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On a Baker's Yeast-Mediated Approach to Verapamil's Optically Active Intermediates

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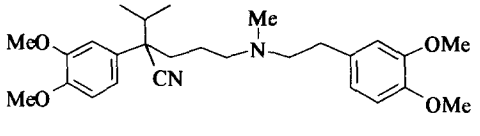
Abstract. Racemic hydroxylactones **11a** and **11b** were converted through the key aldehyde intermediate **21** into the C_6-C_4 acid **22**, showing all the necessary functionalities for the subsequent transformation into verapamil **1**. Baker's yeast reduction of racemic ketolactone **8** provided enantiomerically pure **11a**, close to the diastereoisomer **11b** possessing 0.14 *ee*. The unusual chemical behaviour observed during the synthetic study, such as the conversion of **13** into **14** upon reaction with MeMgI and of **16** into **17** and **18** upon acid treatment, as well as the low yields of a few relevant steps might be due to the crowd of functionalities around the stereogenic carbon atom of the intermediates. This inhibited completion of the work in the optically active series. © 1997 Elsevier Science Ltd.

INTRODUCTION

It is now acknowledged that the two enantiomers of a chiral drug may have pharmacological activity of different entity or nature.[1] Racemic verapamil **1**, for example, has been used to lower blood pressure for a long time. Recent studies have shown that the (S)-enantiomer is the most effective in calcium channel blocking, while the (R)-stereoisomer has been found to be potentially interesting for the treatment of multiple drug resistance during cancer therapy.[2] Thus, the synthesis of both enantiopure (S)- and (R)-verapamil represents an important goal for organic chemists.

The known approaches to the optically active forms of **1** are based either on a classical resolution *via* crystallisation of diastereoisomeric salts at some stage of the sequence[3] or on the use of (2S)-(+)-propane-1,2-diol as the optically active starting material.[4] The recent report[5] on the synthesis of enantiopure analogues of **1**, starting from components of the pool of chirality,[6] prompted us to present our results on the preparation of (S)- and (R)-verapamil, using the baker's yeast reduction of keto lactone **8** as the key step to obtain optical activation.



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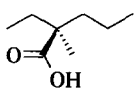

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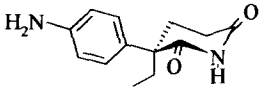
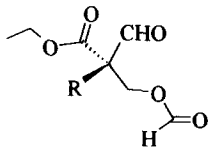
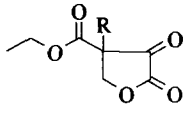
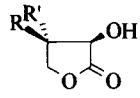


3

We have recently used this enzymic approach to prepare optically active **9a** and **10a** starting from racemic keto lactones **6** and **7**.[7] The two hydroxy lactones easily afforded upon periodic acid cleavage the C_5 molecules **4** and **5**, showing a stereogenic center with four carbon atoms in different oxidation states[7], which were subsequently converted into optically active (2S)-2-ethyl-2-methylpentanoic acid **2**[8] and (R)-aminogluthetimide **3**[9] by simple functional group manipulations.







4 R = Me
5 R = Ph

6 R = Me
7 R = Ph
8 R = C_6H_3 - 3,4 - diOMe

9a R = Me, R' = COOEt
9b R = COOEt, R' = Me
10a R = Ph, R' = COOEt
10b R = COOEt, R' = Ph
11a R = C_6H_3 - 3,4 - diOMe, R' = COOEt
11b R = COOEt, R' = C_6H_3 - 3,4 - diOMe

In order to continue our studies on the synthetic applications of this microbial transformation,[10,11] we have explored the possibility to obtain enantiomerically pure **11a** and/or **11b** by baker's yeast reduction of ketolactone **8**, and to use these derivatives as the starting materials for the preparation of both (S)- and (R)-**1**.

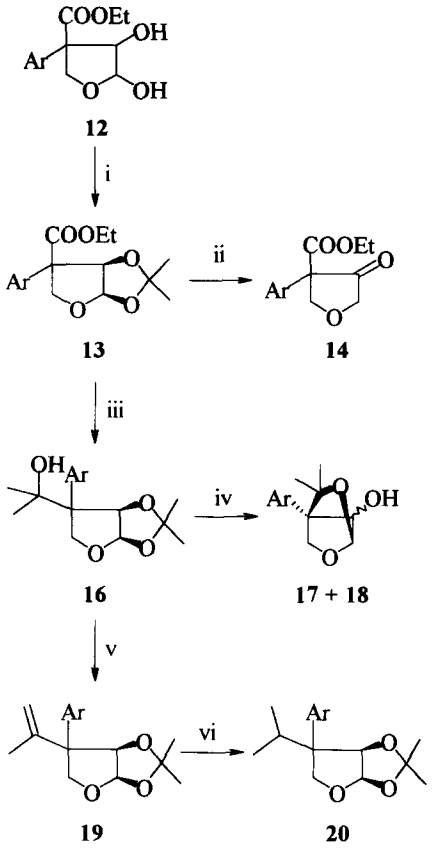
The baker's yeast reduction of substrate **8** proceeded in a satisfactory manner, providing enantiomerically pure **11a**, easily separated by column chromatography from the diastereoisomer **11b**, showing very low *ee*. The synthetic approach to **1** was verified only in the racemic series from the mixture of (±)-**11a** and (±)-**11b** to (±)-**22**, a C_6-C_4 acid showing all the suitable functionalities for the construction of the required target molecule **1**.

The low yields and the unexpected course of certain reactions performed on these intermediates, all bearing a crowd of functionalities around the stereocenter, prevented us from obtaining enantiopure (S)- or (R)-verapamil, but allowed us to get some interesting serendipitous results we would like to report herein.

RESULTS AND DISCUSSION

Baker's yeast reduction of ketolactone **8** afforded two optically active diastereoisomeric hydroxy lactones, separated by column chromatography, as in the case of **6** and **7**. These products, in the order of elution from the column, were shown to possess 0.99 and 0.14 *ee*, respectively, by HPLC analysis on a chiral column. By analogy with **9a,b** and **10a,b**,[7,8] they were assigned structural formulas **11a** and **11b**. The conversion of **11a** into enantiopure (S)-**1** required, not necessarily in this order, the transformation of the carboxyethyl moiety into the isopropyl group and the oxidative extrusion of the C_1 unit of the lactone carbonyl group to provide aldehyde (R)-**21**. Moreover, suitable manipulation of the two functionalities of **21** should eventually provide verapamil. This synthetic sequence was initially explored (Scheme 1) on the mixture of the two racemic diastereoisomers **11a,b**,[8] which was treated with $LiBH_4$ to provide furanose **12** (4 diastereoisomers), and subsequently converted into the crystalline dioxolane

derivative **13**.

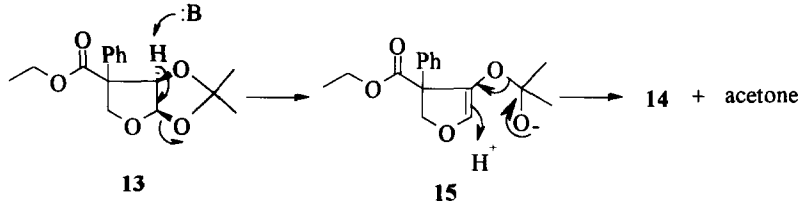


Reagents and conditions: (i) 2,2-dimethoxypropane, p-toluensulfonic acid, acetone; (ii) methyl magnesium iodide, THF; (iii) methyl magnesium chloride, THF; (iv) p-toluensulfonic acid, toluene; (v) phosphorous pentoxide, toluene; (vi) H_2, 10% Pd/C, ethanol.

Scheme 1

This latter compound was found to be a 1:1 mixture of only two diastereoisomers by means of NMR spectroscopy, both of them showing a syn arrangement of the two protected hydroxylic groups. Substrate **13** was reacted with methylmagnesium iodide, in an attempt to obtain a tertiary methyl carbinol, from which, by dehydration and hydrogenation, the isopropyl moiety characteristic of **1** could be constructed. However, reaction of **13** in diethylether or tetrahydrofuran with an excess of MeMgI provided derivative **14** in high yield. This compound seemed formally derived from **13** by elimination of acetone according to the tentative mechanism outlined in Scheme 2.

In the reaction with overcrowded **13** this Grignard reagent did not add to the carboxyethyl moiety, but rather it acted as a base and removed the proton in position 6a of the tetrahydrodioxole derivative, thus promoting the ring opening to intermediate **15**, and eventually conversion into substrate **14** and acetone. The structural assignment of **14** was based on both ^1H and ^{13}C NMR spectra. Indeed, the presence of two AB systems in the range 4.0-5.0 ppm and of a typical ^{13}C carbonyl resonance at 207 ppm was consistent with a furanone derivative rather than with a lactone one.



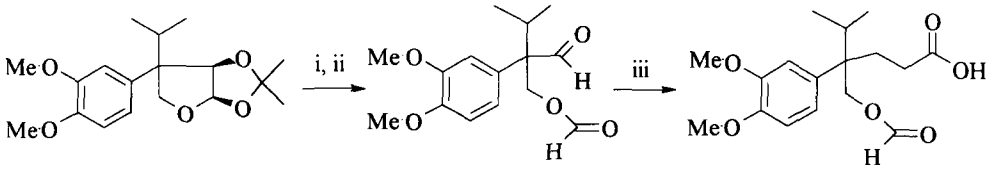
Scheme 2

Conversely, reaction of **13** with methylmagnesium chloride in THF gave the desired carbinol **16** (2 diastereoisomers) in 85% yield. The conversion of tertiary carbinol **16** into the corresponding olefin, precursor of the desired isopropyl moiety of verapamil **1**, resulted quite difficult. Indeed, compound **16** afforded on acid treatment (4-

methylbenzenesulfonic acid in refluxing toluene, trifluoroacetic acid at room temperature and 85% sulphuric acid[12]) bicyclo derivatives **17** and **18**, supposedly formed by intramolecular transketalization of the two diasteroisomeric dioxoles. Protonation of the oxygen atom in position 1 and subsequent cleavage of the corresponding C-O bond, assisted by the oxygen atom of the tetrahydrofuran moiety, could give an oxonium intermediate. On both sides of this latter compound, ring closure might occur to afford the two diastereoisomeric bicyclic derivatives. The synthesis of **17** and **18** is a very relevant result, as the creation of a [2,2,1] bicyclic skeleton is very difficult. Only a few examples are reported in the literature. Palladium(II)-catalysed intramolecular cyclization of (2S,3S)-2-allyl-1,3-butandiol gave (1S,3S,4R)-1,3-dimethyl-2,6-dioxa-bicyclo[2.2.1]heptane in 63% yield.[13] The parent compound 2,6-dioxabicyclo[2.2.1]heptane was obtained by acid -catalysed transketalization of 4,4-diethoxy-2-hydroxymethyl-1-butanol in dioctyl phthalate under high vacuum with vigorous stirring and was distilled as it was formed.[14] Bicyclization of substrate **16** occurred in milder conditions thanks to the rigidity of the molecular skeleton and the favourable steric orientation of the reacting groups in the two diastereoisomers.

Experiments designed to convert carbinol **16** into the corresponding olefin by pyrolysis of the xantogenate derivative failed, since no reaction occurred in the treatment with KH/CS_2.[15] The required isopropenyl derivative **19** was eventually obtained from **16** on treatment with P_2O_5 in dry toluene at room temperature. The yields of the reaction were in the 70-80% range on the 100 mg scale, but decreased significantly on scaling up to a few grams, allowing the recovery of only one diastereoisomer. The following step, consisting in the catalytic hydrogenation (Pd/C) of **19**, afforded the saturated material **20** (1 diastereoisomer) quantitatively.

The subsequent conversion of **20** into **1** required the C_6-C_4 acid **22** as key intermediate (Scheme 3).



20 **21** **22**

Reagents and conditions: (i) trifluoroacetic acid (5:1); (ii) periodic acid, THF; (iii) triphenylphosphonium (carboxy-ethyl)methinylide, CHCl3.

Scheme 3

To this end, the dioxolane moiety of **20** was hydrolysed in trifluoroacetic acid - water (5:1) solution and the resulting diol derivative gave rise to racemic aldehyde **21** on HIO_4 oxidative cleavage in THF. The required chain elongation of **21** was performed by reaction with triphenylphosphonium (carboxybenzyl)methinylide which provided the corresponding unsaturated ester in only 33% yield. Similar reaction on aldehyde **5** with $Ph_3P{=}CHCO_2CH_2C_6H_5$ proceeded in 75% yield. Catalytic hydrogenation of the so obtained material saturated the double bond and revealed the carboxyl moiety of **22**. From this latter material, verapamil **1** seemed to be easily accessible through amide formation with N-methyl homoveratrylamine, reduction of the tertiary amide function and, eventually, oxidative conversion of the $-CH_2OH$ moiety into the nitrile group.[3]

However, due to the low yields of some of the above steps we were unable to repeat the sequence starting from enantiomerically pure **11a** to optically active acid **22**, and hence to (S)-verapamil. Thus, the study was

interrupted at the level of racemic **22**. Despite this limitation, the present work might hold some significance as far as biotransformations are concerned, since it is a further example of the utility of baker's yeast, although on the chemical *scenario* for a long time,[16] in the reduction of synthetic ketolactones related to pantolactone.[17] The enantiomerically enriched educts obtained by this enzymic approach are useful starting materials, alternative to those derived from natural products,[6] in the synthesis of elaborated molecules characterised by a stereogenic carbon atom such as **1**, **2** and **3**.[8,9] As far as the synthetic aspects of the work are concerned, two steps provided disappointingly low yields, *i.e.*, the dehydration of **16** to **19** and the C_2 Wittig homologation of the aldehyde **21**. In the meantime, the unexpected conversion of **13** into **14** and of **16** into **17** and **18**, supports the particular reactivity of the functional groups linked to the quaternary carbon atom of the intermediates, obtained from **11** in the sequence towards **22**.

EXPERIMENTAL

General procedures.

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at room temperature unless otherwise stated, on a Bruker AC-250 spectrometer (250 MHz ^1H). The chemical shift scale is based on internal tetramethylsilane. J values are in Hz. Optical rotations were measured on a Jasco DIP 181 digital polarimeter and the specific rotations calculated in units 10^{-1} deg cm^2 g^{-1}. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. All the chromatographic separations were carried out on silica gel columns. Organic extracts were dried over anhydrous sodium sulphate. HPLC analyses were performed with a Merck-Hitachi L-6200 apparatus, equipped with UV detector L-4200 with D-2500 integrator, on a chiral column (Chiracel OD, Daicel Japan).

Homoveratric acid ethyl ester

A solution of homoveratric acid (150 g, 0.76 mol) in ethanol (500 ml) and concentrated sulphuric acid (30 ml) was refluxed for 4 h. The reaction mixture was concentrated, diluted with water, extracted into diethyl ether, and washed first with a saturated sodium hydrogen carbonate solution, then with water. The combined organic extracts were dried, filtered and concentrated under reduced pressure. The residue was distilled under reduced pressure to give the title compound as a colourless oil (128 g, 75%) bp. 136°C/ 0.5 mbar (Found: C, 64.33; H, 7.23; $C_{12}H_{16}O_4$ requires C, 64.27; H, 7.19%); δ_H 1.25 (3H, t, J 7, $COOCH_2\mathit{CH_3}$), 3.55 (2H, s, $\mathit{CH_2}COOEt$), 3.82 (3H, s, $\mathit{OCH_3}$), 3.88 (3H, s, $\mathit{OCH_3}$), 4.15 (2H, q, J 7, $COO\mathit{CH_2}CH_3$), 6.80 (3H, m, aromatic hydrogens).

2-(3,4-Dimethoxyphenyl)-3-oxo-succinic acid diethyl ester

An equimolar mixture of homoveratric acid ethyl ester (90 g, 0.40 mol) and diethyl oxalate (58 g, 0.40 mol) was dropped into a suspension of sodium ethylate (27 g, 0.40 mol) in dry ethyl ether (500 ml) at 0°C under mechanical stirring. After 3 h at room temperature, the reaction mixture was quenched with HCl 10%, extracted into diethyl ether and washed with water. The organic phase was dried and concentrated under reduced pressure, to afford the title compound (82 g, 63%) which was taken on to the next step without purification. δ_H 1.3 (6H, m, $2COOCH_2\mathit{CH_3}$), 3.85 (6H, s, $2\mathit{OCH_3}$), 4.25 (4H, m, $2COO\mathit{CH_2}CH_3$), 5.31 (1H, s, CH), 6.85 (3H, m, aromatic hydrogens).

3-(3,4-Dimethoxyphenyl)-4,5-dioxo-tetrahydrofuran-3-carboxylic acid ethyl ester (8)

To a solution of the derivative previously described (40 g, 0.12 mol) in diethyl ether (300 ml) and pyridine (15 ml) gaseous formaldehyde was added at -20°C till ester disappearance. The reaction mixture was poured into ice-HCl, extracted with diethyl ether, washed with water, dried, and concentrated under reduced pressure. The residue was purified on a silica gel column, eluting with hexane-ethyl acetate (8:2-5:5), to afford ketolactone **8** (23 g, 62%) as a viscous liquid (Found: C, 58.32; H, 5.34; $C_{15}H_{16}O_7$ requires C, 58.44; H, 5.23%); δ_H 1.26 (3H, t, J 7, $COOCH_2CH_3$), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.26 (2H, q, J 7, $COOCH_2CH_3$), 5.00 (1H, d, J 10, CHH-O), 5.50 (1H, d, J 10, CHH-O), 6.94 (3H, m, aromatic hydrogens).

Bakers' Yeast reduction of ketolactone 8

A mixture of commercial moist bakers' yeast (500 g) and D-glucose (200 g) in tap water (2 L) at 32°C was collected in a 3-L glass jar. As the fermentation started a solution of **8** (5g, 0.016 mol) in ethanol (5 ml) was added under stirring. After 16 h at 23°C, the reaction mixture was filtered on a Celite cake, and the filtrate was extracted with ethyl acetate. The dried organic phase was concentrated under reduced pressure, to give a residue which was chromatographed on a silica gel column, using hexane-ethyl acetate (9.5:0.5-7:3) as eluent. The first eluted fractions gave hydroxy lactone **11a** (2.1 g, 42%), showing 0.99 ee (HPLC) (Found: C, 58.12; H, 5.78; $C_{15}H_{18}O_7$ requires C, 58.06; H, 5.85%; $[\alpha]_D^{25}$ + 2.1 (*c* 0.2, $CHCl_3$); δ_H 1.25 (3H, t, J 7, $COOCH_2CH_3$), 3.9 (6H, s, $2OCH_3$), 4.25 (2H, q, J 7, $COOCH_2CH_3$), 4.60 (1H, d, J 10, CHH-O), 4.85 (1H, d, J 10, CHH-O), 5.05 (1H, s, CHOH), 5.1 (1H, s, CHOH), 6.7-7.1 (3H, m, aromatic hydrogens). The last eluted fractions gave diastereoisomer **11b** (0.98 g, 20%), showing 0.14 ee (HPLC) (Found: C, 57.98; H, 5.78; $C_{15}H_{18}O_7$ requires C, 58.06; H, 5.85%); δ_H 1.26 (3H, t, J 7, $COOCH_2CH_3$), 3.87 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.25 (2H, q, J 7, $COOCH_2CH_3$), 4.35 (1H, d, J 10, CHH-O), 4.70 (1H, s, CHOH), 5.02 (1H, d, J 10, CHH-O), 6.7-7.1 (3H, m, aromatic hydrogens).

(±)-3-(3,4-Dimethoxyphenyl)-4-hydroxy-5-oxo-tetrahydrofuran-3-carboxylic acid ethyl esters (11a and 11b)

To a stirred solution of ketolactone **8** (10 g, 0.032 mol) in ethyl acetate (100 ml) and ethanol (25 ml) sodium borohydride (0.75 g, 0.020 mol) was added keeping the temperature below -10°C. The reaction mixture was treated with HCl 10%, and extracted with ethyl acetate. The organic phase, after washing with water, was dried and concentrated under reduced pressure. The residue was chromatographed on a silica gel column using hexane-ethyl acetate (7:3) as eluent, to give a 1:1 mixture of the two racemic diastereoisomers **11a** and **11b.**

(±)-3-(3,4-Dimethoxyphenyl)-4,5-dihydroxy-tetrahydrofuran-3-carboxylic acid ethyl ester (four diastereoisomers) (12)

A 1.4 M solution of $LiBH_4$ (8 ml) was added dropwise under nitrogen at -5°C into a solution of hydroxylactones **11a** and **11b** (4 g, 0.013 mol) in tetrahydrofuran (25 ml) with a few drops of acetic acid. The reaction mixture was allowed to reach room temperature in about 2h, then poured into ice-HCl and extracted with diethyl ether. The organic phase was dried and concentrated under reduced pressure, to give a residue which was used immediately for the following step.

(±)-6-(3,4-Dimethoxyphenyl)-2,2-dimethyl-tetrahydrofuro[2,3-d][1,3]-dioxole-6-carboxylic acid ethyl ester (13) (two diastereoisomers)

A solution of compound **12** (7.5 g, 0.024 mol) and 2,2-dimethoxypropane (2.5 g, 0.024 mol) in acetone (50 ml) in presence of a trace of *p*-toluenesulfonic acid was refluxed for 8 h. The solvent was removed under reduced pressure to give a residue which was dissolved in ethyl acetate and washed with a saturated solution of sodium hydrogen carbonate. The organic phase was dried and concentrated under reduced pressure. The residue was chromatographed on a silica gel column, using hexane-ethyl acetate (7:3) as eluent, to give **13** (5g, 59%) as a 1:1 mixture of only two diastereoisomers (Found: C, 61.41; H, 6.93; $C_{18}H_{24}O_7$ requires C, 61.35; H, 6.89%); δ_H 1.25 (6H, m, 2COOCH$_2$*CH$_3$*), 1.34 (3H, s, C*CH$_3$*), 1.36 (3H, s, C*CH$_3$*), 1.42 (3H, s, C*CH$_3$*), 1.58 (3H, s, C*CH$_3$*), 3.88 (6H, s, 2*OCH$_3$*), 3.90 (6H, s, 2*OCH$_3$*), 4.15 (4H, m, 2COO*CH$_2$*CH$_3$), 4.25 (1H, d, J 10, CH*H*-O), 4.35 (1H, d, J 10, CH*H*-O), 4.52 (1H, d, J 10, CH*H*-O), 4.66 (1H, d, J 10, CH*H*-O), 4.98 (1H, d, J 4, *CH*-O), 5.40 (1H, d, J 4, *CH*-O), 5.78 (1H, d, J 4, *CH*-O), 5.90 (1H, d, J 4, *CH*-O), 6.7-7.1 (6H, m, aromatic hydrogens).

(±)-3-(3,4-Dimethoxyphenyl)-4-oxo-tetrahydrofuran-3-carboxylic acid ethyl ester (14)

A solution of methylmagnesium iodide (prepared from 0.03 mol of methyl iodide and 0.03 mol of magnesium) in tetrahydrofuran (10 ml) was dropped into a solution of **13** (5 g, 0.014 mol) in tetrahydrofuran (25 ml) at 0°C under nitrogen. After stirring at room temperature for 3h, the reaction mixture was poured into ice-NH_4Cl and extracted with diethyl ether. The combined organic extracts were washed first with a saturated sodium hydrogen carbonate solution, then with water, and dried. The solvent was removed under reduced pressure to give **14**, which was purified by crystallisation from ethanol (1.7 g, 41%), mp 78-79°C (Found: C, 61.29; H, 6.23; $C_{15}H_{18}O_6$ requires C, 61.21; H, 6.17%); δ_H 1.25 (3H, t, J 7, COOCH$_2$*CH$_3$*), 3.85 (3H, s, *OCH$_3$*), 3.88 (3H, s, *OCH$_3$*), 4.05 (1H, d, J 16, CO-*CH*H-O), 4.15 (3H, q + d, COO*CH$_2$*CH$_3$ + CO-CH*H*-O), 4.52 (1H, d, J 10, C-CH*H*-O), 5.00 (1H, d, J 10, C-CH*H*-O), 6.8-7.1 (3H, m, aromatic hydrogens); δ_C 14.24 (CH$_2$*CH$_3$*), 56.28 (*OCH$_3$*), 56.17 (*OCH$_3$*), 62.71 (COO*CH$_2$*CH$_3$), 63.08 (Ar-*C*-CO), 71.62, 75.79 (C-*CH$_2$*-O, CO-*CH$_2$*-O), 111.05, 111.56, 119.70, 126.04, 149.47 (aromatic carbon atoms), 168.66 (*COO*Et), 207.82 (*CO*-CH$_2$); *m/z* (EI) 294 (M$^+$).

(±)-2-[6-(3,4-Dimethoxyphenyl)-2,2-dimethyl-tetrahydrofuro[2,3-d][1,3]-dioxol-6-yl]propan-2-ol (two diastereoisomers) (16)

A 3 M solution of methylmagnesium chloride in tetrahydrofuran (20 ml, 0.060 mol) was dropped into a solution of **13** (10 g, 0.028 mol) in tetrahydrofuran (50 ml) at 0°C under nitrogen. The reaction mixture was refluxed for 3h, then poured into ice-NH_4Cl and extracted with diethyl ether. The combined organic extracts were washed first with a saturated sodium hydrogen carbonate solution, then with water, and dried. The solvent was removed under reduced pressure to give **16**, which crystallised from ethyl acetate as a 3:1 mixture of two diastereoisomers (8.1 g, 85%).(Found: C, 63.81; H, 7.67; $C_{18}H_{26}O_6$ requires C, 63.88; H, 7.74%). A sample of this mixture was chromatographed on a silica gel column using hexane-ethyl acetate (7:3) as eluent, in order to record NMR spectra: maior diasteroisomer (first eluted fraction): δ_H 0.9 (3H, s, C*CH$_3$*), 1.42 (3H, s, C*CH$_3$*), 1.48 (3H, s, C*CH$_3$*), 1.65 (3H,

s, CCH_3), 3.88 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.55 (1H, d, J 10, *CH*H-O), 4.72 (1H, d, J 10, CH*H*-O), 5.20 (1H, d, J 4, *CH*-O), 5.52 (1H, d, J 4, *CH*-O), 6.8-7.1 (3H, m, aromatic hydrogens); minor diastereoisomer (last eluted fraction) δ_H 1.12 (3H, s, CCH_3), 1.22 (3H,s, CCH_3), 1.30 (3H,s, CCH_3), 1.35 (3H,s, CCH_3), 3.88 (6H, s, 2OCH_3), 4.25 (1H, d, J 10, *CH*H-O), 4.52 (1H, d, J 10, CH*H*-O), 5.10 (1H, d, J 4, *CH*-O), 5.84 (1H, d, J 4, *CH*-O), 6.6-6.8 (3H, m, aromatic hydrogens).

4-(3,4-Dimethoxyphenyl)-3,3-dimethyl-2,6-dioxa-bicyclo[2.2.1]-heptan-7-ols (17 and 18)

A solution of carbinol **16** (two diastereoisomers) (1g, 0.03 mol) in toluene in the presence of a trace of *p*-toluenesulfonic acid was refluxed for 30 min. The reaction mixture was poured into a saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic phase was dried and concentrated under reduced pressure, to give a residue which was chromatographed on a silica gel column, using hexane-ethyl acetate (9:1-7:3) as eluent. The first eluted fractions gave compound **17** (0.614 g, 73%) (Found: C, 64.33; H, 7.23; $C_{15}H_{20}O_5$ requires C, 64.27; H, 7.19%); δ_H 1.15 (3H, s, CCH_3), 1.45 (3H, s, CCH_3), 2.15 (1H, d, J 8, CH*OH*), 3.74 (1H, d, J 8, CH*H*-O), 3.78 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.38 (1H, d, J 8, C*H*H-O), 4.45 (1H, d, J 8, *CH*OH), 5.00 (1H, s, O-*CH*-O), 6.72 (1H, d, J 8, H_5 of aromatic ring), 6.85 (1H, dd, J 8, 4, H_6 of aromatic ring), 7.12 (1H, d, J 4, H_2 of aromatic ring); *m/z* (EI): 280 (M^+). The last eluted fractions gave compound **18** (0.148 g, 16%), (Found: C, 60.18; H, 7.23; $C_{15}H_{22}O_6$ requires C, 60.39; H, 7.43%); δ_H 1.20 (3H, s, CCH_3), 1.40 (3H, s, CCH_3), 1.85 (1H, d, J 8, CH*OH*), 3.85 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.20 (1H, d, J 8, CH*H*-O), 4.55 (1H, d, J 8, C*H*H-O), 4.80 (1H, d, J 8, C-*CH*-OH), 5.10 (1H, s, O-*CH*-O), 6.65 (1H, d, J 4, H_2 of aromatic ring), 6.75 (1H, dd, J 8, 4, H_6 of aromatic ring), 6.90 (1H, d, J 8, H_5 of aromatic ring); *m/z* (EI): 280 (M^+).

6-(3,4-Dimethoxyphenyl)-6-isopropenyl-2,2-dimethyl-tetrahydro-furo[2,3-d][1,3]dioxole (19)

A mixture of carbinol **16** (two diastereoisomers) (0.200 g, 0.6 mmol) and phosphorous pentoxide (0.400 g) in toluene (25 ml) was stirred at room temperature for 15 min. The reaction mixture was poured into ice-saturated sodium hydrogen carbonate solution and extracted with ether. The organic layer was dried, concentrated under reduced pressure to give a residue which was chromatographed on a silica gel column, using hexane-ethyl acetate (9:1-8:2) as eluent. The first eluted fractions gave olefin **19** (single diastereoisomer) (0.115 g, 60%) (Found: C, 67.42; H, 7.53; $C_{18}H_{24}O_5$ requires C, 67.48; H, 7.55%); δ_H 1.30 (3H, s, CCH_3), 1.58 (3H, s, CCH_3), 1.65 (3H, s, C=CCH_3), 3.85 (6H, s, OCH_3), 4.08 (1H, d, J 10, CH*H*-O), 4.38 (1H, d, J 10, C*H*H-O), 4.92 (2H, m, C-*CH*-O + C=CH*H*), 5.05 (1H, m, C=*CH*H), 5.90 (1H, d, J 4, O-*CH*-O), 6.8-7.0 (3H, m, aromatic hydrogens).

6-(3,4-Dimethoxyphenyl)-6-isopropyl-2,2-dimethyl-tetrahydro-furo[2,3-d][1,3]dioxole (20)

Compound **19** (2.03 g, 0.0062 mol) was hydrogenated in ethanol solution (10 ml) on 10% palladium on charcoal (0.200 g) at room temperature. The reaction mixture was filtered, concentrated *in vacuo*, and purified on a silica gel column, eluting with hexane-ethyl acetate (8:2), to give substrate **20** (1.58 g, 81%) as a viscous liquid (Found: C, 67.02; H, 8.17; $C_{18}H_{26}O_5$ requires C, 67.06; H, 8.13%); δ_H 0.65 (3H, d, J 7, CHCH_3), 0.96 (3H, d, J 7, CHCH_3), 1.40 (3H, s, CCH_3), 1.59 (3H, s, CCH_3), 2.31 (1H, m, *CH*(CH_3)$_2$), 3.87 (3H, s, OCH_3), 3.92 (3H, s,

OCH$_3$), 3.98 (1H, d, J 10, CH*H*-O), 4.50 (1H, d, J 10, C*H*H-O), 4.96 (1H, d, J 3.5, C-*CH*-O), 5.57 (1H, d, J 3.5, O-*CH*-O), 6.8-7.0 (3H, m, aromatic hydrogens).

4-(3,4-Dimethoxyphenyl)-4-isopropyl-tetrahydrofuran-2,3-diol

A solution of dioxole **20** (1.23 g, 3.82 mmol) in trifluoroacetic acid - water (5:1) (10 ml) was stirred at room temperature for 2h. The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column, using hexane-ethyl acetate (7:3-5:5) as eluent, to give the title compound (0.775 g, 72%) (Found: C, 67.02; H, 8.17; $C_{18}H_{26}O_5$ requires C, 67.06; H, 8.13%); δ_H 0.61 (3H, d, J 7, CH*CH*$_3$), 0.92 (3H, d, J 7, CH*CH*$_3$), 2.36 (1H, m, *CH*(CH$_3$)$_2$), 2.60 (1H, broad s, *OH*) 3.90 (6H, s, 2*OCH*$_3$), 4.12 (1H, d, J 10, CH*H*-O), 4.45 (1H, d, J 10, C*H*H-O), 4.53 (1H, d, J 4, C-*CH*-O), 5.11 (1H, d, J 4,O-*CH*-O), 6.7-7.0 (3H, m, aromatic hydrogens).

Formic acid [2-(3,4-dimethoxyphenyl)-2-formyl-3-methyl]butyl ester (21)

A solution of the previously described diol (0.740 g, 2.62 mmol) in tetrahydrofuran (5 ml) was treated with periodic acid (0.600 g, 2.63 mmol) in tetrahydrofuran (5 ml). After 10 min, a few drops of 1,2-ethanediol were added, and the reaction mixture was filtered, concentrated *in vacuo,* diluted with water and extracted with ethyl acetate. The organic phase was washed with a sodium sulphite solution, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column, to afford compound **21** (0.506 g, 69%) (Found: C, 64.11; H, 7.05; $C_{15}H_{20}O_5$ requires C, 64.27; H, 7.19%); δ_H 0.88 (3H, d, J 7, CH*CH*$_3$), 1.00 (3H, d, J 7, CH*CH*$_3$), 2.55 (1H, m, *CH*(CH$_3$)$_2$), 3.84 (3H, s, *OCH*$_3$), 3.87 (3H, s, *OCH*$_3$), 4.64 (1H, d, J 11, CH*H*-OCHO), 4.69 (1H, d, J 11, C*H*H-OCHO), 6.68 (1H, d, J 2, H_2 of aromatic ring), 6.74 (1H, dd, J 2, 8, H_6 of aromatic ring), 6.89 (1H, d, H_5 of aromatic ring), 7.98 (1H, s, O-*CH*O), 9.79 (1H, s, -*CHO*)..

4-(3,4-Dimethoxyphenyl)-4-formyloxymethyl-3,5-dimethyl-hex-2-enoic acid benzyl ester

A solution of aldehyde **21** (0.480 g, 1.71 mmol) and triphenylphosphonium (carboxyethyl)methinylide (0.771 g, 1.88 mmol) in chloroform (10 ml) was stirred at room temperature for 8 h. The reaction mixture was concentrated under reduced pressure, and chromatographed on silica gel, eluting with hexane-ethyl acetate (7:3-5:5), to afford the title compound (0.230 g, 33%) (Found: C, 69.75; H, 6.89; $C_{24}H_{28}O_6$ requires C, 69.88; H, 6.84%); δ_H 0.87 (3H, d, J 7, CH*CH*$_3$), 1.01 (3H, d, J 7, CH*CH*$_3$), 2.50 (1H, m, *CH*(CH$_3$)$_2$), 3.87 (6H, s, 2 OC*H*$_3$), 4.05 (1H, d, J 11, CH*H*-OCHO), 4.15 (1H, d, J 11, C*H*H-OCHO), 4.70 (2H, s, Ph-*CH*$_2$-OCO), 5.13 (1H, d, J 15,*CH*=CH), 5.27 (1H, d, J 15,CH=*CH*), 6.7-6.9 (3H, m, aromatic hydrogens of dimethoxyphenyl), 7.2-7.4 (5H, m, *Ph*), 9.8 (1H, s, O-*CH*O).

4-(3,4-Dimethoxyphenyl)-4-formyloxymethyl-5-methyl-hexanoic acid (22)

The compound previously described (0.190 g, 0.461 mmol) was hydrogenated in ethanol - acetic acid (1:1) solution (5 ml) in presence of 10% palladium on charcoal (0.019 g) at room temperature. The reaction mixture was filtered, concentrated under reduced pressure, diluted with water, and extracted with ethyl acetate. The organic phase was dried, evaporated *in vacuo*, to give **22** (Found: C, 62.87; H, 7.55; $C_{17}H_{24}O_6$ requires C, 62.95; H, 7.46%); δ_H 0.80 (3H, d, J 7, CH*CH*$_3$), 0.98 (3H, d, J 7, CH*CH*$_3$), 1.20 (2H, m, *CH*$_2$-CH$_2$COOH), 2.30 (2H, m, *CH*$_2$COOH),

2.42 (1H, m, *CH*$(CH_3)_2$), 3.70 (6H, s, 2*OCH*$_3$), 3.95 (1H, d, J 11, *CH*H-OCHO), 4.11 (1H, d, J 11, CH*H*-OCHO), 6.6-6.8 (3H, m, aromatic hydrogens), 9.8 (1H, s, OCHO).

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REFERENCES

1. Cannarsa, J. *Chem.Ind.*, **1996**, 374.
2. Stinson, C. *C&EN*, **1993**, September 27, 38.
3. Ramuz, H. *Helv. Chim. Acta*, **1975**, *58*, 2050 and references therein.
4. Theodore, L.J.; Nelson, W.L. *J. Org. Chem.*, **1987**, *52*, 1309.
5. Gilmore, J.; Prouse, W.; Steggles, D.; Urquhart, M.; Olkowski, J. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 2845.
6. Seebach, D.; Kalinowski, H.O. *Nachr. Chem. Techn.*, **1976**, *24*, 515.
7. Fronza, G.; Fuganti, C.; Grasselli, P.; Malpezzi, L.; Mele, A. *J. Org. Chem.*, **1994**, *59*, 3487.
8. Fronza, G.; Fogliato, G.; Fuganti, C.; Grasselli, P.; Rigoni, R. *Tetrahedron*, **1996**, *52*, 14281.
9. Fogliato, G.; Fronza, G.; Fuganti, C.; Grasselli P.; Servi,, S. *J. Org. Chem.*, **1995**, *60*, 5693.
10. Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G.; Servi, S. *Tetrahedron Lett.*, **1992**, *33*, 5625.
11. Fronza, G.; Fuganti, C.; Pedrocchi-Fantoni, G.; Piergianni, V.; Sarra, A.; Servi, S. *Biotechnol. Lett.*, **1994**, *16*, 1047.
12. Adamson, D.W.; Barrett, P.A. Billinghurst, J.W.; Jones, T.S.G. *J. Chem. Soc.*, **1957**, 2315.
13. Hosokawa, T.; Nakajima, F.; Iwasa, S.; Murahashi, S. *Chem.Lett*, **1990**, 1387.
14. Hall, H.K. Jr.; DeBlauwe, F. *J.Am.Chem.Soc.*,**1975**, *97*, 655.
15. Fletcher, S.R.; Baker, R.; Chambers, M.S.; Herbert, R.H.; Hobbs, S.C.; Thomas, S.R.; Vrrier, H.M.; Watt, A.P.; Ball, R.G. *J.Org.Chem.*, **1994**, *59*, 1771.
16. Servi, S. *Synthesis*, **1990**, 1.
17. Yamada, ; Shimizu, S.; *Angew. Chem. Int. Engl. Ed.*, **1988**, *27*, 622.

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