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PAPER

A quantitative structure-reactivity relationship in *N*-acetyl oxazolidines: an electrostatic interaction controls rotamer population†

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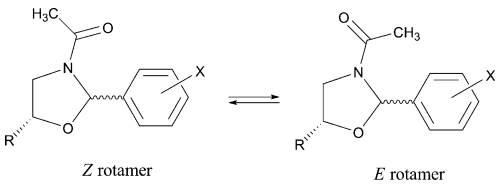
The conformational population of *Z* and *E* isomers of the amide bond in *N*-acetyl oxazolidines is dictated by the electronic nature of the vicinal aryl ring. Experimental and theoretical data support a rationale based on a strong and stereodirecting charge–charge interaction that should be added to the arsenal of non-covalent interactions and whose influence can be more important than once thought.

Introduction

Oxazolidines and *N*-acyloxazolidines constitute a family of important heterocycles found in bioactive natural products.[1] *N*-Acyloxazolidines can be considered as pseudo-prolines and exert a pronounced effect upon backbone conformation in peptides due to their structural similarity with proline itself.[2] It is well established that proline residues play a particular and often key role in peptide and protein secondary structure formation.[3] The prevalence of proline residues in biological processes such as protein folding and protein recognition[4] has led to the development of numerous mimetics[5] and substituted-proline analogs.[6] Therefore, pseudo-*N*-acylprolines may offer new vistas and applications in peptide-based drug and prodrug design, molecular recognition studies, as well as in protein folding and self-aggregation processes.[7] Likewise, DNA-templated syntheses of monocyclic and bicyclic *N*-acyloxazolidines have also been reported and represent the most complex architectures containing these heterocycles and incorporating DNA sequences.[2]

During the course of our studies on chiral imines derived from aminopolyols, we also found a facile and unexpected formation of *N*-acyl-1,3-oxazolidines by simple acylation of such imines.[8] Due to restricted rotation around the amide bond, the resulting *N*-acyl oxazolidines show two sets of signals on the NMR time scale, which correspond to *Z* and *E* rotamers (Scheme 1). *Z*–*E* Isomerization constitutes a dynamic aspect of numerous organic molecules and biomolecules with profound implications and synthetic applications.[9] The interconversion can be driven by external stimuli, a fact that has been exploited for multiple purposes including the design of atropisomeric substrates, chiral switches, and molecular gears.[10]



Scheme 1

Remarkably, the rotameric ratio of polyol *N*-acyl oxazolidines was found to be largely dependent on the substituent in the aromatic ring. Thus, it was decided to explore whether a linear relationship exists between the *Z*/*E* ratio and stereoelectronic parameters of the substituents and, in such a case, to unravel the nature of the associated electronic effect.

Results and discussion

Dependence on the substitution at the aromatic ring

To this end, representative series of *trans*-*N*-acetyl polyacetoxyalkyl-1,3-oxazolidines (**1–10**) having (2*R*,5*S*)-configurations, the corresponding *cis*-(2*S*,5*S*) stereoisomers (**13–22**), and the *O*-unprotected *trans* derivatives (**25–34**) have been evaluated.

Tables 1–3 collect the *Z*/*E* ratio of each *N*-acetyl oxazolidine, which have been determined by ^{1}H NMR spectroscopy in $CDCl_3$ or DMSO-d_6 (for *O*-unprotected compounds), and the corresponding equilibrium constants ($K_{Z/E} = [E]/[Z]$). The Hammett plots (Fig. S1–S3, see Electronic Supplementary Information†) for each series of diastereomeric oxazolidines show a good linear relationship (eqn (1)–(3)).

$$\text{For } \mathbf{1–10}\text{: } \log(K_x/K_0)_{trans} = -0.94\sigma_x - 0.03 \ (r = 0.99) \quad (1)$$

$$\text{For } \mathbf{13–22}\text{: } \log(K_x/_0)_{cis} = -0.80\sigma_x - 0.02 \ (r = 0.99) \quad (2)$$

$$\text{For } \mathbf{25–34}\text{: } \log(K_x/K_0)_{trans} = -0.64\sigma_x - 0.02 \ (r = 0.98) \quad (3)$$

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† Electronic supplementary information (ESI) available: Syntheses of compounds **3a**, **4a**, **3**, **4**, **27**, **28**, and **35**, NMR spectra for all new compounds, along with other graphical and computational data. See DOI: 10.1039/c0ob01039a

Table 1 Z/E Ratios ($CDCl_3$) and substituent effects in compounds **1–12** at 298 K

Compound	X Group	Z	E	$K_{Z/E}$[a]	K/K_0	Log (K/K_0)	σ_x[b]	σ_x[c]	σ_x[c]
12	4-$NHMe_2^+$	79.00	21.00	0.27	0.24	–0.62	0.82[d]	0.82[d]	0.82[d]
1	4-NO_2	83.89	16.11	0.19	0.17	–0.76	0.81	0.78	0.78
2	3-NO_2	84.75	15.25	0.18	0.16	–0.79	0.71	0.71	0.71
3	4-CN	82.64	17.36	0.21	0.19	–0.72	0.70	0.66	0.66
4	4-CF_3	73.53	26.47	0.36	0.33	–0.49	0.53	0.54	0.54
5	3-Br	64.97	35.03	0.54	0.49	–0.31	0.37	0.39	0.39
6	4-AcO	63.07	36.93	0.59	0.53	–0.28	0.31	0.31	0.31
7	4-Cl	63.62	36.38	0.57	0.52	–0.29	0.24	0.23	0.23
8	H	47.50	52.50	1.11	1.00	0.00	0.00	0.00	0.00
9	4-MeO	44.70	55.30	1.24	1.12	0.05	–0.12	–0.27	–0.12[b]
10	4-Me	44.10	55.90	1.27	1.15	0.06	–0.14	–0.17	–0.17
11	4-NMe_2	31.00	69.00	2.23	2.01	0.30	–0.63[d]	–0.63[d]	–0.63[d]
For **1–10**	ρ						–0.94	–0.87	–0.94
	r						0.988	0.974	0.983
For **1–12**	ρ						–0.79	–0.76	–0.79
	r						0.975	0.972	0.972

[a] $K_{Z/E} = [E]/[Z]$. [b] Ref. 11a. [c] Ref. 11b. [d] Ref. 11c.

Table 2 Z/E Ratios ($CDCl_3$) and substituent effects in compounds **13–24** at 298 K

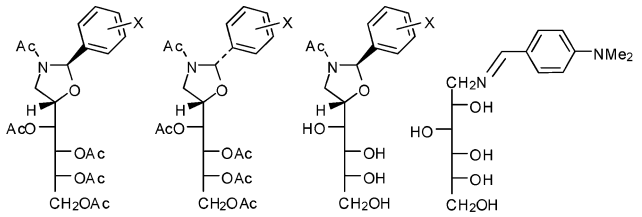
Compound[e]	X Group	Z	E	$K_{Z/E}$[a]	K/K_0	Log (K/K_0)	σ_x[b]	σ_x[c]	σ_x[c]
24	4-$NHMe_2^+$	56.00	44.00	0.79	0.35	–0.46	0.82[d]	0.82[d]	0.82[d]
13	4-NO_2	66.00	34.00	0.52	0.23	–0.65	0.81	0.78	0.78
14	3-NO_2	67.16	32.84	0.49	0.21	–0.67	0.71	0.71	0.71
15	4-CN	60.87	39.13	0.64	0.28	–0.55	0.70	0.66	0.66
16	4-CF_3	54.10	45.90	0.85	0.37	–0.43	0.53	0.54	0.54
17	3-Br	46.43	53.57	1.15	0.51	–0.29	0.37	0.39	0.39
19	4-Cl	43.86	56.14	1.28	0.56	–0.25	0.24	0.23	0.23
20	H	30.50	69.40	2.28	1.00	0.00	0.00	0.00	0.00
21	4-MeO	29.90	70.10	2.34	1.03	0.01	–0.12	–0.27	–0.12[b]
22	4-Me	24.49	75.51	3.08	1.36	0.13	–0.14	–0.17	–0.17
23	4-NMe_2	20.00	80.00	4.00	1.76	0.25	–0.63[d]	–0.63[d]	–0.63[d]
For **13–22**	ρ						–0.80	–0.74	–0.81
	r						0.989	0.975	0.990
For **13–24**	ρ						–0.65	–0.63	–0.64
	r						0.966	0.962	0.959

[a] $K_{Z/E} = [E]/[Z]$. [b] Ref. 11a. [c] Ref. 11b. [d] Ref. 11c. [e] For compound **18** the E/Z ratio could not be determined.

Table 3 Z/E Ratios (DMSO-d_6) and substituent effects in compounds **25–35** at 298 K

Compound[e]	X Group	Z	E	$K_{Z/E}$[a]	K/K_0	Log (K/K_0)	σ_x[b]	σ_x[c]	σ_x[c]
25	4-NO_2	79.00	21.00	0.27	0.37	–0.44	0.81	0.78	0.78
26	3-NO_2	81.00	19.00	0.23	0.32	–0.49	0.71	0.71	0.71
27	4-CN	79.00	21.00	0.27	0.37	–0.44	0.70	0.66	0.66
28	4-CF_3	77.00	23.00	0.30	0.41	–0.38	0.53	0.54	0.54
29	3-Br	66.00	34.00	0.52	0.71	–0.15	0.37	0.39	0.39
30	4-AcO	66.00	34.00	0.52	0.71	–0.15	0.31	0.31	0.31
31	4-Cl	67.00	33.00	0.49	0.68	–0.17	0.24	0.23	0.23
32	H	58.00	42.00	0.72	1.00	0.00	0.00	0.00	0.00
33	4-MeO	50.00	50.00	1.00	1.38	0.14	–0.12	–0.27	–0.12[b]
34	4-Me	53.49	46.51	0.87	1.20	0.08	–0.14	–0.17	–0.17
35	4-NMe_2	42.00	58.00	1.38	1.91	0.28	–0.63[d]	–0.83	–0.63[d]
For **25–34**	ρ						–0.64	–0.61	–0.64
	r						0.977	0.978	0.975
For **25–35**	ρ						–0.58	–0.51	–0.52
	r						0.977	0.969	0.959

[a] $K_{Z/E} = [E]/[Z]$. [b] Ref. 11a. [c] Ref. 11b. [d] Ref. 11c. [e] For compound **36** the E/Z ratio could not be determined.



1 X=4-NO_2	**13** X=4-NO_2	**25** X=4-NO_2	**37**
2 X=3-NO_2	**14** X=3-NO_2	**26** X=3-NO_2	
3 X=4-CN	**15** X=4-CN	**27** X=4-CN	
4 X=4-CF_3	**16** X=4-CF_3	**28** X=4-CF_3	
5 X=3-Br	**17** X=3-Br	**29** X=3-Br	
6 X=4-AcO	**18** X=4-AcO	**30** X=4-AcO	
7 X=4-Cl	**19** X=4-Cl	**31** X=4-Cl	
8 X=H	**20** X=H	**32** X=H	
9 X=4-MeO	**21** X=4-MeO	**33** X=4-MeO	
10 X=4-Me	**22** X=4-Me	**34** X=4-Me	
11 X=4-NMe_2	**23** X=4-NMe_2	**35** X=4-NMe_2	
12 X=4-N^+HMe_2	**24** X=4-N^+HMe_2	**36** X=4-N^+HMe_2	

The negative slope value is evidence that the electronic effect of substituents in the aromatic ring largely dictates the Z/E ratio. The lower magnitude for the *O*-unprotected derivatives (**25–34**) is presumably due to solvent effects as the equilibrium was determined in DMSO-d_6 (ε = 47) having a higher dielectric constant than $CDCl_3$ (ε = 4.8). The choice of different σ_x sets [11] has little or no influence leading to similar correlations. Clearly, electron-withdrawing groups favor the Z conformer, whereas electron-releasing ones shift the equilibrium toward their E counterparts.

The strong dependence of the Z/E equilibrium on the electronic character of the substituent offers a potential means of controlling this equilibrium by a judicious choice of substituent and substitution pattern. Thus pH-responsive systems can be envisaged and, as a consequence, the Z/E ratio could be further fine-tuned. A salient example is provided by an amino group acting as a strong electron donor ($\sigma_p \sim -0.6$), while its protonated form behaves as a good electron acceptor ($\sigma_p \sim +0.8$).[11b,c] To verify this hypothesis, we have prepared an *N*-acetyl oxazolidine bearing such a functionality, specifically the 4-dimethylamino group. Condensation of D-glucamine with 4-dimethylamino benzaldehyde in benzene with azeotropic removal of water led to imine **37**. Its acetylation not only produces the oxazolidine **11** (2*R*,5*S*-configured) but also its 2*S*,5*S* isomer **23**. The *O*-unprotected oxazolidine **35** was isolated after deacetylation of **11** with ammonia in MeOH (see Experimental). A $CDCl_3$ solution of **11** shows an equilibrium Z/E ratio = 31 : 69. Addition of an equimolar amount of CF_3COOH fully switches the ratio to 79 : 21 (*i.e.* protonated form **12**). This conformational inversion is consistent with a stereoelectronic influence exerted by the substituents on the equilibrium (Scheme 2).

Inclusion of equilibria data corresponding to **11** and its protonated form **12** into the Hammett representation led to a good linear relationship (eqn (4), Fig. 1).[12] Likewise, suitable correlations were found for the series of (2*R*,5*S*)-oxazolidines, including **23** and the protonated form **24** (eqn (5), Fig. 2). The oxazolidine derivative **35** shows in DMSO-d_6 a Z/E rotamer population = 42 : 58. The Hammett plot fitted well to eqn (6) (Fig. 3).

$$\text{For } \mathbf{1–12}\text{: } \log(K_x/K_0)_{trans} = -0.79\sigma_x - 0.09 \ (r = 0.98) \qquad (4)$$

$$\text{For } \mathbf{13–24}\text{: } \log(K_x/K_0)_{cis} = -0.65\sigma_x - 0.07 \ (r = 0.97) \qquad (5)$$

$$\text{For } \mathbf{25–35}\text{: } \log(K_x/K_0)_{trans} = -0.58\sigma_x - 0.01 \ (r = 0.98) \qquad (6)$$

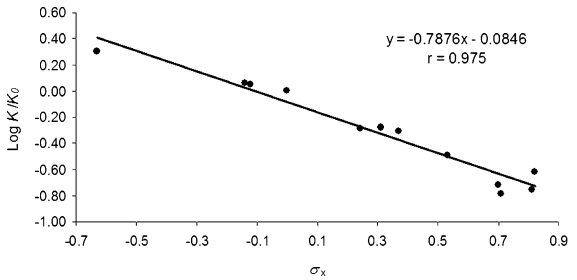


Fig. 1 Relationship between the E/Z ratio and the electron-withdrawing ability of X groups in *N*-acetyl oxazolidines **1–11** and the protonated form **12**.

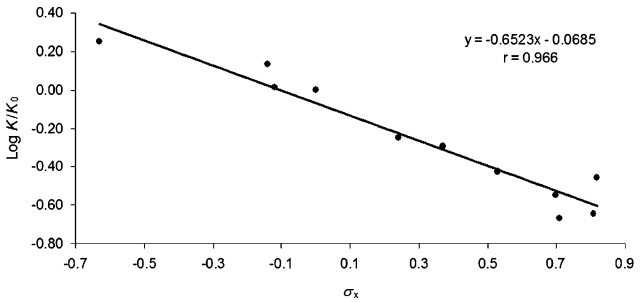


Fig. 2 Relationship between the E/Z ratio and the electron-withdrawing ability of X groups in *N*-acetyl oxazolidines **13–23** and the protonated form **24**.

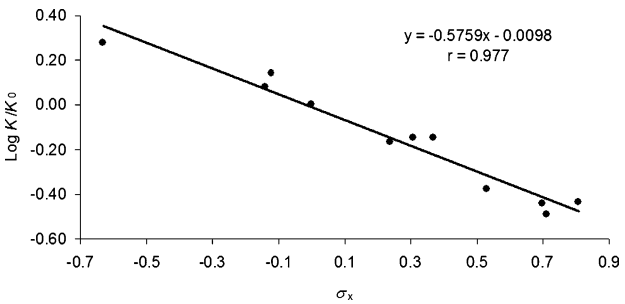
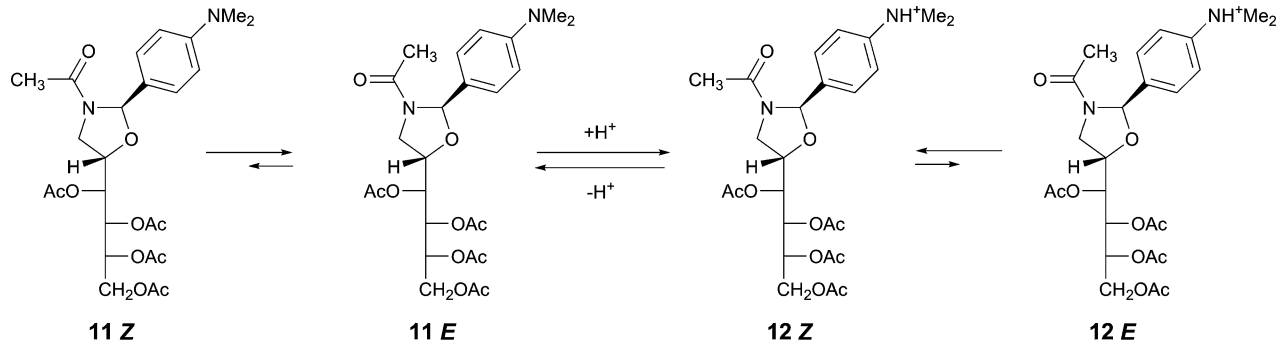


Fig. 3 Relationship between the E/Z ratio and the electron-withdrawing ability of X groups in *O*-unprotected *N*-acetyl oxazolidines **25–35**.

The above representations unambiguously show a stereoelectronic effect, despite the fact that Z/E interconversion of the amide function does not involve formal covalent bonds. This effect cannot be steric in nature, because *meta* and *para* substituents are far from the amide bond.

To confirm the existence of this electronic interaction, theoretical calculations at the B3LYP/6-31G* level of theory have been undertaken.[13,14] The structures of both Z and E isomers of the oxazolidines **1–4** and **6–10** were evaluated, computing the energies of both rotamers, their isomerization energy (ΔG°), and the expected $K_{Z/E}$ value ($K_{Z/E} = e^{-\Delta G^\circ/RT}$). The Hammett plot for these derivatives gives a poor linear correlation (r = 0.805), which could be substantially improved (r = 0.967), after removing the proton and 4-methyl groups from this representation (see ESI†).



Scheme 2

Given the disparate values found for ΔG° through this series of oxazolidines, we thought of different geometric parameters to satisfactorily represent the strength of the non-covalent interaction, such as the distance between the carbonyl oxygen and the *ipso* aromatic position linked to the oxazolidine moiety (d_1), as well as the distance between the carbonyl oxygen and the nearest *ortho* carbon atom (d_2) (Fig. 4 and Table 4).

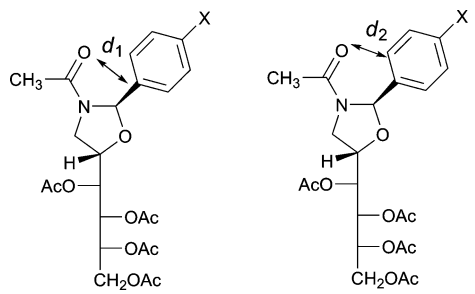


Fig. 4 Schematic definition of d_1 and d_2 parameters in oxazolidines.

A plot of d_1 *versus* σ_x for compounds **1–11** gives rise to a good correlation (r = 0.956) because shorter distances should be expected as the interaction increases. However, d_1 varies only slightly owing to the rigidity of the core framework. More insightful should be a plot of d_2 *versus* σ_x (as actually found, r = 0.962) as rotation around the C_{het}–C_{arom} bond causes greater variations (see ESI†).

The above calculations clearly reproduce the experimental results and support the working hypothesis that there should be an electronic interaction involving the acetamido oxygen and the aromatic ring, which controls the extent of the conformational equilibrium. The origin of such an interaction constitutes the second and main part of this study.

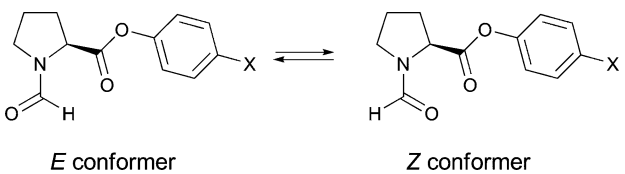
Table 4 Calculated geometric parameters and Hammett parameters (for X groups) according to Fig. 4

Compound	X group	d_1[a]	d_2[a]	σ_x[b]
1	4-NO_2	3.5100	3.2943	0.81
2	4-CN	3.5138	3.3014	0.7
4	4-CF_3	3.5305	3.3279	0.53
6	4-AcO	3.5298	3.3288	0.31
7	4-Cl	3.5315	3.3311	0.24
8	H	3.5617	3.3785	0.00
9	4-MeO	3.5575	3.3776	–0.12
10	4-Me	3.5629	3.3843	–0.14
11	4-NMe_2	3.5720	3.4000	–0.63

[a] In Å. [b] Ref. 11a

On the nature of the electronic interaction

Recently, Raines and Hodges[15] have reported a similar behavior in phenyl esters derived from *N*-formylproline (Scheme 3), for which the population of *Z* conformers increases with the electron-withdrawing character of substituents at the aromatic ring. These authors found a Hammett relationship with ρ = –0.26 and attributed this effect to an n→π* electronic interaction involving one lone pair on the amide carbonyl oxygen and the carbonyl carbon at the ester bond.[16] Due to structural similarities between such proline esters and the *N*-acetyloxazolidines described herein, we thought of the same effect; however, as we shall see this is not the case.



Scheme 3

To elucidate the origin of the electronic effect, four possibilities have been scrutinized: (a) n→π* delocalization between one lone pair on the carbonyl oxygen and one π* orbital of the aromatic ring; (b) dipole–dipole interaction; (c) hydrogen bonding involving the carbonyl oxygen and one *ortho* hydrogen at the aryl group, and (d) charge–charge electrostatic interaction (Fig. 5).

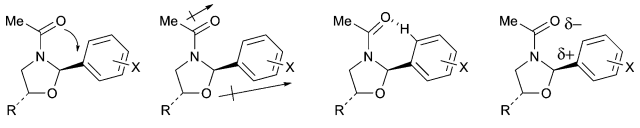


Fig. 5 Possible electronic interactions involving the carbonyl group.

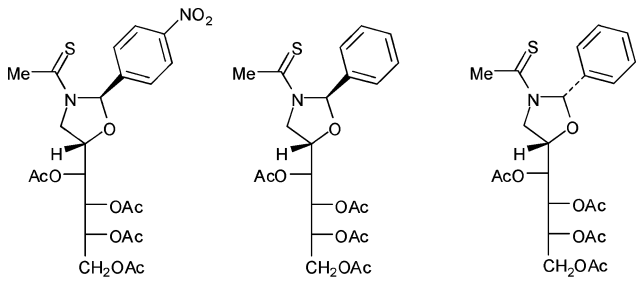
Dipole–dipole and n→π* interactions. Synthesis of *N*-thioacetyl 1,3-oxazolidines

An n→π* interaction involves one lone pair on the carbonyl oxygen and the lowest unoccupied orbital (LUMO, π*) of the aromatic ring. According to the frontier orbital theory[17] the stronger the

interaction, the lower the energy difference between the above-mentioned orbitals. This accounts for more intense interactions as the electron-withdrawing character of the substituents increases, thus lowering the LUMO energy.

To verify the existence of an n→π* interaction, we have employed the same strategy as Raines *et al.*[18] On replacing the amido group by its thio-counterpart, it should be possible to distinguish between n→π* and charge–charge interactions. Such a substitution would reinforce the former as the sulfur atom represents a softer base than the oxygen, and hence a more suitable donor atom. In contrast, the charge–charge interaction would decrease because sulfur is less negatively polarized than oxygen.

To this end, the thio-analog **38** was obtained by treatment of oxazolidine **1** with the Lawesson reagent; however a similar reaction starting from **8** led to a mixture of compounds **39** and **40**, the latter being isolated as a pure isomer by fractional crystallization.



38 **39** **40**

The structures attributed to **38–40** agree with their analytical and spectroscopic data. FT-IR spectra show the stretching band of the amide function at around 1650 cm^{-1}. As expected NMR spectra show two signal sets corresponding to both *Z* and *E* rotamers. The oxazolidine ring remains unaffected as evidenced by resonances at ~6.8–6.0 ppm and ~92 ppm, which are typical of the H-2 and C-2 atoms at the heterocycle (Fig. 6).

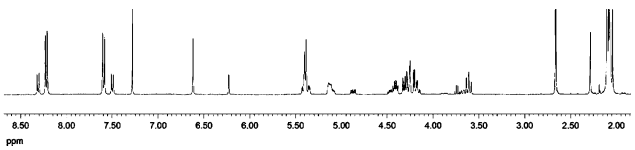


Fig. 6 ^{1}H NMR spectrum of compound **38** in $CDCl_3$.

The thiocarbonyl group causes a larger chemical shift between the protons at C-2 and C-4 in each rotamer than the carbonyl group does. Thus, for the H-2 atom, this difference between the most and less populated rotamer is ~0.5 ppm (*versus* ~0.25 ppm in the corresponding amides). Likewise, the shift difference for the geminal protons at C-4 in the *E* rotamer is ~1.2 ppm and ~0.7 ppm in its *Z* isomer (*versus* ~1.0 ppm and ~0.5 ppm, respectively, in their oxo-analogs). For compounds **38–40** both rotamers can also be easily differentiated on the basis of a significant downfield shift ($\Delta\delta \approx 0.4$ ppm) for the methyl protons of the thioamide function in the *Z* rotamer. In addition, ^{13}C NMR spectra show diagnostic resonances for the thiocarbonyl function at ~196 ppm and its methyl group at ~33 ppm.

Table 5 collects the data for *Z*/*E* equilibria in compounds **38–40** recorded in $CDCl_3$. For comparative purposes, we have also included data for compounds **1**, **8** and **20**. The presence of

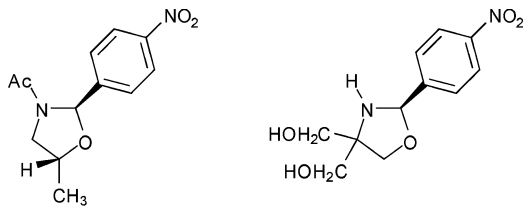
Table 5 *Z*/*E* Equilibria for compounds **1**, **8**, **20** and **38–40**.[a]

Compound	*Z*	*E*	$K_{Z/E}$[b]
1	83.89	16.11	0.19
38	74.07	25.93	0.35
8	47.50	52.50	1.11
39	29.08	70.92	2.44
20	30.50	69.50	2.28
40	27.54	72.46	2.63

[a] In $CDCl_3$. [b] $K_{Z/E} = [E]/[Z]$.

a thioamide function rather than its oxo-counterpart increases markedly the magnitude of $K_{Z/E}$, or in other words, a lower proportion of *Z* rotamers. This result follows the opposite trend to that observed by Raines and associates[18] and would be more consistent with a charge–charge interaction than stabilization *via* n→π* interaction.

Furthermore, NBO (Natural Bond Orbital)[19] analysis helped to rule out the n→π* effect, because no appreciable interactions between the amide oxygen and the aromatic ring could be measured. Second-order interactions found for *E* and *Z* rotamers were essentially identical. Results obtained by calculation using the simplified model **41** at the B3LYP/6-311+G(2d,p) level were similar to those found in **1**, **8** and **9** at the B3LYP/6-31G*. From such data, the anomeric effect, arising from the interaction of the lone pair on the oxazolidine nitrogen with the $\sigma^*_{C\text{-}O}$ orbital (<8.4 kJ mol^{-1}), is much less than that shown by oxazolidines like **42** (~35.1 kJ mol^{-1}).[20] This fact can be attributed to delocalization of the lone pair through the π* orbital of the acetyl C═O bond (~250 kJ mol^{-1}). Such a delocalization implies an almost complete planarity of the nitrogen atom, because the sum of bond angles around this atom in question is close to 360° (**41*Z***, 355.5°; **41*E***, 356.5°); which contrasts with the pyramidalization exhibited by **42** (320.3°). As consequence of this nitrogen planarity, rotamers *E* and *Z* adopt an E_1 conformation, while that in **42** is E_2. The E_1 conformation is also responsible for the reduced anomeric effect at the oxygen atom, varying from ~24.3 kJ mol^{-1} in **42** to <15.5 kJ mol^{-1} in **41**.



41 **42**

A dipole–dipole interaction should likewise be discarded because thioamides usually exhibit larger dipole moments than amides (*e.g.* for the two rotamers of **3**: μ_Z = 5.85 D, μ_E = 1.46 D, whereas in their thio-analogs: μ_Z = 6.24 D, μ_E = 2.28 D). A greater interaction would have been expected, which translates into lower $K_{E/Z}$ values for **38–40**, *i.e.* higher proportions of the *Z* rotamer.

Intramolecular hydrogen-bonding interaction

An interaction involving the amide oxygen and a proximal hydrogen atom at the phenyl ring cannot explain either the

conformation behavior of *N*-acetyl and *N*-thioacetyl oxazolidines. Although the conformational minimum shows that hydrogen close to the carbonyl oxygen, the d_2 distance between the latter and the aromatic carbon (Table 4) invariably exceeds the sum of their van der Waals radii[21] ($r_C^{vdw} + r_O^{vdw} = 1.70 + 1.52 = 3.22$ Å $< d_2$). Thus, Fig. 7 depicts the optimized structures of **1*Z*** and **13*Z***.

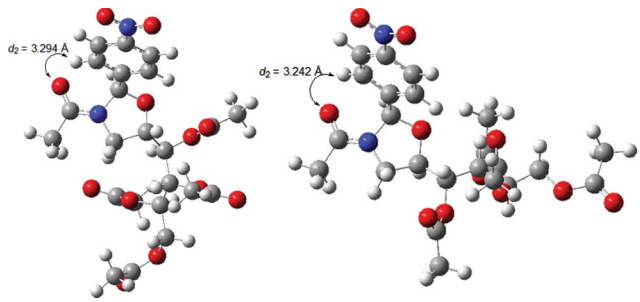


Fig. 7 Optimized geometry for compounds **1*Z*** and **13*Z***.

Moreover, a bonding interaction *via* a hydrogen bridge will also hinder the free rotation of the aryl ring around the bond connected to C-2, thereby altering the magnetic equivalence, in both ^{1}H and ^{13}C NMR spectra, of *ortho* hydrogen and carbon atoms on one hand and of hydrogens and carbons located at the *para* position on the other. However, all the *N*-acetyl and *N*-thioacetyl oxazolidines reported in this work exhibit a complete magnetic equivalence of their *ortho* and *para* positions, which agrees with free rotation of the aryl rings.

Finally, the behavior of rotamers of compound **3** in different solvents also disagrees with the existence of hydrogen bonds. The rotamer population found in different solvent systems appears to be linearly dependent on the corresponding dielectric constants. The linear relationship in Fig. 8, obtained on plotting log $K_{E/Z}$ against $1/\varepsilon$ (Table 6), shows a very good correlation ($r = 0.98$). In stark contrast, no significant correlations were obtained relative to solvatochromic parameters Z and E_T for the same solvents.[22]

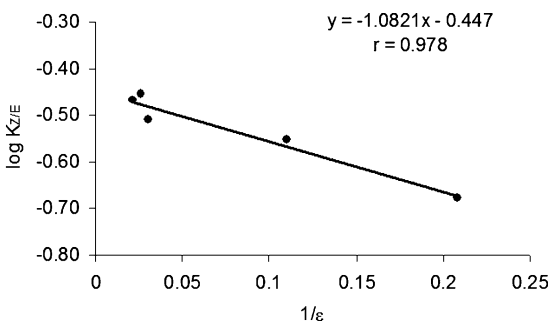


Fig. 8 Plot of log $K_{E/Z}$ *versus* $1/\varepsilon$ of a given solvent.

Table 6 Rotamer populations (%) of **3** in some deuterated solvents

Solvent	*Z*	*E*	$K_{Z/E}$	log $K_{Z/E}$	ε	$1/\varepsilon$
$CDCl_3$	82.64	17.36	0.21	–0.68	4.8	0.21
CD_2Cl_2	78.13	21.88	0.28	–0.55	9.1	0.11
MeOD	76.34	23.66	0.31	–0.51	33.0	0.03
DMF-d_7	74.07	25.93	0.35	–0.46	38.0	0.03
DMSO-d_6	74.63	25.37	0.34	–0.47	47.0	0.02

In addition, this linear relationship suggests a similar influence, though to a different extent, of solvents on the rotameric equilibrium. Solvents capable of participating in hydrogen bonding with the amide carbonyl would disrupt the intramolecular hydrogen bonding, thus altering the *E*/*Z* equilibrium. This effect should be markedly different to that of solvents unable to engage in such hydrogen bonding. The ability is well established in the case of solvents like methanol; even chloroform may bind to the carbonyl groups of peptide bonds, a fact often related to its anesthetic effect. Overall, the whole range of solvents would not fit to a linear correlation, while the empirical data collected in Fig. 8 prove the opposite, thus ruling out any interaction by intramolecular hydrogen bonding.

Charge–charge interaction

Since the amount of *Z* rotamer in **3** decreases as the dielectric constant of either solvent increases, one should reasonably conjecture the existence of charge–charge interactions. On considering the effective charge of all atoms close to the amide oxygen, which is negatively charged, the most important and attractive electrostatic interaction involves the C-1 atom of the aromatic ring that is positively charged; in contrast, the vicinal atoms C-2 and C-6 show negative charges. The hydrogen atoms bound to C-2 and C-6 also possess positive charges, though free rotation of the aromatic ring implies longer distances on average to the carbonyl oxygen, thereby reducing the importance of such attractive interactions.

DFT calculations can be used to determine the total charges on the amide oxygen and C-1 of the aromatic ring, from which a further estimation of the charge–charge interaction can be inferred.

According to Coulomb's law, the electrostatic interaction between two charged particles, $q_1 \cdot e$ and $q_2 \cdot e$, with a separation distance r is given by:

$$F = \frac{q_1 . q_2 . e^2}{4\pi\varepsilon_0 r^2} \tag{7}$$

The stability resulting from such an interaction can be related to work done in moving a positive charge from infinity to a distance dr against the direction of electric field:

$$dW = -F dr \tag{8}$$

And work done by moving the two charges from infinity to a distance d will be obtained by integration of the above expression:

$$W = \frac{q_1 . q_2 . e^2}{4\pi\varepsilon_0 d} \tag{9}$$

By replacing the magnitudes of ε_0 (= $8.8541878176 \times 10^{-12}$ F m^{-1}) and e (= $1.60217653 \times 10^{-19}$ C), the following equations can be obtained:

$$F = 2.307.10^{-8} \frac{q_1 . q_2}{d^2} \tag{10}$$

$$E = W = 2.307.10^{-18} \frac{q_1 . q_2}{d} \tag{11}$$

where q_1 and q_2 are given in atomic units and d in Å, which results in newtons for F and joules for E.

Table 7 Electronic parameters calculated for compounds **1**, **3**, **4**, **6–10**

Comp.	X	q_O[a]	q_{Cl}[a]	F[b] (×10[10])	E[c] (×10[20])	σ_x[d]
1	4-NO_2	–0.509	0.130	–1.239	–4.349	0.81
3	4-CN	–0.510	0.124	–1.182	–4.152	0.70
4	4-CF_3	–0.511	0.120	–1.135	–4.007	0.53
6	4-AcO	–0.513	0.119	–1.130	–3.990	0.31
7	4-Cl	–0.512	0.113	–1.070	–3.780	0.24
8	H	–0.513	0.110	–1.026	–3.655	0.00
9	4-MeO	–0.515	0.110	–1.033	–3.674	–0.12
10	4-Me	–0.513	0.109	–1.016	–3.621	–0.14

[a] In atomic units. [b] In newtons. [c] In joules. [d] Ref. 11.

Table 7 summarizes data for charges as well as calculated values of F and E for diverse *trans*-*N*-acetyl polyacetoxyalkyl-1,3-oxazolidines, *i.e.* those possessing the (2*R*, 5*S*) configuration. The values of d were listed in Table 4 as d_1.

Plots of F or E *versus* σ_x lead to essentially identical linear relationships (Fig. 9) with good correlation coefficients ($r = 0.97$). These results suggest that both F and E result from a direct electronic effect of substituents.

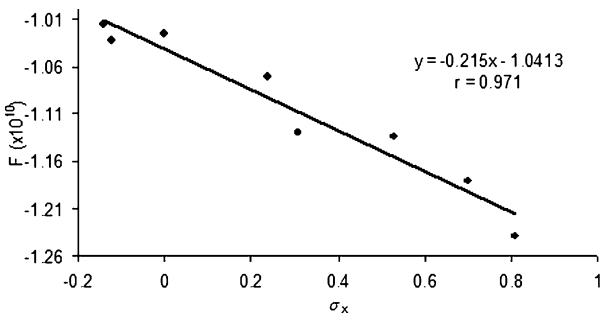


Fig. 9 Plot of F *versus* σ_x for *trans*-*N*-acetyl oxazolidines.

Moreover, the values of $\log(K/K_0)$, which account for experimental data of the E/Z equilibrium, also show a linear relationship with F and E estimated by DFT calculations (Fig. 10 and 11).

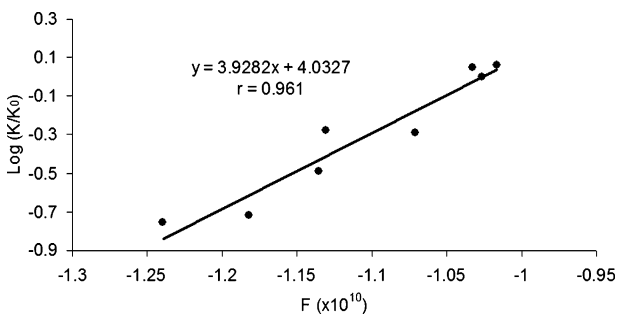


Fig. 10 Plot of $\log(K/K_0)$ *versus* F for *trans*-*N*-acetyl oxazolidines.

Analogous results could be obtained in the case of *cis*-*N*-acetyl polyacetoxyalkyl-1,3-oxazolidines with (2*S*, 5*S*) configurations (Table S1, Fig. S7–S9, see ESI†).

The linear relation between $\log K_{Z/E}$ and $1/\varepsilon$ in Fig. 8 is likewise consistent with a charge–charge interaction as the dominant effect. This dependence can be rationalized by means of a simple model of electrostatic interaction.[23] When the E/Z equilibrium

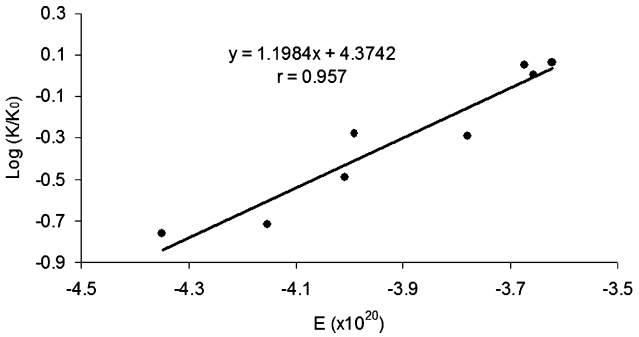


Fig. 11 Plot of $\log(K/K_0)$ *versus* E for *trans*-*N*-acetyl oxazolidines.

is reached, the equilibrium constant is related to the Gibbs free energy variation (ΔG°) between both conformers by:

$$K_{Z/E} = [E]/[Z] = e^{-\Delta G^\circ/RT} \quad (12)$$

or put in logarithmic form:

$$\ln K_{Z/E} = -\Delta G^\circ/RT \quad (13)$$

On the other hand, ΔG° includes both one electrostatic term, ΔG_{ee}°, due to the interaction between charges, and a non-electrostatic and independent term of the charges, ΔG_{nee}°, which corresponds to the free energy variation to an infinite dielectric constant:

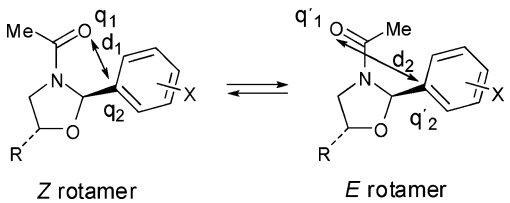
$$\Delta G^\circ = \Delta G_{nee}^\circ + \Delta G_{ee}^\circ \quad (14)$$

Therefore,

$$\ln K_{Z/E} = -(\Delta G_{nee}^\circ + \Delta G_{ee}^\circ)/RT = \ln K_{Z/E}^\circ - \Delta G_{ee}^\circ/RT \quad (15)$$

where $K_{Z/E}^\circ$ is the equilibrium constant to an infinite dielectric constant.

It is obvious that the charge–charge interaction between the amide oxygen and C-1 on the aromatic ring for the Z isomer should be larger than that of its E counterpart owing to a longer distance for the latter, which results in a weaker electrostatic attraction.



The term ΔG_{ee}° equals to work done by moving the charges q_1 and q_2 from infinity to distance d_1 for the Z rotamer minus work done by moving q'_1 and q'_2 from infinity to d_2 for the E rotamer. The resulting expression per mole of substance is:

$$\Delta G_{ee}^\circ = \Delta G_{ee}^\circ(Z) - \Delta G_{ee}^\circ(E) = \frac{q_1 q_2 e^2 N_A}{\varepsilon d_1} - \frac{q'_1 q'_2 e^2 N_A}{\varepsilon d_2} \quad (16)$$

with N_A denoting the Avogadro constant:

By combining eqn (15) and (16) one gets:

$$\ln K_{Z/E} = \ln K_{Z/E}^\circ - \frac{e^2 N_A}{\varepsilon RT}\left(\frac{q_1 q_2}{d_1} - \frac{q'_1 q'_2}{d_2}\right) \quad (17)$$

A more accurate estimation, taking into account all the electrostatic interactions, regardless of their magnitude, is given by:

$$\ln K_{Z/E} = \ln K_{Z/E}^{\circ} - \frac{e^2 N_A}{\varepsilon RT}\left(\sum_Z \frac{q_1 q_2}{d_1} - \sum_E \frac{q_1' q_2'}{d_2}\right) \quad (18)$$

Eqn (17) and (18) are evidence of a linear correlation between log $K_{Z/E}$ and $1/\varepsilon$ with negative slope, because the term in parentheses is always positive: $d_2 \gg d_1$, and agreeing with the plot of Fig. 8.

Conclusions

This investigation demonstrates the existence of a remarkable stereoelectronic interaction that strongly influences the conformational equilibrium of the amide bond in *N*-acetyl oxazolidines (chirality added in turn by an appended sugar chain). This interaction is non-covalent in nature like others found in peptide structures[24] and should most likely have an impact on protein folding. Dynamic control of this stereochemical motif through external stimuli (*e.g.* pH) can also advance further possibilities in nanomachinery. Current efforts are directed towards this goal.

Experimental

General procedures for the synthesis of Schiff bases

Method A. To a solution of D-glucamine (10.0 g, 55.2 mmol) in water (70 mL) was slowly added a solution of the corresponding aldehyde (55.0 mmol) in a small volume of methanol (~30 mL). The mixture was stirred at room temperature, affording a precipitate within a few minutes. The resulting product was collected by filtration and successively washed with cold water, ethanol, and diethyl ether and recrystallized from ethanol.

Method B. To a suspension of D-glucamine (0.91 g, 5.0 mmol) in benzene (15 mL) was added the corresponding aldehyde (7.5 mmol). The mixture was refluxed for 5 h with concomitant water removal (Dean–Stark). The product was filtered and washed with cold benzene and recrystallized from ethanol.

1-Deoxy-1-(3-nitrobenzylidene)amino-D-glucitol (2a)

Method A (66%); mp 137–138 °C; $[\alpha]_D^{22}$ +3; $[\alpha]_{578}^{22}$ +4; $[\alpha]_{546}^{22}$ +4 (*c* 0.5, pyridine); IR (KBr) ν_{max}/cm^{-1} 3400–3000 (OH), 1651 (C═N), 1532 (arom), 1085, 1059, 1020 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (1H, s, CH═N), 8.47 (1H, s, H-arom), 8.30 (1H, d, J = 7.6 Hz, H-arom), 8.17 (1H, d, J = 7.6 Hz, H-arom), 7.76 (1H, t, J = 8.0 Hz, H-arom), 4.76 (1H, d, $J_{C2,OH}$ = 4.4 Hz, OH-2), 4.52 (1H, d, J = 4.8 Hz, OH), 4.50 (1H, d, J = 5.2 Hz, OH), 4.36 (2H, m, OH), 3.89 (1H, m, H-2), 3.86 (1H, m, H-1), 3.71 (1H, m, H-3), 3.62–3.52 (3H, m, H-6′, H-1′, H-5, H-4), 3.40 (1H, dd, $J_{6,OH}$ = 5.6 Hz, $J_{6,6'}$ = 10.4 Hz, H-6′).^{13}C NMR (100 MHz, DMSO-d_6): 160.5 (C═N), 148.6, 138.3, 134.6, 130.8, 125.4, 122.3 (C-arom), 72.8 (C-2), 72.4 (C-4), 72.0 (C-5), 70.4 (C-3), 63.9 (C-6, C-1). Anal. calcd. for $C_{13}H_{18}N_2O_7$ (314.29): C, 49.68; H, 5.77; N, 8.91. Found: C, 49.47; H, 5.98; N, 8.83%.

1-Deoxy-1-(4-dimethylaminobenzylidene)amino-D-glucitol (37)

Method B (66%); mp 188–189 °C; $[\alpha]_D^{21}$ −23; $[\alpha]_{578}^{21}$ −25; $[\alpha]_{546}^{21}$ −30; $[\alpha]_{436}^{21}$ −75 (*c* 0.5, DMSO); IR (KBr) ν_{max}/cm^{-1} 3300–2900 (OH), 1637 (C═N), 1613 (arom), 1088, 1058, 1019 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (1H, s, CH═N), 7.53 (2H, d, J = 8.8 Hz, H-arom), 6.73 (2H, d, J = 8.8 Hz, H-arom), 4.84 (1H, d, $J_{C2,OH}$ = 2.8 Hz, OH-2), 4.65 (1H, d, J = 4.4 Hz, OH), 4.49 (1H, d, J = 4.4 Hz, OH), 4.33 (1H, t, $J_{C6,OH}$ = 5.6 Hz, OH-6), 4.29 (1H, d, J = 6.4 Hz, OH), 3.81 (1H, m, $J_{1,2} = J_{2,3} = J_{C2,OH}$ = 4.6 Hz, H-2), 3.71 (1H, t, H-3), 3.64 (1H, dd, $J_{1,2}$ = 4.4 Hz, $J_{1,1'}$ = 12.0 Hz, H-1), 3.60 (1H, m, H-6), 3.53 (1H, dd, $J_{1,2}$ = 5.6 Hz, $J_{1,1'}$ = 12.8 Hz, H-1′), 3.50 (2H, m, H-5, H-4), 3.39 (1H, dt, $J_{6,OH}$ = 5.4 Hz, $J_{6,6'}$ = 10.6 Hz, H-6′).^{13}C NMR (100 MHz, DMSO-d_6): 161.9 (C═N), 152.2 (C-arom), 129.7 (2C, C-arom), 124.4 (C-arom), 111.9 (2C, C-arom), 73.1 (C-2), 72.3 (C-4), 71.9 (C-5), 70.3 (C-3), 64.0 (C-6), 63.6 (C-1). Anal. calcd. for $C_{15}H_{24}N_2O_5$ (312.37): C, 57.68; H, 7.74; N, 8.97. Found: C, 57.65; H, 7.86; N, 8.91%.

General procedure for the synthesis of *N*-acetyloxazolidines

To a solution of the corresponding 1-(arylmethylene)-amino-1-deoxy-D-glucitol (5.0 mmol) in pyridine (6.7 mL) was added acetic anhydride (6.5 mL). The reaction mixture was kept at 0 °C for 24 h, and then it was poured into ice–water. If the resulting product was an oil this was extracted with chloroform (3 × 50 mL), and the organic layer was sequentially washed with 1 N HCl (2 × 50 mL), a saturated solution of $NaHCO_3$ (2 × 50 mL), and distilled water (2 × 50 mL). The organic layer was dried ($MgSO_4$) and evaporated. If the resulting product was a solid this was separated by filtration and washed with water.

(2*R*,5*S*)-3-Acetyl-2-(3-nitrophenyl)-5-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetrahydroxybutyl-1-yl)oxazolidine (2*E*,*Z*)

(92%). Recrystallized from ethanol, mp 145–146 °C; $[\alpha]_D^{23}$ −12; $[\alpha]_{578}^{23}$ −14; $[\alpha]_{546}^{23}$ −15; $[\alpha]_{436}^{23}$ −14 (*c* 0.5, chloroform); IR (KBr) ν_{max}/cm^{-1} 1745 (C═O), 1654 (C═O, amide), 1215 (C–O–C, ester), 1081, 1051 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (1H, s, H-arom), 8.19 (1H, d, J 8.0 Hz, H-arom), 7.87 (1H, d, J 7.6 Hz, H-arom), 7.53 (1H, t, J 7.8 Hz, H-arom), 6.29 (1H, s, H-2$_Z$), 6.10 (1H, s, H-2$_E$), 5.46 (1H, d, $J_{2',3'}$ = 2.4 Hz, H-2′$_Z$), 5.43 (1H, d, $J_{1',5}$ = 3.2 Hz, H-1′$_Z$), 5.33 (2H, m, H-1′$_E$, H-2′$_E$), 5.16 (1H, m, H-3′$_Z$), 5.09 (1H, m, H-3′$_E$), 4.38 (2H, m, H-5$_Z$ and H-5$_E$), 4.27 (1H, dd, $J_{3',4'}$ = 2.4 Hz, $J_{4',4''}$ = 12.8 Hz, H-4″$_Z$), 4.41–4.18 (3H, m, H-4$_{a,E}$, H-4′$_E$, H-4″$_E$), 4.19 (1H, dd, $J_{3',4''}$ = 4.4 Hz, $J_{4',4''}$ = 12.8 Hz, H-4″$_Z$), 3.97 (1H, dd, $J_{4a,5}$ = 6.0 Hz, $J_{4a,4b}$ = 10.2 Hz, H-4$_{a,Z}$), 3.43 (1H, t, $J_{4b,4a} = J_{4b,5}$ = 10.2 Hz, H-4$_{b,Z}$), 3.28 (1H, t, $J_{4b,4a} = J_{4b,5}$ = 9.6 Hz, H-4$_{b,E}$), 2.17, 2.15, 2.12, 2.10, 2.07 (8 × 3H, s, CH_3), 2.07 (3H, s, CH_3, AcN *Z* isomer), 1.82 (3H, s, CH_3, AcN *E* isomer). ^{13}C NMR (100 MHz, $CDCl_3$): 170.6, 170.5, 170.2, 169.8 (C═O), 168.3 (N–*C*═O, *Z*), 167.8 (N–*C*═O, *E*), 148.6 (C-arom, *E*), 148.3 (C-arom, *Z*), 141.0 (C-arom, *Z*), 140.9 (C-arom, *E*), 133.9 (C-arom, *Z*), 132.8 (C-arom, *E*), 129.2 (C-arom, *Z*), 124.6 (C-arom, *E*), 123.9 (C-arom, *Z*), 122.1 (C-arom, *E*), 121.8 (C-arom, *Z*), 89.1 (C-2$_E$), 88.3 (C-2$_Z$), 77.4 (C-5$_Z$), 77.3 (C-5$_E$), 69.1 (C-2′$_Z$, C-2′$_E$), 68.3 (C-1′$_Z$, C-1′$_E$), 68.0 (C-3′$_Z$, C-3′$_E$), 61.5 (C-4′$_Z$ and C-4′$_E$), 47.6 (C-4$_Z$), 46.5 (C-4$_E$), 23.2 (CH_3, Ac–N *Z* isomer), 22.9 (CH_3, Ac–N *E* isomer), 20.9, 20.8, 20.7, 20.6 (CH_3, acetates). Anal. calcd. for $C_{23}H_{28}N_2O_{12}$ (524.47): C, 52.67; H, 5.38; N, 5.34. Found: C, 52.64; H, 5.30; N, 5.60%.

(2*R*,5*S*)-3-Acetyl-2-(4-dimethylaminophenyl)-5-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetrahydroxybutyl-1-yl)oxazolidine (11*E*,*Z*)

To a solution of imine **37** (5.0 mmol) in pyridine (6.7 mL) was added acetic anhydride (6.5 mL). Solvents were removed after 24 h, and compounds **11** and **23** were purified by crystallization. (55%); Recrystallized from ethanol, mp 168–169 °C; $[\alpha]_D^{21}$ −36; $[\alpha]_{578}^{21}$ −38; $[\alpha]_{546}^{21}$ −43; $[\alpha]_{436}^{21}$ −89 (*c* 0.5, chloroform); IR (KBr) ν_{max}/cm^{-1} 1741 (C═O), 1648 (C═O, amide), 1629 (arom), 1221, 1207 (C–O–C, ester), 1053, 1029 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (2H, d, J = 8.4 Hz, H-arom, *Z*), 7.18 (2H, d, J = 8.8 Hz, H-arom, *E*), 6.69 (4H, d, J = 8.8 Hz, H-arom, *Z* and *E*), 6.18 (1H, s, H-2$_Z$), 5.83 (1H, s, H-2$_E$), 5.43 (2H, m, H-2′$_E$ and H-2′$_Z$), 5.37 (2H, m, H-1′$_E$ and H-1′$_Z$), 5.16 (1H, d, $J_{2',3'}$ = 3.8 Hz, $J_{3',4'}$ = 7.6 Hz, H-3′$_Z$), 5.10 (1H, dd, $J_{2',3'}$ = 3.6 Hz, $J_{3',4'}$ = 7.6 Hz, H-3′$_E$), 4.23 (6H, m, H-4′$_Z$, H-4′$_E$, H-5$_Z$, H-5$_E$, H-4$_{a,E}$, H-4″$_Z$), 4.15 (1H, dd, $J_{4'',5'}$ = 4.2 Hz, $J_{4',4''}$ = 12.6 Hz, H-4″$_E$), 3.86 (1H, dd, $J_{4a,4b}$ = 9.6 Hz, $J_{4a,5}$ = 5.6 Hz, H-4$_{a,Z}$), 3.37 (1H, t, $J_{4b,4a}$ = $J_{4b,5}$ = 10.0 Hz, H-4$_{b,Z}$), 3.29 (1H, t, $J_{4b,4a}$ = $J_{4b,5}$ = 12.2 Hz, H-4$_{b,E}$), 2.97 (6H, s, $(CH_3)_2N$, *E*), 2.95 (6H, s, $(CH_3)_2N$, *Z*), 2.14, 2.10, 2.09, 2.07, 2.03, (9 × 3H, s, CH_3), 1.72 (3H, s, CH_3, *E* AcN isomer). ^{13}C NMR (100 MHz, $CDCl_3$): 170.6, 170.4, 170.3, 170.1, 170.0, 169.9 (C═O), 168.4 (*N*-*C*═O, *E*), 167.9 (N–*C*═O, *Z*), 151.3 (C-arom, *E*), 150.8 (C-arom, *Z*), 128,4 (C-arom, *Z*), 128.2 (C-arom, *E*, *Z*), 127.9 (C-arom, *Z*), 126.5 (C-arom, *Z*), 125.1 (C-arom, *E*), 112.1 (C-arom, *E*), 111.9 (C-arom, *E*), 90.7 (C-2$_E$), 89.5 (C-2$_Z$), 76.4 (C-5$_Z$), 75.7 (C-5$_E$), 69.1 (C-2′$_E$), 69.0 (C-2′$_Z$), 68.7 (C-1′$_Z$), 68.5 (C-1′$_E$), 68.2 (C-3′$_Z$ and C-3$_E$), 61.5 (C-4′$_Z$ and C-4′$_E$), 47.7 (C-4$_Z$), 47.0 (C-4$_E$), 40.5 (2C, $(CH_3)_2N$, *Z*), 40.3 (2C, $(CH_3)_2N$, *E*), 23.4 (CH_3, Ac–N *Z* isomer), 22.8 (CH_3, Ac–N *E* isomer), 20.9, 20.8, 20.7, 20.6 (CH_3, acetates). Anal. calcd. for $C_{25}H_{34}N_2O_{10}$ (522.54): C, 57.46; H, 6.56; N, 5.36. Found: C, 57.39; H, 6.44; N, 5.37%.

(2*S*,5*S*)-3-Acetyl-2-(4-dimethylaminophenyl)-5-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetrahydroxybutyl-1-yl)oxazolidine (23*E*,*Z*)

See compound **11** (31%); Recrystallized from ethanol, mp 188–189 °C; $[\alpha]_D^{21}$ +72; $[\alpha]_{578}^{21}$ +77; $[\alpha]_{546546}^{21\ 21}$ +89; $[\alpha]_{436}^{21}$ +165 (*c* 0.5, chloroform); IR (KBr) ν_{max}/cm^{-1} 1741 (C═O), 1648 (C═O, amide), 1629 (arom), 1221, 1207 (C–O–C, ester), 1053, 1029 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (2H, d, J = 8.4 Hz, H-arom, *Z*), 7.16 (2H, d, J = 8.4 Hz, H-arom, *E*), 6.69 (4H, d, J = 8.4 Hz, H-arom, *Z* and *E*), 6.39 (1H, s, H-2$_Z$), 6.05 (1H, s, H-2$_E$), 5.43 (1H, m, H-2′$_Z$), 5.39 (1H, dd, $J_{2',3'}$ = 5.2 Hz, $J_{2',1'}$ = 1.6 Hz, H-2′$_E$), 5.33 (1H, m, H-1′$_Z$), 5.26 (1H, dd, $J_{1',5'}$ = 7.6 Hz, $J_{1',2'}$ = 1.6 Hz, H-2′$_E$), 5.16 (1H, m, H-3′$_Z$), 5.13 (1H, m, H-3′$_E$), 4.44 (1H, m, H-5$_Z$) 4.26 (4H, m, H-4′$_E$, H-5$_E$, H-4′$_Z$, H-4″$_Z$), 4.16 (1H, dd, $J_{4'',5'}$ = 4.0 Hz, $J_{4',4''}$ = 11.4 Hz, H-4″$_E$), 3.98 (1H, dd, $J_{4a,4b}$ = 12.0 Hz, $J_{4a,5}$ = 4.8 Hz, H-4$_{a,E}$), 3.79 (1H, m, H-4$_{a,Z}$), 3.75 (1H, dd, $J_{4b,4a}$ = 11.8 Hz, $J_{4b,5}$ = 7.0 Hz, H-4$_{b,E}$), 3.63 (1H, dd, $J_{4b,4a}$ = 10.0 Hz, $J_{4b,5}$ = 5.6 Hz, H-4$_{b,Z}$) 2.98 (6H, s, $(CH_3)_2N$, *E*), 2.95 (6H, s, $(CH_3)_2N$, *Z*), 2.14, 2.11, 2.10, 2.09, 2.08 (9 × 3H, s, CH_3), 1.87 (3H, s, CH_3, AcN *E* isomer). ^{13}C NMR (100 MHz, $CDCl_3$): 170.7, 170.6, 170.5, 170.1 (C═O), 168.3 (N–*C*═O, *E*), 167.8 (N–*C*═O, *Z*), 151.2 (C-arom, *E*, *Z*), 127.6, 127.3, 125.3, 112.1 (C-arom), 90.1 (C-2$_E$), 89.6 (C-2$_Z$), 75.7 (C-5$_Z$), 74.4 (C-5$_E$), 69.1 (C-2′$_E$, C-2′$_Z$, C-1′$_E$), 68.3, 68.0 (C-3′$_Z$ and C-3′$_E$), 61.6 (C-4′$_Z$), 61.4 (C-4′$_E$), 47.9 (C-4$_E$), 46.4 (C-4$_Z$), 40.5 (2C, $(CH_3)_2N$, *Z*), 40.4 (2C, $(CH_3)_2N$, *E*), 23.1 (CH_3, Ac–N *Z* isomer), 22.8 (CH_3, Ac–N *E* isomer), 20.9, 20.8, 20.7 (CH_3, acetates). Anal. calcd. for $C_{25}H_{34}N_2O_{10}$ (522.54): C, 57.46; H, 6.56; N, 5.36. Found: C, 57.30; H, 6.40; N, 5.42%.

General procedure for the synthesis of *N* - acetyl - polyhydroxyalkyl-1,3-oxazolidines

To a solution of the corresponding oxazolidine (0.98 mmol) in methanol (16 mL) was added a saturated solution of ammonia in methanol (16 mL). The transformation was monitored by thin layer chromatography (benzene–methanol 9 : 1) and then the mixture was filtered off and evaporated to dryness at a temperature below 30 °C. The title compound was obtained as a solid.

(2*R*,5*S*)-3-Acetyl-2-(3-nitrophenyl)-5-(D-*arabino*-tetrahydroxybutyl-1-yl)oxazolidine (26*E*,*Z*)

(83%); Recrystallized from ethanol, mp 142–143 °C; $[\alpha]_D^{22}$ −27; $[\alpha]_{578}^{22}$ −31; $[\alpha]_{546}^{22}$ −35 (*c* 0.5, pyridine); IR (KBr) ν_{max}/cm^{-1} 3500–3000 (OH), 1637 (C═O), 1524 (arom), 1221 (C–N), 1100, 1079, 1034 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (1H, s, H-arom, *E*), 8.26 (1H, s, H-arom, *Z*), 8.20 (1H, d, J = 8.0 Hz, H-arom, *E*, *Z*), 7.95 (1H, d, H-arom, *E*), 7.92 (1H, d, J = 7.6 Hz, H-arom, *Z*), 7.75 (1H, t, J = 7.8 Hz, H-arom, *E*), 7.67 (1H, t, J = 7.8 Hz, H-arom, *Z*), 6.32 (1H, s, H-2$_E$), 6.13 (1H, s, H-2$_Z$), 4.87 (1H, d, $J_{OH,1}$ = 6.4 Hz, OH-1$_Z$), 4.78 (1H, d, $J_{OH,1}$ = 6.8, Hz OH-1$_E$), 4.57 (1H, d, J = 6.0 Hz, OH, *E*), 4.55 (1H, d, J = 6.0 Hz, OH, *Z*), 4.48 (1H, d, J = 6.0 Hz, OH, *E*), 4.40 (2H, t, $J_{OH,4}$ = 5.6 Hz, OH-4$_Z$ and OH-4$_E$), 4.28 (1H, m, $J_{4b,5}$ = 10.0 Hz, $J_{5,1'}$ = $J_{4a,5}$ = 6.4 Hz, H-5$_Z$), 4.17 (1H, m, H-4$_{a,E}$, H-5$_E$), 3.97 (1H, dd, $J_{4a,5}$ = 5.6 Hz, $J_{4a,4b}$ = 9.6 Hz, H-4$_{a,Z}$), 3.84 (1H, t, $J_{1',5}$ = 6.8 Hz, $J_{1',2'}$ = 0 Hz, H-1′$_Z$), 3.79 (1H, t, $J_{1',5}$ = 6.6 Hz, $J_{1',2'}$ = 0 Hz, H-1′$_E$), 3.61 (2H, m, H-4′$_Z$ and H-4′$_E$), 3.51 (2H, m, H-3′$_Z$ and H-3′$_E$), 3.44 (4H, m, H-4′$_Z$ and H-4″$_E$, H-2′$_Z$ and H-2′$_E$), 3.26 (2H, t, $J_{4b,5}$ = $J_{4b,4a}$ = 7.8 Hz, H-4$_{b,E}$ and H-4$_{b,Z}$), 2.03 (3H, s, CH_3, *Z*), 1.66 (3H, s, CH_3, *E*). ^{13}C NMR (100 MHz, $CDCl_3$): 167.7 (C═O, *E*), 167.1 (C═O, *Z*), 147.9, 147.5, 142.1, 141.9, 134.0, 133.9, 130.4, 129.6, 124.1, 123.3, 122.1, 121.9 (C-arom), 88.0 (C-2$_E$), 87.8 (C-2$_Z$), 80.7 (C-5$_Z$), 80.1 (C-5$_E$), 71.2, 71.1, 70.8, 70.5, 70.3 (C-1′$_Z$ and C-1′$_E$, C-2′$_Z$ and C-2′$_E$, C-3′$_Z$ and C-3′$_E$), 63.2 (C-4′$_Z$ and C-4′$_E$), 47.7 (C-4$_Z$), 46.6 (C-4$_E$), 23.0 (CH_3, *Z*), 22.5 (CH_3, *E*). Anal. calcd. for $C_{15}H_{20}N_2O_8$ (356.33): C, 50.56; H, 5.66; N, 7.86. Found: C, 50.47; H, 5.60; N, 7.84%.

Synthesis of (2*R*,5*S*)-2-(4-nitrophenyl)-5-(1,2,3,4-tetra-*O*-acetyl-D-*arabino* - tetrahydroxybutyl - 1 - yl) - 3 - thioacetyloxazolidine (38*E*,*Z*)

To a solution of the oxazolidine **1** (0.11 mmol) in dry toluene (0.8 mL) was added Lawesson reagent (45 mg, 0.11 mmol) and the mixture was refluxed for 24 h. The reaction mixture was cooled at 4 °C and the resulting product was collected by filtration. (49%); mp 170–171 °C; IR (KBr) ν_{max}/cm^{-1} 1747 (C═O), 1610, 1530, 1460 (arom), 1209 (C═S); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (2H, d, J 8.8 Hz, H-arom$_E$), 8.19 (2H, d, J 8.8 Hz, H-arom$_Z$), 7.57 (2H, t, J 8.8 Hz, H-arom$_Z$), 7.47 (2H, t, J 8.8 Hz, H-arom$_E$), 6.60 (1H, s, H-2$_Z$), 6.21 (1H, s, H-2$_E$), 5.39 (1H, m, H-2′$_E$), 5.37 (2H, m, H-2′$_Z$, H-1′$_Z$), 5.33 (1H, m, H-1′$_E$), 5.11 (1H, m, H-3′$_Z$), 5.07 (1H, m, H-3′$_E$), 4.85 (1H, dd, 1H, dd, $J_{4a,5}$ = 6.0 Hz, $J_{4a,4b}$ = 12.8 Hz, H-4$_{a,E}$), 4.47 (1H, m, H-5$_E$), 4.41 (1H, m, H-5$_Z$), 4.28 (1H, m, H-4$_{a,Z}$), 4.24 (2H, m, H-4′$_Z$, H-4′$_E$), 4.17 (1H, dd, $J_{3',4''}$ = 4.4 Hz, $J_{4',4''}$ = 12.4 Hz, H-4″$_Z$), 4.14 (1H, dd, $J_{3',4''}$ = 4.4 Hz, $J_{4',4''}$ = 12.4

Hz, H-4″$_E$), 3.64 (1H, dd, $J_{4b,4a}$ = 12.8 Hz, $J_{4b,5}$ = 10.0 Hz, H-4$_{b,E}$), 3.59 (1H, t, $J_{4b,4a}$ = $J_{4b,5}$ = 10.6 Hz, H-4$_{b,Z}$), 2.64 (3H, s, CH_3C═S *Z* isomer), 2.26 (3H, s, CH_3C═S *E* isomer), 2.08–2.02 (8 × 3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 197.9 (C═S), 170.5–169.7 (8C, C═O), 149.0–123.5 (C-arom), 92.1 (C-2$_Z$), 91.1 (C-2$_E$), 76.8 (C-5$_Z$), 76.5 (C-5$_E$), 69.0 (C-2′$_E$), 68.9 (C-2′$_Z$), 68.4 (C-1′$_Z$, C-1′$_E$), 68.1 (C-3′$_Z$, C-3′$_E$), 61.4 (C-4′$_Z$ and C-4′$_E$), 53.9 (C-4$_E$), 51.6 (C-4$_Z$), 34.3 (*C*H_3C═S *Z* isomer), 32.8 (CH_3C═S *E* isomer), 20.9–20.5 (CH_3, acetates). Anal. calcd. for $C_{23}H_{28}N_2O_{11}S$ (540.54): C, 51.11; H, 5.22; N, 5.18; S, 5.93. Found: C, 51.33; H, 4.95; N, 5.27; S, 5.84%.

Synthesis of (2*R*,5*S*)-2-(phenyl)-5-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetrahydroxybutyl-1-yl)-3-thioacetyloxazolidine (39*E*,*Z*) and (2*S*,5*S*)-2-(phenyl)-5-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetrahydroxybutyl-1-yl)-3-thioacetyloxazolidine (40*E*,*Z*)

To a solution of the oxazolidine **8** (1.04 mmol) in dry toluene (7 mL) was added Lawesson's reagent (0.46 g, 1.13 mmol) and the mixture was refluxed for 24 h. Solvent was removed under vacuum and the resulting mixture was purified by flash chromatography (hexane–ethyl acetate, 3 : 1), giving a mixture of **39** and **40** (68%). Compound **40** was isolated by recrystallization, (44%); mp 141–142 °C; IR (KBr) ν_{max}/cm^{-1} 1742 (C═O), 1593, 1478 (arom), 1218 (C═S); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.21 (10H, m, H-arom), 6.84 (1H, s, H-2$_Z$), 6.31 (1H, s, H-2$_E$), 5.38 (2H, dd, $J_{2',1'}$ = 2.4 Hz, $J_{2',3'}$ = 8.8 Hz, H-2′$_Z$, H-2′$_E$), 5.33 (2H, dd, $J_{1',2'}$ = 2.4 Hz, $J_{1',5}$ = 6.4 Hz, H-1′$_Z$, H-1′$_E$), 5.11 (2H, m, H-3′$_Z$, H-3′$_E$), 4.47 (1H, m, H-5′$_Z$), 4.34 (1H, m, H-5′$_E$), 4.78 (1H, dd, 1H, dd, $J_{4a,5}$ = 6.0 Hz, $J_{4a,4b}$ = 12.4 Hz, H-4$_{a,E}$), 4.41 (2H, m, H-5$_E$, H-5$_Z$), 4.23–3.88 (8H, H-4$_{a,Z}$, H-4$_{a,E}$, H-4′$_E$, H-4′$_Z$, H-4″$_Z$, H-4″$_E$, H-4$_{b,E}$, H-4$_{b,Z}$), 2.63 (3H, s, CH_3C═S *Z* isomer), 2.37 (3H, s, CH_3C═S *E* isomer), 2.10–2.03 (8 × 3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 196.8 (C═S), 170.9–169.7 (8C, C═O), 136.2–126.4 (C-arom), 93.6 (C-2$_Z$), 92.1 (C-2$_E$), 75.9 (C-5$_Z$), 74.5 (C-5$_E$), 69.7 (C-2′$_Z$), 69.1 (C-2′$_E$), 69.0 (C-1′$_Z$), 68.5 (C-1′$_E$), 68.0 (C-3′$_Z$, C-3′$_E$), 61.5 (C-4′$_Z$ and C-4′$_E$), 53.4 (C-4$_E$), 51.4 (C-4$_Z$), 33.8 (*C*H_3C═S *Z* isomer), 32.6 (*C*H_3C═S *E* isomer), 20.9–20.7 (CH_3, acetates). Anal. calcd. for $C_{23}H_{29}NO_9S$ (495.54): C, 55.75; H, 5.90; N, 2.83; S, 6.47. Found: C, 55.72; H, 5.83; N, 2.84; S, 6.53. **Spectroscopic data for compound 39:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (10H, m, H-arom), 6.58 (1H, s, H-2$_Z$), 6.07 (1H, s, H-2$_E$), 5.38 (4H, m, H-2′$_E$, H-2′$_Z$, H-1′$_Z$, H-1′$_E$), 5.09 (2H, m, H-3′$_Z$, H-3′$_E$), 4.78 (1H, dd, 1H, dd, $J_{4a,5}$ = 6.0 Hz, $J_{4a,4b}$ = 12.4 Hz, H-4$_{a,E}$), 4.41 (2H, m, H-5$_E$, H-5$_Z$), 4.25 (3H, m, H-4$_{a,Z}$, H-4′$_E$, H-4′$_Z$), 4.17 (2H, m, H-4″$_Z$, H-4″$_E$), 3.62 (1H, dd, $J_{4b,4a}$ = 12.0 Hz, $J_{4b,5}$ = 10.8 Hz, H-4$_{b,E}$), 3.55 (1H, t, $J_{4b,4a}$ = $J_{4b,5}$ = 10.6 Hz, H-4$_{b,Z}$), 2.64 (3H, s, CH_3C═S *Z* isomer), 2.22 (3H, s, CH_3C═S *E* isomer), 2.07–2.01 (8 × 3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 192.4 (C═S), 170.6–169.7 (8C, C═O), 136.8–126.4 (C-arom), 93.2 (C-2$_Z$), 92.7 (C-2$_E$), 76.4 (C-5$_Z$), 76.0 (C-5$_E$), 69.1 (C-2′$_E$), 69.0 (C-2′$_Z$), 68.9 (C-1′$_Z$, C-1′$_E$), 68.1 (C-3′$_Z$, C-3′$_E$), 61.4 (C-4′$_Z$ and C-4′$_E$), 54.1 (C-4$_E$), 51.5 (C-4$_Z$), 34.2 (*C*H_3C═S *Z* isomer), 32.7 (*C*H_3C═S *E* isomer), 20.9–20.7 (CH_3, acetates).

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