Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 3487–3491

TETRAHEDRON

New chemo and chemo-enzymatic synthesis of β-benzyl-γ-butyrolactones☆

S. Koul, B. Singh, S. C. Taneja* and G. N. Qazi

Bio-organic Chemistry Section, Regional Research Laboratory, Canal Road, Jammu Tawi 180001, India

Received 2 January 2003; revised 28 February 2003; accepted 21 March 2003

Abstract—β-Benzyl-γ-butyrolactones, important intermediates for the synthesis of butyrolactone lignans, have been synthesized by a new route involving preparation of α-β-unsaturated formyl esters. The formyl esters can easily be converted into the desired butyrolactones either through chemical transformations or by enzymatic methods. © 2003 Published by Elsevier Science Ltd.

1. Introduction

Substituted β-benzyl-γ-butyrolactones are key intermediates in the synthesis of butyrolactone lignans as well as other natural products.[1] Due to various pharmacological and medicinal properties associated with butyrolactone and related lignans, chemical synthesis of the intermediate butyrolactones has been the major target of several synthetic schemes.[2] One of the more common synthetic strategies utilizes Stobbe's condensation of an aromatic aldehyde with alkyl succinates followed by selective reduction.[3] Besides this approach several new methodologies have also been reported for the asymmetric synthesis of the butyrolactones and the lignans.[4] In recent years, asymmetric syntheses of optically active butyrolactones and the corresponding lignans have also been achieved using chemo-enzymatic methods.[5] In this paper a new and facile chemo- and chemo-enzymatic strategy for the synthesis of β-benzyl-γ-butyrolactones is delineated.

2. Results and discussion

The strategy outlined here utilizes Vilsmeier's reaction[6] of substituted 4-hydroxy-4-arylbutanoates in the key step. Thus, the synthetic pathway to β-benzyl-γ-butyrolactones utilizes 4-oxo-4-arylbutanoates which through their reduction followed by formylation leads to the formation of an α,β-unsaturated aldehyde (3-formyl-4-arylbut-3-enoate). The unsaturated aldehyde thus obtained is an ideal prochiral precursor that may easily be reduced chemically as well as bio-catalytically. The partially or fully reduced alcohol undergoes facile cyclisation to produce the desired butyrolactones in moderate yields.

The preparation of substituted 4-oxo-4-arylbutanoic acids was achieved through Friedel–Crafts reaction of substituted benzenes **1** with succinic anhydride in the presence of anhydrous aluminum chloride. The 4-oxoarylbutanoic acids thus obtained were protected through ester formation to give **2**, followed by catalytic reduction using 5% Pd/C and hydrogen gas at 50 psi to furnish the hydroxy esters **3** in quantitative yield. Sodium borohydride reduction of **2** however gave a mixture of **3** and a cyclised product (butanolide). The butanolide may easily be converted into hydroxy butyrate **3** with triethylamine in methanol. The hydroxyester **3** was then subjected to a formylation reaction with Vilsmeier's reagent freshly prepared from phosphoryl chloride and dimethyl formamide. The product, mainly the (*E*)-α,β-unsaturated aldehydes **4** are isolated in 51–60% yield. The reduction of the prochiral aldehydes with borohydride generated primary alcohols **5** which were hydrolyzed with dilute acid to butenolides **6** which were then converted into the desired racemic β-benzyl-γ-butyrolactones **8** through hydrogenation over 5% Pd/C (over all yield of approximately 25% based on starting material). Alternatively, prochiral alcohol **5** can be hydrogenated to furnish racemic hydroxymethyl esters **7** which undergo facile cyclisation in dilute acid to furnish **8** (Scheme 1).

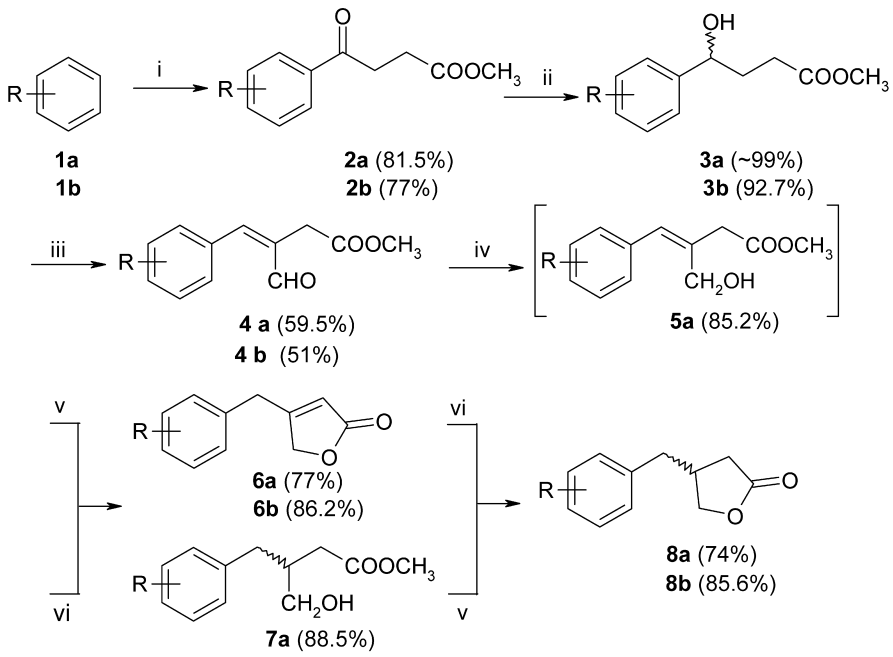
To prepare optically active butyrolactones using a chemo-enzymatic approach, intermediate α,β-unsaturated aldehyde **4a** was subjected to Baker's yeast mediated reduction at 30°C. The intermediate chiral alcohol **7a** isolated in 56.9% yield was converted into optically enriched *R*-(+)-butyrolactone **8a** (ee 47%, chiral HPLC) through acid catalyzed hydrolysis and concomitant cyclisation (Scheme 2). *R*-(+)-Butyrolactone **8a** has also been obtained by asymmetric synthesis (ee ~97%).[3b]

☆ R.R.L. contribution no. 2362.

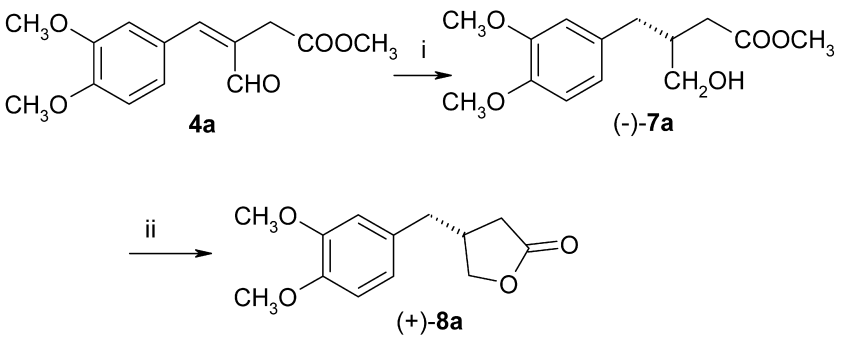
Keywords: β-benzyl-γ-butyrolactones; chemo-enzymatic synthesis; α-β-unsaturated formyl esters; Baker's yeast; bioreduction.

* Corresponding author. Tel.: +91-191-2580329; fax: +91-191-2548607; e-mail: sc_taneja@yahoo.co.in

0040–4020/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1016/S0040-4020(03)00476-9



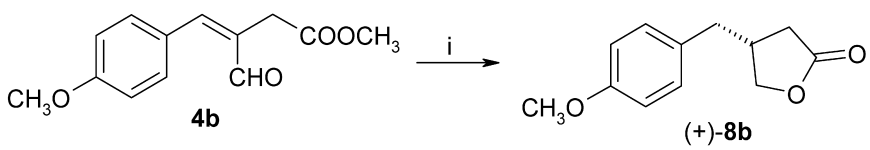
Scheme 1. (a) R=3,4-dimethoxy; (b) R=4-methoxy. (i) (a) Succinic anhydride/$AlCl_3$ (anhydrous), (b) diazomethane/diethyl ether; (ii) H_2, 5% Pd/C; (iii) DMF/$POCl_3$; (iv) $NaBH_4$/CH_3OH; (v) dil. HCl; (vi) H_2, 5% Pd/C.



Scheme 2. (i) Baker's yeast/D-glucose/50 h/30°C; (ii) dil. HCl.

It was observed that when 4-methoxyphenyl precursor **4b** was subjected to bio-reduction, the intermediate chiral primary alcohol could not be detected among the products. Instead Baker's yeast produced the desired optically enriched butyrolactone **8b** (op, 46% based on specific rotation value) directly (Scheme 3). Thus, in this case reduction, hydrolysis and cyclisation are all performed in a single step. The overall yield of the butyrolactone **8b** was comparable to **8a**, however its enantiopurity could not be accurately determined by chiral HPLC. Preparation of butyrolactone **8b** has earlier been reported through a kinetic resolution pathway (ee ~98%) using *meso*-diol ester as the substrate,[5d] present methodology however has a wider scope and applicability in terms of synthesis of **8** through asymmetric reduction or using other biocatalysts.

In conclusion the present new synthetic strategy provides access to both racemic as well as optically enriched β-benzyl-γ-butyrolactones. Although moderate enantiopurity of the final products have been achieved by the present chemoenzymatic approach compared to some reported kinetic resolution methodology and asymmetric synthesis, however for any further improvements in ees, use of other oxido-reductases as well as chiral catalysts using prochiral formyl esters **4** as the substrates would make an interesting study.



Scheme 3. (i) Baker's yeast/D-glucose/45 h/30°C.

3. Experimental

3.1. General

Melting points were determined on a Buchi 510 melting point apparatus. ^{1}H NMR spectra were recorded as δ values at 60, 90 and 200 MHz and ^{13}C NMR at 50 MHz using $CDCl_3$ as a solvent (or as mentioned) and TMS as internal standard. Infrared spectra were recorded as KBr pellets in cm^{-1} on a Hitachi 270-30 model spectrophotometer. Mass spectra were obtained on JEOL MSD-300 mass-spectrometer. Optical rotations were measured on Perkin–Elmer-241 polarimeter. Chiral HPLC was carried out on a Shimadzu LC-10 AT model. Reagents used were AR grade and all solvents for synthesis, extraction and column chromatography were distilled and dried before use.

3.1.1. Methyl 4-(3,4-dimethoxyphenyl)-4-oxobutanoate 2a. (a) In a three necked flask fitted with a guard tube, a mixture of veratrole (3,4-dimethoxy benzene, **1**) (7.0 g, 50 mmol) and anhydrous aluminum chloride (16 g, 120 mmol) in nitrobenzene (50 mL) stirred at 0–5°C and to the mixture was added dropwise a solution of succinic anhydride (6 g, 60 mmol) in nitrobenzene (60 mL). After the addition was over, the stirring mixture was allowed to attain room temperature and heated up to 60°C for a further 3 h till the evolution of hydrochloric acid subsides. The reaction mixture was cooled, poured into ice-cold water (200 mL) and the resulting precipitate was filtered, washed with water. The dried crude acid (10.6 g, 89%) was crystallized from methanol/ethyl acetate (1:9) to give a white powder (9.7 g, 81.4%) mp 162–63°C, [found C, 60.43; H, 5.90% $C_{12}H_{14}O_5$ requires C, 60.49; H, 5.92%]; ν_{max} (KBr) 3332, 1730, 1660, 1592, 1504, 1444, 1414, 1332, 1264, 1240, 1140, 1018 cm^{-1}; δ_H (200 MHz, CD_3OD) 2.67 (2H, t, J=6.6 Hz, CH_2COOMe), 3.27 (2H, t, J=6.6 Hz, COCH_2), 3.86, 3.89 (6H, 2×s, 2×O*Me*), 7.02 (1H, d, J=8.5 Hz, Ar-*H*), 7.65 (1H, d, J=2.0 Hz, Ar-*H*), 7.68 (1H, dd, J=8.5, 2.0 Hz, Ar-*H*); δ_C (50 MHz, CD_3OD) 33.6, 33.7, 56.1, 56.2, 111.2, 111.4, 123.8, 130.8, 150.1, 154.7, 175.0, 198.9.

(b) 4-(3,4-Dimethoxyphenyl)-4-oxobutanoic acid (5 g, 21 mmol) in diethyl ether (150 mL) is esterified with a freshly prepared ethereal solution of diazomethane to furnish the corresponding ester in quantitative yield (5.25 g, ~99%), which on crystallization from ethyl acetate/*n*-hexane gave colorless needles of **2a** (5 g) mp 87°C [found C, 62.14; H, 6.41% $C_{13}H_{16}O_5$ requires C, 61.89; H, 6.39%]; ν_{max} (KBr) 2876, 1714, 1666, 1592, 1446, 1412, 1380, 1244, 1210, 1178, 1148, 1088, 1020, 988, 914, 872 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.76 (2H, t, J=7.0 Hz, CH_2COOMe), 3.22 (2H, t, J=7.0 Hz, COCH_2), 3.56 (3H, s, O*Me*), 3.96 (6H, s, 2×O*Me*), 6.94 (1H, d, J=8.5 Hz, Ar-*H*), 7.60–7.73 (2H, m, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 27.7, 32.2, 51.6, 55.3, 55.4, 109.7, 109.8, 122.1, 129.3, 148.3, 152.7, 174.2, 196.3; M^+ at *m/z* 252 (16), 221 (7), 206 (8), 179 (5), 165 (61), 132 (49), 119 (100), 91 (36), 89 (79), 74 (91).

3.1.2. Methyl 4-(4-methoxyphenyl) methyl-4-oxobutanoate 2b. (a) The title compound was prepared from anisole (11 g, 102 mmol) and succinic anhydride (12 g, 120 mmol) in presence of anhydrous aluminum chloride (30 g, 226 mmol) by the same method as described for **2a** to furnish 4-(4-methoxyphenyl)-4-oxo-butanoic acid (17.9 g, 84.6%), which on purification and crystallization from methanol/ethyl acetate (1:9) produced colorless crystals (16.3 g, 77%), mp 142–43°C [found C, 64.21; H, 5.86% $C_{11}H_{12}O_4$ requires C, 63.45; H, 5.80%]; ν_{max} (KBr) 1670, 1600, 1426, 1358, 1246, 1026, 830 cm^{-1}; δ_H (200 MHz, $CDCl_3$+DMSO-d_6) 2.70 (2H, t, J=6.5 Hz, CH_2COOMe), 3.26 (2H, t, J=6.5 Hz, CH_2CO), 3.93 (3H, s, O*Me*), 7.04 (2H, d, J=8.5 Hz, Ar-*H*), 8.05 (2H, d, J=8.5 Hz, Ar-*H*); δ_C (50 MHz, $CDCl_3$+DMSO-d_6) 28.1, 32.9, 55.4, 114.2, 129.7, 130.1, 162.7, 174.6, 196.7; M^+ at *m/z*, 208 (40), 135 (83), 120 (12), 106 (69), 91 (100), 77 (100).

(b) The butanoic acid (10.16 g,48.8 mmol) was esterified in diethyl ether using freshly prepared diazomethane in quantitative yield to furnish **2b** (10.8 g, 99%),which is crystallized from ethyl acetate/hexane (1:4) as colorless solid mp 46°C [found C, 65.46; H, 6.42% $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.34%]; ν_{max} (KBr) 1670, 1600, 1516, 1426, 1358, 1310, 1240, 1174, 1120, 1022, 944, 830 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.75 (2H, t, J=6.5 Hz, CH_2COOMe), 3.28 (2H, t, J=6.5 Hz, CH_2CO), 3.75 (2H, s, COO*Me*), 3.90 (3H, s, O*Me*), 7.00 (2H, d, J=8.5 Hz, Ar-*H*), 8.05 (2H, d, J=8.5 Hz, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 28.1, 33.0, 51.8, 55.4, 113.8, 129.6, 130.3, 163.6, 173.5, 196.6; M^+ at *m/z*, 222 (13), 191 (19), 135 (100), 107 (18), 97 (27), 92 (27), 77 (37).

3.1.3. Methyl 4-(3,4-dimethoxyphenyl)-4-hydroxybutanoate 3a. The oxoester **2a** (3.3 g, 13 mmol) was reduced in presence of Pd/C (5%) and hydrogen gas at 50 psi in ethanol (30 mL) to quantitatively produce racemic alcohol **3a** (3.3 g, ~99%) [found C, 61.66; H, 7.20% $C_{13}H_{18}O_5$ requires C, 61.40; H, 7.13%]; ν_{max} (KBr) 3256, 1718, 1594, 1332, 1250, 1236, 1144, 1030, 940, 858 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.01–2.12 (2H, m, CH_2), 2.53 (2H, t, J=7.4 Hz, CH_2COO), 3.65 (3H, s, O*Me*), 3.89 (6H, s, 2×O*Me*), 4.69 (1H, t, J=6.6 Hz, *CH*OH), 6.82–6.89 (3H, m, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 30.4, 33.8, 51.9, 55.8, 55.9, 73.2, 108.9, 111.0, 118.0, 136.8, 148.4, 149.1, 174.3; M^+ at *m/z* 254 (6), 236 (1), 234 (5), 218 (7), 216 (4), 204 (5), 188 (6), 182 (8), 174 (10), 164 (22), 162 (17), 137 (22), 136 (100), 121 (17), 105 (18), 90 (27).

3.1.4. Methyl 4-(4-methoxyphenyl)-4-hydroxybutanoate 3b. Reduction of **2b** (7.0 g, 31 mmol) was carried out by a similar process as described for **2a**, the reduced product purified by column chromatography over silica gel using dichloromethane/ethyl acetate (19:1) as eluant to give a semi-solid (6.4 g, 92.7%) [found C, 64.93; H, 7.23% $C_{12}H_{16}O_4$ requires C, 64.27, H, 7.19%]; ν_{max} (KBr) 1678, 1604, 1512, 1362, 1240, 1172, 1114, 1026, 944 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.98–2.10 (2H, m, CH_2), 2.40 (2H, t, J=7 Hz, CH_2COOMe), 3.65 (3H, s, COO*Me*), 3.83 (3H, s, O*Me*), 4.66 (1H, t, J=6.5 Hz, C*H*OH), 6.94 (2H, d, J=8.5 Hz, Ar-*H*), 7.33 (2H, d, J=8.5 Hz, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 30.3, 33.7, 51.5, 55.07, 72.6, 113.6, 126.9, 131.0, 158.8, 174.2; M^+ at *m/z* 224 (2), 223 (6), 206 (3), 205 (7), 191 (15), 149 (21), 136 (100), 134 (21), 108 (28), 93 (12), 76 (29).

3.1.5. Methyl 4-(3,4-dimethoxyphenyl)-3-formyl-3(*E*)-butenoate 4a. To a stirring solution of hydroxy ester **3a**

(2.3 g, 9 mmol) in dimethyl formamide (9 mL) at 0–5°C is added phosphoryl chloride (5 mL) slowly for 30 min. The contents further stirred for one hour maintaining the temperature. The temperature is then raised to 35–40°C and stirring continued for 36 h till the completion of the reaction. The contents were poured in cold water (200 mL) and the resulting precipitate filtered. The aqueous layer was extracted with ethyl acetate (3×20 mL). The combined solid and organic layer were washed with water, dried, concentrated and chromatographed over silica gel using ethyl acetate/dichloromethane (1:4) as eluant to give a light yellow compound **4a** (1.4 g, 59.5%). mp 61°C [found C, 64.11; H, 6.09% $C_{14}H_{16}O_5$ requires C, 63.62; H, 6.10%]; ν_{max} (KBr) 1752, 1590, 1512, 1456, 1424, 1352, 1266, 1240, 1152, 1022, 864 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.56 (2H, s, *CH*$_2$COOMe), 3.64 (3H, s, O*Me*), 3.86 (6H, 2×s, 2×O*Me*), 6.88 (1H, d, *J*=8.5 Hz, Ar-*H*), 7.00 (1H, m, Ar-*H*), 7.05 (1H, s, Ar-*H*), 7.37 (1H, s, =C*H*), 9.56 (1H, s, C*H*O); δ_C (50 MHz, $CDCl_3$) 30.7, 52.2, 55.9, 55.9, 111.2, 112.3, 124.1, 126.9, 133.2, 149.1, 150.9, 152.2, 172.2, 193.2; M^+ at *m/z*: 264 (26), 263 (91), 248 (11), 235 (41), 232 (25), 204 (39), 176 (100), 160 (92), 145 (60), 131 (25), 115 (25), 103 (24), 91 (28), 89 (28).

3.1.6. Methyl 3-(4-methoxyphenyl)-3-formyl-3(*E*)-butenoate 4b. Formylation of **3b** (4.5 g, 20 mmol) was carried out with Vilsmeier's reagent as described for **3a**. The product purified by column chromatography with pet. ether/ethyl acetate (9:1) to furnish **4b** as a light yellow solid (2.38 g, 51%), mp 54–56°C [found C, 67.13; H, 6.09% $C_{13}H_{14}O_4$ requires C, 66.65; H, 6.02%]; ν_{max} (KBr) 1722, 1666, 1632, 1602, 1494, 1438, 1416, 1380, 1254, 1200, 1018, 1004, 942, 912, 878, 834 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.59 (2H, s, C*H*$_2$), 3.72 (3H, s, COO*Me*), 3.89 (3H, s, O*Me*), 7.03 (2H, d, *J*=8.5 Hz, Ar-*H*), 7.53 (1H, s, =C*H*), 7.56 (2H, d, *J*=8.5 Hz, Ar-*H*), 9.66 (1H, s, C*H*O); δ_C (50 MHz, $CDCl_3$) 30.7, 52.3, 55.5, 114.6, 126.8, 131.3, 133.3, 148.3, 161.4, 171.0, 194.3; M^+ at *m/z*: 234 (6), 233 (42), 205 (96), 202 (31), 174 (31), 159 (24), 146 (100), 134 (14), 107 (17).

3.1.7. Methyl 4-(3,4-dimethoxyphenyl)-3-hydroxymethyl-3(*E*)-butenoate 5a. A methanolic solution of **4a** (0.4 g, 1.5 mmol) at 0–5°C was reduced by slow addition of sodium borohydride (40 mg). After the completion of the reaction the contents poured into cold water and extracted with chloroform (4×40 mL). The water washed organic layer was concentrated and passed through a silica gel column using chloroform/ethyl acetate (9:1) as eluant to furnish a semi-solid **5a** (0.34 g, 85.2%) [found C, 63.98; H, 6.86% $C_{14}H_{18}O_5$ requires C, 63.14; H, 6.81%]; ν_{max} (KBr) 3348, 1698, 1597, 1446, 1358, 1260, 1198, 1156, 1074, 866 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.70 (3H, s, O*Me*), 3.90, 3.93 (6H, 2×s, 2×O*Me*), 4.71 (2H, s, C*H*$_2$OH), 5.86 (1H, s, =C*H*), 6.72 (1H, s, Ar-*H*), 6.77 (1H, d, *J*=8.5 Hz, Ar-*H*), 6.89 (1H, d, *J*=8.5 Hz, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 34.9, 55.8, 55.9, 56.0, 72.7, 111.5, 111.6, 116.4, 121.0, 127.9, 133.7, 148.4, 149.4, 169.4; M^+ at *m/z* 266 (3), 205 (10), 204 (29), 178 (3), 173 (10), 159 (23), 147 (13), 145 (11), 134 (19), 121 (100), 108 (37), 91 (17).

3.1.8. 3-(3,4-Dimethoxyphenyl) methyl-2-butenolide 6a. A solution of **5a** (100 mg, 0.37 mmol) in ethanol (1 mL) and dilute hydrochloric acid (10%, 10 mL) was heated at 60–80°C with TLC monitoring. After the completion of the reaction, the contents of the reaction were cooled and extracted with chloroform (5×10 mL). The organic layer washed free of acid, dried, concentrated and chromatographed over silica gel with chloroform/ethylacetate (9:1) to produce colorless gummy mass **6a** (67 mg, 77%) [found C, 66.89; H, 6.04% $C_{13}H_{14}O_4$ requires C, 66.66; H, 6.02%]; ν_{max} (KBr) 1728, 1636, 1514, 1448, 1304, 1250, 1126, 1028, 886 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.66 (2H, s, C*H*$_2$), 3.83, 3.85 (6H, 2×s, 2×O*Me*), 4.68 (2H, s, C*H*$_2$O), 5.77 (1H, s, =C*H*), 6.66 (1H, s, Ar-*H*), 6.70 (1H, d, *J*=8.4 Hz, Ar-H), 6.81 (1H, d, *J*=8.4 Hz, Ar-*H*); M^+ at *m/z* 234 (5), 221 (13), 207 (100), 191 (16), 133 (11), 121 (12), 111 (18), 107 (8).

3.1.9. 3-(4-Methoxyphenyl) methyl-2-butenolide 6b. Sodium borohydride (70 mg) was added in small proportions to a methanolic solution of **4b** (0.6 g, 2.5 mmol) at 0–5°C. After the completion of the reaction (TLC monitored), the contents worked-up as described for the preparation of **5a** to give directly **6b** which was purified on silica column with chloroform/methanol (9:1) as eluant to furnished pure product as a gum (0.45 g, 86.2%) [found C, 71.33; H, 5.99% $C_{12}H_{12}O_3$ requires C, 70.57; H, 5.92%]; ν_{max} (KBr) 1728, 1636, 1514, 1352, 1304, 1250, 1174, 1126, 1028, 886, 832 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.68 (2H, s, C*H*$_2$), 3.80 (3H, s, O*Me*), 4.70 (2H, s, C*H*$_2$O), 5.78 (1H, bs, =C*H*), 6.87 (2H, d, *J*=8.5 Hz, Ar-*H*), 7.13 (2H, d, *J*=8.5 Hz, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 34.4, 55.3, 72.7, 114.2, 116.2, 127.6, 129.2, 158.9, 169.7, 173.8; M^+ at *m/z*: 204 (68), 189 (10), 175 (5), 160 (22), 159 (31), 147 (13), 145 (38), 135 (14), 121 (100), 107 (98), 90 (51), 78 (87).

3.1.10. Racemic methyl 4-(3,4-dimethoxyphenyl)-3-hydroxymethylbutanoate 7a. The compound **5a** (200 mg, 0.75 mmol) was hydrogenated in presence of Pd/C (5%, 60 mg) at 40 psi in ethanol (20 mL) to give racemic semi-solid (178 mg, 88.5%) **7a** after usual workup [found, C, 63.03; H, 7.58% $C_{14}H_{20}O_5$ requires C, 62.67, H, 7.51%]; ν_{max} (KBr) 1710, 1598, 1442, 1322, 1262, 1242, 1152, 1024, 804 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.37–2.48 (3H, m, C*H*$_2$, C*H*), 2.64 (2H, bs, Ar–C*H*$_2$), 3.28 (3H, s, COO*Me*), 3.27–3.30 (2H, m, OC*H*$_2$), 3.87 (6H, s, 2×O*Me*), 6.74–6.84 (3H, m, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 36.0, 36.1, 37.5, 55.8, 55.9, 58.9, 74.3, 111.3, 112.6, 121.4, 132.1, 147.6, 148.9, 178.6.

3.1.11. Racemic 3-(3,4-dimethoxyphenyl) methylbutyrolactone 8a. *Method A*. A suspension of **7a** (100 mg, 0.37 mmol) and dilute hydrochloric acid (10%, 5 mL) heated at 70°C for 20 min with stirring. The cooled solution was diluted with water (10 mL) and extracted with chloroform (4×10 mL). The organic layer washed with water, dried and concentrated under vacuo to furnish a crude solid which was purified by column chromatography over silica gel with chloroform/ethylacetate (9:1) as eluant to give a white powder **8a** (62 mg, 70.5%) mp 110–111°C [found C, 66.14; H, 6.87% $C_{13}H_{16}O_4$ requires C, 66.08; H, 6.82%]; ν_{max} (KBr) 1762, 1584, 1510, 1448, 1408, 1388, 1362, 1260, 1144, 1034, 841 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.33 (1H, dd, *J*=6.6, 17.4 Hz, –C*H*), 2.55–2.84 (4H, m, 2×C*H*$_2$), 3.89 (6H, s, 2×O*Me*), 4.06, 4.30 (2H, dd, *J*=5.7, 9.2 Hz, OC*H*$_2$), 6.66 (1H, s, Ar-*H*), 6.70 (1H, dd, *J*=8.5,

2.4 Hz, Ar-*H*), 6.84 (1H, d, *J*=8.5 Hz, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 34.3, 37.4, 38.7, 56.0, 56.1, 72.7, 111.6, 112.0, 120.9, 130.9, 148.1, 149.3, 176.9; M^+ at *m/z* 236 (22), 181 (7), 152 (15), 151 (100), 137 (6), 121 (8), 106 (12), 90 (130, 78 (11).

3.1.12. Racemic 3-(4-methoxyphenyl) methylbutyrolactone 8b. A solution of **6b** (250 mg, 1.22 mmol) in ethanol (10 mL) was hydrogenated in presence of Pd/C (5%, 50 mg) at 45–50 psi and the product obtained after filtration, removal of the solvent and column chromatography over silica gel with hexane/ethyl acetate (9:1) as a semi solid (215 mg, 85.6%) **8b** [found C, 70.05; H, 6.99% $C_{12}H_{14}O_3$ requires C, 69.89; H, 6.84%]; ν_{max} (KBr) 1732, 1614, 1510, 1460, 1302, 1248, 1176, 1030, 834 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.27 (1H, dd, *J*=6.65, 17.45 Hz, –C*H*), 2.52–2.72 (4H, m, 2×CH_2), 3.80 (3H, s, O*Me*), 4.04 (1H, dd, *J*=5.90, 8.17 Hz, OCH_{2a}), 4.31 (1H, dd, *J*=6.65, 9.03 Hz, –OCH_{2b}), 6.81 (2H, d, *J*=8.5 Hz, Ar-*H*), 7.08 (2H, d, *J*=8.5 Hz, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 34.3, 37.3, 38.0, 55.2, 72.7, 113.8, 130.0, 130.3, 158.5, 177.0; M^+at *m/z* 206 (8), 192 (3), 147 (6), 121 (100), 103 (8), 91 (20), 78 (35).

Method B. Alternatively, **6a** could easily be hydrogenated catalytically to furnish racemic butyrolactone **8a** in 90% yield by the same method as described above for the conversion of **5a** to **7a**.

3.1.13. Optically enriched methyl 4-(3,4-dimethoxyphenyl) 3-hydroxymethylbutanoate 7a. A mixture of Baker's yeast (3 g, dry powder) and D-glucose (3 g) in distilled water (60 mL, pH 6.8) was stirred at 30°C in a fermentation flask with a bubbler for 10 min after which an ethanolic solution (3 mL) of formyl ester **4a** (173 mg, 0.65 mmol) was added to it. The mixture stirred at 30°C for 50 h with TLC monitoring and after the consumption of **4a**, filtered through a pad of celite (2 g) and extracted with chloroform (5×20 mL). The combined chloroform layer was washed and dried (sod. sulfate), concentrated under reduced pressure. The concentrated material was purified over silica gel using chloroform/ethyl acetate (9:1). The purified product **7a** (100 mg, 56.9%) a semi-solid [found C, 62.92; H, 7.55% $C_{14}H_{20}O_5$ requires C, 62.67; H, 7.50%]; $[\alpha]_D^{25}$=−3.4 ($CHCl_3$, *c*, 1.4).

3.1.14. Optically enriched (*R*)-(+)-3-(3,4-dimethoxyphenyl) methyl butyrolactone 8a. A suspension of **7a** (60 mg,0.22 mmol) and dilute hydrochloric acid (10%, 5 mL) heated at 70°C for 20 min with stirring. The product processed as described for the preparation of racemic lactone above to furnish optically enriched **8a** (39 mg, 74%) [ee, 47% on a Chiradex chiral column (β-cyclodextrin) using methanol/water (9:1) as the mobile phase, oven temperature 22°C, detection at 256 nm, flow rate 0.5 mL/min, retention time 13.8 and 18.4 min, respectively], mp 108–109°C [found C, 66.12; H, 6.87% $C_{13}H_{16}O_4$ requires C, 66.08; H, 6.82]; $[\alpha]_D^{25}$=+10.5 ($CHCl_3$, *c*, 0.24); reported $[\alpha]_D^{25}$=+23.8 (op, 97%).[3b]

3.1.15. Optically enriched *R*-(+)-3-(4-methoxyphenyl) methylbutyrolactone 8b. An ethanolic solution (3 mL) of **4b** (160 mg, 0.68 mmol) is added to a stirring mixture of Baker's yeast (dry powder, 2.5 g) and D-glucose (2.1 g) in distilled water (80 mL, pH 6.8) and the contents stirred at 30°C using a bubbler. The reaction is monitored by TLC and after the consumption of the starting material (45 h) the contents worked up by the method as described for **8a** to furnish crude bio-product (0.13 g) which on chromatographic purification on silica gel column and elution with pet. ether/ethyl acetate (9:1) gave (+)-**8b** (80 mg, 57%) [found C, 70.13; H, 6.81% $C_{12}H_{14}O_3$ requires C, 69.89; H, 6.84%]; $[\alpha]_D^{25}$=+2.5 ($CHCl_3$, *c*, 1.6), reported $[\alpha]_D^{25}$=+5.4 (op, 98%) ($CHCl_3$, *c*, 6.8).[5d]

References

1. (a) Ward, R. S. *Nat. Prod. Rep.* **1997**, *14*, 43. (b) Whiting, D. A. *Nat. Prod. Rep.* **1990**, *7*, 349.
2. Ward, R. S. *Tetrahedron* **1990**, *46*, 5029. and references cited therein.
3. (a) Banerji, J.; Biswanath, D. *Heterocycles* **1985**, *23*(3), 661–665. (b) Shao, L.; Miyato, S.; Muramatsui, H.; Kawano, H.; Ishi, Y.; Soburi, M.; Uchida, Y. *J. Chem. Soc. Perkin Trans. 1* **1990**, *5*, 1441–1445. (c) Marimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron* **1993**, *49*(9), 1793–1806.
4. (a) Vanderlei, J. M. de. L.; Coelho, F.; Almeida, W. P. *Synth. Commun.* **1998**, *28*(16), 3047–3055. (b) Carlton, J. L. *Can. J. Chem.* **1997**, *75*(8), 1076–1083. (c) Filho, H. C. A.; Filho, U. F. L.; Pinheiro, S.; Vasconcells, M. L. L. A.; Costa, P. R. R. *Tetrahedron: Asymmetry* **1994**, *5*(7), 1219–1220. (d) Costo Paulo, R. R. V.; Ferreiro, J. *Braz. Chem Soc.* **1996**, *7*(1), 67–73, *Chem. Abstr.*, *124*, 260681y.
5. (a) Chenvert, R.; Mohammadi, Z. G.; Caron, D.; Dasser, M. *Can. J. Chem.* **1999**, *77*(2), 223–226. (b) Brinksma, J.; Vander Deen, H.; van Oeveren, A.; Feringa, B. L. *J. Chem. Soc. Perkin Trans. 1* **1998**, *1*(24), 4159–4164. (c) Alphand, V.; Mazzini, C.; Lebreton, J.; Furstoss, K. *J. Mol. Catal. B. Enzym.* **1998**, *5*(1–4), 219–221. (d) Shiotani, S.; Okada, H.; Yamamoto, T.; Nakamata, K.; Adachi, J.; Nakamoto, H. *Heterocycles* **1996**, *43*(1), 113–126. (e) Mazzini, C.; Lebreton, J.; Furstoss, R. *J. Org. Chem.* **1996**, *91*(1), 8–9. (f) Lemoult, S. C.; Richardson, P. F.; Roberts, S. M. *J. Chem. Soc. Perkin Trans. 1* **1995**, *2*, 89–91. (g) Gagnon, R.; Grogan, G.; Groussain, G. E.; Pedragosa, M.; Sandrine, R.; Paul, F.; Roberts, S. M.; Willets, A. J.; Alphand, V.; Lebreton, J.; Furstoss, R. *J. Chem. Soc. Perkin Trans. 1* **1995**, *2*, 2527–2528. (h) Itoh, T.; Chicka, J. C.; Takagi, Y. *J. Org. Chem.* **1993**, *58*(21), 5117–5123. (i) Kong, S.-K.; Eon, J.-H.; Yamaguchi, T.; Hong, R. K.; Ko, B.-S. *Tetrahedron: Asymmetry.* **1995**, *6*(1), 97–100. (j) Sime, J. T.; Barnes, R. D.; Elson, S. W.; Jarvest, R. L.; OToole, K. J. *J. Chem. Soc. Perkin Trans. 1* **1992**, *13*, 1653–1658. (k) Yang, L. M.; Lin, S. J.; Yang, T. H.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **1996**, *6*(8), 941–944.
6. Reddy, M. P.; Krishna Rao, G. S. *Synthesis* **1980**, 815.