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Chair–boat equilibrium as driving force in epimerization of 3,7-dimethylbicyclo[3.3.1]nonan-2,9-dione derivatives. Stereocontrolled synthesis of the 3-*exo*,7-*exo*- and 3-*endo*,7-*exo*-dimethylbicyclo[3.3.1]nonan-9-ones

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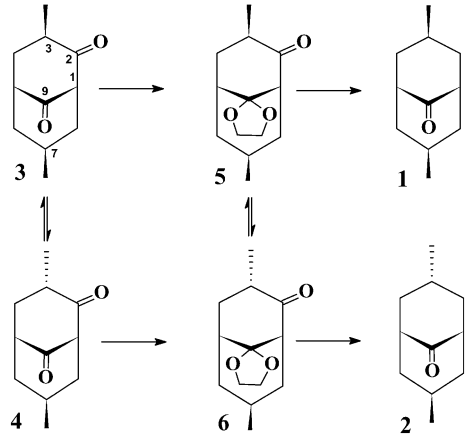
Abstract—Molecular mechanics calculations and experimental ^{1}H NMR data are in close agreement and show that the epimerization equilibrium at C_3 of 3,7-dimethylbicyclo[3.3.1]nonan-2,9-diones is shifted toward the 3-*endo*-epimer in order to reach the lowest energy chair–boat conformation. Introduction of a 1,3-dioxolane moiety at C_9 results in reversal of the equilibrium, in protic solvents, leading mainly to the 3-*exo*-epimer in the most stable chair–chair conformation. These results have been applied to the stereocontrolled synthesis of the title compounds.

Due to their intrinsic ability to undergo transannular reactions,[1–3] fragmentation reactions [2,4,5] and stereospecific skeletal rearrangements,[6–8] bicyclo[3.3.1]nonane derivatives have been widely used as starting templates in the synthesis of more complex molecules and natural products.[2,7–9] Following this approach, we identified the still unknown epimeric bicyclononanones **1** and **2** (Scheme 1) as suitable and versatile starting templates for transferring the resident configurations to functionalised open chain isoprenoid and deoxypropionate subunits to be assembled for the construction of naturally occurring polymethyl alternating systems.[10] However, installation of the required configuration at stereocentres in bicyclononane templates [3,5,11,12] strictly depends on the conformational features[13] of their twin cyclohexane structure.



Scheme 1.

In principle, stereoselective synthesis of compounds **1** and **2**, can be accomplished from the 2,9-diones **3** and **4**, respectively, after chemoselective[14] ketalization[15] at C_9 and deoxygenation[16] at C_2 of the resulting ketals **5** and **6**. However, also diones **3** and **4** are unreported compounds, but can be obtainable, in principle, by applying well established synthetic procedures for similar compounds.[17,18] However, while the 7-*exo* configuration can be rigidly installed in compounds **3**–**6** during the anellation procedure,[17,18] enolization at C_3 gives rise to the equilibria **3**⇄**4** and **5**⇄**6**, with the relative amounts of epimers being determined by their relative stabilities and, in turn, by their conformational features.

As depicted in Scheme 2 for compounds **3**–**6**, bicyclo[3.3.1]nonanes can exist as four conformers: chair–chair (*cc*), chair–boat (*cb*), boat–chair (*bc*) and boat–boat (*bb*), the flattened *cc* conformation being usually the most populated, if not the only conformation, when 3-*exo* and/or 7-*exo* substituents are present.[13] On the other hand, bicyclononanes carrying 3-*endo*- and/or 7-*endo*- substituents exist

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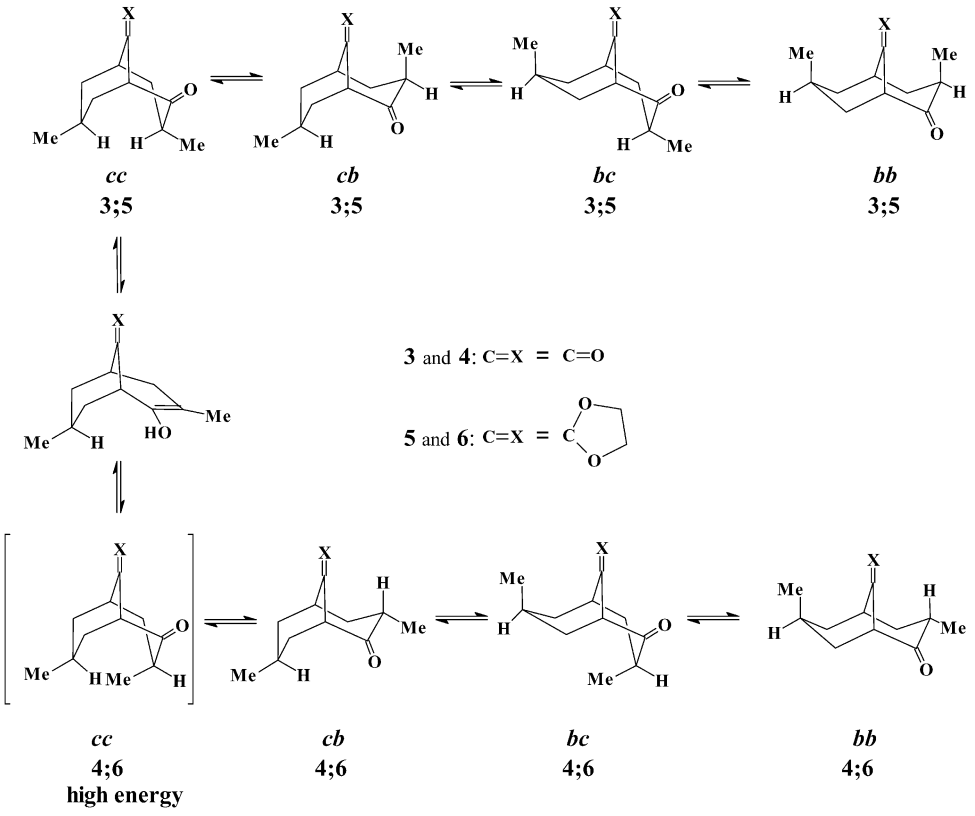


Scheme 2.

with the ring that bears them in the boat conformation, but, if epimerization is allowed, the 3-*exo*- and/or 7-*exo*-configuration is restored to reach the more stable *cc* conformation.[19–21] However, the position, stereochemistry and hybridation of the substituents strongly affect the conformational equilibria.

Carbonyl groups at C_2[12] or C_9[20,22] increase the amount of the *cb* conformation, this latter being likely the most populated in 2,9-diones as shown by X-ray crystallography in the crystals of 7-*exo*-*t*-butyl-1-methylbicyclo[3.3.1]nonan-2,9-dione[18] and by calculation for bicyclo[3.3.1]nonan-2,9-dione itself.[23] Therefore, we hypothesised that the *cb* conformation was the lowest energy one in bicyclononan-2,9-diones also in solution, although experimental evidence is still lacking. As a consequence, the epimerization equilibrium **3**⇄**4** should be driven toward the 3-*endo*-epimer **4** by the higher stability of the **4***cb* conformation in comparison with that of **3***cc* and **3***cb*, excluding the high energy **4***cc* conformation.

On the contrary, rehybridisation at C_9 by introduction of a hindering 1,3-dioxolane group, as in compounds **5** and **6**, should favour the *cc* conformation. In fact, irrespective of the presence of 3-*endo*- and/or 7-*endo*-substituents, introduction of a *gem*-dimethyl group at C_9 has been reported to force the two rings in a flattened *cc* conformation.[24] As a consequence, the epimerization equilibrium **5**⇄**6** should be driven toward the 3-*exo*-epimer **5** by the higher stability of the **5***cc* conformation in comparison with that of **6***cb*, where a negative flagpole interaction is predictable between the pseudo axial hydrogen at C_3 and the dioxolane oxygen at C_9. Therefore, in order to verify and quantify these hypotheses and to take advantage in driving the stereoselective synthesis of compounds **1** and **2**, we calculated the distribution of conformers and the equilibrium position for the epimeric couples **3/4** and **5/6**. Calculation results have been confirmed experimentally and applied to the synthesis of templates **1** and **2**.

1. Results and discussion

In vacuo conformational searches of compounds **3**–**6** were performed using the Monte Carlo Multiple Minimum method (MCMM)[25] of MacroModel/BatchMin[26] and the implemented force field MM2*. All the conformations found in a 40 kJ mol^{-1} window over the energy minimum were collected, in order to gain a complete insight into the conformational properties of these compounds. Three different sets of thermodynamic values were then calculated at 298 K, namely in vacuo, in chloroform and in water.

For calculations in vacuo, the MCMM output geometries were re-minimised to low gradient (0.001 kJ $Å^{-1}$ mol^{-1}), obtaining steric energy values (*E*) and Boltzmann populations for all the conformers of **3**–**6** populated at room temperature, from which the averaged steric energies (E) were calculated. In addition, in an attempt aimed at evaluating the thermal excitation contribution of each populated conformation to enthalpies and entropies, a further value, named $G^{(0-298)}$, was calculated with BatchMin by means of statistical thermodynamics through the application of the normal mode analysis.[27] This $G^{(0-298)}$ value expresses the

Table 1. Differences between the Boltzmann averaged values (kJ mol^{-1}) of the steric energy ($\Delta\underline{E}$) and Gibbs free energy ($\Delta\underline{G}^{298}$) of **3** with respect to **4** and of **5** with respect to **6**, calculated in vacuo, in GB/SA H_2O and in GB/SA $CHCl_3$ at 298 K

Entry	Energy differences (medium)	Compounds (conformation)			
		3 (*cc*)[a]	**4** (*cb*)	**5** (*cc*)[b]	**6** (*cb*)[b]
1	$\Delta\underline{E}$ (vacuum)	4.5	0.0	1.2	0.0
2	$\Delta\underline{E}$ ($CHCl_3$)	4.6	0.0	1.1	0.0
3	$\Delta\underline{E}$ (H_2O)	2.7	0.0	0.0	0.4
4	$\Delta\underline{G}^{298}$ (vacuum)	3.6	0.0	0.3	0.0
5	$\Delta\underline{G}^{298}$ ($CHCl_3$)	3.6	0.0	0.0	0.1
6	$\Delta\underline{G}^{298}$ (H_2O)	1.8	0.0	0.0	1.3

[a] A small amount of the *cb* conformation (about 5%) was also found (see Section 2).
[b] A fairly even mixture of four conformers of the dioxolane ring is present at equilibrium (see Section 2).

thermally averaged translational, rotational and vibrational contributions of a conformer to the thermodynamic quantities when the system is heated from 0 to 298 K because of excitation of the system to higher quantum states. Addition of these terms to the corresponding steric energy values E allowed the calculation[27] of conformational Gibbs free energies G^{298}, and consequently the relative populations were re-evaluated, to obtain the corresponding Boltzmann averaged $\underline{G}^{298}$ values.

For calculations in solvents, the BatchMin GB/SA continuum solvation method was introduced[28] to evaluate the solvation energy contributions to the steric energies of compounds **3**–**6** and all the thermally averaged values of steric energies and Gibbs free energies were calculated again, through energy minimisations to low gradient (0.001 kJ $Å^{-1}$ mol^{-1}), considering both water and chloroform as the solvents. Calculated values (E and G^{298}) for compounds **3**–**6** in the three media and the relative populations of the found conformations are reported in Section 2.

In order to give a better understanding of the physical meaning of the above calculated values, results are reported in Table 1 as the averaged steric energy and Gibbs free energy differences ($\Delta\underline{E}$ and $\Delta\underline{G}^{298}$) between the two epimers (**3**–**4** or **5**–**6**) in the three examined media.

As expected, due to the presence of the two methyl groups at C_3 and C_7, all examined compounds possess a quite rigid geometry for the fused bicyclic system either in vacuo or in solvents. In particular, epimers **3** and **4**, exist in the *cc* and *cb* geometry, respectively, while some conformational freedom (about 5% of *cb* conformation) is allowed for compound **3** only. Accordingly, epimers **5** and **6** are rigidly in the *cc* and *cb* conformation, respectively, the only conformational freedom being attributable to the flexible dioxolane moiety, which gives rise to a fairly even mixture of the theoretically expected four geometries (see Section 2).

Comparison of the differences between the in vacuo calculated Boltzmann energies ($\Delta\underline{E}$) and free energies ($\Delta\underline{G}^{298}$) for compounds **3**–**6** shows a similar trend. Compounds **4** and **6**, in the *cb* conformation, are always more stable than compounds **3** and **5**, in the *cc* conformation, and this can be explained in terms of a better flattening of the bicyclic system in the *cb* conformation, measured by a favourable bending energy contribution. However, $\Delta\underline{G}^{298}$ between the two epimers **3**–**4** and **5**–**6** appears always smaller than the corresponding $\Delta\underline{E}$, so that thermal excitation seems to favour **3** and **5** with respect to **4** and **6** and this can be justified in terms of a higher loss of vibrational freedom due to the flagpole interaction C_9–O/H_3 in the *cb* conformations. Notably, thermodynamic values are strongly affected by a polar solvent. While chloroform does not modify substantially the relative $\Delta\underline{E}$ and $\Delta\underline{G}^{298}$ values calculated in vacuo for each epimeric couple (Table 1), a sharp decrease of these terms for the couple **3**–**4** and a reversal of the relative stabilities for the couple **5**–**6** is observed in water.

Using the above thermodynamic data two sets of equilibrium constants (K_{calc} and K'_{calc} in Table 2) were calculated at 298 K for the epimerizations **3/4** and **5/6**. Constants K_{calc} were obtained from an estimate of the free energy differences (ΔG^{298}) calculated by assuming the enthalpic term (ΔH^{298}) as the difference between the Boltzmann averaged steric energies ($\Delta\underline{E}$) of the two epimers at equilibrium, and the entropic contribution ($\Delta S_{mix}{}^{298}$) simply assumed as mixing entropy and calculated by the expression[29]

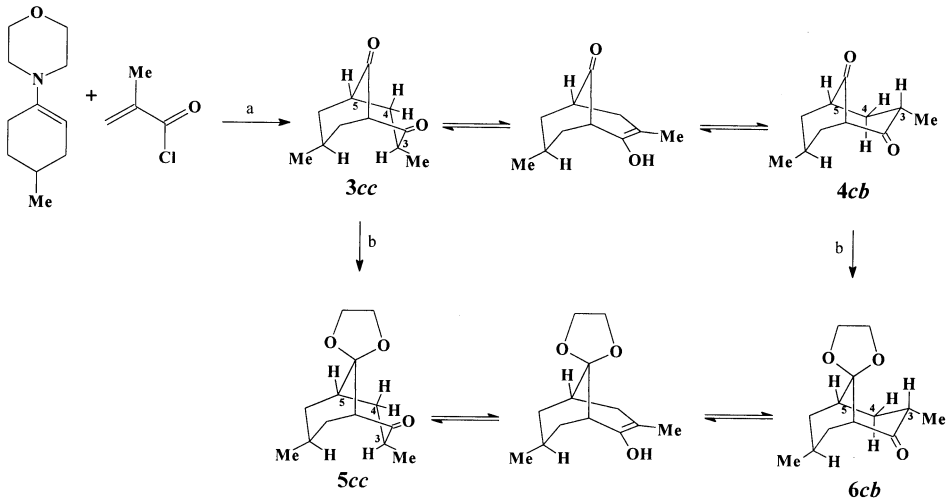
$$\Delta S^{298}_{mix} = S^{298}_X - S^{298}_Y = R[\sum_j p^{298}X_j \ln p^{298}X_j - \sum_j p^{298}Y_j \ln p^{298}Y_j]$$

where $p^{298}X_j$ (or $p^{298}Y_j$) is the relative population of conformer j of compound X (or Y) at 298 K. In the calculation of constants K'_{calc}, the free energy differences ($\Delta\underline{G}^{298}$, Table 1) were directly added to $\Delta S_{mix}{}^{298}$ to give $\Delta G'^{298}$.

Table 2. Equilibrium constants calculated at 298 K and corresponding enthalpy, mixing entropy and free energy differences (kJ mol^{-1}) for the equilibria **3/4** and **5/6**, in vacuo, in GB/SA $CHCl_3$ and in GB/SA H_2O

Entry	Equilibrium	Medium	298 ΔS_{mix}	ΔH^{298}	$\Delta G^{298,a}$	$\Delta G'^{298,b}$	$K_{calc}{}^{a}$	$K'_{calc}{}^{b}$
1	**3**⇄**4**	in vacuo	−0.5	−4.5	−4.0	−3.1	5.0	3.5
2	**3**⇄**4**	$CHCl_3$	−0.5	−4.6	−4.1	−3.1	5.2	3.5
3	**3**⇄**4**	H_2O	−0.3	−2.7	−2.4	−1.5	2.6	1.8
4	**5**⇄**6**	in vacuo	0.0	−1.2	−1.2	−0.3	1.6	1.1
5	**5**⇄**6**	$CHCl_3$	0.0	−1.1	−1.1	0.1	1.6	1.0
6	**5**⇄**6**	H_2O	0.0	0.4	0.4	1.3	0.9	0.6

[a] Values obtained using the contributions coming from ΔH^{298} and 298 ΔS_{mix}.
[b] Values obtained taking into account both the thermal excitation ($\Delta\underline{G}^{298}$ from Table 1) and the 298 ΔS_{mix} contributions to the equilibrium constant.



Scheme 3. (a) PhH, 80°, 93%; (b) $(CH_2–OTMS)_2$/5%TMSOTf, CH_2Cl_2, −78 to −20°, 96%.

Results are reported in Table 2, together with the corresponding enthalpy, entropy and free energy differences.

As hypothesised, the epimerization equilibrium **3**⇄**4** is appreciably shifted toward **4** in vacuo and in chloroform by the higher stability of the **4***cb* conformation, although the vibrational contributions introduced by heating result in some reversal toward **3**. On the contrary, introduction of the 1,3-dioxolane group at C_9 does not afford the hypothesised reversal of the equilibrium **5**⇄**6** in favour of **5**, the epimer **6**, in the *cb* conformation, being still the most stable in vacuo and in chloroform ($K_{calc6/5}$=1.6). However, the excitation free energy contribution coming from heating results in an increased equilibrium amount of the epimer **5** ($K'_{calc6/5}$=1.1 in vacuo and $K'_{calc6/5}$=1.0 in $CHCl_3$).

A more pronounced effect on the calculated equilibrium constants is observed when water is taken into account as a solvent. Here, the **3**⇄**4** equilibrium is still shifted toward **4**, although to a minor extent, while the **5**⇄**6** equilibrium is reversed toward **5**, as the more stable epimer, particularly when heated ($K_{calc6/5}$=0.9 and $K'_{calc6/5}$=0.6).

These results, in close agreement with our initial hypothesis, although the calculated free energy differences are small, were experimentally confirmed through the preparation of compounds **3**–**6**. Synthesis of the novel diones **3** and **4** was carried out as depicted in Scheme 3 by applying a previously described procedure for similar compounds.[17,18] Reaction between *N*-(4-methylcyclohexenyl)-morpholine and methacryloyl chloride afforded compounds **3** and **4** in 93% overall yield together with some epimers at C_7.

As expected from the calculated rigid conformations, ^{1}H NMR spectra of both compounds showed sharp signals for each proton (see Section 2) and decoupling experiments allowed to assign the 3-*endo*-7-*exo*-configuration, in the *cb* conformation, to the more abundant epimer **4**, and the 3-*exo*-7-*exo*-configuration, in the *cc* conformation, to the less abundant dione **3**. Diagnostic signals are the chemical shifts and the coupling constants for the protons at C_3, C_4 and C_5 in both spectra. Namely, the axial proton at C_4 in compound **3** shows a *cis* coupling constant (J=6.1 Hz) with the equatorial proton at C_5 and a *trans* diaxial coupling constant with H_3 (J=10.8 Hz) so indicating the chair conformation for the ring and the *exo* configuration for the equatorial methyl group at C_3. On the contrary, $H_{4\beta}$ in compound **4**, due to the characteristic eclipsing effect observed for boat conformations in bicyclononanes,[21] shows a large coupling constant (J=10.5 Hz) with H_5 and a small constant with H_3 (J=5.8 Hz), the latter proton being shifted upfield (δ=2.30 ppm), with respect to the same proton in compound **3** (δ=2.81 ppm), by the shielding effect of the carbonyl at C_9. This clearly indicates the boat conformation for the ring and the *endo* configuration for the methyl group at C_3 in compound **4**.

Since epimers **3** and **4** are reactive in protic solvents under basic catalysis, the equilibrium constant for the epimerization **3**⇄**4** was measured starting from both pure epimers either without solvent and catalyst or in $CHCl_3$ under acid catalysis (1% TsOH) to give values corresponding to $K_{exp4/3}$=5.3 and 4.0, respectively, very close to the calculated ones (Table 2). This indicates a good agreement between theoretical and experimental data and constitutes the first experimental evidence that, for bicyclononan-2,9-diones, the *cb* conformation is the low energy one also in solution.

Due to the difficult chromatographic separation of the **3/4** epimeric couple, chemoselective ketalization[14] at C_9 was performed on the equilibrium mixture by Noyori's procedure[15] and afforded the epimeric couple **5/6** in high overall yield. As for compounds **3** and **4**, the observation (see Section 2) of a large $H_{4\beta}/H_5$ ^{1}H NMR coupling constant (J=10.5 Hz) together with a pseudo *trans*-diaxial coupling $H_3/H_{4\alpha}$ allowed the assignment of the 3-*endo* configuration in the *cb* conformation to epimer **6**. Conversely, the 3-*exo* configuration in the *cc* conformation was assigned to compound **5** as only small coupling constants are observed for H_5, while H_3, in *trans*-diaxial coupling (J=10.9 Hz) with the axial proton at C_4, resonates upfield (δ=2.44 ppm) if compared with the same proton in the ketal **6**

Table 3. Molar ratios and experimental equilibrium constants for the acid or base catalysed epimerizations of **5** and **6** in aprotic and protic solvents

Entry	Solvent	Catalyst	Temp. (°C)	6:5 ratio	Yield (%)	$K_{exp6/5}$
1	CH_2Cl_2	TMSOTf[a]	−20	9:1.0	95 [b]	–
2	CH_2Cl_2	TMSOTf[a]	25	1:1.6[c]	50	–[c]
3	EtOH[d]	NaOH[e]	25	1:1.9	93	0.5
4	MeOH[d]	NaOH[e]	25	1:2.7	94	0.4
5	H_2O[d,f]	NaOH[e]	25	1:3.3	94	0.3

[a] 5% with respect to the substrate.
[b] Reaction was stopped after 0.5 h and the resulting mixture was used for the other equilibrations.
[c] Reaction was stopped after 2 h. The equilibrium point was not determined because of formation of tarry materials.
[d] Solvents were deoxygenated by an argon stream to avoid competing oxygen insertion in the C_3–H bond[31].
[e] 5% with respect to the solvent.
[f] Containing 20% MeOH.

(δ=2.77 ppm), deshielded by the acetalic oxygen at C_9 in flagpole relationship.

Epimers **5** and **6** were shown to be in very slow equilibration without catalyst, but unstable under acid catalysis in chloroform. Nevertheless, their equilibrium amounts were sharply temperature and reaction time dependent in CH_2Cl_2, under the action of trimethylsilyltriflate (TMSOTf) used as a catalyst in Noyori's ketalization procedure. As shown in Table 3 (entries 1–2), under kinetic control conditions, ketals **6** and **5** were obtained in 9:1 ratio and high yield, while under thermodynamic control the molar ratio reversed to 1:1.6, although the formation of tarry materials unfortunately did not allow the determination of the equilibrium constant.

On the contrary, compounds **5** and **6** were stable under basic catalysis and we explored the effect of protic solvents, able to form H-bonds, on the epimerization equilibrium constant by equilibrating the kinetic 9:1 mixture.

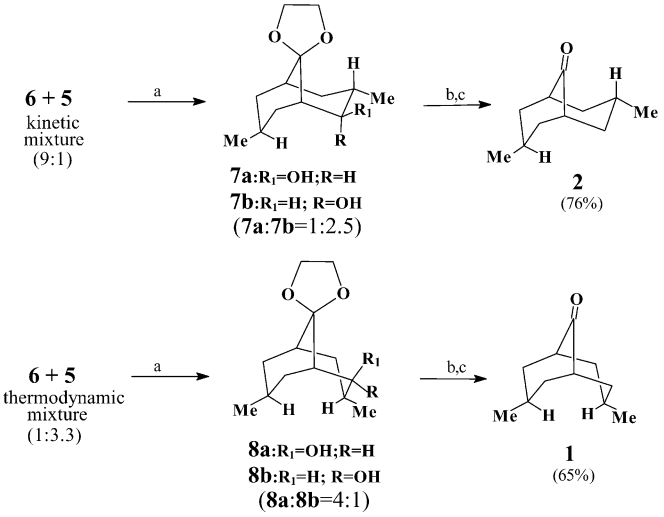
The results and reaction conditions are reported in Table 3 (entries 3–5) and show an increasing equilibrium amount of the 3-*exo*-epimer **5** as the H-bonding ability of the solvent increases. Therefore, experimental equilibrium constants in protic solvents are in good agreement with the calculated ones in water (Table 2, entry 6) and confirm the calculated higher stability of the epimer **5** in polar solvents.

In conclusion, calculated and experimental equilibrium constants indicate that the epimerization equilibria **3/4** and **5/6** are driven by the relative stabilities of their *cc* and *cb* conformations and are tunable by controlling temperature and equilibration medium.

As an application of the above findings, we carried out the stereocontrolled synthesis of the novel ketones **1** and **2** (Scheme 4). Due to their difficult chromatographic separation, the kinetic (9:1) and the thermodynamic (1:3.3, Table 3) mixtures of ketals **5** and **6** were used as starting material to obtain ketones **2** and **1**, respectively, and the pure epimers at C_3 were easily isolated as hydroxyacetals **7a–b** and **8a–b**, respectively.

Thus, LAH reduction of the 9:1 mixture of ketones **6** and **5**, obtained under kinetic conditions, afforded the hydroxyacetals **7a–b** in 85% overall yield and 1:2.5 molar ratio, after chromatographic separation of the 3-*exo*-epimers **8a–b**. In the same way, reduction and chromatographic purification of the 1:3.3 mixture of ketones **6** and **5**, obtained after equilibration in 5% aqueous NaOH, gave the hydroxyacetals **8a–b** (73% overall yield, 4:1 molar ratio). Configurations at C_2 in alcohols **7a–b** and **8a–b** arise from the spectroscopic properties (see Section 2), and the remarkable diastereoselectivity observed in LAH reductions is in agreement with the already reported preference for hydride *exo*-attack at C_2 carbonyl on the boat conformation and *endo*-attack on the chair conformation in similar systems.[12]

Deoxygenation[16] at C_2 of the mixtures **7a–b** and **8a–b**, followed by removal of the dioxolane moiety gave the 3-*endo*-7-*exo*-dimethylketone **2** (76% overall yield) and the 3-*exo*-7-*exo*-dimethylketone **1** (65% overall yield), respectively. Due to the high molecular symmetry, both ^{13}C and ^1H NMR spectra of ketone **1** show only five signals (see Section 2) and the presence of small coupling constants between H_1 (or H_5) and the adjacent protons indicates the *cc*



Scheme 4. (a) LAH, Et_2O, rt, 95%; (b) Ireland's deoxygenation,[16] 94%; (c): 2 M HCl/Me_2CO, reflux, (95%).

conformation. On the contrary, the lesser symmetry in ketone **2** results both in a complex proton spectrum and in a height-signals carbon spectrum, in particular two different methyl groups, while the presence of large coupling constants between H_1 (or H_5) and $H_{2\beta}$ (or $H_{4\beta}$) indicates the *cb* conformation.

In conclusion, tunable chair–boat and chair–chair equilibria drive configuration changes at C_3 in 3,7-dialkyl-bicyclo[3.3.1]nonan-2,9-dione derivatives and this can be applied in controlling the stereochemistry at C_3.

2. Experimental

2.1. General

GC analyses were obtained on a FISON GC 8000 gas-chromatograph with a capillary column (Megawax MEGA, 15 m long, ID 0.25 mm, film thickness 0.25 μm) and GC/MS analyses were performed with the same gas-chromatograph equipped with a capillary column (SE52 MEGA, 30 m long, ID 0.25 mm, film thickness 0.25 μm) coupled with a FISON MD800 mass detector. FT-IR spectra were performed in $CHCl_3$ on a Brucker Vector 22 spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Gemini 200 and VARIAN XL300 spectrometers. Microanalyses were carried out on a CE Instruments EA1110. Chromatographic separations were performed by using a Flash Master Jr apparatus (Alfatech) equipped with CFSi4075 cartridges, while Fluka silica gel TLC plates (5–17 μm, 0.25 mm) were used for TLC analyses. Unless otherwise stated, organic phases from extractions were always dried over anhydrous Na_2SO_4 and evaporated under reduced pressure.

2.2. Molecular modelling studies

All the simulations were done on a Silicon Graphics computer Indigo Entry 4000, using the software package MacroModel/BatchMin version 4.5[26] and the force field MM2*, as implemented in MacroModel. The study was carried out applying molecular mechanics techniques to perform conformational searches and exhaustive energy minimisations. The conformational space of compounds **3**–**6** was searched using the MCMM procedure of Chang et al.,[25] applied to all the N rotatable bonds of each compound (N=6 in the case of compounds **3** and **4**, N=9 in the case of compounds **5** and **6**), accordingly to the MacroModel guidelines.[30] The number of torsion angles allowed to vary simultaneously during each Monte Carlo step ranged from 2 to $N-1$. In each search 1000 steps were performed, even though over 500 steps, almost all the new minima generated were duplicates of previously found conformations. The threshold applied in the de-duplication protocol was fixed to 0.25 Å. To speed up the search, energy minimisations were performed using the Polak–Ribiere conjugate gradient (PRCG) procedure and were terminated after 200 iterations or when the energy gradient root mean square (rms) fell below 0.1 kJ $Å^{-1}$ mol^{-1}. All the conformers differing no more than 40.0 kJ mol^{-1} from the global minimum-energy conformation were saved. At the end of the search, all the conformations were exhaustively minimised, performing again the elimination of duplicates. Exhaustive energy minimisations were terminated according to the convergence criterion of 0.001 kJ $Å^{-1}$ mol and the obtainment of true minima was verified using the MTST command. The normal mode analysis was performed by the MacroModel RRHO method. Calculated conformations for compounds **3**–**6** with the relative populations, steric energies and free energies (kJ mol^{-1}) in vacuo (E_v, G_v^{298}), in $CHCl_3$ (E_c, G_c^{298}) and in H_2O (E_w, G_w^{298}) are reported below. In conformations of compounds **5** and **6** signs (+) and (−) refer to the position in 3D space of the methylene groups of the 1,3-dioxolane moiety at C_9 with respect to the plane defined by the –O–C–O– system: sign (+) indicates a methylene at the same side of the carbonyl at C_2, sign (−) indicates a methylene in the opposite side.

3. *E* (conformation, %): E_v=71.5 (*cc*, 94.8), 78.7 (*cb*, 5.2); E_c=−4.6 (*cc*, 94.6), 2.5 (*cb*, 5.4); E_w=6.8 (*cc*, 97.4), 15.8 (*cb*, 2.6). G^{298} (conformation, %): G_v^{298}=10.6 (*cc*, 95.1), 18.0 (*cb*, 4.9); G_c^{298}=−65.5 (*cc*, 95.0), −58.2 (*cb*, 5.0); G_w^{298}=−54.1 (*cc*, 97.6), −4.9 (*cb*, 2.4).

4. *E* (conformation, %): E_v=67.4 (*cb*, 100.0); E_c=−8.8 (*cb*, 100.0); E_w=4.3 (*cb*, 100.0). G^{298} (conformation, %): G_v^{298}=7.4 (*cb*, 100.0); G_c^{298}=−68.7 (*cb*, 100.0); G_w^{298}=−55.7 (*cb*, 100.0).

5. *E* (conformation, %): E_v=12.8 (*cc* (−,+), 25.6), 13.9 (*cc* (+,−), 16.4), 12.4 (*cc* (−,−), 30.1), 12.6 (*cc* (+,+), 27.8); E_c=−161.6 (*cc* (−,+), 26.5), −160.6 (*cc* (+,−), 17.8), −162.1 (*cc* (−,−), 32.4), −161.3 (*cc* (+,+), 23.5); E_w=−125.3 (*cc* (−,+), 10.2), −124.6 (*cc* (+,−), 7.7), −129.5 (*cc* (−,−), 55.3), −127.7 (*cc* (+,+), 26.8). G^{298} (conformation, %): G_v^{298}=−47.9 (*cc* (−,+), 28.3), −47.9 (*cc* (+,−), 28.3), −47.3 (*cc* (−,−), 22.2), −47.2 (*cc* (+,+), 21.3); G_c^{298}=−222.3 (*cc* (−,+), 29.8), −222.2 (*cc* (+,−), 28.6), −221.7 (*cc* (−,−), 23.4), −221.1 (*cc* (+,+), 18.4); G_w^{298}=−186.7 (*cc* (−,+), 16.2), −187.8 (*cc* (+,−), 25.3), −188.8 (*cc* (−,−), 37.8), −187.3 (*cc* (+,+), 20.6).

6. *E* (conformation, %): E_v=11.6 (*cb* (−,+), 25.6), 12.1 (*cb* (+,−), 20.9), 1.0 (*cb* (−,−), 32.6), 12.1 (*cb* (+,+), 20.9); E_c=−163.1 (*cb* (−,+), 27.0), −162.6 (*cb* (+,−), 22.1), −163.7 (*cb* (−,−), 34.4), −161.9 (*cb* (+,+), 16.6); E_w=−124.6 (*cb* (−,+), 10.6), −124.2 (*cb* (+,−), 9.0), −128.7 (*cb* (−,−), 55.5), −126.7 (*cb* (+,+), 24.8). G^{298} (conformation, %): G_v^{298}=−48.4 (*cb* (−,+), 30.2), −48.3 (*cb* (+,−), 29.0), −47.8 (*cb* (−,−), 23.72), −47.0 (*cb* (+,+), 17.2); G_c^{298}=−222.9 (*cb* (−,+), 30.8), −222.8 (*cb* (+,−), 29.6), −222.4 (*cb* (−,−), 25.2), −221.0 (*cb* (+,+), 14.3); G_w^{298}=−185.4 (*cb* (−,+), 19.4), −185.6 (*cb* (+,−), 21.1), −187.2 (*cb* (−,−), 40.2), −185.4 (*cb* (+,+), 19.4).

2.2.1. 3-*exo*-7-*exo*-Dimethyl-bicyclo[3.3.1]nonan-2,9-dione 3 and 3-*endo*-7-*exo*-epimer 4. Freshly distilled methacryloyl chloride (3.2 ml, 32.6 mmol) in anhydrous benzene (4 ml) was added dropwise and under argon atmosphere to a refluxing solution of *N*-(4-methylcyclohexenyl)-morpholine (5.90 g, 32.6 mmol) in 110 ml of anhydrous benzene. After 2 h reflux, the mixture was brought to room temperature, 20 ml of H_2O were added

and the resulting suspension was stirred for one further hour. The organic phase was then separated, the aqueous phase extracted with diethyl ether and the joined organic extracts were dried and evaporated. The crude product was distilled (108–118°C, 0.5 mmHg) to give 5.46 g (30.32 mmol) of the epimers **3** and **4** (1:5 ratio via GC) together with small amounts (<5% overall) of two other isomers, likely the C_7 epimers, not further investigated. Yield 93%. Small pure samples of the two main products were obtained after repeated chromatography (SiO_2 ratio 1:150) by eluting with hexane: AcOEt (95:5).

3. ^{1}H NMR ($CDCl_3$) δ: 3.23 (1H, ddd, J_s=4.6, 2.7, 2.0$_{(w)}$ Hz, H_1), 2.81 (1H, ddq, J_s=10.8, 8.3, 6.7 Hz, H_{3ax}), 2.71 (1H, ddddd, J_s=6.1, 5.2, 2.1, 2.1, 2.0 Hz, H_5), 2.30–2.10 (4H, m, H_{4eq}+H_{6eq}+H_{8eq}+H_7), 1.79 (1H, dddd, J_s=15.2, 14.2, 4.6, 1.5$_{(w)}$ Hz, H_{8ax}), 1.63 (1H, ddddd, J_s=14.2, 10.8, 5.2, 1.5$_{(w)}$, 1.5$_{(w)}$ Hz, H_{6ax}), 1.61 (1H, dddd, J_s=14.2, 10.8, 6.1, 1.5$_{(w)}$ Hz, H_{4ax}), 1.13 (3H, d, J=6.7 Hz, C_3–CH_3), 0.93 (3H, d, J=5.7 Hz, C_7–CH_3). ^{13}C NMR ($CDCl_3$) δ: 212.02 (C_2), 211.03 (C_9), 65.17 (C_1), 45.40 (C_3), 43.40 (C_5), 43.31 (C_6), 42.45 (C_8), 33.18 (C_4), 26.27 (C_7), 21.13 (C_7–CH_3), 16.41 (C_3–CH_3). MS (*m/z*; %): 180 (M^+, 50), 138 (23), 111 (14), 110 (100), 109 (21), 108 (10), 96 (10), 95 (41), 82 (22), 81 (23), 79 (14), 69 (90), 68 (12), 67 (50), 55 (77), 53 (19). IR (CCl_4): ν_{CO}=1730, 1710 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found C, 73.55; H, 9.06.

4. ^{1}H NMR ($CDCl_3$) δ: 2.90 (1H, ddd, J_s=3.9, 3.9, 2.4$_{(w)}$ Hz, H_1), 2.81 (1H, ddddd, J_s=10.5, 3.2, 2.4$_{(w)}$, 2.3, 1.8 Hz, H_5), 2.41 (1H, dddd, J_s=12.6, 3.9, 3.5, 3.1$_{(w)}$ Hz, H_{8eq}), 2.35 (1H, ddd, J_s=12.5, 10.5, 5.8 Hz, $H_{4\beta}$), 2.30 (1H,ddq, J_s=12.1, 5.8, 6.1 Hz, $H_{3\beta}$), 1.93 (1H, dddd, J_s=12.6, 3.2, 3.2, 3.1$_{(w)}$ Hz, H_{6eq}), 1.75 (1H, ddqdd, J_s=12.6, 12.6, 5.9, 3.5, 3.2, Hz, H_{7ax}), 1.67 (1H, ddd, J_s=12.6, 12.6, 2.3 Hz, H_{6ax}), 1.61 (1H, ddd, J_s=12.6, 12.6, 3.9 Hz, H_{8ax}), 1.37 (1H, ddd, J_s=12.5, 12.1, 1.8 Hz, $H_{4\alpha}$), 1.09 (3H, d, J=6.1 Hz, C_3–CH_3), 0.87 (3H, d, J=5.9 Hz, C_7–CH_3). ^{13}C NMR ($CDCl_3$) δ: 213.02 (C_2), 211.20 (C_9), 60.70 (C_1), 44.72 (C_5 and C_4), 44.54 (C_3), 42.58 (C_8), 30.72 (C_6), 24.13 (C_7), 20.46 (C_7–CH_3), 13.12 (C_3–CH_3). MS (*m/z*; %): 180 (M^+, 58), 138 (29), 111 (15), 110 (99), 109 (31), 108 (15), 96 (11), 95 (29), 82 (20), 81 (21), 79 (12), 69 (100), 68 (12), 67 (50), 56 (12), 55 (90), 54 (12), 53 (20). IR (CCl_4): ν_{CO}=1725, 1705 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found C, 73.50; H, 9.00.

2.2.2. Equilibration of epimers 3–4. All reactions were carried out in duplicate and the reported results are the averaged values. (a) *Without catalyst and solvent*. Pure samples (10 mg) of diones **3** and **4** were held under argon at room temp. for two months. At the end, GC analysis showed a ratio **4/3**=5.3:1, in both cases. Repetition of the analysis after additional two months gave the same result. (b) *Under acid catalysis*. Pure samples (10 mg) of diones **3** and **4** were separately dissolved in dry $CHCl_3$ (1 ml), a small crystal of *p*-toluenesulfonic acid was added and the mixture was stirred under argon at room temp., by monitoring the equilibration progress via GC. In both cases a constant ratio **4/3**=4.0:1 was reached after 48 h.

2.2.3. 9,9-Ethylendioxy-3-*exo*-7-*exo*-dimethyl-bicyclo-[3.3.1]nonan-2-one 5 and 3-*endo*-7-*exo*-epimer 6. *Kinetic mixture*. A mixture of diones **3** and **4** (ratio 1:5 via GC; 4.92 g, 27.32 mmol) was dissolved in 200 ml of anhydrous CH_2Cl_2 under argon atmosphere and 6.8 ml (27.76 mmol) of 1,2-bis(trimethylsilyloxy)ethane were added dropwise. The solution was cooled at −78°C under stirring and trimethylsilyl triflate (0.24 ml) was added by a syringe. The mixture was stirred for 30 min at −20°C, quenched with $NaHCO_3$ (40 ml, satd solution) and extracted with Et_2O. The organic phase was dried and evaporated to afford 5.80 g (25.96 mmol) of the epimers **5** and **6** in a 1:9 ratio via GC. Yield 95%. Pure samples were obtained by preparative TLC eluting with hexane/AcOEt (95:5).

5. ^{1}H NMR ($CDCl_3$) δ: 3.92 (4H, s, O–CH_2–CH_2–O), 2.56 (1H,ddd, J_s=4.8, 2.4, 2.4$_{(w)}$ Hz, H_1), 2.44 (1H, ddq, J_s=10.9, 8.8, 6.6 Hz, H_{3ax}), 1.95 (1H, ddd, J_s=13.7, 8.8, 1.7 Hz, H_{4eq}), 1.96 (1H, ddddd, J_s=3.9, 3.9, 2.4$_{(w)}$, 1.7, 1.7 Hz, H_5), 1.92–1.65 (5H, m, H_{7ax}+H_{4ax}+H_{6ax}+H_{8eq}+H_{6eq}), 1.61 (1H, ddd, J_s=13.5, 12.5, 4.8 Hz, H_{8ax}), 1.08 (d, 3H, J=6.6 Hz, C_3–CH_3), 0.89 (d, 3H, J=5.9 Hz, C_7–CH_3). ^{13}C NMR ($CDCl_3$) δ: 214.05 (C_2), 110.18 (C_9), 64.43 and 64.07 (O–CH_2–CH_2–O),55.18 (C_1), 42.22 (C_3), 38.33 (C_6), 37.22 (C_5), 34.66 (C_4), 34.35 (C_8), 25.60 (C_7), 22.16 (CH_3), 16.24 (CH_3). MS (*m/z*, %): 224 (M^+, 40), 182 (43), 167 (13), 154 (17), 153 (12), 139 (45), 126 (34), 125 (18), 113 (39), 112 (34), 100 (15), 99 (100), 55 (61). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.65; H, 8.93. Found C, 69.90; H, 8.90.

6. ^{1}H NMR ($CDCl_3$) δ: 4.00–3.85 (4H, m, O–CH_2–CH_2–O), 2.77 (1H, ddq, J_s=10.0, 10.0, 6.7 Hz, $H_{3\beta}$), 2.37 (1H, ddd, J_s=13.9, 10.5, 10.0 Hz, $H_{4\beta}$), 2.30 (1H, ddd, J_s=4.1, 4.1, 2.4$_{(w)}$ Hz, H_1), 2.13 (1H, ddddd, J_s=10.5, 2.8, 2.8, 2.4$_{(w)}$, 1.3 Hz, H_5), 1.88 (1H, dddd, J_s=12.7, 4.1, 4.1, 2.4$_{(w)}$ Hz, H_{8eq}), 1.60 (1H, ddd, J_s=12.8, 12.8, 2.8 Hz, H_{6ax}), 1.55 (1H, ddd, J_s=12.7, 12.7, 4.1 Hz, H_{8ax}), 1.47 (1H, dddd, J_s=12.8, 4.1, 2.8, 2.4$_{(w)}$ Hz, H_{6eq}), 1.23 (1H, ddddq, J_s=12.8, 12.7, 4.1, 4.1, 6.3 Hz, H_{7ax}), 1.08 (1H, ddd, J_s=13.9, 10.0, 1.3 Hz, $H_{4\alpha}$), 1.01 (3H, d, J=6.7 Hz, C_3–CH_3), 0.80 (3H, d, J=6.3 Hz, C_7–CH_3). ^{13}C NMR ($CDCl_3$) δ: 217.11 (C_2), 109.73 (C_9), 64.24 and 63.90 (O–CH_2–CH_2–O), 52.05 (C_1), 40.36 (C_4), 40.05 (C_3), 37.36 (C_6), 35.00 (C_5), 31.42 (C_8), 23.19 (C_7), 21.25 (CH_3), 13.86 (CH_3). MS (*m/z*; %): 224 (M^+, 34), 182 (33), 167 (12), 154 (16), 153 (15), 139 (43), 126 (34), 125 (15), 113 (36), 112 (31), 100 (13), 99 (100), 55 (67). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.65; H, 8.93. Found C, 69.85; H, 8.89.

2.2.4. Equilibration of epimers 5–6. All reactions were carried out in duplicate and the reported results are the averaged values. (a) *Under acid catalysis*. A sample (10 mg) of the above kinetic mixture (ratio **6/5**=9:1) was dissolved in dry CH_2Cl_2 (1 ml) under argon and 5 mg of *n*-eicosane were added as an internal GC standard. The solution was cooled at −78°C under stirring and trimethylsilyl triflate (5% with respect to the substrate) was added by a syringe. The temperature was raised to 25°C for 2 h. At the end, quenching with $NaHCO_3$, extraction with Et_2O and GC analysis showed a ratio **6/5**=1:1.6, but loss of the substrates (50% with respect to the internal standard). (b) *Under basic catalysis and protic solvents*. Samples (10 mg) of the above kinetic mixture (ratio **6/5**=9:1) were dissolved in 5% NaOH solutions (1 ml) in the appropriate alcohol (entries 3–5,

Table 3), previously deoxygenated by an argon stream.[31] *n*-Eicosane (5 mg) was added as an internal GC standard and the mixtures were stirred at room temp. by monitoring the equilibration progress via GC. In all cases, constant **6/5** ratios were reached within 3 h and are reported in Table 3 together with GC yields.

2.2.5. 9,9-Ethylendioxy-3-*exo*-7-*exo*-dimethylbicyclo-[3.3.1]nonan-2-one 5 and 3-*endo*-7-*exo*-epimer 6. *Thermodynamic mixture*. The kinetic mixture of ketals **5** and **6** (1:9 ratio, 1.84 g, 8.21 mmol) was dissolved in 50 ml of 5% NaOH solution in H_2O/MeOH (4:1) carefully deoxygenated by an argon stream.[31] After 3 h stirring at room temperature, the mixture was cooled at 0°C and first cautiously neutralised with 45 ml of 5% HCl and then with NH_4Cl (saturated solution) to complete the neutralisation. Methanol was evaporated and the resulting mixture was extracted with AcOEt. The organic phase was dried, evaporated and purified by chromatography to obtain **5** and **6** (1.73 g, 7.72 mmol) in 3.3:1 ratio via GC. Yield 94%.

2.2.6. 9,9-Ethylendioxy-3-*endo*-7-*exo*-dimethylbicyclo-[3.3.1]nonan-2-ols 7a–b. $LiAlH_4$ (0.4 g, 10.5 mmol) was added to a stirred and ice-bath cooled solution of **6** and **5** (kinetic mixture, 9:1 ratio, 1.45 g, 6.47 mmol) in dry Et_2O (50 ml), under an argon atmosphere. After 2 h stirring, the reaction was cautiously quenched with 10 ml of NH_4Cl (satd solution) and filtered by suction through a sintered glass filter. The organic phase was separated, washed with brine, dried and evaporated. The crude product was purified by chromatography (1:50; petroleum ether/AcOEt, 8:2) to obtain, in the first fractions the 2-*endo*-epimer **7b** (0.89 g, 3.95 mmol, 68% with respect to **6**), in the last fractions the 2-*exo*-epimer **7a** (0.36 g, 1.58 mmol, 27% with respect to **6**), while the central fractions afforded compounds **8a** (0.11 g) and **8b** (0.03 g), in elution order (vide infra).

7a. ^{1}H NMR ($CDCl_3$) δ: 4.00–3.75 (4H, m, O–CH_2–CH_2–O), 3.25 (1H, broad dd, J_s=9.0, 4.9 Hz, H_2), 2.10–1.53 (5H, m), 1.55–1.20 (6H, m), 0.98 (3H, d, J=6.1 Hz, C_3–CH_3), 0.83 (3H, 'filled in' d, C_7–CH_3). ^{13}C NMR ($CDCl_3$) δ: 112.07 (C_9), 80.41 (C_2), 64.44 and 63.64 (O–CH_2–CH_2–O), 46.91 (C_1), 39.92 (C_6), 38.15 (C_4), 34.66 (C_3), 33.40 (C_5), 33.07 (C_8), 21.90 (CH_3), 21.67 (CH_3), 19.78 (C_7). MS (*m*/*z*, %): 226 (M^+, 37), 209 (16), 169 (14), 167 (19), 155 (23) 141 (30), 139 (30), 129 (16), 128 (20), 127 (84),125 (17),113 (87), 100 (20), 99 (100), 73 (33), 55 (70). IR (CCl_4): ν_{OH}=3600 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.04; H, 9.74. Found C, 69.10; H, 9.68.

7b. ^{1}H NMR ($CDCl_3$) δ: 4.14 (1H, broad dd, J_s=9.7, 6.4, H_2), 4.00–3.80 (4H, m, O–CH_2–CH_2–O), 2.45 (1H, dddq, J_s=13.2, 6.4, 6.4, 6.4 Hz, H_3), 2.16 (1H, dddd, J_s=9.7, 4.2, 2.4, $2.0_{(w)}$ Hz, H_1), 1.95–1.75 (4H, m), 1.60–1.15 (5H, m), 0.90 (3H, d, J=7.1 Hz, C_3–CH_3), 0.85 (3H, d, J=6.2 Hz, C_7–CH_3). ^{13}C NMR ($CDCl_3$) δ: 112.43 (C_9), 71.58 (C_2), 64.04 and 63.27 (O–CH_2–CH_2–O), 40.58, 39.56, 34.53, 33.10, 32.32, 28.56, 23.10, 21.86, 16.18. MS (*m*/*z*, %): 226 (M^+, 21), 209 (9), 208 (13), 193 (12), 169 (10), 167 (12), 155 (14), 141 (16), 139 (30), 127 (73), 113 (90), 100 (16), 99 (100), 93 (17), 91 (18), 55 (60). IR (CCl_4): ν_{OH}=3630 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.04; H, 9.74. Found C, 69.25; H, 9.72.

2.2.7. 9,9-Ethylendioxy-3-*exo*-7-*exo*-dimethylbicyclo[3.3.1]-nonan-2-ols 8a–b. The reaction was performed as for compounds **7a**–**b** by reducing the thermodynamic mixture of epimers **5** and **6** (3.3:1 ratio, 1.73 g, 7.72 mmol) with $LiAlH_4$ (0.48 g, 12.6 mmol). The crude product was purified by chromatography (1:50; petroleum ether/AcOEt, 8:2) to afford compounds **7b** (0.27 g) and **7a** (0.11 g) in the first and the last fractions, respectively, while the central fractions gave the 2-*exo*-epimer **8a** (1.02 g, 4.50 mmol, 76% with respect to **5**) and the 2-*endo*-epimer **8b** (0.25 g, 1.13 mmol, 19% with respect to **5**).

8a. ^{1}H NMR ($CDCl_3$) δ: 4.00–3.80 (4H, m, O–CH_2–CH_2–O), 3.70 (1H, br s, exchanges with D_2O, OH), 3.63 (1H, ddd, J_s=6.2, 2.0, $2.0_{(w)}$ Hz, H_2), 2.12 (1H, dqdd, J_s=10.0, 6.6, 6.2, $2.2_{(w)}$ Hz, H_3), 2.06–1.40 (9H, m), 0.91 (3H, d, J=6.6 Hz, C_3–CH_3), 0.79 (3H, d, J=6.1 Hz, C_7–CH_3). ^{13}C NMR ($CDCl_3$) δ: 111.85 (C_9), 77.21 (C_2), 64.28 and 63.61 (O–CH_2–CH_2–O), 42.77 (C_1), 38.03 (C_6), 37.07 (C_5), 35.16 (C_4), 34.25 (C_8), 33.00 (C_3), 25.54 (C_7), 23.47 (CH_3), 17.95 (CH_3). MS (*m*/*z*, %): 226 (M^+, 46), 209 (22), 169 (12), 167 (13), 155 (19), 141 (21), 139 (34), 129 (11), 128 (13), 127 (61), 125 (19), 113 (100), 100 (16), 99 (87), 73 (15), 55 (45). IR (CCl_4): ν_{OH} 3520 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.04; H, 9.74. Found C, 68.95; H, 9.78.

8b. ^{1}H NMR ($CDCl_3$) δ: 3.88 (4H, s, O–CH_2–CH_2–O), 3.60 (1H, dd, J_s=10.3, 5.0 Hz, H_2), 2.05–1.20 (11H, m), 0.95 (3H, d, J=6.1 Hz, C_3–CH_3), 0.81 (3H, d, J=5.8 Hz, C_7–CH_3). ^{13}C NMR ($CDCl_3$) δ: 111.63 (C_9), 77.04 (C_2), 64.10 and 63.89 (O–CH_2–CH_2–O), 43.59 (C_1), 38.29 (C_8), 36.89 (C_5), 35.63 (C_6), 35.37 (C_3), 31.24 (C_4), 26.40 (C_7), 23.51 (CH_3), 20.39(CH_3). MS (*m*/*z*, %): 226 (M^+, 37), 169 (16), 167 (20), 155 (27), 141 (27), 139 (36), 129 (17), 128 (23), 127 (100), 125 (16), 115 (21), 113 (85), 100 (17), 99 (96), 95 (17), 93 (18), 91 (18), 73 (39), 55 (96), 41 (53). IR (CCl_4): ν_{OH} 3630 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.04; H, 9.74. Found C, 69.15; H, 9.70.

2.2.8. 3,7-*exo*,*exo*-Dimethylbicyclo[3.3.1]nonan-9-one 1. Deoxygenation at C_2 was carried out by Ireland's procedure.[16] Alcohols **8a**–**b** in mixture (1.20 g, 5.31 mmol, 4:1 ratio) were dissolved in anhydrous THF, (50 ml) under argon atmosphere, and 0.88 ml of TMEDA were added. Temperature was cooled to 0°C and 3.5 ml of BuLi (2.5 M solution in hexane) were added dropwise under stirring. The solution was stirred at room temperature for 0.5 h and freshly distilled tetramethylphosphorodiamidic chloride (1.57 ml, 10.63 mmol) was added dropwise. After 2 h stirring, the reaction was quenched with NH_4Cl (satd solution), extracted with diethyl ether, the organic extracts dried and evaporated to afford a crude product that was purified by chromatography. Elution with petroleum ether/Et_2O (7:3) eliminated the excess reagent while a successive elution with methanol afforded the tetramethylphosphorodiamidic esters (1.80 g) in mixture. These latter were dissolved in anhydrous THF (30 ml) containing *tert*-butanol (1.55 ml, 16.41 mmol) and the resulting solution was added under argon atmosphere to a stirred deep blue suspension of lithium wire (0.38 g) in anhydrous ethylamine (60 ml) at −20°C, paying attention that addition rate was slow enough to maintain the blue colour. After a further 0.5 h at −20°C, the solution was allowed to warm to room temperature,

allowing the amine to evaporate overnight. The residue was neutralised with 6 M HCl and extracted with Et_2O. The organic extracts were dried and the solvent fractionally distilled to give the 9,9-*ethylendioxy*-3,7-*exo*,*exo*-*dimethylbicyclo*[3.3.1]*nonane* (1.018 g, 4.85 mmol, yield 94%): ^{1}H NMR ($CDCl_3$) δ: 3.89 (4H, s, O–CH_2–CH_2–O), 2.09 (2H, dddq, J_s=12.0, 12.0, 6.0, 6.0, 6.2 Hz, $H_{3ax}+H_{7ax}$), 1.75–1.65 (10H, m), 0.81 (6H, d, J=6.2 Hz, C_3–CH_3+C_7–CH_3). ^{13}C NMR ($CDCl_3$) δ: 111.14 (C_9), 63.49 (O–CH_2–CH_2–O), 38.03 ($C_2+C_4+C_6+C_8$), 36.49 (C_1+C_5), 26.38 (C_7+C_3), 29.13 (2 CH_3). MS (*m*/*z*; %): 210 (M^+, 39), 195 (27), 167 (9), 153 (16), 139 (42), 126 (12), 113 (100), 100 (18), 99 (42), 55 (35), 41 (29). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.28; H, 10.48. Found C, 74.40; H, 10.60. This latter compound (1.018 g, 4.85 mmol) was refluxed for 2 h in 60 ml of Me_2CO–2 M HCl (5:1) mixture and then neutralised with $NaHCO_3$ (satd solution). The organic solvent was fractionally distilled and the aqueous residue was extracted with diethyl ether. The organic extracts were dried and slowly distilled at room pressure to give the volatile ketone **1** (0.76 g, 4.56 mmol, yield 95%, yield 76% with respect to the starting 5+6 kinetic mixture): ^{1}H NMR ($CDCl_3$) δ: 2.52 (2H, ddddq, J_s=12.1, 12.1, 6.1, 6.1, 6.2 Hz, H_3+H_7), 2.27 (2H, brs, H_1+H_5), 2.05 (4H, broad dd, J_s=12.6, 6.1 Hz, $H_{2eq}+H_{4eq}+H_{6eq}+H_{8eq}$), 1.60 (4H, ddd, J_s=12.6, 12.1, 5.0 Hz, $H_{2ax}+H_{4ax}+H_{6ax}+H_{8ax}$), 0.83 (6H, d, J=6.2 Hz, C_3–CH_3+C_7–CH_3). ^{13}C NMR ($CDCl_3$) δ: 222.65 (C_9), 46.35 (C_1+C_5), 42.87 ($C_2+C_4+C_6+C_8$), 27.26 (C_3+C_7), 22.53 (2 CH_3). MS (*m*/*z*; %): 166 (M^+, 69), 109 (20), 110 (16), 96 (25), 95 (50), 81 (100), 68 (27), 55 (65). IR (CCl_4): ν_{max} 1730 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O$: C, 79.52; H, 10.84. Found C, 79.75; H, 11.05.

2.2.9. 3-*endo*-7-*exo*-Dimethylbicyclo[3.3.1]nonan-9-one 2. The deoxygenation reaction was performed as for the synthesis of **1**, starting from the mixture of epimers **7a–b** (1:2.5 ratio, 1.20 g, 5.31 mmol) to obtain **9,9-ethylendioxy-3-*endo*-7-*exo*-dimethylbicyclo[3.3.1]nonane** (1.05 g, 4.99 mmol, yield 94%): ^{1}H NMR ($CDCl_3$) δ: 3.98–3.78 (4H, 2m, O–CH_2–CH_2–O), 2.08 (1H, ddddq, J_s=12.9, 12.9, 6.4, 6.4, 6.4 Hz, H_7), 2.07–1.60 (5H,m, $H_{6eq}+H_{8eq}+H_1+H_5+H_3$), 1.45 (2H, ddd, J_s=12.9, 12.9, 3.7 Hz, $H_{6ax}+H_{8ax}$), 1.30 (2H, dddd, J_s=12.7, 11.0, 5.3, 3.7$_{(w)}$ Hz, $H_{2\beta}+H_{4\beta}$), 1.05 (2H, ddd, J_s=12.7, 11.7, 1.5 Hz, $H_{2\alpha}+H_{4\alpha}$), 0.85 (3H, d, J=6.4 Hz, C_7–CH_3), 0.80 (3H, d, J=6.2 Hz, C_3–CH_3). ^{13}C NMR ($CDCl_3$) δ: 112.56 (C_9), 64.03 and 63.26 (O–CH_2–CH_2–O), 39.94 (C_6+C_8), 36.00 (C_2+C_4), 34.32 (C_1+C_5), 22.64 (C_3), 22.25 (C_7), 21.40 (CH_3), 20.17 (CH_3). MS (*m*/*z*; %): 210 (M^+, 27), 195 (20), 139 (35), 113 (100). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.28; H, 10.48. Found C, 74.37; H, 10.55. The dioxolane moiety was removed as described for **1** and gave ketone **2** (0.88 g, 4.74 mmol, yield 95%, yield 65% with respect to the starting **5+6** thermodynamic mixture): ^{1}H NMR ($CDCl_3$) δ: 2.40 (2H, ddddd, J_s=10.3, 3.1, 3.1, 3.1,1.5$_{(w)}$ Hz, H_1+H_5), 2.50–2.20 (1H, m, H_7), 2.10 (2H, ddd, J_s=12.9, 10.3, 4.3, 1.8$_{(w)}$ Hz, $H_{2\beta}+H_{4\beta}$), 1.85 (2H, dddd, J_s=13.2, 4.5, 3.1, 1.8$_{(w)}$ Hz, $H_{6eq}+H_{8eq}$), 1.75–1.35 (5H, m, $H_{2\alpha}+H_{4\alpha}+H_3+H_{6ax}+H_{8ax}$), 0.91 (3H, d, J=6.5 Hz, CH_3), 0.89 (3H, d, J=5.9 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ: 222.40 (C_9), 44.57 (C_1+C_5), 44.41 (C_2+C_4), 38.98 (C_6+C_8), 27.32 (CH_3), 21.63 (C_3), 21.61 (C_7), 20.79 (CH_3); MS (*m*/*z*; %): 166 (M^+, 51), 123 (15), 110 (18), 96 (28), 95 (50), 82 (20), 81 (100), 55 (60). IR (CCl_4): ν_{max} 1730 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O$: C, 79.52; H, 10.84. Found C, 79.72; H, 11.00.

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