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APPLICATIONS OF PIG LIVER ESTERASES (PLE) IN ASYMMETRIC SYNTHESIS

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CONTENTS

1. INTRODUCTION

Enzymes are now widely recognised as practical catalysts for asymmetric synthesis and in many cases the stereochemical control exerted by the enzyme cannot be matched by non-enzymic catalysts. Of the enzymes studied to date, esterases, in particular pig liver esterases (PLE E.C.3.1.1.1) have proven to be the most successful in asymmetric syntheses.[1–4]

PLE has many advantages: it is cheap, stable, does not require a coenzyme and will hydrolyse a wide range of esters. Commercially available preparations are mixtures of isozymes which exhibit essentially the same stereospecificity and can therefore be used in asymmetric synthesis as if they were a single enzyme.[5,6]

2. ASYMMETRIC HYDROLYSIS REACTIONS

2.1. *Initial studies*

The potential of PLE in organic synthesis first emerged when Sih and co-workers reported the PLE-catalysed asymmetric hydrolysis of diesters **1** (Scheme 1).[7] A single enantiomer can be obtained

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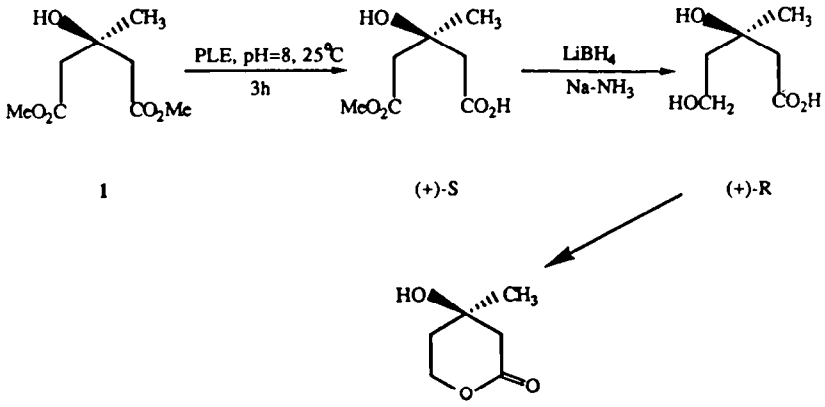


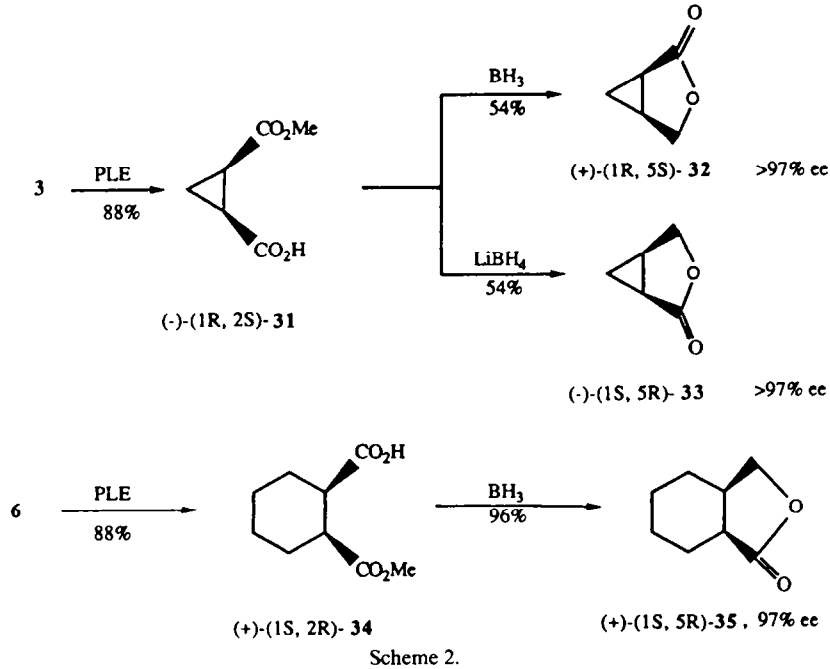
Scheme 1.

with high enantioselectivity starting from either *meso* or prochiral diesters. In addition PLE can be used to resolve racemic monoesters.[8]

PLE has great potential as a catalyst in the asymmetric synthesis of chiral optically active synthons and hence continues to receive wide attention.[9-12]

2.2. *Monocyclic* meso-*diesters*

The PLE-catalysed hydrolysis of a wide range of *meso*-diesters **2–30** has been examined (Scheme 3).[13-16] To date the most successful, in terms of producing chiral synthons, are the hydrolyses of *meso*-dimethyl cyclopropane-, cyclobutane- and cyclohexane-1,2-dicarboxylates (**3**, **4** and **6** respectively). The acid-ester products are readily converted into γ-lactones with 97% *ee* (Scheme 2). Diesters **7**, **8**, **16** and **17** are very similar in structure and the PLE catalyzed hydrolyses are enantiotopically specific for the pro-*S* methoxycarbonyl group although the acid-ester products have different absolute configurations. PLE exhibits different stereospecificity towards *cis* and *trans*



Scheme 2.

hydroxy **19**, **20** and acetoxy **21**, **22** diesters. For the *cis*-diesters **19** and **21**, the hydrolysis is enantiotopically specific for the pro-*S* methoxycarbonyl group, whereas for the *trans*-diesters **20** and **22** the pro-*R* methoxycarbonyl group is hydrolyzed. The detailed results are shown in Table 1.

Hydrolysis of the *meso*-diesters **3** and **4** are enantiotopically specific for the pro-*S* methoxycarbonyl group whereas the pro-*R* methoxycarbonyl group is hydrolysed with the substrates **5** and **6**. The cyclopentyl substrate is hydrolysed with marginal pro-*R* enantiotopic selectivity.

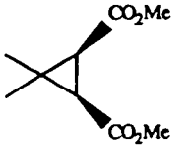
The enantioselective hydrolysis of diesters **9–14** would afford versatile chiral building blocks to be used, for example, in natural product synthesis (Scheme 4).[16a] The monoesters could serve as potential precursors for all possible enantiomers of these systems, (irrespective of the resulting absolute configurations) by carrying out selective group transformations.

Unfortunately the chemical and optical yields of the PLE-catalyzed hydrolysis of **9–14** are not yet sufficient for application in organic synthesis.[14,16] This is not the case, however, for the hydrolysis of *meso*-2-nitro-1,3-propanediols **25–30** in which the products are formed in very good chemical and optical yields.[16c]

Table 1. PLE-catalyzed hydrolysis of monocyclic meso-diesters

Substrate	Product Yield(%)	$[\alpha]_D^{25}$	ee%	Absolute Configuration	Ref.
2	23	- 11.2	43	(-)-(1R,2S)	13a
3	88	- 13.4	>97	(-)-(1R,2S)	13b,14
4	87	- 3.0	>97	(-)-(1R,2S)	13b,14
5	92	+ 1.0	17	(+)-(1S,2R)	13b,14
6	88	+ 4.7	97	(+)-(1S,2R)	13b,14
7	94	+ 2.9 [a]	95	(+)-(1S,2R)	15a
8	84	- 2.8 [b]	68	(-)-(1S,2R)	15b
9	69	+ 5.3 [b]	20	(+)-(1R,2S)[c]	16a
10	54	+ 7.7 [b]	44	(+)-(1R,2S)[c]	16a
11	62	0 [b]	0	-	16a
12	40	+ 0.8 [b]	8	(+)-(1R,2S)[c]	16a
13	31	- 0.9 [b]	4	(-)-(1S,2R)[c]	16a
14	43	+ 7.6 [b]	40	(+)-(1R,2S)[c]	16a
15	86	- 60.8	86	(-)-(1S,2R)	16b
16	30	+ 34.6 [b]	72	(+)-(1S,2R)	15b
17	94	- 7.2 [d]	80	(-)-(1S,2R)	15b
18	63	+ 0.6 [b]	22	(+)-(1R,2S)	15b
19	76	+ 2.6 [b]	80	(+)-(1S,2R)	15b
20	80	- 1.3 [b]	22	(-)-(1R,2S)	15b
21	76	+ 3.0 [b]	52	(+)-(1S,2R)	15b
22	91	- 1.3 [b]	27	(-)-(1R,2S)	15b
23	88	+ 1.2 [b]	58	(+)-(1S,2R)	15b
24	76	- 1.5 [b]	84	(-)-(1R,2S)	15b
25	70	+ 9.8 [e]	>97	(+)-(1S,2S,3R)	16c
26	90	+ 9.4 [e]	>95	(-)-(1S,2S,3R)	16c
27	80	+ 29.1 [e]	>95	(+)-(1S,2S,3R,5S)	16c
28	68	+ 8.9 [e]	-	(-)-(1S,2S,3R,5S)	16c
29	70	- 1.3 [e]	-	(-)-(1S,2S,3R,4S,6R)	16c
30	70	+ 6.0 [e]	>95	(+)-(1S,2S,3R,5R)	16c

[a] T = 22°C.
[b] T = 20°C.
[c] By comparison to ref. 17.
[d] $[\alpha]_{365}^{20}$.
[e] room temperature.



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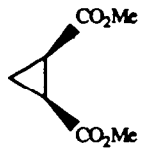

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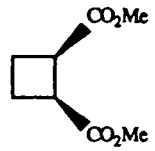

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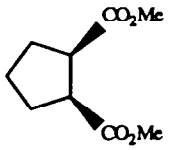

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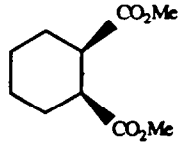

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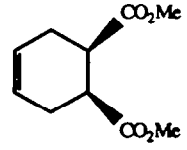

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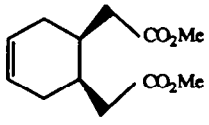

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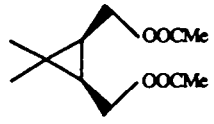

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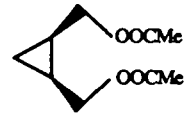

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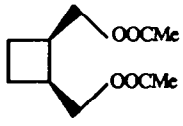

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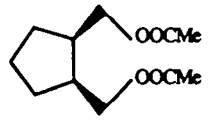

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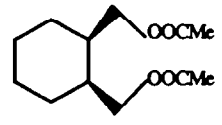

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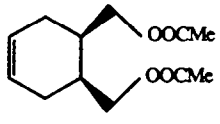

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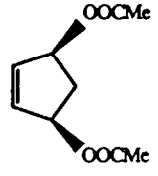

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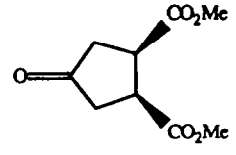

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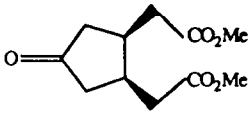

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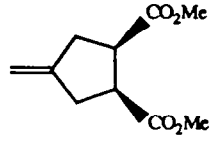

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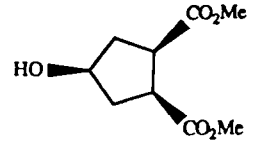

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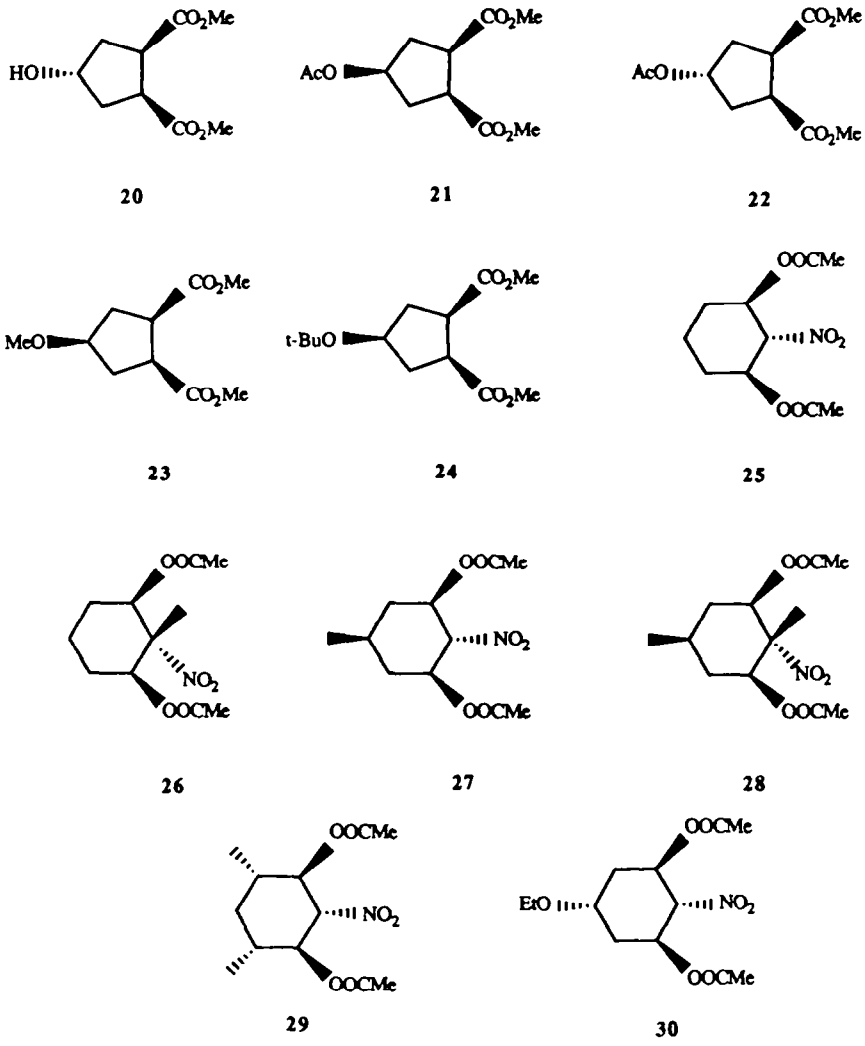


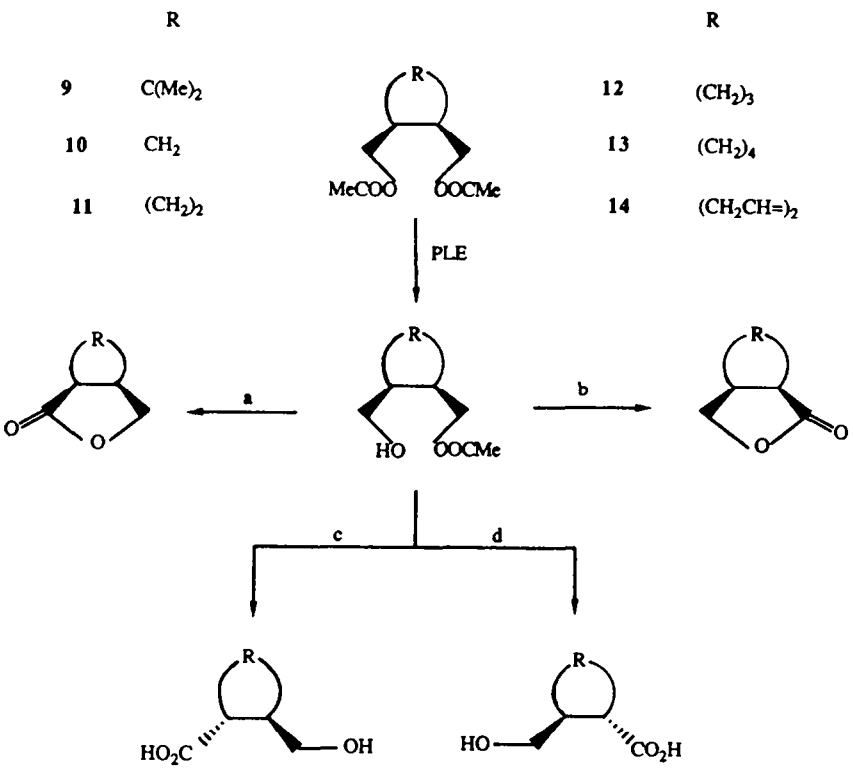
Scheme 3.

2.3. *Heterocyclic diesters*

PLE can also be used as a useful catalyst for the hydrolysis of heterocyclic diesters. Three-membered **36**, **36a**, **36b**, five-membered **37–39** and six-membered **40** heterocyclic *meso* diesters are hydrolyzed by PLE to the half esters **41–45** (Scheme 5).[14,16c,18]

The products obtained from the PLE-catalyzed hydrolysis of the five-membered heterocyclic diesters **46–51** (all *trans* form)[19–22] include the half-esters **52–57** and recovered diesters **58–63** (Scheme 6).

Within the above series of 3,4- and 2,5-diesters, enantiomers of **46** and **47** with the same absolute configuration are hydrolysed preferentially, whereas in **48** the opposite configuration is favoured. Although the optical yields are relatively low, it appears that the stereospecificity of PLE is not influenced by the hetero-atom, but by a substituent adjacent to the chiral centre. For example, the absolute configuration of the hydrolysis product of dimethyl pyrrolidine-2,5-dicarboxylate **49** is (−)-(2*R*,5*R*) whereas dimethyl N-benzylpyrrolidine-2,5-dicarboxylate **50** yields the (−)-(2*S*,5*S*) product.



a. Oxidation b. Protection-Hydrolysis-Oxidation c. Oxidation, Isomerisation
d. Protection-Hydrolysis-Oxidation, Isomerisation.

Scheme 4.

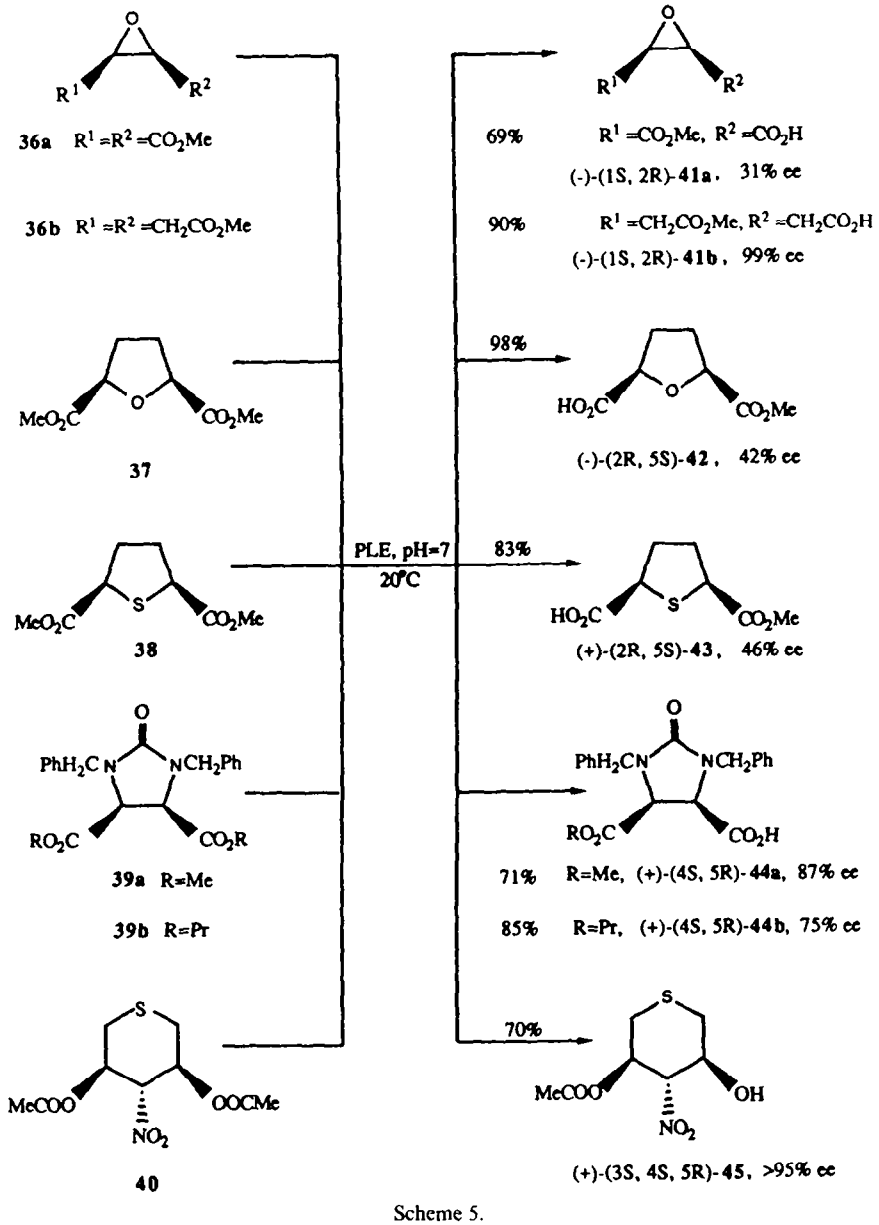
2.4. *Bicyclic mono- and diesters*

Enantiomeric excesses in the range 80–98% are obtained for the PLE catalyzed hydrolysis of bicyclic *meso*-diesters **64–72**.[2b,23,24] The corresponding products can be usefully employed in the synthesis of natural products (Schemes 7 and 8).

Bloch and co-workers[24] have shown that *exo*- and *endo-cis-meso*-oxabicyclo[2.2.1]-heptane diesters **65** and **66** are excellent substrates for PLE catalysed hydrolysis, affording the corresponding half esters with both high chemical and optical yield. In contrast, PLE does not catalyze the hydrolysis of the *endo-cis-meso* bicyclic diesters **84** and **85** (Scheme 9).[2b,24]

Polycyclic monoesters and *trans*-diesters have been examined by Zwanenburg and coworkers.[27,30–32] These investigators used PLE to resolve the tricyclic monoester **86**. This rather bulky monoester proved to be a very good substrate for PLE and the corresponding carboxylic acid **87** and the ester **88** were obtained in excellent chemical and optical yields (Scheme 10).[25,26]

The results of the PLE-catalyzed hydrolysis of a series of *trans*-diesters (Table 2) clearly show that a *trans* relation between vicinal esters is essential for high enantioselectivity. The *trans*-diesters **89**, **90** and **91** undergo rapid and stereoselective hydrolysis affording the corresponding acids with high optical yields. Very little enantioselectivity is observed with the *exo*-esters **92** and **93**, but the more slowly hydrolysed *endo*-ester **94** affords the corresponding acid (30% *ee*). The *endo*-epoxy ester **95** is not hydrolysed at all by PLE.[28] Furthermore, PLE cannot catalyze the hydrolysis of the bicyclo[2,2,2]octane *trans*-diesters **96**, **97** and **98** and only slowly hydrolyses the tricyclic *mono-endo* ester **94**.

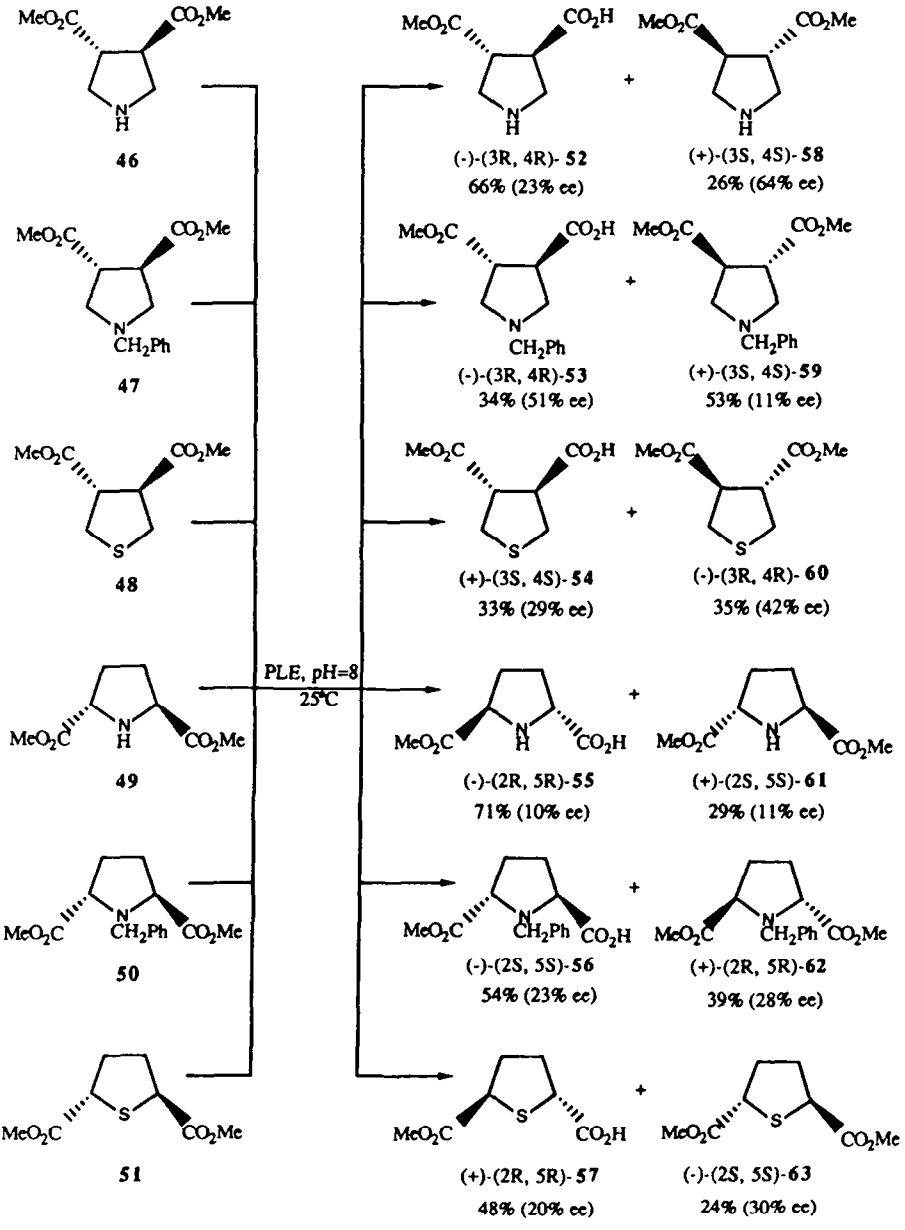


Scheme 5.

Bicyclic *mono*-ester and *trans*-diester derivatives are often useful starting materials in many synthesis schemes. Thus PLE-catalyzed hydrolysis of these compounds will provide chiral synthons for enantioselective syntheses.[29]

2.5. *Straight chain diesters*

In close analogy with the cyclic/bicyclic diesters already discussed, PLE can also stereoselectively catalyze the hydrolysis of straight chain diesters such as 3-substituted glutamates, giving half ester product with high chemical and optical yields under normal hydrolysis conditions. For example, the optically active half ester **100**[30-31] can be obtained from the symmetrical glutamate **99**. Glutamate

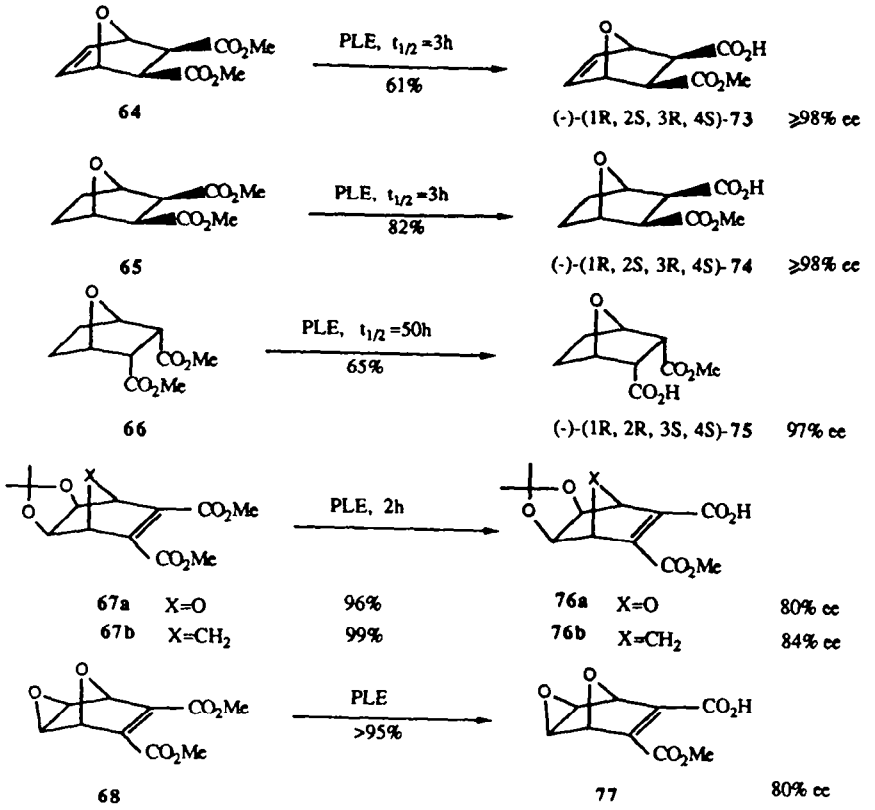


Scheme 6.

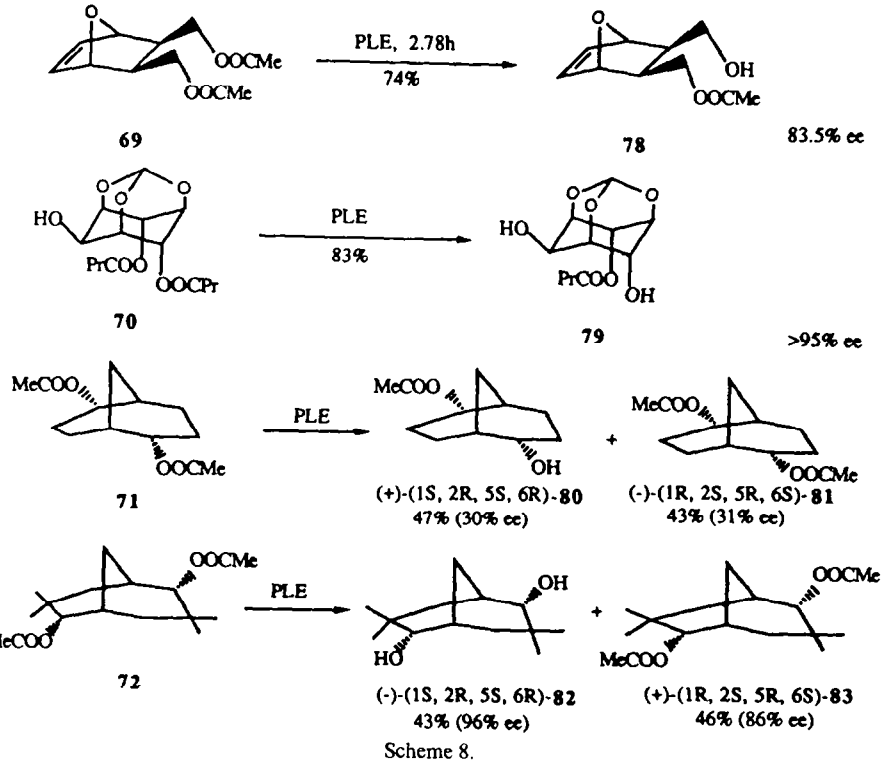
half esters with functionalized substituents at the C-3 position are not readily available from natural sources. However, Jones *et al.* have investigated a series of PLE-catalyzed hydrolysis of 3-substituted glutamates **99**, **101–128** and have obtained very promising results[32 38] (Table 3).

Other straight chain diesters have been stereoselectively hydrolyzed by PLE. For example, dimethyl *cis*-2,4-dimethylglutamate **129** is hydrolyzed to the half ester **130** (85%; 64% *ee*) (Scheme 11).[33]

In acyclic systems the observed stereoselectivity is affected by the proximity of the prochiral centre to the ester group which is hydrolyzed. Dimethyl 2-monosubstituted malonates **131–133**

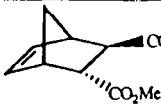
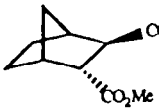
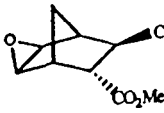
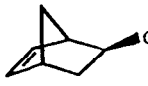
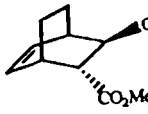
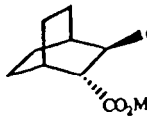
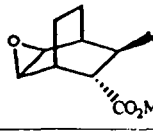


Scheme 7.



Scheme 8.

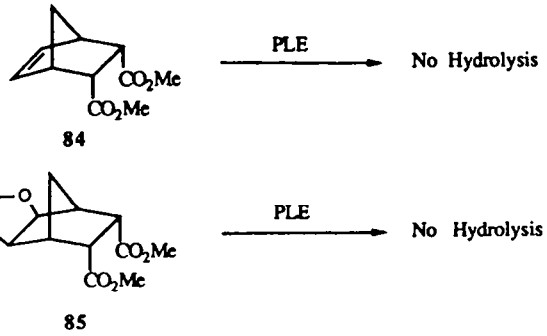
Table 2.

Substrate[a]		Reaction time	Product $[\alpha]_D$[b]	C.Y.(%)	%ee	Absolute configuration
	89a	3h	+ 110.2	45	73	(+)-(2S,3S)
	89b	3h	- 105.0	45	70	(-)-(2R,3R)
	90a	3.5h	+ 31.7	45	82	(+)-(2S,3S)
	90b	3.5h	- 33.2	40	90	(-)-(2R,3R)
	91a	6h	-	45	82	-
	91b	6h	- 71.4	40	95	(-)-(2R,3R)
	92a	1.75h	+ 0.9	45	< 5	(+)-(1R,2S,4R)
	92b	1.75h	- 1.0	45	< 5	(-)-(1S,2R,4S)
	93a	0.5h	-	40	< 2	-
	93b	0.5h	-	40	< 2	-
	94a	18h	+ 44.5	45	30	(+)-(1R,2R,4R)
	94b	18h	- 41.8	45	30	(-)-(1S,2S,4S)
	95	No[c]				
	96	- c				
	97	- c				
	98	- c				

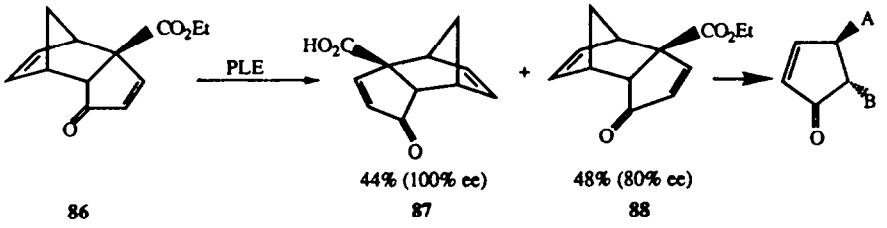
[a] The optically active half esters are designated a (R=H) and the full esters b ($R=CH_3$). The racemic starting esters are denoted by the number alone.

[b] All optical rotations are measured in CH_3OH (c = 1) at room temperature.

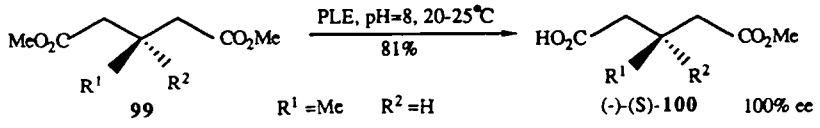
[c] No hydrolysis after 48 h.

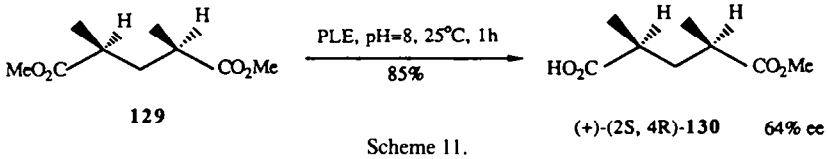


Scheme 9.



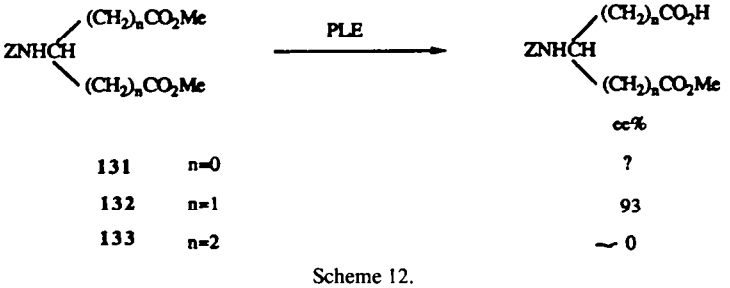
Scheme 10.





Scheme 11.

(Scheme 12) appear to be enantioselectively hydrolyzed by PLE but the resultant half esters are readily equilibrated and inconsistent optical rotations are observed. 2,2-Disubstituted malonates may yield more useful chiral synthons.



Scheme 12.

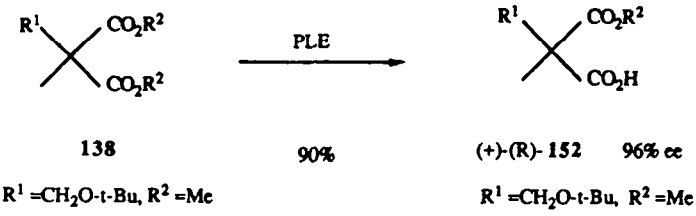
Table 3.

Substrate	R_1	R_2	C.Y.(%)	ee%	Ref
99	Me	H	81	100	30
101	Me	OH	64	99	30
102	CH_2Ph	OH	-	100	31
103	Ph	OH	-	100	31
104	Et	H	77	100	32
105	Pr	H	90	100	32
106	$CHMe_2$	H	61	100	32
107	C_6H_5	H	90	100	32
108	Ph	H	91	100	32
109	CH_2Ph	H	90	100	32
110	NH_2	H	94	41[a]	2b
111	NHAc	H	81	93[a]	2b
112	NHPh	H	94	50[b]	2b
113	NHCOPh	H	60	72[b]	2b
114	$NHCOOCH_2Ph$	H	93	93[b]	2b
115	$NHCOOCMe_3$	H	93	90[b]	2b
116	$(CH_2)_2OBzl$	H	100	54	38b
117	$CH_2CH=CHCH_2OH$[c]	H	100	19	38b
118	$CH_2CH=CHCH_2OTHP$[c]	H	95	74	38b
119	$CH_2CH=CHCH_2OTHP$-4-OMe[c]	H	92	53	38b
120	CH=CHPh[c]	H	100	93	38b
121	CH_2CH_2Ph	H	98	44	38b
122	$CH_2CH=CHPh$[c]	H	95	88	38b
123	$CH_2CH=CHPh$[c,d]	H	100	91	38b
124	$(CH_2)_3Ph$	H	97	88	38b
125	OH	H	87	16	38a
126	O-methoxyethoxymethyl	H	92	38	38a
127	OCH_2Ph	H	87	40	38a
128	CH_2Ph	H	98	73	32

[a] Absolute configuration is R.
[b] Absolute configuration is S.
[c] The stereochemistry of the double bond is *trans*.
[d] The ester group in the diester is Et.

When longer chain diesters e.g. **133** are subjected to PLE-catalyzed hydrolysis very low stereoselectivity is observed.

The PLE catalyzed hydrolysis of substituted malonic esters **134–151** can also provide useful chiral synthons.[39] The detailed results are shown in Table 4. The best substrate in this series is the readily available dimethyl 2-[(tert-butoxy)methyl]-2-methyl malonate **138** which is hydrolyzed by PLE to the (+)-(*R*) acid **152** with high chemical and optical yields (96% *ee*) (Scheme 13). The remarkable diversity of PLE is seen in the enantioselectivity of the PLE-catalyzed hydrolysis of



Scheme 13.

dialkylated propandioic acid esters **139–149**. Up to 73% of the *S*-enantiomer is obtained with substrates which have one methyl substituent and a short alkyl chain **139–141** and **145–147**, whereas those with a long alkyl chain **142–144** and **148** gave the *R*-enantiomer (hexyl **143** and heptyl **144** gave almost 90% *ee*).

3. ASYMMETRIC SYNTHESIS

3.1. *Synthetic strategy*

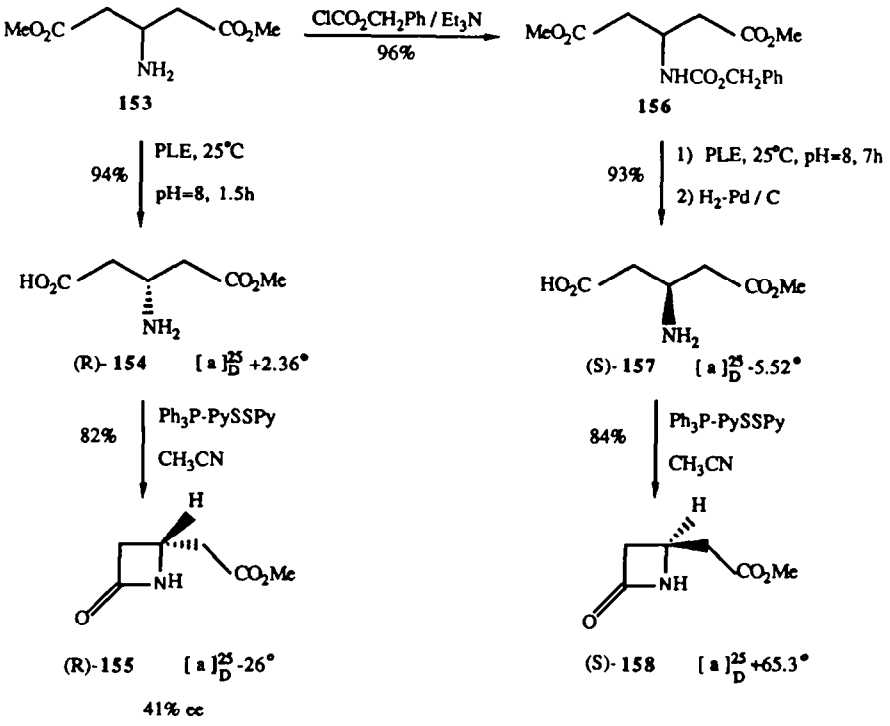
Naturally occurring β-lactam antibiotics of the carbapenem group are still being discovered. Their unique structure and biological activity[41] has provoked intense synthesis studies, most of

Table 4. PLE-catalyzed hydrolysis of malonic esters

Substrate	R_1	R_2	C.Y.(%)	ee(%)	Configuration	Ref
134	$-CH_2OH$	Me	37	6	(-)-S	39a
135	$-CH_2OCH_3$	Me	86	21	(-)-S	39a
136	$-CH_2OSi(CH_3)_2(Bu^t)$	Me	49	95	(+)-R	39a
137	$-CH_2OCH_2Ph$	Me	90	67	(+)-R	39a
138	$-CH_2OBu^t$	Me	90	96	(+)-R	39a
139	$-CH_2CH_3$	Me	a	73	(-)-S	39b
140	$-CH_2CH_2CH_3$	Me	a	52	(-)-S	39b
141	$-CH_2(CH_2)_2CH_3$	Me	a	58	(-)-S	39b
142	$-CH_2(CH_2)_3CH_3$	Me	a	46	(+)-R	39b
143	$-CH_2(CH_2)_4CH_3$	Me	a	87	(+)-R	39b
144	$-CH_2(CH_2)_5CH_3$	Me	a	88	(+)-R	39b
145	$-CH_2CH_3$	Et	a	5	(-)-S	39b,d
146	$-CH_2CH_2CH_3$	Et	a	10	(-)-S	39b,d
147	$-CH_2(CH_2)_2CH_3$	Et	a	25	(-)-S	39b,d
148	$-CH_2(CH_2)_3CH_3$	Et	a	10	(+)-R	39b
149	$-CH_2(CH_2)_6CH_3$	Et	a	5	(-)-S	39b
150	$-CH_2Ph$	Me	a	16(45)[b]	(+)-R	39b
151	$-CH_2Ph$	Et	a	23	(+)-R	39b

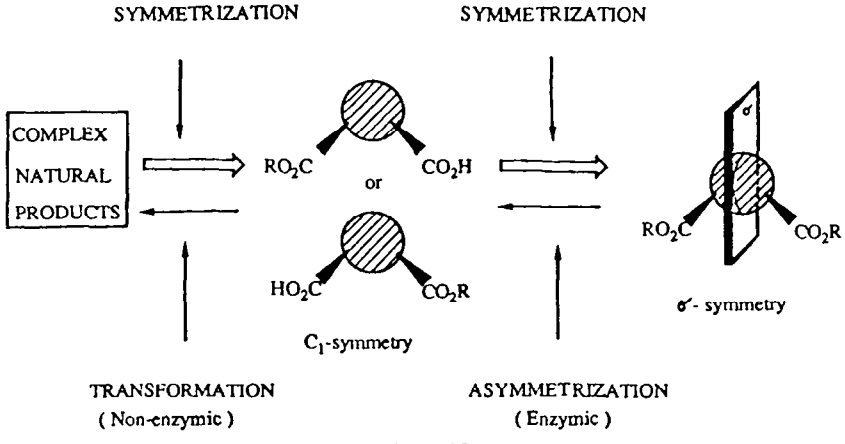
[a] 90-98%.
[b] PLE plus α-chymotrypsin ref. [68].

which have led to racemic carbapenem derivatives. For example, the chiral synthesis of thienamycin and (−)homothienamycin starting from L-aspartate[43] consists of several multistep reactions to produce the azetidinone moiety in low overall yield. An alternative approach is to use PLE and citric acid derivatives as illustrated below. This is an efficient route to (*R*) and (*S*)-4(methoxycarbonyl)methyl]-2-azetidinones **155** and **158** (Scheme 14).[44]



Scheme 14.

The enantioselective total synthesis of many useful natural products can be effectively achieved by a good combination of both enzymic and non-enzymic procedures.[45] Ohno and co-workers have

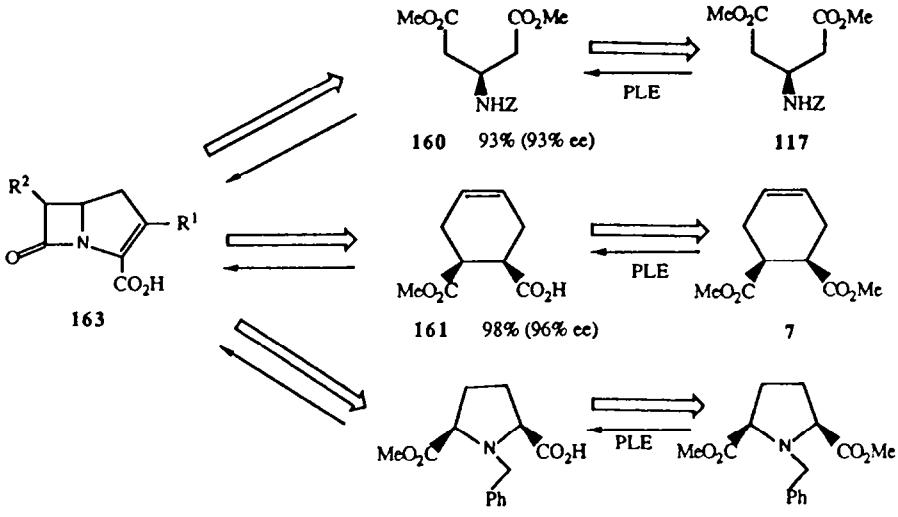


Scheme 15.

developed the following strategy for the preparation of optically active natural products Scheme 15).[26,46]

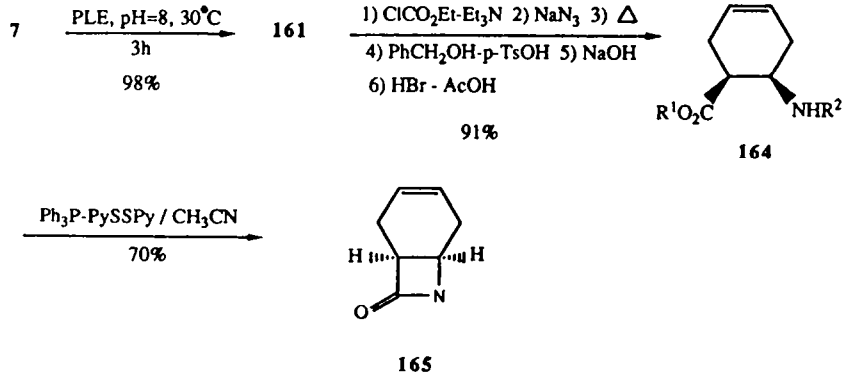
1. Symmetrization: retrosynthesis is performed to generate from the target molecule a simplified symmetric diester in the prochiral or *meso* form.
2. Asymmetrization: the symmetric diester is subjected to PLE catalyzed asymmetric hydrolysis to obtain the chiral half ester.
3. Non-enzymic procedures: the chiral half ester is converted to the target molecule by standard synthesis procedures.

A typical example of the symmetrization–asymmetrization concept is illustrated in the synthesis of the carbapenem antibiotic **163** (Scheme 16).[47-49]



Scheme 16.

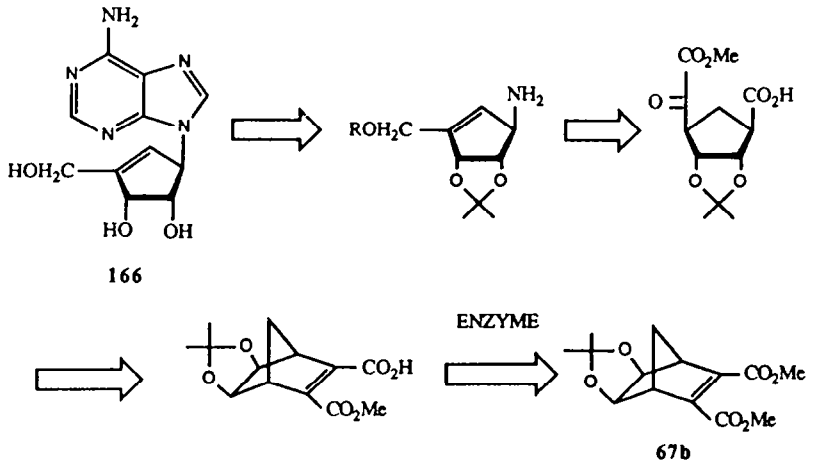
The bicyclic β-lactam **165** is proposed as an intermediate in the symmetrization-retrosynthesis of **163**. The precursor to the β-lactam is the half ester **161** which can be obtained in excellent chemical (98%) and optical yield[50] (96% *ee*) from the PLE-catalyzed hydrolysis of the diester **7** (Scheme 17).



Scheme 17.

Neplanocin **166**, isolated in 1981[51] from *Ampullariella regularis*, is a novel carbocyclic analogue of adenosine incorporating a cyclopentene ring. It exhibits remarkable antitumour activity against L1210 leukaemia in mice.

The chiral carbocyclic grouping is not easily accessible by conventional synthesis routes or by partial degradation of neplanocin A, and to date cyclopentene nucleosides have been prepared only in racemic form. A possible retrosynthesis of **166** based upon the symmetrization–asymmetrization concept is shown below (Scheme 18).



Scheme 18.

In this way various optically active nucleosides have been synthesised. Neplanocin A **166**, aristeromycin **167**, and the cyclopentenylamine moiety of nucleoside Q **168** can be prepared from **67b**, while L-riboside **169**, D-riboside **170**, showdomycin **171** and 6-azepseudouridine **172** can be prepared from **67a** (Scheme 19).[52-57]

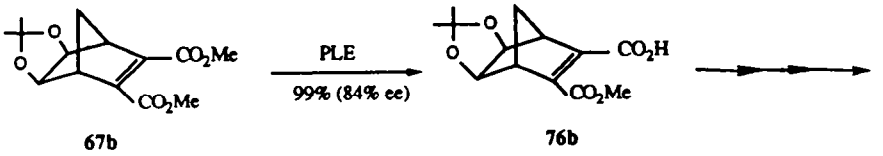
In the first step of the retrosynthesis a simplified symmetric diester is obtained (symmetrization) and then subjected to PLE-catalyzed asymmetric hydrolysis to create the corresponding chiral half ester. This is then converted to the target molecules by standard non-enzymic methods. An important feature of the symmetrization–asymmetrization concept is that it facilitates the design of various forms of a symmetric substrate from one target molecule.

3.2. *Applications of PLE in the synthesis of natural products*

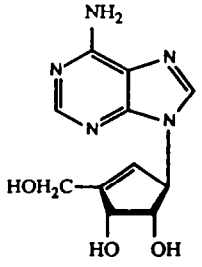
The stereo-controlled introduction of polyfunctional groups into cyclohexane has been well developed in recent years,[58] but the synthons with the desired absolute configuration are not readily accessible from natural sources. Asymmetric Diels–Alder reactions utilizing a chiral auxiliary or starting with a chiral *Z*-diene have led to the formation of several useful chiral cyclohexene derivatives. An alternative method is to use PLE to prepare the chiral building blocks—in this way the iodo lactone **176** can be prepared in high chemical and optical yield (Scheme 20).[50]

Compounds **173**, **174**, **177–179** are derived from **161** and provide useful chiral synthons for preparing amino sugars and macrolide antibiotics (Scheme 21).

Since the discovery of fortimicin A in 1977, a number of related antibiotics[60] have been isolated and characterized as pseudo-disaccharide antibiotics possessing a 4-N-glycl group. In addition to their medicinal importance,[61] these antibiotics possess a unique 1,4-diaminocyclitol skeleton which corresponds with the normal 1,3-skeleton of classical amino glycoside antibiotics such as streptomycin and kanamycin. Considerable synthetic interest has focused on the unique polyfunctional

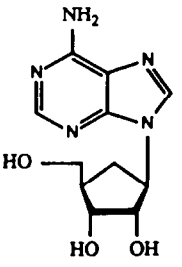


67b 76b



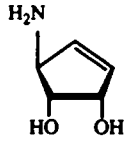
Neplanocin A

166



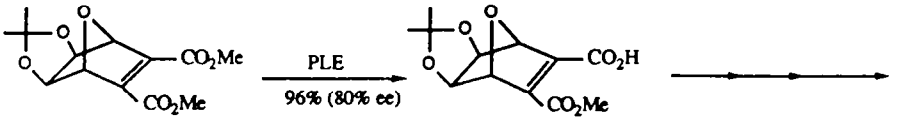
Aristeromycin

167

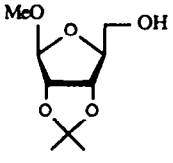


Cyclopentenylamine moiety in nucleoside Q

168

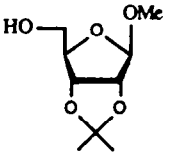


67a 76a



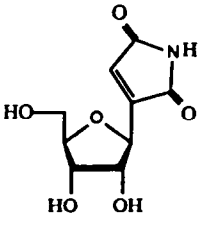
I - riboside

169



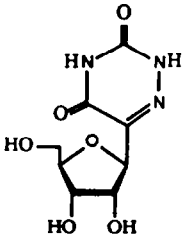
d - riboside

170



Showdomycin

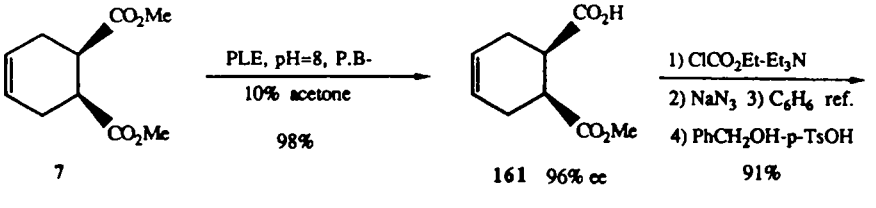
171



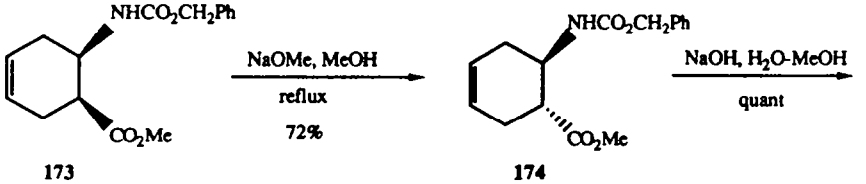
6 - azapseudouridine

172

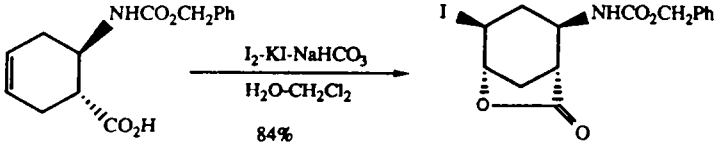
Scheme 19.



7 161 96% ee

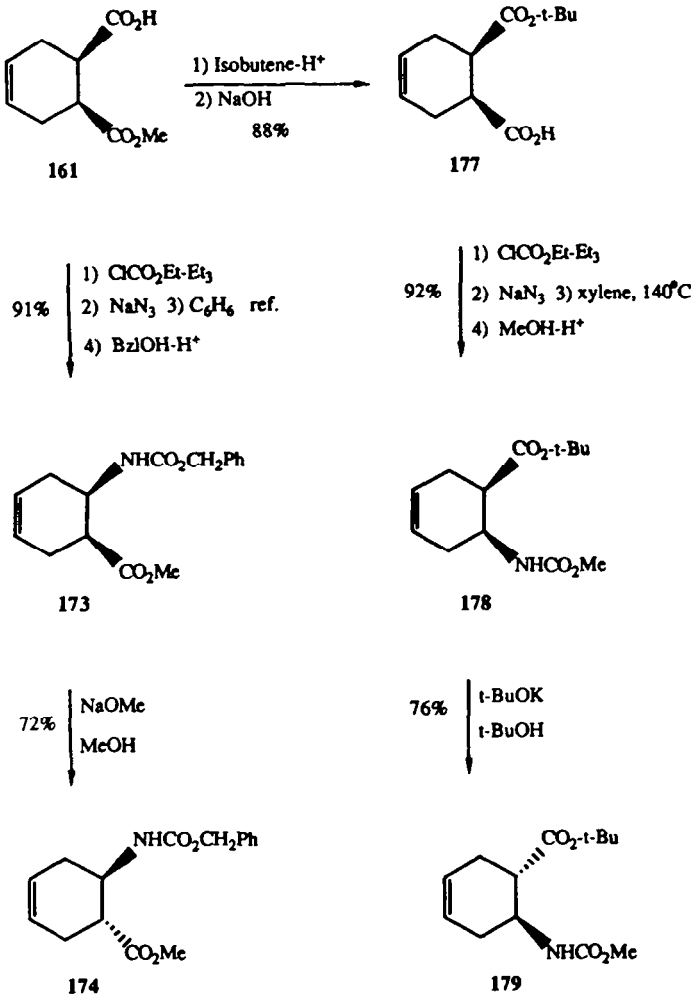


173 174



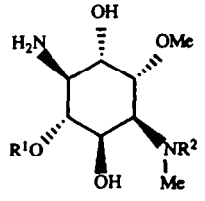
175 176

Scheme 20.



Scheme 21.

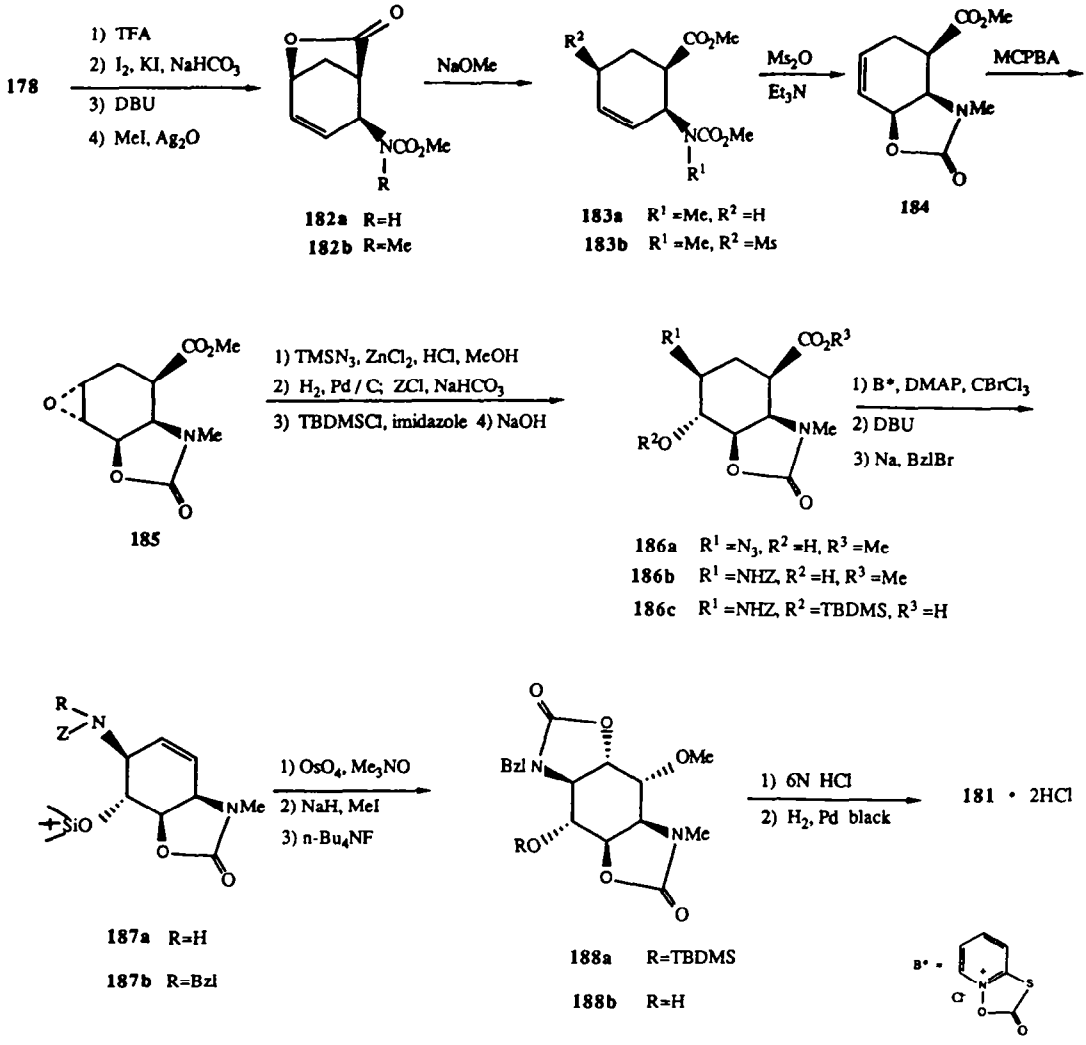
structure of fortamine **181** in which all six carbon atoms are asymmetric. The diastereoselective synthesis of fortamine has been reported by several research groups,[62] but to date optically pure fortamine has been obtained only by the resolution of a racemic intermediate.[62c] This problem can be overcome by employing the enantioselective synthesis outlined below in which the initial step is the PLE catalyzed hydrolysis of the diester **7** to the chiral half ester **161** (Schemes 22 and 23).[63]



180 FORTIMICIN A
R^1 = 6-epi-purpurosamine B
R^2 = $COCH_2NH_2$

181 (-)-FORTAMINE
$R^1 = R^2 = H$

Scheme 22.

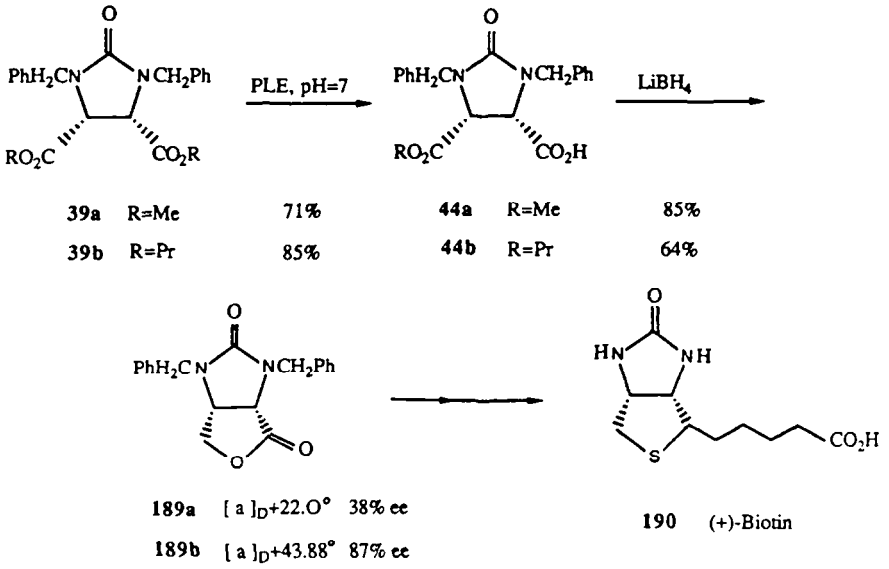


Scheme 23.

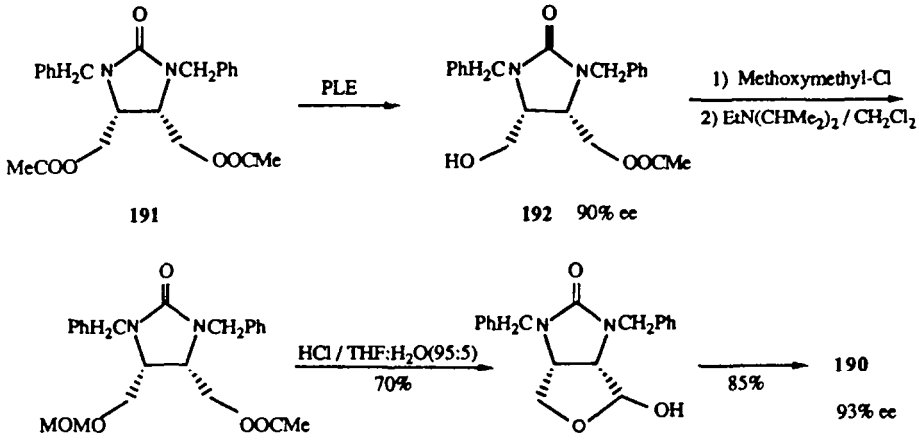
An example of a commercial application of PLE is the synthesis of (+)-biotin **190** which is at present prepared from a reduction of (4*S*,5*R*)-1,3-dibenzyl-5-alkyloxy-carbonyl-2-oxoimidazolidine-4-carboxylic acid **39a–39b**[64,65] via the chiral lactone **189**. An alternative route employing **191** as a starting material is also illustrated below (Schemes 24 and 25).[66]

One of the most successful applications of PLE has been in the synthesis of optically active amino acids. For example, diethyl 3,4-dimethoxybenzyl(methyl)malonate **195** is asymmetrically hydrolyzed by PLE to (*R*)-ethyl 3,4-dimethoxybenzyl(methyl)malonate **196** which can then be converted into (*S*)-α-methyl 3,4-dihydroxyphenylalanine (L-α-methyl-DOPA) **199** (Scheme 26).[34]

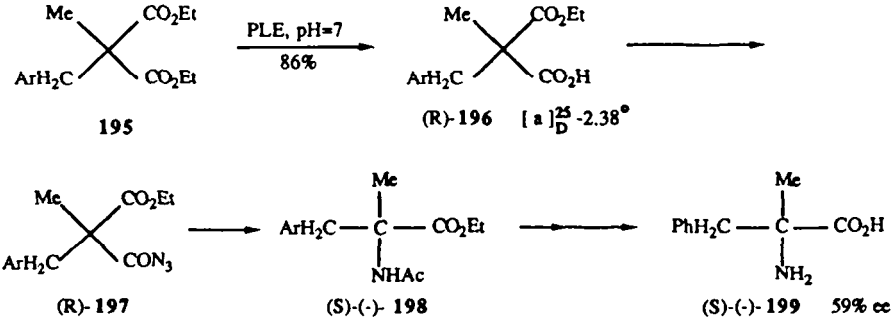
The PLE catalyzed hydrolysis of prochiral diesters has been shown to be an efficient method for the preparation of chiral synthons as reagents or starting materials for the synthesis of more complex compounds of biological and/or pharmacological interest.[15,67] This is illustrated by the PLE and α-chymotrypsin catalyzed hydrolysis of the *meso*-diesters **200a**, **b** and **c** to their corresponding acid-esters which can then be converted into enantiomerically pure (*S*)-α-methylphenylamine **202a**, and (*S*)-α-methyltyrosine **202d** (Scheme 27).[68]



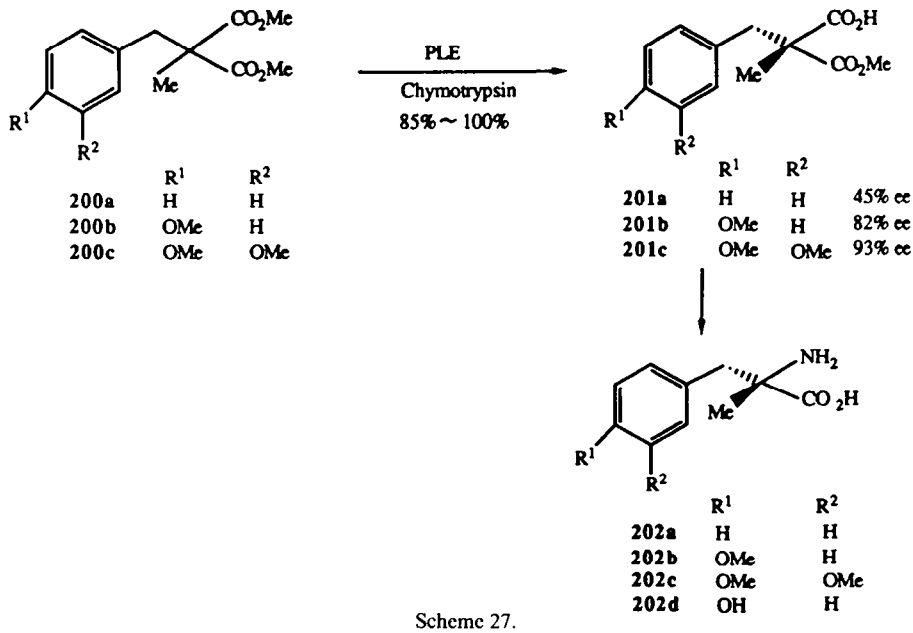
Scheme 24.



Scheme 25.

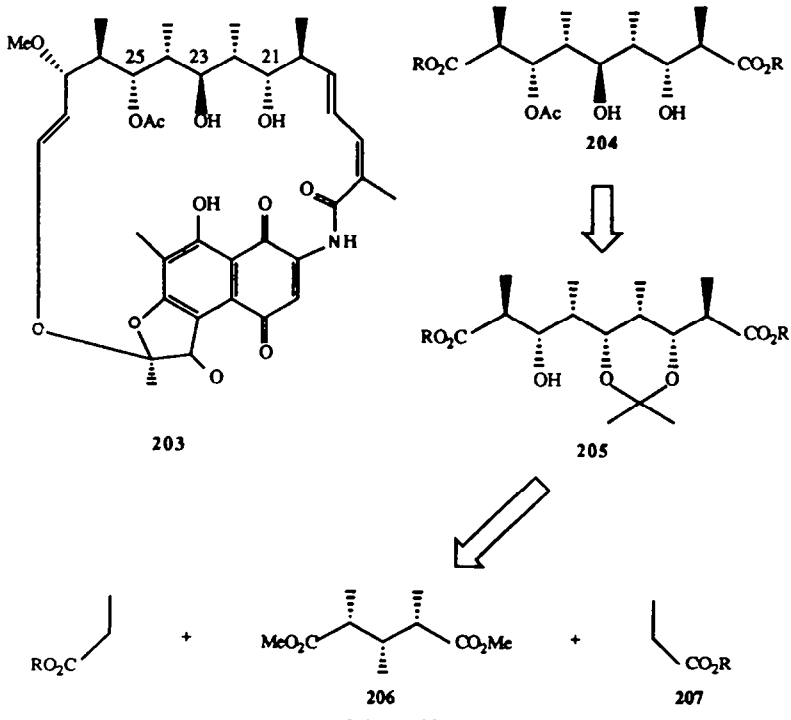


Scheme 26.



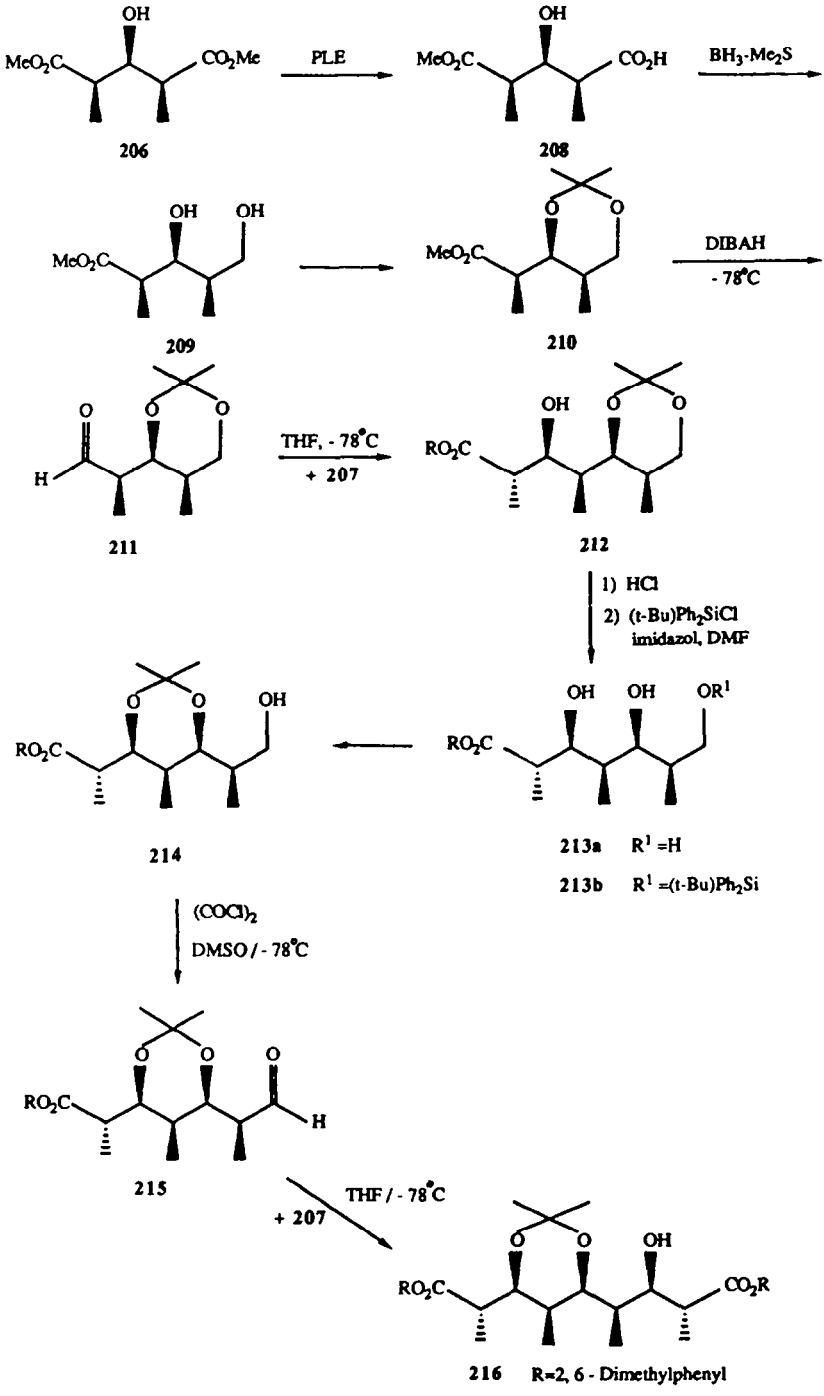
Scheme 27.

The construction of the sequence of the eight chiral centres in the *ansa* moiety of the antibiotic rifamycin *S* **203** provides a great challenge for synthetic chemistry.[69] An important feature of this segment is the presence of a symmetry element at C(23) which plays a leading role in the retrosynthetic analysis of the ester **204** which corresponds to the C(19) to C(27) fragment of **203** (Scheme 28).[70]



Scheme 28.

The diester **204** can be synthesized from dimethylxylo-3-hydroxy-2,4-dimethyl glutamate **206** and two equivalents of propionate **207** via the intermediate **205**. Since the achiral dimethyl ester **206** can be hydrolyzed with high enantioselectivity by PLE[71] the *ansa* chain moiety of rifamycin *S* **203** corresponding to the C(19) to C(27) moiety epimeric at C(23) can be obtained easily (Scheme 29).[72,73]



Scheme 29.

4. CONCLUSIONS

Extensive studies carried out with a wide range of symmetric diesters and monoesters have shown that PLE-catalyzed asymmetric hydrolysis is very useful for the synthesis of optically active chiral synthons which can be applied in the asymmetric synthesis of many natural products. The stereoselectivity of PLE is controlled by the composition of the substrate and small changes in a substrate may completely alter the absolute stereochemistry of the product.

PLE is rapidly increasing in importance as an asymmetric catalyst in organic synthesis. It has already had a great impact in synthetic organic chemistry.[74-76]

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