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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 2459–2474

Cycloaddition reactions on activated *exo*-glycals

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Received 24 May 2005; accepted 15 June 2005

Abstract—Cycloaddition reactions of activated *exo*-glycals and nitrones proceeded only under microwave activation, with excellent facial selectivities on furanoglycosylidenes and good stereocontrol on the nitrone producing only two diastereomeric spiroisoxazolidines. α/β-Spiro sugar-isoxazolidines are obtained from pyrano *exo*-glycals. The cycloaddition reaction with nitrile oxide proceeds at room temperature and gives open-chain isoxazoles due to facile β-elimination of the sugar ring oxygen on the intermediate isoxazoline ring system. All the heterocycles obtained this way can be regarded as nucleoside analogues.

1. Introduction

Cycloaddition reactions have been widely explored as important carbon-carbon bond forming reactions. In particular, the 1,3-dipolar cycloaddition of nitrones and nitrile oxides is amongst the most widely studied reaction forming one carbon–carbon bond and one carbon–oxygen bond. High regioselectivities are generally observed with activated double bonds, the carbon–oxygen bond being formed at the γ-position. The N–O bond cleavage of these heterocycles provides an entry to other classes of compounds such as 1,3-amino alcohols. Numerous applications of the nitrone–olefin cycloaddition (NOC)[1a,b] or nitrile oxide–olefin cycloaddition (INOC) can be found in the literature.[2a,b] Many different olefins have been tested in this type of cycloaddition including carbohydrate-derived olefins.[3a–c]

exo-Glycals are olefinic sugars with an exocylic carbon–carbon double bond at the anomeric centre. This new class of compounds did not attract much attention until recently.[4] Almost at the same time, two general approaches to such compounds from lactones were proposed by us for the synthesis of anomeric dichloroolefins,[5a–c] and by Wilcox using Tebbe methylenation for *exo*-methylene glycals.[6] More recently, we reported the facile formation of activated *exo*-glycals using the Wittig olefination of sugar lactones.[7a,b] Several other approaches to *exo*-glycals have been reported, especially over the last five years, using stepwise procedures,[8a–g] or Ramberg–Bäcklund rearrangements.[9a,b]

INOC or NOC reaction of *exo*-glycals are supposed to yield anomeric spiroisoxazoli(di)ne derivatives, which can be regarded as spironucleoside analogues[10] or as stereodiverse scaffolds.[11] One example of bioactive spiroheterocyclic sugar derivatives is hydantocidin,[12–15] which is believed to be a mimic of adenosine.[16] Moreover some isoxazoli(di)ne derivatives with antibacterial and antifungal properties have recently been reported.[17]

RajanBabu was the first to report the reaction of an anomeric *exo*-methylene sugar with benzonitrile oxide leading with high regio- and stereocontrol to a spiroisoxazoline.[18] Some examples of an NOC reaction of 5,6- and 3,4-unsaturated sugars have been reported and found useful for the synthesis of carbocycles via the Ferrier carbocyclisation.[19] More recently, further examples of nitrile oxide cycloaddition with substituted *exo*-glycals has been reported by Lieberknecht.[20] The cycloaddition of glyoxylic nitrones and nitrile oxide with 1-methylene *exo*-glycals has also been reported by Ikegami et al.[21] while our work was in progress. Subsequent work by the same authors on the thermal cycloaddition of nitrones on *exo*-methylene sugars recently appeared.[22] To the best of our knowledge, activated *exo*-glycals, recently introduced by our group,[7a] have never been considered in cycloaddition reactions.[23]

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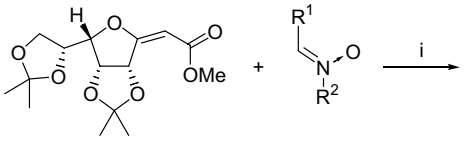
doi:10.1016/j.tetasy.2005.06.027

Herein, we report the details of our first results obtained in nitrones and nitrile oxides cycloadditions on this particular class of *exo*-glycals having an usual capto-dative substituent arrangement on the double bond.[24]

2. Results

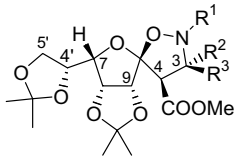
2.1. Nitrone–*exo*-glycal cycloadditions

The readily available *E exo*-glycal **1**[7a] was chosen as the model compound. Reaction with nitrone **2** was first attempted under standard thermal conditions, but no reaction occurred even in refluxing toluene. Microwave activation (MA) in a focussed microwave oven, ensured a clean reaction of nitrone **2** with **1** (*E* isomer), giving a mixture of two isomers in a 4:1 ratio and 50% yield. On the basis of previous studies from our group,[25] all reactions on the olefinic sugar **1** took place from the less hindered β face. Attack of the nitrone was also assumed to take place from this face. The C-4 configuration in the isoxazolidine ring being normally dictated by the geometry of the starting olefin, the two compounds obtained were supposed to be the C-3 epimers **6** and **7** resulting from *endo*/*exo* attacks of the nitrone. Determination of the absolute configuration at C-3 by the $J_{3,4}$ coupling constant measurement proved to be difficult due to very close values, 7.0 and 8.0 Hz. NOE difference spectroscopy, showing no interaction between H4 and H9 in both isomers, as expected from the stereochemistry depicted on Scheme 1, supported the hypothesis of structure **6** and **7**. X-ray analysis[26] of the major isomer **6** obtained as a crystalline material showed a *trans*-orientation of the two substituents at C-3 and C-4 of the isoxazolidine ring and also confirmed the C-4 and C-5 configurations (Fig. 1). As expected, the *E* geometry of **1** gives an (*R*)-configuration at C-4 and the configuration at C-5 results from attack of the less hindered β face



1

2 R^1 = *n*Pr, R^2 = Me
3 R^1 = Ph, R^2 = Me
4 R^1 = *n*Pr, R^2 = CH_2Ph
5 R^1 = H, R^2 = CH_2Ph



6 R^1 = Me, R^2 = *n*Pr, R^3 = H
7 R^1 = Me, R^2 = H, R^3 = *n*Pr
8 R^1 = Me, R^2 = Ph, R^3 = H
9 R^1 = Me, R^2 = H, R^3 = Ph
10 R^1 = CH_2Ph, R^2 = R^3 = H

Scheme 1.

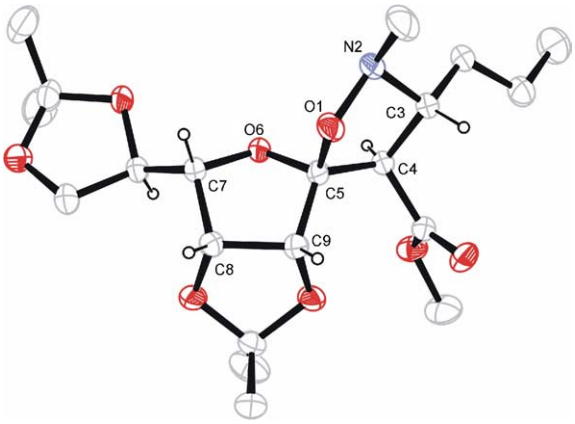


Figure 1. ORTEP diagram corresponding to the X-ray molecular structure of compound **6**.

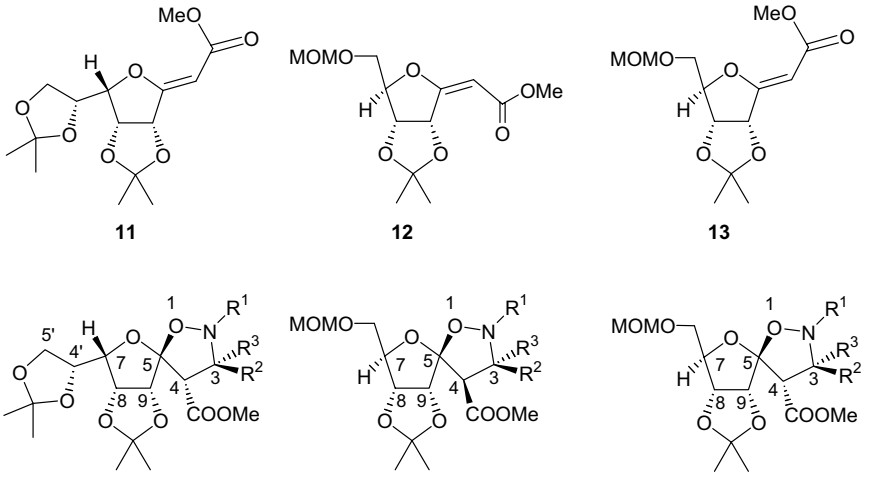
of olefin **1**. As for the *trans*-relationship between the two substituents at C-3 and C-4, this can be the result of cycloaddition in the *endo* mode with the *Z* nitrone or *exo* mode with the *E* nitrone (see below). Nitrone **3** was also submitted to cycloaddition under microwave activation with olefin **1**. As shown by ^{1}H NMR of the crude, the presence of only two isomers was undeniable but they were obtained as an inseparable mixture. From our previous observations, structures **8** and **9** were proposed for these two isomers.

The reaction of the unsubstituted nitrone **5** with **1** under microwave activation both for the formation of the nitrone and the subsequent cycloaddition gave only one isomer **10** in 75% yield (Table 1, entry 3). This confirmed the initial hypothesis that cycloadditions with nitrones **2** and **3** gave two isoxazolidines, epimeric at C-3, rather than an anomeric mixture.

Table 1. Results of cycloadditions of nitrones with furano-*exo*-glycals **1**, **11**, **12** and **13**

Entry	Starting *exo*-glycals	Nitrones	Products	trans/cis Ratio	Yield (%)
1	**1**	**2**	**6**, **7**	4:1	50
2	**1**	**3**	**8**, **9**	2:1	76
3	**1**	**5**	**10**	—	75
4	**11**	**3**	**14**, **15**	2:1	80
5	**11**	**2**	**16**, **17**	1.2:1	65
6	**11**	**5**	**18**	—	84
7	**12**	**3**	**19**, **20**	2.3:1	86
8	**12**	**2**	**21**, **22**	1.7:1	58
9	**12**	**4**	**23**, **24**	1:1	89
10	**12**	**5**	**25**	—	92
11	**13**	**3**	**26**, **27**	7.4:1	94
12	**13**	**2**	**28**, **29**	6:1	57
13	**13**	**4**	**30**, **31**	2.4:1	96
14	**13**	**5**	**32**	—	89

The same set of reactions was carried out with the four nitrones **2**, **3**, **4** and **5** on the *Z* isomer **11** and the two *ribo* derivatives **12** and **13** (Scheme 2). The latter were readily obtained from the corresponding lactones according to our previously described procedure.[25]



14 R^1 = Me, R^2 = Ph, R^3 = H
15 R^1 = Me, R^2 = H, R^3 = Ph
16 R^1 = Me, R^2 = *n*Pr, R^3 = H
17 R^1 = Me, R^2 = H, R^3 = *n*Pr
18 R^1 = Bn, R^2 = R^3 = H

19 R^1 = Me, R^2 = H, R^3 = Ph
20 R^1 = Me, R^2 = Ph, R^3 = H
21 R^1 = Me, R^2 = H, R^3 = *n*Pr
22 R^1 = Me, R^2 = *n*Pr, R^3 = H
23 R^1 = Bn, R^2 = H, R^3 = *n*Pr
24 R^1 = Bn, R^2 = *n*Pr, R^3 = H
25 R^1 = Bn, R^2 = R^3 = H

26 R^1 = Me, R^2 = Ph, R^3 = H
27 R^1 = Me, R^2 = H, R^3 = Ph
28 R^1 = Me, R^2 = *n*Pr, R^3 = H
29 R^1 = Me, R^2 = H, R^3 = *n*Pr
30 R^1 = Bn, R^2 = *n*Pr, R^3 = H
31 R^1 = Bn, R^2 = H, R^3 = *n*Pr
32 R^1 = Bn, R^2 = R^3 = H

Scheme 2.

In all cases, only two isomers were obtained. The results are summarised in Table 1. The first conclusion drawn from these studies is the excellent facial selectivity on the olefin. In each case only one anomer was isolated for each isomer. In the case of *exo*-glycals **1** and **11**, the α face being sterically congested, it is obvious that nitrone attack occurred from the β face. This is less evident for the *ribo* derivatives **12** and **13** where both faces of the lactone are substituted. Previous results from our group showed that reactions on such olefinic bonds usually gave mixture of anomers.[7,25,27] Nevertheless, the steric hindrance induced by the dioxolane group is far larger than that induced by the MOM protected hydroxymethyl at C4, thus only β-anomers were formed. In all cases, (Table 1, entries 6, 10 and 14) the reaction of *exo*-glycals with nitrone **5** gave, in very good yield, a single cycloadduct resulting from attack on the less hindered face.

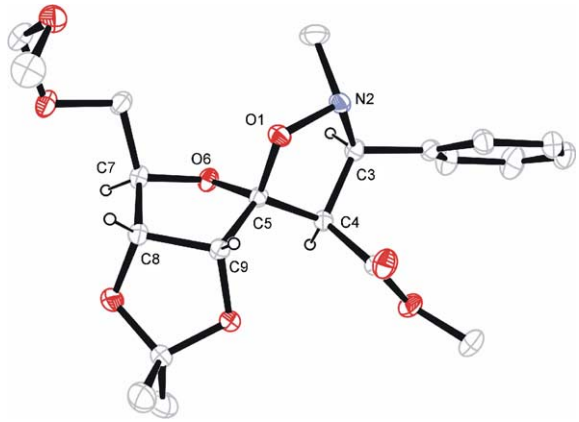


Figure 2. ORTEP diagram corresponding to the X-ray molecular structure of compound **20**.

In all this series, structural evidence for the β configuration at the anomeric carbon (C-5) was first supported by X-ray crystal structure of the *ribo*-isoxazolidine derivative **20** (Fig. 2)[28]. The stereochemical assignments of these structures were also achieved by NOE difference measurements. H4–H9 proton interaction is an indicator of the C-4 configuration. When starting from *Z exo*-glycals, an NOE effect is expected for both α- and β-anomers. Thus, molecular modelling of **27** and its α-anomer showed a H4–H9 distance of about 2.8 and 2.3 Å, respectively. This does not hold true for the cycloadducts obtained from *E-exo*-glycals where no NOE interactions are expected whatever the anomeric configuration. In the crystal structure of β-compounds **6** and **20** formed from *E-exo*-glycals, the H-4 and H-9 protons are located at 3.9 and 3.7 Å, respectively and this distance was estimated at 3.7 Å in the case of the anomeric compound of **6**, thus no NOE interactions are expected in this case. The results of H-4/H-9 NOE measurements, which are given in Table 2, are consistent with this prediction. NOE interactions between H-3 and H-4 were also used to determine the *cis–trans* arrangement of each cycloadduct. The absolute configurations around the isoxazolidine ring were established on this basis by correlation with the known absolute configurations of **6** and **20**. It is also noteworthy that the *trans*-isomers were always the first eluted compounds from the silica gel chromatography.

Table 2 brings together a series of ^{1}H and ^{13}C chemical shifts values, which were also very helpful for stereochemical determination. One can observe that the ^{13}C

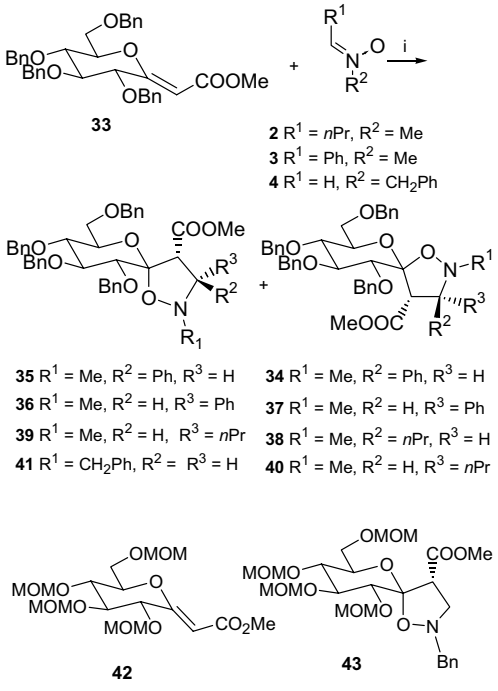
Table 2. NMR parameters for the fused furano-isoxazolidines **6**, **7**, **10** and **14**–**32**

Compounds	^{1}H Chemical shifts (δ)				Coupling constants (Hz)	^{13}C Chemical shifts (δ)			NOE difference measurements (%)	
	H-3	H-4	NCH_3	CO_2CH_3	$J_{3,4}$	NCH_3	C-3	C-4	H-3/H-4	H-4/H-9
D-*gulo* Derivatives										
6	2.84	3.34	2.70	3.65	8.0	43.71	73.82	60.88	—	—
7	3.39	3.55	2.85	3.75	7.0	48.40	69.65	59.04	5	—
8[a]	—	—	2.59	3.61	—	42.70	—	—	—	—
9[a]	—	—	2.86	3.31	—	46.86	—	—	—	—
10	3.55–4.10	3.80	—	3.69	—	—	58.45	54.08	—[c]	—
14	4.32	3.87	2.64	3.68	9.5	43.67	76.2	59.52	—	14
15	3.92	4.18	2.71	3.39	8.0	43.95	74.92	58.22	13	2.7
16	3.42	3.47	2.85	3.72	7.9	45.27	70.22	57.04	—	2.8
17[b]	—	—	—	—	—	—	—	—	—	—
18	3.51–3.67	3.93	—	3.77	—	—	56.37	51.74	—[c]	5
D-*ribo* Derivatives										
19	3.87	3.60–3.69	2.61	3.67	8.5	43.08	78.02	74.46	—	—
20	4.50	3.61–3.70	2.86	3.36	6.8	47.30	73.48	62.76	10	—
21	2.84	3.28	2.66	3.71	8.0	45.85	73.63	62.42	—	—
22	3.24	3.47	2.68	3.75	6.7	47.88	72.92	59.53	8.6	—
23	3.13	3.33	—	3.72	7.9	—	71.59	61.22	—	—
24	3.47–3.58	3.47–3.58	—	3.75	—	—	67.79	59.08	—[d]	—
25	3.52 (2H)	3.90	—	3.72	—	—	71.59	59.45	—[c]	—
26	4.24	3.93	2.64	3.67	9.5	43.44	75.25	59.56	—	3
27	3.93	4.22	2.71	3.40	8.2	44.30	74.91	58.52	7.4	2.6
28	3.34–3.37	3.54	2.81	3.73	7.2	46.01	70.81	58.02	—	—[d]
29	2.63	3.90	2.63	3.74	7.4	43.87	71.24	54.81	2.5	4.2
30	3.66	3.62	—	3.76	—	—	66.64	58.50	—	6
31	3.7–3.82	3.90	—	3.72	8.0	—	67.54	53.80	—[d]	3.5
32	4.20 (2H)	3.91	—	3.74	7.9	—	62.71	51.68	—[c]	—[d]

[a] Compounds **8** and **9** could not be separated.
[b] Compound **17** was not separated from **16**.
[c] Compounds with a methylene group at C3.
[d] NOE difference could not be measured unambiguously.

chemical shifts of C-3 and C-4 of *trans*-isomers are at a lower field compared to the corresponding *cis*-isomers. The opposite tendency was noticed for the ^{13}C chemical shifts values of the N–Me group in cycloadducts **6**–**17** and **19**–**29**. Comparisons of ^{1}H NMR chemical shifts values of H-3, H-4 protons and N–CH_3, CO_2CH_3 methyl groups in both *cis*- and *trans*-isomers were also very fruitful. In cycloadducts bearing a propyl group at C-3 (isomers **6**/**7**, **21**/**22**, **23**/**24** and **30**/**31**), the H-3 and H-4 of the *trans*-isomers are at a lower field than in the corresponding *cis*-isomers. The opposite is observed in the couple of isomers **14**/**15**, **19**/**20** and **26**/**27** all substituted by a phenyl group at C-3. For the latter, one can point out a large difference between the chemical shift values of the methyl ester group between *cis*- and *trans*-isomers. The ^{1}H δ_{CH_3} of *trans*-cycloadducts **14**, **19** and **26** is ≈3.67 ppm while in the corresponding *cis*-cycloadducts **15**, **20** and **27**, due to the presence of a shielding zone, $\delta_{CH_3} \approx 3.39$ ppm.

Our attention next turned to pyranose *exo*-glycals, which could behave differently in the cycloaddition reactions. Some precedents can be found in the literature using *exo*-methylene glycals with nitrile oxides[18,20] and nitrones.[22] The cycloaddition reactions were attempted on **33** (Scheme 3), obtained as a *Z*-isomer only, with nitrones **2** and **3** under microwave activation. The situation appeared much more complex than previously described



Scheme 3. (i) Microwave irradiation.

by us and careful examination of the crude reaction mixtures was needed. With nitrone **3**, four cycloadducts **34**, **35**, **36** and **37** were obtained in a 1.3:8.1:3.5:1 ratio (in order of elution) in 90% yield. **35**, **36** and **37** obtained as pure compounds were completely analysed by NMR spectroscopy. This was not the case of isomer **34** (first eluted compound), which could not be separated from **35** but its presence was shown unambiguously by NMR, in particular by the signals of the N–Me group (δ^1H 2.81 ppm, δ^{13}C 45.48 ppm) and the methyl ester group (δ^1H 3.60 ppm). The configuration of the four synthesised compounds **34**–**37** was performed as follows: assuming a concerted mechanism for NOC reactions, the single configuration at C-4 as depicted in Scheme 3 is related to the *Z* geometry of the starting *exo*-glycal **33**. Thus the four isomers obtained are diastereoisomers at C-3 and/or C-5. Determination of the *cis*/*trans* relationship between substituents at C-3 and C-4 is based on the proton chemical shift of the Me-ester group. As in the furano series it was observed that among the four isomers two have a methyl group, which appear abnormally at a higher field (3.27 and 3.37 ppm) compared to 3.54 and 3.60 ppm (Table 4). As already explained, this shift towards high fields indicates a *cis*-relationship between the C-3 phenyl group and the C-4 methyl ester. The ^{13}C chemical shift of the anomeric carbon is usually a good indicator in sugar chemistry to discriminate between α- and β-isomers.[29] In the case of spirosugar-heterocycles, α-anomers appear at a higher field than the corresponding β-anomers. Accordingly, the first and fourth eluted compounds, which have the higher values for the anomeric carbon (107.80 and 106.95, respectively) were assumed to be the β-anomers **34** and **37** while the second and third eluted compounds are the α-anomers **35** and **36**. It is worth noting that like in the furano series, the two *trans*-isomers **34** and **35** are the less polar compounds and are obtained in a greater amount (*trans*/*cis*: 2:1).

The cycloaddition from the α-face of **33** was favoured (α/β 5:1), in agreement with reported results on the 1,3-dipolar cycloaddition of 1-methylene-sugar with nitrile oxides.[18,20] These results are also consistent with the reported formation of a mixture of anomeric cycloadducts in the Lewis acid catalysed (α/β ~11:1) or thermal (α/β ~1:1) reaction of 1-methylene-analogue of **33** with glyoxylic nitrones (R^1 = COOEt in structure **2**). However, only one epimer at C3 of the isoxazolidine ring was formed accounting for a total facial selectivity on the nitrone.[21] This is in sharp contrast with our results, the observed *trans*/*cis* ratio of the C3–C4 substituents of isoxazolidines is the opposite of the *endo*–*exo* attack. In the case of the cycloaddition of olefin **33** with nitrone **2**, three cycloadducts **38**–**40** were also obtained (**38**/**39**/**40** 5.9:4.1:1, 64% yield, Table 3), a fourth isomer being detected in trace amount. In these compounds the presence of a propyl group at C-3 instead of a phenyl group did not allow us to discriminate between the *cis*- and *trans*-isomers by comparison of the ^{1}H NMR chemical shifts of the ester methyl group. In addition the comparison of the $^3J_{3,4}$ coupling constants was not reliable enough to distinguish between the *cis*- and *trans*-orientation. Nevertheless, the C-3 configuration of cycloadducts **38**–**40** was tentatively assigned by comparison of the ^{13}C NMR spectral data of the N–Me group. In the *cis*-compounds **36** and **37**, the N–Me group appears around 44 ppm while it is at a lower field in the *trans*-cycloadducts **34** and **35** (see Table 4). We took advantage of this difference (>4 ppm) to distinguish between the *cis*- and *trans*-isomers among the three isolated compounds **38**, **39** and **40**. The *cis*/*trans*-arrangement of substituents at C3 and C4 was also determined by NOE difference measurements (see Table 4). Determination of the anomeric configuration was again established by comparison of the ^{13}C data of C-5. Compounds having C-5 chemical shifts at 106.59 and 106. 96 ppm should be the β-isomers and were obtained in the greater proportion, (α/β ~1:1.6). Once more, such as in the furano series, we have noticed that *trans*-isomers are less polar than the *cis* one. This observation reinforces all our structural assignments. The reaction of *exo*-glycal **33** with nitrone **5**, generated in situ was next examined. Interestingly, only one cycloadduct **41** was obtained in 68% yield (Table 3, entry 3), which is the result of a complete α selectivity in this case. Similarly, compound **43** was obtained as the sole isomer (72% yield) from the reaction of olefin **42** with nitrone **5**.

Table 3. Results of nitrone cycloadditions with pyrano-*exo*-glycals **33** and **42**

Entry	Starting *exo*-glycals	Nitrones	Products, ratio	*trans*/*cis* (α/β) Ratio	Yield (%)
1	**33**	**3**	**34**, **35**, **36**, **37** 1.3:8.1:3.5:1	2:1, (5:1)	90
2	**33**	**2**	**38**, **39**, **40** 5.9:4.1:1	1.1:1, (1:1.6)	64
3	**33**	**5**	**41**	(1:0)	68
4	**42**	**5**	**43**	(1:0)	72

Table 4. NMR data for compounds **34**–**40**

Compound	^{1}H δ (ppm) CO_2CH_3	H-3/H-4 NOE difference measurements (%)	^{13}C δ (ppm) C-5	^{13}C δ (ppm) NCH_3
34 (β-*trans*)	3.60	—	107.80	45.48
35 (α-*trans*)	3.54	—	105.78	47.0
36 (α-*cis*)	3.37	14	104.34	44.01
37 (β-*cis*)	3.27	10	106.95	44.14
38 (β-*trans*)	3.61	—	106.96	48.73
39 (α-*cis*)	3.58	5.6	104.16	43.95
40 (β-*cis*)	3.70	[a]	106.59	43.84

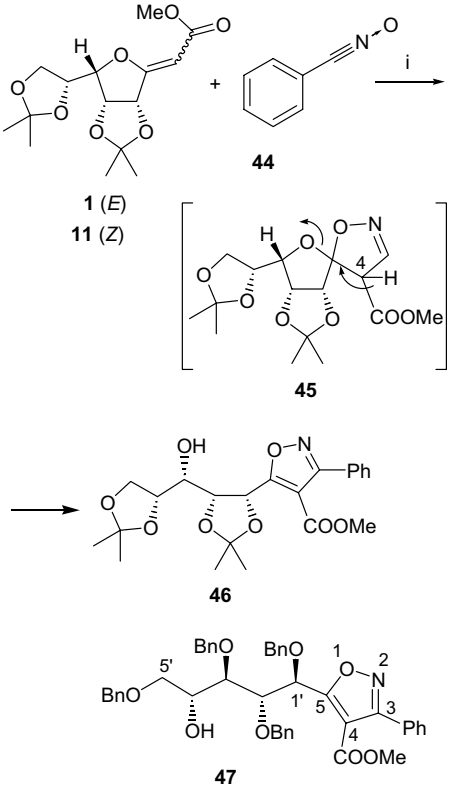
[a] NOE difference could not be measured due to signals overlapping.

2.2. Nitrile oxide-*exo*-glycal cycloadditions

The reaction of nitrile oxide with some activated *exo*-glycals was next examined. Benzonitrile oxide **44**, generated in situ from the corresponding hydroxyiminoyl chloride and triethylamine was reacted with the *E* olefin **1**. This cycloaddition proceeded at room temperature in 6 h to give single adduct **46** in 52% yield. The same

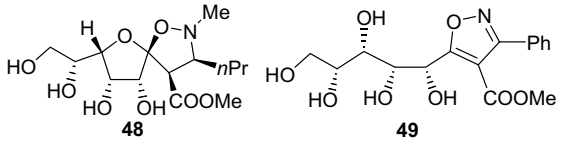
reaction was carried out on *Z*-isomer **11** and gave only one adduct in 72% yield, which proved identical to **46**. This suggested that the stereochemistry at carbon 4 of the expected isoxazoline ring, normally dictated by the olefin stereochemistry, was destroyed during the process. Indeed, careful examination of the ^{1}H NMR spectra of **46** showed that H-4 was no longer present. The presence of a hydroxyl proton was also clear, thus establishing the isoxazole ring structure of **46**. This heterocycle aromatisation can be explained by the initial formation of the expected cycloadduct **45** bearing an acidic proton at C-4, which is abstracted under the rather basic cycloaddition conditions, the sugar ring oxygen elimination follows providing **46**.[24]

The same β-elimination was observed in the reaction of olefin **33** with benzonitrile oxide **44**, which gave only one compound **47** in 35% yield (Scheme 4). This poor yield shows again the low reactivity of **33** compared to the methylene analogue. In fact *exo*-glycals with a methylene group either of the gluco[18] or galacto[21] series or with a methyl or phenyl substituent on the double bond have been reported to be good substrates in the INOC reaction.[20]



Scheme 4. Benzonitrile oxide cycloaddition reactions.

The deprotection of representative compounds bearing acetonides was next examined in order to evaluate the robustness of the synthesised compounds. Removal of the acetonides of compounds **7** and **46** was carried out very cleanly and quantitatively from treatment with 25% v/v TFA in water at room temperature to give the free spirosugar-heterocycle **48** and isoxazole **49** (Scheme 5). It shows that furano-spiroisoxazolidine templates are stable in acidic medium. The equilibration of furano- to pyrano-isoxazolidine does not occur and that the anomeric configuration is also preserved.



Scheme 5. Representative deprotected compounds.

3. Discussion

Not unexpectedly, cycloadditions performed with *exo*-glycals seem very sensitive to the steric hindrance of both the nitrone and the trisubstituted olefinic bond. Excellent yields (75–92%) were obtained upon reaction of furano *exo*-glycals with the unsubstituted nitrone **5** giving only one stereogenic centre at C4 (isoxazolidine numbering), the absolute configuration of which is dictated by the starting olefin geometry. The fact that a single adduct was obtained in each case strongly supports an excellent facial control on the carbohydrate template. The β-selectivity, which is systematically observed with furano *exo*-glycals, can be explained by the overcrowding of the α-face by the fused dioxolane-protecting group.

The importance of stereoelectronic control in the NOC is well known[1a] and the *endo* attack is largely preferred.[30a,b] However, the steric bulk of the two partners play an important role, favouring or disfavouring the *endo* attack. In our cycloaddition reaction, the absolute configuration at C3 is dictated by the *endo*/*exo* attack of the nitrone. Thus, the observed *trans*/*cis* ratio of the C3–C4 substituents of isoxazolidines is the opposite of the *endo*/*exo* attack. In the furano series, the yields and *cis*/*trans* ratio of the different isoxazolidines are significantly different and should deserve comment. The first point is that with nitrones **3**, **4** and **5**, yields are good to excellent between 75% and 96%. This was not the case with the butylidenemethylamine *N*-oxide **2**, which was used as an *E*/*Z* mixture and gave cycloadducts in 50–58% average yields. The lower reactivity of this nitrone cannot be only the fact of steric hindrance because nitrone **4**, which is also substituted by a propyl group, gave better yields (89–96%).

The cycloaddition of nitrone **3** with (*E*)-olefins **1** and **12** (Table 1, entries 2 and 7) gave comparable *trans*/*cis* ratios, 2:1 (76%) and 2.3:1 (86%), respectively. Assuming that nitrone **3** reacts via the more stable *Z* isomer, it is believed that cycloadditions on **1** and **12** preferentially took place via the *endo* attack pictured by **A** (Fig. 3) to provide the observed major *trans*-isomers **8** and **19**. A substantial amount of *cis*-isomers **9** and **20** was formed via the *exo* attack (**B**, Fig. 3). It is worth noting that the corresponding *Z* olefins **11** and **13** behaved differently upon reaction with nitrone **3**. The

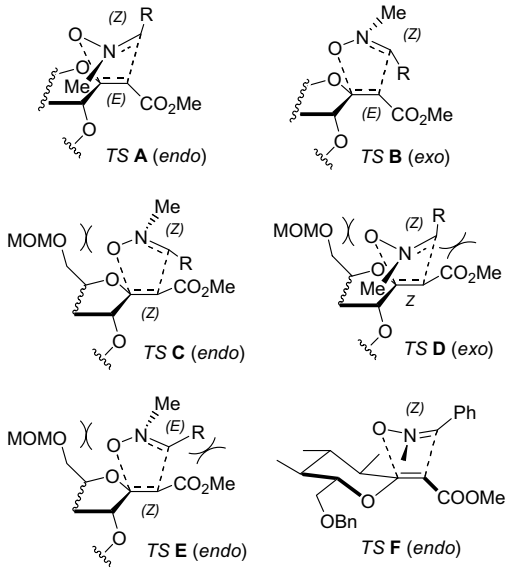


Figure 3. Postulated transition state representation.

trans-selectivity is dramatically enhanced with olefin **13** (*trans*/*cis* 7.4:1, Table 1, entry 11), compared to olefin **11** (*trans*/*cis* 2:1, Table 1, entry 4). It clearly demonstrates the influence of the sugar part in the *endo*/*exo* selectivity of the reaction. Assuming that nitrone **3** reacts as a *Z* form, major isomer **26** would be formed via *TS* **C** (*endo*) and the minor *cis*-isomer **27** via *TS* **D** (*exo*). The low proportion of *cis*-diastereoisomer **27** tends to demonstrate that *TS* **D** (depicted as a *ribo* configuration in Fig. 3) is much more congested in the case of *ribo*-derivatives than in the case of *gulo*-derivatives. This is confirmed by the 6:1 ratio in favour of the *trans*-orientation (compound **28**), obtained when reacting nitrone **2** with olefin **13** (Table 1, entry 12). Indeed the same nitrone **2** gave a 1.2:1 ratio of *trans*/*cis*-isomers when reacting with the (*Z*)-*gulo* olefin **11** (Table 1, entry 5). *endo*-*TS* **E** could also contribute to the formation of the minor *cis*-compound **29** (Table 1, entry 12) if the reaction occur from the *E* form of nitrone **2**. Consequently, *TS* **E** is certainly also very congested in the *ribo* series.

In the case of pyrano *exo*-glycals, facial selectivity was dependent on the nature of the nitrone and decreased when going from nitrone **5** to **3** and then **2**. With the unsubstituted nitrone **5**, facial selectivity on the olefin was complete giving only α cycloadducts **41** and **43** (Table 3, entries 3 and 4). A 5:1 α/β ratio was obtained when reacting olefin **33** with the little crowded nitrone **3** (Table 3, entry 1) and the more crowded nitrone **2** gave opposite results (α/β 1:1.6, Table 3, entry 2). With regard to the *cis*/*trans* ratio, in the reaction of olefin **33** with nitrone **3**, the *trans*-isomers were predominant, in particular the α-*trans*-isomer **35** (*trans*/*cis* 2:1, Table 3, entry 1). Assuming that nitrone **3** reacts in its *Z* form, the reaction of **3** proceeds preferentially via the *endo* attack depicted in **F** giving the *trans* adduct. Reaction of nitrone **2** with olefin **33** was not selective (*trans*/*cis* 1.1:1, Table 3, entry 2).

More insights on these mechanisms should arise from the computational evaluation of the different transition states.[31a,b]

4. Conclusion

The results reported herein show that the capto-dative olefins **1**, **11**, **12** and **13** are good substrates in the nitrone-cycloaddition reaction, provided that the reactions were carried out under microwave activation. Almost no reaction was observed under standard thermal conditions. These cycloadditions provide new spiroheterocycles with good stereoselectivities and yields. Excellent facial selectivities on the sugar olefins were observed with these bicyclic furanose *exo*-glycals due to the presence of the dioxolane-protecting group near the anomeric centre. The *endo* mode for the *Z* nitrone cycloaddition is preferred as postulated in most NOC reactions.

Pyranose *exo*-glycal **33** also gave good yields in NOC reactions with nitrones **2**, **3** and **5**. However, due to the steric hindrance of both faces of the sugar ring, facial selectivity is not complete and the cycloaddition reactions give α/β mixtures. Here again the *endo* mode of cycloaddition is preferred with the *Z* nitrone **3**. The reaction is much more complex to rationalise with nitrone **2** since no selectivity was observed. The reactivity was similar in the nitrile oxide reaction of furano *exo*-glycals **1**, **11** and pyrano *exo*-glycal **33**. A sugar ring opening was observed, may be due to the basic reaction medium giving chiral isoxazoles. All the new compounds formed in these cycloadditions easily obtained chiral scaffolds suitable for the construction of stereodiverse peptidomimetics libraries. All the new compounds, which can be easily deprotected, can also be regarded as spironucleosides and should therefore present interesting biological properties.

5. Experimental

5.1. General methods

5.1.1. General indications. FTIR spectra were recorded on a Perkin–Elmer Spectrum 1000 on NaCl windows or KBr pellets. ^{1}H NMR and ^{13}C spectra were recorded on a Bruker AC 250 or on a Bruker DRX 400 spectrometer. Chemical shifts (δ) are given in ppm and coupling constants (J) in hertz (Hz). Multiplicities of NMR signals are designed as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines). 1H assignments were confirmed by homonuclear 2D COSY correlated experiments. Attribution of ^{13}C signals are based on the *J*-modulated spin-echo sequence and/or heteronuclear two-dimensional techniques. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass spectra were recorded on a Trio 1000 Thermo Quest spectrometer in the electron impact mode or a Platform Micromass spectrometer in the electro spray mode. Specific rotations were determined on a Perkin–Elmer 141 polarimeter (10 cm cell). Elemental

analyses were obtained with a Thermofinnigan Flash EA 1112 apparatus. Analytical thin-layer chromatography was performed on Merck 60 F_{254} pre-coated silica gel plates. Compounds were visualised with UV light and (or) 30% methanolic H_2SO_4-heat as developing agent. Preparative chromatography was performed on silica gel 60 (230–40 mesh ASTM). Reverse phase HPLC was performed with a Gilson 321 apparatus equipped with a C18 chromasil column. Detection was carried out using a Polymer Laboratories evaporator light scattering 1000 (PL ELS 1000). Melting points were determined in capillaries on a Tottoli apparatus and are uncorrected. *N*-Butylidenemethylamine *N*-oxide **2**,[32] *N*-benzylidenemethylamine *N*-oxide **3**[32] and *N*-butylidenebenzylamine *N*-oxide **4**[33] were prepared as described.

5.2. Cycloaddition reactions with *N*-butylidenemethylamine *N*-oxide 2, *N*-benzylidenemethylamine *N*-oxide 3 and *N*-butylidenebenzylamine *N*-oxide 4, under microwave activation. General procedure

A solution of *exo*-glycal **1**, **11**–**13** or **33** and a threefold excess of nitrones **2**–**4** (1.5 equiv) in toluene (0.7 mL/mmol) in a septum-sealed glass tube was heated at 120–140 °C in a focussed microwave oven (Discover® CEM) for 22–100 min until the *exo*-glycal was completely consumed (TLC control). Purification of the crude reaction mixtures by silica gel column chromatography with EtOAc–hexane as eluent afforded spiroisoxazolidines **6**–**9**, **14**–**17**, **19**–**24**, **26**–**31** and **34**–**40** (50–96% yields).

5.2.1. Methyl (3*R*,4*R*,5*S*,7*S*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-methyl-7-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-propyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 6 and methyl (3*S*,4*R*,5*S*,7*S*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-methyl-7-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-propyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 7.

Compound **1** (500 mg, 1.60 mmol) was converted to **6** (200 mg, 0.48 mmol) and **7** (50 mg, 0.12 mmol) according to the general procedure. Reaction time: 25 min; 50% yield. **6**/**7** 4:1.

Eluted first (R_f 0.48, silica gel, 50% EtOAc in hexane) was **6** as a solid; mp 92 °C; $[\alpha]_D^{25} = -159.1$ (*c* 1, $CHCl_3$); ν_{max} (KBr) 2987.04, 2959.59, 2936.62, 1742.82, 1458.12; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, 3H, *J* 7.2 Hz, CH_3 propyl), 1.20 (s, 3H, CH_3 acetal), 1.20–1.35 (m, 2H, CH_2 propyl), 1.35 (s, 3H, CH_3 acetal), 1.36 (s, 3H, CH_3 acetal), 1.40 (s, 3H, CH_3 acetal), 1.45–1.60 (m, 2H, CH_2 propyl), 2.70 (s, 3H, N–CH_3), 2.84 (m, 1H, H-3), 3.34 (d, 1H, $J_{3,4}$ 8.08 Hz, H-4), 3.65 (m, 4H, CO_2CH_3, H-5′), 3.90 (dd, 1H, $J_{7,8}$ 4.0, $J_{4',7}$ 8.1 Hz, H-7), 4.17 (dd, 1H, $J_{4',5'}$ 6.7, J_{gem} 8.4 Hz, H-5′), 4.32 (m, 1H, H-4′), 4.56 (d, 1H, $J_{8,9}$ 5.9 Hz, H-9), 4.62 (dd, 1H, $J_{8,9}$ 5.9, $J_{7,8}$ 4.0 Hz, H-8); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.13 (CH_3 propyl), 19.35 (CH_2 propyl), 25.09, 25.43, 25.67, 26.57 (4 × CH_3 acetal), 33.68 (CH_2 propyl), 43.71 (N–CH_3), 51.82 (CO_2CH_3), 60.88 (C-4), 66.00 (C-5′), 73.82 (C-3), 75.48 (C-4′), 79.71 (C-8), 81.06 (C-7), 83.00 (C-9), 109.80 (C acetal), 112.22 (C-5), 112.87 (C acetal), 172.17 (CO_2CH_3). Anal. Calcd for $C_{20}H_{33}NO_8$: C, 57.82; H, 8.01; N, 3.37. Found: C, 57.68; H, 8.11; N, 3.37.

Eluted second (R_f 0.38, silica gel, 50% EtOAc in hexane) was **7** as a yellow oil; $[\alpha]_D^{26} = -70.1$ (*c* 1.1, $CHCl_3$); ν_{max} (neat) 2986.82, 2959.31, 2936.85, 1744.98, 1458.15; ^{1}H NMR ($CDCl_3$, 400 MHz,): δ 0.91 (t, 3H, *J* 7.0 Hz, CH_3 propyl), 1.22 (s, 3H, CH_3 acetal), 1.26 (m, 2H, CH_2 propyl), 1.38 (s, 3H, CH_3 acetal), 1.39 (s, 3H, CH_3 acetal), 1.43 (s, 3H, CH_3 acetal), 1.50 (m, 2H, CH_2 propyl), 2.85 (s, 3H, N–CH_3), 3.39 (m, 1H, H-3), 3.55 (d, 1H, $J_{3,4}$ 7.0 Hz, H-4), 3.75 (s, 3H, CO_2CH_3), 3.77 (dd, 1H, $J_{4',5'}$ 6.1, J_{gem} 8.6 Hz, H-5′), 3.95 (dd, 1H, $J_{7,8}$ 3.5, $J_{4',7}$ 8.6 Hz, H-7), 4.18 (dd, 1H, $J_{4',5'}$ 6.1 Hz, J_{gem} 8.6 Hz, H-5′), 4.35 (m, 1H, H-4′), 4.63 (m, 1H, H-8), 4.74 (d, 1H, $J_{8,9}$ 6.0 Hz, H-9); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.67 (CH_3 propyl), 20.67 (CH_2 propyl), 25.53, 25.83, 26.21, 26.43 (4 × CH_3 acetal), 32.48 (CH_2 propyl), 48.40 (N–CH_3), 52.14 (CO_2CH_3), 59.04 (C-4), 66.46 (C-5′), 69.65 (C-3), 75.66 (C-4′), 80.17 (C-8), 81.31 (C-7), 84.05 (C-9), 110.28 (C acetal), 113.58 (C-5), 114.68 (C acetal), 169.79 (CO_2CH_3). *m*/*z* (EI+) 416.2 [$(M+1)^+$, 8%], 415.1 [$(M)^+$, 11%], 400.1 [$(M-CH_3)^+$, 13%], 340.1 (25), 102.0 (65), 100.8 (100); HRMS *m*/*z* (ES+) calcd for $C_{20}H_{34}NO_8$ $[M+H]^+$ 416.2284, found 416.2281.

5.2.2. Methyl (3*R*,4*R*,5*S*,7*S*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-methyl-7-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 8 and methyl (3*S*,4*R*,5*S*,7*S*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-methyl-7-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 9.

Compound **1** (429 mg, 1.36 mmol) was converted to **8** and **9** according to the general procedure. Reaction time: 25 min; 76% yield (328 mg, 0.73mmol). **8**/**9** 2:1 (inseparable mixture). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24, 1.37, 1.40, 1.47 (4 × s, CH_3 acetal), 2.59 (s, 0.66 NCH_3, compound **8**), 2.86 (s, 0.34 NCH_3, compound **9**), 3.31 (s, 0.34 CO_2CH_3, compound **9**), 3.61 (s, 0.66 CO_2CH_3, compound **8**), 3.65–4.29 (m, 4H), 4.30–4.48 (m, 1H), 4.59–4.77 (m, 2.66H), 4.86 (br d, 0.34H), 7.20–7.48 (5H, Ar); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 24.8–26.4 (4 × CH_3 acetal), 42.7 (N–CH_3, compound **8**), 46.8 (N–CH_3, compound **9**), 51.1 (CO_2CH_3, compound **9**), 51.6 (CO_2CH_3, compound **8**), 61.3, 63.1, 65.8, 72.7, 75.0, 75.3, 77.9, 79.6, 80.7, 80.9, 82.7, 83.3, 109.5, 112.2, 112.7, 112.9, 114.0, 127.2–128.4 (Ar), 134.7 and 135.6 (C*ipso*), 168.0 (CO_2CH_3, compound **9**), 170.7 (CO_2CH_3, compound **8**). *m*/*z* (EI+) 451.1 [$(M+2)^+$, 4%], 450.1 [$(M+1)^+$, 15%], 449.0 [$(M)^+$, 10%], 434.0 [$(M-CH_3)^+$, 5%], 403.0 (20), 133.9 (100). HRMS *m*/*z* (ES+) calcd for $C_{23}H_{32}NO_8$ $[M+H]^+$ 450.2128, found 450.2115.

5.2.3. Methyl (3*R*,4*S*,5*S*,7*S*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-methyl-7-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 14 and methyl (3*S*,4*S*,5*S*,7*S*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-methyl-7-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 15.

Compound **11** (270 mg, 0.86 mmol) was converted to **14** (170 mg, 0.35 mmol) and **15** (80 mg, 0.16 mmol) according to the general procedure. Reaction time: 16 min, 130 °C; 80% yield. **14**/**15** 2:1. Eluted first (R_f 0.68, silica gel, 50% EtOAc in hexane) was **14** as a glassy solid; mp

178 °C; $[\alpha]_D^{25} = +1.8$ (*c* 1.1, $CHCl_3$); ν_{max} (KBr) 3434.82, 3331.85, 3129.40, 2992.94, 1745.81, 1658.93; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.34 (s, 3H, CH_3 acetal), 1.38 (s, 3H, CH_3 acetal), 1.44 (s, 3H, CH_3 acetal), 1.45 (s, 3H, CH_3 acetal), 2.64 (s, 3H, N–CH_3), 3.68 (s, 3H, CO_2CH_3), 3.75 (dd, 1H, $J_{4',5'}$ 7.2, J_{gem} 8.0 Hz, H-5′), 3.87 (d, 1H, $J_{3,4}$ 9.5 Hz, H-4), 4.09 (ddd, 1H, $J_{4',7} = 7.6$, $J_{7,8}$ 2.5, $J_{7,9}$ 1,0 Hz, H-7), 4.20 (m, 1H, H-5′), 4.26 (pseudo q, 1H, *J* 7.5 Hz, H-4′), 4.32 (d, 1H, $J_{3,4}$ 9.5 Hz, H-3), 4.78–4.80 (m, 2H, H-8, H-9), 7.25–7.41 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 25.18 (CH_3 acetal), 25.99 (2 × CH_3 acetal), 27.07 (CH_3 acetal), 43.67 (N–CH_3), 52.23 (CO_2CH_3), 59.52 (C-4), 66.3 (C-5′), 76.2 (C-3), 76.32 (C-8), 80.20 (C-9), 83.8 (C-4′), 85.9 (C-7), 110.19 (C-5), 111.95 113.76 (2 × C acetal), 128.38–129.11 (5C, Ar), 137.76 (C*ipso*), 168.88 (CO_2CH_3). Anal. Calcd for $C_{23}H_{31}NO_8$: C, 61.46; H, 6.95; N, 3.12. Found: C, 61.91; H, 6.99; N, 3.20.

Eluted second (R_f 0.45, silica gel, 50% EtOAc in hexane) was **15** as a glassy solid; mp. 133–135 °C; $[\alpha]_D^{26} = -50.1$ (*c* 0.4, $CHCl_3$); ν_{max} (KBr) 3431.20, 3330.44, 3129.77, 2990.97, 1759.54, 1654.31; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.33 (s, 3H, CH_3 acetal), 1.35 (s, 3H, CH_3 acetal), 1.43 (s, 3H, CH_3 acetal), 1.47 (s, 3H, CH_3 acetal), 2.71 (s, 3H, N–CH_3), 3.39 (s, 3H, CO_2CH_3), 3.78 (pseudo t, 1H, J_{gem} 8.0 Hz, H-5′), 3.92 (d, 1H, $J_{3,4}$ 8.0 Hz, H-3), 4.11–4.17 (m, 2H, H-5′, H-7), 4.18 (d, 1H, $J_{3,4}$ 8.0 Hz, H-4), 4.30 (m, 1H, H-4′), 4.67 (d, 1H, $J_{8,9}$ 5.9 Hz, H-9), 4.77 (dd, 1H, $J_{7,8}$ 3.8, $J_{8,9}$ 5.9 Hz, H-8), 7.25–7.40 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 24.91, 25.56, 25.66, 26.49 (4 × CH_3 acetal), 43.95 (N–CH_3), 51.22 (CO_2CH_3), 58.22 (C-4), 65.92 (C-5′), 74.92 (C-3), 75.33 (C-4′), 79.84 (C-8), 81.76 (C-7), 85.24 (C-9), 109.67 (C-5), 111.79 113.62 (2 × C acetal), 127.99–128.23 (Ar), 134.42 (C*ipso*), 167.13 (CO_2CH_3). HRMS *m*/*z* (ES+) calcd for $C_{23}H_{32}NO_8$ $[M+H]^+$ 450.2128, found 450.2134.

5.2.4. Methyl (3*S*,4*S*,5*S*,7*S*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-methyl-7-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-propyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 16. Compound **11** (420 mg, 1.34 mmol) was converted to **16** and **17** according to the general procedure. Yield 65% (354 mg, 0.85 mmol). **16/17** 1.2:1. Data for compound **16**: solid; mp 53 °C; R_f 0.40 (silica gel, 30% EtOAc in hexane); $[\alpha]_D^{25} = +3.5$ (*c* 1, $CHCl_3$); ν_{max} (KBr) 3434.80, 3128.92, 2992.93, 1739.12, 1665.16; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, 3H, *J* 7.1 Hz, CH_3 propyl), 1.29 (s, 3H, CH_3 acetal), 1.35 (m, 2H, CH_2 propyl), 1.35 (s, 3H, CH_3 acetal), 1.41 (s, 3H, CH_3 acetal), 1.42 (m, 1H, CH*H* propyl), 1.45 (s, 3H, CH_3 acetal), 1.52 (m, 1H, CH*H* propyl), 2.85 (s, 3H, N–CH_3), 3.42 (m, 1H, H-3), 3.47 (d, 1H, $J_{3,4}$ 7.9 Hz, H-4), 3.69–3.76 (m, 4H, CO_2CH_3, H-5′), 3.99 (dd, 1H, $J_{7,8}$ 3.9, $J_{4',7}$ 7.8 Hz, H-7), 4.15 (dd, 1H, $J_{4',5'}$ 6.7, J_{gem} 8.2 Hz, H-5′), 4.22 (m, 1H, H-4′), 4.57 (d, 1H, $J_{8,9}$ 5.9 Hz, H-9), 4.70 (dd, 1H, $J_{7,8}$ 3.9, $J_{8,9}$ 5.9 Hz, H-8); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.11 (CH_3 propyl), 19.38 (CH_2 propyl), 24.58 (CH_3 acetal), 25.52 (2C, CH_3 acetal), 26.67 (CH_3 acetal), 35.13 (CH_2 propyl), 45.27 (N–CH_3), 51.85 (CO_2CH_3), 57.04 (C-4), 65.88 (C-5′), 70.22 (C-3), 75.70 (C-4′), 79.71 (C-8), 82.52 (C-7), 85.04 (C-9), 109.65 (C-5), 112.79 (C acetal), 113.19 (C acetal), 169.25 (CO_2CH_3). Anal. Calcd for $C_{20}H_{33}NO_8$: C, 57.82; H, 8.01; N, 3.37. Found: C, 57.49; H, 8.10; N, 3.47.

Compound **17** was inseparable from **16**.

5.2.5. Methyl (3*S*,4*R*,5*S*,7*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-methyl-7-[(methoxymethoxy)methyl]-3-phenyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 19 and methyl (3*R*,4*R*,5*S*,7*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-methyl-7-[(methoxymethoxy)methyl]-3-phenyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 20. Compound **12** (200 mg, 0.69 mmol) was converted to **19** (179 mg, 0.42 mmol) and **20** (78 mg, 0.18 mmol) according to the general procedure. Reaction time: 90 min; 86% yield. **19/20** 2.3:1. Eluted first (R_f 0.60, silica gel, 30% EtOAc in hexane) was **19** as a yellow solid; mp 53 °C; $[\alpha]_D^{25} = -127.3$ (*c* 1, $CHCl_3$; ν_{max} (KBr) 3064.22, 3031.72, 2989.66, 2951.01, 1741.82; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.32 (s, 3H, CH_3 acetal), 1.44 (s, 3H, CH_3 acetal), 2.61 (s, 3H, N–CH_3), 3.41 (s, 3H, CH_2OCH_3), 3.60–3.69 (m, 5H, CO_2CH_3, H-4 and 7-CH*H*), 3.83 (dd, 1H, $J_{7,7\text{-}CHH}$ 6.4, J_{gem} 10.2 Hz, 7-CH*H*), 3.87 (br d, 1H, $J_{3,4}$ 8.5 Hz, H-3), 4.35 (dt, 1H, $J_{7,7\text{-}CHH}$ 8.0, $J_{7,8}$ 1,0 Hz, H-7) 4.68 (d, 1H, J_{gem} 6.4 Hz, CH*H*OCH$_3$), 4.70 (d, 1H, $J_{8,9}$ 5.7 Hz, H-9), 4.73–4.79 (m, 2H, CH*H*OCH$_3$ and H-8), 7.31–7.41 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 25.79 (CH_3 acetal), 26.41 (CH_3 acetal), 43.08 (N–CH_3), 52.11 (CO_2CH_3), 55.43 (CH_2OCH_3), 64.46 (C-4), 68.73 (7-CH_2), 78.02 (C-3), 82.54 (C-8), 83.26 (C-9), 84.61 (C-7), 96.81 (CH_2OCH_3), 112.94, 113.98 (C acetal, C-5), 128.21–128.90 (5C, Ar), 136.35 (C*ipso*), 171.36 (CO_2CH_3). Anal. Calcd for $C_{21}H_{29}NO_8$: C, 59.56; H, 6.90; N, 3.31. Found: C, 59.52; H 6.91; N, 3.41.

Eluted second (R_f 0.32, silica gel, 30% EtOAc in hexane) was **20** as a solid; mp 135 °C; $[\alpha]_D^{25} = -9.0$ (*c* 1.1, $CHCl_3$); ν_{max} (KBr) 2979.65, 2948.43, 1749.84; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.29 (s, 3H, CH_3 acetal), 1.43 (s, 3H, CH_3 acetal), 2.86 (s, 3H, N–CH_3), 3.36 (s, 3H, CO_2CH_3), 3.41 (s, 3H, CH_2OCH_3), 3.61–3.70 (m, 2H, H-4 and 7-CH*H*), 3.72 (dd, 1H, $J_{7,7\text{-}CHH}$ 7.6, J_{gem} 10.6 Hz, 7-CH*H*), 4.38 (pseudo t, 1H, *J* 7.5 Hz, H-7), 4.50 (br d, 1H, $J_{3,4}$ 6.8 Hz, H-3), 4.69 (br s, 2H, CH_2OCH_3), 4.75 (d, 1H, $J_{8,9}$ 5.8 Hz, H-8 or H-9), 4.91 (d, 1H, $J_{8,9}$ 5.8 Hz, H-8 or H-9), 7.28–7.40 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 25.36 (CH_3 acetal), 26.47 (CH_3 acetal), 47.30 (N–CH_3), 51.61 (CO_2CH_3), 55.58 (CH_2OCH_3), 62.76 (C-4), 68.69 (7-CH_2), 73.48 (C-3), 82.34 (C-8 or C-9), 83.59 (C-8 or C-9), 84.30 (C-7), 96.92 (CH_2OCH_3), 112.81 (C acetal), 116.07 (C-5), 127.59–128.58 (5C, Ar), 134.88 (C*ipso*), 168.46 (CO_2CH_3). Anal. Calcd for $C_{21}H_{29}NO_8$: C, 59.56; H, 6.90; N, 3.31. Found: C, 59.68; H 6.88, N, 3.30.

5.2.6. Methyl (3*R*,4*R*,5*S*,7*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-methyl-7-[(methoxymethoxy)methyl]-3-propyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 21 and methyl (3*S*,4*R*,5*S*,7*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-methyl-7-[(methoxymethoxy)methyl]-3-propyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 22. Compound **12** (204 mg, 0.71 mmol) was converted to **21** (101 mg,

0.26 mmol) and **22** (58 mg, 0.15 mmol) according to the general procedure. Reaction time: 95 min; 58% yield. **21/22** 1.7:1.

Eluted first (R_f 0.39, silica gel, 30% EtOAc in hexane) was **21** as a yellow oil; $[\alpha]_D^{25} = -89.9$ (c 0.9, $CHCl_3$); ν_{max} (neat) 2958.36, 2935.47, 2875.78, 1742.91, 1459.14; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, 3H, J 7.3 Hz, CH_3 propyl), 1.30 (s, 3H, CH_3 acetal), 1.35 (m, 2H, CH_2 propyl), 1.45 (s, 3H, CH_3 acetal), 1.53 (m, 2H, CH_2 propyl), 2.66 (s, 3H, N–CH_3), 2.84 (m, 1H, H-3), 3.28 (d, 1H, $J_{3,4}$ 8.0 Hz, H-4), 3.37 (s, 3H, CH_2OCH_3), 3.54 (pseudo t, 1H, J 9.7 Hz, 7-CHH), 3.65–3.78 (m, 4H, CO_2CH_3 and 7-CHH), 4.27 (dd, 1H, $J_{7,7\text{-CH}H}$ 7.3, $J_{7,7\text{-CH}H}$ 9.7 Hz, H-7), 4.60–4.73 (m, 4H, H-8, H-9 and CH_2OCH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.24 (CH_3 propyl), 19.51 (CH_2 propyl), 25.65 (CH_3 acetal), 26.42 (CH_3 acetal), 33.98 (CH_2 propyl), 45.85 (N–CH_3), 51.18 (CO_2CH_3), 55.43 (CH_2OCH_3), 62.42 (C-4), 68.69 (7-CH_2), 73.63 (C-3), 82.58 (C-8), 83.29 (C-9), 84.31 (C-7), 96.83 (CH_2OCH_3), 112.78 (C acetal), 116.70 (C-5), 169.51 (CO_2CH_3). m/z (EI+) 390.1 [$(M+1)^+$, 10%], 389.0 [$(M)^+$, 12%], 374.1 [$(M-CH_3)^+$, 6%], 358.0 (8), 343.1 (40), 314.0 (65), 311.1 (100). HRMS m/z (ES+) calcd for $C_{18}H_{32}NO_8$ $[M+H]^+$ 390.2128, found 390.2130.

Eluted second (R_f 0.12, silica gel, 30% EtOAc in hexane) was **22** as a yellow oil; $[\alpha]_D^{25} = -45.7$ (c 1.4, $CHCl_3$); ν_{max} (neat) 2958.34, 2875.45, 1751.04, 1676.28, 1459.02; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.93 (t, 3H, J 5.8 Hz, CH_3 propyl), 1.28 (s, 3H, CH_3 acetal), 1.35 (m, 2H, CH_2 propyl), 1.44 (s, 3H, CH_3 acetal), 1.45 (m, 2H, CH_2 propyl), 2.68 (s, 3H, N–CH_3), 3.24 (m, 1H, H-3), 3.38 (s, 3H, CH_2OCH_3), 3.47 (d, 1H, $J_{3,4}$ 6.7 Hz, H-4), 3.52–3.70 (m, 2H, 7-CH_2), 3.75 (s, 3H, CO_2CH_3), 4.30 (pseudo t, 1H, J 7.3 Hz, H-7), 4.65 (s, 2H, CH_2OCH_3), 4.70 (d, 1H, $J_{8,9}$ 5.8 Hz, H-8 or H-9), 4.78 (d, 1H, $J_{8,9}$ 5.8 Hz, H-8 or H-9); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.18 (CH_3 propyl), 20.21 (CH_2 propyl), 25.16 (CH_3 acetal), 26.31 (CH_3 acetal), 31.70 (CH_2 propyl), 47.88 (N–CH_3), 51.73 (CO_2CH_3), 55.41 (CH_2OCH_3), 59.53 (C-4), 68.41 (7-CH_2), 72.92 (C-3), 83.53 (C-9), 83.95 (C-8), 84.88 (C-7), 96.72 (CH_2OCH_3), 112.59 (C acetal), 117.32 (C-5), 169.47 (CO_2CH_3). m/z (EI+) 391.2 [$(M+2)^+$, 2.5%], 390.1 [$(M+1)^+$, 12%], 389.1 [$(M)^+$, 20%], 374.1 [$(M-CH_3)^+$, 8%], 358.1 (7), 343.1 (40), 314.0 (90), 311.1 (100). HRMS m/z (ES+) calcd for $C_{18}H_{32}NO_8$ $[M+H]^+$ 390.2128, found 390.2119.

5.2.7. Methyl (3*R*,4*R*,5*S*,7*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-benzyl-7-[(methoxymethoxy)methyl]-3-propyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 23 and methyl (3*S*,4*R*,5*S*,7*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-benzyl-7-[(methoxymethoxy)methyl]-3-propyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 24. Compound **12** (300 mg, 1.04 mmol) was converted to **23** (215 mg, 0.46 mmol) and **24** (214 mg, 0.46 mmol) according to the general procedure. Reaction time: 100 min; 89% yield. **23/24** 1:1. Eluted first (R_f 0.52, silica gel, 30% EtOAc in hexane) was **23** as a yellow oil; $[\alpha]_D^{26} = -199.6$ (c 1, $CHCl_3$); ν_{max} (neat) 2953.36, 2875.62, 1742.90, 1497.23, 1455.76; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, 3H, J 7.3 Hz, CH_3 propyl), 1.27 (s, 3H, CH_3 acetal), 1.34 (m, 1H, CHH propyl), 1.43 (s, 3H, CH_3 acetal), 1.44 (m, 1H, CHH propyl), 1.64 (m, 2H, CH_2 propyl), 3.01 (dd, 1H, J_{gem} 9.9, $J_{7,CHH}$ 7.0 Hz, 7-CHH), 3.13 (m, 1H, H-3), 3.26 (m, 4H, CH_2OCH_3, 7-CHH), 3.33 (d, 1H, $J_{3,4}$ 7.9 Hz, H-4), 3.72 (s, 3H, CO_2CH_3), 3.76 (d, 1H, J 13.9 Hz, CHHPh), 4.13 (dd, 1H, $J_{7,8}$ 3.8, $J_{7,CHH}$ 7.0 Hz, H-7), 4.14 (d, 1H, J 13.0 Hz, CHHPh), 4.34 (d, 1H, J_{gem} 16.0 Hz, CHHOCH$_3$), 4.35 (d, 1H, J_{gem} 16.0 Hz, CHHOCH$_3$) 4.58 (pseudo s, 2H, H-8, H-9), 7.24–7.37 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.22 (CH_3 propyl), 19.21 (CH_2 propyl), 25.54 (CH_3 acetal), 26.18 (CH_3 acetal), 33.87 (CH_2 propyl), 51.91 (CO_2CH_3), 55.12 (CH_2OCH_3), 60.50 (CH_2Ph), 61.22 (C-4), 68.09 (7-CH_2), 71.59 (C-3), 82.37 (C-9), 83.07 (C-8), 83.86 (C-7), 96.25 (CH_2OCH_3), 112.50 (C-5), 113.20 (C acetal), 127.0–128.8 (5C, Ar), 137.51 (C*ipso*), 172.28 (CO_2CH_3). m/z (EI+) 466.4 [$(M+1)^+$, 3%], 465.2 [$(M)^+$, 18%], 450.2 [$(M-CH_3)^+$, 4%], 434.2 (5), 422.1 (7), 390.1 (63), 343.1 (50), 311.1 (100). HRMS m/z (ES+) calcd for $C_{24}H_{36}NO_8$ $[M+H]^+$ 466.2441, found 466.2437.

Eluted second (R_f 0.38, silica gel, 30% EtOAc in hexane) was **24** as a yellow oil; $[\alpha]_D^{26} = -27.0$ (c 1, $CHCl_3$); ν_{max} (neat) 2955.62, 2875.20, 1751.74, 1497.42; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.84 (t, 3H, J 7.1 Hz, CH_3 propyl), 1.17–1.42 (m, 7H, CH_3 acetal, 2 × CH_2 propyl), 1.46 (s, 3H, CH_3 acetal), 3.35 (s, 3H, CH_2OCH_3), 3.47–3.58 (m, 3H, 7-CHH, H-3, H-4), 3.65 (dd, 1H, J_{gem} 10.0, $J_{7,CHH}$ 7.6 Hz, 7-CHH), 3.75 (s, 3H, CO_2CH_3), 4.02 (d, 1H, J 13.5 Hz, CHHPh), 4.26 (d, 1H, J 13.0 Hz, CHHPh), 4.34 (pseudo t, 1H, J 7.6 Hz, H-7), 4.58 (**2**, 2H, J_{gem} 10.7 Hz, CH_2OCH_3), 4.67 (dd, 1H, $J_{8,9}$ 6.0, $J_{4,9}$ 0.7 Hz, H-9), 4.79 (d, 1H, $J_{8,9}$ 6.0 Hz), 7,25–7.40 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.05 (CH_3 propyl), 19.99 (CH_2 propyl), 25.09 (CH_3 acetal), 26.27 (CH_3 acetal), 32.45 (CH_2 propyl), 51.61 (CO_2CH_3), 55.35 (CH_2OCH_3), 59.08 (C-4), 65.21 (CH_2Ph), 67.79 (C-3), 68.26 (7-CH_2), 81.96 (C-8), 83.41 (C-9), 84.03 (C-7), 96.54 (CH_2OCH_3), 112.52 (C-5), 116.20 (C acetal), 127.20–128.82 (5C, Ar), 137.29 (C*ipso*), 169.38 (CO_2CH_3). m/z (EI+) 466.4 [$(M+1)^+$, 10%], 465.2 [$(M)^+$, 28%], 450.2 [$(M-CH_3)^+$, 7%], 434.1 (7), 422.1 (9), 390.1 (85), 311.1 (92), 105.9 (100). HRMS m/z (ES+) calcd for $C_{24}H_{36}NO_8$ $[M+H]^+$ 466.2441, found 466.2455.

5.2.8. Methyl (3*R*,4*S*,5*S*,7*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-methyl-7-[(methoxymethoxy)methyl]-3-phenyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 26 and methyl (3*S*,4*S*,5*S*,7*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-methyl-7-[(methoxymethoxy)methyl]-3-phenyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 27. Compound **13** (200 mg, 0.69 mmol) was converted to **26** (243 mg, 0.57 mmol) and **27** (33 mg, 0.08 mmol) according to the general procedure. Reaction time: 90 min; 94% yield. **26/27** 7.4:1. Eluted first (R_f 0.46, silica gel, 30% EtOAc in hexane) was **26** as a yellow oil; $[\alpha]_D^{25} = -11.8$ (c 1.1, $CHCl_3$); ν_{max} (neat) 3033.18, 2989.38, 2951.95, 1742.76; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.39 (s, 3H, CH_3 acetal), 1.50 (s, 3H, CH_3 acetal), 2.64 (s, 3H, N–

CH_3), 3.39 (s, 3H, CH_2OCH_3), 3.54 (dd, 1H, $J_{7,7\text{-}CHH}$ 8.7, J_{gem} 10.2 Hz, 7-CH*H*), 3.67 (s, 3H, CO_2CH_3), 3.71 (dd, 1H, $J_{7,7\text{-}CHH}$ 5.8, J_{gem} 10.2 Hz, 7-CH*H*), 3.93 (d, 1H, $J_{3,4}$ 9.5 Hz, H-4), 4.24 (br d, 1H, $J_{3,4}$ 9.5 Hz, H-3), 4.35 (dd, 1H, $J_{7,7\text{-}CHH}$ 5.8, $J_{7,CHH}$ 8.6 Hz, H-7) 4.68 (s, 2H, CH_2OCH_3), 4.81 (br s, 2H, H-8 and H-9), 7.28–7.39 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 25.14 (CH_3 acetal), 26.11 (CH_3 acetal), 43.44 (N–CH_3), 51.91 (CO_2CH_3), 55.37 (CH_2OCH_3), 59.56 (C-4), 68.16 (7-CH_2), 75.25 (C-3), 82.01 (C-8 or C-9), 84.92 (C-7), 84.61 (C-8 or C-9), 96.77 (CH_2OCH_3), 113.04, 113.14 (C acetal and C-5), 127.98–128.74 (5C, Ar), 137.31 (C*ipso*), 168.98 (CO_2CH_3). Anal. Calcd for $C_{21}H_{29}NO_8$: C, 59.56; H, 6.90; N, 3,31. Found: C, 59.45; H, 6.84; N, 3.42.

Eluted second (R_f 0.21, silica gel, 30% EtOAc in hexane) was **27** as a solid; mp. 65 °C; $[\alpha]_D^{25} = -169.7$ (*c* 1, $CHCl_3$); ν_{max} (KBr) 3430.24, 3128.86, 2993.47, 1753.44; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.39 (s, 3H, CH_3 acetal), 1.52 (s, 3H, CH_3 acetal), 2.71 (s, 3H, N–CH_3), 3.37 (s, 3H, CH_2OCH_3), 3.40 (s, 3H, CO_2CH_3), 3.61 (pseudo t, 1H, *J* 9.7 Hz, 7-CH*H*), 3.84 (dd, 1H, $J_{7,7\text{-}CHH}$ 4.9, J_{gem} 9.7, 7-CH*H*), 3.93 (br d, 1H, $J_{3,4}$ 8.2 Hz, H-3), 4.22 (d, 1H, $J_{3,4}$ 8.2 Hz, H-4), 4.36 (dd, 1H, $J_{7,7\text{-}CHH}$ 9.4, $J_{7,7\text{-}CHH}$ 4.8 Hz, H-7) 4.68 (AB, 2H, CH_2OCH_3), 4.71 (d, 1H, $J_{8,9}$ 6.0 Hz, H-8 or H-9), 4.85 (d, 1H, $J_{8,9}$ 6.0 Hz, H-8 or H-9), 7.25–7.41 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 25.29 (CH_3 acetal), 26.17 (CH_3 acetal), 44.30 (N–CH_3), 51.43 (CO_2CH_3), 55.53 (CH_2OCH_3), 58.52 (C-4), 67.24 (7-CH_2), 74.91 (C-3), 82.22 (C-8 or C-9), 85.56 (C-7), 87.89 (C-8 or C-9), 96.97 (CH_2OCH_3), 113.36, 113.44 (C acetal and C-5), 127.95–128.35 (5C, Ar), 134.83 (C*ipso*), 167.35 (CO_2CH_3). Anal. Calcd for $C_{21}H_{29}NO_8$: C, 59.56; H, 6.90; N, 3.31. Found: C, 59.47; H, 6.90; N, 3.11.

5.2.9. Methyl (3*S*,4*S*,5*S*,7*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-methyl-7-[(methoxymethoxy)methyl]-3-propyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 28 and methyl (3*R*,4*S*,5*S*,7*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-methyl-7-[(methoxymethoxy)methyl]-3-propyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 29. Compound **13** (300 mg, 1.04 mmol) was converted to **28** (200 mg, 0.51 mmol) and **29** (30 mg, 0.08 mmol) according to the general procedure. Reaction time: 45 min; 57% yield. **28/29** 6:1. Eluted first (R_f 0.43, silica gel, 30% EtOAc in hexane) was **28** as a yellow oil; $[\alpha]_D^{25} = -9.3$ (*c* 1.1, $CHCl_3$); ν_{max} (neat) 2956.83, 2875.94, 1742.36, 1458.44; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, *J* 7.2 Hz, 3H, CH_3 propyl), 1.20–1.42 (m, 6H, CH_3 acetal, CH_2 and CH*H* propyl), 1.51 (m, 4H, CH_3 acetal, CH*H* propyl), 2.81 (s, 3H, N–CH_3), 3.34–3.37 (m, 4H, CH_2OCH_3 and H-3), 3.52 (dd, 1H, $J_{7,CHH}$ 9.2, J_{gem}10.3 Hz, 7-CH*H*), 3.54 (d, 1H, $J_{3,4}$ 7.2 Hz, H-4), 3.65 (dd, 1H, $J_{7,CHH}$ 5.6, J_{gem} 10.3 Hz, 7-CH*H*), 3.73 (s, 3H, CO_2CH_3), 4.30 (dd, 1H, $J_{7,CHH}$ 5.6, $J_{7,CHH}$ 5.8 Hz, H-7), 4.60 (d, 1H, $J_{8,9}$ 6.0 Hz, H-9), 4.64 (s, 2H, CH_2OCH_3), 4.74 (d, 1H, $J_{8,9}$ 6.0 Hz, H-8); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.51 (CH_3 propyl), 19.87 (CH_2 propyl), 25.38 (CH_3 acetal), 26.43 (CH_3 acetal), 35.73 (CH_2 propyl), 46.01 (N–CH_3), 52.37 (CO_2CH_3), 55.75 (CH_2OCH_3), 58.02 (C-4), 68.53 (7-CH_2), 70.81 (C-3), 82.38 (C-8), 84.92 (C-7), 85.76 (C-9), 97.11 (CH_2OCH_3), 113.38 (C-5), 115.33 (C acetal), 170.23 (CO_2CH_3). Anal. Calcd for $C_{18}H_{31}NO_8$: C, 55.51; H, 8.02; N, 3,60. Found: C, 55.87; H, 8.04; N, 3.80.

Eluted second (R_f 0.17, silica gel, 30% EtOAc in hexane) was **29** as a yellow oil; $[\alpha]_D^{25} = -131.7$ (*c* 0.9, $CHCl_3$); ν_{max} (neat) 2958.49, 2875.61, 1750.56, 1458.53; ^{1}H NMR ($CDCl_3$ 400 MHz): δ 0.91 (t, 3H, *J* 7.3 Hz CH_3 propyl), 1.26 (m, 2H, CH_2 propyl), 1.34 (s, 3H, CH_3 acetal), 1.50 (s, 3H, CH_3 acetal), 1.87 (m, 1H, CH*H* propyl), 2.63 (m, 4H, N–CH_3 and H-3), 3.34 (s, 3H, CH_2OCH_3), 3.53 (pseudo t, 1H, *J* 9.9 Hz, 7-CH*H*), 3.68–3.74 (m, 4H, CO_2CH_3, 7-CH*H*), 3.90 (d, 1H, $J_{3,4}$ 7.4 Hz, H-4), 4.27 (dd, 1H, $J_{7\text{-}CHH}$ 4.9, $J_{7,CHH}$ 4.9 Hz, H-7), 4.57 (d, 1H, $J_{8,9}$ 5.9 Hz, H-9), 4.61 (AB, 2H, CH_2OCH_3), 4.77 (d, 1H, $J_{8,9}$ 5.9 Hz, H-8); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.20 (CH_3 propyl), 20.11 (CH_2 propyl), 24.97 and 25.89 (2 × CH_3 acetal), 29.14 (CH_2 propyl), 43.87 (N–CH_3), 51.44 (CO_2CH_3), 54.81 (C-4), 55.26 (CH_2OCH_3), 68.22 (7-CH_2), 71.24 (C-3), 83.12 (C-8), 83.55 (C-7), 84.99 (C-9), 96.75 (CH_2OCH_3), 112.98 and 113.38 (C-5 and C acetal), 168.02 (CO_2CH_3). *m*/*z* (EI+) 390.0 [$(M+1)^+$, 8%], 389.1 [$(M)^+$, 9%], 374.1 [$(M-CH_3)^+$, 5%], 358.1 (8), 343.1 (32), 314.0 (50), 311.1 (82), 101.9 (95), 85.9 (100). HRMS *m*/*z* (ES+) calcd for $C_{18}H_{32}NO_8$ $[M+H]^+$ 390.2128, found 390.2137.

5.2.10. Methyl (3*S*,4*S*,5*S*,7*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-benzyl-7-[(methoxymethoxy)methyl]-3-propyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 30 and methyl (3*R*,4*S*,5*S*,7*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-benzyl-7-[(methoxymethoxy)methyl]-3-propyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 31. Compound **13** (200 mg, 0.069 mmol) was converted to **30** (220 mg, 0.47 mmol) and **31** (90 mg, 0.19 mmol) according to the general procedure. Reaction time: 100 min; 96% yield. **30/31** 2.4:1. Eluted first (R_f 0.58, silica gel, 30% EtOAc in hexane) was **30** as an oil; $[\alpha]_D^{25} = -40.3$ (*c* 1.1, $CHCl_3$); ν_{max} (neat) 2954.84, 2875.51, 1740.68, 1496.73; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.74 (t, 3H, *J* 7.2 Hz, CH_3 propyl), 1.10 (m, 1H, CH*H* propyl), 1.25–1.38 (m, 2H, CH_2 propyl), 1,35 (s, 3H, CH_3 acetal), 1.47–1.60 (m, 4H, CH_3 acetal, CH*H* propyl), 3.32 (s, 3H, CH_2OCH_3), 3,45 (pseudo t, 1H, J_{gem} 10.1 Hz, 7-CH*H*), 3.60 (dd, 1H, J_{gem} 10.1, $J_{7,7\text{-}CHH}$ 5.6 Hz, 7-CH*H*), 3.62 (d, 1H, $J_{3,4}$ 4.7, H-4) 3.66 (m, 1H, H-3), 3.76 (s, 3H, CO_2CH_3), 4.15 (d, 1H, *J* 12.8 Hz, CH*H*Ph), 4.29–4.37 (m, 2H, *J* 12.7, $J_{7,CHH}$ 7.3 Hz, CH*H*Ph, H-7), 4.55 (s, 2H, CH_2OCH_3), 4.58 (d, 1H, $J_{8,9}$ 6.0 Hz, H-9), 4.71 (d, 1H, $J_{8,9}$ 6.0 Hz, H-8), 7,25–7.46 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 13.73 (CH_3 propyl), 19.47 (CH_2 propyl), 24.98 and 25.98 (CH_3 acetal), 36.75 (CH_2 propyl), 52.13 (CO_2CH_3), 55.39 (CH_2OCH_3), 58.50 (C-4), 62.30 (CH_2Ph), 66.64 (C-3), 68.14 (7-CH_2), 82.00 (C-8), 84.26 (C-7), 85.38 (C-9), 96.74 (CH_2OCH_3), 113.13 (C-5), 117.81 (C acetal), 127.3–129.5 (5C, Ar), 137,50 (C*ipso*), 170.45 (CO_2CH_3). Anal. Calcd for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58; N, 3.01. Found: C, 61.96; H, 7.57; N, 3.15.

Eluted second (R_f 0.42, silica gel, 30% EtOAc in hexane) was **31** as an oil; $[\alpha]_D^{25} = -97.4$ (*c* 0.9, $CHCl_3$); ν_{max} (neat) 3088.35, 3063.27, 3030.10, 2954.94, 1748.12, 1496.92; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.90 (t, 3H, *J* 7.2 Hz, CH_3 propyl), 1.17–1.40 (m, 5H, CH_3 acetal and CH_2 propyl), 1,50 (s, 3H, CH_3 acetal), 1.62 (m, 1H, CH*H* propyl), 1.91 (m, 1H, CH*H* propyl), 3,24 (m, 1H, 7-CH*H*), 3.29 (s, 3H, CH_2OCH_3), 3.53 (m, 1H, 7-CH*H*), 3.72 (s, 3H, CO_2CH_3), 3.70–3.82 (m, 2H, H-3 and CH*H*Ph) 3.90 (br d, 1H, $J_{3,4}$ 8.0 Hz, H-4), 4.16–4.30 (m, 2H, H-7, CH*H*Ph), 4.44 (br s, 2H, CH_2OCH_3), 4.56 (d, 1H, $J_{8,9}$ 5.8 Hz, H-9), 4.71 (d, 1H, $J_{8,9}$ 5.8 Hz, H-8), 7.25–7.46 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.28 (CH_3 propyl), 20.32 (CH_2 propyl), 25.08 and 26.01 (CH_3 acetal), 29.77 (CH_2 propyl), 51.65 (CO_2CH_3), 53.80 (C-4), 55.37 (CH_2OCH_3), 60.55 (CH_2Ph), 67.54 (C-3), 68.20 (7-CH_2), 82.18 (C-8 or C-9), 83.81 (C-7), 85.35 (C-8 or C-9), 96.71 (CH_2OCH_3), 113.06, 113.18 (C-5 and C acetal), 127.3–129.5 (5C, Ar), 137,50 (C*ipso*), 168.16 (CO_2CH_3). *m*/*z* (EI+) 465.3 [$(M)^+$, 2.5%], 450.2 [$(M-CH_3)^+$, 1%], 390.2 (7), 343.1 (7), 311.0 (11), 161.9 (12), 90.9 (100). Anal. Calcd for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58; N, 3.01. Found: C, 62.00; H, 7.48; N, 3.34.

5.2.11. Methyl (3*R*,4*S*,5*S*,7*R*,8*R*,9*S*,10*R*)-8,9,10-tris(benzyloxy)-7-[(benzyloxy)methyl]-2-methyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]decane-4-carboxylate 34, methyl (3*S*,4*R*,5*R*,7*R*,8*R*,9*S*,10*R*)-8,9,10-tris(benzyloxy)-7-[(benzyloxy)methyl]-2-methyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]-decane-4-carboxylate 35, methyl (3*R*,4*R*,5*R*,7*R*,8*R*,9*S*,10*R*)-8,9,10-tris(benzyloxy)-7-[(benzyloxy)methyl]-2-methyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]decane-4-carboxylate 36 and methyl (3*S*,4*S*,5*S*,7*R*,8*R*,9*S*,10*R*)-8,9,10-tris(benzyloxy)-7-[(benzyloxy)methyl]-2-methyl-3-phenyl-1,6-dioxa-2-azaspiro[4.5]decane-4-carboxylate 37. Compound **33** (311 mg, 0.50 mmol) was converted to **34** (33 mg, 0.043 mmol), **35** (212 mg, 0.27 mmol), **36** (90 mg, 0.117 mmol) and **37** (26 mg, 0.034 mmol) according to the general procedure. Reaction time: 36 min; 90% yield. **34/35/36/37** 1.3:8.1:3.5:1. Eluted first was **34**, mixed with **35**. Eluted second was **35**, (R_f 0.45, silica gel, 30% EtOAc in hexane), oil; $[\alpha]_D^{25} = +18.0$ (*c* 1, $CHCl_3$), ν_{max} (neat) 3088.23, 3063.66, 3031.26, 2917.80, 2869.77, 1747.97, 1652.77, 1496.44; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.83 (s, 3H, N–CH_3), 3.54 (s, 3H, CO_2CH_3), 3.70–3.82 (m, 4H, H-3, H-4, H-8 and 7-C*H*H), 3.84 (dd, 1H, J_{gem} 10.9, *J* 8.0 Hz, 7-CH*H*), 3.94 (d, 1H, $J_{9,10}$ 10.2 Hz, H-10), 4.03–4.15 (m, 2H, H-7 and H-9), 7.25–7.60 (m, 25H, Ar); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 47.0 (N–CH_3), 51.1 (C-4), 52.0 (CO_2CH_3), 60.8 (C-3), 68.5 (7-CH_2), 72.7 (C-7), 73.3 (CH_2Ph), 75.3 (CH_2Ph), 75.7 (CH_2Ph), 75.8 (CH_2Ph), 78.3 (C-8), 78.6 (C-10), 83.9 (C-9), 105.8 (C-5), 127.3–128.6 (25C, Ar), 135.1–138.8 (5 × C*ipso*), 167.5 (CO_2CH_3). HRMS *m*/*z* (ES+) calcd for $C_{45}H_{48}NO_8$ $[M+H]^+$ 730.3380, found 730.3394.

Eluted third was **36**, (R_f 0.42, silica gel, 30% EtOAc in hexane), oil; $[\alpha]_D^{25} = +38.6$ (*c* 0.4, $CHCl_3$); ν_{max} (neat) 2869.31, 1748.15, 1496.39, 1454.00; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.80 (s, 3H, N–CH_3), 3.37 (s, 3H, CO_2CH_3), 3.64 (d, 1H, $J_{3,4}$ 8.4 Hz, H-4), 3.82 (dd, 1H, $J_{7,7\text{-CH}H}$ 1.5 J_{gem} 11.6 Hz, 7-CH*H*), 3.84 (d, 1H, $J_{9,10}$ 9.5 Hz, H-10), 3.95 (m, 3H, H-3, H-8, 7-CH*H*), 4.09 (pseudo t, 1H, $J_{8,9}$ 9.5, $J_{9,10}$ 9.5 Hz, H-9), 4.16 (m, 1H, H-7), 4.57 (d, 1H, *J* 12.1 Hz, CH*H*Ph), 4.63 (d, 1H, *J* 12.1 Hz, CH*H*Ph), 4.78 (d, 1H, *J* 10.8 Hz, CH*H*Ph), 4.85 (d, 1H, *J* 11.8 Hz, CH*H*Ph), 4.94 (d, 1H, *J* 10.8 Hz, CH*H*Ph), 5.02 (AB, 2H, *J* 11.0 Hz, CH_2Ph), 5.18 (d, 1H, J 11.7 Hz, CH*H*Ph), 7.28–7.43 (m, 25H, Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 44.01 (N–CH_3), 51.1 (CO_2CH_3), 59.2 (C-4), 68.2 (7-CH_2), 72.9 (C-7), 73.3 (CH_2Ph), 74.3 (C-3), 75.0 75.4 75.7 (3 × CH_2Ph), 78.1 (C-8), 80.3 (C-10), 83.7 (C-9), 104.2 (C-5), 127.4–128.5 (25C, Ar), 135.3, 138.0, 138.2, 138.5, (5 × C*ipso*), 170.0 (CO_2CH_3). Anal. Calcd for $C_{45}H_{47}NO_8$: C, 74.05; H, 6.49; N, 1.92. Found: C, 74.2; H, 6.56; N, 2.03.

Eluted fourth was **37**, (R_f 0.28, silica gel, 30% EtOAc in hexane), oil; $[\alpha]_D^{26} = +16.6$ (*c* 2.5, $CHCl_3$); ν_{max} (neat) 3088.20, 3063.31, 1753.11, 1719.85, 1496.53; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.72 (s, 3H, N–CH_3), 3.18 (d, 1H, $J_{7,\text{CH}H}$ 9.2 Hz, H-7), 3.27 (s, 3H, CO_2CH_3), 3.63–3.70 (m, 2H, H-9, H-10), 3.73 (dd, 1H, $J_{7,\text{CH}H}$ 10.6, $J_{7,7\text{-CH}H}$ 1.8 Hz, 7-CH*H*), 3.75–3.87 (m, 2H, H-8, 7-CH*H*), 4.03 (d, 1H, $J_{3,4}$ 7.3 Hz, H-4), 4.12 (d, 1H, $J_{3,4}$ 7.3 Hz, H-3), 4.49 (d, 1H, *J* 12.1 Hz, CH*H*Ph), 4.59 (d, 1H, *J* 10.6 Hz, CH*H*Ph), 4.71 (d, 1H, *J* 12.0 Hz, CH*H*Ph), 4.81 (d, 1H, *J* 10.6 Hz, CH*H*Ph), 4.89 (d, 1H, *J* 10.9 Hz, CH*H*Ph), 4.95 (d, 1H, *J* 10.9 Hz, CH*H*Ph), 4.96 (d, 1H, *J* 10.9 Hz, CH*H*Ph), 5.05 (d, 1H, *J* 11.0 Hz, CH*H*Ph), 7.12–7.16 (m, 2H, PhH), 7.27–7.33 (m, 23H, PhH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 44.14 (N–CH_3), 52.09 (CO_2CH_3), 58.46 (C-4), 68.86 (7-CH_2), 73.97 (CH_2Ph), 74.9 (C-7), 75.48, 76.18, 76.4 (3 × CH_2Ph), 77.60 (2C, C-3, C-8), 82.6 (C-10), 84.5 (C-2), 107.20 (C-5), 127.5–128–6 (25C, Ar), 134.38, 138.45, 138.56, 138.7, 138.9 (5 × C*ipso*), 168.4 (CO_2CH_3). Anal. Calcd for $C_{45}H_{47}NO_8$: C, 74.05; H, 6.49; N, 1.92. Found: C, 73.91; H, 6.44; N, 1.65.

5.2.12. Methyl (3*S*,4*S*,5*S*,7*R*,8*R*,9*S*,10*R*)-8,9,10-tris(benzyloxy)-7-[(benzyloxy)methyl]-2-methyl-3-propyl-1,6-dioxa-2-azaspiro[4.5]decane-4-carboxylate 38, methyl (3*S*,4*R*,5*R*,7*R*,8*R*,9*S*,10*R*)-8,9,10-tris(benzyloxy)-7-[(benzyloxy)methyl]-2-methyl-3-propyl-1,6-dioxa-2-azaspiro[4.5]-decane-4-carboxylate 39 and methyl (3*R*,4*S*,5*S*,7*R*,8*R*,9*S*,10*R*)-8,9,10-tris(benzyloxy)-7-[(benzyloxy)methyl]-2-methyl-3-propyl-1,6-dioxa-2-azaspiro[4.5]decane-4-carboxylate 40. Compound **33** (500 mg, 0.84 mmol) was converted to **38** (200 mg, 0.28 mmol), **39** (140 mg, 0.20 mmol) and **40** (34 mg, 0.048 mmol) according to the general procedure. Reaction time: 33 min, 64% yield. **38/39/40** 5.9:4.1:1. Eluted first (R_f 0.42, silica gel, 30% EtOAc in hexane) was **38** as a yellow oil; $[\alpha]_D^{25} = +13.0$ (*c* 0.5, $CHCl_3$); ν_{max} (neat) 2929.47, 2956.21, 2871.72, 1746.62, 1454.35, 1361.74; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, 3H, *J* 7.2 Hz, CH_3 propyl), 1.29–1.67 (m, 4H, 2 × CH_2 propyl), 2.92 (s, 3H, N–CH_3), 3.35 (d, 1H, $J_{3,4}$ 8.7 Hz, H-4), 3.55 (m, 1H, H-3), 3.61 (s, 3H, CO_2CH_3), 3.65 (dd, 1H, $J_{gem} = 11.4$, $J_{7,7\text{-CH}H}$ 1.5 Hz, 7-CH*H*), 3.77 (pseudo t, 1H, *J* 9.3 Hz, H-8), 3.83 (dd, 1H, J_{gem} 11.4, $J_{7,7\text{CH}H}$ 3.6 Hz, 7-CH*H*), 3.89 (d, 1H, $J_{9,10}$ 9.9 Hz, H-10), 3.98–4.07 (m, 2H, H-7, H-

9), 4.51 (d, 1H, J_{AB} 12.4 Hz, C*H*HPh), 4.60 (d, 1H, J_{AB} 12.4 Hz, C*H*HPh), 4.69 (d, 1H, J_{AB} 10.8 Hz, C*H*HPh), 4.82 (d, 1H, J_{AB} 11.6 Hz, C*H*HPh), 4.88–4.98 (m, 3H, 3 × CH*H*Ph), 5.06 (d, 1H, J_{AB} 11.6 Hz, C*H*HPh); ^{13}C NMR ($CDCl_3$, 100.6 MHz,): δ 14.09 (CH_3 propyl), 19.22 (CH_2 propyl), 35.67 (CH_2 propyl), 48.73 (N–CH_3), 51.91 (CO_2CH_3), 58.10 (C-4), 67.1 (C-3), 68.31 (7-*C*H_2), 72.54 (C-7), 73.15 (*C*H_2Ph), 75.11 (*C*H_2Ph), 75.28 (*C*H_2Ph), 75.60 (*C*H_2Ph), 78.21 and 78.25 (C-8 and C-10), 83.66 (C-9), 106.80 (C-5), 127.1 and 128.4 (20C, Ar), 138.13, 138.16, 138.41, 138.59 (4 × C*ipso*), 168.48 (*C*O_2CH_3). Anal. Calcd for $C_{42}H_{49}NO_8$: C, 72.49; H, 7.10; N, 2.01. Found: C, 71.32; H, 7.24; N, 2.07.

Eluted second (R_f 0.23, silica gel, 30% EtOAc in hexane) was **39** as a yellow oil; $[\alpha]_D^{25} = +31.8$ (*c* 1.1, $CHCl_3$); ν_{max} (neat) 2929.69, 2956.39, 2871.63, 1751.54, 1496.91, 1453.99; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, 3H, *J* 7.2 Hz, CH_3 propyl), 1.10–1.35 (m, 2H, CH_2 propyl), 1.45 (m, 1H, CH*H* propyl), 2.01 (m, 1H, CH*H* propyl), 2.73 (m, 4H, N–CH_3, H-3), 3.32 (d, 1H, $J_{3,4}$ 7.2 Hz, H-4), 3.58 (s, 3H, CO_2CH_3), 3.70–3.80 (m, 2H, H-10, 7-CH*H*), 3.84–3.92 (m, 2H, H-8, 7-CH*H*), 3.97 (m, 1H, H-9), 4.03 (m, 1H, $J_{7,8}$ 9.7 Hz, H-7), 4.49 (d, 1H, *J* 12.2 Hz, CH*H*Ph), 4.59 (d, 1H, *J* 12.2 Hz, CH*H*Ph), 4.72 (d, 1H, *J* 10.9 Hz, CH*H*Ph), 4.75 (d, 1H, *J* 11.8 Hz, CH*H*Ph), 4.87 (d, 1H, *J* 12.2 Hz, CH*H*Ph), 4.93 (d, 1H, *J* 11.1 Hz, CH*H*Ph), 4.96 (d, 1H, *J* 11.1 Hz, CH*H*Ph), 5.08 (d, 1H, *J* 12.2 Hz, CH*H*Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.15 (CH_3 propyl), 20.39 (CH_2 propyl), 29.02 (CH_2 propyl), 43.95 (NCH_3), 51.45 (CO_2CH_3), 55.98 (C-4), 68.21 (7-*C*H_2), 70.73 (C-3), 72.77 (C-7), 73.33 (*C*H_2Ph), 74.98 (*C*H_2Ph), 75.39 (*C*H_2Ph), 75.61 (*C*H_2Ph), 77.99 (C-8), 79.97 (C-10), 83.72 (C-9), 104.00 (C-5), 127.35–128.44 (20C, Ar), 137.99, 138.27, 138.56, (4 × C*ipso*), 168.17 (*C*O_2CH_3). *m*/*z* (EI+) 697.3 [$(M+2)^+$, 3.7%], 695.9 [$(M+1)^+$, 5.2%], 694.8 [$(M)^+$, 1.2%], 605.2 [$(M+1-Bn)^+$, 2.7%], 604.2 [$(M-Bn)^+$, 2.8%], 541.5 (5), 419.1 (10), 104.8 (100); HRMS *m*/*z* (ES+) calcd for $C_{42}H_{50}NO_8$ $[M+H]^+$ 696.3536, found 696.3536.

Eluted third (R_f 0.11, silica gel, 30% EtOAc in hexane) was **40** as a yellow oil, $[\alpha]_D^{25} = +12.4$ (*c* 0.4, $CHCl_3$); ν_{max} (neat) 2960, 1734, 1454; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86–1.0 (m, 3H, CH_3 propyl), 1.23–1.45 (m, 2H, CH_2 propyl), 1.45–1.70 (m, 1H, CH*H* propyl), 2.01 (m, 1H, CH*H* propyl), 2.69 (br s, 3H, N–CH_3), 2.83 (m, 1H, H-3), 3.28 (m, 1H, H-7), 3.56–3.75 (m, 6H, H-8, H-9, H-10 and CO_2CH_3), 3.90 (m, 2H, H-10, 7-CH*H*), 4.48–4.94 (CH_2Ph), 7.17–7.34 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 13.98 (CH_3 propyl), 20.02 (CH_2 propyl), 29.45 (CH_2 propyl), 43.84 (NCH_3), 52.07 (CO_2CH_3), 55.17 (C-4), 68.88 (7-*C*H_2), 73.48 (C-3), 73.76 (*C*H_2Ph), 74.82 (C-7), 75.00 (*C*H_2Ph), 75.85 (*C*H_2Ph), 76.03 (*C*H_2Ph), 77.60 (C-8), 82.00 (C-10), 83.83 (C-9), 106.59 (C-5), 127.28–129.81 (20C, Ar), 138.24, 138.49, 138.62, 138.80 (4 × C*ipso*), 169.11 (*C*O_2CH_3). *m*/*z* (EI+) 695.9 [$(M)^+$, 2.1%], 595.3 [$(M-100.6)^+$, 6%], 563.2 (7%), 180.9 (83%), 91.0 (100%); HRMS *m*/*z* (ES+) calcd for $C_{42}H_{50}NO_8$ $[M+H]^+$ 696.3536, found 696.3510.

5.3. Cycloaddition reactions with *N*-methylidenebenzylamine *N*-oxide 5 formed in situ under microwave activation. General procedure

A solution of *N*-benzylhydroxylamine (prepared by $NaBH_3CN$ reduction of benzaldehyde oxime,[34] 0.75 mmol, 1.25 equiv) and paraformaldehyde (1.1 mmol, 1.8 equiv) in EtOH (0.7 mL) in a septum-sealed glass tube was heated at 40 °C in a focussed microwave oven (Discover® CEM) for 10 min The *exo*-glycal **1**, **11**–**13**, **33** or **42** (0.6 mmol) was added and the mixture heated in the microwave oven at 80 °C for 20 min The reaction was monitored by TLC before a new addition of *N*-benzylhydroxylamine (0.75 mmol) and paraformaldehyde (1.1 mmol). After heating at 80 °C for 20 min, the reaction was controlled again. A third addition of *N*-benzylhydroxylamine (0.75 mmol) and paraformaldehyde (1.1 mmol) was performed and after heating at 80 °C for another 20 min the reaction was complete. Silica gel column chromatography of the crude mixture with EtOAc-hexane as eluent afforded spiroisoxazolidines **10**, **18**, **25**, **32**, **41** and **43** (68–92% yields).

5.3.1. Methyl (4*R*,5*S*,7*S*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-benzyl-7-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 10. Compound **1** (178 mg, 0.56 mmol) was converted to **10** (189 mg, 0.42 mmol) in 75% yield. Yellow oil; R_f 0.59 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{26} = -91.2$ (*c* 2.0, $CHCl_3$); ν_{max} (neat) 3063.66, 3030.59, 2987.22, 1742.69; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24 (s, 3H, CH_3 acetal), 1.42 (s, 6H, $2CH_3$ acetal), 1.50 (s, 3H, CH_3 acetal), 3.55 (m, 1H, H-3), 3.69 (m, 4H, CO_2CH_3, H-5′), 3.80 (m, 1H, H-4), 3.85 (m, 1H, H-7), 4.10 (m, 1H, H-3), 4.20 (pseudo t, 1H, *J* 7.6 Hz, H-5′), 4.39 (m, 1H, $J_{4',5'}$ 7.0 Hz, H-4′), 4.61 (dd, 1H, $J_{8,9}$ 5.5, $J_{7,8}$ 4.1 Hz, H-8), 4.69 (m, 1H, H-9), 7.26–7.43 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 25.25, 25.57, 25.96, 26.94 (4× CH_3 acetal), 52.14 (CO_2CH_3), 54.08 (C-4), 58.45 (C-3), 66.14 (C-5′), 75.45 (C-4′), 79.83 (C-8), 81.41 (C-7), 83.31 (C-9), 110.02 (C acetal), 113.26 (C acetal), 116,0 (C-5), 127.4–128.9 (5C, Ar), 137.07 (C*ipso*), 171.57 (*C*O_2CH_3). *m*/*z* (EI+) 450.4 [$(M+1)^+$, 3%], 449.1 [$(M)^+$, 7%], 434.2 [$(M-CH_3)^+$, 7%], 418.3 (5), 417.1 (20), 100.8 (14), 90.9 (100); HRMS *m*/*z* (ES+) calcd for $C_{23}H_{32}NO_8$ $[M+H]^+$ 450.2128, found 450.2121.

5.3.2. Methyl (4*S*,5*S*,7*S*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-benzyl-7-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 18. Compound **11** (176 mg, 0.56 mmol) was converted to **18** (213 mg, 0.47 mmol) in 84% yield. Glassy solid; R_f 0.24 (silica gel, 30% EtOAc in hexane); $[\alpha]_D^{26} = +25.5$ (*c* 1 $CHCl_3$; ν_{max}) (KBr) 2986.72, 2940.56, 1741.37; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.29 (s, 3H, CH_3 acetal), 1.40 (s, 3H, CH_3 acetal), 1.48 (s, 3H, CH_3 acetal), 1.50 (s, 3H, CH_3 acetal), 3.51 (m, 1H, H-3), 3.67 (m, 1H, H′-3), 3.72 (pseudo t, 1H, *J* 7.7 Hz, H-5′), 3.77 (s, 3H, CO_2CH_3), 3.93 (m, 2H, H-4, H-7), 4.06 (d, 1H, J_{gem} 12.8 Hz, CH_2Ph), 4.18 (dd, 1H, J_{gem} 7.7, $J_{4',5'}$ 7.5 Hz, H-5′), 4.26 (pseudo q, 1H, $J_{4',5'} = 7.5, J_{4',7}$ 7.2 Hz, H-4′), 4.45 (m, 1H, CH*H*Ph), 4.55 (d, 1H, $J_{8,9}$ 5.8 Hz, H-9), 4.64

(dd, 1H, $J_{8,9}$ 5.8, $J_{7,8}$ 4.0 Hz, H-8), 7.25–7.46 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 24.64, 25.50, 25.68, 26.07 ($4\times CH_3$ acetal), 51.74 (C-4), 52.13 (CO_2CH_3), 56.37 (C-3), 62.99 (CH_2Ph), 66.08 (C-5′), 75.82 (C-4′), 79.95 (C-8), 82.48 (C-7), 84.89 (C-9), 109.87 (C acetal), 113.55 (C acetal), 115.71 (C-5), 127.4–129.5 (5C, Ar), 137.70 (C*ipso*), 169.94 (CO_2CH_3). *m/z* (EI+) 450.4 [$(M+1)^+$, 2%], 449.1 [$(M)^+$, 7%], 434.2 [$(M-CH_3)^+$, 7%], 418.3 (5), 417.1 (20), 100.8 (18), 90.9 (100); HRMS *m/z* (ES+) calcd for $C_{23}H_{32}NO_8$ $[M+H]^+$ 450.2128, found 450.2124.

5.3.3. Methyl (4*R*,5*S*,7*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-benzyl-7-[(methoxymethoxy)methyl]-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 25. Compound **12** (180 mg, 0.62 mmol) was converted to **25** (242 mg, 0.57 mmol) in 92% yield. Yellow oil; R_f 0.28 (silica gel, 30% EtOAc in hexane); $[\alpha]_D^{26} = -80.6$ (*c* 1.3, $CHCl_3$); ν_{max} (neat) 3030.48, 2988.08, 2949.80, 1742.50; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30 (s, 3H, CH_3 acetal), 1.46 (s, 3H, CH_3 acetal), 3.32 (s, 3H, CH_2OCH_3), 3.52 (m, 2H, $2\times$H-3), 3.68 (pseudo t, 1H, *J* 7.7 Hz, 7-CH*H*), 3.72 (s, 3H, CO_2CH_3), 3.90 (m, 1H, H-4), 4.02 (d, 1H, *J* 12.7 Hz, CH*H*Ph), 4.10 (m, 1H, H-7), 4.25 (m, 1H, 7-CH*H*), 4.47 (m, 3H, CH_2OCH_3 and CH*H*Ph), 4.65 (m, 1H, H-8), 4.68 (s, 1H, H-9), 7.27–7.34 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 25.66 (CH_3 acetal), 26.43 (CH_3 acetal), 52.13 (CO_2CH_3), 54.77 (CH_2OCH_3), 55.38 (CH_2Ph), 59.45 (C-4), 62.85 (7-CH_2), 71.59 (C-3), 82.37 (C-9), 83.07 (C-8), 83.86 (C-7), 96.25 (CH_2OCH_3), 112.50 (C-5), 113.20 (C acetal), 127.62–129.17 (5C, Ar), 137.51 (C*ipso*), 172.28 (CO_2CH_3). *m/z* (EI+) 424.2 [$(M+1)^+$, 1.5%], 423.1 [$(M)^+$, 3%], 408.1 [$(M-CH_3)^+$, 1%], 392.1 (5), 391.1 (20), 389.9 (2), 90.9 (100); HRMS *m/z* (ES+) calcd for C_{21} $H_{30}NO_8$ $[M+H]^+$ 424.1971, found 424.1984.

5.3.4. Methyl (4*S*,5*S*,7*R*,8*R*,9*R*)-8,9-isopropylidenedioxy-2-benzyl-7-[(methoxymethoxy)methyl]-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 32. Compound **13** (180 mg, 0.62 mmol) was converted to **32** (235 mg, 0.55 mmol) in 89% yield. Yellow oil; R_f 0.30 (silica gel, 30% EtOAc in hexane); $[\alpha]_D^{26} = -44.7$ (*c* 0.8, $CHCl_3$); ν_{max} (neat) 2986.83, 2948.86, 1741.33; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.35 (s, 3H, CH_3 acetal), 1.55 (s, 3H, CH_3 acetal), 3.32 (s, 3H, CH_2OCH_3), 3.41 (m, 1H, 7-CH*H*), 3.58 (dd, 1H, $J_{7,CHH}$ 5.4, J_{gem} 11,0 Hz, 7-CH*H*), 3.74 (s, 3H, CO_2CH_3), 3.91 (d, 1H, $J_{3,4}$ 7.9 Hz, H-4), 4.13 (m, 2H, CH_2Ph), 4.20 (m, 2H, H-3), 4.31 (m, 1H, H-7), 4.53 (m, 2H, CH_2OCH_3), 4.61 (d, 1H, $J_{8,9}$ 6.0 Hz, H-8), 4.73 (d, 1H, $J_{8,9}$ 6.0 Hz, H-9), 7.26–7.41 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 24.89 (CH_3 acetal), 25.88 (CH_3 acetal), 51.68 (C-4), 52.07 (CO_2CH_3), 55.37 (CH_2OCH_3), 56.20 (CH_2Ph), 62.71 (C-3), 68.07 (7-CH_2), 82.03 (C-9), 84.44 (C-7), 85.11 (C-8), 96.73 (CH_2OCH_3), 113.13 (C acetal), 116.77 (C-5), 127.4–129.2 (5C, Ar), 136.83 (C*ipso*), 170.04 (CO_2CH_3). *m/z* (EI+) 424.3 [$(M+1)^+$, 1.5%], 423.1 [$(M)^+$, 4%], 408.2 [$(M-CH_3)^+$, 2%], 392.2 (6), 391.1 (20), 389.9 (2), 90.9 (100). HRMS *m/z* (ES+) calcd for $C_{21}H_{30}NO_8$ $[M+H]^+$ 424.1971, found 424.1964.

5.3.5. Methyl (4*R*,5*R*,7*R*,8*R*,9*S*,10*R*)-8,9,10-tris(benzyloxy)-7-[(benzyloxy)methyl]-2-benzyl-1,6-dioxa-2-azaspiro[4.5]decane-4-carboxylate 41. Compound **33** (178 mg, 0.30 mmol) was converted to **41** (147 mg, 0.20 mmol) in 68% yield, yellow oil; R_f 0.47 (silica gel, 30% EtOAc in hexane); $[\alpha]_D^{26} = +35.0$ (*c* 1, $CHCl_3$); ν_{max} (neat) 3088.00, 3062.94, 3030.27, 2919.33, 2865.47, 1745.72, 1496.70; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.63 (s, 3H, CO_2CH_3), 3.64–4.20 (m, 11H, $J_{7\text{-}CHH,7\text{-}CHH}$ 11.5, $J_{7,CHH}$ 4.9 Hz, $2\times$H-3, H-4, H-7, H-8, H-9, H-10, $2\times$7-CH*H* and NCH_2Ph), 4.52 (d, 1H, *J* 12.1Hz, CH*H*Ph), 4.62 (d, 1H, *J* 12.1 Hz, CH*H*Ph), 4.71 (d, 1H, *J* 10.9 Hz, CH*H*Ph), 4.85 (d, 1H, *J* 11.6 Hz, CH*H*Ph), 4.90 (d, 1H, *J* 10.9 Hz, CH*H*Ph), 4.95 (s, 2H, CH_2Ph), 5.12 (d, 1H, *J* 11.6 Hz, CH*H*Ph), 7.30–7.36 (m, 25H, Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 52.17 (CO_2CH_3), 53.74 (C-3), 68.78 (7-CH_2), 72.87 (1C), 73.31 (CH_2Ph), 75.21 (CH_2Ph), 75.73 (2C, CH_2–Ph), 78.24 (1C), 78.36 (1C), 83.95 (1C), 106.21 (C-5), 127.50–127.98 (25C, Ar), 138.21–138.75 (5C, C*ipso*), 168.56 (CO_2CH_3). Anal. Calcd for $C_{45}H_{47}NO_8$: C, 74.05; H, 6.49; N, 1.92. Found: C, 74.41; H, 6.43; N, 2.03.

5.3.6. Methyl (4*R*,5*R*,7*R*,8*R*,9*S*,10*R*)-8,9,10-tris(methoxymethoxy)-7-[(methoxymethoxy)methyl]-2-benzyl-1,6-dioxa-2-azaspiro[4.5]decane-4-carboxylate 43. Compound **42** (180 mg, 0.44 mmol) was converted to **43** (172 mg, 0.31 mmol) in 72% yield, yellow oil; R_f 0.23 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{25} = +27$ (*c* 0.9, $CHCl_3$); ν_{max} (neat) 2949, 1743, 1454; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.35, 3.42, 3.44, 3.46 (4s, 12H, CH_3 acetal), 3.50–4.20 (m, 14H, $2\times$H-3, H-4, 7-CH_2, H-7, H-8, H-9, H-10, CO_2CH_3, CH_2Ph), 4.62 (br s, 2H, CH_2OCH_3), 4.73 (d, 1H, *J* 6.5 Hz, CH*H*OCH_3), 4.80–4.87 (m, 4H, $2\times CH_2OCH_3$), 4.96 (d, 1H, *J* 6.5 Hz, CH*H*OCH_3), 7.27–7.42 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 52.17 (CO_2CH_3), 54.18, 55.20, 55.40 (CH_3 acetal), 65.88 (CH_2OCH_3), 72.06, 76.40, 78.53, 81.18, (C-7, C-8, C-9, C-10), 96.72, 98.48, 98.85, 99.41 (CH_2OCH_3), 105.97 (C-5), 127.62–129.52 (Ar), 136.67 (C*ipso*), 168.87 (CO_2CH_3). *m/z* (EI+) 546.4 [$(M+1)^+$, 5%], 545.1 [$(M)^+$, 10%], 514.1 [$(M-CH_3O)^+$, 20%], 452.1 [(M−Bn), 27%], 360.0 (55), 90.9 (100); HRMS *m/z* (ES+) calcd for $C_{25}H_{40}NO_{12}$ $[M+H]^+$ 546.2551, found 546.2533.

5.4. Cycloaddition reaction with benzonitrile oxide 44. General procedure

A solution of benzohydroximoyl chloride (0.30 g, 2 mmol, 2 equiv) and triethylamine (0.266 mL, 2 mmol, 2 equiv) in dichloromethane (5 mL) was added to a solution of *exo*-glycal **1**, **11** or **33** (1 mmol) in dichloromethane (2 mL) and the mixture stirred at room temperature for 6 h. The solvent was then evaporated and the solid residue purified by silica gel column chromatography to afford compounds **46** (52% yield from **1**, 72% from **11**) and **47** (32% yield from **33**).

5.4.1. Methyl (1′*R*,2′*R*,3′*S*,4′*R*)-3-phenyl-5[(1′,2′-4′,5′-diisopropylidenedioxy,3′-hydroxy)pentyl]-isoxazole-4-carboxylate 46. Compound **1** (300 mg, 0.95 mmol) was

converted to **46** (210 mg, 0.48 mmol) in 52% yield. Yellow oil; R_f 0.40 (silica gel, 30% EtOAc in hexane); $[\alpha]_D = +26.2$ (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.34 (s, 3H, CH_3 acetal), 1.41 (s, 3H, CH_3 acetal), 1.49 (s, 3H, CH_3 acetal), 1.72 (s, 3HCH_3 acetal), 2.32 (d, 1H, *J* 5.1 Hz, OH), 3.60 (m, 1H, H-3′), 3.73 (s, 3H, CO_2CH_3), 3.83 (dd, 1H, $J_{4',5'}$ 7.3, J_{gem} 8.0 Hz, H-5′), 3.95 (dd, 1H, $J_{4',5'}$ 7.3, J_{gem} 8.0 Hz, H-5′), 4.08 (m, 1H, H-4′), 4.60 (dd, 1H, $J_{1',2'}$ 6.6, $J_{2',3'}$ 3.6 Hz, H-2′), 5.90 (d, 1H, $J_{1',2'}$ 6.6 Hz, H-1′), 7.43–7.44 (m, 3H, PhH), 7.58–7.60 (m, 2H, PhH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 25.12, 25.16, 26.10, 26.18 (4 × CH_3 acetal), 51.88 (CO_2CH_3), 65.58 (C-5′), 68.59 (C-3′), 71.61 (C-1′), 76.17 (C-4′), 78.34 (C-2′), 109.40 (C-4), 109.51, 110.95 (2 × C acetal), 127.94–129.80 (6C, Ar), 161.77, 161.98 (C-3, C-5), 174.85 (CO_2CH_3). Anal. Calcd for $C_{22}H_{27}NO_8$: C, 60.96; H, 6.28; N, 3.23. Found: C, 60.60; H, 6.32; N, 3.13.

5.4.2. Methyl (1′*R*,2′*S*,3′*R*,4′*R*)-3-phenyl-5-[4′-hydroxy-1′,2′,3′,5′-tetra(benzyloxy)pentyl]-isoxazole-4-carboxylate 47. Compound **33** (838 mg, 1.40 mmol) was converted to **47** (350 mg, 0.49 mmol) in 35% yield. Yellow oil; R_f 0.48 (silica gel, 30% EtOAc in hexane); $[\alpha]_D^{25} = +38.7$ (*c* 0.6, $CHCl_3$); ν_{max} (neat) 3088.02, 3030.90, 1731.72, 1596.39; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.95 (d, 1H, *J* 5.1 Hz, OH), 3.52 (s, 3H, CO_2CH_3), 3.62 (dd, 1H, $J_{4',5'}$ 5.5, J_{gem} 9.7 Hz, H-5′), 3.67 (dd, H, $J_{4',5'}$ 3.6, J_{gem} 9.7 Hz, H-5′), 3.70 (dd, 1H, $J_{2',3'}$ 5.2, $J_{3',4'}$ 6.8 Hz, H-3′), 4.07 (m, 1H, H-4′), 4.39 (dd, 1H, $J_{1',2'}$ 6.1, $J_{2',3'}$ 4.6 Hz, H-2′), 4.45–4.59 (m, 4H, 2 × CH_2Ph), 4.63 (d, 1H, *J* 11.6 Hz, CH*H*Ph), 4.69 (d, 1H, *J* 11.6 Hz, CH*H*Ph), 4.78 (d, 1H, *J* 11.4 Hz, CH*H*Ph), 4.83 (d, 1H, *J* 11.3 Hz, CH*H*Ph), 5.63 (d, 1H, $J_{1',2'}$ 6.1 Hz, H-1′), 7.20–7.35 (m, 20H, PhH), 7.45–7.52 (m, 3H, PhH), 7.56–7.61 (m, 2H, PhH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 51.62 (CO_2CH_3), 70.78 (C-4′), 70.96 (C-5′), 72.83, 73.15, 73.34 (3 × CH_2Ph), 74.68 (C-1′), 75.12 (CH_2Ph), 77.66 (C-3′), 79.81 (C-2′), 109.88 (C-4), 127.47–129.89 (26C, Ar), 137.14, 137.57, 137.95, 137.98 (4 × C*ipso*), 161.56 (C-5), 162.03 (C-3), 174.52 (CO_2CH_3). Anal. Calcd for $C_{44}H_{43}NO_8$: C, 74.03; H, 6.07; N, 1.96. Found: C, 73.94; H, 6.10; N, 2.08.

5.5. Deprotection of 7 and 46

The same protocol was applied for the deprotection of **7** and **46**. The procedure was described for compound **7**. Compound **7** (140 mg, 0.33 mmol) was treated with a 25 vol % TFA/H_2O solution (2 mL) at room temperature until the complete disappearance of the starting material (R_f 0.38, silica gel, 50% EtOAc in hexane). The mixture was concentrated in vacuo and coevaporated with toluene (3×) and MeOH (3×) to quantitatively give compound **48**.

5.5.1. Methyl (3*S*,4*R*,5*S*,7*S*,8*R*,9*R*)-8,9-dihydroxy-7-[(1′*R*)-1′,2′-dihydroxyethyl]-2-methyl-3-propyl-1,6-dioxa-2-azaspiro[4.4]nonane-4-carboxylate 48. Compound **7** (47 mg, 0.11 mmol) was converted to **48** (37 mg) quantitatively. Solid, mp 105–108 °C; $[\alpha]_D^{25} = -21.2$ (*c* 1.0, CH_3OH); ^1H NMR (400 MHz, D_2O): δ 0.86 (t, 3H, *J* 7.2 Hz, Me–propyl), 1.36 (m, 2H, CH_2 propyl), 1.54 (m, 1H, H–(CH_2) propyl), 1.82 (m, 1H, H–(CH_2) propyl), 3.22 (s, 3H, N–Me), 3.54 (dd, 1H, $J_{1',2'}$ 6.4, J_{gem} 12.0 Hz, H-2′), 3.65 (dd, 1H, $J_{1',2'}$ 4.0, J_{gem} 12.0 Hz, H-2′), 3.70 (s, 3H, Me ester), 3.78 (d, 1H, $J_{3,4}$ 5.8 Hz, H-4), 3.87 (m, 1H, H-1′), 4.14 (dd, 1H, $J_{7,8}$ 6.4, $J_{1',7}$ 4.3 Hz, H-7), 4.33 (m, 2H, H-8, H-3), 4.39 (d, 1H, $J_{8,9}$ 5.0 Hz, H-9); ^{13}C NMR (100 MHz, D_2O): δ 15.38 (Me propyl), 21.87 (CH_2 propyl), 29.96 (CH_2 propyl), 47.89 (N–Me), 55.51 (Me ester), 58.22 (C-4), 64.71 (C-2′), 72.46 (C-1′), 73.05 (C-8), 74.98 (C-3), 76.22 (C-9), 83.10 (C-7), 120.42 (C-5), 172.24 (*C*(O)OMe). HRMS *m/z* (ES+) calcd for $C_{14}H_{25}NO_8Na$ $[M+Na]^+$ 358.1478, found 358.1482.

5.5.2. Methyl (1′*R*,2′*R*,3′*S*,4′*R*)-3-phenyl-5[(1′,2′,3′,4′,5′-hydroxy)pentyl]-isoxazole-4-carboxylate 49. Compound **46** (59 mg, 0.13 mmol) was converted to **49** (48 mg) quantitatively. Solid, mp 103 °C; $[\alpha]_D^{25} = +13.2$ (*c* 0.8, CH_3OH); ν_{max} (KBr) 3338.32, 3139.26, 1708.71, 1608.14; ^1H NMR (CD_3OD, 400 MHz): δ 3.67 (dd, 1H, $J_{4',5'}$ 8.8, J_{gem} 19.0 Hz, H-5′), 3.77 (dd, 1H, $J_{4',5'}$ 8.8, J_{gem} 19.0 Hz, H-5′), 3.82 (s, 3H, CO_2CH_3), 3.91 (m, 1H, H-4′), 3.98 (dd, 1H, H-3′, $J_{2',3'}$ 2.7, $J_{3',4'}$ 9.6 Hz, H-3′), 4.20 (dd, 1H, $J_{2',3'}$ 2.7, $J_{1',2'}$ 14.3 Hz, H-2′), 5.56 (d, 1H, $J_{1',2'}$ 14.3 Hz, H-1′), 7.57–7.62 (m, 5H, PhH); ^{13}C NMR (CD_3OD, 100.6 MHz): δ 52.32 (CO_2CH_3), 64.06 (C-5′), 67.13 (C-1′), 70.53 (C-3′), 74.01 (C-2′), 75.02 (C-4′), 111.09 (C-4), 129.20–130.92 (6C, Ar), 163.57, 163.73 (C-3, C-5), 179.18 (CO_2CH_3). HRMS *m/z* (ES+) calcd for $C_{16}H_{19}NO_8Na$ $[M+Na]^+$ 376.1008, found 376.1012.

Acknowledgements

We thank the 'Service Commun de Diffraction X sur Monocristaux (Université Henri Poincaré, Nancy 1) for providing access to crystallographic experimental facilities.

References

1. (a) Tufariello, J. J. In *Nitrones in 1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley Interscience: New York, 1984; Vol. 2, p 1; (b) Confalone, P. N.; Huie, E. M. *Org. React. (NY)* **1988**, *36*, 1.
2. (a) Frederickson, M. *Tetrahedron* **1997**, *53*, 403–425; (b) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909.
3. For reviews see: (a) Giuliano, R. M. In *Cycloaddition Reactions in Carbohydrate Chemistry*; Giuliano, R. M., Ed.; American Chemical Society: Washington, DC, 1992, pp 1–23; (b) Paton, R. M. The Nitrile Oxide Isoxazoline Route to C-Disaccharides. In *Carbohydrate Mimics*; Chapleur, Y., Ed.; Wiley, VCH: Weinheim, 1998, pp 49–66, Chapter 3; (c) Osborn, H. M. I.; Gemmell, N.; Harwood, L. M. *J. Chem. Soc. Perkin Trans. 1* **2002**, 2419–2438.
4. Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263–292.
5. (a) Chapleur, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 449–450; (b) Lakhrissi, M.; Chapleur, Y. *Synlett* **1991**, 583–587; (c) Lakhrissi, M.; Chapleur, Y. *J. Org. Chem.* **1994**, *59*, 5752–5757.

6. Wilcox, C. S.; Long, G. W.; Suh, H. *Tetrahedron Lett.* **1984**, *25*, 395–398.
7. (a) Lakhrissi, M.; Chapleur, Y. *Angew. Chem., Int. Ed.* **1996**, *35*, 750–752; (b) Lakhrissi, M.; Taillefumier, C.; Chaouch, A.; Didierjean, C.; Aubry, A.; Chapleur, Y. *Tetrahedron Lett.* **1998**, *39*, 6457–6460.
8. (a) Ousset, J. B.; Mioskowski, C.; Yang, Y.-L.; Falck, J. R. *Tetrahedron Lett.* **1984**, *25*, 5903–5906; (b) Csuk, R.; Glanzer, B. I. *Tetrahedron* **1991**, *47*, 1655–1664; (c) Praly, J. P.; Chen, G. R.; Gola, J.; Hetzer, G.; Raphoz, C. *Tetrahedron Lett.* **1997**, *38*, 8185–8188; (d) Lieberknecht, A.; Griesser, H.; Bravo, R. D.; Colinas, P. A.; Grigera, R. J. *Tetrahedron* **1998**, *54*, 3159–3168; (e) Yang, W.-B.; Wu, C.-Y.; Chang, C.-C.; Wang, S.-H.; Teo, C.-F.; Lin, C.-H. *Tetrahedron Lett.* **2001**, *42*, 6907–6910; (f) Toth, M.; Somsak, L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 942–943; (g) Gomez, A. M.; Pedregosa, A.; Valverde, S.; Lopez, J. C. *Chem. Commun.* **2002**, 2022–2023.
9. (a) Griffin, F. K.; Murphy, P. V.; Paterson, D. E.; Taylor, R. J. *Tetrahedron Lett.* **1998**, *39*, 8179–8182; (b) Belica, P. S.; Franck, R. W. *Tetrahedron Lett.* **1998**, *39*, 8225–8228; (c) Taylor, R. J. K. *Chem. Commun.* **1999**, 217–227.
10. Taillefumier, C.; Thielges, S.; Chapleur, Y. *Tetrahedron* **2004**, *60*, 2213–2224.
11. For an introduction to the stereodiversity concept we introduced recently, see: Moitessier, N.; Dufour, S.; Chrétien, F.; Thiery, J.-P.; Maigret, B.; Chapleur, Y. *Bioorg. Med. Chem.* **2001**, *9*, 511–523.
12. Nakajima, M.; Itoi, K.; Takamatsu, Y.; Kinoshita, T.; Okazaki, T.; Kawakubo, K.; Shindo, M.; Honma, T.; Tohjigamori, M.; Haneishi, T. *J. Antibiot.* **1991**, *44*, 293–300.
13. For a review see: Frueh, T.; Chemla, P.; Ehrler, J.; Farooq, S. *Pestic. Sci.* **1996**, *46*, 37–47.
14. For syntheses see: (a) Chemla, P. *Tetrahedron Lett.* **1993**, *34*, 7391–7394; (b) Matsumoto, M.; Kirihara, M.; Yoshino, T.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1993**, *34*, 6289–6292; (c) Harrington, P. M.; Jung, M. E. *Tetrahedron Lett.* **1994**, *35*, 5145–5148; (d) Nakajima, N.; Matsumoto, M.; Kirihara, M.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron* **1996**, *52*, 1177–1194; (e) Shiozaki, M. *Carbohydr. Res.* **2002**, *337*, 2077–2088.
15. For hydantocidin analogues, see: (a) Sano, H.; Mio, S.; Kitagawa, J.; Sugai, S. *Tetrahedron: Asymmetry* **1994**, *5*, 2233–2240; (b) Fairbanks, A. J.; Fleet, G. W. J. *Tetrahedron* **1995**, *51*, 3881–3894; (c) Bichard, C. J. F.; Mitchell, E. P.; Wormald, M. R.; Watson, K. A.; Johnson, L. N.; Zographos, S. E.; Koutra, D. D.; Oikonomakos, N. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 2145–2148; (d) Sano, H.; Sugai, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1143–1150; (e) Brandstetter, T. W.; Wormald, M. R.; Dwek, R. A.; Butters, T. D.; Platt, F. M.; Tsitsanou, K. E.; Zographos, S. E.; Oikonomakos, N. G.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1996**, *7*, 157–170; (f) Brandstetter, T. W.; de la Fuente, C.; Kim, Y. H.; Johnson, L. N.; Crook, S.; Lilley, P. M. D. Q.; Watkin, D. J.; Tsitsanou, K. E.; Zographos, S. E.; Chrysina, E. D.; Oikonomakos, N. G.; Fleet, G. W. J. *Tetrahedron* **1996**, *52*, 10721–10736; (g) Agasimundin, Y. S.; Mumper, M. W.; Hosmane, R. S. *Bioorg. Med. Chem.* **1998**, *6*, 911–923; (h) Hanessian, S.; Sanceau, J. Y.; Chemla, P. *Tetrahedron* **1995**, *51*, 6669–6678; (i) Osz, E.; Sos, E.; Somsak, L.; Szilagyi, L.; Dinya, Z. *Tetrahedron* **1997**, *53*, 5813–5824.
16. Heim, D. R.; Cseke, C.; Gerwick, B. C.; Murdoch, M. G.; Green, S. B. *Pestic. Biochem. Physiol.* **1995**, *53*, 138–145.
17. (a) Barbachyn, M. R.; Cleek, G. J.; Dolak, L. A.; Garmon, S. A.; Morris, J.; Seest, E. P.; Thomas, R. C.; Toops, D. S.; Watt, W.; Wishka, D. G.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H.; Adams, W. J.; Friis, J. M.; Slatter, J. G.; Sams, J. P.; Oien, N. L.; Zaya, M. J.; Wienkers, L. C.; Wynalda, M. A. *J. Med. Chem.* **2003**, *46*, 284–302; (b) Basappa, M. P.; Sadashiva, K. M.; Swamy, S. N.; Rangappa, K. S. *Bioorg. Med. Chem.* **2003**, *11*, 4539–4544; (c) Mishra, R. C.; Tewari, N.; Verma, S. S.; Tripathi, R. P.; Kumar, M.; Shukla, P. K. *J. Carbohydr. Chem.* **2004**, *23*, 353–374.
18. RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458–5461.
19. Gallos, J. K.; Koftis, T. V. *J. Chem. Soc., Perkin Trans. 1* **2001**, 415–423.
20. Colinas, P. A.; Jager, V.; Lieberknecht, A.; Bravo, R. D. *Tetrahedron Lett.* **2003**, *44*, 1071–1074.
21. Li, X. L.; Takahashi, H.; Ohtake, H.; Ikegami, S. *Heterocycles* **2003**, *59*, 547–571.
22. Li, X. L.; Takahashi, H.; Ohtake, H.; Ikegami, S. *Tetrahedron Lett.* **2004**, *45*, 4123–4126.
23. Taillefumier, C.; Enderlin, G.; Chapleur, Y. *Lett. Org. Chem.* **2005**, *2*, 226–230.
24. Jimenez, R.; Perez, L.; Tamariz, J.; Salgado, H. *Heterocycles* **1993**, *35*, 591–598.
25. Taillefumier, C.; Lakhrissi, Y.; Lakhrissi, M.; Chapleur, Y. *Tetrahedron: Asymmetry* **2002**, *13*, 1707–1711.
26. Crystallographic data have been deposited with the Cambridge Crystallographic Data centre as supplementary publication number CCDC 256012. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2, 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
27. Lakhrissi, M.; Chapleur, Y. *Tetrahedron Lett.* **1998**, *39*, 4659–4662.
28. Crystallographic data have been deposited with the Cambridge Crystallographic Data centre as supplementary publication number CCDC 256013. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
29. Li, X.; Takahashi, H.; Ohtake, H.; Shiro, M.; Ikegami, S. *Tetrahedron* **2001**, *57*, 8053–8066.
30. For a theoretical explanation of the stereoselectivity of nitrone electron poor olefins cycloaddition, see: (a) Burdisso, M.; Gandolfi, R.; Grünanger, P.; Rastelli, A. *J. Org. Chem.* **1990**, *55*, 3427–3429; (b) Busque, F.; de March, P.; Figueredo, M.; Font, J.; Monsalvatje, M.; Virgili, A.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1996**, *61*, 8578–8585.
31. For computational studies on 1,3-dipolar cycloadditions, see: (a) Pascal, Y. L.; Chanetray, J.; Vessiere, R.; Zeroual, A. *Tetrahedron* **1992**, *48*, 7197–7208; (b) Merino, P.; Revuelta, J.; Tejero, T.; Chiacchio, U.; Rescifina, A.; Romeo, G. *Tetrahedron* **2003**, *59*, 3581–3592.
32. Hassan, A.; Wazeer, M. I. M.; Perzanowski, H. P.; Ali, Sk. A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 411–418.
33. Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *24*, 2537–2550.
34. Borch, R. F.; Bernstein, M. D.; Dupont Durst, H. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.