J. Braz. Chem. Soc., Vol. 7, No. 1, 67-73, 1996.
Printed in Brazil.

Carbohydrates and Terpenes as Chiral Auxiliaries: the Stereoselective Synthesis of (+) or (-)-β-Piperonyl-γ-Butirolactone

Paulo R.R. Costa,[*a] ***Vitor Francisco Ferreira,***[*b]
Hiram C.A. Filho[a] ***and Sergio Pinheiro***[b]

[a] *Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro,*
CCS-Bloco H, CEP 21941-900, Rio de Janeiro, Brazil
[b] *Universidade Federal Fluminense, Curso de Mestrado em Química Orgânica-GQO,*
Niterói, 24210-150 RJ, Brazil

Received: July 14, 1995; November 10, 1995

Reações de alquilação assimétrica de enolatos de lítio obtidos a partir dos ésteres **11a-f**, utilizando auxiliares quirais derivados de terpenos e carboidratos, forneceram produtos alquilados com excessos diastereoisomérico de 10-78 %. Os ésteres quirais foram transformados em duas etapas na β-piperonil-γ-butirolactona (+) ou (-)-**2**, que são importantes materiais de partida para a síntese de lignanas naturais com importantes atividade biológicas.

Kinetic asymmetric alkylation reactions of lithium enolates derived from chiral esters **11a-f** prepared by using either terpene or carbohydrate derivatives as chiral auxiliaries occur in 10-78% d.e. The allylated chiral esters **12d** were transformed in two steps into the β-piperonyl-γ-butirolactone (+) or (-)-**2**, which are importants starting materials for the synthesis of biologically active naturally occurring lignans.

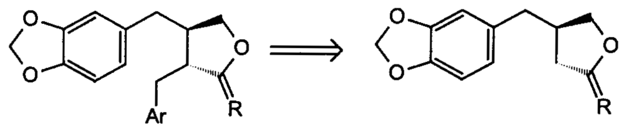
Keywords: *lignans, alkylation, asymmetric synthesis*

Introduction

Lignans belong to a class of natural products widely distributed in plants[1] and most of them have important biological properties such as **1**[2,3]. Due to their activities and varied structures they have been very attractive target molecules for organic synthesis[4]. Indeed, recent progress in synthetic methods has resulted in several new developments for the asymmetric synthesis of lignans[5], mainly using (+)-β-piperonyl-γ-butirolactone **2** as the key intermediate. This compound has been prepared enantioselectively by many routes from moderate to high enantiomeric excess[5]. However, none of the methods explored the asymmetric α-alkylation reaction of chiral esters using either terpene or carbohydrate derivatives as the chiral auxiliaries for the preparation of **2**.

Results and Discussion

Herein we report the study of the asymmetric α-alkylation of chiral esters as the key step in the preparation of **2**, by using the terpene derivatives **3-5** and the carbohydrate derivatives **6-8** as chiral auxiliaries (Fig. 1)[6-9].



1, R=O
R=H,H
R=H,OR

(+)-**2**

In previous work[10] we converted the naturally abundant safrole **9** into the acid **10** in two steps. Compound **10** was used as the starting material for preparing the chiral esters **11a-f** (Scheme 1). These compounds were obtained from **10** by using the appropriated chiral auxiliaries **3-8** upon esterification with DCC/DMAP[11] in yields ranging from 43-83% (entries 1-6, Table 1). As shown in Table 1 this method gave poor results for the preparation of ester **11a** with the alcohol (-)-**3** (entry 1), but this yield was improved (65%) by using the procedure described by Oppolzer[12].

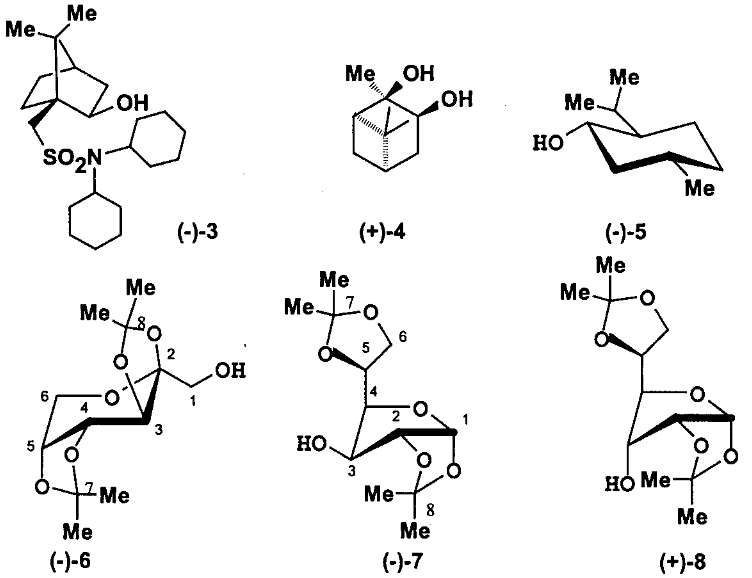
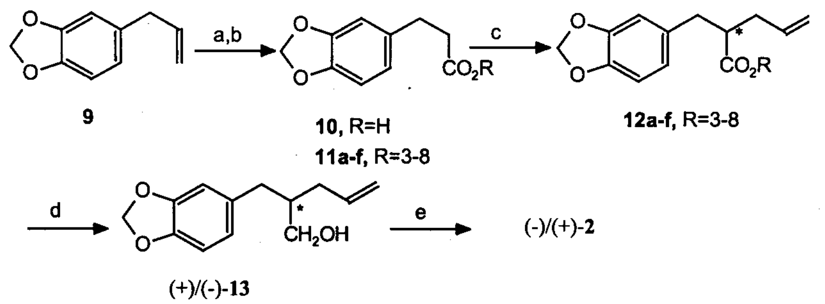


Figure 1. Chiral auxiliaries **3-8** used in the asymmetric α-alkylation of **11a-f.**



Scheme 1. Synthesis of β-piperonyl-γ-butirolactone (+) or (-)-**2**.
a) Ref.10; b) DCC /.DMAP / CH_2Cl_2, alcohol **3-8**, r.t.; c) LDA / THF, -78 °C, then allyl bromide; d) LiAl H_4/THF, 0 °C; e) $NaIO_4$/ cat. $KMnO_4$/ t-BuOH, pH 8.

Table 1. Asymmetric α-allylation of esters **11a-f.**

Entry	R-OH	11 (%)	12 (%)	d.e. % (R:S)
1	**(-)-3**	**11a** (43)[a]	**12a** (60)	78(11:89)
2	**(+)-4**	**11b** (66)	**12b** (11)[b]	72(14:86)
3	**(-)-5**	**11c** (81)	**12c** (61)	10(45:55)
4	**(-)-6**	**11d** (83)	**12d** (56)	40(70:30)
5	**(-)-7**	**11e** (74)	**12e** (52)	16(58:42)
6	**(+)-8**	**11f** (70)	**12f** (44)	40(30:70)

a) Compound **11a** was obtained in a 65% yield by using $C_2H_4Cl_2$/benzene and then AgCN/(-)-**3**[12]; b) 3.0 eq. of LDA was used in the kinetic deprotonation.

The chiral esters **11a-f** were kinetically deprotonated with lithium diisopropylamide (LDA, 1.5 eq., -78 °C)[8] and allowed to react with allyl bromide (1.2 eq.) in THF. The usual work up and purification by column chromatography afforded the diastereomeric mixtures of allyl esters **11a-f**. Compound **12d** was reduced to the allyl alcohol **(+)-13** in an 82% yield with lithium aluminum hydride in THF. Finally, cleavage of the double bond with $NaIO_4$/cat. $KMnO_4$/t-BuOH followed by *in situ* oxidation yielded the corresponding β-piperonyl-γ-butirolactone **(-)-2** in a 64% yield[13].

Optical purity (d.e.) of the alkylated esters **12a-b** were determined directly either by HPLC analysis using Lichrocart-RP-18 (18.5 μm) or by ^{1}H-NMR (**12d**). The absolute configuration of these products was determined by converting **12a-f** into the corresponding well known chiral lactone **(-)-2** and measuring its optical rotation (see Experimental).

From the results in the Table, it is clear that, as expected, the diastereoselectivity was very dependent on the structure of the chiral auxiliaries. It is notable that except for the esters derived from 2,3:4,5-di-O-isopropylidene-β-D-fructopyranose **(-)-6** and 1,2;5,6-di-O-isopropylidene-α-D-glucofuranose **(-)-7** (entries 4 and 5), the configuration of the major allyl esters was always S. The best diastereomeric excess was obtained from 10-dicyclohexylsulfamoyl-D-isoborneol **(-)-3** and (+)-pinanediol **(+)-4** (entries 1 and 2).

However, the chemical yield for the alkylation of **11b** (entry 2) was very poor, probably due to the presence of the free hydroxyl group. It is worth nothing that diastereomeric alkylations obtained with 1,2;5,6-di-O-isopropylidene-α-D-allose **(+)-8** (entry 6) and with **(-)-6** (entry 4) resulted in products with the same moderate d.e., but with a different sense of stereoselection. These compounds can be considered as a "enantiomeric pairs" with different structures.

Many studies indicate that regio- and stereochemistry of the reaction of lithium enolates with nucleophiles depends on stereochemistry and the degree of aggregation of the enolates[14-19]. In the literature it is known that the enolates generated from **11a** and **11d** (entries 1 and 4) mainly have the E(O) geometry (proven by ketene-silyl-acetals)[8,15].

These results suggest the possibility that the enolates generated from esters **11b-c** and **11e-f** probably also exist with E(O) geometry. The origin of the high Si facial diastereoselectivity found in the alkylation of **11a-b** (entries 1 and 2) is probably related to the pronounced intramolecular complexing ability of lithium cation of enolate by the oxygen atoms of **(-)-3** and **(+)-4**, enhancing the rigidity of the main conformation in the transition states of the alkylation step. Another possible explanation is that these auxiliaries can increase the degree of the aggregation state of the enolates (*e.g.* dimers, tetramers, hexamers, etc.)[15-17]. Since there is no functionality present in the chiral auxiliary **(-)-5** of ester **11c** to complex with lithium (entry 3) very low diastereoface selection was found[15].

The complex-forming ability of carbohydrate auxiliaries is strongly affected by several possible sites for complexation with lithium in the alkylation step (entries 4-6). Apart from the E/Z preference of the enolates of ester **11e**, this compound showed practically no diastereodifferentiation. On the other hand, the enolates derived from esters **11d** and **11f** gave moderate differentiation of the π-faces (Re and Si, respectively).

The above discussion which is intended to give some insights into the asymmetric -alkylation of esters **11a-f** using some natural product derivatives such as chiral auxiliaries took mainly taking into account the complexing ability of these chiral auxiliaries. However, in another work it was postulated that chirality based on chelation does not affect the transition states of these reactions[20].

Conclusion

In summary, asymmetric α-alkylation of the chiral enolates **11a-f** with stereodiscriminating auxiliaries derived from terpenes and carbohydrates offer a variety of possibilities for spatial differentiation on a reactive site. The best result was found with the most expensive chiral auxiliary **(-)-3** that gave alcohol as **13** having **S** absolute configuration and the natural occurring lignans show the **R** configuration at C(3). However, (+)-pinanediol **(+)-4** is very promising, and the chemical yield of the alkylation is being improved in our laboratory. In addition to the fact that the carbohydrates **6-8** have shown moderate optical yield, they are very inexpensive, and the chiral information that they contain can be exploited in stereodifferentiating selection. The diastereomeric allylated esters were successfully transformed into the important intermediate β-piperonyl-γ-butirolactone (+)-2 or **(-)-2** for the asymmetric synthesis of biologically active lignans.

Experimental Details

General procedures

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The solvents used were of analytical grade and were purified and dried by using the procedure described in the literature[21]. The chiral auxiliaries (-)-10-dicyclohexylsulfamoyl-D-isoborneol **(3)**, (1S,2S,3R,5S)-pinanediol **(4)**, and (1R,2S,5R)-(-)-menthol **(5)** were purchased from Aldrich Chemical Co., and 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose **(6)**, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **(7)** and 1,2:5,6-di-*O*-isopropylidene-α-D-xylofuranose **(8)** were prepared from D-glucose and D-fructose by known procedures[22-23]. Optical rotations were recorded with a Perkin-Elmer 243-B polarimeter. Column chromatography was performed on silica gel 60 (Merck). Infrared spectra were recorded with a Perkin-Elmer 783 spectrophotometer. NMR spectra were recorded with either a Varian VXR (300 MHz) or a Gemini (200 MHz), or with a Varian XL-100-12 (100 MHz) for solutions in $CDCl_3$. High (HRMS) and low resolution mass spectra (MS) were measured on an Autospec VG spectrometer. HPLC analyses were recorded on a Waters 441 chromatograph (by using a Lichrocart-RP-18 column).

General Procedure for Preparing Chiral Esters 11a-f

A mixture of **10** (1.1 equiv.), 1.0 equivalent of each of the chiral alcohols shown in Figure 1, DCC (1.2 equiv.) and DMAP (0.2 equiv.) in dry CH_2Cl_2 (5 mL / mmol of the chiral alcohol) was stirred under a N_2 atmosphere for 48 hours. The mixture was diluted with ethyl ether and filtered on celite. The filtrate was washed successively with 5% aqueous $NaHCO_3$ and brine. Drying over anhydrous Na_2SO_4 was followed by solvent evaporation. The crude esters were purified by column chromatography on silica gel (with AcOEt/n-hexane solutions as eluants).

1-O-[2-(3,4-methylenedioxy)phenyl]-propionate-1-(10-dicyclohexylsulfamoyl)-D-isobornene (11a)

Colorless solid m.p. 250-251 °C, $[\alpha]_D 25$ -26.2° (c. 1.23, $CHCl_3$) in a 43% yield from a 10% solution of AcOEt in n-hexane as the eluant. IR (KBr) 2940, 1734, 1508, 1492, 1445, 1248, 1052 cm^{-1}; ^{1}H-NMR (100 MHz, $CDCl_3$) δ 0.88 (s, 3H, Me), 0.92 (s, 3H, Me), 1.08-1.38 (m, 7H, CH and CH_2), 1.44-2.08 (m, 21H, CH and CH_2), 2.41-3.64 (m, 5H, CH (bridge) and CH_2), 3.24 (d, 2H, J=13 Hz, $HCSO_2$), 4.88-5.06 (m, 1H, H-C-O), 5.92 (s,2H, OCH_2O), 6.67 (sl, 3H, H-Ar) ppm.

1-O-[2-(3,4-methylenedioxy)phenyl]-propionate-2-(1S,2S,3R,5S)-pinane-1-ol (11b):

Yellowish oil, $[\alpha]_D25$ +7.3° (c. 3.34, $CHCl_3$) in a 66% yield from a 20% solution of AcOEt in n-hexane as the eluant. IR (neat) 3640, 2925, 1731, 1501, 1491, 1442, 1246, 1036 cm^{-1}; ^{1}H-NMR (100 MHz, $CDCl_3$) δ 0.99 (s, 3H, Me), 1.25 (s, 3H, Me), 1.28 (s, 3H, CH_3-COH), 1.56 (d, 1H, J=11Hz, CH), 1.60-2.58 (m, 5H, CH and CH_2), 2.64-3.06 (m, 4H, CH_2Ar and CH_2C=O), 5.10(dd, 1H, J=10 and 6 Hz, HC-OCO), 5.96 (s, 2H, OCH_2O), 6.70 (sl, 3H, H-Ar) ppm.

1-O-[2-(3,4-methylenedioxy)phenyl]-propionate-(1R-2S,5R)-menthane (11c)

Colorless solid m.p. 41-44 °C, $[\alpha]_D25$ -55.6° (c. 1.02, $CHCl_3$) in an 81% yield from a 10% solution of AcOEt in n-hexane as the eluant. IR (neat) 2957, 2885, 1728, 1505, 1495, 1446, 1251, 1043 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.67 (d, 3H, J=6.94 Hz, Me), 0.82 (d, 3H, J=7.04 Hz, Me), 0.85 (d, 3H, J=6.56 Hz, Me), 0.88-0.92 (m, 9H, CH_2 and CH), 2.52 (t, 2H, J=7.31 Hz, CH_2-Ar), 2.83 (t, 2H, J=7.31 Hz, CH_2C=O), 4.63 (dt, 1H, J=10.48 and 4.35 Hz, H-CO), 5.88 (s, 2H, OCH_2O), 6.58-6.71 (m, 3H, H-Ar) ppm.

1-O-[2-(3,4-methylenedioxy)phenyl]-propionate-2,3;4,5-di-O-isopropylidene-β-D-fructopyranose (11d)

Viscous yellow oil, $[\alpha]_D25$ -21.5° (c. 3.30, $CHCl_3$) in an 83% yield from a 20% solution of AcOEt in n-hexane as the eluant. IR (neat) 2998, 2930, 1744, 1502, 1491, 1442, 1160, 1074 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.31 (s, 3H, Me), 1.33 (s, 3H, Me), 1.44 (s, 3H, Me), 1.50 (s, 3H, Me), 2.59 (t, 2H, J=7.25 Hz, CH_2-Ar), 2.85 (t, 2H, J=7.25 Hz, CH_2C=O), 3.72 (dd, 1H, J=12.94 and 1.80 Hz, H_6), 3.83 (dd, 1H, J=12.94 and 1.80 Hz, H_7), 4.00 (d, 1H, J=11.80 Hz, H_1), 4.19-4.21 (m, 2H, H_3 and H_5), 4.35 (d, 1H, J=11.80 Hz, H_1), 4.56 (dd, 1H, J=7.82 and 2.60 Hz, H_4), 5.88 (s, 2H, OCH_2O), 6.58-6.71 (m, 3H, H-Ar) ppm; MS, m/z (relative intensity) 421 (M^+-15, base), 83(65), 57(37); HRMS calcd.for $C_{21}H_{25}O_9$ (421.1498). Found: 421.1487.

1-O-[2-(3,4-methylenedioxy)phenyl]-propionate-1,2;5,6-di-O-isopropylidene-α-D-gluco furanose (11e)

Viscous yellow oil, $[\alpha]_D25$ -15.8° (c. 1.42, $CHCl_3$) in a 74% yield from a 20% solution of AcOEt in n-hexane as the eluant. IR (neat) 2994, 2938, 1741, 1501, 1490, 1442, 1370, 1246, 1077, 1032 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.32 (s, 3H, Me), 1.33 (s, 3H, Me), 1.43 (s, 3H, Me), 1.53 (s, 3H, Me), 2.58 (t, 2H, J=7.73 Hz, CH_2-Ar), 2.84 (t, 2H, J=7.73 Hz, CH_2C=O), 4.00 (m, 2H, H_6), 4.13 (m, 2H, H_4 and H_5), 4.29 (d, 1H, J=3.68 Hz, H_2), 5.19 (d, 1H, J=2.13 Hz, H_3), 5.74 (d, 1H, J=3,68 Hz, H_1), 5.87 (s, 2H, OCH_2O), 6.57-6.71 (m, 3H, H-Ar) ppm.

1-O-[2-(3,4-methylenedioxy)phenyl]-propionate-1,2;5,6-di-O-isopropylidene-β-D-lyxofuranose (11f)

Viscous yellow oil, $[\alpha]_D25$ +25.4° (c. 0.7, $CHCl_3$) in a 70% yield from a 20% solution of AcOEt in n-hexane as the eluant. ^{1}H-NMR (300 Mhz, $CDCl_3$) δ 1.34 (s, 6H, 2 Me), 1.40 (s, 3H, Me), 1.54 (s, 3H, Me), 2.65 (t, 2H, J=7.61 Hz,CH_2-Ar), 2.89 (t, 2H, J=7.61 Hz,CH_2C=O), 3.86 (dd,1H, J=8.51 and 5.71 Hz, H_6), 4.05 (dd, 1H, J=8.51 and 6.96 Hz, H_6), 4.15 (dd, 1H, J=7.94 and 4.26 Hz, H_4), 4.28 (m, 1H, H_5), 4.81-4.88 (m, 2H, H_2 and H_3), 5.82 (d, 1H, J=3.45 Hz, H_1), 5.92 (s, 2H, OCH_2O), 6.64-6.75 (m, 3H, H-Ar) ppm.

General procedure for Preparing Allyl-Esters 12 a-f

To a -78 °C cooled 0.8 M solution of LDA (1.5 equiv. of LDA for esters **11a**, **11c-f**, and 3.0 equiv. of LDA for ester **11b**) in dry THF under a nitrogen atmosphere was added dropwise 1M solutions of esters **11a-f** (1.0 equiv.) in dry THF and the pale yellow solutions were stirred at -78 °C for one hour. A 2 M solution of allyl bromide (1.2 equiv.) in THF was added dropwise, and the mixture was stirred for one hour. Saturated aqueous NH_4Cl was added, and the mixture was allowed to rise to room temperature. The mixture was extracted with ethyl acetate and washed successively with 5% aqueous NH_4Cl and brine. Drying over anhydrous Na_2SO_4 was followed by solvent evaporation. The crude esters were purified by column chromatography on silica gel (AcOEt/ n-hexane solutions as eluants) giving **12a-f** in the ratios shown in the table.

1-O-[2-allyl,3-(3,4-methylenedioxy)-phenyl]-propionate-1-(10-dicyclohexylsulfamoyl)-D-isobornene (12a)

Colorless solid in a 60% yield from a 10% solution of AcOEt in n-hexane as the eluant. This compound has a 78% d.e. by HPLC. IR (KBr) 3070, 2940, 2858, 1727, 1640, 1609, 1501, 1489, 1442, 1245, 1044 cm^{-1}; ^{1}H-NMR (100 MHz, $CDCl_3$) δ 0.70 (s, 3H, Me of the S-isomer), 0.81 (s, 3H, Me of the S-isomer), 0.84 (s, 3H, Me of the R-isomer), 0.96(s, 3H, Me of the R-isomer),1.0- 2.0 (m, 27H, CH_2 and CH), 2.2-3.4 (m, 8H, CH_2SO_2, CH-N and $ArCH_2CHCH_2C$=C), 4.2-5.2 (m, 2H, H_2C=C), 5.6-5.9 (m, 1H, H_2C=CH), 5.82 (s,2H, OCH_2O), 6.58 (s, 3H, H-Ar) ppm.

1-O-[2-allyl,3-(3,4-methylenedioxy)-phenyl]-propionate-2-(1S,2S,3R,5S)-pinane-1-ol (12b)

Yellowish oil in an 11% yield from a 20% solution of AcOEt in n-hexane as the eluant. This compound has a 72%

d.e. by HPLC. IR (neat) 3568, 3067, 2913, 2865, 1729, 1639, 1608, 1500, 1489, 1442, 1244, 1037 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.92 (s, 3H, Me of the R and S-isomers), 1.04 (s, 3H, $\underline{H}_3C$-C-O of the S-isomer), 1.19 (s, 3H, $\underline{H}_3C$-C-O of the R-isomer), 1.22 (s, 3H, Me of the R and S-isomers), 1.28-1.55 (m, 3H, CH_2 and CH), 1.84-1.92 (m, 2H, CH_2), 2.09-2.36 (m, 4H, $C\underline{H}_2$-C=C,CH and OH), 2.73-2.87 (m, 3H, $ArC\underline{H}_2C\underline{H}C$=O), 4.98-5.12 (m, 3H, $\underline{H}$-CO and $\underline{H}_2C$=C), 5.67-5.86 (m, 1H, $H_2C=C\underline{H}$), 5.87 (s, 2H, $OC\underline{H}_2O$), 6.58-6.72 (m, 3H, $\underline{H}$-Ar) ppm.

1-O-[2-allyl,3-(3,4-methylenedioxy)-phenyl]-propionate-(1R-2S,5R)-menthane (12c)

Yellowish oil in a 61% yield was obteined from a 10% solution of AcOEt in n-hexane as the eluant. This compound has a 10% d.e. by HPLC. IR (neat) 3077, 2957, 2869, 1726, 1641, 1609, 1505, 1492, 1446, 1249, 1040 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.54 (d, 3H, J=6.86 Hz, $(C\underline{H}_3)_2CH$ of the R-isomer), 0.65 (d, 3H, J=6.92 Hz, $(C\underline{H}_3)_2CH$ of the S-isomer), 0.73 (d, 3H, J=6.96 Hz, $(C\underline{H}_3)_2CH$ of the R-isomer), 0.84 (d, 3H, J=6.52 Hz, $(C\underline{H}_3)_2CH$ of the S-isomer), 0.82 (d, 3H, J=6.78 Hz, Me of the R and S-isomers), 0.87-1.65 (m, 9H, CH_2 and CH), 2.22-2.30 (m, 2H, $C\underline{H}_2C$=C), 2.62-2.79 (m, 3H, $ArC\underline{H}_2C\underline{H}C$=O), 4.57 (dt, 1H, $\underline{H}$-C-O), 4.96-5.09 (m, 2H, $\underline{H}_2C$=C), 5.68-5.72 (m, 1H,$\underline{H}C=CH_2$), 5.87 (s, 2H, $OC\underline{H}_2O$), 6.56-6.69 (m, 3H, $\underline{H}$-Ar) ppm.

1-O-[2-allyl,3-(3,4-methylenedioxy)-phenyl]-propionate -2,3;4,5-di-O-isopropylidene-β-D-fructopyranose (12d)

Viscous colorless oil in a 56% yield from a 30% solution of AcOEt in n-hexane as the eluant. This compound has a 40% d.e. by HPLC. IR (neat) 3077, 2983, 2927, 1742, 1639, 1604, 1501, 1489, 1442, 1380, 1247, 1070 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 6H, Me), 1.47 (s, 3H, Me), 1.52 (s, 3H, Me), 2.22-2.56 (m, 2H, $\underline{H}_2C$-C=C), 2.60-3.04 (m, 3H, $ArC\underline{H}_2C\underline{H}C$=O), 3.73 (d, 1H of R-isomer, J=12.90 Hz, H_6), 3.87 (d, 1H of S-isomer, J=12.90 Hz, H_6), 4.04 (d, 1H, J=11.60 Hz, H_1), 4.13 (d, 1H, J=11.60 Hz, H_1), 4.18-4.29 (m, 2H, H_3 and H_5), 4.53 (dd, 1H of R-isomer, J=7.90 and 2.20 Hz, H_4), 4.59 (dd, 1H of S-isomer, J=7.90 and 2.20 Hz, H_4), 5.06-5.15 (m, 2H, $\underline{H}_2C$=C), 5.70-5.86 (m, 1H, $\underline{H}C=CH_2$), 5.91 (s, 2H of R-isomer, $OC\underline{H}_2O$), 5.92 (s, 2H of S-isomer, $OC\underline{H}_2O$), 6.58-6.78 (m, 3H, $\underline{H}$-Ar) ppm; ^{13}C-NMR ($CDCl_3$, DEPT) δ 24.43 (CH_3), 25.57(CH_3), 25.65(CH_3), 26.21(CH_3), 26.82(CH_3), 26.86(CH_3), 36.13(CH_2), 36.22(CH_2), 37.49(CH_2), 38.14(CH_2), 47.84(CH), 48.15(CH), 61.54(CH_2), 61.57(CH_2), 65.43(C), 65.80(C), 70.30(CH), 70.37(CH), 70.45(CH), 70.81(CH), 71.12(CH_2), 71.14(CH_2), 101.16(C), 101.68(C), 101.75(C), 108.53(C), 108.70(C), 109.04(C), 109.43(C), 109.46(CH), 109.52(CH), 109.58(CH), 109.71(CH), 117.72(CH_2), 117.86(CH_2), 122.27(CH), 122.32(CH), 132.93(C), 135.19($CH_{.2}$), 135.25(CH), 146.06(C), 148.02(C), 174.46(C=O), 174.51(C=O) ppm; HRMS calcd. for $C_{25}H_{32}O_9$ (476.52): C,63.01; H,4.61. Found : C,63.13; H,4.70.

1-O-[2-allyl,3-(3,4-methylenedioxy)-phenyl]-propionate -1,2;5,6-di-O-isopropylidene-α-D-glucofuranose (12e)

Viscous colorless oil in a 52% yield from a 20% solution of AcOEt in n-hexane as the eluant. This compound has a 16% d.e. by HPLC. IR (neat) 3083, 2989, 2941, 1744, 1642, 1610, 1506, 1491, 1443, 1383, 1249, 1073 cm^{-1}; ^{1}H-NMR (300 MHz, CDC_{13}) δ 1.16 (s, 3H, Me), 1.18 (s, 3H, Me), 1.19 (s, 3H, Me), 1.21 (s, 3H, Me), 1.30 (s, 3H, Me), 1.31 (s, 3H, Me), 1.40 (s, 3H, Me), 2.15-2.44 (m, 2H, $\underline{H}_2C$-C=C), 2.60-2.89 (m, 3H, $ArC\underline{H}_2C\underline{H}C$=O), 3.81-3.92 (m, 2H, H_6), 3.95-4.08 (m, 1H, H_5), 4.10 (dd, 1H, J=7.52 and 2.36 Hz, H_4), 4.17 (d, 1H, J=3,64 Hz, H_2), 4.93-5.04 (m, 2H, $\underline{H}_2C$=C), 5.06 (d, 1H, J=2.36 Hz, H_3), 5.48 (d, 1H of S-isomer, J=3.64 Hz, H_1), 5.60-5.74 (m, 1H, $\underline{H}C=CH_2$), 5.71 (d, 1H of R-isomer, J=3.64 Hz, H_1), 5.82 (s, 2H, $OC\underline{H}_2O$), 6.49-6.63 (m, 3H, $\underline{H}$-Ar) ppm; ^{13}C-NMR ($CDCl_3$, DEPT) δ 25.24(CH_3), 25.28(CH_3), 26.09(CH_3), 26.22(CH_3), 26.83(CH_3), 26.85(CH_3), 36.11(CH_2), 36.44(CH_2), 37.44(CH_2), 38.28(CH_2), 47.53(CH), 48.07(CH), 67.16(CH_2), 67.56(CH_2), 72.33(CH), 72.57(CH), 75.90(CH), 76.39(CH), 79.86(CH), 80.00(CH), 83.13(CH), 83.30(CH), 101.03(CH_2), 105.14(CH), 108.24(CH), 108.29(C), 109.33(C), 109.40(C), 109.44(C), 109.55(C), 112.36(CH), 117.42(CH_2), 117.56(CH_2), 121.97(CH), 122.18(CH), 132.44(C), 132.64(C), 134.87(CH), 134.96(CH), 146.33(C), 147.70(C), 147.76(C), 173.38(C=O), 173.62(C=O) ppm.

1-O-[2-allyl,3-(3,4-methylenedioxy)-phenyl]-propionate -1,2;5,6-di-O-isopropylidene-α-D-xylofuranose (12f)

Viscous colorless oil in a 44% yield from a 20% solution of AcOEt in n-hexane as the eluant. This compound has a 40% d.e. by HPLC. IR (neat) 3076, 2986, 2932, 1738, 1642, 1609, 1503, 1490, 1442, 1381, 1246, 1028 cm^{-1}; ^{1}H-NMR (300 MHz, CDC_{13}) δ 1.33 (s, 3H, Me), 1.35 (s, 3H, Me), 1.42 (s, 3H, Me), 1.50 (s, 3H, Me), 1.54 (s, 3H, Me), 2.22-2.49 (m, 2H, $\underline{H}_2C$-C=C), 2.66-2.80 (m, 2H, $C\underline{H}_2$-Ar), 2.81-2.98 (m, 1H, $\underline{H}C$-C=O), 3.73 (dd, 1H of S-isomer, J=8.33 and 6.20 Hz, H_6), 3.87 (dd, 1H of R-isomer, J=8.33 and 6.20 Hz, H_6), 3.98 (dd, 1H of S-isomer, J=8.33 and 6.69 Hz, H_6), 4.05 (dd, 1H of R-isomer, J=8.33 and 6.69 Hz, H_6), 4.13-4.32 (m, 2H, H_4 and H_5), 4.67-4.88 (m, 2H, H_2 and H_3), 5.02-5.17 (m, 2H, $\underline{H}_2C$=C), 5.73-5.94 (m ,1H, $\underline{H}C=CH_2$), 5.82 (d, 1H, J=3.72 Hz, H_1), 5.92 (s, 2H, $OC\underline{H}_2O$), 6.61-6.78 (m, 3H, $\underline{H}$-Ar) ppm; ^{13}C-NMR ($CDCl_3$, DEPT) δ 25.05(CH_3), 25.13(CH_3), 26.19(CH_3), 26.23(CH_3), 26.59(CH_3), 26.63(CH_3), 26.67(CH_3), 26.73(CH_3), 35.65(CH_2), 35.84(CH_2), 37.07(CH_2), 37.16(CH_2), 47.04(CH), 47.33(CH), 65.33(CH_2), 65.62(CH_2), 72.69(CH), 72.88(CH), 74.97(CH), 75.10(CH), 77.65(CH), 77.60(CH), 100.79(CH_2), 100.86(CH_2), 104.12(CH), 104.19(CH), 108.11(C), 108.15(C), 109.36(CH), 109.43(CH), 109.86(CH), 109.94(CH), 112.97(CH), 117.22(CH_2), 117.38(CH_2), 121.91(CH), 122.01(CH), 132.62(C), 135.00(CH), 135.03(CH), 146.26(C), 147.63(C), 173.88(C=O) ppm.

1-O-[2-(3,4-methylenedioxy)phenyl]-2-allyl-propanol (13)

To a suspension of $LiAlH_4$ (0.99 mmol) in dry THF (2 mL) cooled at 0 °C under a nitrogen atmosphere was added dropwise a 1 M solution of ester **12d** (0.33 mmol) in dry THF and the mixture was stirred for 1 h. The addition of ethyl ether was followed by water, 15% aqueous NaOH and water. After 10 min the mixture was filtered through celite and concentrated in vacuum, giving a yellow oil. Column chromatography on silica gel (20% solution of AcOEt in n-hexane as the eluant) gave **13** as a pale yellow oil in an 82% yield ([α]D25 + 5.2° (c. 2.57, $CHCl_3$); b.p. 190-191 °C / 14 mmHg). IR (neat) 3390, 3084, 2935, 1637, 1605, 1502, 1491, 1442, 1244, 1040 cm^{1}; MS (70eV) 220 (M^+, 18%), 135 (100%), 77(11%); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.56 (sl, 1H, OH), 1.77-1.95 (m, 1H, CH), 2.12 (t, 2H, J=6.80 Hz, $CH_2CH{=}CH_2$), 2.56 (d, 2H, J=7.60 Hz, CH_2-Ar), 3.54 (d, 2H, J=5.24 Hz, CH_2OH), 5.02-5.17 (m, 2H, $H_2C{=}C$), 5.72-5.96 (m, 1H, $HC{=}CH_2$), 5.94 (s, 2H, OCH_2O), 6.58-6.77 (m, 3H, H-Ar) ppm.

β-piperonyl-γ-butirolactone (2)

To a solution of $NaIO_4$ (0.944 g; 4.4 mmol) in water (20 mL) was added $KMnO_4$ (2.9 mg). The mixture was stirred at room temperature for 15 min and the pH was adjusted to 8 by adding 5% aqueous K_2CO_3. The solution was cooled to 0 °C, and a solution of **12d** (0.0968 g; 0.44 mmol) in t-BuOH (10 mL) was added. After stirring for 17 h at room temperature, ethyleneglycol (0.1 mL) was added, and the mixture was stirred for an additional 3 h. The solid residue was removed by filtration and washed with water (20 mL), and the solution was acidified with 10% HCl until pH 1, and stirred at room temperature for one hour. The solution was concentrated in vacuum and partitioned with AcOEt (30 mL).The organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuum, to give a residue that was purified by column chromatography (30% solution of AcOEt in n-hexane as the eluant) to give **(-)-2** (0.0619 g; 64%) as a pale yellow oil [α]D25-1.8° [c. 3.89, $CHCl_3$; lit. [α] D25-4.78° C (c.1.7, $CHCl_3$)].[24] IR (neat) 3021, 2925, 2864, 1772, 1503, 1490, 1442, 1244, 1173, 1040 cm^{-1} ; MS (70 eV) 220 (M^+, 21%), 136 (15%), 135 (100%), 77 (24%); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 2.10-3.00 (m, 5H, $ArCH_2CHCH_2C{=}O$), 4.00 (dd, 1H, J=9.0 and 6.0 Hz, H-C-O), 4.32 (dd, 1H, J=9.0 and 6.0 Hz, H-C-O), 5.93 (s, 2H, OCH_2O), 6.50-6.90 (m, 3H, H-Ar) ppm.

Acknowledgments

Part of this work was supported by CAPES and funds from CNPq (rhe National Council of Research of Brazil).

References and Notes

1. Rao, C.B.S.;*Chemistry of Lignans*; Andhra University Press; Visakhapathnam, Andra Pradesh, 1978.
2. Hartwell, J.L.; Schrecker, A.W.; *J. Am. Chem . Soc.* **1951**, *73*, 2909.
3. Jardine, I.; *Anticancer Agents Based on Natural Models*; Academic Press; New York, 1980; p 319.
4. Ward, R.S.; *Chem. Soc. Rev.* **1982**, *11*, 75.
5. Ward, *R.S.; Tetrahedron* **1990**, *46*, 5029, and references cited therein.
6. Reetz, M.T.; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531.
7. Kunz, H.; Rück, K. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 336.
8. Costa, P.R.R.; Ferreira, V.F.; Filho, H.C.A.; Alencar, K.G.; Pinheiro, S.; Ferreira, C.M.; *J. Carbohydr. Chem.* **1996**, *15; Filho, H.C.A.; Filho, U.F.L.; Pinheiro, S.; Vasconcellos, M.L. A.A.; Costa, P.R.R.; Tetrahedron:Asymm.* **5**, 1219 (1994).
9. Duhamel, L.; Duhamel, P.; Fouguay, S.; Eddine, J.J.; Peschard, O.; Plasquevent, J.-C.;Ravard, A.; Solliard, R.; Velnot, J.-Y.; Vincens, *H.; Tetrahedron* **1988**, *44*, 5495.
10. Costa, P.R.R.; Barreiro, E.J.L.; Coelho, F.A.S.; Farias, F.M.C.; *J.Chem. Res. (M)* **1985**, 220.
11. A.; Hassner, V.; Alexanian, *Tetrahedron Lett.* **1978**, 4475 .
12. Oppolzer, W.; Rodrigues, I.; Bragg, J.; Bernadinelli, G.; *Helv. Chim. Acta.* **1989**, *72*, 123.
13. The chiral esters **12a**, **12e** and **12f** were similarly reduced to the corresponding alcohols (-)-**13** by this procedure. Reduction of **12a** and **12f** led to the S(-)-**13** in 73% and 79% yields ([α]D25 -10° C; c. 0.5, $CHCl_3$) and ([α]D25 -5.5° C; c. 1.27, $CHCl_3$), respectively. Reduction of **12e** led to R(+)-**13** in a 76% yield ([α]D25 +2.3° C; c. 1.96, $CHCl_3$).
14. Jackman, L.M.; Rakiewicz, E.F.; *J. Am. Chem. Soc.* **1977**, *99*, 4954.
15. Jackman, L.M.; Dune, T.S.; *J. Am. Chem. Soc.* **1985**, *107*, 1810.
16. Jackman, L.M.; Rakiewicz, E.F.; *J. Am. Chem. Soc.* **1991**, *113*, 1202.
17. Seebach, D.; Thaler, A.; Beck, *A.K.; Helv. Chim. Acta.* **1989**, *72*, 857.

18. Oppolzer, W.; Moretti, R.; *Tetrahedron* **1988**, *44*, 5541 .
19. Uragami, M.; Tomioka, K.; Koga, K.; *Tetrahedron:Asymmetry* **1995**, *6*, 701.
20. Mulze, J.; Steffen, U.; Rorn, L.; Scneider, C.; Weinhold, E.; Münch, W.; Rüdert, R.;Luger, P.; Harth, H.; *J. Am. Chem. Soc.* **1988**, *110*, 4640.
21. Ferreira, V.F.; *Quimica Nova*, **1992**, *15*, 348.
22. Verhart, C.G.J.; Caris, B.M.G.; Zwonerburg, B.; Chittenden, G.J.F.; *Rec.Trav. Chim.-Pays-Bas.* **1992**, *111*, 348.
23. Austin, G.N.; *Tetrahedron Lett.* **1987**, *43*, 3095.
24. Tomioka, K.; Koga, K.; *Tetrahedron Lett.* **1979**, 3315.