Pergamon

Tetrahedron Letters, Vol. 38, No. 49, pp. 8503-8506, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10299-4

Enzymatic resolution of endo-bicyclo[4.1.0]heptan-2-ols.

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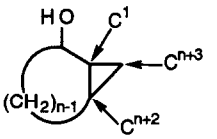
Abstract: Optically active endo-bicyclo[4.1.0]heptan-2-ols compounds were prepared by lipase-catalyzed transesterifications with the racemic alcohols. High enantioselectivities and reaction rates were observed using the lipase from *Candida antarctica*. © 1997 Elsevier Science Ltd.

Cleavage of the C^1-C^{n+3} or C^{n+2}-C^{n+3} cyclopropanic bond of bicyclo[n.1.0]alkan-2-ols allows the synthesis of various types of compounds bearing one or several chiral atoms.[1] Fission of the C^1-C^{n+3} bond occurred generally without change of the C^{n+2} absolute configuration [1b,c] whereas inversion of the configuration of this carbon was observed after C^{n+2}-C^{n+3} bond cleavage.[1a] Thus, the preparation of enantiomerically enriched bicyclo[n.1.0]alkan-2-ols derivatives [2] should give an access to various types of compounds in an optically active form.



Optically active bicyclo[n.1.0]alkan-2-ols derivatives are generally prepared by cyclopropanation of optically active cycloalk-2-en-1-ols compounds [3] or by diastereoselective addition of nucleophiles to enantiomerically enriched bicyclo[n.1.0]alkan-2-ones compounds.[1c]

This paper is dealing with the lipase-catalyzed kinetic resolution of racemic endo-bicyclo[4.1.0]heptan-2-ol **1a** and of the corresponding 6-methyl and 1-methyl substituted compounds **1b** and **1c**.[4] In order to allow an easy recovery of these small hydrophilic compounds, only transesterification and esterification reactions in an organic solvent have been tested. These two types of reactions were run at 37°C in *tert*-butylmethylether. In the first one, an acylating agent (isopropenyl acetate or a linear carboxylic acid) was reacted with a bicycloheptanol **1a-c** [5] (Scheme 1) and, in the second type, the corresponding bicyclo[4.1.0] hept-2-yl chloroacetates **3a-c** [6] (Scheme 2) were treated with n-propanol.

In preliminary experiments achieved with the unsubstituted bicycloheptanol **1a** and isopropenyl acetate using porcine pancreatic lipase [7] or lipase from *Candida rugosa* [7], no reaction was observed after 24 hours. However with the lipases from *Pseudomonas cepacia* (LP),[7] *Mucor miehei* (LMM) [7] and *Candida antarctica* (LCA) [7] transesterification occurred. Various conditions using these three enzymes and bicycloheptanols **1a**, **1b** and **1c** were attempted. Our results are reported in Table 1.

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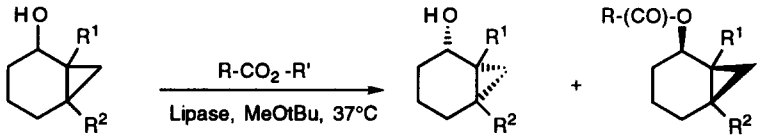


rac-endo-1 (1*R*, 2*S*, 6*S*)-1 (1*S*, 2*R*, 6*R*)-2

Scheme 1

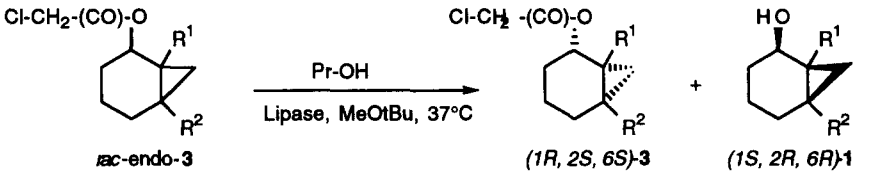
Table 1. *Enzymatic acylation of endo-bicyclo[4.1.0]heptan-2ols* ***1*** [8a,9]

Entry	Substrate			Lipase	Acylating agent	Time (h)	Recovered alcohol **1** ee (%) [10]	Ester **2** ee (%) [10]	c [16]	E [17]
		R^1	R^2							
1	**1a**	H	H	LP	isopropenyl acetate	3	87 [11]	63	0.58	12
2				"	hexanoic acid	113	68 [11]	83 [12]	0.45	22
3				LMM	isopropenyl acetate	20	35 [11]	64	0.35	6
4				"	hexanoic acid	163	34 [11]	44 [12]	0.44	4
5				LCA	isopropenyl acetate	0.75	98 [14]	84	0.54	51
6	**1b**	H	Me	LP	isopropenyl acetate	20	84	72	0.54	16
7				"	hexanoic acid	289	65	90 [13]	0.42	37
8				LMM	isopropenyl acetate	20	31	81	0.28	13
9				"	butanoic acid	264	64	85 [13]	0.43	24
10				"	hexanoic acid	264	77	90 [13]	0.46	44
11				"	octanoic acid	48	77	78 [13]	0.50	19
12				"	decanoic acid	48	76	75 [13]	0.50	16
13				LCA	isopropenyl acetate	0.75	99 [15]	86	0.53	70
14				" [8b]	isopropenyl acetate	0.70	56 [15]	95 [13, 15]	0.37	64
15	**1c**	Me	H	LP	isopropenyl acetate	94	68	73	0.48	13
16				"	hexanoic acid	291	21	89 [13]	0.19	21
17				LMM	isopropenyl acetate	318	12	81	0.13	11
18				"	hexanoic acid	312	26	80	0.245	12
19				LCA	isopropenyl acetate	1.25	97 [15]	90	0.52	81

Low enantiomeric ratios E were observed in the reactions of **1a**, **1b** and **1c** with isopropenyl acetate in the presence of LP (entries 1, 6, 15) or LMM (entries 3, 8, 17) and the presence of the methyl substituent close to the hydroxyl group in **1c** decreases the reaction rate (compare entry 15 to 1 and 6 and entry 17 to 3 and 8). The influence of the acyl reagent size was checked in the case of the 6-methylbicycloheptanol **1b** in the presence of LMM.[18] From acetyl to butanoyl and hexanoyl reagent there is a continuous increase of the E value and a large decrease of the reaction rate (compare entry 8 with 9 and 10). With the longer octanoic and decanoic acids the reaction rates are increased but the E values were closed to those observed with the acetylated reagent (compare entries 11 and 12 to 8). With **1a** and **1c** there is no improvement of LMM catalyzed reaction with hexanoic acid compared to the corresponding reaction with isopropenyl acetate (compare entry 4 to 3 and 18 to 17). The E values of the LP catalyzed reactions were also increased using

hexanoic acid instead of isopropenyl acetate (compare entry 2 to 1, 7 to 6 and 16 to 15). The highest E values were observed for LCA catalyzed transesterification of isopropenyl acetate (see entries 5, 13 and 18) and the reaction rates were greatly increased with this enzyme. As expected in this type of kinetic resolutions, it is possible to isolate the product or the unreacted substrate with a good ee by running the reaction to less or more than 50% conversion (see entries 13 and 14).

The results of the transesterification of bicyclo[4.1.0]hept-2-yl chloroacetates **3a-c** with n-propanol in the presence of LP and LMM are reported in Table 2. The reaction of the 2-methyl substituted ester **3c** with LMM shows higher E value and reaction rate than those of the LMM catalyzed reaction of the corresponding alcohol **1c** with isopropenyl acetate. Except the reactions of **3b** and **3c** in the presence of LMM, for all the other attempts, the enantioselectivity and the reaction rate were simultaneously low. So these reaction conditions seem less attractive from a synthetic point of view.



rac-endo-**3** (1R, 2S, 6S)-**3** (1S, 2R, 6R)-**1**

Scheme 2

Table 2. *Enzymatic transesterification of endo bicyclo[4.1.0]heptan-2-yl chloroacetate 3 with propanol* [8c, 9]

	Substrate R1	R2	Lipase	time/h	Recovered ester **3** ee (%) [10]	Alcohol **1** ee (%) [10]	c [16]	E [17]
3a	H	H	LP	120	64	71 [11]	0.47	11
			LMM	120	54	35 [11]	0.61	3
3b	H	Me	LP	120	54	76	0.41	13
			LMM	120	50	81	0.37	17
3c	Me	H	LP	120	58	60	0.49	7
			LMM	120	74	85	0.46	27

In conclusion, a new method to prepare optically active endo-bicyclo[4.1.0]heptan-2-ols compounds by lipase-catalyzed transesterification was reported herein. With the lipases from *Pseudomonas cepacia* , *Mucor miehei* and *Candida antarctica* the *(1S, 2R, 6R)*-enantiomers [19] react faster and the better enantioselectivities were obtained using the last enzyme.

References and notes

1. a) Collum, D.B.; Still, W.C.; Mohamadi, F. *J. Am. Chem. Soc.* **1986**, *108*, 2094-2096. b) Batey, R.A.; Harline, J.D.; Motherwell, W.B. *Tetrahedron* **1996**, *52*, 11421-11444. c) Clive, D.L.J.; Daigneault, S. *J. Org. Chem.* **1991**, *56*, 3801-3814.
2. For an example of an optically active bicyclo[n.1.0]alkan-2-ol isolated from a natural source see: Hiyamoto, T.; Ebisawa, Y.; Higuchi, R. *Tetrahedron Lett.* **1995**, *36*, 6073-6074.
3. a) Hill, R.K.; Morgan, J.W. *J. Org. Chem.* **1968**, *33*, 927-928. b) Barbachyn, M.R.; Johnson, C.R.; Glick, M.D. *J. Org. Chem.* **1984**, *49*, 2746-2748.
4. For other examples of lipase catalyzed preparation of optically active cyclopropyl methyl alcohols derivatives, see: Csuk, R.; von Scholz, Y. *Tetrahedron* **1996**, *52*, 6383-6396 ; Krief, A.; Surleraux, D.; Ropson, N. *Tetrahedron: Asymmetry* **1993**, *4*, 289-292 ; Theil, F.; Schick, H.; Winter, G.; Reck, G. *Tetrahedron* **1991**, *47*, 7569-7582 ; Granjean, D.; Pale, P.; Chuche, J. *Tetrahedron* **1991**, *47*, 1215-1230 ; Ader, U.; Breitgoff, D.; Klein, P.; Laumen, K.E.; Schneider, M.P.

Tetrahedron Lett. **1989**, *30*, 1793-1796 ; Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1985**, *26*, 2073-2076 ; Rasel, W.; Hultin, P.G.; Jones, J.B. *J. Chem. Soc. Chem. Commun.* **1985**, 1563-1564.

5. The starting endo bicycloheptanols **1a**, **1b** and **1c** were prepared by the well-known hydroxyl directed cyclopropanation [20] (Et_2Zn, CH_2I_2) of cyclohex-2-en-1-ol and the corresponding 2- and 3-methylsubstituted compounds in 1,2-dichloroethane at 0°C (2 hours).[21] The beneficial influence of the presence of oxygen [22] on the reaction yields should be underlined (due to the high inflammability of Et_2Zn, the cyclopropanating reagent was prepared under argon in the presence of the allylic alcohol then the argon inlet was replaced by a calcium chloride guard-tube). Exo diastereomers were not noticed in these reactions. Purification was done by silicagel column chromatography (eluent : pentane/Et_2O : 80/20) (Yield : 75-80%).
6. The chloroacetates **3a-c** were prepared by treatment of bicycloheptanols **1a-c** with chloroacetic anhydride in dichloromethane at 0°C (2 hours) in the presence of 4-dimethylaminopyridine and were purified by silicagel column chromatography (eluent : pentane/Et_2O : 93/7) (Yield : 65-75%).
7. Lipase from porcine pancreas and lipase from *Candida rugosa* were purchassed from Sigma Chemical co. Lipases from *Pseudomonas cepacia* and *Pseudomonas fluorescens* (AK) were purchassed from Amano Pharmaceutical co. Resins containing the lipase from *Mucor miehei* or the lipase from *Candida antarctica* named respectively Lipozyme® and Novozyme® were used, they were purchassed from Novo Nordisk.
8. a) 1 mmol of alcohol **1** was treated with 1.05 eq. of acylating agent and 192 mg of Novozyme ® or 300 mg of an other lipase in 2 mL of dry tBuOMe. b) Except the amount of Novozyme® (48 mg) the above conditions were used. c) 1 mmol of chloroacetate **3** was treated with 100 mg of dry 1-propanol and 300 mg of lipase in 2 mL of dry tBuOMe.
9. The reaction was stopped by removing the enzyme by filtration. The unreacted substrate and the product were separated by silica gel column chromatography (eluent : pentane/Et_2O : 85/15 then 70/30).
10. Unless otherwise noticed, enantiomeric excesses were determined by integration of ^1H NMR spectra (C_6D_6) in the presence of the chiral lanthanide complex $Eu(hfc)_3$: For **2a** (R = CH_3) when the signal of methyl protons were moved from 1.77 to 12.35 ppm, two signals (probably from one of the C_3-protons) appeared at 8.47 (1*R*,2*S*,6*S*) and 8.25 ppm (1*S*,2*R*,6*R*); For **3a** the signals of the C_2 proton were moved from 5.22 ppm to 14.02 (1*S*,2*R*,6*R*) and 13.81 ppm (1*R*,2*S*,6*S*); For **1b** when the signal of the methyl protons was moved from 0.96 to 3.42 ppm, two signals appeared at 13.87 (1*S*,2*R*,6*R*) and 13.48 ppm (1*R*,2*S*,6*S*); For **2b** (R = CH_3) the singlets of the acetoxy group protons were moved fro 1.78 ppm to 12.19 (1*S*,2*R*,6*R*) and 11.88 ppm (1*R*,2*S*,6*S*); For **3b** the signals of C_2 proton were moved from 5.22 to 8.68 (1*S*,2*R*,6*R*) and 8.49 ppm (1*R*,2*S*,6*S*); For **1c** the signals of the methyl protons were moved from 1.09 to 5.41 ppm (1*R*,2*S*,6*S*) and 5.20 ppm (1*S*,2*R*,6*R*); For **2c** (R = CH_3) the singlets of the methyl protons linked to the cyclopropane were moved from 1.14 to 4.04 ppm (1*S*,2*R*,6*R*) and 3.93 ppm (1*R*,2*S*,6*S*); **2c** (R = C_5H_{11}) the singlets of the methyl protons linked to the cyclopropane were moved from 1.13 to 4.32 ppm (1*S*,2*R*,6*R*) and 4.24 ppm (1*R*,2*S*,6*S*); For **3c** the singlets of the methyl protons were moved from 1.04 to 2.48 ppm (1*R*,2*S*,6*S*) and 2.42 ppm (1*S*,2*R*,6*R*).
11. Enantiomeric excess was measured on the corresponding acetate (Ac_2O, DMAP, CH_2Cl_2).
12. Enantiomeric excess was measured on the corresponding acetate (1- $LiAlH_4$, Et_2O, 2- Ac_2O, DMAP, CH_2Cl_2).
13. Enantiomeric excess was measured on the corresponding alcohol ($LiAlH_4$, Et_2O).
14. Enantiomeric excess was termined by HPLC of the corresponding phenyl carbamate on a 250mm x 4.5mm Chiralcel OD-H column (eluent : hexane/isopropanol : 85/15) ; Flow rate : 1 ml/min): Retention time : **1a**-(1*R*,2*S*,6*S*)-phenylurethane : 16 min; **1a**-(1*S*,2*R*,6*R*)-phenylurethane : 21 min.
15. Enantiomeric excess were determined by GLC on a 25m x 0.33mm ID CYDEX B column (Flow carrier: He, P = 0.8 Bar, 65°C). Retention time **1b**-(1*R*,2*S*,6*S*) : 24 min; **1b**-(1*S*,2*R*,6*R*) : 20 min; **1c**-(1*R*,2*S*,6*S*) : 25 min; **1c**-(1*R*,2*R*,6*R*) : 34 min.
16. The conversion ratio c calculated using the formula $c = ee_s / (ee_s + ee_p)$.
17. E values were calculated from ee_s and ee_p using the equation: $E = Ln [(1-ee_s) (ee_p/(ee_s + ee_p))] / Ln [(1-ee_s) (ee_p/(ee_s + ee_p))]$, see: Chen, C.S.; Fujimoto, Y.; Girdaukas, G.; Sih C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294-7298.
18. The influence of the acyl chain length on the enantiomeric ratio of kinetic resolution of linear secondary alcohols in the presence of Lipozyme was reported: Sonnet, P.E. *J. Org. Chem.* **1987**, *52*, 3477-3479.
19. The absolute configuration of alcohol **1a**-(1*R*,2*S*,6*S*) (98% ee ; $[\alpha]_D^{20}$ = -77, $CHCl_3$, c = 1) was assigned by comparison of its chiroptical properties with those described in the literature for the (1*S*,2*R*,6*R*)-enantiomer (7% ee ; $[\alpha]_D^{20}$ = +4.2, $CHCl_3$, c = 1).[3b]
    The absolute configuration of alcohols **1b**-(1*R*,2*S*,6*S*) (99% ee ; $[\alpha]_D^{20}$ = -73, $CHCl_3$, c = 1) and **1c**-(1*R*,2*S*,6*S*) (97% ee ; $[\alpha]_D^{20}$ = -0.5, THF, c = 1.3) were attributed from their GC and chiroptical properties. Samples of **1b**-(1*R*,2*S*,6*S*) (57% ee ; $[\alpha]_D^{20}$ = -49, THF, c = 1) and **1c**-(1*R*,2*S*,6*S*) (18% ee; $[\alpha]_D^{20}$ = -0.3, THF, c = 1) were prepared by cyclopropanation of respectively (*S*)-3-methylcyclohex-2-en-1-ol (56% ee ; $[\alpha]_D^{20}$ = -46, $CHCl_3$, c = 1) and (*S*)-2-methylcyclohex-2-en-1-ol ($[\alpha]_D^{20}$ = -23, $CHCl_3$, c = 1) which are obtained by Lipase AK [7] (for the former) and Lipase LP [7] (for the latter) catalyzed transesterification of isopropenyl acetate with the racemic alcohol.
20. Winstein, J.; Sonneberg, J.; Devries, L. *J. Am. Chem. Soc.* **1959**, *81*, 6523-6524; Dauben, W.G.; Berezin, G.H. *J. Am. Chem. Soc.* **1963**, *85*, 468-472. For a review on "Substrate-directable chemical reactions" where are reported various examples of hydroxyl directed cyclopropanation of allylic alcohols, see: Hoveyda, A.H.; Evans, D.A.; Fu, G.C. *Chem. Rev.* **1993**, *93*, 1307-1370.
21. Denmark, S.E.; Edwards, J.P. *J. Org. Chem.* **1991**, *56*, 6974-6981.
22. Miyano, S.; Izumi, Y.; Fujii, H.; Hashimoto, H. *Synthesis* **1977**, 700-701.

(*Received in France* 15 *August* 1997; *accepted* 2 *October* 1997)