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An Efficient Method for Hydrolysis of *N*-Monosubstituted Amides Utilization of Intramolecular N–O Acyl Migration in Hydroxypivalimides

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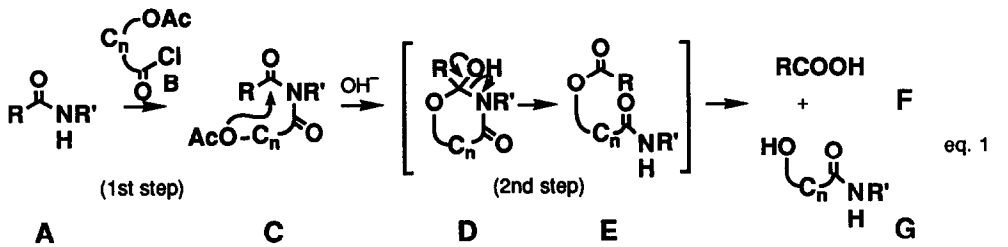
Abstract *: An efficient and versatile method for the hydrolysis of* N*-monosubstituted carboxamides has been developed. The method consists of two steps: the conversion to acetoxypivalimides (≥90% yield) and their mild alkaline hydrolysis (70~90% yield). No epimerization at the α-position of the acyl group took place in the process. The amine part of the original amides can be recovered in good yield.*

The classical procedures for the hydrolysis of amide linkage require severe conditions (strong bases or acids, and elevated temperatures) incompatible with substrates containing acid- or base-sensitive groups.[1] In order to overcome this limitation, a number of highly efficient methods has been developed for the hydrolysis of *N*-nonsubstituted and *N*,*N*-disubstituted amides.[2] For *N*-monosubstituted amides, however, the presently available methods seem to still suffer from serious limitations.[3] Recently, Grieco *et al.* have converted *N*-monosubstituted amides to *t*-butoxycarboximides which, on mild alkaline hydrolysis, yielded the desired carboxylic acids.[4] Sonnet has also reported a two-step procedure in which a β-hydroxyethyl group was introduced to the amide nitrogen and then the resulted amides were hydrolyzed smoothly under acidic conditions as the consequence of N–O acyl migration.[5] In the course of our study that required the hydrolysis of *N*-monosubstituted amides without epimerization at α-position of the acyl groups,[6] we had to develop a new method because both the Grieco and Sonnet methods were found unsatisfactory for our objective.[7] In this paper, we present an efficient and versatile process for hydrolysis of *N*-monosubstituted amides under mild conditions.[8]

General Strategy

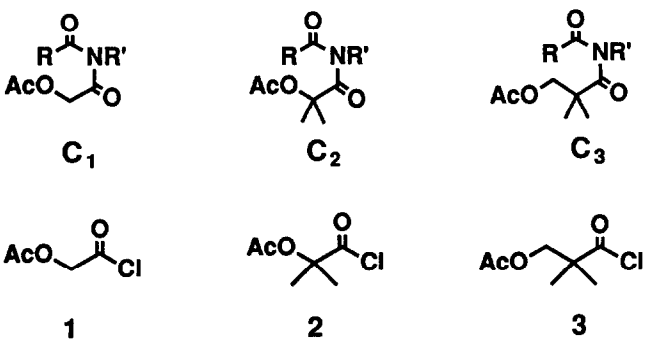
In planning a new hydrolysis methodology, we had in our mind two principles, *i.e.* i) much faster hydrolysis of imides than of amides, and ii) intramolecular nucleophilic attack of oxygen to carbonyl carbon and the subsequent C–N bond cleavage (N–O acyl migration). The logical consequence is shown in eq. 1.



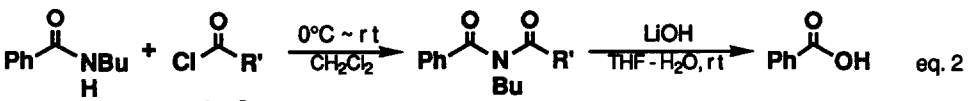
The original amides **A** are acylated with acetoxyacyl chlorides **B** to the corresponding imides **C** in the 1st step. In the 2nd step, the intramolecular nucleophilic attack of the alkoxide group produced by the hydrolysis of the acetoxy group in **C** attacks the carbonyl group of the original amides to form the esters **E** through the cyclic intermediates **D**. Finally, the esters **E** are hydrolyzed to the desired acids **F** and hydroxycarboxamides **G**. By adjusting the length of the carbon chain in **B**, the nucleophilic attack of the alkoxide group would be directed preferentially to the desired carbonyl group.

Selection of Acetoxyacyl Chlorides B

For the chain length in the acetoxyacyl group in the imides **C**, we considered $(CH_2)_1$ (acetoxyacetyl) and $(CH_2)_2$ (acetoxypropanoyl) in order for the hydrolysis to proceed through the 5-membered and 6-membered intermediates **D**,[9] respectively, and also two *gem*-methyl groups at α-position to avoid intermolecular hydrolysis at the undesired carbonyl group and to direct both desired reaction centers in the proper positions for the steric reason (cf. C_1, C_2 and C_3). Thus, the three acylchlorides, **1**,[10] **2**,[11] and **3**,[12] were selected.



Using *N*-butylbenzamide (**4**), the efficiency of the three acid chlorides **1**, **2** and **3**, was compared (eq. 2). The benzamide **4** was treated with an excess of **1**, **2** or **3** in CH_2Cl_2 at 0 °C~rt in the presence of an equivalent amount of pyridine or triethylamine and a catalytic amount of *N*, *N*-dimethylaminopyridine (DMAP). The result is shown in Table I.



5 R' : -CH_2OAc
6 R' : -$C(Me)_2OAc$
7 R' : -$C(Me)_2CH_2OAc$

Table I Hydrolysis of *N*-Butylbenzamide (**4**).

Entry	Acid chloride	1st step (Acylation)					2nd step (Hydrolysis)		
		Base	Temp.	Time (hr)	Imides	Yield (%)	Base	Time (hr)	Yield (%)
1	**1** (3eq)	Pyridine (3eq) DMAP (0.1eq)	0 °C	20	**5**	55	LiOH (2 2eq)	20	28
2	**2** (5eq)	Et_3N (5eq) DMAP (0.2eq)	rt	20	**6**	14	LiOH (4eq)	41	72
3	**3** (3eq)	Et_3N (3eq) DMAP (0.1eq)	rt	19	**7**	99	LiOH (2.2eq)	19	87

While 3 mol equivalents of **1** gave the corresponding imide **5** in moderate yield after 20 h (entry 1), **2** gave the imide **6** only in low yield even with a much larger excess of the reagents (entry 2). Steric hindrance may be responsible for the low yield. By far the best result was obtained with **3**, which gave the imide **7** in excellent yield after 19 h with 3 mol eqivalents of **3** and triethylamine (entry 3).

The imides **5~7** were then hydrolyzed in aq. THF at room temperature using 2 mol equivalents of LiOH. After 19 h, **7** gave benzoic acid (**8**) in 87% yield (entry 3), while **5** suffered from reduced selectivity (entry 1).[13] The reaction of **6** was much slower and needed twice as much base and a longer reaction period to produce **8** in reasonable yield (entry 2). The result clearly indicates that the formation of the 6-membered intermediate **D** is easier than that of the 5-membered counterpart, and that as expected *gem*-dimethyl groups at α-position are needed for successful hydrolysis. From these experiments, acetoxypivaloyl chloride (**3**) was concluded to be the reagent of choice for further elaboration of our methodology.

Scope of Reaction Sequence

The reaction sequence was applied to various *N*-monosubstituted amides under the standard conditions described above (eq. 3). The result is shown in Table II.

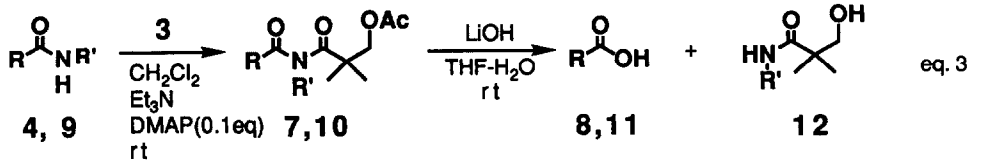


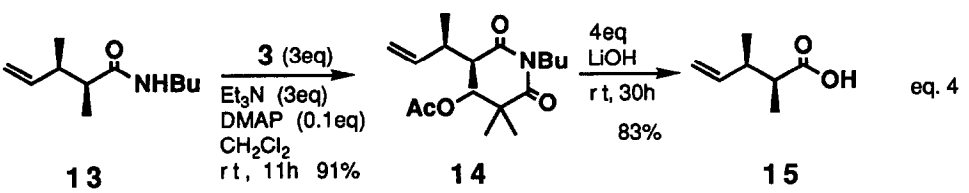
Table II Hydrolysis of Various *N*-Monosubstituted Amides.

Entry	Amides			3 and	1st step (Acylation)			2nd step (Hydrolysis)		
		R	R'	Et_3N	Period (h)	Imides	Yield (%)	Period (h)	Acids	Yield (%)
1	**9a**	n-Pent	n-Bu	2 eq	0.75	**10a**	91	19	**11a**	74
2	**9b**	c-Hex	n-Bu	2 eq	2.5	**10b**	89	19	**11b**	87 [a]
3	**9c**	c-Hex	$PhCH_2$	2 eq	6	**10c**	90	24	**11b**	73
4	**4**	Ph	n-Bu	3 eq	19	**7**	99	17	**8**	87
5	**9d**	c-Hex	1-Phenethyl	5 eq	8	**10d**	92	24	**11b**	89

a. The original amide **9b** was recovered in 10% yield.

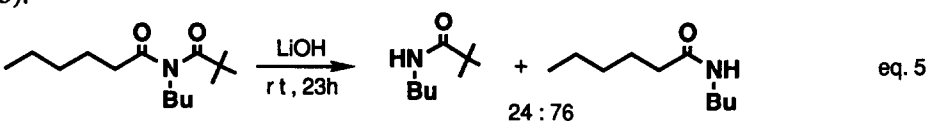
Although the amount of the acid chloride **3** and triethylamine, and the reaction period vary from one substrate to another, the acylation reaction (1st step) monitored by TLC gives the desired imides in 89% or better yields at room temperature in the presence of 0.1 mol equivalent of DMAP for straight-chain (entry 1), branched-chain aliphatic (entries 2, 3) and aromatic (entry 4) acid derivatives of butyl- or benzylamines. The sterically hindered amides, *e.g. N*-1-phenethylcyclohexanecarboxamide (**9d**), can also be acylated smoothly with a large excess of acylating reagents (entry 5). For the 2nd step, the standard procedure also monitored by TLC worked nicely to a wide variety of the carboximides **7** and **10,** and the desired carboxylic acides **8** or **11** were obtained in 70% or better yields (often nearly 90% yield).

In order to test the mildness of the hydrolytic conditions, (2*S**,3*R**)-*N*-butyl-2,3-dimethylpent-4-enamide (**13**) (syn:anti=99.5:0.5)[6] was subjected to the reaction sequence (eq. 4). The carboxylic acid **15** obtained in 76% overall yield through **14** showed practically no indication of epimerization during the reactions (syn:anti=99.2:0.8).



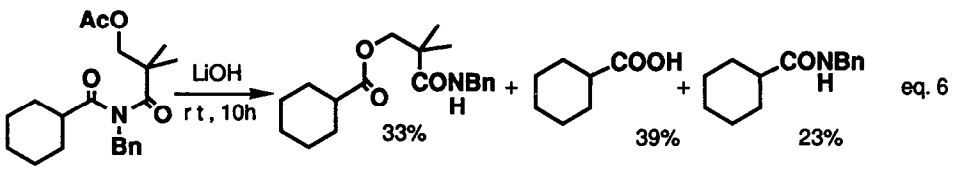
The importance of the neighboring group participation in the 2nd step was verified by the following reaction. *N*-Butyl-*N*-hexanoylpivalamide (**16**), statically very similar to **10a** but lacking the crucial oxygen function, gave a 24:76 mixture of *N*-butylpivalamide (**17**) and

N-butylhexanamide (**18**) under the same conditions (2 mol eq. LiOH, rt, 23 h) as in entry 1, Table II, disclosing that steric hindrance did not protect the pivaloyl carbonyl group but rather prevented the hexanoyl carbonyl group from the attack of hydroxide and, therefore, that the increase in bulkiness of acylchloride alone is not essential to the desired hydrolysis (eq. 5).



16 **17** **18**

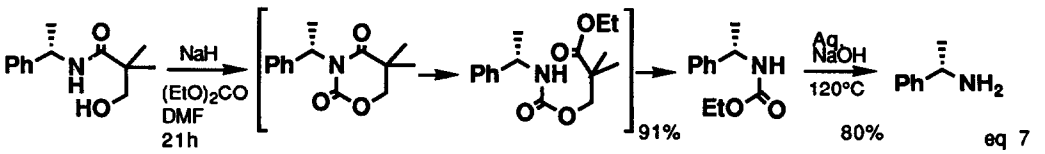
Furthermore, when the hydrolysis of *N*-benzyl-*N*-(cyclohexanecarbonyl)acetoxypivalamide (**10c**) (entry 3, Table II) was quenched after 10 h, *N*-benzylcyclohexanecarboxypivalamide (**19**), the rearrangement product, was isolated in 33% yield along with the desired and undesired hydrolysis products **11b** and **9c**, respectively (eq. 6). This is the convincing evidence for the intervening N–O acyl migration.



10c **19** **11b** **9c**

Recovery of Amines.

The recovery of amines from the by-product **12** is often necessary, especially when chiral amines are used in asymmetric synthesis. We tried to isolate (1*S*)-phenethylamine (**23**) from (1*S*)-*N*-(1-phenethyl)hydroxypivalamide (**12a**), the by-product corresponding to **G** in the hydrolysis of (1'*S*, 2*R*, 3*S*)-*N*-(1'-phenethyl)-2,3-dimethylpent-4-enamide.[14] While heating of **12a** with a large excess of NaOH in ethylene glycol at 180 °C induced no reaction, the hydrolytic conditions with 6 M HCl at 100 °C gave styrene dimer in good yield.[15] Thus, we developed a new two-step procedure for the hydrolysis of **12a** as shown in eq. 7.



12a **20** **21** **22** **23**

The amide **12a** was converted to the carbamate **22** in 91% yield by the reaction with diethyl carbonate (1.4 eq) and NaH (2.8 eq) in DMF at room temperature for 21 h. Since the

carbamate **21** was isolated in 27% yield along with **22** (18% yield) and the starting amide **12a** (42% yield) when the reaction was stopped after 30 min, it was clear that the reaction proceeded *via* the cyclic and acyclic carbamates **20** and **21**. The carbamate **22** was smoothly hydrolyzed with 12 M NaOH (large excess) at 120 °C to give (1*S*)-1-phenethylamine **23** in 80% yield. The optical purity of **23** was perfectly retained.

EXPERIMENTAL

General

IR spectra were measured with either neat liquid films or KBr pellets on a JASCO IRA-2 or IR-260-10 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL FX90Q (90 MHz) or a Varian XL-200 (200 MHz) in $CDCl_3$. Mass spectra (MS) were obtained using electron impact at 70, 25, 15, or 13.5 eV on a Hitachi M-52 or a Shimadzu LKB-9000B. All the melting points were determined on a Yanaco MP-3 apparatus and are uncorrected. Optional rotations were measured on a Perkin-Elmer 141 or a JEOL DIP-140 polarimeter using 10 cm microcell. Gas chromatographic analyses were performed on a Shimadzu GC-14A gas chromatograph equipped with a flame ionization detector and CBP1 or CBP10 fused silica capillary column (HiCap CBP1 or HiCap CBP10), 25 m x 0.2 mm i.d., film thickness 0.25 μm. Peak areas were measured by electronic integration on a Shimadzu C-R5A chromatopac. Elemental analyses were performed at the Instrumental Analysis Center of Tohoku University or Tokushima Bunri University.

In general, solvents of reagent grade were used. Tetrahydrofuran (THF) was distilled prior to use under argon atmosphere over sodium/benzophenoneketyl. *N,N*-Dimethylformamide (DMF) was distilled over CaH_2 under reduced pressure. Dichloromethane, triethylamine and pyridine were distilled over CaH_2 under argon. Analytical thin layer chromatography (TLC) was performed on precoated Merck silica-gel 60 F-254 glass plates (0.2 mm layers) with fluorescent indicator. For column chromatography Merck silica-gel 60 (70-230 mesh) was used.

Preparation of Imides. General Procedure.

To a 0.5 M solution of carboxamide (6 mmol) in dry CH_2Cl_2 were successively added the required amounts of triethylamine (or pyridine), DMAP and the acid chlorides at 0 °C under argon atmosphere. After the reaction was completed (monitored by TLC), the resulting mixture was poured into 1 M HCl aq. (30 mL) and extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were washed with saturated $NaHCO_3$ aq. and dried over Na_2SO_4. Removal of the solvent *in vacuo* followed by column chromatography (hex-AcOEt as eluents) gave the desired imides.

N-*Benzoyl*-N-*butylacetoxyacetamide (5)*. Obtained in 55% yield as a colorless oil: IR (neat) 1760, 1725, 1700 cm^{-1}; ^{1}H NMR δ 7.8-7.3 (5H, m), 4.94 (2H, s), 3.72 (2H, t-like), 2.16 (3H, s), 1.74-0.98 (4H, m), 0.78 (3H, t, J=6.6); MS m/z 277 (M^+), 105 (base). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.69; H, 6.90; N, 5.20.

N-*Benzoyl*-N-*butyl-2-acetoxy-2-methylpropanamide (6)*. Obtained in 14% yield as a colorless oil: IR (neat) 1750, 1690 cm^{-1}; ^1H NMR δ 7.8 (2H, m), 7.5 (3H, m), 3.61 (2H, t-like), 1.74 (6H, s), 1.71 (3H, s), 1.54-0.98 (4H, m), 0.83 (3H, t, J=6.5); MS m/z 305 (M^+), 105 (base). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.70; H, 7.62; N, 4.43.

N-*Benzoyl*-N-*butyl-3-acetoxy-2,2-dimethylpropanamide (7)*. Obtained in 99% yield as a colorless oil: IR (neat) 1740, 1695 cm^{-1}; ^1H NMR δ 7.8-7.35 (5H, m), 4.20 (2H, s), 3.56 (2H, t-like), 2.06 (3H, s), 1.7-1.0 (4H, m), 1.31 (6H, s), 0.84 (3H, t, J=6.8); MS m/z 319 (M^+), 143 (base), 115. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.33; H, 7.85; N, 4.30.

N-*Butyl*-N-*hexanoyl-3-acetoxy-2,2-dimethylpropanamide (10a)*. Isolated in 91% yield as a colorless oil: IR (neat) 1755, 1690 cm^{-1}; ^1H NMR δ 4.18 (2H, s), 3.56 (2H, t-like), 2.44 (2H, t, J=7.2), 2.03 (3H, s), 1.9-1.2 (10H, m), 1.32 (6H, s), 0.94 (3H, t, J=7.3) 0.91 (3H, t, J=6.4); MS m/z 314 (M^++1), 198, 143 (base), 115. Anal. Calcd for $C_{17}H_{31}NO_4$: C, 65.14; H, 9.97; N, 4.47. Found: C, 65.01; H, 9.79; N, 4.62.

N-*Butyl*-N-*cyclohexanecarbonyl-3-acetoxy-2,2-dimethylpropanamide (10b)*. Obtained in 89% yield as a colorless oil: IR (neat) 1750, 1680 cm^{-1}; ^1H NMR δ 4.17 (2H, s), 3.54 (2H, t-like), 2.50 (1H, m), 2.04 (3H, s), 2.0-1.1 (14H, m), 1.31 (6H, s), 0.94 (3H, t, J=6.5); MS m/z 326 (M^++1), 325(M^+), 210, 197, 143 (base). Anal. Calcd for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N, 4.30. Found: C, 66.20; H, 9.80; N, 4.25.

N-*Benzyl*-N-*cyclohexanecarbonyl-3-acetoxy-2,2-dimethylpropanamide (10c)*. Isolated in 90% yield as a colorless crystal, m.p. 46-47 °C: IR (KBr) 1745, 1685 cm^{-1}; ^1H NMR δ 7.28 (5H, br s), 4.81 (2H, s), 4.17 (2H, s), 2.54 (1H, m), 1.94 (3H, s), 1.8-1.1 (10H, m), 1.32 (6H, s); MS m/z 359 (M^+), 248 (base), 216, 143. Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.16; H, 8.16; N, 3.90.

N-*Cyclohexanecarbonyl*-N-*(1-phenethyl)-3-acetoxy-2,2-dimethyl-propanamide (10d)*. Obtained in 92% yield as colorless needles, m.p. 77 °C: IR (KBr) 1740, 1670 cm^{-1}; ^1H NMR δ 7.5-7.2 (5H, m), 5.26 (1H, q, J=7.3), 4.17 (1H, d, J=10.8), 4.09 (1H, d, J=10.8), 2.24 (1H, m), 2.03 (3H, s), 1.74 (3H, d, J=7.3), 1.85-0.8 (10H, m), 1.29 (3H, s), 1.26 (3H, s); MS m/z 374(M^++1) 231, 105 (base); Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.48; H, 8.34; N, 3.59.

***(2S*,3R*)*- N-*Butyl*-N-*2,3-dimethylpent-4-enoyl-3-acetoxy-2,2-dimethyl-propanamide (14)*.** Obtained in 91% yield as a colorless oil: IR (neat) 3040, 1745, 1675 cm^{-1}; ^1H NMR δ 5.81 (1H, ddd, J=17.2, 10.8, 7.6), 5.05 (1H, br.d, J=17.2), 5.02 (1H, br d, J=10.8), 4.19 (2H, s), 3.57 (2H, t-like), 2.52 (2H, m), 2.04 (3H, s), 1.8-1.0 (4H, m), 1.36 (3H, s), 1.33 (3H, s), 1.18 (3H, d, J=6.5), 1.04 (3H, d, J=6.5), 0.94 (3H, t, J=6.8); MS m/z 325 (M^+), 168, 83, 43 (base). Anal. Calcd for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N, 4.30. Found: C, 66.22; H, 9.61; N, 4.19.

N-*Butyl*-N-*hexanoyl-2,2-Dimethylpropanamide (16)*. Obtained in 94% yield as a colorless oil: IR (neat) 1700 cm^{-1}; ^1H NMR δ 3.56 (2H, t-like), 2.41 (2H, t, J=7.9), 1.8-1.2

(10H, m), 1.30 (9H, s), 1.0-0.8 (6H, m); MS m/z 255(M^+), 198, 142, 115(base), 99, 71. Anal. Calcd for $C_{15}H_{29}NO_2$: C, 70.54; H, 11.45; N, 5.48. Found: C, 70.69; H, 11.71; N, 5.36.

Hydrolysis of Imides. General Procedure.

To a solution of imides (1.5 mmol) in THF (7.5 mL) was added a 1 M aqueous solution of LiOH (3.3 mL, 2.2 eq) and the mixture was stirred at ambient temperature. The reaction was monitored by TLC. After the reaction was completed, the mixture was poured into a 1 M NaOH aq (30 mL) and extracted with CH_2Cl_2 (10 mL x 3). The organic extracts were dried (K_2CO_3), and evaporated to give the starting amides **4** or **9** and the hydroxy-carboxamides **12**. The aqueous layer was acidified with 2 M HCl aq (25 mL) and extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography (hexane-AcOEt) to yield the desired acids. Acids obtained were identified by IR, ^1H NMR and MS.

(2S*,3R*)-2,3-Dimethylpent-4-enoic acid (15). Obtained in 83% yield as a colorless oil starting from **14** (syn:anti=99.5:0.5).[6] The syn/anti ratio (99.2:0.8) was determined by capillary GLC (CBP1, 65 °C) after the esterification with CH_2N_2.

Hydrolysis of* N-*butyl*-N-*hexanoyl-2,2-dimethylpropanamide (16).

To a solution of the imide **16** (129 mg, 0.50 mmol) in THF (2.5 mL) was added an aqueous solution of LiOH (1.0 M, 1.1 mL) and the mixture was stirred for 23 h. The mixture was poured into a 1 M NaOH aq (30 mL) and extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were dried (K_2CO_3) and evaporated to yield 86 mg of a colorless oil. ^1H NMR (200 MHz) of the oil showed it to be a 24:76 mixture of **17** and **18**.

Partial Hydrolysis of* N-*Benzyl*-N-*cyclohexanecarbonyl-3-acetoxy-2,2-dimethylpropanamide (10c).

The standard hydrolysis (*vide supra*) was stopped after 10 hr. The resulting mixture was poured into a 1 M NaOH aq (30 mL) and extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were dried (K_2CO_3) and evaporated. The column chromatography of the resulting residue gave an unseparable oily mixture (233 mg) of the ester **19** (33% yield) and the amide **9c** (23% yield) as determined by ^1H NMR (200 MHz). The aqueous solution was acidified with a 2 M HCl aq (30 mL) and extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were dried ($MgSO_4$), evaporated, and purified by column chromatography to give 75 mg of cyclohexanecarboxylic acid (**11b**) (39% yield).

Synthesis of* N-*Benzyl-3-cyclohexanecarboxy-3,3-dimethylpropanamide (19).

To a pyridine (2.5 mL) solution of *N*-benzyl-3-hydroxy-2,2-dimethylpropanamide (181 mg, 0.87 mmol) was added cyclohexanecarbonyl chloride (1.10 g, 7.48 mmol) with stirring at rt After 2 h, the reaction mixture was poured into 1M HCl aq (30 ml) and extracted with CH_2Cl_2 (10 mL x 3). The combined extracts were dried (Na_2SO_4), evaporated, and purified by column chromatography to afford 222 mg (94% yield) of the ester **19**, colorless needles,

m.p. 64 °C: IR (KBr) 3325, 1725, 1650 cm^{-1}; ^1H NMR δ 7.29 (5H, s), 6.14 (1H, m), 4.44 (2H, d, J=5.5), 4.10 (2H, s), 2.25 (1H, m), 2.0-1.0 (10H, m), 1.23(6H, s); MS m/z 317 (M^+), 206, 106 (base), 91. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.69; H, 8.57; N, 4.37.

Hydrolysis of (1S)-N-1-Phenethyl-3-hydroxy-2,2-dimethylpropanamide (12a).

Reaction of 12a with diethyl carbonate. To a solution of the amide **12a** (779 mg, 3.53 mmol) in dry DMF (7 mL) was added sodium hydride (392 mg, 60% in oil, 9.80 mmol) at 0 °C under argon atmosphere. After 10 min, diethyl carbonate (0.6 mL, 4.95 mmol) was added with a syringe and the mixture was stirred for 21 h at ambient temperature. After 5 mL of a saturated NH_4Cl aq was added, the resulting mixture was poured into 100 mL of water and extracted with ether (50 mL x 4). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and evaporated. The residue was chromatographed to provide the carbamate **22** (617 mg, 91%) as a colorless solid: $[\alpha]_D^{14}$-91.3° (c=1.02, MeOH), m.p. 29-30 °C: IR (KBr) 3300, 1705, 1685 cm^{-1}; ^1H NMR δ 7.31 (5H, br s), 4.85 (2H, m), 4.11 (2H, q, J=7.0), 1.48 (3H, d, J=6.2), 1.22 (3H, t, J=7.0); MS m/z 193 (M^+, base), 178, 164, 120, 106. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.27; H, 7.85; N, 7.05. Found: C, 68.37; H, 7.82; N, 7.25.

Isolation of the intermediate 21. The above reaction with 220 mg (1.0 mmol) of **12a**, 111 mg (2.8 mmol) of NaH and 117 mg (1.4 mmol) of diethyl carbonate was stopped after 0.5 h. The same work-up procedure afforded **21** (79 mg, 27%), **22** (35 mg, 18%) and **12a** (93 mg, 42%). **21**: colorless oil: IR (neat) 3350, 1740, 1725, 1710, 1695 cm^{-1}; ^1H NMR δ 7.31 (5H, br s), 4.9 (2H, m), 4.12 (2H, q, J=6.8), 4.09 (2H, s), 1.47 (3H, d, J=6.6), 1.21 (3H, t, J=6.8), 1.17 (6H, s); MS m/z 293 (M^+), 132, 105 (base). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.78. Found: C, 65.35; H, 7.86; N, 4.55.

Hydrolysis of the carbamate 22. A mixture of **22** (883 mg, 4.57 mmol), NaOH (1.10 g), H_2O (1.2 mL), and ethylene glycol (3.0 mL) was heated at 110 °C for 13 h. The reaction mixture was poured into 2M HCl aq (40 mL) and extracted with ether (100 mL x 1). The ethereal extracts were washed with 1M HCl aq (30 mL x 3). The combined aqueous layer was treated with 6M NaOH aq (adjusted to pH 13) and extracted with CH_2Cl_2 (40 mL x 5). The combined organic extracts were washed with water (20 mL), dried (K_2CO_3), and evaporated to afford (1*S*)-1-phenethylamine (**23**) (444 mg, 80%) as a colorless oil [$[\alpha]_D^{16}$-28.1° (c=3.16, MeOH)] which was identified by comparison with the authentic sample [$[\alpha]_D^{16}$-26.8° (c=3.14, MeOH)].[16)]

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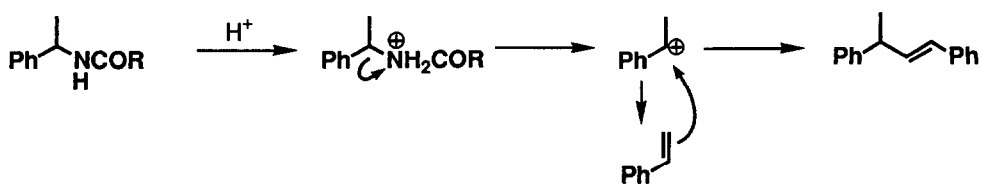

16. The value of **23** (Wako, special grade) used for the experiment.