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Highly regio- and stereoselective iodocyclization of chiral 3-alkoxycarbonyl-4-propenyl-2,2-dimethyl-1,3-oxazolidines: a computational investigation

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Abstract

The iodocyclization of allylic carbamates **3a** and **3b** proceeded with high regio- and stereoselection to give 2-oxobicyclo[4.3.0]nonane **5a** as the major product. Both the regio- and diastereoselection of the reaction were investigated with the help of molecular mechanics and quantomechanical calculations. The energetic difference between the competing transition states TS-**5a** and TS-**5b** is in good agreement with the experimental results and from the calculated transition structures it appears that steric factors direct the discrimination.

1. Introduction

In recent years, highly regio- and stereoselective iodocyclizations of allylic and homoallylic carbamates, have been used to obtain heterocyclic intermediates, suitable for conversion into polyfunctionalized structures by cleavage of the heterocyclic ring.[1,2]

As part of a programme aimed at synthesizing polyfunctionalized acyclic molecules with biological activity, in the present paper we describe the facile preparation of (4*S*,5*S*,6*S*)-1-aza-5-iodo-4,9,9-trimethyl-3,8-dioxa-2-oxobicyclo[4.3.0]nonane **5a**, which can be a precursor of bioactive products such as L-2,5-dideoxy-2-aminoarabinose[3] **1** and β,γ-dihydroxy-α-amino acids[4] such as **2** (Scheme 1).

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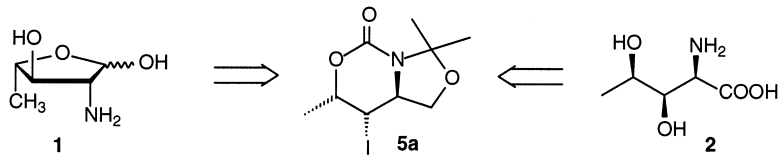
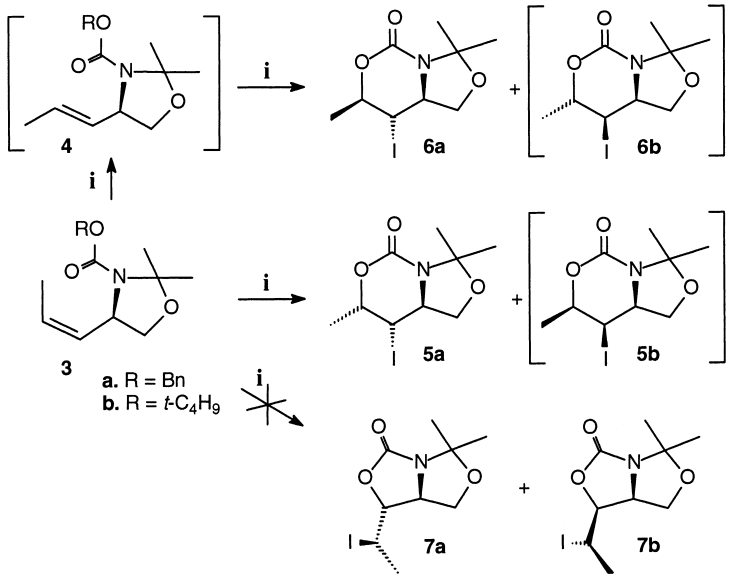


Scheme 1.

2. Results and discussion

Both *N*-Cbz and *N*-Boc derivatives **3a**[5] and **3b**[6] underwent highly regio- and stereoselective iodocyclization on treatment with iodine or *N*-iodosuccinimide (NIS) in dichloromethane or chloroform, to give, in moderate to low yield, the cyclization products **5a** (major) and **6a**, which were easily isolated by column chromatography. The possible bicyclic products **5b**, **6b**, **7a** and **7b** were never observed in the reaction mixture (Scheme 2; Table 1).[7,8,14]



Scheme 2. Reagents and conditions: i. I_2 or NIS in CH_2Cl_2 or $CHCl_3$, 3 days (see Table 1)

These compounds were first assigned as 2-oxobicyclo[4.3.0]nonanes owing to the observed IR absorption at 1703 cm^{-1}, which is diagnostic for a six-membered ring carbamate.[2e] The stereochemistry of the products was subsequently accomplished by ^1H NMR spectroscopy supported by molecular mechanics calculations. Thus, the minimum energy conformations and significant dihedral angles for **5a**,**b** and **6a**,**b** were calculated by using the AMBER* force field programme[9] and are reported in Fig. 1. Compound **5a** showed resonances for H_5 at δ 3.95 (dd, $J_{5,6}$ 11.3 and $J_{4,5}$ 4.8 Hz), for H_4 at δ 4.68 (dq, $J_{4,1'}$ 6.6 and $J_{4,5}$ 4.8 Hz) and for H_6 at δ 4.09 (ddd, $J_{5,6}$ 11.3, $J_{6,7A}$ 9.5 and $J_{6,7B}$ 5.1). Both the large value of $J_{5,6}$ (11.3 Hz) and the small value of $J_{4,5}$ (4.8 Hz) are typical of a 4,5-*cis*-, 5,6-*trans*-relationship and were in agreement with the calculated dihedral angles H_5–C_5–C_6–H_6 and H_4–C_4–C_5–H_5, respectively. This assignment was confirmed by the ^{13}C NMR spectrum, which showed three CH sp^3-carbon signals [at δ 18.4 (C_5), 56.5 (C_6) and 76.5 (C_4)], and further supported by a two-dimensional ^1H–^{13}C COSY spectrum which shows a pronounced cross peak between H_5 and C_5.

On the other hand, the minor product of the reaction could not be assigned as **3b**, arising from addition

Table 1
Product distribution for cyclization of compounds **3a** and **3b**

Substrate	Reagent	Solvent	**5a** (%)[a]	**6a** (%)[a]	d.r.
3a	I_2	CH_2Cl_2	45	3	94:6
3a	I_2	$CHCl_3$	29	1	97:3
3a	NIS	CH_2Cl_2	7	1	88:12
3b	NIS	CH_2Cl_2	37	2	95:5
3b	I_2	CH_2Cl_2	12	1	92:7
3b	I_2	$CHCl_3$	17	1	94:6

[a]Yields refer to pure, isolated products.

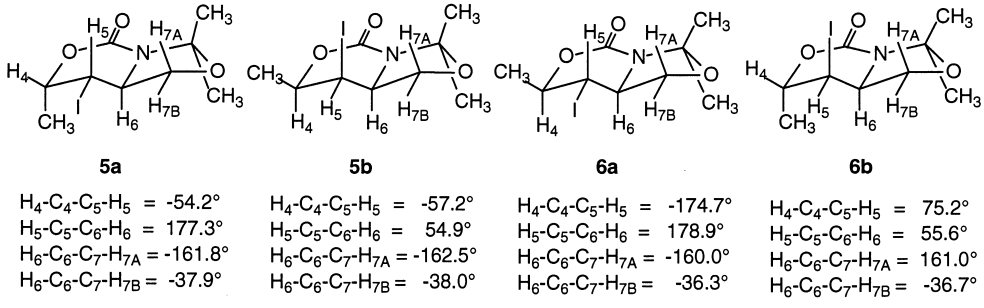
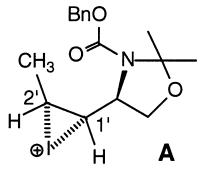


Figure 1. Preferred conformations and significant dihedral angle values for compounds **5a**, **5b**, **6a** and **6b**

to a *Z*-double bond, although three CH sp^3-carbon signals [at δ 22.7 (C_5), 61.5 (C_6) and 79.4 (C_4)] were present in its ^{13}C NMR spectrum. In fact, both coupling constants and splitting pattern of H_5 (δ 3.55, dd, *J* 10.6 and *J* 10.9) clearly showed a *trans*,*trans*-relationship of H_5 with both H_4 and H_6, so that the minor product was assigned as **6a**, arising from iodocyclization of a small amount of both **4a** and **4b**, which probably forms under the reaction conditions. These observations allowed us to assign the major product **5a** as (4*S*,5*S*,6*S*)-1-aza-5-iodo-4,9,9-trimethyl-3,8-dioxa-2-oxobicyclo[4.3.0]nonane and the minor one **6a** as its (4*R*,5*S*,6*S*)-isomer.

The reaction proceeded with total regioselection, since 2-oxobicyclo[4.3.0]nonanes **5a** and **6a** arising from a 6-*endo* mode closure were exclusively isolated from the reaction mixture, whereas products such as **7a** and **7b**, which would form through a 5-*exo* mode cyclization were missing.[10] In order to explain the regioselection of the cyclization, in which electronic effects are not clearly present as in previously reported examples,[2e] we first considered the intermediate iodonium ion **A** derived from **3a** (Fig. 2). Thus, we calculated the frontier electron density for nucleophile (f_r^N) for both C_1', leading to 5-*exo* closure, and C_2', leading to 6-*endo* closure, and the values turned out to be 2.35×10^{-3} and 0.634, respectively, in agreement with a 6-*endo* closure pathway.[11]

Subsequently, the search for transition states (TSs) leading to bicyclic compounds **5a**,**b**, **6a**,**b** and **7a**,**b** starting from the corresponding iodonium ions was carried out using the synchronous transit quadratic method at the AM1 level and the calculated structures are reported in Figs. 3 and 4.[12] In addition, the formation enthalpy values ($\Delta H^{\#}$) of all the considered transition structures were calculated and



A

Figure 2.

are summarized in Table 2. Firstly, it resulted in both TS-**7a** and TS-**7b** being largely disfavored with respect to TS-**5a** and TS-**5b**, according to the observed regioselection.[13] Moreover, by considering the transition states TS-**5a**/TS-**5b**, leading to **5a** and **5b**, and TS-**6a**/TS-**6b**, leading to **6a** and **6b**, the observed diastereoselection could also be explained (Table 2). The energetic difference occurring between TS-**5a** and TS-**5b** ($\Delta\Delta H^{\#}$=1.16 kcal/mol) and TS-**6a** and TS-**6b** ($\Delta\Delta H^{\#}$=1.66 kcal/mol), respectively, is in good agreement with the related experimental results (only **5a** and **6a** were observed in the reaction mixture).

The role of the heterocyclic ring on the stereoselection of the reaction can be appreciated by inspection of the AM1-optimized transition state geometries of both TS-**5a** and TS-**5b**, as reported in Fig. 3. As a matter of fact, it results in the steric factors governing the energy differences between these transition states. In TS-**5b** a sterically demanding interaction takes place between the ring and CH_3-3′, which is otherwise lacking in TS-**5a**, the distance between the heterocyclic ring and CH_3-3′ being 3.33 Å.

Eventually, the molecular mechanics calculations data confirmed that the cyclization reaction proceeds under kinetic control. In fact, by comparison with **5a**, compound **5b** was found to be more stable by 1.01 kcal/mol, although only **5a** was isolated from the reaction mixture, owing to the irreversible cyclization proceeding through the lower energy transition state.[9,12] The same behavior was also observed for compound **6a** with respect to **6b**.

3. Conclusion

The iodocyclization reaction of allylic carbamates **3a** and **3b** proceeds with high regio- and stereoselection leading to 2-oxobicyclo[4.3.0]nonanes **5a** and **6a** and this behavior has been explained by molecular mechanics and quantum-mechanical calculations. The major product **5a** could be a precursor of biologically active compounds and work in progress on this subject will be reported in due course.

4. Experimental

4.1. General

All reactions involving air-sensitive reagents were performed under nitrogen using syringe–septum cap techniques. All glassware was flame-dried prior to use. Flash chromatography was performed using silica gel (Merck 60, 70–230 mesh). Optical rotations were measured at rt on a Perkin–Elmer 241 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 250 and 69.2 MHz on a Bruker AC-250 spectrometer. Carbon was determined via DEPT and ^{13}C–^{1}H COSY techniques. High-resolution mass spectra were obtained on a VG Autospec, TRIO 1000 (Fisons) instrument. The ionization modes used in mass spectrometric analysis were chemical ionization (CI) at 70 eV or fast atom bombardment (FAB).

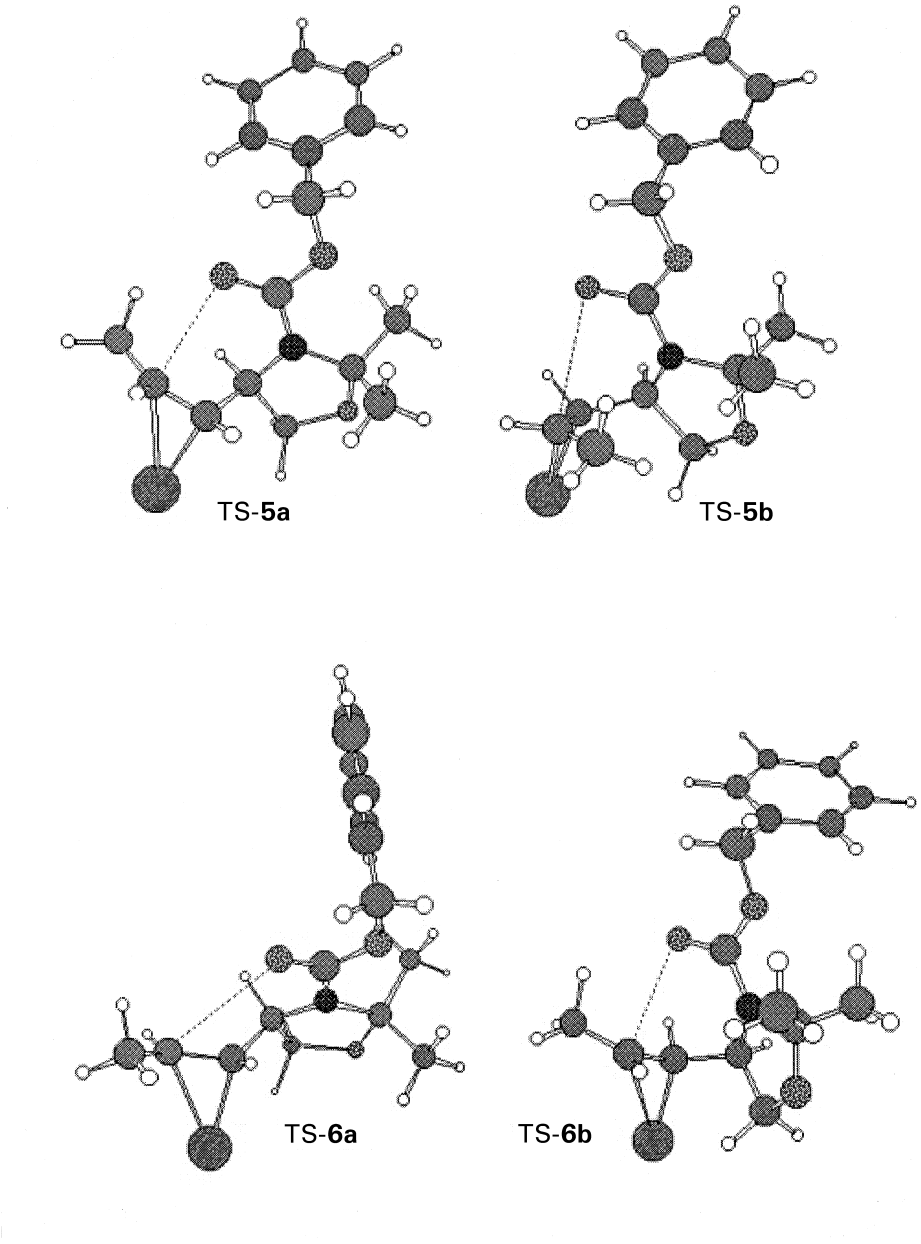


Figure 3. Transition states for cyclization of both **3a** and **4a** in 6-*endo* mode

4.2. Materials

(*S*)-*N*-Benzyloxycarbonyl-4-formyl-2,2-dimethyl-1,3-oxazolidine[5] and (*Z*,*R*)-3-*t*-butoxycarbonyl-2,2-dimethyl-4-(1-propenyl)-1,3-oxazolidine[6] **3b** were prepared following literature methods.

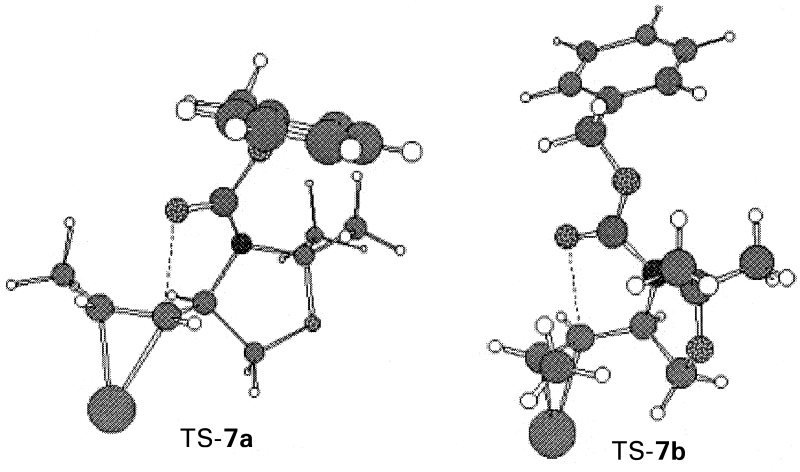


Figure 4. Transition states for cyclization of **3a** in 5-*exo* mode

Table 2
Formation enthalpies (kcal/mol) of both the theoretical transition state structures (TSs) and the corresponding iodonium ions

TS	ΔH_f (TS)	ΔH_f (iodonium ion)	$\Delta H^{\#}$
TS-5a	125.67	125.03	0.64
TS-5b	129.26	127.41	1.85
TS-6a	131.56	129.34	2.22
TS-6b	127.29	123.41	3.88
TS-7a	129.99	125.03	4.96
TS-7b	132.27	127.04	5.23

*4.3. (Z,R)-3-Benzyloxycarbonyl-2,2-dimethyl-4-(1-propenyl)-1,3-oxazolidine **3a***

To a suspension of ethyl triphenylphosphonium halide (17.5 mmol) in dry THF (115 ml) under an argon atmosphere cooled to −78°C, *n*-BuLi (2 M solution in hexane; 17.5 mmol; 8.75 ml) was added dropwise. The mixture was stirred for 15 min, allowing the temperature to reach 0°C, and the resulting dark red solution was stirred for an additional hour. After cooling to −78°C, (*S*)-*N*-benzyloxycarbonyl-4-formyl-2,2-dimethyl-1,3-oxazolidine[5] (10 mmol) dissolved in dry THF (22 ml), was added dropwise over a 10 min period. The reaction mixture was stirred under argon until the temperature reached 25°C and then for a further 90 min. The mixture was quenched with saturated aqueous NH_4Cl (115 ml) and extracted with ethyl acetate (3×55 ml). The combined organic phases were washed with water (60 ml) and brine (60 ml) and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (hexane:ethyl acetate, 80:20) to give **3a** in 70% yield as a colorless oil. Both ^1H and ^{13}C NMR spectra showed two sets of signals at room temperature, due to the presence of a dynamic equilibrium between two conformers (α and β, the α form being predominant).

^{1}H NMR: 1.34–1.64 (m, 9H), 3.53 (dd, 1H, *J*=8.8, *J*=2.2), 3.92 (dd, 1H, *J*=8.8, *J*=5.9), 4.51–4.62 (m, 1H), 4.96 (s, 2H), 5.30–5.36 (m, 2H), 7.19 (s, 5H); ^{13}C NMR: 12.6 (q, $CH_3)_{\alpha+\beta}$, 23.7 (q, $CH_3)_\alpha$, 25.0 (q, $CH_3)_\beta$, 26.3 (q, $CH_3)_\alpha$, 27.2 (q, $CH_3)_\beta$, 53.7 (d, CHN)$_\alpha$, 54.5 (d, CHN)$_\beta$, 66.5 (t, $OCH_2C_6H_5)_{\alpha+\beta}$, 68.8 (t, $CH_2O)_{\alpha+\beta}$, 94.0 (s, $C_2)_{\alpha+\beta}$, 125.8 (d, =CH)$_{\alpha+\beta}$, 127.8 (d, $2CH_{ar})_{\alpha+\beta}$, 127.9 (d, $CH_{ar})_{\alpha+\beta}$, 128.2 (d, $2CH_{ar})_{\alpha+\beta}$, 129.6 (d, =CH)$_{\alpha+\beta}$, 136.4 (s, $C_{ar})_{\alpha+\beta}$, 152.2 (s, CON)$_{\alpha+\beta}$. $[\alpha]_D^{25}$=85.9 (*c* 1.23, $CHCl_3$). Exact mass (CI) calcd for $C_{16}H_{21}O_3N$ (M^+): 275.1517; found: 275.1521.

*4.4. Iodocyclization of carbamates **3a**,**b***

4.4.1. General procedure

Method A. To a solution of alkenyloxazolidine **3a** or **3b** (10 mmol) in dichloromethane or chloroform (50 ml), I_2 (5.1 g, 20 mmol) was added at room temperature. After 3 days, the reaction was diluted with dichloromethane or chloroform (50 ml), the organic phase washed with 10% aqueous $Na_2S_2O_3$ (50 ml), then extracted with dichloromethane (3×50 ml) and the combined organic layers were washed with water (75 ml), brine (75 ml), and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (hexane:ethyl acetate, 60:40) to give compounds **5a** and **6a** as colorless oils. Yields and d.r.s are reported in Table 1.

Method B. To a solution of alkenyloxazolidine **3a** or **3b** (10 mmol) in dichloromethane (50 ml), NIS (2.7 g, 12 mmol) was added at room temperature. After stirring for 3 days, the reaction was diluted with dichloromethane (50 ml), the solution was washed with 10% aqueous $Na_2S_2O_3$ (50 ml), extracted with dichloromethane (3×50 ml) and the combined organic layers were washed with 10% HCl (30 ml), 10% aqueous $NaHCO_3$ solution (30 ml) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (hexane:ethyl acetate, 70:30) to give compounds **5a** and **6a** as colorless oils. Yields and d.r.s are reported in Table 1.

*4.5. (4S,5S,6S)-1-Aza-5-iodo-4,9,9-trimethyl-3,8-dioxa-2-oxobicyclo[4.3.0]nonane **5a***

IR (CH_2Cl_2): 1703 cm^{-1}. ^{1}H NMR: 1.60 (s, 3H), 1.61 (s, 3H), 1.63 (d, 3H, *J*=6.6), 3.59 (dd, 1H, H_{7A}, *J*=8.7, *J*=9.5), 3.95 (dd, 1H, H_5, *J*=4.8, *J*=11.3), 4.09 (ddd, 1H, H_6, *J*=5.1 *J*=9.5, *J*=11.3), 4.30 (dd, 1H, H_{7B}, *J*=5.1, *J*=8.7), 4.68 (dq, 1H, H_4, *J*=6.6, *J*=4.8). ^{13}C NMR: 17.9 (q, CH_3), 18.4 (d, CHI), 23.6 (q, CH_3), 26.4 (q, CH_3), 56.5 (d, CHN), 70.2 (t, CH_2O), 76.5 (d, CHO), 97.3 (s, C), 148.2 (s, CON). $[\alpha]_D^{25}$=−46.8 (*c* 1, $CHCl_3$). Exact mass (FAB) calcd for $[C_9H_{15}O_3NI]^+$ (MH^+): 312.0096; found: 312.0098.

*4.6. (4R,5S,6S)-1-Aza-5-iodo-4,9,9-trimethyl-3,8-dioxa-2-oxobicyclo[4.3.0]nonane **6a***

IR (CH_2Cl_2): 1705 cm^{-1}. ^{1}H NMR: 1.60 (d, 3H, *J*=6.2), 1.62 (s, 3H), 1.64 (s, 3H), 3.55 (dd, 1H, H_5, *J*=10.6, *J* 10.9), 3.59 (dd, 1H, H_{7A}, *J*=9.5, *J*=8.7), 4.04 (ddd, 1H, H_6, *J*=10.6, *J*=5.8, *J*=9.5), 4.33 (dd, 1H, H_{7B}, *J*=5.8, *J*=8.7), 4.50 (dq, 1H, H_4, *J*=10.9, *J*=6.2). ^{13}C NMR: 20.4 (q, CH_3), 22.7 (d, CHI), 23.8 (q, CH_3), 26.2 (q, CH_3), 61.5 (d, CHN), 70.1 (t, CH_2O), 79.4 (d, CHO), 97.1 (s, C), 148.5 (s, CON). $[\alpha]_D^{25}$=−85.0 (*c* 1.02, $CHCl_3$). Exact mass (FAB) calcd for $[C_9H_{15}O_3NI]^+$ (MH^+): 312.0096; found: 312.0097.

4.7. Computational studies

All simulations were carried out using the BATCHMIN simulation program as implemented in Macromodel molecular modeling package, version 5.5.[9] The AMBER* force field was used, and the conformational search varied all internal degrees of freedom, by using a Monte Carlo algorithm included in the package. All conformers with energies within 3.0 kcal/mol were considered. All the calculations were performed on a Silicon Graphics Indigo2 workstation R10000, 175 MHz.

Transition states (TSs) leading to compounds **5a**,**b**, **6a**,**b** and **7a**,**b** were localized by using the AM1 Hamiltonian combined with the synchronous transit method, included in HyperChem Software Package 5.1.[12] In particular, the quadratic synchronous transit method (QST) was employed, which searches for a maximum along a parabola-connecting reagent and products, and for a minimum in all directions perpendicular to the parabola. The TS structures found have only one imaginary frequence normal mode which corresponds to the coordinate of reaction, consisting of a synchronous motion of the two centers of reaction (O···C).[14,15]

Acknowledgements

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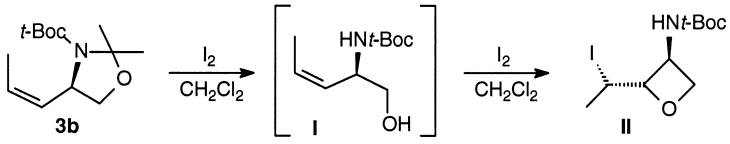
7. No reaction was observed starting from both (*R*)-3-benzyloxycarbonyl-2,2-dimethyl-4-(1-propenyl)-1,3-oxazolidine and (*E*,*R*)-3-benzyloxycarbonyl-2,2-dimethyl-4-(2-ethoxycarbonylethenyl)-1,3-oxazolidine. This result was surprising, in comparison with those reported for analogous systems (see Ref. 2e and h), although an explanation seems rather difficult to find.
8. When halocyclization of **3b** was carried out with I_2 in CH_2Cl_2, besides the bicyclic derivatives **5a** and **6a**, (2*S*,3*S*,1′*S*)-3-*t*-butoxycarbonylamino-2-(1′-iodoethyl)oxetane **II** was also isolated (10%), which arises from 4-*exo* cyclization of the intermediate **I** formed by acetonide ring cleavage of **3b** under reaction conditions.[14] ^{1}H NMR: 1.19 (s, 9H), 1.90 (d, 3H,

J=6.9), 3.40 (dd, 1H, H_{4B} *J*=7.3, *J*=8.7), 3.47 (dd, 1H, H_{4A}, *J*=4.8, *J*=8.7), 3.78 (m, 1H, H_3), 4.18 (dd, 1H, H_2 *J*=4.4, *J*=3.5), 4.26 (dq, 1H, *J*=6.9, *J*=3.5), 6.40 (br s, 1H, NH). ^{13}C NMR: 21.9 (q, CH_3), 27.0 (d, CHI), 27.3 (q, $3CH_3$), 56.2 (d, CHN), 64.2 (t, CH_2O), 73.6 (s, C), 81.5 (d, CHO), 158.7 (s, CON). $[\alpha]_D^{25}$ −53.2 (*c* 1.00, $CHCl_3$). Exact mass (FAB) calcd for $[C_{10}H_{19}O_3NI]^+$ (MH^+): 328.0409; found: 328.0424. The *trans* relationship between H_2 and H_3 was confirmed by inspection of the corresponding coupling constant ($J_{2,3}$ 3.5 Hz); whereas the (*S*)-configuration for the stereogenic center in the side chain was tentatively assigned from mechanistic considerations, by assuming an *anti*-addition mechanism to the *Z*-double bond.



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14. The frequency values are the following: for TS-**5a**, −59.33 cm^{-1}; for TS-**5b**, −29.92 cm^{-1}; for TS-**6a**, −43.18 cm^{-1}; for TS-**6b**, −67.12 cm^{-1}; for TS-**7a**, −276.90 cm^{-1}; for TS-**7b**, −205.35 cm^{-1}.
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