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DIVISION DE NUEVAS CREACIONES

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Re: Expediente No. 02.111.163

Solicitud de patente a nombre de

AstraZeneca UK Ltd.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 94-76, Of. 305, obrando como apoderada de la sociedad AstraZeneca UK Ltd., domiciliada en Stanhope Gate, Londres, Gran Bretaña, solicitante de la patente de la referencia, en respuesta al oficio No. 2374 notificado por fijación en lista el 16 de febrero de 2007, relacionado con el concepto técnico No. 0211, me permito acompañar los siguientes documentos solicitados por el examinador:

- JUN-ICHI SAKAKI: "LIPASE CATALYSED ASYMETRIC SYNTHESIS OF 6-(3-CHLORO-2-HYDROXYPROPYL)-1,3-DIOXIN-4-ONES"
TETRAHEDRON: ASYMETRY, vol.2, No. 5, 1991, páginas 343-6
XP002178271
ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM,
NL
ISSN:0957-4166
- F. BENNETT ET AL: "METHYL (3R)-3-HYDROXYHEX-5-ENOATE"
JOURNAL OF THE CHEMICAL SOCIETY, PERKIN
TRANSACTIONS 1.
Vol 1, 1991, páginas 133-140, XP002178272
CHEMICAL SOCIETY, LETCHWORTH, GB
ISSN: 1472-7781

Espero con esto haber dado cabal cumplimiento a lo solicitado por ese despacho y de conformidad con lo indicado en los artículos 3º, inciso 3, 35 inciso 2 y 59 inciso 2 del CCA, al analizar este memorial, atentamente solicito se traten todas las cuestiones planteadas con motivo del mismo.

Señor Superintendente,


JIMENA ESCOBAR URIBE

C.C. 39.779.452 de Usaquen

T.P. 68.228

Cod. 5376

EUA/ra.

Lipase-catalyzed Asymmetric Synthesis of 6-(3-Chloro-2-hydroxypropyl)-1,3-dioxin-4-ones and Their Conversion to Chiral 5,6-Epoxyhexanoates¹

Jun-ichi Sakaki,* Hiroko Sakoda, Yoshiaki Sugita,
Masayuki Sato, and Chikara Kaneko

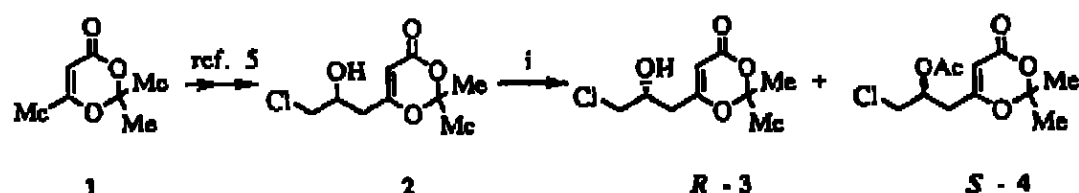
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(Received 20 March 1991)

Abstract: Highly enantioselective syntheses of (*R*)- and (*S*)-6-(3-chloro-2-hydroxypropyl)-1,3-dioxin-4-ones by means of lipase-catalyzed kinetic resolutions are described. Chiral dioxinones thus obtained have been converted to optically active 5,6-epoxyhexanoates, which are important precursors for a series of biologically active compounds.

During recent years enzyme-catalyzed asymmetric synthesis has been well recognized as one of the most effective methods for the synthesis of chiral building blocks.² Previously, we reported that prochiral methyl ketones having 4-oxo-1,3-dioxin-6-yl group as the terminal unit were enantioselectively reduced by baker's yeast.³ The same reduction if applied to the higher methylene homologs (RCO: R≠Me), however, gave poor chemical and optical yields. For the purpose of creating more versatile chiral synthons, we have been interested in the lipase-catalyzed asymmetric synthesis of (*R*)- and/or (*S*)-6-(3-chloro-2-hydroxypropyl)-1,3-dioxin-4-ones (*R*-3, *S*-3). Since the dioxinones are known as the manipulatable synthons in a variety of ways under mild conditions,⁴ chiral ones if obtained as EPC can be converted to optically active 5,6-epoxyhexanoates: the precursors either of chiral 6-substituted δ -lactones or of 4-hydroxy δ -lactones.

According to the two-step procedure elaborated recently by us,⁵ racemic chloroalcohol (2) was prepared from 2,2,6-trimethyldioxinone (1). After some preliminary screening to find the suitable enzyme for asymmetric transesterification of 2 in vinyl acetate, Amano PS (*Pseudomonas* sp.) was found to be the best choice.⁶

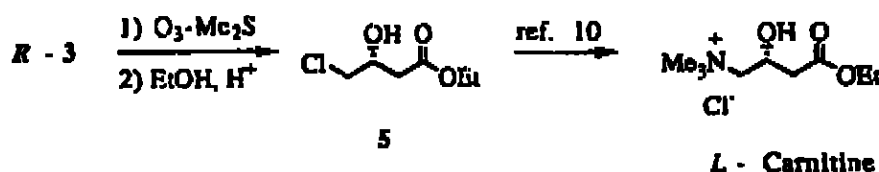


Conditions: i) Amano PS, vinyl acetate, 28 °C, 7 d.

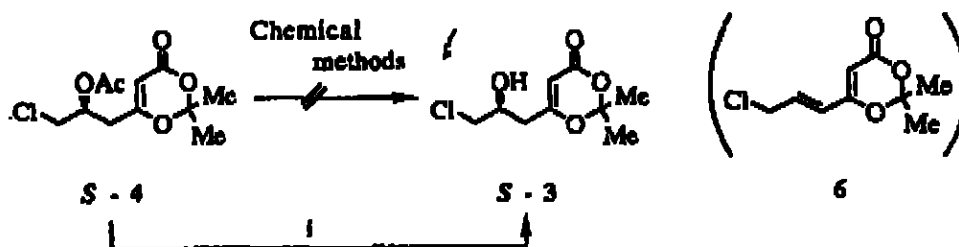
Scheme 1

Both isomers (*R*-3, *S*-4)⁷ were obtained in quantitative chemical yields with high enantiomeric excesses ($\geq 98\%$ e.e.).⁸

The absolute configuration of chiral chloroalcohol [*R*-3: $[\alpha]_D^{20} +19.3$ (c 1.67, CHCl_3)] thus obtained was determined by conversion to ethyl (*R*)-4-chloro-3-hydroxybutanoate (5)⁹ (degradation of a dioxinone ring by ozonolysis followed by acid mediated esterification), which was synthesized previously by Sih *et al.* as the key intermediate of *L*-carnitine (Scheme 2).¹⁰ Attempted hydrolysis of the acetylated product [*S*-4: $[\alpha]_D^{20} +0.12$ (c 1.20, CHCl_3)] in basic medium failed to give the desired alcohol and the deacetylated product (6) was obtained as the major product, irrespective of the reaction conditions (e.g. $\text{K}_2\text{CO}_3/\text{MeOH}$, $2N$ NaOH/ether , etc.). It has been found, however, that enzyme-mediated hydrolysis of *S*-4 by lipase MY (Meito, *Candida cylindracea* nov. sp.) proceeded smoothly to give the antipode (*S*-3) in 83% chemical yield with $\geq 98\%$ e.e.



Scheme 2

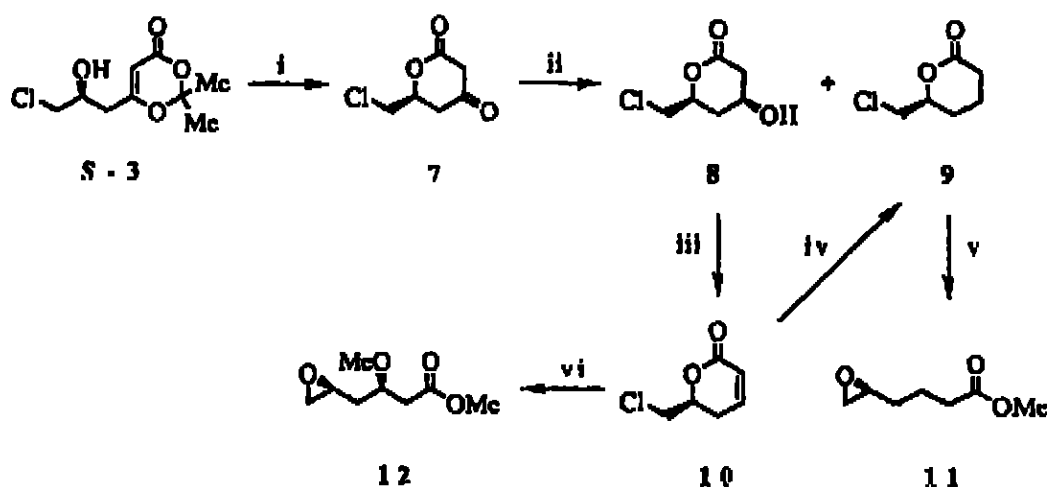


Conditions: i) Lipase MY, 0.1M pH 7.2 phosphate buffer, 28 °C, 4 d

Scheme 3

5,6-Epoxyhexanoates are known as efficient precursors for 6-substituted δ -lactone derivatives which are fairly common units among natural products and in a variety of biologically active molecules.¹¹ Thus 5,6-epoxyhexanoate derivatives (11, 12) were prepared from the corresponding chiral chloroalcohol (*S*-3). Following one-

pot lactonization reaction developed in our laboratory,¹² 6-chloromethyl- β -keto- δ -lactone (7: mp 98-99 °C, $[\alpha]_D^{25}$ -83.4 (c 1.07, MeOH)) was prepared from S-3 in 84% yield. Catalytic hydrogenation of keto lactone (7) over PtO₂ gave *cis*-4-hydroxy lactone (8: $[\alpha]_D^{20}$ +13.3 (c 1.25, CHCl₃)) and its deoxy derivative (9: $[\alpha]_D^{30}$ -0.77 (c 1.03, CHCl₃)) in 73% and 20% yields, respectively. The latter lactone (9) was also prepared by two-step procedure¹³ (acid-catalyzed dehydration followed by catalytic hydrogenation over 10% Pd-C) from 8 via unsaturated lactone (10: $[\alpha]_D^{23}$ -144.8 (c 3.09, CHCl₃)) in satisfactory overall yield. When saturated lactone (9) was treated with K₂CO₃ in MeOH at room temperature, epoxyster (11: $[\alpha]_D^{24}$ -15.7 (c 1.94, CHCl₃); lit.¹¹ $[\alpha]_D^{23}$ -16.2 (c 0.58, CHCl₃)) was obtained directly in 79% yield. The reaction proceeded obviously by methoxide mediated lactone ring opening followed by formation of epoxide ring. Nishida *et al.* has demonstrated that this epoxide (11) can be used as the common precursor for a variety of optically active 6-substituted δ -lactones.¹¹ Finally, methyl (3*R*, 5*S*)-5,6-epoxy-3-hydroxyhexanoate (12),¹⁴ which is the important precursor¹⁵ for compactin or mevinolin (HMG-CoA reductase inhibitor), has been synthesized as a sole product from unsaturated lactone (10) by treatment with sodium methoxide in methanol.¹⁶



Conditions: i) K₂CO₃, MeOH, room temp., 84%; ii) H₂, PtO₂, AcOEt, 1 atm, 7 h; iii) *p*-TsOH, benzene, Δ , 1.5 h, 88%; iv) H₂, Pd-C, MeOH, 30 min, 90%; v) K₂CO₃, MeOH, room temp., 5 h, 79%; vi) NaOMe, MeOH, -50 °C - room temp., 49%

Scheme 4

In summary, successful use of lipase to the readily available chloroalcohol (2) provided highly enantioselective route to the versatile synthons [(*R*)- and (*S*)-6-(3-chloro-2-hydroxypropyl)-1,3-dioxin-4-ones] which were efficiently converted to chiral 5,6-epoxyhexanoates.

References and Notes

1. Synthesis of 1,3-Dioxin-4-ones and Their Use in Synthesis. XXX. XXIX: M Sato, Y. Abe, H. Ohuchi, and C. Kaneko, *Heterocycles*, **31**, 2115 (1990).
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3. J. Sakaki, M. Suzuki, S. Kobayashi, M. Sato, and C. Kaneko, *Chemistry Lett.*, 1990, 901.
4. C. Kaneko, M. Sato, J. Sakaki, and Y. Abe, *J. Heterocycl. Chem.*, **27**, 25 (1990).
5. J. Sakaki, Y. Sugita, M. Sato, and C. Kaneko, *J. Chem. Soc., Chem. Commun.*, in press.
6. The reaction was monitored by HPLC analysis. When the integrals due to alcohol (*R*-3) and acetate (*S*-4) became almost equal, the reaction was terminated.
7. All new compounds exhibited satisfactory spectroscopic (NMR, IR) and combustion or high-resolution mass spectral analytical data.
8. Determined by HPLC analysis using chiral columns [3: Chiralcell OD, 4: Chiralcell OJ (Daicel)].
9. 5: $[\alpha]_D^{26} +21.1^\circ$ (c 3.11, CHCl₃), *S*-Isomer (55% a.c.); lit.¹⁰ $[\alpha]_D^{23} -11.7^\circ$ (c 0.75, CHCl₃).
10. B. Zhou, A. S. Gopalan, F. VanMiddlesworth, W.-R. Shieh, and C. J. Sih, *J. Am. Chem. Soc.*, **105**, 5925 (1983).
11. F. Nishida, Y. Mori, N. Rokkaku, S. Isobe, T. Furuse, M. Suzuki, V. Meevootisom, T. W. Flegel, Y. Thebtaranonth, and S. Intararungsorn, *Chem. Pharm. Bull.*, **38**, 2381 (1990).
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13. M. Sato, J. Sakaki, Y. Sugita, T. Nakano, and C. Kaneko, *Tetrahedron Lett.*, **31**, 7463 (1990).
14. 12: $[\alpha]_D^{24} -19.1^\circ$ (c 3.55, CHCl₃). IR (CHCl₃): 1735 cm⁻¹. 500 MHz-¹H-NMR (CDCl₃) δ : 1.70-1.77 (1H, m, C₄-H), 1.84-1.91 (1H, m, C₄-H), 2.50 (1H, dd, *J*=3.8, 2.4 Hz, C₂-H), 2.55 (1H, dd, *J*=15.6, 5.8 Hz, C₆-H), 2.68 (1H, dd, *J*=15.6, 7.7 Hz, C₆-H), 2.78 (1H, t, 3.8 Hz, C₂-H), 3.01-3.07 (1H, m, C₃-H), 3.38 (3H, s, CO₂Me), 3.71 (3H, s, OMe), 3.82-3.89 (1H, m, C₃-H).
15. B. D. Roth and W. H. Roark, *Tetrahedron Lett.*, **29**, 1255 (1988).
16. When this reaction was carried out at higher temperature (-5°--10 °C), the diastereomeric excess (d.e.) lowered to 33%.

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

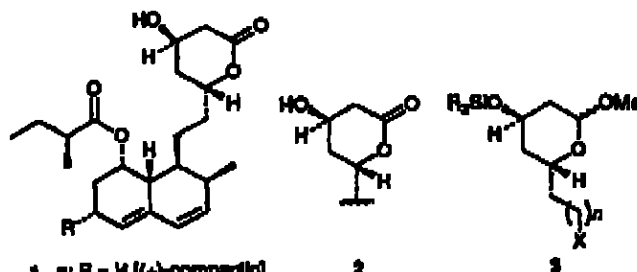
Frank Bennett,^a David W. Knight^{a,*} and Garry Fenton^b

^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 (5*S*)-(+) -parasorbic acid 23.

The ability of the mevinic acids, most notably compactin 1a¹ and mevinolin 1b² 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

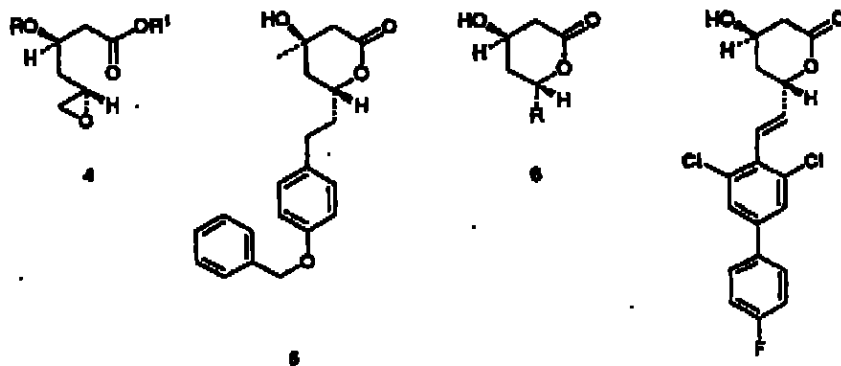


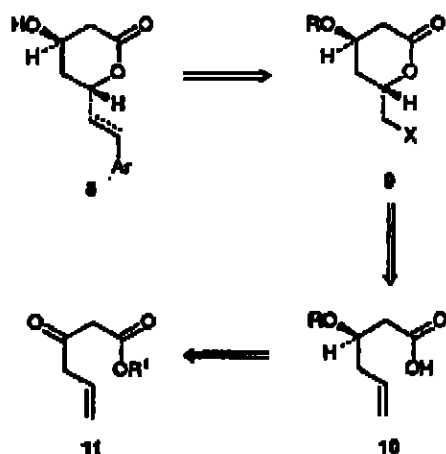
intermediate in the terpenoid biosynthetic pathway leading to cholesterol. The compounds act as potent inhibitors of the pathway by blocking a major rate-limiting enzyme, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCoA reductase) which is responsible for the conversion of HMGCoA into mevalonic 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 intermediate has often been obtained by carbohydrate degrad-

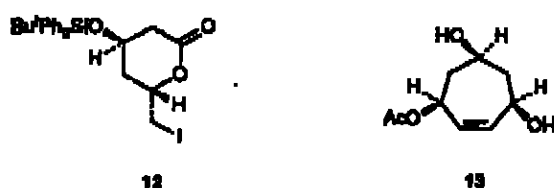
ation^{7,8} as well as from L-malic acid,⁹ (5*S*)-4-hydroxymethylbutyrolactone,¹⁰ and from an asymmetric [1,3]-dipolar cycloaddition.¹¹ Chiral as well as racemic material has been obtained using a Diels-Alder reaction as the key step¹² as well as by other approaches.^{6,13,14} Other viable intermediates are the chiral epoxy esters 4 which have been obtained from a variety of precursors¹⁵ and which undergo extremely efficient couplings with aryl cuprate reagents leading directly to mevinic acid analogues. Alternative open-chain precursors, based on β-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 (5*E*)-arylethonyl,¹⁴ 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.¹⁸ 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 5 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





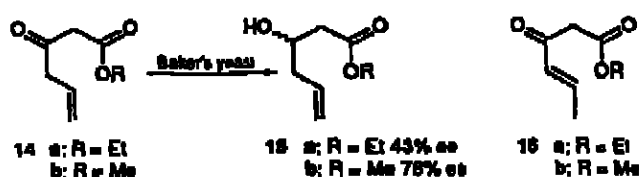
viability of these lactones in such syntheses has been emphasised by alternative approaches which were reported²⁰ prior to the completion of our studies.²¹ Thus, the optically pure



iodolactone 12 was prepared from α -D-glucose in 17 steps whereas its (4S,6R)-enantiomer with 70% enantiomeric enrichment was obtained from acetonedihydroxybutyric 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 α -cyano 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

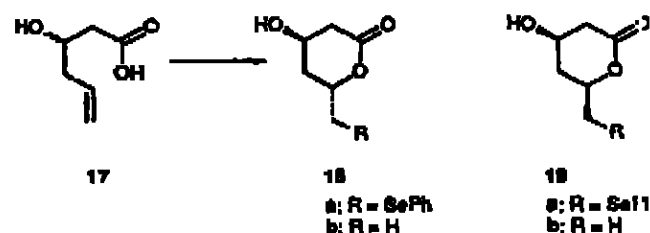


ethyl 14a and methyl 14b esters were prepared in this way and both could be isolated as pure regioisomers by vacuum distillation below 70°C. Above this temperature, both compounds displayed a marked tendency to isomerize to the conjugated hex-4-enoate isomers 16. An alternative and more efficient approach to these esters is by the procedure of Hamana and Sugawara²⁶ in which the same cyanoacetates are

condensed with allyltrimethylsilane in the presence of boron trichloride. However, this more expensive procedure was not 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 yeast²⁷ 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 key 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 derivatives²⁹ 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.^{27,30} Attempts to increase the enantioselectivity of the yeast reduction by the addition of allyl alcohol,³⁰ by reduction of the corresponding carboxylate salt³¹ or by changes to the concentration or reactant ratios³² were not successful. Our samples of the hydroxy ester 15b (78% ee) showed $[\alpha]_D^{25} -23.5^\circ$ (c 1.1; CHCl₃). 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.³³ These authors quote $[\alpha]_D^{25} -12.6^\circ$ (c 1; CHCl₃) 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 fractional crystallization effect, we cannot offer an explanation for this discrepancy.

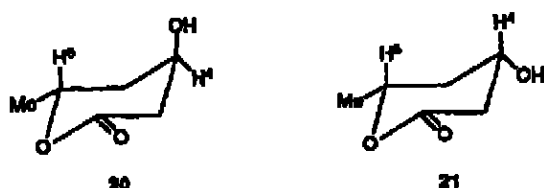
The absolute configuration of the major enantiomer of the hydroxy ester 15b was determined during our first investigation into ways to convert the hydroxy esters 15 into mevinic acid analogues. Hydrolysis of the ester 15b led to the hydroxy acid 17, $[\alpha]_D^{25} -27.3^\circ$ (c 1.0; CHCl₃) which, upon selenolactonization under kinetic conditions³⁴ gave a ca 10:1 mixture of the selenolactones 18a and 19a but in only a modest 40% yield. In



contrast, selenolactonization using thermodynamic conditions gave an improved 65% isolated yield of the same lactones, but a ratio of 1:1. The relative stereochemistries of these lactones were determined by reductive removal of the seleno group using triphenyltin hydride³⁴ prior to separation of the resulting methyl-substituted lactones 18b and 19b by column chromatography. The less polar isomer exhibited resonances: δ 4.38 (br quin, J/Hz: 3.7) and at δ 4.87 (ddq, J/Hz: 11.3, 6.4, 1.1).

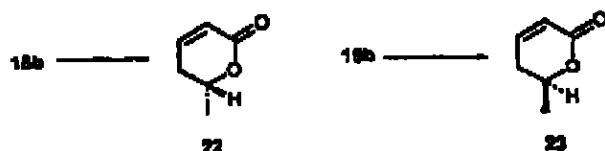
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3.1) which were assigned to the 4-H and 6-H, respectively, on the basis of appropriate decoupling and COSY experiments. On the reasonable assumption that the larger methyl group will adopt an equatorial position, this is the *trans* isomer 18b which 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



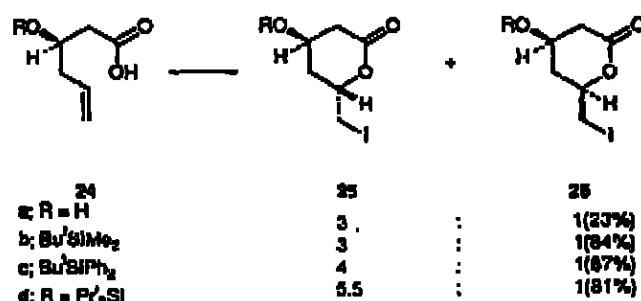
19b which exists in the conformation 21, in which both the 4- and 6-protons are in axial positions. The downfield shift of the 6-H resonance in the *trans* isomer ($\Delta\delta$ 0.5 ppm) is also consistent with a [1,3]-diaxial relationship between this proton and the 4-hydroxy group.

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 $+206^\circ$ (c 1; EtOH) and the (6*S*)-configuration 23.³¹ 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 $[\alpha]_D$ $+98^\circ$ (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



from our samples were $\pm 159^\circ$, based on the maximum value of the natural compound ($+206^\circ$) 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 conditions³⁸ 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 allyl 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 allyl ether function resulted in higher

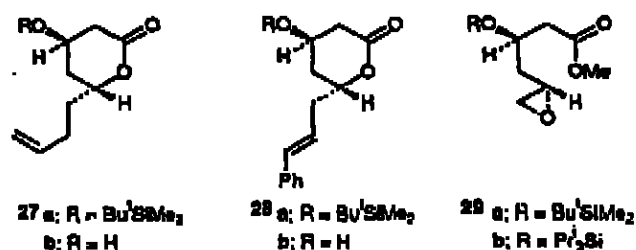


Scheme 1

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.³⁹ 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.³¹ 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, treatment of the stereochemical mixture of lactones 25b and 26b with allyltributylstannane (AIBN, toluene, 80 $^\circ$ C, 16 h)⁴⁰ followed by column chromatography gave an isomerically pure sample of the *trans*-butenyl lactone 27a. A similar coupling⁴¹ 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 yields 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



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-workers²² 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 $\text{C}_7\text{H}_{10}\text{O}_3$: 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 Sugawara.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%). $[\alpha]_{\text{D}}^{25} -23.5^\circ$ (c 1.1; CHCl_3) [$[\alpha]_{\text{D}}^{25} -12.6^\circ$ (c 1.3; CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ 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%, $\text{C}_7\text{H}_{11}\text{O}_2$, M – OH), 126 (16, M – H_2O), 103 (30, $\text{C}_6\text{H}_9\text{O}_2$, M – C_2H_5), 85 (100, $\text{C}_5\text{H}_7\text{O}$, M – CO_2CH_3) and 67 (73, C_4H_7 , M – CO_2CH_3 and H_2O) (Found: M⁺ – C_7H_9 , 103.0389. Calc. for $\text{C}_7\text{H}_{12}\text{O}_3$: 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 esters²⁹ (0.043 g, 66%) as a yellow oil. $\nu_{\text{max}}/\text{cm}^{-1}$ 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_{HF} 1.0, (R)- OCF_3], 3.54 [0.66 H, q, J_{HF} ca. 1.0, (S)- OCF_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* 183 (100%, $\text{C}_{10}\text{H}_8\text{F}_3\text{O}_3$), 127 (21, $\text{C}_7\text{H}_{11}\text{O}_2$) 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, $[\alpha]_{\text{D}}^{25} -27.3^\circ$ (c 1.0; CHCl_3) or $[\alpha]_{\text{D}}^{25} -26.5^\circ$ (c 2.1; CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ 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, OH and CO_2H); *m/z* 112 (5%, $\text{C}_6\text{H}_8\text{O}_2$, M – H_2O), 89 (94, $\text{C}_5\text{H}_8\text{O}$, M – C_2H_5) and 71 (100, $\text{C}_3\text{H}_3\text{O}_2$) (Found: M⁺ – C_3H_5 , 89.0245. $\text{C}_5\text{H}_8\text{O}$ 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-phenylselenomethyl tetrahydropyran-2-one 18a and 19a.—Benzene-selenenyl 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 0.7 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 (0.11 g, 42%) as a colourless oil, $\nu_{\text{max}}/\text{cm}^{-1}$ 3400 and 1725; δ_{H} 1.57–2.51 (2 H, m), 2.64 (2 H, apparent d, *J* 4.05, 3- CH_2), 2.97–3.31 (2 H, m, PbSeCH_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⁺, $\text{C}_{12}\text{H}_{14}\text{O}_3^{80}\text{Se}$), 171 (34, $\text{C}_7\text{H}_7^{80}\text{Se}$), 158 (47, $\text{C}_6\text{H}_6^{80}\text{Se}$), 111 (54, $\text{C}_6\text{H}_7\text{O}_2$), 97 (59, $\text{C}_5\text{H}_5\text{O}_2$), 77 (91, C_4H_6) and 73 (100, $\text{C}_3\text{H}_5\text{O}_2$) (Found: M⁺, 286.0083. $\text{C}_{12}\text{H}_{14}\text{O}_3^{80}\text{Se}$ 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 benzene-selenenyl 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, 1 mmol) in dry toluene (5 ml) was added to the mixture of selenolactones 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, $[\alpha]_{\text{D}}^{25} +23.1^\circ$ (c 1.0; CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ 3405 and 1725; δ_{H} (400 MHz) 1.41 (3 H, d, *J* 6.4, 6- CH_3), 1.72 (1 F, 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, ddd, *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⁺, $\text{C}_6\text{H}_{10}\text{O}_3$), 115 (8, $\text{C}_5\text{H}_9\text{O}_2$, M – CH_3), 97 (6, $\text{C}_5\text{H}_8\text{O}_2$, M – CH_3 and H_2O) and 44 (100, $\text{C}_2\text{H}_4\text{O}$) (Found: M⁺, 130.0627. $\text{C}_6\text{H}_{10}\text{O}_3$ 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 $[\alpha]_D^{20} -20.7^\circ$ (c 0.92; CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ 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, 5 β -H), 2.29 (1 H, dddd, J 13.8, 5.6, 2.9 and 1.3, 5 α -H), 2.45 (1 H, dd, J 17.1 and 7.6, 3 β -H), 2.87 (1 H, ddd, J 17.1, 5.6 and 1.3, 3 α -H), 3.57 (1 H, br s, OH), 4.25 (1 H, dddd, J 9.1, 7.6, 5.8 and 5.6, 4 α -H), and 4.37 (1 H, ddq, J 11.7, 6.2 and 3.0, 6 α -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^+ , $\text{C}_6\text{H}_{10}\text{O}_3$), 115 (34, $\text{C}_5\text{H}_9\text{O}_3$), $\text{M} - \text{CH}_3$), 97 (18, $\text{C}_5\text{H}_9\text{O}_3$, $\text{M} - \text{CH}_3$ and H_2O) and 44 (100, $\text{C}_2\text{H}_4\text{O}$) (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 (4R,6R)-*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 eluent to give the (R)-lactone 22 (0.023 g, 61%) as a colourless oil, $[\alpha]_D^{20} -111.5^\circ$ (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.²⁵

(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 (4R,6S)-*cis*-hydroxy lactone 19b (0.032 g, 0.3 mmol) gave the (S)-lactone 23 (0.018 g) which showed $[\alpha]_D^{20} +98^\circ$ (c 1.8; EtOH) and was otherwise identical to parasorbic acid.²⁵

(3R)-3-[*t*-Butyldimethylsilyloxy]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 $\times$ 15 ml). The separated organic phase was dried and evaporated to provide the crude silyl ester which showed $\nu_{\text{max}}/\text{cm}^{-1}$ 1717 and 1639; δ_{H} 0.04 (6 H, s, 2 $\times$ CH_3), 0.24 (6 H, s, 2 $\times$ CH_3), 0.86 (9 H, s, $\text{C}(\text{CH}_3)_3$), 0.90 [9 H, s, $\text{C}(\text{CH}_3)_3$], 2.16–2.64 (4 H, m, 2 $\times$ CH_2), 4.19 [1 H, quin, J 5.4, $\text{CH}(\text{OH})$], 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 $\times$ 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, $[\alpha]_D^{20} -19.6^\circ$ (c 1.2; CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ 2692, 1710, and 1641; δ_{H} 0.01 (3 H, s, SiMe), 0.03 (3 H, s, SiMe), 0.84 (9 H, s, $\text{C}(\text{CH}_3)_3$), 2.15–2.57 (4 H, m, 2 $\times$ CH_2), 4.15 [1 H, quin, J 5.4, $\text{CH}(\text{OSi})$], 4.91–5.20 (2 H, m, CH_2CH) and 5.42–6.02 (1 H, m, CH_2CH); m/z 203 (13%, $\text{C}_9\text{H}_{19}\text{O}_3\text{Si}$, $\text{M} - \text{C}_3\text{H}_7$), 187 (31, $\text{C}_8\text{H}_{17}\text{O}_3\text{Si}$, $\text{M} - \text{C}_4\text{H}_9$), 115 (33, $\text{C}_6\text{H}_{15}\text{O}_3\text{Si}$), 101 (27, $\text{C}_6\text{H}_{15}\text{OSi}$), 75 (100, $\text{C}_2\text{H}_5\text{OSi}$) and 73 (57, $\text{C}_2\text{H}_5\text{Si}$) (Found: M^+ - C_3H_7 , 203.1104. $\text{C}_9\text{H}_{19}\text{O}_3\text{Si}$ requires 203.1102).

(3R)-3-[*t*-Butyldiphenylsilyloxy]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, $[\alpha]_D^{20} -20.7^\circ$ (c 1.0; CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ 1713, 1632 and 1589; δ_{H} 1.01 [9 H, s, $\text{C}(\text{CH}_3)_3$], 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, $\text{CH}(\text{OSi})$], 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%, $\text{C}_{19}\text{H}_{27}\text{O}_3\text{Si}$, $\text{M} - \text{C}_4\text{H}_9$), 269 (15, $\text{C}_{18}\text{H}_{25}\text{O}_3\text{Si}$, $\text{M} - \text{C}_4\text{H}_9$ and C_2H_5), 199 (100, $\text{C}_{12}\text{H}_{11}\text{OSi}$) (Found: M^+ - C_4H_9 , 311.1082. $\text{C}_{19}\text{H}_{27}\text{O}_3\text{Si}$ requires M , 311.1093).

Methyl (3R)-3-[Trisopropylsilyloxy]hex-5-enoate.—Imidazole (3.71 g, 55 mmol) was added to a stirred solution of trisopropylsilyl chloride (5.05 g, 22 mmol) and the hydroxy ester 15h (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, $[\alpha]_D^{20} -23.9^\circ$ (c 1.3; CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ 1739 and 1646; δ_{H} 0.68 (21 H, br s, 6 $\times$ CH_2CH and 3 $\times$ CH_2CH), 1.86–2.20 (4 H, m, 2 $\times$ CH_2), 3.28 (3 H, s, OCH_3), 3.99 [1 H, p, J 6.3, $\text{CH}(\text{OSi})$], 4.55–4.86 (2 H, m, CH_2CH) and 5.26–5.70 (1 H, m, CH_2CH); m/z 257 (85%, $\text{C}_{15}\text{H}_{29}\text{O}_3\text{Si}$, $\text{M} - \text{C}_2\text{H}_5$), 145 (100, $\text{C}_7\text{H}_{17}\text{OSi}$), 117 (22, $\text{C}_6\text{H}_{15}\text{OSi}$) and 89 (21, $\text{C}_2\text{H}_5\text{OSi}$) (Found: M^+ - C_2H_5 , 257.1568. $\text{C}_{15}\text{H}_{29}\text{O}_3\text{Si}$ requires M , 257.1570).

(3R)-3-(Trisopropylsilyloxy)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 $\times$ 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, $[\alpha]_D^{20} -12.0^\circ$ (c 0.97; CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ 1723 and 1640; δ_{H} 0.82 (21 H, br s, 6 $\times$ CH_2CH and 3 $\times$ CH_2CH), 2.13–2.50 (4 H, m, 2 $\times$ 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%, $\text{C}_{15}\text{H}_{27}\text{O}_3\text{Si}$, $\text{M} - \text{C}_2\text{H}_5$), 131 (100, $\text{C}_6\text{H}_{13}\text{OSi}$), 103 (39, $\text{C}_6\text{H}_{11}\text{OSi}$) and 75 (55, $\text{C}_2\text{H}_5\text{OSi}$) (Found: M^+ - C_2H_5 , 243.1397. $\text{C}_{15}\text{H}_{27}\text{O}_3\text{Si}$ 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-iodo-methyltetrahydropyran-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 $\times$ 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 $\nu_{\text{max}}/\text{cm}^{-1}$ 3397 and 1729 and m/z 256 (2%, M^+ , $\text{C}_6\text{H}_9\text{IO}_3$), 129 (7, $\text{C}_6\text{H}_9\text{O}_3$, $\text{M} - \text{I}$), 127 (3, 1), 115 (5, $\text{C}_5\text{H}_7\text{I}$), $\text{M} - \text{CH}_2\text{I}$), 111 (42, $\text{C}_6\text{H}_7\text{O}_3$, $\text{M} - \text{H}_2\text{O}$ and I), 58 (29, $\text{C}_2\text{H}_4\text{O}$) and 43 (100).

$C_9H_{10}O$ (Found: M^+ 255.9599. $C_9H_{10}O$ 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_2H_2), 3.38 (dd, J 10.8 and 5.6, CH_2H_2), 4.37 (br quin, J ca. 3.3, 4- H_{ax}), 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}), 2.45 (dd, J 17.2 and 7.7, 3- H_{ax}), 2.81 (dd, J 17.2 and 7.7, 3- H_{eq}), 3.39 (d, J 4.8, CH_2), 4.16 (m, 4- and 6- H); δ_C 6.4, 37.6, 39.1, 63.2, 75.8 and 170.0.

(4R,6S)-*trans*-4-[(*t*-Butyldimethyl)silyloxy]-6-iodomethyl-tetrahydropyran-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, $[\alpha]_D^{20}$ –10.3° (c 2.1; $CHCl_3$); ν_{max}/cm^{-1} 1740; δ_H 0.09 (6 H, s, $2 \times SiCH_3$), 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}), 2.98 (2 H, d, J 3.2, 3- CH_2), 3.39 (2 H, d, J 4.8, CH_2), 4.33 (1 H, br quin, J ca. 3.3, 4- H_{ax}) 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%, $C_9H_{14}IO_2Si$, $M - C_4H_9$), 271 (13, $C_9H_{13}IO_2Si$, $M - C_4H_9$ and CH_2CO), 145 (57, $C_9H_9O_2Si$) and 101 (100, C_4H_9OSi) (Found: C , 39.2; H , 6.5. $C_{14}H_{21}IO_2Si$ 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_2), 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*-Butyldiphenyl)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_2), 3.23 (1.6 H, d, J 5.2, *trans* CH_2), 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_{ax}), 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%, $C_{18}H_{24}IO_2Si$, $M - C_6H_5$), 395 (6, $C_{18}H_{23}IO_2Si$), 313 (5, $C_{17}H_{21}IO_2Si$), 269 (8, $C_{17}H_{20}IO_2Si$), 225 (100, $C_{16}H_{19}OSi$) and 199 (71, $C_{12}H_{11}OSi$) (Found: M^+ – C_6H_5 , 437.0082. $C_{18}H_{24}IO_2Si$ requires M , 437.0072).

(4R,6S)-*trans*- and (4R,6R)-*cis*-4-[(*T*riisopropyl)silyloxy]-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, $3 \times (CH_3)_2CH$], ca. 1.08 [3 H, m, $3 \times (CH_3)_2CH$], ca. 1.6 (0.15 H, m, *cis*-5- H_{ax}), 1.78 (0.85 H, ddd, J 14.0, 11.4 and 2, *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}), 2.5 (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. 3.3 (0.30 H, m, *cis*- CH_2), 3.41 (1.7 H, d, J 5.1, *trans*- CH_2), 4.2 (0.15 H, m, *cis* 6 H), 4.71 (0.15 H, m, *trans*-4- H_{ax}) 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%, $C_{10}H_{16}IO_2Si$, $M - C_3H_7$), a π (CH_2CO), 201 (43, $C_9H_{11}O_2Si$), 157 (100, C_8H_9OSi) and 125 (30, C_4H_9OSi) (Found: M^+ – C_3H_7 and CH_2CO , 327.0277. $C_{10}H_{16}IO_2Si$ requires 327.0279).

(4RS,6RS)-*trans*-6-(3'-Phenylprop-2'-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 azobisisobutyronitrile (AIBN) (0.018 g) was added and the resulting solution heated to 80°C for 16 h. The iodolactone 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, $2 \times CH_3$), 0.96 (9 H, s, $C(CH_3)_3$), 1.20–2.08 (4 H, m, $2 \times CH_2$), 2.20–2.27 (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 $\times$ 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 1647; δ_H (400 MHz) 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_{ax}), 2.73 (1 H, dd, J 17.7 and 4.7, 3- H_{eq}), ca. 2.74 (1 H, br s, OH), 4.38 (1 H, br quin, J ca. 3.8, 4- H_{ax}), 4.73 (1 H, dddd, J 11.4, 7.7, 4.9 and 3.2, 6- H_{ax}), 5.51 (1 H, dtd, J 10.3, 1.7 and ca. 1.1, CH_2CH), 5.07 (1 H, apparent dq, J 17.0 and 1.7, CH_2CH) and 5.82 (1 H, ddd, J 17.0, 10.3 and 6.6, CH_2CH); 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, $C_8H_{10}O_2$), 115 (43, $C_8H_9O_2$), 97 (48, $C_7H_9O_2$), 92 (92, $C_7H_8O_2$) and 73 (100, $C_7H_8O_2$) (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 -stannylstyrene⁴⁴ (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 x 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, $\nu_{\text{max}}/\text{cm}^{-1}$ 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_{ax}), 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%, $\text{C}_{10}\text{H}_{14}\text{O}_2$, $\text{M} - \text{H}_2\text{O}$), 117 (33, C_9H_{12}) and 97 (100, $\text{C}_3\text{H}_5\text{O}_2$) (Found: $\text{M}^+ - \text{H}_2\text{O}$, 214.1006, $\text{C}_{10}\text{H}_{14}\text{O}_2$ requires M , 214.0999).

Methyl (3R,5S)-3-[1-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-hexane (1:3) then gave the epoxy ester 29a (0.153 g, 93%) as a colourless oil, $[\alpha]_{\text{D}}^{20} -23.2^\circ$ (c 1.0, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ 1736; δ_{H} (400 MHz) 0.07 (3 H, s, SiCH_3), 0.08 (3 H, s, SiCH_3), 0.88 [9 H, s, $\text{C}(\text{CH}_3)_2$], 1.69 (1 H, ddd, J 14.3, 6.9 and 4.8, 4- H_{ax}), 1.82 (1 H, ddd, J 14.3, 5.6 and 4.7, 4- H_{eq}), 2.47 (1 H, dd, J 5.0 and 2.7, 6- H_{ax}), 2.56 (1 H, dd, J 15.0 and 5.6, 2- H_{ax}), 2.63 (1 H, dd, J 15.0 and 7.3, 2- H_{eq}), 2.77 (1 H, dd, J 5.0 and 4.2, 6- H_{eq}), 3.08 (1 H, dtd, J 6.9, $ca.$ 4.4 and 2.7, 5- H), 3.68 (3 H, s, OCH_3) and 4.37 (1 H, dtd, 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%, $\text{C}_{13}\text{H}_{23}\text{O}_3\text{Si}$, $\text{M} - \text{OCH}_3$), 217 (25, $\text{C}_9\text{H}_{17}\text{O}_4\text{Si}$, $\text{M} - \text{C}_4\text{H}_9$), 185 (18, $\text{C}_9\text{H}_{13}\text{O}_3\text{Si}$, $\text{M} - \text{CH}_2\text{OH}$ and C_4H_9), 161 (30, $\text{C}_8\text{H}_{13}\text{O}_3\text{Si}$), 157 (24, $\text{C}_7\text{H}_{13}\text{O}_3\text{Si}$), 143 (58, $\text{C}_6\text{H}_{11}\text{O}_3\text{Si}$), 115 (51, $\text{C}_5\text{H}_{11}\text{O}_3\text{Si}$), 89 (67, $\text{C}_3\text{H}_9\text{O}_3\text{Si}$) and 75 (100, $\text{C}_2\text{H}_7\text{O}_3\text{Si}$) (Found: $\text{M}^+ - \text{C}_4\text{H}_9$, 217.0889, $\text{C}_9\text{H}_{17}\text{O}_4\text{Si}$ requires 217.0895) (Found: C, 56.7; H, 9.7. $\text{C}_{13}\text{H}_{23}\text{O}_3\text{Si}$ 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 $\nu_{\text{max}}/\text{cm}^{-1}$ 3463 and 1738; δ_{H} 0.10 (3 H, s, SiCH_3), 0.12 (3 H, s, SiCH_3), 0.92 [9 H, s, $\text{C}(\text{CH}_3)_2$], 1.75-1.96 (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_2 and 3- H), 3.75 (3 H, s, OCH_3) and 4.41 (1 H, quin, J 6.8, 3- H); m/z 345 (1%, $\text{C}_9\text{H}_{11}\text{IO}_4\text{Si}$, $\text{M} - \text{C}_4\text{H}_9$), 271 (18, $\text{C}_8\text{H}_{11}\text{IO}_4\text{Si}$), 253 (28, $\text{C}_7\text{H}_{11}\text{IO}_4\text{Si}$), 145 (72, $\text{C}_5\text{H}_9\text{IO}_4\text{Si}$) and 101 (100, $\text{C}_4\text{H}_9\text{O}_4\text{Si}$) (Found: $\text{M}^+ - \text{C}_4\text{H}_9$, 345.0032, $\text{C}_9\text{H}_{11}\text{IO}_4\text{Si}$ 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, $\nu_{\text{max}}/\text{cm}^{-1}$ 1738; δ_{H} (400 MHz) 1.05 [0.45 H, m, *anti*-(CH_2)₂CH], 1.06 [2.55 H, m, *syn*-(CH_2)₂CH], 1.066 [15.3 H, br s, *anti*-(CH_2)₂CH], 1.073 [2.7 H, br s, *syn*-(CH_2)₂CH], 1.69 (0.85 H, ddd, J 14.3, 7.2 and 4.0, *syn*-4- H_{ax}), 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_{eq}), 2.47 (0.85 H, dd, J 5.1 and 2.7, *syn*-6- H_{ax}), 2.49 (0.15 H, dd, J 5.1 and 2.7, *anti*-6- H_{ax}), 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_{eq}), 2.79 (0.15 H, dd, J 5.0 and 4.1 Hz, *anti*-6- H_{eq}), 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%, $\text{C}_{13}\text{H}_{23}\text{O}_4\text{Si}$, $\text{M} - \text{C}_2\text{H}_5$), 217 (64, $\text{C}_{10}\text{H}_{21}\text{O}_3\text{Si}$), 199 (24, $\text{C}_{10}\text{H}_{19}\text{O}_3\text{Si}$), 171 (53, $\text{C}_9\text{H}_{19}\text{O}_3\text{Si}$), and 75 (100, $\text{C}_2\text{H}_7\text{O}_3\text{Si}$) (Found: $\text{M}^+ - \text{C}_2\text{H}_5$, 273.1521, $\text{C}_{13}\text{H}_{23}\text{O}_4\text{Si}$ requires M , 273.1522).

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Paper 0/03303

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020/
Bogotá, D.C.,

Doctora
Jimena Escobar
Apoderada

Oficio N° 6927

REFERENCIA	Radicación	02 111163
	Trámite	002
	Evento	001
	Actuación	430
	Folios	008

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 02 111163, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 26-32
- . Ejemplos: folios 32-35
- . Capítulo reivindicatorio estudiado: folios 36-38
- . Se reivindica prioridad, presentada en Holanda el 19.07.00, bajo el número 1015744

Objeto de la Invención

Según las reivindicaciones 1 a 15 de la presente solicitud, se refiere a un procedimiento para la preparación de un derivado de ácido 2-(6—sustituido-1,3-dioxan-4-il) acético de fórmula (1), partiendo de un compuesto de fórmula (2), haciendo uso de un agente acetilzante, en presencia de un catalizador ácido.

Clasificación Internacional de patentes A 61 K 31/357

Claridad de la solicitud

El art. 30 de la decisión 486 contempla que *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*

Los términos "grupo fácilmente eliminable", "agente acetilzante" y "catalizador ácido" usados en la reivindicación 1 son muy amplios y pueden llegar a incluir grupos, agentes y catalizadores que no se encuentran revelados en la descripción.

En la reivindicación 11 se dice que X es "como se ha definido anteriormente", esto debe aclarar, porque no se hace referencia específica a alguna reivindicación.

Favor hacer las aclaraciones y correcciones del caso

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 31.05.00-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	WO 9113876	"Imidazoles"	19.09.91
2		"Síntesis asimétrica catalizada por lipasa de 6-(3-cloro-2-hidroxiopropil)-1,3-dioxin-4-onas"	1991
3		"Metil-(3R)-3-hidroxihex-5-enoato"	1991
4	US 5278313	"Procedimiento para la preparación de derivados de 1,3-dioxano útiles en la preparación de inhibidores de HMG-CoA reductasa"	11.06.94

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la NOVEDAD

El artículo 16 de la decisión 486 establece que *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica"*

La publicación WO 9113876 se relaciona con la síntesis de imidazoles, en la página 57, revela el compuesto 4-hidroxi-6-iodometilpiran-2-ona

El artículo *"Síntesis asimétrica catalizada por lipasa de 6-(3-cloro-2-hidroxiopropil)-1,3-dioxin-4-onas"*, enseña la síntesis de esta clase de compuestos, además revela dentro de su contenido el compuesto 8

El artículo *"Metil-(3R)-3-hidroxihex-5-enoato"*, enseña que éste compuesto es un precursor de análogos del ácido mevinico quiral; además revela dentro de su contenido los compuestos 18a y 19a.

Comparando elemento por elemento, el compuesto de la reivindicación 11 es igual a al compuesto 4-hidroxi-6-iodometilpiran-2-ona de WO 9112876, al compuesto 8 de D2 y a los compuestos 18a y 19a de D3. De igual manera, el compuesto de la reivindicación 15 es igual al compuesto 8 de D2.

Evaluación del NIVEL INVENTIVO

El artículo 18 de la decisión 486 establece que *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*

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. dentro de dichos compuestos se incluyen los



. que son intermediarios para la preparación de

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 9113876	11, 15	Novedad
2	"Síntesis asimétrica catalizada por lipasa de 6-(3-cloro-2-hidroxipropil)-1,3-dioxin-4-onas",	11, 15	Novedad
3	"Metil-(3R)-3-hidroxi-hex-5-enoato"	11, 15	Novedad
4	US 5278313	13-14	Nivel Inventivo

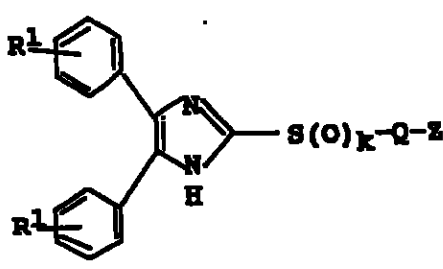
Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001

08 JAN 2007

El anterior requerimiento fue notificado por fijación en lista, de fecha

CONCEPTO TÉCNICO Número 0812	EXAMINADOR TÉCNICO Código 202024
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification S : C07D 233/84, A61K 31/415 C07D 403/12, 403/12	A1	(11) International Publication Number: WO 91/13876 (43) International Publication Date: 19 September 1991 (19.09.91)
(21) International Application Number: PCT/GB91/00408 (22) International Filing Date: 15 March 1991 (15.03.91) (30) Priority data: 9005966.8 16 March 1990 (16.03.90) GB (71) Applicant (for all designated States except US): RHONE-POULENC ROVER LIMITED [GB/GB]; Rainham Road South, Dagenham, Essex RM10 7XS (GB). (72) Inventors; and (73) Inventors/Applicants (for US only): BRIDGE, Andrew, William [GB/GB]; COFFEE, Edward, Charles, John [GB/GB]; HARRIS, Neil, Victor [GB/GB]; LYTHGOE, David, John [GB/GB]; SMITH, Christopher [GB/GB]; Rhone-Poulenc Rover Limited, Rainham Road South, Dagenham, Essex RM10 7XS (GB).		(74) Agents: BENTHAM, Stephen et al.; J.A. Kemp & Co, 14 South Square, Gray's Inn, London WC1R 5LX (GB). (81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.
(54) Title: IMIDAZOLES  (II) (57) Abstract Imidazole derivatives of general formula (II) in which R^1 is hydrogen or one or more substituents, k is 0, 1 or 2, Q is a straight or branched alkylene group and Z is hydrogen or a substituent group and pharmaceutically acceptable salts thereof possess useful pharmacological properties as inhibitors of acyl coenzyme-A: cholesterol-o-acyl transferase and as inhibitors of the binding of thromboxane TXA_2 to its receptors, and are useful in therapy.		

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- 57 -

Calculated:- C,70.38;H,6.16;N,7.14;S,8.17%.

By again proceeding in a similar manner, but replacing the 5-(iodomethyl)-2-furanone by (4R,4S) (6R,6S)-4-hydroxy-6-iodomethylpyran-2-one, there was obtained, after chromatography:-

BQ (4R,4S) (6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-3,4,5,6-tetrahydropyran-2-one, m.p. 191-192°C.

[Elemental analysis:- C,66.2;H,5.26;N,7.3;S,8.2%;

Calculated:- C,66.29;H,5.30;N,7.36;S,8.43%] and

BQ (3R,3S) (5R,5S)-ethyl 6-[(4,5-diphenylimidazol-2-yl)thio]-3,5-dihydroxyhexanoate, m.p. 94-95°C.

[Elemental analysis:- C,64.4;H,6.02;N,6.48;S,7.5 %;

Calculated:- C,64.77;H,6.14;N,6.57;S,7.52%].

NMR (in CDCl₃):- 1.21(3H,t), 1.5-2.1(2H,m),

2.22-2.6(2H,m), 2.9-3.2(2H,m), 4.16(2H,q), 2.2-2.4(2H,m).

EXAMPLE 17

Compound BR

A mixture of 4,5-diphenylimidazole-2-thiol (3.5g) and anhydrous potassium carbonate (2.9g) in anhydrous dimethylformamide (60ml) was stirred at room temperature for 30 minutes. It was then treated with (2R,2S)-2-(iodomethyl)-6-oxo-1,4-dioxane (3.4g) and the resulting mixture stirred at room temperature for 3 days. The mixture was poured into water (600ml) and the product collected by filtration and dried at

United States Patent [19]

Thottathil et al.

US005278313A

[11] Patent Number: 5,278,313

[45] Date of Patent: Jan. 11, 1994

[54] PROCESS FOR THE PREPARATION OF 1,3-DIOXANE DERIVATIVES USEFUL IN THE PREPARATION OF HMG-COA REDUCTASE INHIBITORS

[75] Inventors: John K. Thottathil, Robbinsville; Yadingri Pandri, Old Bridge; Wen-San Li, Lincroft, all of N.J.; David R. Kromenthal, Yardley, Pa.

[73] Assignee: E. R. Squibb & Sons, Inc., Princeton, N.J.

[21] Appl. No.: 888,907

[22] Filed: Mar. 27, 1992

[31] Int. Cl.⁵ C07D 307/04; C07D 257/00

[32] U.S. Cl. 548/252; 548/253; 549/230

[58] Field of Search 548/252, 253; 549/430

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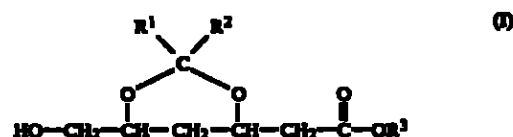
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Primary Examiner—David B. Springer

Attorney, Agent, or Firm—John M. Kilcoyne

[57] ABSTRACT

A novel, overall process for the preparation of a compound of the formula I:



where

R¹ and R² are each independently hydrogen, an alkyl group, a cycloalkyl group, an aryl group or, taken together with the carbon atom to which they are attached, form a cycloalkyl group; and

R³ is hydrogen, an alkyl group, or an aryl group,

or salts thereof, useful as intermediates in the preparation of HMG-CoA reductase inhibitors; novel methods within the overall process; and novel intermediates produced by those methods.

4 Claims, No Drawings

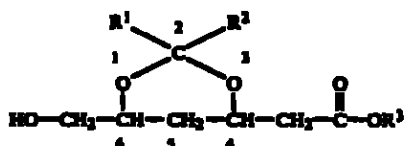
PROCESS FOR THE PREPARATION OF 1,3-DIOXANE DERIVATIVES USEFUL IN THE PREPARATION OF HMG-COA REDUCTASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of 1,3-dioxane derivatives useful in the preparation of HMG-CoA reductase inhibiting compounds. The instant invention also relates to the novel intermediates produced.

SUMMARY OF THE INVENTION

The instant invention provides a process for the preparation of compounds of the formula I:



where

R¹ and R² are each independently hydrogen, an alkyl group, a cycloalkyl group, an aryl group or, taken together with the carbon atom to which they are attached, form a cycloalkyl group; and

R³ is hydrogen, an alkyl group or an aryl group; and salts thereof,

and especially for the preparation of optically active such compounds.

Compounds of the formula I are useful as intermediates in the preparation of inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which inhibitors are useful, for example, in the treatment of hypercholesterolemia, hyperlipoproteinemia, hyperlipidemia and atherosclerosis. The instant invention provides a convenient process for the preparation of compounds of the formula I in good yields, particularly for the preparation of chiral compounds of the formula I having the 4R,6S configuration which are preferred in the preparation of HMG-CoA reductase inhibitors.

The process of the instant invention comprises the steps of:

(a) condensing a compound of the formula II:



where

X is a halogen atom; and

R⁴ is an alkyl group, a cycloalkyl group or an aryl group,

with a compound of the formula III, or a salt thereof:



where R³ is as defined above for the formula I; in the presence of a condensation agent, to form a compound of the formula IV, or a salt thereof:



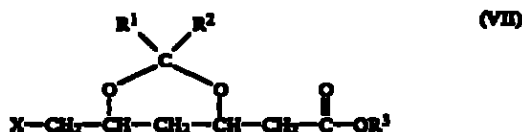
where X is as defined in formula II and R³ is as defined in formula I;

(b) reducing, in the presence of a reducing agent, the compound of the formula IV or salt thereof prepared in step (a) to form a compound of the formula V, or a salt thereof:



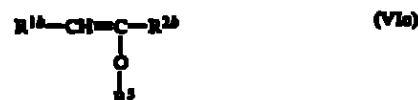
where X is as defined in formula II and R³ is as defined in formula I;

(c) preparing a compound of the formula VII, or a salt thereof:



where

R¹, R² and R³ are as defined in formula I; and X is as defined in formula II, by reacting the compound of formula V or salt thereof prepared in step (b) with a compound of the formula VIa, VIb or VIc:



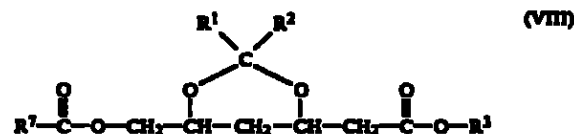
where

R¹ and R² are as defined in the formula I;

R^{1b} and R^{2b} are each independently hydrogen, an alkyl group, a cycloalkyl group, an aryl group or, taken together with the carbon atoms to which they are attached, form a 1,2-cycloalkenyl group; and

R³ and R⁴ are each independently an alkyl group, in the presence of an acidic condensation agent;

(d) preparing a compound of the formula VIII, or a salt thereof:



where

The method of step (d) is novel. Further, compounds of the formula VIII where R⁷ is an alkyl group are novel, and are preferably prepared by the instant method. Use of compounds of the formula VIII having as R⁷ an alkyl group, most preferably a lower alkyl group such as methyl, facilitates the hydrolysis procedure of step (e) described below. In particular, the by-products formed by the use of such compounds in step (e), such as methyl acetate or acetic acid, are volatile and are readily separated from the desired compound of the formula I relative to the by-products formed when a compound of the formula VIII where R⁷ is aryl is employed.

In the method of step (e), a compound of the formula I is prepared by hydrolyzing the compound of the formula VIII prepared in step (d) above. Any hydrolyzing agent effecting the reaction of step (e) may be employed. Exemplary hydrolyzing agents are basic compounds such as alkali metal hydroxides (for example, sodium hydroxide, potassium hydroxide or lithium hydroxide), or any other hydroxide base. Potassium carbonate is particularly preferred as the hydrolyzing agent. The molar ratio of hydrolyzing agent to the compound of the formula VIII is preferably from about 2:1 to about 1:2, most preferably from about 1:1 to about 1:2.

Use of a mildly basic medium is particularly advantageous in step (e). A "mildly basic medium", as used in this specification, denotes a reaction medium at a pH which selectively hydrolyzes the R⁷-C(O)-O- ester group of the compound of the formula VIII, relative to hydrolysis of the R³-O-C(O)- ester group. Preferably, a pH of from about 7 to about 12, most preferably from about 8 to 10, is employed. It is particularly desirable to employ a medium such that substantially all of the product formed in step (e) is the compound of the formula I, for example, an amount greater than about 99% of the product formed.

It is further preferred to employ a mild base to achieve the mildly basic medium described above. As used in this specification, a "mild base" is a base having a pK_a of from about 5 to about 12, most preferably from about 6 to about 10. Exemplary mild bases include alkali metal carbonates such as sodium carbonate, and particularly potassium carbonate as discussed above. pK_a may be determined by the method described in Cookson, Chem. Rev., 74, 5-28 (1974).

In addition to allowing selective hydrolysis, use of a mild base and mildly basic medium is advantageous in avoiding instability of the compound of formula I, for example, elimination of the group -O-C(R¹)(R²)-O- (ring opening), which may occur under strongly basic conditions.

The method of step (e) is preferably conducted at a temperature of from about 0° C. to about 100° C., most preferably from about 10° C. to about 40° C. Alcoholic solvents are preferably employed, exemplified by alcohols such as methanol.

The method of step (e) is novel where (i) a mild base or mildly basic medium is employed and/or (ii) a compound of the formula VIII is employed where R⁷ is an alkyl group. Use of a compound of the formula VIII where R⁷ is an alkyl group is particularly advantageous for the reasons described above.

Exemplary compounds falling within the scope of the present invention include:

(S)-6-chloro-5-hydroxy-3-oxohexanoic acid, 1,1-dimethylethyl ester (formula IV);

(S)-6-bromo-5-hydroxy-3-oxohexanoic acid, 1,1-dimethylethyl ester (formula IV);

(R,S)-6-chloro-3,5-dihydroxyhexanoic acid, 1,1-dimethylethyl ester (formula V);

(R,S)-6-bromo-3,5-dihydroxyhexanoic acid, 1,1-dimethylethyl ester (formula V);

(4R-cis)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester (formula VII);

(4R-cis)-6-(bromomethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester (formula VII);

(4R-cis)-6-[(acetyloxy)methyl]-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester (formula VIII);

(4R-cis)-6-[(benzyloxy)methyl]-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester (formula VIII); and

(4R-cis)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester (formula I).

In each of the above steps (a) through (e), solvates, as well as the salt or free form of the compounds, may be employed as starting materials or prepared as products. Solvates may be organic solvates or, preferably, hydrates. Salts include acidic or basic salts with inorganic or organic acids or bases. Exemplary salts include salts formed with nontoxic cations such as alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example, calcium or magnesium) cations or ammonium salts formed with nontoxic anions such as trialkylamines, dibenzylamine, pyridine, N-methylmorpholine, N-methylpiperidine and the like.

The term "alkyl", as used in this specification, preferably denotes a straight or branched saturated carbon chain having from 1 to 21 carbon atoms. Exemplary alkyl groups include methyl, ethyl, *i*-propyl, *n*-propyl, *t*-butyl and *n*-butyl.

The term "lower alkyl", as used in this specification, preferably denotes an alkyl group as described above having from 1 to 8, most preferably 1 to 6, carbon atoms.

The term "cycloalkyl", as used in this specification, preferably denotes a saturated carbocyclic ring system having from 1 to 3 rings and from 3 to 21 carbon atoms. Exemplary cycloalkyl groups include cyclopentyl, cyclohexyl and cycloheptyl.

The term "cycloalkenyl", as used in this specification, preferably denotes a partially unsaturated carbocyclic ring system having from 1 to 3 rings and from 3 to 21 carbon atoms. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl and cycloheptenyl.

The term "aryl", as used in this specification, preferably denotes an unsaturated monocyclic or bicyclic carbocyclic ring system having from 6 to 12 carbon atoms. Exemplary aryl groups include phenyl, biphenyl and naphthyl.

Each of the alkyl (including lower alkyl), cycloalkyl, cycloalkenyl or aryl groups described above may optionally be substituted. Appropriate substituents include those groups allowing preparation according to the methods of the present invention. For example, the cycloalkyl, cycloalkenyl or aryl groups described above may be substituted by one or more alkyl groups.

The term "halogen", as used in this specification, denotes fluorine, iodine or preferably, bromine or chlorine.

The present invention contemplates preparation of any of the compounds herein which may be in the form

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ANTERIORIDADES ENCONTRADAS		
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