parent C atoms. Further details concerning the treatment of the H atoms are in the supplementary material. In the structure of **6b**, the sulfino group was found to be disordered; for the S and the (S=)O atom two partly occupied positions were found and refined to occupancies of 60% and 40%, respectively. The two partly occupied (S=)O positions could only be refined isotropically. Parameters refined were the overall scale factor, an isotropic extinction parameter g ($F_o = F_c/(1 + gI_c)$), positional and anisotropic thermal parameters for non-H atoms, and positional and isotropic thermal parameters for H atoms. Refinement converged with shift/error ratios less than unity. Final difference Fourier maps showed no significant features. All calculations were done with SDP.[32]

Acknowledgment. We thank P. Telleman for his contribution to a part of this work. We also acknowledge J. M. Visser and J. L. M. Vrielink for recording the NMR spectra, T. W. Stevens for recording the mass spectra, and A. M. Montanaro-Christenhusz for performing the elemental analysis.

(32) *Structure Determination Package*; B. A. Frenz and Associates Inc.; College Station, TX; Enraf Nonius, Delft, 1983.

Registry No. **1a**, 111982-21-9; **1b**, 55440-88-5; **1c**, 111982-22-0; **1d**, 111982-23-1; **1e**, 111982-24-2; **1f**, 111982-25-3; **1g**, 102096-98-0; **3a**, 116748-69-7; **3b**, 116748-70-0; **3d**, 116748-71-1; **3e**, 116748-72-2; **3f**, 116748-73-3; **3g**, 116748-74-4; **4b**, 116748-75-5; **4c**, 116748-76-6; **4d**, 116748-77-7; **4e**, 116748-78-8; **4g**, 116748-79-9; **5a**, 55440-82-9; **5b**, 55440-83-0; **5c**, 55440-84-1; **5d**, 103304-41-2; **5e**, 103304-43-4; **5f**, 55440-85-2; **5g**, 103304-45-6; **6a**, 111982-26-4; **6b**, 111970-24-2; **6c**, 111970-25-3; **6d**, 111970-26-4; **6e**, 111970-27-5; **6f**, 111970-28-6; **6g**, 111970-29-7; **8a**, 65112-35-8; **8b**, 65112-36-9; **8c**, 94707-40-1; **8d**, 116748-80-2; **8e**, 116748-81-3; **8f**, 116748-82-4; **8g**, 116748-83-5; $HO((CH_2)_2O)_3H$, 112-27-6; $HO((CH_2)_2O)_4H$, 112-60-7; $HO((CH_2)_2O)_5H$, 4792-15-8; $HO((CH_2)_2O)_6H$, 2615-15-8; $HO((CH_2)_2O)_7H$, 5617-32-3; $HO((CH_2)_2O)_8H$, 5117-19-1; $HO((CH_2)_2O)_9H$, 3386-18-3; 2-bromo-1,3-bis(bromomethyl)benzene, 25006-88-6; benzo-15-crown-5, 14098-44-3; benzo-18-crown-6, 14098-24-9; 3-(methylthio)benzo-15-crown-5, 116748-84-6; 3-(methylthio)benzo-18-crown-6, 116748-85-7.

Supplementary Material Available: Tables of positional and thermal parameters of all atoms, bond distances and angles, and torsion angles in the macrocycle, for the crystal structures of compounds **1b** and **6b** (10 pages). Ordering information is given on any current masthead page.

Stereoselective Intramolecular Haloamidation of N-Protected 3-Hydroxy-4-pentenylamines and 4-Hydroxy-5-hexenylamines

Yoshinao Tamaru,* Shin-ichi Kawamura, Takashi Bando, Kunitada Tanaka, Makoto Hojo, and Zen-ichi Yoshida*

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Kyoto 606, Japan

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Haloamidation of *N*-(*p*-tolylsulfonyl)-3-hydroxy-4-pentenylamines proceeds regio- and stereoselectively to provide *cis*-2-(halomethyl)-3-hydroxypyrrolidines in high yields. The tosylamides with phenyl and dimethyl substituents at C-5 cyclize to give six-membered piperidine products. *N*-(Methoxycarbonyl)-3-hydroxy-4-pentenylamines undergo a similar cyclization to furnish *cis*-*N*-(methoxycarbonyl)-2-(halomethyl)-3-hydroxypyrrolidines, which further undergo a cyclization to give bicyclic oxazolidones (1-aza-3-oxabicyclo[3.3.0]octan-2-ones). The above reactions proceed *in the dark*, while the haloamidation of *N*-(*p*-tolylsulfonyl)-4-hydroxy-5-hexenylamine only proceeds *upon exposure to ambient light* and provides 2-(halomethyl)-3-hydroxypiperidine.

Diastereoselective electrophilic addition to the double bond of allylic alcohols has attracted considerable interest in recent literature, and numerous experimental[1] and theoretical[2] approaches to this subject have appeared. The intramolecular version of the methodology, based on diastereoselective intramolecular addition of hetero nucleophiles, directed by an allylic hydroxyl group, has proved to be useful for the syntheses of heterocyclic compounds with stereochemically defined structures,[3] as exemplified by the syntheses of many natural products and their synthetic intermediates.

Most of these examples, however, are confined to the cyclization with oxygen nucleophiles. For example, 3-hydroxy-4-pentenoic acids[4] (and acid derivatives)[5] and 3-hydroxy-4-pentenols,[6] when treated with halogenating agents, stereoselectively provide *cis*-3-hydroxy-4-(halo-

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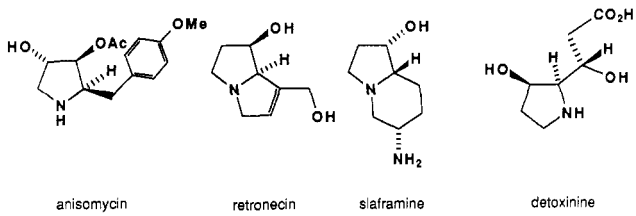

Figure 1.

methyl)-γ-butyrolactones and *cis*-2-(halomethyl)-3-hydroxytetrahydrofurans, respectively, in a synthetically useful level. Interestingly, despite the high potential as a methodology for the synthesis of the stereochemically defined nitrogen heterocycles, the hydroxyl group directed intramolecular amination of unsaturated hydroxy amines has been less studied. Except for our previous study,[7] to our knowledge, there has been reported only one example, which deals with a mercurioamination of 4-(benzyloxy)-5-hexenylamines.[8] In this reaction, which forms a six-membered piperidine ring, the allylic benzyloxy group seems not to exert its ability to control the diastereoselection. In this context, it seems important to clarify the regio- and stereoselectivity in the cyclization of 3-hydroxy-4-pentenylamines and 4-hydroxy-5-hexenylamines with wide structural characteristics.

In this paper, we describe the haloamidation of N-protected 3-hydroxy-4-pentenylamines **2** and **9** (eq 1 and 2) and *N*-(*p*-tolylsulfonyl)-4-hydroxy-5-hexenylamines **14** (eq 5).

The cyclization of **2** and **9** proceeds regio- and stereoselectively and provides *cis*-2-(halomethyl)-3-hydroxypyrrolidines **3** and **10**, respectively, in high yields. The usefulness of the reaction may be apparent from the structures of these products: (1) The cis configuration of the C-2 substituent with respect to the C-3 hydroxyl group in the pyrrolidine ring is abundantly observed in many interesting alkaloids (e.g., anisomycin,[9] retronecin,[10] slaframine,[11] detoxinine,[12] etc.,[13] Figure 1). (2) The halomethyl group in **3** and **10** is a versatile functionality and might be used for further manipulation to construct desired molecules. The usefulness of the present reaction may be further augmented by the ease with which the starting materials (and hence the products) with a wide structural variety could be prepared.

Some iodoamidation products **10** spontaneously undergo a further cyclization to furnish bicyclic 2-oxazolidone **13** (eq 3 and 9). This one-flask conversion of **9** to **13** may be regarded as a regio- and stereoselective vicinal hydroxyamination of a double bond and may be efficiently used for the synthesis of detoxinine[12] (eq 4 and Figure 1).

The above cyclization of **2** and **9** proceeds *in the dark*, while the cyclization of **14**, the one-carbon-higher homologue of **2**, only proceeds *upon exposure to ambient light* (eq 5).

A detailed mechanistic rationale for the stereoselective cis cyclization has been described elsewhere,[4b,6e] and in this

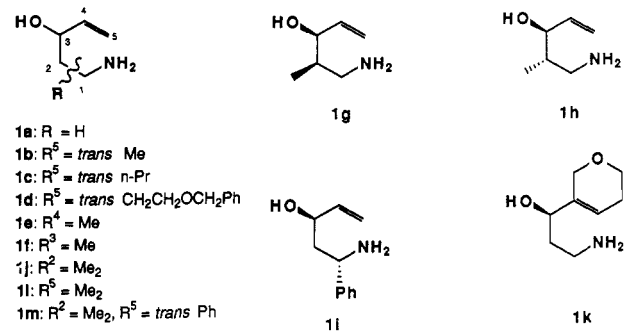

Figure 2. The structures of 3-hydroxy-4-pentenylamines 1.

paper our attention will be focused on the scope and limitation of the haloamidation from a synthetic point of view.

Effect of N-Protecting Groups on Haloamidation. The reactivity of unsaturated hydroxy amines **1** (Figure 2) toward haloamidation largely depends on the kind of amine protecting groups. As N-protecting groups, we examined tolylsulfonyl (sulfonamide), methoxycarbonyl (carbamate), (phenylamino)carbonyl (urea), and acyl (acid amide) groups. Among them, sulfonamide **2** showed the highest reactivity, and all the sulfonamides examined (**2a–m**) underwent haloamidation at a reasonable rate. Carbamates undergo the cyclization rather slowly and suffer from limited structural flexibility. Ureas react very slowly and provide complex mixtures of products. All the acid amide derivatives of **1a**, despite our extensive examination of the reaction conditions and the steric and electronic nature of acyl groups ($COCH_3$, COPh, $COCH{=}CH_2$, $COCH_2Cl$, $COCHCl_2$, $COCCl_3$, $COCF_3$, $COCH_2COCH_3$), were totally unreactive toward the cyclization. Mostly, they provide either halohydrins under aqueous conditions (conditions A, vide infra) or the starting material under anhydrous conditions (conditions D and E, vide infra).

The observed relative reactivity toward haloamidation among sulfonamides, carbamates, and ureas is in good accord with a general tendency: the more acidic the NH, the higher the nucleophilic reactivity.[14] However, taking into consideration that the acidities of trichloro- and trifluoroacetamides, though the accurate values are not known, are comparably as high as those of sulfonamide and carbamates, the low reactivity of these acid amides is rather surprising.

Recently, we have pointed out that the relative nucleophilic reactivity of amides based on their acidity is reversed in the palladoamidation of N-protected 4-pentenylamines and 5-hexenylamines, where ureas are most reactive and carbamates are more reactive than tosylamides.[15] Also in this case, acid amides are totally unreactive toward cyclization. The ready palladoamidation and mercurioamidation of *N*-acyl-*o*-allylanilines, reported by Hegedus[16] and Danishefsky,[17] respectively, should be referred to.

All these observations suggest that aminocyclization is strongly affected not only by the acidity of amides but also by the kind of electrophile and steric environment in a transition state or in the product. The complete immunity

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Table I. Stereoselective Haloamidation of *N*-(*p*-Tolylsulfonyl)-4-pentenylamines 2 (Eq 1)

entry	substrate 2	rctn condtns[a] (temp,[b] time)	product ratio (% isolated yield)
1	**2a**	A (−5, 1 h)	**3a**/**4a** = 95/5 (88)
2	**2a**	C (−5, 4 h)	**3a**/**4a** = 96/4 (86)
3	**2a**	D (0, 2 h)	**3a**/**4a**/**7a** = 60/4/36 (88)
4	**2b**	A (−5, 15 min)	**3b**/**4b** = 94/6 (82)
5	**2b**	C (−5, 4 h)	**3b**/**4b** = 95/5 (91)
6	**2c**	C (rt, 24 h)	**3c**/**4c** = 97/3 (86)
7	**2e**	A (rt, 5 min)	**3e**/**4e**/**8e** = 58/7/35 (86)
8	**2e**	A (−15, 20 min)	**3e**/**4e** = 93/7 (95)
9	**2e**	B (−78, 2 h)	**3e**/**4e** = 93/7 (99)
10	**2e**	C (rt, 1 h)	**3e**/**4e** = 86/14 (95)
11	**2e**	C (−5, 5 h)	**3e**/**4e** = 92/8 (78)
12	**2e**	E (−50, 4 h)	**3e**/**4e** = 89/11 (99)
13	**2f**	A (0, 1 h)	**3f**/**4f**/**5f** = 90/3/7 (84)
14	**2g**	A (0, 1 h)	**3g**/**4g** = 97/3 (80)
15	**2h**	A (0, 1 h)	**3h**/**4h** = 97/3 (82)
16	**2i**	A (0, 2 h)	**3i**/**4i** = 95/5 (88)
17	**2j**	A (0, 1 h)	**3j**/**4j** = 95/5 (80)
18	**2k**	A (0, 3 h)	**3k**/**4k** = 95/5 (80)[c]
19	**2k**	C (rt, 12 days)	**3k**/**4k** = 95/5 (76)[d]
20	**2l**	C (rt, 40 h)	**5l**/**6l** = 52/48 (53)
21	**2m**	A (0, 1 h)	**5m** (98)

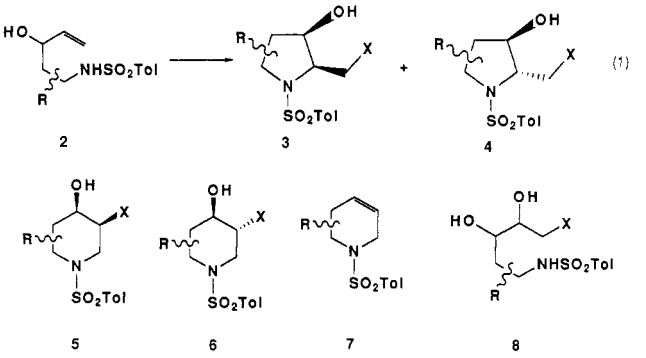
[a] Haloamidation of **2** was undertaken under the following conditions. A: NBS (1.2 mmol), DME–H_2O (4 mL–1 mL)/mmol of **2**. B: NBS (1.2 mmol), dichloromethane (5 mL)/mmol of **2**. C: I_2 (1.5 mmol), $NaHCO_3$ (1.5 mmol), Et_2O–H_2O (5 mL–2 mL)/mmol of **2**. D: I_2 (1.5 mmol), acetonitrile (5 mL)/mmol of **2**. E: NIS (1.2 mmol), dichloromethane (5 mL)/mmol of **2**. [b] Temperature is in °C; rt = room temperature. [c] Yield is based on 50% conversion. [d] Yield is based on 42% conversion.

of our acid amides from haloamidation might primarily be attributed to an A(1,3) strain[18] between 2-halomethyl and 1-acyl groups in the pyrrolidine products, which is expected to decrease in the order of acid amide, carbamate (urea), and tosylamide, as judged from the rotational barrier around their CO–N and SO_2–N bonds.

As mentioned above, depending on the kind of N-protecting group, the reactivity and structural flexibility (and also the product stability) largely differ, and hence it seems reasonable to discuss the haloamidation of tosylamides **2** and carbamates **9** separately.

Haloamidation of *N*-(*p*-Tolylsulfonyl)-3-hydroxy-4-pentenylamines 2. Haloamidation of **2** was examined under five different sets of conditions (conditions A–E, see footnote *a* in Table I), employing either aqueous or nonaqueous media and different halogenating agents. Generally the haloamidation of **2** proceeds smoothly at ambient temperature or below. The reaction is highly regio- and stereoselective and provides *cis*-*N*-(tolylsulfonyl)-2-(halomethyl)-3-hydroxypyrrolidine **3** as a major product (eq 1). The minor trans isomer **4** could not be isolated from the reaction mixture in a pure form, and **4** was only detected spectroscopically. The product ratio, determined by the combination of ^1H NMR spectra and/or HPLC, seems to reflect kinetic selectivity, since neither a prolonged reaction nor an exposure of the isolated product mixture to the halogenation conditions altered the ratio.

Except for entries 20 and 21, the selectivity of **3** over **4** was high and did not depend on the reaction conditions (A–E). However, under certain conditions, some byproducts were produced. For example, iodocyclization of **2a** with I_2 in dry acetonitrile (conditions D) provided tetrahydropyridine **7a** in a considerable amount in addition to

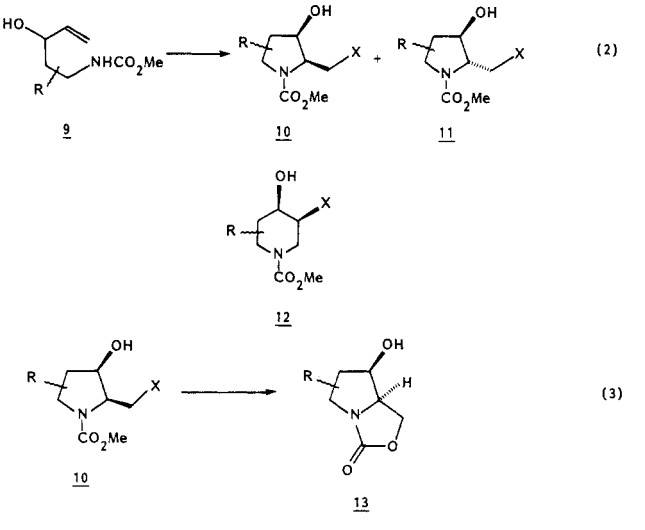


3a and **4a** (entry 3, Table I). The tetrahydropyridine **7a** may be a product of an iodine-catalyzed nucleophilic displacement of the hydroxyl group with the amide nitrogen atom. The reaction of **2e** with *N*-bromosuccinimide (NBS) in 1,2-dimethoxyethane–H_2O at ambient temperature gave a mixture of **3e**, **4e**, and a bromohydrin **8e** (entry 7, Table I). This bromohydrin may be produced due to unfavorable approach of the amide nitrogen to the hindered tertiary carbenium ion center. This byproduct could be completely eliminated by conducting the reaction at the lower temperature (entry 8).

Despite a wide structural range of substrates, the cis-selective cyclization seems to be quite general. Especially rewarding is the cyclization of **2e–h** and **2k**. The reaction of **2e** and **2k** involves a quarternary C–N bond formation, and the cyclization of **2f** is directed by the quarternary hydroxyl group. The similarly high cis selectivity in the cyclization of a pair of diastereomers **2g** and **2h** is also impressive. All of these results seem to indicate that the allylic hydroxyl group controls the diastereofacial selection and the other substituents are not involved.

In contrast to all of the others, the last two substrates, **2l** and **2m**, selectively cyclize to give piperidine derivatives, **5** and **6** (entries 20–22). The drastic change of regioselectivity may be attributed to stabilization of the carbenium ion at the C-5 position by the phenyl and methyl groups attached to this carbon. Partial formation of **5f** in the cyclization of **2f** may be due to steric congestion among the substituents on N, C-2, and C-3 in the pyrrolidine product (entry 13).

Haloamidation of *N*-(Methoxycarbonyl)-3-hydroxy-4-pentenylamines 9. Compared with tosylamide **2**, the reactivity of the corresponding carbamate **9** is low. Hence, for completion of the reaction, the higher temperatures and the longer reaction times were required. Even under such forcing conditions, some carbamates, e.g., **9i** and **9k**, were unreactive and were recovered unchanged.



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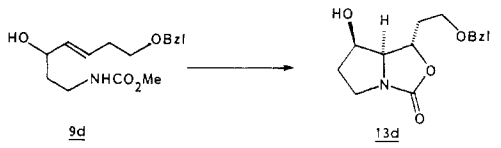
The stereoselectivity in the haloamidation of **9** is almost the same as that of **2**, and the cis isomer **10** was produced predominantly over the trans isomer **11** (eq 2). In some cases, the regioselectivity in the cyclization of **9** is significantly different from that of **2**. The sulfonamide **2c** provides pyrrolidines (**3c** and **4c**) exclusively, while the corresponding carbamate **9c** cyclizes to give a mixture of pyrrolidine **13c** (likely via an intermediate **10c**, vide infra) and piperidine **12c** in a comparable amount (entry 3, Table II). A similar trend was also observed in the cyclization of **9d** (entry 4). Judging from the exclusive formation of a pyrrolidine derivative **13b** (likely via an intermediate **10b**, vide infra, entry 2) from the C-5 methyl substituted carbamate **9b**, and exclusive formation of piperidine **12m** from the C-5 phenyl substituted carbamate **9m** (entry 13), the cyclization of carbamates **9c** and **9d** is just an intermediate case of the above two extremes and seems to sensitively reflect the relative stability of the C-4 and C-5 carbenium ions. Here, the phenyl group stabilizes the C-5 carbenium ion most strongly, the propyl group more than the (benzyloxy)ethyl group, and the latter more than the methyl group.

The C-5 monosubstituted carbamates **9b**, **9c**, and **9d**, presumably after cyclization to pyrrolidines **10b**, **10c**, and **10d**, undergo a further spontaneous cyclization to furnish bicyclic oxazolidones **13b**, **13c**, and **13d**, respectively (see, for example, eq 9). All the other pyrrolidine carbamates **10**, possessing primary C–I bonds, are rather stable under the haloamidation conditions and can be isolated. These pyrrolidine carbamates, however, undergo the second cyclization to give **13** in good yields upon heating in acetonitrile at reflux (eq 3). The ease of the second cyclization is largely dependent on the substitution pattern on the pyrrolidine ring. The large difference in reactivity between the two diastereomers **10g** and **10h** (entries 7 and 8, Table II) as well as the low reactivity of **10f** and **10j** (entries 6 and 10) are very impressive and may be an interesting subject to pursue further in relation to conformational analyses of the pyrrolidine rings.



(4)

9d 13d

The present transformation of **9** to **13** may be regarded, as a whole, as a doubly stereoselective geminal hydroxyamination of the double bond of **9**. The first stereoselection is due to hydroxyl group directed cyclization to form the cis-substituted pyrrolidine ring, and the second stereoselection is due to a trans iodoamination across the double bond, followed by a nucleophilic displacement of iodide with an inversion of configuration around the carbon bearing iodide. The stereospecific formation of **13b**, with a 4*S*,6*R* structure (eq 9), supports the sequence of the reactions.

Although the yield is not satisfactory yet, the one-flask conversion of **9d** to **13d** may be a useful approach to the synthesis of detoxinine[12] (eq 4 and Figure 1), since **13d** possesses many desirable structural features for the further conversion to this physiologically interesting alkaloid: (1) an N-protected pyrrolidine ring, (2) two hydroxyl groups with correct configuration, and (3) a propanol side chain at the 2-position of the pyrrolidine ring, protected as a benzyl ether. The propanol group may be readily transformed to a propionic acid.

Haloamidation of *N*-(Tolylsulfonyl)-4-hydroxy-5-hexenylamines 14. As an extension of the above-mentioned cyclization of **2** and **9**, we next examined the cyclization of *N*-(tolylsulfonyl)-4-hydroxy-5-hexenylamines **14**, the one-carbon-higher homologues of **2**, in the expectation of the stereoselective cyclization to obtain *cis*-2-(halomethyl)-3-hydroxypiperidines **15** (eq 5). All attempts at the cyclization of **14a** to **15a**, however, were not successful. Under the conditions successfully applied for the cyclization of **2** and **9**, or even under the other conditions, **14a** was either unreactive or provided an intractable mixture of products or bromohydrins. For example, the attempted bromoamidation of **14a** with NBS (1.2 equiv) in dry dichloromethane (conditions B) or in dry THF at ambient temperature for 2 h gave at least seven or eight products, which did not contain the expected cyclization product, as judged from TLC. On the other hand, treatment of **14a** with NBS (1.2 equiv) in methanol at ambient temperature for 30 min cleanly provided a single product, whose structure was assigned as *N*-(tolylsulfonyl)-4-hydroxy-5-methoxy-6-bromohexylamine. All the attempts for the iodoamidation of **14a** resulted in the recovery of the starting material: I_2 (1.5 equiv), $NaHCO_3$ (1.5 equiv) in ethyl ether–H_2O at ambient temperature for 1 week (conditions C); I_2 (1.5 equiv), NaH (2 equiv) in dry THF at 0 °C for 1 day; *N*-iodosuccinimide (NIS, 1.2 equiv) in dry dichloromethane at ambient temperature for 12 h (conditions E).

Selenoamidation of **14a** with benzeneselenenyl chloride (2 equiv) or *N*-(phenylseleno)phthalimide (2 equiv) in dry dichloromethane at ambient temperature for 3 h also resulted in no reaction.

(5)

14a; R = H
14b; R = Me

15b; R = Me

Recently Bernotas[8] reported that mercurioamidation was effective for piperidine synthesis via a cyclization of 4-(benzyloxy)-5-hexenylamines. Accordingly, we examined a mercurioamidation by treating **14a** with mercuric acetate (1.2 equiv) in THF at ambient temperature for 1 day. However, this attempt also turned out to be fruitless.

Eventually, we found that **14b** (*but not 14a*) cleanly undergoes the expected haloamidation under somewhat unusual conditions. According to the following procedure, *N*-(tolylsulfonyl)-2-(halomethyl)-3-hydroxy-3-methylpiperidine (**15b**) was obtained in 70–80% yields. Amide **14b** was treated with NBS (3 equiv) in dry dichloromethane at 0 °C *in the dark until the starting material completely disappeared*, and then the reaction mixture was exposed *to ambient light* at the same temperature. The reaction was reproducible, and the progress of the reaction could be conveniently monitored by TLC: **14b** (R_f 0.5 on a silica gel plate, benzene–ethyl acetate, 1/1 v/v), an intermediate (R_f 0.7), **15b** (R_f 0.6). Both the complete formation of an intermediate in the dark and the irradiation of the resultant mixture by ambient light are essential for a clean cyclization. Quenching of the reaction mixture with aqueous Na_2SO_3 without the light irradiation provides **14b**, contaminated with many unidentified products. This is in marked contrast to the cyclization of **2** and **9**, which proceeds in the dark.

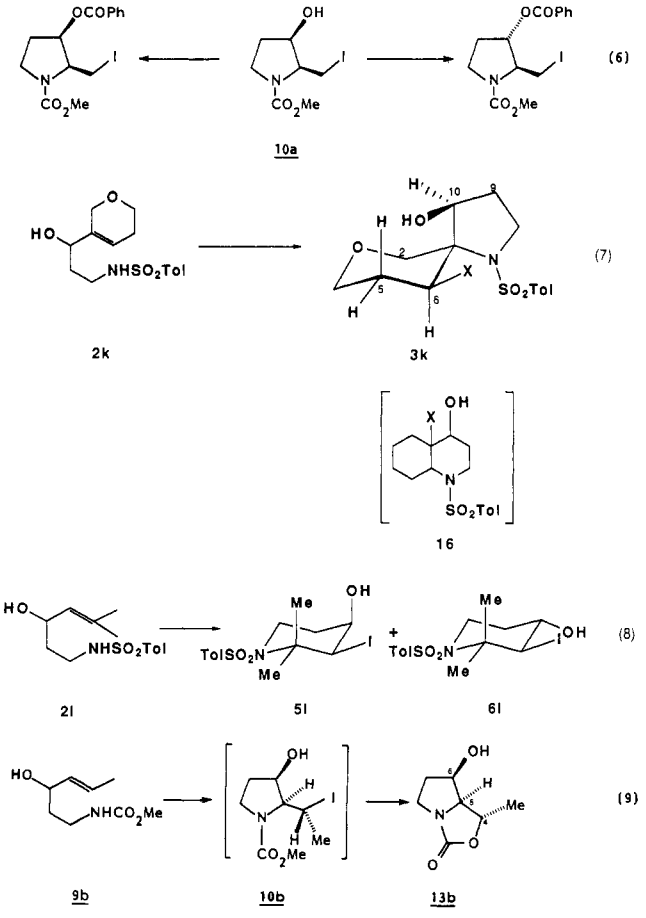
In order to get a further insight into this unique behavior, we followed the reaction by ^1H NMR spectroscopy. When **14b** was treated with 2 equiv of NBS in $CDCl_3$ in the dark, all the resonances of **14b**, including the olefinic

protons, remained almost unchanged, except for the methylene protons α to the nitrogen atom, which significantly shifted downfield (3.23 ppm from 2.92 ppm).

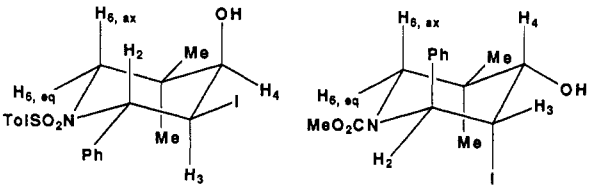
These observations suggest that the reaction in the dark involves formation of an intermediate, most likely N-brominated **14b**, and the cyclization, initiated upon exposure to ambient light, proceeds via a homolytic fission of the N–Br bond of the intermediate. Similar treatment of **14b** with NIS also provides **15b** (X = I) in a similar yield; however, in this case, **14b** remains unchanged during the reaction in the dark and no intermediate is detected. The proposed radical mechanism may be further supported by the failure of cyclization of **14a**, which possesses an allylic hydrogen, susceptible to radical species.

Although the stereochemistry of **15b** has not yet been determined, its high homogeneity, as judged from ^{1}H NMR, ^{13}C NMR, HPLC, and sharp melting point, indicates that the cyclization of **14b** is highly stereoselective.

Structure Determination of Products. The cis configuration of the main products **3** and **10** was deduced from the higher field resonances of the halomethyl group by ca. 3–5 ppm compared with those of the corresponding trans isomers **4** and **11** in the ^{13}C NMR spectra.[19] For example, the iodomethyl carbon of the benzoate of **10a** resonates at 1.32 ppm, while that of the benzoate of **11a** appears at 5.53 ppm. The authentic sample of **11a** (benzoate) was prepared from **10a** by Mitsunobu inversion[20] (eq 6). The structures of **3f** and **10f** were tentatively assigned from a mechanistic analogy, since we could not prepare the authentic trans isomers **4f** and **10f**, respectively, according to this procedure.



(19) (a) Gaudemer, A. In *Stereochemistry*; Kagan, H. B., Ed.; George Thieme Verlag: Stuttgart, 1977. (b) Levy, G. C.; Lichter, R. L.; Nelson, G. L. *Carbon-13 NMR Spectroscopy*, 2nd ed.; Wiley: New York, 1980.
(20) Mitsunobu, O. *Synthesis* **1981**, 1.



5m	12m
H_2; 4.57 (d, 9.0 Hz)	H_2; 5.86 (d, 3.9 Hz)
H_3; 4.87 (dd, 2.4, 9.0 Hz)	H_3; 5.15 (dd, 3.7, 3.9 Hz)
H_4; 3.50 (m)	H_4; 2.99 (br s)
H_{6ax}; 3.27 (d, 12.5 Hz)	H_{6ax}; 2.73 (d, 13.7 Hz)
H_{6eq}; 3.54 (d, 12.5 Hz)	H_{6eq}; 3.80 (d, 13.7 Hz)

Figure 3. ^{1}H NMR spectra of **5m** and **12m**.

The structure determination of **3k** is rather complicated. The structure was determined as follows (eq 7). The spiro[5.4] structure of **3k** was discriminated from another possible bicyclic [4.4.0] structure **16** on the basis of the presence of a tertiary C-6–halogen bond. That is, in the ^{13}C NMR spectra of **3k** (X = I and Br), only the doublets (C-6): X = I, 30.7 ppm; X = Br, 53.5 ppm), which coalesce to singlets by selective irradiations of protons at 5.37 and 5.33 ppm respectively, differ significantly. The equatorial C-6–halogen configuration is assigned from the coupling pattern of the axial proton attached to C-6 (X = I, dd, J = 4.9 and 12.7 Hz; X = Br, dd, J = 5.1 and 12.8 Hz) characteristic of the chair-form cyclohexane ring. The syn orientation of the C-10 hydroxyl group to the halogen moiety is most likely on the basis of an anomalous low-field resonance of the C-5–H(axial) proton (2.91 ppm) compared with that of the C-5–H(equatorial) proton (2.25 ppm), which may be caused by a steric compression[21] of the former with the hydroxyl group in close proximity.

The cyclization of **2l** provides a 1:1 mixture of stereoisomeric piperidines (**5l**, R_f 0.5 on a silica gel plate, benzene–ethyl acetate, 2/1 v/v, $J_{H(3)H(4)}$ = 2.9 Hz; **6l**, R_f 0.6, $J_{H(3)H(4)}$ = 10.0 Hz, eq 8). The piperidine structure of these products is apparent from their coupling pattern of the C(3)C(4) ring protons characteristic of a chair-form six-membered ring. The structure was further verified by a separate reduction of **5l** and **6l** with $(n\text{-Bu})_3$SnH, which provided the identical product, showing two methyl singlets in the ^{1}H NMR spectrum. On the basis of the above results, neither one of the products nor both of the products could be pyrrolidine derivatives, since, if this were the case, two different products would have been produced by the reduction. Furthermore, if the cyclization products of **2l** were a mixture of **3l** and **4l**, the two diastereomeric methyl groups of the isopropyl side chain would likely appear as two doublets for each product.

Both **2m** and **9m** also specifically cyclize to give piperidine derivatives **5m** and **12m** with the same configuration, respectively. However, the ^{1}H NMR spectra of these products differ significantly (Figure 3). The coupling constants $J_{H(2)H(3)}$ = 9.0 Hz and $J_{H(3)H(4)}$ = 2.4 Hz for **5m** (X = I) are typical for axial–axial and axial–equatorial couplings in cyclohexane systems, respectively.

In **12m**, on the other hand, the small coupling constant $J_{H(2)H(3)}$ = 3.9 Hz indicates an equatorial–equatorial coupling and hence an axial orientation of the C-2 phenyl group. The axial phenyl conformation seems to be reflected in the unusual high-field resonances of the two axial

(21) Winstein, S.; Carter, P.; Anet, F. A. L.; Bourn, A. J. R. *J. Am. Chem. Soc.* **1965**, *87*, 5247.

protons (2.99 and 2.73 ppm) attached to C-4 and C-6, respectively. These protons are located in a shielding region of the axial phenyl group. The phenyl group most likely occupies an axial position in order to minimize an A(1,3) strain[18] against the methoxycarbonyl group.

Interestingly, all the halo carbamates **10** showed their carbonyl absorptions at unusually low wave numbers (e.g., **10f**, 1670 cm^{-1}) when their IR spectra were measured in KBr disk or as neat films. When the hydroxyl group was protected as an ester or when their IR spectra were taken as dilute CCl_4 solutions, the carbonyl absorptions shifted to a normal position (e.g., acetate of **10f**, 1700 cm^{-1}). Similarly, oxazolidones **13** exhibit their carbonyl absorptions at low wave numbers (e.g., **13a**, 1700 cm^{-1}), which are restored to a standard position by acylation (e.g., benzoate of **13a**, 1760 cm^{-1}). Judging from these observations, these anomalies may be ascribed to an intermolecular hydrogen bonding between the hydroxyl and carbamate carbonyl groups.

Finally, the structure determination of **13b** was based on the differential NOE experiments, which indicated that the following two pairs of protons were located in close proximity: C-4–H and OH protons and C-4–Me and C-5–H protons (eq 9). As being general for the cyclopentane ring, the coupling constants of the ring protons in **3**, **10**, and **13** were useless for the structure determination (e.g., **13b**, $J_{H(4)H(5)}$ = 3.6, $J_{H(5)H(6)}$ = 2.7 Hz).

Experimental Section

Melting points were determined in capillary tubes with a Büchi apparatus and were not corrected. Unless otherwise specified, short-path (bulb to bulb) distillations were carried out in a Kugelrohr apparatus. Microanalyses were performed by the Microanalysis Center of Kyoto University. Analyses agreed with the calculated values within ±0.3%. Infrared spectra were measured with a Hitachi Model EPI-G3 grating spectrophotometer. Proton magnetic resonance spectra were determined either at 60 MHz on a JEOL JNM-PMX60 instrument, at 90 MHz on a JEOL FX90Q instrument, or at 400 MHz on a JEOL-GX400 instrument with tetramethylsilane as an internal standard. Carbon-13 NMR spectra were determined at 22.4 MHz on a JEOL FX90Q instrument with tetramethylsilane as an internal standard. Mass spectra were measured either on a Hitachi Model RMU6C or on a JEOL D-300 instrument (high-resolution mass spectrophotometer).

Solvents and Reagents. Tetrahydrofuran (THF) and ethyl ether were dried and distilled from benzophenone and sodium immediately prior to use under an argon atmosphere. Trichloromethane, dichloromethane, and acetonitrile were distilled over P_2O_5 under an argon atmosphere. Benzeneselenenyl chloride and *N*-(phenylseleno)phthalimide were purchased from Aldrich Chemical Co. *N*-Iodosuccinimide, *N*-bromosuccinimide, methyl chloroformate, and *p*-toluenesulfonyl chloride were purchased from Wako Pure Chemical Industries, Ltd and used without further purification.

Haloamidation of 2 and 9. The reactions under conditions B, D, and E were undertaken under a nitrogen atmosphere, and all reagents were added under a nitrogen flow. All through the reaction, the flask was covered with aluminum foil, and the reaction was monitored with a silica gel TLC plate (Merck precoated silica gel plate, 60F254) by using benzene–ethyl acetate mixed solvents as eluents. The reaction mixture was quenched by the addition of aqueous Na_2SO_3. The products **10**, **11**, and **12**, and especially **13**, were highly soluble in water, especially under acidic conditions, and hence the aqueous Na_2SO_3 layer was extracted three or four times with ethyl acetate.

Bromoamidation of 2i under Conditions A (Entry 16, Table I). Into a solution of **2i** (1 mmol) in 1,2-dimethoxyethane–H_2O (4 mL–1 mL), kept at 0 °C with an ice bath, was added *N*-bromosuccinimide (1.2 mmol) in one portion. After being stirred at the same temperature for 2 h, the mixture was treated with aqueous Na_2SO_3 and extracted with ether (30 mL × 2). The combined extracts were washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated to give a colorless solid, which was purified by means of column chromatography over silica gel (benzene–ethyl acetate gradient) to give a mixture of **3i** and **4i** as a solid. The reaction was monitored by means of TLC (R_f(**2i**) 0.2, R_f(**3i**,**4i**) 0.6 in benzene–ethyl acetate, 4/1 v/v).

Bromoamidation of 2e under Conditions B (Entry 9, Table I). Into a 10-mL two-necked round-bottomed flask, connected with a nitrogen inlet, was added a solution of **2e** (1 mmol) in 5 mL of dichloromethane via a syringe through a serum cap. The flask was covered with aluminum foil and immersed in a dry ice–acetone bath kept at −78 °C. *N*-Bromosuccinimide (1.2 mmol) was added into the stirred mixture in one portion during back-flushing with nitrogen. The mixture was stirred at the same temperature for 2 h and then quenched by the addition of aqueous Na_2SO_3. The mixture was diluted with ether, washed with saturated NaCl and aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated to give a colorless oil, which was chromatographed over silica gel. A mixture of **3e** and **4e** (R_f 0.55, benzene–ethyl acetate, 4/1 v/v) was isolated as a solid in 99% yield.

Iodoamidation of 2a under Conditions C (Entry 2, Table I). Into a 20-mL round-bottomed flask, wrapped with aluminum foil, were added **2a** (2 mmol, 510 mg), $NaHCO_3$ (3 mmol, 252 mg), ether (10 mL), and H_2O (4 mL). Into the stirred solution in an ice–salt bath (−5 °C) was added iodine (760 mg, 3 mmol) in one portion, and the mixture was stirred at the same temperature for 4 h. Excess iodine was quenched by the addition of aqueous Na_2SO_3, and the colorless solution was extracted with ethyl acetate (30 mL × 2). The combined extracts were washed with saturated NaCl and aqueous $NaHCO_3$, then dried ($MgSO_4$), and concentrated to give a sticky oil, which was chromatographed over silica gel to give a mixture of **3a** and **4a** as a solid in 86% yield (R_f 0.55, benzene–ethyl acetate, 4/1 v/v).

Iodoamidation of 9d under Conditions C (Entry 4, Table II). A solution of **9d** (1.07 g, 3.65 mmol), $NaHCO_3$ (460 mg, 5.5 mmol), and I_2 (1.4 g, 5.5 mmol) in ether (18 mL) and H_2O (7 mL) was stirred at ambient temperature for 2 weeks in a flask covered with aluminum foil. Excess iodine was quenched by the addition of aqueous Na_2SO_3, and the mixture was extracted with ethyl acetate (30 mL × 4). The combined extracts were washed with minimum amounts of saturated NaCl and aqueous $NaHCO_3$, then dried ($MgSO_4$), and concentrated to give a brown oil, which was subjected to column chromatography over silica gel (benzene–ethyl acetate gradient, 1/1–1/4 v/v) to give a mixture of **12d** and **13d** (316 mg, R_f 0.5, silica gel plate, ethyl acetate). The mixture of **12d** and **13d** (316 mg) was refluxed in 7 mL of dry THF for 12 h under argon in the presence of benzoic anhydride (306 mg, 1.35 mmol), pyridine (0.73 mL, 9 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (20 mg). The mixture was diluted with ethyl acetate and washed with 10 mL of 1 N HCl. The water layer was extracted with ethyl acetate (10 mL × 4), and the combined organic extracts were washed with saturated NaCl and aqueous $NaHCO_3$, then dried ($MgSO_4$), and condensed to give a brown oil, which was subjected to column chromatography over silica gel (R_f: benzoate of **12d**, 0.4; benzoate of **13d**, 0.55; benzene–ethyl acetate, 2/1 v/v) to give the benzoate of **12d** (134 mg, 7% yield based on **9d**) and the benzoate of **13d** (223 mg, 16% yield based on **9d**).

Iodoamidation of 2a under Conditions D (Entry 3, Table I). Into a 20-mL two-necked round-bottomed flask, connected with a nitrogen inlet, was added a solution of **2a** (2 mmol) in 10 mL of dry acetonitrile via a syringe. The flask was covered with aluminum foil and immersed in an ice bath. Iodine (3 mmol) was added into the stirred mixture in one portion while back-flushing with nitrogen. After stirring for 2 h at 0 °C, the excess iodide was quenched by the addition of aqueous Na_2SO_3 at the same temperature. The colorless mixture was extracted with ethyl acetate (30 mL × 2), and the combined extracts were washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated to give a sticky oil, which was chromatographed over silica gel to give a mixture of **3a** and **4a** as a solid in 56% yield (R_f 0.55, benzene–ethyl acetate, 4/1 v/v) and **7a** (R_f 0.65, benzene–ethyl acetate, 4/1, v/v).

Iodoamidation of 9m under Conditions E (Entry 13, Table II). This reaction was undertaken in analogy to the procedure described for conditions B, using *N*-iodosuccinimide (1.2 mmol per mole of **9m**) in place of *N*-bromosuccinimide.

***cis*-*N*-(*p*-Tolylsulfonyl)-2-(bromomethyl)-3-hydroxypyrrolidine (3a, X = Br)**: mp 124.5–125.0 °C (benzene–hexane); IR (KBr disk) 3450 (vs), 2900 (w), 1580 (w), 1318 (s), 1218 (m), 1140 (s), 1110 (w), 1075 (m), 1020 (m), 955 (w), 895 (w), 850 (w), 810 (w), 745 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (m, 1 H), 1.75 (m, 1 H), 2.31 (br s, 1 H), 2.44 (s, 3 H), 3.49–3.99 (m, 5 H), 4.43 (br s, 1 H), 7.33 (d, J = 8.3 Hz, 2 H), 7.73 (d, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.6 (MePh), 30.7 (CH_2Br), 32.8 (C-4), 48.1 (C-5), 64.5 (C-1), 72.0 (C-3), 127.6, 130.0, 133.9, 144.0 (Ph); mass spectrum, m/z (relative intensity) 254 (M – Br, 48), 240 (M – CH_2Br, 100), 155 (M – SO_2Tol, 34), 91 (16). Anal. Calcd for $C_{12}H_{16}NO_3BrS$: C, 43.12; H, 4.83; N, 4.19; O, 14.36. Found: C, 42.82; H, 4.80; N, 4.01; O, 14.39.

***cis*-*N*-(*p*-Tolylsulfonyl)-2-(iodomethyl)-3-hydroxypyrrolidine (3a, X = I)**: mp 136.0–137.0 °C (benzene–hexane); IR (KBr disk) 3390 (vs), 2880 (m), 1580 (w), 1395 (w), 1310 (m), 1215 (w), 1140 (m), 1070 (m), 1015 (m), 955 (m), 900 (w), 835 (w), 807 (w), 730 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (m, 1 H), 1.74 (m, 1 H), 2.30 (br s, 1 H), 2.43 (s, 3 H), 3.35–3.83 (m, 5 H), 4.44 (m, 1 H, coalescing to t, J = 4.0 Hz, by irradiation at 1.74, coalescing to d, J = 3.5 Hz, by irradiation at 1.33), 7.33 (d, J = 8.6 Hz, 2 H), 7.72 (d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 4.0 (CH_2I), 21.4 (MePh), 32.7 (C-4), 48.4 (C-5), 65.0 (C-2), 72.4 (C-3), 127.3, 129.8, 133.8, 143.8 (Ph); mass spectrum, m/z (relative intensity) 381 (M, 0.1), 254 (M – I, 100), 240 (M – CH_2I, 49), 210 (17), 155 (52), 91 (28). Anal. Calcd for $C_{12}H_{16}NO_3I$: C, 37.80; H, 4.23; N, 3.67; O, 12.59. Found: C, 38.02; H, 4.07; N, 3.77; O, 12.60.

***N*-(*p*-Tolylsulfonyl)-2(*S*)-[1′(*R*)-bromoethyl]-3(*R*)-hydroxypyrrolidine (3b, X = Br)**: mp 85.0–86.0 °C (benzene–hexane); IR (KBr disk) 3480 (s), 2900 (s), 1595 (s), 1490 (w), 1438 (w), 1475 (w), 1340 (s), 1300 (m), 1230 (w), 1155 (vs), 1085 (m), 1030 (m), 970 (w), 900 (w), 815 (m), 710 (m), 655 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38–1.80 (m, 2 H), 1.97 (d, J = 7.3 Hz, 3 H), 2.44 (s, 3 H), 3.43 (dd, J = 8.3, 4.9 Hz, 2 H), 3.95 (dd, J = 7.8, 6.1 Hz, 1 H), 4.38 (m, 1 H), 4.42 (m, 1 H, coalescing to d, J = 7.3 Hz, by irradiation at 1.97), 7.33 (d, J = 8.6 Hz, 2 H), 7.72 (d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.5 (MePh), 23.8 (Me), 33.4 (C-4), 47.2 (C-5), 50.0 (CHBr), 67.5 (C-2), 73.0 (C-3), 127.5, 129.8, 134.7, 144.0 (Ph); mass spectrum, m/z (relative intensity) 348 (M, 0.7), 268 (6), 240 (M – CHBrMe, 100), 155 (37), 91 (16). Anal. Calcd for $C_{13}H_{18}NO_3BrS$: C, 44.83; H, 5.21; N, 4.02; O, 13.78. Found: C, 44.75; H, 5.22; N, 3.96; O, 13.97.

***N*-(*p*-Tolylsulfonyl)-2(*S*)-[1′(*R*)-iodoethyl]-3(*R*)-hydroxypyrrolidine (3b, X = I)**: mp 129.5 –130.0 °C; IR (KBr disk) 3500 (vs), 2900 (m), 1590 (s), 1490 (m), 1480 (m), 1440 (s), 1375 (s), 1330 (vs), 1300 (s), 1207 (s), 1150 (vs), 1080 (s), 1030 (m), 980 (m), 960 (m), 900 (m), 870 (m), 830 (m), 815 (s), 710 (s), 698 (s), 645 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–1.90 (m, 2 H), 2.13 (d, J = 7.1 Hz, 3 H), 2.44 (s, 3 H), 3.43 (dd, J = 8.5, 4.9 Hz, 2 H), 3.87 (dd, J = 8.1, 6.1 Hz, 1 H), 4.42 (dq, J = 8.1, 7.1 Hz, 1 H, coalescing to d, J = 8.1 Hz, by irradiation at 2.1), 4.43 (m, 1 H), 7.32 (d, J = 8.3 Hz, 2 H), 7.73 (d, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.4 (MePh), 25.8 (Me), 27.2 (CHI), 33.3 (C-4), 47.7 (C-5), 68.0 (C-2), 73.0 (C-3), 127.4, 129.7, 134.5, 143.9 (Ph); mass spectrum, m/z (relative intensity) 395 (M, 0.1), 268 (M – I, 31), 240 (M – CHIMe, 100), 155 (33), 91 (21). Anal. Calcd for $C_{13}H_{18}NO_3IS$: C, 39.50; H, 4.59; N, 3.54; O, 12.14. Found: C, 39.70; H, 4.57; N, 3.47; O, 12.18.

***N*-(*p*-Tolylsulfonyl)-2(*S*)-[1′(*R*)-iodobutyl]-3(*R*)-hydroxypyrrolidine (3c)**: IR (neat film) 1340 (s), 1160 (s), 1090 (m), 955 (m), 905 (m), 810 (s), 715 (m), 660 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, J = 7.1 Hz, 3 H), 1.17–2.20 (m, 6 H), 2.43 (s, 3 H), 3.45 (dd, J = 4.9, 8.5 Hz, 2 H), 3.88 (br t, J = 6.5 Hz, 1 H), 4.28–4.56 (m, 2 H), 7.23–7.44 (m, 3 H), 7.65–7.83 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.8 (C-4′), 23.1 (C-3′), 33.0 (C-4), 37.5 (C-1′), 38.1 (C-2′), 46.7 (C-5), 66.4 (C-2), 72.7 (C-3). Anal. Calcd for $C_{15}H_{22}NO_3IS$: C, 42.56; H, 5.24; N, 3.31; O, 11.34. Found: C, 42.55; H, 5.12; N, 3.30; O, 11.34.

***cis*-*N*-(*p*-Tolylsulfonyl)-2-methyl-2-(bromomethyl)-3-hydroxypyrrolidine (3e, X = Br)**: mp 126.0–127.0 °C (benzene–hexane); IR (KBr disk) 3390 (vs), 3040 (w), 2970 (s), 1595 (s), 1490 (m), 1440 (s), 1395 (m), 1373 (s), 1330 (vs), 1150 (vs), 1110 (s), 1050 (m), 1010 (m), 980 (m), 940 (w), 910 (m), 875 (w), 855 (w), 810 (s), 710 (s), 665 (vs); ^1H NMR ($CDCl_3$) δ 1.52 (s, 3 H), 1.97 (m, 2 H), 2.44 (s, 3 H), 2.80 (s, 1 H), 3.54 (dd, J = 6.3, 5.4 Hz, 2 H), 3.74 (d, J = 9.5 Hz, 1 H), 4.10 (d, J = 9.5 Hz, 1 H), 4.10 (br s, 1 H), 7.27 (d, J = 8.3 Hz, 2 H), 7.71 (d, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.4 (MePh), 22.8 (Me), 30.1 (CH_2Br), 37.5 (C-4), 47.6 (C-5), 70.3 (C-2), 79.2 (C-3), 126.9, 129.5, 137.6, 143.2 (Ph); mass spectrum, m/z (relative intensity) 348 (M, 1), 268 (13), 254 (M – CH_2Br, 100), 155 (27), 98 (15), 91 (16), 82 (16). Anal. Calcd for $C_{13}H_{18}NO_3BrS$: C, 44.83; H, 5.21; N, 4.02; O, 13.78. Found: C, 44.80; H, 5.18; N, 3.82; O, 13.95.

***cis*-*N*-(*p*-Tolylsulfonyl)-2-methyl-2-(iodomethyl)-3-hydroxypyrrolidine (3e, X = I)**: mp 103.0–103.5 °C (benzene–hexane); IR (KBr disk) 3480 (vs), 3030 (w), 2950 (s), 2930 (m), 1590 (m), 1490 (m), 1440 (m), 1395 (w), 1370 (m), 1320 (vs), 1300 (s), 1150 (vs), 1080 (vs), 1045 (m), 1010 (m), 980 (m), 910 (s), 870 (m), 810 (s), 730 (m), 710 (s), 665 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (s, 3 H), 1.6–2.2 (m, 2 H), 2.41 (s, 3 H), 3.50 (d, J = 9.3 Hz, 1 H), 3.50 (m, 2 H), 4.04 (d, J = 9.3 Hz, 1 H), 4.10 (br s, 1 H), 7.28 (d, J = 8.6 Hz, 2 H), 7.72 (d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.3 (CH_2I), 21.3 (MePh), 23.8 (Me), 30.1 (C-4), 48.0 (C-5), 69.6 (C-2), 79.8 (C-3), 126.9, 129.4, 138.0, 143.1 (Ph); mass spectrum, m/z (relative intensity) 395 (M, 0.1), 268 (M – I, 75), 254 (M – CH_2I, 100), 155 (43), 91 (27). Anal. Calcd for $C_{13}H_{18}NO_3IS$: C, 39.50; H, 4.59; N, 3.54; O, 12.14. Found: C, 39.60; H, 4.65; N, 3.44; O, 12.09.

***cis*-*N*-(*p*-Tolylsulfonyl)-2-(bromomethyl)-3-hydroxy-3-methylpyrrolidine (3f)**: mp 91.0–92.0 °C (benzene–hexane); IR (KBr disk) 3400 (vs), 2950 (m), 1590 (m), 1480 (w), 1440 (w), 1370 (m), 1330 (vs), 1290 (s), 1230 (s), 1150 (vs), 1113 (m), 1080 (vs), 1040 (s), 990 (m), 970 (w), 830 (s), 810 (s), 700 (s), 660 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (s, 3 H), 1.45 (ddd, J = 12.7, 7.1, 6.5 Hz, 1 H), 1.99 (dt, J = 12.7, 7.1 Hz, 1 H), 2.45 (s, 3 H), 3.17 (dt, J = 7.1, 10.6 Hz, 1 H), 3.50 (ddd, J = 10.6, 7.1, 6.5 Hz, 1 H), 3.54 (dd, J = 8.8, 2.9 Hz, 1 H), 3.72 (dd, J = 10.0, 8.8 Hz, 1 H), 3.82 (dd, J = 10.0, 2.9 Hz, 1 H), 7.36 (d, J = 8.2 Hz, 2 H), 7.74 (d, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.3 (MePh), 27.8 (Me), 32.0 (CH_2Br), 38.9 (C-4), 45.9 (C-5), 66.7 (C-2), 77.9 (C-3), 127.1, 129.6, 133.4, 143.8 (Ph); mass spectrum, m/z (relative intensity) 348 (M, 0.3), 268 (100), 155 (70), 91 (45). Anal. Calcd for $C_{13}H_{18}NO_3BrS$: C, 44.83; H, 5.21; N, 4.02; O, 13.78. Found: C, 45.12; H, 5.27; N, 4.22; O, 13.54.

***cis*-*N*-(*p*-Tolylsulfonyl)-3-bromo-4-hydroxy-4-methylpiperidine (5f)**: mp 126.0–127.0 °C (benzene–hexane); IR (KBr disk) 3500 (s), 3050 (s), 2950 (m), 2900 (w), 2870 (w), 2830 (w), 1590 (m), 1485 (w), 1465 (m), 1435 (w), 1370 (s), 1340 (vs), 1300 (m), 1210 (m), 1155 (vs), 1120 (m), 1080 (m), 1040 (m), 950 (m), 930 (m), 905 (s), 805 (s), 730 (m), 690 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, 3 H), 1.69 (br s, 1 H), 1.86 (ddd, J = 14.0, 12.6, 4.8 Hz, 1 H), 2.00 (dt, J = 2.7, 14.0 Hz, 1 H), 2.44 (s, 3 H), 2.70 (dt, J = 2.7, 12.6 Hz, 1 H), 2.84 (t, J = 11.5 Hz, 1 H), 3.61 (d of m, J = 12.6 Hz, 1 H), 3.92 (ddd, J = 11.5, 4.9, 2.1 Hz, 1 H), 4.15 (dd, J = 11.5, 4.9 Hz, 1 H), 7.35 (d, J = 10.2 Hz, 2 H), 7.65 (d, J = 10.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.4 (MePh), 29.3 (Me), 37.1 (C-5), 41.8 (C-6), 48.7 (C-2), 59.2 (C-3), 68.4 (C-4), 127.4, 129.7, 133.4, 143.7 (Ph); mass spectrum, m/z (relative intensity) 348 (M, 8), 250 (88), 194 (42), 192 (43), 155 (60), 85 (100). Anal. Calcd for $C_{13}H_{18}NO_3BrS$: C, 44.83; H, 5.21; N, 4.02; O, 13.78. Found: C, 44.74; H, 5.32; N, 3.91; O, 13.48.

***cis,cis*-*N*-(*p*-Tolylsulfonyl)-2-(bromomethyl)-3-hydroxy-4-methylpyrrolidine (3g)**: mp 134.0–135.0 °C (benzene–hexane); IR (KBr disk) 3430 (s), 3020 (w), 2930 (m), 2850 (m), 1590 (m), 1340 (vs), 1290 (m), 1215 (m), 1150 (vs), 1110 (m), 1060 (s), 1020 (m), 975 (s), 920 (m), 905 (m), 880 (m), 800 (s), 755 (m), 700 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, J = 6.6 Hz, 3 H), 1.39 (m, 1 H), 2.21 (br s, 1 H), 2.44 (s, 3 H), 3.20 (t, J = 11.2 Hz, 1 H), 3.4–4.0 (m, 5 H), 4.20 (br s, 1 H, coalescing to t, J = 3.4 Hz, by irradiation at 2.21), 7.33 (d, J = 8.3 Hz, 2 H), 7.72 (d, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 10.2 (Me), 21.3 (MePh), 30.4 (CH_2Br), 37.4 (C-4), 54.1 (C-5), 65.8 (C-2), 73.8 (C-3); mass spectrum, m/z (relative intensity) 348 (M, 0.6), 268 (56), 254 (100), 155 (46). Anal. Calcd for $C_{13}H_{18}NO_3BrS$: C, 44.83; H, 5.21; N, 4.02; O, 13.78. Found: C, 44.99; H, 5.11; N, 3.78; O, 13.82.

***cis,trans*-*N*-(*p*-Tolylsulfonyl)-2-(bromomethyl)-3-hydroxy-4-methylpyrrolidine (3h)**: mp 173.0–174.0 °C ($CHCl_3$); IR (KBr disk) 3480 (vs), 3040 (w), 2900 (m), 1590 (m), 1490 (w), 1430 (m), 1390 (w), 1325 (vs), 1265 (m), 1215 (s), 1150 (vs), 1110 (s), 1080 (s), 1025 (vs), 930 (w), 915 (w), 865 (s), 820 (m), 800 (m), 770 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (d, J = 6.6 Hz, 3 H), 2.21 (m, 1 H), 2.45 (s, 3 H), 2.88 (dd, J = 10.0, 6.5 Hz, 1 H), 3.18 (d,

J = 4.9 Hz, 1 H), 3.61 (dd, J = 10.0, 6.8 Hz, 1 H), 3.6–3.8 (m, 4 H), 7.45 (d, J = 8.3 Hz, 2 H), 7.76 (d, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 15.6 (Me), 21.7 (MePh), 32.1 (CH_2Br), 39.8 (C-4), 54.3 (C-5), 63.7 (C-2), 78.0 (C-3), 116.78, 128.8, 131.0 (Ph); mass spectrum, m/z (relative intensity) 348 (M, 0.4), 268 (25), 254 (100), 155 (35). Anal. Calcd for $C_{13}H_{18}NO_3BrS$: C, 44.83; H, 5.21; N, 4.02; O, 13.78. Found: C, 44.58; H, 5.23; N, 4.04; O, 13.56.

***cis,trans*-*N*-(*p*-Tolylsulfonyl)-2-(bromomethyl)-3-hydroxy-5-phenylpyrrolidine (3i)**: mp 146.0–147.0 °C (benzene–hexane); IR (KBr disk) 3500 (vs), 3030 (w), 3003 (w), 2880 (w), 1590 (m), 1490 (m), 1445 (s), 1413 (w), 1315 (vs), 1295 (s), 1280 (s), 1268 (s), 1255 (s), 1225 (w), 1175 (m), 1145 (vs), 1115 (vs), 1080 (s), 1043 (s), 1005 (m), 803 (s), 690 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.08 (ddd, J = 12.7, 6.8, 3.4 Hz, 1 H), 2.29 (s, 1 H), 2.34 (s, 3 H), 2.57 (dt, J = 8.5, 12.7 Hz, 1 H), 3.80–4.13 (m, 2 H), 4.34 (dt, J = 2.7, 6.8 Hz, 1 H), 4.80 (dt, J = 6.6, 15.1 Hz, 1 H), 5.08 (dd, J = 8.8, 3.4 Hz, 1 H), 6.97–7.25 (m, 9 H); mass spectrum, m/z (relative intensity) 410 (M, 0.1), 316 (100), 155 (25). Anal. Calcd for $C_{18}H_{20}NO_3BrS$: C, 52.68; H, 4.91; N, 3.41; O, 11.70. Found: C, 52.96; H, 4.99; N, 3.39; O, 11.55.

***cis*-*N*-(*p*-Tolylsulfonyl)-2-(bromomethyl)-3-hydroxy-4,4-dimethylpyrrolidine (3j)**: mp 133.0–134.0 °C (benzene–hexane); IR (KBr disk) 3500 (s), 3030 (w), 2915 (s), 2850 (s), 1587 (s), 1487 (w), 1440 (s), 1340 (vs), 1300 (v), 1280 (s), 1185 (m), 1130 (vs), 1080 (s), 1026 (vs), 1080 (m), 955 (m), 880 (m), 810 (m), 760 (m), 700 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.39 (s, 3 H), 1.02 (s, 3 H), 2.13 (d, J = 4.2 Hz, 1 H), 2.43 (s, 3 H), 3.25 (d, J = 10.6 Hz, 1 H), 3.39 (d, J = 10.6 Hz, 1 H), 3.66 (m, 1 H), 3.84 (m, 1 H, coalescing to d, J = 3.4 Hz, by irradiation at 2.13), 3.84 (m, 1 H), 4.08 (dt, J = 3.4, 7.6 Hz, 1 H), 7.32 (d, J = 8.3 Hz, 2 H), 7.74 (d, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.4 (MePh), 19.8, 23.8 (Me–C-4), 30.4 (CH_2Br), 41.4 (C-4), 51.9 (C-5), 64.0 (C-2), 78.8 (C-3), 127.2, 129.7, 134.6, 143.7 (Ph); mass spectrum, m/z (relative intensity) 362 (M, 0.9), 282 (23), 268 (100), 282 (22), 210 (34), 155 (45), 91 (23). Anal. Calcd for $C_{14}H_{20}NO_3BrS$: C, 46.41; H, 5.56; N, 3.87; O, 13.25. Found: C, 46.47; H, 5.64; N, 3.85; O, 12.25.

***N*-(*p*-Tolylsulfonyl)-6(*S*)-bromo-10(*S*)-hydroxy-7-aza-3-oxaspiro[4.5]decane (3k, X = Br)**: mp 172.0–173.0 °C (benzene–hexane); IR (KBr disk) 3430 (vs), 2950 (m), 2850 (m), 1590 (m), 1445 (m), 1315 (s), 1305 (s), 1295 (s), 1285 (m), 1260 (w), 1225 (w), 1180 (w), 1150 (vs), 1095 (vs), 1075 (s), 1045 (s), 980 (s), 880 (w), 830 (m), 810 (s), 680 (m), 650 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05 (ddd, J = 14.4, 12.8, 7.5 Hz, 1 H, C_3H), 2.16 (dt, J = 6.7, 12.8 Hz, 1 H, C_3H), 2.25 (d of m, J = 12.8 Hz, 1 H, C_9H_{eq}), 2.43 (s, 3 H), 2.91 (dq, J = 5.7, 12.8 Hz, 1 H, C_9H_{ax}), 3.27–3.34 (m, 2 H, C_2H), 3.56 (ddd, J = 12.8, 11.6, 2.7 Hz, 1 H, C_8H_{eq}), 3.67 (dd, J = 11.3, 1.2 Hz, 1 H, C_6H_{ax}), 4.00 (br dd, J = 11.6, 5.7 Hz, 1 H, C_8H_{eq}), 4.20 (d, J = 11.3 Hz, 1 H, C_6H_{ax}), 4.64 (t, J = 6.7 Hz, 1 H, C_4H), 5.33 (dd, J = 12.8, 5.1 Hz, 1 H, C_{10}H), 7.32 (d, J = 8.5 Hz, 2 H), 7.84 (d, J = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.3 (MePh), 35.5 (C-9), 45.6 (C-2), 53.5 (C-10), 68.5 (C-8), 69.4 (C-5), 75.5 (C-6), 80.5 (C-3, C-4), 127.6, 129.4, 137.1, 143.5 (Ph); mass spectrum, m/z (relative intensity) 390 (M, 18), 310 (17), 260 (34), 236, 234 (100), 189 (24), 155 (33), 91 (17). Anal. Calcd for $C_{15}H_{20}NO_4BrS$: C, 46.16; H, 5.17; N, 3.59; O, 16.4. Found: C, 46.45; H, 5.28; N, 3.30; O, 16.43.

***N*-(*p*-Tolylsulfonyl)-6(*S*)-iodo-10(*S*)-hydroxy-7-aza-3-oxaspiro[4.5]decane (3k, X = I)**: mp 119 °C dec (benzene–hexane); IR (KBr disk) 3320 (vs), 2950 (m), 2900 (w), 2860 (m), 1590 (m), 1445 (m), 1376 (w), 1310 (vs), 1302 (vs), 1295 (s), 1282 (s), 1258 (m), 1245 (m), 1200 (w), 1180 (w), 1145 (vs), 1090 (vs), 1070 (vs), 1040 (s), 1005 (s), 980 (vs), 810 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.93–2.24 (m, 2 H), 2.43 (s, 3 H), 2.48 (d, J = 9.5 Hz, 1 H), 2.75–3.6 (m, 7 H), 3.59 (d, J = 11.0 Hz, 1 H), 3.86 (dd, J = 5.6, 11.5 Hz, 1 H), 4.25 (d, J = 11.0 Hz, 1 H), 4.64 (dt, J = 7.1, 9.5 Hz, 1 H, coalescing to d, J = 7.1 Hz, by irradiation at 2.1), 5.37 (dd, J = 12.7, 4.9 Hz, 1 H), 7.30 (d, J = 8.5 Hz, 2 H), 7.87 (d, J = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.4 (MePh), 30.7 (C-10), 32.1 (C-3), 37.1 (C-9), 45.4 (C-2), 69.4 (C-8), 75.2 (C-6), 80.3 (C-4), 127.7, 129.4, 136.6, 143.7 (Ph); mass spectrum, m/z (relative intensity) 437 (M, 0.5), 310 (100), 155 (85), 154 (42), 138 (38), 108 (30), 91 (81). Anal. Calcd for $C_{15}H_{20}NO_4IS$: C, 41.20; H, 4.60; N, 3.20; O, 14.64. Found: C, 41.41; H, 4.56; N, 3.04; O, 14.34.

***cis*-*N*-(*p*-Tolylsulfonyl)-2,2-dimethyl-3-iodo-4-hydroxypiperidine (5l, X = I)**: oil; IR (neat film) 3475 (s), 2900 (m), 2850 (m), 1590 (m), 1490 (w), 1437 (s), 1390 (m), 1315 (vs), 1250 (m), 1195 (m), 1150 (vs), 1117 (m), 1080 (vs), 1030 (m), 1000 (s), 960 (m), 910 (s), 890 (m), 810 (m), 725 (m), 700 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 3 H), 1.56 (s, 3 H), 1.94 (m, 2 H), 2.24 (d, J = 6.1 Hz, 1 H), 2.41 (s, 3 H), 3.36 (m, 1 H), 3.50 (m, 1 H), 3.96 (dt, J = 5.4, 13.7 Hz, 1 H), 4.46 (d, J = 2.9 Hz, 1 H), 7.27 (d, J = 8.3 Hz, 2 H), 7.72 (d, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.4 (MePh), 24.8, 31.0 (Me), 32.5 (C-5), 40.8 (C-6), 59.4 (C-3), 60.9 (C-2), 67.7 (C-4), 127.0, 129.3, 139.4, 143.0 (Ph).

***trans*-*N*-(*p*-Tolylsulfonyl)-2,2-dimethyl-3-iodo-4-hydroxypiperidine (6l, X = I)**: oil; IR (neat film) 3500 (s), 2920 (s), 1595 (m), 1440 (m), 1390 (m), 1370 (s), 1310 (vs), 1210 (m), 1180 (m), 1150 (vs), 1120 (m), 1085 (vs), 1018 (w), 960 (s), 916 (w), 860 (w), 800 (s), 730 (m), 690 (vs) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3 H), 1.58 (s, 3 H), 1.6–2.4 (m, 3 H), 2.42 (s, 3 H), 3.23 (dt, J = 2.4, 14.4 Hz, 1 H), 3.85–4.07 (m, 1 H), 4.15 (d, J = 10 Hz, 1 H), 4.33 (ddd, J = 14.4, 5.1, 2.9 Hz, 1 H), 7.26 (d, J = 8.3 Hz, 2 H), 7.66 (d, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 30.0 (MePh, Me), 34.6 (C-5), 41.1 (C-6), 56.3 (C-3), 61.5 (C-2), 71.2 (C-4), 126.7, 129.5, 140.1, 143.1 (Ph).

***cis*-*N*-(*p*-Tolylsulfonyl)-2,2-dimethyl-3-bromo-4-hydroxypiperidine (5l, X = Br)**: oil; IR (neat film) 3490 (s), 2920 (s), 1590 (s), 1490 (w), 1440 (s), 1370 (s), 1320 (vs), 1210 (m), 1185 (m), 1150 (vs), 1087 (vs), 1020 (w), 965 (s), 910 (s), 865 (w), 805 (s), 730 (vs), 705 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 3 H), 1.55 (s, 3 H), 1.6–2.3 (m, 3 H), 2.41 (s, 3 H), 3.22 (dt, J = 2.7, 14.4 Hz, 1 H), 3.91 (m, 2 H), 4.32 (ddd, J = 14.4, 4.9, 2.7 Hz, 1 H), 7.26 (d, J = 8.3 Hz, 2 H), 7.68 (d, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.3 (MePh), 19.6, 27.8 (Me–C-2), 34.1 (C-5), 41.0 (C-6), 61.8 (C-2), 69.9 (C-3), 70.3 (C-4), 126.6, 129.5, 140.0, 143.1 (Ph).

Reduction of 5l and 6l with (n-Bu)$_3$SnH. A mixture of **5l** or **6l** (X = I, 0.1 mmol), (n-Bu)$_3$SnH (0.25 mmol), and azobis(isobutyronitrile) (0.005 mmol) in 5 mL of dry benzene was refluxed for 2 h under argon. After evaporation of the solvent, the residue was dissolved in ether–hexane (1/4 v/v) and kept in a refrigerator to give *N*-(*p*-tolylsulfonyl)-2,2-dimethyl-4-hydroxypiperidine as a colorless crystalline solid (87% yield from **5l**, 78% yield from **6l**): IR (KBr disk) 3550 (s), 1315 (m), 1300 (s), 1145 (s), 1085 (m), 1065 (m), 950 (m), 900 (m), 810 (m), 690 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 3 H), 1.43 (s, 3 H), 1.4–2.2 (m, 4 H), 2.41 (s, 3 H), 3.18 (ddd, J = 2.9, 11.5, 13.4 Hz, 1 H), 3.9 (m, 1 H), 4.03 (dt, J = 13.4, 4.4 Hz, 1 H); high-resolution mass spectrum calcd for $C_{14}H_{21}NO_3S$ 283.1241, found m/z (relative intensity) 283.1222 (M, 1), 168 (100), 155 (40).

***trans,cis*-*N*-(*p*-Tolylsulfonyl)-2-phenyl-3-bromo-4-hydroxy-5,5-dimethylpiperidine (5m, X = Br)**: mp 156.0–156.5 °C (benzene–hexane); IR (KBr disk) 3560 (vs), 2950 (m), 2910 (m), 2865 (m), 1600 (m), 1495 (s), 1468 (m), 1440 (s), 1400 (m), 1370 (w), 1360 (m), 1320 (s), 1300 (s), 1220 (w), 1160 (vs), 1100 (m), 1080 (vs), 1070 (s), 1040 (vs), 965 (s), 817 (s), 740 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (s, 3 H), 1.14 (s, 3 H), 2.18 (br s, 1 H), 2.39 (s, 3 H), 3.36 (m, 2 H), 3.51 (d, J = 2.4 Hz, 1 H), 4.78 (dd, J = 7.3, 2.4 Hz, 1 H), 4.89 (d, J = 7.3 Hz, 1 H), 7.10–7.50 (m, 4 H), 7.20 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.3 (MePh), 22.8, 24.9 (Me), 36.7 (C-5), 52.1 (C-6), 60.0 (C-3), 63.6 (C-2), 74.1 (C-4), 127.6, 127.9, 128.6, 129.0, 136.8, 142.9 (Ph); mass spectrum, m/z (relative intensity) 438 (M, 10), 340 (79), 260 (82), 202 (100), 155 (83), 91 (47), 70 (85). Anal. Calcd for $C_{20}H_{24}NO_3BrS$: C, 54.79; H, 5.52; N, 3.02; O, 10.95. Found: C, 55.16; H,5.46; N, 3.12; O, 10.62.

***trans,cis*-*N*-(*p*-Tolylsulfonyl)-2-phenyl-3-iodo-4-hydroxy-5,5-dimethylpiperidine (5m, X = I)**: IR (neat film) 3500 (s), 3050 (m), 2950 (vs), 2820 (m), 1720 (m), 1595 (s), 1330 (vs), 1150 (vs), 1090 (vs), 1030 (s), 1005 (m), 960 (m), 905 (s), 810 (s), 775 (s), 730 (s), 700 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.22 (s, 3 H), 2.28 (br s, 1 H), 2.37 (s, 3 H), 3.27 (d, J = 12.5 Hz, 1 H), 3.50 (m, 1 H), 3.54 (d, J = 12.5 Hz, 1 H), 4.57 (d, J = 9.0 Hz, 1 H), 4.87 (dd, J = 9.0, 2.4 Hz, 1 H), 7.10 (d, J = 8.3 Hz, 2 H), 7.31 (d, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.3 (MePh), 23.9, 24.5 (Me–C-5), 36.6 (C-5), 43.8 (C-3), 51.9 (C-6), 63.6 (C-2), 75.6 (C-4), 125.0, 126.7, 127.3, 127.4, 128.0, 128.9, 129.1, 136.0, 137.9, 142.8 (Ph).

The following products **10** were, owing to their instability, characterized through derivation to the corresponding cyclic carbamates **13**.

***cis*-*N*-(Methoxycarbonyl)-2-(iodomethyl)-3-hydroxypyrrolidine (10a)**: IR (neat film) 3400 (vs), 2950 (m), 2880 (m), 1670 (vs), 1100 (m), 1450 (s) cm^{-1}; ^1H NMR ($CDCl_3$ at 60 °C) δ 2.0 (m, 2 H), 2.61 (d, J = 4.9 Hz, 1 H), 3.16–3.56 (m, 3 H), 3.71 (s, 3 H), 3.99 (ddd, J = 3.7, 4.9, 10.0 Hz, 2 H), 4.60 (m, 1 H); ^{13}C NMR ($CDCl_3$ at 60 °C) δ 2.7 (CH_2I), 32.1 (C-4), 45.4 (C-5), 52.4 (OMe), 62.1 (C-2), 71.7 (C-3), 155.8 (C=O).

***cis*-*N*-(Methoxycarbonyl)-2-(iodomethyl)-3-(benzoyloxy)pyrrolidine (Benzoate of 10a).** A solution of **10a** (1 mmol), triethylamine (3 mmol), benzoic anhydride (1.5 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (0.1 mmol) in dry THF (7 mL) was stirred at room temperature overnight. The solution was diluted with ether and washed with 2 N HCl, saturated NaCl, and then aqueous $NaHCO_3$. After drying over anhydrous magnesium sulfate, the solvent was evaporated and the residue was purified by column chromatography (silica gel, benzene–ethyl acetate, 8/1 v/v): oil; IR (neat film) 2940 (w), 1720 (s), 1700 (s), 1440 (m), 1260 (m), 1100 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.22 (m, 2 H), 3.28–3.92 (m, 4 H), 3.75 (s, 3 H), 4.31 (ddd, J = 9.5, 5.9, 3.9 Hz, 1 H, coalescing to dd, J = 9.5, 3.9 Hz, by irradiation at 5.73), 5.73 (m, 1 H, coalescing to d, J = 5.6 Hz, by irradiation at 2.22), 7.36–7.70 (m, 3 H), 7.92–8.19 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 1.3 (CH_2I), 30.2 (C-4), 45.3 (C-5), 52.6 (OMe), 60.5 (C-2), 74.4 (C-3), 128.3, 129.5, 133.2 (Ph), 155.5, 165.3 (C=O).

***trans*-*N*-(Methoxycarbonyl)-2-(iodomethyl)-3-(benzoyloxy)pyrrolidine (Benzoate of 11a, Mitsunobu Inversion, Eq 6).** Into a solution of **10a** (1 mmol), Ph_3P (1.1 mmol), and benzoic acid (1.1 mmol) in dry THF (5 mL) was added diethyl azodicarboxylate (1.1 mmol) dropwise at 0 °C. After being stirred at 0 °C for 5 h, the mixture was diluted with ethyl ether and washed with 2 N HCl, saturated NaCl, and then aqueous $NaHCO_3$. The extract was dried ($MgSO_4$) and condensed to give an oil, which was chromatographed over silica gel (benzene–ethyl acetate, 8/1 v/v): oil; IR (neat film) 2950 (w), 1720 (s), 1700 (s), 1440 (m), 1380 (m), 1270 (m), 1105 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.97–2.65 (m, 2 H), 3.46–3.74 (m, 4 H), 3.74 (s, 3 H), 4.11 (m, 1 H), 5.49 (br s, 1 H), 7.36–7.68 (m, 3 H), 7.96–8.10 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 5.5 (CH_2I), 29.5 (C-4), 45.4 (C-5), 52.6 (OMe), 63.9 (C-2), 78.5 (C-3), 128.3, 129.5, 133.3 (Ph), 155.2, 165.6 (C=O); high-resolution mass spectrum calcd for $C_{14}H_{16}NO_4I$ – I 262.1079, found m/z (relative intensity) 389 (M^+, 0.2), 262.1087 (M – I, 34), 248 (32), 140 (28), 105 (100).

***cis*-*N*-(Methoxycarbonyl)-2-(iodomethyl)-2-methyl-3-hydroxypyrrolidine (10e)**: IR (neat film) 3400 (m), 2940 (w), 1665 (s), 1440 (s), 1370 (s), 1190 (w), 1070 (w) cm^{-1}; ^1H NMR ($CDCl_3$ at 60 °C) δ 1.48 (s, 3 H), 2.00 (m, 2 H), 3.50–3.70 (m, 4 H), 3.68 (s, 3 H), 4.15 (m, 2 H).

***cis*-*N*-(Methoxycarbonyl)-2-(iodomethyl)-3-hydroxy-3-methylpyrrolidine (10f)**: IR (neat film) 3400 (s), 2950 (m), 2880 (w), 1670 (s), 1450 (m), 1380 (m), 1110 (m) cm^{-1}; ^1H NMR ($CDCl_3$ at 60 °C) δ 1.46 (s, 3 H), 1.67–2.33 (m, 2 H), 3.36–3.81 (m, 5 H), 3.71 (s, 3 H); ^{13}C NMR ($CDCl_3$ at 60 °C) δ 3.5 (br, CH_2I), 28.3 (C-3-*Me*), 36.7, 37.6 (2 br, C-4), 43.4 (C-5), 52.2 (OMe), 64.59 (C-2), 76.5 (br, C-3), 155.1 (C=O).

***cis*,*cis*-*N*-(Methoxycarbonyl)-2-(iodomethyl)-3-hydroxy-4-methylpyrrolidine (10g)**: IR (KBr disk) 3300 (s), 2950 (m), 1670 (s), 1445 (m), 1380 (m) cm^{-1}; ^1H NMR ($CDCl_3$ at 60 °C) δ 1.08 (d, J = 6.8 Hz, 3 H), 1.91–2.34 (m, 1 H), 2.34 (d, J = 4.6 Hz, 1 H), 3.14 (t, J = 11.0 Hz, 1 H), 3.23 (dd, J = 11.0, 9.0 Hz, 1 H), 3.70 (s, 3 H), 3.70–4.14 (m, 3 H), 4.34 (dd, J = 4.6, 4.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$ at 60 °C) δ 3.0 (br, CH_2I), 10.6 (Me–C-4), 37.4 (C-4), 52.6 (C-5, OMe), 64.3 (br, C-1), 74.4 (C-3), 155.8 (C=O).

***cis*,*trans*-*N*-(Methoxycarbonyl)-2-(iodomethyl)-3-hydroxy-4-methylpyrrolidine (10h)**: IR (neat film) 3400 (m), 2950 (w), 1670 (s), 1445 (m), 1380 (m) cm^{-1}; ^1H NMR ($CDCl_3$ at 60 °C) δ 1.03 (d, J = 6.8 Hz, 3 H), 2.30 (m, 3 H), 3.08–3.64 (m, 4 H), 3.70 (s, 3 H), 4.10 (m, 1 H); ^{13}C NMR ($CDCl_3$, at 60 °C) δ 2.8 (CH_2I), 15.7 (Me–C-4), 38.1 (C-4), 51.2 (C-5), 52.5 (OMe), 60.2 (br, C-2), 76.9 (C-3), 155.8 (C=O).

***cis*-*N*-(Methoxycarbonyl)-2-(iodomethyl)-3-hydroxy-4,4-dimethylpyrrolidine (10j)**: IR (KBr disk) 3400 (s), 2940 (m), 2500 (w), 1665 (s), 1450 (s), 1380 (s) cm^{-1}; ^1H NMR ($CDCl_3$ at 60 °C) δ 0.95 (s, 3 H), 1.10 (s, 3 H), 2.27 (d, J = 4.4 Hz, 1 H), 3.10–3.97 (m, 4 H), 3.70 (s, 3 H), 3.90 (t, J = 4.4 Hz, 1 H), 4.10 (dt, J = 11.2, 4.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$ at 60 °C) δ 2.5 (CH_2I), 19.5 (Me–C-4), 24.7 (Me–C-4), 41.2 (C-4), 52.3 (OMe), 57.5 (C-5), 62.7 (C-2), 78.5 (C-3), 156.1 (C=O); mass spectrum, m/z (relative intensity) 313 (M, 2), 186 (74), 172 (38), 114 (100). Anal. Calcd for $C_9H_{16}NO_3I$: C, 34.52; H, 5.15; N, 4.47; O, 15.33. Found: C, 34.74; H, 5.23; N, 4.39; O, 15.09.

***trans*,*cis*-*N*-(Methoxycarbonyl)-2-phenyl-3-iodo-4-hydroxy-5,5-dimethylpiperidine (12m)**: mp 140 °C dec; IR (KBr disk) 3420 (s), 2950 (m), 1680 (s) cm^{-1}; ^1H NMR ($CDCl_3$ at 60 °C) δ 0.88 (s, 3 H), 1.22 (s, 3 H), 2.23 (br s, 1 H), 2.73 (d, J = 13.7 Hz, 1 H), 2.99 (br s, 1 H), 3.73 (s, 3 H), 3.80 (d, J = 13.7 Hz), 5.15 (dd, J = 3.7, 3.9 Hz, 1 H), 5.86 (d, J = 3.9 Hz, 1 H), 7.29 (br s, 5 H); ^{13}C NMR ($CDCl_3$ at 60 °C) δ 21.2, 27.3 (Me × 2), 36.5 (C-6), 37.4 (C-5), 50.0 (C-3), 53.2 (OMe), 62.9 (C-2), 72.9 (C-4), 126.3, 127.7, 128.8, 138.2 (Ph), 156.9 (C=O); mass spectrum, m/z (relative intensity) 389 (M, 0.003), 261 (35), 244 (100), 190 (27). Anal. Calcd for $C_{15}H_{20}NO_3I$: C, 46.28; H, 5.18; N, 3.60; O, 12.13. Found: C, 46.19; H, 5.01; N, 3.61; O, 12.09.

6-*endo*-Hydroxy-1-aza-3-oxabicyclo[3.3.0]octan-2-one (13a): mp 107.0–108.0 °C (ethyl acetate); IR (KBr disk) 3370 (m), 2940 (w), 1700 (s), 780 (w) cm^{-1}; ^1H NMR ($CDCl_3$ at 60 °C) δ 1.99–2.19 (m, 2 H), 3.08–3.34 (m, 2 H), 3.51–3.92 (m, 2 H), 4.20 (br s, 1 H), 4.29–4.63 (m, 2 H); ^{13}C NMR (CD_3CN) δ 35.4 (C-7), 44.5 (C-8), 63.9 (C-4), 64.9 (C-5), 70.5 (C-6), 163.3 (C-2); mass spectrum, m/z (relative intensity) 143 (12), 99 (33), 86 (19), 71 (99), 56 (100). Anal. Calcd for $C_6H_9NO_3$: C, 50.34; H, 6.34; N, 9.79. Found: C, 50.9; H, 6.37; N, 9.49.

4-*exo*-Methyl-6-*endo*-hydroxy-1-aza-3-oxabicyclo[3.3.0]-octan-2-one (13b): mp 111.0–111.3 °C (ethyl acetate); IR (KBr disk) 3400 (s), 1720 (s), 1400 (m), 1260 (m), 1055 (m), 820 (m), 770 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (d, J = 6.6 Hz, 3 H, Me), 2.08 (m, 2 H, C_7H), 3.01 (br s, 1 H, OH), 3.20 (ddd, J = 10.7, 8.1, 3.7 Hz, 1 H, coalescing to d, J = 10.7 Hz, by irradiation at 2.08, C_8H), 3.41 (dd, J = 3.6, 2.7 Hz, 1 H, C_5H), 3.4–3.8 (m, 1 H, coalescing to d, J = 10.7 Hz, by irradiation at 2.08, C_8H), 4.18 (br s, 1 H), 4.80 (dq, J = 3.6, 6.6 Hz, 1 H, coalescing to d, J = 3.6 Hz, by irradiation at 1.46, C_4H); ^{13}C NMR ($CDCl_3$) δ 21.3 (Me), 35.4 (C-7), 43.4 (C-8), 69.7 (C-6), 71.7 (C-5), 71.8 (C-4), 162.3 (C-2). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.06; N, 8.91. Found: C, 53.50; H, 7.18; N, 8.88. Differential NOE: increases of area intensities of C_4H and C_5H, C_4H and C_6H, and Me and C_6H by irradiations at Me, OH, and C_5H protons, respectively.

***trans*,*cis*-*N*-(Methoxycarbonyl)-2-propyl-3-iodo-4-(benzoyloxy)piperidine (benzoate of 12c)**: oil; IR (neat film) 1700 (br s), 1450 (s), 1385 (m), 1270 (s), 1200 (m), 1105 (s), 1070 (m), 1025 (m), 770 (m), 715 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70–1.00 (m, 3 H), 1.30–1.55 (m, 4 H), 2.22 (q, J = 7.1 Hz, 2 H, coalescing to t, J = 7.1 Hz, by irradiation at 5.52), 3.40–3.83 (m, 2 H), 3.75 (s, 3 H), 3.85–4.10 (m, 2 H), 5.52 (q, J = 5.9 Hz, coalescing to d, J = 5.9 Hz, by irradiation at 2.18), 7.33–7.72 (m, 3 H), 7.95–8.15 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.7, 18.6, 20.0, 37.2, 44.9, 63.8, 70.6, 73.9, 157.6, 165.6; high-resolution mass spectrum calcd for $C_{17}H_{22}NO_4I$ – PhCO, I, 199.1208, found m/z (relative intensity) 304 (M – I, 0.3), 199.1192 (M – PhCOI, 5), 144 (30), 105 (100).

4-*exo*-Propyl-6-*endo*-(benzoyloxy)-1-aza-3-oxabicyclo-[3.3.0]octan-2-one (benzoate of 13c): IR (neat film) 2960 (s), 1750 (s), 1720 (s), 1450 (m), 1380 (m), 1270 (s), 1110 (m), 1070 (m), 1030 (m), 960 (m), 780 (m), 710 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 6.6 Hz, 3 H), 1.16–1.95 (m, 4 H), 2.18–2.41 (m, 2 H, C_7H), 3.16–3.53 (m, 1 H, C_8H, coalescing to d, J = 11.2 Hz, by irradiation at 2.30), 3.58–4.00 (m, 2 H, C_5H and C_8H), 4.48 (dt, J = 2.9, 6.6 Hz, 1 H, C_4H), 5.47 (br q, J = 2.7 Hz, 1 H, C_6H), 7.35–7.65 (m, 2 H), 7.85–8.16 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.5 (C-3′), 17.7 (C-2′), 32.8 (C-7), 37.1 (C-1′), 43.5 (C-8), 67.8 (C-5), 73.5 (C-6), 74.8 (C-4), 161.4 (C-2), 165.5 (PhCO); high-resolution mass spectrum calcd for $C_{16}H_{19}NO_4$ – PhCO 184.0973, found m/z (relative intensity) 289 (M, 0.2), 184.0972 (M – PhCO, 28), 167 (M – $PhCO_2$, 40), 105 (100).

***trans*,*cis*-*N*-(Methoxycarbonyl)-2-[2′-(benzyloxy)-ethyl]-3-iodo-4-(benzoyloxy)piperidine (benzoate of 12d)**: IR (neat film) 1720 (br s), 1450 (s), 1390 (m), 1270 (s), 1100 (s), 705 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86 (q, J = 6.3 Hz, 2 H, $C_{1'}H$), 2.26 (q, J = 6.3 Hz, 2 H, C_5H), 3.46–3.70 (m, 4 H, $C_{2'}H$ and C_6H), 3.71 (s, 3 H), 4.04–4.26 (m, 2 H, C_2H and C_3H), 4.45 (s, 2 H), 5.50 (q, J = 6.3 Hz, coalescing to d and t, by irradiations at 2.26 and 4.15, respectively, C_4H), 7.22 (s, 5 H), 7.28–7.55 (m, 3 H), 7.96–8.13 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 29.6 (C-5), 34.7 (C-1′), 44.6 (C-6), 52.5 (Me), 63.0 (C-3), 67.8 (C-2′), 69.4 ($PhCH_2$), 72.9 (C-2), 73.6 (C-4),

Table II. Stereoselective Haloamidation of *N*-(Methoxycarbonyl)-4-pentenylamines 9 (Eq 2 and 3)

entry	substrate 9	rctn condtns[a] (days)(eq 2)	product ratio (% isolated)	rctn condtns[b] (h) (eq 3)	product (% isolated)
1	**9a**	C (6)	**10a**/**11a** = 93/7 (83)	16	**13a** (80)
2	**9b**	C (2)	**13b** (38)		
3	**9c**	C (5)	**12c** (5),[c] **13c** (8)[c]		
4	**9d**	C (14)	**12d** (7),[c] **13d** (16)[c]		
5	**9e**	C (2)	**10e**/**11e** = 92:8 (87)	5	**13e** (90)
6	**9f**	C (2)	**10f**/**11f** = 95/5 (93)	24	**13f** (94)[d]
7	**9g**	C (4)	**10g**/**11g** = 95/5 (97)	6	**13g** (93)
8	**9h**	C (4)	**10h**/**11h** = 91:10 (81)	31	**13h** (94)
9	**9i**	C (4)	no rctn		
10	**9j**	C (0.1)	**10j** (97)	45	**13j** (73)[e]
11	**9k**	**C** (4)	no rctn		
12	**9k**	E (4)	no rctn		
13	**9m**	E (2)	**12m** (86)		

[a] Haloamidation was undertaken under the following conditions. C: room temperature, I_2 (1.5 mmol), $NaHCO_3$ (1.5 mmol), Et_2O–H_2O (5 mL–2 mL)/mmol of **9**. E: room temperature, NIS (1.2 mmol), CH_2Cl_2 (5 mL)/mmol of **9**. [b] The reaction was undertaken in acetonitrile at reflux. [c] Yield refers to the isolated yield after benzoylation of the hydroxyl group. [d] Yield is based on 60% conversion. [e] Yield is based on 73% conversion.

157.2 (NCO), 165.6 (PhCO); high-resolution mass spectrum calcd for $C_{23}H_{26}NO_5I$ – PhCO, HI, 290.1392, found *m/z* (relative intensity) 290.1391 (4), 259 (15), 248 (27), 200 (11), 168 (15), 144 (41), 138 (17), 127 (100).

4-*exo*-[2′-(Benzyloxy)ethyl]-6-*endo*-(benzoyloxy)-1-aza-3-oxabicyclo[3.3.0]octan-2-one (benzoate of 13d): IR (neat film) 1750 (s), 1715 (s), 1445 (m), 1370 (m), 1265 (s), 1100 (s), 1065 (m), 1020 (m), 710 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (br q, J = 5.9 Hz, 2 H), 2.18–2.41 (m, 2 H, C_7H), 3.20–3.50 (m, 1 H, C_8H, coalescing to d, J = 11.2 Hz, by irradiation at 2.30), 3.59–3.75 (m, 3 H, $C_{2'}H$ and C_8H), 3.78–3.94 (m, 1 H, C_5H, coalescing to d, J = 2.9 Hz, by irradiation at 5.42), 4.48 (s, 2 H), 4.72 (dt, J = 2.9, 6.6 Hz, 1 H, C_4H, coalescing to d, J = 2.9 Hz, by irradiation at 2.10), 5.32–5.52 (m, 1 H, C_6H, coalescing to d, J = 2.9 Hz, by irradiation at 2.30), 7.26 (br s, 5 H), 7.41–7.62 (m, 3 H), 7.92–8.05 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 32.4 (C-7), 34.9 (C-1′), 43.2 (C-8), 65.4 (C-2′), 67.4 (C-5), 72.6 (C-4), 72.7 ($PhCH_2$), 73.2 (C-6), 161.0 (C-2), 165.1 (PhCO); high-resolution mass spectrum calcd for $C_{22}H_{23}NO_5$ – $PhCO_2H$ 259.1208, found *m/z* (relative intensity) 259.1208 (M – $PhCO_2H$, 58), 168 (26), 138 (42), 125 (34), 105 (PhCO).

5-Methyl-6-*endo*-hydroxy-1-aza-3-oxabicyclo[3.3.0]octan-2-one (13e): mp 91.5–92.5 °C (ethyl acetate); IR (KBr disk) 3350 (m), 2950 (m), 1720 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 3 H), 2.00–2.51 (m, 3 H), 3.21 (ddd, J = 11.3, 9.0, 3.9 Hz, 1 H), 3.70 (dt, J = 11.3, 8.5 Hz, 1 H), 3.90 (br s, 1 H), 4.00 (d, J = 8.8 Hz, 1 H), 4.69 (d, J = 8.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.3 (Me), 33.5 (C-7), 42.4 (C-8), 69.9, 70.1 (C-4, C-5), 74.2 (C-6), 162.4 (C-2); mass spectrum, *m/z* (relative intensity) 129 (14), 113 (66), 98 (100), 97 (74), 53 (40), 42 (60). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.06; N, 8.91. Found: C, 53.48; H, 7.12; N, 8.91.

6-*endo*-Hydroxy-6-*exo*-methyl-1-aza-3-oxabicyclo[3.3.0]-octan-2-one (13f): mp 124.0–125.0 °C (ethyl acetate); IR (KBr disk) 3350 (s), 2950 (m), 1710 (s), 770 (m) cm^{-1}; ^1H NMR ($CDCl_3$ at 60 °C) δ 1.32 (s, 3 H), 1.92–2.12 (m, 2 H), 2.34 (br s, 1 H), 3.27 (ddd, J = 11.2, 8.5, 3.1 Hz, 1 H), 3.54–3.86 (m, 2 H), 4.34–4.4 (m, 2 H, coalescing to s, by irradiation at 3.6); ^{13}C NMR (CD_3CN) δ 23.4 (Me), 42.0 (C-7), 46.2 (C-8), 64.6 (C-4), 68.9 (C-5), 77.5 (C-6), 164.3 (C-2); mass spectrum, *m/z* (relative intensity) 113 (11), 98 (20), 86 (16), 71 (35), 70 (57), 56 (100). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.06; N, 8.91. Found: C, 53.37; H, 6.95; N, 8.92.

6-*endo*-Hydroxy-7-*endo*-methyl-1-aza-3-oxabicyclo-[3.3.0]octan-2-one (13g): mp 112.0–113.0 °C (ethyl acetate); IR (KBr disk) 3400 (s), 2950 (m), 1720 (s), 1400 (m), 1250 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (d, J = 6.8 Hz, 3 H), 2.39 (m, 2 H), 3.06 (t, J = 8.6 Hz, 1 H), 3.60 (d, J = 4.5 Hz, 1 H), 4.56 (dd, J = 4.4, 8.6 Hz, 1 H), 3.89–4.26 (m, 2 H), 4.31 (d, J = 8.7 Hz, 1 H), 4.54 (dd, J = 8.7, 4.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.5 (Me), 40.5 (C-7), 50.3 (C-8), 63.6 (C-4), 64.7 (C-5), 72.2 (C-6), 162.5 (C-2). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.06; N, 8.91. Found: C, 53.59; H, 7.11; N, 8.90.

6-*endo*-Hydroxy-7-*exo*-methyl-1-aza-3-oxabicyclo[3.3.0]-octan-2-one (13h): IR (neat film) 3400 (s), 2950 (m), 1720 (m), 1400 (m), 1250 (m), 1080 (m), 1015 (m), 780 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (d, J = 7.3 Hz, 3 H), 2.42 (m, 1 H), 3.77–3.90 (m, 2 H), 3.98 (t, J = 4.4 Hz, 1 H), 4.38 (d, J = 8.8 Hz, 1 H), 4.48 (s, 1 H), 4.53 (dd, J = 8.8, 4.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.4 (Me), 42.0 (C-7), 50.9 (C-8), 61.5, 63.0 (C-4, C-5), 75.3 (C-6), 162.4 (C-2); high-resolution mass spectrum calcd for $C_7H_{11}NO_3$ 157.0739, found *m/z* (relative intensity) 157.0759 (M, 4), 99 (33), 85 (25), 70 (43), 56 (100).

6-*endo*-Hydroxy-7,7-dimethyl-1-aza-3-oxabicyclo[3.3.0]-octan-2-one (13j): mp 143.0–143.5 °C (MeCN–hexane); IR (KBr disk) 3350 (m), 2950 (m), 1705 (s), 770 (w) cm^{-1}; ^1H NMR (CD_3CN) δ 1.06 (s, 3 H), 1.10 (s, 3 H), 2.87 (dd, J = 10.5, 1.5 Hz, 1 H), 3.19 (d, J = 10.5 Hz, 1 H), 3.31–3.49 (m, 2 H), 4.32 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 21.8, 26.7 (Me), 46.0 (C-7), 58.0 (C-8), 63.5, 64.2 (C-4, C-5), 78.1 (C-6), 163.2 (C-2); mass spectrum, *m/z* (relative intensity) 171 (M, 0.02), 100 (44), 97 (38), 56 (100), 55 (43). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 55.97; H, 7.71; N, 8.17.

***N*-(*p*-Tolylsulfonyl)-2-(iodomethyl)-3-hydroxy-3-methylpiperidine (15b, X = I)**: A 30-mL round-bottomed flask containing *N*-iodosuccinimide (3 mmol) and a magnetic stirring bar was purged with nitrogen and covered with aluminum foil. Into this was added 10 mL of dry dichloromethane. After stirring at 0 °C for 10 min, a solution of **14b** (1 mmol) in 5 mL of dry dichloromethane was introduced into the mixture via a syringe. The mixture was stirred for about 1 h until TLC monitoring showed the complete disappearance of the starting material (R_f 0.5, silica gel plate, benzene–ethyl acetate, 1/1 v/v) and then exposed to ambient light by removal of the aluminum foil. After about 2 h (product **15b**: R_f 0.6), the reaction mixture was quenched by the addition of aqueous Na_2SO_3, and the mixture was extracted with ethyl ether (30 mL × 2). The extracts were washed with saturated NaCl and aqueous $NaHCO_3$ and dried ($MgSO_4$). The solvent was evaporated, and the residual mixture was separated by preparative TLC: mp 114.5–115.5 °C (benzene); IR (KBr disk) 3500 (s), 2930 (m), 1595 (m), 1490 (w), 1460 (w), 1440 (w), 1370 (m), 1310 (s), 1245 (w), 1215 (m), 1200 (s), 1145 (s), 1090 (S), 1060 (s), 1020 (s), 995 (m), 960 (m), 940 (s), 905 (w), 840 (m), 820 (s), 760 (m), 710 (s), 695 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.20–1.88 (m, 4 H), 2.41 (s, 3 H), 2.61–2.88 (m, 2 H), 3.14 (dd, J = 11.0, 9.5 Hz, 1 H), 3.35 (dd, J = 11.0, 5.3 Hz, 1 H), 3.60 (m, 1 H, coalescing to d, J = 11.4 Hz, by irradiation at 1.50), 4.20 (dd, J = 9.3, 5.3 Hz, 1 H), 7.29 (d, J = 8.6 Hz, 2 H), 7.87 (d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 1.8 (CH_2I), 19.6 (C-5), 21.1 (MePh), 27.3 (Me), 31.3 (C-4), 38.8 (C-6), 64.1 (C-2), 69.1 (C-3), 127.5, 129.0, 136.6, 142.9 (Ph); mass spectrum, *m/z* (relative intensity) 282 (17), 85 (100). Anal. Calcd for $C_{14}H_{20}NO_3SI$: C, 41.10; H, 4.93; N, 3.42; O, 11.73. Found: C, 41.23; H, 4.94; N, 3.50.

***N*-(*p*-Tolylsulfonyl)-2-(bromomethyl)-3-hydroxy-3-methylpiperidine (15b, X = Br)**: IR (KBr disk) 3470 (m), 2900 (m), 1715 (s), 1590 (w), 1300 (s), 1145 (s) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 19.8 (C-5), 21.2 (MePh), 27.0 (Me), 28.9 (CH_2Br), 31.9 (C-4), 39.2 (C-6), 63.7 (C-2), 69.1 (C-3); mass spectrum, *m/z* (relative

intensity) 282 (8), 85 (100). Anal. Calcd for $C_{14}H_{20}NO_3SBr$: C, 46.41; H, 5.56; N, 3.87; O, 13.25. Found: C, 46.51; H, 5.56; N, 3.87; O, 13.35.

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Supplementary Material Available: Synthetic procedure for 3-hydroxy-4-pentenylamines **1a-m**, 4-hydroxy-5-hexenylamines, and their N-protected derivatives **2a-m**, **9a-m**, and **14a,b** and their spectral data (IR, ^1H, ^{13}C NMR) (9 pages). Ordering information is given on any current masthead page.

2-Iminooxetane Chemistry. 2. General Synthesis from Ketene Imine-Aldehyde Cycloadditions[1]

Gaetano Barbaro, Arturo Battaglia,* and Patrizia Giorgianni

Istituto dei Composti del Carbonio Contenenti Eteroatomi, Loro Applicazioni del CNR, 40064 Ozzano Emilia, Italy

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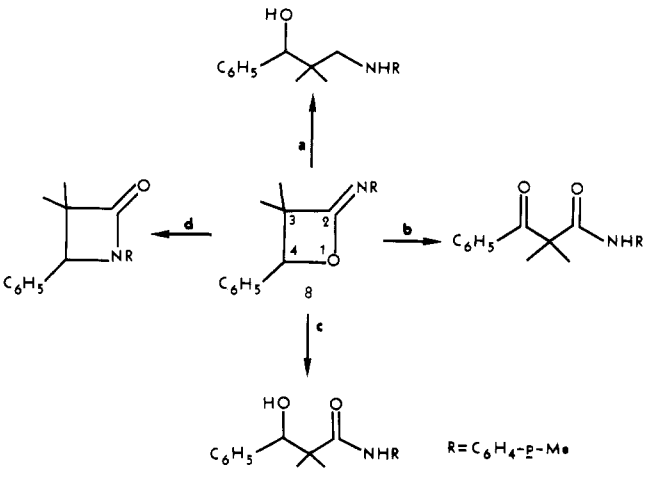
2-Iminooxetanes, versatile synthons of highly functionalized γ-amino alcohols, β-keto amides, β-hydroxy amides, and β-lactams, are synthesized by regiospecific 2 + 2 cycloadditions of aldehydes to ketene imines in the presence of lanthanide shift reagents (Yt^{3+} or Eu^{3+}). In a few cases, the nature of the peripheral substitution on the reagents influences the selectivity of the cycloaddition, causing the formation of other isomeric products.

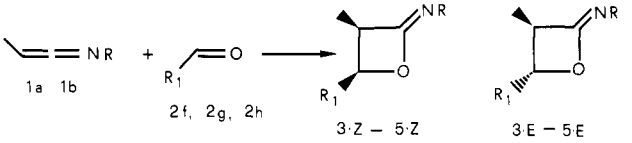
We have recently described the cycloaddition of dimethylketene *N*-*p*-tolylimine (**1d**) with benzaldehyde (**2f**),[1] in the presence of 1 mol % of lanthanide shift reagents, such as $Yt(fod)_3$ or $Eu(fod)_3$,[2] yielding the oxetane **8** as sole regioisomer. An exploratory investigation (Scheme I) showed that **8** is the intermediate key that can be transformed into the corresponding γ-amino alcohol (path a), β-keto amide (path b), and β-hydroxy amide (path c), depending on the medium. In addition, the catalyzed ring isomerization (path d) produced the regioisomeric β-lactam.

The possibility of developing a new strategy for syntheses of β-lactams having diverse functionality, via path d directly, or via β-keto amides and β-hydroxy amides as intermediates, prompted us to test the generality of our procedure for the synthesis of 2-iminooxetanes. So far we have studied the role of peripheral substituents in the reagents on the stereoselectivity of the heterocycloaddition among a selected number of ketene imines and aldehydes. This preliminary investigation is essential because alternative sources are not available for the production of 2-iminooxetanes. In fact, the literature reports only a few examples of photochemically induced cycloadditions of ketene imines and aldehydes or ketones.[3] However, these reactions produced only moderate amounts of mixtures of the regioisomeric 2- and 3-iminooxetanes, the latter being more often the major isomers. The thermally induced cycloaddition of diphenylketene *N*-*p*-tolylimine with the electron-deficient bis(trifluoromethyl) ketone to give the corresponding 2-iminooxetane has also already been described.[4]

Scheme I



Scheme II



R: a = C_6H_4-p-OMe; b = C_6H_4-p-Me

R_1: f = C_6H_5; g = n-Pr; h = i-Pr

	R	R_1
3:	a	C_6H_5
4:	a	n-Pr
5:	b	i-Pr

(1) Barbaro, G.; Battaglia, A.; Giorgianni, P. *Tetrahedron Lett.* **1987**, *28*, 2995.

(2) The IUPAC and, in parentheses, the commercial names of the lanthanides used were as follows: tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium or -europium [$Yt(fod)_3$ or $Eu(fod)_3$]; tris(2,2,6,6-tetramethyl-3,5-heptanedionato)ytterbium [$Yt(thd)_3$]; tris-[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]ytterbium or -europium [$Yt(hfc)_3$ or $Eu(hfc)_3$]; tris[3-[(trifluoromethyl)hydroxymethylene]-(+)-camphorato]europium [$Eu(tfc)_3$].

(3) (a) Singer, L. A.; Bartlett, P. D. *Tetrahedron Lett.* **1964**, 1887. (b) Singer, L. A.; Davis, G. A.; Muralidharan, V. P. *J. Am. Chem. Soc.* **1969**, *91*, 897 and references therein.

(4) Weidler-Kubanek, A.; Litt, M. *J. Org. Chem.* **1968**, *33*, 1844.

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