Tandem Cycloaddition–Enzymatic Transesterification. An Enantioselective Diels–Alder Reaction Equivalent

Cecilia Andreu, J. Alberto Marco, and Gregorio Asensio*
Departamento de Química Orgánica, Facultad de Farmacia, Avda. Blasco Ibáñez, 13 E–46010 Valencia, Spain

Tandem cycloaddition–enzymatic transesterification with pancreatic pig lipase or the lipase from *Candida ciclindracea* carried out in ethyl, vinyl, or isopropenyl acetate gives rise to optically active Diels–Alder type derivatives from symmetrical precursors with both high enantioselectivity and chemical yield.

Efficient control of stereochemistry in enantioselective carbon–carbon bond formation in cycloadditions remains a formidable synthetic challenge and several methodologies have been devised to achieve it based on competing transition states which differ in energy to the greatest extent.[1,2]

Here we report that a tandem cycloaddition–enzymatic transesterification in an organic solvent gives rise to cycloadducts derived from common symmetrical dienes and dienophiles with both high enantioselectivity and chemical yield; in this sense, therefore, it can be considered as the simplest and most convenient way to asymmetric Diels–Alder products. The furan (**1**) reacts with maleic anhydride (**2**) to afford the *exo*-adduct (**3**)[3] which by catalytic hydrogenation followed by lithium aluminium hydride reduction gives the corresponding *meso*-diol (**5**).[4] Asymmetric monoacetylation of this by transesterification with ethyl, vinyl, or isopropenyl acetate in the presence of pancreatic pig lipase (PPL) (see Scheme 1 and Table), gave 99.0% ee of the (2*S*,3*R*)-(+)-(**6**) enantiomer[5] in ethyl or vinyl acetate as solvent; no transesterification took place in isopropenyl acetate. In contrast the lipase of *Candida cylindracea* (CCL) gave 96.5% ee of the (2*R*,3*S*)-(−)-(**6**)enantiomer[5] in isopropenyl acetate as solvent and 76.0% ee in vinyl acetate; no transesterification took place in ethyl acetate.

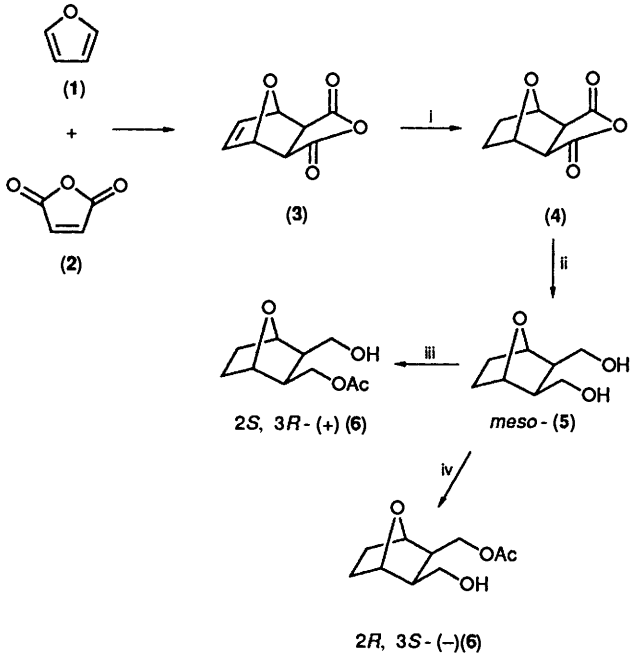
The reaction of furan (**1**) and dimethyl acetylendicarboxylate (**7**)[3] followed by catalytic hydrogenation and lithium aluminium hydride reduction affords the *meso*-diol *endo*-(**10**)[4] which gives the monoacetate (2*R*,3*S*)-(+)-(**11**)[5] with different degrees of enantioselectivity depending on the lipase and reaction conditions used (see Scheme 2 and Table). The best enantioselectivity (87.3% ee) was obtained with CCL and vinyl acetate. All solvents and reagents, including enzymes, were used without previous drying or purification.

It is noteworthy that CCL and PPL catalyze the

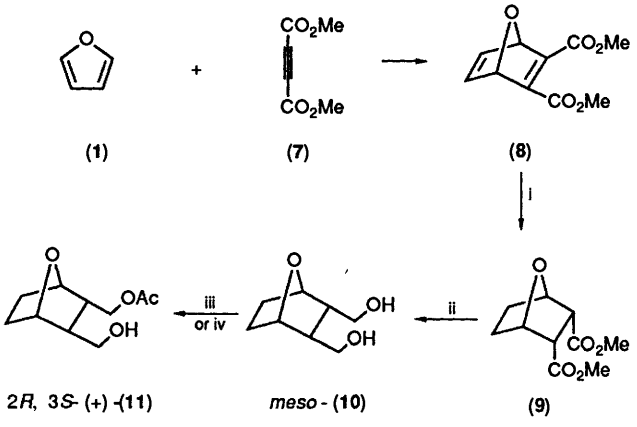
Table. Enzymatic transesterification, in an organic solvent, of *meso*-(**5**) and *meso*-(**10**) in the presence of PPL or lipase from CCL.

Substrate	Enzyme	Solvent[a]	*t*(°C)	Product	% Yield	$[\alpha]_D^{20}$ [b]	%Ee[c]
meso-(**5**)	PPL	E.A.	40	(+)-(**6**)	68.0	+15.1	>99
meso-(**5**)	PPL	V.A.	20	(+)-(**6**)	92.0	+15.1	>99
meso-(**5**)	CCL	I.A.	40	(−)-(**6**)	76.0	−14.6	96.5
meso-(**5**)	CCL	V.A.	20	(−)-(**6**)	70.0	−11.5	76.0
meso-(**10**)	PPL	V.A.	40	(+)-(**11**)	38.2	+1.02	8.34
meso-(**10**)	CCL	V.A.	20	(+)-(**11**)	72.0	+10.7	87.3

[a] E.A., ethyl acetate; V.A., vinyl acetate; I.A., isopropenyl acetate. [b] *c* 0.2 Ethyl acetate; [c] % Ee determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ [hfc$_3$ = 3-(heptafluoropropylhydroxymethylene)-(+)-camphorato], as a chiral shift reagent.



Scheme 1. *Reagents and conditions:* i, H_2,Pd/C 10%; ii, $LiAlH_4$, THF, reflux; iii, PPL, ethyl or vinyl acetate; iv, CCL, isopropenyl or vinyl acetate.



Scheme 2. *Reagents and conditions:* i, H_2, Pd/C 10%; ii, $LiAlH_4$, THF, reflux; iii, PPL, vinyl acetate; iv, CCl, vinyl acetate.

transesterification of the *exo*-adduct (**5**) with great enantioselectivity each leading to a different enantiomer. Conversely, the diol *endo*-(**10**) is a worse substrate for the enzymatic transesterification since only a low enantiomeric excess is obtained with PPL and also because PPL and CCL show preference for the same enantiotopic group.

Our methodology for optically active 7-oxabicyclo[2.2.1]-heptane derivatives has the merit of providing a single *enantiomer from a meso* precursor with high chiral economy, enantioselectivity, and chemical yield. The use of a solvent as acylating agent avoids the problems of dry solvents and labile, activated esters.[6] An alternative and valuable enzymatic approach to optically active compounds *via* Diels–Alder synthesis[7] is based on the resolution by hydrolysis of racemic starting materials and hence, a <50% yield of the desired stereoisomer is obtained in the base case.

Experimental

Synthesis of cis-exo-2,3-*Bis(hydroxymethyl)*-7-*oxabicyclo*-[2.2.1]*heptane* (**5**).—The anhydride (**3**)[3] (4.15 g, 25 mmol) in ethyl acetate (100 ml) containing 10% Pd–C (100 mg) was hydrogenated under H_2 (1 atm) to give compound (**4**). The latter (4.16 g, 25 mmol) was reduced with $LiAlH_4$ (0.95 g, 25 mmol) in dry THF (200 ml), to give the *meso*-diol (**5**) (2.4 g, 60.7%); m.p. 63 °C (lit.,[8] m.p. 62 °C); δ_H(200 MHz, $CDCl_3$) 1.57 (4 H, m), 2.18 (2 H d of t, *J* 5 Hz, 1.5 Hz), 3.4–3.8 (4 H, m), 4.1 (2 H, br s, OH), and 4.35 (2 H, t, *J* 3 Hz).

Synthesis of cis-endo-2,3*Bis(hydroxymethyl)*-7-*oxabicyclo*-[2.2.1]*heptane* (**10**).—The adduct (**8**)[3] (5.25 g, 25 mmol), in ethyl acetate (100 ml) containing 10% Pd–C (100 mg) was hydrogenated under H_2 (1 atm) to give compound (**9**). The latter (5.35 g, 25 mmol) was reduced with $LiAlH_4$ (0.95 g, 25 mmol) in dry THF (200 ml) to yield the *meso*-diol (**10**) (2.3 g, 60%); m.p. 49 °C (lit.,[9] 49–50 °C); δ_H(200 MHz, $CDCl_3$) 1.55 (4 H, s), 2.2–2.6 (2 H, m), 3.4–3.8 (4 H, m), 4.1 (2 H, br s, OH), and 4.5 (2 H, br s).

Lipase-catalyzed Transesterifications: Typical Procedure.—The *meso* diol (**5**) or (**10**) (1 g, 6.3 mmol) was dissolved in ethyl, vinyl, or isopropenyl acetate (50 ml). Lipase PPL or CCL (1.9 g) was added and the mixture was stirred at 20 or 40 °C. The course of the reaction was followed by monitoring of the optical activity. At the optimum time, the reaction was stopped by enzyme filtration. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (hexane–ethyl acetate, 5:3). The yield in the products (**6**) or (**11**) are given in the Table: (**6**) δ_H(200 MHz, $CDCl_3$) 1.5–1.7 (4 H, m), 2.0 (3 H, s), 2.12 (2 H, m), 2.5 (1 H, br s, OH), 3.5 (2 H, m), 4.0 (2 H, m), 4.36 (1 H, t, *J* 2.5 Hz), and 4.45 (1 H, t, *J* 2.6).

(**11**) δ_H(200 MHz, $CDCl_3$) 1.4–1.7 (4 H, m), 2.0 (3 H, s), 2.7 (2 H, m), 3.4–3.6 (2 H, m), 3.8–4.0 (2 H, m), and 4.5 (2 H, m).

Acknowledgements

We acknowledge financial support from the Direccion General de Investigación Científica y Ténica (Project No. PB86-0461) and (C. A.) to the Conselleria de Cultura, Educación y Ciencia de la Generalitat Valenciana.

References

1 L. Paquette in D. Morrison (ed.), 'Asymmetric Synthesis,' 1984, **3**, 455. Academic Press, Inc. Orlando, Fl.
2 G. Helmchen, R. Karge and J. Weetman in R. Schelfold (ed.), *Modern Synth. Methods*, 1986, **4**, 262.
3 M. C. Kloetzel and H. L. Holmes, in R. Adams, *Org. React.* (N.Y.), 1948, **4**, 1.
4 J. B. Jones and C. J. Francis, *Can. J. Chem.*, 1984, **62**, 2578.
5 Absolute configuration was determined by partial oxidation and lactonisation. The specific rotation of the lactones was compared with literature data (see ref. 4).
6 J. V. Eycken, M. Vandewalle, G. Heinemann, K. Laumen, M. P. Schneider, J. Kredel and J. Sauer, *J. Chem. Soc., Chem. Commun.*, 1989, 306.
7 P. Cesti, A. Zaks and A. M. Klibanov, *Appl. Biochem Biotechnol.*, 1985, **11**, 401.
8 J. Johvet, *Ann. Chim* (Paris), 1960, **5**, 1198.
9 T. A. Eggelte, H. de Koning and H. O. Huisman, *Tetrahedron*, 1973, **29**, 2445.

Paper 0/03240I
Received 18*th April* 1990
Accepted 18*th July* 1990