Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

The Use of Chiral Auxiliaries Prepared from (-)-β-Pinene in Stereoselective Reduction of β-Ketobutyrates

Karla G. Alencar [a] , Ubiracir F.L. Filho [a] , Mário L. A. A. Vasconcellos [a] & Paulo R.R. Costa [b]

[a] Laboratório H1-029 , Brazil E-mail:

[b] Laboratório de Sintese Assimétrica (LASA), Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro, Centro de Ciěncias da Saúde, Bloco H, Ilha da Cidade Universitária , 21941--590, RJ, Rio de Janeiro, Brazil E-mail:

Published online: 04 Dec 2007.

To cite this article: Karla G. Alencar , Ubiracir F.L. Filho , Mário L. A. A. Vasconcellos & Paulo R.R. Costa (2000) The Use of Chiral Auxiliaries Prepared from (-)-β-Pinene in Stereoselective Reduction of β-Ketobutyrates, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 30:3, 455-468, DOI: 10.1080/00397910008087342

To link to this article: http://dx.doi.org/10.1080/00397910008087342

SYNTHETIC COMMUNICATIONS, 30(3), 455–468 (2000)

THE USE OF CHIRAL AUXILIARIES PREPARED FROM (-)-β-PINENE IN STEREOSELECTIVE REDUCTION OF β-KETOBUTYRATES

Karla G. Alencar, Ubiracir F.L. Filho,

Mário L.A.A. Vasconcellos[1]* and Paulo R.R.Costa [2]*

[1]Laboratório H1-029 and [2]Laboratório de Síntese Assimétrica (LASA), Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro, Centro de Ciências da Saúde, Bloco H, Ilha da Cidade Universitária, 21941-590, RJ, Rio de Janeiro, Brazil, Email: mlaav@nppn.ufrj.br or prrc@nppn.ufrj.br.

ABSTRACT: Chiral auxiliaries previously prepared from (-)-β–pinene (**3**), alcohols **5a-e** and **6**, were transformed into β–ketobutyrates **7a-e** and **8** respectively. These compounds were stereoselectively reduced by $NaBH_4$ in the presence of additives ($MnCl_2$ or $CaCl_2$), leading to the corresponding β-hydroxy butyrates **10a-e** and **11** in good chemical yield and poor to moderate stereoselectivities (de 0%-60%). The configuration at the newly generated stereogenic center in **10a** was determined to be **S** through its transformation into S-(+)-butanediol.

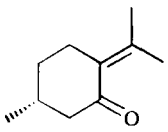
INTRODUCTION

Terpenes play an essential role as natural source of chirality in asymmetric synthesis. They have been employed to obtain useful chiral bases, ligands, catalysts and auxiliaries.[1-5] The landmark in this field was the report by Corey in 1975,[2] on the synthesis of (+)-8-phenylmenthol (**2**) from (-)-pulegone (**1**) (figure 1). A number of derivatives of **2** were synthesized, where the phenyl group was replaced by more bulky aromatic groups.[2b] Several pro-chiral esters obtained from **2**, its derivatives or its enantiomer, undergo different types of stereoselective reactions in excellent de.[6] On the other hand, (–)–β-pinene (**3**) was used by Oppolzer et al to prepare alcohol **4**, a 8-phenyl menthol based chiral auxiliary (figure 1).[4] The Diels-Alder reaction between the acrylate prepared from **4** and cyclopentadiene occurred in 85% de, while reduction of the corresponding β-ketobutyrate with $ZnBH_4$ occurred in 43% de.[4]

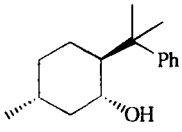
Recently we reported the stereoselective synthesis of new 8-phenylmenthol based chiral auxiliaries, alcohols *cis*-**5a-e** and *trans*-**6**, from (-)-β-pinene (**3**).[7] These auxiliaries are structurally related to the Oppolzer auxyliary **4** but the absence of a second phenyl group in their structures makes their syntheses easier and more economic. In addition, most of them have a *cis*-relationship between the hydroxy and the benzyl group, in contrast with the *trans*-relationship observed in menthol derivatives.

The reaction of the corresponding β-ketobutytates, *cis*-**7a-e** and *trans*-**8** (figure 2) with trypthophol in the presence of Lewis acids was recently studied.[8,9] In these cases, a Friedel-Crafts type reaction occurs involving the pro-chiral diastereotopic keto group in these β-ketobutyrates, leading to analogs of the drug ethodolac. A high level of steric induction was observed when *cis*-**7a-b** were used as substrates.[9]

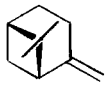
In this paper, we describe the stereoselective reduction of these β-ketobutyrates, **7a-e** and **8**, with $NaBH_4$ in the presence of complexing additives as $CaCl_2$ and $MnCl_2$.[10]



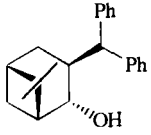
1



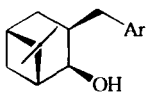
2



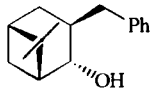
3



4

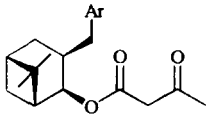


5a; Ar =Ph
5b; Ar = p-OMePh
5c; Ar = o-OMePh
5d; Ar = α-naphtyl
5e; Ar = β-naphtyl

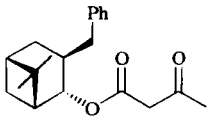


6

Figure 1



7a ; Ar = Ph
7b; Ar = p-OMePh
7c; Ar = o-OMePh
7d; Ar = α-naphtyl
7e; Ar = β-naphtyl

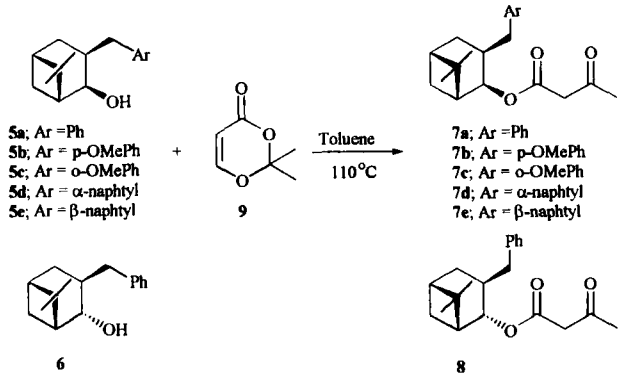


8

Figure 2

RESULTS

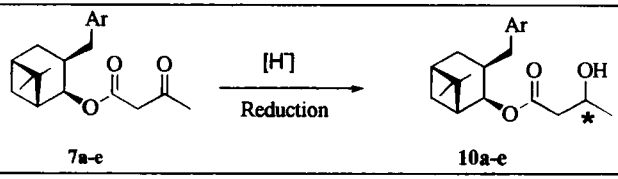
The preparation of the β-ketobutyrates **7a-e** and **8** was accomplished in high yield through the reaction of alcohols *cis*-**5a-e** and *trans*-**6** respectively, with 2,2,6-trimethyl-4H-1,3-dioxyn-4-one (**9**) (scheme 1).[11] Despite the fact that these alcohols have differents steric hindrances, the reaction of acetoacetoxylation reactions proceeded in excellents yield in all cases studied.



Scheme 1

Reaction of **7a** with $NaBH_4$ in the absence of additives led to the β-hydroxybutyrate **10a** as an equimolecular mixture of diastereomers (entry 1, scheme 2). The stereoselectivity increased in the presence of $CaCl_2$ (entry 2) but the best result was obtained in the presence of $MnCl_2$, owing to the higher complexing power of this additive (entry 3).[10] Similarly, better stereoselection for the reduction of **7b** was also obtained in the presence of $MnCl_2$ (entry 5) . The comparison of the results shown in entries 3, 5 and 6 suggests that the methoxy group at the aromatic ring in **7b** and **7c** are not involved in the control of the stereochemical outcome of the reduction. In an attempt to improve the observed stereoselectivities, the reduction of **7d** and **7e**, substituted with more bulky aromatic groups at the pinene nucleus (α and β naphtyl, respectively), was investigated. While in the first case only 17% de was obtained, the stereoselection increased to 60% de in the second case (entries 7 and 8, respectively).

The reduction of *trans*-**8** with $NaBH_4$ in the presence of $MnCl_2$ was also accomplished (scheme 3). A low de (4%) was observed, contrasting with the result obtained from **7a** (40% de, scheme 2, entry 3).

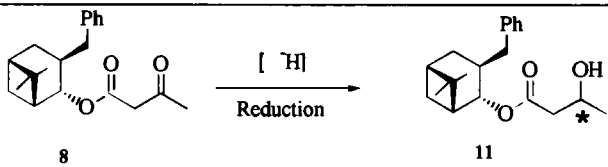


7a-e 10a-e

Entry	Product	Reducting system	Yield (%)	de (%)[a]
1	10a	$NaBH_4$	60	0
2	10a	$NaBH_4$/ $CaCl_2$	75	14
3	10a	$NaBH_4$/ $MnCl_2$	78	40
4	10b	$NaBH_4$/ $CaCl_2$	90	20
5	10b	$NaBH_4$/ $MnCl_2$	70	40
6	10c	$NaBH_4$/ $MnCl_2$	90	37
7	10d	$NaBH_4$/ $MnCl_2$	82	17
8	10e	$NaBH_4$/ $MnCl_2$	60	60

a-diasteromeric excess measured by quantitative ^{13}C NMR (C=O ~ 172δ)

Scheme 2



8 11

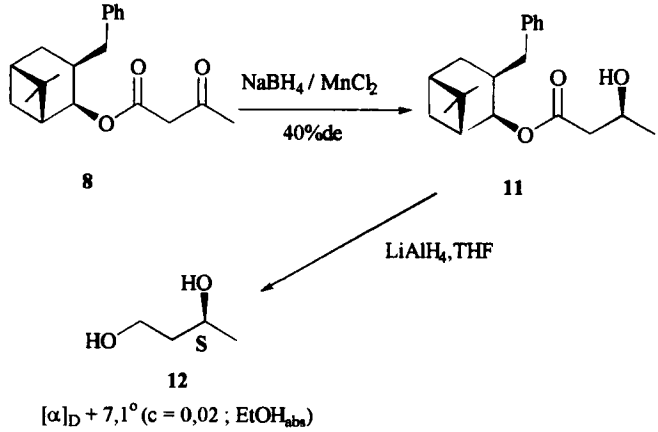
Entry	Product	Reducting system	Yield (%)	de (%)[a]
1	11	$NaBH_4$/ $MnCl_2$	80	4

a-diasteromeric excess measured by quantitative ^{13}C NMR (C=O ~ 172δ)

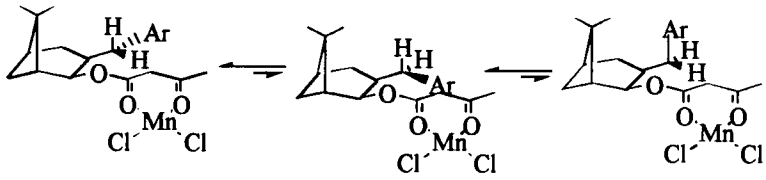
Scheme 3

The absolute configuration at the newly generated asymmetric center in **10a** was determined by chemical correlation. The **S** stereochemistry was assigned based on its reduction into (S)-(+)-butanediol (**12**) (scheme 4). [12]

In scheme 5 are shown the possible conformers generated by rotation around the C-CH_2Ar bound in β-ketobutyrates **7a-e** chelated with $MnCl_2$. Based



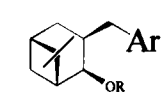
Scheme 4



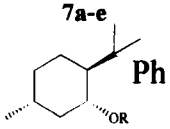
Scheme 5

on the analysis of molecular models, the participation of the axial conformer can be ruled out since a strong steric interaction occurs between the aryl group and the methyl group at the pinene nucleus. On the other hand, both stacked and trans conformers could occur in the conformational equilibrium.

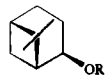
The occurrence of stacked conformers in the β-ketobutyrate **15**, derived from **2**, had been previously suggested by ^{1}H NMR studies[16] (table). The methylene and the methyl group in **15** are shielded when compared with the values observed for **14**. In addition, the methylene group in **14** appears as a singlet while



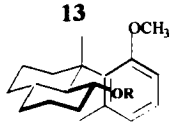
7a-e



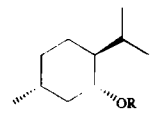
15



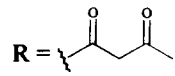
13



16
17; R = H



14



Entry	β-ketobutyrates	CH_2 (δ ppm)	CH_3(δ ppm)
1	7a	3,55(s)	2,22
2	7b	3,40(s)	2,24
3	7c	3,40(s)	2,21
4	7d	3,30(s)	2,13
5	7e	3,40(s)	2,19
6	13	3,38(s	2,25
7	14	3,46(s)	2,28
8	15	2,74(d,1H) ; 2,61(d,1H)	2,18
9	16	2,28(d,1H) ; 2,21(d,1H)	1,67

Table

in **15** a double dublet is observed (entry 7 and 8). The same effect on the chemical shift and multiplicity occurs in β–ketobutyrate **16**, derived from chiral auxiliary **17** (entry 9). In this case, the phenyl group is locked in the stacked position.[16] In contrast, in β-ketobutyrates **7a-e**, the methylene group appears as a singlet and the chemical shift are very similar to that obtained for **13** (entry 1-6). These data suggest that, in our case, only *trans* conformers should be present in solution and the stereoselections observed in the reduction resulted from the attach of hydride to the *Re* face of these conformers.

In conclusion, we described in this work another application of the auxiliary **5e**, easily prepared (three steps) from the β-pinene **3**. The reduction of the β-ketobutyrate derivative **7e**, occourred stereoselectivily (8:2) in excellent chemical yield. The use of $MnCl_2$-$NaBH_4$ in methanol showed to be more practice than the use of the pyrophoric $Zn(BH4)_2$ in anhydrous THF, usualy employed in this type of reduction.

EXPERIMENTAL SECTION

General methods: ^1H NMR Varian spectra were recorded at 200MHz in $CDCl_3$ with $CHCl_3$ as internal reference (7,26ppm). ^{13}C NMR spectra were recorded at 50.0 MHz in $CDCl_3$ solution with $CHCl_3$ (77.00ppm) as internal reference. The $[\alpha]_D$ value were measured in Perkin-Elmer polarimeter model 243-B in ethanol as solvent, (c=0,02). 2,2,6-Trimethyl-4H-1,3-dioxin-4-one yellows with time but generally retains a high assay even when it has become an orange-red color. It can be purified by distillation if the pot temperature in kept below 90^0C (bp $65\text{-}67^0C$; 0,2 torr).

General Procedure for Acetoacetylation with Dioxinone: A solution of alcohols *trans*-**4** and *cis*-**5a-e** (50 mmol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (50 mmol) in 10mL of toluene was placed in balloon flask 50 mL connected reflux condenser. The system was immersed in an oil bath that had been preheated at approximated 120 ^0C, and the solution was vigorously stirred. The evolution of acetone became apparent within several minutes; heating was continued for a total of two hours. At the end of the reaction the toluene and acetone produced were removed by distillation , and the yellow oil resultant was dissolved in CH_2Cl_2. A resultant solution was washed with solution of $NaCO_3$ (10%) (10mLx1) and solution saturated of NaCl (10mLx1). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. Purification of the product by silica-gel column chromatography gave a β-ketobutyrates (7 or 8a-e) in good yield (80-90%).

β-Ketobutyrate 7a: IR (film, υ (cm^{-1}): 1717, 1646 ; ^1H MNR ($CDCl_3$): δ 7,5-7,2 (m, 5H, H_{ar}), 5,5 (dd, 1H, H_2, J= 7,7/ 4,2), 3,35 (s, 2H, H_{13}), 2,9-2,53 (m, 3H, H_3, H_{10}/ $H_{10'}$), 2,22 (s, 3H, Me_{15}), 2,1-2,35 (m, H_{7ex}/ H_1), 1,97-1,89 (m, 1H, H_5), 1,78-1,69 (m, 2H, $H_{4\alpha,\beta}$), 1,37 (d, 1H, H_{7en}, J= 10,3), 1,28 (s, 3H, Me_9), 0,98 (s, 3H, Me_8); ^{13}C MNR ($CDCl_3$): δ 45,00 (CH), 77,30 (CH), 32,30 (CH), 30,80 (CH_2), 40,50 (CH), 38,30 (C), 24,90 (CH_2), 22,70 (CH_3), 27,05 (CH_3), 36,81 (CH_2), 140,20 (C), 166,40 (C), 50,20 (CH_2), 200,00 (C), 30,00 (CH_3); MS (70eV): m/z M^+314 (<1%), 212(42%), 121 (54%), 91 (100%)..HRMS m/z (%) mass: 314.188734 ($C_{20}H_{26}O_3$); calculated, 314.188195.

β-Ketobutyrate 7b: IV (film, υ (cm^{-1}): 1718, 1646; ^1H MNR ($CDCl_3$): δ 7,13-7,06 (m, 2H, H_{ar}), 6,85-6,77 (m, 2H, H_{ar}), 5,5 (dd, 1H, H_2, J= 7,7/ 5), 3,77 (s, 3H, Me_{16}), 3,38 (s, 2H, H_{13}), 2,82- 2,46 (m, 3H, H_3/ H_{10}/ $H_{10'}$), 2,16-2,33 (m, 2H, H_{7ex}/ H_1), 2,24 (s, 3H, Me_{15}), 1,98-1,91 (m,1H, H_5), 1,77-1,66 (m, 2H, $H_{4\alpha,\beta}$), 1,33 (d, 1H, H_{7en}, J= 10,2), 1,19 (s, 3H, Me_9), 0,98 (s, 3H, Me_8); δ ^{13}C MNR ($CDCl_3$): δ 45,00 (CH), 77,29 (CH), 32,50 (CH), 30,78 (CH_2), 40,49 (CH), 38,27 (C), 24,87 (CH_2), 22,69 (CH_3), 27,05 (CH_3), 35,83 (CH2), 129,3 (C), 200,3 (C), 50,2 (CH_2), 166,4 (C), 30,0 (CH_3), 55,00 (OCH_3); MS (70eV): m/z M^+344 (2%), 242 (23%), 121 (100%)..HRMS m/z (%) mass: 344.199583 ($C_{21}H_{28}O_4$); calculated, 344.198759.

β-Ketobutyrate 7c: ^1H NMR ($CDCl_3$): J em Hz): δ 7,2-7,1 (m, 2H, H_{ar}), 6,9-6,8 (m, 2H, H_{ar}), 5,75 (dd, 1H, H_2, J= 8/ 4), 3,8 (s, 3H, Me_{16}), 3,4 (s, 2H, H_{13}), 2,9-2,7 (m, 2H, H_{10}/ $H_{10'}$), 2,6-2,48 (m, 1H, H_3), 2,3-2,15 (m, 2H, H_{7ex}/H_1), 2,21 (s, 3H, Me_{15}), 1,95-185 (1H, m, H_5), 1,70-1,6 (m, 2H, $H_{4\alpha,\beta}$), 1,32 (d, 1H, H_{7en}, J=10,3), 1,19 (s, 3H, Me_8), 1,0 (s, 3H, Me_9); ^{13}C NMR ($CDCl_3$): δ 45,1 (CH), 77,7 (CH), 30,3 (CH), 30,8 (CH_2), 40,6 (CH), 38,3 (C), 24,9 (CH_2), 22,7 (CH_3), 27,1 (CH_3), 36,8 (CH_2), 128,5 (C), 166,5 (C), 50,3 (CH_2), 200,4 (C), 30,5 (CH_3), 55,1 (OCH3); MS (70eV): m/z = M^+ 344 (2%), 242 (15%), 121 (100%). HRMS m/z (%) mass: 344.197298 ($C_{21}H_{28}O_4$); calculated, 344.198759.

β-Ketobutyrate 7d: ^1H MNR ($CDCl_3$): δ 8,0 -7,2 (7H ,H_{ar}), 5,58 (dd, 1H, H_2, J=6/4), 3,3 (s, 2H, H_{13}), 2,9-2,70 (m, 3H, H_3/ H_{10} / $H_{10'}$), 2,0-2,3 (m, 2H, H_{7ex}/

H_1), 2,13 (s, 3H, Me_{15}), 1,9-1,83 (m, 1H, H_5), 1,75-1,5 (m, 2H, $H_{4\alpha,\beta}$), 1,23 (d, 1H, H_{7en}, J= 10), 1,15 (s, 3H, Me_9), 1,0 (s, 3H, Me_8); ^{13}C MNR:($CDCl_3$): δ 40,95 (CH), 73,26 (CH), 27,74 (CH), 27,23 (CH_2), 36,35 (CH), 34,18 (C), 20,73 (CH_2), 18,65 (CH_3), 22,91 (CH_3), 29,35 (CH_2), 131,89 (CH), 129,63 (C), 127,52 (C), 124,56 (CH), 119,22 (CH), 162,47 (C), 45,98 (CH_2), 196,03 (C), 25,84 (CH_3).

β-Ketobutyrate 7e: ^1H NMR ($CDCl_3$): δ 7,9-7,4 (7H ,H_{ar}), 5,58 (dd, 1H, H_2, J=7,6/ 5), 3,4 (s, 2H, H_{13}), 3,04-2,69 (m, 3H, H_3/ H_{10} / $H_{10'}$), 2,35-2,15(m, 2H, H_{7ex}/ H_1), 2,19 (s, 3H, Me_{15}), 1,98-1,93 (m, 1H, H_5), 1,78-1,72 (m, 2H, $H_{4\alpha,\beta}$), 1,36 (d, 1H, H_{7en}, J= 10,2), 1,2 (s, 3H, Me_9), 1,03 (s, 3H, Me_8); ^{13}C NMR: ($CDCl_3$): δ 45,15 (CH), 78,00 (CH), 32,36 (CH), 30,95 (CH_2), 40,60 (CH), 38,37 (C), 25,00 (CH_2), 22,81 (CH_3), 27,12 (CH_3), 37,06 (CH_2), 154,00 (C), 50,29 (CH_2), 30,04 (CH_3), 137,83 (CH); 127,79-125,09 (CH); MS (70eV): m/z = M^+ 364 (17%); 262 (35%), 141 (100%), 122 (45%), 85 (77%).

β-Ketobutyrate 8: IR (film, υ (cm^{-1}): 1718; 1646 ; ^1H MNR ($CDCl_3$): δ 7,4-7,1 (m, 5H, H_{ar}), 5,18 (d, 1H, H_2, J=6), 3,18 (s, 2H, H_{13}), 2,9-2,6 (m, 3H, H_3, H_{10}/ $H_{10'}$), 2,2 (s, 3H, Me_{15}), 2,34-2,2 (m, 1H, H_1), 2,12-2,0 (m, 1H, H_{7ex}), 1,96-1,82 (m, 1H, H_5), 1,58-124 (m, 2H, $H_{4\alpha,\beta}$), 1,53 (d, 1H, H_{7en}, J= 10), 1,22 (s, 3H, Me_9), 0,84(s, 3H, Me_8); ^{13}C MNR ($CDCl_3$): δ 45,02 (CH), 79,11 (CH), 29,92 (CH), 29,81 (CH_2), 40,33 (CH), 29,50 (C), 23,10 (CH_2), 19,64 (CH_3), 26,36 (CH_3), 40,14 (CH_2), 140,18 (C), 166,68 (C), 50,04 (CH_2), 200,00 (C), 35,56 (CH_3); MS: (70eV): m/z M^+314 (<1%), 212(27%), 121 (36%), 91 (100%).HRMS m/z (%) mass: 314.189385 ($C_{20}H_{26}O_3$); calculated, 314.188195.

General Procedure for reductions of β-Ketobutyrates 7a-e or 8: Calcium chloride or magnesium chloride (2,0 mmol) was added to a methanol (10 mL) solution of β-ketobutyrates (7 or 8-a-e) (1,0mmol) at 25°C and the resulting clear solution was stirred for 30 min at 25°C. The mixture was cooled to 0 °C and $NaBH_4$ (40 mg, 1 mmol) was added. Vigorous gas evolution occurred. After stirring for 10 min at 0 °C, the reaction mixture was poured into aq. HCl (1N) and extracted with ethyl acetate (10mL x 2). The combined organic layers were dried

over Na_2SO_4 and concentrated in vacuum. The crude products was obtained in good yield (60-90%) and the isomeric ratio was determined by ^{13}C NMR (50,0 MHz).

β-Hydroxybutyrate 10a: IR (film, υ (cm^{-1})): 3442 (O-H), 1729 (C=O).; ^1H NMR ($CDCl_3$): δ 7,32-7,15 (m, 5H, H_{ar}), 5,5 (dd, 1H, H_2, J= 7,4/ 4,9), 4,26-4,04 (m, 1H, H_{14}), 2,87-2,59 (m, 3H, H_3/ H_{10}/ $H_{10'}$), 2,44 (d, 1H, H_{13}, J= 1,74), 2,42 (d, 1H, $H_{13'}$, J=2,84), 2,34- 2,13 (m, 2H, H_{7ex}/ H_1), 1,97 (q, 1H, H_5, J=5), 1,82-1,65 (m, 2H, $H_{4\alpha}$/ $H_{4\beta}$), 1,36 (d, 1H, H_{7en}, J=10), 1,24 (dl, 3H, Me_{15}), 1,2 (s, 3H, Me_9), 1,04 (s, 3H, Me_8); ^{13}C NMR ($CDCl_3$, Major diastereomer): δ 45,10 (CH), 76,25 (CH), 32,50 (CH), 30,90 (CH_2), 40,50 (CH), 38,30 (C), 25,00 (CH_2), 22,23 (CH_3), 27,14 (CH_3), 36,86 (CH_2), 140,20 (C), 172,20 (C), 42,80 (CH_2), 64,00 (CH), 22,78 (CH_3); MS (70eV): m/z M^+ 316 (≤1%),225 (3%), 212 (36%), 121(81%), 91 (100%). HRMS m/z (%) mass: 316.204002 ($C_{20}H_{28}O_3$); calculated, 316.203845.

β-Hydroxybutyrate 10b: IR (film, υ (cm^{-1})): 3425 (O-H), 1728 (C=O); ^1H NMR ($CDCl_3$): δ 7,1-6,8 (m, 4H, H_{ar}), 5,47 (dd, 1H, H_2, J= 6,9/ 5,0), 4,2-4,08 (m, 1H, H_{14}), 3,8 (s, 3H, Me_{16}), 2,8-2,5 (m, 3H, H_3/ H_{10}/ $H_{10'}$), 2,43-2,36 (m, 2H, H_{13}/ $H_{13'}$), 2,32-2,10 (m, 2H, H_1/ H_{7ex}), 1,94 (q, 1H, H_5, J= 4,8), 1,84-1,6 (m, 2H, $H_{4\alpha}$/ $H_{4\beta}$), 1,33 (d, 1H, H_{7en}, J=10,2), 1,21 (dd, 3H, Me_{15}, J= 6,32/ 0,9), 1,17 (s, 3H, Me_9), 1,01 (s, 3H, Me_8); ^{13}C NMR ($CDCl_3$, Major diastereomer): δ 41,1 (CH), 72,1 (CH), 28,6 (CH), 26,7 (CH_2), 38,8 (CH), 34,2 (C), 20,8 (CH_2), 23,1 (CH_3), 18,7 (CH_3), 31,8 (CH_2), 128,1 (CH), 168,1 (C), 50,9 (CH_2), 59,8 (CH), 18,1 (CH_3), 36,5 (OCH_3); MS (70eV): m/z M^+ 346 (2%), 121 (100%). HRMS m/z (%) mass: 346.213886 ($C_{21}H_{30}O_4$); calculated, 346.214409.

β-Hydroxybutyrate 10c: IR (film, υ (cm^{-1})): 3430 (O-H), 1728 (C=O); ^1H NMR($CDCl_3$): δ 7,2-7,0 (d, 2H, H_{ar}, J=8,8), 6,9-6,7 (d, 2H, H_{ar}, J=8,5), 5,47 (dd, 1H, H_2, J= 6,9/ 5,0), 4,2-4,08 (m, 1H, H_{14}), 3,8 (s, 3H, Me_{16}), 2,8-2,5 (m, 3H, H_3/ H_{10}/ $H_{10'}$), 2,43-2,36 (m, 2H, H_{13}/ $H_{13'}$), 2,32-2,10 (m, 2H, H_1/ H_{7ex}), 1,94 (q, 1H, H_5, J= 4,8), 1,84-1,6 (m, 2H, $H_{4\alpha}$/ $H_{4\beta}$), 1,33 (d, 1H, H_{7en}, J=10,2), 1,21 (dd, 3H,

Me_{15}, J= 6,32/ 0,9), 1,17 (s, 3H, Me_9), 1,01 (s, 3H, Me_8); ^{13}C NMR ($CDCl_3$, Major diastereomer): δ 41,1 (CH), 72,1 (CH), 28,6 (CH), 26,7 (CH_2), 38,8 (CH), 34,2 (C), 20,8 (CH_2), 18,7 (CH_3), 23,1 (CH_3), 31,8 (CH_2), 128,5 (CH), 168,1 (C), 36,5 (CH_2), 59,8 (CH), 18,1 (CH_3), 50,9 (OCH_3); MS (70eV): m/z M^+ 346 (1%) 242 (25%), 121 (100%), 91 (55%). HRMS m/z (%) mass: 346.214303 ($C_{21}H_{30}O_4$); calculated, 346.214409.

β-Hydroxybutyrate 10d: IR (film, υ (cm^{-1})): 3441 (O-H), 1714 (C=O); ^1H NMR($CDCl_3$): δ 8,15-7,25 (7H, H_{ar}), 5,63 (dd, 1H, H_2, J= 7,6/ 5,0), 4,3-4,0 (m, 1H, H_{14}), 3,43-3,33 (m, 1H, H_3), 3,0-2,88 (m, 2H, H_{10}/ $H_{10'}$), 2,46-2,36 (m, 2H, H_{13}/ $H_{13'}$), 2,33-2,1 (m, 2H, H_1/ H_{7ex}), 1,97-1,87 (m, 1H, H_5), 1,8-1,60 (m, 2H, $H_{4\alpha,\beta}$), 1,30 (d, 1H, H_{7en}, J= 10,6), 1,19 (d, 3H, Me_{15}, J=6,17), 1,21 (s, 3H, Me_9), 1,10 (s, 3H, Me_8); ^{13}C NMR ($CDCl_3$, Major diastereomer): δ 45,14 (CH), 72, 48 (CH), 27,37 (CH), 26,99 (CH_2), 38,87 (CH), 34,39 (C), 20,93 (CH_2), 23,15 (CH_3), 18,92 (CH_3), 29,60 (CH_2), 168,40 (C), 36,59 (CH_2), 59,99 (CH), 18,26 (CH_3); MS (70eV): m/z M^+ 366 (5%), 262 (32%), 141 (90%), 91 (100%). HRMS m/z (%) mass: 366.218997 ($C_{24}H_{30}O_3$); calculated, 366.219495

β-Hydroxybutyrate 10e: ^1H NMR ($CDCl_3$): δ 7,82-7,26 (7H, H_{ar}), 5,57 (dd, 1H, H_2, J= 8/ 5), 4,29-4,02 (m, 1H, H_{14}), 3,03-2,7 (m, 3H, H_3,/ H_{10}/ $H_{10'}$), 2,51-2,43 (m, 2H, H_{13}/ $H_{13'}$), 2,36-2,15 (m, 2H, H_1/ H_{7ex}), 2,02-1,94 (m, 1H, H_5), 1,82-1,75 (m, 2H, $H_{4\alpha,\beta}$), 1,39 (d, 1H, H_{7en}, J= 10,3), 1,26-1,22 (m, 3H, Me_{15}), 1,23 (s, 3H, Me_9), 1,10 (s, 3H, Me_8); ^{13}C NMR ($CDCl_3$, Major diastereomer): δ 42,85 (CH), 76, 41 (CH), 32,58 (CH), 30,99 (CH_2), 42,85 (CH), 38,38 (C), 24,96 (CH_2), 22,26 (CH_3), 27,17 (CH_3), 37,11 (CH_2), 137,80 (CH), 172,30 (C), 40,58 (CH_2), 64,04 (CH), 22,84 (CH_3). HRMS m/z (%) mass: 366.219470 ($C_{24}H_{30}O_3$); calculated, 366.219495

β-Hydroxybutyrate 11: ^1H NMR ($CDCl_3$) δ 7,3-7,1 (m, 5H, H_{ar}), 5,13 (dd, 1H, H_2, J= 7,0/ 1,0), 4,09-3,89 (m, 1H, H_{14}), 2,83-2,6 (m, 1H, H_{13}), 2,34- 1,83 (m, 8H, H_3/ H_{10}/ $H_{10'}$/ H_5/ $H_{13'}$/ H1/ $H7_{ex}$/ $H_{4\alpha}$), 1,5-1,4 (m, 1H, $H_{4\beta}$), 1,53 (d, 1H, H_{7en}, J=10), 1,21 (s, 3H, Me_9), 1,13 (dd, 3H, Me_{15}, J=6,3/ 3,1), 0,85 (s, 3H, Me_8); ^{13}C

NMR ($CDCl_3$, Major diastereomer): δ 45,13 (CH), 78, 31 (CH), 35,56 (CH), 30,00 (CH_2), 40,30 (CH), 29,55 (C), 23,09 (CH_2), 19,61 (CH_3), 26,32 (CH_3), 42,42 (CH_2), 140,10 (C), 172,50 (C), 40,19 (CH_2), 64,03 (CH), 22,13 (CH_3), 128,8-125,7 (CH).

Acknowledgments: National Research Council of Brazil (CNPq), José Bonifácio University Foundation (FUJB-Brazil) and Research Foundation of Rio de Janeiro (FAPERJ) it goes financial support. Dr. A.J.R. Silva, E. Miguez goes NMR spectra (NPPN-UFRJ).

REFERENCES

1. Oppolzer, W. *Tetrahedron* **1987**, *43, 1969.*
2. (a)Corey, E.J. and Ensley, H.E. *J.Am.Chem.Soc.* **1975**, *97*, 6908. (b) Chapman, B. J. and Jones, G. B. *Synthesis* **1995**, *475*. (c)Herzog, H.; Scharf, H.D. *Synthesis* **1986**, 420 and references cited therein.
3. (a)El Achaagar, THE., Boumzebra, M., Roumestant, M.L., Viallefont, P. *Tetrahedron* **1988**, *44, 5319.* (b) Matterson, D. S. *Chem. Rev.* **1989**, *89*, 1535.(c) Solladie-Cavallo, T. and Koesseler, J.L. *J.Org.Chem* **1994**, *59*, 3240 and references cited therein.
4. Oppolzer, W., Kurth, M., Reichlin, D., Chapuis, C., Monhaupt, M., Moffart,F. *Helv.Chim.Acta* **1981**, *64, 2802.*
5. Vasconcellos,M.L.A.A., D'Angelo, J., Desmaele, D., Costa, P.R.R.and Potin, D. *Tetrahedron:Asymmetry* **1991**, *2, 353.*
6. Dumas, F., Mezrhab, B., D'Angelo, J. and Riche, C. *J.Org.Chem.***1996**, *61, 2293.*
7. Dumas, F., Alencar,K., Mahuteau, J.; Barbero, M.J.L., Miet,C., Gérard, F., Vasconcellos, M.L.A.A and Costa, P.R.R. *Tetrahedron:Asymmetry* **1997**, *8*, 579.
8. Cabral, L.M., Costa ,P.R.R., Vasconcellos, M.L.A.A., Barreiro, E.J. and Castro,R.N. *Synth. Commun.***1996**, *26*, 3671.

9. Costa, P.R.R., Cabral, L.M., Alencar, K., Schmidt, L.L. and Vasconcellos, M.L.A.A. *Tetrahedron Lett.* **1997**, *38*, 7021

10.(a)Fujii, H., Oshima, K. and Ultimoto, K. *Chemistry Lett.* **1992**, 967. (b) Fraga, C. A. M., Barreiro, E. J. *Synth. Commun.* **1995**, *25*, 1133.

11.Clemens, R.J. and Hyatt, J.A. *J.Org.Chem* **1985**, *50*, 2431.

12. (S)-(+)-1,3-Butanediol, $[\alpha]_{20} = +30$ (c = 1, EtOH), is commercially available from Aldrich Chemical Company.

13.Taber, D.F., Deker, P.B., Gaul, M. A. *J.Am.Chem.Soc* **1987**, *109*, 7488.

14.Maddaluno, J.F.; Gresh, N.; Giessner-Prettre, C.,*J.Org.Chem.* **1994**, *59*, 793.

15.Maddaluno, J.F ; D'Angelo *J.Am.Chem.Soc* **1986**, *108*, 8112.

16.Hamon, D.P.G.; Holman, J.W.; Massy-Westropp, R.A .*Tetrahedron* **1993**, *42*, 9593.

(Received in the USA 07 June 1999)