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1,3-Oxazin-2-ones vs tetrahydrofurans by iodocyclisation of 2-alkoxycarbonylamino-3-alken-1-ols

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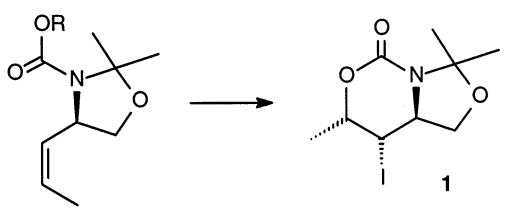
Abstract

Iodocyclisation of primary homoallylic alcohols **2a**–**d**, containing either a 2-*t*-butoxy- or a benzyloxycarbonylamino group, was studied, in order to establish the nucleophilic group involved in cyclofunctionalisation. In fact, the *N*-*t*-Boc derivative **2a** gave the oxazinone **3**, exclusively, whereas starting from the *N*-Cbz derivative **2b** a diastereomeric mixture of substituted tetrahydrofurans **4** and **5** resulted in ratios depending upon the reaction conditions. These results were rationalised by means of computational methods. On the contrary, migration of both the *t*-butyl or benzyl group to the hydroxy group was observed when both **2c** and **2d** underwent cyclisation to give the corresponding 5-alkoxymethyl oxazolidin-2-ones **7a**,**b** in low yield, but with high regio- and stereocontrol.

1. Introduction

In continuation of our interest in the stereoselective synthesis of polyfunctionalised molecules,[1] we recently reported iodocyclisation of homochiral *N*-*t*-Boc and *N*-Cbz allylic carbamates to give the bicyclic derivative **1** with high stereoselection (Scheme 1).[2]



Scheme 1.

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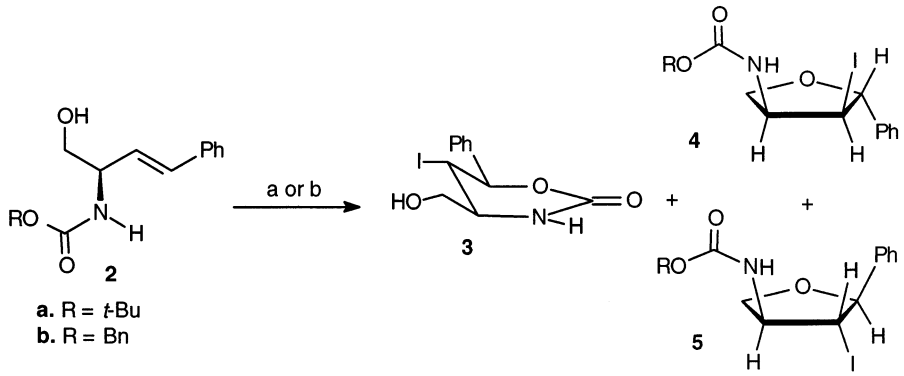
2. Results and discussion

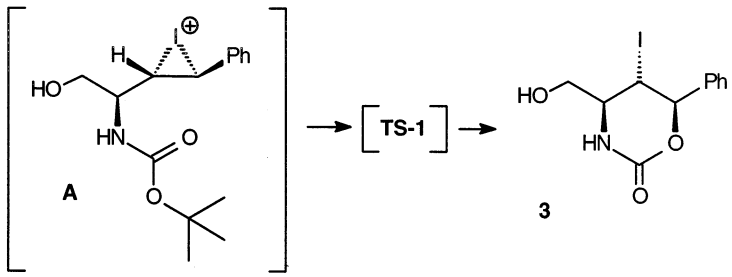
As an extension of our cyclisation strategy towards polyfunctionalised molecules, we report here on the iodocyclisation of 2-alkoxycarbonylamino-3-alken-1-ols **2a**–**d**,[3,4] in which both hydroxy- and alkoxycarbonyl groups can act as nucleophiles, leading to cyclic carbamates as well as to cyclic ethers, through competing reaction pathways.

Thus, when the *N*-*t*-Boc derivative **2a** underwent iodocyclisation, the oxazinone **3** was exclusively obtained in moderate yield, whose structure was assigned by comparison of its IR and ^{1}H NMR data with those of related compounds,[5] and subsequently confirmed by the ^{13}C NMR and two-dimensional ^{1}H–^{13}C COSY spectra. Eventually, the configuration of **3** was determined by the coupling constant values ($J_{4,5}=8.0$, $J_{5,6}=8.5$ Hz), which agree with a *trans*,*trans*-relationship. In this case the exclusive 6-*endo* cyclisation mode seems to be due to electronic factors, i.e. the phenyl ring stabilisation of the incipient carbocation (Scheme 2).[6]



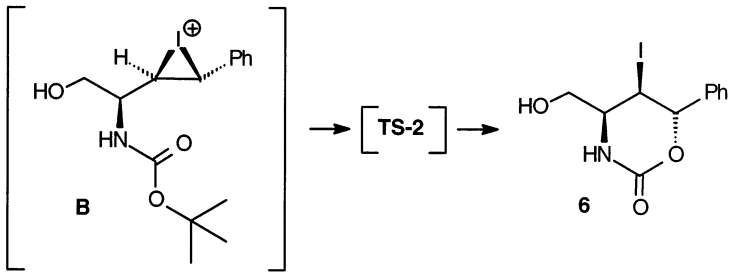
Scheme 2. *Reagents and conditions:* (a) NIS in CH_2Cl_2, rt, R = *t*-Bu, **3** (53%), **4** (0%), **5** (0%); R = Bn, **3** (traces), **4** (31%), **5** (9%); (b) I_2 in CH_2Cl_2, rt, R = Bn, **3** (traces), **4** (7%), **5** (13%)

Thus, the energies of both **3** (58.81 kcal/mol) and the corresponding intermediate iodonium ion **A** (70.48 kcal/mol) were calculated and then the transition state **TS-1**, leading to **3**, was localised ($\Delta H_f=79.99$ kcal/mol).[7–9] For this transition state, the 3D shapes for HOMO and LUMO were obtained ($E_{HOMO}=-13.677654$ eV and $E_{LUMO}=-6.337213$ eV) with the result that the HOMO lies mainly on the carbonyl oxygen and nitrogen ($f^{E}_{r(HOMO)}$ 0.129 and 0.537, respectively), whereas the LUMO lies mainly at C-4 ($f^{N}_{r(LUMO)}$, C-4, 0.455, and C-3, 7.38×10^{-4}, respectively) (Scheme 3).



Scheme 3.

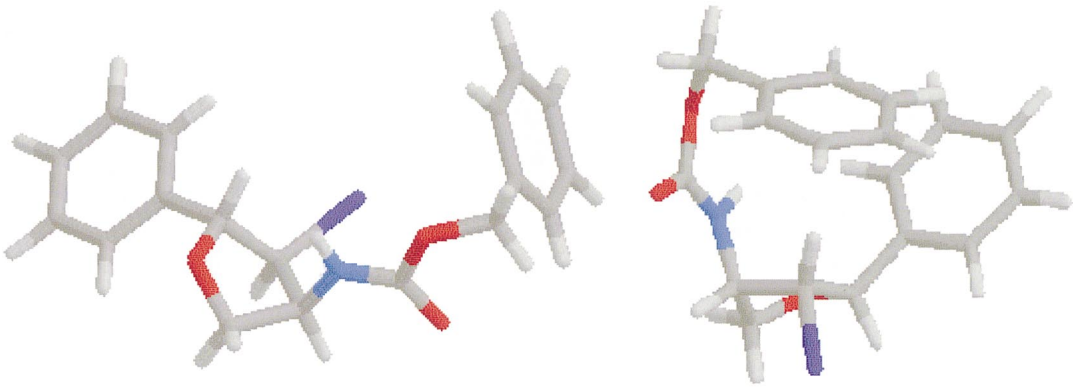
Starting from **2a**, we considered the formation pathway of oxazinone **6**, a diastereomer of **3**, although it was not observed in the reaction mixture, in order to explain the total stereoselection of the cyclisation process. Therefore, the energies of both iodonium **B** (80.92 kcal/mol) and **6** (61.59 kcal/mol) were calculated and transition state **TS-2**, leading to **6**, was localised ($\Delta H_f = 83.206$ kcal/mol). In addition, the corresponding 3D shapes for both the HOMO and LUMO were obtained ($E_{HOMO} = -13.599336$ eV and $E_{LUMO} = -6.337$ eV) with the result that the HOMO lies mainly on carbonyl oxygen and nitrogen ($f^{E}_{r(HOMO)}$ 0.184 and 0.461, respectively), whereas the LUMO lies mainly at C-4 ($f^{N}_{r(LUMO)}$, C-4, 0.454, and C-3, 6.77×10^{-4}, respectively). Thus, the overall process is largely disfavoured, owing to the higher energies involved, although the formation of **6** via a 6-*endo* mode is allowed (Scheme 4).[6]



Scheme 4.

On the other hand, when the *N*-Cbz derivative **2b** was treated with NIS in CH_2Cl_2, besides traces of the oxazinone **3**, a diastereomeric mixture of tetrahydrofurans **4** and **5** was obtained, whose structures were assigned by inspection of their ^1H and ^{13}C NMR spectra supported by molecular mechanics calculations (Scheme 2).[10,11]

First, the PhCHO- and -CHI functions in all-*trans* iodo-tetrahydrofuran **5** were easily identified by both their coupling pattern (δ H-3: 4.27, 1H, dd, $J_{3,2} = 6.5$ and $J_{3,4} = 6.2$ Hz; δ H-2: 5.19, 1H, d, $J_{2,3} = 6.5$ Hz) and ^1H–^{13}C correlation spectrum, relying on the upfield shift of the methine attached to iodine (δ 37.3) and the downfield shift of the methine attached to oxygen (δ 88.6). Then, the configuration of **4** and **5** was definitely assigned by comparison of their chemical shifts and coupling constant values. In fact, the minimum energy conformations have been calculated, in order to explain the corresponding ^1H NMR spectra, and are reported in Fig. 1.



4 **5**

Figure 1. Minimum energy conformations and significant dihedral angles for compounds **4** and **5**. (H-2)–(C-2)–(C-3)–(H-3) = −156.0°, (H-2)–(C-2)–(C-3)–(H-3) = 127.9°, (H-3)–(C-3)–(C-4)–(H-4) = 43.4°, (H-3)–(C-3)–(C-4)–(H-4) = −96.8°, (H-4)–(C-4)–(C-5)–(H-5_A) = −45°, (H-4)–(C-4)–(C-5)–(H-5_A) = −46.2°, (H-4)–(C-4)–(C-5)–(H-5_B) = 76.8°, (H-4)–(C-4)–(C-5)–(H-5_B) = 76.7°

Thus, H-4 in **4** resonates at lower field (δ 4.57) than in **5** (δ 4.08), owing to the shielding effect of the C-3 halogen *cis* to H-4. Moreover, as a result of the phenyl group shielding, in **4**, H-3 resonates upfield (δ 3.85) with respect to **5** (δ 4.27).

A tentative explanation of the reaction outcome can arise from inspection of the minimum energy conformations of the corresponding iodonium ions **C** and **D**, leading to **4** and **5**, respectively.[11] In fact, owing to a π-stacking effect[12] between the phenyl groups, the carbonyl group is constrained far from C-4, whereas the distance between the hydroxy group and C-4 seems appropriate for the cyclisation (2.64 and 2.68 Å, for both **C** and **D**, respectively), thus favouring formation of tetrahydrofurans **4** and **5**, vs 1,3-oxazin-2-one **3** (Fig. 2).

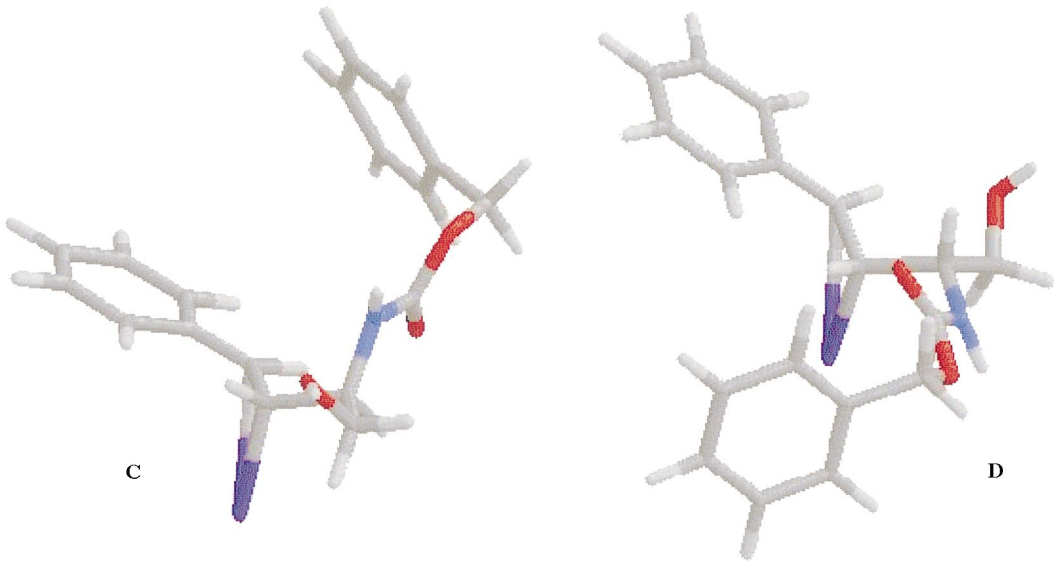
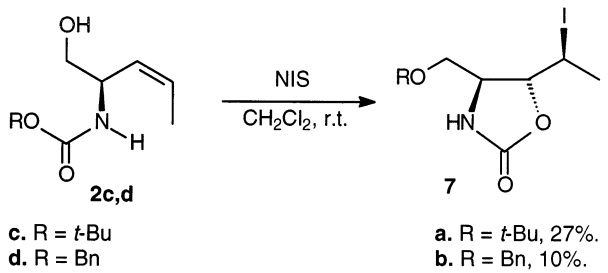


Figure 2. Minimum energy conformation for iodonium ions **C** and **D**

Furthermore, it is worth mentioning that the d.r. strongly depends upon the cyclisation conditions. In fact, when NIS in CH_2Cl_2 was employed, diastereomeric tetrahydrofurans **4** and **5** were obtained in 78:22 d.r., as determined from the ^{13}C NMR spectrum. On the contrary, cyclisation carried out with iodine in dichloromethane afforded **4** and **5** in low yield and 35:65 d.r. This result could be explained in terms of kinetic vs thermodynamic control of the cyclisation process.[13] In fact, molecular mechanics calculations carried out by using the AMBER* force field have shown that **5** is 0.9 kcal/mol more stable than **4**, owing to a π-stacking effect[12] between the phenyl groups. In agreement with these results, under kinetically controlled conditions (NIS in CH_2Cl_2) **4** is the major component of the reaction mixture. On the contrary, when the reaction was carried out under thermodynamic control (iodine in CH_2Cl_2), equilibration takes place to give **5** as the major product.[13]

Eventually, a rather surprising result was observed when both **2c** and **2d** underwent cyclisation with NIS in dichloromethane since oxazolidin-2-ones **7a**,**b** were exclusively obtained in low yield but with high regio- and stereoselection (Scheme 5).



c. R = *t*-Bu
d. R = Bn

a. R = *t*-Bu, 27%.
b. R = Bn, 10%.

Scheme 5.

The structural assignment of **7a**,**b** was performed on the basis of their spectral data. In fact, the observed carbonyl absorption of **7a** and **7b** at 1760 and 1754 cm^{-1}, respectively, was diagnostic for a five-membered ring carbamate.[14] In addition, in the ^1H NMR spectrum of **7a**, a peak at 1.17 δ suggested that the *t*-Boc group had been converted to a *t*-butyl ether.[15] On the other hand, for oxazolidinone **7b** the change of the chemical shift of the benzyloxy group from δ 5.06 (in compound **2d**) to δ 4.48 confirmed the presence of a benzyl ether moiety. Eventually, the relative stereochemistry of the oxazolidinone ring in both **7a** and **7b** was assigned as *trans*, on the basis of the values of the coupling constants ($J_{4,5}=4.0$ and 4.5 Hz, respectively).[14]

3. Conclusion

In summary, we showed that the iodocyclisation of 2-alkoxycarbonylamino-3-alken-1-ols **2a**–**d** strongly relies on either the substituents of the double bond and the nitrogen protecting group, which in agreement with computational results direct the process towards formation of 1,3-oxazin-2-one, or tetrahydrofuran derivatives with high stereoselection. Applications of this process to the synthesis of polyfunctionalised bioactive compounds are currently under study in our laboratory and will be reported in due course.

4. Experimental

4.1. Materials and methods

Mps were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded at 250 and 69.2 MHz, respectively, on a Bruker AC-250 spectrometer. Chemical shifts are relative to tetramethylsilane (TMS) and coupling constants (J) are given in Hz. All assignments were determined via DEPT and ^{13}C–^1H COSY techniques. Optical rotations were measured at rt on a Perkin–Elmer 241 polarimeter. High-resolution mass spectra were obtained on a VG Autospec, TRIO 1000 (Fisons) instrument. The ionisation mode used in mass spectra were electron impact (EI), chemical ionisation (CI) at 70 eV or fast atom bombardment (FAB). Flash chromatography was performed using silica gel (Merck 60, 70–230 mesh). Compounds **2a**–**d** were prepared according to the literature method.[3]

4.2. (E,R)-2-t-Butoxycarbonylamino-4-phenyl-3-butenol **2a**

Yield 66%. White solid. Mp 97–99°C. ^{1}H NMR: 1.36 (s, 9H), 3.15 (br s, 1H, OH), 3,53 (dd, 1H, $J=11.0$, $J=5.5$), 3.64 (dd, 1H, $J=11.0$, $J=4.4$), 4.26 (m, 1H, NH), 5.16 (br s, 1H), 6.03 (dd, 1H, $J=16.0$, $J=6.0$), 6.46 (d, 1H, $J=16.0$), 7.19–7.24 (m, 5ArH). ^{13}C NMR: 28.3, 54.4, 65.1, 79.8, 126.4, 126.9, 127.6, 128.4, 131.5, 136.4, 156.0. $[\alpha]_D$ −40.1 (*c* 1.2, $CHC1_3$). CI-HRMS (MH^+) = 264.1593. Calculated for $C_{15}H_{22}NO_3$ 264.1599.

4.3. (E,R)-2-Benzyloxycarbonylamino-4-phenyl-3-butenol **2b**

Yield 60%. White solid. Mp 110–112°C. ^{1}H NMR: 2.50 (br s, 1H), 3.64 (dd, 1H, $J=11.0$, $J=5.5$), 3.74 (dd, 1H, $J=11.0$, $J=4.0$), 4.37 (m, 1H), 5.03 (s, 2H), 5.31 (d, 1H, $J=7.7$), 6.04 (dd, 1H, $J=15.7$, $J=5.9$), 6.49 (d, 1H, $J=15.7$), 7.19–7.24 (m, 10ArH). ^{13}C NMR: 54.9, 65.1, 67.0, 126.5, 127.8, 128.2, 128.6, 132.0, 136.2, 156.3. $[\alpha]_D$−34.4 (*c* 1.05, $CHC1_3$). EI-HRMS (M^+) = 297.1364. Calculated for $C_{18}H_{19}NO_3$ = 297.1364.

4.4. (Z,R)-2-t-Butoxycarbonylamino-3-penten-1-ol **2c**

Yield 78%. White solid. Mp 54–56°C. ^{1}H NMR 1.45 (s, 9H), 1.73 (dd, 3H, $J=6.9$, $J=1.8$), 2.75 (br s, 1H), 3.57–3.62 (m, 2H), 4.48–4.53 (m, 1H), 4.75 (d, 1H, NH, $J=6.6$), 5.29 (ddq, 1H, $J=10.6$, $J=8.8$, $J=1.8$), 5.68 (ddq, 1H, $J=10.6$, $J=6.9$, $J=1.8$). ^{13}C NMR 13.5, 28.4, 50.4, 66.4, 79.9, 127.2, 127.7, 156.3. $[\alpha]_D$ 39.2 (*c* 1.0, $CHCl_3$) [lit.[3] $[\alpha]_D$ 40.7 (*c* 1.1, MeOH)]. CI-HRMS (MH^+) = 202.1434. Calculated for $C_{10}H_{20}NO_3$ 202.1443.

4.5. (Z,R)-2-Benzyloxycarbonylamino-3-pentenol **2d**

Yield 76%. Colourless oil. ^{1}H NMR: 1.77 (br s, 3H), 3.07 (br s, 1H), 3.52–3.57 (m, 2H), 4.52 (m, 1H), 5.06 (s, 2H), 5.23–5.38 (m, 2H), 5.59–5.66 (m, 1H), 7.30 (m, 5ArH). ^{13}C NMR: 13.3, 50.4, 65.2, 66.8, 127.1, 127.9, 128.0, 128.4, 136.2, 156.5. $[\alpha]_D$ 42.1 (*c* 1.1, $CHC1_3$). EI-HRMS (MH^+) = 236.1281. Calculated for $C_{13}H_{18}NO_3$ 236.1286.

4.6. The iodocyclisation reaction

4.6.1. Method A

To a solution of the appropriate amino alcohol **2** (10 mmol) in dichloromethane (50 ml), NIS (4.5 g, 20 mmol) was added at room temperature. After stirring for 24 h, the reaction was diluted with dichloromethane (50 ml), the organic phase washed with 10% aqueous $Na_2S_2O_3$ (50 ml), and then extracted with dichloromethane (3×50 ml). The combined organic layers were washed with 10% NaCl (30 ml), 10% aqueous $NaHCO_3$ solution (30 ml) and dried (Na_2SO_4), and after removal of the solvent under reduced pressure, the residue was purified by silica gel flash chromatography using gradient elution (hexane:ethyl acetate, 80:20 to 30:70).

4.6.2. Method B

To a solution of alcohol **2c**,**d** (10 mmol) in dichloromethane (50 ml), I_2 (7.65 g, 30 mmol) was added at room temperature. After 24 h, the reaction was diluted with dichloromethane (50 ml), the organic phase washed with 10% aqueous $Na_2S_2O_3$ (50 ml), then extracted with (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, 80:20).

4.6.3. (4S,5S,6R)-4-Hydroxymethyl-5-iodo-6-phenyl-1,3-oxazin-2-one ***3***

Starting from **2a**, the title compound was obtained in 53% yield following Method A. White solid. Mp 164–165°C. IR (CH_2Cl_2): 3321, 1716 cm^{-1}. ^1H NMR: 2.63 (s, 1H, OH), 4.04–4.20 (m, 3H, H-4, H-$7_{a,b}$), 4.43 (dd, 1H, H-5, $J=8.5$, $J=8.0$), 4.93 (d, 1H, H-6, $J=8.0$), 5.90 (br s, 1H, NH), 7.32 (m, 5ArH). ^{13}C NMR: 41.7 (d, CHI), 55.6 (d, CHN), 72.4 (t, CH_2OH), 79.3 (d, CHO), 126.7 (d, $2CH_{Ar}$), 128.9 (d, $2CH_{Ar}$), 129.1 (d, C_{Ar}), 140.9 (s, C_{Ar}), 159.1 (s, CON). $[\alpha]_D$−39.5 (*c* 1.06, CH_3OH). EI-HRMS (MH^+): 332.9860. Calculated for $C_{11}H_{12}INO_3$ 332.9862.

4.6.4. (2R,3S,4S)-4-(Benzyloxycarbonylamino)-3-iodo-2-phenyltetrahydrofuran ***4*** *and its (2S,3R,4S)-isomer* ***5***

When iodocyclisation was carried out according to Method A starting from **2b**, a diastereomeric mixture of **4** and **5** was obtained in 40% overall yield. D.r. 78:22. Compound **4**. Yield 31%. White solid. Mp 70–73°C. ^1H NMR: 3.85–3.93 (m, 2H, H-5_A, H-3), 4.24 (dd, 1H, H-5_B, $J=8.7$, $J=7.3$), 4.57 (m, 1H, H-4), 5.10 (m, 3H, H-2+CH_2Ph), 5.37 (d, 1H, NH, $J=7.3$), 7.25 (m, 10ArH). ^{13}C NMR: 31.0 (d, CHI), 62.3 (d, CHN), 67.1 (t, CH_2OPh), 71.5 (t, CH_2O), 88.9 (d, CHO), 126.1 (d, $2CH_{Ar}$), 128.1 (d, CH_{Ar}), 128.3 (d, CH_{Ar}), 128.5 (d, CH_{Ar}), 128.6 (d, $2CH_{Ar}$), 135.9 (s, C_{Ar}), 138.1 (s, C_{Ar}), 155.6 (s, CON). $[\alpha]_D$ 22.1 (*c* 1.02, $CHCl_3$). CI-HRMS (M^+)= 424.0425. Calculated for $C_{18}H_{19}INO_3$=424.0410. Compound **5**. Yield 9%. Colourless oil. ^1H NMR: 3.77 (dd, 1H, H-5_B $J=8.8$, $J=6.2$), 4.08 (m, 1H, H-4), 4.27 (dd, 1H, H-3, $J=6.5$, $J=6.2$), 4.34 (dd, 1H, H-5_A, $J=8.8$, $J=6.5$), 5.07 (m, 3H), 5.19 (d, 1H, H-2, $J=6.5$), 7.29 (m, 10ArH). ^{13}C NMR: 37.3 (d, CHI), 53.1 (d, CHN), 67.3 (t, OCH_2Ph), 71.3 (t, CH_2O), 88.6 (d, CHO), 125.8 (d, $2CH_{Ar}$), 128.2 (d, CH_{Ar}), 128.3 (d, CH_{Ar}), 128.5 (d, CH_{Ar}), 128.6 (d, $2CH_{Ar}$), 128.7 (d, $2CH_{Ar}$), 136.0 (s, C_{Ar}), 139.2 (s, C_{Ar}), 155.5 (s, CON). $[\alpha]_D$ 12.9 (*c* 1.08, $CHC1_3$). CI-HRMS (M^+)=424.0418. Calculated for $C_{18}H_{19}INO_3$ 424.0410.

4.6.5. (2R,3S,4S)-4-(Benzyloxycarbonylamino)-3-iodo-2-phenyltetrahydrofuran ***4*** *and its (2S,3R,4S)-isomer* ***5***

When iodocyclisation according to Method B was carried out starting from **2b**, besides tars, a diastereomeric mixture of **4** and **5** was obtained, in 20% overall yield. D.r. 35:65.

*4.6.6. (4S,5R,1′S)-4-*t*-Butoxymethyl-5-(1′-iodoethyl)-1,3-oxazolidin-2-one* ***7a***

When iodocyclisation was carried out according to Method A starting from **2c**, tars were obtained, together with compound **7a** which was recovered in 27% yield. White solid. Mp 68–70°C. IR (CH_2Cl_2): 3288, 1760 cm^{-1}. ^1H NMR: 1.17 (s, 9H), 1.90 (d, 3H, $J=6.8$), 3.40 (dd, 1H, $J=7.3$, $J=8.7$), 3.47 (dd, 1H, H, $J=4.8$, $J=8.7$), 3.78 (m, 1H, H-4), 4.18 (dd, 1H, H-5, $J=4.2$, $J=3.6$), 4.26 (dq, 1H, $J=6.8$, $J=3.6$), 6.43 (br s, 1H, NH). ^{13}C NMR: 21.8 (q, CH_3), 27.0 (d, CHI), 27.3 (q, $3CH_3$), 55.2 (d, CHN), 64.2 (t, CH_2O), 73.6 (s, C), 81.5 (d, CHO), 158.7 (s, CON). $[\alpha]_D$−49.6 (*c* 1.3, $CHCl_3$). FAB-HRMS (MH^+) 328.0424. Calculated for $C_{10}H_{19}INO_3$ 328.0409.

4.6.7. (4S,5R,1′S)-4-Benzyloxymethyl-5-(1′-iodoethyl)-1,3-oxazolidin-2-one ***7b***

When iodocyclisation was carried out according to Method A starting from **2d**, tars were obtained, together compound **7b** which was recovered in 10% yield. Colourless oil. IR (CH_2Cl_2):

3284, 1754 cm^{-1}. ^1H NMR: 1.81 (d, 3H, $J=7.0$), 3.43 (dd, 1H, $J=9.5$, $J=6.2$), 3.49 (dd, 1H, $J=9.5$, $J=4.7$), 3.76 (m, 1H, H-4), 4.11 (dd, 1H, H-5, $J=4.0$, $J=3.5$), 4.16 (dq, 1H, $J=7,0$, $J=3.5$), 4.48 (s, 2H), 6.13 (br s, 1H), 7.22–7.25 (m, 5ArH). ^{13}C NMR: 21.8 (q, CH_3), 26.6 (d, CHI), 55.7 (d, CHN), 71.9 (t, CH_2O), 73.5 (t, CH_2O), 81.2 (d, CHO), 127.7 (d, $2CH_{Ar}$), 128.0 (d, CH_{Ar}), 128.6 (d, $2CH_{Ar}$), 137.2 (s, C_{Ar}), 158.5 (s, CON). $[\alpha]_D$−51.1 (*c* 0.8, $CHCl_3$). EI-HRMS (MH^+) = 362.0262. Calculated for $C_{13}H_{17}INO_3$ 362.0253.

4.7. Computational methods

Semiempirical calculations were carried out by using the AM1 Hamiltonian as implemented in HyperChem 5.1 software package. Transition structures were always located by means of the eigenvector following algorithm and on the optimised structures a complete vibrational analysis was carried out in order to check the nature of the true transition states. All these **TS** structures have only one imaginary normal mode which correspond to the expected c.d.r.

The conformational analysis of the cyclic products was carried out by using the BatchMin V.5.5 simulation program as implemented in Macromodel molecular modelling package. The AMBER* force field was used, and the simulation varied all internal degree of freedom (including the torsional angle of the ring). The conformational search was performed by using a MonteCarlo algorithm[16] included in the package and all the conformers with the energy within 3.0 kcal/mol were considered.

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