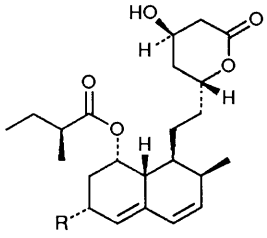
Methyl (3*R*)-3-Hydroxyhex-5-enoate as a Precursor to Chiral Mevinic Acid Analogues

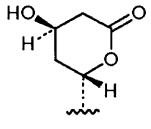
Frank Bennett,[a] David W. Knight*,[a] and Garry Fenton[b]
[a] *Chemistry Department, University Park, Nottingham NG7 2RD, UK*
[b] *Rhone-Poulenc Ltd., Dagenham, Essex, UK*

Baker's yeast reduction of methyl 3-oxohex-5-enoate **14b** provides methyl (3*R*)-3-hydroxyhex-5-enoate **15b** with 78% enantiomeric enrichment. Subsequent seleno- and iodo-lactonization of derived hex-5-enoic acids leads to valerolactones **18**, **19**, **25** and **26** which are suitable for the subsequent elaboration of a variety of mevinic acid analogues. The absolute configuration of the major enantiomer produced in the initial yeast reduction was determined by correlation with natural (*S*)-(+)-parasorbic acid **23**.

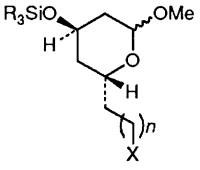
The ability of the mevinic acids, most notably compactin **1a**[1] and mevinolin **1b**[2] as well as a number of closely related compounds,[3] effectively to inhibit the biosynthesis of cholesterol in humans has generated a considerable amount of interest both in the synthesis of the natural materials as well as in the design and elaboration of simpler and possibly more potent synthetic analogues. The key structural feature common to all the mevinic acids is the β-hydroxyvalerolactone function **2** which, in its open form, closely mimics mevalonic acid, a crucial



1 **a**; R = H [(+)-compactin]
b; R = Me [(+)-mevinolin]



2

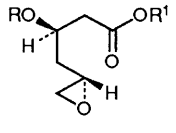


3

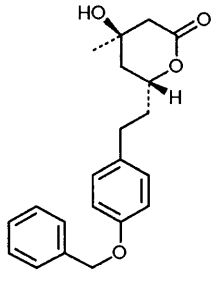
intermediate in the terpenoid biosynthetic pathway leading to cholesterol. The compounds act as potent inhibitors of the pathway by blocking a major rate-limiting enzyme, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCoA reductase) which is responsible for the conversion of HMGCoA into mevalonic acid.[4,5]

A commonly used tactic for incorporation of the key chiral hydroxy lactone function **2** in syntheses of both the natural compounds and synthetic analogues thereof is to employ the masked lactol **3** as an electrophilic species.[6] This type of intermedate has often been obtained by carbohydrate degradation[7,8] as well as from L-malic acid,[9] (*S*)-4-hydroxymethylbutyrolactone,[10] and from an asymmetric [1,3]-dipolar cycloaddition.[11] Chiral as well as racemic material has been obtained using a Diels–Alder reaction as the key step[12] as well as by other approaches.[6,13,14] Other viable intermediates are the chiral epoxy esters **4** which have been obtained from a variety of precursors[15] and which undergo extremely efficient couplings with aryl cuprate reagents leading directly to mevinic acid analogues. Alternative open-chain precursors, based on δ-hydroxy β-keto ester systems have been obtained in optically active form using a number of chiral auxiliaries.[16] The asymmetric Sharpless epoxidation has also been used to prepare some related chiral intermediates.[17]

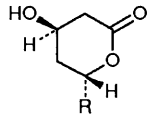
The design of synthetic analogues of compactin **1a** and mevinolin **1b** has been governed by two major considerations, namely the requirement for a hydroxyvalerolactone function **2** and the desirability of having a much simpler array in place of the complex decalin systems present in the natural products. Initial work focussed on the preparation of a variety of mevalonate analogues, of which lactone **5** was a notable example in terms of its bioactivity.[14] The related analogues **6**, which lack a 4-methyl substituent and which therefore more closely resemble the mevinic acids, were generally most active when the substituent R was arylethyl or (*E*)-arylethenyl,[18] an example being the lactone **7** which in its dihydroxy acid form displays 2.8 times the activity of natural compactin **1a** in HMGCoA reductase inhibition.[19] The requirement for rapid access to a wide range of chiral lactones **8** suggested that the seleno- or iodo-lactones **9** (X = SePh or I) could be valuable intermediates in this respect. We reasoned that the lactones **9** should be available from the unsaturated hydroxy acids **10** which, in turn, should be obtainable in optically active form by asymmetric reduction of the corresponding keto esters **11**. The



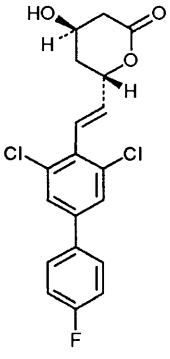
4



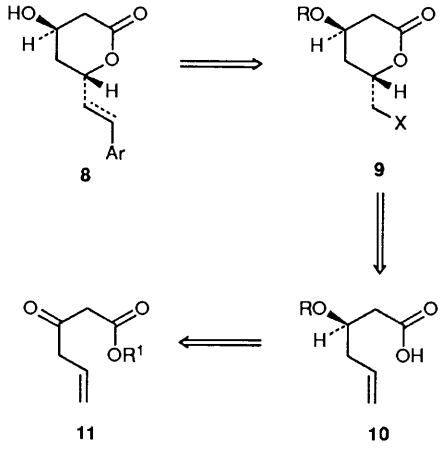
5



6

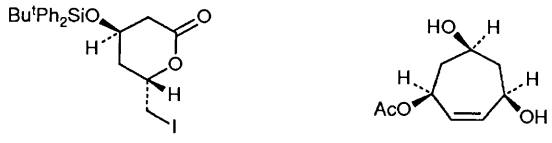


7



8 9 11 10

viability of these lactones in such syntheses has been emphasised by alternative approaches which were reported[20] prior to the completion of our studies.[21] Thus, the optically pure

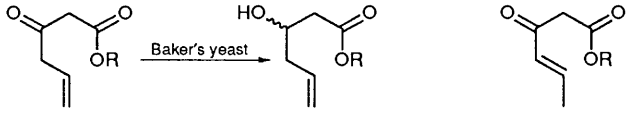


12 13

iodolactone **12** was prepared from α-D-glucose in 17 steps whereas its (4*S*,6*R*)-enantiomer with 70% enantiomeric enrichment was obtained from acetonedicarboxylic acid, the key asymmetric step being partial saponification of the corresponding dipropyl ester using porcine liver esterase (PLE).[20] Others have also been more or less successful in achieving such an enzyme mediated preparation of chiral 3-hydroxyglutarate derivatives.[22,23] Very recently, a related enzymic hydrolysis by electric eel acetylcholinesterase has been used to prepare the cycloheptenetriol derivative **13** from which either enantiomer of a chiral *trans*-mevinic acid analogue **8** can be prepared by appropriate protection steps followed by oxidation, ring cleavage and coupling to an aryl cuprate.[24]

Results and Discussion

Our studies began with syntheses of the 3-oxohex-5-enoates **11**. Such esters can be prepared by a Grignard reaction between allylmagnesium bromide and a cyanoacetate followed by mild hydrolysis of the resulting enamino ester.[25] Although this procedure is not particularly efficient, the yields were improved by using tetrahydrofuran (THF) in place of ether as the solvent for the Grignard step; the mitigating feature of the method is that it can be conveniently carried out on a large scale. Both the

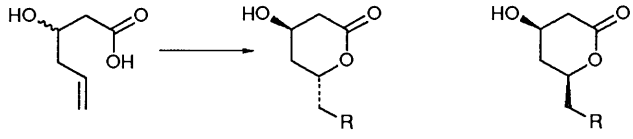


14 a; R = Et, b; R = Me — **15** a; R = Et 43% ee, b; R = Me 78% ee — **16** a; R = Et, b; R = Me

ethyl **14a** and methyl **14b** esters were prepared in this way and both could be isolated as pure regioisomers by vacuum distillation below 70 °C. Above this temperature, both compounds displayed a marked tendency to isomerize to the conjugated hex-4-enoate isomers **16**. An alternative and more efficient approach to these esters is by the procedure of Hamana and Sugasawa[26] in which the same cyanoacetates are condensed with allyltrimethylsilane in the presence of boron trichloride. However, this more expensive procedure was not so amenable to large scale preparations of esters **14**.

Of a number of possibilities for the asymmetric reduction of these β-keto esters, the use of baker's yeast[27] seemed to offer a number of advantages, notably cheapness and ease of handling as well as the innocuous nature of this 'reagent'. Using the method described in detail by Seebach and his colleagues,[28] incubation of the esters **14** with fermenting baker's yeast for *ca.* 24 h at 30 °C led to the hydroxy esters **15** in 65–70% isolated yields. The use of tap water was essential; in deionized water, the reductions tended to stop at around 50% conversion. If the keto ester substrates were contaminated with varying amounts of the corresponding hex-4-enoates **16** (*vide supra*), this was of little consequence as no products arising from these compounds were isolated. Possibly these conjugated isomers react by a Michael addition process; although the fate of the resulting species is unclear, hydrolysis and decarboxylation to give volatile fragments would seem a distinct possibility. The initial yeast reduction products **15** were virtually free from impurities when isolated by a simple solvent extraction. Conversion into the Mosher's ester derivatives[29] and subsequent NMR analysis showed the ethyl ester **15a** to have an enantiomeric enrichment of 43% (71.5:28.5) while the corresponding value for the methyl ester **15b** was 78% (89:11). The higher ee value associated with the smaller methyl ester function follows a pattern typical of such yeast reductions.[27,28] Attempts to increase the enantioselectivity of the yeast reduction by the addition of allyl alcohol,[30] by reduction of the corresponding carboxylate salt[31] or by changes to the concentration or reactant ratios[32] were not successful. Our samples of the hydroxy ester **15b** (78% ee) showed $[\alpha]_D$ −23.5° (*c* 1.1; $CHCl_3$). While our work was in progress, Tamm and his colleagues reported an alternative preparation of this compound by a kinetic hydrolysis of racemic methyl 3,4-epoxybutanoate catalysed by PLE, followed by coupling with vinylmagnesium bromide in the presence of copper(I) iodide.[22] These authors quote $[\alpha]_D$ −12.6° (*c* 1.3; $CHCl_3$) but no enantiomeric enrichment value. However, conversion of the initial 3,4-epoxy ester into γ-amino-β-hydroxybutyric acid (GABOB) gave material with an ee of 97%, based on the rotation of a recrystallized sample. Other than a fractional crystallization effect, we cannot offer an explanation for this discrepancy.

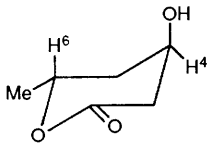
The absolute configuration of the major enantiomer of the hydroxy ester **15b** was determined during our first investigations into ways to convert the hydroxy esters **15** into mevinic acid analogues. Hydrolysis of the ester **15b** led to the hydroxy acid **17**, $[\alpha]_D$ −27.3° (*c* 1.0; $CHCl_3$) which, upon selenolactonization under kinetic conditions[33] gave a *ca* 10:1 mixture of the selenolactones **18a** and **19a** but in only a modest 40% yield. In



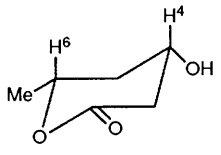
17 — **18** a; R = SePh, b; R = H — **19** a; R = SePh, b; R = H

contrast, selenolactonization using thermodynamic conditions gave an improved 65% isolated yield of the same lactones, but in a ratio of 1:1. The relative stereochemistries of these two lactones were determined by reductive removal of the selenium group using triphenyltin hydride[34] prior to separation of the resulting methyl-substituted lactones **18b** and **19b** by column chromatography. The less polar isomer exhibited resonances at δ 4.38 (br quin, *J*/Hz: 3.7) and at δ 4.87 (ddq, *J*/Hz: 11.3, 6.4 and

3.1) which were assigned to the 4-H and 6-H, respectively, on the basis of appropriate decoupling and COSY experiments. On the reasonable assumption that the larger methyl group will adopt an equatorial position, this is the *trans* isomer **18b** which exists in the chair conformation **20**. In contrast, the more polar isomer exhibited the corresponding resonances at δ 4.25 (dddd, *J*/Hz: 9.1, 7.6, 5.8 and 5.6, 4-H) and δ 4.37 (ddq, *J*/Hz: 11.7, 6.2 and 3.0, 6-H). These data are consistent with this being the *cis* isomer



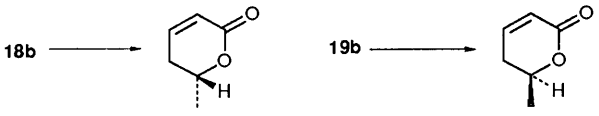
20



21

19b which exists in the conformation **21**, in which both the 4- and 6-protons are in axial positions. The downfield shift of the 6-H resonance in the *trans* isomer (Δδ 0.5 ppm) is also consistent with a [1.3]-diaxial relationship between this proton and the 4-hydroxy group.

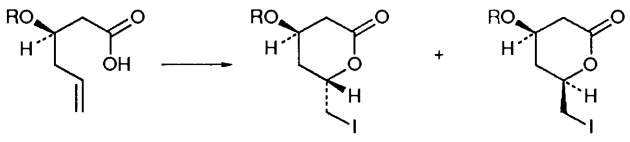
The absolute configurations of these lactones and hence of the initial yeast reduction product **15b** were determined by conversion of both seleno lactone isomers into parasorbic acid, a metabolite of the mountain ash or rowan (*Sorbus aucuparia* L.). The natural material has an $[\alpha]_D$ of +206° (*c* 1; EtOH) and the (6*S*)-configuration **23**.[35] Dehydration of the *trans*-hydroxy lactone **18b** by treatment with phosphorus oxychloride in warm pyridine gave the dihydropyran-2-one **22** which showed $[\alpha]_D$ −112° (*c* 0.87; EtOH) and which is therefore the non-natural (6*R*) enantiomer. Similar treatment of the *cis*-hydroxy lactone **19b** led to a pyran-2-one which showed $[\alpha]_D$ +98° (*c* 1.8; EtOH) corresponding to the stereochemistry of natural parasorbic acid **23**. Therefore, the absolute configurations of the lactones **18** and **19** are as depicted and the major enantiomer produced during the yeast reduction has the 3*R* absolute configuration **24**. Significantly, this corresponds to the natural stereochemistry of the mevinic acids and to that of the more biologically active analogues.[19] The somewhat lower than expected optical rotations of the two synthetic samples is unlikely to be due to racemization and is more likely associated with the difficulties in handling and purifying small amounts of the volatile and sensitive lactones **22** and **23**. The maximum rotations expected



22 23

from our samples were ± 159°, based on the maximum value of the natural compound (+206°) and an optical purity of 78% (*vide supra*).[36] The synthetic utility of the seleno lactones **18a** and **19a** and higher homologues has been exemplified in an alternative strategy in which the initial yeast reduction product **15b** is homologated prior to lactonization.[37]

We then turned our attention to iodolactonizations of the hydroxy acid (*cf.* **17**) and some of its derivatives. Direct iodolactonization under kinetically controlled conditions[38] led to a poor yield (23%) of the iodo lactones **25a** and **26a** in a ratio of 3:1 (Scheme 1). However, such cyclizations were much more productive when carried out on the corresponding silyl ethers. Thus, the t-butyldimethylsilyl derivative **24b** gave a similar 3:1 *trans*–*cis* ratio of the expected iodo lactones **25b** and **26b**, respectively in 84% isolated yield. The *trans* isomer **26b** could be separated by fractional crystallization from pentane. Increases in the bulk of the silyl ether function resulted in higher



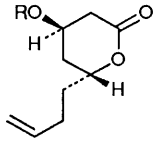
24	25		26
a; R = H	3	:	1(23%)
b; Bu^tSiMe_2	3	:	1(84%)
c; Bu^tSiPh_2	4	:	1(87%)
d; R = Pr^i_3Si	5.5	:	1(81%)

Scheme 1

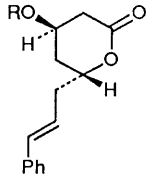
stereoselections; the t-butyldiphenylsilyl ether **24c** gave a *trans*–*cis* ratio of 4:1 which was improved to 5.5:1 in the case of the triisopropylsilyl ether **24d**. Although the isomers were not separated in this latter example, conditions for obtaining the *trans* isomer **25c** (=**12**) have recently been reported.[20] The relative stereochemistries of all the foregoing isomers were deduced from proton NMR spectra in exactly the same manner as outlined above for the seleno lactones **18a** and **19a**. Attempts to effect similar selenolactonizations of the silyl ethers **24** were not successful.

The origins of the stereoselections observed in the iodolactonizations are not clear. Such cyclizations of 3-methylhex-5-enoic acid, under kinetic or thermodynamic conditions, lead to a preponderance of the *cis*-4,6-disubstituted lactone which is consistent with the involvement of a chair-like transition state.[38] As the stereoselection of the present cyclizations increases in favour of the *trans* isomer with an increase in the bulk of the silyloxy group, complexation between the carboxylic acid function and the silyloxy group would appear not to be the controlling factor. Later work established that incorporation of substituents at the distal end of the 3-silyloxy acid increases the stereoselection of cyclization even further.[39] It is therefore possible that the cyclizations proceed predominantly *via* a boat-like transition state, perhaps brought about by the steric demands of the bulky silyloxy and iodonium substituents.

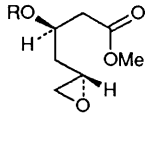
The major products obtained from these iodolactonizations have the same absolute stereochemistry of the mevinic acids and their biologically most active analogues. One way to gain access to such compounds from the iodo lactones is by direct, radical-mediated coupling reactions with a variety of stannanes. For example, treatement of the stereochemical mixture of lactones **25b** and **26b** with allyltributylstannane (AIBN, toluene, 80 °C, 16 h)[40] followed by column chromatography gave an isomerically pure sample of the *trans*-butenyl lactone **27a**. A similar coupling[41] with β-tributylstannylstyrene led to the phenylpropenyl derivative **28a**. Both products were cleanly deprotected by treatment with hydrogen fluoride to give the corresponding hydroxy lactones **27b** and **28b**, respectively. Both coupling reactions proceeded in unoptimized yeilds of *ca.* 40%; a more efficient method for the elaboration of a wide variety of mevinic acid analogues is to convert the iodo lactones into the corresponding epoxy esters **29a** and **29b** (*cf.* **4** by treatment with



27 **a**; R = Bu^tSiMe_2
b; R = H



28 **a**; R = Bu^tSiMe_2
b; R = H



29 **a**; R = Bu^tSiMe_2
b; R = Pr^i_3Si

sodium carbonate in methanol.[42] The epoxy esters were isolated in 93% and 85% yields, respectively. Such derivatives, differing only in the type of hydroxy protecting group, have been found to give essentially quantitative yields of mevinic acid analogues by coupling with a range of benzylic Grignard reagents in the presence of copper(I) bromide–dimethyl sulphide complex.[15]

Experimental

General Details.—For general details, see ref. 43. All *J* values are in Hz.

Methyl and Ethyl 3-oxohex-5-enoate **14a** *and* **14b**.—Large scale preparations were carried out using the method of Anderson and co-workers[25] by reaction between the appropriate cyanoacetate ester and allylmagnesium bromide. Yields were improved when THF rather than ether was employed as the solvent. In a typical run, methyl cyanoacetate (35 g) gave methyl 3-oxohex-5-enoate **14b** (13 g) which showed b.p. 63–64 °C at 3 mmHg: δ_H 3.36 (2 H, d, *J* 6.3, CH_2CHCH_2), 3.54 (2 H, s, $COCH_2CO$), 3.79 (3 H, s, CO_2CH_3), 5.06–5.40 (2 H, m, CH_2CH) and 5.61–6.39 (1 H, m, CH_2CH) (Found: C, 59.5; H, 7.2. Calc. for $C_7H_{10}O_3$: C, 59.2; H, 7.1%).

Somewhat smaller quantities of these esters were prepared by Lewis-acid catalysed addition of allyltrimethylsilane to the same cyanoacetates according to the procedure of Hamana and Sugasawa.[26] Isolated yields were typically 65–70%.

Methyl (3R)-3-*Hydroxyhex-5-enoate* **15b**.—A suspension of methyl 3-oxohex-5-enoate **14b** (5.87 g) in tap water (425 ml) was maintained at 30 °C and treated successively with sucrose (78 g) and dried baker's yeast (52 g). The resulting mixture was stirred gently for 24 h at this temperature and then cooled, treated with Celite (30 g) and suction filtered. The solid was thoroughly washed with water and the filtrate extracted with chloroform (4 × 100 ml). The combined extracts were dried and evaporated. Subsequent chromatography of the residue over silica gel eluted with 20% ether in hexanes gave the *hydroxy ester* **15b** as a colourless oil (4.04 g, 69%), $[\alpha]_D$ −23.5° (*c* 1.1; $CHCl_3$) [lit.,[22] $[\alpha]_D$ −12.6° (*c* 1.3; $CHCl_3$)]; ν_{max}/cm^{-1} 3470, 1728 and 1644; δ_H 2.20–2.65 (4 H, m, 2 × CH_2), 3.16 (1 H, br s, OH), 3.75 (3 H, s, OCH_3), 4.16 (1 H, apparent quin, *J* 6.8, CHOH), 5.02–5.33 (2 H, m, CH_2CH) and 5.68–6.14 (1 H, m, CH_2CH); *m/z* 127 (85%, $C_7H_{11}O_2$, M − OH), 126 (16, M − H_2O), 103 (30, $C_4H_7O_3$, M − C_3H_5), 85 (100, C_5H_9O, M − CO_2CH_3) and 67 (73, C_5H_7, M − CO_2CH_3 and H_2O) (Found: $M^+ - C_3H_5$, 103.0389. Calc. for $C_4H_7O_3$: M, 103.0394).

Methyl (3R)- *and* (3S)-3-[(R′)-3,3,3-*Trifluoro*-2-*methoxy*-2-*phenylpropionyloxy*]*hex*-5-*enoate*.—A solution of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(+)-MTPA] (0.094 g, 0.4 mmol) in freshly distilled thionyl chloride (1.7 ml) was heated at reflux for 18 h and then evaporated. To the residue was added a solution of the hydroxy ester **15b** (0.029 g, 0.2 mmol) in dry carbon tetrachloride (1 ml) and dry pyridine (8 drops). The resulting solution was stirred at ambient temperature for 48 h and then a second equal portion of the acid chloride was added. After a further 16 h, the solution was diluted with water and extracted with ether (2 × 5 ml). The combined ether solutions were washed with 2M HCl and water then dried and evaporated. Chromatography of the residue over silica gel eluted with ether–hexanes (1:10) afforded the Mosher's esters[29] (0.043 g, 66%) as a yellow oil, ν_{max}/cm^{-1} 1741 and 1641; δ_H(400 MHz) 2.42 [1.78 H, ddt, *J* 7.1, 6.6 and 1.0, (*R*)-$CHCH_2$], 2.52 [0.22 H, ddt, *J ca.* 7.0, 6.5 and 1.0, (*S*)-$CHCH_2$], 2.61–2.72 [2 H, m, (*R*) and (*S*) CH_2CO_2], 3.53 [2.34 H, q, $J_{H,F}$ 1.0, (*R*)-OCH_3], 3.54 [0.66 H, q, $J_{H,F}$ *ca.* 1.0, (*S*)-OCH_3], 3.57 [0.66 H, s, (*S*)-OCH_3], 3.66 [2.34 H, s, (*R*)-OCH_3], 5.03–5.18 (2 H, m), 5.33–5.81 (2 H, m), 7.26–7.41 (3 H, m) and 7.51–7.53 (2 H, m); *m/z* 189 (100%, $C_9H_8F_3O_3$), 127 (21, $C_7H_{11}O_2$) and 91 (7, C_7H_7).

(3R)-(−)-3-*Hydroxyhex*-5-*enoic Acid* **17**.—Aqueous sodium hydroxide (30 ml; 2M) was added to the methyl ester **15b** (2.48 g, 19.7 mmol) and the mixture stirred at ambient temperature for 24 h. The reaction mixture was then washed with chloroform, acidified to pH 2 using 2M HCl and continuously extracted with chloroform for 18 h. The resulting chloroform solution was dried and evaporated to give the *acid* **17** (2.45 g, 96%) as an oil, $[\alpha]_D$ −27.3° (*c* 1.0; $CHCl_3$) or $[\alpha]_D$ −26.5° (*c* 2.1; $CHCl_3$); ν_{max}/cm^{-1} 3360, 1710 and 1642; δ_H 2.15–2.77 (4 H, m, 2 × CH_2), 4.13 (1 H, apparent quin, *J* 6.3 CHOH), 5.00–5.33 (2 H, m, CH_2), 5.60–6.11 (1 H, m, CH) and 6.25 (2 H, br s, O*H* and CO_2H); *m/z* 112 (5%, $C_6H_8O_2$, M − H_2O), 89 (94, $C_3H_5O_3$, M − C_3H_5) and 71 (100, $C_3H_3O_2$) (Found: $M^+ - C_3H_5$, 89.0245. $C_3H_5O_3$ requires M, 89.0238). The compound was at least 95% pure according to TLC and the NMR data.

(4R,6R)- *and* (4R,6S)-4-*Hydroxy*-6-*phenylselenomethyltetrahydropyran*-2-*one* **18a** *and* **19a**.—Benzeneselenenyl chloride (0.18 g, 0.94 mmol) was added portionwise to a stirred solution of the acid **17** (0.11 g, 0.84 mmol) in dry THF (10 ml) maintained below −70 °C using a solid CO_2–acetone bath. The resulting orange solution was stirred at this temperature for 0.5 h and then allowed to warm to ambient temperature during 0.75 h. The solvent was removed under reduced pressure and the residue chromatographed on silica gel using ether as the eluant to give an inseparable mixture of the *selenides* **18a** and **19a** (0.10 g, 42%) as a colourless oil, ν_{max}/cm^{-1} 3400 and 1725; δ_H 1.57–2.51 (2 H, m), 2.64 (2 H, apparent d, *J* 4.05, 3-CH_2), 2.97–3.38 (2 H, m, PhSeCH_2), 3.52 (1 H, br s, OH), 4.35 (1 H, apparent quin, *J* 3.5, 4β-H), 4.90 (1 H, m, 6α-H), 7.21–7.29 (3 H, m) and 7.43–7.59 (2 H, m): *m/z* 286 (96%, M^+, $C_{12}H_{14}O_3{}^{80}Se$), 171 (34, $C_7H_7{}^{80}Se$), 158 (47, $C_6H_6{}^{80}Se$), 111 (54, $C_6H_7O_2$), 97 (59, $C_5H_5O_2$), 77 (91, C_6H_5) and 73 (100, $C_3H_5O_2$) (Found: M^+, 286.0083. $C_{12}H_{14}O_3{}^{80}Se$ requires 286.0106).

The isomer ratio could not be determined very accurately from these data, but was approximately 10:1 in favour of the *trans* isomer [*vide infra*].

In another run, 2 equiv. of benzeneselenenyl chloride were used with ether in place of THF as the solvent and triethylamine (0.5 ml) was added after warming to ambient temperature. The resulting solution was then stirred for 72 h prior to work-up as above and gave an approximately 1:1 mixture of the two isomers in a combined yield of 65%.

(4R,6R)- *and* (4R,6S)-4-*Hydroxy*-6-*methyltetrahydropyran*-2-*one* **18b** and **19b**.—A solution of triphenyltin hydride (1.73 g, 5 mmol) in dry toluene (5 ml) was added to the mixture of seleno lactones **18a** and **19a** (1:1) (0.47 g, 1.6 mmol) obtained by the latter route (prolonged reaction in ether in the presence of triethylamine) and the resulting solution was heated at reflux for 2.5 h. It was then cooled and evaporated under reduced pressure. Careful chromatography over silica gel eluted with ether gave first the (4R,6R)-trans *lactone* **18b** (0.053 g, 25%) as a colourless oil, $[\alpha]_D$ = +23.1° (*c* 1.0; $CHCl_3$); ν_{max}/cm^{-1} 3405 and 1725; δ_H(400 MHz) 1.41 (3 H, d, *J* 6.4, 6-CH_3), 1.72 (1 H, ddd, *J* 14.4, 11.3 and 3.2, 5β-H), 2.00 (1 H, dddd, *J* 14.4, 3.7, 3.1 and 1.6, 5α-H), 2.62 (1 H, ddd, *J* 17.2, 3.6 and 1.6, 3α-H), 2.72 (1 H, dd, *J* 17.2 and 3.6, 3β-H), 2.85 (1 H, br s, OH), 4.38 (1 H, br quin, *J* 3.7, 4β-H) and 4.87 (1 H, ddq, *J* 11.3, 6.4 and 3.1, 6α-H); δ_C 20.4 (CH_3), 36.4 (CH_2), 37.3 (CH_2), 61.5 (CH), 71.9 (CH) and 170.5 (CO); *m/z* 130 (4%, M^+, $C_6H_{10}O_3$), 115 (8, $C_5H_7O_3$, M − CH_3), 97 (6, $C_5H_5O_2$, M − CH_3 and H_2O) and 44 (100, C_2H_4O) (Found: M^+, 130.0627. $C_6H_{10}O_3$ requires 130.0630). Secondly, a mixture of the two isomers was eluted (0.04 g, 19%) with a *trans–cis* ratio of 1:3 and finally the more polar (4R,6S)-

cis *lactone* **19b** (0.046 g, 22%) was eluted as a colourless oil which showed $[\alpha]_D$ −20.7° (*c* 0.92; $CHCl_3$); ν_{max}/cm^{-1} 3409 and 1726; δ_H(400 MHz) 1.41 (3 H, d, *J* 6.2, CH_3), 1.57 (1 H, ddd, *J* 13.8, 11.7 and 9.1, 5β-H), 2.29 (1 H, dddd, *J* 13.8, 5.6, 2.9 and 1.3, 5α-H), 2.45 (1 H, dd, *J* 17.1 and 7.6, 3β-H), 2.87 (1 H, ddd, *J* 17.1, 5.6 and 1.3, 3α-H), 3.57 (1 H, br s, OH), 4.25 (1 H, dddd, *J* 9.1, 7.6, 5.8 and 5.6, 4α-H), and 4.37 (1 H, ddq, *J* 11.7, 6.2 and 3.0, 6α-H); δ_C 21.3 (CH_3), 39.2 (CH_2), 39.3 (CH_2), 63.4 (CH), 74.0 (CH) and 171.8 (CO): *m/z* 130 (10%, M^+, $C_6H_{10}O_3$), 115 (34, $C_5H_7O_3$, M − CH_3), 97 (18, $C_5H_5O_2$, M − CH_3 and H_2O) and 44 (100, C_2H_4O) (Found: M^+, 130.0626).

(6R)-6-*Methyl*-5,6-*dihydro*-2H-*pyran*-2-*one* **22**.—Phosphorus oxychloride (0.056 g, 0.4 mmol) in dry pyridine (1.5 ml) was added to a stirred solution of the (4*R*,6*R*)-*trans*-hydroxy lactone **18b** (0.049 g, 0.4 mmol) in pyridine (0.5 ml) at 0 °C. The resulting solution was stirred without cooling for 15 min and then heated at 65 °C for 50 min. The mixture was cooled, ice was added and the mixture acidified to pH 2 with 2M HCl, saturated with sodium chloride and then continuously extracted with ether for 12 h. The residue obtained after evaporation of the dried ether extract was chromatographed over silica gel using ether–hexanes (2:3) as eluant to give the (R)-*lactone* **22** (0.023 g, 61%) as a colourless oil, $[\alpha]_D$ − 111.5° (*c* 0.87; EtOH), which exhibited spectral data (IR, ^1H and ^{13}C NMR and MS) identical to that displayed by an authentic sample of parasorbic acid **23** isolated from Rowan berries.[35]

(6S)-6-*Methyl*-5,6-*dihydro*-2H-*pyran*-2-*one* (*Parasorbic Acid*) **23**.—In exactly the same manner as in the foregoing reaction, dehydration of the (4*R*,6*S*)-*cis*-hydroxy lactone **19b** (0.032 g, 0.3 mmol) gave the (*S*)-lactone **23** (0.018 g) which showed $[\alpha]_D$ + 98° (*c* 1.8; EtOH) and was otherwise identical to parasorbic acid.[35]

(3R)-3-[*t*-*Butyl*(*dimethyl*)*silyloxy*]*hex*-5-*enoic Acid* **24b**.—Imidazole (4.53 g, 67 mmol) was added to a stirred solution of the *R*-hydroxy acid **17** (1.24 g, 10 mmol) and t-butyldimethylsilyl chloride (3.58 g, 24 mmol) in dry dimethylformamide (25 ml). The solution was stirred at 45 °C for 3 h and then cooled, diluted with pentane (60 ml) and washed with water (3 × 15 ml). The separated organic phase was dried and evaporated to provide the crude silyl ester which showed ν_{max}/cm^{-1} 1717 and 1639; δ_H 0.04 (6 H, s, 2 × CH_3), 0.24 (6 H, s, 2 × CH_3), 0.86 (9 H, s, $C(CH_3)_3$), 0.90 [9 H, s, $C(CH_3)_3$], 2.16–2.64 (4 H, m, 2 × CH_2), 4.19 [1 H, quin, *J* 5.4, C*H*(OH)], 4.93–5.25 (2 H, m, CH_2CH) and 5.50–6.12 (1 H, m, CH_2CH).

The crude ester was dissolved in a mixture of methanol (100 ml) and THF (35 ml) and treated with a solution of potassium carbonate (3.29 g) in water (35 ml). After 1 h at ambient temperature, the mixture was concentrated under reduced pressure, cooled to 0 °C, acidified to pH 4 with 1M aqueous potassium hydrogen sulphate and extracted with ether (3 × 40 ml). The combined extracts were washed with saturated brine and then dried and evaporated. Chromatography of the residue over silica gel eluted with ether–hexanes (1:5) then gave the *acid* **24b** (1.71 g, 74%) as a colourless oil, $[\alpha]_D$ − 19.6° (*c* 1.2; $CHCl_3$); ν_{max}/cm^{-1} 2692, 1710, and 1641; δ_H 0.01 (3 H, s, SiMe), 0.03 (3 H, s, SiMe), 0.84 (9 H, s, $C(CH_3)_3$], 2.15–2.57 (4 H, m, 2 × CH_2), 4.15 [1 H, quin, *J* 5.4, CH(OSi)], 4.91–5.20 (2 H, m, CH_2CH) and 5.42–6.02 (1 H, m, CH_2CH): *m/z* 203 (13%, $C_9H_{19}O_3Si$, M − C_3H_5), 187 (31, $C_8H_{15}O_3Si$, M − C_4H_9), 115 (33, $C_6H_{15}Si$), 101 (27, C_4H_9OSi), 75 (100, C_2H_7OSi) and 73 (57, C_3H_9Si) (Found: M^+ − C_3H_5, 203.1104. $C_9H_{19}O_3Si$ requires 203.1102).

(3R)-3-[*t*-*Butyl*(*diphenyl*)*silyloxy*]*hex*-5-*enoic Acid* **24c**.—This compound was prepared in exactly the same manner as the foregoing method by silylation of the hydroxy acid **17** (0.57 g, 4 mmol) using t-butyldiphenylsilyl chloride (3.02 g, 11 mmol) and imidazole (2.10 g, 31 mmol) in dimethylformamide (15 ml). Subsequent saponification of the resulting silyl ester (1.50 g) using potassium carbonate in methanol (24 ml), water (8 ml) and THF (8 ml) then gave the *acid* **24c** (0.41 g, 51%) as a colourless oil, $[\alpha]_D$ −20.7° (*c* 1.0; $CHCl_3$); ν_{max}/cm^{-1} 1713, 1632 and 1589; δ_H 1.01 [9 H, s, $C(CH_3)_3$], 2.20 (2 H, br t, *J ca.* 6.3, $CHCH_2$), 2.41 (2 H, d, *J* 6.3), 4.19 [1 H, quin, *J* 6.3, CH(OSi)], 4.77–5.07 (2 H, m, CH_2CH), 5.36–5.91 (1 H, m, CH_2CH), 7.23–7.48 (6 H, m, aryl CH), 7.57–7.85 (4 H, m, aryl CH) and 11.44 (1 H, br s, CO_2H); *m/z* 311 (25%, $C_{18}H_{19}O_3Si$, M − C_4H_9), 269 (15, $C_{15}H_{13}O_3Si$, M − C_4H_9 and C_3H_6), 199 (100, $C_{12}H_{11}OSi$) (Found: M^+ − C_4H_9, 311.1082. $C_{18}H_{19}O_3Si$ requires M, 311.1093).

Methyl (3R)-3-[*Triisopropylsilyloxy*]*hex*-5-*enoate*.—Imidazole (3.71 g, 55 mmol) was added to a stirred solution of triisopropylsilyl chloride (5.05 g, 22 mmol) and the hydroxy ester **15b** (3.14 g, 22 mmol) in dimethylformamide (6 ml). The resulting solution was stirred at ambient temperature for 48 h and then worked up as in the foregoing reaction to give, after chromatography over silica gel eluted with ether–hexanes (1:20), the corresponding *silyl ether* (5.67 g, 87%) as a colourless oil, $[\alpha]_D$ −23.9° (*c* 1.3; $CHCl_3$); ν_{max}/cm^{-1} 1739 and 1646; δ_H 0.68 (21 H, br s, 6 × CH_3CH and 3 × CH_3CH), 1.86–2.20 (4 H, m, 2 × CH_2), 3.28 (3 H, s, OCH_3), 3.99 [1 H, p, *J* 6.3, CH(OSi)], 4.55–4.86 (2 H, m, CH_2CH) and 5.26–5.70 (1 H, m, CH_2CH), *m/z* 257 (85%, $C_{13}H_{25}O_3Si$, M − C_3H_7), 145 (100, $C_7H_{17}OSi$), 117 (22, $C_5H_{13}OSi$) and 89 (21, C_3H_9OSi) (Found: M^+ − C_3H_7, 257.1568. $C_{13}H_{25}O_3Si$ requires M, 257.1570).

(3R)-3-(*Triisopropylsilyloxy*)*hex*-5-*enoic Acid* **24d**.—A solution of potassium hydroxide (0.19 g, 3.4 mmol) in methanol (5 ml) was added to the foregoing ester (0.52 g, 1.7 mmol) and the resulting solution stirred at ambient temperature for 20 h and then diluted with water (15 ml) and washed with ether. The aqueous solution was then acidified to pH 2 using 2M HCl and extracted with ether (3 × 15 ml). The combined extracts were dried and evaporated. Chromatography of the residue over silica gel eluted with ether–hexanes (1:10) gave the *acid* **24d** (0.36 g, 74%) as a colourless oil, $[\alpha]_D$ −12.0° (*c* 0.97: $CHCl_3$); ν_{max}/cm^{-1} 1723 and 1640, δ_H 0.82 (21 H, br s, 6 × CH_3CH and 3 × CH_3CH), 2.13–2.50 (4 H, m, 2 × CH_2), 4.13 (1 H, quin, *J* 6.3, CHOSi), 4.84–5.16 (2 H, m, CH_2CH), 5.50–6.05 (1 H, m, CH_2CH), and 9.70 (1 H, br s, CO_2H); *m/z* 243 (85%, $C_{12}H_{23}O_3Si$, M − C_3H_7), 131 (100, $C_6H_{15}OSi$), 103 (39, $C_4H_{11}OSi$) and 75 (55, C_2H_7OSi) (Found: M^+ − C_3H_7, 243.1397. $C_{12}H_{23}O_3Si$, requires M, 243.1415).

Unchanged methyl ester (0.10 g, 19%) was also isolated.

(4RS,6SR)- *and* (4RS,6RS)-trans- *and* cis-4-*Hydroxy*-6-*iodomethyltetrahydropyran*-2-*one* **25a** *and* **26a**.—Anhydrous sodium hydrogen carbonate (0.95 g, 11 mmol) was added to a stirred solution of a racemic sample of the hydroxy acid **17** (0.049 g, 0.4 mmol) in dry acetonitrile at 0 °C. After 5 min, iodine (0.29 g, 1.1 mmol) was added and the resulting mixture stirred for a further 3 h. It was then diluted with ether (40 ml) and washed with 10% aqueous sodium thiosulphate, until the excess of iodine was removed, and water (1 × 15 ml). The separated organic solution was dried and evaporated to leave the *iodo lactones* **25a** and **26a** (0.022 g, 23%) as an unstable red oil. NMR spectral data indicated an isomer ratio of 3:1 in favour of the *trans* isomer, but the material was too unstable to permit further purification and/or isomer separation. The sample showed ν_{max}/cm^{-1} 3397 and 1729 and *m/z* 256 (2%, M^+, $C_6H_9IO_3$), 129 (7, $C_6H_9O_3$, M − I), 127 (3, I), 115 (5, $C_5H_7O_3$, M − CH_2I), 111 (42, $C_6H_7O_2$, M − H_2O and I), 58 (29, C_3H_6O) and 43 (100,

C_2H_3O) (Found: M^+ 255.9599. $C_6H_9O_3I$ requires M, 255.9597). The major *trans* isomer **25a** exhibited δ_H(250 MHz) 1.77 (ddd, *J* 14.2, 11.2 and 2.4, 5-H_{ax}), 2.13 (br d, *J ca.* 14.2, 5-H_{eq}), 2.62 (apparent d, *J* 3.6, 3-CH_2), 3.32 (dd, *J* 10.8 and 4.4, CH_aH_bI), 3.38 (dd, *J* 10.8 and 5.6, CH_aH_bI), 4.37 (br quin, *J ca.* 3.3, 4-H_{eq}), and 4.59 (dddd, *J* 11.2, 5.6, 4.4 and *ca.* 3.0, 6-H_{ax}) and δ_C 8.6, 35.8, 38.2, 62.4, 74.1 and 169.9. The minor *cis* isomer **26a** showed δ_H 1.66 (ddd, *J* 13.6, 10.8 and 9.7, 5-H_{ax}), *ca.* 2.42 (obscured, m, 5-H_{eq}), 2.44 (dd, *J* 17.2 and 7.7, 3-H), 2.83 (dd, *J* 17.2 and 5.7, 3-H), *ca.* 3.33 (m, CH_2I and OH), 4.18 (m, 6-H_{ax}) and 4.26 (m, 4-H_{ax}): δ_C 6.4, 37.6, 39.1, 63.2, 75.8 and 170.0.

(4R,6S)-trans-4-[*t-Butyl(dimethyl)silyloxy*]-6-*iodomethyltetrahydropyran-2-one* **25b**.—Anhydrous sodium hydrogen carbonate (1.23 g, 15 mmol) was added to a stirred solution of the acid **24b** (0.12 g, 0.5 mmol) in dry acetonitrile (1.6 ml) cooled in an ice-bath. After 5 min, iodine (0.37 g, 1.5 mmol) was added and the mixture stirred for a further 4 h. It was then worked up as described in the foregoing experiment to give a 3:1 mixture of the trans and cis *lactones* **25b** and **26b** (0.15 g, 84%). Fractional crystallization from pentane then gave the pure *trans isomer* **25b** (0.06 g) as colourless needles, m.p. 55–57 °C, $[\alpha]_D$ −10.3° (*c* 2.1; $CHCl_3$); ν_{max}/cm^{-1} 1740; δ_H 0.09 (6 H, s, 2 × $SiCH_3$), 0.88 [9 H, s, $C(CH_3)_3$], 1.75 (1 H, ddd, *J* 13.9, 11.4 and 2.3, 5-H_{ax}), 2.09 (1 H, dddd, *J* 13.9, 4.2, 3.7 and 1.6 Hz, 5-H_{eq}), 2.58 (2 H, d, *J* 3.2, 3-CH_2), 3.39 (2 H, d, *J* 4.8, CH_2I), 4.33 (1 H, br quin, *J ca.* 3.3, 4-H_{eq}) and 4.58 (1 H, ddt, *J* 11.4, 4.8 and 3.7, 6-H_{ax}); δ_C −4.9, 8.8, 17.9, 25.8, 36.4, 38.8, 63.2, 74.1 and 169.2; *m/z* 313 (8%, $C_8H_{14}IO_3Si$, M − C_4H_9), 271 (13, $C_6H_{12}IO_2Si$, M − C_4H_9 and CH_2CO), 145 (57, $C_5H_9O_3Si$) and 101 (100, C_4H_9OSi) (Found: C, 39.2; H, 6.5. $C_{12}H_{23}IO_3Si$ requires C, 38.9; H, 6.3%).

The *cis* isomer **26b** showed the following NMR data: δ_H 0.09 (s, $SiCH_3$), 0.88 [s, $C(CH_3)_3$], 1.70 (m, 5-H), 2.32 (m, 5-H), 2.44 (m, 3-H), 2.77 (m, 3-H), 3.39 (d, *J* 4.8, CH_2I), 4.16–4.25 (m, 4- and 6-H); δ_C −4.8, 7.3, 17.9, 25.8, 37.8, 39.7, 64.0, 75.6 and 169.4.

(4R,6S)-trans- *and* (4R,6R)-cis-4-[*t-Butyl(diphenyl)silyloxy*]-6-*iodomethyltetrahydropyran-2-one* **25c** *and* **26c**.—Using the foregoing procedure, iodolactonization of the (*R*)-t-butyl-(diphenyl)silyloxy acid **24c** (0.16 g, 0.44 mmol) afforded an inseparable mixture of the *lactones* **25c** and **26c** (0.20 g, 87%) in a *trans–cis* ratio of 4:1, as a pale yellow oil, ν_{max}/cm^{-1} 1741 and 1580: δ_H(400 MHz) 0.97 [9 H, s, $C(CH_3)_3$], 1.49 (0.8 H, ddd, *J* 13.8, 11.6 and 2.0, *trans*-5-H_{ax}), 1.67 (0.2 H, ddd, *J* 13.6, 10.9 and 8.9, *cis*-5-H_{ax}), 1.95 (0.8 H, dddd, *J* 13.8, *ca* 5.2, 2.9 and *ca.* 1.5, *trans*-5-H_{eq}), 2.12 (0.2 H, m, *cis*-5-H_{eq}), 2.31 (0.8 H, dd, *J* 17.6 and 4.0, *trans*-3-H_{ax}), 2.39 (0.2 H, dd, *J* 17.2 and 7.6 Hz, *cis*-3-H_{ax}), 2.48 (0.8 H, ddd, *J* 17.6, 3.1 and *ca.* 1.5, *trans*-3-H_{eq}), 2.54 (0.2 H, ddd, *J* 17.2, 5.6 and *ca.* 1.5, *cis*-3-H_{eq}), 3.17 (0.4 H, m, *cis* CH_2I), 3.23 (1.6 H, d, *J* 5.2, *trans* CH_2I), 3.87 (0.2 H, m, *cis*-4-H_{ax}), 4.07 (0.2 H, m, *cis*-6-H_{ax}), 4.21 (0.8 H, m, *trans*-4-H_{eq}), 4.63 (0.8 H, dtd, *J* 11.6, 5.2 and 2.9, *trans*-6-H_{ax}), 7.21 (6 H, m) and 7.51–7.60 (4 H, m); δ_C(c = *cis*; t = *trans*) 7.2 (c), 8.5 (t), 18.8 (c), 18.9 (t), 26.7 (c), 26.8 (t), 35.8 (t), 37.7 (c), 38.4 (t), 39.2 (c), 64.1 (t), 64.7 (c), 74.2 (t), 75.1 (c), 127.8 (c + t), 130.0 (c + t), 132.7 (c + t), 135.4 (c + t), 168.8 (t) and 169.1 (c); *m/z* 437 (9%, $C_{18}H_{18}IO_3Si$, M − C_4H_9), 395 (6, $C_{16}H_{16}IO_2Si$), 313 (5, $C_{18}H_{21}O_3Si$), 269 (8, $C_{15}H_{13}O_3Si$), 225 (100, $C_{14}H_{13}OSi$) and 199 (71, $C_{12}H_{11}OSi$) (Found: M^+ − C_4H_9, 437.0082. $C_{18}H_{18}IO_3Si$ requires M, 437.0072).

(4R,6S)-trans- *and* (4R,6R)-cis-4-(*Triisopropylsilyloxy*)-6-*iodomethyltetrahydropyran-2-one* **25d** *and* **26d**.—In exactly the same manner as above, iodolactonization of the (*R*)-triisopropylsilyloxy acid **24d** (0.111 g, 0.388 mmol) gave the *lactones* **25d** and **26d** as an oil (0.13 g, 81%) in a *trans–cis* isomer ratio of 5.5:1 which were inseparable by column chromatography; the mixture showed ν_{max}/cm^{-1} 1743; δ_H(400 MHz) 1.06 [18 H, d, *J* 3.8, 3 × $(CH_3)_2CH$], *ca.* 1.08 [3 H, m, 3 × $(CH_3)_2CH$], *ca.* 1.64 (0.15 H, m, *cis*-5-H_{ax}), 1.78 (0.85 H, ddd, *J* 14.0, 11.4 and 2.3, *trans*-5-H_{ax}), 2.20 (0.85 H, dddd, *J* 14.0, 3.9, 3.3 and 1.4, *trans*-5-H_{eq}), 2.43 (0.15 H, dddd, *J* 13.3, 4.6, 3.0 and 1.5, *cis*-5-H_{eq}), 2.52 (0.15 H, dd, *J* 17.2 and 7.9, *cis*-3-H_{ax}), 2.64 (0.85 H, dd, *J* 17.6 and 3.9, *trans*-3-H_{ax}), 2.66 (0.85 H, ddd, *J* 17.6, 3.4 and 1.4, *trans*-3-H_{eq}), 2.87 (0.15 H, ddd, *J* 17.2, 5.7 and 1.5, *cis*-3-H_{eq}), *ca.* 3.38 (0.30 H, m, *cis*-CH_2I), 3.41 (1.7 H, d, *J* 5.1, *trans*-CH_2I), 4.21 (0.15 H, m, *cis*-6-H_{ax}), 4.31 (0.15 H, m, *cis*-4-H_{ax}), 4.46 (0.85 H, m, *trans*-4-H_{eq}) and 4.64 (0.85 H, dtd, *J* 11.4, 5.1 and 3.3, *trans*-6-H_{ax}); δ_C 7.0 (c), 8.5 (t), 12.0 (t), 12.3 (c), 17.7 (c), 18.0 (t), 36.7 (t), 38.5 (c), 39.1 (t), 40.0 (c), 63.5 (t), 64.4 (c), 74.1 (t), 75.6 (c), 169.2 (t) and 169.5 (c); *m/z* 327 (9%, $C_{10}H_{20}IO_2Si$, M − C_3H_7 and CH_2CO), 201 (43, $C_9H_{17}O_3Si$), 157 (100, $C_8H_{17}OSi$) and 129 (30, $C_6H_{13}OSi$) (Found: M^+ − C_3H_7 and CH_2CO, 327.0277. $C_{10}H_{20}IO_2Si$ requires 327.0279).

(4RS,6RS)-trans-6-(*But-3-enyl*)-4-*hydroxytetrahydropyran-2-one* **27b**.—A solution of allyltributyltin (0.48 g, 1.1 mmol) in dry toluene (2 ml) was added to the iodo lactones **25b** and **26b** (0.27 g, 0.73 mmol, *trans–cis* ratio 3:1). The solution was stirred for 5 min then azoisobutyronitrile (AIBN) (0.018 g) was added and the resulting solution heated to 80 °C for 16 h. The cooled reaction mixture was evaporated and the residue chromatographed on silica gel using ether–hexanes (1:5) as the eluant to give the intermediate alkylated lactone **27a** (0.062 g) which showed ν_{max}/cm^{-1} 1737 and 1641; δ_H 0.09 (6 H, s, 2 × CH_3), 0.96 [9 H, s, $C(CH_3)_3$], 1.20–2.08 (4 H, m, 2 × CH_2), 2.20–2.57 (2 H, m, $CHCH_2$), 2.74 (2 H, apparent d, *J* 4.3, 3-CH_2), 4.56 (1 H, quin, *J* 3.6, 4-H), 4.83–5.16 (1 H, m, 6-H), 5.19–5.52 (2 H, m, CH_2CH), and 5.91–6.44 (1 H, m, CH_2CH).

The foregoing silyl ether was dissolved in acetonitrile (2 ml), the solution cooled to 0 °C and treated with aqueous hydrogen fluoride (40%; 1 ml). After 4 h at this temperature, the solution was concentrated under reduced pressure and the residue partitioned between chloroform (10 ml) and water (5 ml). The separated organic layer was washed with water (2 × 5 ml) and then dried and evaporated. Chromatography of the residue over silica gel eluted with ether afforded the trans *lactone* **27b** (0.029 g, 31% overall), as an oil, ν_{max}/cm^{-1} 3410, 1725 and 1642; δ_H(400 mmHg) 1.58–1.90 (3 H, m, 1-CH_2 and 5-H_{ax}), 2.07 (1 H, dddd, *J* 14.5, 3.5, 3.2 and 1.6, 5-H_{eq}), 2.12–2.37 (2 H, m, $CHCH_2$), 2.58 (1 H, ddd, *J* 17.7, 3.7 and 1.6, 3-H_{eq}), 2.73 (1 H, dd, *J* 17.7 and 4.7, 3-H_{ax}), *ca.* 2.74 (1 H, br s, OH), 4.38 (1 H, br quin, *J ca.* 3.8, 4-H_{eq}), 4.73 (1 H, dddd, *J* 11.4, 7.7, 4.9 and 3.2, 6-H_{ax}), 5.01 (1 H, ddt, *J* 10.3, 1.7 and *ca.* 1.1, CH_cH_tCH), 5.07 (1 H, apparent dq, *J* 17.0 and 1.7, CH_cH_tCH) and 5.82 (1 H, ddd, *J* 17.0, 10.3 and 6.6, CH_cH_tCH); δ_C 28.0, 33.7, 34.9, 37.6, 61.6, 74.3, 114.5, 136.3 and 169.8; *m/z* 152 (8%, $C_9H_{12}O_2$, M − H_2O), 128 (30, $C_6H_8O_3$), 115 (43, $C_5H_7O_3$), 97 (48, $C_5H_5O_2$) 92 (92, C_7H_8) and 73 (100, $C_3H_5O_2$) (Found: M^+ − H_2O, 152.0833. $C_9H_{12}O_2$ requires M, 152.0836).

(4RS,6RS,2′E)-trans-6-(3′-*Phenylprop-2′-enyl*)-4-*hydroxytetrahydropyran-2-one* **28b**.—A solution of β-stannylstyrene[44] (0.42 g, 1.1 mmol) in dry toluene (1.0 ml) was added to the iodo lactones **25b** and **26b** (0.2 g, 0.54 mmol, *trans–cis* ratio 3:1) followed by AIBN (0.014 g). The resulting solution was stirred at 80 °C; after 12 h, a further aliquot of AIBN was added. This procedure was continued for 72 h and then further aliquots were added every 24 h for 96 h. After a total of 168 h, the solution was cooled and evaporated. The crude silyl ether **28a** (0.11 g) was isolated by rapid filtration of the residue through silica gel eluted with ether–hexanes (1:5).

The crude silyl ether **28a** (0.11 g) was dissolved in acetonitrile (3 ml), cooled to 0 °C and treated with aqueous hydrogen fluoride (40%; 1.5 ml). After 3 h at this temperature, the solvent was evaporated and the residue partitioned between chloroform

(25 ml) and water (10 ml). The separated organic layer was washed with water (1 × 10 ml) and then dried and evaporated. Chromatography of the residue over silica gel using ether as the eluant then gave the trans *lactone* **28b** (0.033 g, 35% overall) as an oil, ν_{max}/cm^{-1} 3405, 1720 and 1598: δ_H(400 MHz) 1.75 (1 H, ddd, *J* 14.4, 11.5 and 3.1, 5-H_{ax}), 2.00 (1 H, dddd, *J* 14.4, 3.6, 3.1, and 1.4, 5-H_{eq}), 2.60 (5 H, m, 3- and 1′-CH_2 and OH), 4.36 (1 H, br quin, *J* 3.7, 4-H_{eq}), 4.84 (1 H, dtd, *J* 11.5, 6.0 and 3.1, 6-H_{ax}), 6.21 (1 H, dt, *J* 15.9 and 7.2, 2′-H), 6.51 (1 H, d, *J* 15.9, 3′-H), and 7.10–7.37 (5 H, Ph); δ_C 35.2, 38.6, 38.8, 62.6, 75.5, 123.8, 126.2, 127.5, 128.3, 137.0, 137.7 and 170.6; *m/z* 214 (9%, $C_{14}H_{14}O_2$, M − H_2O), 117 (33, C_9H_9) and 97 (100, $C_5H_5O_2$) (Found: M^+ − H_2O, 214.1006, $C_{14}H_{14}O_2$ requires M, 214.0999).

Methyl (3R,5S)-3-[*t-Butyl(dimethyl)silyloxy*]-5,6-*epoxyhexanoate* **29a**.—Anhydrous sodium carbonate (0.075 g, 0.75 mmol) was added to a stirred solution of the iodo lactone **25b** (0.24 g, 0.6 mmol) in methanol (7.5 ml). The resulting mixture was stirred in the dark for 16 h at ambient temperature and then evaporated and the residue partitioned between ether (40 ml) and water (10 ml). The separated organic phase was dried and evaporated. Chromatography of the residue over silica gel eluted with ether–hexanes (1:3) then gave the *epoxy ester* **29a** (0.153 g, 93%) as a colourless oil, $[\alpha]_D$ −23.2° (*c* 1.0; $CHCl_3$): ν_{max}/cm^{-1} 1736; δ_H(400 MHz) 0.07 (3 H, s, $SiCH_3$), 0.08 (3 H, s, $SiCH_3$), 0.88 [9 H, s, $C(CH_3)_3$], 1.69 (1 H, ddd, *J* 14.3, 6.9 and 4.8, 4-H_aH_b), 1.82 (1 H, ddd, *J* 14.3, 5.6 and 4.7, 4-H_aH_b), 2.47 (1 H, dd, *J* 5.0 and 2.7, 6-H_aH_b), 2.56 (1 H, dd, *J* 15.0 and 5.6, 2-H_aH_b), 2.63 (1 H, dd, *J* 15.0 and 7.3, 2-H_aH_b), 2.77 (1 H, dd, *J* 5.0 and 4.2, 6-H_aH_b), 3.08 (1 H, ddt, *J* 6.9, *ca.* 4.4 and 2.7, 5-H), 3.68 (3 H, s, OCH_3) and 4.37 (1 H, ddt, *J* 7.3, 5.6 and 4.8, 3-H); δ_C −4.9, −4.6, 18.0, 25.8, 40.3, 42.3, 46.5, 48.9, 51.6, 67.6 and 172.0; *m/z* 243 (3%, $C_{12}H_{23}O_3Si$, M − OCH_3), 217 (25, $C_9H_{17}O_4Si$, M − C_4H_9), 185 (18, $C_9H_{13}O_3Si$, M − CH_3OH and C_4H_9), 161 (30, $C_6H_{13}O_3Si$), 157 (24, $C_7H_{13}O_2Si$), 143 (58, $C_6H_{11}O_2Si$), 115 (51, $C_5H_{11}OSi$), 89 (67, C_3H_9OSi) and 75 (100, C_2H_7OSi) (Found: M^+ − C_4H_9, 217.0889. $C_9H_{17}O_4Si$ requires 217.0895) (Found: C, 56.7; H, 9.7. $C_{13}H_{26}O_4Si$ requires C, 56.9; H, 9.6%).

If the reaction was terminated after a shorter period, according to the length of time varying amounts of the intermediate iodohydrin could be isolated using the same chromatographic system as above. The iodohydrin showed ν_{max}/cm^{-1} 3463 and 1738; δ_H 0.10 (3 H, s, $SiCH_3$), 0.12 (3 H, s, $SiCH_3$), 0.92 [9 H, s, $C(CH_3)_3$], 175—1.96 (2 H, m, 4-CH_2), 2.61 (2 H, d, *J* 7.2, 2-CH_2), 2.87 (1 H, br s, OH), 3.27–3.49 (3 H, m, CH_2I and 5-H), 3.75 (3 H, s, OCH_3) and 4.41 (1 H, quin, *J* 6.8, 3-H); *m/z* 345 (1%, $C_9H_{18}IO_4Si$, M − C_4H_9), 271 (18, $C_6H_{12}IO_2Si$), 253 (28, $C_7H_{10}IO_2$), 145 (72, $C_5H_9O_3Si$) and 101 (100, C_4H_9OSi) (Found: M^+ − C_4H_9, 345.0032. $C_{19}H_{18}IO_4Si$ requires M, 345.0021).

Methyl (3R,5S)- *and* (3R,5R)-3-[*Triisopropylsilyloxy*]-5,6-*epoxyhexanoate* **29b**.—Using exactly the same method as in the foregoing reaction, treatment of the iodo lactones **25d** and **26d** (*trans–cis* 5.5:1) (0.10 g, 0.24 mmol) with sodium carbonate (0.028 g, 0.27 mmol) in methanol (3.5 ml) gave the *epoxy esters* **29b** (0.064 g, 85%) as a colourless oil, ν_{max}/cm^{-1} 1738; δ_H (400 MHz) 1.05 [0.45 H, m, *anti*-$(CH_3)_2CH$], 1.06 [2.55 H, m, *syn*-$(CH_3)_2CH$], 1.066 [15.3 H, br s, *anti*-$(CH_3)_2CH$], 1.073 [2.7 H, br s, *syn*-$CH_3)_2CH$], 1.69 (0.85 H, ddd, *J* 14.3, 7.2 and 4.0, *syn*-4-H_aH_b), 1.73–1.85 (0.3 H, m, *anti*-4-CH_2), 1.94 (0.85 H, ddd, *J* 14.3, 6.1 and 4.3 Hz, *syn*-4-H_aH_b), 2.47 (0.85 H, dd, *J* 5.1 and 2.7, *syn*-6-H_aH_b), 2.49 (0.15 H, dd, *J* 5.1 and 2.7, *anti*-6-H_aH_b), 2.60–2.73 (0.3 H, m, *anti*-2-CH_2), 2.67 (1.7 H, apparent t, *J* 6.3, *syn*-2-CH_2), 2.76 (0.85 H, dd, *J* 5.0 and 4.1, *syn*-6-H_aH_b), 2.79 (0.15 H, dd, *J* 5.0 and 4.1 Hz, *anti*-6-H_aH_b), 3.05 (0.15 H, dddd, *J* 6.6, 5.1, 4.0 and 2.6, *anti*-5-H), 3.11 (0.85 H, dtd, *J* 7.2, 4.1 and 2.7, *syn*-5-H), 3.67 (3 H, *syn* and *anti* OCH_3) and 4.47–4.54 (1 H, m, *syn* and *anti*-3-H); δ_C 12.5 (*syn*), 12.6 (*anti*), 17.7 (*syn*), 18.1 (*anti*), 40.2 (*syn*), 40.7 (*anti*), 41.9 (*syn*), 42.9 (*anti*), 46.5 (*syn*), 47.3 (*anti*), 48.7 (*syn*), 49.1 (*anti*), 51.5 (*syn* and *anti*) OCH_3), 67.6 (*anti*), 68.0 (*syn*), 171.7 (*anti*) and 171.9 (*syn*); *m/z* 273 (60%, $C_{13}H_{25}O_4Si$, M − C_3H_7), 217 (64, $C_{10}H_{21}O_3Si$), 199 (24, $C_{10}H_{19}O_2Si$), 171 (53, $C_9H_{19}OSi$), and 75 (100, C_2H_7OSi) (Found: M^+ − C_3H_7, 273.1521. $C_{13}H_{25}O_4Si$ requires M, 273.1522).

Acknowledgements

We are grateful to Rhone-Poulenc (Dagenham) and the SERC for financial support through the CASE award scheme. We are grateful to Professor L. Crombie for a generous supply of natural parasorbic acid **23**.

References

1 A. G. Brown, T. C. Smale, T. J. King, R. Hasenkamp and R. H. Thompson, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1165; A. Endo, M. Kuroda and M. Tsujita, *J. Antibiot.*, 1976, **29**, 1346.

2 A. W. Alberts, J. Chen, G. Kuron, V. Hunt, J. Huff, C. Hoffman, J. Rothrock, M. Lopez, H. Joshua, E. Harris, A. Patchett, R. Monaghan, S. Currie, E. Stapley, G. Albers-Schonberg, O. Hensens, J. Hirshfield, K. Hoogsteen, J. Liesch and J. Springer, *Proc. Natl. Acad. Sci.*, 1980, **77**, 3957; A. Endo, *J. Antibiot.*, 1979, **32**, 852.

3 These include 3,4-dihydrocompactin: Y. K. Lam, V. P. Gullo, R. T. Goegelman, D. Jorn, L. Huang, C. De Riso, R. L. Monaghan and I Putter, *J. Antibiot.*, 1981, **34**, 614; 3,4-dihydromevinolin: G. Albers-Shonberg, H. Joshua, M. B. Lopez, O. D. Hensens, J. P. Springer, J. Chen, S. Ostrove, C. H. Hoffman, A. W. Alberts and A. A. Patchett, 1981, **34**, 507; monacolins J and L; A. Endo, K. Hasumi and S. Negishi, 1985, **38**, 420; monacolin M: A. Endo, D. Komagata and H. Shimada, 1986, **39**, 1670; monacolin X and several dihydromonacolins: A. Endo, K. Hasumi, T. Nakamura, M. Kunishima and M. Masuda, 1985, **38**, 321.

4 For reviews, see A. Endo, *J. Med. Chem.*, 1985, **28**, 401 and L. Vega and S. Grundy, *J. Am. Med. Assoc.*, 1987, **257**, 33. For an example of a β-lactone which is an HMGCoA reductase inhibitor, see Y-C. P. Chiang, S. S. Yang, J. V. Heck, J. C. Chabala and M. N. Chang, *J. Org. Chem.*, 1989, **54**, 5708, and references therein.

5 For some earlier examples of such inhibitors, see F. M. Singer, J. P. Januszka and A. Barman, *Proc. Soc. Exper. Biol. Med.*, 1959, **102**, 270; F. H. Hulcher, *Arch. Biochem. Biophys.*, 1971, **146**, 422.

6 For a comprehensive review of mevinic acid syntheses, see T. Rosen and C. H. Heathcock, *Tetrahedron*, 1986, **42**, 4909. For some recent synthetic studies, see D. L. J. Clive, K. S. Keshava Murthy, A. G. H. Wee, J. S. Prasad, G. V. J. Da Silva, M. Majewski, P. C. Anderson, R. D. Haugen and L. D. Heerze, *J. Am. Chem. Soc.*, 1988, **110**, 6914; S. D. Burke, K. Takeuchi, C. W. Murtiashaw and D. W. M. Liang, *Tetrahedron Lett.*, 1989, **30**, 6299; A. E. DeCamp, T. R. Verhoeven and I. Shinkai, *J. Org. Chem.*, 1989, **54**, 3207.

7 T. Rosen, M. J. Taschner and C. H. Heathcock, *J. Org. Chem.*, 1984, **49**, 3994.

8 J. D. Prugh and A. A. Deana, *Tetrahedron Lett.*, 1982, **23**, 281; C. David, J. P. Gesson and J. C. Jacquesy, 1989, **30**, 6015.

9 M. Majewski, D. L. J. Clive and P. C. Anderson, *Tetrahedron Lett.*, 1984, **25**, 2101.

10 A. H. Davidson, C. D. Floyd, C. N. Lewis and P. L. Myers, *J. Chem. Soc., Chem. Commun.*, 1988, 1417.

11 A. P. Kozikowski and C-S. Li, *J. Org. Chem.*, 1985, **50**, 778.

12 S. Danishefsky, S. Kobayashi and J. F. Kerwin, jr., *J. Org. Chem.*, 1982, **47**, 1981; Y-L. Yang and J. R. Falk, *Tetrahedron Lett.*, 1982, **23**, 4305.

13 I. Fleming, N. L. Reddy, K. Takaki and A. C. Ware, *J. Chem. Soc., Chem. Commun.*, 1987, 1472; J. D. Prugh and A. A. Deana, *Tetrahedron Lett.*, 1988, **29**, 37; K. Prasad and O. Repic, 1984, **25**, 2435.

14 A. Sato, A. Ogiso, H. Noguchi, S. Mitsui, I. Kaneko and Y. Shimada, *Chem. Pharm. Bull.*, 1980, **28**, 1509.

15 Y. Guindon, C. Yoakin, M. A. Bernstein and H. E. Morton, *Tetrahedron Lett.*, 1985, **26**, 1185; B. D. Roth and W. H. Roark, 1988, **29**, 1255.

16 T. Rosen and C. H. Heathcock, *J. Am. Chem. Soc.*, 1985, **107**, 3731; J. E. Lynch, R. P. Volante, R. V. Wattley and I. Shinkai, *Tetrahedron Lett.*, 1987, **28**, 1385; W. S. Johnson, A. B. Kelson and J. D. Elliott,

1988, **29**, 3757. For a review of some aspects of this type of chemistry, see T. Oishi and T. Nakata, *Acc. Chem. Res.*, 1984, **17**, 338.
17 K. Prasad and O. Repic, *Tetrahedron Lett.*, 1984, **25**, 3391; F. Bonadies, R. Di Fabio, A. Gubbiotti, S. Mecozzi and C. Bonini, 1987, **28**, 703.
18 G. E. Stokker, W. F. Hoffman, A. W. Alberts, E. J. Cragoe, Jr., A. A. Deana, J. L. Gilfilan, J. W. Huff, F. C. Novello, J. D. Prugh, R. L. Smith and A. K. Willard, *J. Med. Chem.*, 1985, **28**, 347; W. F. Hoffman, A. W. Alberts, E. J. Cragoe, Jr., A. A. Deana, B. E. Evans, J. L. Gilfilan, N. P. Gould, J. W. Huff, F. C. Novello, J. D. Prugh, K. E. Rittle, R. L. Smith, G. E. Stokker and A. K. Willard, 1986, **29**, 159.
19 G. E. Stokker, A. W. Alberts, P. S. Anderson, E. J. Cragoe, Jr., A. A. Deana, J. L. Gilfilan, J. Hirshfield, W. J. Holtz, W. F. Hoffman, J. W. Huff, T. J. Lee, F. C. Novello, J. D. Prugh, C. S. Rooney, R. L. Smith and A. K. Willard, *J. Med. Chem.*, 1986, **29**, 170.
20 E. Baader, W. Bartmann, G. Beck, A. Bergmann, H.-W. Fehlhaber, H. Jendralla, K. Kesseler, R. Saric, H. Schussler, V. Teetz, M. Weber and G. Wess, *Tetrahedron Lett.*, 1988, **29**, 2563.
21 For a preliminary report, see F. Bennett, D. W. Knight and G. Fenton, *Tetrahedron Lett.*, 1988, **29**, 4865.
22 P. Mohr, L. Rosslein and C. Tamm, *Helv. Chim. Acta*, 1987, **70**, 142.
23 R. Roy and A. W. Rey, *Tetrahedron Lett.*, 1987, **28**, 4935.
24 C. R. Johnson and C. H. Senanayake, *J. Org. Chem.*, 1989, **54**, 735.
25 G. W. Anderson, I. F. Halvstadt, W. H. Miller and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, 1945, **67**, 2197, and references therein.
26 H. Hamana and T. Sugasawa, *Chem. Lett.*, 1985, 921.
27 For some recent reviews, see C. J. Sih and C. S. Chen, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 570; S. Butt and S. M. Roberts, *Nat. Prod. Rep.*, 1986, **3**, 489; S. Servi, *Synthesis*, 1990, 1.
28 D. Seebach, M. A. Sutter, R. H. Weber and M. F. Zuger, *Org. Synth.*, 1985, **63**, 1, and references therein.
29 J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.
30 K. Nakamura, K. Inoue, K. Ushio, S. Oka and A. Ohno, *Chem. Lett.*, 1987, 679.
31 M. Hirama, M. Shimizu and M. Iwashita, *J. Chem. Soc., Chem. Commun.*, 1983, 599; K. Hayakawa, F. Nogatsugi and K. Kanematsu, *J. Org. Chem.*, 1988, **53**, 860.
32 A. Manzocchi, R. Casati, A. Fiecchi and E. Santaniello, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2753.
33 K. C. Nicolaou and Z. Lysenko, *J. Am. Chem. Soc.*, 1977, **99**, 3185.
34 D. L. J. Clive, G. Chittattu and C. K. Wong, *J. Chem. Soc., Chem. Commun.*, 1978, 41.
35 R. Kuhn and K. Kum, *Chem. Ber.*, 1962, **95**, 2009; R. Lukes, J. Jary and J. Nemec, *Coll. Czech. Chem. Commun.*, 1962, 735; *Chimica (Switz.)*, 1959, **13**, 336; L. Crombie and P. A. Firth, *J. Chem. Soc. C*, 1968, 2852.
36 A similarly low value ($[\alpha]_D$ +126.3°) has recently been recorded for the optical rotation of parasorbic acid **23**, although the value was obtained in chloroform rather than in ethanol; see G. Procter, A. T. Russell, P. J. Murphy, T. S. Tan and A. N. Mather, *Tetrahedron*, 1988, **44**, 3953. See also A. T. Russell and G. Procter, *Tetrahedron Lett.*, 1987, **28**, 2041.
37 F. Bennett and D. W. Knight, *Tetrahedron Lett.*, 1988, **29**, 4625.
38 P. A. Bartlett, D. P. Richardson and J. Myerson, *Tetrahedron*, 1984, **40**, 2317
39 F. Bennett, D. W. Knight and G. Fenton, *Heterocycles*, 1989, **29**, 639.
40 G. E. Keck and J. B. Yates, *J. Am. Chem. Soc.*, 1982, **104**, 5829.
41 J. E. Baldwin and D. R. Kelly, *J. Chem. Soc., Chem. Commun.*, 1985, 682.
42 P. A. Bartlett and J. Myerson, *J. Org. Chem.*, 1979, **44**, 1625.
43 C. D. Buttery, A. G. Cameron, C. P. Dell and D. W. Knight, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1601.
44 M. L. Saihi and M. Pereye, *Bull. Soc. Chim. Fr.*, 1977, 1251.

Paper 0/03303K
Received 23*rd July* 1990
Accepted 20*th August* 1990