Stereoselectivity of 1,3-Dipolar Cycloadditions of D-Erythrose and D-Threose Derived Nitrones with Methyl Acrylate

Juraj Kubáň,[a] Andrej Kolarovič,[a] Lubor Fišera,*[a] Volker Jäger,*[b] Otakar Humpa,[c] Nada Prónayová,[d] Peter Ertl[a]

[a] Department of Organic Chemistry, Slovak University of Technology, SK-812 37 Bratislava, Slovak Republic

[b] Institute of Organic Chemistry, University of Stuttgart, D-70569 Stuttgart, Germany

[c] Department of Organic Chemistry, Masaryk University, CZ-611 37 Brno, Czech Republic

[d] Central Laboratory of Chemical Techniques, Slovak University of Technology, SK-812 37 Bratislava, Slovak Republic
E-mail: fisera@cvt.stuba.sk

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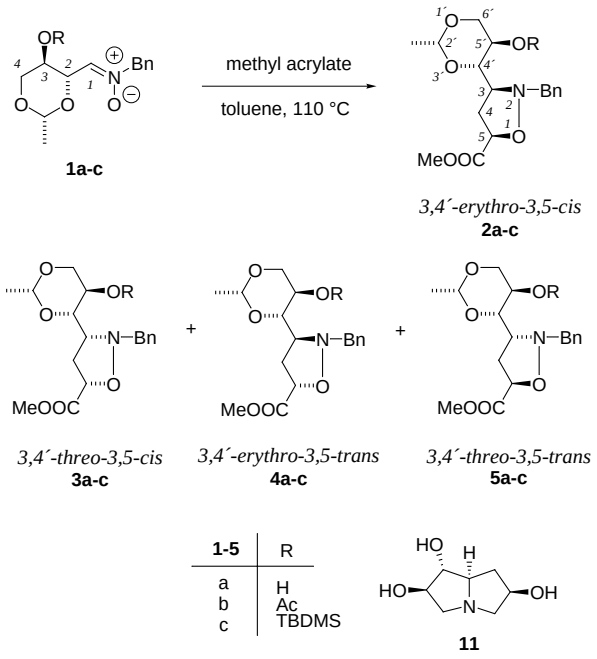
Abstract: 1,3-Dipolar cycloadditions between the D-erythrose and D-threose derived nitrones and methyl acrylate proceed in a regiospecific manner to afford the corresponding 3,5-disubstituted diastereomeric isoxazolidines in good yields. The stereoselectivity was dependent on the steric hindrance of the nitrone. The major products were found to have the C-3/C-4´ *erythro* and C-3/C-5 *cis* relative configuration. Its formation can be rationalized by less hindered *endo* attack of the *Z*-nitrone in an antiperiplanar manner with respect to the largest group of the cyclic acetal.

Key words: cycloadditions, nitrones, isoxazolidines, stereoselectivity, heterocycles

The nitrone-olefin 1,3-dipolar cycloaddition is a powerful reaction in that it can create as many as three new contiguous stereogenic centres in a single step.[1] Based on an evaluation of the nitrone cycloaddition, it was felt that the stereochemistry of these new centers could be controlled if the reaction system were properly designed.[2,3] Regio- and stereoselective nitrone cycloaddition, followed by reduction of the N-O bond to produce both an amino and a hydroxy function, allows the synthesis of many products of potential interest.[4] With our continuing efforts to utilize chiral 1,3-dipolar cycloadditions,[5] and with the goal of developing a simple route to the synthesis of polyhydroxylated derivatives of pyrrolizidines,[6] which have been shown to display antiviral activity,[7] via an asymmetric 1,3-dipolar cycloaddition we have recently published the preparation of new D-erythrose-**1a** and D-threose-**6a** derived nitrones and the stereoselectivity of their cycloadditions to styrene.[8] We now report the stereoselectivity of the cycloaddition of chiral sugar-derived nitrones **1a**–**c**, **6a** and **6b** with methyl acrylate.

The results are presented in the Table. In all cases the reactions were highly regiospecific, leading to the formation of diastereomeric isoxazolidines **2**–**5** (Scheme 1) and **7**–**10** (Scheme 2) as a mixture of three or four diastereoisomers in a good overall yield.[9] Purification by flash chromatography allowed the isolation of the pure major diastereoisomers **2a**–**c, 7a** and **7b**, while the isolation and/or characterization of minor isomers was possible only for some of them.[10]



Scheme 1

When, methyl acrylate was used instead of styrene,[8] selectivity decreased. Only 48% of major diastereomer **2a** for nitrone **1a** (Table, entry 1) versus 81% in the case of styrene as dipolarophile[8] was deemed unacceptable. The usefulness of the chiral 1,3-dipolar cycloaddition depends on the diastereoselectivity achieved, since the major diastereoisomers **2a** will be used subsequently for the synthesis of pyrrolizidines **11**.[11] In light of these differences; we undertook a systematic study of the possibility to influence the selectivity of the cycloaddition. Our objective was the study of diastereoselectivity of cycloadditions stemming from the nitrone part. In the case of the cycloadditions with styrene we have found, that the stereoselectivity of the cycloaddition was influenced by the steric hindrance of both the *N*- and *C*-substituent of the nitrone, i.e. the selectivity increases as the nitrogen substituent of the nitrone becomes bulkier.[8] The best diastereoselectivity was achieved with the *N*-benzyl nitrones **1a** and **6a**. Therefore, in addition to the parent chiral sugar-derived nitrones **1a** and **6a**, the hydroxy group protected nitrones **1b, 1c** and **6b** have also been prepared and used for the improvement of the selectivity of the cycloaddition.

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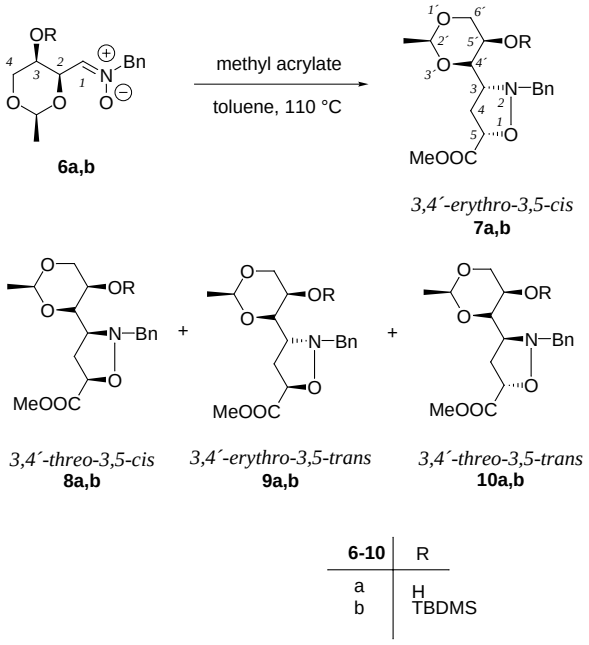
Table 1,3-Dipolar Cycloaddition of Nitrones **1a–c**, **6a** and **6b** to Methyl Acrylate

Entry	Nitrone	Yield (%)	*erythro-cis*	*threo-cis*	*erythro-trans*	*threo-trans*	*erythro: threo*	*cis:trans*
1	**1a**	85	48	18	29	5	77:23	66:34
2	**1b**	77	73	3	24	-	97:3	76:24
3	**1c**	82	87	5	6	2	93:7	92:8
4	**6a**	68	62	11	19	8	81:19	73:27
5	**6b**	65	96	1	3	-	99:1	97:3



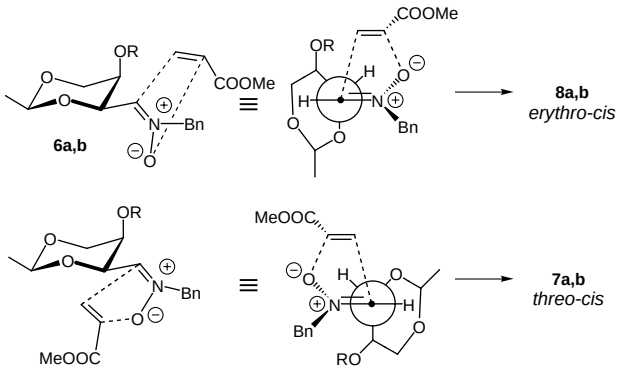
Scheme 2

The regiochemistry of the cycloadducts **2**–**5** and **7**–**10** were readily deduced from resonance positions and spin multiplicity of protons H-3, H-4 and H-5[10] and the relative stereochemistry of these adducts was indicated from NOE studies. The major adduct formed has the same configuration of stereogenic centres as with styrene[8] meaning an *erythro* relationship between the existing centre C-4' on the sugar moiety and the hydrogen at C-3, and 3,5-*cis* configuration between isoxazolidine centres. While the configuration on C-3 and C-5 was confirmed by NOE measurement of cycloadducts, relationship between stereocentres at C-3 and C-4' was confirmed by conversion into rigid pyrrolizidine **11**.[11] The *cis* relationship of substituents at C-3 and C-5 in **2a** was assigned on the basis of NOEDS. The composition of diastereoisomers was determined analogously to previously[8] from peak integration of C-4 in quantitative ^{13}C NMR analysis.

Decline of the stereoselectivity in the cycloaddition of the nitrones **1a** and **6a** with methyl acrylate compelled us to focus on the nitrone reactive conformations, that can lead to the prediction of this stereoselectivity. The MM2 calculations[12] suggest that sugar moiety of D-nitrones **1a** and **6a** adopts the most favorable conformation around the C-1−C-2 bond having dihedral angle between the protons H-1 and H-2 close to ~180°. From this point of view, the front side attack of the dipolarophile leads to the *erythro* isoxazolidines, while the backside approach to the *threo* products (Scheme 3). As has been already mentioned, the nitrone **1a** imposes only the moderate selectivity in its reaction with methyl acrylate (Table, entry 1). Conformational consideration indicates that an increase of the size of the hydroxyl-protecting group resulted in an increase of the induced stereoselectivity. The more bulky protection of the free hydroxy group of the nitrone can effectively hinder the approach of the alkene from the backside. The front side attack is then favored and leads to the major *erythro-cis* product **7a** (Scheme 3). The results obtained using β-hydroxy protected nitrones **1b**, **1c** and **6b** support this hypothesis. Indeed, even the use of the acetyl protecting group improves the selectivity of the nitrone **1b** (Table, entry 2). The strong preference for the *erythro-cis* products **2c** and **7b** provided more sterically demanding *O-tert*-butyldimethylsilyl group. The induced selectivity increased from 77:23 to 93:7 and also the growth of the simple selectivity was observed (66:34 *versus* 92:8) in the cycloaddition of the nitrones **1a** and **1c**, respectively (entries 1 and 3). These results concur with AM1 calculations of the rotation barrier.[12] Activation energy of the possible isomerization for the nitrone **1a** has been calculated to be 36 kcal/mol, while for the silylated nitrone **1c** it is 60−65 kcal/mol. The higher energy barrier in the *O*-protected nitrone **1c** is fully in accord with the aforementioned higher simple selectivity.

The analysis of the product configuration in D-*threo* nitrones **6a** and **6b** indicates that the major cycloadduct **7** arises from the cycloaddition that has occurred on the more sterically accessible face of the nitrone (Scheme 3). This conclusion, that steric factors are important for the orientation of the nitrone, is also supported by the fact, that cycloaddition of D-*threo* nitrone **6b** proceeds with the best *anti*-facial (99:1) and *endo*-facial (97:3) preference in this series (entry 5, Table).

The cycloadditions of nitrones are thus rationalized by *anti* approach with respect to the alkyl group of the heterocyclic acetal to afford the major *erythro* pair **7a**, **9a**. The *endo* transition state results in the formation *cis* diastereoisomer **7a**, while the *exo* transition state gives the corre-



Scheme 3

sponding *trans* isomer **9a**. On the other hand, the corresponding *syn* orientation in the transition state is responsible for the formation of the *threo* products. The C–COOMe functionalized isoxazolidine **2a** represents subunit with potential for the cleavage and recyclization to form a pyrrolizidine **11**. This opens a new route to the stereocontrolled formation of polyhydroxysubtituted pyrrolizidines, which is described in the subsequent paper.[11]

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References

(1) (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, **1984**, Chap. 9, 83. (b) Gothelf, K. V.; Jorgensen, K. V. *Chem. Rev.* **1988**, *98*, 863.

(2) Frederickson, M. *Tetrahedron* **1997**, *53*, 403.

(3) (a) Baggiolini, E. G.; Iacobelli, J. A.; Hennesy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098. (b) Brandi, A.; Cicchi, S.; Goti, A.; Pietrusiewicz, K. M. *Tetrahedron: Asymmetry* **1991**, *2*, 1063. (c) Saito, S.; Ishikawa, T.; Kishimoto, N.; Kohara, T.; Moriwake, T. *Synlett* **1994**, 282. (d) Kametani, T.; Chu, S. D.; Honda, T. *Heterocycles* **1987**, *25*, 241. (e) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1998**, *63*, 2371. (f) Bernet, B.; Vasella, A. *Helv. Chim. Acta*. **1979**, *62*, 2411.

(4) (a) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates*; VCH Publishers Inc.: New York, **1988**. (b) Grünanger, P.; Vita-Finzi, P. *Isoxazoles. Part One., In The Chemistry of Heterocyclic Compounds*; Taylor, E. C.; Weissberger, E., Eds.; Wiley: New York, **1991**.

(5) (a) Fišera, L.; Al-Timari, U. A. R.; Ertl, P. In *Cycloadditions in Carbohydrate Chemistry*; ACS Monograph., American Chemical Society: Washington, **1992**, 158. (b) Al-Timari, U. A. R.; Fišera, L.; Ertl, P.; Goljer, I.; Prónayová, N. *Monatsh. Chem.* **1992**, *123*, 999. (c) Kubán, J.; Blanáriková, I.; Fišera, L.; Prónayová, N. *Chem. Pap.* **1997**, *51*, 378. (d) Kubán, J.; Blanáriková, I.; Fengler-Veith, M.; Jäger, V.; Fiera, L. *Chem. Pap.* **1998**, *52*, 780. (e) Blanáriková, I.; Dugovi, B.; Fiera, L.; Hametner, C. *ARKIVOC* **2001**, *2*, 1091.

(6) (a) Denmark, S. E.; Hurd, R. A.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668. (b) McGaig, A. E.; Meldrum, K. P.; Wightman, R. H. *Tetrahedron* **1998**, *54*, 9429. (c) Hall, A.; Meldrum, K. P.; Therond, P. R.; Wightman, R. H. *Synlett* **1997**, 123. (d) Müller, R.; Leibold, T.; Pätzel, M.; Jäger, V. *Angew. Chem., Int. Ed. Engl*. **1994**, 1295. (e) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905.

(7) (a) Taylor, D. L.; Nash, R.; Fellows, L. E.; Kang, M. S.; Syms, A. S. *Antiviral Chem. Chemother.* **1992**, *3*, 273. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. V. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645.

(8) Kubán, J.; Blanáriková, I.; Fišera, L.; Jarošková, L.; Fengler-Veith, M.; Jäger, V.; Kozíšek, J.; Humpa, O.; Langer, V. *Tetrahedron* **1999**, *55*, 9501.

(9) Typical experimental procedure: To a stirred solution of nitrone (4.0 mmol) in toluene (12 mL) was added methyl acrylate (4.6 mmol) and the reaction mixture was heated at reflux for 4 h. The solvent was evaporated in a rotary evaporator and the dark brown oil thus obtained was purified by flash chromatography (silica gel, hexanes–ethyl acetate 90:10).

(10) Selected data: **Methyl (3*S*,5*R*,2'*R*,4'*S*,5'*R*)-2-*N*-benzyl-3-(5-hydroxy-2-methyl-1,3-dioxan-4-yl)isoxazolidine-5-carboxylate** (**2a**): Colorless solid, mp 118-120 °C; yield 43%; $[\alpha]_D$ = –54.2 (CH_2Cl_2, *c* 0.21); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 5 H, NCH_2Ph), 5.17 (s, 1 H, OH), 4.66 (dd, 1 H, $J_{4b,5}$ = 8.8 Hz, $J_{4a,5}$ = 8.7 Hz, H-5), 4.61 (q, 1 H, $J_{2',CH3}$ = 5.1 Hz, H-2'), 4.32 (d, 1 H, *J* = 12.4 Hz, NCH_2Ph), 4.05 (dd, 1 H, $J_{6'a,6'e}$ = 10.3 Hz, $J_{5',6'e}$ = 4.7 Hz, H-6'e), 3.82 (s, 3 H, $COOCH_3$), 3.80 (d, 1 H, *J* = 12.4 Hz, NCH_2Ph), 3.51 (dd, 1 H, 3.33 $J_{3,4'}$ = 9.5 Hz, $J_{3,4a}$ = 7.0 Hz, H-3), 3.33 (dd, 1 H, $J_{6'a,6'e}$ = 10.3 Hz, $J_{5',6'a}$ = 10.1 Hz, H-6'a), 3.28 (ddd, 1 H, $J_{5',6'a}$ = 10.1 Hz, $J_{4',5'}$ = 8.2 Hz, $J_{5',6'e}$ = 4.7 Hz, H-5'), 3.14 (dd, 1 H, $J_{3,4'}$ = 9.5 Hz, $J_{4',5'}$ = 8.2 Hz, H-4'), 2.85 (dd, 1 H, $J_{4a,4b}$ = 13.3 Hz, $J_{4b,5}$ = 8.8 Hz, H-4b), 2.69 (ddd, 1 H, $J_{4a,4b}$ = 13.3 Hz, $J_{4a,5}$ = 8.7 Hz, $J_{3,4a}$ = 7.0 Hz, H-4a), 1.27 (d, 3 H, $J_{2',CH3}$ = 5.1 Hz, 2'-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.7 ($COOCH_3$), 135.4, 129.4, 128.8, 128.2 (NCH_2Ph), 99.1 (C-2'), 77.7 (C-4'), 77.5 (C-5), 69.8 (C-6'), 68.4 (C-3), 66.0 (C-5'), 62.4 (NCH_2Ph), 52.6 ($COOCH_3$), 33.3 (C-4), 20.4 (2'-CH_3); $C_{17}H_{23}NO_6$ (337.37) calcd C 60.52, H 6.87, N 4.15; found: C 60.33, H 7.01, N 4.24. **Methyl (3*S*,5*S*,2'*R*,4'*S*,5'*R*)-2-*N*-benzyl-3-(5-hydroxy-2-methyl-1,3-dioxan-4-yl)isoxazolidine-5-carboxylate** (**4a**): Colorless solid, mp 136-137 °C; yield 24%; $[\alpha]_D$ = –26.3 (CH_2Cl_2, *c* 0.24); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.28 (m, 5 H, NCH_2Ph), 5.00 (s, 1 H, OH), 4.85 (dd, 1 H, $J_{4b,5}$ = 10.0 Hz, $J_{4a,5}$ = 5.6 Hz, H-5), 4.60 (q, 1 H, $J_{2',CH3}$ = 5.1 Hz, H-2'), 4.12 (d, 1 H, *J* = 12.4 Hz, NCH_2Ph), 4.03 (dd, 1 H, $J_{6'a,6'e}$ = 10.3 Hz, $J_{5',6'e}$ = 4.7 Hz, H-6'e), 3.79 (s, 3 H, $COOCH_3$), 3.77 (d, 1 H, *J* = 12.4 Hz, NCH_2Ph), 3.45-3.27 (m, 4 H, H-3, H-4', H-5', H-6'a), 2.79 (dd, 1 H, $J_{4a,4b}$ = 13.6 Hz, $J_{4b,5}$ = 10.0 Hz, H-4b), 2.64 (ddd, 1 H, $J_{4a,4b}$ = 13.6 Hz, $J_{4a,5}$ = 5.6 Hz, $J_{3,4a}$ = 1.7 Hz, H-4a), 1.26 (d, 3 H, $J_{2',CH3}$ = 5.1, 2'-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8 ($COOCH_3$), 134.7, 129.2, 128.8, 128.2 (NCH_2Ph), 99.0 (C-2'), 78.3 (C-4'), 75.5 (C-5), 69.7 (C-6'), 67.6 (C-3), 66.1 (C-5'), 60.9 (NCH_2Ph), 52.5 ($COOCH_3$), 33.6 (C-4), 20.4 (2'-CH_3). **Methyl (3*S*,5*R*,2'*R*,4'*S*,5'*R*)-2-*N*-benzyl-3-(5-acetoxy-2-methyl-1,3-dioxan-4-yl)isoxazolidine-5-carboxylate** (**2b**): Colorless solid, mp 74-75 °C; yield 62%; $[\alpha]_D$ = -37.1 (CH_2Cl_2, *c* 0.23); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43-7.36 (m, 5 H, NCH_2Ph), 4.71 (dd, 1 H, $J_{4a,5}$ = 8.3 Hz, $J_{4b,5}$ = 7.7 Hz, H-5), 4.66 (q, 1 H, $J_{2',CH3}$ = 5.1 Hz, H-2'), 4.34 (d, 1 H, *J* = 12.4 Hz, NCH_2Ph), 4.00 (d, 1 H, *J* = 12.4 Hz, NCH_2Ph), 3.92 (dd, 1 H, $J_{6'a,6'e}$ = 10.1 Hz, $J_{5',6'e}$ = 4.0 Hz, H-6'e), 3.83 (s, 3 H, $COOCH_3$), 3.61-3.43 (m, 3 H, H-3, H-

4', H-5'), 3.34 (dd, 1 H, $J_{6'a,6'e}$ = 10.1 Hz, $J_{5',6'a}$ = 9.0 Hz, H-6'a), 2.94 (ddd, 1 H, $J_{4a,4b}$ = 12.1 Hz, $J_{4b,5}$ = $J_{3,4b}$ = 7.7 Hz, H-4b), 2.51 (ddd, 1 H, $J_{4a,4b}$ = 12.1 Hz, $J_{4a,5}$ = 8.3 Hz, $J_{3,4a}$ = 4.1 Hz, H-4a), 1.79 (d, 3 H, $OCOCH_3$), 1.37 (d, 3 H, $J_{2',CH3}$ = 5.1, 2'-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6 and 170.0 ($COOCH_3$ and $OCOCH_3$), 136.4, 129.3, 128.6, 128.4 (NCH_2Ph), 98.7 (C-2'), 80.4 (C-4'), 77.3 (C-5), 70.9 (C-6'), 64.2 (C-3), 63.5 (C-5'), 61.8 (NCH_2Ph), 52.4 ($COOCH_3$), 32.5 (C-4), 20.5 and 20.4 (2'-CH_3 and $OCOCH_3$); $C_{19}H_{25}NO_7$ (379.41) calcd C 60.15, H 6.64, N 3.69; found: C 59.87, H 6.23, N 3.95. **Methyl (3*S*,5*R*,2'*R*,4'*S*,5'*R*)-2-*N*-benzyl-3-(5-*tert*-butyldimethylsilyloxy-2-methyl-1,3-dioxan-4-yl)isoxazolidine-5-carboxylate** (**2c**): Colorless solid, mp 66-68 °C; yield 78%; $[\alpha]_D$ = -69.7 (CH_2Cl_2, *c* 0.23); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32-7.14 (m, 5 H, NCH_2Ph), 4.57-4.51 (m, 2 H, H-5, H-2'), 4.19 (d, 1 H, *J* = 13.2 Hz, NCH_2Ph), 3.86 (dd, 1 H, $J_{6'a,6'e}$ = 10.2 Hz, $J_{5',6'e}$ = 4.5 Hz, H-6'e), 3.85 (d, 1 H, *J* = 13.2 Hz, NCH_2Ph), 3.68 (s, 3 H, $COOCH_3$), 3.43 (dd, 1 H, $J_{3,4a}$ = 8.1 Hz, $J_{3,4b}$ = 4.1 Hz, H-3), 3.39-3.36 (m, 1 H, H-4'), 3.32 (ddd, 1 H, $J_{4',5'}$ = $J_{5',6'a}$ = 9.3 Hz, $J_{5',6'e}$ = 4.5 Hz, H-5'), 3.19 (dd, 1 H, $J_{6'a,6'e}$ = 10.2 Hz, $J_{5',6'a}$ = 9.3 Hz, H-6'a), 2.70 (dd, 1 H, $J_{4a,4b}$ = 12.3 Hz, $J_{4b,5}$ = 9.0 Hz, $J_{3,4b}$ = 4.1 Hz, H-4b), 2.64 (ddd, 1 H, $J_{4a,4b}$ = 12.3 Hz, $J_{3,4a}$ = 8.1 Hz, $J_{4a,5}$ = 7.3 Hz, H-4a), 1.21 (d, 3 H, $J_{2',CH3}$ = 5.1 Hz, 2'-CH_3), 0.67 (s, 9 H, $OSiC(CH_3)_3$), -0.01 and -0.02 (2 × s, 2 × 3 H, $OSi(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9 ($COOCH_3$), 137.0, 129.1, 128.4, 127.4 (NCH_2Ph), 98.7 (C-2'), 82.3 (C-4'), 77.4 (C-5), 71.0 (C-6'), 63.7 (C-3), 63.5 (C-5'), 63.0 (NCH_2Ph), 52.2 ($COOCH_3$), 32.4 (C-4), 25.5 ($OSiC(CH_3)_3$), 20.4 (2'-CH_3), 17.6 ($OSiC(CH_3)_3$), -4.4 and -5.0 ($OSi(CH_3)_2$); $C_{23}H_{37}NO_6Si$ (451.63) calcd.: C 61.17, H 8.26, N 3.10; found: C 60.79, H 8.23, N 3.17. **Methyl (3*R*,5*S*,2'*S*,4'*R*,5'*R*)-2-*N*-benzyl-3-(5-hydroxy-2-methyl-1,3-dioxan-4-yl)isoxazolidine-5-carboxylate** (**7a**): Colorless solid, mp 87-88 °C; yield 47%; $[\alpha]_D$ = +71.2 (CH_2Cl_2, *c* 0.26); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48-7.37 (m, 5 H, NCH_2Ph), 4.70 (q, 1 H, $J_{2',CH3}$ = 5.1 Hz, H-2'), 4.56 (dd, 1 H, $J_{4b,5}$ = 8.6 Hz, $J_{4a,5}$ = 7.8 Hz, H-5), 4.25 (d, 1 H, $J_{CH2a,CH2b}$ = 13.2 Hz, NCH_2Ph), 4.01 (d, 1 H, $J_{CH2a,CH2b}$ = 13.2 Hz, NCH_2Ph), 3.98-3.85 (m, 4 H, H-4'. H-5', H-6'a, H-6'e), 3.72 (s, 3 H, $COOCH_3$), 3.69 (ddd, 1 H, $J_{3,4'}$ = 8.5 Hz, $J_{3,4a}$ = 7.8 Hz, $J_{3,4b}$ = 5.0 Hz, H-3), 2.94 (ddd, 1 H, $J_{4a,4b}$ = 13.1 Hz, $J_{4b,5}$ = 8.6 Hz, $J_{3,4b}$ = 5.0 Hz, H-4b), 2.59 (ddd, 1 H, $J_{4a,4b}$ = 13.1 Hz, $J_{3,4a}$ = $J_{4a,5}$ = 7.8 Hz, H-4a), 1.33 (d, 3 H, $J_{2',CH3}$ = 5.1 Hz, 2'-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.8 ($COOCH_3$), 136.3, 129.4, 128.7, 127.9 (NCH_2Ph), 99.3 (C-2'), 80.5 (C-4'), 78.2 (C-5), 71.9 (C-6'), 64.7 (C-3), 62.3 (C-5'), 60.8 (NCH_2Ph), 53.1 ($COOCH_3$), 33.5 (C-4), 20.5 (2'-CH_3); $C_{17}H_{23}NO_6$ (337.37) calcd C 60.52, H 6.87, N 4.15; found: C 60.17, H 6.79, N 3.99. **Methyl (3*R*,5*S*,2'*S*,4'*R*,5'*R*)-2-*N*-benzyl-3-(5-*tert*-butyldimethylsilyloxy-2-methyl-1,3-dioxan-4-yl)isoxazolidine-5-carboxylate** (**7b**): Colorless oil; yield 65%; $[\alpha]_D$ = +40.0 (CH_2Cl_2, *c* 0.19); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46-7.29 (m, 5 H, NCH_2Ph), 4.72 (dd, 1 H, $J_{4a,5}$ = 8.4 Hz, $J_{4b,5}$ = 7.8 Hz, H-5), 4.73 (q, 1 H, $J_{2',CH3}$ = 5.1 Hz, H-2'), 4.21 (d, 1 H, $J_{CH2a,CH2b}$ = 13.2 Hz, NCH_2Ph), 4.06-4.04 (m, 2 H, H-6'e and NCH_2Ph), 3.78 (d, 1 H, $J_{6'a,6'e}$ = 12.1 Hz, H-6'a), 3.79-3.77 (m, 1 H, H-5'), 3.76 (s, 3 H, $COOCH_3$), 3.62 (ddd, 1 H, $J_{3,4'}$ = 8.7 Hz, $J_{3,4b}$ = 7.9 Hz, $J_{3,4a}$ = 4.9 Hz, H-3), 3.52 (d, 1 H, $J_{3,4'}$ = 8.7 Hz, H-4'), 2.95 (ddd, 1 H, $J_{4a,4b}$ = 13.0 Hz, $J_{3,4b}$ = 7.9 Hz, $J_{4b,5}$ = 7.8 Hz, H-4b), 2.39 (s, 1 H, OH), 2.21 (ddd, 1 H, $J_{4a,4b}$ = 13.0 Hz, $J_{4a,5}$ = 8.4 Hz, $J_{3,4a}$ = 4.9 Hz, H-4a), 1.36 (d, 3 H, $J_{2',CH3}$ = 5.1 Hz, 2'-CH_3), 0.92 (s, 9 H, $OSiC(CH_3)_3$), 0.14 and 0.08 (2 × s, 2 × 3 H, $OSi(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7 ($COOCH_3$), 137.1, 128.9, 128.3, 127.4 (NCH_2Ph), 99.1 (C-2'), 78.8 (C-4'), 74.8 (C-5), 71.4 (C-6'), 63.4 (C-3), 62.3 (C-5'), 60.7 (NCH_2Ph), 52.3 ($COOCH_3$), 33.6 (C-4), 26.0 ($OSiC(CH_3)_3$), 21.0 (2'-CH_3), 17.3 ($OSiC(CH_3)_3$), -4.0 and -4.2 ($OSi(CH_3)_2$).

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(12) The quantum-chemical calculations (AM1 and MM2) were carried out with MOPAC version 6 (on Silicon Graphics Oxygen 2). Geometry optimization and calculation of electronic parameters of reactants, products and transition states was done by semi-empirical methods (AM1 parameters), in all cases using the PRECISE keyword. Transition states were identified by performing force field calculations.