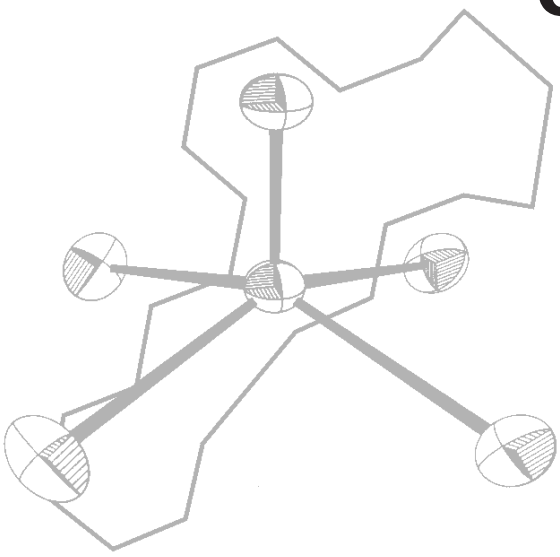
CSIRO PUBLISHING

Australian Journal of Chemistry



Volume 53, 2000

A journal for the publication of original research
in all branches of chemistry and chemical technology

www.publish.csiro.au/journals/ajc

All enquiries and manuscripts should be directed to
The Managing Editor
Australian Journal of Chemistry
CSIRO PUBLISHING
PO Box 1139 (150 Oxford St)
Collingwood Telephone: 61 3 9662 7630
Vic. 3066 Facsimile: 61 3 9662 7611
Australia Email: john.zdysiewicz@publish.csiro.au

Published by **CSIRO** PUBLISHING
for CSIRO and
the Australian Academy of Science

Aust. J. Chem., 2000, **53**, 659–664

Improved Synthetic Route to Enantiomerically Pure Samples of the Tetrahydropyran-2-ylacetic Acid Core Associated with the Phytotoxic Polyketide Herboxidiene

Martin G. Banwell,[A,B] *Malcolm D. McLeod,*[A,C] *Rajaratnam Premraj*[A] *and Gregory W. Simpson*[D]

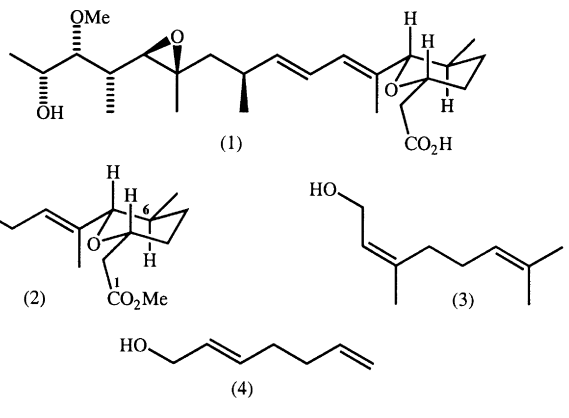
[A] Research School of Chemistry, Institute of Advanced Studies,
The Australian National University, Canberra, A.C.T. 0200.
[B] To whom correspondence should be addressed.
[C] School of Chemistry, F11, University of Sydney, Camperdown, N.S.W. 2006.
[D] CSIRO Molecular Science, Bag 10, Clayton South, Vic. 3169.

The phosphine oxide (2), which embodies the tetrahydropyran-2-ylacetic acid core associated with the phytotoxic polyketide herboxidiene (1) and which is a key intermediate in a projected synthesis of this natural product, has been prepared in a highly enantio- and diastereo-selective manner. The pivotal steps in this new and improved synthesis of compound (2) involve Katsuki–Sharpless asymmetric epoxidation of the allylic alcohol (4) to give epoxide (7) and subsequent ring-cleavage of the latter compound with trimethylaluminium to give diol (9). The derived acetate (10) is then readily ozonolysed to give the previously reported aldehyde (11), although now in high enantiomeric excess. Compound (11) can be elaborated, by established chemistry, to the target oxide (2).

Keywords. Dess–Martin oxidation; Michaelis–Arbuzov reaction; Mosher esterification; Parikh–Doering oxidation; Katsuki–Sharpless asymmetric epoxidation; Still oxidation; Still–Gennari olefination; synthesis.

Introduction

In 1992 a group at Monsanto (U.S.A.) detailed[1] the near complete structural elucidation of the polyketide herboxidiene (1) (also known as TAN-1609) which the researchers had isolated from *Streptomyces chromofuscus* A7847. The same group also revealed[1] that the molecule displays potent and highly selective phytotoxic properties so that at application rates of 35 g/acre it selectively controls various crop pests such as oilseed rape, wild buckwheat and morning glory while being harmless to wheat. Such properties, which are remarkable for a polyketide, prompted efforts by Edmunds's group at Novartis AG[2] to reisolate herboxidiene and then, through a combination of X-ray crystallographic, chemical degradation and chemical synthesis studies, to establish the full stereochemistry associated with compound (1). Several Japanese groups[3–5] have also isolated herboxidiene and one has determined[5] that the compound up-regulates the gene expression of the low-density lipoprotein receptor while another has reported (Horiguchi *et al.*[3]) that it inhibits the growth of various murine and human tumour cell lines. The interesting biological profile of this natural product has prompted various attempts to effect its preparation by total synthesis.[2,6–9] In connection with our own efforts in this area[8,9] we have reported[9] a 12-step route to phosphine oxide (2) which embodies the tetrahydropyran-2-ylacetic acid core associated with compound (1). However, a deficiency associated with our synthesis of (2) is the need to carry out, at the initial stage, a Katsuki–Sharpless asymmetric epoxidation of nerol (3) which delivers the corresponding epoxy alcohol in only *c*. 50% enantiomeric excess (e.e.).[9] Since, with the exception of target (2), all the compounds in the reaction sequence, including the initially formed epoxy alcohol, are oils the only opportunity to obtain enantiopure phosphine oxide (2) was by repeated recrystallization of this compound. However, the attendant loss of material was significant thus prompting us to examine alternative routes to this com-

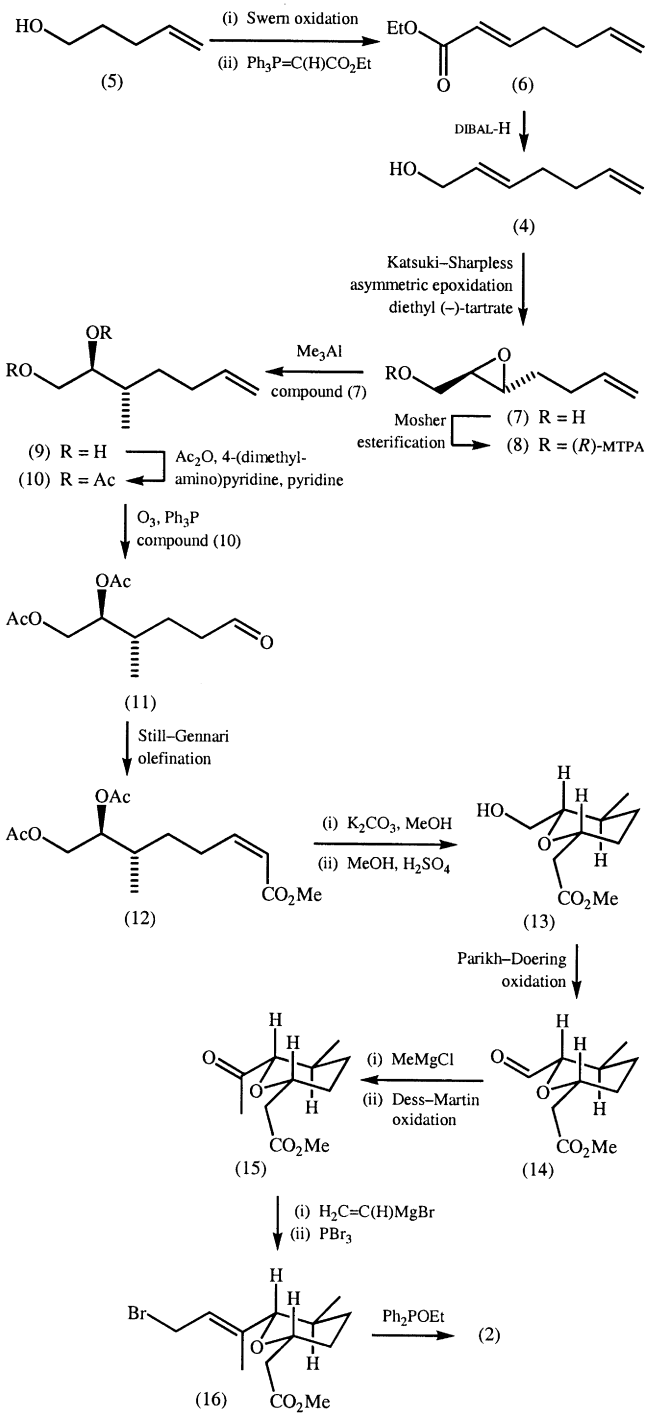


Manuscript received 26 June 2000 10.1071/CH00083 0004-9425/00/080659

pound. As a consequence, we now describe a new synthesis, of phosphine oxide (2), that circumvents the above-mentioned problems.

Results and Discussion

In contrast to the situation with (*Z*)-1,2,2-trisubstituted alkenes (e.g. nerol), the Katsuki–Sharpless asymmetric epoxidation of allylic alcohols proceeds in high enantiomeric excess when (*E*)-1,2-disubstituted alkenes are employed as substrates.[10] Consequently, the allylic alcohol (4) was chosen as the substrate for Katsuki–Sharpless asymmetric epoxidation



Scheme 1

on the basis that the product epoxide would be obtained in high e.e. In addition, it was expected that nucleophilic methylation of the product epoxide could be achieved in a regio- and diastereo-selective manner so as to install the methyl group required at C 6 in the target molecule (2). The pivotal alkene (4) was readily prepared (Scheme 1) by a one-pot procedure involving initial oxidation of commercially available (Aldrich) alcohol (5) to the corresponding aldehyde. Using a modification of procedures reported by Barrett,[11] Lee[12] and Taylor,[13] this latter compound was subjected to *in situ* Wittig olefination with (methoxycarbonylmethylidene)triphenylphosphorane. In this manner the α,β-unsaturated ester (6) (98%) was obtained and the illustrated (*E*)-configuration about the Δ^2-double bond was established by ^{1}H n.m.r. analysis ($J_{H2,H3}$ 15.6 Hz). DIBAL-H-promoted 1,2-reduction of compound (6) proceeded smoothly to give the target alcohol (4) in 85% yield and the various spectroscopic data derived from this material were in full accord with the assigned structure. Katsuki–Sharpless asymmetric epoxidation of compound (4) was effected under standard conditions by using catalytic quantities of diethyl D-(–)-tartrate and in this manner the expected epoxy alcohol (7) (70%) was obtained. This latter material was converted, under standard conditions, into the corresponding Mosher ester (8) (42%) which was obtained as a single diastereoisomer (as determined by ^{1}H n.m.r. analysis) and thus suggesting that the precursor alcohol was of >95% e.e. This interpretation was confirmed by, *inter alia*, converting the racemic modification of epoxide (7) [prepared by treating alkene (4) with *m*-chloroperbenzoic acid] into the corresponding 1 : 1 mixture of compound (8) and its diastereoisomer and observing that these Mosher esters were readily differentiated from one another by 300 MHz ^{1}H n.m.r. spectroscopy (see Experimental section).

Treatment of epoxy alcohol (7) with 3 mol. equiv. of trimethylaluminium[14] in CH_2Cl_2 at 18°C for 10 h resulted in its smooth conversion into diol (9) (83%) the structure of which follows from its transformation into the previously reported[9] aldehyde (11). Thus, twofold acetylation of compound (9) was achieved under standard conditions and the resulting diacetate (10) (96%) was subjected to ozonolytic cleavage followed by reductive workup with triphenylphosphine to give the aldehyde (11) (79%). This last compound proved identical (as judged by ^{1}H n.m.r., ^{13}C n.m.r., i.r. and mass spectral analysis) with the samples of the aldehyde obtained by our previous route.[9] As expected, however, the specific rotation of the material generated by the present route was effectively double {$[\alpha]_D$ +7.3 versus $[\alpha]_D$ +3.8} that observed for the sample of aldehyde (11) obtained earlier.[9]

The completion of the synthesis of the target phosphine oxide (2) followed the route established earlier, although various minor modifications to the previously reported methods[9] are detailed herein. Thus, subjection of compound (11) to Still–Gennari modification[15] of the Wadsworth–Emmons reaction afforded the alkene (12) (80%) as the only isolable product of reaction. The (*Z*)-configuration about the double bond in this product follows from the magnitude of the vicinal spin–spin coupling (*J* 11.5 Hz) observed between H 2 and H 3 in the ^{1}H n.m.r. spectrum of this material. Treatment of compound (12) with potassium carbonate in methanol

resulted in removal of the acetate groups and a subsequent intramolecular Michael addition reaction to give the tetrahydropyran-2-ylacetic acid ester (13) which was accompanied by varying quantities of the corresponding acid. Consequently, the crude reaction mixture was treated with acidic methanol and in this manner compound (13) was obtained in 71% yield. Oxidation of hydroxy ester (13) under Parikh–Doering conditions (pyridine–SO_3 activated Me_2SO)[16] afforded the corresponding aldehyde (14) (60%) which proved spectroscopically identical with the sample we had obtained by our previous route. In addition, the optical rotation of this material effectively matched that reported[2] by Edmunds for enantiomerically pure material. The conversion of aldehyde (14) into methyl ketone (15) proved especially troublesome and, thus far, we have not been able to satisfactorily resolve these difficulties. After considerable experimentation with a range of nucleophilic methylating agents, methylmagnesium chloride proved to be most effective in adding to the aldehyde moiety associated with compound (14). The resulting mixture of diastereoisomeric secondary alcohols was immediately oxidized with the Dess–Martin periodinane[17] and the corresponding methyl ketone (15) thereby obtained albeit in only 17% yield. Nevertheless, the optical rotation of this compound matched that reported for a sample obtained by ozonolytic cleavage of herboxidiene itself.[2]

Elaboration of ketone (15) to the target phosphine oxide (2) followed previously established procedures[9] and involved initial reaction of the former compound with vinylmagnesium bromide. This resulted in generation of the desired tertiary alcohol (60%) which was treated with phosphorus tribromide to afford the allylic bromide (16) (93%). The latter compound engaged in a Michaelis–Arbuzov reaction with ethoxydiphenylphosphine to deliver the target compound (2) (85%) as a crystalline solid after flash chromatography. The melting point (125–126°C) of this compound matched that reported for the multiply recrystallized material obtained by the previous route.[9] However, the specific rotation of compound (2) produced by the method described here was much lower $\{[\alpha]_D$ –0.4 versus $[\alpha]_D$ –33$\}$ than that reported[9] for material generated by the earlier route. Fortunately a sample of compound (2) derived by the earlier sequence was still available and a redetermination of the specific rotation resulted in a value identical to that observed for the newly prepared sample. Consequently, we believe our earlier determination[9] of the optical rotation for compound (2) to be in error. Given the absence of any racemization pathways in the synthetic sequence just described as well as the high levels of enantioselectivity obtained in the Katsuki–Sharpless asymmetric epoxidation reaction leading to compound (7) we conclude that phosphine oxide (2) produced by the method described here has been obtained in >95% e.e.

Efforts are now under way to exploit compound (2) as a key building block in the total synthesis of herboxidiene.[8] Results will be described in due course.

Experimental

Melting points were recorded with a Kofler hot-stage apparatus and are uncorrected. Proton (^{1}H) and carbon (^{13}C) n.m.r. spectra were recorded with a Varian Gemini 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon. All such spectra were recorded in (D)chloroform solution at 22°C. The protonicities of the carbon atoms observed in ^{13}C n.m.r. spectra were determined by attached proton test (a.p.t.) experiments. Infrared spectra (ν_{max}) were recorded with either a Perkin–Elmer 983G infrared spectrophotometer or a Perkin–Elmer 1800 Fourier-transform infrared spectrophotometer. Unless otherwise specified, samples were analysed as thin liquid films on potassium bromide plates. Low-resolution electron-impact mass spectra (*m/z*) were recorded at 70 eV on a VG Micromass 7070F mass spectrometer. High-resolution mass spectra were recorded with the same instrument. Unless otherwise stated, optical rotations were measured in spectroscopic grade chloroform at 22°C by means of a Perkin–Elmer 241 polarimeter. Diethyl ether (Et_2O) and tetrahydrofuran (thf) were distilled under nitrogen from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc) and hexane were each distilled from calcium hydride. Ethanol and methanol (MeOH) were distilled from their respective magnesium alkoxide salts. Ozonolyses were performed using a Wallace and Tiernan Ozonator with the oxygen flow rate and power set at approximately 25 l/h and 200 V, respectively. Flash chromatographic separations were conducted according to the method of Still *et al*.[18]

Ethyl (E)-*Hepta-2,6-dienoate (6)*

Dimethyl sulfoxide (23.7 ml, 334 mmol) was added to a magnetically stirred solution of oxalyl chloride (13.4 ml, 153 mmol) in CH_2Cl_2 (480 ml) maintained under a nitrogen atmosphere at –78°C. After 0.1 h, pent-4-en-1-ol (5) (12.0 g, 139 mmol, ex Aldrich) was added, dropwise, followed, after a further 0.25 h, by triethylamine (134 ml, 961 mmol). The resulting mixture was stirred for 0.5 h at –78°C, then warmed to room temperature and treated with (ethoxycarbonylmethylidene)triphenylphosphorane[19] (72.8 g, 209 mmol) in dry CH_2Cl_2 (110 ml). After 2 h at 18°C the reaction mixture was quenched with water (200 ml) and the separated aqueous layer was extracted with CH_2Cl_2 (3×100 ml). The combined organic layers were washed with brine (1×75 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. An ethyl acetate/hexane (1 : 9 v/v) solution of this material was filtered through a short pad of t.l.c. grade silica gel to afford, after concentration of the filtrate, the title ester (6)[12,20] (21.0 g, 98%) as a light-yellow oil. ν_{max} 3078, 2980, 2933, 1721, 1655, 1446, 1367, 1315, 1266, 1206, 1176, 1044, 989, 914, 852 cm^{-1}. ^{1}H n.m.r. δ 6.93, dt, *J* 15.6 and 5.7 Hz, 1H; 5.84–5.73, complex m, 2H; 5.06–4.96, complex m, 2H; 4.15, q, *J* 7.1 Hz, 2H; 2.32–2.17, complex m, 4H; 1.26, t, *J* 7.1 Hz, 3H. ^{13}C n.m.r. δ 166.5 (C), 148.2 (CH), 137.0 (CH), 121.6 (CH), 115.4 (CH_2), 60.1 (CH_2), 32.0 (CH_2), 31.4 (CH_2), 14.2 (CH_3). Mass spectrum *m/z* 154 (6%, $M^{+\bullet}$), 109 [30, $(M-C_2H_5O^{\bullet})^+$], 81 [100, $(M-C_2H_5OCO^{\bullet})^+$]. This material was of sufficient purity for use in the next step of the reaction sequence.

(E)-*Hepta-2,6-dien-1-ol (4)*

Diisobutylaluminium hydride (325 ml of a 1.0 M solution in hexane, 325 mmol, ex Aldrich) was added dropwise (via syringe) to a magnetically stirred solution of ethyl (*E*)-hepta-2,6-dienoate (6) (20.0 g, 130 mmol) in CH_2Cl_2 (650 ml) maintained under a nitrogen atmosphere at –78°C. The resulting mixture was stirred for 2 h at –78°C then warmed to 18°C and quenched with tartaric acid (200 ml of a 1 M aqueous solution). Stirring was continued until two distinct layers were observed (0.25 h). The separated aqueous layer was extracted with CH_2Cl_2 (3×200 ml) and the combined organic phases were washed with brine (1×200 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the material thus obtained to flash chromatography (silica gel, 1 : 4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_F 0.25) afforded the title compound (4)[12,21] (12.4 g, 85%) as a light-yellow oil. ν_{max} 3326, 2923, 1641, 1437, 1087, 1000, 970, 911 cm^{-1}. ^{1}H n.m.r. δ 5.85–5.65, complex m, 3H; 5.04–4.94, complex m, 2H; 4.07, d, *J* 4.4 Hz, 2H; 2.15–2.13, complex m, 4H; 1.67, s, 1H. ^{13}C n.m.r. δ 138.0 (CH), 132.4 (CH), 129.3 (CH), 114.8 (CH_2), 63.7 (CH_2), 33.2 (CH_2), 31.5 (CH_2). Mass spectrum *m/z* 111 [1%, $(M-H^{\bullet})^+$], 94 [13, $(M-H_2O)^{+\bullet}$], 79 (100).

(*2*R-trans)-*2,3-Epoxyhept-6-en-1-ol* (+)-*(7)*

Katsuki–Sharpless asymmetric epoxidation of allylic alcohol (4), so as to afford epoxide (+)-(7), was carried out according to the method of ref. 22. Thus, a magnetically stirred suspension of finely powdered and activated 4 Å molecular sieves (1.0 g) in dry CH_2Cl_2 (137 ml) was cooled to –40°C then treated, sequentially, with diethyl D-(–)-tartrate (0.92 ml, 5.38 mmol), $Ti(OPr^i)_4$ (1.32 ml, 4.50 mmol) and t-butyl hydroperoxide (17.2 ml of a 5.2 M solution in isooctane, 89 mmol—prepared by extraction of 70% aqueous t-butyl hydroperoxide ex Aldrich[22]). The resulting mixture was stirred at –40°C for 0.5 h then a solution of compound (4) (5.0 g, 44.6 mmol) in CH_2Cl_2 (20 ml) was added, via cannula, at such a rate as to maintain the reaction temperature below –20°C. After an additional 3 h at –20°C the reaction mixture was warmed to 0°C then treated with water (26 ml). The reaction mixture was then warmed to 18°C and after a further 1 h treated with NaOH (6.0 ml of a 30% aqueous solution saturated with sodium chloride) and stirred vigorously. After *c*. 0.2 h of stirring, the mixture was filtered through a small pad of Celite™ then the separated aqueous layer was extracted with CH_2Cl_2 (3×150 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 3 : 7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_F 0.3) afforded the title compound (7) (4.00 g, 70%) as a clear colourless oil, $[\alpha]_D$ +33 (*c*, 1.2). ν_{max} 3401, 3078, 2979, 2928, 1641, 1449, 1088, 1030, 997, 914, 882, 642 cm^{-1}. ^1H n.m.r. δ 5.90–5.73, complex m, 1H; 5.10–4.95, complex m, 2H; 3.94–3.88, complex m, 1H; 3.66–3.58, m, 1H; 3.01–2.90, complex m, 2H; 2.20, m, 2H; 1.76, t, *J* 6.5 Hz, 1H; 1.71–1.64, complex m, 2H. ^{13}C n.m.r. δ 137.4 (CH), 115.3 (CH_2), 61.7 (CH_2), 58.6 (CH), 55.4 (CH), 30.8 (CH_2), 30.1 (CH_2). Mass spectrum *m/z* 97 [18%, $(M-HOCH_2^{\bullet})^+$], 67 (100).

(±)-trans-*2,3-Epoxyhept-6-en-1-ol* (±)-*(7)*

A magnetically stirred solution of allylic alcohol (4) (50 mg, 0.45 mmol) in CH_2Cl_2 (2.5 ml) was treated, portionwise, with *m*-chloroperbenzoic acid (132 mg of technical grade material containing *c*. 70% peracid, *c*. 0.54 mmol). After 2 h the reaction mixture was quenched with $Na_2S_2O_5$ (5 ml of a 1 M aqueous solution). The separated organic phase was washed with $NaHCO_3$ (1×5 ml) and water (1×5 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 1 : 4 v/v ethyl acetate/hexane elution) followed by concentration of the appropriate fractions (R_F 0.3) then afforded the title compound (±)-(7) (25 mg, 44%) as a clear, colourless oil. This material was identical, as judged by ^1H n.m.r., ^{13}C n.m.r., mass spectral and infrared analysis, with the material obtained using the Katsuki–Sharpless asymmetric epoxidation protocol described above.

Mosher Ester Analysis of Epoxides (+)-*(7) and* (±)-*(7). Formation of Ester (8) and a Diastereoisomer Thereof*

A nitrogen atmosphere was established over a magnetically stirred solution of 4-(dimethylamino)pyridine (18 mg, 0.15 mmol) and triethylamine (0.1 ml) in CH_2Cl_2 (0.5 ml) which was then treated with epoxide (+)-(7) (19.2 mg, 0.15 mmol) and (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[22] (0.04 ml, 0.20 mmol). The resulting solution became warm and turned orange in colour. After 0.1 h the reaction mixture was treated with $NaHCO_3$ (5 ml of a saturated aqueous solution) and extracted with CH_2Cl_2 (2×10 ml). The combined organic extracts were washed with brine (1×5 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale-yellow oil which was subjected to flash chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_F 0.4) afforded Mosher ester (8) (22 mg, 42%) as a clear, colourless oil. ^1H n.m.r. (C_6D_6) δ 7.82, d, *J* 7.6 Hz, 2H; 7.35–7.05, complex m, 3H; 5.69, m, 1H; 5.00, m, 2H; 4.30, dd, *J* 12.2 and 3.2 Hz, 1H; 3.80, dd, *J* 12.2 and 5.8 Hz, 1H; 3.54, s, 3H; 2.63, m, 1H; 2.53, m, 1H; 1.97, m, 2H; 1.32, m, 2H.

The racemic epoxide (±)-(7) (25 mg, 0.20 mmol) was converted into the corresponding mixture of diastereoisomeric Mosher esters by reaction with (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride under the conditions described immediately above. ^1H n.m.r. analysis of this material revealed it to be a 1 : 1 mixture of compound (8) and the diastereoisomeric ester derived from *ent*-(7). The most diagnostic ^1H n.m.r. signals due to the (R)-MTPA ester derivative of *ent*-(7) appear (in C_6D_6) at δ 4.14 (dd, *J* 12.2 and 3.2 Hz, 1H) and 3.90 (dd, *J* 12.2 and 5.8 Hz, ^1H) [the corresponding signals for (8) appear at δ 4.30 and 3.80 respectively (see preceding paragraph)].

*(2*S*,3*S*)-3-Methylhept-6-ene-1,2-diol (9)*

Trimethylaluminium (131 ml of a 2.0 M solution in hexane, 262 mmol, ex Aldrich) was added, dropwise, to a magnetically stirred solution of epoxide (7) (11.15 g, 87 mmol) in CH_2Cl_2 (90 ml) maintained at 0°C under a nitrogen atmosphere. After addition was complete, the reaction mixture was stirred at 18°C for 10 h and then chilled (0°C) and quenched (CAUTION) with HCl (75 ml of 1 M aqueous solution). The aqueous layer was extracted with CH_2Cl_2 (3×150 ml) and the combined organic layers were washed with water (1×100 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 1 : 1 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_F 0.4) afforded the *title compound (9)* (10.4 g, 83%) as a clear, colourless oil, $[\alpha]_D$ –5.7 (*c*, 1.2) [Found: $(M-H^{\bullet})^+$, 143.1070. $C_8H_{16}O_2$ requires $(M-H^{\bullet})^+$, 143.1072]. ν_{max} 3368, 3077, 2962, 2928, 1640, 1458, 1380, 1073, 995, 909, 880 cm^{-1}. ^1H n.m.r. δ 5.78, m, 1H; 5.03–4.88, complex m, 2H; 3.70–3.60, complex m, 1H; 3.53–3.40, complex m, 2H; 3.20, br s, 2H; 2.20–2.08, complex m, 1H; 2.05–1.90, complex m, 1H; 1.70–1.54, complex m, 2H; 1.29–1.18, complex m, 1H; 0.88, d, *J* 7.0 Hz, 3H. ^{13}C n.m.r. δ 138.8 (CH), 114.5 (CH_2), 76.1 (CH), 64.6 (CH_2), 35.5 (CH), 31.6 (CH_2), 31.1 (CH_2), 15.1 (CH_3). Mass spectrum *m/z* 145 [3%, $(M+H)^+$], 144 (3, $M^{+\bullet}$), 143 [2, $(M-H^{\bullet})^+$], 95 (100), 71 (53).

*(2*S*,3*S*)-3-Methylhept-6-ene-1,2-diol Diacetate (10)*

A magnetically stirred solution of diol (9) (5.54 g, 38.5 mmol) in pyridine (21 ml) was treated with acetic anhydride (12.7 ml, 134 mmol) and 4-(dimethylamino)pyridine (10 mg, 0.08 mmol). The resulting mixture was stirred at 18°C for 3 h then poured onto ice (*c*. 50 g) and extracted with ether (1×100 ml). The separated organic phase was washed with HCl (2×20 ml of a 1 M aqueous solution), $NaHCO_3$ (2×20 ml of a saturated aqueous solution) and brine (1×20 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 3 : 7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_F 0.7) afforded the *title compound (10)* (8.40 g, 96%) as a clear, colourless oil, $[\alpha]_D$ +5.24 (*c*, 1.3) [Found: $(M+H)^+$, 229.1440. $C_{12}H_{20}O_4$ requires $(M+H)^+$, 229.1440]. ν_{max} 2973, 2937, 1744, 1641, 1458, 1371, 1227, 1048, 1020, 913, 605 cm^{-1}. ^1H n.m.r. δ 5.76, m, 1H; 5.03–4.90, complex m, 3H; 4.27, dd, *J* 12.0 and 3.0 Hz, 1H; 4.05, dd, *J* 12.0 and 4.2 Hz, 1H; 2.15–1.90, complex m, 2H; 2.06, s, 3H; 2.03, s, 3H; 1.85–1.73, complex m, 1H; 1.50, m, 1H; 1.23, m, 1H; 0.92, d, *J* 6.9 Hz, 3H. ^{13}C n.m.r. δ 170.8 (C), 170.6 (C), 138.2 (CH) 114.8 (CH_2), 74.9 (CH), 63.6 (CH_2), 33.6 (CH), 31.3 (CH_2), 31.0 (CH_2), 21.0 (CH_3), 20.9 (CH_3), 15.0 (CH_3). Mass spectrum *m/z* 229 [2%, $(M+H)^+$], 213 [24, $(M-H_3C^{\bullet})^+$], 115 (76), 114 (78), 108 (90), 95 (100), 93 (96), 79 (70).

[S-(R*,R*)]-*5,6-Bis(acetyloxy)-4-methylhexanal (11)*

A magnetically stirred solution of diacetate (10) (10.50 g, 45.65 mmol) in CH_2Cl_2 (575 ml) was cooled to –78°C then treated with a stream of ozone gas until a blue colour persisted. The reaction mixture was then warmed to –30°C and triphenylphosphine (12.0 g, 45.65 mmol) was carefully added in portions. After the addition was complete, the reaction mixture was allowed to warm to room temperature. The solvent was then removed under reduced pressure and the residue thereby obtained was subjected to flash chromatography (silica gel, 3 : 7 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_F 0.3) gave the title compound (11)[9] (8.40 g, 79%) as a pale-yellow oil, $[\alpha]_D$ +7.3 (*c*, 2.0 in MeOH) [Found: $(M+H)^+$, 231.1232.

Calc. for $C_{11}H_{18}O_5$: $(M+H)^+$, 231.1232]. ν_{max} 2967, 2727, 1744, 1371, 1227, 1048, 959, 605 cm^{-1}. ^1H n.m.r. δ 9.77, s, 1H; 4.94, m, 1H; 4.31, dd, *J* 12.1 and 2.9 Hz, 1H; 4.05, dd, *J* 12.1 and 6.8 Hz, 1H; 2.60–2.30, complex m, 2H; 2.07, s, 3H; 2.04, s, 3H; 1.90–1.72, complex m, 2H; 1.54–1.44, complex m, 1H; 0.93, d, *J* 6.8 Hz, 3H. ^{13}C n.m.r. δ 201.8 (CH), 170.8 (C), 170.6 (C), 74.5 (CH), 63.4 (CH_2), 41.2 (CH_2), 33.5 (CH), 24.1 (CH_2), 21.0 (CH_3), 20.8 (CH_3), 15.1 (CH_3); Mass spectrum *m/z* 231 [15%, $(M+H)^+$], 115 (60), 103 (53), 97 (100), 84 (48).

Methyl {S-[R*,R*-(Z)]}*-7,8-Bis(acetyloxy)-6-methyloct-2-enoate (12)*

$KN(SiMe_3)_2$ (73.0 ml of a 0.5 M solution in toluene, 36.5 mmol) was added, dropwise, to a magnetically stirred solution of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (7.73 ml, 36.5 mmol) and 18-crown-6/MeCN complex[23] (48.3 g, 183 mmol) in dry thf (140 ml) maintained at –78°C under an atmosphere of nitrogen. The reaction mixture was stirred at –78°C for 0.5 h then treated with aldehyde (11) (8.4 g, 36.52 mmol). After 1 h at this temperature, the reaction mixture was quenched with NH_4Cl (60 ml of a saturated aqueous solution) then allowed to warm to room temperature. The resulting mixture was extracted with ether (3×50 ml) and the combined organic phases were washed with water (1×100 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the material thus obtained to flash chromatography (silica gel, 3 : 7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_F 0.4) afforded the title ester (12)[9] (8.35 g, 80%) as a pale-yellow oil, $[\alpha]_D$ +9.9 (*c*, 5.4) [Found: $(M+H)^+$, 287.1495. Calc. for $C_{14}H_{22}O_6$: $(M+H)^+$, 287.1495]. ν_{max} 2953, 1743, 1645, 1439, 1371, 1226, 1176, 1048, 821 cm^{-1}. ^1H n.m.r. δ 6.18, m, 1H; 5.78, br d, *J* 11.5 Hz, 1H; 4.95, td, *J* 6.8 and 2.9 Hz, 1H; 4.29, dd, *J* 12.0 and 2.9 Hz, 1H; 4.06, dd, *J* 12.0 and 7.1 Hz, 1H; 3.70, s, 3H; 2.68, m, 2H; 2.07, s, 3H; 2.04, s, 3H; 1.82, m, 1H; 1.65–1.50, complex m, 1H; 1.35–1.20, complex m, 1H; 0.96, d, J 7.0 Hz, 3H. ^{13}C n.m.r. δ 170.8 (C), 170.6 (C), 166.7 (C), 149.8 (CH), 119.7 (CH), 74.9 (CH_3), 63.5 (CH_2), 51.0 (CH), 33.9 (CH), 31.3 (CH_2), 26.3 (CH_2), 21.0 (CH_3), 20.8 (CH_3), 15.0 (CH_3). Mass spectrum *m/z* 287 [5%, $(M+H)^+$], 166 (52), 153 (70), 139 (100), 107 (74), 81 (90).

*Methyl [2*R*-(2α,5β,6α)]-6-(Hydroxymethyl)-5-methyltetrahydro-2*H*-pyran-2-acetate (13)*

A mixture of methyl ester (12) (8.35 g, 29.20 mmol), K_2CO_3 (20.2 g, 146 mmol) and methanol (42 ml) was stirred at 18°C for 24 h then filtered through a sintered glass funnel. Water (100 ml) was added to the filtrate which was acidified to pH 2–3 with HCl (concentrated aqueous solution). The resulting mixture was extracted with diethyl ether (3×50 ml) and the combined extracts were dried ($MgSO_4$), filtered and then concentrated under reduced pressure. The light-yellow oil obtained in this manner was suspended in methanol (50 ml) containing H_2SO_4 (6 drops of 98% acid) and the resulting mixture stirred at 18°C for 16 h then poured onto ice (50 g) and extracted with diethyl ether (3×50 ml). The combined organic extracts were washed with $NaHCO_3$ (1×50 ml of a saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 3 : 7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_F 0.25) afforded the title compound (13)[9] (4.18 g, 71%) as a clear colourless oil, $[\alpha]_D$ +9.8 (*c*, 1.0) {lit.[2] $[\alpha]_D$ +9.4} [Found: $(M-H_2O)^{+\bullet}$, 184.1097. Calc. for $C_{10}H_{18}O_4$: $(M-H_2O)^{+\bullet}$, 184.1099). ν_{max} 3458, 2928, 2873, 1738, 1437, 1199, 1087, 1019 cm^{-1}. ^1H n.m.r. δ 3.80–3.63, complex m, 2H; 3.65, s, 3H; 3.47, ddd, *J* 11.4, 7.1 and 4.3 Hz, 1H; 3.10, ddd, *J* 9.8, 7.1 and 2.7 Hz, 1H; 2.53, dd, *J* 15.2 and 7.7 Hz, 1H; 2.40, dd, *J* 15.2 and 5.4 Hz, 1H; 2.21, dd, *J* 8.2 and 4.4 Hz, 1H; 1.80–1.72, complex m, 1H; 1.70–1.60, complex m, 1H; 1.48–1.12, complex m, 3H; 0.80, d, *J* 6.5 Hz, 3H. ^{13}C n.m.r. δ 171.6 (C), 83.5 (CH), 74.0 (CH), 63.7 (CH_2), 51.6 (CH_3), 41.1 (CH_2), 32.1 (CH_2), 31.5 (CH_2), 31.1 (CH), 17.1 (CH_3). Mass spectrum *m/z* 203 [26%, $(M+H)^+$], 171 [100, $(M-H_3CO^{\bullet})^+$], 139 (73), 129 (57), 97 (54).

*Methyl [2*R*-(2α,5β,6α)]-6-Formyl-5-methyltetrahydro-2*H*-pyran-2-acetate (14)*

A solution of alcohol (13) (1.0 g, 4.95 mol) and triethylamine (4.5 ml, 32.1 mmol) in CH_2Cl_2 (14.2 ml) was added, dropwise, to a magnetically stirred solution of sulfur trioxide/pyridine complex (2.52 g, 15.8 mmol, ex Aldrich) in Me_2SO/CH_2Cl_2 (15.6 ml of a 3 : 2 v/v mixture) maintained at 0°C (icebath) under a nitrogen atmosphere. The reaction mixture was warmed to 18°C and after stirring for a further 1 h it was treated with water (130 ml) then extracted with hexane (3×7 ml). The combined organic phases were washed with brine (1×50 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash chromatography (silica gel, 3 : 7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_F 0.4) then afforded the title compound (14)[9] (594 mg, 60%) as a clear colourless oil, $[\alpha]_D$ –65 (*c*, 0.45) {lit.[2] $[\alpha]_D$ –62 (*c*, 0.5 in $CHCl_3$)} [Found: $(M-CHO^{\bullet})^+$, 171.1020. Calc. for $C_{10}H_{16}O_4$: $(M-CHO^{\bullet})^+$, 171.1021). ν_{max} 2932, 1740, 1437, 1200, 1090, 1021, 857 cm^{-1}. ^1H n.m.r. δ 9.51, d, *J* 2.3 Hz, 1H; 3.80, m, 1H; 3.67, s, 3H; 3.41, dd, *J* 10.6 and 2.3 Hz, 1H; 2.61, dd, *J* 15.4 and 7.6 Hz, 1H; 2.44, dd, *J* 15.4 and 5.4 Hz, 1H; 1.88, m, 1H; 1.70, m, 1H; 1.64–1.50, complex m, 1H; 1.45–1.20, complex m, 2H; 0.91, d, *J* 6.6 Hz, 3H. ^{13}C n.m.r. δ 200.6 (CH), 171.4 (C), 86.7 (CH), 73.5 (CH), 51.7 (CH_3), 41.0 (CH_2), 32.1 (CH_2), 30.8 (CH_2), 30.5 (CH), 16.3 (CH_3). Mass spectrum *m/z* 201 [14%, $(M+H)^+$], 171 [100, $(M-CHO^{\bullet})^+$], 139 (88), 127 (52), 111 (57), 97 (88), 81 (57), 69 (59).

*Methyl [2*R*-(2α,5β,6α)]-6-Acetyl-5-methyltetrahydro-2*H*-pyran-2-acetate (15)*

Methylmagnesium chloride (0.83 ml of a 3 M solution in thf, 2.5 mmol) was added, dropwise, to a magnetically stirred solution of aldehyde (14) (500 mg, 2.5 mmol) in thf (12.5 ml) maintained at –78°C under a nitrogen atmosphere. After addition was complete the reaction mixture was allowed to warm to 0°C, stirred at this temperature for a further 1 h then poured onto a mixture of ice (*c*. 20 g) and NH_4Cl (20 ml of a saturated aqueous solution). The resulting mixture was extracted with ether (3×20 ml) and the combined organic phases were washed with water (1×30 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a light-yellow oil (190 mg). Subjection of this material to flash chromatography (silica gel, 3 : 7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_F 0.3) afforded the expected mixture of diastereoisomeric secondary alcohols as a clear, colourless oil. This material was dissolved in CH_2Cl_2 (8.0 ml) and the resulting solution treated with the Dess–Martin periodinane[17] (560 mg, 1.32 mmol). The mixture thus obtained was stirred at 18°C for 1 h then diluted, successively, with diethyl ether (10 ml), $NaHCO_3$ (5 ml of a saturated aqueous solution) and $Na_2S_2O_3$ (5 ml of a 1 M aqueous solution). Stirring was continued until two layers became apparent. The separated aqueous phase was extracted with diethyl ether (3×10 ml) and the combined organic phases were washed with brine (1×10 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica gel, 3 : 7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_F 0.3) then afforded the title compound (15)[9] (90 mg, 17%) as a clear colourless oil $[\alpha]_D$ –91 (*c*, 1.2) {lit.[2] $[\alpha]_D$ –95 (*c*, 1.5 in $CHCl_3$)} [Found: $(M+H)^+$, 215.1282. Calc. for $C_{11}H_{18}O_4$: $(M+H)^+$, 215.1283]. ν_{max} 2931, 1741, 1719, 1437, 1354, 1199, 1083, 1022, 894 cm^{-1}. ^1H n.m.r. δ 3.78, m, 1H; 3.67, s, 3H; 3.41, d, *J* 10.2 Hz, 1H; 2.57, dd, *J* 15.1 and 7.6 Hz, 1H; 2.44, dd, *J* 15.1 and 5.4 Hz, 1H; 2.14, s, 3H; 1.87, m, 1H; 1.72–1.67, complex m, 1H; 1.60–1.18, complex m, 3H; 0.82, d, *J* 6.6 Hz, 3H. ^{13}C n.m.r. δ 207.9 (C), 171.5 (C), 89.0 (CH), 73.7 (CH), 51.7 (CH_3), 41.1 (CH_2), 32.2 (CH_2), 31.8 (CH_3), 31.1 (CH_2), 25.8 (CH), 16.9 (CH_3). Mass spectrum *m/z* 215 [5%, $(M+H)^+$], 171 [100, $(M-CH_3CO^{\bullet})^+$], 139 (95), 111 (61), 97 (92).

*Methyl {2*R*-[2α,5β,6α(E)]}-6-(3-Bromo-1-methylprop-1-enyl)-5-methyltetrahydro-2*H*-pyran-2-acetate (16)*

Vinylmagnesium bromide (1.6 ml of a 1 M solution in thf, 1.58 mmol, ex Aldrich) was added, dropwise, to a magnetically stirred solution of ketone (15) (339 mg, 1.58 mmol) in thf (65 ml) maintained

at –78°C under a nitrogen atmosphere. The resulting mixture was stirred at –78°C for a further 1 h then warmed to 0°C, poured into NH_4Cl (25 ml of a saturated aqueous solution) and extracted with diethyl ether (3×50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil (203 mg) which was subjected to flash chromatography (silica gel, 1 : 4 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_F 0.3) then afforded the expected vinyl alcohol which was immediately subjected to the brominative rearrangement reaction. Thus, PBr_3 (50 µl, 0.5 mmol) was injected, via syringe, into a magnetically stirred solution of the vinyl alcohol (100 mg, 0.41 mmol) in diethyl ether (10 ml) maintained at 0°C under a nitrogen atmosphere. After the addition was complete, the reaction mixture was stirred at 0°C for a further 1 h and then poured onto ice (*c*. 10 g). The resulting mixture was extracted with diethyl ether (1×30 ml) and the separated organic phase dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 1 : 4 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_F 0.3), the title bromide (16)[9] (117 mg, 93%) as a clear, colourless oil, $[\alpha]_D$ –29 (*c*, 2.1) {lit.[9] $[\alpha]_D$ –5.2 (*c*, 1.5 in $CHCl_3$)} [Found: $(M-Br^{\bullet})^+$, 225.1495. Calc. for $C_{13}H_{21}BrO_3$: $(M-Br^{\bullet})^+$, 225.1491]. ν_{max} 2951, 2926, 1740, 1436, 1200, 1069, 1019, 865 cm^{-1}. ^1H n.m.r. δ 5.69, t, *J* 9.0 Hz, 1H; 4.00, m, 2H; 3.80–3.70, complex m, 1H; 3.66, s, 3H; 3.35, d, *J* 9.8 Hz, 1H; 2.58, dd, *J* 15.2 and 6.5 Hz, 1H; 2.40, dd, *J* 15.2 and 6.5 Hz, 1H; 1.90–1.80, complex m, 1H; 1.69, s, 3H; 1.70–1.65, complex m, 1H; 1.62–1.47, complex m, 1H; 1.40–1.15, complex m, 2H; 0.71, d, *J* 6.7 Hz, 3H. ^{13}C n.m.r. δ 171.7 (C), 141.5 (C), 123.9 (CH), 89.5 (CH), 73.8 (CH), 51.6 (CH_3), 41.2 (CH_2), 32.3 (CH), 32.2 (CH_2), 31.5 (CH_2), 28.2 (CH_2), 17.4 (CH_3), 11.5 (CH_3). Mass spectrum *m/z* 224 [8%, $(M-HBr)^{+\bullet}$], 121 (100).

*Methyl {2*R*-[2*α*,5*β*,6*α*(*E*)]}-6-[3-(Diphenylphosphinoyl)-1-methyl-prop-1-enyl]-5-methyltetrahydro-2*H*-pyran-2-acetate (2)*

A magnetically stirred solution of bromide (16) (100 mg, 0.33 mmol) and ethoxydiphenylphosphine (143 µl, 0.66 mmol, ex Aldrich) in thf (10 ml) was heated at reflux until the starting materials had been consumed (*c*. 2 h). The cooled reaction mixture was concentrated under reduced pressure and the resulting solid recrystallized (diethyl ether) to give the phosphine oxide (2)[9] (119 mg, 85%) as a fine white powder, m.p. 125–126°C (lit.[9] 125–126°C), $[\alpha]_D$ –0.4 (*c*, 1.4) {lit.[9] $[\alpha]_D$ –32.8 (*c*, 0.5 in $CHCl_3$)—see text} (Found: $M^{+\bullet}$, 426.1962. Calc. for $C_{25}H_{31}O_4P$: $M^{+\bullet}$, 426.1960). ν_{max} (KBr disk) 2924, 2847, 1736, 1437, 1180, 1120, 1069, 1018, 745, 719, 697, 555, 512 cm^{-1}. ^1H n.m.r. δ 7.74, m, 4H; 7.50, m, 6H; 5.50, m, 1H; 3.72–3.60, complex m, 1H; 3.63, s, 3H; 3.26, d, *J* 9.7 Hz, 1H; 3.23–3.10, complex m, 2H; 2.54, dd, *J* 15.1 and 6.5 Hz, 1H; 2.37, dd, *J* 15.1 and 6.4 Hz, 1H; 1.75, dm, *J* 13.5 Hz, 1H; 1.63, dm, *J* 13.5 Hz, 1H; 1.47, br s, 3H; 1.45–1.10, complex m, 3H; 0.42, d, *J* 6.6 Hz, 3H. ^{13}C n.m.r. δ 171.7 (C), 140.0 (d, C), 133.2 (d, C), 131.9 (CH), 131.0 (d, CH), 128.5 (d, CH), 116.9 (d, CH), 90.0 (CH), 73.8 (CH), 51.5 (CH_3), 41.3 (CH_2), 32.1 (CH_2), 32.0 (CH_3), 31.5 (CH_2), 30.7 (d, CH_2), 17.2 (CH), 12.2 (CH_3) [d denotes doublet due to ^{13}C–^{31}P coupling]. ^{31}P n.m.r. δ 31.0. Mass spectrum *m/z* 426 (51%, $M^{+\bullet}$), 202 [100, $(Ph_2POH)^{+\bullet}$], 201 [94, $(Ph_2PO)^+$].

Acknowledgments

The Institute of Advanced Studies and Dunlena Pty Ltd are thanked for generous financial support. R.P. thanks the Australian Research Council for the provision of an APA(I) Ph.D. Scholarship.

References

[1] Miller-Wideman, M., Makkar, N., Tran, M., Isaac, B., Biest, N., and Stonard, R., *J. Antibiot*., 1992, **45**, 914; Isaac, B. G., Ayer, S. W., Elliott, R. C., and Stonard, R. J., *J. Org. Chem*., 1992, **57**, 7220.
[2] Edmunds, A. J. F., Trueb, W., Oppolzer, W., and Cowley, P., *Tetrahedron*, 1997, **53**, 2785.
[3] Tanida, S., Shirasaki, M., and Horiguchi, T., Jpn Kokai Tokkyo Koho JP 06 22,770 [94 22,770] (*Chem. Abstr*., 1994, **121**, 33284r); Horiguchi, T., Shirasaki, M., and Tanida, S., *Takeda Kenkyushoho*, 1996, **55**, 149 (*Chem. Abstr*., 1996, **125**, 185223r).
[4] Mizukami, T., Sakai, Y., Yoshida, T., Uosaki, Y., Ochiai, K., and Akinaga, S., Eur. Pat. Appl. EP 781,772 (*Chem. Abstr*., 1997, **127**, 108054a).
[5] Koguchi, Y., Nishio, M., Kotera, J., Omori, K., Ohnuki, T., and Komatsubara, S., *J. Antibiot*., 1997, **50**, 970.
[6] Smith, N. D., Kocienski, P. J., and Street, S. D. A., *Synthesis*, 1996, 652.
[7] Blakemore, P. R., Kocienski, P. J., Morley, A., and Muir, K., *J. Chem. Soc., Perkin Trans. 1*, 1999, 955.
[8] Banwell, M. G., Bui, C. T., Hockless, D. C. R., and Simpson, G. W., *J. Chem. Soc., Perkin Trans. 1*, 1997, 1261.
[9] Banwell, M. G., Bui, C. T., and Simpson, G. W., *J. Chem. Soc., Perkin Trans. 1*, 1998, 791.
[10] Pfenninger, A., *Synthesis*, 1986, 89.
[11] Barrett, A. G. M., Hamprecht, D., and Ohkubo, M., *J. Org. Chem*., 1997, **62**, 9376.
[12] Lee, E., Yoon, C. H., Lee, T. H., Kim, S. Y., Ha, T. J., Sung, Y-s., Park, S.-H., and Lee, S., *J. Am. Chem. Soc*., 1998, **120**, 7469.
[13] Wei, X., and Taylor, R. J. K., *Tetrahedron Lett*., 1998, **39**, 3815; *J. Org. Chem*., 2000, **65**, 616.
[14] Suzuki, T., Saimoto, H., Tomioka, H., Oshima, K., and Nozaki, H., *Tetrahedron Lett*., 1982, **23**, 3597; Roush, W. R., Adam, M. A., and Peseckis, S. M., *Tetrahedron Lett*., 1983, **24**, 1377.
[15] Still, W. C., and Gennari, C., *Tetrahedron Lett*., 1983, **24**, 4405.
[16] Parikh, J. R., and Doering, W. von E., *J. Am. Chem. Soc*., 1967, **89**, 5505.
[17] Boeckman, R. K., Shao, P., and Mullins, J. J., *Org. Synth*., 1999, **77**, 141.
[18] Still, W. C., Kahn, M., and Mitra, A., *J. Org. Chem*., 1978, **43**, 2923.
[19] Denney, D. B., and Ross, S. T., *J. Org. Chem*., 1962, **27**, 998.
[20] Booker-Milburn, K. I., Barker, A., Brailsford, W., Cox, B., and Mansley, T. E., *Tetrahedron*, 1998, **54**, 15321.
[21] Colonge, J., and Poilane, G., *Bull. Soc. Chim. Fr*., 1955, 953.
[22] Gao, Y., Hanson, R. M., Klunder, J. M., Ko, S. Y., Masamune, H., and Sharpless, K. B., *J. Am. Chem. Soc*., 1987, **109**, 5765.
[23] Gokel, G. W., Cram, D. J., Liotta, C. L., Harris, H. P., and Cook, F. L., *J. Org. Chem*., 1974, **39**, 2445.