C), yielded 1.8 g of a low-melting solid. Further crystallization from methanol/water produced 0.8 g (46% yield) of benzophenone, mp 47–48 °C (lit.[10]a mp 48 °C). Its identity was confirmed by infrared spectroscopy[11] and the 2,4-dinitrophenylhydrazone derivative, mp 238–239 °C (lit.[10a] mp 238 °C).

Carbon dioxide (as $BaCO_3$), accounting for an approximately 20% yield based on loss of one phenyl group, was isolated from 4-h, biphasic reactions of **5a**. For these reactions, hypochlorite solutions containing tetra-*n*-butylammonium hydroxide as catalyst were saturated with $Ba(OH)_2$, and the $BaCO_3$ formed from CO_2 in the bleach was filtered prior to use.

Oxidation of 1,1-Diphenylethanol (5b). The alcohol (1.0 g, 0.005 mol) and 0.11 g of TBAHS in 50 mL of dichloromethane were stirred magnetically with 100 mL of aqueous hypochlorite set at pH 9.5. After 17 h, the pH had dropped to 8.2, and GC analysis indicated almost complete consumption of the alcohol. After raising the pH to 12 and stirring with the dichloromethane layer, the aqueous hypochlorite layer was separated. Excess hypochlorite was decomposed by the addition of powdered sodium bisulfite until the pH was reduced to 5. (The solution warmed, and considerable effervescence occurred.) Upon lowering the pH to 1 with 6 M HCl, 0.16 g of a white precipitate, mp 119–120 °C (lit.[10]b mp for benzoic acid 122 °C), was isolated. Diethyl ether extracts of the aqueous solution provided an additional 0.17 g of crude benzoic acid for a total yield of approximately 50%.

Acetophenone and benzophenone were detected (10–31% and 3–7%, respectively) by GC and LC analysis of 2–4-h, phase transfer catalyzed reactions of **5b** with hypochlorite. Acidification of 3.5-h reaction mixtures blanketed and flushed with nitrogen resulted in isolation of carbon dioxide, as $BaCO_3$ from $Ba(OH)_2$ traps, in yields of approximately 40%, based on loss of one phenyl group.

Oxidation of 2-Phenyl-2-propanol (5c). Procedures employed strictly were analogous to those used in phase transfer catalyzed hypochlorite reactions of alcohol **5b**. LC and GC analyses showed alcohol **5c** to be converted to >50% yield to acetophenone in 4 h. Benzoic acid was isolated in 27–37% yield upon acidification of reaction mixtures maintained at pH 8–9 for 24 h.

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Registry No. **2**, 611-73-4; **4a**, 595-91-5; **4b**, 5558-66-7; **5a**, 76-84-6; **5b**, 599-67-7; **5c**, 617-94-7; **6a**, 93-99-2; **6b**, 98-86-2; **7**, 117-34-0; benzoic acid, 65-85-0.

(10) (a) Pavia, D. L.; Lampman, G. M.; Kritz, G. S. *Introduction to Organic Laboratory Techniques*, 2nd ed.; Saunders: Philadelphia, 1982; p 637; (b) *Ibid.* p 638.

(11) *Sadtler Standard Spectra*, Midget Edition; Sadtler Research Laboratories: Philadelphia, 1962; Spectrum No. 14800.

Derivatives of the Thebaine Anion. 2. 5-Methylmorphine, 5-Methylcodeine, 5-Methylheroin, and Some Related Compounds

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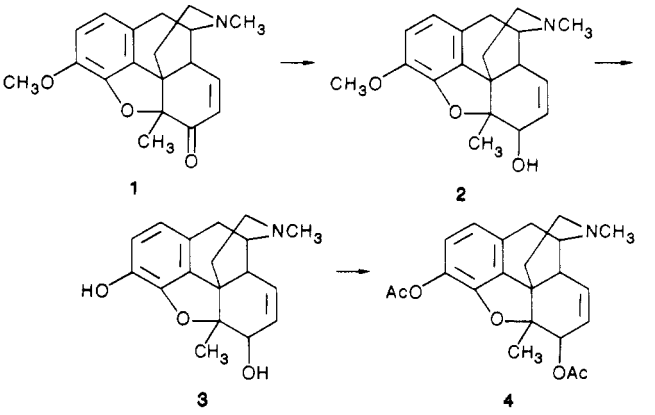
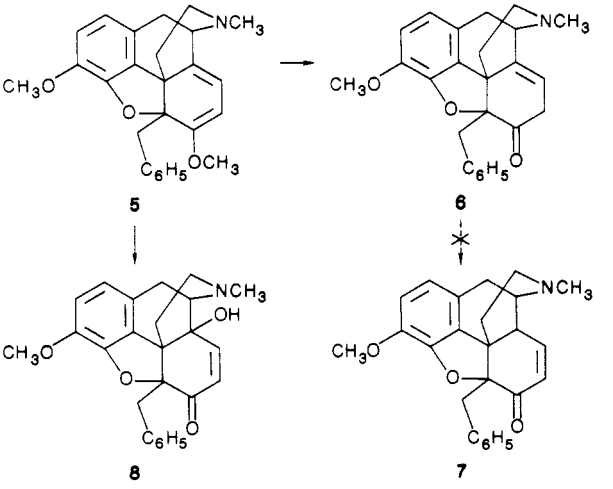
Simple direct routes to 5-methylmorphine, 5-methylcodeine, and 5-methylheroin from the recently described[1] thebaine anion are herein described.

(1) Boden, R. M.; Gates, M.; Ho, S. P.; Sundararaman, P. *J. Org. Chem.* **1982**, *47*, 1347.

5-Methylcodeinone (**1**)[1] on reduction with sodium borohydride[2] gives 5-methylcodeine (**2**) in high yield. Cleavage of the phenolic methoxyl group of **2** with sodium ethanethiolate gives 5-methylmorphine (**3**) likewise in excellent yield, and acetylation of **3** provides 5-methyldiacetylmorphine (5-methylheroin) (**4**). That **2**, **3**, and **4** have the natural codeine configuration at C_6 was shown conclusively by an X-ray crystallographic structure determination carried out on **4** (5-methylheroin) by Professor William D. Jones of these laboratories.[3]



The alkylation of the thebaine anion with benzyl chloride yields 5-benzylthebaine (**5**), but application to **5** of the procedure of Dauben, Baskin, and von Riel[4] for the conversion of thebaine to codeinone yields only the β,γ-unsaturated ketone, 5-benzylneopinone (**6**) and all attempts to isomerize this to the α,β-isomer, 5-benzylcodeinone (**7**),



failed and with it our projected preparation of 5-benzylmorphine. 5-Benzylthebaine is, however, readily converted into 5-benzyl-14-hydroxycodeinone (**8**) with hydrogen peroxide in formic acid. 5-Carbethoxythebaine (**9**), prepared by the action of ethyl chloroformate on the thebaine anion, is readily transformed into 5-carbethoxycodeinone (**10**) from which 5-(hydroxymethyl)codeine (**11**) is produced by reduction with sodium borohydride.

The results of screening for antinociceptive activity are tabulated in Table I. These tests were carried out for us

(2) Gates, M. *J. Am. Chem. Soc.* **1953**, *75*, 4340.

(3) A 3-dimensional ORTEP drawing of 5-methylheroin (**4**), tables of fractional atomic coordinates, anisotropic thermal parameters, bond angles and distances, and observed and calculated structure factors will be made available on request.

(4) Dauben, W. G.; Baskin, C. P.; van Riel, H. C. A. *J. Org. Chem.* **1979**, *44*, 1567.

0022-3263/89/1954-0972$01.50/0