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Experimental and theoretical study of the 1,3-dipolar cycloaddition between D-glyceraldehyde nitrones and acrylates. Diastereoselective approach to 4-hydroxy pyroglutamic acid derivatives

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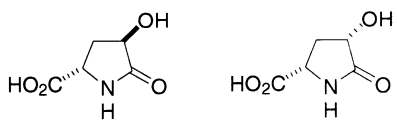
Abstract—The 1,3-dipolar cycloaddition reactions of five D-glyceraldehyde nitrones with alkyl acrylates and Oppolzer's sultam acrylamide have been studied in detail, the study including double chiral induction experiments. A complete theoretical study of the reaction has also been carried out using density functional methods (B3LYP/6-31G*) in which both *ortho* and *meta* channels leading to 3,5- and 3,4-disubstituted isoxazolidines, respectively, were considered. The adducts obtained from the cycloaddition reactions have been further used for the stereoselective synthesis of protected 4-hydroxy pyroglutamic acids, particularly the (2*S*,4*S*)-isomer, which is prepared from the major adducts of the cycloaddition reactions.

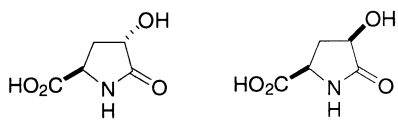
1. Introduction

Enantiomerically pure functionalized derivatives of pyroglutamic acid have stirred up great interest among synthetic chemists since they can be used both for the construction of peptide-based drugs[1] and as building blocks in asymmetric synthesis.[2] Pyroglutamic acid derivatives can also be considered as conformationally constrained glutamate analogues of biological interest.[3] In spite of the growing interest in highly functionalized pyrrolidines related to pyroglutamic acid,[4] the synthesis of 4-hydroxy-pyroglutamic acids **1** has received little attention.

These compounds, in addition to their potential as synthetic intermediates, constitute an entry to γ-substituted glutamic acid analogues. Thus, γ-hydroxyglutamic acids (the open-chain form of **1**) have been reported to be amenable to conventional resolution using alkaloids[5] and the (4*S*)-isomer has been prepared using chiral auxiliary methodology.[6] There is only one reported synthesis of racemic 4-hydroxypyroglutamic acids[7] and three reports on their preparation in homochiral form. Among them, Nozoe et al.[8] described the oxidation of the enolate derived from L-pyroglutamic acid; however, this procedure has been reported to give low chemical yields due to side reactions.[9] While preparing this work, Zhang et al.[10] reported the oxidation of *trans*-4-hydroxy-L-proline to give **1a** in excellent yield. However, these oxidative processes are limited to the availability of starting materials (chiral pool). Alternatively, it is possible to construct the pyrrolidine ring in a stereoselective way. We[11] and others[12] have been exploring the utility of nitrones as starting materials for the preparation of 5-substituted-3-hydroxy-2-pyrrolidinones according to the general route depicted in Scheme 1.



1a **1b**



ent-**1a** *ent*-**1b**

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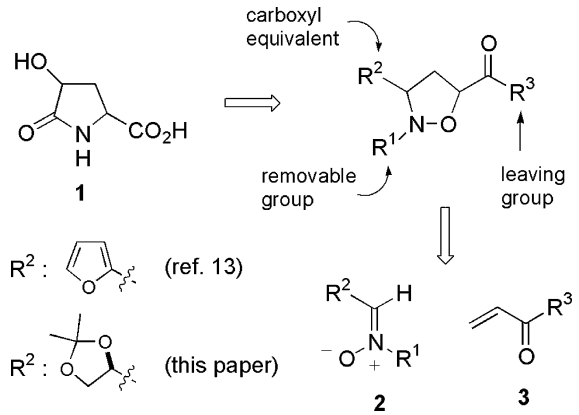


Scheme 1.

In this vein, we have reported the first enantioselective synthesis of the *cis*-isomer *ent*-**1b** formally derived from D-pyroglutamic acid, by using Oppolzer's sultam as a chiral auxiliary and the furan ring as an effective carboxyl group equivalent.[13] Herein, we report the synthesis of enantiomerically pure protected derivatives of **1b** by using a diastereoselective version of the approach illustrated in Scheme 1. We use as starting materials D-glyceraldehyde derived nitrones **2** and acrylates **3**. The choice of the starting materials was made upon three criteria: (i) the oxygen atom of the nitrone should allow the installation of the hydroxyl group at the 3-position of the pyrrolidine ring; (ii) the nitrogen atom of the cycloadduct should carry an easily removable substituent to facilitate the construction of unprotected derivatives and (iii) the 1,3-dioxolane moiety should be used as both a chiral inductor and as a surrogate of the carboxyl group.[14] The methodology is amenable to large scale synthesis. The preparation of other 4-hydroxy pyroglutamates **1** is described and a DFT study of the key reaction, i.e. the 1,3-dipolar cycloaddition between **2** and **3** is also presented.

2. Results and discussion

2.1. 1,3-Dipolar cycloadditions

The 1,3-dipolar cycloaddition between 2,3-*O*-isopropylidene-D-glyceraldehyde nitrone **2a** and methyl acrylate **3a** was reported by White et al. in 1986,[15] the stereochemistry of the adducts not being assigned unequivocally. Subsequent studies by the same authors[16] clarified the absolute configuration of the major adduct. However, only two products were reported to be obtained from the reaction.

A detailed inspection of the crude mixture of the reaction revealed to us the formation of at least four isomers consisting of one major product (ca. 63% of the total isomeric amount) besides the other minor products (Table 1, entry 1). HPLC allowed high accuracy in measuring isomeric ratios. Moreover, when the reaction was carried out on a multigram scale (ca. 10 g) traces of a minor 3,4-regioisomer could be detected. All isomers were separated and fully characterized (see Section 4).

The relative *cis*/*trans* configuration of the isoxazolidine ring substituents has been assigned on the basis of NOE experiments (Fig. 1). Thus, for *trans* compounds **4a** and **4d**, irradiation of H-3 produced a strong enhancement of only H-4a (15–17%) and irradiation of H-5 produced enhancement of only H-4b (11–13%). In addition, irradiation of H-4a and H-4b in the same experiment produced enhancements of H-3 (9–11%) and H-5 (8–12%). For compound **4e**, irradiation of H-4 produced an enhancement of only H-5a and no NOE was observed between H-3 and H-4 upon irradiation of H-3. For *cis* compounds **4b** and **4c**, irradiation of H-4a produced strong enhancements of both H-3 (14–16%) and H-5 (9–12%). Irradiation of H-5 produced enhancement of H-4a (14–17%) and a much smaller enhancement of H-4b (2–3%, not indicated in Fig. 1). Irradiation of H-3 only produced enhancement of H-4a (12–14%).

The relative configuration between isoxazolidine and 1,3-dioxolane rings could not be determined by spectroscopic means but the major isomer crystallized and was shown by X-ray crystallography[17] to be the (3*S*,5*S*,1′*S*) isomer **4a** (Fig. 2).[18] This assignment also served to confirm the absolute configuration of the other *trans*-isomer **4d**. The absolute configuration of *cis* adducts **4b**

Table 1. 1,3-Dipolar cycloaddition of nitrones **2** with dipolarophiles **3**[a]

Entry	Nitrone	Acrylate[b]	**a**:**b**:**c**:**d**[c,d]	Adduct	Yield (%)[e]
1	**2a**	**3a**	63:23:11:3	**4**	95
2	**2a**	**3b**	53:20:16:11	**5**	66
3	**2b**	**3a**	35:25:20:20	**6**	88
4	**2c**	**3a**	75:15:8:2	**7**	94
5	**2d**	**3a**	25:25.25:25	**8**	93
6	**2a**	**3c**	60:20:20:0	**9**	94
7	**2e**	**3a**	52:18:15:15	**10**	93

[a] All reactions were carried out neat except for entry 6 which was carried out in toluene as a solvent.
[b] 20 equiv. of dipolarophile were used except for **3c** (10 equiv.).
[c] **a**:**b**:**c**:**d** ratio corresponds to *anti–trans*/*anti–cis*/*syn–cis*/*syn–trans*.
[d] Ratios of products were determined by HPLC chromatography.
[e] All yields are based on mixtures of adducts isolated by radial chromatography.

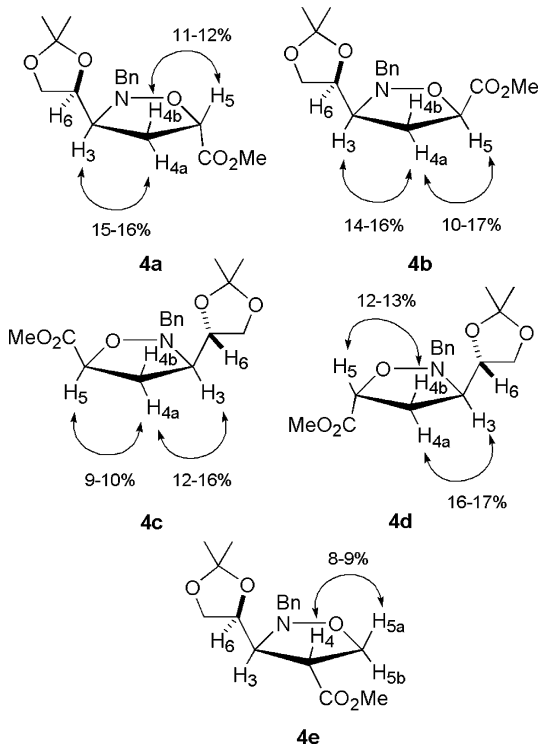


Figure 1. Selected NOE observed for **4** (η_{obs} given as percent of η_{max}).

and **4c** was determined by chemical correlation as discussed below. For the 3,4-regioisomer **4e**, although the *cis*/*trans* stereochemistry has been confirmed by NOE experiments, the assignment of the absolute configuration is only tentative.

A survey of reported stereoselective nitrone cycloaddition reactions with α-alkoxy nitrones indicates that substituents at both the nitrone nitrogen and the dipolarophile influence the steric course of the reaction.[19] Armed with this observation we studied differentially substituted nitrones and acrylates (Scheme 2). The results are collected in Table 1.

When *tert*-butyl acrylate was employed as dipolarophile (entry 2), the reaction showed similar diastereoselectivity as was observed with **3a**. In addition, lower chemical yields were obtained for this reaction due to considerable thermally induced polymerization of the dipolarophile.[20] Increasing the bulk of the nitrogen substituent of the nitrone led to a considerable lack of selectivity (entry 3). No substantial changes were observed with nitrone **2e** (entry 7). Double chiral induction experiments were also carried out (entries 4–6) and in the case of cycloaddition between nitrone **2c** and methyl acrylate **3a**, an increasing amount of the major adduct **8a** was obtained (entry 4), the reaction showing good diastereofacial selectivity (*anti*/*syn*, 90:10). No selectivity was observed with nitrone **2d** (entry 5). With nitrone **2a**, a better diastereofacial selectivity was obtained by using the chiral acrylate **3c** (entry 6).

Not all the isomeric cycloadducts corresponding to entries 2–7 in Table 1 could be separated, and the yields reported in Table 1 refer to the yield of the mixture of isomers after purification of the crude product by column chromatography. The isomeric ratio was measured by NMR spectroscopy or HPLC, when possible. Compounds **5a**, **5d**, **6a**, **7a–d**, **8a–c**, **9a** and **10a–d** were separated and fully characterized (see Section 4).

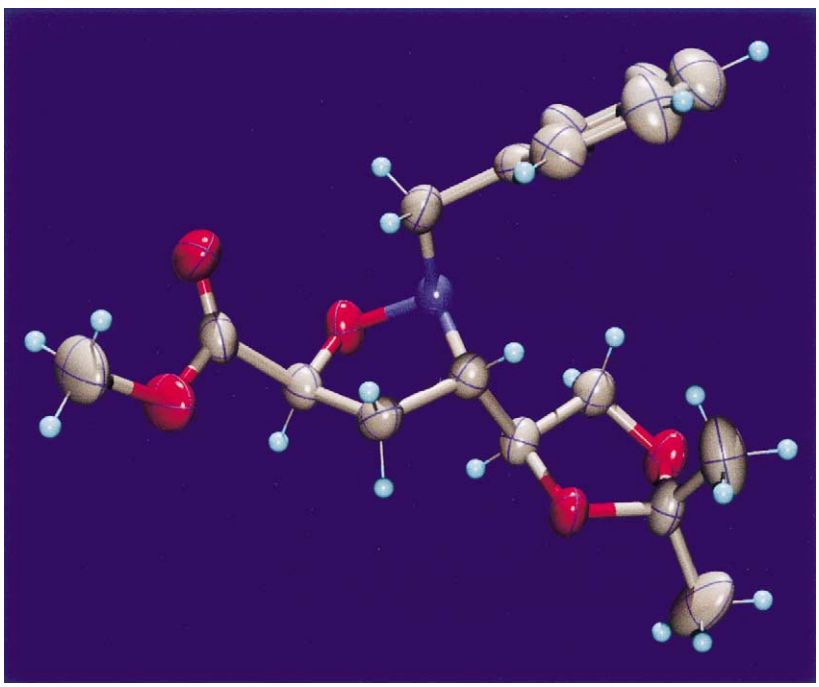
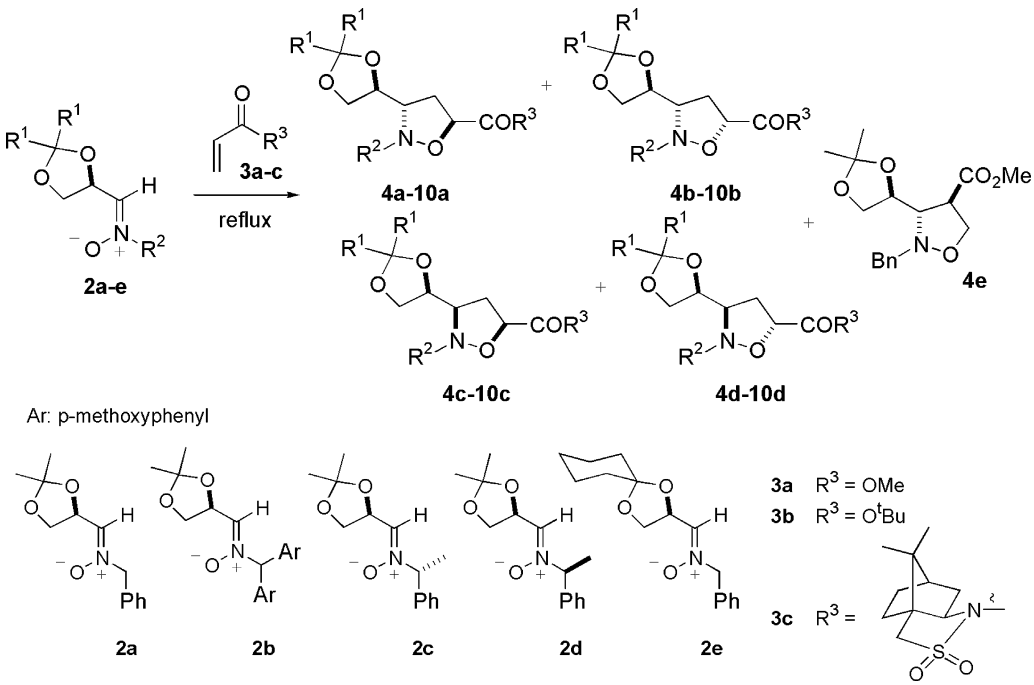


Figure 2. Perspective view (ORTEP) of **4a**. Non-hydrogen atoms are drawn as 50% thermal ellipsoids while hydrogens are drawn at an arbitrary size. Only the atoms refined with anisotropic thermal parameters are drawn with the principal axes indicated; the isotropic atoms are represented as simple circles.



Scheme 2.

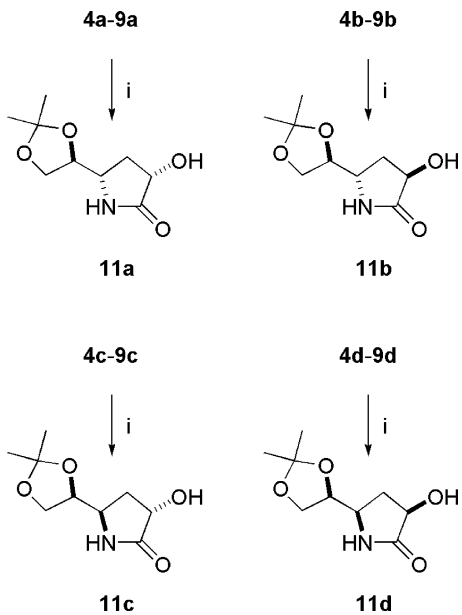
The stereochemical assignments of compounds **5–9** were made by their further conversion into the corresponding 3-hydroxy-2-pyrrolidinones **11**, which can also be obtained in pure form from compounds **4a–d** (Scheme 3). Both isolated compounds and mixtures of adducts were cyclized into **11**. In all instances the observed ratio of isomers determined by HPLC was maintained after the cyclization process. In the case of cyclization of mixtures of isomers, compounds **11** were more easily separated by chromatographic methods than the precursor isoxazolidines. In the case of compounds **10a–d**, the configurational assignment was made by transformation of pure compounds into the corresponding isopropylidene derivatives **4a–d** (Scheme 4).

The absolute configuration of the *cis*-isomers **11a** and **11d** was known since the isoxazolidine precursors (**4a** and **4d**, respectively) had been unequivocally identified by NMR spectroscopy and X-ray analysis, as indicated above. The stereoconfiguration of *trans*-isomers **11b** and **11c** was determined by transformation of **11b** into the corresponding *p*-nitrobenzoyl derivative **12** (Scheme 5). This compound proved to be identical to that obtained from **11a** by Mitsunobu reaction with *p*-nitrobenzoic acid.

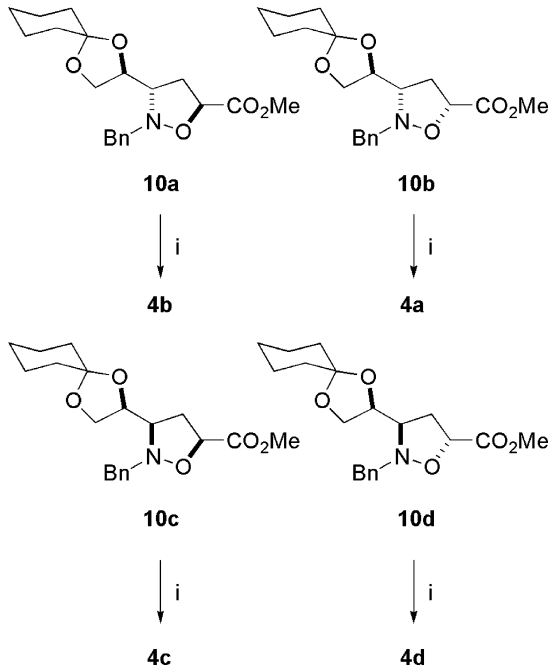
Since the absolute configuration of **11a** was known, the reactions shown in Scheme 5 demonstrated the *anti* relative configuration between the dioxolane ring and the isoxazolidine ring in **11b**. Thus, the absolute configurations of **11b** and, by extension, that of **11c** were also confirmed. Complementary NOE experiments performed on compounds **11a–d** and **12** are fully consistent with the relative *cis*/*trans* assignments made for C(3) and C(5) substituents of the pyrrolidinone ring.

2.2. Synthesis of 4-hydroxy pyroglutamic acid derivatives

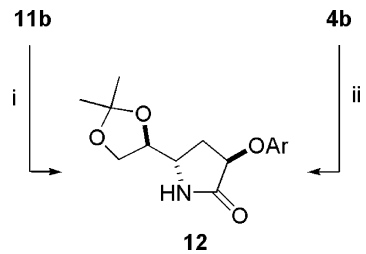
Our initial target was the isoxazolidine **16**, from which pyroglutamic acid **1b** can be obtained by hydrogenolytic *N–O* bond cleavage and subsequent cyclization.[21] In a first attempt, the conversion of the major adduct of the cycloaddition **4a** to **14** was accomplished in two steps by using catalytic *p*-toluenesulfonic



Scheme 3. (i) H_2/Pd(OH)$_2$–C/MeOH/150 bar/24 h.



Scheme 4. (i) (1) HCl/MeOH; (2) acetone/*p*-TosOH/$MgSO_4$.



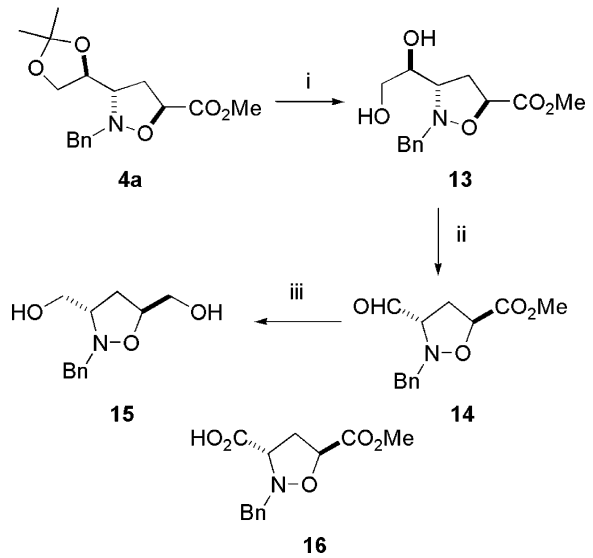
Scheme 5. (i) 4-Nitrobenzoyl chloride/Py/CH_2Cl_2; (ii) 4-nitrobenzoic acid/DIAD. Ar: *p*-nitrobenzoyl.

acid in MeOH and subsequent treatment of the resulting 1,2-diol **13** with $NaIO_4$ (Scheme 6).

Unfortunately, attempted oxidation of formyl isoxazolidine **14** with $KMnO_4$, $NaClO_2$ or TEMPO/BAIB led to extensive decomposition. Alternatively, we explored the oxidation of the completely reduced diol **15**, obtained by reduction of **14** with sodium borohydride. Also in this case, all the oxidation conditions examined failed. These unsuccessful results are probably due to the presence of a basic nitrogen, which may suffer collateral oxidations. Therefore, we decided to change the strategy and to form the pyrrolidine ring before oxidizing the dioxolane moiety.

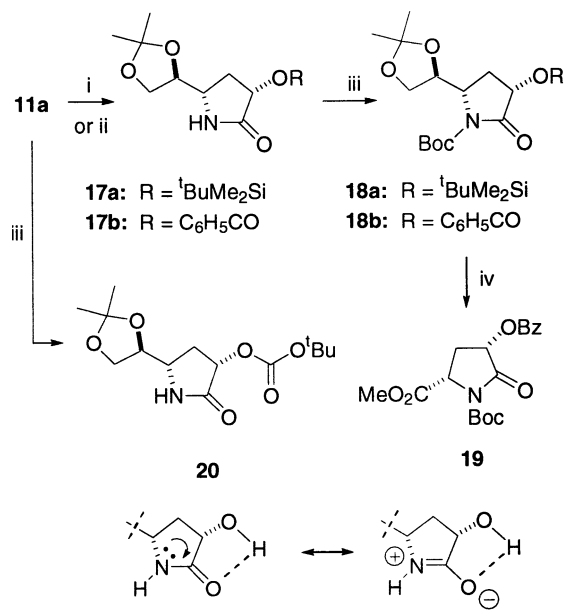
The pyrrolidinone derivative **11a** was protected with both *tert*-butyldimethylsilyl and benzoyl groups to give compounds **17a** and **17b**, respectively. These products were treated with di-*tert*-butyldicarbonate to afford the completely protected pyrrolidinones **18a** and **18b** (Scheme 7).

Attempts to introduce the Boc group at the nitrogen atom prior to *O*-protection only led to *O*-*tert*-butoxycarbonyl derivative **20**.[22] The failure of **11a** to undergo *N*-protection can be rationalized by the presence of an intramolecular hydrogen bond interaction which compromises the lone pair of the lactam nitrogen.



Scheme 6. (i) MeOH, *p*-TosOH; (ii) $NaIO_4$; (iii) $NaBH_4$.

Exposure of **18a** to the acidic conditions needed for the transformation of the dioxolane ring into the carboxyl group (the first step should be deacetalyzation) led to loss of the TBS group. On the other hand, release of the carboxylic function could be made by treatment of **18b** with periodic acid and subsequent in situ oxidation of the resulting aldehyde with sodium chlorite, according to a protocol previously described by us.[14b] After esterification with diazomethane the protected (2*S*,4*S*)-4-hydroxy pyroglutamic acid **19** was obtained.



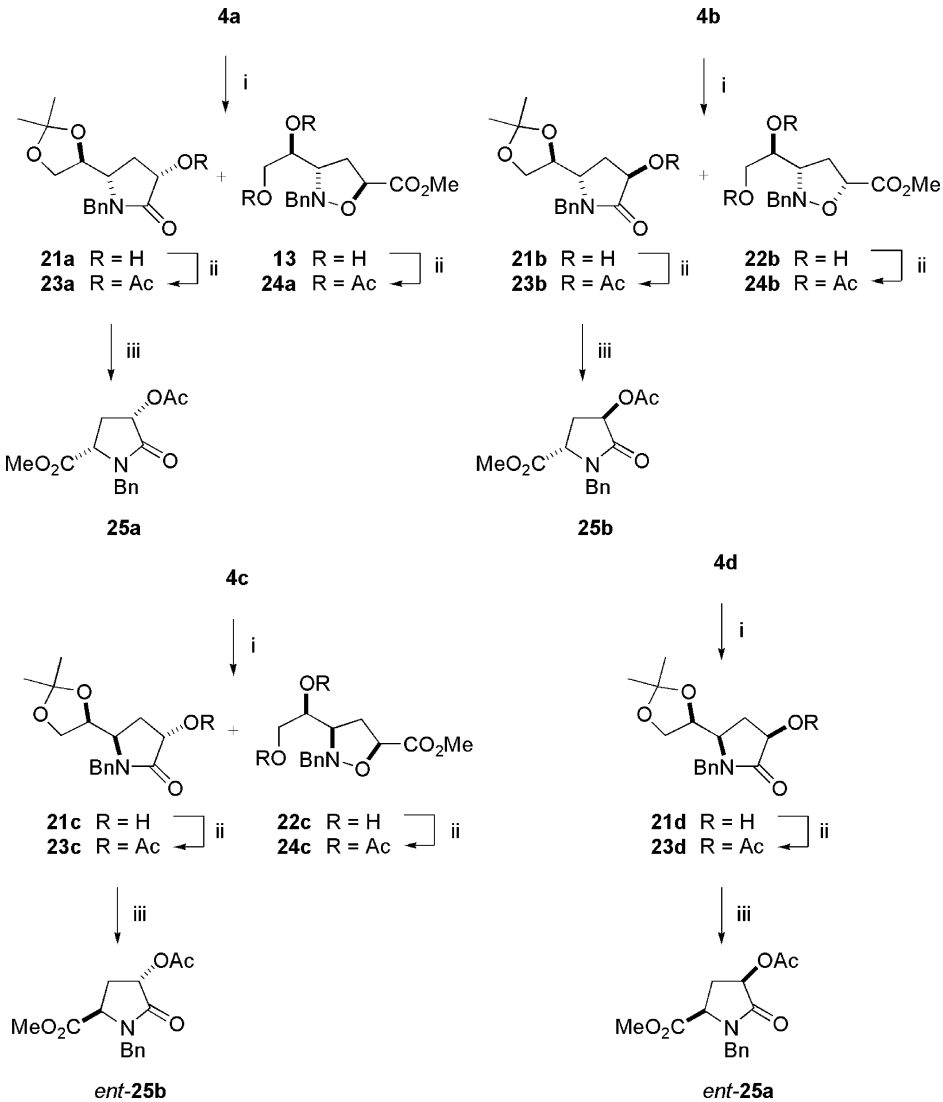
Scheme 7. (i) TBSCl, DMF; (ii) PhCOCl, CH_2Cl_2; (iii) Boc_2O, DMAP; (iv) H_5IO_6, then $NaClO_2$, NaH_2PO_4, then CH_2N_2.

Nevertheless, the protecting groups present in **19** cannot be considered to be orthogonal, since two ester functionalities are present in the molecule. As a consequence, competitive reactions might be found in further synthetic transformations. In order to avoid these troubles a different protecting group system was studied.

As an alternative, it is also possible to reduce the *N–O* bond in adducts **4** without debenzylating the nitrogen atom. Thus, treatment of the major adduct **4a** with zinc in acidic media provided a mixture of pyrrolidinone **21a** and deprotected isoxazolidine **13** (Scheme 8). Because of the nature of this reduction reaction, we were unable to find conditions that avoided concomitant deprotection of the acetonide moiety, although in any case the yield of **13** was higher than 10%, the total chemical yield of the reaction being 86%.

Due to difficult chromatographic separation, purification of compounds **21a** and **13** was made as the corresponding acetylated derivatives **23a** and **24a**. This protocol was repeated for all adducts obtained from the cycloaddition reaction (Scheme 8). Also, for the reduction of adducts **4b** and **4c** minor amounts of deacetalyzed isoxazolidines **22b** and **22c** were obtained, respectively. Only reduction of **4d** afforded pure pyrrolidinone **21d**. In all cases, the products were isolated and fully characterized as the corresponding acetylated derivatives **23b–d**.

Finally, all of the possible isomers of 4-hydroxy pyroglutamic acid were prepared by unmasking the carboxyl group. Conversion of the dioxolane moiety into the carboxylic functionality was achieved by treatment of compounds **23a–d** with periodic acid and sodium chlorite, as described above for compound **18b**. Both **25a** and **25b**, and their antipodes were prepared. Compounds **25b** and ent-**25a** had been prepared previously in our laboratories.[13] Thus, this also served to confirm previous configurational assignments. The orthogonal protection of compounds **25** should allow their further use as building blocks in organic synthesis.

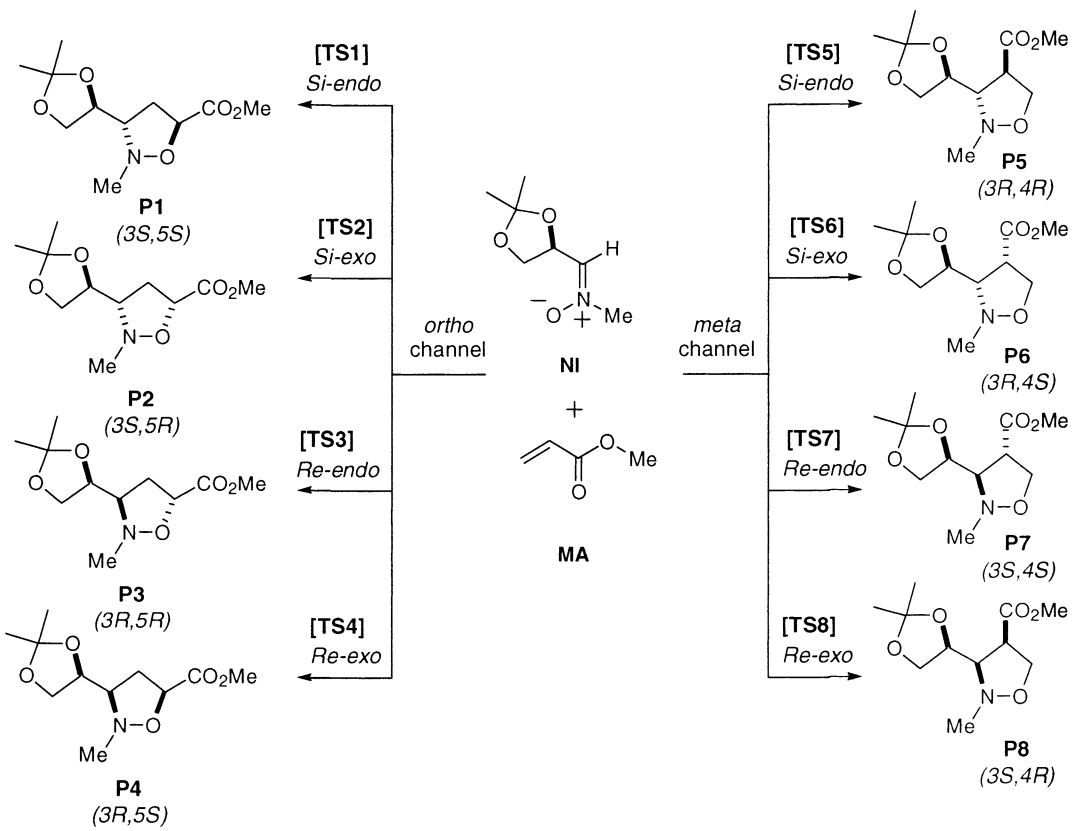


Scheme 8. (i) Zn, AcOH; (ii) Ac_2O, Py; (iii) H_5IO_6, then $NaClO_2$, NaH_2PO_4, then CH_2N_2.

2.3. Theoretical study

In order to rationalize the above 1,3-dipolar cycloadditions we have also performed a computational study of the reaction between **2a** and **3a** using transition state (TS) modelling. Several studies concerning 1,3-dipolar cycloadditions of nitrones with electron-rich[23] and electron-poor[24] dipolarophiles have recently been carried out.[25] From these and other[26–28] related work, we found B3LYP/6-31G(d) level of theory to be quite promising in this respect. Therefore, stationery points (reactants, transition structures and products) were fully characterized[29] as minima or first-order saddle points by diagonalizing the Hessian matrices of the optimized structures at that level.[30] All transition structures were found to have only one negative eigenvalue with the corresponding eigenvector involving the formation of the newly created C–C and C–O bonds. Vibrational frequencies were calculated (1 atm, 298.15 K) for all B3LYP/6-31G(d) optimized structures and used, unscaled, to compute both ZPVE and activation energies. The only simplification of the calculations consisted of replacement of the benzyl group by a methyl group.

We studied all types of selectivity, i.e. regio- and diastereoselectivity, the latter including both *endo*/*exo* and π-facial selectivity. Consequently, a total of eight transition states leading to the eight corresponding cycloadducts, have been located. For each transition state the most stable conformation of the dioxolane ring has been chosen. We considered two reaction channels, *ortho* and *meta*, corresponding to the formation of 3,5- and 3,4-disubstituted isoxazolidines, respectively. *Endo* and *exo* approaches by *Re* and *Si* faces completed the study. The nomenclature used for defining stationary points is given in Scheme 9. Starting from **TS1**–**TS8**, the minima associated with the final cycloadducts, **P1**–**P8** have also been located. The optimized geometries of transition states **TS1**–**TS4**, leading to the formation of the 3,5-cycloadducts, are displayed[31] in Fig. 3 (the geometries of **TS5**–**TS8**, **P1**–**P8** and the reagents are available from the authors upon request). The values of total and relative energies for the different stationery points as well as selected geometrical parameters are given in Table 2. In all cases the cycloaddition reactions are exothermic in the range of −17 to −20 kcal/mol, the most stable product being the (3*R*,5*S*)-isomer. Slightly higher energy differences are observed for 3,5-cycloadducts (*ortho* channel) with respect to the reagents, than for 3,4-cycloadducts (*meta* channel). Clearly, the most favoured reaction channel corresponds to the *ortho* one, through an *endo* approach by the *Si* face of the nitrone. The energy activation value for the corresponding transition state **TS1** is 11.7 kcal/mol. From the analysis of the other activation energies, in several cases not different enough for the calculation errors, a mixture of products can be expected. Thus, although **TS6** and **TS8** can be discarded, very close energy barriers are observed for **TS2**, **TS3**, **TS4**, **TS5** and **TS7** (0.4 kcal/mol maximum difference).



Scheme 9.

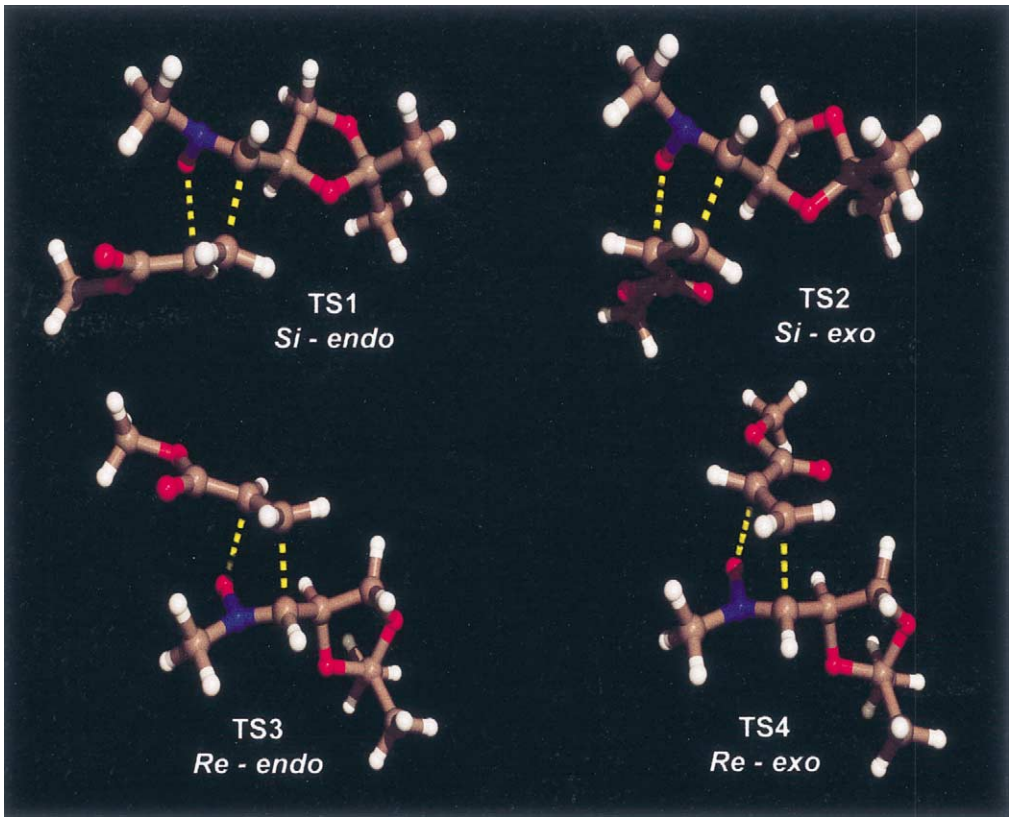


Figure 3. Optimized (B3LYP/6-31G(d) transition structures (bond lengths in Å) for cycloaddition of nitrone **2a** and methyl acrylate **3a**. Only transition structures, **TS1**, **TS2**, **TS3** and **TS4**, leading to 3,5-regiosiomers are shown.

Table 2. Total energies (au), relative energies (kcal/mol) and selected geometrical parameters for the reactants, transition structures and products of the cycloaddition between **NI** and **MA**

	Total energy	Relative energy[a]	O1–N2	N2–C3	C4–C5	O1–C5	O1–C4	C3–C4	C3–C5	*v* imag
NI	−554.696533		1.280	1.306	–	–	–	–	–	–
MA	−306.365295		–	–	1.335	–	–	–	–	–
TS1	−861.043148	11.7	1.285	1.352	1.390	2.337	–	2.053	–	−395.1
TS2	−861.041232	12.9	1.288	1.350	1.389	2.320	–	2.081	–	−397.0
TS3	−861.040746	13.2	1.281	1.352	1.390	2.291	–	2.086	–	−378.8
TS4	−861.040979	13.1	1.282	1.353	1.389	2.295	–	2.102	–	−378.7
TS5	−861.041129	13.0	1.311	1.337	1.400	–	1.961	–	2.288	−418.5
TS6	−861.038162	14.9	1.315	1.335	1.400	–	1.948	–	2.340	−416.6
TS7	−861.041445	12.8	1.313	1.332	1.404	–	1.883	–	2.369	−388.7
TS8	−861.034063	17.4	1.313	1.333	1.406	–	1.882	–	2.404	−378.7
P1	−861.091394	−18.6	1.479	1.476	1.535	1.414	–	1.533	–	–
P2	−861.088992	−17.0	1.476	1.492	1.530	1.416	–	1.549	–	–
P3	−861.091521	−18.6	1.485	1.473	1.538	1.411	–	1.533	–	–
P4	−861.093299	−19.7	1.470	1.480	1.544	1.413	–	1.549	–	–
P5	−861.090914	−18.3	1.440	1.476	1.546	–	1.435	–	1.566	–
P6	−861.090124	−17.8	1.438	1.467	1.544	–	1.445	–	1.569	–
P7	−861.090188	−17.8	1.464	1.485	1.536	–	1.418	–	1.545	–
P8	−861.087840	−16.3	1.464	1.478	1.556	–	1.414	–	1.569	–

[a] Relative to **NI**+**MA**.

These results are in agreement with the experimental observations, since the energy of **TS1** is only 1.2 kcal/mol higher than that of **TS2**, thus justifying the preferential, but not only, formation of **P1**. However, the proximity of energy values mentioned above means that the experimentally observed 3,5-regioselectivity cannot be said to be completely predictable by B3LYP/6-31G(d) calculations. Nevertheless, DFT calculations are the only ones that correctly predicted the preferential formation of **P1**. Hartree–Fock calculations or DFT single point calculations using the same basis set (6-31G(d)) suggest the formation of other cycloadducts (data corresponding to lower level calculations are available from the authors upon request). This strong

dependence on the method for predicting regioselectivity in 1,3-dipolar cycloadditions of nitrones has previously been described and discussed by Marco and Domingo,[25] and Cossio.[28]

The geometry of the transition structures is consistent with a rather asynchronous process. For **TS1**–**TS4** (*ortho* channel), the C–O forming bond is longer than the C–C forming bond. On the other hand, for **TS5**–**TS8** (*meta* channel), the C–C bond is longer than the C–O bond. Although differences of values of forming bonds are not comparable for measuring asynchronicity since C–O bonds are shorter than C–C bonds, what is clear is that the cycloaddition reaction has a high character of *Michael addition* of the nitrone to the dipolarophile.[32] In all cases the shorter forming bond corresponds to that in which C(3) of methyl acrylate is involved. Marco and Domingo[25] have described this observation previously for other electron-poor dipolarophiles.

The imaginary frequencies for the transition states are in the range of −378.7 to −418.5, indicating that the processes are associated with displacement of heavy atoms. Those values corresponding to the *ortho* channel (−378.7 to −397.0) are slightly lower than those corresponding to the *meta* channel (−388.7 to −418.45).

3. Conclusions

We have studied in detail the stereoselective 1,3-dipolar cycloadditions of D-glyceraldehyde-derived nitrones with methyl acrylate and other dipolarophiles. This study has allowed us to assign unequivocally the absolute configuration of the obtained adducts. The observed regio- and stereochemical results can be explained by means of computational methods using density functional theory. In addition, the present method offers a facile route for the stereoselective preparation of protected (2*S*,4*S*)-4-hydroxy pyroglutamic acids. Since the (2*R*,4*R*)- and (2*S*,4*R*)-isomers can be readily prepared as described before by us[13] and others,[10] respectively, the present strategy provides a complementary method for constructing advanced synthetic intermediates such as polyfunctionalized pyrrolidines.

4. Experimental

The reaction flasks and other glass equipment were heated in an oven at 130°C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the position of the spots was detected with 254 nm UV light or by spraying with one of the following staining systems: 50% methanolic sulfuric acid, 5% ethanolic phosphomolybdic acid and iodine. Preparative flash column chromatography was performed on silica gel (40–60 microns) columns. Preparative medium pressure liquid chromatography (MPLC) was performed on a Buchi B-680 chromatography system using dry-filled columns with silica gel (10–15 microns) as stationary phase, and the eluting solvents were delivered by the pump at a flow rate of 16–20 mL min^{-1}. Preparative centrifugally accelerated radial thin-layer chromatography (PCAR-TLC) was performed with a Chromatotron® Model 7924 T (Harrison Research, Palo Alto, CA, USA); the rotors (1 or 2 mm layer thickness) were coated with silica gel Merck grade type 7749, TLC grade, with binder and fluorescence indicator (Aldrich 34,644-6) and the eluting solvents were delivered by the pump at a flow rate of 0.5–1.5 mL min^{-1}. All solvents used for preparative chromatography were distilled prior to use. HPLC analyses were carried out using a Waters 2695 Alliance System, peaks being detected with a 2996 photodiode array detector. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity or on a Bruker 300 instrument in $CDCl_3$ at 55°C. Chemical shifts are reported in ppm (δ) relative to $CHCl_3$ ($\delta = 7.26$) in $CDCl_3$. Optical rotations were obtained at 25°C on a Perkin–Elmer 241 polarimeter. Elemental analyses were performed on a Perkin Elmer 240B microanalyzer.

4.1. 1,3-Dipolar cycloaddition of nitrones 2 with acrylates 3. General procedure

The corresponding nitrone (20 mmol) was dissolved in acrylate (20 equiv.) and the resulting solution was stirred under reflux until no more nitrone was observed (TLC). (In the case of cycloaddition with acrylamide **3c**, the reaction was conducted in toluene (600 mL) at reflux.) The reaction mixture was evaporated to dryness and the residue purified by MPLC to give the adducts (eluent is given in brackets). In the case of nitrone **2a** the reaction was repeated with 10.6 g (45 mmol) of starting material and the same results were obtained.

4.1.1. (3*S*,5*S*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-isoxazolidine-5-carboxylic acid methyl ester 4a. (hexane/EtOAc, 90:10); 3.856 g (60%); mp 72–74°C; $[\alpha]_D^{25}$ +20 (*c* 0.17, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.37 (s, 3H), 2.62 (ddd, 1H, $J = 2.2$, 7.7, 15.5 Hz), 2.75 (ddd, 1H, $J = 7.3$, 8.4, 15.5 Hz), 3.23 (ddd, 1H, $J = 2.2$, 7.3, 8.6 Hz), 3.50 (dd, 1H, $J = 5.1$, 8.3 Hz), 3.74 (s, 3H), 3.76 (d, 1H, $J = 12.9$ Hz), 3.91 (ddd, 1H, $J = 5.1$, 6.2, 8.6 Hz), 4.00 (dd, 1H, $J = 6.2$, 8.3 Hz), 4.21 (d, 1H, $J = 12.9$ Hz), 4.58 (dd, 1H, $J = 7.7$, 8.4 Hz), 7.30–7.50 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 25.2, 26.9, 34.2, 52.6, 62.7, 67.4, 68.2, 75.5, 77.3, 109.6, 127.8, 128.6, 129.4, 137.0, 173.2. Anal. calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.48; H, 7.11; N, 4.49%.

4.1.2. (3*S*,5*R*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-isoxazolidine-5-carboxylic acid methyl ester 4b. (hexane/EtOAc, 90:10); 1.414 g (22%); oil; $[\alpha]_D^{25}$ −12 (*c* 0.18, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.38 (s, 3H), 2.56 (ddd, 1H, $J = 2.7$, 5.6, 13.3 Hz), 2.79 (ddd, 1H, $J = 8.0$, 9.9, 13.3 Hz), 3.16 (ddd, 1H, $J = 2.7$, 8.0, 8.3 Hz), 3.51 (dd, 1H, $J = 5.3$, 8.2 Hz), 3.77 (s, 3H), 3.82 (d, 1H, $J = 12.9$ Hz), 4.00 (dd, 1H, $J = 5.3$, 8.2 Hz), 4.04 (d, 1H, $J = 12.9$ Hz), 4.05 (ddd, 1H, $J = 5.3$, 6.2, 8.3 Hz), 4.79 (dd, 1H, $J = 5.6$, 9.9 Hz), 7.30–7.50 (m, 5H).

^{13}C NMR ($CDCl_3$) δ 25.2, 26.8, 34.7, 52.4, 61.3, 66.4, 67.9, 75.5, 76.3, 109.2, 127.8, 128.5, 129.1, 136.2, 171.5. Anal. calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.46; H, 7.38; N, 4.25%.

4.1.3. (3*R*,5*S*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-isoxazolidine-5-carboxylic acid methyl ester 4c. (hexane/EtOAc, 90:10); 0.643 g (10%); mp 40–42°C; $[\alpha]_D^{25}$ +61 (*c* 0.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.38 (s, 3H), 2.25 (ddd, 1H, J=5.5, 6.5, 13.2 Hz), 2.58 (ddd, 1H, J=8.5, 9.1, 13.2 Hz), 3.08 (dd, 1H, J=6.5, 8.5 Hz), 3.71 (dd, 1H, J=6.8, 8.0 Hz), 3.75 (s, 3H), 4.00 (d, 1H, J=14.5 Hz), 4.00 (dd, 1H, J=6.4, 8.0 Hz), 4.10 (ddd, 1H, J=6.4, 6.8, 8.0 Hz), 4.36 (d, 1H, J=14.5 Hz), 4.57 (dd, 1H, J=5.5, 9.1 Hz), 7.19–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 25.1, 26.6, 34.8, 52.1, 60.8, 66.6, 66.9, 74.2, 76.8, 109.8, 127.1, 128.1, 129.3, 136.9, 172.2. Anal. calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.65; H, 7.44; N, 4.28%.

4.1.4. (3*R*,5*R*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-isoxazolidine-5-carboxylic acid methyl ester 4d. (hexane/EtOAc, 90:10); 0.193 g (3%); oil; $[\alpha]_D^{25}$ +57 (*c* 0.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.39 (s, 3H), 2.35 (ddd, 1H, J=7.0, 9.1, 15.9 Hz), 2.50 (ddd, 1H, J=5.5, 7.6, 15.9 Hz), 3.25 (q, 1H, J=7.3 Hz), 3.73 (dd, 1H, J=6.5, 8.3 Hz), 3.76 (s, 3H), 3.98 (dd, 1H, J=6.5, 8.3 Hz), 4.08 (q, 1H, J=6.8 Hz), 4.14 (d, 1H, J=13.6 Hz), 4.20 (d, 1H, J=13.6 Hz), 4.51 (dd, 1H, J=5.5, 9.1 Hz), 7.29–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 25.2, 26.8, 33.9, 53.0, 62.4, 66.5, 67.8, 75.4, 75.9, 109.9, 127.4, 128.3, 129.2, 137.1, 172.0. Anal. calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.32; H, 7.32; N, 4.50%.

4.1.5. (3*S*,4*R*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-isoxazolidine-4-carboxylic acid methyl ester 4e. (hexane/EtOAc, 90:10); traces (when the reaction was conducted with 10 g of **2a**, ca. 80 mg (about 0.6%) of **4e** could be isolated); white foam; $[\alpha]_D$ +18 (*c* 0.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.35 (s, 3H), 3.24 (ddd, 1H, J=4.8, 6.0, 8.8 Hz), 3.56 (dd, 1H, J=4.8, 6.2 Hz), 3.74 (s, 3H), 3.80 (dd, 1H, J=6.0, 8.8 Hz), 3.99 (dd, 1H, J=6.0, 8.8 Hz), 4.10 (q, 1H, J=6.0 Hz), 4.12 (d, 2H, J=14.8 Hz), 4.13 (t, 1H, J=8.8 Hz), 4.25 (dd, 1H, J=7.0, 8.8 Hz), 7.24–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 24.6, 26.2, 49.9, 52.4, 53.7, 60.7, 65.9, 68.9, 69.6, 109.5, 127.5, 128.3, 129.3, 136.7, 173.2. Anal. calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.39; H, 7.41; N, 4.58%.

4.1.6. (3*S*,5*S*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)]-isoxazolidine-5-carboxylic acid *tert*-butyl ester 5a. (hexane/EtOAc, 85:15); 2.542 g (35%); oil; $[\alpha]_D^{25}$ +33 (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.32 (s, 3H), 1.49 (s, 9H), 2.62 (dt, 1H, J=7.6, 12.9, 12.7 Hz); 2.73 (ddd, 1H, J=2.0, 8.5, 12.9 Hz), 3.22 (dt, 1H, J=2.0, 7.4 Hz), 3.50 (dd, 1H, J=5.2, 8.3 Hz), 3.79 (d, 1H, J=13.3 Hz), 3.93 (ddd, 1H, J=5.2, 6.1, 7.4 Hz), 4.01 (dd, 1H, J=6.1, 8.3 Hz), 4.26 (d, 1H, J=13.3 Hz), 4.50 (t, 1H, J=7.3 Hz), 7.26–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 25.2, 26.8, 28.0, 34.1, 62.7, 67.2, 68.1, 75.4, 78.0, 81.9, 109.4, 127.6, 128.4, 129.3, 137.1, 171.8. Anal. calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 65.96; H, 8.11; N, 3.69%.

4.1.7. (3*S*,5*R*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)]-isoxazolidine-5-carboxylic acid *tert*-butyl ester 5b and (3*R*,5*S*)-2-benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)]-isoxazolidine-5-carboxylic acid *tert*-butyl ester 5c. (hexane/EtOAc, 85:15); 1.743 g (24%) of a mixture of **5b** and **5c** was obtained: **5b** (selected signals): ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.39 (s, 3H), 1.48 (s, 9H), 2.26 (ddd, 1H, J=4.8, 7.2, 12.7 Hz); 2.74 (ddd, 1H, J=8.0, 9.5, 12.7 Hz), 3.16 (q, 1H, J=7.6 Hz), 3.50 (dd, 1H, J=5.1, 8.1 Hz), 3.95 (d, 1H, J=13.8 Hz), 4.10–4.28 (m, 2H), 4.29 (d, 1H, J=13.8 Hz), 4.49 (dd, 1H, J=4.2, 8.1 Hz), 7.20–7.50 (m, 5H).

5c (selected signals): ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 6H), 1.47 (s, 9H), 2.49–2.61 (m, 2H), 3.19 (dt, 1H, J=2.4, 7.2 Hz), 3.74 (dd, 1H, J=6.4, 8.3 Hz), 3.84 (d, 1H, J=13.3 Hz), 4.10–4.30 (m, 2H), 4.32 (d, 1H, J=13.3 Hz), 4.64 (dd, 1H, J=4.8, 9.5 Hz), 7.20–7.50 (m, 5H).

4.1.8. (3*R*,5*R*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)]-isoxazolidine-5-carboxylic acid *tert*-butyl ester 5d. (hexane/EtOAc, 85:15); 0.508 g (7%); oil; $[\alpha]_D^{25}$ +44 (*c* 0.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.39 (s, 3H), 1.49 (s, 9H), 2.36 (ddd, 1H, J=7.1, 8.8, 12.7 Hz); 2.45 (ddd, 1H, J=5.6, 7.6, 12.7 Hz), 3.24 (q, 1H, J=7.4 Hz), 3.71 (dd, 1H, J=6.9, 8.0 Hz), 4.00 (t, 1H, J=8.1 Hz), 4.18 (q, 1H, J=6.6 Hz), 4.20 (s, 2H), 4.42 (dd, 1H, J=5.6, 8.8 Hz), 7.29–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 25.3, 26.5, 28.0, 35.2, 62.7, 66.3, 66.6, 76.5, 76.8, 81.9, 109.7, 127.3, 128.3, 129.2, 137.6, 171.2. Anal. calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 66.13; H, 8.25; N, 3.96%.

4.1.9. (3*S*,5*S*)-2-[Bis-(4-methoxyphenyl)-methyl]-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-isoxazolidine-5-carboxylic acid methyl ester 6a. (hexane/EtOAc, 80:20); 2.834 g (31%); oil; $[\alpha]_D^{25}$ +28 (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 3H), 1.30 (s, 3H), 2.70–2.80 (m, 2H), 3.35 (ddd, 1H, J=2.9, 4.8, 8.6 Hz), 3.51 (dd, 1H, J=5.7, 8.1 Hz), 3.62 (s, 3H), 3.74 (s, 6H), 3.99 (dt, 1H, J=6.2, 8.6 Hz), 4.10 (dd, 1H, J=6.4, 8.1 Hz), 4.54 (t, 1H, J=8.1 Hz), 4.94 (s, 1H), 6.76–6.84 (m, 4H), 7.22–7.26 (m, 2H), 7.38–7.42 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 25.4, 26.7, 33.3, 52.4, 55.2 (2C), 65.7, 68.5, 72.7, 75.7, 77.8, 109.4, 113.7, 114.3, 128.2, 129.0, 133.9, 135.1, 158.3, 159.2, 173.2. Anal. calcd for $C_{25}H_{31}NO_7$: C, 65.63; H, 6.83; N, 3.06. Found: C, 63.70; H, 7.00; N, 3.29%.

4.1.10. (3*S*,5*S*)-3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2-[(1*R*)-1-phenylethyl]-isoxazolidine-5-carboxylic acid methyl ester 7a. (hexane/EtOAc, 90:10); 4.763 g (71%); oil; $[\alpha]_D^{25}$ +79 (*c* 0.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 3H), 1.24 (s, 3H), 1.51 (d, 3H, J=6.3 Hz), 2.55 (ddd, 1H, J=7.5, 8.8, 12.9 Hz), 2.70 (ddd, 1H, J=0.8, 9.6, 12.9 Hz), 3.14 (td, 1H, J=0.8, 8.5 Hz), 3.26 (dd, 1H, J=5.8, 8.5 Hz), 3.79 (s, 3H), 3.83 (ddd, 1H, J=5.8, 6.3, 8.3 Hz), 3.85 (q, 1H, J=6.3 Hz), 3.95 (dd, 1H, J=6.3, 8.5 Hz), 4.60 (dd, 1H, J=7.5, 8.5 Hz), 7.20–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 21.3, 25.2, 26.5, 33.3, 52.1, 65.6, 66.2, 68.2, 75.6, 76.5, 109.1, 127.7, 127.8, 128.6,

142.9, 173.1. Anal. calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.38; H, 7.49; N, 4.02%.

4.1.11. (3*S*,5*R*)-3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2-[(1*R*)-1-phenylethyl]-isoxazolidine-5-carboxylic acid methyl ester 7b. (hexane/EtOAc, 90:10); 0.939 g (14%); oil; $[\alpha]_D^{25}$ +36 (*c* 0.21, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.15 (s, 3H), 1.22 (s, 3H), 1.45 (d, 3H, $J=6.3$ Hz), 2.53 (ddd, 1H, $J=1.8$, 5.5, 13.2 Hz), 2.66 (ddd, 1H, $J=7.7$, 9.9, 13.2 Hz), 3.06 (ddd, 1H, $J=1.8$, 7.7, 8.8 Hz), 3.23 (dd, 1H, $J=5.8$, 9.1 Hz), 3.73 (q, 1H, $J=6.3$ Hz), 3.76 (s, 3H), 3.95 (dd, 1H, $J=6.3$, 9.1 Hz), 3.99 (ddd, 1H, $J=5.8$, 6.3, 8.8 Hz), 4.60 (dd, 1H, $J=5.5$, 9.9 Hz), 7.24–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 21.1, 25.4, 26.8, 34.5, 52.3, 64.2, 65.6, 68.4, 75.7, 76.6, 109.0, 127.9, 128.2, 128.8, 142.4, 171.3. Anal. calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.48; H, 7.77; N, 4.26%.

4.1.12. (3*R*,5*S*)-3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2-[(1*R*)-1-phenylethyl]-isoxazolidine-5-carboxylic acid methyl ester 7c. (hexane/EtOAc, 90:10); 0.537 g (8%); oil. This compound was impurified with 10% of **7d** which could not be separated. ^1H NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.43 (s, 3H), 1.57 (d, 3H, $J=6.8$ Hz), 2.29 (ddd, 1H, $J=5.5$, 8.8, 12.9 Hz), 2.44 (ddd, 1H, $J=6.3$, 8.1, 12.9 Hz), 3.40 (dt, 1H, $J=5.9$, 8.5 Hz), 3.59 (dd, 1H, $J=7.0$, 8.4 Hz), 3.71 (q, 1H, $J=6.8$ Hz), 3.74 (s, 3H), 3.99 (dd, 1H, $J=6.5$, 8.4 Hz), 4.11 (q, 1H, $J=6.6$ Hz), 4.40 (dd, 1H, $J=6.3$, 8.4 Hz), 7.23–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 21.6, 25.4, 26.5, 34.5, 52.0, 62.9, 64.2, 66.5, 74.3, 75.6, 109.7, 127.1, 127.9, 128.6, 142.1, 171.7.

4.1.13. (3*R*,5*R*)-3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2-[(1*R*)-1-phenylethyl]-isoxazolidine-5-carboxylic acid methyl ester 7d. (hexane/EtOAc, 90:10); 0.134 g (2%); oil; $[\alpha]_D^{25}$ +46 (*c* 0.14, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.42 (s, 3H), 1.56 (d, 3H, $J=6.4$ Hz), 2.15 (dt, 1H, $J=6.6$, 12.8 Hz), 2.31 (dt, 1H, $J=8.1$, 12.8 Hz), 3.18 (dt, 1H, $J=6.8$, 7.8 Hz), 3.63 (dd, 1H, $J=6.6$, 8.5 Hz), 3.70 (q, 1H, $J=6.4$ Hz), 3.75 (s, 3H), 3.98 (dd, 1H, $J=6.6$, 8.5 Hz), 4.15 (q, 1H, $J=6.8$ Hz), 4.33 (dd, 1H, $J=6.6$, 8.5 Hz), 7.26–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 20.8, 25.3, 26.7, 35.1, 52.2, 63.5, 63.6, 66.7, 74.3, 75.4, 109.8, 127.4, 128.0, 129.2, 140.7, 171.8. Anal. calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.42; H, 7.41; N, 4.29%.

4.1.14. (3*S*,5*S*)-{2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-isoxazolidin-5-yl}-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-yl)-methanone 9a. (hexane/EtOAc, 80:20); 5.652 g (56%); oil; $[\alpha]_D^{25}$ −8 (*c* 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.93 (s, 3h), 1.10 (s, 3H), 1.31 (s, 3H), 1.34 (s, 3H), 1.50–1.60 (m, 2H), 1.80–1.90 (m, 2H), 2.03 (dd, 1H, $J=8.0$, 13.6 Hz), 2.08–2.12 (m, 1H), 2.38 (ddd, 1H, $J=6.3$, 8.5, 12.9 Hz), 2.70 (ddd, 1H, $J=5.5$, 7.7, 12.9 Hz), 3.32 (t, 1H, $J=7.0$ Hz), 3.35 (d, 1H, $J=13.6$ Hz), 3.46 (d, 1H, $J=13.6$ Hz), 3.68 (dd, 1H, $J=7.0$, 8.2 Hz), 3.85 (dd, 1H, $J=5.2$, 7.7 Hz), 4.00 (dd, 1H, $J=6.6$, 8.2 Hz), 4.10 (q, 1H, $J=7.0$ Hz), 4.17 (d, 1H, $J=14.3$ Hz), 4.23 (d, 1H, $J=14.3$ Hz), 4.97 (dd, 1H, $J=5.2$, 8.5 Hz), 7.20–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 19.1, 19.9, 25.3, 26.3, 26.5, 26.7, 26.9, 36.5, 44.6, 47.8, 48.9, 53.0, 53.8, 61.4, 62.9, 66.5, 68.8, 75.4, 109.4, 127.5, 128.9, 129.3, 136.8, 171.0. Anal. calcd for $C_{26}H_{36}N_2SO_6$: C, 61.88; H, 7.19; N, 5.55. Found: C, 61.74; H, 7.32; N, 5.40%.

4.1.15. (3*S*,5*S*)-2-Benzyl-3-(1,4-dioxa-spiro[4.5]dec-2-yl)-isoxazolidine-5-carboxylic acid methyl ester 10a. (hexane/EtOAc, 85:15); 3.470 g (48%); oil; $[\alpha]_D^{25}$ −1 (*c* 0.22, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.28–1.63 (m, 10H), 2.68 (dt, 1H, $J=7.8$, 12.7 Hz), 2.76 (ddd, 1H, $J=2.0$, 8.3, 12.7 Hz), 3.25 (dt, 1H, $J=2.0$, 7.8 Hz), 3.50 (dd, 1H, $J=5.4$, 8.3 Hz), 3.76 (s, 3H), 3.78 (d, 1H, $J=13.2$ Hz), 3.92 (ddd, 1H, $J=5.4$, 6.3, 7.8 Hz), 4.00 (dd, 1H, $J=6.3$, 8.3 Hz), 4.22 (d, 1H, $J=13.2$ Hz), 4.58 (t, 1H, $J=8.1$), 7.23–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 23.7, 23.9, 25.1, 34.3, 34.8, 36.6, 52.1, 53.8, 62.7, 67.6, 67.7, 75.2, 110.0, 127.5, 128.3, 129.2, 137.1, 172.9. Anal. calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.39; H, 7.50; N, 3.71%.

4.1.16. (3*S*,5*R*)-2-Benzyl-3-(1,4-dioxa-spiro[4.5]dec-2-yl)-isoxazolidine-5-carboxylic acid methyl ester 10b. (hexane/EtOAc, 85:15); 1.229 g (17%); oil; $[\alpha]_D^{25}$ +16 (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.10–1.61 (m, 10H), 2.58 (ddd, 1H, $J=2.9$, 5.5, 13.2 Hz), 2.78 (ddd, 1H, $J=8.3$, 9.8, 13.2 Hz), 3.17 (dt, 1H, $J=2.9$, 8.1 Hz), 3.50 (dd, 1H, $J=4.9$, 8.1 Hz), 3.74 (s, 3H), 3.82 (d, 1H, $J=13.2$ Hz), 3.98 (d, 1H, $J=13.2$ Hz), 4.02 (dd, 1H, $J=5.1$, 8.1 Hz), 4.10 (dt, 1H, $J=5.0$, 8.1 Hz), 4.74 (dd, 1H, $J=5.5$, 9.8 Hz), 7.19–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 23.7, 24.0, 25.1, 34.6, 34.8, 36.6, 52.4, 61.4, 66.6, 67.6, 75.4, 75.9, 109.8, 127.7, 128.5, 129.1, 136.3, 171.5. Anal. calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.32; H, 7.68; N, 3.75%.

4.1.17. (3*R*,5*S*)-2-Benzyl-3-(1,4-dioxa-spiro[4.5]dec-2-yl)-isoxazolidine-5-carboxylic acid methyl ester 10c. (hexane/EtOAc, 85:15); 1.012 g (14%); oil; $[\alpha]_D^{25}$ +2 (*c* 0.31, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.15–1.63 (m, 10H), 2.25 (ddd, 1H, $J=5.4$, 7.3, 12.7 Hz), 2.56 (dt, 1H, $J=8.8$, 12.7 Hz), 3.06 (q, 1H, $J=7.3$ Hz), 3.68 (dd, 1H, $J=6.8$, 8.3 Hz), 3.73 (s, 3H), 4.00 (dd, 1H, $J=6.8$, 8.3 Hz), 4.01 (d, 1H, $J=14.3$ Hz), 4.11 (q, 1H, $J=6.8$ Hz), 4.38 (d, 1H, $J=14.3$ Hz), 4.54 (dd, 1H, $J=5.4$, 8.8 Hz), 7.22–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 23.7, 24.0, 25.1, 34.8, 34.9, 36.4, 52.0, 60.9 (2C), 66.4, 66.9, 74.3, 109.9, 127.3, 128.3, 129.1, 137.3, 173.6. Anal. calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.56; H, 7.59; N, 3.93%.

4.1.18. (3*R*,5*R*)-2-Benzyl-3-(1,4-dioxa-spiro[4.5]dec-2-yl)-isoxazolidine-5-carboxylic acid methyl ester 10d. (hexane/EtOAc, 85:15); 1.012 g (14%); oil; $[\alpha]_D^{25}$ −5 (*c* 0.11, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.29–1.60 (m, 10H), 2.48 (ddd, 1H, $J=4.4$, 7.8, 12.7 Hz), 2.54 (ddd, 1H, $J=8.3$, 9.2, 12.7 Hz), 3.35 (q, 1H, $J=7.8$ Hz), 3.65 (dd, 1H, $J=6.4$, 8.3 Hz), 3.79 (s, 3H), 4.04 (dd, 1H, $J=6.3$, 8.3 Hz), 4.29 (d, 1H, $J=14.1$ Hz), 4.50 (d, 1H, $J=14.1$ Hz), 4.71 (dd, 1H, $J=4.4$, 8.3), 7.25–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 23.5, 24.1, 24.8, 33.8, 34.5, 37.2, 52.9, 55.1, 64.6, 67.5, 69.3, 74.9, 110.1, 127.2, 128.1, 129.3,

137.0, 173.1. Anal. calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.68; H, 7.43; N, 3.80%.

4.2. Synthesis of pyrrolidin-2-ones

4.2.1. (3*S*,5*S*)-5-((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-pyrrolidin-2-one 11a. A solution of **4a** (1.0 g, 3.11 mmol) in methanol (50 mL) was treated with Pearlman's catalyst, $Pd(OH)_2$–C (120 mg), and stirred under hydrogen at room temperature and 2000 psi. After 24 h the reaction mixture was filtered through a pad of Celite, which was washed with methanol. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel (EtOAc/MeOH, 5:1) to afford pure **11a** (0.576 g, 92%) as a white solid; mp 148–149°C; $[\alpha]_D$ −5 (*c* 0.92, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.43 (s, 3H), 1.68 (dt, 1H, $J=8.0$, 16.0 Hz), 2.56 (ddd, 1H, $J=6.8$, 8.3, 16.0 Hz), 3.10 (bs, 1H, ex. D_2O), 3.74 (dddd, 1H, $J=1.8$, 4.4, 6.8, 8.0 Hz), 3.79 (dd, 1H, $J=6.3$, 8.5 Hz), 4.02 (dd, 1H, $J=6.5$, 8.5 Hz), 4.14 (dt, 1H, $J=4.4$, 6.4 Hz), 4.32 (t, 1H, $J=8.2$ Hz), 6.69 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ 24.7, 26.3, 32.3, 52.1, 64.9, 69.1, 77.3, 109.7, 177.8. Anal. calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.60; H, 7.58; N, 7.13%.

The same procedure was applied to **5a** (1.0 g, 2.75 mmol), **6a** (1.0 g, 2.19 mmol), **7a** (1.0 g, 2.98 mmol) and **9a** (1.0 g, 1.98 mmol), and pure **11a** (0.498 g, 90%; 0.405 g, 92%; 0.540 g, 90% and 0.351 g, 88%, respectively) was obtained in all cases, the physical and spectroscopic properties being identical to those obtained for the compound prepared from **4a**.

4.2.2. (3*S*,5*R*)-5-((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-pyrrolidin-2-one 11b. The same procedure described above for the conversion of **4a** to **11a** was applied to **4b** (1.0 g, 3.11 mmol). After flash chromatography (EtOAc/MeOH, 5:1) of the crude product, pure **11b** (0.563, 90%) was obtained as a white solid; mp 118–120°C; $[\alpha]_D^{25}$ −30 (*c* 0.43, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.40 (s, 3H), 2.12 (ddd, 1H, $J=7.6$, 8.6, 16.3 Hz), 2.42 (ddd, 1H, $J=2.6$, 8.4, 16.3 Hz), 3..80 (bs, 1H, ex. D_2O), 3.63 (m, 1H), 3.75 (m, 1H), 4.03 (m, 2H), 4.36 (t, 1H, $J=8.2$ Hz), 7.07 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ 24.9, 26.4, 31.4, 53.3, 65.9, 68.3, 77.4, 109.9, 178.7. Anal. calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.81; H, 7.60; N, 7.08%.

The same procedure was applied to **7b** (0.9 g, 2.68 mmol) and pure **11b** (0.491 g, 91%) was obtained, the physical and spectroscopic properties being identical to those obtained for the compound prepared from **4b**.

4.2.3. (3*R*,5*S*)-5-((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-pyrrolidin-2-one 11c. The same procedure described above for the conversion of **4a** to **11a** was applied to **4c** (0.5 g, 1.56 mmol). After flash chromatography (EtOAc/MeOH, 5:1) of the crude product, pure **11c** (0.292 g, 93%) was obtained as a white solid; mp 112–114°C; $[\alpha]_D^{25}$ −22 (*c* 0.21, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.31 (s, 3H), 1.62 (dt, 1H, $J=7.7$, 12.9 Hz), 2.38 (ddd, 1H, $J=1.5$, 8.1, 12.9 Hz), 3.53 (m, 1H), 3.74 (dd, 1H, $J=5.3$, 8.2 Hz), 4.00, 4.11 (m, 2H), 4.40 (t, 1H, $J=8.0$ Hz), 6.20 (bs, 1H), 7.02 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ 25.0, 26.5, 32.4, 53.6, 65.7, 68.6, 78.9, 109.8, 177.9. Anal. calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.76; H, 7.42; N, 7.25%.

The same procedure was applied to **7c** (0.5 g, 1.49 mmol) and pure **11c** (0.276 g, 92%) was obtained, the physical and spectroscopic properties being identical to those obtained for the compound prepared from **4c**.

4.2.4. (3*R*,5*R*)-5-((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-hydroxypyrrolidin-2-one 11d. The same procedure described above for the conversion of **4a** to **11a** was applied to **4d** (0.150 g, 0.47 mmol). After flash chromatography (EtOAc/MeOH, 5:1) of the crude product, pure **11d** (87 mg, 92%) was obtained as a white solid; mp 133–135°C; $[\alpha]_D^{25}$ −19 (*c* 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.40 (s, 3H), 1.64 (dt, 1H, $J=8.0$, 15.8 Hz), 2.46 (ddd, 1H, $J=6.7$, 8.3, 15.8 Hz), 3.52 (m, 1H), 3.70 (dd, 1H, $J=4.9$, 8.3 Hz), 3.97 (q, 1H, $J=6.7$ Hz), 4.05 (dd, 1H, $J=6.4$, 8.3 Hz), 4.31 (t, 1H, $J=8.3$ Hz), 4.40 (bs, 1H, ex. D_2O), 6.70 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ 25.1, 26.7, 32.3, 53.8, 65.9, 69.0, 79.1, 110.1, 177.4. Anal. calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.91; H, 7.46; N, 6.84%.

The same procedure was applied to **7d** (0.12 g, 0.36 mmol) and pure **11d** (62 mg, 86%) was obtained, the physical and spectroscopic properties being identical to those obtained for the compound prepared from **4d**.

4.3. Transketalization of isoxazolidines 10a–d

A solution of the corresponding isoxazolidine **10** (0.5 g, 1.38 mmol) in dry acetone (50 mL) was treated with *p*-toluensulfonic acid (30 mg, 0.174 mmol) and the resulting solution was stirred at ambient temperature for 8 h, at which time saturated aqueous sodium bicarbonate (10 mL) was added. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc (100 mL) and brine (100 mL). The organic layer was separated, dried over magnesium sulphate and evaporated. The crude product was purified by flash chromatography (hexane/EtOAc, 4:1) to give the corresponding isoxazolidines **4**. Starting from **10a**, **10b**, **10c** and **10d**, compounds **4a** (0.390 g, 88%), **4b** (0.381 g, 86%), **4c** (0.392 g, 88%) and **4d** (0.373 g, 84%) were obtained, respectively. In all cases, the physical and spectroscopic properties of these compounds were identical to those obtained for the corresponding compounds prepared from nitrone **2a**.

4.4. 4-Nitrobenzoic acid (3*R*,5*S*)-5-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxo-pyrrolidin-3-yl ester 12

From **11a**: To a stirred solution of **11a** (0.2 g, 1 mmol), triphenylphosphine (1.28 g, 4.92 mmol) and *p*-nitrobenzoic acid (0.730 g, 4.38 mmol) in dry toluene (30 mL) at ambient temperature was added slowly diisopropylazodicarboxylate (1.30 g, 6.4 mmol). After 6 h, the

reaction mixture was evaporated to dryness and the residue was purified by flash chromatography (hexane/EtOAc, 2:3) to give pure **12** (0.235 g, 67%) as a white foam; $[\alpha]_D^{25}$ −19 (*c* 0.40, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.50 (s, 3H), 2.26 (dt, 1H, $J=8.8$, 13.9 Hz), 2.65 (ddd, 1H, $J=1.8$, 8.5, 13.9 Hz), 3.67 (dd, 1H, $J=5.9$, 8.5 Hz), 3.84 (ddd, 1H, $J=1.8$, 3.7, 8.8 Hz), 4.10 (dd, 1H, $J=7.0$, 8.5 Hz), 4.19 (ddd, 1H, $J=3.7$, 5.9, 7.0 Hz), 5.62 (t, 1H, $J=8.6$ Hz), 6.28 (s, 1H), 7.40–7.51 (m, 2H), 8.00–8.13 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 24.7, 26.4, 30.2, 38.6, 53.0, 67.1, 69.5, 109.9, 125.6, 131.4, 138.3, 151.6, 165.7, 172.1. Anal. calcd for $C_{16}H_{18}N_2O_7$: C, 54.86; H, 5.18; N, 8.00. Found: C, 54.92; H, 5.33; N, 8.42%.

From **11b**: A solution of **11b** (0.2 g, 1 mmol) in dry dichloromethane (20 mL) was treated with 4-nitrobenzoyl chloride (0.223 g, 1.2 mmol) and pyridine (0.158 g, 2 mmol), and the resulting solution was stirred at ambient temperature for 12 h. The reaction mixture was washed sequentially with 2N HCl and saturated aqueous sodium bicarbonate. The organic layer was separated, dried over magnesium sulphate and concentrated to dryness. The residue was purified by radial chromatography (hexane/EtOAc, 2:3) to give pure **12** (0.287 g, 82%). The physical and spectroscopic properties of this compound were identical to those obtained for the compound prepared from **11a**.

4.5. (3*S*,5S)-2-Benzyl-3-formyl-isoxazolidine-5-carboxylic acid methyl ester 14

To a solution of **4a** (0.32 g, 1 mmol) in MeOH (60 mL) was added *p*-TsOH (43 mg, 0.25 mmol) and the resulting solution was heated under reflux for 4 h. The reaction mixture was cooled at room temperature and neutralized with Amberlite IRA-400. The mixture was filtered and the filtrate was evaporated under reduced pressure. The crude diol **13** (^1H NMR ($CDCl_3$+D_2O) δ 2.58 (dt, 1H, $J=7.3$, 13.2 Hz), 2.81 (ddd, 1H, $J=3.4$, 8.8, 13.2 Hz), 3.29 (m, 1H), 3.51 (m, 2H), 3.74 (s, 3H), 3.85 (d, 1H, $J=12.7$ Hz), 4.16 (m, 1H), 4.23 (d, 1H, $J=12.7$ Hz), 4.58 (dd, 1H, $J=7.3$, 8.8 Hz), 7.15–7.32 (m, 5H) was taken up into a 1:1 mixture of MeOH:H_2O (30 mL), cooled at 0°C and treated with $NaIO_4$ (0.214 g, 1 mmol). The resulting suspension was stirred at 0°C for 1 h, filtered and rotatory evaporated to give **14** as a yellow oil (0.19 mg; 78%). ^1H NMR ($CDCl_3$) δ 2.40 (ddd, 1H, $J=2.2$, 4.4, 13.2 Hz), 2.60 (ddd, 1H, $J=6.4$, 8.8, 13.2), 3.54 (m, 1H), 3.74 (s, 3H), 3.78 (d, 1H, $J=12.4$ Hz), 3.82 (d, 1H, $J=12.4$), 4.42 (dd, 1H, $J=4.4$, 8.8 Hz), 7.15–7.45 (m, 5H), 9.42 (bs, 1H). The aldehyde was immediately used in the next step without further purification.

4.6. (3*S*,5*S*)-2-Benzyl-3,5-bis(hydroxymethyl-isoxazolidine 15

A solution of **14** (0.19 g, 0.76 mmol) in aqueous methanol (10 mL) was cooled to 0°C and treated with $NaBH_4$ (0.117 g, 3 mmol). After stirring at the same temperature for 2 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give pure **15** as a light yellow oil (188 mg, 80%). $[\alpha]_D^{25}$ +8 (*c* 0.78, $CHCl_3$); ^1H NMR ($CDCl_3$+D_2O) δ 2.22 (ddd, 1H, $J=1.8$, 7.3, 13.2 Hz), 2.36 (ddd, 1H, $J=3.4$, 8.8, 13.2 Hz), 3.22 (m, 1H), 3.56 (dd, 1H, $J=6.4$, 14.8), 3.59 (dd, 1H, $J=6.2$, 14.8), 3.62 (dd, 1H, $J=6.8$, 14.8 Hz), 3.81 (dd, 1H, $J=6.5$, 14.8), 4.03 (d, 1H, $J=14.4$), 4.12 (d, 1H, $J=14.4$ Hz), 4.21 (m, 1H), 7.15–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 30.0, 32.7, 62.7, 64.1, 66.6, 79.0, 127.8, 128.7, 129.3, 137.8. Anal. calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.70; H, 7.80; N, 6.10%.

4.7. (3*S*,5*S*)-5-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(*tert*-butyldimethylsiloxy)-pyrrolidin-2-one 17a

A solution of **11a** (0.402 g, 2 mmol) in DMF (15 mL) was treated with imidazole (0.756 g) and *tert*-butyldimethylsilyl chloride (0.452 g, 3 mmol). The resulting solution was stirred at 70°C until no more starting material was observed by TLC (ca. 4 h). Methanol (5 mL) and water (50 mL) were added and the resulting mixture was extracted with EtOAc (3×40 mL). The organic layers were combined, dried over magnesium sulfate and evaporated under reduced pressure to give crude **17a**, which was purified by flash chromatography (hexane/EtOAc, 2:3) to afford pure **17a** (0.467 g, 74%) as an oil; $[\alpha]_D^{25}$ +9 (*c* 0.28, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.12 (s, 3H), 0.14 (s, 3H), 0.89 (s, 9H), 1.33 (s, 3H), 1.42 (s, 3H), 1.66 (dt, 1H, $J=7.4$, 13.1 Hz), 2.50 (ddd, 1H, $J=7.1$, 8.1, 13.1 Hz), 3.68 (dt, 1H, $J=4.5$, 7.3 Hz), 3.83 (dd, 1H, $J=6.0$, 8.2 Hz), 4.03 (dd, 1H, $J=6.2$, 8.2 Hz), 4.07 (q, 1H, $J=6.1$ Hz), 4.27 (t, 1H, $J=7.8$ Hz), 6.8 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ −5.2, −4.6, 18.2, 24.9, 25.7, 26.5, 34.1, 51.8, 65.2, 70.1, 77.9, 109.4, 176.5. Anal. calcd for $C_{15}H_{29}NO_4Si$: C, 57.11; H, 9.27; N, 4.44. Found: C, 57.03; H, 9.42; N, 4.37%.

4.8. Benzoic acid (3*S*,5*S*)-5-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxo-pyrrolidin-3-yl ester 17b

The same procedure described above for the conversion of **11b** to **12** was applied to **11a** (0.402 g, 2 mmol). After flash chromatography (hexane/EtOAc, 2:3) of the crude product, pure **17b** (0.519 g, 85%) was obtained as a white foam; $[\alpha]_D^{25}$ +17 (*c* 0.20, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.43 (s, 3H), 1.90 (dt, 1H, $J=7.8$, 13.7 Hz), 2.86 (ddd, 1H, $J=6.8$, 8.8, 13.7 Hz), 3.84 (dt, 1H, $J=6.7$, 8.0 Hz), 3.88 (dd, 1H, $J=6.4$, 8.3 Hz), 4.05 (dd, 1H, $J=6.4$, 8.3 Hz), 4.18 (q, 1H, $J=6.4$ Hz), 5.54 (t, 1H, $J=8.3$ Hz), 7.40 (bs, 1H), 7.48–7.52 (m, 3H), 7.59–7.63 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 24.8, 26.4, 30.5, 38.1, 52.2, 65.0, 70.6, 109.8, 128.4, 129.2, 129.9, 1233.4, 165.8, 173.2. Anal. calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.10; H, 6.11; N, 4.70%.

4.9. (3*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-5-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(*tert*-butyldimethylsiloxy)-pyrrolidin-2-one 18a

A solution of **17a** (0.4 g, 1.27 mmol) in CH_2Cl_2 (20 mL) was treated with Boc_2O (0.44 g, 2 mmol), Et_3N (0.30 mL, 2 mmol) and DMAP (0.244 g, 2 mmol). The

reaction mixture was stirred at ambient temperature for 12 h, at which time 1N $KHSO_4$ (20 mL) was added. The organic layer was separated, washed with water (1×15 mL) and brine (1×15 mL), dried over magnesium sulfate and evaporated to give crude **8**, which was purified by flash chromatography (hexane/EtOAc, 4:1) to afford pure **18a** (0.464 g, 88%) as a solid which solidified upon standing; mp 69–71°C; $[\alpha]_D^{25}$ −44 (*c* 0.48, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.12 (s, 3H), 0.14 (s, 3H), 0.89 (s, 9H), 1.31 (s, 3H), 1.40 (s, 3H), 1.52 (s, 9H), 2.11 (dt, 1H, $J=4.9$, 13.6 Hz), 2.24 (dt, 1H, $J=7.9$, 13.6 Hz), 3.75 (dd, 1H, $J=7.2$, 8.6 Hz), 4.01 (dd, 1H, $J=6.2$, 8.6 Hz), 4.05 (ddd, 1H, $J=4.6$, 6.2, 7.8 Hz), 4.23 (dd, 1H, $J=5.1$, 8.0 Hz), 4.40 (dt, 1H, $J=6.2$, 7.2 Hz). ^{13}C NMR ($CDCl_3$) δ −5.2, −4.5, 18.2, 25.5, 25.8, 26.4, 28.1, 29.4, 56.8, 67.7, 71.1, 79.4, 83.7, 109.1, 150.7, 172.5. Anal. calcd for $C_{20}H_{37}NO_6Si$: C, 57.80; H, 8.97; N, 3.37. Found: C, 57.96; H, 9.12; N, 3.12%.

4.10. (3*S*,5*S*)-5-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-(benzoyloxy)-2-oxo-pyrrolidine-1-carboxylic acid *tert*-butyl ester 18b

The same procedure described above for the conversion of **17a** to **18a** was applied to **17b** (0.410 g, 1.17 mmol). After flash chromatography (hexane/EtOAc, 4:1) of the crude product, pure **18b** (0.403 g, 85%) was obtained as an oil; $[\alpha]_D^{25}$ −49 (*c* 0.57, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.34 (s, 3H), 1.57 (s, 9H), 2.24 (dt, 1H, $J=4.9$, 5.9, 14.2 Hz), 2.63 (ddd, 1H, $J=8.3$, 9.3, 14.2 Hz), 3.70 (dd, 1H, $J=6.8$, 8.8 Hz), 4.10 (dd, 1H, $J=6.8$, 8.8 Hz), 4.24 (ddd, 1H, $J=3.9$, 4.9, 8.3 Hz), 4.60 (dt, 1H, $J=3.9$, 6.8 Hz), 5.55 (dd, 1H, $J=5.9$, 9.3 Hz), 7.44–7.55 (m, 3H), 7.60–7.63 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 24.7, 26.0, 27.9, 36.6, 38.1, 56.5, 66.8, 70.6, 84.2, 109.6, 128.4, 129.9 (2C), 133.4, 150.1, 165.6, 169.1. Anal. calcd for $C_{21}H_{27}NO_7$: C, 62.21; H, 6.71; N, 3.45. Found: C, 62.42; H, 6.61; N, 3.55%.

4.11. (2*S*,4*S*)-4-(Benzoyloxy)-5-oxo-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester 19

To a well-stirred suspension of periodic acid (0.536 g, 2.35 mmol) in dry diethyl ether (50 mL), compound **18b** (0.450 g, 1 mmol) was added at ambient temperature under an argon atmosphere in one portion. Stirring was maintained for additional 4 h at which time the reaction mixture was filtered. The filtrate was evaporated under reduced pressure and the residue was dissolved in CH_3CN (5 mL). To the resulting mixture, a solution of $NaClO_2$ (0.133 g, 1.53 mmol) in water (5 mL) was added dropwise. The resulting mixture was then treated with a solution of NaH_2PO_4 (29 mg, 0.25 mmol) in H_2O (2 mL) and 35% H_2O_2 (82 μL, 0.88 mmol) keeping the temperature of the mixture below 10°C. After stirring for 1 h, Na_2SO_3 (9 mg, 0.17 mmol) was added and the resulting mixture was acidified (pH 2–3) with 10% aqueous HCl. The resulting mixture was partitioned between brine (30 mL) and EtOAc (30 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3×25 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give a residue which was taken up in diethyl ether (20 mL) and treated with a freshly distilled ethereal solution of diazomethane at 0°C for 5 min. The solvent was removed under reduced pressure and the residue was subjected to purification by radial chromatography (hexane/EtOAc, 9:1) to give the pure **19** (0.218 g, 60%) as a colorless oil; $[\alpha]_D^{25}$ −10 (*c* 0.19, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.49 (s, 9H), 2.40 (dt, 1H, $J=6.8$, 13.7 Hz), 2.85 (dt, 1H, $J=8.3$, 13.7 Hz), 3.75 (s, 3H), 4.59 (dd, 1H, $J=6.8$, 7.8 Hz), 5.57 (dd, 1H, $J=7.3$, 8.3), 7.38–7.41 (m, 3H), 7.97–8.04 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 27.8, 27.9, 52.7, 55.8, 70.1, 84.5, 128.5, 130.0, 133.7, 149.0, 165.3, 168.1 (2C), 170.8. Anal. calcd for $C_{18}H_{21}NO_7$: C, 59.50; H, 5.83; N, 3.85. Found: C, 59.37; H, 5.72; N, 4.75%.

4.12. Carbonic acid *tert*-butyl ester (3*S*,5*S*)-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxo-pyrrolidin-3-yl ester 20

The same procedure described above for the conversion of **17a** to **18a** was applied to **11a** (0.2 g, 1 mmol). After radial chromatography (hexane/EtOAc, 1:1) of the crude product, pure **20** (0.223 g, 74%) was obtained as an oil; $[\alpha]_D^{25}$ −4 (*c* 0.14, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.36 (s, 3H), 1.43 (s, 9H), 1.67 (dt, 1H, $J=8.4$, 16.7 Hz), 2.57 (ddd, 1H, $J=6.7$, 8.6, 16.7 Hz), 3.53 (ddd, 1H, $J=6.7$, 7.4, 8.4 Hz), 3.66 (dd, 1H, $J=4.6$, 8.3 Hz), 3.93 (ddd, 1H, $J=4.6$, 6.4, 7.4 Hz), 4.00 (dd, 1H, $J=6.4$, 8.3 Hz), 5.11 (t, 1H, $J=8.7$ Hz), 6.70 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ 25.1, 26.7, 27.7, 30.0, 53.4, 65.7, 72.1, 78.8, 83.2, 110.2, 152.7, 171.9. Anal. calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.62; H, 7.48; N, 4.45%.

4.13. Reduction of isoxazolidines 4

4.13.1. (3*S*,5*S*)-1-Benzyl-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-pyrrolidin-2-one 21a and (3*S*,5*S*)-2-benzyl-3-[(1*S*)-1,2-dihydroxy-ethyl]-isoxazolidine-5-carboxylic acid methyl ester 13. A solution of **4a** (0.82 g, 2.55 mmol) in THF (25 mL) was treated with glacial acetic acid (40 mL) and Zn dust (0.196 g, 3 mmol); the resulting solution was heated at 60°C for 1 h. After cooling at ambient temperature, the reaction mixture was treated with a saturated aqueous solution of sodium carbonate and the resulting mixture was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated to yield a residue which after a short flash chromatography (hexane/EtOAc, 1:4) afforded a 90:10 mixture of compounds **21a** and **13**, which were used in the next acetylation step without further purification.

21a: ^1H NMR ($CDCl_3$+D_2O) δ (selected signals) 1.30 (s, 3H), 1.46 (s, 3H), 1.88 (td, 1H, $J=6.3$, 12.7 Hz), 2.35 (td, 1H, $J=7.8$, 12.7 Hz), 3.50 (m, 1H), 3.98 (dd, 1H, $J=6.5$, 8.9 Hz), 4.14 (d, 1H, $J=15.1$ Hz), 4.30–4.40 (m, 3H), 5.05 (d, 1H, $J=15.1$ Hz), 7.15–7.32 (m, 5H).

13: The ^{1}H NMR spectra of this compound was identical to that observed for the same product obtained from **4a** as described above.

4.13.2. (3*R*,5*S*)-1-Benzyl-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-pyrrolidin-2-one 21b and (3*S*,5*R*)-2-benzyl-3-[(1*S*)-1,2-dihydroxy-ethyl]-isoxazolidine-5-carboxylic acid methyl ester 22b. The same procedure described above for the conversion of **4a** to **21a** and **13** was applied to **4b** (0.68 g, 2.12 mmol). After a short flash chromatography (hexane/EtOAc, 1:4) of the crude product, a 93:7 mixture of **21b** and **22b** was obtained and used in the next acetylation step without further purification.

21b: ^{1}H NMR ($CDCl_3$+D_2O) δ (selected signals) 1.29 (s, 3H), 1.42 (s, 3H), 1.87 (dt, 1H, J=8.8, 13.2 Hz), 2.40 (ddd, 1H, J=1.9, 8.2, 13.2 Hz), 3.45 (dt, 1H, J=2.3, 8.6 Hz), 3.54 (dd, 1H, J=6.3, 8.5 Hz), 3.93 (dd, 1H, J=7.3, 8.5 Hz), 4.09 (d, 1H, J=15.1 Hz), 4.27 (dt, 1H, J=2.2, 7.0 Hz), 4.59 (t, 1H, J=8.5 Hz), 5.0 (sd, 1H, J=15.1 Hz), 7.32–7.45 (m, 5H).

22b: ^{1}H NMR ($CDCl_3$+D_2O) δ (selected signals) 2.25–2.65 (m, 2H), 3.19 (dt, 1H, J=5.1, 8.5 Hz), 3.56–3.63 (m, 2H), 3.75 (s, 3H), 3.91 (d, 1H, J=12.8 Hz), 3.98 (m, 1H), 4.05 (d, 1H, J=12.8 Hz), 4.72 (dd, 1H, J=5.5, 8.8 Hz), 7.31–7.42 (m, 5H).

4.13.3. (3*S*,5*R*)-1-Benzyl-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-pyrrolidin-2-one 21c and (3*R*,5*S*)-2-benzyl-3-[(1*S*)-1,2-dihydroxy-ethyl]-isoxazolidine-5-carboxylic acid methyl ester 22c. The same procedure described above for the conversion of **4a** to **21a** and **13** was applied to **4c** (0.44 g, 1.36 mmol). After a short flash chromatography (hexane/EtOAc, 1:4) of the crude product, a 90:10 mixture of **21c** and **22c** was obtained and used in the next acetylation step without further purification.

21c: ^{1}H NMR ($CDCl_3$+D_2O) δ (selected signals) 1.31 (s, 3H), 1.37 (s, 3H), 1.85–2.10 (m, 2H), 3.30 (m, 1H), 3.56 (dd, 1H, J=6.3, 8.6 Hz), 4.11 (dd, 1H, J=4.8, 8.6 Hz), 4.30 (d, 1H, J=14.7 Hz), 4.31 (m, 1H), 4.50 (t, 1H, J=8.5 Hz), 5.13 (d, 1H, J=14.7 Hz), 7.28–7.39 (m, 5H).

22c: ^{1}H NMR ($CDCl_3$+D_2O) δ (selected signals) 2.34 (ddd, 1H, J=2.2, 5.5 12.9 Hz), 2.76 (1H, J=8.1, 9.6, 12.9 Hz), 3.43, 3.60 (m, 3H), 3.78 (s, 3H), 3.84 (d, 1H, J=13.0 Hz), 4.08 (d, 1H, J=13.0 Hz), 4.11 (m, 1H), 4.78 (dd, 1H, J=5.5, 9.6 Hz), 7.30–7.40 (m, 5H).

4.13.4. (3*R*,5*R*)-1-Benzyl-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-pyrrolidin-2-one 21d. The same procedure described above for the conversion of **4a** to **21a** and **13** was applied to **4d** (0.3 g, 0.94 mmol). After a short flash chromatography (hexane/EtOAc, 1:4) of the crude product, only **21d** was obtained and used in the next acetylation step without further purification. ^{1}H NMR ($CDCl_3$+D_2O) δ 1.30 (s, 3H), 1.34 (s, 3H), 1.58 (dt, 1H, J=7.3, 13.7 Hz), 2.36 (dt, 1H, J=7.8, 13.7 Hz), 3.43 (q, 1H, J=7.3 Hz), 3.57 (1H, J=7.8 Hz), 3.91 (dd, 1H, J=6.8, 8.1 Hz), 4.12 (q, 1H, J=6.8 Hz), 4.38 (t, 1H, J=7.8 Hz), 4.47 (d, 1H, J=14.6 Hz), 4.91 (d, 1H, J=14.6 Hz), 7.33–7.41 (m, 5H).

4.14. Acetylation of pyrrolidin-2-ones 21 and diols 22

4.14.1. Acetic acid (3*S*,5*S*)-1-benzyl-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxo-pyrrolidin-3-yl ester 23a and (3*S*,5*S*)-2-benzyl-3-[(1*S*)-1,2-diacetoxy-ethyl]-isoxazolidine-5-carboxylic acid methyl ester. The above described mixture of compounds **21a** and **13** was dissolved in dry dichloromethane (30 mL) and treated with acetic anhydride (2.44 g, 24 mmol) and pyridine (3.20 g, 40 mmol), and the resulting solution was stirred at ambient temperature for 12 h. The reaction mixture was washed sequentially with 2N HCl and saturated aqueous sodium bicarbonate. The organic layer was separated, dried over magnesium sulfate and concentrated to dryness. The residue was purified by MPLC (hexane/EtOAc, 3:2) to give pure **23a** and **24a**.

23a: 0.621 g (73%); oil; $[\alpha]_D^{25}$ −45 (c 0.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3H), 1.47 (s, 3H), 1.85 (td, 1H, J=7.4, 13.2 Hz), 2.12 (s, 3H), 2.50 (ddd, 1H, J=7.3, 8.8, 13.2 Hz), 3.50 (dt, 1H, J=2.9, 7.0 Hz), 3.54 (dd, 1H, J=6.6, 8.5 Hz), 3.96 (dd, 1H, J=7.0, 8.5 Hz), 4.10 (d, 1H, J=15.4 Hz), 4.30 (dt, 1H, J=2.9, 6.6 Hz), 5.12 (d, 1H, J=15.4 Hz), 5.32 (dd, 1H, J=7.4, 8.8 Hz), 7.30–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 20.9, 24.6, 26.0, 26.5, 44.9, 54.9, 65.4, 70.1, 73.4, 109.8, 127.8, 127.9, 128.8, 135.6, 170.4, 170.8. Anal. calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.69; H, 6.80; N, 4.38%.

24a: 65 mg (7%); oil; $[\alpha]_D^{25}$ −56 (c 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.82 (s, 3H), 2.03 (s, 3H), 2.50 (ddd, 1H, J=2.6, 8.8, 13.2 Hz), 2.66 (td, 1H, J=7.4, 13.2 Hz), 3.49 (dt, 1H, J=2.2, 7.7 Hz), 3.77 (s, 3H), 3.80 (d, 1H, J=12.9 Hz), 4.12 (dd, 1H, J=4.8, 12.1 Hz), 4.21 (d, 1H, J=12.9 Hz), 4.26 (dd, 1H, J=2.6, 12.1 Hz), 4.58 (t, 1H, J=8.5 Hz), 4.94 (ddd, 1H, J=2.9, 4.8, 7.9 Hz), 7.31–7.46 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 20.6, 20.9, 33.3, 52.5, 62.3, 62.8, 63.3, 70.4, 76.9, 127.7, 128.5, 129.4, 136.5, 170.3, 170.5, 172.7. Anal. calcd for $C_{18}H_{23}NO_7$: C, 59.17; H, 6.34; N, 3.83. Found: C, 59.28; H, 6.26; N, 3.91%.

4.14.2. Acetic acid (3*R*,5*S*)-1-benzyl-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxo-pyrrolidin-3-yl ester 23b and (3*S*,5*R*)-2-benzyl-3-[(1*S*)-1,2-diacetoxy-ethyl]-isoxazolidine-5-carboxylic acid methyl ester 24b. The same procedure described above for the conversion of the mixture of **21a** and **13** to **23a** and **24a** was applied to the mixture of **21b** and **22b**. After MPLC (hexane/EtOAc, 3:2) pure **24b** and **24b** were obtained.

23b: 0.516 g (73%); oil; $[\alpha]_D^{25}$ +18 (c 0.41, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3H), 1.48 (s, 3H), 1.83 (dt, 1H, J=8.8, 12.9 Hz), 2.13 (s, 3H), 2.58 (dd, 1H, J=8.5, 12.9 Hz), 3.43 (dt, 1H, J=1.8, 9.2 Hz), 3.51 (dd, 1H, J=5.9, 8.5 Hz), 3.96 (dd, 1H, J=78.4, 8.5 Hz), 4.08 (d, 1H, J=15.1 Hz), 4.30 (ddd, 1H, J=2.2, 5.9, 7.7 Hz),

5.08 (d, 1H, $J=15.1$ Hz), 5.47 (dd, 1H, $J=8.5$, 9.2 Hz), 7.32–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 20.9, 24.3, 25.9, 27.5, 44.7, 56.1, 65.7, 70.8, 72.9, 110.2, 127.8, 127.9, 128.8, 135.5, 170.3, 170.9. Anal. calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.69; H, 6.80; N, 4.38%.

24b: 46 mg (6%); oil; $[\alpha]_D^{25}$ +3 (*c* 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.82 (s, 3H), 1.99 (s, 3H), 2.43 (ddd, 1H, $J=3.3$, 4.7, 13.6 Hz), 2.73 (ddd, 1H, $J=8.1$, 9.9, 13.6 Hz), 3.38 (dt, 1H, $J=2.9$, 7.7 Hz), 3.75 (s, 3H), 3.85 (d, 1H, $J=12.9$ Hz), 4.12 (d, 1H, $J=12.9$ Hz), 4.15 (dd 1H, $J=4.8$, 12.1 Hz), 4.32 (dd, 1H, $J=2.9$, 12.1 Hz), 4.75 (dd, 1H, $J=4.7$, 9.9 Hz), 4.99 (ddd, 1H, $J=2.9$, 4.8, 7.7 Hz), 7.33–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 20.8, 21.2, 36.1, 51.4, 63.0, 63.5(2C), 69.7, 73.1, 127.6, 128.4, 129.5, 136.0, 170.1, 170.6, 173.0. Anal. calcd for $C_{18}H_{23}NO_7$: C, 59.17; H, 6.34; N, 3.83. Found: C, 59.08; H, 6.43; N, 3.69%.

4.14.3. Acetic acid (3*S*,5*R*)-1-benzyl-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxo-pyrrolidin-3-yl ester 21c and (3*R*,5*S*)-2-benzyl-3-[(1*S*)-1,2-diacetoxy-ethyl]-isoxazolidine-5-carboxylic acid methyl ester 22c. The same procedure described above for the conversion of the mixture of **21a** and **13** to **23a** and **24a** was applied to the mixture of **21c** and **22c**. After MPLC (hexane/EtOAc, 3:2) pure **23c** and **24c** were obtained.

23c: 0.304 g (67%); oil; $[\alpha]_D^{25}$ −49 (*c* 0.38, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.38 (s, 3H), 1.95 (dt, 1H, $J=8.8$, 13.7 Hz), 2.13 (s, 3H), 2.18 (ddd, 1H, $J=2.4$, 9.3, 13.7 Hz), 3.46 (ddd, 1H, $J=2.4$, 7.3, 8.8 Hz), 3.55 (dd, 1H, $J=5.6$, 8.3 Hz), 4.00 (dd, 1H, $J=6.8$, 8.3 Hz), 4.09 (q, 1H, $J=6.4$ Hz), 4.29 (d, 1H, $J=15.1$ Hz), 5.12 (d, 1H, $J=15.1$ Hz), 5.40 (t, 1H, $J=8.3$ Hz), 7.29–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 20.8, 25.0, 26.4, 29.7, 45.9, 56.4, 66.6, 70.2, 79.0, 110.58, 127.7, 128.4, 128.7, 136.1, 170.4, 170.6. Anal. calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.73; H, 6.86; N, 4.15%.

24c: 35 mg (7%); oil; $[\alpha]_D^{25}$ +27 (*c* 0.27, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.92 (s, 3H), 2.02 (s, 3H), 2.41 (ddd, 1H, $J=5.9$, 10.3, 13.2 Hz), 2.73 (dt, 1H, $J=9.2$, 13.2 Hz), 3.39 (ddd, 1H, $J=5.5$, 9.2, 10.3 Hz), 3.8 (s, 3H), 3.91 (d, 1H, $J=13.2$ Hz), 4.05 (d, 1H, $J=13.2$ Hz), 4.08 (dd, 1H, $J=5.1$, 12.1 Hz), 4.18 (dd, 1H, $J=4.0$, 12.1 Hz), 4.70 (dd, 1H, $J=5.9$, 9.2 Hz), 5.04 (dt, 1H, $J=4.0$, 5.3 Hz), 7.30–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 20.6, 20.9, 34.1, 52.5, 61.5, 63.1, 63.2, 72.0, 75.3, 127.7, 128.5, 129.1, 136.2, 170.3, 170.4, 171.0. Anal. calcd for $C_{18}H_{23}NO_7$: C, 59.17; H, 6.34; N, 3.83. Found: C, 59.04; H, 6.31; N, 3.95%.

4.14.4. Acetic acid (3*R*,5*R*)-1-benzyl-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxo-pyrrolidin-3-yl ester 23d. The same procedure described above for the conversion of the mixture of **21** and **13** to **23a** and **24a** was applied to **21d**. After flash chromatography (hexane/EtOAc, 3:2) pure **23d** (0.235 g, 75%) was obtained as an oil; $[\alpha]_D^{25}$ −27 (*c* 0.32, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.33 (s, 3H), 1.46 (dt, 1H, $J=7.0$, 13.7 Hz), 2.14 (s, 3H), 2.50 (ddd, 1H, $J=7.3$, 8.8, 13.7 Hz), 3.50 (q, 1H, $J=7.3$ Hz), 3.52 (dd, 1H, $J=6.8$, 8.3 Hz), 3.86 (dd, 1H, $J=6.8$, 8.3 Hz), 4.10 (q, 1H, $J=6.8$ Hz), 4.46 (d, 1H, $J=14.6$ Hz), 4.90 (d, 1H, $J=14.6$ Hz), 5.25 (dd, 1H, $J=7.0$, 8.8 Hz), 7.32–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 20.9, 25.2, 26.3, 28.1, 45.8, 56.9, 65.8, 70.2, 78.8, 110.5, 127.6, 128.5, 128.7, 136.6, 170.3, 170.6. Anal. calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.96; H, 6.88; N, 4.16%.

4.15. Synthesis of *N*-benzyl pyroglutamates 25

4.15.1. (2*S*,4*S*)-4-Acetoxy-1-benzyl-5-oxo-pyrrolidine-2-carboxylic acid methyl ester 25a. The same procedure described above for the conversion of **18b** to **19** was applied to **23a** (0.2 g, 0.6 mmol). After radial chromatography (hexane/EtOAc, 4:1) pure **25a** (0.115 g, 66%) was obtained as an oil; $[\alpha]_D^{25}$ +17 (*c* 0.46, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.00 (dt, 1H, $J=6.4$, 13.9 Hz), 2.07 (s, 3H), 2.77 (dt, 1H, $J=8.5$, 13.9 Hz), 3.65 (s, 3H), 3.92 (dd, 1H, $J=6.4$, 8.5 Hz), 4.13 and 5.13 (2d, 2H, $J=14.9$ Hz), 5.29 (dd, 1H, $J=6.4$, 8.5), 7.10–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.6, 29.9, 45.8, 52.5, 55.4, 69.5, 128.0, 128.4, 128.7, 134.8, 170.0, 170.1, 170.8. Anal. calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.62; H, 5.99; N, 4.67%.

4.15.2. (2*S*,4*R*)-4-Acetoxy-1-benzyl-5-oxo-pyrrolidine-2-carboxylic acid methyl ester 25b. The same procedure described above for the conversion of **18b** to **19** was applied to **23b** (0.15 g, 0.45 mmol). After radial chromatography (hexane/EtOAc, 4:1) pure **25b** (90 mg, 69%) was obtained as an oil; $[\alpha]_D^{25}$ −7 (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.15 (dt, 1H, $J=8.9$, 13.4 Hz), 2.15 (s, 3H), 2.64 (ddd, 1H, $J=1.5$, 8.9, 13.4 Hz), 3.67 (s, 3H), 4.00 (dd, 1H, $J=1.5$, 8.9 Hz), 4.06 and 4.98 (2d, 2H, $J=14.8$ Hz), 5.46 (t, 1H, $J=8.9$), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.8, 30.6, 46.2, 52.7, 55.9, 69.7, 128.1, 128.7, 128.8, 134.7, 170.2, 170.5, 171.3. Anal. calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.95; H, 6.02; N, 4.74%.

4.15.3. (2*R*,4*S*)-4-Acetoxy-1-benzyl-5-oxo-pyrrolidine-2-carboxylic acid methyl ester ent-25b. The same procedure described above for the conversion of **18b** to **19** was applied to **23c** (0.12 g, 0.36 mmol). After radial chromatography (hexane/EtOAc, 4:1) pure ent-**25b** (70 mg, 67%) was obtained. The physical and spectroscopic properties of this compound were identical to those of **23b** except for the sign of the optical rotation: $[\alpha]_D^{25}$ +7 (*c* 0.22, $CHCl_3$). Anal. calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.79; H, 6.00; N, 4.89%.

4.15.4. (2*R*,4*R*)-4-Acetoxy-1-benzyl-5-oxo-pyrrolidine-2-carboxylic acid methyl ester ent-25a. The same procedure described above for the conversion of **18b** to **19** was applied to **23d** (0.14 g, 0.42 mmol). After radial chromatography (hexane/EtOAc, 4:1) pure ent-**25a** (86 mg, 70%) was obtained. The physical and spectroscopic properties of this compound were identical to those of **23a** except for the sign of the optical rotation: $[\alpha]_D^{25}$ −16 (*c* 0.40, $CHCl_3$). Anal. calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.83; H, 5.81; N, 4.90%.

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References

1. (a) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2172–2175; (b) Cai, C.; Soloshonok, V. A.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1339–1350.
2. For some recent examples: (a) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295–4303; (b) Honda, T.; Kimura, M. *Org. Lett.* **2000**, *2*, 3925–3927. For an excellent review, see: Najera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245–2303.
3. (a) Ali, A.; Ahmad, V. U.; Ziemer, B.; Liebscher, J. *Tetrahedron: Asymmetry* **2000**, *11*, 4365–4375; (b) Dyer, J.; Keeling, S.; Moloney, M. G. *Chem. Commun.* **1998**, 461–462; (c) Bailey, J. H.; Cherry, D. T.; Dyer, J.; Moloney, M. G.; Bamford, M. J.; Keeling, S.; Lamont, R. B. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2783–2792; (d) Dyer, J.; King, A.; Keeling, S.; Moloney, M. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2793–2804; (e) Goswami, R.; Moloney, M. G. *Chem. Commun.* **1999**, 2333–2334.
4. (a) Snider, B. B.; Gu, Y. *Org. Lett.* **2001**, *3*, 1761–1763; (b) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V.; Yamazaki, T. *J. Org. Chem.* **2000**, *65*, 6688–6696; (c) Fujita, M.; Kitagawa, O.; Yamada, Y.; Izawa, H.; Hasegawa, H.; Taguchi, T. *J. Org. Chem.* **2000**, *65*, 1108–1114; (d) Kim, Y. J.; Takatsuki, A.; Kogoshi, N.; Kitahara, T. *Tetrahedron* **1999**, *55*, 8353–8364; (e) Dudot, B.; Chiaroni, A.; Royer, J. *Tetrahedron Lett.* **2000**, *41*, 6355–6359; (f) Ostendorf, M.; Dijkink, J.; Rutjes, F. P. J. T.; Hiemstra, H. *Eur. J. Chem.* **2000**, 115–124; (g) Langlois, N.; Moro, A. *Eur. J. Chem.* **1999**, 3483–3488; (h) Chan, P. W. H.; Cottrell, I. F.; Moloney, M. G. *Tetrahedron: Asymmetry* **1999**, *10*, 3887–3891; (i) Bryans, J. S.; Large, J. M.; Parsons, A. F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2905–2910.
5. Lee, Y. K.; Kaneko, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3494–3498.
6. Gefflaut, T.; Bauer, U.; Ariola, K.; Koskinen, A. M. P. *Tetrahedron: Asymmetry* **1996**, *7*, 3099–3102.
7. Heinz, L. J.; Lunn, W. H.; Murff, R. E.; Paschal, J. W.; Spangle, L. A. *J. Org. Chem.* **1996**, *61*, 4838–4841.
8. Ohta, T.; Hosoi, A.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 329–332.
9. Avent, A. G.; Bowler, A. N.; Doyle, P. M.; Marchand, C. M.; Young, D. W. *Tetrahedron Lett.* **1992**, *33*, 1509–1512. We have also confirmed in our laboratories low chemical yields for this reaction in agreement with Young et al. See: Merino, P.; Franco, S.; Merchan, F. L.; Revuelta, J.; Tejero, T. Proceedings of ECSOC-5, The Fifth International Electronic Conference on Synthetic Organic Chemistry, http://www.mdpi.org/ecsoc-5.htm, September 1–30, 2001. Kappe, O.; Merino, P., Marzinzik, A.; Wennemers, H.; Wirth, T.; Vanden Eynde, J.-J.; Lin, S.-K., Eds.; CD-ROM, ISBN 3-906980-06-5. Paper A0010.
10. Zhang, X.; Schmitt, C.; Jiang, W. *Tetrahedron Lett.* **2001**, *42*, 5335–5338.
11. (a) Merino, P.; Anoro, S.; Merchan, F.; Tejero, T. *Heterocycles* **2000**, *53*, 861–875; (b) Tejero, T.; Dondoni, A.; Rojo, I.; Merchan, F. L.; Merino, P. *Tetrahedron* **1997**, *53*, 3301–3318; (c) Casuscelli, F.; Di Bella, M. R.; Romeo, G.; Chiacchio, U.; Rescifina, A. *Gazz. Chim. Ital.* **1977**, *127*, 367–371.
12. (a) Shimazaki, M.; Okazaki, F.; Nakasima, F.; Ishikawa, T.; Ohta, A. *Heterocycles* **1993**, *36*, 1823–1836; (b) White, J. D.; Badger, R. A.; Kezar, H. J., III; Pallenberg, A. J.; Schieser, G. A. *Tetrahedron* **1989**, *45*, 6631–6644; (c) Burdisso, M.; Gamba, A.; Gandolfi, R.; Oberti, R. *Tetrahedron* **1988**, *44*, 3735–3748; (d) Herczegh, P.; Kovacs, I.; Szilagyi, L.; Varga, T.; Dinya, Z.; Sztaricskai, F. *Tetrahedron Lett.* **1993**, *34*, 1211–1214; (e) Coutouli-Argyropoulou, E.; Malamidou-Xenikaki, E.; Stampelos, X. N.; Alexopoulou, I. N. *Tetrahedron* **1997**, *53*, 707–718.
13. Merino, P.; Anoro, S.; Franco, S.; Merchan, F. L.; Tejero, T.; Tunon, V. *J. Org. Chem.* **2000**, *65*, 1590–1596.
14. For recent examples of a similar use of the 1,3-dioxolane moiety, see inter alia: (a) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron* **1998**, *54*, 12301–12322; (b) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1998**, *63*, 2371–2374.
15. Schiehser, G. A.; White, J. D.; Matsumoto, G.; Pezzanite, J. O.; Clardy, J. *Tetrahedron Lett.* **1986**, *27*, 5587–5590.
16. White, J. D.; Badger, R. A.; Kezar, H. S., III; Pallenberg, A.; Schieser, G. A. *Tetrahedron* **1989**, *45*, 6631–6644.
17. The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre, CCDC 179303. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
18. The graphic view showed in Fig. 2 was made with ORTEP3 software. Copyright by Farrugia, L. J. University of Glasgow, 1997–2000.
19. For representative 1,3-dipolar cycloadditions of α-alkoxy nitrones, see inter alia: (a) Kuban, J.; Blanarikova, I.; Fisera, L.; Jaroskova, L.; Fengler-Veith, M.; Jager, V.; Kosizek, J.; Humpa, O.; Pronayova, N.; Langer, V. *Tetrahedron* **1999**, *55*, 9501–9514; (b) Bruche, L.; Arnone, A.; Bravo, P.; Panzeri, W.; Presenti, C.; Viani, F. *Eur. J. Chem.* **1999**, 1665–1670; (c) Borrachero, P.; Cabrera, F., Dianez, M. J.; Estrada, M. D.; Gomez-Guillen, M.; Lopez-Castro, A.; Moreno, J. M.; de Paz, J. L.; Perez-Garrido, S. *Tetrahedron: Asymmetry* **1999**, *10*, 77–98; (d) Torrente, S.; Noya, B.; Paredes, M. D.; Alonso, R. *J. Org. Chem.* **1997**, *62*, 6710–6711; (e) Xu, Z.; Johannes, C. W.; La, D. S.; Hofilena, G. E.; Hoveyda, A. H. *Tetrahedron* **1997**, *53*, 16377–16390; (f) Saito, S.; Ishikawa, T.; Kishimoto, N.; Kohara, T.; Moriwake, T. *Synlett* **1994**, 282–283; (g) Goti, A.; Cicchi, S.; Brandi, A.; Pietrusiewicz, K. M. *Tetrahedron: Asymmetry* **1991**, *2*, 1371–1378; (h) DeShong, P.; Li, W.; Kennington, J. W., Jr.; Ammon, H. L.; Leginus, J. M. *J. Org. Chem.* **1991**, *56*, 1364–1373; (i) Fray, M. J.; Jones, R. H.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2753–2761; (j) DeShong, P.; Dicken, C. M.; Leginus, J. M.; Whittle, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 5598–5602; (h) Chiacchio, U.; Corsaro, A.; Gumina, G.; Rescifina, A.; Ian-

nazzo, D.; Piperno, A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **1999**, *64*, 9321–0327
20. Even in the presence of an inhibitor such as 2,6-di-*tert*-butyl-4-methylphenol, polymerization was observed to a great extent.
21. Conversion of **16** into **1b** only should require catalytic hydrogenation, since the formation of the lactam ring is preferred to the formation of the lactone ring (see Ref. 11c).
22. For a complete study on the reaction of di-*tert*-butyldicarbonate with amines and alcohols in the presence of DMAP, see: Basel, Y.; Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368–6380.
23. Domingo, L. R. *Eur. J. Org. Chem.* **2000**, 2265–2272.
24. (a) Kanemasa, S.; Ueno, N.; Shirahase, M. *Tetrahedron Lett.* **2002**, *43*, 657–660; (b) Tanaka, J.; Kanemasa, S. *Tetrahedron* **2001**, *57*, 899–905.
25. For a recent report with references to previous related articles, see: Carda, M.; Portoles, M.; Murga, J.; Uriel, S.; Marco, J. A.; Domingo, L. R.; Zaragoza, R. J.; Roper, H. *J. Org. Chem.* **2000**, *65*, 7000–7009.
26. Rastelli, A.; Gandolfi, R.; Sarzi-Amade, M.; Carboni, B. *J. Org. Chem.* **2001**, *66*, 2449–2458.
27. Di Valentin, C.; Freccero, M.; Gandolfi, R.; Rastelli, A. *J. Org. Chem.* **2000**, *65*, 6112–6120.
28. Cossio, F.; Morao, I.; Jiao, H. *J. Am. Chem. Soc.* **1999**, *121*, 6737–6746.
29. All calculations were performed using the Gaussian 98 Revision A.9 suite of programs. Frisch, J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, 1999.
30. Structures were optimized through step by step calculations starting with the semi-empirical calculations (PM3), then moving to the ab initio calculation with a low level of basis set using Hartree Fock methods (HF/3-21G) and finally the calculation was completed at a higher level of theory using density functional methods (B3LYP/6-31G(d)). For the purpose of comparison single points calculations were also carried out at HF/6-31G(d)//3-21G and B3LYP/6-31G(d)//HF/3-21G levels.
31. The graphic views showed in Fig. 3 were made with PovChem software. Copyright by Thiessen, P.A., 1999–2000.
32. A nitrone is isoelectronic with an allylic anion; so it can be considered as a nucleophile when it is made to react with electron-poor dipolarophiles.