Synthesis of (−)-Frontalin from the (2*S*,3*R*)-Diol prepared from α-Methylcinnamaldehyde and Fermenting Baker's Yeast

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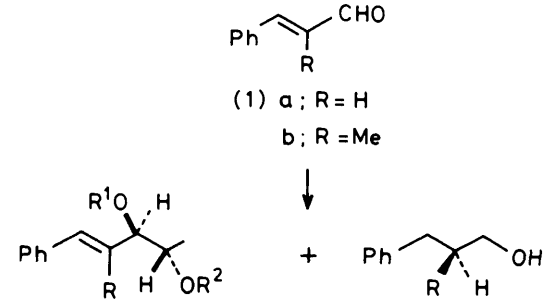
The synthesis of (−)-frontalin (13) from the (2*S*,3*R*)-diol (2b), through the intermediacy of the C_5 (3*S*,4*S*) methyl ketone (6) and of the C_{11} adduct (8), is reported.

The approach to enantiomerically pure synthetic products based on the chemical optical resolution of racemic material at some stage of the sequence, is of limited value in the field of insect pheromones, since the compounds are invariably volatile oils lacking of suitable functionality.[1] Accordingly, most of the preparations of optically active forms of representative members of this class of compounds have relied on the use as starting materials, of optically active substances which are members of the so called 'pool of chirality',[2] *i.e.*, the whole of easily available chiral materials produced by Nature including, among others, carbohydrates, amino-acids, hydroxy-acids and terpenes. However the present composition of the 'pool of chirality', is far from being satisfactory, the major limitation arising from the fact that most of the components are really available in only one enantiomeric form ‡ and, furthermore, the choice of types of chirality is rather poor, those of the type R,R^{1}CHX, where X = oxygen or nitrogen functions being particularly abundant, whereas those of the type R,R′,R″CH and R,R′,R″C(OR‴), quite frequent amongst the insect pheromones, occur rather rarely. Consequently there is at present an interest in expanding the composition of the 'pool of chirality' and new chiral products are expected to arise from the microbial transformations of non-conventional substrates.[3] In this context, the baker's yeast-mediated transformations of aromatic α,β-unsaturated aldehydes,[4] proceeding according to the Scheme, appeared likely to be quite fruitful from the synthetic point of view.

Indeed from the (2*S*,3*R*) diols (2), we have obtained deoxy and C-methyl branched deoxy-sugars of the L-series,[5,6] *N*-trifluoroacetyl-L-acosamine and L-daunosamine,[7] D-(−)-*allo*-muscarine,[8] the *N*-benzoyl derivatives of the 3-*C*-methyl branched deoxy-aminosugars L-vancosamine and of its configurational isomers,[9] and in the field of insect pheromones, the enantiomeric forms of γ-hexanolide [10] and (+) and (−) *exo*- and *endo*-brevicomin.[11] Now, as a further example of the synthetic significance of the set of the chiral products indicated in the Scheme, we report on the preparation of (−)-frontalin (13), the pheromone of the *Dendroctonus frontalis* bark beetle,[12] possessing a chiral centre of the type R,R′,R″C(OR″′), from the (2*S*,3*R*)-diol (2b), prepared in fermenting baker's yeast from α-methylcinnamaldehyde (1).[4] The dioxabicyclo[3.2.1]octane system of (−)-frontalin (13) can be viewed as formed by internal ketalization of the dihydroxyketone (4) and the above system has already been obtained in enantiomerically pure form, from D-glucose, the most abundant source of chirality present in Nature.

Our approach starts off with the C_5 methyl ketone (6), formed by ozonolysis from the isopropylidene derivative (3). Its (3*S*,4*S*) absolute configuration rests on the formation of the



(2) a ; R = R^1 = R^2 = H
b ; R = Me ; R^1 = R^2 = H
(3) R = Me ; R^1,R^2 = Me$_2$C

Scheme

N-benzoyl derivative of the 2,3,6-trideoxy-3-C-methyl-3-amino-L-*arabino*-hexose.[9] Clark-Still [13] has recently shown that chiral α-alkoxy-ketones undergo highly stereoselective addition of Grignard reagents under various conditions, with a strong predominance of the *threo*-isomer. As expected, addition of the organomagnesium reagent (7) (diethyl ether, 2 °C), onto the chiral ketone (6) takes place with complete selectivity to give as the sole C_{11} adduct, compound (8) (60%), which was shown to be homogeneous on the basis of chromatographic and spectroscopic criteria. Indeed the adduct (8) obtained by *O*-benzylation of (9) and subsequent hydrolysis, gave (10) (65%), shown by ^{1}H n.m.r. studies to possess a single resonance relative to the C-Me at position 6, at δ 1.24. Analogous compounds available [5] in the two series which are diastereomeric because of the different configuration at C-6, show distinct chemical shifts for the C-Me group. Furthermore, the *threo*-stereochemistry relative to positions 6 and 7 of (8), rests on the conversion of (10) into (−)-frontalin (13): periodic acid oxidation of the 7,8 C–C bond of (10), followed by *in situ* $NaBH_4$ reduction of the formed aldehyde, gave the C_9 intermediate (11) (77%). The latter compound on ozonolysis, yields the C_8 ketone (12), from which (−)-frontalin (13) was obtained in 27% total yield from (8), after hydrogenolysis and spontaneous cyclization. The ^{1}H n.m.r. spectra of a distilled sample of (13) recorded in the presence of the chiral shift reagent Eu(facam)$_3$, was compared with the data reported in the literature [14] for the two enantiomers of frontalin under identical conditions, showing our sample to be enantiomerically pure. By g.l.c. analysis it has been shown to be *ca.* 93% pure {$[\alpha]_D^{20}$ resulted −45° (*c* 1, diethyl ether); lit.,[14] −52° (*c* 1, diethyl ether)}.

The preparation of (−)-frontalin (13) from the methyl

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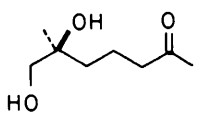
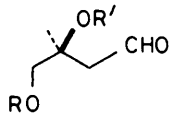
‡ In this context, unnatural (+)-frontalin has been obtained from natural (−)-linalool (P. Magnus and G. Roy, *J. Chem. Soc., Chem. Commun.*, 1978, 297).

§ Tris[3-(trifluoromethylhydroxymethylene)-(±)-camphorato]-europium(III).



(4)



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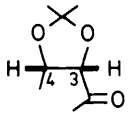
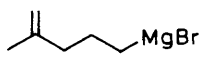


(6)



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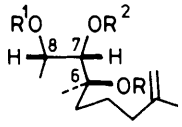
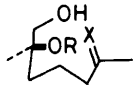
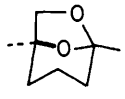


(8) R = H; R^1,R^2 = Me_2C
(9) R = CH_2Ph; R^1,R^2 = Me_2C
(10) R = CH_2Ph; R^1 = R^2 = H



(11) R = CH_2Ph; X = CH_2
(12) R = CH_2Ph; X = O



(13)

ketone (6), represents an alternative to the procedure based on D-glucose [15,16] as a source of chirality.* In our scheme, the two chiral centres present in (6), served to induce the required chirality, and are destroyed in subsequent steps of the synthetic sequence. We have recently reported two other synthetic applications of the C_5 methyl ketone (6),[9,17] both based on the use of the two chiral centres to induce stereocontrol in the addition of carbon nucleophiles onto the adjacent sp^2 carbon.[18] All these results lend support to the value of the approach to enantiomerically pure synthetic products based on the use of relatively small, highly functionalized chiral, acyclic starting materials, as an alternative to the one which uses the stereochemical bias and the rich array of chiral centres present in natural carbohydrates.[19]

Experimental

^{1}H N.m.r. spectra were recorded at 90 MHz. Chemical shifts are in p.p.m. (δ) from $SiMe_4$ as internal standard. Flash chromatography was performed with Merck Si gel (0.040—0.069 mm), and t.l.c. with Merck HF_{254} Si gel. G.l.c. analysis were performed on a DANI 3800 gas chromatograph, equipped with FID detector. Carrier N_2 25 ml/min 2-m Pyrex columns, i.d. 2 mm packed with: 5% SP 1000 on 100/120 mesh Supelcoport and 10% UCC W-982 Silicone, on Chromosorb W A.W. DMCS-acid washed 80/100 mesh. Analytical samples were prepared by bulb-to-bulb distillation or by crystallization.

(3R,4S)-2-*Methyl*-1-*phenylpent*-1-*ene*-3,4-*diol* (2b).—To a solution of glucose (2 kg) and Na_2HPO_4 (100 g) in water (10 l) in an open vessel with an efficient mechanical stirrer, commercial baker's yeast (2.5 kg) was added. The temperature was initially set at 30 °C and α-methylcinnamaldehyde (83 g) was added dropwise during 30 min. Stirring was continued for 12 h. Two extractions with ethyl acetate (5 l), gave a crude material from which the (3*R*,4*S*)-diol (20 g) was recovered after chromatography (hexane–ethyl acetate–ethyl acetate), m.p. 106—107 °C (from CH_2Cl_2), $[\alpha]_D^{20}$ +32° (*c* 1, EtOH) (Found: C, 74.6; H, 8.35. $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39%), δ($CDCl_3$) 7.35 (5 H, s, ArH), 6.7 (1 H, s, C=CH), 4.18 (1 H, d, OCH), 4.08 (1 H, m, OCH), 2.3 and 2.1 (2 H, m, 2 × OH), 1.9 (3 H, s, C=CCH), 1.2 (3 H, d, CH_3, *J* 7 Hz).

(3R,4S)-3,4-*Isopropylidenedioxy*-2-*methyl*-1-*phenylpent*-1-*ene* (3).—Compound (2b) (70 g) in anhydrous CH_2Cl_2 (300 ml) were treated with an excess of 2,2-dimethoxypropane (90 g) and with toluene-*p*-sulphonic acid (0.05 g). The solution was left at room temperature and periodically examined by t.l.c. (hexane–ethyl acetate (8 : 2) [diol R_F 0.15, (3) R_F 0.6]. After 3 h the reaction was complete. The solution was then washed with aqueous $NaHCO_3$, dried, and evaporated. The oily product (90%), pure on t.l.c., was used directly for the subsequent step; $[\alpha]_D^{20}$ −74° (neat), δ($CDCl_3$) 7.35 (5 H, s, ArH), 6.6 (1 H, s, C=CH), 4.6 (2 H, m, OCHCHO), 1.8 (3 H, s, C=CCH_3), 1.6 (3 H, s, CCH_3), 1.4 (3 H, s, CCH_3), and 1.1 (3 H, d, CH−CH_3, *J* 6 Hz).

(3S,4S)-3,4-*Isopropylidenedioxypentan*-2-*one* (6).—Compound (3) (23 g) dissolved in anhydrous CH_2Cl_2 (80 ml) was ozonized at −78 °C during a period of 2 h; PPh_3 (56 g) was then added. The mixture was evaporated and extracted with pentane; the precipitated phosphine oxide was removed by suction filtration. The mixture was chromatographed [hexane–benzene(1 : 1)/benzene] to yield the (3*S*,4*S*)-ketone (6) (12 g, 81%); $[\alpha]_D^{20}$ −80° (*c* 1, $CHCl_3$), δ($CDCl_3$), 4.5 (2 H, m, OCHCHO), 2.2 (3 H, s, O=CCH_3), 1.6 (3 H, s, CCH_3), and 1.25 (3 H, d, HCCH_3, *J* 6 Hz) (Found: C, 60.5; H, 8.8. $C_8H_{14}O_3$ requires C, 60.74; H, 8.92), g.l.c. SP 1000 105/220 °C 3 °C/min R_t 5.2 min.

Methyl 4-*Vinylpentanoate*.—A solution of methylsulphinyl carbanion, was prepared from NaH (50% oily dispersion, 14.8 g) and Me_2SO (600 ml), by warming under N_2 at 70—80 °C for 1 h. To this solution, finely grounded methylenetriphenylphosphonium iodide (0.306 mol, 124 g) was added at room temperature and the mixture was stirred for 10 min. Methyl laevulinate (0.3 mol, 35 g) in Me_2SO (150 ml) was then added while the temperature was kept <10 °C. The dark solution was kept at room temperature for 24 h and then poured in a ice-brine mixture (2 l); it was then extracted with pentane (2 l). The precipitated phosphine oxide was filtered off and washed with pentane and the combined extracts were evaporated at atmospheric pressure. The crude material was distilled at 60 °C, 20 mm/Hg to give the *title* compound (*18* g, 50%), δ($CDCl_3$) 4.72 (2 H, d, *J* 6 Hz), 3.7 (3 H, s), 2.4 (4 H, m), and 1.85 (3 H, s) (Found: C, 62.1; H, 10.3. $C_7H_{12}O_2$ requires C, 62.04; H, 10.41%).

4-*Methylpent*-4-*en*-1-*ol*.—This compound was obtained in 80% purified yield, by $LiAlH_4$ reduction of the corresponding ester. Distillation of the crude material afforded a product whose spectral and physicochemical properties were identical with those described in the literature.[20]

1-*Bromo*-4-*methylpent*-4-*ene*.—This compound was prepared from the corresponding alcohol with the *N*-bromosuccinimide/PPh_3 procedure, as described in the literature.[20]

(6S,7S,8S)-7,8-*Isopropylidenedioxy*-2,6-*dimethylnon*-1-*en*-6-*ol* (8).—To a solution of 4-methylpent-4-enylmagnesium

* For a synthesis of (−)-frontalin from (*S*)-citrmalic acid, see R. Batner and J. Hübscher, unpublished results, quoted in ref. 3, p. 323.

bromide (7) in anhydrous diethyl ether (45 ml), prepared from the corresponding bromide (5 g) and magnesium turnings, using a drop of 1,2-dibromoethane as initiator, (6) (4.4 g) in ether (25 ml) was added dropwise, while the internal temperature was kept at 2 °C. Stirring was continued for 1 h after which the temperature was raised to 22 °C. The mixture was poured in an ice–brine mixture and extracted with ether (3 × 40 ml). Flash chromatography(hexane–ethyl acetate, 8 : 2) gave (8) as an almost colourless liquid (4 g, 60%) single spot on t.l.c. (hexane–ethyl acetate, 8 : 2; R_F 0.26), δ($CDCl_3$) 4.9 (2 H, s, C=CH_2), 4.28 (1 H, m, ROCH), 3.88 (1 H, d, OCH), 2.3 (1 H, s, OH), 2 (2 H, C=CCH_2m), 1.75 (3 H, C=CH_3,s), 1.6 (d, CH_3CH), 1.32 (s, CH_3CO), 1.25 (s, CH_3CO), and 1.2 (s, CH_3CO); $[\alpha]_D^{20}$ −42.2 (*c* 1, $CHCl_3$) (g.l.c. 92% pure sample); *m/z* 242, 227, 167, 159, 149, 142, 127, 115, 101, and 97 (Found: C, 69.1; H, 10.7. $C_{14}H_{26}O_3$ requires C, 69.38; H, 10.81%); g.l.c. SP 1000 132/220 °C 6 °C/min R_t 14 min.

(6S,7S,8S)-6-*Benzyloxy*-2,6-*dimethyl*-7,8-*isopropylidene-dioxynon*-1-*ene* (9).—Compound (8) (2,6 g) in dimethylformamide (DMF) (20 ml), was added to a suspension of NaH (50% oily dispersion, 0.470 g) in DMF (20 ml). The mixture was stirred at room temperature for 1 h and for an additional hour at 60 °C, whereupon the solution turned dark brown. Benzyl bromide (3,6 g) was then added at room temperature. The mixture was stirred for 1 h at room temperature and then 1 h at 60 °C; it was then poured into iced water and extracted with pentane (3 × 50 ml). The crude material, after flash chromatography (hexane–ethyl acetate, 9 : 1; R_F 0.45) afforded (9) as a colourless oil (3 g, 85%), δ($CDCl_3$) 7.33 (5 H, s, ArH), 4.8 (2 H, s, C=CH_2), 4.6 (2 H, s, $ArCH_2$) 4,5 (1 H, m, CH_3CHO) 3.65 (1 H, d, CHO, *J* 3 Hz), 2 (2 H, m, C=CH_2), 1.7 (3 H, s, C=CCH_3), 1.4 (3 H, s, $OCCH_3$), 1.3 (3 H, s, $OCCH_3$), and 1.1 (3 H, s, $OCCH_3$); $[\alpha]_D^{20}$ −19.5 (*c* 1, $CHCl_3$) (g.l.c. 90% pure sample) (M^+) 332, 317, 274, 249, 217, 199, 183, 157, 139, 111, 91, 81, 69, 59, and 45; g.l.c. UCC W 220 °C isot.; R_t 8 min (Found: C, 75.95; H, 9.4. $C_{21}H_{32}O_3$ requires C, 75.86; H, 9.70%).

(6S,7S,8S)-6-*Benzyloxy*-2,6-*dimethylnon*-1-*ene*-7,8-*diol* (10).—A solution of compound (9) (4.4 g) in CH_3CN (23 ml) and 50% acetic acid (7 ml) was heated on a water-bath (temp. 75 °C). The reaction followed by t.l.c. (hexane–ethyl acetate, 7 : 3, starting material R_F 0.8, diol R_F 0.2) was complete after 30 min. The mixture was diluted with water and extracted with ether. The crude material (4 g) was chromatographed (7 : 3 hexane–ethyl acetate) to give a low melting solid (3g), $[\alpha]_D^{20}$ −9.1 (*c* 1, $CHCl_3$) (g.l.c. 94% pure sample), δ($CDCl_3$) 7.4 (5 H, s, ArH), 4.73 (2 H, s, C=CH_2), 4.5 (2 H, s, $ArCH_2$), 3.9 (1 H, m, OH), 3.6 (1 H, m, OCH), 2.8 (1 H, m, OH), 2.03 (2 H, m, C=CH_2), 1.7 (3 H, s, C=CH_3), 1.24 (3 H, $OCCH_3$, s), and 1.22 (3 H, d, $HOCHCH_3$, *J* 6 Hz) (Found: C, 74.0; H, 9.5. $C_{18}H_{28}O_3$ requires C, 73.93; H, 9.65%); g.l.c. UCC W 220 °C R_t 9 min.

(6S)-6-*Benzyloxy*-6-*methyl*-2-*vinylheptan*-7-*ol* (11).—To a solution of (10) (1.5 g) in anhydrous tetrahydrofuran (THF) (25 ml), $HIO_4 2H_2O$ (1.06 g) in THF (70 ml) was added in one portion at room temperature; immediately, the solution became cloudy. A few drops of ethylene glycol were added, and the precipitated HIO_3 filtered off; the filtrate was then evaporated under reduced pressure and the residue dissolved in EtOH and treated with an excess of $NaBH_4$. The resulting mixture was poured in iced water, extracted with pentane, and the extract dried and the solvent removed under reduced pressure. The crude material (1 g, 77%) was purified on t.l.c. (hexane–ethyl acetate, 7 : 3; R_F 0.38) $[\alpha]_D^{20}$ −2.2 (*c* 1, $CHCl_3$) (g.l.c. 98% pure sample); δ($CDCl_3$) 7.4 (5 H, s, ArH), 4.75 (2 H, s, C=CH_2), 4.5 (2 H, s, $ArCH_2$), 3.5 (2 H, s, $COCH_2$), 2.1 (2 H, m, C=CH_2), 1.7 (3 H, s, C=CCH_3), 1.3 (3 H, s, $OCCH_3$); *m/z* 248, 225, 217, 199, 191, 165, 157, 143, 117, 107, 91, 77, 65, 51, and 43 (Found: C, 77.1; H, 9.9. $C_{16}H_{24}O_2$ requires C, 77.37; H, 9.74%); g.l.c. SP 1000 210 °C, R_t 18.2 min.

(6S)-6-*Benzyloxy*-7-*hydroxy*-6-*methylheptan*-2-*one* (12).—Compound (11) (1g) was ozonized at −78 °C in methanol (40 ml). The ozonide was decomposed with an excess of Me_2S, at room temperature (1 h) and then heated at 60 °C for 30 min. The solution gave after evaporation of the solvent and flash chromatography (hexane–ethyl acetate 7 : 3, R_F 0.2) (12) a pale yellow oil (0.640 g, 65%), $[\alpha]_D^{20}$ −28.2 (*c* 1, $CHCl_3$) (g.l.c. 92% pure sample) *m/z* 250, 235, 201, 186, 159, 116, 107, 105, 91, 77, 65, 51, and 43 (Found: C, 71.0; H, 8.6. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%), g.l.c. SP 1000 75/250 °C 5 °C/min R_t 27 min.

(S)-(−)-1,5-*Dimethyl*-6,8-*dioxabicyclo*[3.2.1]*octane*: (S)-(−)-*Frontalin* (13).—Compound (12) (0.540 g) dissolved in methanol (14 ml), was hydrogenated in a Parr apparatus with 10% Pd/C (0.150 g) during a period of 12 h. The catalyst was removed by filtration and the solvent distilled through a short Vigreux column at atmospheric pressure. The crude material was carefully distilled in a bulb-to-bulb apparatus at 100 mmHg, 95 °C to yield (13) (0.2 g 65%), 93% pure by g.l.c., $[\alpha]_D^{20}$ −45° (*c* 1, diethyl ether), δ(CCl_4) 3.8 (1 H, d, OCH, *J* 7 Hz), 3.3 (1 H, d, OCH, *J* Hz), 1.55 (m, 6 H), 1.3 (3 H, s, CCH_3), and 1.25 (3 H, s, CH_3). Addition of Eu(facam)$_3$ (0.1 g) caused a downfield shift of the signals without any change in pattern of the two methyl singlets and of the OCH_2O AB quartet. Conditions were: 20 mg of (13) in CCl_4 (0.2 ml) + Eu(facam)$_3$ (107 mg). The spectra was recorded after 2 and 4 h; δ 4.63 (1 H, d, OCH_2O, *J* 7 Hz), 4.12 (1 H, d, OCH_2O, *J* 7 Hz) 1.94 (3 H, s, CH_3), 1.93 (6 H, m), and 1.51 (3 H, s, CH_3); *m/z* 142, 112, 100, 72, 67, 54, and 43; g.l.c. SP 1000 100/210 °C 3 °C/min, R_t 3.39 min (93%), 6.8 min (1.52%), and 12.27 min (2.8%).

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References

1 J. M. Brand, J. Chr. Young, and R. H. Silverstein, *Fortschr. Chem. Org. Naturst.*, 1979, **37**, 1—190.
2 D. Seebach and H. O. Kalinowski, *Nachr. Chem. Tech.*, 1976, **24**, 415.
3 A. Fischli in 'Modern Synthetic Methods,' R. Scheffold ed., Salle und Sauerländer, Frankfurt am Main, 1980, vol. 2, p. 269.
4 C. Fuganti and P. Grasselli, *Chem. Ind. (London)*, 1977, 983.
5 C. Fuganti and P. Grasselli, *J. Chem. Soc., Chem. Commun.*, 1978, 299.
6 C. Fuganti, P. Grasselli, and G. Marinoni, *Tetrahedron Lett.*, 1979, 1161.
7 G. Fronza, C. Fuganti, and P. Grasselli, *J. Chem. Soc., Chem. Commun.*, 1980, 442.
8 G. Fronza, C. Fuganti, and P. Grasselli, *Tetrahedron Lett.*, 1978, 3941.
9 G. Fronza, C. Fuganti, P. Grasselli, and G. Pedrocchi-Fantoni, *Tetrahedron Lett.*, 1981, 5073.
10 R. Bernardi, C. Fuganti, P. Grasselli, and G. Marinoni, *Synthesis*, 1980, 50.
11 R. Bernardi, C. Fuganti, and P. Grasselli, *Tetrahedron Lett.*, 1981, 4021.
12 G. W. Kinzer, A. F. Fentiman, jun., T. F. Page, jun., R. L. Foltz, J. P. Vite, and G. B. Pitman, *Nature (London)*, 1969, **221**, 447; T. E. Stewart, E. L. Plumer, L. L. McCandless, J. R. West, and R. M. Silverstein, *J. Chem. Ecol.*, 1977, **3**, 27.

13 W. Clark-Still and J. H. McDonald III, *Tetrahedron Lett.*, 1980, 1031.
14 K. Mori, *Tetrahedron Lett.*, 1975, **31**, 1381.
15 B. R. Hicks and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, 1976, 869.
16 H. Ohrui and S. Emoto, *Agric. Biol. Chem.*, 1976, **40**, 2267.
17 C. Fuganti and P. Grasselli, *J. Chem. Soc., Chem. Commun.*, 1982, 205.
18 P. A. Bartlett, *Tetrahedron*, 1980, **36**, 2.
19 S. Hanessian, *Acc. Chem. Res.*, 1979, **12**, 159; A. Vasella in 'Modern Synthetic Methods,' R. Scheffold ed., Salle und Sauerländer, Frankfurt am Main, 1980, vol. 2, p. 173.
20 M. C. Pirrung, *J. Am. Chem. Soc.*, 1981, **103**, 82.

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