An Example of Kinetic Resolution by Bakers' Yeast: Synthesis of Enantiomers of *endo*-Brevicomin from the Same Precursor

Sowmianarayanan Ramaswamy and Allan C. Oehlschlager*

Department of Chemistry, Simon Fraser University, Burnaby, British Columbia, Canada V5A 1S6

Received July 6, 1988

The southern pine beetle, *Dendroctonus frontalis*, is attracted to baits containing racemic α-pinene, *trans*-verbenol, and racemic frontalin.[1,2] When (1*S*,7*R*)-(+)-*endo*-brevicomin ((+)-**1a**) is added to this mixture attractancy is dramatically increased, but when the mixture is constituted with (1*R*,7*S*)-(−)-*endo*-brevicomin ((−)-**1a**) an unattractive mixture is obtained, suggesting that (−)-**1a** is repellant.[3] Development of a semiochemical-based management system for this insect requires efficient routes to the enantiomers of *endo*-brevicomin, **1a**. The most efficient routes to the enantiomers of **1a** in terms of overall chemical and optical yield are based on the Sharpless oxidation.[4] The present investigation was undertaken to develop an efficient route to enantiomers of **1a** from a single inexpensive precursor.

Bakers' yeast reductions of ketones are highly *si* selective.[5] When the ketone carries a substituent capable of coordination through hydrogen bonding or lone pair interaction the reductions are additionally *erythro* selective.[6]

Reductions of **2a**[7-9] or **3a** by bakers' yeast could give either enantiomer of **4a**, which are precursors of enantiomers of *exo*-brevicomin, **5a**, or the enantiomers of **6a**, which are the precursors of the enantiomers of **1a** (Figure 1). By analogy with the reduction of other α-hydroxycarbonyl derivatives,[6] it was anticipated that racemic **2a** or the ring-opened form **3a** would undergo stereoselective reduction by bakers' yeast to give to (6*R*,7*S*)-**6a** and thence (+)-**1a**. The remaining enantiomer of **2a** (or **3a**) would possess the *S* configuration at the hydroxyl-bearing carbon and would lead to (6*S*,7*R*)-**6a** upon *erythro* selective chemical reduction.[10]

Shaking **2a** with actively growing bakers' yeast under anaerobic conditions resulted in initial (12 h) formation of racemic **3a** and subsequent formation of (+)-**1a** (ee 99%)[11] and minor amounts of nearly racemic **5a** (Figure 1). The reaction was sluggish (6 days) and required large quantities of yeast (ca. 15 g dry weight per g of the substrate). Extraction of the yeast culture gave 29% of a mixture of **1a** and **5a** in the ratio of 16:1 and 36% of **3a**. The chiral purity of the brevicomins was determined by chiral complexation gas chromatography.[11] The presumed dihydroxy ketone intermediates (**4a** and **6a**) were not detected in the ether extract.

Although we initially considered that in situ conversion of **2a** to **3a** would lead to complications arising from competing methyl ketone reduction, no products arising from reduction of the methyl ketone were detectable by gas chromatographic/mass spectral analysis of the crude ether extract of the yeast culture.

The length of the alkyl chain appended to the carbonyl affected the enantio- and diastereoselectivity of reduction. Shortening the alkyl chain (i.e., reduction of **2b**) dramatically increased the rate of reduction and the enantioselectivity in the formation of **5b**. The exo and endo isomers of the norbrevicomins, **5b** and **1b**, respectively, formed from **2b**, were each produced in high chiral purity.[11] Whereas **2a** gave primarily endo product (**1a**) via *erythro* selective reduction, the exo isomer of **5b** predominated (2:1) in the reduction of **2b**. The observation of the opposite diastereoselectivity in the reduction of **2a** compared to **2b** can be attributed to loss of the precursor, (*R*) hydroxy diketone, for 1*S*,7*R* endo product by biodegradation.

Reduction of **2c**, which contained a propyl group attached to the reactive carbonyl, proceeded very slowly (only 9% reduction after 7 days) to give **5c** and **1c** in a ratio of 1:2. However, when the acyclic form of the ketone, viz. **3c**, was used as the substrate, this ratio increased to 1:30. The use of **3a** and **3b** in place of substrates **2a** and **2b** did not alter the exo:endo ratios produced in these reductions. Complexation gas chromatographic analysis[11] of the product derived from yeast reduction of **2c** revealed an optical purity of 98% for **1c** in which (+)-**1c** predominated and 33% for the **5c** in which (−)-**5c** predominated.

The *erythro* selective chemical reduction of the C-7 ketone of recovered enantiomeric **3a** followed by cyclization gave (−)-**1a**. This sequence required selective protection of the C-2 ketone, which proved difficult under a variety of conditions. Selective protection of the C-2 ketone was achieved by initial cyclization of **3a** to the chiral dihydropyran, **2a**, in 66% yield using oxalic acid as the catalyst. The dihydropyran underwent selective ketalization with ethylene glycol at the C-2 carbonyl in the presence of oxalic acid to give an enantiomer of **7** in 82% yield. Chelation-controlled reduction of **7** with $Zn(BH_4)_2$ in THF at −78 °C afforded 88% of a mixture of (−)-**5a** and (−)-**1a** with 91% optical purity as shown by complexation gas chromatographic analysis.[11]

Experimental Section

NMR spectra were recorded on Bruker WM400 and SY100 spectrometers. Mass spectra were recorded with an ionizing voltage of 70 eV. Gas chromatographic analysis utilized a J+W

(1) Borden, J. H. "Aggregation Pheromones" in *Comprehensive Insect Physiology Biochemistry, and Pharmacology*; Kerkut, G. A., Gilbert, L. I., Eds.; Pergamon Press: Oxford, 1985; Vol. 9, 257.

(2) Vité, J. P.; Billings, R. F.; Ware, C. W.; Mori, K. *Naturwissenschaften* **1985**, *72*, 99.

(3) In 1983 more than 10^8 ft^3 of timber was lost to *D. frontalis*. U.S. Forest Insect and Disease Conditions in the U.S. 1985, USDA Forest Service Report, 1985.

(4) (a) Oehlschlager, A. C.; Johnston, B. D. *J. Org. Chem.* **1987**, *52*, 940 and references therein. The enantiomers of *endo*-brevicomin prepared in this study were shown to possess the following optical purities by complexation gas chromatography[11] (+)-**1a**, ee 88%, (−)-**1a**, ee 90%. For other syntheses of chiral *endo*-brevicomins, see: (b) Redlich, H.; Bruns, W.; Francke, W.; Schurig, V.; Payne, T. L.; Vité, J. P. *Tetrahedron* **1987**, *43*, 2029 and references therein.

(5) Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119.

(6) (a) Buisson, D.; Sanner, C.; Larcheveque, M.; Azerad, R. *Tetrahedron Lett.* **1987**, *28*, 3939. (b) Sato, T.; Tsurumaki, M.; Fujisawa, T. *Chem. Lett.* **1986**, 1367. (c) Sakai, T.; Nakamura, T.; Fukuda, K.; Amano, E.; Utaka, M.; Takeda, A. *Bull. Chem. Soc. Jpn.* **1986**, 3185. (d) Lee, L. G.; Whitesides, G. M. *J. Org. Chem.* **1986**, *51*, 25.

(7) Prepared by the method of Chaquin, P.; Morizur, J.-P.; Kossanyi, J. *J. Am. Chem. Soc.* **1977**, *99*, 903.

(8) Sodium borohydride reduction of this substrate has been reported to give an exo–endo ratio of 3:2. See: Lipkowitz, K. B.; Scarpone, S.; Mundy, B. P.; Bornmann, W. G. *J. Org. Chem.* **1979**, *44*, 486.

(9) While our investigation was in progress, a preliminary report on the bakers' yeast mediated reductions of **2a** and **2b** was reported by Ibrahim, N.; Dixon, L. A.; Urbanek, T.; Eggiman, T.; Wieser, H. 70th Canadian Chemical Congress and Exhibition, 155 (1987). The present work and that reported by Ibrahim et al. are in substantial agreement in that comparable optical yields were obtained in the bakers' yeast reduction.

(10) For an excellent discussion, see: Nogradi, M. *Stereoselective Synthesis*; VCH Publishers: New York, 1986; pp 131–148.

(11) Schurig, V.; Weber, R.; Nicholson, G. J.; Oehlschlager, A. C.; Pierce, H. D., Jr.; Pierce, A. M.; Borden, J. H.; Ryker, L. C. *Naturwissenschaften* **1983**, *70*, 92. The determination of optical purities of **1a** and **5a** was by complexation chromatography on a fused silica column coated with Ni-4-Pin. Assignments of absolute configuration for **1a** and **5a** and analogues were based on retention behavior of the enantiomers of **1a**[12] and **5a**.[4a] The order of elution on this chiral phase column is (+)-**5a**, (−)-**5a**, (+)-**1a** and (−)-**1a**.

0022-3263/89/1954-0255$01.50/0

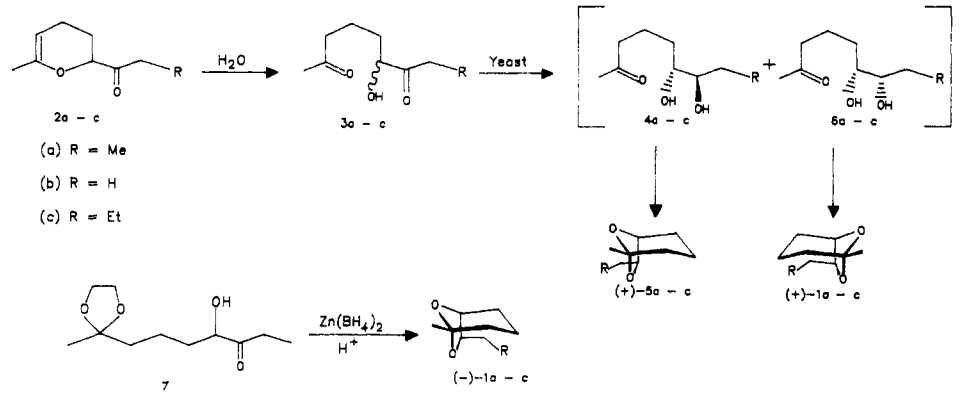


Figure 1. Synthetic routes to (+)- and (−)-*endo*-brevicomin.

fused silica DB-1 capillary column (15 m × 0.25 mm) and linear oven temperature programs initiated at 60 °C (program 1) or 100 °C (program 2) and increased at 5 °C/min to 200 °C. Complexation chromatography was performed on a fused silica capillary column (25 m × 0.25 mm) coated with Ni-4-Pin (op), purchased from Capillary Columns and Complexation Chromatography, Kirchentellinsfurt, FRG, and a linear oven temperature program initiated at 85 °C and increased at 0.1 °C/min to 90 °C.

Bakers' yeast was purchased locally and was manufactured by Fleischmann. Solvents and reagents were used as supplied from commercial sources with the following exceptions. Chromatography solvents were distilled before use. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. All reactions involving air- or moisture-sensitive reagents were performed under an argon atmosphere.

Preparation of 2-Butanoyl-6-methyl-2,3-dihydro-4*H*-pyran (2c) from 2b. This compound was prepared by adaptation of the literature procedure.[7] To 5.75 g (25 mmol) of the *N*-cyclohexyl imine of **2b** in 20 mL of THF was added 15 mL of 2 M ethylmagnesium bromide in ether. After removal of the ether, the remaining THF solution was refluxed and 2.0 mL of bromoethane was added. The reaction mixture was stirred at 25 °C for 18 h. Hydrolysis of the alkylated imine intermediate by addition of acetic acid followed by the usual extractive workup yielded **2c**: 3.27 g, 78%; bp 60 °C (0.25 mmHg) Kugelrohr; IR (film) 1720 and 1683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.0 Hz, 3 H), 1.37–2.1 (m, 6 H), 1.77 (d, J = 1.0 Hz, 3 H), 2.54 (m, 2 H), 4.26 (m, 1 H), 4.49 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.55, 16.39, 19.06, 19.77, 23.51, 39.75, 80.02, 96.09, 149.79, 210.97; M_r calcd for $C_{10}H_{16}O_2$ (M^+) 168.1150, found (high resolution MS) 168.1151.

Bakers' Yeast Reduction of 2a. To a vigorously stirred slurry of 40 g of bakers' yeast in 120 mL of tap water was added 10 g of sucrose. Vigorous fermentation ensued in a few minutes at which point 4.62 g (30 mmol) of **2a** was added in a single portion followed by 0.5 mL of ethanol, which was used to wash the addition pipette. Sucrose (5 g) and yeast (10 g) were added every 48 h to the vigorously stirred suspension. Aliquots (1 mL) for analysis were withdrawn at 12 h, 24 h, and thereafter every 48 h. Each aliquot was extracted with ether (5 mL), which was dried over anhydrous $MgSO_4$, filtered, and analyzed by gas chromatography/mass spectrometry. The starting material (**2a**) was substantially converted to hydroxy diketone **3a** within 12 h. The latter was partially consumed over 6 days, after which time consumption appeared to stop. At this point the reaction mixture was centrifuged, the supernatant decanted, and the sedimented yeast cells shaken with 3 × 75 mL portions of acetone. Each extraction was centrifuged and the supernatant removed by decantation. The combined acetone extracts were concentrated in vacuo and combined with the aqueous solution decanted earlier. This extract was extracted with ether continuously over 24 h. The ether extract was dried over anhydrous $MgSO_4$ and concentrated in vacuo at 0 °C to afford, upon Kugelrohr distillation, 60 °C (20 mmHg), lit.[13] bp 96 °C (77 mmHg), **1a**, 1.38 g, 29%; **1a**:**5a**, 16:1, DB-1, program 1. Optical purity: (+)-**1a**, ee >99%; **5a** ee 0% (complexation chromatography, Ni-4-Pin). Also obtained by distillation, (*S*)-**3a**:[14] 1.86 g, 36%, hygroscopic liquid, **bp** 110–120 °C (0.25 mmHg); $[\alpha]^{22}_D$ +23.86° ($CHCl_3$, c = 1.4); IR (film) 3450, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (t, J = 6.6 Hz, 3 H), 1.68 (m, 4 H), 2.13 (s, 3 H), 2.49 (m, 4 H), 3.61 (br s, 1 H), 4.15 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 7.07, 18.74, 29.41, 30.66, 32.50, 42.56, 75.80, 208.73, 212.82; low resolution CIMS (isobutane), m/e 173 ($M + H^+$). Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 62.84; H, 9.70.

Cyclization of (*S*)-3a into (*S*)-2a. Kugelrohr distillation (50 °C at 0.25 mmHg) of a mixture of 0.35 g (2.03 mmol) of recovered (*S*)-**3a** from the yeast reduction afforded 0.21 g (66%) of (*S*)-**2a**: $[\alpha]^{22}_D$ = +6.32° ($CHCl_3$, c = 2.5); spectral characteristics of this product were identical with those of racemic **2a**.

Preparation of Ketal (*S*)-7. A mixture of 0.15 g (1 mmol) of (*S*)-**2a**, 0.080 g (1.3 mmol) of ethylene glycol, and 5 mg of oxalic acid monohydrate was stirred at 25 °C for 48 h. The mixture was then chromatographed on neutral activity 3 alumina using 10–30% ether in hexanes (v/v, gradient) to afford 0.177 g (82%) of (*S*)-**7**, as a colorless, thermally unstable oil used immediately following chromatography: $[\alpha]^{22}_D$ = +12.78° ($CHCl_3$, c = 1.8); IR (film) 3450, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.027 (t, J = 7.3 Hz, 3 H), 1.20 (t, J = 7.2 Hz, 2 H), 1.38 (s, 3 H), 1.4–2.05 (m, 4 H), 2.60 (m, 2 H), 3.50 (m, 4 H), 3.72 (br t, 1 H), 4.08 (dd, J = 11.7, 3 Hz, 1 H); low resolution CIMS (isobutane), m/e 217 ($M + H^+$). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H 9.32. Found: C, 61.02; H, 9.25.

Preparation of (−)-*endo*-Brevicomin. To a solution of 0.108 g (0.5 mmol) of the chiral ketal, (*S*)-**7**, in 2 mL of dry THF cooled to −78 °C under an atmosphere of argon was added 0.5 mL of a 0.56 M solution of $Zn(BH_4)_2$ in THF through the sides to ensure precooling of the reagent. The reaction was stirred at −78 °C for 1 h and then warmed to room temperature, treated with 2 mL of 2 M H_2SO_4, and extracted with 3 × 10 mL of ether. The ether extract was dried over anhydrous $MgSO_4$ and concentrated in vacuo at 0 °C to afford 0.07 g (88%) of (−)-*endo*-brevicomin, ee 91% (complexation chromatography, Ni-4-Pin).[11]

Bakers' Yeast Reduction of 2b. Reduction of **4b** by bakers' yeast was essentially as above for **2a** except that 1.5 g (10.7 mmol) of **2b** was reduced in a fermenting medium initially containing 4 g of sucrose and 12 g of bakers' yeast with subsequent addition of 3 g of sucrose every 24 h. The intermediate hydroxy diketone was completely consumed in 72 h. Workup was as above and the reduction yielded, upon Kugelrohr distillation, 50 °C (20 mmHg), **1b** and **5b**:[15] 0.472 g, 32%, **1b**:**5b**, 2:1, DB-1, program 1. Optical purity: (+)-**1b**, ee >99%; (−)-**5b**, ee 98% (complexation chromatography, Ni-4-Pin).[11]

Bakers' Yeast Reduction of 2c. To an actively fermenting mixture of 3 g of sucrose and 3 g of bakers' yeast in 10 mL of tap

(12) Johnston, B. D.; Oehlschlager, A. C. *J. Org. Chem.* **1982**, *47*, 5384. The enantiomers of *exo*-brevicomin prepared in this study were shown to possess the following optical purities by complexation gas chromatography:[11] (+)-**1a**, ee = 86%; (−)-**1a**, ee = 86%.

(13) Mori, K.; Seu, Y.-B. *Tetrahedron* **1985**, *41*, 3431.

(14) The configuration of the recovered **3a** was determined to be *S* by conversion to (−)-*exo*-brevicomin by yeast reduction.

(15) The ^1H NMR spectrum obtained corresponded to that reported in the literature[16] except that our chemical shifts are consistently 0.13 ppm higher than those reported. This discrepency is probably due to a systematic error in referencing.

(16) Mundy, B. P.; Lipkowitz, K. B.; Dirks, G. W. *Synth. Commun.* **1975**, *5*, 7.

water was added 0.168 g (1 mmol) of **2c**. The reaction mixture was stirred and mixtures of 2 g of sucrose and 3 g of yeast were added every 48 h. After 1 week the consumption of **3c**, which formed within 12 h, had slowed appreciably and the reaction was stopped by centrifugation and extraction of the supernatant with ether (4 × 25 mL). The extract was dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford 0.19 g of an oil, which upon evaporation under 0.25 mmHg with trapping on a cold finger at −78 °C afforded **1c** and **5c**: 15 mg, 9%, **1c**:**5c**, 2:1, DB-1, program 1. Optical purity: (+)-**1c**, ee 92%; (−)-**5c**, ee 45% (complexation chromatography, Ni-4-Pin). ^1H NMR ($CDCl_3$) δ: 0.97 (t, J = 7.5, 3 H), 1.44 (s, 3 H), 1.3–1.9 (m, 10 H), 4.04 (m, 1 H), 4.18 (m, 1 H). M_r calcd for $C_{10}H_{18}O_2$ 170.1307, found (high resolution MS) 170.1307. The residue upon Kugelrohr distillation afforded 0.08 g (43%) of **3c** as a hygroscopic liquid, bp 120 °C (0.2 mmHg): IR (film) 3450, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, J = 7.5 Hz, 3 H), 1.20–2.04 (m, 6 H), 2.14 (s, 3 H), 2.50 (m, 4 H), 3.09 (br s, 1 H), 4.15 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.62, 16.99, 19.08, 29.76, 32.74, 39.64, 42.87, 76.15, 187.23, 190.87; low resolution CIMS (isobutane), m/e 187 ($M + H^+$). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.76; H, 10.05.

Bakers' Yeast Reduction of 3c. Ketone **2c**, 0.33 g (2 mmol), was stirred with 2 mL of 0.05 M KH_2PO_4 for 20 h and the resulting clear solution was added to an actively fermenting mixture of 3 g of bakers' yeast and 0.5 g of sucrose in 10 mL of water. Additional 0.5-g amounts of sucrose were added every 24 h and 1.5-g quantities of yeast every 48 h. After stirring for 8 days and workup as above were obtained **1c** and **5c**: 0.026 g, 7.5%, **1c**:**5c**, 30:1, DB-1, program 1. Optical purity: (+)-**1c**, ee 98%; (−)-**5c**, ee 34% (complexation chromatography, Ni-4-Pin).[11]

Acknowledgment. This work was funded by a Natural Sciences and Engineering Research Council Strategic Grant (Biotechnology) and an Operating Grant to A.C.O. We thank Professor Hal Wieser and Dr. Elizabeth Dixon of the Department of Chemistry at the University of Calgary for helpful discussions and preliminary communication of their work in this area.

Registry No. (+)-**1a**, 22625-19-0; (−)-**1a**, 80952-67-6; (+)-**1b**, 117957-12-7; (+)-**1c**, 117897-06-0; (*S*)-**2a**, 117957-11-6; (±)-**2a**, 117957-10-5; (±)-**2b**, 84498-69-1; (±)-**2b** *N*-cyclohexyl imine, 117897-02-6; (±)-**2c**, 117897-03-7; (*S*)-**3a**, 117897-04-8; (−)-**5b**, 117957-13-8; (−)-**5c**, 117957-14-9; (*S*)-**7**, 117897-05-9; bromoethane, 74-96-4.

Some Observations on the Mechanism of the Mitsunobu Reaction

David Crich,* Hubert Dyker, and Robert J. Harris

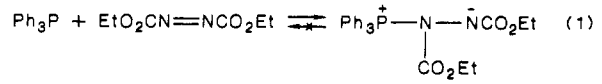
Department of Chemistry, University College London, 20, Gordon Street, London, WC1H OAJ, U.K.

Received June 27, 1988

During a search for a stereoselective preparation of secondary alkyl hydroperoxides, we examined some aspects of the mechanism of the Mitsunobu reaction and studied the use of *m*-chloroperoxybenzoic acid (MCPBA) as a nucleophile.

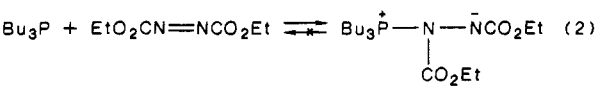
The triphenylphosphine (TPP)/diethyl azodicarboxylate (DEAD) mediated esterification of an alcohol with an acid, with clean inversion of configuration for asymmetric alcohols, known[1] as the Mitsunobu reaction, has been subjected[2] to considerable mechanistic scrutiny in recent years. The majority of this work relates to the later stages of the mechanism and concerns the intermediacy of alkoxyphosphonium salts and/or dialkoxyphosphoranes. The work described below focuses on the initial stages of the mechanism and provides supportive evidence for the irreversibility[2b] of the addition of TPP to DEAD.

Literature methods for the stereoselective preparation of secondary alkyl hydroperoxides involving[3] the displacement of mesylates by alkaline hydrogen peroxide give at best meagre yields, although application[4] to primary mesylates is more efficient. The use of potassium superoxide/18-crown-6 in dimethyl sulfoxide/dimethylformamide yields[5] alcohols and not hydroperoxides. More efficient methods for the preparation of secondary hydroperoxides involve either free radical[6] or carbocation[7] intermediates and are nonstereoselective. We conceived that the use of MCPBA as nucleophile in the Mitsunobu reaction with a secondary alcohol would provide secondary peroxyesters, with clean inversion of configuration, and that alkaline hydrolysis would then yield[8] diastereomerically pure secondary alkyl hydroperoxides. Obvious problems such as oxidation of TPP by the peracid would be circumvented by prior formation of the betaine and dialkoxyphosphoranes before addition of MCPBA. Such an approach relies on clean, *irreversible*, betaine formation. Although Guthrie and Jenkins noted[2b] that the ^{31}P NMR chemical shift of the betaine showed little solvent dependence (δ +43.9 in benzene; +44.7 in chloroform; +45.4 in dimethylformamide) and took this to imply little or no equilibrim with TPP and DEAD, we sought more conclusive evidence for the irreversibility of this reaction (eq 1).



$$Ph_3P + EtO_2CN{=}NCO_2Et \rightleftharpoons Ph_3\overset{+}{P}-\underset{\displaystyle CO_2Et}{\underset{|}{N}}-\overset{-}{N}CO_2Et \quad (1)$$

Equimolar amounts of TPP and DEAD were allowed to react in THF to give the betaine. Clean formation of the betaine (δ +43) was observed, and all of the TPP (δ −5.3) was consumed. An equimolar quantity of tributylphosphine (TBP) was then added and the ^{31}P NMR spectrum recorded after 20 min. Some formation of triphenylphosphine oxide (δ +23) was observed, presumably due to hydrolysis by extraneous water, but, significantly, no TPP was liberated, indicating that the reaction of eq 1 is not reversible, at least on the time scale of a typical Mitsunobu reaction. This observation was given further credence when addition of TPP to a preformed solution of the betaine from TBP and DEAD (eq 2) (δ +46) did not lead to the liberation of TBP (δ −32) or formation of the TPP/DEAD betaine.



$$Bu_3P + EtO_2CN{=}NCO_2Et \rightleftharpoons Bu_3\overset{+}{P}-\underset{\displaystyle CO_2Et}{\underset{|}{N}}-\overset{-}{N}CO_2Et \quad (2)$$

Secure in the knowledge that prior betaine formation would exclude the reaction of TPP with MCPBA, we attempted the formation of peresters by the Mitsunobu se-

(1) Mitsunobu, O. *Synthesis* **1981**, 1 and references therein.
(2) (a) Grochowski, E.; Hitton, B. D.; Kupper, R. J.; Michejda, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 6876. (b) Guthrie, R. D.; Jenkins, I. D. *Aust. J. Chem.* **1982**, *35*, 767. (c) von Itzstein, M.; Jenkins, I. D. *Aust. J. Chem.* **1983**, *36*, 557. (d) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235.
(3) Williams, H. R.; Mosher, H. S. *J. Am. Chem. Soc.* **1954**, *76*, 2987.
(4) (a) Williams, H. R.; Mosher, H. S. *J. Am. Chem. Soc.* **1954**, *76*, 2984. (b) Wawzonek, S.; Klimstra, P. D.; Kallio, R. E. *J. Org. Chem.* **1960**, *25*, 621.
(5) Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, 3186.
(6) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.
(7) Cagliotti, L.; Gasparrini, F.; Misiti, D.; Palmieri, G. *Tetrahedron* **1978**, *34*, 135.
(8) Milas, M. A.; Surgenor, D. M. *J. Am. Chem. Soc.* **1946**, *68*, 642.

0022-3263/89/1954-0257$01.50/0