Synthesis of Nitrogen-Functionalized Cyclohexanes Using Chemoselective Conjugate Addition of Phenyllithium to Linear ω-Nitro-α,β,ψ,ω-Unsaturated Ester and Subsequent Stereoselective Intramolecular Nitro-Michael Cyclization

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Nitrogen-functionalized cyclohexane derivatives with three contiguous chiral centers were synthesized by nitroalkene-selective conjugate addition of phenyllithium to a ω-nitro-α,β,ψ,ω-unsaturated ester and subsequent stereocontrolled intramolecular nitro-Michael cyclization with cesium fluoride and a quaternary ammonium bromide. The cyclohexanes were applicable to the total synthesis of α-, β- and γ-lycoranes.

Key words nitroolefin; conjugate addition; nitro-Michael cyclization; lycorane

The conjugate addition reaction of a carbonucleophile to a nitroalkene[1] has been proven to be one of the powerful methodologies for a carbon–carbon bond formation.[2—14] An organolithium reagent rapidly undergoes the Michael addition to a nitroalkene with reasonably high stereoselectivity[15,16] and were incorporated in the total syntheses of biologically active compounds as the critical step[17,18] As well the nitro-Michael reaction has been attracted much attentions due to its relevance in the strategy of synthetic chemistry.[19—23] Based on these progresses, we designed a synthesis of carbocycles with three contiguous chiral centers by the sequential two reactions of the conjugate addition of a nucleophile to a nitroalkene moiety of a ω-nitro-α,β,ψ,ω-unsaturated ester and subsequent intramolecular Michael addition of a nitronate to an enoate moiety.[24—27] We have been involved in the development of the conjugate addition[28]-based cyclization methodology in these years.[29—35] Described herein is the full details of a new methodology for the construction of nitrogen-functionalized cyclohexanes with three contiguous chiral centers **1** by the sequential nitroalkene-selective conjugate addition of phenyllithium to a ω-nitro-α,β,ψ,ω-unsaturated ester **3** and subsequent stereoselective intramolecular nitro-Michael cyclization of **2** (Chart 1).

Nitroalkene-Selective Conjugate Addition of Phenyllithium The key to our approach sits on the possible chemoselectivity in the conjugate addition of a carbonucleophile to a nitroalkene moiety in the presence of another Michael acceptor, an enoate in the same molecule **3**. We found the chemoselectivity was available from a model reaction. The reaction of one equiv of phenyllithium with a mixture of an equal amount of *trans*-β-nitrostyrene (**4**) and *tert*-butyl *trans*-3-phenylpropenoate (**5**) in an each 0.05 M THF solution at −78 °C for 15 min afforded a nitroalkene-selective conjugate addition product, 2-nitro-1,1-diphenylethane (**6**) in 88% isolated yield, and 95% of **5** was recovered unchanged (Chart 2). This reaction clearly demonstrated that the reactivity of a nitroalkene is superior to an enoate, and a nitroalkene-selective reaction is possible with an organolithium reagent.

Nitroalkene-Selective Conjugate Addition of Phenyllithium to ω-Nitro-α,β,ψ,ω-Unsaturated Ester A ω-nitro-α,β,ψ,ω-unsaturated ester **3** was prepared *via* four steps from **7** in 65% overall yield by the modified procedure developed by Denmark[36] (Chart 3). The Wittig reaction of **7** gave an alcohol **8**, which was then oxidized by the Pfitzner–Moffat method to give a *trans*-aldehyde **9** after chromatographical separation of Z-isomer. The nitro-aldol reaction of **9** with nitromethane was catalyzed by triethylamine giving **10** and was followed by dehydration with trifluoroacetic anhydride and triethylamine to afford **3** in 65% overall yield from **7**.

The reaction of **3** with phenyllithium in a 0.05 M THF solution at −78 °C for 15 min gave a nitroalkene-selective addition product **11** in 91% isolated yield (Table 1, entry 3). The

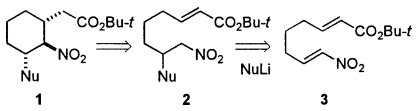

Chart 1. A Synthetic Way to **1** by Nitroalkene-Selective Conjugate Addition of Organolithium to **3** and Nitro-Michael Cyclization of **2**

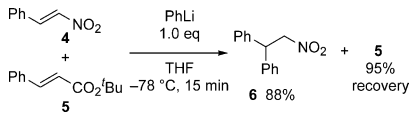

Chart 2. The Nitroalkene-Selective Michael Addition Reaction of Phenyllithium with a Mixture of a Nitroalkene **4** and an Enoate **5**

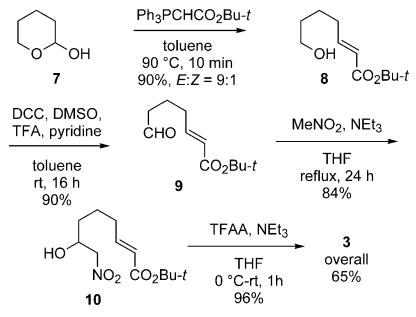

Chart 3. The Four-Step Synthesis of **3** from **7**

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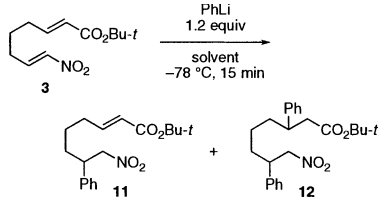
Table 1. The Conjugate Addition of Phenyllithium to **3** in Different Concentrations and Solvents



Entry	Solvent	Concentration (M)	**11** (%)	**12** (%)	**3** (%)
1	THF	1.0	16	16	
2	THF	0.1	77		
3	THF	0.05	91		
4[a)]	THF	0.05	16	16	16
5	DME	0.1	76		
6	*t*-BuOMe	0.1	69		
7	Et_2O	0.1	58		
8	Toluene	0.1	50		
9	Hexane	0.1	0		62

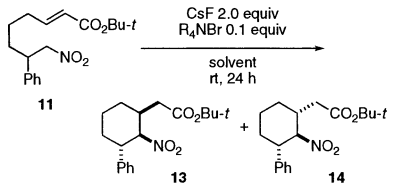
a) A THF solution of **3** was added to a 0.05 M solution of PhLi.

selectivity and chemical yield were highly affected by the concentration of **3**. In the 1.0 M concentration of **3**, the reaction afforded a mixture of **11** (16%) and a double phenylation product **12** in 16% yield (entry 1). A 0.1 M solution gave **11** as a sole product in 77% yield (entry 2). An excess presence of phenyllithium to **3** suffers from the concentration influence, and thus addition of THF solution of **3** to a 0.05 M THF solution of phenyllithium resulted in 16% yield of **11** along with 16% of **12** (entry 4). No observation of an enoate-selective adduct in every conditions indicates the efficient reaction chemoselectivity in THF.

Although THF and dimethoxyethane (DME) were the good solvents for high yields (entries 3, 5), other ethereal solvents, *tert*-butyl methyl ether and diethyl ether were also relatively good solvents, affording chemoselective adduct **11** in 69% and 58% yields, respectively (entries 6, 7). Toluene was a comparable solvent giving **11** in 50% yield (entry 8). Hexane was the inapplicable solvent, recovering **3** in 62% yield (entry 9).

Intramolecular Nitro-Michael Cyclization of 11 An intramolecular nitro-Michael cyclization reaction of **11** was examined using cesium fluoride as a nitronate-generating reagent.[35)] Treatment of **11** with 2.0 eq of cesium fluoride and 0.1 eq of myristyltrimethylammonium bromide in THF at rt for 24 h afforded a 2.3 : 1 mixture of the cyclization products **13** and **14** in 67% combined yield (Table 2, entry 2). Cyclization in dichloromethane gave a highly selective 1 : 11 mixture of **13** and **14** in 62% combined yield (entry 9). Diastereomerically pure all-substituents equatorial **14** was obtained by a nitro-Michael addition in chloroform (entry 10). The reaction in ethanol did not give the product, recovering **11** unchanged (entry 1). Other ammonium bromides were also effective in THF to give a 2 : 1 to 1 : 1.5 mixture in high yield (entries 11—13). It is noteworthy that only two of four possible stereoisomers were observed. The highly selective and specific formation of all equatorial-**14** in methylene chloride and chloroform implies the thermodynamic control is operative in these bromide and fluoride dissolving solvents.

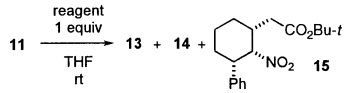
Table 2. The Intramolecular Nitro-Michael Cyclization of **11** with Cesium Fluoride and Ammonium Bromide in Different Solvents



Entry	Solvent	R_4NBr	Yield (%)	**13** : **14** [a)]
1	EtOH	$C_{13}H_{27}Me_3$	0	
2	THF	$C_{13}H_{27}Me_3$	67	2.3 : 1
3	Dioxane	$C_{13}H_{27}Me_3$	90	1 : 1
4	DME	$C_{13}H_{27}Me_3$	73	1 : 1
5	DMF	$C_{13}H_{27}Me_3$	73	1 : 1.3
6	Et_2O	$C_{13}H_{27}Me_3$	70	1 : 1.3
7	MeCN	$C_{13}H_{27}Me_3$	80	1 : 1.4
8	Toluene	$C_{13}H_{27}Me_3$	87	1 : 1
9	CH_2C_{12}	$C_{13}H_{27}Me_3$	62	1 : 11
10	CHC_{13}	$C_{13}H_{27}Me_3$	77	0 : 1
11	THF	Me_4	80	2 : 1
12	THF	Et_4	90	1.3 : 1
13	THF	*n*-Bu_4	97	1 : 1.5

a) Determined by ^{1}H-NMR.

Table 3. Ammonium Bases for the Intramolecular Nitro-Michael Cyclization of **11**.



Entry	Reagent	Time	Yield (%)	**13** : **14** : **15**[a)]
1	Me_4NF	5 min	99	1.4 : 1 : 1
2	Et_4NF	5 min	99	1.5 : 1 : 1.4
3	*n*-Bu_4NF	5 min	99	1.4 : 1 : 1
4	Triton B	5 min	70	1 : 1.3 : 0.9

a) Determined by ^{1}H-NMR.

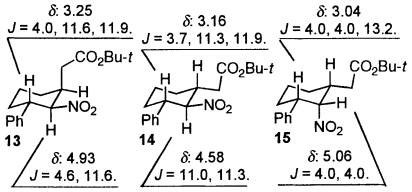


Fig. 1. ^{1}H-NMR of **13**—**15**

Tetraalkylammonium fluorides were found to be more effective to give the cyclization products within 5 min (Table 3). It is interesting to find that the third diastereomer **15** was observed in a comparable yield. Prolonged 24 h reaction with ammonium fluoride gave the same level of diastereoselectivities, indicating that the reactions are kinetically as well as thermodynamically controlled.

Determination of the Stereochemistry of 13—15 The stereochemistry of **13**—**15** was well determined by ^{1}H-NMR (Fig. 1). Vicinal coupling constants of methine protons attached by phenyl and nitro groups indicate that phenyl, nitro and acetate groups are all equatorial in **14**, two are equatorial and one is axial in **13**, and two are equatorial excepting an axial nitro group in **15**.

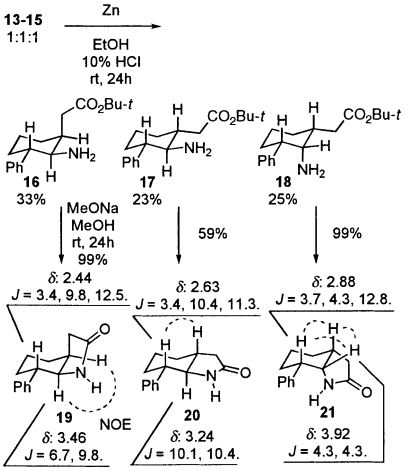


Chart 4. Reduction of a Nitro Group and Lactam Formation.
Hatched Lines Indicate NOE.

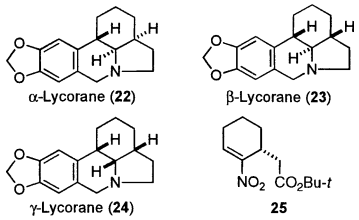


Fig. 2. α-, β-, γ-Lycoranes **22**—**24** and a Cyclonitroalkene **25**

A nitro group of a mixture of an almost equal amount of **13**—**15** was reduced with zinc powder[37] and 10% HCl in ethanol at rt for 24 h gave a mixture of chromatographically easily separable amines **16**, **17** and **18** in 33%, 23% and 25% isolated yields, respectively (Chart 4). Cyclization of **16**—**18** was carried out by treatment with sodium methoxide in methanol at rt for 24 h to give the corresponding lactams **19**, **20** and **21** in 99%, 59% and 99% yields, respectively.

Vicinal coupling constants and NOEs of methine protons of **19**, **20** indicate that phenyl, amino, and acetyl moieties are equatorial, equatorial, and axial in **19**, all equatorial in **20**, and equatorial, axial, and equatorial in **21**, confirming the stereochemical assignments of **13**—**15**. (Fig. 1, Chart 4). The stereochemical pathway in the cyclization is the subject of the future studies.

In conclusion, we have developed the nitroalkene-selective conjugate addition of an phenyllithium to a ω-nitro-α,β,ψ,ω-unsaturated ester and following intramolecular nitro-Michael cyclization for the synthesis of nitrogen-functionalized cycloalkanes with three contiguous chiral centers. We have already accomplished total syntheses of (±)-α-[38,39] and (±)-β-lycoranes (**22**, **23**)[40] using these sequential addition reactions with **3** (Fig. 2).[41] Further application was achieved in the total synthesis of (±)-γ-lycorane (**24**)[39,42—44] by developing a stereoselective conjugate addition of an aryllithium to a cyclic nitroalkene **25**.[45]

Experimental

Combined organic layers for extraction were dried over sodium sulfate, and then concentrated unless otherwise noted. Silica gel column chromatography was carried out for purification. All melting points are uncorrected. NMR (500 or 270 MHz for a proton, 125 or 67.8 MHz for a carbon) was measured in $CDCl_3$. Chemical shift values were expressed in ppm relative to internal tetramethylsilane. *J* values were shown in Hz. The IR spectroscopy was presented in cm^{-1} for the wave numbers of maximum absorption peaks.

2-Nitro-1,1-diphenylethane (6) To a solution of a mixture of *trans*-β-nitrostyrene (**4**, 149 mg, 1.0 mmol) and *tert*-butyl 3-phenylpentenoate (**5**, 204 mg, 1.0 mmol) in THF (20 ml) was added phenyllithium (1.81 M cyclohexane–ether, 0.55 ml, 1.0 mmol) at −78 °C. The mixture was stirred for 15 min, and was then successively treated at −78 °C with methanol (1 ml), sat. NH_4Cl (20 ml), and brine (20 ml). The mixture was extracted with ethyl acetate (20 ml×3). Chromatography (hexane : AcOEt=50 : 1 to 1 : 1) gave 194 mg (95% recovery) of **5** as a colorless oil and 199 mg (88%) of the known **6**[46] as pale yellow crystals of mp 69—70 °C (ethanol). ^{1}H-NMR: 4.81—4.91 (3H, m), 7.16—7.28 (10H, m). ^{13}C-NMR: 48.9, 79.2, 127.5, 127.6, 129.0, 139.2. IR ($CHCl_3$): 1545. MS *m/z*: 227 (M^+), 150 (M^+-Ph).

2,2-Dimethylethyl 7-Hydroxyhept-2-enoate (2*E* : 2*Z*=9 : 1) (8) To a solution of **7** (0.5 g, 4.9 mol) in toluene (10 ml) was added at rt $Ph_3P{=}CHCO_2{}^tBu$. The mixture was stirred at 60 °C for 10 min. Hexane (50 ml) was added at 0 °C. The mixture was filtrated and concentrated. Hexane (50 ml) was again added and the mixture was filtrated again. Concentration and chromatography (hexane : AcOEt=3 : 2) gave 0.891 g (91%) of a 9 : 1 mixture of *E*- and *Z*-**8** as a colorless oil. ^{1}H-NMR: 1.48 (9H, s), 1.53—1.65 (4H, m), 2.21 (1.8H, ddt, *J*=1.5, 7.1, 7.3, *E*), 2.64 (0.2H, ddt, *J*= 1.5, 7.3, 7.6, *Z*), 3.67 (2H, t, *J*=6.4), 5.69 (0.1H, dt, *J*=1.5, 11.6, *Z*), 5.75 (0.9H, dt, *J*=1.5, 15.6, *E*), 6.13 (0.1H, dt, *J*=7.6, 11.3, *Z*), 6.85 (0.9H, dt, *J*=7.1, 15.6, *E*). ^{13}C-NMR: 24.2 (E), 25.1 (Z), 28.1 (E), 28.2 (Z), 31.7, 32.0, 62.4 (Z), 62.5 (E), 80.1, 121.7 (Z), 123.2 (E), 147.5 (E), 148.5 (Z), 166.1. IR (neat): 3440, 1735. MS *m/z*: 201 (M^++H).

2,2-Dimethylethyl (2*E*)-7-Oxohept-2-enoate (9) To a solution of a 9 : 1 mixture of **8** above (400 mg, 2.0 mmol) in toluene (7.0 ml) were successively added at rt DMSO (7 ml), pyridine (0.16 ml, 2.0 mmol), trifluoroacetic acid (0.08 ml, 1.0 mmol), and DCC (1.2 g, 6.0 mmol). The mixture was stirred at rt for 18 h. After addition of toluene (30 ml), the mixture was filtrated and washed with water (30 ml×3) and brine (20 ml), and then dried over sodium sulfate. Chromatography (hexane : AcOEt=10 : 1) gave 358 mg (90%) of **9** as a colorless oil. ^{1}H-NMR: 1.48 (9H, s), 1.80 (2H, tt, *J*=7.1, 7.3), 2.23 (2H, ddt, *J*=1.6, 7.1, 7.7), 2.49 (2H, dt, *J*=1.5, 7.3), 5.76 (1H, dt, *J*=1.6, 15.6), 6.81 (1H, dt, *J*=7.1, 15.6), 9.78 (1H, t, *J*=1.5). ^{13}C-NMR: 20.4, 28.1, 31.1, 43.0, 80.2, 124.0, 146.2, 165.8, 201.7. IR (neat): 1710. MS *m/z*: 199 (M^++H).

2,2-Dimethylethyl (2*E*)-7-Hydroxy-8-nitrooct-2-enoate (10) A solution of **9** (198 mg, 1.0 mmol), nitromethane (0.17 ml, 1.0 mmol) and 2 drops of triethylamine in THF (2 ml) was stirred at reflux for 12 h. Concentration and chromatography (hexane : AcOEt=8 : 1) gave 219 mg (84%) of **10** as a colorless oil. ^{1}H-NMR: 1.40—1.70 (4H, m), 1.44 (9H, s), 2.19 (2H, dt, *J*=6.4, 6.7), 3.02 (1H, br s), 4.29—4.41 (3H, m), 5.72 (1H, d, *J*=15.6), 6.78 (1H, dt, *J*=6.7, 15.6). ^{13}C-NMR: 23.7, 28.1, 31.4, 33.0, 68.3, 80.3, 80.6, 123.6, 146.8, 166.1. IR (neat): 3420, 1700, 1550. MS *m/z*: 260 (M^++H), 203 ($M^+-{}^t$Bu+H). *Anal*. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.60; H, 8.21; N, 5.62.

2,2-Dimethylethyl 8-Nitroocta-2,7-dienoate (3) Triethylamine (0.9 ml, 7.0 mmol) was added dropwise over 3 min at 0 °C to a solution of **10** (900 mg, 3.5 mmol) and trifluoroacetic anhydride (0.5 ml, 3.5 mmol) in THF (10 ml). The mixture was stirred at rt for 1 h, and then was diluted with 20 ml of $CHCl_3$. The whole was washed with water (20 ml), sat. NH_4Cl (20 ml), and brine (20 ml). Combined water layers were extracted with $CHCl_3$ (20 ml×2). Chromatography (hexane : AcOEt=8 : 1) gave 804 mg (96%) of **3** as a colorless oil. ^{1}H-NMR: 1.49 (9H, s), 1.70 (2H, tt, *J*=7.4, 7.7), 2.25 (2H, dt, *J*=6.7, 7.4), 2.31 (2H, dt, *J*=7.3, 7.7), 5.77 (1H, d, *J*=15.6), 6.81 (1H, dt, *J*=6.7, 7.4), 6.99 (1H, d, *J*=13.4), 7.26 (1H, dt, *J*=7.3, 13.4). ^{13}C-NMR: 26.1, 27.7, 28.1, 31.1, 80.4, 124.2, 141.6, 145.7, 145.7, 165.7. IR (neat): 1710. HR-FAB-MS *m/z*: Calcd for $C_{12}H_{19}NO_4$: 242.1392. Found: 242.1389.

2,2-Dimethylethyl 7-Phenyl-8-nitrooct-2-enoate (11) (Table 1, Entry 3) A solution of phenyllithium (1.84 M, 0.65 ml, 1.2 mmol) was added at −78 °C over 1 min to a solution of 3 (241 mg, 1.0 mmol) in THF (20 ml). After stirring for 15 min, methanol (1 ml) and sat. NH_4Cl (20 ml) and brine (20 ml) were added at −78 °C to the mixture. The mixture was extracted with AcOEt (20 ml×3). Chromatography (hexane : AcOEt=50 : 1 to 1 : 1) gave 291 mg (91%) of **11** as a pale yellow. ^{1}H-NMR: 1.40 (2H, m), 1.52 (9H, s), 1.76 (2H, dt, *J*=7.6, 7.9), 2.2 (2H, m), 3.50 (1H, ddt, *J*=7.7, 7.9, 8.0), 4.60 (1H, dd, *J*=8.0, 12.2), 4.63 (1H, dd, *J*=7.7, 12.2), 5.73 (1H, dt, *J*=1.6, 15.6), 6.79 (1H, dt, *J*=7.1, 15.6), 7.32 (2H, d, *J*=7.6), 7.33 (1H, t, *J*=7.1), 7.40 (2H, dd, *J*=7.1, 7.6). ^{13}C-NMR: 25.4, 28.1, 31.6, 32.4, 44.2, 80.2, 80.8, 123.5, 127.5, 127.7, 129.0, 138.9, 146.7, 165.9. IR (neat): 1710, 1650. HR-MS *m/z*: Calcd for $C_{18}H_{26}NO_4$: 320.1862. Found: 320.1856.

2,2-Dimethylethyl 3,7-Diphenyl-5-yl-8-nitrooctanoate (12) (Table 1, Entry 1) ^{1}H-NMR: 0.93—1.07 (m), 1.24—1.78 (m), 1.43 (s), 1.47 (s), 2.06—2.24 (2H, m), 2.65—2.78 (1H, m), 3.29 (br s), 3.45 (br s), 4.41—4.46 (m), 4.50 (m), 4.57 (m), 7.02—7.45 (10H, m). ^{13}C-NMR: 23.8, 25.0, 27.5, 28.1, 32.7, 32.9, 33.2, 34.0, 44.1, 44.3, 43.9, 80.0, 130.1, 139.4, 142.5, 142.5, 172.0, 172.1. IR (neat): 1720. HR-MS *m/z*: Calcd for $C_{24}H_{35}NO_4$: 398.2331. Found: 398.2340.

2,2-Dimethylethyl (2-Nitro-3-phenylcyclohexyl)acetate (13—15) (Table 2, Entry 2) A suspension of **11** (32 mg, 0.1 mmol), CsF (30 mg, 0.2 mmol) and myristyltrimethylammonium bromide (134 mg, 0.2 mmol) in THF (1 ml) was stirred at rt for 24 h, and was quenched with brine (20 ml). The mixture was extracted with AcOEt (20 ml×3). Chromatography (hexane : AcOEt=10 : 1) gave 20 mg (67%) of the 2.3 : 1 mixture of **13** and **14** as a pale yellow oil.

14 (from Entry 10): ^{1}H-NMR: 1.34 (1H, m), 1.45 (9H, s), 1.52—1.66 (2H, m), 1.86 (2H, m), 1.99—2.08 (2H, m), 2.16 (1H, dd, *J*=8.5, 15.9), 2.31 (1H, dd, *J*=3.4, 15.9), 2.40—2.55 (1H, m), 3.16 (1H, ddd, *J*=3.7, 11.3, 11.6), 4.58 (1H, dd, 11.0, 11.3), 7.18 (2H, d, *J*=7.0), 7.23 (1H, t, *J*=7.6), 7.30 (2H, dd, *J*=7.0, 7.6). ^{13}C-NMR: 24.9, 28.1, 30.1, 32.9, 38.3, 38.9, 48.7, 81.0, 95.1, 127.1, 127.6, 128.8, 140.2, 170.3. IR (neat): 1720. FAB-MS *m/z*: 320 (M^++H). *Anal*. Calcd for $C_{18}H_{24}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.77; H, 7.91; N, 4.59. 3.

13 (Data Selected from a 1 : 1 Mixture of **13** and **14**): ^{1}H-NMR: 1.44 (9H, s), 1.49—1.76 (3H, m), 1.82—1.94 (2H, m), 1.99—2.08 (3H, m), 2.40—2.55 (3H, m), 3.09 (1H, br s), 3.26 (1H, ddd, *J*=4.0, 11.6, 11.9), 4.96 (1H, dd, *J*=4.6, 11.6), 7.18—7.29 (5H, m). ^{13}C-NMR: 19.9, 28.0, 29.3, 33.5, 33.7, 34.6, 41.9, 81.0, 91.8, 127.0, 127.3, 128.7, 141.0, 170.6. IR (neat): 1720. FAB-MS *m/z*: 320 (M^++H).

2,2-Dimethylethyl (2-Amino-3-phenylcyclohexyl)acetate (16—18) A mixture of **13**, **14** and **15** (1 : 1 : 1) (1.6 g, 5.0 mmol), and Zn powder (1.0 g, 15.4 mmol) in EtOH (60.0 ml) and 10% HCl aq. (10 ml) was stirred at rt for 1 d. The mixture was filtrated and concentrated. The residue was diluted with 40 ml of AcOEt, and was washed with sat. $NaHCO_3$ (20 ml) and brine (20 ml). The combined organic layers were dried over sodium sulfate. Concentration and chromatography (hexane : AcOEt=10 : 1 to 1 : 1) gave 478 mg (33%) of **16**, 333 mg (23%) of **17** and 362 mg (25%) of **18**.

16: A colorless oil. ^{1}H-NMR: 1.26—1.63 (6H, m,), 1.46 (9H, s), 1.80 (2H, br s), 2.27 (1H, dd, *J*=9.5, 15.0), 2.40 (1H, ddd, *J*=3.6, 10.7, 11.6), 2.45 (1H, br s), 2.70 (1H, dd, *J*=4.6, 15.0), 3.14 (1H, dd, *J*=4.6, 10.7), 7.21—7.32 (5H, m). ^{13}C-NMR: 20.6, 28.1, 29.5, 32.6, 36.6, 46.8, 56.3, 80.1, 126.5, 127.7, 128.6, 144.3, 173.6. IR (neat): 1720. MS *m/z*: 289 (M^+). HR-MS *m/z*: Calcd for $C_{18}H_{27}NO_2$: 289.2042. Found: 289.2033.

17: A colorless oil. ^{1}H-NMR: 1.22—1.29 (5H, m), 1.26 (9H, s), 1.75—1.84 (4H, m), 2.12 (1H, dd, *J*=8.0, 15.0), 2.32 (1H, ddd, *J*=2.5, 10.1, 12.0), 2.56 (1H, dd, *J*=10.1, 10.1), 2.66 (1H, dd, *J*=5.2, 15.0), 7.19—7.34. ^{13}C-NMR: 26.0, 28.0, 28.1, 32.0, 40.2, 42.3, 54.0, 58.9, 80.1, 126.5, 127.8, 128.6, 144.5, 172.9. IR (neat): 1720. MS *m/z*: 289 (M^+). HR-MS *m/z*: Calcd for $C_{18}H_{27}NO_2$: 289.2042. Found: 289.2051.

18: A colorless oil. ^{1}H-NMR: 1.13 (2H, br s), 1.39—1.56 (3H, m), 1.49 (9H, s), 2.20 (1H, m), 2.26 (1H, dd, *J*=7.3, 14.3), 2.36 (1H, dd, *J*=7.0, 14.3), 2.88 (1H, ddd, *J*=2.0, 3.0, 13.1), 3.16 (1H, dd, *J*=1.7, 1.9), 7.24—7.27 (5H, m). ^{13}C-NMR: 22.9, 25.5, 25.9, 28.1, 39.9, 40.1, 48.2, 54.6, 80.2, 126.2, 127.6, 128.4, 144.3, 172.6. IR (neat): 1720. MS *m/z*: 289 (M^+). HR-MS *m/z*: Calcd for $C_{18}H_{27}NO_2$: 289.2042. Found: 289.2054.

7-Phenyloctahydroindol-2-one (19—21) (Chart 4) A solution of **16** (289 mg, 1.0 mmol) in MeOH (1 ml) was added at rt to a solution of sodium (115 mg, 5.0 mmol) in MeOH (2 ml). After stirring for 24 h at rt, brine (10 ml) was added. The mixture was extracted with AcOEt (20 ml×3). Recrystallization from $CHCl_3$/hexane gave 213 mg (99%) of **19** as colorless needles of mp 188—190 °C. ^{1}H-NMR: 1.47—1.58 (2H, m), 1.69—1.89 (4H, m), 2.21 (1H, dd, *J*=8.5, 16.5), 2.39 (1H, dd, *J*=12.3, 16.5), 2.44 (1H, ddd, *J*=3.4, 9.8, 12.5), 2.76 (1H, br s), 3.46 (1H, dd, *J*=6.7, 9.8), 5.57 (1H, br s), 7.18 (2H, d, *J*=7.0), 7.24 (1H, t, *J*=7.3), 7.32 (2H, dd, *J*=7.0, 7.3). ^{13}C-NMR: 21.1, 26.1, 30.3, 33.4, 34.9, 48.6, 59.9, 126.9, 127.6, 128.8, 143.2, 177.6. IR ($CHCl_3$): 1680. MS *m/z*: 215 (M^+). *Anal*. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.97; H, 7.92; N, 6.50.

20: Colorless needles of mp 231—232 °C ($CHCl_3$). ^{1}H-NMR: 1.37—1.47 (1H, m), 1.49—1.67 (2H, m), 1.91—2.07 (4H, m), 2.12 (1H, dd, *J*=12.8, 15.3), 2.37 (1H, dd, *J*=6.4, 15.3), 2.63 (1H, ddd, *J*=3.4, 10.4, 11.3), 3.24 (1H, dd, *J*=10.1, 10.4), 5.28 (1H, br s), 7.18 (2H, d, *J*=7.4), 7.24 (1H, t, *J*=7.1), 7.32 (2H, dd, *J*=7.1, 7.4). ^{13}C-NMR: 26.1, 28.2, 32.8, 38.0, 44.8, 48.7, 65.1, 126.9, 127.1, 128.9, 142.3, 177.7. IR ($CHCl_3$): 1680. MS *m/z*: 215 (M^+). *Anal*. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.23; H, 7.97; N, 6.46.

21: Colorless needles of mp: 225—226 °C ($CHCl_3$). ^{1}H-NMR: 1.26—1.40 (1H, m), 1.74—1.89 (5H, m), 2.00 (1H, d, *J*=15.7), 2.44 (1H, m), 2.52 (1H, dd, *J*=7.1, 15.7), 2.88 (1H, ddd, *J*=3.7, 4.3, 12.8), 3.92 (1H, dd, *J*=4.3, 4.3), 4.92 (1H, br s), 7.19—7.36 (5H, m). ^{13}C-NMR: 23.8, 24.3, 27.6, 35.3, 40.3, 44.0, 58.7, 127.0, 128.9, 129.0, 142.4, 177.9. IR ($CHCl_3$): 1680. MS *m/z*: 215 (M^+). *Anal*. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.33; H, 8.01; N, 6.66.

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