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Dynamic kinetic resolution of racemic *N*-phthalyl amino acids using (*S*)-α-methylpantolactone as the chiral auxiliary

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Abstract

A dynamic kinetic resolution of racemic *N*-phthalyl amino acids by stereoselective esterification was examined using (*S*)-α-methylpantolactone as the chiral auxiliary. The reaction of various racemic *N*-phthalyl amino acids with this chiral alcohol in the presence of both DCC and DMAP afforded predominantly the (*S*,*S*)-esters in nearly quantitative yield.

1. Introduction

Kinetic resolution of racemic mixtures is an effective tool for the preparation of enantiomerically enriched compounds,[1] but in this reaction the expected product can be obtained at most in 50% yield. Procedures which allow in situ epimerisation of the substrate prior to the reaction, viz dynamic kinetic resolution,[2] have the advantage of theoretically quantitative conversion of the starting material into a single stereoisomer.

Dynamic kinetic resolution processes have been used previously for the synthesis of optically active α-amino acids or esters via stereoselective amination of the corresponding α-bromo compounds.[3] Moreover, the direct dynamic kinetic resolution of racemic α-amino acid derivatives has also been reported[4] but essentially only for enzymatically catalyzed reactions.

Yus et al.[5] have described the kinetic resolution of racemic carboxylic acids by using the dicyclohexylcarbodiimide (DCC) esterification method with optically active alcohols. With one equivalent each of DCC and 4-dimethylaminopyridine (DMAP), this reaction applied to *N*-protected amino acids should allow a dynamic kinetic resolution process due to the propensity of the corresponding acyl (4-dimethylamino)pyridinium salt to racemize[6] (Scheme 1). Therefore, we decided to examine this

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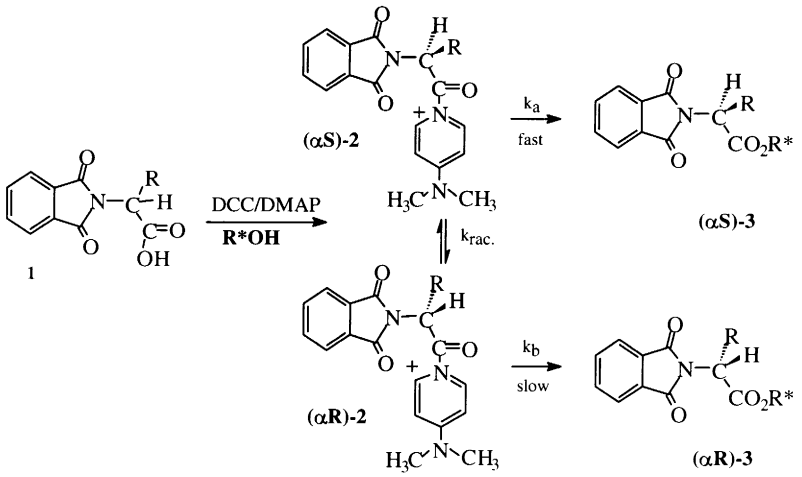
esterification reaction starting from various racemic *N*-phthaloyl amino acids and a chiral alcohol. The use of the phthalimido protecting group has the advantage of being easily introduced and removed.



Scheme 1. Dynamic kinetic resolution of *N*-phthalyl amino acids using DCC/DMAP and a chiral alcohol

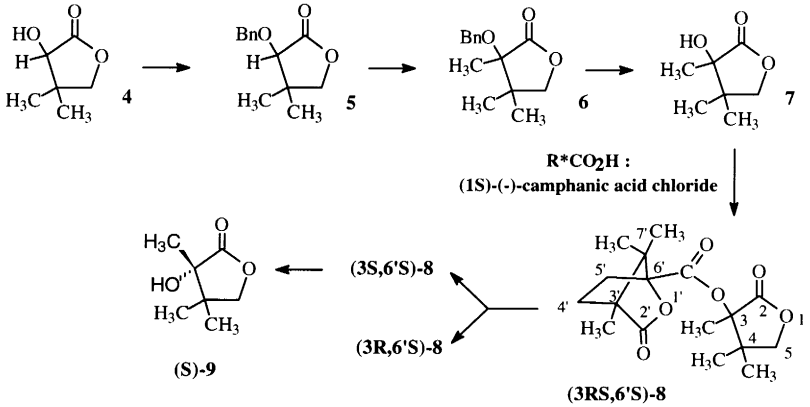
2. Results and discussion

To obtain a dynamic kinetic resolution under the experimental conditions used, with for example formation of (α*S*)-**3** compound, **2** should easily racemize and both k_{rac}/k_a and k_a/k_b values should be sufficiently high (Scheme 1). Therefore we first verified that a total racemization of different enantiomerically pure *N*-phthalyl amino acids takes place rapidly in the presence of one equivalent each of DCC and DMAP. Initially, we decided to use (*R*)-pantolactone as the chiral alcohol since it is both an efficient auxiliary[3b,7] and commercially available. We tested the esterification reaction of various racemic *N*-phthalyl amino acids using this chiral alcohol and DCC/DMAP at different temperatures. Under these conditions the corresponding esters were formed quantitatively after 15 hours but with no significant diastereoselectivity. It was reasonable to speculate that the absence of stereoselectivity obtained by using (*R*)-pantolactone might result from too small a difference between k_{rac}, k_a and k_b. These results are close to those obtained by Koh et al.[8] and Camps et al.[9] in the case of esterification of α-bromo carboxylic acids with the same alcohol.

We then investigated the use of a tertiary instead of a secondary alcohol with the aim of modifying the values of the reaction constants thus allowing a dynamic kinetic resolution process. To conserve the pantolactone structure, we decided to synthesize and to test the enantiomerically pure α-methyl substituted derivative (*S*)-**9**: (*S*)-3,4,4-trimethyl-3-hydroxy-γ-butyrolactone or (*S*)-α-methyl pantolactone.

To prepare (*S*)-**9**, pantolactone **4** was first converted into the corresponding benzyl ether as described recently[10] (Scheme 2). Then, alkylation of **5** was achieved in good yield in THF after deprotonation at low temperature (−40°C) by using lithium diisopropylamine as base and DMPU as co-solvent. The benzyl ether was easily cleaved by hydrogenolysis affording racemic **7** which was then transformed, using DCC/DMAP and (1*S*)-camphanic acid chloride, into the diastereoisomeric mixture of **8**. Enantiomerically pure (3*S*,6′*S*)-**8** was isolated by fractional crystallization of the mixture of the two diastereoisomers **8**,[11] and (*S*)-**9** was then obtained by simple saponification. The structure of (3*S*,6′*S*)-**8**

was ascertained from the spectral data,[12] and its stereochemistry from the X-ray diffraction analysis (Fig. 1).[13] The stereochemistry of (3*S*,6′*S*)-**8** allowed us to establish that of compound (*S*)-**9**.[14]



Scheme 2. Synthesis of (*S*)-**9**

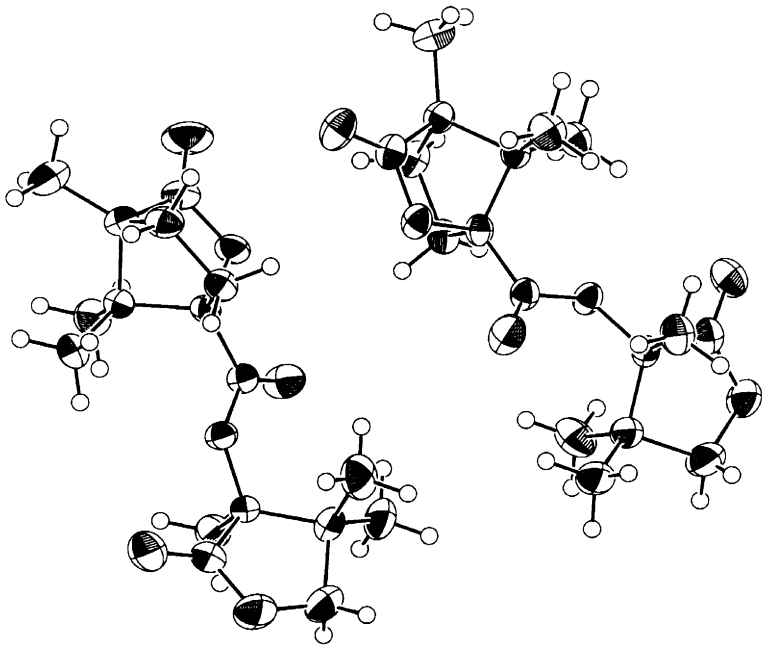


Fig. 1. ORTEP drawing of ester (3*S*,6′*S*)-**8**

We first studied the dynamic kinetic resolution of racemic *N*-phthalyl alanine using (*S*)-**9** and one equivalent of DCC and DMAP under various conditions of solvent, temperature and reaction time (Table 1).[15]

A dynamic kinetic resolution was observed in each case since a non-equivalent mixture of the two diastereoisomers was obtained in nearly quantitative yield. Therefore, under the experimental conditions used, the racemization of the *N*-phthalyl alanine was sufficiently rapid with respect to the esterification rate. Moreover, the reaction rates of (*R*)-**2** and (*S*)-**2** with (*S*)-α-methyl pantolactone were substantially different. This was confirmed by similar results obtained starting from (*RS*), (*R*) or (*S*)-*N*-phthalyl alanine.

The best results were obtained after 15 hours at room temperature (Table 1, entries 3 and 6). The diastereoselectivity was affected by the solvent. Toluene gives better results than dichloromethane but

Table 1
Dynamic kinetic resolution of racemic *N*-phthalyl alanine

Entries	Solvent	Reaction time (h) /T°C	Yield %	Ratio (S,S/R,S)
1	CH_2Cl_2	2h/25°C	70	78/22
2	CH_2Cl_2	5h/25°C	85	77/23
3	**CH_2Cl_2**	**15h/25°C**	**95**	**78/22**
4	CH_2Cl_2	36h/25°C	95	73/27
5	CH_2Cl_2	96h/25°C	97	62/38
6	**toluene**	**15h/25°C**	**90**	**85/15**
7	CH_2Cl_2	15h/0°C	75	71/29
8	toluene	15h/0°C	55	87/13
9	CH_2Cl_2	0.5h/40°C	50	78/22
10	CH_2Cl_2	5h/40°C	85	71/29
11	CH_2Cl_2	15h/40°C	96	68/32

in this case, the yields are slighty lower probably due to a lower solubility of the substrate. Moreover, a noticeable decrease in diastereoselectivity was obtained when the reaction mixture was allowed to stand for several days at room temperature, probably due to the prolonged exposure of the substrate to the basic DMAP (Table 1, entries 4 and 5). When the reaction was carried out at 0°C an important decrease in yield was observed, whatever the solvent with no increase in stereoselectivity (Table 1, entries 7 and 8). On the other hand, after only 30 minutes in refluxing dichloromethane, the same stereoselectivity as at room temperature was observed. However, the reaction took place in only 50% yield, and prolonged reaction times provided lower stereoselectivity (Table 1, entries 9, 10 and 11).

Reaction of (*S*)-**9** at room temperature with other racemic *N*-phthalyl amino acids was then studied. In each case we observed after one night, as previously, a dynamic kinetic resolution process affording in high yield the corresponding optically active esters (Table 2). Variation of the R side chain of the amino acid was possible without significant influence on yields or stereoselectivity. As in the case of *N*-phthalyl alanine, toluene afforded slightly higher diastereoselectivity except when the less soluble phenylalanine compound was used, in which case essentially no reaction took place.

Table 2
Dynamic kinetic resolution of various racemic *N*-phthalyl amino acids

Entries	R	Solvent/reaction time (h)	Yield %	Ratio (S,S/R,S)
12	CH_3	CH_2Cl_2/15h	95	78/22
13	**CH_3**	**toluene/15h**	**90**	**85/15**
14	CH_2CH_3	CH_2Cl_2/15h	85	78/22
15	**CH_2CH_3**	**toluene/15h**	**80**	**81/19**
16	**$CH_2C_6H_5$**	**CH_2Cl_2/15h**	**90**	**84/16**
17	$CH_2C_6H_5$	toluene/15h	7	86/14
18	$CH_2C_6H_5$	toluene/36h	8	89/11
19	$CH_2CH(CH_3)_2$	CH_2Cl_2/15h	95	81/19
20	**$CH_2CH(CH_3)_2$**	**toluene/15h**	**95**	**90/10**
21	$(CH_2)_3CH_3$	CH_2Cl_2/15h	98	79/21
22	**$(CH_2)_3CH_3$**	**toluene/15h**	**98**	**84/16**
23	$CH(CH_3)_2$	CH_2Cl_2/15h	50	78/22
24	$CH(CH_3)_2$	toluene/15h	65	88/12
25	**$CH(CH_3)_2$**	**toluene/48h**	**76**	**87/13**

Hydrolysis of **3** under acidic conditions[7c] gave the corresponding (*S*)-amino acids in good yield. The (*S*) configuration was assigned by the specific rotation values and by HPLC analysis after derivatization

with Marfey's reagent[16] indicating that the (*S*,*R*) ester was mainly formed during this dynamic kinetic resolution process.

In conclusion, a new example of dynamic kinetic resolution using (*S*)-α-methyl pantolactone as the chiral auxiliary has been developed. This method provides an easy access to optically active α-amino acids and can be applied to other α-substituted acids.

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11. All new described products were isolated by chromatography on silica gel, or by recrystallization, and satisfactory analytical data have been obtained.
12. Fractional crystallization of (3*SR*,6′*S*)-**8** from a mixture of CH_2Cl_2 and hexane gave diastereomerically pure (3*S*,6′*S*)-**8**. (3*S*,6′*S*)-**8** has the following physical data: mp 186°C; $[\alpha]_D=-11.5$ (c=2 in CH_2Cl_2); HPLC (Chiraspher (Merck), hexane:isopropanol: 97:3): rt 19.9 min; ^{1}H NMR ($CDCl_3$) δ=1.03 (s, 3H, 3′-C*H*$_3$), 1.14 (s, 3H, 4-C*H*$_3$), 1.15 (s, 6H, 7′-C*H*$_3$), 1.25 (s, 3H, 4-C*H*$_3$), 1.65 (s, 3H, 3-C*H*$_3$), 1.71 (m, 1H, 5′-HC*H*), 1.96 (m, 1H, 5′-HC*H*), 2.05 (m, 1H, 4′-HC*H*), 2.45 (m, 1H, 4′-HC*H*), 3.96 (d, J=8.8 Hz, 1H, 5-HC*H*), 4.14 (d, J=8.8 Hz, 1H, 5-HC*H*); ^{13}C NMR ($CDCl_3$) δ=10.0 ($C_{7'}(CH_3)$), 17.0 ($C_3(CH_3)$), 17.2 ($C_{3'}(CH_3)$, $C_{7'}(CH_3)$), 21.2 ($C_4(CH_3)$), 22.3 ($C_4(CH_3)$), 29.3 ($C_{5'}$), 31.0 ($C_{4'}$), 43.2 (C_4), 54.8 ($C_{7'}$), 55.2 ($C_{3'}$), 77.6 ($C_{5'}$), 85.3 (C_3), 91.2 ($C_{6'}$), 166.2 (CO), 173.0 (CO), 178.3 (CO).
13. The diffraction data were collected on an Enraf–Nonius KappaCCD diffractometer using graphite-monochromate Mo-Kα radiation and the φ-scan technique up to θ=25.41. Crystal data of (3*S*,6′*S*)-**8**: Molecular formula $C_{17}H_{24}O_6$, molecular weight=324, triclinic, space group P1, cell constants: *a*=6.5157(3) Å, *b*=10.8843(6) Å, *c*=12.5148(7) Å, *V*=833.1(1) Å^3, *Z*=2, *Dc*=1.29 mg m^{-3}, *T*=298 K, final *R*=0.032, final *Rw*=0.045. Details of the crystal structure determination have been deposited at the Cambridge Crystallographic Data Centre (deposition number CCDC137179).
14. (*S*)-**9** has the following physical data: mp 129°C; $[\alpha]_D^{20}=+30.5$ (c=2.7 in D_2O); ^{1}H NMR ($CDCl_3$) δ=1.08 (s, 3H, 4-C*H*$_3$), 1.14 (s, 3H, 4-C*H*$_3$), 1.34 (s, 3H, 3-C*H*$_3$), 3.08 (br, 1H, O*H*), 3.92 (d, J=8.7 Hz, 1H, 5-HC*H*), 4.08 (d, J=8.7 Hz, 1H, 5-HC*H*); ^{13}C NMR ($CDCl_3$) δ=19.6 ($C_3(CH_3)$), 20.4 ($C_4(CH_3)$), 20.5 ($C_4(CH_3)$), 42.5 (C_4), 76.6 (C_3), 77.7 (C_5), 180.6 (CO).
15. The diastereoisomeric composition was determined for the crude product from the NMR spectra ($CDCl_3$) by integration of the α-methyl signal of the pantolactonyl moiety of the pair of diastereoisomers and/or by HPLC (Chiraspher column (Merck)).
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