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Stereoselective Radical-Mediated Cyclization of Norephedrine Derived α-Iodoamides: Synthesis of Enantiopure Pyrrolidines and Transition State Modelling[1]

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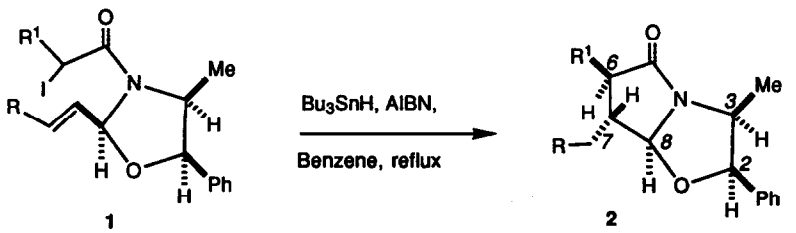
Abstract: *Radical-mediated cyclization of norephedrine derived α-iodoamides 1 was found to be highly stereoselective (≥97:3) favouring diastereoisomer 2. Bicyclic lactams 2 were transformed in high yields into enantiomerically pure pyrrolidines 10. Transition state modelling with a force field developed* ad hoc *nicely predicts the stereochemical results.*

The understanding of the factors that control relative stereochemistry in radical cyclization reactions is a topic of continuous interest.[2] As part of a long term project aimed at investigating the stereodirecting effects of allylic stereocentres in addition reactions to π-systems[3] (e.g. nucleophilic[4] and electrophilic[5]), we became interested in the stereoselectivity of radical additions to double bonds[6] (Scheme 1). The radical mediated cyclization of norephedrine derived α-iodoamides **1** was found to be highly stereoselective (≥97:3) favouring diastereoisomer **2**.[1] This high level of stereocontrol was somehow unexpected, and was lacking of both experimental precedents and stereochemical rationalizations based on the existing models. For example, transition state modelling using the "radical force field" developed by K. Houk and coworkers[7e] predicted ratios which are disappointingly lower than the experimental ones [e.g. *trans-cis* (C-7/C-8) ratio 66:34]. In this paper we report on the radical cyclization reactions of norephedrine derived α-iodoamides **1** to give bicyclic lactams **2** and on the subsequent transformation of **2** into enantiomerically pure pyrrolidines **10**. The stereochemical outcome of the cyclization reaction was rationalized using a "radical force field" developed *ad hoc*, which models a transition state for the radical addition to the double bond which is "earlier" along the reaction coordinate compared to other force fields.[7]

Scheme 1. Radical mediated cyclizations.



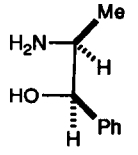
1

R = H, Me, COOMe; R^1 = H
R = H; R^1 = Me

2

α-Iodoamides **1** were synthesized as outlined in Scheme 2. Norephedrine **3** was treated with the suitable α-chloroacyl chloride (Shotten Baumann) to give the α-chloroamide. Subsequent reaction with α,β-unsaturated dimethylacetals [refluxing benzene, pyridinium tosylate (Py-Ts), 4-Å mol. sieves] gave the corresponding oxazolidines in very good yield and high *cis* selectivity (Table 1).[8] Substitution of the chloride with iodide (NaI, acetone) gave oxazolidines **1** in good overall yield.

Scheme 2. Synthesis of α-iodoamides 1.

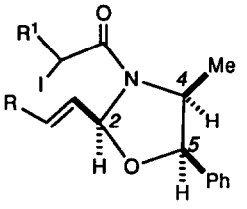


3

a) $R^1CHClCOCl$, H_2O, NaOH (90-92%)

b) RCH=CHCH(OMe)$_2$, Py-Ts, benzene reflux, 4-Å Mol.Sieves (80-90%)

c) NaI, acetone (80-92%)



1

R = H, Me, COOMe; R^1 = H

R = H; R^1 = Me

Table 1. ***Cis-trans*** **ratios and yields of Py-Ts mediated cyclizations [3→1].**

Entry	Compound **1**	*cis:trans* (C-2/C-4) ratio[a]	cyclization yield (%)
1	R=H; R^1=H	≥95: 5[b]	90
2	R=Me; R^1=H	80:20[c]	90
3	R=H; R^1=Me	92: 8[d]	90
4	R=CO_2Me; R^1=H	≥95: 5[e]	80

[a]see footnote 8. [b]benzene, reflux, 10 hr, 0.25 mol.eq. Py-Ts. [c]benzene, reflux, 13 hr, 0.25 mol.eq. Py-Ts. [d]benzene, reflux, 14 hr, 0.25 mol.eq. Py-Ts. [e]benzene, reflux, 70 hr, 0.40 mol.eq. Py-Ts.

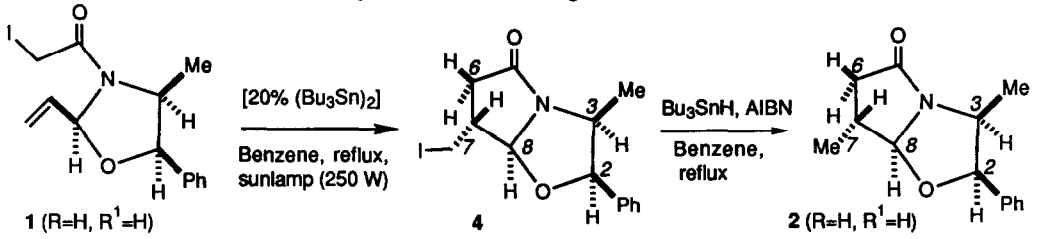
Slow addition (6 hr) of a 0.08 M solution of Bu_3SnH (1.1 mol.eq.) in benzene containing a catalytic amount of AIBN (0.05 mol.eq.) to a 0.02 M refluxing benzene solution of α-iodoamide **1** (1 mol.eq.) gave, after work-up (KF-H_2O) and chromatography, bicyclic compounds **2** (Scheme 1, Table 2).[9,10] In the case of R^1=H (Table 2, entries 1,2,4), the major side-products of the Bu_3SnH mediated reaction at 80°C were the reduction products (acetamides), which were the only isolated products when the reaction was run at room temperature. No reduction product was observed in the case of R^1=Me (Table 2, entry 3).

Table 2. Diastereomeric ratios and yields of radical-mediated cyclizations [1→2].[10]

Entry	Compound **2**	*trans-cis* (C-7/C-8) ratio	*si-re* face (C-6) ratio	%yield
1	R=H; R^1=H	≥97:3	-	75
2	R=Me; R^1=H	≥97:3	-	60
3	R=H; R^1=Me	≥97:3	≥97:3	85
4	R=CO_2Me; R^1=H	≥97:3	-	32

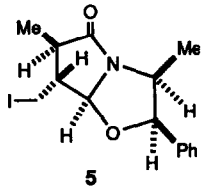
The problem of Bu_3SnH competitive reduction of iodoacetamides was solved using the alternative "atom-transfer cyclization reaction" developed by D. Curran and coworkers (Scheme 3).[11] Using this methodology the cyclization yields were high (≥ 80%) not only in refluxing benzene (1 h at 80°C), but also in toluene at 25°C, although under these last conditions longer reaction times were required (3 h).[11a] Final reduction of the γ-iodo carbonyl product **4** gave the desired bicyclic lactam **2** in quantitative yield.

Scheme 3. Radical mediated cyclizations via halogen-transfer.



1 (R=H, R^1=H) **4** **2** (R=H, R^1=H)

It is interesting to observe that no *endo-(6)* ring closure product was observed, in contrast with the high *endo-(6) : exo-(5)* ratios reported for the cyclization reactions of α-keto radicals (carbonyl group inside the forming ring).[11b] It is also interesting to observe that variable amounts of compound **5** were formed as by-product of the Bu_3SnH-mediated radical cyclization reaction of α-iodopropionamide **1** [R=H; R^1=Me (Table 2; entry 3)] when 1.1 mol.eq. of the hydride were used instead of 1.5 mol.equiv..[10]



5

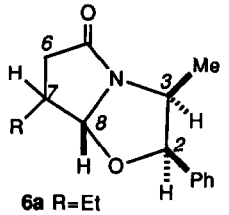
Iodoamides **1** are particularly good substrates for both the atom-transfer and the Bu_3SnH-mediated cyclization reactions, in comparison with the literature precedents. Usually, N-allyl α-chloro and α-iodoacetamides give only minute amounts of butyrolactams under Bu_3SnH-mediated radical cyclization conditions.[9a,12] Good cyclization yields were reported with the atom-transfer protocol, but only at 80°C (boiling benzene).[11a]

All new compounds have been fully characterized by ^1H- and ^{13}C-n.m.r. spectroscopy, IR, MS, and elemental analysis. Stereochemical ratios were checked by ^1H and ^{13}C n.m.r. analysis of the crude mixtures, and by capillary VPC. The stereostructure of bicyclic compounds **2** was proved by careful analysis of the ^1H-^1H coupling constants, and by n.O.e. difference experiments (both mono and bidimensional). This analysis was assisted by comparison with the calculated atomic distances, dihedral angles, and coupling constants of bicyclic compounds **2**, obtained using molecular mechanics in conjunction with Altona's equation[13] as implemented by MacroModel[14] (see Experimental section).

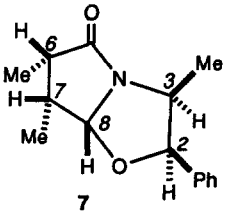
The electrophilic nature of the α-carbamoyl radicals, in analogy with other radicals α-substituted with electronwithdrawing groups,[2b,15] is well documented by the low cyclization yield in the case of the electron-poor

olefin **1** [R=CO_2Me, R^1=H (Table 2, Entry 4)]. It is worth noting that the secondary radical generated from a racemic α-iodopropionate tether (Scheme 1, R^1=Me) undergoes stereocontrolled cyclization to give γ-butyro lactam **2** [R=H, R^1=Me (Table 2, Entry 3)] in which the newly formed stereogenic centre (C-6) bearing the original propionate methyl group is of high stereochemical purity (≥ 97% *si* face selectivity).[6c]

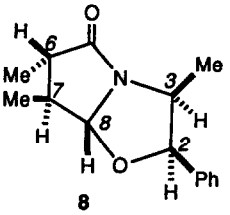
"Large scale" preparations (10 mmol) permitted in some cases the isolation and characterization of minor diastereoisomers of bicyclic lactams **2**, all originating from the minor C-2 epimers of α-iodoamides **1** (C-2/C-4 *trans*). For example, α-iodoamide **1** [R=Me; R^1=H (Table 1, entry 2)] is a 80:20 (C-2/C-4) *cis:trans* mixture. The minor (C-2/C-4) *trans* isomer gave the cyclization product **6a** (stereochemistry at C-7 not attributed) in 60% yield. In the cyclization reaction of α-iodopropionamide **1** (R=H; R^1=Me), the minor C-2/C-4 *trans* isomer [(Table 1, entry 3), 8%] gave the cyclization product **7** and traces of **8**.



6a R=Et
6b R=Me



7

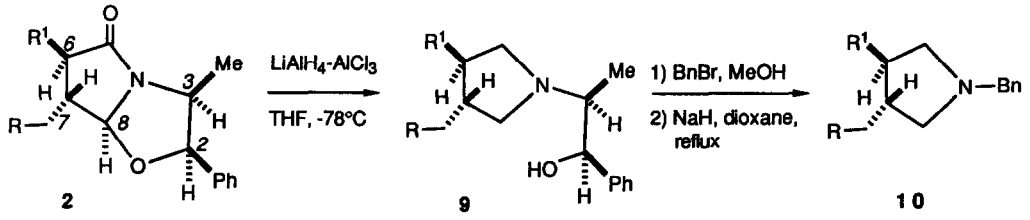


8

No diastereoisomers due to the radical cyclization process and originating from the major series (**1**, C-2/C-4 *cis*) were ever detected in the reaction mixtures.

Bicyclic lactams **2** were transformed in high yields into enantiomerically pure pyrrolidines **10** according to Scheme 4.[16] Treatment with $LiAlH_4$-$AlCl_3$ (AlH_3) in THF at -78°C proceeded to reduce the carbonyl group and simultaneously cleave the oxazolidine ring of **2** to give pyrrolidines **9** (80-85% yield). Bicyclic lactams **2** were reductively cleaved using only $LiAlH_4$ in boiling THF in the absence of $AlCl_3$, but reductions using $LiAlH_4$-$AlCl_3$ (AlH_3) were consistently cleaner.[17] Pyrrolidines **9** were treated with benzyl bromide (BnBr) in methanol to give the corresponding N-benzyl ammonium bromides (90% after chromatography), which were cleaved to pyrrolidines **10** (90%) and (1R, 2R)-*trans* -β-methylstirene oxide using sodium hydride in boiling dioxane.

Scheme 4. Synthesis of enantiomerically pure pyrrolidines.



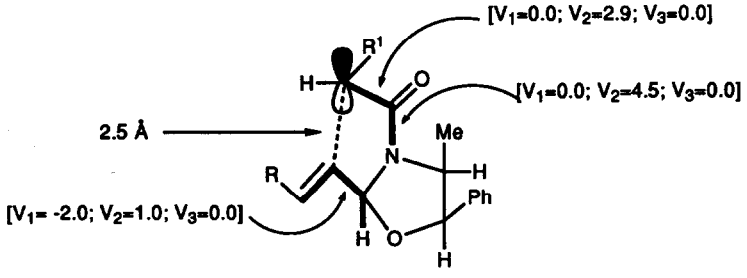
2 **9** **10**

Bicyclic lactam **2** (R=H, R^1=Me) gave the chiral (C_2), enantiomerically pure pyrrolidine **10** (R=H, R^1=Me), while the minor distereoisomer **7** gave the corresponding meso compound, offering an additional proof for the stereochemical attribution.

Application of MM-Force Field Calculations to Model Transition Structures

The stereoselectivity of the cyclization reactions was analyzed in detail with the application of MM-force field calculations to model transition structures.[7] Our first model was based upon MM-X force field,[18] with two new parameters and one constraint devised from the following considerations: (a) a constrained C(radical)-C(alkene) distance = 2.5 Å was imposed, 17% longer than the *ab initio* calculated value for the malononitrile radical addition to ethylene (2.14 Å);[7h] (b) a rotational barrier (10.3 kcal mol^{-1}) was imposed around the C(radical)-C(carbonyl) bond [the X-C(rad)-C(acyl)-Y torsional parameters were assigned values of V_1=0.0; V_2=2.9; V_3=0.0] to mimick the experimental restrained rotation of α-carbamoyl radicals;[19a,b] (c) a conformational preference was imposed for the rotamer with the C-C double bond eclipsed with the allylic hydrogen [the H-C(stereocentre)-C(alkene)-C(alkene) torsional parameters were assigned values of V_1= -2.0; V_2=1.0; V_3=0.0] (Scheme 5).

Scheme 5. Constrained model based upon MM-X force field.

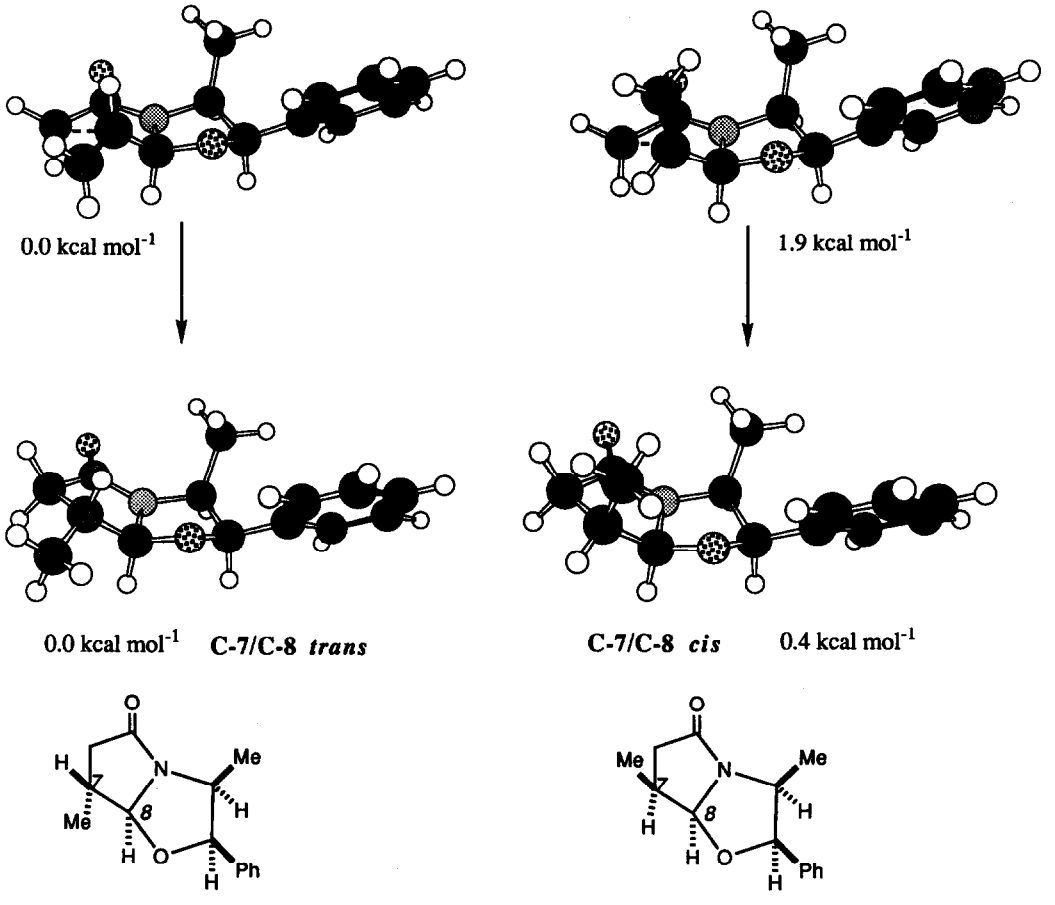


This model corresponds to an "early" transition state, with the radical and the olefin trigonal carbon atoms slightly pyramidalized, which retains the conformational preferences of the starting functional groups (α-carbamoyl radical and olefin). The rotamer with the allylic hydrogen eclipsed with the double bond is usually the most stable conformer for alkenes;[20] in 2-alkenyl-oxazolidines this rotamer is favoured both in the crystal structure (X-ray) and in $CDCl_3$ solutions (n.O.e. difference experiments).[8] Because of the early transition state, factors that influence the ground-state alkene conformation would also be expected to influence the transition state in the addition reaction. Predictions of stereochemical ratios based on this model (Table 3) were in good agreement with the experimental results. It is interesting to observe that ground-state calculations (MM-X[18] or MMOD[14]) on reaction products **2** (*trans*) and on their C-7 epimers (*cis*) predict almost no selectivity (ΔE ca. 0.4 kcal mol^{-1} in favour of the *trans*). One example [R=H; R^1=H (Table 3, entry 1)] is shown in Scheme 6.

Table 3. Prediction of diastereomeric ratios based on transition structure modelling.[21] Constrained model based upon MM-X force field.

Entry	Compound **2**	*trans-cis* (C-7/C-8) ratio	*si-re* face (C-6) ratio
1	R=H; R^1=H	94:6 [ΔE =1.9 kcal mol^{-1}]	-
2	R=Me; R^1=H	93:7 [ΔE =1.8 kcal mol^{-1}]	-
3	R=H; R^1=Me	94:6 [ΔE =1.9 kcal mol^{-1}]	99:1 [ΔE = 3.3 kcal mol^{-1}]
4	R=CO_2Me; R^1=H	90:10 [ΔE =1.5 kcal mol^{-1}]	-

Scheme 6. **Transition structure models of the radical cyclization leading to compound 2 [R=H; R^1=H (*trans*)] and its C-7 epimer (*cis*) (Table 3, entry 1). Constrained model based upon MM-X force field.**



Although recent *ab initio* calculations suggest a somewhat later transition state for the reaction of carbonyl-substitued alkyl radicals compared to that of addition of alkyl radicals,[7h] the only way to reproduce the experimental C-7/C-8 *trans* selectivity was to use a "radical force field" which models a transition state for the radical addition to the double bond which is "earlier" along the reaction coordinate compared to other force fields.[7] For example, transition state modelling using the force field for intramolecular additions of acyl-substituted radicals to alkenes developed by K. Houk and J. Broeker[7e] predicted regiochemical 5-*exo*/6-*endo* ratios in good agreement with the experimental values (5-*exo*/6-*endo* ratios 100:0), but stereochemical ratios which are disappointingly lower than the experimental ones [e.g. *trans-cis* (C-7/C-8) ratio 66:34].

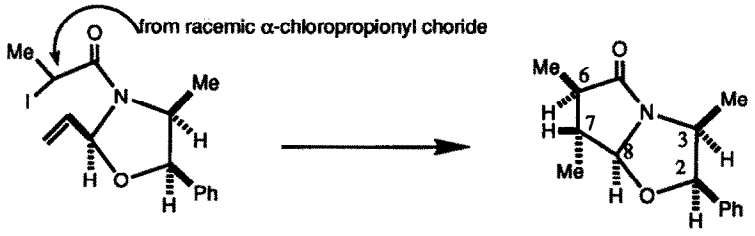
Our second approach was based on a completely "flexible model" in which all atoms are free to move and optimized in the calculation. Standard MM2 parameters as available in MacroModel[14] were used for atoms not involved in the bond breaking or bond making process. Most of the parameters for bond lengths, bond angles,

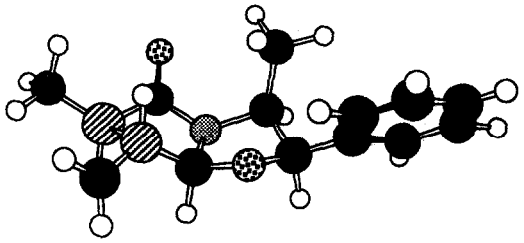
and torsional angles regarding atoms involved in the reaction process were taken directly from the Broeker-Houk parameter set.[7e] Parameters newly developed or modified for this force field are discussed in the following text: (a) The equilibrium bond length for the C(radical)-C(alkene) forming bond was assigned a value of 2.14 Å on the basis of the *ab initio* calculated value for the malononitrile radical addition to ethylene.[7h] (b) The H-$C_{sp}3$-C_{alkene}-C_{alkene} torsional parameters were assigned values of V_1= 0.0; V_2=0.0; V_3= - 0.3 (atom type 5-1-2-2) and the $C_{sp}3$-$C_{sp}3$-C_{alkene}-C_{alkene} values of V_1= -0.54; V_2=0.44; V_3= - 0.6 (atom type 1-1-2-2).[20b] These values were recently proposed by Houk *et al.*[20b] and Pettersson *et al.*[20c] in order to fit the *ab initio* potential energy surfaces for a series of alkenes. (c) The atom type equivalence for C(rad)-C(alkene)-C(alkene) was changed from atom type 1-atom type 1-atom type 2 to atom type 2-atom type 2-atom type 2. That is, all parameters for C(rad), C(alkene), C(alkene) not defined were assigned values equal to the analogous parameters for atom type 2. This modification generates a force field that models a transition state which is "earlier" along the reaction coordinate compared to the Broeker-Houk force field. As a result, the predicted *trans-cis* (C-7/C-8) ratio for compound 2 (R=H, R^1=H) was improved from 66:34 to 92:8 using this modified force field, while the predicted regiochemical 5-*exo*/6-*endo* ratio remained 100:0. The calculated *trans-cis* (C-7/C-8) ratios are very sensitive to the X-C(stereocentre)-C(alkene)-C(alkene) torsional parameters (X = O, N): calculations using the values of V_1= 0.0; V_2=0.0; V_3= -1.0 for both X = N and O (instead of the previously used 0.0, 0.0, 0.0) gave ratios in good agreement with the experimental results (Table 4). One example [R=H; R^1=Me (Table 4, entry 3)] is shown in Scheme 7, while the relative energies of all the transition structures relevant for Table 4 are given in the Computational Section. 5-*Exo*/6-*endo* ratios = 100:0 were calculated with this force field, in good agreement with the experimental results (no 6-*endo* product detected).

Table 4. Prediction of diastereomeric ratios based on transition structure modelling.[21] Flexible model based upon MM2 force field and newly developed parameters.

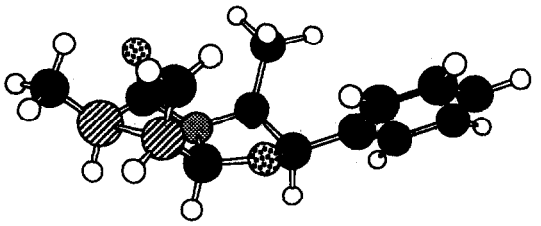
Entry	Compound **2**	*trans-cis* (C-7/C-8) ratio	*si-re* face (C-6) ratio
1	R=H; R^1=H	98:2	-
2	R=Me; R^1=H	98:2	-
3	R=H; R^1=Me	98:2	99:1
4	R=CO_2Me; R^1=H	99:1	-

Scheme 7. Transition structure models of the radical cyclization leading to compound 2 (R=H; R^1=Me) and its diastereoisomers (Table 4, entry 3). Flexible model based upon MM2 force field and newly developed parameters.

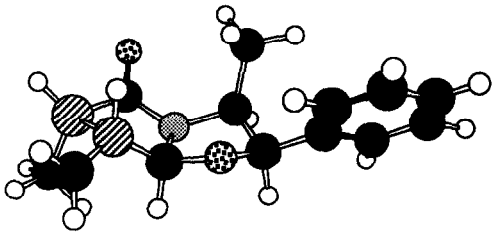




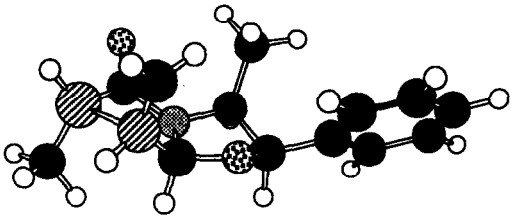
0.0 kcal mol^{-1} C7-C8-Trans C6-si



+ 2.68 kcal mol^{-1} C7-C8-Cis C6-si



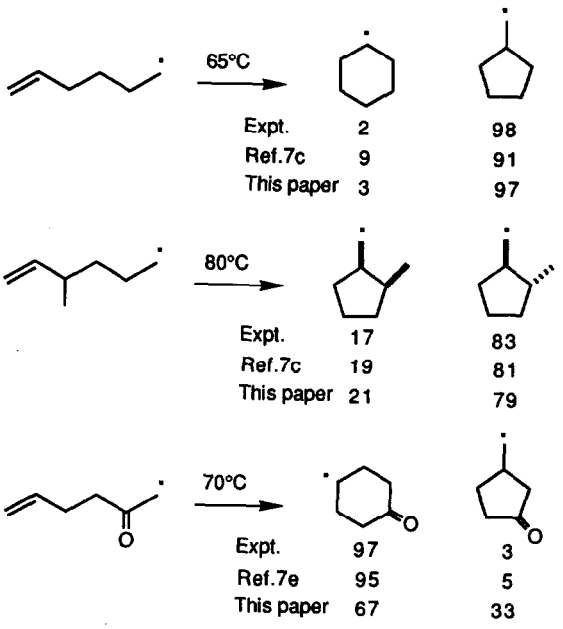
+ 3.13 kcal mol^{-1} C7-C8-Trans C6-re



+ 5.82 kcal mol^{-1} C7-C8-Cis C6-re

We tested our modified force field in a few of the cases reported by Houk and coworkers,[7c,e] in order to see if the agreement between the calculated and experimental literature data is still good (Scheme 8).

Scheme 8. Comparison between calculated and experimental literature data.



The regioselectivity (*5-exo*/*6-endo*) was checked in the cyclization of the 5-hexenyl radical and 2-oxo-5-hexenyl radical, while the stereoselectivity (*cis*/*trans*) was checked in the *5-exo* cyclization of 4-methyl-5-hexenyl radical (Scheme 8). Our force field correctly predicts the regio- and stereochemistry for the cyclization of alkyl-radicals, while the calculated *endo-exo* ratio for the cyclization of acyl-substituted radicals (carbonyl inside the forming ring) is lower than the experimental value.

The construction of an improved force field suitable for all radical cyclization reactions is currently underway in our laboratory.

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Computational Section

Using the Broeker-Houk parameter set,[7e] modified as described in the main text, MacroModel[14] was used to generate accessible transition structures for the radical cyclization reaction of interest. The conformational space was searched with the Still-Chang-Guida usage-directed torsional Monte Carlo search[22] as implemented by the BATCHMIN program.[23] Two separate Monte Carlo runs were necessary: one for the structures leading to the *trans* compound and the other for the ones leading to the *cis* compound. An alternative procedure made use of Multiconformer[24] using a 30° or 60° resolution for each dihedral angle. The two methods usually gave comparable results and were used in concert to make sure that our conformational analysis was not dependent on the search method used.[25] The transition structures found by these searches were analyzed by a Boltzmann distribution at +80°C (353°K) of the various conformers leading to each of the possible stereoisomers (see **Table 4** and details below). 6-*Endo* transition structures were all higher in energy (> 5 kcal mol^{-1}), and are not reported.

Table 4, entry 1.
Structure 1 (trans) 0.00 kcal mol^{-1}; Structure 2 (trans) 2.14 kcal mol^{-1}; Structure 3 (cis) 2.79 kcal mol^{-1}.
Table 4, entry 2.
Structure 1 (trans) 0.00 kcal mol^{-1}; Structure 2 (trans) 2.14 kcal mol^{-1}; Structure 3 (cis) 2.84 kcal mol^{-1}.
Table 4, entry 3.
Structure 1 (trans-si) 0.00 kcal mol^{-1}; Structure 2 (trans-si) 2.12 kcal mol^{-1}; Structure 3 (cis-si) 2.68 kcal mol^{-1}; Structure 4 (trans-re) 3.13 kcal mol^{-1}; Structure 5 (trans-re) 4.85 kcal mol^{-1}; Structure 6 (cis-re) 5.82 kcal mol^{-1}.
Table 4, entry 4.
Structure 1 (trans) 0.00 kcal mol^{-1}; Structure 2 (trans) 1.18 kcal mol^{-1}; Structure 3 (trans) 2.10 kcal mol^{-1}; Structure 4 (cis) 3.07 kcal mol^{-1}; Structure 5 (trans) 3.31 kcal mol^{-1}; Structure 6 (cis) 3.69 kcal mol^{-1}; Structure 7 (trans) 4.62 kcal mol^{-1}; Structure 8 (trans) 6.75 kcal mol^{-1}; Structure 9 (cis) 6.76 kcal mol^{-1}.

Experimental Section

All new compounds were fully characterized by ^{1}H and ^{13}C n.m.r. spectroscopy (reported), IR, MS, and elemental analysis (reported only for selected compounds).

Synthesis of α-iodoamides 1 (Scheme 2, Table 1). A solution of L-Norefedrine **3** (3.51 g, 23.21 mmol) in water (35 ml) was treated at 0°C with 2 N NaOH in water (12.8 ml, 25.5 mmol) and α-chloroacetyl chloride (2.22 ml, 27.85 mmol). The two reagents were added slowly, simultaneously, and under vigorous stirring, so

that the pH was kept constantly around 7. At the end of the addition the temperature was raised to 25°C, and the mixture was stirred overnight at room temperature. The white precipitate (Norefedrine α-chloroacetamide) was filtered under vacuum, washed with water, and dried under vacuum in the presence of P_2O_5 (4.87 g, 92% yield). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.05 (3H, CH_3, d, J=7 Hz), 2.82 (1H, OH, br.s), 4.09 (2H, CH_2Cl, s), 4.35 (1H, NCH, m), 4.90 (1H, CHO, d, J=5 Hz), 6.80 (1H, NH, s), 7.35 (5H, Ar-H, m). Anal. Calcd for $C_{11}H_{14}NO_2Cl$: C, 58.03; H, 6.20; N, 6.15. Found: C, 57.95; H, 6.30; N, 6.07.

Following the above described procedure, treatment with α-chloropropionyl chloride (2.49 ml, 27.88 mmol) gave Norefedrine α-chloropropionamide (5.05 g, 90%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.98 (50% 3H, CH_3-C-N, d, J=7 Hz), 1.02 (50% 3H, CH_3-C-N, d, J=7 Hz), 1.70 (3H, CH_3-C-Cl, d, J=7.2 Hz), 2.80-3.10 (1H, OH, br.s), 4.10-4.55 (2H, CHCl and CHN, m), 4.65 (1H, CHO, d, J=5 Hz), 6.60-6.80 (1H, NH, br.s), 7.20-7.40 (5H, Ar-H, m). Anal. Calcd for $C_{12}H_{16}NO_2Cl$: C, 59.63; H, 6.67; N, 5.79. Found: C, 59.52; H, 6.75; N, 5.70.

(Table 1, entry 1). A solution of Norefedrine α-chloroacetamide (3.02 g, 13.26 mmol) in dry benzene (83 ml) was treated with acrolein dimethylacetal (4.71 ml, 39.79 mmol) and pyridinium tosylate (0.83 g, 3.31 mmol). The mixture was stirred and heated at reflux under nitrogen for 10 hr using a reflux condenser equipped with 4-Å molecular sieves. The crude mixture was then evaporated, and the residue purified by flash-chromatography (n-hexane/ethyl acetate 3:1) to give the corresponding oxazolidine (3.17 g, 90%) with a *cis:trans* (C-2/C-4) ratio ≥ 95:5. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.90 (3H, CH_3-C-N, d, J=7 Hz), 4.05 (2H, CH_2Cl, s), 4.29 (1H, CH-N, m), 5.15-5.75 (1H, CH-O, d, J=5.2 Hz; 1H, *Hcis*CH=CH-, d, J=11 Hz; 1H, *Htrans*CH=CH-, d, J=16 Hz; 1H, O-CH-N), 5.95 (1H, C=CH-C, m), 7.35 (5H, Ar-H, m). A solution of N-chloroacetyloxazolidine (2.3 g, 8.65 mmol) was treated with a saturated solution of NaI in acetone (216 ml). The mixture was stirred at room temperature, in the dark and under nitrogen, for 1 hr (NaCl precipitates). The mixture was then evaporated under vacuum, and the crude product purified by flash chromatography (n-hexane/ethyl acetate 3:1) to give **N-iodoacetyloxazolidine 1 (R=H; R^1=H)**(2.84 g, 92%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.87 (50% 3H, CH_3-C-N. d, J=7 Hz), 0.96 (50% 3H, CH_3-C-N, d, J=7 Hz), 3.75 (2H, CH_2I, s), 4.15-4.30 (50% 1H, CH-N, m), 4.55-4.68 (50% 1H, CH-N, m), 5.15 (50% 1H, CH-O, d, J=7.0 Hz), 5.20 (50% 1H, CH-O, d, J=7.0 Hz), 5.40-5.75 (3H, CH_2=C, O-CH-N, m), 5.80-6.08 (1H, C=CH-C, m), 7.25-7.50 (5H, Ar-H, m). The ^{1}H-NMR spectrum was recorded in C_5D_5N at 80°C: at this temperature coalescence of the signals due to the presence of Z (50%) and E (50%) amide bond was observed. Anal. Calcd for $C_{14}H_{16}NO_2I$: C, 47.08; H, 4.52; N, 3.92. Found: C, 47.17; H, 4.60; N, 3.86.

(Table 1, entry 2). Following the above described procedure, treatment of Norefedrine α-chloroacetamide (3.02 g, 13.26 mmol) with crotonaldehyde dimethylacetal (5.29 ml, 39.79 mmol), pyridinium tosylate (0.83 g, 3.22 mmol), and heating at reflux for 13 hr gave the corresponding *trans* C-2/C-4 oxazolidine (0.668 g, 18%) and *cis* C-2/C-4 oxazolidine (2.67 g, 72%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.88 (3H, CH_3-C-N, m), 1.80 (3H, CH_3-C=C, d, J=6.5 Hz), 3.90-4.10 (2H, CH_2Cl, s), 4.25 (30% 1H, CH-N, m), 4.60 (70% 1H, CH-N, m), 5.15 (1H, CH-O, d, J=6 Hz), 5.50-5.80 (1H, N-CH-O, d, J=5.0 Hz; 1H, CH=C, dd, J=18.6, 5.0 Hz), 6.05-6.20 (1H, CH=C, dq, J=18.6, 6.5 Hz), 7.35 (5H, Ar-H, m). A solution of N-chloroacetyloxazolidine (2.3 g, 8.22 mmol) was treated with a saturated solution of NaI in acetone (205.5 ml). The mixture was stirred at room temperature, in the dark and under nitrogen, for 1 hr (NaCl precipitates). The mixture was then evaporated under vacuum, and the crude product purified by flash chromatography (n-hexane/ethyl acetate 3:1) to give **N-iodoacetyloxazolidine 1 (R=Me; R^1=H)**(2.78 g, 91%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.8-1.0 (50% 3H, CH_3-C-N, d, J=6.5 Hz; 50% 3H, CH_3-C-N, d, J=6.5 Hz), 1.75-1.95 (50% 3H, CH_3-C=C, d, J=6.5 Hz; 50% 3H, CH_3-C=C, d, J=6.5 Hz), 3.60-3.85 (2H, CH_2I, m), 4.15-4.33 (50% 1H, CH-N, m), 4.50-4.60 (50% 1H, CH-N, m), 5.08 (50% 1H, CH-O, d, J=6.0 Hz), 5.12 (50% 1H, CH-O, d, J=6.0 Hz), 5.50-5.80 (2H, Me-C=C*H*, O-CH-N, m), 6.0-6.2 (1H, Me-C*H*=C, m), 7.25-7.45 (5H, Ar-H, m). The ^{1}H-NMR spectrum was recorded in C_5D_5N at 80°C: at this temperature coalescence of the signals due to the presence of Z (50%) and E (50%) amide bond was observed. Anal. Calcd for $C_{15}H_{18}NO_2I$: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.59; H, 4.95; N, 3.69.

(Table 1, entry 3). Following the above described procedure, treatment of Norefedrine α-chloropropionamide (3.20 g, 13.26 mmol) with acrolein dimethylacetal (4.71 ml, 39.79 mmol), pyridinium tosylate (0.83 g, 3.22 mmol), and heating at reflux for 14 hr gave the corresponding *trans* C-2/C-4 oxazolidine (0.267 g, 7.2%) and *cis* C-2/C-4 oxazolidine (3.07 g, 82.8%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.85 (3H, CH_3-C-N, d, J=7.0 Hz), 1.65 (3H, CH_3-C-Cl, d, J=6.6 Hz), 4.20-4.50 (1H, CH-N, m; 1H, CH-Cl, q, J=6.6 Hz), 5.18 (1H, CH-O, d, J=6.5 Hz), 5.45 (1H, N-CH-O, m), 5.70-5.85 (2H, CH_2=C, m), 5.90-6.00 (1H, C=CH, m), 7.35 (5H, Ar-H, m). A solution of N-α-chloropropionyloxazolidine (2.3 g, 8.22 mmol) was treated with a saturated solution of NaI in acetone (205.5 ml). The mixture was stirred at 50°C, in the dark and under nitrogen, for 1 hr (NaCl precipitates). The mixture was then evaporated under vacuum, and the crude product purified by flash chromatography (n-hexane/ethyl acetate 85:15) to give **N-α-iodopropionyloxazolidine 1 (R=H;**

R^1=Me)(2.44 g, 80%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.82 (50% 3H, CH_3-C-N, d, J=7.0 Hz), 0.91 (50% 3H, CH_3-C-N, d, J=7.0 Hz), 1.95 (50% 3H, CH_3-C-I, d, J=6.6 Hz), 2.00 (50% 3H, CH_3-C-I, d, J=6.6 Hz), 4.10-4.80 (1H, CH-N, m; 1H, CH-I, q, J=6.6 Hz), 5.10-5.50 (1H, CH-O, m; 1H, N-CH-O, m), 5.70-6.00 (2H, CH_2=C, m; 1H, C=CH, m), 7.15-7.45 (5H, Ar-H, m). The ^{1}H-NMR spectrum was recorded in C_5D_5N at 80°C: at this temperature coalescence of the signals due to the presence of Z (50%) and E (50%) amide bond was observed. Anal. Calcd for $C_{15}H_{18}NO_2I$: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.61; H, 4.93; N, 3.67.

(Table 1, entry 4). Following the above described procedure, treatment of Norefedrine α-chloroacetamide (3.02 g, 13.26 mmol) with monomethylester monofumaraldehyde dimethylacetal (6.37 g, 39.79 mmol), pyridinium tosylate (1.33 g, 5.30 mmol), and heating at reflux for 70 hr gave the corresponding oxazolidine (3.43 g, 80%) with a *cis:trans* (C-2/C-4) ratio ≥ 95:5. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.89 (3H, CH_3-C-N, d, J=7.0 Hz), 3.80 (3H, CH_3OOC, s), 4.08 (2H, Cl-CH_2-CON, s), 4.35 (1H, CH-N, dq, J=7.0, 5.3 Hz), 5.25 (1H, CH-O, d, J=5.3 Hz), 5.93 (1H, N-CH-O, d, J=5.0 Hz), 6.38 (1H, OOC-CH=C, d, J=16.0 Hz), 7.03 (1H, OOC-C=CH, dd, J=16.0, 5.0 Hz), 7.35 (5H, Ar-H, m). A solution of N-chloroacetyloxazolidine (2.3 g, 7.10 mmol) was treated with a saturated solution of NaI in acetone (177.5 ml). The mixture was stirred at room temperature, in the dark and under nitrogen, for 1 hr (NaCl precipitates). The mixture was then evaporated under vacuum, and the crude product purified by flash chromatography (n-hexane/ethyl acetate 3:1) to give **N-iodoacetyloxazolidine 1 (R=CO_2Me; R^1=H)**(2.65 g, 90%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.92 (3H, CH_3-C-N, d, J=7.0 Hz), 3.75 (2H, I-CH_2-CON, s), 3.80 (3H, CH_3OOC, s), 4.23 (1H, CH-N, m), 5.21 (1H, CH-O, d, J=5.5 Hz), 5.84 (1H, N-CH-O, d, J=5.0 Hz), 6.36 (1H, OOC-CH=C, d, J=16.0 Hz), 7.02 (1H, OOC-C=CH, dd, J=16.0, 5.0 Hz), 7.35 (5H, Ar-H, m). Anal. Calcd for $C_{16}H_{18}NO_4I$: C, 46.28; H, 4.37; N, 3.37. Found: C, 46.35; H, 4.45; N, 3.30.

Bu_3SnH Mediated Radical Cyclizations. Synthesis of Bicyclic Lactams 2 (Scheme 1, Table 2).

(Table 2, entry 1). A 0.08 M solution of Bu_3SnH (0.85 ml, 3.2 mmol) in benzene (40.0 ml) containing AIBN (24 mg, 0.146 mmol) was slowly added via syringe pump (6 hr) to a boiling 0.02 M solution of N-iodoacetyloxazolidine **1** (R=H; R^1=H)(1.04 g, 2.91 mmol) in benzene (146 ml), under nitrogen, with stirring. At the end of the addition, the mixture was cooled to room temperature, treated with a saturated aqueous solution of KF (90 ml) and stirred for 2 hr. The two layers were separated, the aqueous phase extracted with ethyl ether, and the combined organic extracts were dried (Na_2SO_4) and evaporated. The crude product was purified by flash-chromatography (n-hexane-ethyl acetate 55:45) to give **bicyclic lactam 2 (R=H; R^1=H)**(0.505 g, 75%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.98 (3H, CH_3-C-N, d, J=6.5 Hz), 1.30 (3H, CH_3-C-C, d, J=6 Hz), 2.40-2.60 (1H, CH-CNO, m; 1H, *H*CH-C=O, m), 2.75 (1H, *H*CH-C=O, m), 4.0 (1H, CH-N, quint., J=6.5 Hz), 5.02 (1H, O-CH-N, d, J=5.4 Hz), 5.35 (1H, CH-O, d, J=6.5 Hz), 7.24-7.42 (5H, Ar-H, m). ^{13}C-NMR (200 MHz, $CDCl_3$) δ (selected data): 13.530 (CH_3), 16.711 (CH_3), 36.915 (CH_2), 43.508 (CH), 54.115 (CH-N), 86.172 (CH-O), 98.085 (N-CH-O), 126.183 (CH=), 128.079 (CH=), 128.331 (CH=). N.O.E. difference experiments, positive response: C(8)-H and C(3)-H; C(8)-H and C(2)-H; C(8)-H and C(7)-Me; C(7)-H and C(3)-Me. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.79; H, 7.50; N, 6.01. MS (CI, methane): *m/e* 232 (M^++1).

The major side-product (only isolated product when the reaction was run at room temperature) was the **reduction product (N-acetyloxazolidine)**(n-hexane-ethyl acetate 1:1, 0.135 g, 20%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.85 (50% 3H, CH_3-C-N, d, J=7 Hz), 0.89 (50% 3H, CH_3-C-N, d, J=7 Hz), 2.05 (50% 3H, CH_3-CO-N, s), 2.15 (50% 3H, CH_3-CO-N, s), 4.13 (50% 1H, CH-N, m), 4.65 (50% 1H, CH-N, m), 5.11 (50% 1H, CH-O, d, J=6 Hz), 5.18 (50% 1H, CH-O, d, J=6 Hz), 5.40 (50% 1H, N-CH-O, d, J=10 Hz), 5.50-5.75 (50% 1H, N-CH-O; 2H, CH_2=C, m), 5.85-6.10 (1H, C=CH-C, m), 7.25-7.45 (5H, Ar-H, m). The ^{1}H-NMR spectrum was recorded in C_5D_5N at 80°C: at this temperature coalescence of the signals due to the presence of Z (50%) and E (50%) amide bond was observed. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.80; H, 7.48; N, 5.97.

(Table 2, entry 2). Following the procedure described for entry 1, treatment of N-iodoacetyloxazolidine **1** (R=Me; R^1=H)(1.11 g, 3.0 mmol) gave, after flash chromatography (n-hexane-ethyl acetate 6:4), **bicyclic lactam 2 (R=Me; R^1=H)**(0.44 g, 60%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.95 (3H, CH_3-C-N, d, J=6.5 Hz), 1.05 (3H, CH_3-CH_2-C, t, J=7.5 Hz), 1.55-1.80 (2H, CH_3-CH_2-C, m), 2.35-2.45 (1H, CH-CNO, m), 2.40-2.50 (1H, *H*CH-C=O, m), 2.65-2.80 (1H, *H*CH-C=O, m), 3.95 (1H, CH-N, dq, J=6.5, 7.0 Hz), 5.05 (1H, O-CH-N, d, J=5.5 Hz), 5.34 (1H, CH-O, d, J=7.0 Hz), 7.20-7.40 (5H, Ar-H, m). ^{13}C-NMR (200 MHz, $CDCl_3$) δ (selected data): 11.917 (CH_3), 13.359 (CH_3), 25.192 (CH_2), 41.408 (CH_2), 43.532 (CH), 53.742 (CH-N), 85.875 (CH-O), 96.855 (N-CH-O), 126.045 (CH=), 127.850 (CH=), 128.110 (CH=), 172.020 (C=O). N.O.E. difference experiments, positive response: C(8)-H and C(3)-H; C(8)-H and C(2)-H; C(8)-H and C(7)-CH_2; C(8)-H and C(7)-C-Me; C(7)-H and C(3)-Me. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.52; H, 7.90; N, 5.65. MS (CI, methane): *m/e* 246 (M^++1).

The major side-product (only isolated product when the reaction was run at room temperature) was the **reduction product (N-acetyloxazolidine)**(n-hexane-ethyl acetate 6:4, 0.257 g, 35%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.85 (50% 3H, CH_3-C-N, d, J=7 Hz), 0.87 (50% 3H, CH_3-C-N, d, J=7 Hz), 1.75-1.85 (50% 3H, CH_3-C=C, d, J=5.5 Hz; 50% 3H, CH_3-C=C, d, J=5.5 Hz), 2.00 (50% 3H, CH_3-CO-N, s), 2.15 (50% 3H, CH_3-CO-N, s), 4.12 (50% 1H, CH-N, dq, J=7.0, 5.5 Hz), 4.63 (50% 1H, CH-N, dq, J=7.0, 5.5 Hz), 5.07 (50% 1H, CH-O, d, J=5 Hz), 5.13 (50% 1H, CH-O, d, J=5 Hz), 5.55 (50% 1H, N-CH-O, d, J=6.5 Hz), 5.60 (1H, CH_3-C*H*=C, ddq, J=13.5, 5.5, 0.8 Hz), 5.73 (50% 1H, N-CH-O, d, J=6.5 Hz), 5.90-6.18 (1H, Me-C=C*H*, m), 7.25-7.40 (5H, Ar-H, m). The ^{1}H-NMR spectrum was recorded in C_5D_5N at 80°C: at this temperature coalescence of the signals due to the presence of Z (50%) and E (50%) amide bond was observed. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.34; H, 7.91; N, 5.60.

(Table 2, entry 3). A 0.08 M solution of Bu_3SnH (4.59 ml, 17.37 mmol) in benzene (219 ml) containing AIBN (96 mg, 0.579 mmol) was slowly added via syringe pump (6 hr) to a boiling 0.02 M solution of N-iodoacetyloxazolidine **1** (R=H; R^1=Me)(4.29 g, 11.58 mmol) in benzene (579 ml), under nitrogen, with stirring. At the end of the addition, the mixture was cooled to room temperature, treated with a saturated aqueous solution of KF (488 ml) and stirred for 2 hr. The two layers were separated, the aqueous phase extracted with ethyl ether, and the combined organic extracts were dried (Na_2SO_4) and evaporated. The crude product was purified by flash-chromatography (n-hexane-ethyl acetate 7:3) to give **bicyclic lactam 2 (R=H; R^1=Me)**(2.414 g, 85%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.92 (3H, CH_3-C-N, d, J=7.0 Hz), 1.19 (3H, CH_3-C-C=O, d, J=7.0 Hz), 1.25 (3H, CH_3-C-CNO, d, J=7.0 Hz), 1.98 (1H, CH-CNO, ddq, J=7.0, 7.0, 12.0 Hz), 2.42 (1H, CH-C=O, dq, J=12.0, 7.0 Hz), 3.96 (1H, CH-N, quint., J=7.0 Hz), 4.92 (1H, O-CH-N, d, J=7.0 Hz), 5.32 (1H, CH-O, d, J=7.0 Hz), 7.20-7.40 (5H, Ar-H, m). ^{13}C-NMR (200 MHz, $CDCl_3$) δ: 13.42 (CH_3), 13.59 (CH_3), 14.98 (CH_3), 45.59 (CH), 48.17 (CH), 53.67 (CH-N), 86.00 (CH-O), 95.80 (N-CH-O), 126.01 (CH=), 127.91 (CH=), 128.19 (CH=), 135.70 (C=), 174.30 (C=O). N.O.E. difference experiments, positive response: C(3)-H and C(8)-H; C(8)-H and C(2)-H; C(8)-H and C(7)-Me; C(6)-H and C(7)-Me (4.3%); C(6)-H and C(8)-H (2.6%). Calculated[13,14] and experimental coupling constants: Expt. J [C(8)-H / C(7)-H] = 7.0 Hz, J [C(7)-H / C(6)-H] = 12.0 Hz; calcd. J [C(8)-H / C(7)-H/ trans] = 8.1 Hz, J [C(7)-H / C(6)-H/ trans] = 11.9 Hz; calcd. J [C(8)-H / C(7)-H/ cis] = 6.3 Hz, J [C(7)-H / C(6)-H/ cis] = 6.4 Hz; calcd. J [C(8)-H / C(7)-H/ trans] = 8.2 Hz, J [C(7)-H / C(6)-H/ cis] = 7.3 Hz; calcd. J [C(8)-H / C(7)-H/ cis] = 6.4 Hz, J [C(7)-H / C(6)-H/ trans] = 0.4 Hz. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.50; H, 7.88; N, 5.63. MS (CI, methane): *m/e* 246 (M^++1).

When the above described reaction was run using only 3.37 ml (12.738 mmol) of Bu_3SnH, 1.56 g (55%) of bicyclic lactam **2** (R=H; R^1=Me) were obtained together with 0.946 g (22%) of **bicyclic lactam 5**. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.98 (3H, CH_3-C-N, d, J=6.6 Hz), 1.28 (3H, CH_3-C-CNO, d, J=7.0 Hz), 2.03 (1H, CH-CNO, m), 2.72 (1H, CH-C=O, m), 3.35 (1H, CH-I, dd, J=10.5, 6.0 Hz), 3.58 (1H, CH-I, dd, J=10.5, 4.5 Hz), 4.02 (1H, CH-N, m), 5.15 (1H, O-CH-N, d, J=5.0 Hz), 5.37 (1H, CH-O, d, J=7.0 Hz), 7.20-7.40 (5H, Ar-H, m). Anal. Calcd for $C_{15}H_{18}NO_2I$: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.61; H, 4.95; N, 3.68.

(Table 2, entry 4). Following the procedure described for entry 1, treatment of N-iodoacetyloxazolidine **1** (R=CO_2Me; R^1=H)(1.246 g, 3.0 mmol) gave, after flash chromatography (n-hexane-ethyl acetate 6:4), an inseparable mixture (0.8 g) of the bicyclic lactam **2** (R=CO_2Me; R^1=H) and of the reduction product (N-acetyloxazolidine). A solution of this mixture (0.8 g, 2.76 mmol) in dichloromethane (55.2 ml) was treated at room temperature, under nitrogen, with stirring, with Me_3NO-$2H_2O$ (0.613 g, 5.5 mmol) and $OsCl_3$ (41 mg, 0.138 mmol). The disappearance of one of the two picks of the starting mixture was followed by capillary VPC. The reaction mixture was treated with a $NaHSO_3$ saturated aqueous solution, the two layers were separated, the aqueous phase extracted with ethyl ether, and the combined organic extracts were dried (Na_2SO_4) and evaporated. The crude product was purified by flash-chromatography (n-hexane-ethyl acetate 3:7) to give **bicyclic lactam 2 (R=CO_2Me; R^1=H)**(0.278 g, 32%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.99 (3H, CH_3-C-N, d, J=7.0 Hz), 2.50-2.65 (1H, *H*CH-C=O, m), 2.50-2.65 (1H, *H*CH-C=O, m), 2.74-2.95 (2H, $OOCCH_2$, m; 1H, CH-CNO, m), 3.74 (3H, $COOCH_3$, s), 4.0 (1H, CH-N, m), 5.16 (1H, O-CH-N, d, J=5.6 Hz), 5.35 (1H, CH-O, d, J=6.8 Hz), 7.20-7.40 (5H, Ar-H, m). ^{13}C-NMR (200 MHz, $CDCl_3$) δ (selected data): 13.499 (CH_3), 35.941 (CH_2), 38.098 (CH), 41.317 (CH_2), 51.858 (CH_3O), 54.170 (CH-N), 86.089 (CH-O), 95.621 (N-CH-O), 126.113 (CH=), 128.100 (CH=), 128.168 (CH=), 135.786 (C=), 171.485 (C=O). N.O.E. difference experiments, positive response: C(8)-H and C(3)-H; C(8)-H and C(2)-H; C(8)-H and C(7)-CH_2; C(7)-H and C(3)-Me. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.50; H, 6.72; N, 4.75. MS (CI, methane): *m/e* 290 (M^++1).

Minor diastereoisomers of bicyclic lactams 2, originating from the minor C-2 epimers of α-iodoamides 1 (C-2/C-4 *trans*): bicyclic lactams 6a, 6b, 7, 8.

α-Iodoamide **1** [R=Me; R^1=H (Table 1, entry 2)] is a 80:20 (C-2/C-4) *cis:trans* mixture. In the Bu_3SnH-mediated cyclization reaction of α-iodoamide **1** (R=Me; R^1=H), the minor (C-2/C-4) *trans* isomer gave the **bicyclic lactam 6a** in 60% yield. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.78 (3H, CH_3-C-N, d, J=6.5 Hz), 1.04 (3H, C*H*$_3$-CH_2-C, t, J=7.0 Hz), 1.55-1.80 (2H, CH_3-C*H*$_2$-C, m), 2.25 (1H, CH-CNO, m), 2.40 (1H, *H*CH-C=O, dd, J=16.0, 10.0 Hz), 2.65 (1H, *H*CH-C=O, dd, J=16.0, 8.5 Hz), 4.52 (1H, CH-N, dq, J=6.5, 5.5 Hz), 5.03 (1H, CH-O, d, J=5.5 Hz), 5.30 (1H, N-CH-O, d, J=4.5 Hz), 7.25-7.40 (5H, Ar-H, m). N.O.E. difference experiments, positive response: C(8)-H and C(3)-Me; C(8)-H and C(7)-CH_2; C(8)-H and C(7)-C-Me; C(3)-H and C(2)-H. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.40; H, 7.89; N, 5.61. MS (CI, methane): *m/e* 246 (M^++1).

α-Iodoamide **1** [R=H; R^1=H (Table 1, entry 1)] is a 95:5 (C-2/C-4) *cis:trans* mixture. In the Bu_3SnH-mediated cyclization reaction of α-iodoamide **1** (R=H; R^1=H), the minor (C-2/C-4) *trans* isomer gave the **bicyclic lactam 6b** in 75% yield. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.98 (3H, CH_3-C-N, d, J=6.5 Hz), 1.08 (3H, CH_3-C-C, d, J=7.0 Hz), 2.20 (1H, *H*CH-C=O, d, J=16.0), 2.74 (1H, CH-CNO, m), 2.95 (1H, *H*CH-C=O, dd, J=16.0, 6.5 Hz), 4.00 (1H, CH-N, dq, J=6.5, 6.5 Hz), 5.42 (1H, CH-O, d, J=6.5 Hz), 5.45 (1H, N-CH-O, d, J=5.0 Hz), 7.25-7.40 (5H, Ar-H, m). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.81; H, 7.50; N, 5.98. MS (CI, methane): *m/e* 232 (M^++1).

α-Iodopropionamide **1** [R=H; R^1=Me (Table 1, entry 3)] is a 92:8 (C-2/C-4) *cis:trans* mixture. In the Bu_3SnH-mediated cyclization reaction of α-iodopropionamide **1** (R=H; R^1=Me), the minor C-2/C-4 *trans* isomer gave the **bicyclic lactam 7** in 80% yield. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.90 (3H, CH_3-C-N, d, J=6.6 Hz), 1.00 (3H, CH_3-C-CNO, d, J=7.0 Hz), 1.10 (3H, CH_3-C-C=O, d, J=7.2 Hz), 2.74 (1H, CH-CNO, m), 2.94 (1H, CH-C=O, dq, J=7.0, 7.2 Hz), 3.96 (1H, CH-N, dq, J=7.0, 6.6 Hz), 5.38 (1H, O-CH-N, d, J=4.8 Hz), 5.40 (1H, CH-O, d, J=7.0 Hz), 7.20-7.40 (5H, Ar-H, m). ^{13}C-NMR (200 MHz, $CDCl_3$) δ: 9.56 (CH_3), 12.82 (CH_3), 14.00 (CH_3), 37.81 (CH), 44.28 (CH), 52.73 (CH-N), 85.85 (CH-O), 91.50 (N-CH-O), 125.87 (CH=), 127.89 (CH=), 128.22 (CH=), 135.84 (C=), 173.52 (C=O). N.O.E. difference experiments, positive response: C(8)-H and C(3)-Me; C(6)-H and C(8)-H (3%), C(8)-H and C(7)-H (4.5%), C(8)-H and C(6)-H (3.5%). Calculated[13,14] and experimental coupling constants: Expt. J [C(8)-H / C(7)-H] = 4.8 Hz, J [C(7)-H / C(6)-H] = 7.0 Hz; calcd. J [C(8)-H / C(7)-H/ cis] = 6.4 Hz, J [C(7)-H / C(6)-H/ cis] = 6.3 Hz; calcd. J [C(8)-H / C(7)-H/ trans] = 7.9 Hz, J [C(7)-H / C(6)-H/ trans] = 11.9 Hz; calcd. J [C(8)-H / C(7)-H/ cis] = 6.5 Hz, J [C(7)-H / C(6)-H/ trans] = 0.4 Hz; calcd. J [C(8)-H / C(7)-H/ trans] = 8.0 Hz, J [C(7)-H / C(6)-H/ cis] = 7.3 Hz. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.59; H, 7.91; N, 5.63. MS (CI, methane): *m/e* 246 (M^++1). Traces of **bicyclic lactam 8** (5%) were also detected. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.80 (3H, CH_3-C-N, d, J=7.3 Hz), 1.30 (3H, CH_3-C-C=O, d, J=7.1 Hz), 1.40 (3H, CH_3-C-CNO, d, J=6.8 Hz), 1.85 (1H, CH-CNO, ddq, J=6.8, 5.5, 11.0), 2.39 (1H, CH-C=O, dq, J=11.0, 7.1 Hz), 4.49 (1H, CH-N, dq, J=7.3, 5.0 Hz), 4.96 (1H, CH-O, d, J=5.0 Hz), 5.20 (1H, O-CH-N, d, J=5.5 Hz), 7.20-7.40 (5H, Ar-H, m). ^{13}C-NMR (200 MHz, $CDCl_3$) δ: 13.02 (CH_3), 13.72 (CH_3), 15.49 (CH_3), 45.27 (CH), 47.06 (CH), 53.35 (CH-N), 81.30 (CH-O), 94.63 (N-CH-O), 125.96 (CH=), 127.57 (CH=), 128.12 (CH=), 136.44 (C=), 177.99 (C=O). N.O.E. difference experiments, positive response: C(8)-H and C(6)-H; C(8)-H and C(7)-Me, C(6)-H and C(7)-Me, C(8)-H and C(3)-Me, C(2)-H and C(3)-H, C(2)-H and C(7)-H, C(7)-H and C(6)-Me, C(3)-Me and C(7)-Me. Calculated[13,14] and experimental coupling constants: Expt. J [C(8)-H / C(7)-H] = 5.5 Hz, J [C(7)-H / C(6)-H] = 11.0 Hz; calcd. J [C(8)-H / C(7)-H/ trans] = 7.9 Hz, J [C(7)-H / C(6)-H/ trans] = 11.9 Hz; calcd. J [C(8)-H / C(7)-H/ cis] = 6.4 Hz, J [C(7)-H / C(6)-H/ cis] = 6.3 Hz; calcd. J [C(8)-H / C(7)-H/ cis] = 6.5 Hz, J [C(7)-H / C(6)-H/ trans] = 0.4 Hz; calcd. J [C(8)-H / C(7)-H/ trans] = 8.0 Hz, J [C(7)-H / C(6)-H/ cis] = 7.3 Hz. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.50; H, 7.93; N, 5.62. MS (CI, methane): *m/e* 246 (M^++1).

$(Bu_3Sn)_2$-mediated Radical Cyclizations via Halogen-transfer (Scheme 3).

A solution of N-iodoacetyloxazolidine **1** (R=H; R^1=H)(1.78 g, 5.0 mmol) and $(Bu_3Sn)_2$ (0.506 ml, 1.0 mmol) in benzene (166 ml), under nitrogen, with stirring, was heated ("air bath") to 80°C and irradiated for 60 min with a 250-W sunlamp positioned at a distance of 2 cm. Then the mixture was cooled to room temperature, treated with a saturated aqueous solution of KF (30 ml) and stirred for 2 hr. The two layers were separated, the aqueous phase extracted with ethyl ether, and the combined organic extracts were dried (Na_2SO_4) and evaporated. The crude product was purified by flash-chromatography (n-hexane-ethyl acetate 1:1) to give **bicyclic lactam 4** (1.46 g, 82%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.0 (3H, CH_3-C-N, d, J=6.5 Hz), 2.57-

2.90 (1H, CH-CNO, m; 1H, *H*CH-C=O, m; 1H, *H*CH-C=O, m), 3.40 (2H, CH_2-I, d, J=4.5 Hz), 4.0 (1H, CH-N, dq, J=6.5, 7.0 Hz), 5.14 (1H, O-CH-N, d, J=4.35 Hz), 5.36 (1H, CH-O, d, J=7.0 Hz), 7.25-7.45 (5H, Ar-H, m). Anal. Calcd for $C_{14}H_{16}NO_2I$: C, 47.08; H, 4.52; N, 3.92. Found: C, 47.16; H, 4.60; N, 3.85.

A solution of bicyclic lactam **4** (260 mg, 0.728 mmol) in benzene (36.5 ml) was treated with Bu_3SnH (0.23 ml, 0.874 mmol) and AIBN (6 mg, 0.0364 mmol), under nitrogen, with stirring. The mixture was heated at reflux for 60 min, then cooled to room temperature, treated with a saturated aqueous solution of KF (25 ml) and stirred for 2 hr. The two layers were separated, the aqueous phase extracted with ethyl ether, and the combined organic extracts were dried (Na_2SO_4) and evaporated. The crude product was purified by flash-chromatography (n-hexane-ethyl acetate 60:40) to give **bicyclic lactam 2 (R=H; R^1=H)**(165 mg, 98%).

Synthesis of pyrrolidines 9 and 10 (Scheme 4).

A suspension of $LiAlH_4$ (0.47 g, 12.4 mmol) in dry THF (73 ml) was treated under nitrogen, with stirring, with $AlCl_3$ (0.55 g, 4.12 mmol). The mixture was stirred at room temperature until LiCl precipitation was completed. To this mixture, cooled to -78°C, a solution of bicyclic lactam **2** (R=Me; R1=H)(1.34 g, 5.5 mmol) in THF (37 ml) was added dropwise. After 60 min at -78°C, the reaction was quenched by subsequent addition of water (0.626 ml), 15% NaOH (0.626 ml), and water (1.252 ml). The resulting mixture was treated with Na_2SO_4, diluted with ethyl ether, and stirred for 1 hr. Filtration of the various salts and evaporation of the organic phase gave a crude product which was purified by flash chromatography (dichloromethane-methanol-triethylamine 95:5:1) to yield **pyrrolidine 9 (R=Me; R^1=H)**(1.03 g, 80%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.80 (3H, CH_3-C-N, d, J=6.5 Hz), 0.93 (3H, C*H*$_3$CH$_2$, t, J=7.5 Hz), 1.2-1.5 (2H, CH_3CH_2, m; 1H, *H*CH-CH_2-N, m), 1.92-2.15 (1H, *H*CH-CH_2-N, m; 1H, C-C*H*-CH_2-N, m), 2.22 (1H, C-CH-C*H*H-N, dd, J=6.5, 8.5 Hz), 2.50 (1H, C*H*Me-N, dq, J=2.6, 6.5 Hz), 2.75 (2H, CH_2CH_2-N, m), 3.10 (1H, C-CH-C*H*H-N, J=6.5, 7.5 Hz), 5.00 (1H, CHO, d, J=2.6 Hz), 7.20-7.40 (5H, Ar-H, m). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.29; H, 9.99; N, 5.91. MS (CI, methane): *m/e* 234 (M^++1).

Pyrrolidine 9 N-hydrochloride (R=Me; R^1=H) ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.93 (3H, C*H*$_3$CH$_2$, t, J=7.5 Hz), 1.03 (3H, CH_3-C-N^+, d, J=6.5 Hz), 1.46 (2H, CH_3CH_2, m, J=7.5, 6.0 Hz), 1.56 (1H, *H*CH-CH_2-N^+, m, J=6.0, 8.0, 1.5 Hz), 2.2 (1H, *H*CH-CH_2-N^+, m, J=6.0, 8.0, 1.5 Hz), 2.2 (1H, C-C*H*-CH_2-N^+, m, J=6.0, 8.0, 1.5 Hz), 2.64 (1H, C-CH-C*H*H-N^+, dd, J=8.5, 10.5 Hz), 3.0 (1H, C*H*Me-N^+, dq, J=2.0, 6.5 Hz), 3.22 (2H, CH_2CH_2-N^+, m, J=6.0, 8.0 Hz), 3.58 (1H, C-CH-C*H*H-N^+, J=7.5, 10.5 Hz), 5.32 (1H, CHO, d, J=2.0 Hz), 6.85 (1H, N^+H, br.s), 7.20-7.40 (5H, Ar-H, m). Anal. Calcd for $C_{15}H_{24}NOCl$: C, 66.77; H, 8.97; N, 5.19. Found: C, 66.65; H, 9.06; N, 5.11. MS (F.A.B.$^+$) = 234 (M^+).

Following the above described procedure, bicyclic lactam **2** (R=H; R^1=Me) was reduced to **pyrrolidine 9 (R=H; R^1=Me)**(85%). ^{1}H-NMR (200 MHz, CD_3OD) δ: 0.88 (3H, CH_3-C-N, d, J=6.6 Hz), 1.07 (2 x 3H, C*H*$_3$CH, d, J=6.1 Hz), 1.67-1.73 (2 x 1H, CH_3C*H*, m), 2.51 (2 x 1H, C-CH-C*H*H-N, dd, J=8.3, 9.3 Hz), 2.63 (1H, C*H*Me-N, dq, J=2.6, 6.6 Hz), 3.12 (2 x 1H, C-CH-C*H*H-N, dd, J=7.2, 9.3 Hz), 5.03 (1H, CHO, d, J=2.6 Hz), 7.15-7.40 (5H, Ar-H, m). ^{13}C-NMR (200 MHz, CD_3OD + $CDCl_3$) δ: 9.96 (CH_3), 17.12 (2 x CH_3), 39.73 (2 x CH), 59.32 (2 x CH_2-N), 65.48 (CH-N), 72.19 (CH-O), 125.33 (2 x CH=), 126.47 (CH=), 127.58 (2 x CH=), 141.47 (C=). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.13; H, 10.01; N, 5.93. MS (CI, methane): *m/e* 234 (M^++1).

A solution of pyrrolidine **9** (R=H; R^1=Me)(0.928 g, 3.97 mmol) in methanol (14 ml) was treated with benzyl bromide (0.972 ml, 7.95 mmol). After stirring at room temperature for 15 hr, the solvent was evaporated and the crude product was flash chromatographed (CH_2Cl_2, CH_2Cl_2-MeOH 9:1) to yield **pyrrolidine 9 N-benzyl bromide (R=H; R^1=Me)** (1.445 g, 90%). ^{1}H-NMR (200 MHz, CD_3OD) δ: 0.92 (3H, C*H*$_3$CH, d, J=6.1 Hz), 0.93 (3H, C*H*$_3$CH, d J=6.1 Hz), 1.45 (3H, CH_3-C-N^+, d, J=6.5 Hz), 1.90-2.20 (2 x 1H, CH_3C*H*, m), 3.62 (1H, C-CH-C*H*H-N^+, dd, J=12.5, 12.5 Hz), 3.72 (1H, C*H*Me-N^+, dq, J=1.0, 6.5 Hz), 4.00 (2 x 1H, C-CH-C*H*H-N^+, d, J=9.5 Hz), 4.20 (1H, C-CH-C*H*H-N^+, dd, J=12.5, 8.4 Hz), 4.65 (1H, Ph-C*H*H-N^+, d, J=12.8 Hz), 5.03 (1H, Ph-C*H*H-N^+, d, J=12.8 Hz), 5.60 (1H, CHO, d, J=1.0 Hz), 7.20-7.75 (10H, Ar-H, m).

A suspension of pyrrolidine **9** N-benzyl bromide (R=H, R^1=Me) (1.34 g, 3.3 mmol) in dioxane (33 ml) and DMF (6 ml) was treated with NaH (50% in oil, 0.192 g, 4.0 mmol). The mixture was stirred at reflux for 6 hr, then cooled to room temperature, diluted with ethyl ether (100 ml) and washed with 5% Na_2SO_4 aqueous solution (2 x 50 ml). Evaporation of the solvent gave a crude mixture which was purified by flash chromatography (n-hexane-EtOAc 9:1 to 1:1) to yield (1R, 2R)-*trans* -β-methylstirene oxide and **pyrrolidine 10 (R=H, R^1=Me)**, which was further purified by chromatography on [70-230 mesh ASTM]-neutral alumina (n-hexane-ethyl ether 95:5) (0.562 g, 90%). $[\alpha]_D^{25}$= +35.46° (c 1.1, $CHCl_3$). ^{1}H-NMR (200 MHz, CD_3OD) δ: 1.04 (2 x 3H, C*H*$_3$CH, d, J=6.0 Hz), 1.75 (2 x 1H, CH_3C*H*, ddq, J=7.1, 7.5, 6.0 Hz), 2.27 (2 x 1H, C-CH-C*H*H-N, dd, J=7.1, 9.0 Hz), 2.80 (2 x 1H, C-CH-C*H*H-N, dd, J=7.5, 9.0 Hz), 3.57 (1H, PhCH*H*N, AB system, J=13.0 Hz), 3.67 (1H, PhCH*H*N, AB system, J=13.0 Hz), 7.20-7.40 (5H, Ar-H, m). ^{13}C-NMR (200 MHz, $CDCl_3$) δ: 18.470 (2 x CH_3), 40.752 (2 x CH), 60.990 (Ph-*C*H_2-N), 62.194 (2 x CH_2-N), 126.752 (CH=), 128.155 (2 x CH=), 128.800 (2 x CH=), 139.446 (C=). IR ($CHCl_3$) ν (selected data): 3080, 2950,

2920, 2900, 2860, 2780, 1490, 1450, 1370 cm^{-1}. Anal. Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.50; H, 10.20; N, 7.29. MS (CI, methane): *m/e* 190 (M^++1). **Pyrrolidine 10 N-hydrochloride (R=H; R^1=Me)**: MS (F.A.B.$^+$) = 190 (M^+, 100%), 91 (53%). Anal. Calcd for $C_{13}H_{20}NCl$: C, 69.16; H, 8.93; N, 6.20. Found: C, 69.11; H, 9.05; N, 6.11.

References and Notes

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