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Highly stereoselective synthesis of perhydropyrano[2,3-*b*]pyrans from the new 3-methylidenepentane-1,5-dianion synthon

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Dedicated to the memory of Professor Marcial Moreno Mañas

Abstract—4-Phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**2**) is a new 3-methylidenepentane-1,5-dianion synthon which on reaction with an excess of lithium powder and a catalytic amount of DTBB (2.5%) in the presence of a carbonyl compound in THF at 0 °C, leads, after hydrolysis, to the expected methylidenic diols **3**. These diols when subjected to successive hydroboration–oxidation and final oxidation, undergo spontaneous cyclisation to furnish a series of *cis*-perhydropyrano[2,3-*b*]pyrans (**4**) in a highly diastereoselective manner (>99% de). Acid-catalysed isomerisation of the *cis*-perhydropyrano[2,3-*b*]pyrans (**4**) leads, also stereoselectively, to the corresponding *trans*-perhydropyrano[2,3-*b*]pyrans (**5**). A discussion about the stability of **4** and **5** is also included.

1. Introduction

The perhydropyrano[2,3-*b*]pyran unit can be found in nature as a substructure of natural products, some of which exhibit interesting biological activities such as macralstonidine (**I**, from *Alstonia* species, with antimalarial activity)[1] or sapogenin triterpene **II** (from *Emmenospermum pancherianum*),[2] as well as in dipyranosides like **III** (key precursors for ansamycins)[3] (Chart 1). The perhydropyrano[2,3-*b*]pyran moiety also plays an important role in the synthesis and modification of carbohydrate scaffolds.[4] There is a variety of strategies that allow the construction of the perhydropyrano-[2,3-*b*]pyran skeleton, which normally involves intramolecular cyclisation over a preformed tetrahydropyran derivative

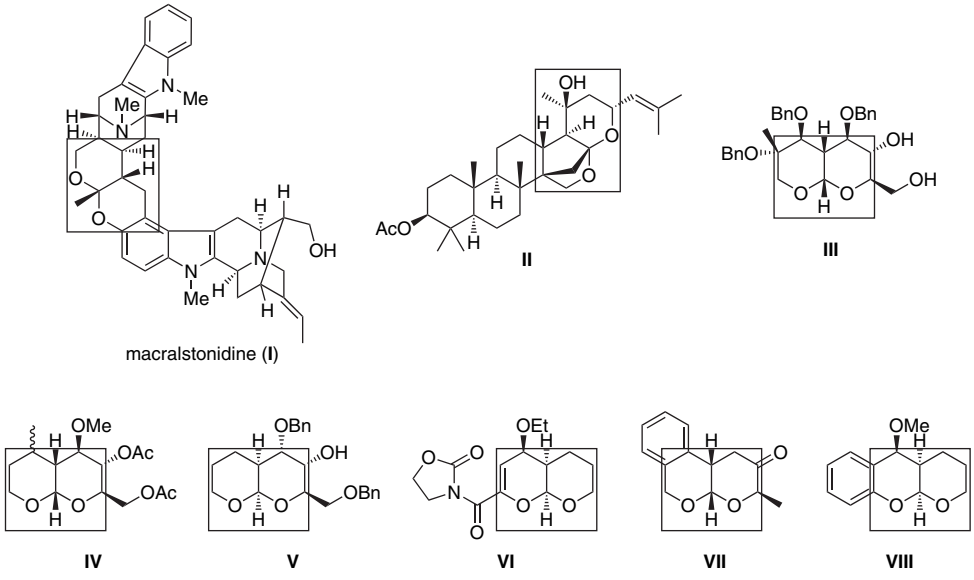

Chart 1.

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under radical,[4a,4c,5] acidic,[4b,6] Diels–Alder[4d,4e,7] or Heck[8] conditions. For instance, compound **IV** was obtained by 6-*exo* radical cyclisation of a but-3-enyl-2-deoxy-2-iodo-α-D-glycoside.[4a] Acid catalysis promoted the intramolecular cyclisation of a 2-deoxy-2-hydroxyalkyl-α-D-altropyranoside to give **V**.[4b] Compound **VI** is one example of intermolecular hetero Diels–Alder reaction of a substituted 1-oxabuta-1,3-diene with dihydro-2*H*-pyran,[7] whereas intramolecular Heck reaction of a hex-2-enepyranoside led to compound **VII**. More recently, different groups have focussed on the synthesis of pyranobenzopyrans of the type **VIII** by Lewis-acid catalysed intermolecular cyclisation of 3,4-dihydro-2*H*-pyran and salicylaldehyde derivatives.[9]

Due to our ongoing interest in the synthesis of fused bicyclic[10] and spirocyclic[11] polyether skeletons, we have preliminary reported about a new 3-methylidenepentane-1,5-dianion synthon, 4-phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**2**), that has found application in the straight synthesis of 1,7-dioxaspiro[4.5]decanes,[12a] perhydropyrano[2,3-*b*]pyrans[12a] and 1,6-dioxaspiro[4.4]nonanes.[12b] We want to report herein a more detailed study on the application of **2** to the stereoselective synthesis of *cis*-perhydropyrano [2,3-*b*]pyrans, including the synthesis of some enantiopure compounds, as well as to report about their acid-catalysed isomerisation to the corresponding trans derivatives. A discussion about the kinetically and thermodynamically controlled formation of the products is also included.

2. Results and discussion

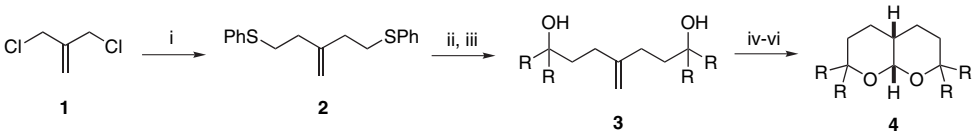
The general protocol followed for the obtention of perhydropyrano[2,3-*b*]pyrans is shown in Scheme 1. As already reported,[12] 4-phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**2**) was easily prepared from commercially available 3-chloro-2-(chloromethyl)prop-1-ene (**1**) with an organocuprate reagent derived from $PhSCH_2Li$ and CuCN. Reductive lithiation[13] of the carbon–sulfur bonds in **2** with an excess of lithium powder and a catalytic amount of DTBB (4,4′-di-*tert*-butylbiphenyl), in the presence of different ketones (Barbier conditions)[14] in THF, at 0 °C for 2 h, led after hydrolysis with water, to the corresponding methylidenic diols **3** (Table 1).[15] It is worthy to note that when the chiral ketones (−)-menthone and (−)-fenchone were used as electrophiles, the corresponding C_2-symmetric diols **3g** and **3h**, respectively, were obtained as single enantiomers.[15]

The transformation of diols **3** into the corresponding perhydropyrano[2,3-*b*]pyrans **4** was effected by successive hydroboration–oxidation with borane–hydrogen peroxide, and final oxidation with PCC (Scheme 1 and Table 1).[10] Under the reaction conditions shown in Scheme 1 (step vi), the spontaneous intramolecular ketalisation occurred in most of the cases with exclusive formation of the cis diastereoisomers and in high yields. Especially interesting from the structural point of view are the products derived from cyclic ketones (in particular polyether **4e**), which contain both spiro and fused bicyclic moieties. Compounds **4a** and **4c** showed to be in equilibrium with small amounts (~10%) of the corresponding precursor lactols (Table 1). The cis stereochemistry in **4** was initially assigned by comparison of the ^1H NMR chemical shift of H_{8a} (acetal proton) and the J H_{8a}, H_{4a} with the values appeared in the literature,[6b] as well as by NOE experiments, and unambiguously established by X-ray crystallography of compound **4f** (Fig. 1). The derivative of (−)-menthone (**4g**) was obtained as an enantiomerically pure compound, whereas **4h** (74%) was obtained together with the corresponding trans diastereoisomer (13%).

To the best of our knowledge this is the first procedure that allows the straight preparation of perhydropyrano[2,3-*b*]pyrans from a completely acyclic precursor and in a stereoselective manner. This methodology is, in fact, clearly advantageous by comparison with those based on the acidic treatment of 2-alkoxy-3-(3-hydroxypropyl)tetrahydropyran derivatives and reported independently by the groups of Deslongchamps[6a] and Duhamel.[6b] In these studies, perhydropyrano[2,3-*b*]pyrans were obtained in 10–90% de, as a result the acidic medium promoted both intramolecular cyclisation and cis–trans isomerisation. In contrast, the methodology described herein, due to the mild and inert reaction conditions utilised, allowed a complete kinetically controlled ketalisation, leading to *cis*-perhydropyrano[2,3-*b*]pyrans (**4**) in >99% de.

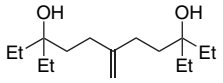
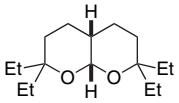
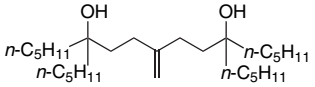
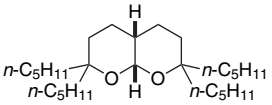
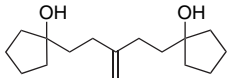
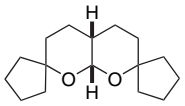
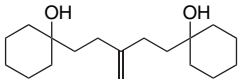
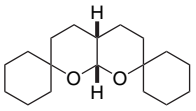
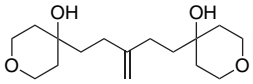
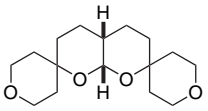
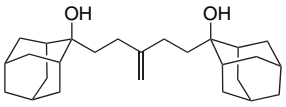
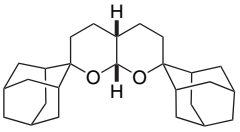
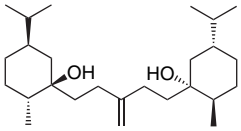
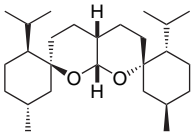
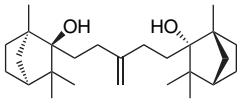
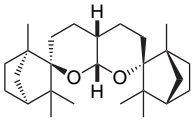
It must be noted that in contrast to the results obtained in Table 1, the cyclisation of the diol derived from diisopropylketone (**3i**) furnished a mixture of perhydropyrano[2,3-*b*]pyrans in a 1:3.5 cis/trans ratio, whereas the diol derived from di-*tert*-butylketone (**3j**) was exclusively obtained as the trans isomer (Scheme 2).[16]

We devised the possibility of obtaining stereoselectively *trans*-perhydropyrano[2,3-*b*]pyrans from the corresponding cis derivatives. Thus, by treating a variety of *cis*-perhydropyrano[2,3-*b*]pyrans **4** with *p*-toluenesulfonic acid in $CHCl_3$ at rt, a progressive isomerisation to the corresponding *trans*-perhydropyrano[2,3-*b*]pyrans **5** was observed (Scheme 3 and Table 2). Figure 2 shows the evolution of the cis–trans isomerisation vs time for compounds **4a**,**b**, **c**,**d**,**f**. A conversion of ≥80% was reached in all the cases after 35 h. The different substituents at the 2 and 7 positions seem to exert a little influence on the cis–trans isomerisation since most values for the trans isomers are near 85% after total equilibration. However, a high 8:92 cis/trans ratio after total equilibration was obtained for compound **4c** (Table 2,



Scheme 1. Reagents and conditions: (i) $PhSCH_2Li$, CuCN, LiCl, 0 °C, 2 h; (ii) Li, DTBB (2.5 mol %), R_2CO, THF, 0 °C, 2 h; (iii) H_2O; (iv) BH_3·THF, 0 °C, 6 h; (v) 33% H_2O_2, 3 M NaOH, 0 °C, 8 h; (vi) PCC, CH_2Cl_2, rt, 8 h.

Table 1. Preparation of the perhydropyrano[2,3-*b*]pyrans **4**

Product **3**[a]			Product **4**[a]		
No.	Structure	Yield (%)[b]	No.	Structure	Yield (%)[c]
3a		55	**4a**		82
3b		50	**4b**		91
3c		57	**4c**		84
3d		58	**4d**		87
3e		37[d]	**4e**		87
3f		33[e]	**4f**		76[f]
3g		48	**4g**		93[g]
3h		49	**4h**		74[h]

[a] All products were ≥95% pure (GLC and/or 300 MHz ^{1}H NMR) and were fully characterised by spectroscopic means (IR, ^{1}H and ^{13}C NMR, and MS).
[b] Isolated yield after column chromatography, unless otherwise stated (silica gel, hexane/EtOAc), based on the starting compound **2**.
[c] Yield of pure compounds **4** from the reaction crude (unless otherwise stated) based on the starting diol **3**.
[d] Purification by column chromatography was carried out with EtOAc/MeOH as eluant.
[e] Isolated yield after recrystallisation with hexane.
[f] Isolated yield after column chromatography (silica gel, hexane), based on the corresponding diol **3f**.
[g] As a single enantiomer.
[h] The corresponding trans diastereoisomer was obtained in 13% yield.

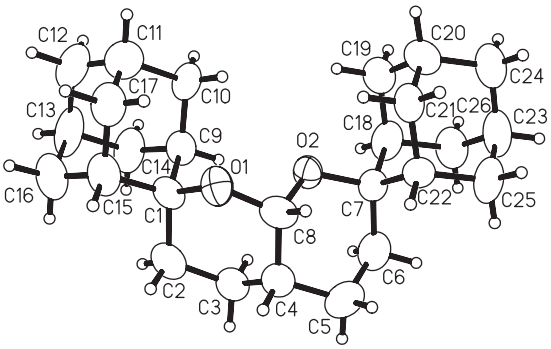
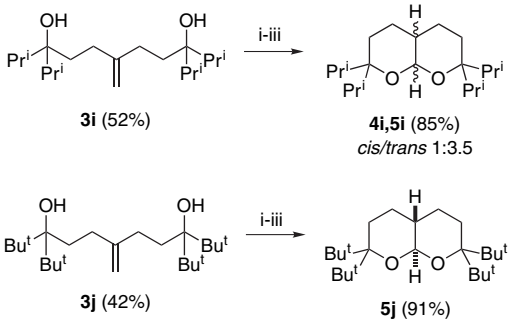
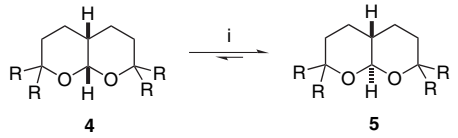


Figure 1. Plot showing the X-ray structure and atomic numbering of compound **4f**.



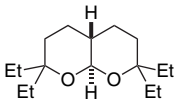
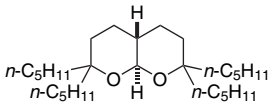
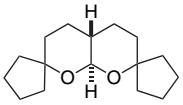
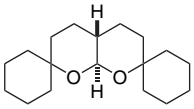
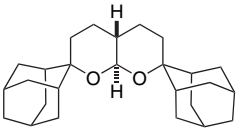
Scheme 2. (i) $BH_3 \cdot THF$, 0 °C, 6 h; (ii) 33% H_2O_2, 3 M NaOH, 0 °C, 8 h; (iii) PCC, CH_2Cl_2, rt, 8 h.

entry 3). This isomerisation is in favour of the trans products **5**, which showed to be more stereoselective than those reported previously.[6b] The trans stereochemistry in compounds **5** was assigned by comparing their δ H_{8a} (4.30–4.58 ppm) and J H_{8a}, H_{4a} (7.5–8.6 Hz) with those of the cis stereochemistry in compounds **4** (4.94–5.06 ppm, J=1.9–2.8 Hz). Nonetheless, this spectroscopic-structure correlation could be additionally confirmed by X-ray crystallography of compound **5f** (Fig. 3).



Scheme 3. (i) *p*-TsOH (cat.), $CHCl_3$ and rt.

Table 2. Isomerisation of the *cis*-perhydropyrano[2,3-*b*]pyrans **4**

Starting material	Product **5**		
	No.	Structure	Conversion (%)[a]
4a	**5a**		86
4b	**5b**		84
4c	**5c**		92
4d	**5d**		86
4f	**5f**		85

[a] Conversion determined by ^{1}H NMR.

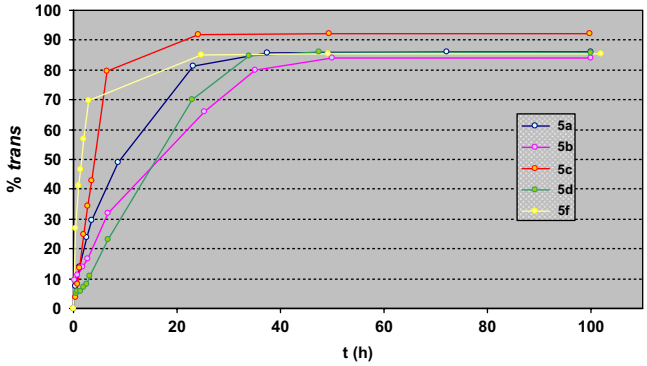


Figure 2. Graphic showing the cis–trans isomerisation of compounds **4** to **5** vs time, under the conditions depicted in Scheme 3.

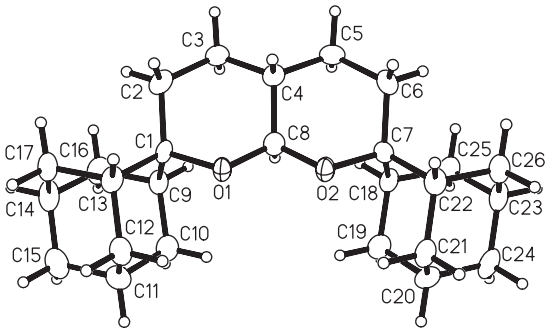
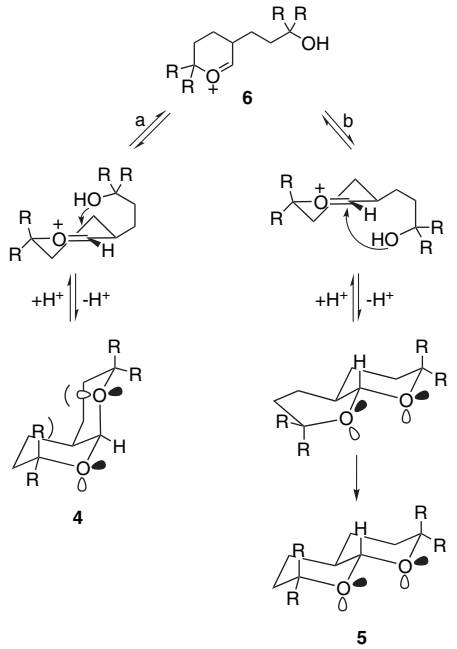


Figure 3. Plot showing the X-ray structure and atomic numbering of compound **5f**.

The high diastereo-control achieved in the cyclisation reaction to the *cis*-perhydropyrano[2,3-*b*]pyrans **4** can be explained if we accept that the hydroxyalkyl substituent adopts a pseudoequatorial position in the cation **6** and the nucleophilic attack occurs along a pseudoaxial trajectory to maximise the overlap of the HOMO of the nucleophile with the LUMO of the oxonium ion (Scheme 4, pathway a). This argument is equivalent to consider, as Deslongchamps et al. did,[6a] that the acetal formation will take place with minimum energy only when the intermediate oxonium ion **6** can develop an electron pair which becomes antiperiplanar to the newly formed carbon–oxygen bond in the final product (pathway a). Under these conditions, nucleophilic attack from the bottom face of the oxonium ion (α attack) cannot yield the *trans*-acetal directly in its more stable conformation (Scheme 4, pathway b), but must provide a disfavoured twist-boat conformation. The latter would then undergo a conformational change to the more stable chair–chair conformation of the *trans*-acetal **5**. On the other hand, the formation of the *cis*-perhydropyrano[2,3-*b*]pyrans **4** is expected to be favoured by a lower-energy, chair-like transition state (pathway a).[17]



Scheme 4. Kinetic vs thermodynamic ketalisation.

The specific conversion of the diols **3** into the *cis*-perhydropyrano[2,3-*b*]pyrans **4** can be considered as a result of a kinetically controlled reaction. The above described equilibration studies show that, at 25 °C, *cis*-acetals **4** are less stable than the trans isomers **5** by 0.99–1.47 kcal/mol (Table 3). Descotes et al. carried out the equilibration of *cis*- and *trans*-hexahydro-2*H*-pyrano[2,3-*b*]pyrans **7** and the resulting mixture contained 57% of cis and 43% of trans isomer at 80 °C (Chart 2).[18] Therefore, the cis isomer was more stable by 0.17 kcal/mol with an estimated value of 1.4 kcal/mol for the anomeric effect. Similar studies by Duhamel et al. on the dimethyl derivative **8** showed, however, that the *cis*-acetal (31%) was less stable than the trans isomer (69%) by 0.52 kcal/mol.[6b] The higher diastereoselectivity achieved in our equilibration studies [7.7–15.9% (cis), 84.1–92.3% (trans)], in comparison with the aforementioned examples, might be due to an extra and unfavourable 1,3-diaxial interaction, which is present in **4** (Chart 2). This 1,3-diaxial interaction could account for the major and exclusive formation of the trans diastereoisomers in the cyclisation reaction of the diols **3i** and **3j**, respectively, where the bulkier isopropyl and *tert*-butyl groups cannot be easily accommodated in a cis chair–chair conformation.

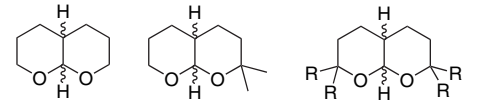


Chart 2. Equilibration studies of different 1,8-dioxadecalins.

The different results obtained in the equilibration studies of the *cis*- and *trans*-1,8-dioxadecalins shown in Chart 2, together with the anomalous behaviour observed in the cyclisation of the diols **3i**,**j**, encouraged us to carry out a short computational study about the geometry optimisation of some of the compounds of **4** and **5**, that allowed us to compare the calculated values with the experimental data.

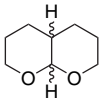
Table 3

Compound no.	ΔG° (kcal/mol)[a]	$\Delta(\Delta H_f)$ (kcal/mol)[b]
4a, **5a**	−1.079	2.858
4b, **5b**	−0.987	—
4c, **5c**	−1.469	0.459
4d, **5d**	−1.053	1.177
4e, **5e**	—	0.635
4f, **5f**	−1.039	1.221
4i, **5i**	—[c]	−1.311
4j, **5j**	—[d]	−1.819[e]

[a] Standard Gibbs energy was experimentally determined at 298 K for the isomerisation of the *cis*-perhydropyrano[2,3-*b*]pyrans **4** to the *trans*-perhydropyrano[2,3-*b*]pyrans **5** (see Scheme 3).
[b] Difference in heat of formation of compounds **4** and **5** [ΔH_f (**5**)−ΔH_f (**4**)] in a chair–chair conformation, unless otherwise stated, calculated by the PM3 semi-empirical method.
[c] Isomerisation of **4i** to **5i** was accompanied by decomposition.
[d] No isomerisation of **5j** (the starting material in this case) was observed after 20 min but only decomposition.
[e] Difference in heat of formation of compounds **4j** and **5j** in a chair–twist boat and chair–chair conformations, respectively.

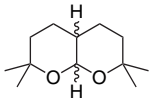
Theoretical studies dealing with the conformational analysis and relative stabilities of 1,8-dioxadecalins are very scarce.[19] In our case, PM3 semi-empirical calculations[20] were carried out for any of the derivatives **4a**,**c**,**d**,**e**,**f**,**i**,**j** and **5a**,**c**,**d**,**e**,**f**,**i**,**j**. In all the cases, the heat of formation was determined for a fused chair–chair conformation in the perhydropyrano[2,3-*b*]pyran core, as other conformations resulted to be less stable (Table 3). One exception was, however, compound **4j**, wherein a high steric hindrance of the *tert*-butyl substituents did not allow fixing of a chair–chair but a chair–twist boat conformation.

From Table 3 and as already mentioned above, the standard Gibbs energy for the isomerisation of the *cis*-perhydropyrano[2,3-*b*]pyrans **4** to the *trans*-perhydropyrano[2,3-*b*]pyrans **5**, clearly reveals that the latter (thermodynamic product) are more stable than the former (kinetic product), though the difference is in most cases around 1 kcal/mol. This result is, however, contradictory with the heats of formation calculated for compounds **4** and **5** (except for **4i**,**j** and **5i**,**j**), which indicate that compounds **4** are thermodynamically more stable than compounds **5**. The same trend was observed for the heats of formation of the simplest *cis*- and *trans*-hexahydro-2*H*-pyrano[2,3-*b*]pyrans **7** (Chart 3). In order to confirm the validity of the PM3 calculations, the simpler substituted *cis*- and *trans*-2,2,7,7-tetramethylperhydropyrano[2,3-*b*]pyrans **9** were subjected to both PM3 and DFT geometry optimisation at the B3LYP/6-31G* level.[21] Also in this case, the similar differences in energy point to the diastereoisomer *cis*-**9** as the more stable one (Chart 3). Therefore, we can conclude that, in general, the *cis*-perhydropyrano[2,3-*b*]pyrans **4** are more stable than the *trans*-perhydropyrano[2,3-*b*]pyrans **5**, under the calculation conditions (i.e., in the gas phase). It is not our aim to carry out a more detailed study about the effect of the solvent on the relative stability of *cis*- and *trans*-1,8-dioxadecalins. On the other hand, it is worthy to note that the only two cases for which the trans diastereoisomer has been calculated to be more stable than the cis one, namely **5i** and **5j**, are the only ones that have been experimentally obtained as the major and exclusive trans diastereoisomers, respectively. In these two cases, important repulsive interactions (1,3-diaxial and others) involving the isopropyl and *tert*-butyl substituents seem to dominate over the stabilising stereoelectronic effects (e.g., the anomeric effect), disfavouring the formation of the cis diastereoisomers.



7

E_{trans} - E_{cis} = 2.107 kcal/mol (PM3)



9

E_{trans} - E_{cis} = 0.951 kcal/mol (PM3)
E_{trans} - E_{cis} = 1.094 kcal/mol (DFT)

Chart 3.

3. Conclusion

A variety of symmetrically substituted *cis*-perhydropyrano[2,3-*b*]pyrans (kinetic products) have been synthesized stereoselectively from a new 3-methylidenepentane-1,5-dianion synthon and the acid-promoted isomerisation of the former to the corresponding trans isomers (thermodynamic products) also proceeds diastereoselectively.

4. Experimental

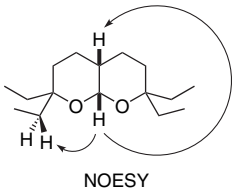
4.1. General

Melting points were obtained with a Reichert Thermovar apparatus. Optical rotations were measured with a Perkin–Elmer 341 polarimeter with a thermally jacketed 10 cm cell at approximately 20 °C. Concentrations (c) are given in g/100 mL and [α] values are given in units of 10^{-1} deg cm^2/g. NMR spectra were recorded on a Bruker Avance 300 and Bruker Avance 400 (300 and 400 MHz for ^{1}H NMR, and 75 and 100 MHz for ^{13}C NMR, respectively) using $CDCl_3$ as solvent and TMS as an internal standard; chemical shifts are given in (δ) parts per million and coupling constants (J) in hertz. Mass spectra (EI) were obtained at 70 eV on a Shimadzu QP-5000 and Agilent 5973 spectrometers, fragment ions in m/z with relative intensities (%) in parenthesis. HRMS analyses were carried out on a Finnigan MAT95S spectrometer. Elemental analyses were performed on a Carlo Erba CHNS-O EA1108 elemental analyser. The purity of volatile compounds and the chromatographic analyses (GLC) were determined with a Hewlett Packard HP-5890 instrument equipped with a flame ionisation detector and a 30 m capillary column (0.32 mm diameter, 0.25 μm film thickness), using nitrogen (2 mL/min) as carrier gas, $T_{injector}$=275 °C, T_{column}=60 °C (3 min) and 60–270 °C (15 °C/min); retention times (t_R) are given under these conditions. Column chromatography was performed using silica gel 60 of 40–60 microns. Thin-layer chromatography was carried out on TLC plastic sheets with silica gel 60 F_{254} (Merck). THF was directly used without any purification (Acros, 99.9%). Lithium powder was commercially available (MEDALCHEMY S. L.). PM3 calculations were carried out with the HyperChem7.5 molecular modelling package, whereas DFT calculations were carried out with the Gaussian03 package.[22]

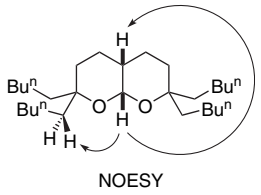
4.2. General procedure for the preparation of the *cis*-perhydropyrano[2,3-*b*]pyrans (4)

$BH_3\cdot$THF (1 M, 5 mL, 5 mmol) was added to a solution of the diol **3** (1 mmol) in THF (10 mL). After stirring for 6 h at rt, the reaction mixture was hydrolysed with water (5 mL) at 0 °C (ca. 5 min), followed by the consecutive addition of a 3 M NaOH (10 mL) and 33% vol of H_2O_2 (10 mL) solutions. The resulting mixture was stirred for 8 h followed by extraction with EtOAc (3×15 mL). The organic phases were dried over anhydrous Na_2SO_4 and the solvents were removed under reduced pressure (15 Torr), affording the corresponding triol crudes, which were subjected to oxidation as follows: pyridinium chlorochromate (2.4 mmol, 517 mg) was added to a solution of the corresponding triol in dichloromethane (10 mL) and the reaction mixture was stirred for 8 h. Then, it was filtered through a pad containing silica gel (bottom layer) and Celite (top layer), and washed with hexane, in order to remove the chromium salts. After removal of the solvents at reduced pressure (15 Torr), the expected *cis*-perhydropyrano[2,3-*b*]pyrans were obtained without any further purification, except in the case of compound **4f**, which was purified by column chromatography (silica gel, hexane).

4.2.1. 2,2,7,7-Tetraethyl-*cis*-perhydropyrano[2,3-*b*]pyran (4a). Colourless oil; t_R 13.32; R_f 0.67 (hexane/EtOAc 8:2); ν (film) 1087 cm^{-1} (CO); δ_H 0.83, 0.87 (12H, 2t, J=7.5, 4×CH_3), 1.20–1.70 (17H, m, 8×CH_2, C*H*CHO), 5.02 (1H, d, J=2.8, CHO); δ_C 7.6, 7.8 (4×CH_3), 21.5, 27.7, 29.1, 30.2 (8×CH_2), 34.2 (*C*HCHO), 76.6 (2×C), 93.3 (CHO); m/z 225 (M$^+$−29, 100%), 207 (30), 189 (57), 153 (15), 140 (23), 136 (10), 135 (86), 133 (50), 124 (12), 123 (19), 111 (21), 109 (19), 98 (12), 97 (17), 95 (35), 85 (13), 84 (14), 83 (25), 81 (12), 69 (39), 67 (11), 57 (42), 55 (45). HRMS calcd for $C_{16}H_{30}O_2$ 254.2246, found 254.2248.



4.2.2. 2,2,7,7-Tetrapentyl-*cis*-perhydropyrano[2,3-*b*]pyran (4b). Colourless oil; t_R 17.56; R_f 0.67 (hexane/EtOAc 8:2); ν (film) 1075 cm^{-1} (CO); δ_H 0.80–0.95 (12H, m, 4×CH_3), 1.15–2.00 (41H, m, 20×CH_2, C*H*CHO), 5.02 (1H, d, J=2.5, CHO); δ_C 14.1, 14.2 (4×CH_3), 21.6, 22.6, 22.7, 22.8, 22.9, 23.0, 23.2, 30.1, 32.6, 32.7, 38.6 (20×CH_2), 34.3 (*C*HCHO), 78.1 (2×C), 93.4 (CHO); m/z 407 (M$^+$−15, <1%), 338 (24), 337 (100). HRMS calcd for $C_{28}H_{54}O_2$ 422.4124, found 422.4117.



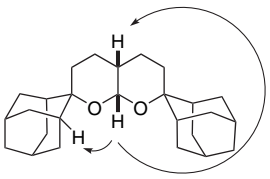
4.2.3. Dispiro[cyclopentane-1,2′-*cis*-tetrahydropyrano-[2,3-*b*]pyran-7′,1″-cyclopentane] (4c). Colourless oil; t_R 14.73; R_f 0.58 (hexane/EtOAc 8:2); ν (film) 1071 cm^{-1} (CO); δ_H 1.20–2.10 (25H, m, 12×CH_2, C*H*CHO), 4.94 (1H, d, J=2.5, CHO); δ_C 23.7, 23.9, 32.4, 36.8, 39.1, 39.5 (12×CH_2), 34.2 (*C*HCHO), 83.9 (2×C), 95.1 (CHO); m/z 250 (M$^+$, 47%), 169 (18), 151 (52), 150 (14), 147 (14), 139 (13), 138 (100), 137 (12), 136 (10), 135 (23), 134 (12), 133 (47), 132 (37), 123 (46), 122 (65), 121 (23), 120 (46), 119 (11), 109 (21), 108 (14), 107 (24), 105 (10), 97 (13), 96 (17), 95 (49), 94 (44), 93 (41), 91 (23), 85 (17), 83 (19), 82 (37), 81 (89), 80 (57), 79 (48), 77 (15), 69 (13), 68 (11), 67 (93), 57 (17), 55 (52), 54 (10), 53 (16). HRMS calcd for $C_{16}H_{26}O_2$ 250.1933, found 250.1940.

4.2.4. Dispiro[cyclohexane-1,2′-*cis*-tetrahydropyrano-[2,3-*b*]pyran-7′,1″-cyclohexane] (4d). Colourless oil; t_R

15.80; R_f 0.63 (hexane/EtOAc 8:2); ν (film) 1050 cm^{-1} (CO); δ_H 1.20–1.90 (29H, m, 14×CH_2, C*H*CHO), 5.03 (1H, d, J=2.5, CHO); δ_C 21.4, 21.8, 22.1, 23.8, 25.6, 26.3, 32.5 (14×CH_2), 34.7 (*C*HCHO), 73.4 (2×C), 93.1 (CHO); *m/z* 278 (M^+, 64%), 183 (20), 181 (10), 166 (15), 165 (100), 152 (36), 149 (11), 147 (43), 146 (36), 137 (15), 136 (31), 135 (11), 134 (14), 122 (14), 121 (39), 109 (22), 108 (17), 107 (15), 96 (19), 95 (49), 94 (26), 93 (13), 91 (12), 83 (12), 81 (64), 79 (25), 69 (12), 68 (10), 67 (42), 55 (43). HRMS calcd for $C_{18}H_{30}O_2$ 278.2246, found 278.2246.

4.2.5. Dispiro[oxacyclohexane-4,2′-*cis*-tetrahydropyrano-[2,3-*b*]pyran-7′,4″-oxacyclohexane] (4e). Colourless oil; t_R 17.34; R_f 0.55 (hexane/EtOAc 1:1); ν (film) 1101 cm^{-1} (CO); δ_H 1.20–2.05 (17H, m, 4×C$H_2$$CH_2$O, 2×C$H_2CH_2$CH, C*H*CHO), 3.62–3.72, 3.77–3.90 (8H, 2m, 4×CH_2O), 5.06 (1H, d, J=1.9, CHO); δ_C 20.8, 33.2, 35.3, 35.4 (4×*C*$H_2$$CH_2$O, 2×*C*$H_2$*C*$H_2$CH), 34.2 (*C*HCHO), 63.4, 63.9 (4×CH_2O), 70.9 (2×C), 93.2 (CHO); *m/z* 282 (M^+, 14%), 268 (86), 222 (18), 210 (14), 170 (14), 168 (17), 167 (78), 157 (17), 155 (37), 137 (12), 127 (19), 121 (14), 114 (35), 112 (18), 111 (22), 109 (15), 101 (28), 99 (40), 97 (21), 96 (100), 95 (14), 94 (11), 93 (10), 83 (21), 81 (19), 79 (30), 71 (12), 70 (10), 69 (10), 67 (29), 55 (39), 53 (12). HRMS calcd for $C_{16}H_{26}O_4$ 282.1831, found 282.1810.

4.2.6. Dispiro[adamantane-2,2′-*cis*-tetrahydropyrano-[2,3-*b*]pyran-7′,2″-adamantane] (4f). Colourless solid; R_f 0.72 (hexane/EtOAc 8:2); mp 180 °C (dec); ν (KBr) 1083 cm^{-1} (CO); δ_H 1.20–1.95, 2.00–2.10, 2.20–2.30, 2.40–2.50 (37H, 4m, 9×C*H*CH_2, 14×CH_2), 5.13 (1H, d, J=2.2, CHO); δ_C 21.3, 29.2, 29.7, 32.4, 33.1, 34.2, 34.4, 38.5 (14×CH_2), 27.7, 27.8 (4×*C*HCH_2*C*H), 37.4 (*C*HCHO), 77.2 (2×C), 92.7 (CHO); *m/z* 382 (M^+, 2%), 204 (48), 189 (18), 188 (23), 149 (19), 148 (100), 91 (10), 79 (11). Anal. calcd for $C_{26}H_{38}O_2$ C, 81.62; H, 10.01, found C, 81.60; H, 9.89.



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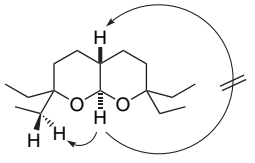
4.2.7. Dispiro[(1*S*,2*S*,4*R*)-1-isopropyl-4-methylcyclohexane-2,2′-*cis*-tetrahydropyrano[2,3-*b*]pyran-7′,2″-{(1*S*,2*S*,4*R*)-1-isopropyl-4-methylcyclohexane}] (4g). Colourless oil; t_R 18.43; R_f 0.59 (hexane/EtOAc 8:2); $[\alpha]_D$ −45.3 (*c* 2.3, $CHCl_3$); ν (film) 1040 cm^{-1} (CO); δ_H 0.75–1.00 (18H, m, 6×CH_3), 1.15–2.55 (27H, m, 4×C*H*CH_3, 3×C*H*CH_2, 10×CH_2), 4.94 (1H, d, J=1.9, CHO); δ_C 18.4, 20.1, 22.6, 22.7, 24.1, 25.5, 25.7, 26.1, 26.4, 27.2 (6×CH_3, 4×*C*HCH_3), 18.9, 20.7, 22.1, 24.9, 26.3, 32.7, 35.9, 36.0, 39.8, 46.3 (10×CH_2), 35.4 (*C*HCHO), 50.8, 52.2 (2×*C*HCHCH_3), 74.7, 77.7 (2×CO), 92.9 (CHO); *m/z* 391 (M^++1, 24%), 390 (81), 347 (32), 329 (30), 305 (16), 239 (21), 221 (23), 208 (20), 203 (50), 202 (100), 193 (10), 165 (12), 164 (39), 159 (12), 149 (17), 147 (14), 137 (19), 123 (11), 121 (12), 110 (10), 109 (27), 107 (12), 105 (11), 97 (11), 95 (32), 93 (14), 83 (14), 81 (31), 79 (11), 69 (32), 67 (17), 55 (30). HRMS calcd for $C_{26}H_{46}O_2$ 390.3498, found 390.3493.

4.2.8. Dispiro[(1*R*,2*S*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]-heptane-2,2′-*cis*-tetrahydropyrano[2,3-*b*]pyran-7′,2″-{(1*R*,2*S*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]heptane}] (4h). Colourless oil; t_R 19.19; R_f 0.60 (hexane/EtOAc 8:2); ν (film) 1036 cm^{-1} (CO); δ_H 0.85–2.35 (41H, m, 6×CH_3, 3×C*H*CH_2, 10×CH_2), 5.03 (1H, d, J=2.3, CHO); δ_C 18.2, 18.8, 22.6, 22.8, 23.1, 23.3 (6×CH_3), 21.8, 22.9, 24.7, 25.3, 25.8, 26.0, 29.7, 29.9, 41.3, 43.6 (10×CH_2), 30.4 (*C*HCHO), 45.2, 47.1 (4×*C*CH_3), 48.9, 50.3 (2×*C*HCH_2C), 82.6, 83.1 (2×CO), 94.3 (CHO); *m/z* 386 (M^+, 8%), 261 (24), 125 (16), 123 (45), 122 (17), 121 (14), 109 (13), 107 (32), 105 (11), 95 (12), 93 (13), 82 (10), 81 (100), 80 (14), 79 (23), 69 (30), 67 (17), 57 (12), 55 (36), 53 (10), 43 (44), 41 (61). HRMS calcd for $C_{26}H_{42}O_2$ 386.3185, found 386.3191.

4.3. General procedure for the preparation of the *trans*-perhydropyrano[2,3-*b*]pyrans (5)

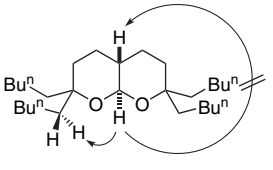
The *cis*-perhydropyrano[2,3-*b*]pyran **4** (30 mg) was dissolved in $CDCl_3$ (1 mL) and this solution was introduced into an NMR tube. *p*-Toluensulfonic acid (ca. 0.5 mg) was added to the NMR tube, the resulting mixture being monitored by ^1H NMR at different time intervals until no variation in the cis/trans rate was observed.

4.3.1. 2,2,7,7-Tetraethyl-*trans*-perhydropyrano[2,3-*b*]pyran (5a). Colourless oil; t_R 13.16; R_f 0.67 (hexane/EtOAc 8:2); ν (film) 1086 cm^{-1} (CO); δ_H 0.85, 0.88 (12H, 2t, J=7.5, 4×CH_3), 1.20–1.70 (17H, m, 8×CH_2, C*H*CHO), 4.33 (1H, d, J=8.4, CHO); δ_C 6.8, 7.7 (4×CH_3), 23.2, 25.0, 31.8, 32.6 (8×CH_2), 40.6 (*C*HCHO), 78.3 (2×C), 93.8 (CHO); *m/z* 225 (M^+−29, 100%), 207 (31), 189 (61), 153 (15), 140 (21), 135 (84), 133 (51), 124 (10), 123 (18), 111 (19), 109 (19), 97 (14), 95 (33), 85 (11), 84 (12), 83 (20), 81 (11), 69 (32), 57 (31), 55 (34). HRMS calcd for $C_{16}H_{30}O_2$ 254.2246, found 254.2242.



NOESY

4.3.2. 2,2,7,7-Tetrapentyl-*trans*-perhydropyrano[2,3-*b*]pyran (5b). Colourless oil; t_R 17.53; R_f 0.670 (hexane/EtOAc 8:2); ν (film) 1070 cm^{-1} (CO); δ_H 0.80–0.95 (12H, m, 4×CH_3), 1.15–2.00 (41H, m, 20×CH_2, C*H*CHO), 4.39 (1H, d, J=8.4, CHO); δ_C 14.1 (4×CH_3), 22.2, 23.9, 24.3, 25.1, 31.4, 33.5, 34.4, 36.0, 40.2, 41.6 (20×CH_2), 43.3 (*C*HCHO), 78.2 (2×C), 94.0 (CHO); *m/z* 407 (M^+−15, <1%), 338 (21), 337 (100). HRMS calcd for $C_{28}H_{54}O_2$ 422.4124, found 422.4119.



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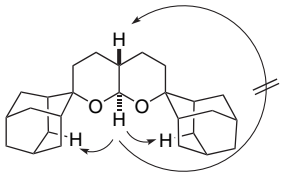
4.3.3. Dispiro[cyclopentane-1,2′-*trans*-tetrahydropyrano[2,3-*b*]pyran-7′,1″-cyclopentane] (5c). Colourless oil; t_R 14.28; R_f 0.60 (hexane/EtOAc 8:2); ν (film) 1075 cm^{-1} (CO); δ_H 1.20–2.10 (25H, m, 12×CH_2, C*H*CHO), 4.30 (1H, d, J=7.8, CHO); δ_C 22.5, 24.3, 30.0, 35.6, 38.2, 38.9 (12×CH_2), 39.5 (*C*HCHO), 80.1 (2×C), 92.7 (CHO); *m/z* 251 (M^++1, 10%), 250 (52), 169 (19), 151 (54), 150 (14), 147 (13), 139 (13), 138 (100), 137 (12), 136 (10), 135 (23), 134 (11), 133 (46), 132 (37), 123 (44), 122 (67), 121 (22), 120 (47), 119 (12), 109 (21), 108 (14), 107 (24), 105 (10), 97 (12), 96 (16), 95 (49), 94 (43), 93 (42), 91 (23), 85 (17), 83 (18), 82 (34), 81 (86), 80 (56), 79 (46), 77 (13), 69 (12), 68 (11), 67 (90), 57 (16), 55 (50), 54 (10), 53 (15). HRMS calcd for $C_{16}H_{26}O_2$ 250.1933, found 250.1929.

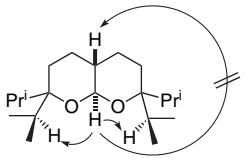
4.3.4. Dispiro[cyclohexane-1,2′-*trans*-tetrahydropyrano[2,3-*b*]pyran-7′,1″-cyclohexane] (5d). Colourless oil; t_R 15.76; R_f 0.65 (hexane/EtOAc 8:2); ν (film) 1070 cm^{-1} (CO); δ_H 1.20–2.00 (29H, m, 14×CH_2, C*H*CHO), 4.54 (1H, d, J=8.2, CHO); δ_C 21.6, 21.8, 24.9, 26.2, 30.7, 35.0, 40.1 (14×CH_2), 41.8 (*C*HCHO), 75.3 (2×C), 93.3 (CHO); *m/z* 278 (M^+, 60%), 183 (18), 166 (17), 165 (100), 152 (35), 149 (11), 147 (40), 146 (36), 137 (16), 136 (30), 134 (17), 122 (16), 121 (38), 109 (24), 108 (15), 107 (15), 96 (19), 95 (48), 94 (27), 93 (11), 91 (13), 83 (12), 81 (64), 79 (24), 69 (11), 67 (39), 55 (44). HRMS calcd for $C_{18}H_{30}O_2$ 278.2246, found 278.2252.

4.3.5. Dispiro[adamantane-2,2′-*trans*-tetrahydropyrano[2,3-*b*]pyran-7′,2″-adamantane] (5f). Colourless solid; R_f 0.71 (hexane/EtOAc 8:2); mp 165 °C (dec); ν (KBr) 1090 cm^{-1} (CO); δ_H 1.20–1.95, 2.00–2.35, 2.40–2.50 (37H, 3m, 9×C*H*CH_2, 14×CH_2), 4.55 (1H, d, J=7.8, CHO); δ_C 24.6, 27.5, 31.6, 31.9, 32.7, 33.8, 34.4, 38.3, 39.8 (14×CH_2), 27.8, 29.5 (4×*C*HCH_2*C*H), 41.5 (*C*HCHO), 79.0 (2×C), 91.5 (CHO); *m/z* 382 (M^+, <1%), 204 (50), 189 (17), 188 (24), 149 (23), 148 (100), 79 (10). Anal. calcd for $C_{26}H_{38}O_2$ C, 81.62; H, 10.01, found C, 81.69; H, 9.99.



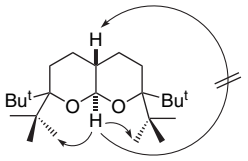
NOESY

4.3.6. 2,2,7,7-Tetraisopropyl-*trans*-perhydropyrano[2,3-*b*]pyran (5i). Colourless oil; t_R 15.16; R_f 0.68 (hexane/EtOAc 8:2); ν (film) 1367, 1384, 1074 cm^{-1} (CO); δ_H 0.85–1.05 (24H, m, 8×CH_3), 1.20–1.75 (9H, m, 4×CH_2, C*H*CHO), 2.00–2.10, 2.30–2.40 (4H, 2m, 4×C*H*CH_3), 4.58 (1H, d, J=8.6, CHO); δ_C 16.9, 18.3, 18.6, 19.0 (8×CH_3), 24.7, 25.0 (4×CH_2), 30.2, 32.9 (4×*C*HCH_3), 40.6 (*C*HCHO), 81.8 (2×C), 94.5 (CHO); *m/z* 310 (M^+, <1%), 268 (19), 267 (100), 249 (47), 231 (20), 181 (10), 179 (13), 165 (10), 163 (58), 161 (13), 137 (12), 125 (15), 123 (11), 121 (14), 111 (14), 109 (16), 107 (24), 99 (12), 97 (13), 95 (20), 93 (13), 83 (17), 81 (12), 71 (37), 69 (41), 67 (10), 57 (14), 55 (22). HRMS calcd for $C_{20}H_{38}O_2$ 310.2872, ($M^+-C_3H_7$) 267.2319, found 267.2296.



NOESY

4.3.7. 2,2,7,7-Tetra-*tert*-butyl-*trans*-perhydropyrano[2,3-*b*]pyran (5j). Colourless oil; t_R 16.75; R_f 0.74 (hexane/EtOAc 9:1); ν (film) 1041 cm^{-1} (CO); δ_H 1.06, 1.11 (36H, 2s, 12×CH_3), 1.20–1.85 (9H, m, 4×CH_2, C*H*CHO), 5.04 (1H, d, J=8.7, CHO); δ_C 25.5, 28.1 (4×CH_2), 30.6 (12×CH_3), 35.2 (*C*HCHO), 43.2, 43.6 (4×*C*CH_3), 83.8 (2×CO), 98.1 (CHO); *m/z* 366 (M^+, 2%), 309 (19), 291 (17), 235 (20), 153 (20), 151 (33), 135 (19), 123 (12), 109 (25), 107 (14), 97 (11), 95 (14), 83 (31), 57 (100), 55 (14). HRMS calcd for $C_{24}H_{46}O_2$ 366.3498, found 366.3501.



NOESY

4.4. X-ray crystallography

Compounds **4f** and **5f** were recrystallised from hexane. Data collection was performed on a Bruker Smart CCD diffractometer, based on three ω-scan runs (starting ω=−34°) at the values of ϕ=0, 120, 240° with the detector at 2θ=−32°. For each of these runs, 606 frames were collected at 0.3° intervals. An additional run at ϕ=0° of 100 frames was collected to improve redundancy. The diffraction frames were integrated using the SAINT[23] programme and the integrated intensities were corrected for Lorentz-polarisation effects with SADABS.[24]

X-ray data for **4f**: $C_{26}H_{38}O_2$, M=382.56; monoclinic, a=13.490(4) Å, b=11.681(3) Å, c=27.054(7) Å, β=102.798(5)°; V=4157.2(19) Å^3; space group $P21/c$; Z=8; D_c=1.222 Mg/m^{-3}; λ=0.71073 Å; μ=0.075 mm^{-1}; $F(000)$=1680; T=22±1 °C. The structure was solved by direct methods[25] and refined to all 6531 unique F_o^2 by full matrix least squares (SHELX97).[26] All the hydrogen atoms were placed at idealised positions and refined as rigid atoms. Final $wR2$=0.1806 for all data and 506 parameters; R_1=0.1045 for 2197 $F_o>4\sigma(F_o)$.

X-ray data for **5f**: $C_{26}H_{38}O_2$, M=382.56; monoclinic, a=13.1663(16) Å, b=6.6471(8) Å, c=23.712(3) Å, β=101.292(3)°; V=2035.1(4) Å^3; space group $P21/c$; Z=4; D_c=1.249 Mg/m^{-3}; λ=0.71073 Å; μ=0.076 mm^{-1}; $F(000)$=840; T=−100±1 °C. The structure was solved by direct methods[25] and refined to all 3590 unique F_o^2 by full matrix least squares (SHELX97).[26] All the hydrogen atoms were placed at idealised positions and refined as rigid atoms. Final $wR2$=0.1448 for all data and 253 parameters; R_1=0.1349 for 2010 $F_o>4\sigma(F_o)$.

Crystallographic data (excluding structure factors) for compounds **4f** and **5f** have been deposited in the Cambridge

Crystallographic Data Center as supplementary publication numbers CCDC 291410 and 294666. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; email: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk/data_request/cif).

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