RADICAL β-FRAGMENTATION OF BICYCLO[3.3.0]-CARBINOLAMIDES: SYNTHESIS OF FIVE- AND EIGHT-MEMBERED CYCLIC IMIDES

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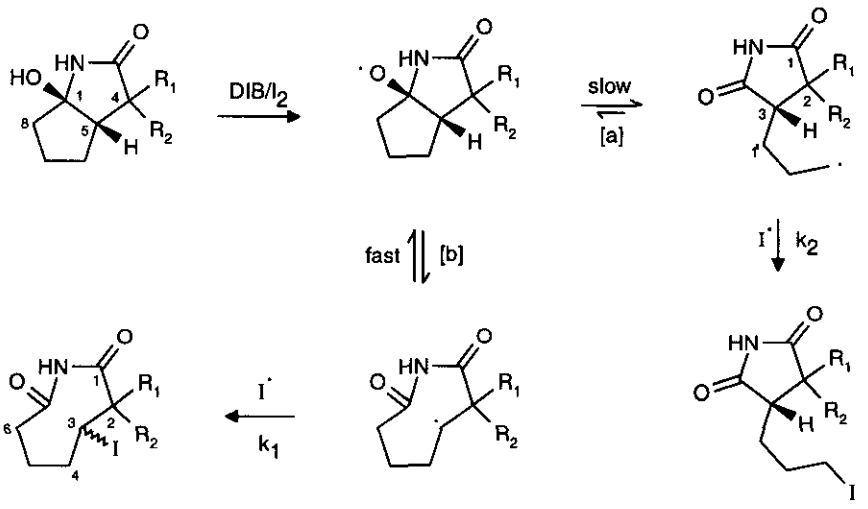
Abstract—The influence of 4-alkyl or 4-aryl substituents in the regioselectivity of the β-fragmentation of carbinolamidyl radicals generated from the corresponding carbinolamides (**7-13**) by irradiation with visible light in the presence of (diacetoxyiodo)benzene and iodine is described. In the case of the less hindered carbinolamides 1-hydroxyazabicyclo[3.3.0]octan-3-one (**7**) and 4-(2'-phenylethyl)-1-hydroxyazabicyclo[3.3.0]octan-3-one (**8**) important amounts of 8-membered cyclic imides were obtained together with the expected 5-membered imides (succinimides).

In a previous paper[1] we have described the radical β-fragmentation of bicyclic carbinolamides by reaction with hypervalent organoiodine reagents and iodine as a method for the synthesis of succinimides. In the case of the 1-hydroxyazabicyclo[3.3.0]octan-3-one derivatives studied the reaction promoted by β-scission of the initially generated alkoxy radicals was completely regioselective. The fragmentation occurs exclusively between C_1 and C_8 to give 2,2-dialkyl-substituted succinimides in good yield (Scheme 1, path [a], $R_1 = R_2$ = alkyl). Products coming from the alternative C_1-C_5 bond cleavage (path [b]) could not be found, only small amounts of isocyanates being formed as by-products by amidyl radical rearrangement.[2]

This observed regioselectivity is in apparent contradiction with the general rule that, in the β-fragmentation of alkoxy radicals, the relative rates of bond cleavage reflect the stabilities of the final products, and in general secondary radical intermediates are formed in preference to primary ones.[3] However, it is not unprecedented in the literature, and Beckwith *et al.*[4] have studied a similar case during the β-fission of the 9-decalinoxyl radical. Taking these studies into account we have proposed the mechanism outlined in Scheme 1 for the radical fragmentation of carbinolamides.

The carbinolamidyl radical may undergo a fast but reversible β-fragmentation of the C_1-C_5 bond to give the secondary C-radical and a slower but essentially irreversible C_1-C_8 bond cleavage to afford the primary C-radical. The second step rate would be dependent on the efficiency of the radical trapping. In hindered carbinolamides ($R_1 = R_2$ = alkyl) k_2 must be greater than k_1, and succinimide derivatives are formed exclusively.[1]

However, with less hindered carbinolamides (R_1 = and/or R_2 = H) we would expect an easier trapping of the secondary radical by the iodine atom directing the equilibrium to the formation of 8-membered cyclic imides. In this paper we describe the preparation of 1-hydroxy-2-azabicyclo[3.3.0]octan-3-one (**7**) and its 4-monosubstituted derivatives (**8-13**) in order to study the influence of the C-4 tether in the trapping reaction and consequently in the regioselectivity of the carbinolamidyl radical β-fragmentation.



Scheme 1. DIB = (diacetoxyiodo)benzene

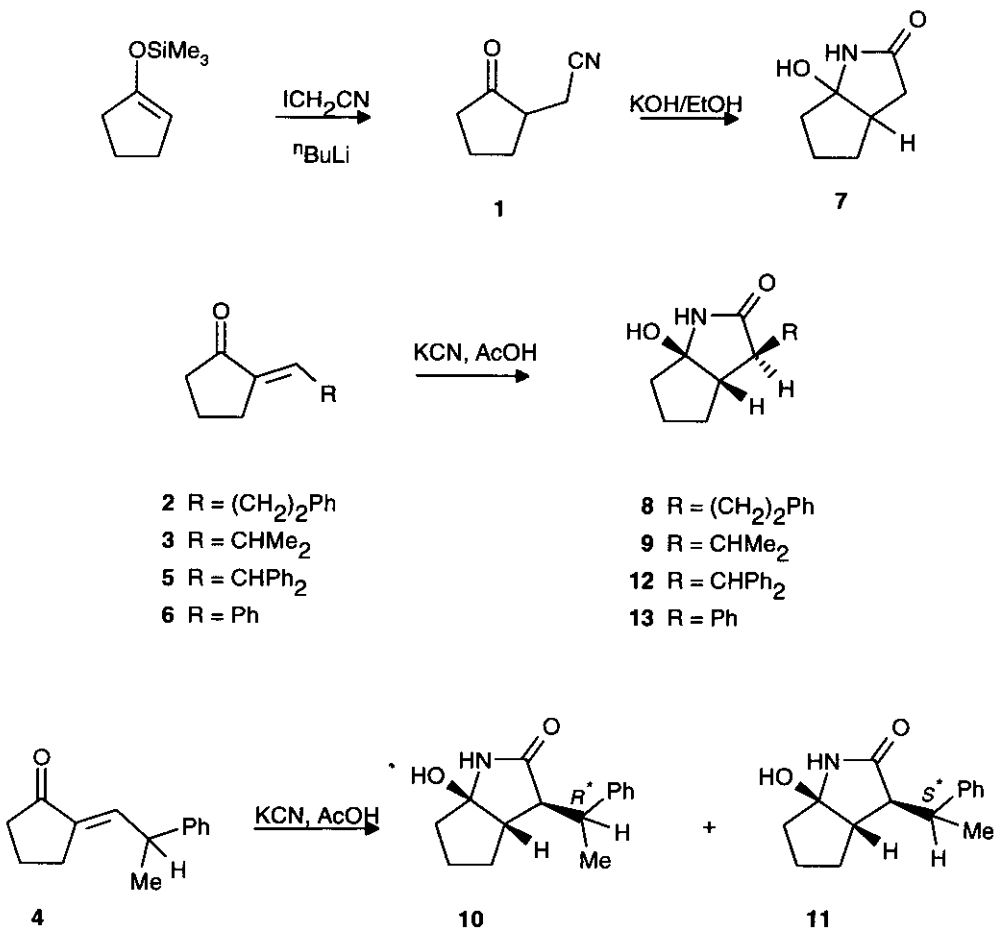
Although small ring imides, in particular succinimides and glutarimides, can be easily prepared by a variety of intramolecular reactions,[5] the method gives low yields in the case of seven-membered rings,[6] and e.g. adipimide is preferently prepared by oxidation of caprolactam.[7] To our knowledge, 8-membered cyclic imides have not been previously prepared. Nevertheless, eleven-[8] and fourteen-membered[9] macroimides have been synthesized using different ring expansion methodology.

RESULTS AND DISCUSSION

Synthesis of Carbinolamides (7-13). Carbinolamide (**7**) was synthesized by alkylation of cyclopentanone lithium enolate, generated from 1-[(trimethylsilyl)oxy]-1-cyclopentene and methyllithium, in the presence of HMPA and chlorotitanium triisopropoxide, with iodoacetonitrile following the Noyori procedure.[10] The nitrile (**1**) obtained was subsequently hydrolysed[11] with 7.5% KOH in MeOH-H_2O to give the required carbinolamide (**7**) (Scheme 2).

The α,β-unsaturated ketones (**2-6**) were prepared by aldol condensation of cyclopentanone with the corresponding aldehydes under basic conditions.[12] Treatment of these enones with KCN in EtOH-H_2O-AcOH gave the corresponding carbinolamides (**8-13**).[13]

In all cases only one carbinolamide was obtained, with the C-4 tether in the more stable *exo* position. We have found, using molecular mechanics calculations, that *exo* isomers are *ca.* 1 Kcal/mol more stable than the corresponding *endo* isomers. The observed coupling constants (2-4 Hz) between H-C_4 and H-C_5 for the *exo* isomers are in good agreement with the calculated ones over a minimized structure using the program PCMODEL[14] (2-2.5 Hz). The calculated coupling constants between H-C_4 and H-C_5 for the *endo* isomers are



Scheme 2. All products are racemates although only one enantiomer is shown

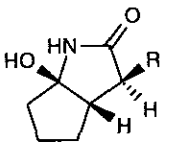
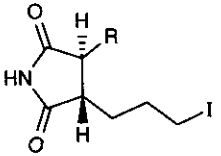
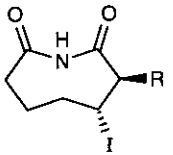
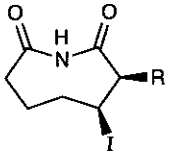
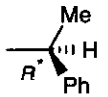
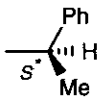
in the range of 7-8 Hz.

The reaction of enone (**4**) with KCN/AcOH deserves special comment. In this case two isomeric carbinolamides (**10**) and (**11**) were obtained. After a ^{1}H-nmr spectroscopic study these carbinolamides seem to be diastereoisomeric at C-1'. The relative stereochemistry of this carbon will be established by X-ray crystallographic analysis of imide(**25**)(*vide infra*).

Fragmentation of Carbinolamides (7-13). The β-fragmentations of carbinolamides (**7-13**) were performed by irradiation with visible light (two 100 W tungsten filament lamps) in the presence of (diacetoxyiodo)benzene and iodine using dichloromethane as solvent under the conditions summarized in Table 1.

The fragmentation of carbinolamides (**7**) gave a *ca.* equimolecular mixture of succinimide (**14**) and 8-membered cyclic imide (**15**) (Entry 1). Compound (**15**) shows in its ir spectrum a band at 1686 cm^{-1} instead of the typical two-band system of the succinimides [*e.g.* 1786 (m) and 1709 (s) cm^{-1} in the spectrum of **14**]. The 8-membered cyclic structure of imide (**15**) can be established by ^{1}H-nmr and ^{13}C-nmr spectroscopy. The proton at C-3 appears at δ 4.64 as a one-proton multiplet, while the C-3 is at δ 21.68 (d, DEPT experiment). The carbon bearing the iodine atom in the succinimide structure should be more shielded [δ 5.24 (t) in the

Table 1. Fragmentation of Carbinolamides (**7-13**)[a]

Entry		Reagents[b] (mmol)	Conditions Time (min)	Conditions Temp. (°C)			
1	**7** R = H	1.5/1.0	120	25	**14** (24)[c]	**15** (20)	
2	**8** R = $(CH_2)_2Ph$	1.5/1.0	30	20	**16** (39)	**17** (32)	**18** (9)
3	**9** R = $CHMe_2$	1.6/1.0	45	25	**19** (59)	**20** (2)	**21** (7)
4	**10** R = 	1.5/1.0	40	25	**22** (56)	**24** (2)	**25** (3)
5	**11** R = 	1.5/1.0	50	25	**23** (61)	**26** (3)	**27** (10)
6	**12** R = $CHPh_2$	1.7/0.9	45	20	**28** (52)	**29** (7)	**30** (8)
7	**13** R = Ph	1.5/1.0	30	25	**31** (64)	**32** (2)[d]	

a) All reactions were performed by irradiation with two 100 W tungsten-filament lamps.
b) Mmol of (diacetoxyiodo)benzene/mmol of I_2 per mmol of substrate in CH_2Cl_2.
c) Yields are in parenthesis.
d) Only one isomeric iodine was obtained and the C-3 stereochemistry remains undetermined.

spectrum of **14**]. A better yield but similar regioselectivity was obtained when the reaction was performed with carbinolamide (**8**) (Entry 2).

When the β-fragmentation reaction was realized with a carbinolamide possessing a bulkier substituent at C-4 **9-13** (Entries 3-7) the β-scission occurs preferentially at the C_1-C_8 bond to give the succinimide derivatives in good yield (52-64 %). In these cases the alternative C_1-C_5 bond fragmentation occurs in low yield (2-15 %) to give a mixture of C-3 epimeric iodine derivatives.

The structure and relative stereochemistry of the 8-membered cyclic imides were determined by a single crystal X-ray analysis[15] of compound (**25**) (Figure 1) obtained from carbinolamide (**10**) (Entry 4). The eight-membered ring displays a quasi-boat conformation with the C_2-C_3 bond nearly parallel to the C_5-C_6 linkage. The ring conformation is very similar to the boat-chair conformation of cyclooctane[16] with the imide group and adjacent carbons in a plane. For a structure such as (**25**) the relative configuration is $2R^*$, $3S^*$, $1'S^*$. Consequently, the relative configuration of the macroimide (**24**) is $2R^*$, $3R^*$, $1'S^*$.

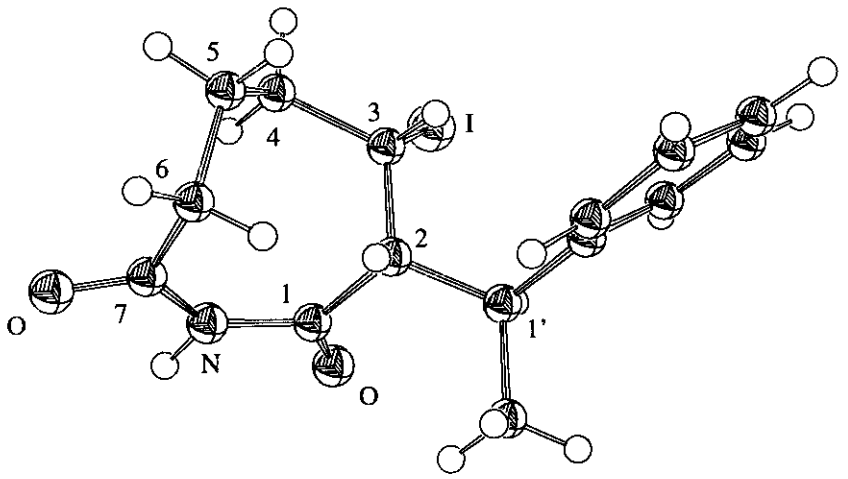


Figure 1. X-Ray structure of **25**

The ring conformation of **25** leads the $3S^*$ iodine atom into a *quasi*-axial position while the $2R^*$ substituent is in equatorial orientation. In its ^{1}H-nmr spectrum the coupling constant between H-C_2 and H-C_3 is 4.1 Hz while this constant has a value of 11.4 Hz in the ^{1}H-nmr spectrum of the C-3 epimeric compound (**24**). These experimental coupling constants are in good agreement with those calculated over a minimized structure (4 and 11 Hz, respectively). The assignments of the stereochemistry of the other medium cyclic C-3 epimeric pairs have been realized taking into account this difference between the H-C_2 and H-C_3 coupling constants.

In the fragmentation reaction of carbinolamide (**13**) only one 8-membered imide could be isolated in low yield (Entry 7). Due to the superimposed of the H-C_2 and H-C_3 signals in its ^{1}H-nmr spectrum the stereochemistry at C-3 could not be determined.

Although the yields of macroimides are too small to be of preparative value, the formation of these compounds through some light on the mechanism of the fragmentation of carbinolamides.

EXPERIMENTAL SECTION

Melting points were determined with a Mettler FP 82 hot-stage apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 1605/FTIR spectrophotometer in $CHCl_3$ solutions. ^{1}H-Nmr (200 MHz) and ^{13}C-nmr (50.3 MHz) spectra were recorded on a Bruker WP 200 SY spectrometer for solutions in $CDCl_3$ with Me_4Si as internal standard and chemical shifts are expressed in parts per million (δ units) relative to internal reference (δ 0.00) and to the centre peak of $CDCl_3$ (δ 77.00), respectively. Low-resolution mass spectra were determined with Hewlett Packard 5930 A and VG Micromass ZAB-2F spectrometers and high-resolution mass spectra on a VG Micromass ZAB-2F spectrometer. Merck silica gel 0.063-0.2 mm was used for column chromatography. Circular layers of 1 mm of Merck silica gel 60 PF 254 were used on a Harrison Chromatotron for centrifugally assisted chromatography. Tlc analyses were conducted on silica gel plates and were visualized by spraying with 0.5% vanillin in H_2SO_4-EtOH (4:1) and further heating until development of color. Commercial reagents and solvents were analytical grade or were purified by standard procedures prior to use.[17] (Diacetoxyiodo)benzene 98% was purchased from Aldrich.

(2-Oxocyclopentyl)acetonitrile (1). To a solution of 1-[(trimethylsilyl)oxy]-1-cyclopentene (1.95 g, 12.5 mmol), in ether (30 ml), was added dropwise a 1.6 M ethereal solution of methyllithium (8.6 ml, 1.1 equiv.) for 30 min under an argon atmosphere at room temperature. The solvent was evaporated under vacuum and dry tetrahydrofuran (100 ml) was added and the mixture was cooled to -50 °C and then hexamethylphosphoramide (22 ml, 125 mmol), chlorotitanium triisopropoxide (3 ml, 12.5 mmol), and iodoacetonitrile (4.5 ml, 62.5 mmol) were added, and the resulting solution was stirred at this temperature for 10 h. The reaction mixture was allowed to reach room temperature and then poured into water and extracted with CH_2Cl_2. The organic phase was washed with 5% HCl and H_2O, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (hexane-EtOAc, 85:15) to give cyanide derivative **(1)** (600 mg, 39%): amorphous; ir ν_{max} 2252, 1745 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.6-2.6 (8H, m), 2.75 (1H, m); ^{13}C-nmr (50.3 MHz) δ 17.15 (t), 20.08 (t), 28.81 (t), 36.98 (t), 45.32 (d), 117.88 (s), 216.05 (s); ms m/z (rel intensity) 123 (M^+, 49), 94 (9), 80 (10), 68 (61), 55 (100), 41 (94); hrms Calcd for C_7H_9NO 123.06841. Found 123.06805. *Anal.* Calcd for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 67.98; H, 7.60; N, 11.06.

General Procedure for the Synthesis of Enones (2-6). To a solution of cyclopentanone (8.4 g, 100 mmol) and aldehyde (0.5-1 equiv.) in methanol (50 ml), at 0 °C and with stirring, was added dropwise for 30 min, 0.5 M NaOH in methanol-H_2O (14:1) (60 ml). The mixture was allowed to warm up to room temperature and the stirring continued for the time stated in each case, then it was poured into water and the resulting aqueous solution acidulated with 5 % HCl and extracted with dichloromethane. Evaporation of the solvent led to a residue which was dissolved in benzene (100 ml) and treated with *p*-toluenesulfonic acid (*p*-tsa) (4.7 g, 25 mmol, 0.25 equiv.) at room temperature overnight, then poured into water and extracted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$, H_2O, dried (anhydrous Na_2SO_4), and concentrated. The crude product was purified by chromatography.

2-(3'-Phenylpropylidene)cyclopentanone (2). Cyclopentanone (18.25 g, 217 mmol) and 3-phenylpropionaldehyde (15.29 g, 114 mmol) in MeOH (50 ml) were treated with 2.7 % NaOH methanolic solution (75 ml) for 1 h, and the residue in C_6H_6 (65 ml) with *p*-tsa (10.2 g, 54.3 mmol) according to the general method. Column chromatography of the residue (hexane-EtOAc, 9:1) gave **2** (8.4 g, 37 %): amorphous; ir ν_{max} 3075,

3050, 1710, 1640, 1600, 1490, 1450, 1410, 1380, 1285, 1260, 1170, 695, 650 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.83 (2H, qui, *J* = 7.4 Hz, 4-H_2), 2.27 (2H, t, *J* = 7.9 Hz, 5-H_2), 2.44 (4H, m, 3-H_2, 2'-H_2), 2.75 (2H, t, *J* = 7.5 Hz, 3'-H_2), 6.56 (1H, m, 1'-H), 7.22 (5H, m, Ar-H_5); ^{13}C-nmr (20.1 MHz) δ 19.71 (t), 26.66 (t), 31.49 (t), 34.56 (t), 38.47 (t), 126.09 (d), 128.37 (4xd), 134.45 (d), 137.97 (s), 141.09 (s), 206.43 (s). *Anal.* Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.14; H, 7.91.

2-Isobutylidenecyclopentanone (3). Cyclopentanone (9.5 g, 113 mmol) and isobutyraldehyde (7.2 g, 99.8 mmol) in methanol (50 ml) were treated with 2.8 % NaOH methanolic solution (75 ml, 52.5 mmol) for 24 h, and the residue purified by column chromatography (hexane-ethyl acetate, 90:10) to give **3** (4.96 g, 36 %): amorphous; ir ν_{max} 1712, 1635 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.04 (6H, d, *J* = 6.6 Hz, 2'-Me_2), 1.93 (2H, qui, *J* = 7.4 Hz, 4-H_2), 2.33 (2H, t, *J* = 7.9 Hz, 5-H_2), 2.46 (1H, m, 2'-H), 2.60 (2H, dt, *J* = 7.4, 2.6 Hz, 3-H_2), 6.40 (1H, dm, *J* = 9.6 Hz, 1'-H); ^{13}C-nmr (50.3 MHz) δ 19.65 (t), 21.49 (2xq), 26.23 (t), 28.81 (d), 38.19 (t), 134.81 (s), 141.67 (d), 205.79 (s). *Anal.* Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.43; H, 9.98.

(±)-2-(2'-Phenylpropylidene)cyclopentanone (4). Cyclopentanone (9.94 g, 118.3 mmol) and (±)-2-phenylpropionaldehyde (16.18 g, 120.6 mmol) in methanol (50 ml) were treated with NaOH (4.2 g, 105 mmol) in methanol-H_2O (15:1) (160 ml) for 2 h at 0 °C. The residue in C_6H_6 (50 ml) was treated with *p*-tsa (10.5 g, 55.9 mmol) according to the general method. Column chromatography of the residue (hexane-ethyl acetate, 97:3) gave **4** (13.98 g, 58 %): amorphous; ir ν_{max} 3080, 3060, 1713, 1642, 1605, 1490, 1450, 1400, 1375, 1290, 1270, 1190, 1050, 1030, 830, 700 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.42 (3H, d, *J* = 7.0 Hz, 1'-Me), 1.93 (2H, qui, *J* = 7.4 Hz, 4-H_2), 2.33 (2H, t, *J* = 8.4 Hz, 5-H_2), 2.63 (2H, dt, *J* = 7.2, 2.6 Hz, 3-H_2), 3.63 (1H, m, 2'-H), 6.67 (1H, dt, *J* = 9.6, 2.7 Hz, 1'-H), 7.27 (5H, m, Ar-H_5); ^{13}C-nmr (50.3 MHz) δ 19.69 (t), 21.37 (q), 26.71 (t), 38.39 (t), 40.03 (d), 126.51 (d), 126.99 (2xd), 128.64 (2xd), 135.93 (s), 139.34 (d), 144.30 (s), 207.06 (s). *Anal.* Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.17; H, 7.81.

2-(2',2'-Diphenyethylidene)cyclopentanone (5). Cyclopentanone (8.53 g, 101.4 mmol) and diphenylacetaldehyde (9.95 g, 50.7 mmol) in methanol (80 ml) were treated with NaOH (2.1 g, 52.5 mmol) in methanol-H_2O (9:1) (53 ml) for 24 h. The residue in C_6H_6 (45 ml) was treated with *p*-tsa (9.5 g) and led to a crude which was purified by column chromatography (hexane-ethyl acetate, 95:5) to give **5** (7.57 g, 57 %): mp 80-81 °C (EtOAc-hexane); ir ν_{max} 1715, 1650, 1605, 1495, 1455, 1410, 1362, 1180, 1040, 990, 910, 700 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.95 (2H, qui, *J* = 7.4 Hz, 4-H_2), 2.36 (2H, t, *J* = 7.7 Hz, 5-H_2), 2,66 (2H, dt, *J* = 7.2, 2.6 Hz, 3-H_2), 4.83 (1H, d, *J* = 9.9 Hz, 1'-H), 7.03 (1H, dt, *J* = 9.9, 2.7 Hz, 1'-H), 7.17 (10H, m, Ar-H_{10}); ^{13}C-nmr (50.3 MHz) δ 19.43 (t), 26.63 (t), 38.33 (t), 50.75 (d), 126.56 (2xd), 127.97 (4xd), 128.48 (4xd), 136.02 (d), 137.20 (s), 142.33 (2xs), 206.85 (s); ms m/z (rel intensity) 262 (M^+, 100), 247 (10), 244 (7), 232 (6), 217 (6), 206 (81), 205 (51), 191 (28), 178 (13), 167 (19), 165 (43), 152 (18), 143 (21), 129 (21), 115 (24), 91 (63), 77 (13); hrms Calcd for $C_{19}H_{18}O$ 262.1358. Found 262.1367. *Anal.* Calcd for $C_{19}H_{18}O$: C, 86.99; H, 6.92. Found: C, 86.88; H, 7.15.

2-Benzylidenecyclopentanone (6). To a mixture of cyclopentenone (10.9 g, 130 mmol) and benzaldehyde (6.58 g, 62 mmol) was added a solution of NaOH (7.17 g, 179.3 mmol) in water (864 ml) for 10 h. Column chromatograhy of the residue gave **6** (7.46 g, 70 %): mp 69-70 °C (pentane) (lit.,[18] 69-71 °C); ir ν_{max} 1712, 1624, 1576, 1493, 1451, 1410, 1308, 1290, 1275, 1180, 692 cm^{-1}; ^{1}H-nmr (200 MHz) δ 2.03 (2H, qui, *J* = 7.4 Hz, 4-H_2), 2.41 (2H, t, *J* = 7.7 Hz, 5-H_2) 2.99 (2H, dt, *J* = 7.2, 2.8 Hz, 3-H_2), 7.41 (6H, m, 1'-H and

Ar-H_5); ^{13}C-nmr (50.3 MHz) δ 20.01 (t), 29.17 (t), 37.48 (t), 128.54 (2xd), 129.14 (d), 130.34 (2xd), 131.95 (d), 135.37 (s), 135.96 (s), 207.68 (s); ms m/z (rel intensity) 172 (M^+, 83), 171 (100), 157 (1), 143 (6), 129 (32), 115 (32), 102 (4), 91 (4), 89 (5), 77 (3), 71 (6); hrms Calcd for $C_{12}H_{12}O$ 172.0888. Found 172.0886. *Anal.* Calcd for $C_{12}H_{12}NO_2$: C, 83.69; H, 7.02. Found: C, 83.54; H, 7.06.

(±)-(1*R,5*S**)-1-Hydroxy-2-azabicyclo[3.3.0]octan-3-one (7).** To a solution of cyanide **(1)** (50 mg, 4.07 mmol) in EtOH (14 ml) was added 7.5% KOH in MeOH-H_2O (9:1) (40 ml, 50.8 mmol) and the resulting mixture was stirred at room temperature for 48 h. Chromatotron chromatography of the residue (EtOAc-acetone, 75:25) gave the carbinolamide **(7)** (320 mg, 56%): mp 138-140 °C (acetone); ir ν_{max} 3601, 3423, 1702 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.46 (1H, m, 6-H), 1.74 (2H, m, 7-H_2), 1.94 (2H, dd, *J* = 5.3, 7.8 Hz, 8-H_2), 2.06 (1H, dd, *J* = 3.8, 17.8 Hz, 4-H), 2.14 (1H, m, 6-H), 2.55 (1H, m, 5-H), 2.83 (1H, dd, *J* = 9.6, 17.8 Hz, 4-H), 5.20 (1H, m, O-H), 7.43 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 24.45 (t), 33.97 (t), 37.69 (t), 39.77 (t), 45.69 (d), 98.27 (s), 177.70 (s); ms m/z (rel intensity) 141 (M^+, 14), 126 (4), 112 (100), 98 (36), 84 (22), 69 (16), 55 (36); hrms Calcd for $C_7H_{11}NO_2$ 141.07898. Found 141.07993. *Anal.* Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.42; H, 7.99; N, 9.83.

General Procedure for the Synthesis of 4-Alkyl-1-hydroxy-2-azabicyclo[3.3.0]octan-3-ones (8-13). To a solution of enone (10 mmol) in ethanol (25 ml) was added a solution of KCN (1.3 g, 20 mmol) in EtOH-water (20:1) (25 ml). To the resulting mixture was added dropwise acetic acid (0.3 ml, 5 mmol) in EtOH (15 ml) and the mixture stirred for the time and temperature stated in each case, then poured over water and extracted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ and water, dried, evaporated, and the residue purified by chromatography.

(±)-(1*R,4*S**,5*S**)-4-(2-Phenylethyl)-1-hydroxy-2-azabicyclo[3.3.0]octan-3-one (8).** Enone **(2)** (6 g, 30 mmol) in EtOH (150 ml) and water (7.5 ml) was allowed to react for 20 h at 45 °C with KCN (3.9 g, 60 mmol) and acetic acid (0.9 ml, 15 mmol) according to the general method. Column chromatography of the residue (hexane-EtOAc, 1:1) gave the carbinolamide **(8)** (3.89 g, 53 %): mp 162-163 °C (EtOAc); ir ν_{max} 3585, 3400, 3080, 3060, 1680, 1585, 1490, 1450, 1300, 1290, 1180, 1080, 698 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.4-1.9 (6H, m), 2.0-2.3 (3H, m), 2.5-2.8 (3H, m), 6.41 (1H, br s, O-H), 6.52 (1H, br s, N-H), 7.23 (5H, m, Ar-H_5); ^{13}C-nmr (50.3 MHz) δ 24.73 (t), 33.52 (2xt), 33.83 (t), 40.28 (t), 49.52 (d), 52.29 (d), 96.71 (s), 125.92 (d), 128.34 (2xd), 128.45 (2xd), 141.34 (s), 179.43 (s); ms m/z (rel intensity) 245 (M^+, 2), 227 (4), 182 (4), 168 (5), 155 (15), 141 (100), 124 (38), 113(19), 91 (79), 77 (16); hrms Calcd for $C_{15}H_{19}NO_2$ 245.1416. Found 245.1438. *Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.53; H, 7.68; N, 5.85.

(±)-(1*R,4*S**,5*S**)-4- Isopropyl -1-hydroxy-2-azabicyclo[3.3.0]octan-3-one (9).** Enone **(3)** (4.83 g, 35 mmol) in EtOH (200 ml) and H_2O (9 ml) was treated with KCN (4.55 g, 70 mmol) and AcOH (1.05 ml, 17.5 mmol) for 30 h at 50 °C. Column chromatography of the residue (benzene-EtOAc, 65:35) gave the carbinolamide **(9)** (3.66 g, 57 %): mp 123-124 °C (acetone-pentane); ir ν_{max} 3590, 3405, 1685 cm^{-1}; ^{1}H-nmr (200 MHz) δ 0.90 (3H, d, *J* = 6.8 Hz, 1'-Me), 0.98 (3H, d, *J* = 6.8 Hz, 1'-Me), 1.4-1.95 (6H, m), 2.0-2.3 (3H, m), 2.54 (1H, m, O-H), 6.33 (1H, m, N-H); ^{13}C-nmr 18.02 (q), 20.47 (q), 24.76 (t), 28.27 (d), 34.32 (t), 40.69 (t), 47.32 (d), 56.41 (d), 96.31 (s), 178.86 (s); ms m/s (rel intensity) 183 (M^+, 19), 168 (20), 165 (1), 154 (7), 140 (100), 124 (16), 122 (13), 112 (20), 99 (27), 85 (41); hrms Calcd for $C_{10}H_{17}NO_2$: 183.1259. Found 183.1255. *Anal.* Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.39; H, 9.38; N, 7.78.

(±)-(1*R,4*S**,5*S**,1'*S**)- and (±)-(1*R**,4*S**,5*S**,1'*R**)-4-(1-Phenylethyl)-1-hydroxy-2-azabicyclo[3.3.0]octan-3-ones (10) and (11).** Enone **(4)** (10 g, 50 mmol) was treated as described previously at 50 °C for 12 h. Column chromatography of the residue (hexane-EtOAc, 60:40) gave the carbinolamides **(10)** (6.49 g, 53 %) and **(11)** (1.2 g, 10 %).

Compound **(10)**: mp 122-123 °C (hexane); ir ν_{max} 3530, 3515, 3418, 3090, 3060, 1680, 1600, 1495, 1450, 1405, 1370, 1290, 1080, 1045, 1002, 700 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.42 (3H, d, *J* = 8.0 Hz, 1'-Me), 1.35-1.75 (6H, m), 2.15 (1H, m, 5-H), 2.19 (1H, m, O-H), 2.37 (1H, dd, *J* = 3.2, 2.4 Hz, 4-H), 3.64 (1H, dq, *J* = 3.4, 7.2 Hz, 1'-H), 5.83 (1H, m, N-H), 7.32 (5H, m, Ar-H_5); ^{13}C-nmr (50.3 MHz) δ 18.66 (q), 24.45 (t), 34.52 (t), 39.18 (t), 39.46 (d), 47.24 (d), 57.13 (d), 96.14 (s), 126.93 (d), 128.00 (2xd), 128.38 (2xd), 142.54 (s), 178.10 (s); ms m/s (rel intensity) 245 (M^+, 42), 230 (3), 227 (5), 202 (10), 162 (58), 145 (17), 141 (73), 124 (23), 122 (13), 115 (17), 105 (100), 91(27), 85 (59), 77(34); hrms Calcd for $C_{15}H_{19}NO_2$ 245.1415. Found 245.1410. *Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.35; H, 8.01; N, 5.66.

Compound **(11)**: mp 142-144 °C (acetone-hexane); ir ν_{max} 3610, 3515, 3418, 3085, 3060, 1690, 1600, 1492, 1451, 1408, 1385, 1130, 1080, 1050, 1000, 705 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.50 (3H, d, *J* = 7.0 Hz, 1'-Me), 1.2-1.9 (6H, m), 2.00 (1H, m), 2.24 (1H, dt, *J* = 9.3, 3.7 Hz, 5-H), 2.45 (1H, t, *J* = 3.8 Hz, 4-H), 3.27 (1H, dq, *J* = 4.0, 6.9 Hz, 1'-H), 6.25 (1H, m, O-H), 6.31 (1H, m, N-H), 7.30 (5H, m, Ar-H_5); ^{13}C-nmr (50.3 MHz) δ 16.41 (q), 24.59 (t), 34.19 (t), 40.21 (d), 40.23 (t), 49.78 (d), 56.71 (d), 96.00 (s), 126.61 (d), 127.60 (2xd), 129.51 (2xd), 143.62 (s), 177.43 (s); ms m/z (rel intensity) 245 (M^+, 56), 230 (4), 227 (6), 202 (11), 162 (100), 145 (29), 141 (47), 129 (10), 124 (17), 115 (13), 105 (85), 91 (22), 85 (37), 77 (26); hrms Calcd for $C_{15}H_{19}NO_2$ 245.1415. Found 245.1409. *Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.48; H, 7.70; N, 5.83.

(±)-(1*R,4*S**,5*S**)-4-Diphenylmethyl-1-hydroxy-2-azabicyclo[3.3.0]octan-3-one (12).** Compound **(5)** (2 g, 7.63 mmol) was treated as described above, for 24 h at 50 °C. To the residue in EtOH (50 ml) was added NaOH (0.5 g, 12.5 mmol) and the resulting solution stirred at room temperature for 24 h. Column chromatography of the residue (hexane-EtOAc, 1:1) gave the carbinolamide **(12)** (1.478 g, 63 %): mp 174-175.5 °C (acetone-hexane); ir ν_{max} 3550, 3420, 1695, 1600, 1490, 1450, 1400, 1340, 1085, 1000, 975, 695 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.7-1.9 (5H, m), 2.3-2.6 (2H, m), 3.02 (1H, t, *J* = 2.4 Hz, 4-H), 4.95 (1H, d, *J* = 2.4 Hz, 1'-H), 6.06 (1H, m, N-H), 7.28 (10H, m, Ar-H_{10}); ^{13}C-nmr (50.3 MHz) δ 24.40 (t), 34.67(t), 39.20 (t), 47.80 (d), 50.72 (d), 54.42 (d), 96.32 (s), 126.58 (d), 127.24 (d), 128.35 (2xd), 128.46 (2xd), 128.52 (2xd), 129.56 (2xd), 141.95 (s), 142.28 (s), 178.15 (s); ms m/z (rel intensity) 307 (M^+, 29), 289 (6), 244 (1), 224 (62), 207 (24), 178 (14), 167 (100), 165 (64), 152 (34), 128 (10), 115 (14), 91 (6), 77 (6); hrms Calcd for $C_{20}H_{21}NO_2$ 307.1572. Found 307.1580. *Anal.* Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.93; H, 7.02; N, 4.53.

(±)-(1*R,4*R**,5*S**)-4-Phenyl-1-hydroxy-2-azabicyclo[3.3.0]octan-3-one (13).** Compound **(6)** (5 g, 29.1 mmol) was treated according to the procedure described for **(4)**. Column chromatography of the residue (hexane-EtOAc, 30:70) gave the carbinolamide **(13)** (3.92 g, 62 %): mp 145-147 °C (hexane); ir ν_{max} 3615, 3440, 1705, 1603, 1500, 1457, 1400, 1080, 1010, 990 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.6-2.0 (5H, m), 2.18 (1H, m), 2.61 (1H, dt, *J* = 8.8, 3.8 Hz, 5-H), 3.34 (1H, d, *J* = 4.5 Hz, 4-H), 4.45 (1H, m, O-H), 6.68 (1H, m, N-H), 7.25 (5H, m, Ar-H_5); ^{13}C-nmr (50.3 MHz) δ 24.68 (t), 33.43 (t), 40.37 (t), 55.00 (d), 56.79 (d), 96.42 (s),

127.07 (d), 128.09 (2xd), 128.80 (2xd), 139.69 (s), 177.47 (s); ms m/s (rel intensity) 217 (M^+, 71), 199 (37), 174 (100), 170 (35), 156 (14), 146 (33), 117 (53), 115 (70), 103 (21), 91 (59), 77 (21); hrms Calcd for $C_{13}H_{15}NO_2$ 217.1103. Found 217.1103. *Anal.* Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.95; H, 7.04; N, 6.30.

Fragmentation of 4-Alkyl-1-hydroxy-2-azabicyclo[3.3.0]octan-3-one Derivatives (7-13): General Procedure. A solution of the carbinolamide (1 mmol) in CH_2Cl_2 (20 to 50 ml dried over 3-4 Å molecular sieves, in accord with the solubility of carbinolamide), containing (diacetoxyiodo)benzene (483 mg, 1.5 mmol) and I_2 (254 mg, 1 mmol), was irradiated with 2x100 W tungsten-filament lamps for the time and temperature stated in each case. The reaction mixture was then poured into aqueous sodium thiosulfate and extracted with CH_2Cl_2, dried over Na_2SO_4, concentrated, and the residue purified by chromatotron chromatography.

Fragmentation of (±)-(1R*,5S*)-1-Hydroxy-2-azabicyclo[3.3.0]octan-3-one (7). Carbinolamide (**7**) (242 mg, 1.72 mmol) in CH_2Cl_2 (86 ml) under Ar was treated with (diacetoxyiodo)benzene (831 mg, 2.58 mmol) and iodine (438 mg, 1.72 mmol) as described previously at 25 °C for 2 h, to give after chromatotron chromatography (hexane-EtOAc, 70:30) (±)-2-(3'-iodopropyl)succinimide (**14**) (110 mg, 24%) and (±)-3-iodoperhydroazocine-2,8-dione (**15**) (90 mg, 20%).

Compound (**14**): mp 93.5-95 °C (acetone-pentane); ir ν_{max} 3404, 1786, 1709 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.68 (1H, m), 1.8-2.1 (3H, m), 2.41 (1H, dd, *J* = 8.3, 21.6 Hz, 2-H), 2.86 (1H, m, 3-H), 2.90 (1H, dd, *J* = 8.9, 21.3 Hz, 2-H), 3.19 (2H, m, 3'-H_2), 9.80 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 5.24 (t), 30.45 (t), 31.94 (t), 35.49 (t), 40.26 (d), 177.07 (s), 180.24 (s); ms m/z (rel intensity) 268 (M^+ + 1, 6), 155 (12), 140 (100), 127 (29), 97 (20), 69 (98); hrms Calcd for $C_7H_{11}NO_2I$ 267.98346. Found 267.98429. *Anal.* Calcd for $C_7H_{10}NO_2I$: C, 31.48; H, 3.77; N, 5.24. Found: C, 31.60; H, 3.65; N, 5.28.

Compound (**15**): mp 119-121 °C (acetone-pentane); ir ν_{max} 3351, 1686 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.8-2.05 (2H, m, 4-H, 5-H), 2.05-2.25 (2H, m, 4-H, 5-H), 2.80 (1H, ddd, *J* = 7.3, 10.7, 14.0 Hz, 6-H), 3.07 (1H, ddd, *J* = 4.8, 13.6, 14.0 Hz, 6-H), 3.06 (1H, dd, *J* = 7.1, 14.8 Hz, 2-H), 3.71 (1H, dd, *J* = 10.2, 14.8 Hz, 2-H), 4.62 (1H, m, 3-H); ^{13}C-nmr (50.3 MHz) δ 21.68 (d), 22.49 (t), 34.12 (t), 35.00 (t), 48.33 (t), 169.56 (s), 172.50 (s); ms m/z (rel intensity) 267 (M^+, 13), 140 (31), 127 (35), 122 (6), 112 (11), 98 (79), 97 (75), 69 (100); hrms Calcd for $C_7H_{10}NO_2I$ 266.97563. Found 266.97585. *Anal.* Calcd for $C_7H_{10}NO_2I$: C, 31.48; H, 3.77; N, 5.24. Found: C, 31.51; H, 3.86; N, 5.12.

Fragmentation of (±)-(1*R,4*S**,5*S**)-4-(2'-Phenylethyl)-1-hydroxy-2-azabicyclo[3.3.0]octan-3-one (8).** A solution of carbinolamide (**8**) (0.5 g, 2.04 mmol), (diacetoxyiodo)benzene (985 mg, 3.06 mmol) and iodine (518 mg, 2.04 mmol) in CH_2Cl_2 (50 ml) was allowed to react according to the general method. After 30 min at 20 °C and usual work-up, the residue gave, after column chromatography (hexane-EtOAc, 90:10), (±)-(2*R**,3*R**)-2-(2'-phenylethyl)-3-iodoperhydroazocine-2,8-dione (**17**) (242 mg, 32 %) and a polar fraction which was separated by fractional crystallization from EtOAc to give (±)-(2*S**,3*S**)-2-(2'-phenylethyl)-3-(3"-iodopropyl)succinimide (**16**) (295 mg, 39 %) and (±)-(2*R**,3*S**)-2-(2'-phenylethyl)-3-iodoperhydroazocine-2,8-dione (**18**) (68 mg, 9 %).

Compound (**16**): mp 95-96 °C (EtOAc); ir ν_{max} 3395, 3087, 3060, 1770, 1720, 1705, 1595, 1487, 1445, 1340, 1170, 695 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.6-2.1 (5H, m), 2.1- 2.3 (1H, m), 2.54 (2H, m, 2-H, 3-H), 2.80 (2H, t, *J* = 7.8 Hz, 2'-H_2), 3.17 (2H, t, *J* = 6.3 Hz, 3"-H_2), 7.23 (5H, m, Ar-H_5), 8.93 (1H, m, N-H); ^{13}C-nmr

(20.1 MHz) δ 5.35 (t), 29.91 (t), 31.58 (t), 32.30 (t), 32.52 (t), 45.78 (d), 46.05 (d), 126.05 (d), 128.13 (2xd), 128.32 (2xd), 140.22 (s), 179.25 (s), 179.40 (s); ms m/z (rel intensity) 371 (M^+, 4), 267 (40), 244 (46), 140 (100), 123 (13), 112 (33), 105 (23), 98 (39), 91 (97), 77 (14); hrms Calcd for $C_{15}H_{18}NO_2I$ 371.0384. Found 371.0338. *Anal.* Calcd for $C_{15}H_{18}NO_2I$: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.57; H, 4.75; N, 3.83.

Compound (**17**): mp 133-135 °C (pentane); ir ν_{max} 3335, 3080, 3055, 1685, 1595, 1485, 1440, 1400, 1350, 1320, 1250, 1155, 1140, 700 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.6-2.9 (10H, m), 3.27 (1H, dt, *J* = 9.9, 2.7 Hz, 2-H), 4.22 (1H, dt, *J* = 10.8, 1.7 Hz, 3-H), 7.24 (5H, m, Ar-H_5), 8.20 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ: 23.39 (t), 33.13 (t), 33.36 (t), 33.89 (d), 34.27 (t), 35.16 (t), 53.61 (d), 126.27 (d), 128.42 (2xd), 128.54 (2xd), 140.56 (s), 170.34 (s), 172.33 (s); ms m/z (rel intensity) 371 (M^+, 6), 244 (13), 227 (1), 216 (2), 199 (3), 181 (5), 171 (3), 155 (3), 140 (100), 123 (72), 117 (45), 112 (55), 105 (16), 104 (29), 95 (46), 91 (98), 77 (32); hrms Calcd for $C_{15}H_{18}NO_2I$ 371.0384. Found 371.0377. *Anal.* Calcd for $C_{15}H_{18}NO_2I$: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.72; H, 4.63; N, 3.79.

Compound (**18**): mp 179-180 °C (EtOAc); ir ν_{max} 3340, 3080, 3060, 1690, 1600, 1490, 1450, 1380, 1350, 1320 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.6-1.9 (3H, m), 2.2-2.8 (8H, m), 4.24 (1H, dt, *J* = 12.4, 4.6 Hz, 3-H), 7.25 (5H, m, Ar-H_5), 8.13 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 24.31 (t), 32.13 (d), 32.32 (t), 36.13 (t), 36.52 (t), 38.19 (t), 45.81 (d), 126.50 (d), 128.40 (2xd), 128.77 (2xd), 140.81 (s), 169.95 (s), 171.53 (s); ms m/z (rel intensity) 371 (M^+, 1), 244 (8), 227 (3), 216 (3), 199 (11), 181 (6), 171 (3), 155 (2), 140 (68), 123 (22), 117 (15), 105 (7), 104 (12), 95 (12), 91 (100), 77 (11); hrms Calcd for $C_{15}H_{18}NO_2I$ 371.0384. Found 371.0392. *Anal.* Calcd for $C_{15}H_{18}NO_2I$: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.65; H, 4.93; N, 3.52.

Fragmentation of (±)-(1*R,4*S**,5*S**)-4-(1'-Methylethyl)-1-hydroxy-2-azabicyclo[3.3.0]octan-3-one (9).** Carbinolamide (**9**) (410 mg, 2.24 mmol) in CH_2Cl_2 (75 ml) was irradiated in the presence of (diacetoxyiodo)benzene (1.15 g, 3.58 mmol) and I_2 (0.57 g, 2.24 mmol) for 45 min at 25 °C as described previously to give, after chromatography (hexane-EtOAc, 85:15), (±)-(2*S**,3*S**)-2-(1'-isopropyl)-3-(3"-iodopropyl)-succinimide (**19**) (408 mg, 59 %), (±)-(2*R**,3*R**)-2-(1'-isopropyl)-3-iodo-perhydroazocine-2,8-dione (**20**) (14 mg, 2 %), and (±)-(2*R**,3*S**)-2-(1'-isopropyl)-3-iodo-perhydroazocine-2,8-dione (**21**) (45 mg, 6.5 %).

Compound (**19**): amorphous; ir ν_{max} 3395, 1775, 1725, 1700, 1460, 1170 cm^{-1}; ^{1}H-nmr (200 MHz) δ 0.98 (3H, d, *J* = 7.0 Hz, 1'-Me), 1.04 (3H, d, *J* = 7.0 Hz, 1'-Me), 1.7-2.1 (4H, m, 1"-H_2, 2"-H_2), 2.25 (1H, m, 1'-H), 2.47 (1H, t, *J* = 4.2 Hz, 2-H), 2.59 (1H, dt, *J* = 4.2, 6.7 Hz, 3-H), 3.20 (2H, t, *J* = 6.4 Hz, 3"-H_2), 9.18 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 5.81 (t), 18.12 (q), 19.59 (q), 28.99 (d), 30.05 (t), 32.60 (t), 42.11 (d), 52.76 (d), 179.57 (s), 180.18 (s); ms m/z (rel intensity) 309 (M^+, 1), 294 (1); 266 (2), 237 (1), 223 (1), 194 (2), 182 (100), 155 (6), 140 (9), 127 (6), 111 (30); hrms Calcd for $C_{10}H_{16}NO_2I$ 309.0228. Found 309.09228. *Anal.* Calcd for $C_{10}H_{16}NOI$: C, 38.85; H, 5.22; N, 4.53. Found: C, 38.98; H, 5.36; N, 4.32.

Compound (**20**): mp 144-146 °C (hexane); ir ν_{max} 3340, 1690, 1455, 1445, 1360, 1295, 1140 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.08 (3H, d, *J* = 7.0 Hz, 1'-Me), 1.16 (3H, d, *J* = 7.0 Hz, 1'-Me), 1.7-2.1 (2H, m, 4-H, 5-H), 2.15-2.4 (3H, m, 1'-H, 4-H, 5-H), 2.76 (1H, dd, *J* = 6.1, 13.5 Hz, 6-H), 3.16 (1H, dt, *J* = 6.7, 14.0 Hz, 6-H), 3.34 (1H, dd, *J* = 11.6, 4.0 Hz, 2-H), 4.51 (1H, dm, *J* = 11.5 Hz, 3-H), 8.02 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 15.47 (q), 20.81 (q), 23.49 (t), 31.51 (d), 31.86 (d), 33.51 (t), 35.53 (t), 57.00 (d), 170.52 (s), 172.34 (s); ms m/z (rel intensity) 309 (M^+, 5), 214 (3), 182 (100), 165 (66), 154 (18), 137 (46), 127 (14), 123 (11), 109 (25), 98 (30), 95 (56); hrms Calcd for $C_{10}H_{16}NO_2I$ 309.0228. Found 309.0200. *Anal.* Calcd for

$C_{10}H_{16}NO_2I$: C, 38.85; H, 5.22; N, 4.52. Found: C, 38.89; H, 5.19; N, 4.41.

Compound (**21**): mp 167-169 °C (acetone-hexane); ir ν_{max} 3330, 1690, 1600, 1455, 1375, 1360, 1280, 1160, 1110 cm^{-1}; ^{1}H-nmr (200 MHz) δ 0.98 (3H, d, *J* = 6.4 Hz, 1'-Me), 1.01 (3H, d, *J* = 6.5 Hz, 1'-Me), 1.7-2.1 (3H, m, 4-H, 5-H_2), 2.25 (1H, m, 1'-H), 2.33 (1H, dd, $J_{2,1'}$ = 8.9, $J_{2,3}$ = 4.1 Hz, 2-H), 2.67 (1H, dq, *J* = 4.6, 15.1 Hz, 4-H), 2.93 (1H, dd, *J* = 8.3, 14.5 Hz, 6-H), 3.07 (1H, dd, *J* = 8.8, 11.7 Hz, 6-H), 4.32 (1H, dt, *J* = 4.7, 12.6 Hz, 3-H), 8.28 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 18.89 (q), 21.40 (q), 24.59 (t), 30.56 (d), 32.20 (d), 36.68 (t), 38.06 (t), 55.29 (d), 170.13 (s), 171.55 (s); ms m/z (rel intensity) 309 (M^+, 28), 266 (1), 182 (100), 165 (60), 154 (46), 139 (19), 137 (48), 127 (36), 123 (15), 109 (38), 98 (43), 95 (98); hrms Calcd for $C_{10}H_{16}NO_2I$ 309.0228. Found 309.0237. *Anal.* Calcd for $C_{10}H_{16}NO_2I$: C, 38.85; H, 5.22; N, 4.52. Found: C, 38.76; H, 5.17; N, 4.58.

Fragmentation of (±)-(1*R,4*S**,5*S**,1'*S**)-4-(1'-Phenylethyl)-1-hydroxy-2-azabicyclo[3.3.0]octan-3-one (10).** Carbinolamide (**10**) (2.02 g, 8.24 mmol) in CH_2Cl_2 (162 ml) was irradiated in the presence of (diacetoxyiodo)benzene (4 g, 12,4 mmol) and I_2 (2.1 g, 8.24 mmol) as above for 40 min at 25 °C to give, after chromatography (hexane-EtOAc, 95:5), (±)-(2*S**,3*S**,1'*S**)-(2-(1'-phenylethyl)-3-(3"-iodopropyl)succinimide (**22**) (1.71 g, 55.9 %), (±)-(2*R**,3*R**,1'*S**)-2-(1'-phenylethyl)-3-iodoperhydroazocine-2,8-dione (**24**) (60 mg, 2 %), and (±)-(2*R**,3*S**,1'*S**)-2-(1'-phenylethyl)-3-iodoperhydroazocine-2,8-dione (**25**) (93 mg, 3 %).

Compound (**22**): mp 86-88 °C (acetone); ir ν_{max} 3410, 3070, 1780, 1725, 1065, 1455, 1350, 1180, 705 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.51 (3H, d, *J* = 7.0 Hz, 1'-Me), 1.6-1.9 (4H, m), 2.55 (1H, dt, *J* = 3.9, 6.5 Hz, 3-H), 2.71 (1H, dd, *J* = 3.4, 7.0 Hz, 2-H), 3.06 (2H, dt, *J* = 2.7, 6.3 Hz, 3"-H_2), 3.34 (1H, dq, *J* = 7.0, 6.6 Hz, 1'-H), 7.27 (5H, m, Ar-H_5), 8.23 (1H, m, N-H); ^{1}H-nmr (200 MHz, C_6D_6) δ 1.19 (3H, d, *J* = 7.7 Hz, 1'-Me), 1.1-1.4 (4H, m), 2.15 (2H, m, 2-H, 3-H), 2.45 (2H, dt, *J* = 1.2, 6.6 Hz, 3"-H_2), 2.85 (1H, qui, *J* = 6.9 Hz, 1'-H), 7.0 (6H, m, N-H, Ar-H_5); ^{13}C-nmr (50.3 MHz) δ 5.49 (t), 18.63 (q), 29.48 (t), 31.84 (t), 40.16 (d), 43.22 (d), 52.70 (d), 126.70 (d), 127.24 (2xd), 128.16 (2xd), 141.33 (s), 178.40 (s), 179.10 (s); ms m/z (rel intensity) 372 (M^++1, 7), 244 (44), 173 (3), 145 (5), 140 (6), 128 (7), 117 (7), 105 (100), 91 (14), 77 (21); hrms Calcd for $C_{15}H_{19}NO_2I$ 372.0462. Found 372.0458. *Anal.* Calcd for $C_{15}H_{18}NO_2I$: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.71; H, 4.75; N, 3.69.

Compound (**24**): mp 148.5-149 °C (EtOAc-hexane); ir ν_{max} 3340, 3100, 3080, 1690, 1600, 1490, 1460, 1405, 1360, 1340, 1285, 1140, 700 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.57 (3H, d, *J* = 7.0 Hz, 1'-Me), 1.7-2.3 (4H, m), 2.69 (1H, dd, *J* = 6.0, 13.2, 6-H), 3.07 (1H, dt, *J* = 6.5, 13.8 Hz, 6-H), 3.51 (1H, dq, *J* = 4.3, 7.2 Hz, 1'-H), 3.66 (1H, dd, *J* = 4.3, 11.4 Hz, 2-H), 4.57 (1H, dm, *J* = 11.5 Hz, 3-H), 7.23 (5H, m, Ar-H_5), 7.77 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 13.18 (q), 23.56 (t), 31.80 (d), 33.57 (t), 35.51 (t), 42.34 (d), 58.62 (d), 126.80 (d), 128.04 (2xd), 128.47 (2xd), 143.36 (s), 170.07 (s), 171.87 (s); ms m/z (rel intensity) 371 (M^+, 40), 244 (77), 227 (28), 216 (21), 199 (22), 181 (13), 145 (22), 129 (31), 117 (17), 115 (18), 105 (100), 91 (28), 77 (23); hrms Calcd for $C_{15}H_{18}NO_2I$ 371.0384. Found 371.0389. *Anal.* Calcd for $C_{15}H_{18}NO_2I$: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.37; H, 5.03; N, 3.79.

Compound (**25**): ir ν_{max} 3340, 3080, 3060, 1704, 1694, 1600, 1490, 1460, 1440, 1400, 1380, 1370, 1360, 1270, 1160, 1070, 1015, 702 cm-1; ^{1}H-nmr (200 MHz) δ 1.33 (3H, d, *J* = 6.7 Hz, 1'-Me), 1.60 (1H, m), 1.90 (1H, m), 2.20 (1H, m), 2.45 (1H, m), 2.96 (1H, dd, *J* = 9.0, 14.5 Hz, 6-H), 3.06 (1H, dd, *J* = 4.1, 9.7 Hz, 2-H), 3.13 (1H, m, 6-H), 3.32 (1H, dq, *J* = 9.7, 6.6 Hz, 1'-H), 3.69 (1H, ddd, *J* = 4.1, 5.9, 13.4 Hz, 3-H), 7.32

(5H, m, Ar-H_5), 8.24 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 21.32 (q), 24.12 (t), 31.43 (d), 36.84 (t), 37.97 (t), 43.14 (d), 53.95 (d), 127.16 (d), 127.85 (2xd), 128.99 (2xd), 142.44 (s), 169.65 (s), 171.48 (s); ms m/z (rel intensity) 371 (M^+, 44), 244 (25), 227 (25), 216 (24), 199 (29), 183 (22), 157 (21), 145 (41), 129 (44), 115 (23), 105 (100), 91 (35), 77 (30); hrms Calcd for $C_{15}H_{18}NO_2I$ 371.0384. Found 371.0381. *Anal.* Calcd for $C_{15}H_{18}NO_2I$: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.67; H, 4.75; N, 3.83. X-ray analysis: $C_{15}H_{18}NO_2I$, orthorhombic, space group $P2_1/c$, Z = 4, a = 17.508(3), b = 7.192, c = 11.931 Å; β = 95.01 (5)°. Crystal size: 0.2x0.3x0.05 mm. The data were measured on a Philips PW-1100 four-circle automatic diffractometer operating with Cu-K_α radiation (λ = 1.5418 Å) monochromated by graphite. The orientation matrix of the crystal was calculated from the angular setting of 25 randomly distributed reflections found in the range $10^\circ<\theta>25^\circ$. The structure was solved by means of direct methods and refined with isotropic factors. Owing to the small size of the crystal and the small number of reflections above the 2σ level, only the iodine atom was refined anisotropically. Most of the hydrogen atoms (64 % of the total) were located on successive Fourier-difference maps, and introduced with a fixed isotropic thermal factor equal to that of the bonded carbon. The others were imposed at their theoretical places. An important decomposition was found during the data collection and the crystal life-time is about 10 h, the crystal turning brown upon I_2 release. Only one crystal was used in the data collection. A very high-speed recording technique was adopted: no background measurements during the data collection and a 15 sec scanning time per reflection. The background was *a posteriori* evaluated from an extrapolated curve of stationary counts (time = 30 s) obtained at different θ angles. The intensities, measured up to $\theta = 65^\circ$, were merged and averaged after scaling as usual with an overall R_{symm} = 7.6 % for 2321 measured reflections. They were reduced to **F** structural factors by means of standard Lorentz and polarization corrections and considered as observed above the 2σ background level. The unique data set contains 1394 reflections of which 828 are above the 2σ background level.

Fragmentation of (±)-(1*R,4*S**,5*S**,1'*R**)-4-(1'-Phenylethyl)-1-hydroxy-2-azabicyclo[3.3.0]octan-3-one (11).** Carbinolamide (**11**) (0.6 g, 2.45 mmol) in CH_2Cl_2 (60 ml) was irradiated in the presence of (diacetoxyiodo)benzene (1.18 g, 3.7 mmol) and I_2 (0.62 g, 2.45 mmol) as above, at 25 °C for 50 min, to give, after chromatography (hexane-EtOAc, 90:10), (±)-(2*S**,3*S**,1'*R**)-2-(1'-phenylethyl)-3-(3"-iodopropyl)succinimide (**23**) (554 mg, 61 %), (±)-(2*R**,3*R**,1'*R**)-2-(1'-phenylethyl)-3-iodoperhydroazocine-2,8-dione (**26**) (27 mg, 3 %), and (±)-(2*R**,3*S**,1'*R**)-2-(1'-phenylethyl)-3-iodoperhydroazocine-2,8-dione (**27**) (91 mg, 10 %).

Compound (**23**): mp 100-101 °C (acetone-hexane); ir ν_{max} 3395, 1775, 1720, 1600, 1450, 1355, 1345, 1170, 650 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.36 (3H, d, *J* = 7.2 Hz, 1'-Me), 1.3-1.6 (4H, m), 2.59 (1H, dt, *J* = 4.3, 5.7 Hz, 3-H), 2.81 (1H, dd, *J* = 4.2, 4.2 Hz, 2-H), 2.93 (2H, t, *J* = 6.3 Hz, 3"-H_2), 3.55 (1H, dq, *J* = 7.2, 4.2 Hz, 1'-H), 7.31 (5H, m, Ar-H_5), 8.29 (1H, m, N-H); ^{1}H-nmr (200 MHz, C_6D_6) δ 1.12 (3H, d, *J* = 7.2 Hz, 1'-Me), 0.9-1.3 (4H, m), 2.33 (1H, m, 3-H), 2.4-2.7 (3H, m, 2-H and 3"-H_2), 3.37 (1H, m, 1'-H), 7.04 (5H, m, Ar-H_5), 9.50 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 5.22 (t), 14.14 (q), 29.69 (t), 32.14 (t), 38.61 (d), 41.59 (d), 53.80 (d), 127.25 (3xd), 128.80 (2xd), 141.70 (s), 178.60 (s), 179.67 (s); ms m/z (rel intensity) 371 (M^+, 10), 244 (94), 216 (2), 173 (5), 145 (18), 129 (7), 117 (8), 105 (100), 91 (13), 77 (17); hrms Calcd for $C_{15}H_{18}NO_2I$ 371.0384. Found 371.0391. *Anal.* Calcd for $C_{15}H_{18}NO_2I$: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.71; H, 4.93; N, 3.65.

Compound (**26**): amorphous; ir ν_{max} 3340, 1690, 1600, 1450, 1400, 1340, 1265, 1150, 1125, 905, 650 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.49 (3H, d, *J* = 7.0 Hz, 1'-Me), 1.7 (1H, m), 1.9-2.15 (2H, m), 2.3 (1H, m), 2.76 (1H, dm, *J* = 14.6 Hz, 6-H), 3.20 (1H, dt, *J* = 5.9, 14.3 Hz, 6-H), 3.59 (1H, dq, *J* = 5.7, 7.0 Hz, 1'-H), 3.63 (1H, dd, *J* = 5.7, 15.8 Hz, 2-H), 4.16 (1H, m, 3-H), 7.31 (3H, m, Ar-H_3), 7.63 (2H, m, Ar-H_2), 7.87 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 19.97 (q), 24.82 (t), 32.20 (d), 33.23 (t), 35.04 (t), 41.50 (d), 59.16 (d), 127.01 (d), 128.00 (2xd), 129.70 (2xd), 141.31 (s), 170.19 (s), 172.31 (s); ms m/z (rel intensity) 371 (M^+, 30), 244 (71), 227 (21), 216 (20), 199 (20), 171 (10), 157 (12), 145 (24), 129 (33), 115 (19), 105 (100), 91 (32), 77 (26); hrms Calcd for $C_{15}H_{18}NO_2I$ 371.0384. Found 371.0379. *Anal.* Calcd for $C_{15}H_{18}NO_2I$: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.73; H, 4.95; N, 3.50.

Compound (**27**): mp 194.5-196 °C (acetone-hexane); ir ν_{max} 3340, 1700, 1600, 1360, 1330, 1280, 1160 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.29 (3H, d, *J* = 7.0 Hz, 1'-Me), 1.8-2.1 (2H, m), 2.3 (1H, m), 2.75 (1H, m), 2.75-3.2 (3H, m), 3.33 (1H, dd, *J* = 9.8, 7.1 Hz, 1'-H), 4.46 (1H, dt, *J* = 4.4, 12.5 Hz, 3-H), 7.25 (5H, m, Ar-H_5), 7.86 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 19.14 (q), 24.71 (t), 30.11 (d), 36.80 (t), 38.17 (t), 43.45 (d), 54.12 (d), 126.73 (d), 127.59 (2xd), 128.71 (2xd), 144.47 (s), 168.86 (s), 171.07 (s); ms m/z (rel intensity) 371 (M^+, 75), 244 (23), 226 (7), 216 (26), 199 (13), 183 (10), 171 (7), 157 (12), 145 (45), 131 (10), 129 (29), 115 (18), 105 (100), 91(30), 77(32); hrms Calcd for $C_{15}H_{18}NO_2I$ 371.0384. Found 371.0387. *Anal.* Calcd for $C_{15}H_{18}NO_2I$: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.64; H, 4.87; N, 3.50.

Fragmentation of (±)-(1*R,4*R**,5*S**)-4-Diphenylmethyl-1-hydroxy-2-azabicyclo[3.3.0]octan-3-one (12).** Carbinolamide (**12**) (225 mg, 0.73 mmol) in CH_2Cl_2 (35 ml) was irradiated for 45 min at 25 °C as described previously to give, after chromatography (hexane-EtOAc, 98:2), (±)-(2*S**,3*S**)-2-diphenylmethyl-3(3"-iodopropyl)succinimide (**28**) (171 mg, 52 %), (±)-(2*R**,3ξ)-2-diphenylmethyl-3-iodoperhydroazocine-2,8-dione (**29**) (22 mg, 7 %), and (±)-(2*R**,3ξ)-2-diphenylmethyl-3-iodoperhydroazocine-2,8-dione (**30**) (26 mg, 8 %).

Compound (**28**): mp 124.5-126 °C (acetone-hexane); ir ν_{max} 3398, 1782, 1727, 1601, 1500, 1453, 1345, 1170 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.7-1.8 (4H, m), 2.75 (1H, dt, *J* = 6.1, 3.8 Hz, 3-H), 3.05 (2H, m, 3"-H_2), 3.38 (1H, dd, *J* = 3.8, 7.0 Hz, 2-H), 4.43 (1H, d, *J* = 7.0 Hz, 1'-H), 7.31 (10H, m, Ar-H_{10}), 8.09 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 5.41 (t), 29.68 (t), 32.40 (t), 44.61 (d), 51.31 (d), 52.58 (d), 127.16 (d), 127.33 (d), 128.28 (2xd), 128.55 (2xd), 128.66 (2xd), 128.82 (2xd), 140.21 (s), 140.56 (s), 177.49 (s), 178.78 (s); ms m/z (rel intensity) 433 (M^+, 9), 306 (3), 278 (1), 207 (9), 167 (100), 152 (10), 128 (3), 115 (6), 91 (4), 77 (3); hrms Calcd for $C_{20}H_{20}NO_2I$ 433.0539. Found 433.0556. *Anal.* Calcd for $C_{20}H_{20}NO_2I$: C, 55.44; H, 4.65; N, 3.23. Found: C, 55.23; H, 4.73; N, 3.25.

Compound (**29**): mp 193-195 °C (acetone); ir ν_{max} 3350, 1710, 1600, 1490, 1450, 1405, 1355, 1325, 1290, 1260, 1140, 695 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.85 (1H, m), 2.0-2.4 (3H, m), 2.80 (1H, dm, *J* = 14.7 Hz, 6-H), 3.28 (1H, dt, *J* = 14.4, 5.8 Hz, 6-H), 4.27 (2H, m, 2-H, 3-H), 4.29 (1H, s, 3-H), 4.75 (1H, d, *J* = 7.0 Hz, 1'-H), 7.28 (8H, m, Ar-H_8), 7.51 (2H, m, Ar-H_2), 7.78 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 24.84 (t), 29.76 (d), 33.42 (t), 35.01 (t), 54.45 (d), 57.62 (d), 127.02 (d), 127.10 (d), 128.57 (2xd), 128.60 (2xd), 129.15 (2xd), 129.50 (2xd), 140.20 (s), 140.95 (s), 170.45 (s), 172.32 (s); ms m/z (rel intensity) 433 (M^+, 11), 306 (M^+-I, 7), 278 (9), 261 (5), 207 (46), 178 (3), 167 (100), 152 (26), 129 (20), 115 (26), 91 (22), 77 (12); hrms Calcd for $C_{20}H_{20}NO_2$ 306.1494. Found 306.1487. *Anal.* Calcd for $C_{20}H_{20}NO_2I$: C, 55.44; H, 4.65; N, 3.23. Found: C, 55.47; H, 4.85; N, 3.11.

Compound (**30**): mp 188-190 °C (acetone-hexane); ir ν_{max} 3347, 3090, 3060, 1770, 1600, 1494, 1452, 1375, 1362, 1318, 1278, 1232, 1158 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.76 (1H, m), 2.00 (1H, m), 2.30 (1H, m), 2.60 (1H, m), 3.04 (1H, dd, *J* = 8.9, 14.4 Hz, 6-H), 3.39 (1H, ddd, *J* = 11.2, 2.0, 9.1 Hz, 6-H), 3.85 (1H, dd, *J* = 3.8, 10.3 Hz, 2-H), 3.92 (1H, m, 3-H), 4.52 (1H, d, *J* = 10.3 Hz, 1'-H), 7.31 (10H, m, Ar-H_{10}), 8.08 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 24.27 (t), 31.18 (d), 37.12 (t), 38.00 (t), 51.04 (d), 54.82 (d), 126.82 (d), 127.28 (2xd), 127.32 (d), 128.34 (2xd), 128.99 (2xd), 129.19 (2xd), 140.52 (s), 142.37 (s), 168.64 (s), 171.21 (s); ms m/z (rel intensity) 433 (M^+, 18), 306 (2), 278 (5), 266 (3), 224 (7), 207 (89), 178 (13), 167 (100), 165 (60), 152 (26), 129 (26), 115 (24), 105 (17), 91 (23), 77 (17); hrms Calcd for $C_{20}H_{20}NO_2I$ 433.0539. Found 433.0546. *Anal.* Calcd for $C_{20}H_{20}NO_2I$: C, 55.44; H, 4.65; N, 3.23. Found: C, 55.48; H, 4.53; N, 3.37.

Fragmentation of (±)-(1*R,4*R**,5*S**)-4-Phenyl-1-hydroxy-2-azabicyclo[3.3.0]octan-3-one (13).** A solution of carbinolamide (**13**) (825 mg, 3.9 mmol) in CH_2Cl_2 (90 ml) was irradiated in the presence of (diacetoxyiodo)benzene (1.88 g, 5.85 mmol) and I_2 (0.99 g, 3.9 mmol) for 30 min at 25 °C as described previously to give, after chromatography (hexane-EtOAc, 80:20), (±)-(2*R**,3*S**)-2-phenyl-3-(3"-iodopropyl)succinimide (**31**) (834 mg, 64 %) and (±)-(2*R**,3ξ)-2-phenyl-3-iodoperhydroazocine-2,8-dione (**32**) (26 mg, 2 %).

Compound (**31**): mp 110-111 °C (MeOH); ir ν_{max} 3440, 3025, 1790, 1730, 1603, 1500, 1460, 1355, 1340, 1160 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.8-2.15 (4H, m), 3.01 (1H, dt, *J* = 5.8, 7.5 Hz, 3-H), 3.13 (2H, t, *J* = 6.4 Hz, 3"-H_2), 3.71 (1H, d, *J* = 5.9 Hz, 2-H), 7.31 (5H, m, Ar-H_5), 8.39 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 5.58 (t), 30.12 (t), 31.23 (t), 48.97 (d), 53.69 (d), 127.73 (2xd), 127.96 (d), 129.12 (2xd), 136.20 (s), 177.72 (s), 178.96 (s); ms m/z (rel intensity) 343 (M^+, 5), 272 (14), 217 (51), 216 (100), 188 (7), 174 (21), 145 (90), 128 (23), 117 (91), 115 (95), 103 (24), 91 (87), 77 (34); hrms Calcd for $C_{13}H_{15}NO_2I$ 344.0148. Found 344.0150. *Anal.* Calcd for $C_{13}H_{14}NO_2I$: C, 45.50; H, 4.11; N, 4.08. Found: C, 45.71; H, 4.08; N, 3.87.

Compound (**32**): mp 188-189 °C (acetone-hexane); ir ν_{max} 3375, 1705, 1602, 1500, 1452, 1410, 1365, 1340, 1310, 1290, 1190, 1145, 695 cm^{-1}; ^{1}H-nmr (200 MHz) δ 1.9-2.2 (2H, m), 2.25-2.4 (2H, m), 2.90 (1H, dd, *J* = 5.7, 15.8 Hz, 6-H), 3.35 (1H, dt, *J* = 7.4, 15.9 Hz, 6-H), 4.70 (2H, m, 2-H, 3-H), 7.35 (5H, m, Ar-H_5), 8.03 (1H, m, N-H); ^{13}C-nmr (50.3 MHz) δ 23.46 (t), 32.29 (t), 34.12 (d), 35.59 (t), 60.67 (d), 128.43 (2xd), 128.55 (d), 129.09 (2xd), 137.01 (s), 169.34 (s), 172.12 (s); ms m/z (rel intensity) 343 (M^+, 6), 216 (72), 188 (20), 173 (43), 155 (11), 145 (38), 130 (54), 129 (55), 117 (60), 115 (78), 106 (67), 98 (35), 91 (100), 77 (16); hrms Calcd for $C_{13}H_{15}NO_2I$ 344.0148. Found 344.0144. *Anal.* Calcd for $C_{13}H_{14}NO_2I$: C, 45.50; H, 4.11; N, 4.08. Found: C, 45.39; H, 4.25; N, 4.05.

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