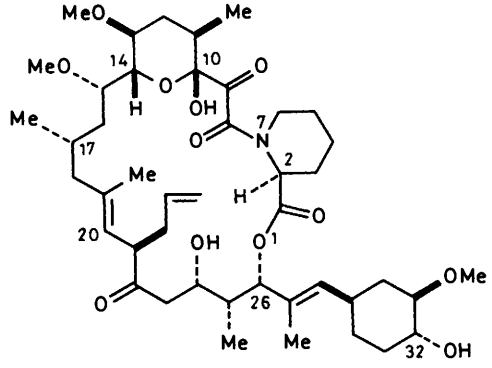
An Approach to the Cyclohexyl Moiety of the Immunosuppressive Agent FK-506

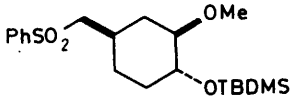
Anthony J. Pearson* and Brian A. Roden
Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106, USA

Tricarbonyl(3-methoxycyclohexadienyl)iron hexafluorophosphate, which is readily prepared from 1,3-dimethoxybenzene, was treated with the enolate of methyl phenylsulphonylacetate to give an adduct which was decarboxylated and decomplexed to give 5-phenylsulphonylmethylcyclohexenone. This compound was converted by a four-step, highly stereoselective, sequence to the trisubstituted cyclohexane (**2**), which represents a cyclohexyl moiety building block for FK-506.

At the present time there is considerable interest in the synthesis of FK-506 (**1**), owing to its potent activity as an immunosuppressant.[1,2] This macrolide is able to suppress *in vitro* immune systems at concentrations 100-fold lower than that required for cyclosporin A,[2] a compound which is currently used to prevent tissue rejection following organ transplant surgery. Recently, Schreiber and Smith[1a] described the synthesis of compound (**2**), a proposed synthetic building block which represents the cyclohexyl moiety of FK-506. The synthesis afforded optically pure (**2**) in twelve steps and *ca.* 10% overall yield from penta-1,4-dien-3-ol, using the Sharpless asymmetric epoxidation/kinetic resolution method. We report a highly stereoselective synthesis of (**2**) in racemic form, which we anticipate can ultimately be modified to give optically pure material.



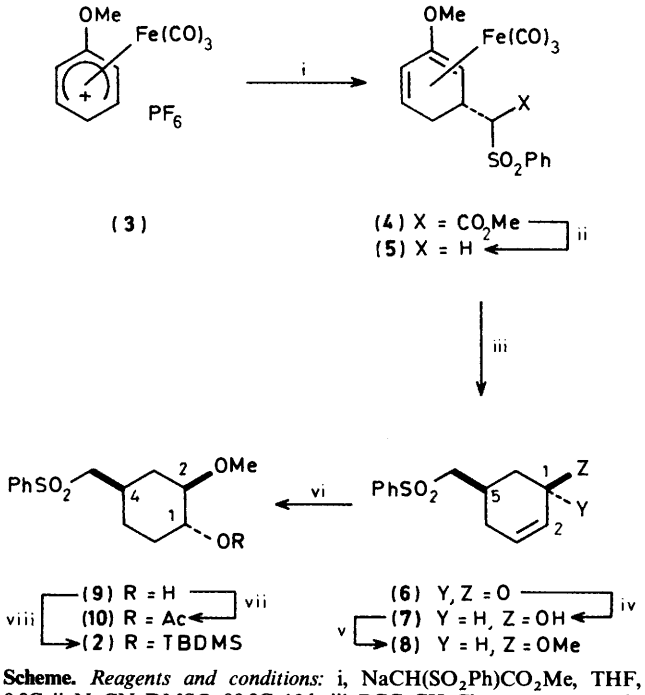
(**1**)



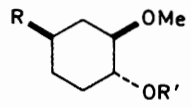
(**2**)

The cyclohexadienyl-Fe(CO)$_3$ complex (**3**) is readily prepared in multigram quantities from 1,3-dimethoxybenzene, using the method of Kelly *et al.*[3] Treatment of (**3**) with NaCH(SO$_2$Ph) CO$_2$Me gave (**4**) in excellent yield, which was decarboxylated without diene rearrangement or decomposition to afford (**5**) in 87% overall yield from (**3**). Treatment of (**5**) with pyridinium chlorochromate (PCC) gave the cyclohexenone (**6**) in 88% yield after purification by flash chromatography. Borohydride reduction of (**6**) (NaBH$_4$, CeCl$_3$, EtOH) proceeded with excellent stereocontrol to give the equatorial alcohol (**7**), as the major product (>20:1) by NMR spectroscopy (91% yield), which was then converted to the methyl ether (**8**) (see Scheme). The stereochemical assignment was readily confirmed by ^{1}H NMR spectroscopy, which showed diaxial coupling of 8–9 Hz between H(1)/H(6) and between H(5)/H(6).

Hydroboration of (**8**) furnished the alcohol (**9**), as expected, which was converted to the silyl-protected derivative (**2**), spectroscopically identical to the material prepared by Schreiber and Smith.[1a] Further confirmation of relative stereochemistry was accomplished by converting (**9**) to the acetate (**10**), which showed better separation of peaks in the ^{1}H NMR spectrum. Diaxial couplings were evident for H(1) (ddd, *J* 10.2, 8.6, 4.6 Hz), H(2) (ddd, *J* 10.2, 9.4, 4.5 Hz) and for H(3β) (ddd, J_{gem} 10 Hz, $J_{2,3}$ 9.4 Hz, $J_{2,4}$ 8 Hz). This is in agreement with couplings reported for the cyclohexyl moiety of rapamycin,[4] which is structurally related to FK-506. In addition, the NMR assignments were confirmed by COSY 2-D techniques.



Scheme. *Reagents and conditions:* i, NaCH(SO$_2$Ph)CO$_2$Me, THF, 0 °C; ii, NaCN, DMSO, 80 °C, 10 h; iii, PCC, CH$_2$Cl$_2$, room temp., 4 h; iv, NaBH$_4$, CeCl$_3$·7H$_2$O, EtOH, 0 °C, 1 h; v, NaH, THF, MeI, room temp., 24 h; vi, BH$_3$·THF, room temp., 24 h, then H$_2$O$_2$, NaOH, H$_2$O, room temp., 24 h; vii, Ac$_2$O, py, −20 °C, 16 h; viii, TBDMSOTf, Et$_3$N, CH$_2$Cl$_2$, room temp., 24 h.



(11)

In summary, this synthesis furnishes the FK-506 cyclohexyl moiety in racemic form in six steps and *ca.* 41% overall yield from complex (**3**), which is itself prepared from 1,3-dimethoxybenzene by a four-step sequence. This approach is potentially useful for constructing cyclohexane derivatives of *general* structure (**11**) in optically active form, since we have found[5] that reaction of (**3**) with enolate nucleophiles bearing chiral auxiliaries, such as those derived from optically pure sulphoximinyl esters[6] or the Evans *N*-acyloxazolidinone systems,[7] occurs with asymmetric induction. While the enantiomeric excesses (30–70% e.e.) obtained are not high enough at this stage to be of real practical value, we anticipate that this can be improved sufficiently to allow asymmetric synthesis of compounds related to (**3**).

Experimental

General.—Infra-red spectra were recorded using a Perkin-Elmer 1420 instrument, ^{1}H NMR spectra were recorded on a Varian XL 200 for solutions in deuteriochloroform using Me_4Si as an internal reference, and mass spectra were measured in-house on a Kratos MS 25A instrument. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN. Solvents were purified by distillation as follows: dichloromethane and pyridine from calcium hydride; tetrahydrofuran (THF) from sodium benzophenone ketyl. NMR assignments were confirmed by decoupling experiments for compounds (**7**), (**8**), (**9**), and by COSY for (**2**).

Tricarbonyl{methyl(2-4-η-3-methoxycyclohexa-2,4-dienyl)-phenylsulphonylacetate}iron (**4**).—Methyl phenylsulphonylacetate (64 mg, 0.3 mmol) was converted to its sodio-derivative by treatment with NaH (0.3 mmol) in THF (5 ml). The stirred solution was cooled to 0 °C and the dienyl complex (**3**) (100 mg, 0.25 mmol) was added. Stirring was continued until the THF-insoluble complex had disappeared, the mixture was quenched with water (5 ml) and poured into ether (30 ml). The ether phase was washed with brine, water, dried ($MgSO_4$) and evaporated to yield the crude complex (**4**) as a yellow foam (113 mg, 97%). An analytical sample was prepared by flash chromatography on 10 mg of the crude product (80% recovery), but the crude compound was used in the next step, $\nu_{max}(CHCl_3)$ 2 040, 1 972, and 1 735 cm^{-1}; δ_H 7.82 (4 H, m, Ph, both diastereomers), 7.53 (6 H, m, Ph, both diastereomers), 5.15 (2 H, dm, $J_{3,4}$ 6.5 Hz, H-4, both diastereomers), 3.83 (1 H, d, *J* 7.3 Hz, C*H*(CO_2CH_3)-SO_2Ph, one diastereomer), 3.64 (1 H, d, *J* 7.3 Hz, C*H*(CO_2-CH_3)SO_2Ph, one diastereomer), 3.59 (3 H, s, CO_2CH_3, one diastereomer), 3.58 (3 H, s, CO_2CH_3, one diastereomer), 3.56 (3 H, s, OCH_3, one diastereomer), 3.45 (3 H, s, OCH_3, one diastereomer), 3.08 (2 H, m, H-2, both diastereomers), 2.93 (1 H, m, H-1, one diastereomer), 2.66 (1 H, m, H-1, one diastereomer), 2.61 (2 H, m, H-5 both diastereomers), 2.04 (2 H, m, H-1 *exo*, both diastereomers), and 1.74 (2 H, dm, J_{gem} 11 Hz, H-1 *endo*, both diastereomers) (Found: C, 49.20; H, 3.95. Calc. for $C_{19}H_{16}FeO_8S$: C, 49.59; H, 3.50%).

Tricarbonyl[2-4-η-(3-methoxycyclohexa-2,4-dienyl)methyl-phenylsulphone]iron (**5**).—The crude complex (**4**) (100 mg, 0.22 mmol) was dissolved in degassed dimethylsulphoxide (10 ml) under argon in a 25 ml flask fitted with a reflux condenser and magnetic stir bar. To this was added sodium cyanide (54 mg, 1.10 mmol) and water (0.1 ml) and the stirred mixture was heated at 80 °C until infra-red spectroscopy showed complete disappearance of the ester (1 735 cm^{-1}; reaction time approx. 10 h). The cooled solution was poured onto crushed ice and saturated with NaCl. Ether extraction, followed by washing with water, brine, drying ($MgSO_4$) and evaporation afforded the crude complex (**5**) (79 mg, 90%) as a yellow foam which was used directly in the next step. An analytical sample was obtained by flash chromatography (30% EtOAc in hexane) on 10 mg, giving (**5**) as a viscous yellow oil; $\nu_{max}(CHCl_3)$ 2 040 and 1 970 cm^{-1}; δ_H 7.56 (2 H, m, Ph), 7.31 (3 H, m, Ph), 4.86 (1 H, dd, *J* 6, 2 Hz, H-4), 3.31 (3 H, s, OCH_3), 2.86 (1 H, dd, J_{gem} 10.5 Hz, J_{vic} 7 Hz, CH_2SO_2Ph), 2.59 (1 H, dd, J_{gem} 10.5 Hz, J_{vic} 9 Hz, CH_2SO_2Ph), 2.33 (2 H, m, H-1, H-5), 1.67 (1 H, ddd, *J* 15.3, 10, 4 Hz, H-6 *endo*), and 1.10 (1 H, dm, J_{gem} 15.3 Hz, H-6 *exo*) (Found: C, 46.30; H, 3.45. Calc. for $C_{17}H_{14}FeO_6S$: C, 46.16; H, 3.19%).

5-Phenylsulphonylmethylcyclohex-2-en-1-one (**6**).—Complex (**5**) (65 mg, 0.16 mmol) was stirred in dry dichloromethane (3 ml) while pyridinium chlorochromate (170 mg) was added in one portion. The mixture was stirred until the reaction was complete (TLC, 30% ethyl acetate in hexane; *ca.* 4 h). Filtration of the mixture through silica gel and washing with 20% EtOAc–hexane, followed by flash chromatography (50% EtOAc–hexane) gave (**6**) as a white crystalline compound, m.p. 135–137 °C (35 mg, 88%); $\nu_{max}(CHCl_3)$ 1 675 cm^{-1}; δ_H 7.86 (2 H, d, *J* 7 Hz, Ph), 7.58 (3 H, m, Ph), 6.93 (1 H, ddd, *J* 9.5, 4.3, 3.0 Hz, H-3), 6.03 (1 H, d br, *J* 9.5 Hz, H-2), 3.13 (1 H, d, *J* 7.2 Hz, CH_2SO_2Ph), 3.10 (1 H, d, *J* 4.8 Hz, CH_2SO_2Ph), 2.81 (2 H, m, H-5), 2.73 (1 H, m, H-4), 2.62 (1 H, dd, *J* 16, 3.8 Hz), and 2.38 (1 H, dm, J_{gem} 10.3 Hz), 2.19 (1 H, dd, *J* 16, 4.8 Hz) (Found: C, 62.30; H, 5.65. Calc. for $C_{13}H_{14}O_3S$: C, 62.38; H, 5.64%).

5-Phenylsulphonylmethylcyclohex-2-en-1-ol (**7**).—The enone (**6**) (35 mg, 0.14 mmol) was stirred in ethanol (3 ml) containing cerium(III) chloride heptahydrate (72 mg, 0.21 mmol) at 0 °C while sodium borohydride (8 mg, 0.21 mmol) was added. After 1 h, the reaction mixture was treated with water (several drops), warmed to room temperature and poured into ethyl acetate (15 ml). The solution was washed with brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure to give (**7**) as a white foam (32 mg, 91%). [NMR spectroscopy showed >90% diastereomeric excess (minor diastereomer shows vinyl protons at δ 5.85)] $\nu_{max}(CHCl_3)$ 3 320 cm^{-1}; δ_H 7.88 (2 H, d, *J* 7.3 Hz, Ph), 7.35 (3 H, m, Ph), 5.66 (2 H, s br, vinyl), 4.29 (1 H, m, H-1), 3.17 (1 H, dd, *J* 9, 6.8 Hz, CH_2SO_2Ph), 3.09 (1 H, dd, *J* 9, 4.8 Hz, CH_2SO_2Ph), 2.39 (1 H, m, H-5), 2.36 (2 H, m), 1.89 (1 H, dm, J_{gem} 14 Hz, one of H-6), 1.62 (1 H, s br, exch. D_2O, OH), and 1.44 (1 H, ddt, *J* 14, 9 Hz, one of H-6) [Found: 253.0890. Calc. for $C_{13}H_{17}O_3S$ (*M* + H): 253.0898.

5-Phenylsulphonylmethylcyclohex-2-enyl methyl ether (**8**).—The alcohol (**6**) (32 mg, 0.13 mmol) was stirred in dry THF (2.5 ml) under argon with sodium hydride (50% dispersion in mineral oil; 30 mg, 0.65 mmol NaH) for 1 h at room temperature. Methyl iodide (185 mg, 0.08 ml, 1.3 mmol) was added *via* syringe and stirring was continued for 24 h. The mixture was cooled to 0 °C and water (several drops) was added. The solution was poured into ethyl acetate (10 ml) and this was washed thoroughly with brine. Separation of the organic layer, followed by drying ($MgSO_4$), removal of solvent under reduced pressure and purification by flash chromatography (50% EtOAc–hexane) gave (**8**) as a colourless oil (28 mg, 82%); $\nu_{max}(CHCl_3)$ 1 320 and 1 150 cm^{-1}; δ_H 7.90 (2 H, d, *J* 6.6 Hz, Ph), 7.59 (3 H, m, Ph), 5.72 (2 H, s br, vinyl), 3.84 (1 H, m,

H-1), 3.32 (3 H, s, OCH_3), 3.11 (2 H,d, J 9 Hz, CH_2SO_2Ph), 2.37 (1 H, m, H-5), 1.97 (1 H, m, H-6), and 1.38 (1 H, ddd, J_{gem} 15, 8.3, 8.7 Hz, axial H-6) [Found: 267.0993. calc. for $C_{14}H_{19}O_3S$ (M + H): 267.0983] (Found: C, 63.40; H, 6.75. Calc. for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81%).

2-Methoxy-4-phenylsulphonylmethylcyclohexan-1-ol (**9**).—The methyl ether (**8**) (5 mg, 0.02 mmol) was stirred in THF (1 ml) at 0 °C while borane–THF (1.0M solution; 0.02 ml) was added. The mixture was stirred for 24 h, allowing to warm to room temperature, and 30% aqueous hydrogen peroxide (0.07 ml) and 3M aqueous sodium hydroxide (0.01 ml) were added. Stirring was continued for 24 h, and the mixture was poured into ethyl acetate, washed with water and brine, and then dried ($MgSO_4$). Removal of solvent under reduced pressure gave a pale yellow oil which was not purified but used directly in the next step; $\nu_{max}(CHCl_3)$ 3 560 cm^{-1}; $\delta_H(CDCl_3)$ 7.90 (2 H, d, J 6.6 Hz, Ph), 7.60 (3 H, m, Ph), 3.36 (3 H, s, OCH_3), 3.35 [1 H, m(obs), H-1], 3.00 (2 H, d, J 6.2 Hz, CH_2SO_2Ph), 2.96 (1 H, td, J 8.7, 4.1 Hz, H-2), 2.63 (1 H, s br, OH); 2.36 (1 H, dm, J 11.2 Hz, H-3), 2.10 (1 H, m, H-4), 2.02 (1 H, m, H-5), 1.89 (1 H, dm, J 9 Hz, H-6), 1.35 (1 H, dm, J 13 Hz, H-5), 1.11 (1 H, dm, J 9 Hz, H-6), and 0.94 (1 H, dd, J 11.1, 12.4 Hz, H-3) [Found: 285.1178. Calc. for $C_{14}H_{21}O_4S$ (M + H): 285.1161].

2-Methoxy-4-phenylsulphonylmethylcyclohexyl acetate (**10**).—The total crude product (**9**) from the preceding reaction was dissolved in pyridine (1 ml) and cooled to −20 °C. Acetic anhydride (0.02 ml) was added, the mixture was stirred overnight, then poured into water (5 ml) and extracted with ethyl acetate. The combined organic extracts were washed with water, then brine, dried ($MgSO_4$) and evaporated. Purification by preparative TLC (silica gel, 30% EtAOc–hexane) gave the acetate (**10**) as a pale yellow oil (4 mg, 71%) $\nu_{max}(CHCl_3)$ 1 720, 1 295, 1 140, and 1 080 cm^{-1}; δ_H 7.90 (2 H, d, J 7 Hz, Ph), 7.56 (3 H, m, Ph), 4.63 (1 H, ddd, J 10.2, 8.6, 4.6 Hz, H-1), 3.34 (3 H, s, OCH_3), 3.16 (1 H, ddd, obscured, J 10.2, 9.4, 4.5 Hz, H-2), 3.01 (2 H, d, J 6.1 Hz, CH_2SO_2Ph), 2.35 (1 H, dm, J 8 Hz, H-6), 2.23 (1 H, m, H-4), 1.98 (1 H, m, H-5), 1.96 (1 H, m, H-6), 1.29 (1 H, m, H-5), 1.16 (1 H, dm, J_{gem} 10 Hz, H-3), and 1.09 (1 H, ddd, J_{gem} 10 Hz, $J_{2,3}$ 9.4 Hz, $J_{3,4}$ 8 Hz, H-3) [Found: 327.1261. Calc. for $C_{16}H_{23}O_5S$ (M + H): 327.1266].

1-(t-Butyldimethylsilyloxy)-2-methoxy-4-phenylsulphonylmethylcyclohexane (**2**).—The crude alcohol (**9**) (5 mg, 0.02 mmol) was dissolved in dry methylene chloride (0.5 ml) under argon. Triethylamine (5 μl, 0.03 mmol) and t-butyldimethylsilyl triflate (10 μl, 0.03 mmol) were added and the reaction mixture was stirred for 24 h. The mixture was diluted with methylene chloride (10 ml), the solution was washed with water (5 ml), 10% aq. HCl (5 ml), brine (5 ml), and dried ($MgSO_4$). Removal of solvent under reduced pressure, followed by preparative TLC (silica gel, 30% EtOAc–hexane) gave (**2**) as a colourless oil, identical (except optical rotation) to the sample kindly provided by Professor Schreiber, $\nu_{max}(CHCl_3)$ 1 295, 1 140, and 1 080 cm^{-1}; $\delta_H(CDCl_3)$ 7.89 (2 H, d, J 6.6 Hz, Ph), 7.57 (3 H, m, Ph), 3.37 (1 H, td, obscured, J 8.4, 4.5 Hz, H-1), 3.34 (3 H, s, OCH_3), 3.00 (2 H, d, J 6.2 Hz, CH_2SO_2Ph), 2.89 (1 H, ddd, J 10.5, 8.4, 4.3 Hz, H-2), 2.16 (1 H, dm, J_{gem} 12 Hz, H-3), 2.11 (1 H, m, H-4), 1.83 (2 H, m, H-6, H-5), 1.32 (1 H, dm, J_{gem} 10.5 Hz, H-6), 1.12 (1 H, dm, J_{gem} 13 Hz, H-5), 0.97 (1 H, dm, J_{gem} 12 Hz, H-3), 0.85 (9 H, s, $SiBu^t$), and 0.03 and 0.02 (3 H, s, $SiCH_3$) (Found: C, 60.75; H, 8.80. Calc. for $C_{20}H_{34}O_4SSi$: C, 60.3; H, 8.54%.

Acknowledgements

Financial support from the National Institutes of Health (GM 32114) and from the Graduate Alumni of Case Western Reserve University (Fellowship to B. A. R.) is gratefully acknowledged. We are also grateful to Professor Stuart Schreiber for a copy of the ^1H NMR spectrum of (**3**) and for providing a generous sample of this compound.

References

1 Synthetic studies: (*a*) S. L. Schreiber and D. B. Smith, *J. Org. Chem.*, 1989, **54**, 9; (*b*) M. Egberton and S. J. Danishefsky, *ibid.*, p. **11**; (*c*) A. Villalobos and S. J. Danishefsky, *ibid.*, p. 12; (*d*) S. L. Schreiber, T. Sammakia, and D. E. Uehling, *ibid.*, p. 15; (*e*) A. B. Jones, M. Yamaguchi, A. Patten, S. J. Danishefsky, J. A. Ragan, D. B. Smith, and S. L. Schreiber, *ibid.*, p. 17; (*f*) D. Askin, R. P. Volante, R. A. Reamer, K. M. Ryan, and I. Shinkai, *Tetrahedron Lett.*, 1988, **29**, 277; (*g*) S. Mills, R. Desmond, R. A. Reamer, R. P. Volante, and I. Shinkai, *ibid.*, p. 281. (*h*) P. Kocienski, M. Stocks, D. Donald, M. Cooper, and A. Manners, *ibid.*, 1988, **29**, 4481; (*i*) D. R. Williams and J. W. Benbow, *J. Org. Chem.*, 1988, **53**, 4643; (*j*) R. E. Ireland and P. Wipf, *Tetrahedron Lett.*, 1989, **30**, 919; (*k*) A. B. Smith, III and K. J. Hale, *ibid.*, p. 1037. Total synthesis: (*l*) T. K. Jones, S. G. Mill, R. A. Reamer, D. Askin, R. Desmond, R. P. Volante, and I. Shinkai, *J. Am. Chem. Soc.*, 1989, **111**, 1157.

2 Immunosuppressive properties: H. Tanaka, A. Kuroda, H. Marusawa, H. Hatanaka, T. Kino, T. Goto, M. Hashimoto, and T. Taga, *J. Am. Chem. Soc.*, 1987, **109**, 5031; T. Kino, H. Hatanaka, M. Hashimoto, M. Nishiyama, T. Goto, M. Okuhara, M. Kohsaka, H. Aoki, and H. Imanaka, *J. Antibiot.*, 1987, 1249; T. Kino, H. Hatanaka, S. Miyata, N. Inamura, M. Nishiyama, T. Yajima, T. Goto, M. Okuhara, M. Kohsaka, H. Aoki, and T. Ochiai, *ibid.*, 1987, 1256.

3 L. F. Kelly, P. Dahler, A. S. Narula, and A. J. Birch, *Tetrahedron Lett.*, 1981, **22**, 1433.

4 J. A. Findlay and L. Radics, *Can. J. Chem.*, 1980, **58**, 579; D. C. N. Swindells, P. S. White, and J. A. Findlay, *ibid.*, 1978, **56**, 2491.

5 A. J. Pearson, S. L. Blystone, H. Nar, A. S. Pinkerton, B. A. Roden, and J. Yoon, *J. Am. Chem. Soc.*, 1989, **111**, 134; A. J. Pearson, V. D. Khetani, and B. A. Roden, *J. Org. Chem.*, 1989, **54**, 5141.

6 C. R. Johnson, *Acc. Chem. Res.*, 1973, **6**, 341; *Aldrichimica Acta*, 1985, **18**, 3.

7 D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127; D. A. Evans, M. D. Ennis, and D. Mathre, *ibid.*, 1982, **104**, 1737; D. A. Evans, *Aldrichimica Acta*, 1982, **15**, 23; D. A. Evans, E. B. Sjorgen, J. Bartroli, and R. L. Dow, *Tetrahedron Lett.*, 1986, **27**, 4957.

Paper 9/03709H
Received 31*st August* 1989
Accepted 19*th September* 1989