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Efficient kinetic resolution of racemic 3-nitro-cyclopent(or hex)-2-en-1-yl acetates

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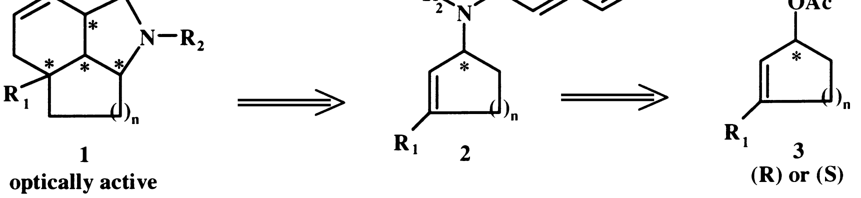
Abstract

The kinetic resolution of 3-nitro-cyclopent(or hex)-2-en-1-yl acetates via enzymatic hydrolysis using *Pseudomonas cepacia* lipase is described. A model, based on a strong interaction between the nitro group and the active site, accounts for the structural selectivity and the stereoselectivity observed. © 2000 Elsevier Science Ltd. All rights reserved.

During the course of our study on the synthesis of optically active polycyclic ring systems **1**, based on the intramolecular Diels–Alder reaction (IMDA) of cyclenic trienes **2**,[1] a practical and economical method for the synthesis of cyclic allylic acetates **3** in high enantiomeric excess as key intermediates was required (Scheme 1). Such compounds and their derivatives are versatile intermediates in organic synthesis and their optically active forms are especially useful in the asymmetric synthesis of terpenes[2] and other natural products[3,4] and for the preparation of a variety of biologically active compounds.[5] Despite their simple structures, practically, it is not easy to obtain compounds **3** in enantiomerically pure forms. Several procedures are available, such as for example the asymmetric reduction of cyclohex-2-en-1-one,[6] the enantioselective



Scheme 1.

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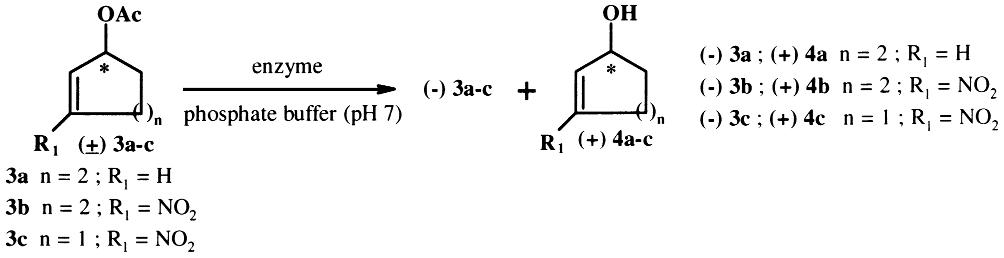
deprotonation of epoxides[7] or the catalytic asymmetric allylic oxidation of olefins.[8] However, few methods provide high (> 90%) enantiomeric excesses. An alternative approach, that would provide derivatives of both enantiomers of the required building block, is the kinetic resolution of suitable racemic compounds[9] or their synthetic equivalents.[10] We report herein the lipase-mediated resolution of racemic acetates **3a–c**, under hydrolytic conditions using mixtures of phosphate buffer and diethyl ether.

Nitro-cyloalkenyl acetates **3b–c** were prepared in three steps from the corresponding cycloalkenes by a procedure reported by Corey.[12] The enzymatic hydrolyses of acetates **3a–c** in phosphate buffer were investigated and lipase PS from *Pseudomonas cepacia* (Amano pharmaceutical) was selected after the screening of several commercially available lipases (Scheme 2). The main results are summarized in Table 1.



Scheme 2.

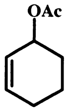
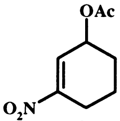
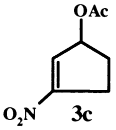
As previously described,[10] we have found that the simplest compound **3a** of the series gave poor enantioselectivity probably due to the conformational mobility of this molecule and the similarity in size of the substituents at the stereocenter (CH_2–CH_2 vs CH=CH). In order to increase the enantioselectivity, the classical strategy is to incorporate a bulky and hydrophobic substituent, close to the stereocenter. Thus, increasing the difference in size of the substituents may help the hydrolase distinguish between the two enantiomers.[11]

In the present paper we show that a polar group such as nitro, which is able to establish hydrogen bonds with the polar pocket of the active site, may be a good way to improve the fit of one enantiomer in the active site.

The acetates **3b** and **3c** are successfully resolved in the presence of lipase Amano PS. The presence of a polar nitro group on the double bond close to the stereocenter results in a different anchorage of the two enantiomers and significantly increases the discrimination between them. Enantioselectivity decreases as the ring size of the cycloalkenylacetates becomes smaller. These observations and the enantioselectivity [(*R*)-enantiopreference of lipase)] are consistent with the model proposed by Kazlauskas et al.[15] for the hydrolysis of secondary acetates as shown in Scheme 3.

Parts (a) and (b) of Scheme 3 depict the projected binding modes of (*R*)- and (*S*)-enantiomers of the acetates **3b**. In Scheme 3(a) the acetate is positioned in the serine sphere and the nitro group in the polar pocket P_F according to the Jones model.[16] The hydrophobic cyclohexyl fits well into the H_L pocket with considerable room to spare. This is not the case for the other enantiomer, where as described in Scheme 3(b) the same binding mode requires an orientation of the large cyclohexyl group in the small H_S pocket. The model forecasts the high enantiomeric excess level observed for product **3b**, because for this substrate the choices are so clear-cut between the two enantiomers.

Table 1
Enzymatic hydrolysis of cyclic allylic acetates **3a**–**c**[13]

Substrate	Enzyme	Amount (eq.)[a]	Reaction Time (h)	Convers.[b] (%)	(S)-**3**-acetate[c] Yield[d] (%)	(S)-**3**-acetate[c] e.e.[e] (%)	(R)-**4**-alcohol[c] Yield[d] (%)	(R)-**4**-alcohol[c] e.e.[e] (%)	E[f]
 **3a**	Amano PS	1.2	1	40	30	19.5	26	18.5	1.7
 **3b**	PLAP[g]	0.3	3	33	61	50	29	20	2.3
	Amano PS	4.4	0.15	43	40	>99	28	>99	>100
		2.2	0.25	50	43	>99	32	>99	>100
		0.3	1.6	43.5	51	95	39	>99	>100
 **3c**	Amano PS	2.2	0.25	50	45	88	34	42	46

[a] Equivalent by weight *vs* substrate

[b] Calculated from the amount of base consumed during hydrolysis

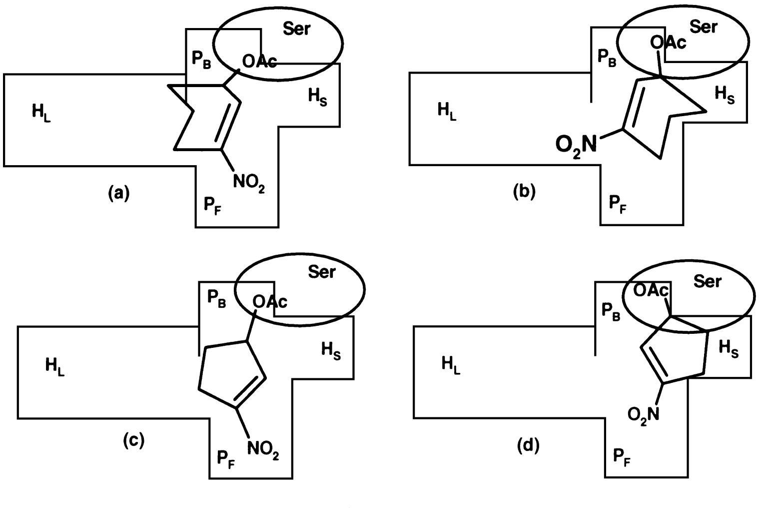
[c] Absolute configuration (**3a**, **4a**) was assigned by comparison of the sign of the specific rotation reported in the literature[10,11] or by chemical correlation (**3b-c**) after direct nitration[12] of the corresponding (S)-cycloalkenyl acetates

[d] Isolated yield

[e] Determined by chiral HPLC (Daicel Chiralpack AD column)

[f] Enantiomeric ratio E was calculated according to ref.14

[g] PLAP Pig Liver Acetone Powder



Scheme 3.

The lower selectivity observed for the cyclopentenyl derivatives **3c** is consistent with the fact that the totally flat cyclopentene ring is only marginally bigger than the small H_S pocket and both enantiomers of acetates **3c** give acceptable active-site fits as shown in Scheme 3(c) and (d). In such a situation, where there is no preferred binding mode when the ester group is located within the spherical locus of the catalytically active serine function, the model forecasts that the level of discrimination will be lower for the cyclopentenyl derivatives.

In conclusion, we have described an efficient procedure for the kinetic resolution of 3-nitro-cyclopent(or hex)-2-en-1-yl acetates **3**. Some useful characteristics of the present process are the use of a very cheap enzyme in reasonable quantity and the velocity of the transformation. Due to their potential as chiral building blocks, this procedure is very attractive for the development of these compounds in organic synthesis.

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13. A general experiment is as follows: substrate **3** (1.8 mmol) dissolved in diethyl ether (2 mL) was added to a stirred mixture of phosphate buffer (20 mL) containing enzyme (amount: see Table 1). The pH was maintained at 7.00 by automatic titration with NaOH (0.2N). After the consumption of base indicating a 33–50% conversion, the reaction mixture was extracted with diethyl ether (4×100 mL). The combined extracts were dried over anhydrous sodium sulfate and concentrated under vacuum and the resulting oil was purified by chromatography on silica gel. Analytical data of all compounds **3** or **4** were identical to data reported in the literature.
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