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Selective Ammonolysis and Aminolysis of Dimethyl Succinate. Synthesis of Optically Active *N*-Alkylsuccinimides

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Abstract: *Candida antarctica* lipase catalyzes the selective monoammonolysis and aminolysis of dimethyl succinate with ammonia and aliphatic amines, respectively, in dioxane as solvent. This enzyme shows a high enantioselectivity when racemic amines are used. Optically active amidoesters are also obtained in the reaction of dimethyl succinate with racemic α -methylalkylamines in hexane as solvent. In this medium, the enzyme catalyzes the formation of *N*-alkylsuccinimides or optically active *N*-alkyl- α -methylsuccinimides from dimethyl succinate or α -methylsuccinate and amines.

INTRODUCTION

Presently, it is well established that lipase-catalyzed aminolysis of esters is an useful reaction in organic synthesis, this method being a complement or alternative to other more usual as the enzymatic hydrolysis, esterification and transesterification processes.¹ This methodology has the advantage of the irreversibility because of the low protease activity of the lipases. Moreover, the formation of amide bond is always an operation of synthetic utility due, in some cases, to the difficulty to obtain these compounds in mild conditions and, in general, for the ubiquity of the amide group in bioactive compounds.²

Recently, we have demonstrated that the lipase from *Candida antarctica* efficiently catalyzes the ammonolysis of β -ketoesters³ and α,β -unsaturated esters.⁴ Other authors⁵ have shown that ammonia also can be used to the resolution of some esters with more satisfactory results than in the corresponding hydrolysis.

In this work we have investigated the potential of *Candida antarctica* lipase (CAL) to catalyze the aminolysis and ammonolysis of dimethyl succinate and α -methylsuccinate. Optically active derivatives of succinic esters are valuable synthetic intermediates of biological active compounds.⁶ In addition, a simple enzymatic method to achieve *N*-alkylsuccinimides is reported too, these compounds having importance as herbicides and plant growth regulators.⁷

RESULTS AND DISCUSSION

The ammonolysis of dimethyl succinate is carried out at 30 °C using a 2% solution of ammonia in

dioxane in presence of *Candida antarctica* lipase. After 31 h, the corresponding amidoester **3a** is isolated as the sole product of the reaction in very high yield (Table 1).

This lipase also catalyzes the selective monoaminolysis of dimethyl succinate when aliphatic amines such as butyl, allyl and benzylamine are used. In these cases the reactions are carried out at 30°C using an equimolecular amount of diester and amine, and dioxane as solvent. In these conditions, the reactions happen with total selectivity, with percentages of conversion in amidoesters **3b-d** >95%, in such a way that further steps of purification are not necessary.

If the aminolysis reactions are conducted in hexane, longer reaction times are necessary to get similar values of conversions, and a mixture of products containing compound **3** (**3b**, 62%; **3c**, 60%; **3d**, 32%) and *N*-alkylsuccinimide (**4**) is obtained (see Scheme 1 and Table 1). The formation of compounds **4** probably takes place by heterocyclization of the amidoester **3**, with a nucleophilic role of the amide nitrogen. The ammonolysis reaction could not be carried out in hexane because of the low solubility of ammonia in this solvent.

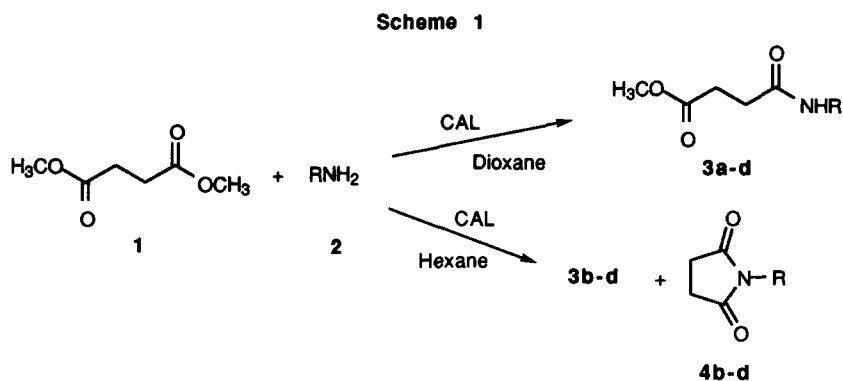


Table 1. Ammonolysis and aminolysis of dimethyl succinate catalyzed by CAL

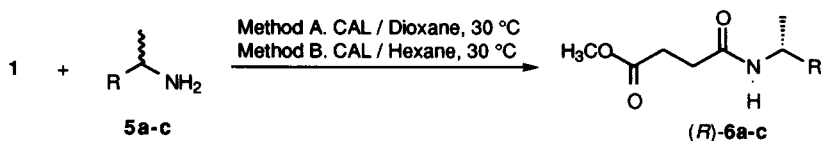
Product	R	Reaction time, h	Yield, %	mp, °C	Product	R	Reaction time, days	Yield, %	mp, °C
3a^a	H	31	92	72-74	4b^b	Butyl	7	35	oil
3b^a	Butyl	48	96	oil	4c^b	Allyl	7	30	oil
3c^a	Allyl	24	95	oil	4d^b	Benzyl	8	44	97-99
3d^a	Benzyl	48	98	58-60					

^a Solvent: dioxane. ^b Solvent: hexane; amidoesters **3** are also obtained: see text

In order to investigate the enantioselectivity of the lipase in this kind of processes, aminolysis of dimethyl succinate is carried out with some racemic amines, α -methylpropyl (**5a**), α -methylhexyl (**5b**) and α -methylbenzylamine (**5c**), using both dioxane and hexane as solvents (Scheme 2, Table 2). In both organic media the enzyme shows the same stereochemical preference towards the *R* enantiomer of the amine, the corresponding amidoesters **6** being obtained with high enantiomeric excesses, especially if dioxane is used as

solvent (method A). The aminolysis of dimethyl succinate in hexane (method B) is again more slow than it is in dioxane, although the enzyme does not catalyze in any case the heterocyclization of amidoesters **6**, in contrast to the aminolysis with achiral amines **2** in hexane (*vide infra*). This fact suggests that the presence of the methyl group in the α -position to the amide nitrogen in compounds **6** hinders the adequate fitting of the amidoester in the catalytic site of the enzyme, precluding in this way the subsequent cyclization.

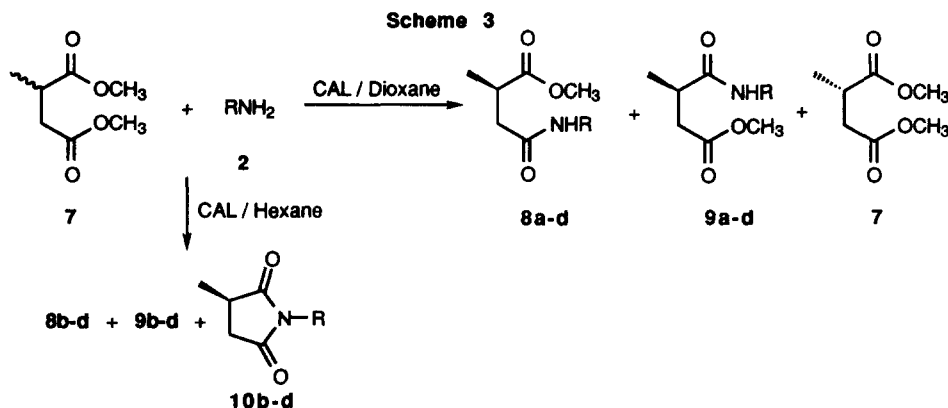
Scheme 2

Table 2. Aminolysis of **1** with racemic amines (**5**) catalyzed by CAL

Product	R	Method	Reaction time, days	Conv., %	$[\alpha]_D^{22}$ (c CHCl ₃)	ee, %
6a^a	Ethyl	A	1	40	- 5.5 (1.14)	90
6a		B	5	13	- 4.3 (1.40)	70
6b^b	Pentyl	A	2	32	+ 3.7 (1.18)	92
6b		B	9	37	+ 3.8 (1.18)	95
6c^a	Phenyl	A	2	28	+ 70.2 (1.00)	97
6d		B	5	10	+ 50.9 (0.63)	70

^aOil; ^bmp 36-38 °C.

On the other hand, we have also studied the enzymatic aminolysis and ammonolysis of racemic dimethyl α -methylsuccinate **7** (Scheme 3). When dioxane is used as solvent, a mixture of regioisomeric amidoesters **8** and **9** are formed (Table 3). The ratio of regioisomers is determined by ¹H-NMR and by GC. In all cases the aminolysis of the less hindered ester group preferably takes place, affording compounds **8** as the major products. As all attempts to separate the regioisomers failed, we tried to determine the optical purity of the mixture of amidoesters **8** and **9** by ¹H-NMR, using Eu(hfc)₃ as chiral shift reagent. The results are collected in Table 3. However, this method was unsuccessful for the mixture of **8b** and **9b**, whose optical purity was assigned on the basis of the e.e of the remaining ester and the percentage of conversion.⁸ In another attempt to determine the optical purity of these compounds, we have also carried out the heterocyclization of the mixture of regioisomeric amidoesters with NaH in THF. In all cases, the corresponding succinimide **10** was obtained with a high percentage of racemization; as an exception, the mixture **8a:9a** (obtained in the ammonolysis process) yielded the (*R*)- α -methylsuccinimide (**10a**) with 72% e.e.

**Table 3.** Enzymatic ammonolysis and aminolysis of dimethyl α -methylsuccinate (7) in dioxane

2	R	Reaction time, h	Conv., % (8 + 9)	8 : 9 ratio	e.e. (%)		
					8	9	7
a	H	24	42	79 : 21	81	21	47
b	Butyl	48	54	70 : 30	— 49 ^a —		58
c	Allyl	45	48	76 : 24	45	47	42
d	Benzyl	45	51	78 : 22	59	73	61

^a E.e. of the mixture **8b-9b**, calculated from the percentage of conversion and e.e. of **7** (Ref. 8)

In hexane as solvent, the enzyme efficiently catalyzes the aminolysis of the diester **7** with amines **2** displaying a similar behaviour as in the analogous reaction with diester **1** (see Scheme 1 and Scheme 3), that is, in these processes *N*-alkylsuccinimides (**10b-d**) are achieved besides smaller amounts of the corresponding amidoesters **8** and **9**. Compounds **10b-d** are obtained with very good chemical and optical yields, the enzyme showing the same stereochemical preference in all the cases.

Table 4. Enzymatic aminolysis of diester **7** in hexane.

2	R	Reaction time, days	Conv., %	10		8 + 9
				Conv., %	$[\alpha]_D^{22}$ (c, CHCl ₃)	ee, %
b	Butyl	7	45	+ 11.8 (0.95)	99	8
c	Allyl	3	37	+ 13.4 (0.88)	70	17
d	Benzyl	4,5	35	+ 14.4 (1.39)	80	20

It is of note the high enantioselectivity achieved in the formation of **10b-d** in hexane (which probably happens in two steps) in comparison with those observed in the one-step aminolysis of **7** in dioxane (see Table 3 and 4). Although the former step leading to the *N*-alkylsuccinimides **10b-d** in hexane [*i.e.*, monoaminolysis

of diester (\pm)-**7** could take place with low or modest enantioselectivity, this should be big enough to accentuate the enantioselectivity of the latter step (intramolecular amidation). The coupling of two consecutive enantioselective steps has been successfully used to get enantioselectivity enhancement in the resolution of racemic alcohols⁹ and diols.¹⁰

The enantiomeric excesses were determined as follows. Compounds **6c**, **10b**, **10c** and **10d** were determined by ¹H-NMR using Eu(hfc)₃ as chiral shift reagent. For compounds **6a** and **6b** comparison of the optical rotation with an authentical sample prepared from **1** and the corresponding optically active (*R*)-amine. For compound **10a** by comparing of the optical rotation with an optically pure sample obtained by enzymatic ammonolysis of (*R*)-(+)-**7**. The absolute configuration of every compound was established by comparing of the optical rotation with authentical samples prepared from the corresponding optically pure reagent.

CONCLUSION

The enzymatic ammonolysis and aminolysis of dimethyl succinate is a very simple and efficient method to prepare amidoesters, which display optical activity if racemic amines are employed. The biologically interesting *N*-alkylsuccinimides and optically active *N*-alkyl- α -methylsuccinimides are efficiently prepared by enzymatic aminolysis of dimethyl succinate and α -methylsuccinate, respectively, with hexane as solvent. In addition, the method described here opens a new route for the enzymatic preparation of different kind of optically active heterocycles.

EXPERIMENTAL SECTION

General. *Candida antarctica* lipase, SP 435, was gifted by Novo Nordisk Co. All reagents were of commercial quality and were purchased from Aldrich Chemie. Solvents were distilled over an adequate desiccant and stored under nitrogen. Precoated TLC plates silica gel 60 F₂₅₄ from Merck were used, and for column chromatography, Merck silica gel 60/230-400 mesh was used. Mp's were taken using a Gallenkamp apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 1720-X FT Infrared spectrophotometer. ¹H- and ¹³C-NMR were obtained with CDCl₃ as solvent and TMS (tetramethylsilane) as internal standard; using a Bruker AC-200 (¹H- 200 MHz and ¹³C- 50 MHz) spectrometer. Mass spectra were recorded on a Hewlett-Packard 5987 A spectrometer. Microanalyses were performed on a Perkin-Elmer 240B elemental analyser.

General Procedure for the Enzymatic Aminolysis of Diesters. 5 mmol of ester and 5 mmol of amine are added to a suspension of CA lipase (300 mg) in dioxane (20 mL) or hexane (20 mL) under nitrogen atmosphere. The mixture is shaken at 30°C and 250 rpm during the time indicated in Tables. Then, the enzyme is filtered, washed with dichloromethane and the organic solvents are evaporated. The residue is subjected to column chromatography using hexane-ethyl acetate 1:1 as eluent.

Methyl 3-carbamoylpropanoate (3a): IR (nujol) 1742 cm⁻¹; ¹H NMR δ 2.40-2.85 (m, 4H, 2CH₂), 3.71 (s, 3H, CH₃), 5.82 (bs, 2H, NH₂); ¹³C NMR δ 28.93 (CH₂), 30.02 (CH₂), 51.82 (CH₃), 173.44

(C=O), 174.29 (C=O); MS (70 eV) m/z 131 (M^+ , 3), 88 (100). Anal. Calcd. for $C_5H_9NO_3$: C, 45.80; H, 6.92; N, 10.68. Found: C, 45.71; H, 7.05; N, 10.59.

Methyl 3-(N-butylcarbamoyl)propanoate (3b): IR (neat) 1740 cm^{-1} ; 1H NMR δ 0.93 (t, 3H, CH_3), 1.19-1.65 (m, 4H, $2CH_2$), 2.47 (t, 2H, CH_2), 2.68 (t, 2H, CH_2), 3.25 (q, 2H, CH_2), 3.70 (s, 3H, CH_3), 5.73 (bs, 1H, NH); ^{13}C NMR δ 13.29 (CH_3), 19.60 (CH_2), 28.99 (CH_2), 30.32 (CH_2), 31.12 (CH_2), 38.86 (CH_2), 51.27 (CH_3), 171.21 (C=O), 173.10 (C=O); MS (70 eV) m/z 187 (M^+ , 2), 115 (100). Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.61; H, 9.03; N, 7.36.

Methyl 3-(N-allylcarbamoyl)propanoate (3c): IR (neat) 1730 cm^{-1} ; 1H NMR δ 2.43-2.81 (m, 4H, $2CH_2$), 3.68 (s, 3H, CH_3), 3.88 (m, 2H, CH_2), 5.16 (m, 2H, CH_2), 5.83 (m, 1H, CH), 6.18 (bs, 1H, NH); ^{13}C NMR δ 28.52 (CH_2), 29.79 (CH_2), 41.15 (CH_2), 51.04 (CH_3), 114.99 (CH_2), 133.62 (CH), 171.27 (C=O), 172.82 (C=O); MS (70 eV) m/z 171 (M^+ , 1.5), 56 (100). Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.18; H, 7.73; N, 8.06.

Methyl 3-(N-benzylcarbamoyl)propanoate (3d): IR (nujol) 1728 cm^{-1} ; 1H NMR δ 2.51 (t, 2H, CH_2), 2.70 (t, 2H, CH_2), 3.68 (s, 3H, CH_3), 4.43 (d, 2H, CH_2), 6.03 (bs, 1H, NH), 7.31 (m, 5H, Ph); ^{13}C NMR δ 29.02 (CH_2), 30.50 (CH_2), 43.23 (CH_2), 51.54 (CH_3), 127.10 (CH), 127.40 (CH), 128.34 (CH), 138.11 (C), 171.22 (C=O), 173.27 (C=O); MS (70 eV) m/z 221 (M^+ , 2), 91 (100). Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.20; H, 6.76; N, 6.40.

N-Butylsuccinimide (4b): IR (neat) 1697 cm^{-1} ; 1H NMR δ 0.91 (t, 3H, CH_3), 1.30 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 2.70 (s, 4H, $2CH_2$), 3.50 (t, 2H, CH_2); ^{13}C NMR δ 13.28 (CH_3), 19.71 (CH_2), 27.78 (CH_2), 29.36 (CH_2), 38.19 (CH_2), 177.08 (C=O); MS (70 eV) m/z 155 (M^+ , 14), 100 (100). Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.80; H, 8.47; N, 9.14.

N-Allylsuccinimide (4c): IR (neat) 1707 cm^{-1} ; 1H NMR δ 2.72 (s, 4H, $2CH_2$), 4.08 (m, 2H, CH_2), 5.08-5.28 (m, 2H, CH_2), 5.62-5.88 (m, 1H, CH); ^{13}C NMR δ 27.91 (CH_2), 40.54 (CH_2), 117.87 (CH_2), 130.46 (CH), 176.64 (C=O); MS (70 eV) m/z 139 (M^+ , 100). Anal. Calcd. for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.35; H, 6.40; N, 10.13.

N-Benzylsuccinimide (4d): IR (nujol) 1692 cm^{-1} ; 1H NMR δ 2.70 (s, 4H, $2CH_2$), 4.64 (s, 2H, CH_2), 7.17-7.48 (m, 5H, Ph); ^{13}C NMR δ 28.05 (CH_2), 42.22 (CH_2), 127.83 (CH), 128.48 (CH), 128.76 (CH), 135.61 (C), 176.80 (C=O); MS (70 eV) m/z 189 (M^+ , 100), 91 (47). Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.71; H, 5.77; N, 7.35.

Methyl (R)-3-[N-(1-methylpropyl)carbamoyl]propanoate (6a): IR (neat) 1739 cm⁻¹; ¹H NMR δ 0.90 (t, 3H, CH₃), 1.13 (d, 3H, CH₃), 1.46 (m, 2H, CH₂), 2.39-2.79 (m, 4H, 2CH₂), 3.67 (s, 3H, CH₃), 3.90 (m, 1H, CH), 5.66 (bs, 1H, NH); ¹³C NMR δ 10.03 (CH₃), 19.91 (CH₃), 28.60 (CH₂), 29.16 (CH₂), 30.66 (CH₂), 46.37 (CH), 51.45 (CH₃), 170.83 (C=O), 173.28 (C=O); MS (70 eV) *m/z* 187 (M⁺, <1), 115 (100). Anal. Calcd. for C₉H₁₇NO₃: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.81; H, 9.03; N, 7.57.

Methyl (R)-3-[N-(1-methylhexyl)carbamoyl]propanoate (6b): IR (nujol) 1736 cm⁻¹; ¹H NMR δ 0.88 (t, 3H, CH₃), 1.11 (d, 3H, CH₃), 1.20-1.52 (m, 8H, 4CH₂), 2.36-2.53 (t, 2H, CH₂), 2.58-2.76 (t, 2H, CH₂), 3.69 (s, 3H, CH₃), 3.96 (m, 1H, CH), 5.53 (bs, 1H, NH); ¹³C NMR δ 13.91 (CH₃), 20.79 (CH₃), 22.46 (CH₂), 25.54 (CH₂), 29.40 (CH₂), 31.17 (CH₂), 31.57 (CH₂), 36.75 (CH₂), 45.28 (CH), 51.72 (CH₃), 170.64 (C=O), 173.48 (C=O); MS (70 eV) *m/z* 229 (M⁺, <1), 115 (100). Anal. Calcd. for C₁₂H₂₃NO₃: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.72; H, 10.06; N, 6.19.

Methyl (R)-3-[N-(1-phenylethyl)carbamoyl]propanoate (6c): IR (neat) 1730 cm⁻¹; ¹H NMR δ 1.42 (d, 3H, CH₃), 2.34-2.68 (m, 4H, 2CH₂), 3.61 (s, 3H, CH₃), 5.04 (m, 1H, CH), 5.89 (bs, 1H, NH), 7.11-7.34 (m, 5H, Ph); ¹³C NMR δ 21.49 (CH₃), 28.89 (CH₂), 30.26 (CH₂), 40.30 (CH), 51.29 (CH₃), 125.65 (CH), 126.63 (CH), 128.03 (CH), 143.17 (C), 170.33 (C=O), 173.08 (C=O); MS (70 eV) *m/z* 235 (M⁺, 4), 120 (100). Anal. Calcd. for C₁₃H₁₇NO₃: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.41; H, 7.19; N, 5.84.

(R)-N-Butyl-α-methylsuccinimide (10b): IR (neat) 1705 cm⁻¹; ¹H NMR δ 0.92 (t, 3H, CH₃), 1.18-1.44 (m, 5H, CH₃, CH₂), 1.45-1.66 (m, 2H, CH₂), 2.18-2.42 (m, 1H, CHH), 2.72-3.02 (m, 2H, CH, CHH), 3.49 (t, 2H, CH₂); ¹³C NMR δ 13.34 (CH₃), 16.52 (CH₃), 19.75 (CH₂), 29.46 (CH₂), 34.32 (CH), 36.10 (CH₂), 38.25 (CH₂), 176.33 (C=O), 180.46 (C=O); MS (70 eV) *m/z* 169 (M⁺, 10), 114 (100). Anal. Calcd. for C₉H₁₅NO₂: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.90; H, 8.84; N, 8.35.

(R)-N-Allyl-α-methylsuccinimide (10c): IR (neat) 1709 cm⁻¹; ¹H NMR δ 1.35 (d, 3H, CH₃), 2.20-2.47 (m, 1H, CHH), 2.73-3.06 (m, 2H, CH, CHH), 4.08 (m, 2H, CH₂), 5.06-5.29 (m, 2H, CH₂), 5.65-5.91 (m, 1H, CH); ¹³C NMR δ 16.66 (CH₃), 34.56 (CH), 36.29 (CH₂), 40.70 (CH₂), 118.02 (CH₂), 130.60 (CH), 175.89 (C=O), 180.02 (C=O); MS (70 eV) *m/z* 153 (M⁺, 100). Anal. Calcd. for C₈H₁₁NO₂: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.62; H, 7.31; N, 9.05.

(R)-N-Benzyl-α-methylsuccinimide (10d): IR (neat) 1696 cm⁻¹; ¹H NMR δ 1.30 (d, 3H, CH₃), 2.14-2.45 (m, 1H, CHH), 2.70-3.07 (m, 2H, CH, CHH), 4.60 (s, 2H, CH₂), 7.30 (m, 5H, Ph); ¹³C NMR δ 16.40 (CH₃), 34.47 (CH), 36.14 (CH₂), 42.07 (CH₂), 127.63 (CH), 128.44 (CH), 135.66 (C), 175.89 (C=O), 180.02 (C=O); MS (70 eV) *m/z* 203 (M⁺, 100), 91 (53). Anal. Calcd. for C₁₂H₁₃NO₂: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.01; H, 6.56; N, 6.85.

General Procedure for the Heterocyclization of 8 and 9. To a solution of the mixture of regioisomers **8** and **9** (1 mmol) in THF (40 ml) is added NaH (1.5 mmol, 36 mg). The reaction mixture is heated at 70 °C under nitrogen during 2.5 h. Then, the solvent is evaporated and the solid residue is extracted with dichloromethane. The evaporation of the solution affords the corresponding compound **10b-d**. To isolate compound **10a**, before the evaporation of the solvent, acetic acid (1.5 mmol) is added to the reaction mixture.

(R)- α -Methylsuccinimide (10a): mp, 56-58°C, $[\alpha]_D^{22} +19.2$ (c, 0.70, CHCl₃), 72% e.e., IR (nujol) 1715 cm⁻¹; ¹H NMR δ 1.34 (d, 3H, CH₃), 2.24-2.54 (m, 1H, CHH), 2.81-3.14 (m, 2H, CH, CHH), 8.90 (bs, 1H, NH); ¹³C NMR δ 16.43 (CH₃), 36.06 (CH), 37.49 (CH₂), 176.71 (C=O), 180.98 (C=O); MS (70 eV) *m/z* 113 (M⁺, 56), 42 (100). Anal. Calcd. for C₅H₇NO₂: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.15; H, 6.16; N, 12.49.

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