Enzymatic Preparation of Optically Active Bicyclo[2.2.1]heptene Derivatives, Building Blocks for Terpenoid Natural Products. An Attractive Alternative to Enantioselective Diels–Alder Syntheses

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Bicyclo[2.2.1]heptene derivatives (**1**)—(**3**), building blocks for terpenoid natural products, have been prepared with high enantiometric purities by enzymatic hydrolysis of their racemic esters in the presence of porcine liver esterase (PLE) and an ester hydrolase from *Pseudomonas sp.* (SAM-II).

Functionalized bicyclo[2.2.1]heptenes like (**1**)—(**3**) are important chiral building blocks for terpenoid natural products as documented in the synthesis of iridoids, *e.g.* specionin (**4**)[1] and 1-*O*-methyl loganin aglucone (**5**).[2,3] Their preparation in enantiomerically enriched or pure form can be achieved either by classical resolution or, more recently, *via* enantioselective (Lewis acid catalysed) [4 + 2] cycloadditions, based on the use of classical chiral auxiliaries like camphorsulphonic[2] or lactic acid.[4]

These methods on a large synthetic scale, however, suffer considerable practical drawbacks with protocols requiring either multistep sequences towards the chiral auxiliaries and/or careful optimisations of critical reaction conditions in order to obtain high stereocontrol.

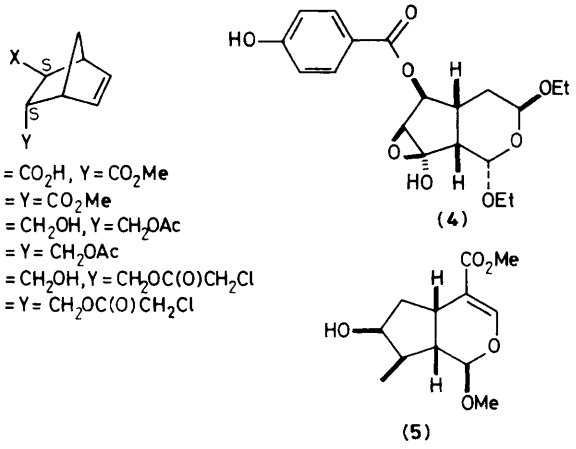
Clearly, if enantiomerically pure molecules of this kind could be prepared conveniently and in preparatively attractive quantities from readily available racemic starting materials like (±)-(**1b**)—(**3b**), this would constitute an interesting alternative to the above methods.

Enzymes are well known for their capability of enantiomer differentiation in racemic substrates and the enantioselective, enzymatic hydrolysis of (±)-(**1b**)—(**3b**) could, in principle,

Table 1. Enzymatic hydrolysis of (±)-(**1b**)—(**3b**) in presence of ester hydrolases.

Entry	Substrate	Enzyme	Conversion (%)	Product	Yield (%)	$[\alpha]_D^{20}$ [d]	% E.e.[f]	E[g]
1	(±)-(**1b**)[a]	PLE	35	(*S*,*S*)-(**1a**)	46	132.8	88[b]	35
				(*R*,*R*)-(**1b**)	48	−108.5	75	
2	(±)-(**1b**)	PLE	40	(*S*,*S*)-(**1a**)	34	131.5	92[c]	45
				(*R*,*R*)-(**1b**)	52	−88.7	62	
3	(±)-(**1b**)	PLE	64	(*S*,*S*)-(**1a**)	55	75.9	53	>10
				(*R*,*R*)-(**1b**)	32	−141	>95	
4	(±)-(**2b**)	SAM-II	23.5	(*R*,*R*)-(**2a**)	43	−62.1	96	>100
				(*S*,*S*)-(**2b**)	50	49.6	85	
5	(±)-(**2b**)	SAM-II	25.5	(*R*,*R*)-(**2a**)	45	−59.2	91	>80
				(*S*,*S*)-(**2b**)	47	55.7	>95	
6	(±)-(**3b**)	SAM-II	23.2	(*R*,*R*)-(**3a**)	36	−36.5[e]	83	23
				(*S*,*S*)-(**3b**)	55	30.3[e]	72	

[a] 10% acetone added. [b] (*R*)-Phenylethylamide. [c] Eu(hfc)$_3$ [hfc = 3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]. [d] *c* 1 MeOH. [e] *c* 1 $CHCl_3$. [f] Enantiomeric excess. [g] See text and Ref. 6; $E = K_R/K_S$, calculated ratio of hydrolysis rates for the two enantiomers.



provide an alternative route to the above target molecules (equations 1,2).

$$(\pm)\text{-(1b)} \xrightarrow{\text{PLE}} (S,S)\text{-(1a)} + (R,R)\text{-(1b)} \quad (1)$$

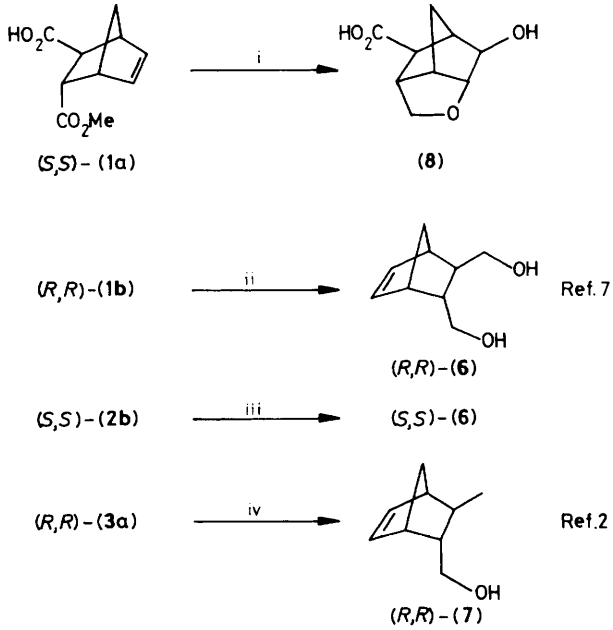
$$(\pm)\text{-(2b),(3b)} \xrightarrow{\text{SAM-II}} (R,R)\text{-(2a),(3a)} + (S,S)\text{-(2b),(3b)} \quad (2)$$

Conditions: phosphate buffer, pH 7, 1 M NaOH.

We report here some highly successful experiments of this kind using (i), porcine liver esterase (PLE) and (ii), a microbial lipase from *Pseudomonas sp*,† by the action of which this whole class of compounds becomes accessible, conveniently, in good quantities and with very high optical purities.

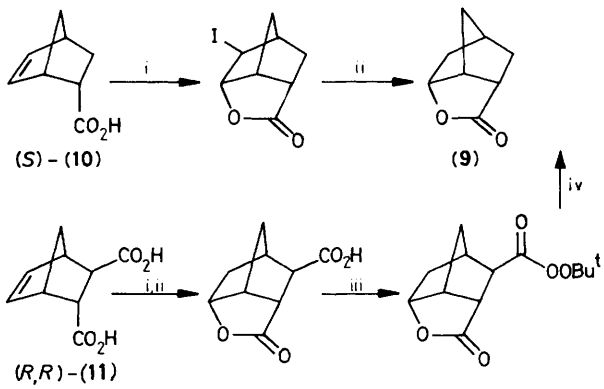
In typical experiments (±)-(**1b**) (20—80 mmol) was hydrolysed enzymatically, by the method described earlier,[5] by continuous addition of 1 M NaOH using 0.1 M phosphate buffer (40—150 g, pH 7, 20 °C) and 1.25 mg PLE (125 units, standard: ethyl butyrate) (equation 1).

After the desired degree of conversion all reactions were terminated by extraction of (*R*,*R*)-(**1b**), the monoester (*S*,*S*)-(**1a**) being isolated from the aqueous phase by continuous extraction after acidification to pH 3. The enantiomeric purities were determined by ^{1}H n.m.r. spectroscopy either on the (*R*)-(+)-phenylethylamides [for (*S*,*S*)-(**1a**)] or directly with (*R*,*R*)-(**1b**) using Eu(hfc)$_3$ [hfc = 3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] as a chiral shift reagent. They are conversion dependent (compare entries 2 and 3, Table 1), a reflection of the selectivity factors[6] of $E < 100$ for these transformations. Similarly the racemic acetate (±)-(**2b**) (50 mmol) and the chloroacetate (±)-(**3b**) (5 mmol) were hydrolysed using 0.1 M phosphate buffer: for (±)-(**2b**): 35 g, pH 7, 20 °C; for (±)-(**3b**): 25 g, pH 7, 35 °C and 100 mg (3200 units, standard: tributyrin) lipase SAM-II. Both reactions became markedly slower after *ca.* 25% conversion, corresponding to the hydrolysis of one ester function. As shown in Table 1 (entries 4 and 5), the enantiomeric purities of the products obtained are again conversion dependent; they can be maximised for both enantiomers by choosing the optimal termination point.



Scheme 1. *Reagents and conditions*: i, Li, liq. NH_3, then *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, room temp.; ii, $LiAlH_4$, Et_2O, reflux; iii, K_2CO_3, MeOH; iv, *p*-$MeC_6H_4SO_2Cl$, NEt_3, 4-dimethylaminopyridine, CH_2Cl_2, room temp., then $LiAlH_4$/THF, reflux.

† Lipase SAM-II from Amano Pharmaceutical Co., supplied by Fluka AG, CH-9470 Buchs, Switzerland (Cat. Nr. 62312) and Mitsubishi Int. GmbH, D-4000 Düsseldorf, Germany.



Scheme 2. *Reagents and conditions*: i, I_2–KI; ii, H_2/Pt; iii, Bu^{t}OOH, pyridine; iv, heat.

Regiochemistry, optical purities, and absolute configurations were unequivocally established by chemical correlation with known compounds (Schemes 1 and 2).

The regioselective hydrolysis of the *exo*-ester function in (*S*,*S*)-(**1a**) was confirmed both by ^{1}H n.m.r. spectroscopy and its transformation into the tricyclic ether (**8**) (Scheme 1). (*R*,*R*)-(**1b**) was reduced to the known[7] diol (*R*,*R*)-(**6**); the hydrolysis of (*S*,*S*)-(**2b**) produced its enantiomer (*S*,*S*)-(**6**). The absolute configuration of (*R*,*R*)-(**3a**) [and thus indirectly also of (*R*,*R*)-(**2a**)] was secured by its transformation into (*R*,*R*)-(**7**), the enantiomer of which [(*S*,*S*)-(**7**)] had been transformed earlier into (−)-l-*O*-methyl-loganin aglucone (−)-(**5**).[2]

Chemical hydrolysis (10 M aqueous NaOH/THF/MeOH, 1:2:1) of (*R*, *R*)-(**1b**) yielded (*R*, *R*)-(**11**) which had been prepared earlier in enantiomerically pure form together with (*S*, *S*)-(**11**) by classical resolution using (−)-quinine or (−)-menthol as chiral auxiliaries.[8] (*R*, *R*)-(**11**) was converted independently into the lactone (**9**), which in turn could be correlated to the known[9] norbornene carboxylic acid (*S*)-(**10**) (Scheme 2).

We feel that the above results, which are currently being optimised in our laboratories, provide an alternative to (i), classical resolution techniques and (ii), enantioselective Diels–Alder reactions for the synthesis of optically active norbornene derivatives and should further help to increase the scope of enzymatic transformations in organic synthesis.‡

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‡ *Added in proof*: The results with (±)—(**1b**) were first documented in the diploma thesis of G. H., Wuppertal, 1985. For recent studies see: A. J. H. Klunder, F. J. C. van Gastel, and B. Zwanenburg, *Tetrahedron Lett.*, 1988, **29**, 2697.