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STEREOCONTROLLED SYNTHESIS BY ANOMERIC EFFECTS OF SUBSTITUTED 1-AZA-3,7-DIOXABICYCLO[3.3.0]OCTANES

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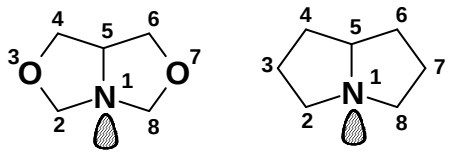
ABSTRACT. First coherent examples of stereocontrolled ring closure in 1-aza-3,7-dioxabicyclo[3.3.0]octane series were found to originate in the anomeric effects of the aminalic part of this heterobicyclic saturated system; experimental data were in agreement with the theoretical calculation; the roll of the bulky substituents is also pointed out.

1. INTRODUCTION

The heterocyclic saturated system 1-aza-3,7-dioxabicyclo[3.3.0] octane (**A**) was discovered in 1945 by Senkus;[1,2] the elucidation of the structure soon after by chemical methods by Pierce[3,4] revealed the analogy between **A** (as 3,7-dioxa analogue and fused 1,3-oxazolidine system) and the core alkaloid, namely pyrrolizidine (**B**, **Scheme 1**).



A **B**

Scheme 1

Presumably, because of this resemblance, very large series of substituted derivatives of **A** were prepared along more than a half of century since they revealed significant useful applications.[5-14] On the other hand, their most convenient synthesis (nucleophilic cyclocondensation between *C*-substituted 2-amino-1,3-propanediols, the so called *"serinols"* and carbonyl compounds) is simple, direct and efficient with high yields (**Scheme 2**).

Furthermore, the multiple applications of the title compounds largely prevailed the structural investigations (conformational analysis, chirality, diastereoisomerism, etc).[15-18]

The first hypothesis regarding their diastereomerism at the aminalic stereocenters C-2, -8 belongs to Edgerton as early as 1959 (**Scheme 2**, compound **3b**, R^2 = Ph).[19,20] In the period of '70's, Crabb postulated the global stereochemistry of the bicycle as *cis*-fused oxazolidine flipping system[15-17] (the lone pair at N-1 and the ligand at C-5

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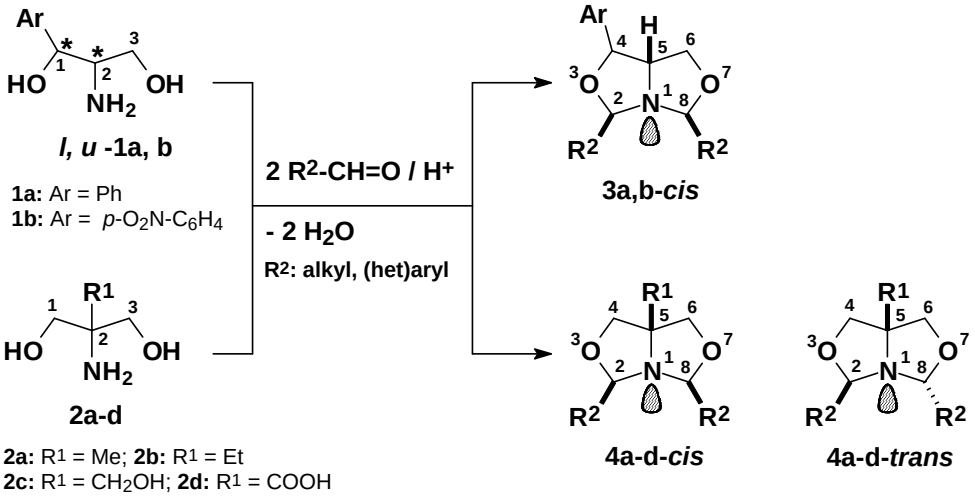
as references). Soon later this basic geometry was independently confirmed by the X-rays determined structure by O'Connor (**Scheme 2**, compound **4d,** R^1 = COOH, R^2 = H, cooper salt).[21] In 2000, another X-rays determined structure by Pavia (**Scheme 2**, compound **4c-*cis***, R^2 = Ph) made known the importance of the anomeric effects in each oxazolidine ring supported by the contraction of the bonds N-C-2(8) with respect to N-C-5.[22-26]



Scheme 2

All these structural assignments confirmed the heterofacial type of the molecular skeleton.

However, in our days, minor attention was paid to enlargement of the diastereomerism in this class.[9,11] Thus, in the series **3a, b**, considering the configuration at C-4 kept identical with C-1 (as in the starting materials **1a, b**), the cyclocondensation would yield four diastereomers about the new chiral centers C-2 and C-8: 2*R*,8*S*; 2*S*,8*R*; 2*S*,8*S*; 2*R*,8*R*. Indeed, under kinetic control, our preceding findings revealed the existence of all these four diastereomers (**Scheme 2**, compound **3b**, R^2 = Ph). In contrast, under thermodynamic control, in a large sequence of syntheses performed with (het)aryl aledhydes, the serinol **1b** (as *like* enantiomerically pure diastereomer, 1*S*,2*S*) yielded diastereoselectively the structures **3b** possessing all ligands (C-2, -4, -8) *cis*-oriented with respect to the *cis*-junction of the bicyle (hence, an absolute configuration 1*R*,2*R*,4*S*,5*S*,8*S*).[27-30] We called this spatial arrangement *"all cis"* : the lone pair at N-1 and all the ligands attached at C-2, -4, –8.

Later investigations by us in the series **2a-d** evidenced the same stereochemical behaviour: indeed, compounds possessing the *"all cis"* arrangement (the lone pair at N-1 and the ligands attached at C-2, -5 and –8, **4-*cis***, **Scheme 2**) were basically dominant with respect to **4-*trans***[!] (diastereomeric ratios from 80:20 to 100:0 ***cis*** *vs.*

[!] A previous detailed by us discussion of this diastereomerism indicated series **4 *cis*** as *meso* forms meanwhile **4 *trans*** are intrinsic chiral about C-2 and C-8; for the present discussion, entering into all these details is not necessary.[31] The same is valid for conformational chirality exhibited by this heterocyclic system.[32,33]

trans).[31] Therefore, hereafter we kept this more simple nomenclature as ***cis*** or ***trans*** restricted to orientation of the ligands linked at C-2(8) (**Scheme 2**).

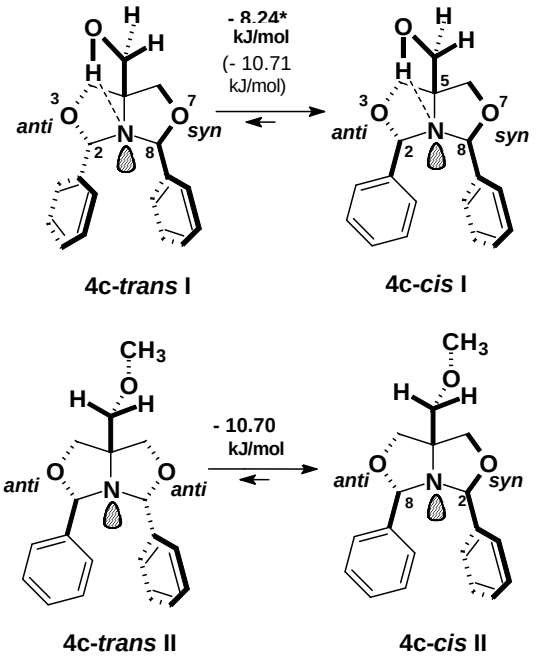
To our knowledge, no explanation was provided so far for this diastereoselectivity. In addition, recently reported more sophisticated structures of type **4** were surprisingly not defined from this point of view.[13]

2. RESULTS AND DISCUSSION

2.1. Theoretical approach by means of RHF 6/31-G* molecular orbital calculation

We start the present discussion by examining the compound **4c I** and its *O*-methyl derivative **4c II** (**Scheme 3**).

The compound **4c I** was readily available by cycloondensation between TRIS® **2c** and benzaldehyde (**Scheme 2**). According to the NMR spectra of the crude reaction mixture, the diastereoselectivity under thermodynamic control (24 hrs, 110°C) was 5:1 **4c-*cis* I** : **4c-*trans* I**, consequently a ΔG value about 5 kJ/mol. The calculated difference between the total energy of these diastereomers (ΔΔE values), as shown in **Scheme 3**, was not quite consistent with the experiment; indeed, it was found 10.7 kJ/mol. It is of note that in **Scheme 3** the fully optimised geometry is given for the most stable conformer belonging each to the series **4c-*cis* I** or **4c-*trans* I**.



4c-*trans* I **4c-*cis* I**

4c-*trans* II **4c-*cis* II**

***in boldface:** ΔΔE values by considering the orientation of the hydroxymethyl group; in brackets, the ΔΔE value by neglecting the orientation of the hydroxymethyl group.

Scheme 3

Unpredictably, in each series, the ΔΔE values between considerable *conformational* diasteromers (*e.g.* issued from the rotation about C-O-C bonds, including also the possible phenyl rotamers (not depicted) were found slightly greater than the difference between *configurational* diastereomers ***cis-trans***. The diverse orientations of the C-5 hydroxymethyl group in **4c-*cis* I** or **4c-*trans* I** (not depicted) as well as the same diference between the *O*-methyl forms **4c-*cis* II** and **4c-*trans* II** indicated no importance in comparison with the basic **4c-I**.

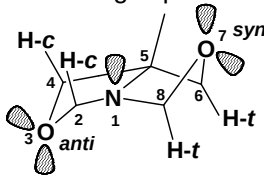
2.2. Theoretical approach by means of anomeric effects

In this approach, we considered the 1-aza-3,7-dioxabicyclo[3.3.0]octane system as two "independent" 1,3-oxazolidines, possessing the phenyl ligand at C-2 (oxazolidine numbering) but differently oriented, *e.g.*, in ***trans***. Next, for the compound **4c-*trans* I** we estimated the anomeric effects as main delocalising interactions in the aminalic zone of the heterocycle O-C-N (kJ/mol). The results are collected in **Table 1** and detailed in **Scheme 4**.

Thus, the two-oxazolidine rings are oriented in opposite sense (O-3-*anti* and O-7-*syn*) as two frozen *O*-envelope conformers. Since the problem under examination, refer to the *pseudo*-equatorial orientation of the two phenyl rings, we strictly focused on the hyperconjugation involving the two *pseudo*-axial $\sigma_{C\text{-}H}$ bonds in the aminalic part of the molecule (O-C-N-C-O), as quantitative manifestation of the anomeric effects. One must observe that in the O-7-*syn* oxazolidine ring, the position C-8 was a significant anomeric center and the corresponding delocalising interactions are $lp_{O\text{-}7\text{-}ax.} \rightarrow \sigma^*_{C\text{-}8\text{-}H\text{-}8\text{-}t}$ and $lp_{N\text{-}1} \rightarrow \sigma^*_{C\text{-}8\text{-}H\text{-}8\text{-}t}$. Indeed, only the depicted orbitals were antiperiplanar and from energetic point of view, their total interaction was about 67 kJ/mol. On the contrary, in the O-3-*anti* oxazolidine ring but one similar interaction was found: $lp_{O\text{-}3\text{-}ax.} \rightarrow \sigma^*_{C\text{-}2\text{-}H\text{-}2\text{-}c}$ supported by about 41 kJ/mol. That is, the O-7-*syn* oriented oxazolidine ring was much more hyperconjugated with respect to the O-*C(H)*-N bond. Its structure can also be described by *two* non-bonding formulae (**Scheme 4**) meanwhile for the O-3-*anti* oxazolidinie ring but *one* non-bonding structure can be imagined.

Table 1

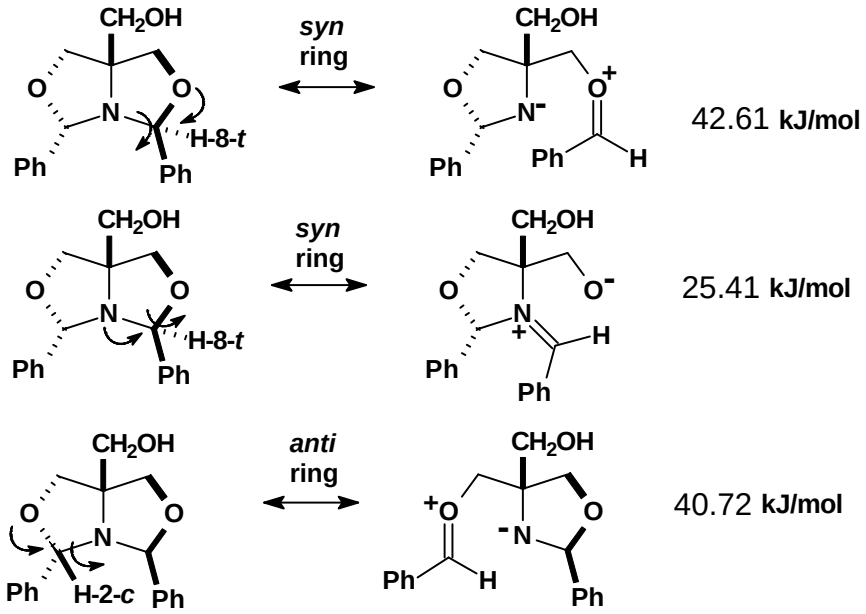
Calculated main delocalising interactions (selected as E > 25 kj/mol) for the compound **4c-*trans* I** (for reason of simplicity, atoms and groups not discussed are omitted in formulae).



4c-*trans* I

NMO Donors (lp)[a]	Acceptors MO (σ*, kj/mol)						
	C2-O3	**N1-C2**	**N1-C8**	**C2-H2-*c***	**C8-H8-*t***	**C4-H4-*c***	**C6-H6-*t***
N-1	46.38	**-**	**-**	**-**	25.41	**-**	**-**
O-3-ax[b]	-	**-**	**-**	40.72	**-**	39.64	**-**
O-3-eq	-	31.93	**-**	-	**-**	-	**-**
O-7-ax	-	**-**	**-**	-	42.61	-	38.51
O-7-eq	-	**-**	31.73	-	**-**	-	**-**

[a] depicted lone pairs as **N**on bonding **M**olecular **O**rbital
[b] orientation of the involved NMO as axial (or equatorial)



Scheme 4

To conclude, our diagnostic is that the **4c-*trans* I** should be less stable than **4c-*cis* I** in which both benzyl carbons C-2, -8 should be comparably hyperconjugated.[32]

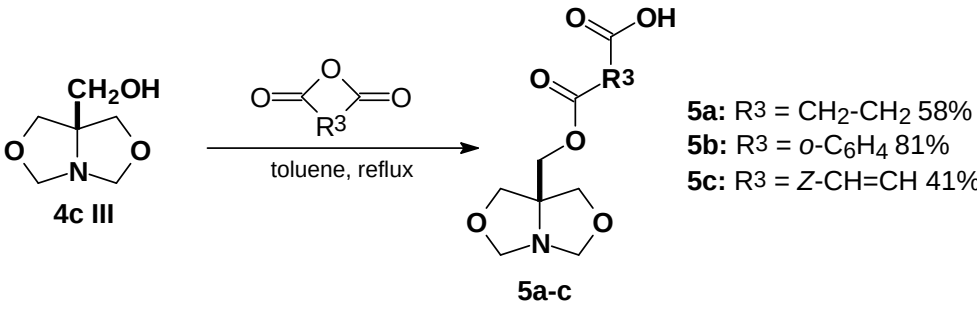
There are two experimental evidence to prove the importance of the delocalisations of type lp-O(N) $\rightarrow$ σ*-C-H in 1,3-oxazolidine ring. Thus, if the aryl aldehyde involved in the ring closure have a strong withdrawing substituent at the *para* position *vs.* the benzyl carbon (*p*-nitrobenzaldehyde and 4-pyridyl aldehyde), the diastereoselectivity is reversed: 100:0 **4c *trans*** *vs.* ***cis*** and 75:25 respectively.[9,11,31] That is, diastereoselectivity is sensitive to the polarity of the C-2(8)-H bond and its corresponding E_{LUMO}.

2.3. Experimental evidence for the anomeric effect from the bridged nitrogen

The calculation resumed in **Table 1** also indicated a strong hyperconjugation involving the bridged nitrogen: $lp_N \rightarrow \sigma^*_{C\text{-}2\text{-}O\text{-}3}$: 46.38 kJ/mol. As recently emphasised in the literature,[22] this interaction is specific for the geometry of the compound **4c-*cis* I**. In the absence of the two phenyl groups linked at C-2, -8 (compound **4c III**, R^2 = H, **Scheme 2**), the same anomeric effect calculated by us was smaller: 40.46 kcal/mol.

We attempted at checking the meaning of this effect: we converted the compound **4c III** in carboxylic derivatives by *O*-acylation (**Scheme 5**).

In the ^{1}H NMR spectra of the compounds **5a-c** the carboxylic proton was unambiguously located in the region 10 – 11 ppm (typical broad singlet), as in authentic COO*H* groups. Hence, no amfionic form we could assign for any of the compounds **5a-c** since the lone pair of the bridged nitrogen was too involved in hyperconjugation and presumably insensitive to proton donors possessing K_a values in the domain 10^{-4} - 10^{-5}.



Scheme 5

2.4. The *trans* stereocontroll by bulky substituents

In the present research, we were also interested in orienting the (complete ?) diastereoselectivty of the double ring closure in 1-aza-3,7-dioxabicyclo[3.3.0]ctanes towards ***trans*** diastereomers. Since ring closure with aryl aldehydes appeared to be governed by the anomeric effects, we considered the long-established influence of a bulky substituent attached to the carbonyl functionality.

Before discussing the results, some conclusions arising from earlier research of our group[31] should be reminded (**Scheme 2**): the *"all cis"* arrangement **4c *cis*** operated in each of the below cases:

i) if but one of the ligands was Ar (*e.g.* ring closure with two different aldehydes from which one is formaldehyde).

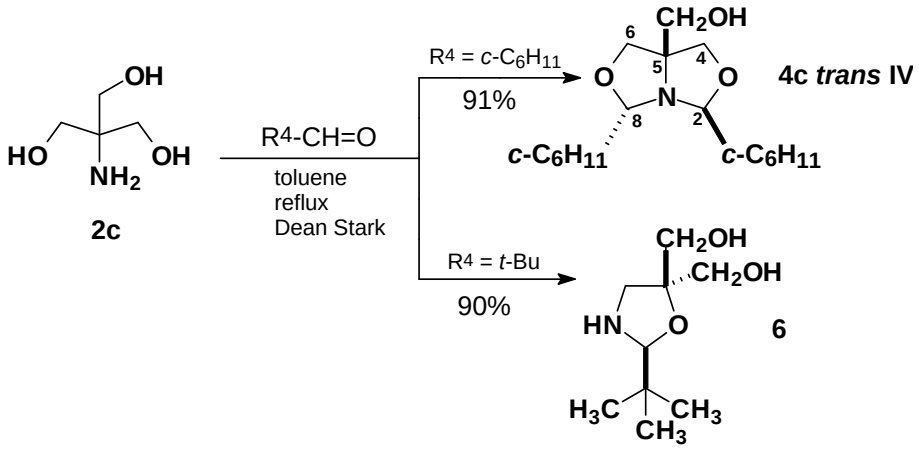
ii) if one of the ligand is Ar and the other oxazolidine was a spiranic structure (*e.g.* ring closure with two different carbonyl compounds: an aryl aldehyde and a C-5-7-cyclanone)

iii) for bulky aldehydes [*e.g.* $R^4 = (Ph)_3CCH_2$] if the bulkiness was remote by at least one carbon from the reaction site.

Keeping in mind these examples, we treated TRIS® **2c** with two bulky aldehydes in 1:2 molar ratio (thermodynamic control: 24 hrs in refluxing toluene with continuous removal of water). The syntheses are described in **Scheme 6**.

The cyclocondensation with cyclohexancarboxaldehyde gave directly **4c *trans* IV** with complete ***trans*** diastereoselectivity; surprisingly, the reaction carried out with 1:1 molar ratio **2c** : aldehyde afforded the same compound (together with the corresponding amount of unreacted TRIS®) to prove that the intermediate mono oxazolidine was more reactive than **2c** itself (hence, non isolable). Careful inspection of Drieding models supported the ***trans*** stereochemistry for **4c IV** together with its NMR spectra (see **EXPERIMENTAL**).

In contrast, if trimethylacetaldehyde was used, constantly only one ring closure took place (mono oxazolidine **6**) to demonstrate the anticipated steric hindrance promoted by the bulky substituent, *t*-Butyl. It seemed to us the behaviour of trimethylacetaldehyde in the above conditions as similar with the C-5-7-cyclanones: but one ring closure took place (to yield the corresponding spiro mono oxazolidines, previously reported by us).



Scheme 6

3. CONCLUSION

The ***cis*** or ***trans*** diastereososelectivity in the ring closure of C-2-, -8 substituted 1-aza-3,7-dioxabicyclo[3.3.0]octanes in reaction with carbonyl compounds can be explained taking into account:

i) the anomeric effects in the final structure (reaction with aryl aldehydes); they favour an *"all cis"* stereochemistry.

ii) the bulky substituents linked directly to carbonyl group promoted either the ***trans*** diastereoselectivity or but a single ring closure, to yield simple C-2-substituted-1,3-oxazolidines.

4. EXPERIMENTAL

General

Melting points are uncorrected; they were carried out on ELECTROTHERMAL® 9100 instrument.

NMR spectra were recorded on Brucker® AM300 instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei respectively. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. All NMR spectra were measured in anhydrous commercially available deuterated solvents. All chemical shifts (δ values) were given throughout in ppm; all coupling patterns (*J* values) were given throughout in Hz. Locking, shimming and acquisition were made without spinning.

IR spectra were performed on a Perkin-Elmer® 16 PC FT-IR spectrometer. Only relevant absorptions were listed [throughout in cm^{-1}: weak (w), medium (m) or (s) strong].

Molecular orbital calculation: the conformational space of the systems have been investigated by using the "Conformer Distribution" facility (MMFF force field) from Spartan'o2® [Spartan'o2, Wavefunction, Inc. Irvine, CA]. The set of conformers thus generated has been subjected, within the same package, to full geometry optimization at the RHF/6-31G* *ab initio* level. The default convergence criteria (Energy = 0.000001 hartrees, rms gradient = 0.000450 hartrees/bohr) have been imposed throughout all the *ab initio* computations.

Natural bond orbital analysis[34] has been carried out with the Gaussian 98 system [Gaussian 98, Revision A.11.3, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, N. Rega, P. Salvador, J. J. Dannenberg, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 2002.] run under Linux.

The syntheses of the discussed compounds: **4c-*cis* I**, **4c-*trans* I**, **4c-*cis* II**, and **4c III** were made according to literature[1-4] or previous published data by us.[31,32]

Typical procedure for the synthesis of the compounds 5a-c

r-1-Aza-*c*-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octane (1.45 g, 10 mmol) **4c III** (**Scheme 5**) and the corresponding anhydride (10 mmol) in dry toluene (25 mL) were refluxed with vigorous stirring. The reaction was monitored by TLC (eluent benzene : methanol 3:1 v/v; double visualisation whenever possible: I_2 bath and UV 254 nm) and stopped when the starting materials where detected in small traces only (8 – 16 hrs). The reaction mixture was filtered hot and the toluene solution was evaporated under vacuum to dryness. The crude product was isolated by crystallisation from ether to yield the title compounds **5a-c**.

***r*-1-Aza-*c*-5-succinyloxymethyl-3,7-dioxabicyclo[3.3.0]octane (5a)** (58%) white crystalline powder mp 71-73 ^oC (Et_2O); [Found: C, 49.09; H, 6.01; N, 5.88. $C_{10}H_{15}NO_6$ requires C, 48.97; H, 6.16; N, 5.71%]; R_f (75% benzene/methanol) 0.60; ν_{max} (CH_3Cl film) 3430 (w), 2950 (s), 2503 (m), 1772 (s), 1479 (m), 1408 (m), 1371 (s), 1344 (s), 1272 (s), 1220 9s), 1172 9s), 1172 9s), 1119 9s), 1060 (s), 1022 9s), 995 (s), 973 (s), 932 (s), 844 (s), 760 (s), 681 (s), 661 (s) cm^{-1}; δ_H (300 MHz $CDCl_3$) 10.40 (1H, bs, COOH), 4.47 (2H, d, *J*=5.5 Hz, H-2 -8), 4.41 (2H, d, *J*=5.5 Hz, H-2, -8), 4.15 (2H, s, CH_2O), 3.76 (4H, s, H-4, -6); δ_C (75 MHz $CDCl_3$) 171.9 (1C, COOH), 167.6 (1C, COO), 87.9 (2C, C-2, -8), 73.7 (2C, C-4, -6), 71.3 (1C, C-5), 66.3 (1C, 5-CH_2O), 28.8 (2C, CH_2).). MS (CI, CH_4); m/z (rel. int.): 244.8 (<2), 145.1 (25), 127.2 (100), 100.1 (19).

***r*-1-Aza-*c*-5-phthaloyloxymethyl-3,7-dioxabicyclo[3.3.0]octane (5b)** (81%) white crystalline powder mp 121-123 ^oC (Et_2O); [Found: C, 56.98; H, 5.01; N, 4.88. $C_{14}H_{15}NO_6$ requires C, 57.33; H, 5.15; N, 4.77%]; R_f (75% benzene/methanol) 0.75; ν_{max} (CH_3Cl film) 3441 (w), 2875 9s), 2854 (s), 2475 (m), 1731 (s), 1692 (s), 1600 (m), 1579 (s), 1291 (s), 1262 (s), 1126 (s), 1096 (s), 1038 (s), 950 (s), 804 (s), 773 (s), 744 9s), 710 (s), 699 (s), 584 (m) cm^{-1}; δ_H (300 MHz $CDCl_3$) 11.0 (1H, bs, COOH), 7.82 (1H, m), 7.62 (1H, m), 7.54 (2H, m), 4.55 (2H, d, *J*=5.2 Hz, H-2 -8), 4.40 (2H, d, *J*=5.2 Hz, H-2, -8), 4.40 (2H, s, CH_2O), 3.88 (2H, d, *J*=9.2 Hz, H-4, -6), 3.83 (2H, d, *J*=9.2 Hz, H-4, -6); δ_C (75 MHz $CDCl_3$) 171.1 (1C, COOH), 168.2 (1C, COO), 132.7 (1C, Cq arom.), 132.2 (1C, CH arom.), 131.5 (1C, CH arom.), 131.2 (1C, Cq arom.), 130.0 (1C, CH arom.), 129.0 (1C, CH arom.), 87.9 (2C, C-2, -8), 74.0 (2C, C-4, -6), 71.4 (1C, C-5), 67.7 (1C, 5-CH_2O); MS (CI, CH_4); m/z (rel. int.): 244.8 (<2), 145.1 (25), 127.2 (100), 100.1 (19); MS (CI, CH_4); m/z (rel. int.): 293 (<1), 148.1 (50), 127.2 (100), 99.3 (5).

***r*-1-Aza-*c*-5-maleyloxymethyl-3,7-dioxabicyclo[3.3.0]octane (5c)** (41%) white crystalline powder mp 83-86 ^{o}C (Et_2O); [Found: C, 48.99; H, 5.01; N, 5.88. $C_{10}H_{13}NO_6$ requires C, 49.38; H, 5.38; N, 5.75%]; R_f (75% benzene/methanol) 0.65; ν_{max} (CH_3Cl film) 3400 (s), 2884 (m), 1742 (s), 1648 (m), 1583 (m), 1370 (m), 1252 (s), 1218 (s), 1172 (s), 1069 (s), 1057 (s), 928 (s), 828 (m), 815 (m), 761 (s), 664 (m), 572 (m) cm^{-1}; δ_H (300 MHz $CDCl_3$) 10.20 (1H, bs, COOH), 6.31 (1H, d, *J*=12.0 Hz), 6.22 (1H, d, *J*=12.0 Hz), 4.51 (2H, d, *J*=5.2 Hz, H-2 -8), 4.41 (2H, d, *J*=5.2 Hz, H-2, -8), 4.25 (2H, s, CH_2O), 3.78 (4H, s, H-4, -6); δ_C (75 MHz $CDCl_3$) 167.6 (1C, COOH), 166.0 (1C, COO), 133.0 (1C, CH=), 128.8 (1C, CH=), 87.1 (2C, C-2, -8), 74.0 (2C, C-4, -6), 71.6 (1C, C-5), 67.5 (1C, 5-CH_2O). MS (CI, CH_4); m/z (rel. int.): 243.1 (<2), 145.3 (30), 126.8 (100), 97.8 (40).

Typical procedure for the synthesis of the compounds 4c *trans* IV and 6

TRIS®(3.69 g, 30 mmol) **2c** (**Scheme 2**, **6**) and cyclohexanecarboxaldehyde (7.07g, 63 mmol) in dry toluene (100 mL) were refluxed with vigorous stirring for 24 hrs in a Dean Stark trap with continuous removal of water. The reaction was monitored by TLC (eluent benzene : methanol 3:1 v/v; visualisation in I_2 bath) and stopped when the starting materials where detected in small traces only. The reaction mixture was filtered hot and the toluene solution was evaporated under vacuum to dryness. The crude product was isolated by crystallisation from ether to yield the title compound **4c *trans* IV**.

In identical conditions compound **6** was prepared, starting from TRIS® **2c** (1.545 g, 12.8 mmol), and trimethylacetaldehyde (2.30 g, 3 mL, 26.7 mmol).

***r*-1-Aza-*c*-2-*t*-8-dicyclohexyl-*c*-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octane (4c *trans* IV)** (91%) white crystalline powder mp 118-119 ^{o}C (Et_2O); [Found: C, 70.07; H, 9.90; N, 4.88. $C_{18}H_{31}NO_3$ requires C, 69.87; H, 10.08; N, 4.52%]; R_f (75% benzene/methanol) 0.50; δ_H (300 MHz $CDCl_3$) 4.46 (1H, d, *J*=6.0 Hz, H-8-*c*), 4.17 (1H, d, *J*=6.0 Hz, H-2-*t*), 3.73 (1H, d, *J*=10.9 Hz, H-6-*t*), 3.63 (1H, d, *J*=8.5 Hz, H-4-*t*), 3.57 (2H, d, *J*=10.9 Hz, C$H_a$$H_b$OH, H-6-*c*), 3.46 (1H, d, *J*=11.9 Hz, $CH_a$$H_b$OH), 3.37 (1H, d, *J*=8.5 Hz, H-4-*c*), 1.9 – 1.4 (11H, m), 1.3 – 0.9 (11H, m);δ_C (75 MHz $CDCl_3$) 104.7 (1C, CH), 95.7 (1C, CH), 70.1 (1C, CH_2), 66.7 (1C, Cq), 65.6 (1C, CH_2), 64.7 (1C, CH_2), 42.5 (1C, CH), 42.2 (1C, CH), 29.1 (1C, CH_2), 28.7 (1C, CH_2), 27.4 (1C, CH_2), 26.8 (1C, CH_2), 26.6 (1C, CH_2), 26.2 (1C, CH_2), 26.1 (1C, CH_2), 26.0 (1C, CH_2). MS (CI, CH_4); m/z (rel. int.) 308.8 (<3), 214.8 (11), 182.9 (18), 148.5 (<3), 131.1 (21), 103.2 (100).

2-*t*-Butyl-4,4,-dihydroxymethyl-1,3-oxazolidine (6) (90%) yellowish crystalline powder mp 47-49 ^{o}C (Et_2O); [Found: C, 56.80; H, 9.90; N, 7.77. $C_9H_{19}NO_3$ requires C, 57.12; H, 10.11; N, 7.41%]; R_f (75% benzene/methanol) 0.60; δ_H (300 MHz $CDCl_3$) 4.13 (1H, s, H-2), 3.66 (2H, d, *J*=10.9 Hz, CH_2OH), 3.61 (1H, bs, NH), 3.57 (1H, d, *J*=8.6 Hz, H-4), 3.55 (1H, d, *J*=10.9 Hz, CH_2OH), 3.53 (1H, d, *J*=8.3, H-4), 3.50 (1H, d, *J*=10.9 Hz, CH_2OH), 3.43 (1H, d, *J*=9.0 Hz, OH), 3.40 (1H, d, *J*=7.9 Hz, OH);δ_C (75 MHz $CDCl_3$) 98.5 (1C, C-2), 70.3 (1C, C-4), 66.6 (1C, C-5), 64.4 (1C, CH_2OH), 64.0 (1C, CH_2OH), 33.9 [1C, $C(CH_3)_3$], 25.4 [1C, $C(CH_3)_3$]. MS (CI, CH_4); m/z (rel. int.) 132.0 [100, M-(*t*-Bu)], 84 (14), 57 (60).

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