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ENZYMATIC RESOLUTION OF ENDO-BICYCLO[2.2.1]HEPT-2-YL BUTYRATES AND RELATED COMPOUNDS: STERIC REQUIREMENTS IN THE BRIDGE-REGION

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Abstract - Butyrates of *endo*-bicyclo[2.2.2]octanols and *endo*-bicyclo[2.2.1]heptan-2-ols, the latter bearing substituents of different size at C-7, were hydrolysed enzymatically using *Candida cylindracea* lipase. Steric factors were found to influence enantioselection: In the bicyclo[2.2.1]heptane series substrates having small substituents on C-7 were generally resolved with better enantioselection (70 to >80% e.e.) than those with bulky ones (30-60% e.e.). This method gives access to enantiomerically enriched building blocks for the synthesis of cyclopentane and -hexane systems.

INTRODUCTION

In previous studies[1-3] we showed that enzymatic resolution of norbornane-type esters is a valuable tool for an access to a number of optically active bicyclic building blocks useful for homochiral syntheses. To increase the applicability of this method by extending it to structurally different substrates and to gain more information about the relationship between substrate structure and enantioselectivity of the enzymatic reaction[4] we initiated this study on the influence of steric factors in the bridge-region of bicyclic esters on the enantioselection of *Candida cylindracea* lipase. Thus, a number of butyrates of bicyclo[2.2.1]heptanols bearing substituents on C-7 differing in size and substrates possessing the bicyclo[2.2.2]octane framework (a formal exchange of the methylene bridge by a CH_2-CH_2 unit) were subjected to enzymatic resolution.

Compounds of both of these types have frequently been used as starting material for the synthesis of monocyclic target molecules: By means of regioselective ring fission reactions[5] or photochemical rearrangement[6], cyclopentanoid systems can be obtained from bicyclo[2.2.1]heptanes[7] and with bicyclo[2.2.2]octanes access is provided for cyclohexane derivatives[8]. Furthermore, the majority of substrates used in this study has successfully been used for the synthesis of natural products[9-11] such as alkaloids[8], prostaglandins, terpenes and steroids[12]. Among the methods for the resolution of these types of compounds hitherto employed[13,14], microbial transformations *via* biohydroxylation[15] or enantioselective reduction of ketones[16,17] recently have gained increasing interest. Since all of them are impeded by either being

laborious[13,14], giving poor yields[15,17] or leading to products with undetermined optical purity[16], the use of enzymatic methods[18] which permit a handling of molar quantities[19] seemed to be an attractive alternative.

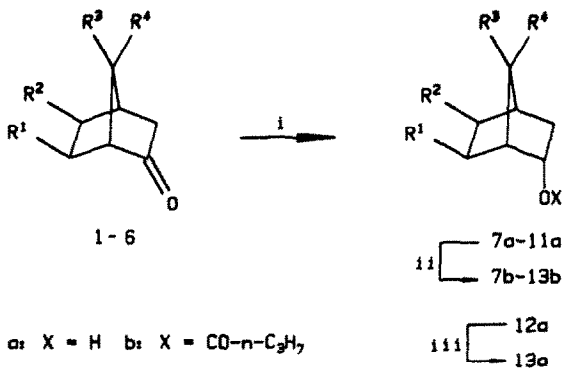
RESULTS AND DISCUSSION

1) SYNTHESIS OF RACEMIC SUBSTRATES[20]

a) Bicyclo[2.2.1]heptane Systems

Since it has been shown[2] that only *endo*-configurated esters possessing the bicyclo[2.2.1]heptane framework in contrast to their corresponding *exo*-isomers were resolved by lipases with a high degree of enantioselection, only substrates of the former type were considered in this study.

SCHEME I: Synthesis of bicyclo[2.2.1]heptane esters[20]



i) $NaBH_4$, MeOH, -10°; ii) Butyric anhydride/DMAP/Py, CH_2Cl_2; iii) H_2/5% Pd on C, EtOH.

Compound	R^1	R^2	R^3	R^4
1, 7a,b	H	Br	CO_2Me	H
2, 8a,b	H	H	CO_2Me	H
3, 9a,b	H	H	CO_2-*t*-Bu	H
4, 10a,b	bond		CO_2Me	H
5, 11a,b	H	H	O-CH_2Ph	H
12a,b	bond		OMe	OMe
6, 13a,b	H	H	OMe	OMe

Entry to compounds bearing a carboxylic ester on C-7 (1-4, 7a,b-10a,b) was accomplished *via* Prins reaction[21] starting from norbornadiene: 1 and 4 were prepared as described[21,22], esters 2[23] and 3 were synthesized from the corresponding acid[21] by standard procedures[24,25]. Ketone 5[26] was obtained from *anti*-7-benzyloxynorborn-2-ene[27] in two steps: Hydroboration[28] and subsequent

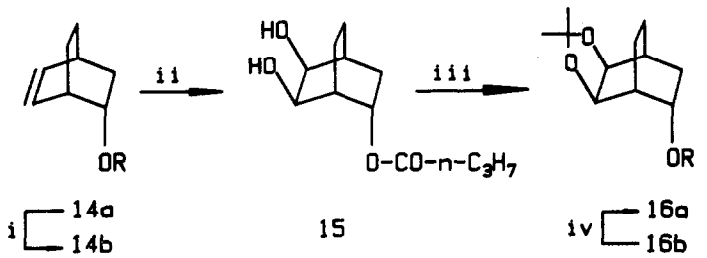
oxidation[29] of the mixture of *endo/exo* alcohols gave **5** in 65 % overall yield. As expected[2], reduction of ketones **1-5** at low temperature proceeded in >98 % stereoselectivity (GLC-analysis) yielding the desired *endo*-alcohols **7a-11a**. Catalytic hydrogenation[2] of the unsaturated 7,7-dimethoxy derivative **12a**[11,30] gave **13a**[31] almost quantitatively. To achieve reasonable rates of conversion in enzymatic hydrolyses of esters, alcohols **7a-13a** were transformed into their butyrates **7b-13b** by a standard method[32].

b) Bicyclo[2.2.2]octane Systems

Due to the low stereoselectivity in the reduction of bicyclo[2.2.2]oct-5-en-2-one[8] (*endo/exo* alcohols 5:2) the most convenient way for the preparation of substrates **14b** and **16b** was as follows:

Diels Alder reaction of 1,3-cyclohexadiene with vinyl acetate[33] gave an 4:1 *endo/exo*-mixture of bicyclic acetates, from which after transesterification pure *endo*-alcohol **14a**[33] was obtained by silica gel chromatography. Esterification[32] gave **14b**, which in turn could be *cis*-dihydroxylated[34,35] stereoselectively to give the intermediate diol **15**. Transacetalisation led to **16b**, whose *exo/endo*-ratio with respect to the dioxolane moiety was shown to be >98:2 by GLC-analysis.

SCHEME II: Synthesis of bicyclo[2.2.2]octane esters[20]



a: R = H; b: R = CO-n-C_3H_7

i) Butyric anhydride/DMAP/Py, CH_2Cl_2; ii) OsO_4/N-methylmorpholine-N-oxide·H_2O, acetone; iii) 2,2-dimethoxypropane/H^+; iv) NaOMe/MeOH.

2) ENZYMATIC HYDROLYSES

To obtain an optimum in both *chemical and optical* yield upon kinetic resolution of racemic substrates[36] we applied a two-step process discussed elsewhere[2,37]. Among the hydrolases tested, *Candida cylindracea* lipase[38] exhibited sufficient activity on all substrates (**7b-14b, 16b**) whereas others showed moderate rates of hydrolysis on some esters only - too low for preparative purposes: Lipase from *Pseudomonas sp.*[39] (active on **10b, 12b**), from *Aspergillus sp.*[40] (**8b, 9b, 13b**) and from porcine pancreas[41] (**7b-10b, 12b, 14b**).

SCHEME III: Enzymatic hydrolyses[20]

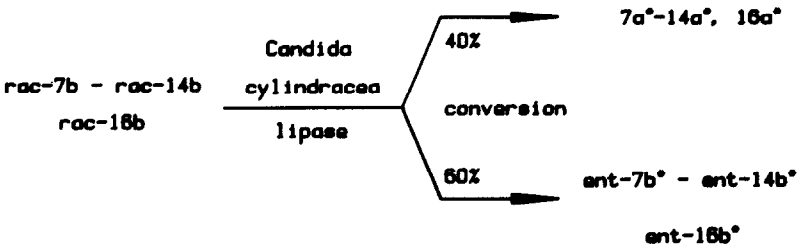
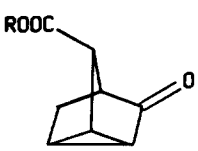


TABLE I: Optical purity of products

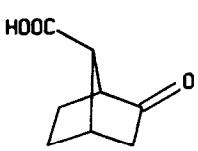
Substrate[20]	Conversion 40 %		Conversion 60 %	
	Product	e.e.[%][a]	Product	e.e.[%][b]
rac-7b	7a*	58	*ent*-7b*	20
rac-8b	8a*	73	*ent*-8b*	52
rac-9b	9a*	36	*ent*-9b*	33
rac-10b	10a*	76	*ent*-10b*	75
rac-11b	11a*	45	*ent*-11b*	51
rac-12b	12a*	71	*ent*-12b*	76
rac-13b	13a*	62	*ent*-13b*	49
rac-14b	14a*	60	*ent*-14b*	47
rac-16b	16a*	75	*ent*-16b*	83

[a] Determined by ^{1}H and/or ^{19}F-NMR spectroscopy of the corresponding MTPA-ester[42]. [b] Determined as above from MTPA-esters of alcohols *ent*-7a* - *ent*-14a* and *ent*-16a* which were obtained by transesterification of the corresponding butyrates.

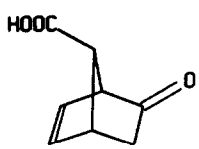
The absolute configuration of products was determined as follows: Swern oxidation[43] of alcohols 7a*-11a* and 13a* gave ketones 1*-6*. HBr Elimination on 1* and hydrolysis of ester 17* led to keto acid 18* with known configuration[44]. Similarly, esters 2*, 3* and 4* were hydrolysed to give known acids 19* and 20*[22]. Catalytic hydrogenation of 12a* yielded 13a*[31]. *Ent*-16b* was correlated with authentical material independently synthesized from *ent*-14b* whose absolute configuration was determined using known optical rotation values of 14a*[45,46].



17* R = CH_3
18* R = H



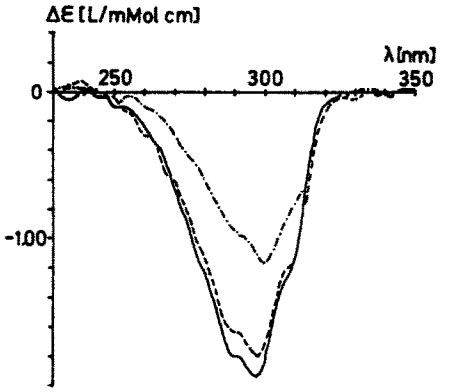
19*



20*

The absolute configuration of **11a*** was determined by comparison of the CD spectrum of its corresponding ketone **5*** with those of ketones **2***[22] and **6***[31]. As figure I shows, all of them exhibited a negative $\Delta\varepsilon$ value for the $n\rightarrow\pi^*$ transition indicating their identical absolute configuration. Additionally, these results are in agreement with an expected $\Delta\varepsilon<0$ when the octant rule was applied to these compounds[47].

FIGURE I: CD-Spectra of ketones **2***, **5*** and **6***, recorded in acetonitrile



2*
5*
6*

Compound	2*	5*	6*
λ_{max} [nm]	300.8	301.8	296.6
$\Delta\varepsilon$ [L/mMolcm]	-1.17	-1.80	-1.94
c [mMol/L]	3.40	0.91	1.18

Upon examination of the results depicted in table I the following characteristics[4] of enzymatic resolution by *Candida cylindracea* lipase are found:

1) *endo*-Esters possessing an (*R*)-configurated alcoholic center are cleaved preferentially being in accordance with previous findings[1-3].

2) Increasing the steric requirements of substituents on C-7 of bicyclo[2.2.1]heptanols drastically reduces the enantioselection of enzymatic hydrolysis: Substrates **8b** and **10b** are resolved with higher e.e. in contrast to **9b** and **11b**, carrying more bulky substituents. Consequently, **16b** having the smallest bridge gives the best results. For the relatively low enantioselection of ester **14b** we assume that the small steric difference between the -CH=CH- and $-CH_2-CH_2-$ bridges, causing an almost spherical shape of the asymmetric moiety of the substrate, is responsible.

3) Esters bearing π-electrons in 5,6-position (**10b**, **12b**) give better results than their saturated counterparts **8b** and **13b**.

4) In general it we observed that in contrast to C-7 unsubstituted norbornane-type esters[1,2] and their 7-oxa analogues[3], where the optical purities of products frequently reached >97 %, bridgehead substituents reduce this value to the range of 70-80 %.

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EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured in $CHCl_3$ solution on a Perkin Elmer 141 or a Jasco DIP 370 polarimeter. For CD-spectra a Jobin-Yvon-ISA dichrographe Mark III was used. ^1H- and ^{19}F-NMR spectra were recorded in $CDCl_3$ on a Bruker WH 90 or a Bruker MSL 300 spectrometer. Chemical shifts are reported in δ from TMS or CCl_3F as internal standard, respectively. GLC analyses were performed on a Dani 8500 chromatograph (25 m capillary column, Chrompack WCOT CP-Sil5-CB) equipped with FID. Elemental analyses (C, H, N) for all novel compounds were within 0.4 % of the calculated values.

TABLE II: Optical rotation values in $CHCl_3$ solution[20]

Compound	$[\alpha]_D^{20}$	c [g/100ml]	e.e. [%]	absolute configuration
7a*	+0.9	13.5	58	1*S*,2*S*,4*S*,5*R*,7*R*
ent-7b*	-0.5	13.5	20	1*R*,2*R*,4*R*,5*S*,7*S*
8a*	+5.80	7.18	73	1*S*,2*R*,4*S*,7*S*
ent-8b*	-24.6	7.30	52	1*R*,2*S*,4*R*,7*R*
9a*	+2.9	9.40	36	1*S*,2*R*,4*S*,7*S*
ent-9b*	-12.3	7.80	33	1*R*,2*S*,4*R*,7*R*
10a*	+84.7	10.4	76	1*S*,2*R*,4*R*,7*S*
ent-10b*	-90.5	4.33	75	1*R*,2*S*,4*S*,7*R*
11a*	-2.1	5.21	45	1*R*,2*R*,4*S*,7*S*
ent-11b*	-1.7	6.03	51	1*R*,2*S*,4*R*,7*R*
12a*	+56.2	8.63	71	1*R*,2*R*,4*R*
ent-12b*	-74.4	6.86	76	1*S*,2*S*,4*S*
13a*	-0.6	10.7	62	1*R*,2*R*,4*S*
ent-13b*	-10.5	12.7	49	1*S*,2*S*,4*R*
14a*	+44.2[46]	3.53	60	1*R*,2*R*,4*R*
ent-14b*	-23.1	9.73	47	1*S*,2*S*,4*S*
16a*	-3.0	4.96	75	1*R*,2*R*,6*S*,7*S*,8*R*
ent-16b*	+17.4	4.48	83	1*S*,2*S*,6*R*,7*S*,8*S*

***endo*-Alcohols 7a, 8a[23] and 9a-11a** were prepared in >90 % yield by $NaBH_4$ reduction of the corresponding ketones (see above) according to a previously published procedure[4]:

(1*RS*,2*RS*,4*RS*,5*SR*,7*SR*)-Methyl 2-bromo-5-hydroxybicyclo[2.2.1]heptan-7-carboxylate (7a)[49]: Bp 90-100°/0.03 mbar[49]; mp 64-6°. ^1H-NMR: 1.0 (dd, J=14 and 4 Hz, *endo*-H on C-6), 1.2-3.0 (m, 6H), 2.0 (s, OH, D_2O exchangeable), 3.65 (s, OCH_3), 3.9-4.4 (m, H on C-2 and C-5).

(1*RS*,2*SR*,4*RS*,7*RS*)-*t*-Butyl 2-hydroxybicyclo[2.2.1]heptan-7-carboxylate (9a): Bp 120-5°/0.3 mbar[48]; mp 66-9°. ^1H-NMR: 0.93 (dd, J=12 and 4 Hz, *endo*-H on C-3), 1.1-2.6 (m, 8H), 1.45 [s, $C(CH_3)_3$], 2.10 (s, OH, D_2O exchangeable), 4.25 (dt, J=10 and 4 Hz, H on C-2).

(1*RS*,2*SR*,4*SR*,7*RS*)-Methyl 2-hydroxybicyclo[2.2.1]hept-5-en-7-carboxylate (10a): Bp 100-10°/0.04 mbar[48]. ^1H-NMR: 0.90 (dd, J=13 and 3 Hz, *endo*-H on C-3), 2.05-2.3 (m, *exo*-H on C-3 and OH), 2.35-2.6 (m, H on C-4), 3.1-3.4 (m, H on C-1 and C-7), 3.65 (s, OCH_3), 4.50 (dt, J=8 and 4 Hz, H on C-2), 5.9-6.6 (m, H on C-5 and C-6).

(1*RS*,2*RS*,4*SR*,7*SR*)-7-Benzyloxybicyclo[2.2.1]heptan-2-ol (11a): Bp 120-30°/0.02 mbar[48]. ^1H-NMR: 0.95 (dd, J=10 and 4 Hz, *endo*-H on C-3), 1.1-2.4 (m, 7H), 1.75 (s, OH, D_2O exchangeable), 3.65 (m, H on C-7), 4.10 (dt, J=10 and 5 Hz, H on C-2), 4.45 (s, Ph-CH_2), 7.3 (broad s, Ar-H).

Esters 7b-14b were prepared in 85-96 % yield by esterification of alcohols **7a-14a** using a standard procedure[32]:

(1*RS*,2*RS*,4*RS*,5*SR*,7*SR*)-Methyl 2-bromo-5-butyryloxybicyclo[2.2.1]heptan-7-carboxylate (7b): Mp 65-8°. ^1H-NMR: 0.98 (t, J=7 Hz, ω-CH_3), 1.1-3.0 (m, 11H), 3.70 (s, OCH_3), 4.05 (dd, J=8 and 5 Hz, H on C-2), 4.92 (dt, J=10 and 4 Hz, H on C-5).

(1*RS*,2*SR*,4*RS*,7*RS*)-Methyl 2-butyryloxybicyclo[2.2.1]heptan-7-carboxylate (8b): Bp 100-10°/0.03 mbar[48]. ^1H-NMR: 0.95 (t, J=7 Hz, ω-CH_3), 1.1-2.8 (m, 13H), 3.71 (s, OCH_3), 4.98 (dt, J=10 and 4 Hz, H on C-2).

(1*RS*,2*SR*,4*RS*,7*RS*)-*t*-**Butyl 2-butyryloxybicyclo[2.2.1]heptan-7-carboxylate (9b):** Bp 130-40°/1 mbar[48]. ^{1}H-NMR: 0.95 (t, J=7 Hz, ω-CH$_3$), 1.05 (dd, J=9 and 4 Hz, *endo*-H on C-3), 1.2-2.8 (m, 12H), 1.45 [s, C(CH$_3$)$_3$], 4.95 (dt, J=10 and 4 Hz, H on C-2).

(1*RS*,2*SR*,4*SR*,7*RS*)-**Methyl 2-butyryloxybicyclo[2.2.1]hept-5-en-7-carboxylate (10b):** Bp 100-10°/0.03 mbar[48]. ^{1}H-NMR: 0.8-3.3 (m, 12H), 3.65 (s, OCH$_3$), 5.30 (dt, J=8 and 3 Hz, H on C-2), 5.75-6.35 (m, H on C-5 and C-6).

(1*RS*,2*SR*,4*RS*,7*RS*)-**7-Benzyloxybicyclo[2.2.1]heptan-2-yl butyrate (11b):** Bp 85-90°/0.02 mbar[48]. ^{1}H-NMR: 0.95 (t, J=7 Hz, ω-CH$_3$), 1.05 (dd, J=10 and 3 Hz, *endo*-H on C-3), 1.2-2.7 (m, 11H), 3.7 (m, H on C-7), 4.45 (s, Ph-C*H*$_2$), 4.90 (dt, J=9 and 3 Hz, H on C-2), 7.3 (broad s, Ar-H).

(1*RS*,2*RS*,4*RS*)-**7,7-Dimethoxybicyclo[2.2.1]hept-5-en-2-yl butyrate (12b):** Bp 90-100°/0.01 mbar[48]. ^{1}H-NMR: 0.85-2.75 (m, 10H), 2.95 (m, H on C-1), 3.25 (s, OCH$_3$), 3.35 (s, OCH$_3$), 5.4 (m, H on C-2), 5.9-6.55 (m, H on C-5 and C-6).

(1*RS*,2*RS*,4*SR*)-**7,7-Dimethoxybicyclo[2.2.1]hept-2-yl butyrate (13b):** Bp 90-100°/0.04 mbar[48]. ^{1}H-NMR: 0.8-2.4 (m, 15H), 3.30 (s, OCH$_3$), 3.35 (s, OCH$_3$), 5.20 (dt, J=8 and 3 Hz, H on C-2).

(1*RS*,2*RS*,4*RS*)-**Bicyclo[2.2.2]oct-5-en-2-yl butyrate (14b):** Bp 118-9°/13 mm. ^{1}H-NMR: 0.92 (t, J=7 Hz, ω-CH$_3$), 1.05-2.1 (m, 8H), 2.15 (t, J=7 Hz, α-CH$_2$), 2.58 (broad s, H on C-4), 2.75 (broad s, H on C-1), 4.85-5.03 (m, H on C-2), 6.18 (dt, J=16 and 5 Hz, H on C-5 and C-6).

(1*RS*,4*RS*,7*RS*)-*t*-**Butyl 2-oxobicyclo[2.2.1]heptan-7-carboxylate (3)** Acid catalysed esterification of the corresponding keto acid[21] using 2-methylpropene in CH_2Cl_2 as described elsewhere[20] gave 3 in 65 % yield. Bp 110-20°/0.8 mbar[48] ^{1}H-NMR: 1.45 [s, C(CH$_3$)$_3$], 1.7-2.3 (m, 6H), 2.7-3.0 (m, H on C-1 and C-3).

(1*RS*,2*RS*,4*RS*)-**7,7-Dimethoxybicyclo[2.2.1]hept-5-en-2-ol (12a)**[10,11,30] was synthesized according to ref. 11 and 30. Bp 120-40°/16 mm[48]. ^{1}H-NMR: 0.90 (dd, J=10 and 2 Hz, *endo*-H on C-3), 1.85 (s, OH, D_2O exchangeable), 2.3-2.9 (m, *exo*-H on C-3 and H on C-4), 3.0 (m, H on C-1), 3.30 (s, OCH$_3$), 3.35 (s, OCH$_3$), 4.5-4.9 (m, H on C-2), 6.1-6.65 (m, H on C-5 and C-6).

(1*RS*,2*RS*,6*SR*,7*SR*,8*RS*)-**4,4-Dimethyl-3,5-dioxatricyclo[5.2.2.0^{2,6}]undecan-8-ol (16a):** Transesterification of **16b** as described[2] gave alcohol **16a** in 95 % yield. Mp 108°. ^{1}H-NMR: 1.08-1.14 (m, 2H), 1.24-1.34 (m, 2H), 1.37 (s, CH$_3$), 1.55 (s, CH$_3$), 1.62 (broad s, OH, D_2O exchangeable), 1.71-2.2 (m, 4H), 4.12 (dt, J=9 and 3.5 Hz, H on C-8), 4.20 (dd, J=8 and 4 Hz, H on C-2), 4.48 (dd, J=8 and 4 Hz, H on C-6).

(1*RS*,2*RS*,6*SR*,7*RS*,8*RS*)-**4,4-Dimethyl-3,5-dioxatricyclo[5.2.2.0^{2,6}]undec-8-yl butyrate (16b)** was obtained in 81 % overall yield from **14b** by a two step sequence: OsO_4 catalysed *cis*-dihydroxylation[2] gave crude diol **15** which was directly protected as its acetal using a previously described procedure[2]. Bp 85-90°/0.02 mbar[48]. ^{1}H-NMR: 0.95 (t, J=7 Hz, ω-CH$_3$), 1.08-2.18 (m, 10 H), 1.37 (s, CH$_3$), 1.52 (s, CH$_3$), 2.25 (t, J=7 Hz, α-CH$_2$), 4.17 (dd, J=7 and 3 Hz, H on C-2), 4.36 (dd, J=7 and 3 Hz, H on C-6), 5.01 (dt, J=9 and 3 Hz, H on C-8).

For a detailed description of enzymatic resolution on a 1-20 g scale see ref.3.

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