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A direct synthesis of 1,7-dioxaspiro[4.5]decanes from the new 3-methylidenepentane-1,5-dianion synthon

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Dedicated to Professor Víctor Riera on occasion of his 70th birthday

Abstract—4-Phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**2**) has proved to be an appropriate and new 3-methylidenepentane-1,5-dianion synthon. The reaction of **2** 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 undergo double intramolecular iodoetherification promoted by a silver salt, to furnish the corresponding 1,7-dioxaspiro[4.5]decanes (**4**) in very high yields. The oxidation of compounds **4** to the corresponding lactones is also studied.

1. Introduction

A variety of different methylidene dianion synthons have been developed during the last decade in order to study their reactivity and possible applications. Most of the attention has been devoted to the trimethylenemethane dianion synthons (**I**) since they are readily accessible and can react with one or two electrophiles, allowing the incorporation of two equal or different moieties, respectively.[1] The versatility of the resulting structures resides on the presence of a methylidenic unit, which can be subjected to further transformations. Less attention has been paid, however, to trimethylenemethane dianion homologue synthons such as 2-methylidenebutane-1,4- (**II**)[2] or 3-methylidenepentane-1,5-dianion (**III**) synthons (Chart 1).

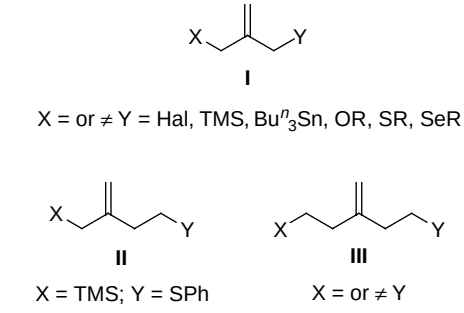

Chart 1.

On the other hand, spirocyclic ethers are widespread in Nature and have attracted much attention from the synthetic point of view. Especially abundant are the 1,5-dioxaspiro[2.4]heptane[3] and 1,7-dioxaspiro[4.4]nonane[4] skeletons, which can be found in many natural products with interesting biological activities. Within the 1,*n*-dioxaspiro[4.5]decane series, those in the ketal form like 1,4-dioxa- (Chart 2, $n=4$) and 1,6-dioxaspiro[4.5]decanes (Chart 2, $n=6$) are well known and easy to prepare, whereas compounds containing the 1,8-dioxaspiro[4.5]decane unit[5] (Chart 2, $n=8$) are less frequent but have also been deeply studied in the last decade.

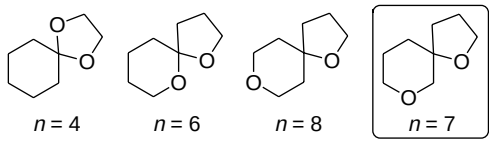

Chart 2. 1,*n*-Dioxaspiro[4.5]decanes.

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In contrast, the 1,7-dioxaspiro[4.5]decane moiety (Chart 2, $n=7$) is very uncommon in Nature and has been little studied at a methodological and synthetic level. Thus, it can be found, in its lactone form, in the structure of camelliatannin G (**IV**, isolated from the leaves of *Camellia japonica* and belonging to a family of complex tannins that show *anti*-HIV activity)[6] or in stemotinine (**V**) and isostemotinine (isolated from the roots of *Stemona tuberose* Lour., which are used in Chinese medicine as insecticides and anticough agents).[7] The mentioned unit is also present in the widely studied reduction products of both artemisinin and its derivatives (i.e., **VI**)[8] as well as in a variety of compounds with use as plant growth regulators and herbicides (i.e., **VII**).[9]

Most of the synthetic chemistry directed to the preparation of the title compounds involves specific carbohydrate scaffolds in which different type of substituents on a preformed tetrahydropyran[10] or tetrahydrofuran[11] ring are subjected to intramolecular cyclisation. For instance, the spirocyclic compound **VIII** was prepared by intramolecular six-membered lactol formation,[11] whereas **IX** was obtained by ring-closing metathesis of a 3-allyloxy-3-vinyl tetrahydropyran moiety.[12] To the best of our knowledge there is only one methodology that starts from a completely acyclic precursor and gives the desired spirocyclic unit (but unsaturated) in one step. This strategy gives rise to spirocyclic dihydropyrans like **X** by double ring-closing metathesis of a proper dioxatetraene precursor.[13] A more indirect route, also from an acyclic precursor, utilised the ring-closing metathesis and hydroformylation reactions as the key steps.[14] 1,7-Dioxaspiro[4.5]decane lactones have received even less attention and have been always synthesized as 1,7-dioxaspiro[4.5]decan-2-ones [see the spirocyclic unit highlighted in stemotinine (**V**), Chart 3].[15] However, no report refers to the synthesis of 1,7-dioxaspiro[4.5]decan-6-ones [see the spirocyclic unit highlighted in camelliatannin G (**IV**), Chart 3].

In recent years, we have shown an increasing interest in developing new and versatile methylidenic dianion synthons. As a result of different studies, we found out that 2-chloromethyl-3-chloroprop-1-ene (**XI**) and 2-chloromethyl-3-(2-methoxyethoxy)prop-1-ene (**XII**) allowed the incorporation of two equal or different electrophilic fragments, respectively, through a one-pot arene-catalysed lithiation (Chart 4).[16] These two dianion synthons were successfully applied to the synthesis of fused bicyclic[17] and spirocyclic[18] polyether structures. In a more recent study, we have preliminary introduced 4-phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**2**), as a new 3-methylidenepentane-1,5-dianion synthon that has found application in the straight synthesis of 1,7-dioxaspiro[4.5]decanes and perhydropyrano[2,3-*b*]pyrans.[19]

We want to report herein about the scope and limitations of 4-phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**2**) as a dianion synthon by studying its reactivity against a large variety of carbonyl compounds, including chiral ketones and aldehydes. The resulting diols can be cyclised to the corresponding 1,7-dioxaspiro[4.5]decanes under the promotion of a silver salt. An improved method to oxidise 1,7-dioxaspiro[4.5]decanes to the corresponding lactones is also described.

2. Results and discussion

We tried first to prepare 4-phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**2**) by nucleophilic

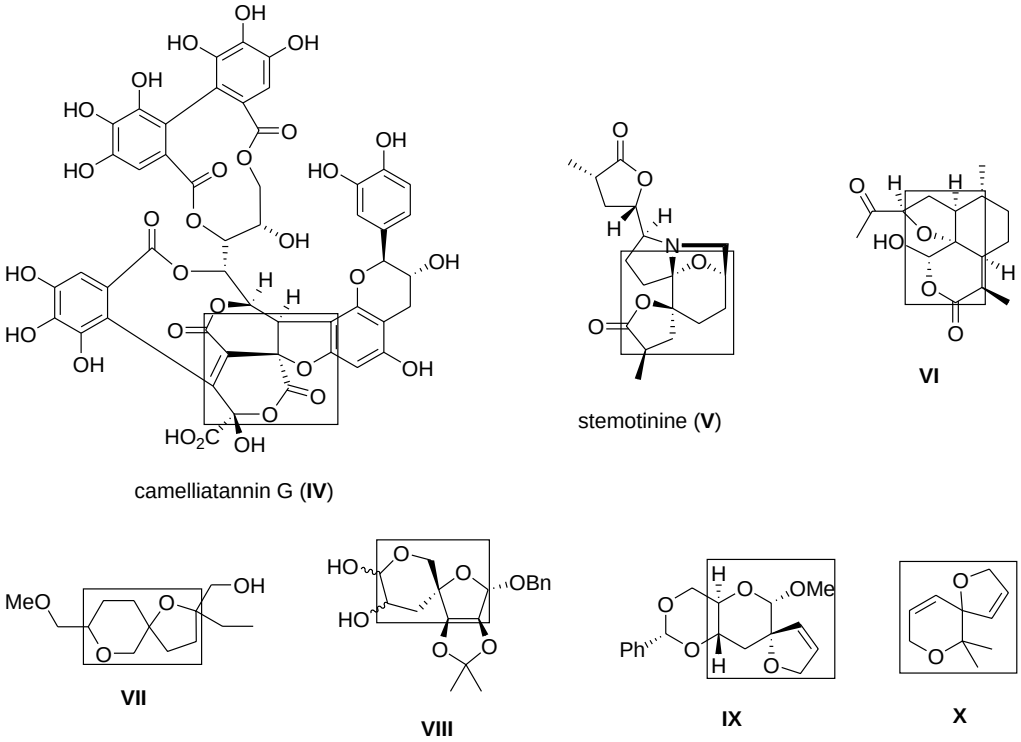


Chart 3.

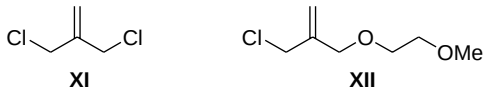


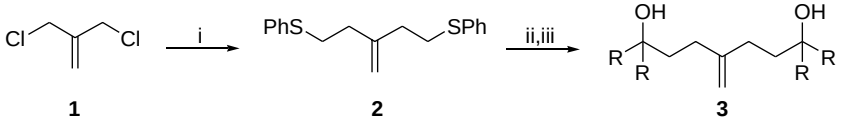
Chart 4.

substitution from commercially available 2-chloromethyl-3-chloroprop-1-ene (**1**) and phenylthiomethyllithium, following Corey's method.[20] This reaction, however, failed and instead, a variant had to be introduced involving the organocuprate reagent derived from $PhSCH_2Li$ and CuCN, affording **2** in 82% yield (Scheme 1). Treatment of compound **2** with an excess of lithium powder (1:7 molar ratio) and a catalytic amount of DTBB (4,4′-di-*tert*-butylbiphenyl, 1:0.1 molar ratio, 2.5 mol%), in the presence of different carbonyl compounds (Barbier conditions)[21] in THF, at 0 °C for 2 h, led, after hydrolysis with water, to the corresponding methylidenic diols **3** (Scheme 1 and Table 1). A wide variety of ketones were studied as electrophiles including linear (Table 1, entries 1 and 2), branched (Table 1, entries 3 and 4), cycloalkyl substituted (Table 1, entry 5), cyclic (Table 1, entries 6 and 7), heterocyclic (Table 1, entries 8 and 9) and polycyclic (Table 1, entry 10) ketones, the corresponding methylidenic diols **3** being obtained in modest yields after column chromatography. More interesting was the use of the chiral ketones (−)-menthone (Table 1, entry 11), (±)-norcamphor (Table 1, entry 12), and (−)-fenchone (Table 1, entry 13) as electrophiles. The reaction of the intermediate organolithium species with these electrophiles led to the corresponding C_2-symmetric diols as single diastereoisomers. The nucleophilic attack to the carbonyl group was equatorial for (−)-menthone and *exo* for (±)-norcamphor and (−)-fenchone, diols **3k** and **3m** being obtained as single enantiomers. A crystallographic study of compounds **3l** and **3m** is included in Section 3. In contrast to the reactivity exhibited by ketones, aldehydes were somewhat more reluctant to react under the above described conditions. Nonetheless, an example using pivalaldehyde is included, which gave a ca. 1:1 mixture of diastereoisomers.

With the methylidenic diols **3** in hand, we tried to cyclise them under our previously published iodoetherification conditions.[18] However, the reaction with the system I_2, Ag_2O, dioxane/H_2O 7:1, rt, gave mainly the intermediate iodohydrin, whereas the starting diol remained practically unaltered with the system NaH, THF, I_2, 0 °C to rt. New reaction conditions were developed and optimised by varying the base (Na_2CO_3, Et_3N) and the silver source (AgOTf, AgOAc), the best results being achieved using I_2, AgOTf, and Na_2CO_3 in THF at rt. Under those reaction conditions, some of the diols **3** readily underwent double intramolecular cyclisation to the corresponding 1,7-dioxaspiro[4.5]decanes **4** in excellent isolated yields without any further purification (Scheme 2 and Table 2). It is worthy of note that those diols containing electrophilic fragments derived from cyclic ketones rendered structurally interesting trispiro compounds in a very straight manner (Table 2, entries 5–9). Among them, compound **4h** (Table 2, entry 7) is of a particular interest due to its trispirocyclic polyether skeleton. Compound **4m** (Table 2, entry 9) was obtained as a 1.73:1 mixture of diastereoisomers, the chiral nature of the precursor diol exhibiting, therefore, a low asymmetric induction toward the generation of the new stereocentre in the spirocyclic core. The presence of the 1,7-dioxaspiro[4.5]decane moiety in compounds **4** was determined by spectroscopic means, and unequivocally established by X-ray crystallography of compound **4j** (Table 2, entry 8) (see Section 3).

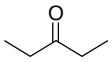
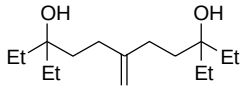
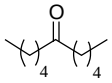
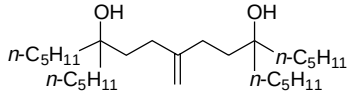
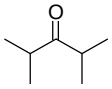
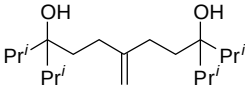
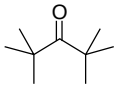
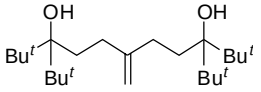
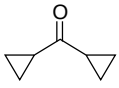
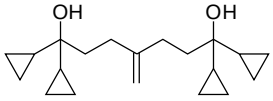
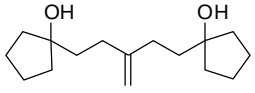
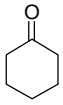
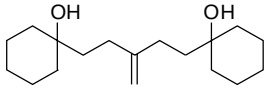
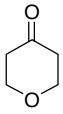
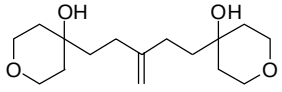
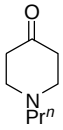
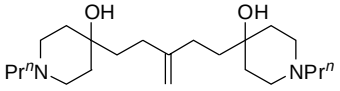
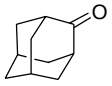
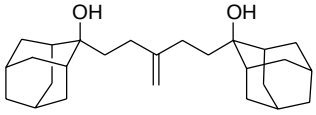
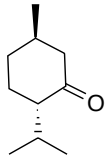
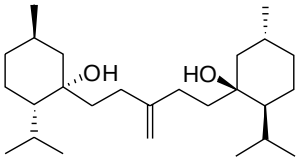
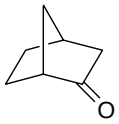
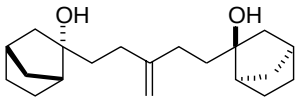
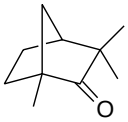
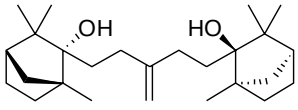
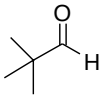
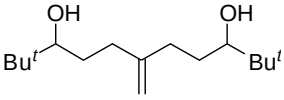
It is noteworthy that, in contrast to the homologous 1,5-dioxaspiro[2.4]heptanes,[18b] 1,6-dioxaspiro[3.4]octanes,[18a] or 1,7-dioxaspiro[4.4]nonanes,[18c,d] which exhibited in ^1H NMR a standard AB system for the CH_2O group in the tetrahydrofuran ring, in the present case the situation is quite different. In fact, all the 1,7-dioxaspiro[4.5]decanes prepared showed one of the CH_2O protons split (as a dd), inside an AB system (see Section 5.4). This particular behaviour was attributed to a long-range 4σ-bond coupling involving the equatorial protons attached to the carbon atoms 6 and 10 (Figs. 1 and 2). The different $^4J_{eq-eq}$ values observed lie in the 0–2 Hz range expected for that spin–spin coupling in cyclohexanes,[22] what additionally confirms the presence of a tetrahydro-2*H*-pyran ring.

We devised the possibility to transform diols **3** into the corresponding 1,7-dioxaspiro[4.5]decan-6-ones by oxidation adjacent to the tetrahydropyran oxygen atom. Compound **4b** was used as a model substrate and subjected to the ruthenium-catalysed oxidation under the conditions described in the literature[23] and applied by us to other homologue spirocyclic ethers.[18b–d] This compound, however, showed to be reluctant to oxidation when treated with a catalytic amount of RuO_2 (0.15 equiv) and an excess of $NaIO_4$ (4.88 equiv), in CCl_4–H_2O (1/1) at rt (Scheme 3). Thus, only 29% conversion was obtained after the standard reaction time of 24 h (Table 3, entry 1). A moderate conversion of 61% was reached after 1 week, whereas the more desired 95% conversion was only achieved after a prohibitive reaction time of 36 days (Fig. 3). We made an effort in order to improve the above mentioned results by varying the different parameters involved in this transformation, namely: the ruthenium catalyst, the stoichiometric oxidising agent, the solvent, presence or absence of a phase-transfer agent, as well as the reaction conditions. As it is shown in Table 3, very poor results were obtained in most cases, independently of the parameters and reaction conditions used. Even the methodology developed by Balavoine et al. for the oxidation of cyclic ethers, involving the use of hydrated $RuCl_3$, failed (Table 3, entry 10).[24] We observed, however, that, in general, these low conversions were reached irrespective of the reaction time. From this

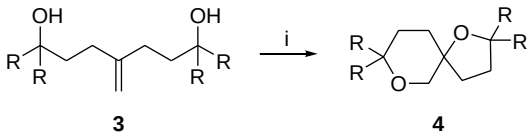


Scheme 1. Reagents and conditions: (i) $PhSCH_2Li$, CuCN, LiCl, 0 °C, 2 h; (ii) Li, DTBB (2.5 mol%), R_2CO, THF, 0 °C, 2 h; (iii) H_2O.

Table 1. Preparation of the methylidenic diols **3**

Entry	Electrophile	Product **3**[a]		
		No.	Structure	Yield (%)[b]
1		**3a**		55
2		**3b**		50
3		**3c**		52
4		**3d**		54
5		**3e**		41
6		**3f**		57
7		**3g**		58
8		**3h**		37[c]
9		**3i**		35[c]
10		**3j**		33[d]
11		**3k**		48[e]
12		**3l**		47[f]
13		**3m**		49[e]
14		**3n**		42[g]

[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] Purification by column chromatography was carried out with EtOAc/MeOH as eluant.
[d] Isolated yield after recrystallisation with hexane.
[e] As a single enantiomer.
[f] As a single diastereoisomer.
[g] As a ca. 1:1 mixture of diastereoisomers.



Scheme 2. I_2, AgOTf, Na_2CO_3, THF, rt, 5–12 h.

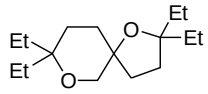
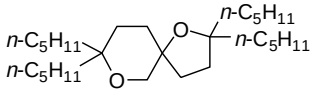
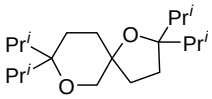
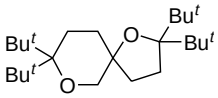
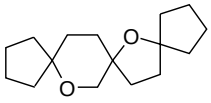
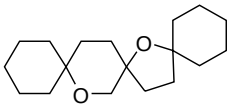
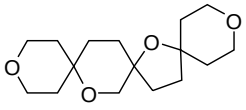
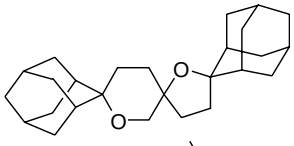
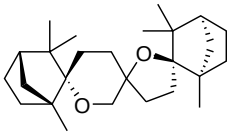
3. X-ray crystallographic study

The structure of compounds **3l**, **3m**, and **4j** was unequivocally established by X-ray crystallography.

3.1. Compound 3l [(±)-norcamphor derivative]

Figure 4 shows a single molecule of the diol **3l** in which it can be seen how the dianion attack to the carbonyl group of

Table 2. Preparation of the 1,7-dioxaspiro[4,5]decanes **4**

Entry	Reaction time (h)	Product 4[a]		
		No.	Structure	Yield (%)[b]
1	12	**4a**		95
2	12	**4b**		96
3	12	**4c**		94
4	5	**4d**		94
5	12	**4f**		95
6	12	**4g**		99
7	12	**4h**		94
8	6	**4j**		98
9	6	**4m**		90[c]

[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 of pure **4** from the reaction crude, unless otherwise stated, based on the starting diol **3**.
[c] Isolated yield after column chromatography (silica gel, hexane/EtOAc), based on the starting compound **3**. Compound obtained as a 1.73:1 mixture of diastereoisomers.

observation it might be inferred that the reaction proceeds fast at the beginning but at some stage the catalyst gets completely deactivated and interrupts the catalytic cycle. This fact led us to try the addition of the catalyst and the stoichiometric oxidising agent in several portions, this method providing the best conversion within a reasonable reaction time (Table 3, entry 13). By using this procedure, several representative 1,7-dioxaspiro[4.5]decanes were transformed into the corresponding lactones, 1,7-dioxaspiro[4.5]decan-6-ones, in fair yields (Chart 5).

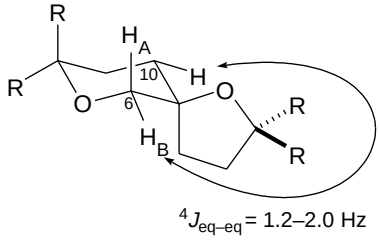


Figure 1. Long-range 4σ-bond diequatorial coupling in the tetrahydro-2*H*-pyran ring of the 1,7-dioxaspiro[4.5]decanes **4**.

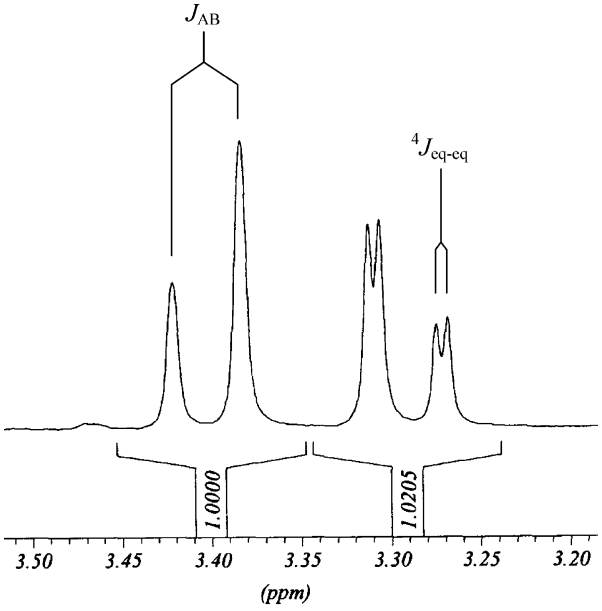
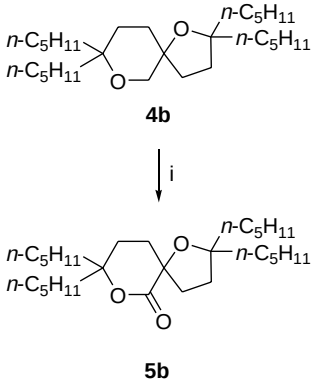


Figure 2. Typical ^{1}H NMR region for the CH_2O group of the 1,7-dioxaspiro[4.5]decanes **4**.



Scheme 3. (i) RuO_2 (cat.), $NaIO_4$, CCl_4, H_2O, rt.

(±)-norcamphor took place following an *exo* direction, giving rise to the corresponding *endo* diol. Interestingly, intermolecular hydrogen bonding was observed involving the four hydroxyl groups of two diol molecules (Fig. 5). A cross-shape orientation of the two diol molecules minimised steric hindrance facilitating the intermolecular hydrogen bonding through a near-square arrangement of the four hydroxyl groups. In addition, one of the diol molecules in the asymmetric part of the unit cell exhibits a static disorder for one of the norbornyl moieties, in such a way that 50% of the molecules at that position have a symmetry binary axis, whereas for the other 50% of the molecules this kind of axis is absent (Fig. 5).

3.2. Compound 3m [(−)-fenchone derivative]

The structure of enantiomerically pure **3m** could be also confirmed by X-ray crystallographic analysis. In this case, as in the case of compound **3l**, an *exo* dianion attack to the carbonyl group of (−)-fenchone was also preferred (Fig. 6). A 50% disorder is observed affecting the hydroxyl group hydrogen (Fig. 6). At one of the positions, a hydrogen bond is formed involving the hydroxyl group of a neighbour molecule. At the other position, however, has no acceptor within the bonding distance (Fig. 6). In the crystal, the hydroxyl group hydrogen atoms are 50% located at the positions showed in bold bond, whereas the other 50% are located as shown in hashed bond (Figs. 7 and 8). In contrast with the hydrogen bonding observed for diol **3l**, in this case each hydroxyl group is hydrogen-bonded to a different diol molecule, thus leading to a wavy three-dimensional scaffold (Fig. 8).

3.3. Compound 4j

X-ray crystallographic analysis of compound **4j** unequivocally confirmed the presence of the 1,7-dioxaspiro[4.5]-decane moiety in compounds **4** (Fig. 9). The crystal is a non-merohedric twin, which can be solved after calculating the twin law matrix using the ROTAX programme.[25]

Table 3. Oxidation of compound **4b**

Entry	Catalyst	Re-oxidant	Solvent	Additive	Physical activation	Time (h)	Conversion (%)[a]
1	RuO_2	$NaIO_4$	CCl_4–H_2O	—	—	24	29
2	RuO_2	$NaIO_4$	CCl_4–H_2O	—	Thermal (50 °C)	24	25
3	RuO_2	$NaIO_4$	CCl_4–H_2O	—	Thermal (reflux)	48	39
4	RuO_2	$NaIO_4$	CCl_4–H_2O–MeCN	—	—	24	7
5	RuO_2	$NaIO_4$	CCl_4–H_2O–MeCN	—	MW (3–10 bar, 65–80 °C)	0.17	15
6	RuO_2	$NaIO_4$	CCl_4–H_2O–MeCN	—	MW (3–10 bar, 65–80 °C) followed by ultrasounds	0.17+1	15
7	RuO_2	aq NaClO	CCl_4–H_2O	—	—	24	13
8	RuO_2	aq NaClO	CCl_4–H_2O	TBAB[b]	—	24	14
9	RuO_2	aq NaClO	CCl_4–H_2O	TBAB	MW (10 bar, 80 °C)	0.17	12
10	$RuCl_3 \cdot xH_2O$	aq NaClO	CH_2Cl_2	CTAB[c]		24	31
11	$RuCl_3 \cdot xH_2O$	$NaIO_4$	CH_2Cl_2	CTAB	Thermal or MW	24	30
12	$RuCl_3 \cdot xH_2O$	$NaIO_4$	CCl_4–H_2O	CTAB	—	24	48
13	$RuCl_3 \cdot xH_2O$[d]	$NaIO_4$	CCl_4–H_2O	CTAB	Thermal (reflux)	5	61

[a] Determined by GLC.
[b] TBAB, tetra-*n*-butylammonium bromide.
[c] CTAB, cetyltriethylammonium bromide.
[d] Added together with $NaIO_4$ as a water solution in five portions at intervals of 1 h.

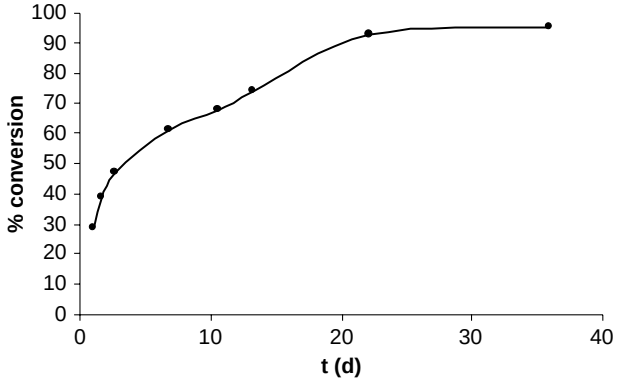
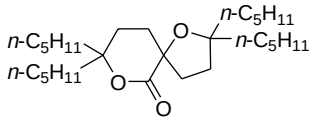
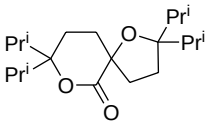


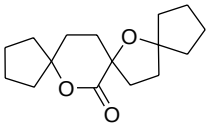
Figure 3. Graphic showing the oxidation of compound **4b** to **5b** versus time, under the conditions depicted in Scheme 3.



5b (61%)



5c (51%)



5f (52%)

Chart 5. Oxidation of compounds **4b**,**c**,**f** under the conditions shown in Table 3, entry 13.

4. Conclusion

In conclusion, we have developed a new 3-methylidene-pentane-1,5-dianion synthon, which has demonstrated to be very useful for the preparation of symmetrically substituted methylidenic 1,7-diols. These diols can be transformed into the corresponding 1,7-dioxaspiro[4.5]decanes in excellent yields and in a straightforward manner under the promotion of a silver salt. In addition, an improved method allows the oxidation of the mentioned spirocyclic ethers to the corresponding lactones.

5. Experimental

5.1. General

Melting points were obtained with a Reichert Thermovar apparatus. Optical rotations were measured with a Perkin-Elmer 341 polarimeter with a thermally jacketted 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^{-1}. 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 internal standard; chemical shifts are given in δ (ppm) and coupling constants (*J*) in Hz. 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 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 diametre, 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.).

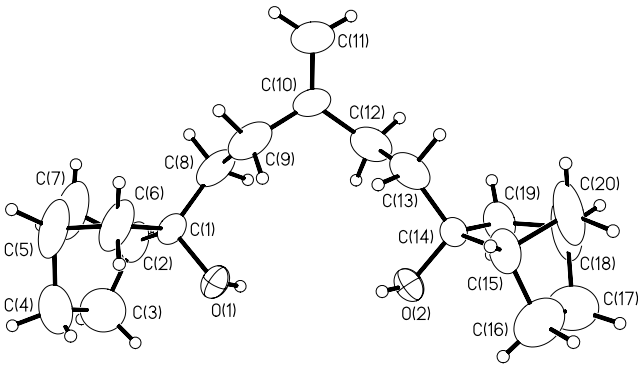


Figure 4. Plot showing the X-ray structure and atomic numbering for one non-disordered molecule of the diol **3l**.

5.2. Procedure for the preparation of 4-phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (2)

n-BuLi (14.00 mL, 22 mmol) was added to a solution of thioanisole (2.34 mL, 20 mmol) in dry THF (50 mL), the resulting solution being stirred for 15 min at rt. Then, a light-blue solution of LiCl (1.86 g, 44 mmol) and CuCN (2.00 g, 22 mmol) in dry THF (50 mL) was added at 0 °C. Once the deep-brown organocopper reagent was generated (ca. 15 min), 2-chloromethyl-3-chloroprop-1-ene (**1**) (1.17 mL, 10 mmol) was added at 0 °C. The mixture was stirred for 2 h and hydrolised with water (10 mL), followed by the addition of aq 25% ammonia (10 mL) and extraction with hexane (3×30 mL). It is recommended to wash the organic phase with more aq ammonia solution in the case of some remaining emulsion. The organic phases were dried over anhydrous $MgSO_4$, the solvents were evaporated under reduced pressure (15 Torr), and the residue was purified by column chromatography (silica gel, hexane/EtOAc), furnishing 2.42 g (82% yield) of compound **2**.

5.2.1. 4-Phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (2). Orange oil; t_r 19.00; R_f 0.35 (hexane); ν (film) 3073, 3057, 1644, 896, 737, 690 (C=CH), 1941, 1868, 1791 cm^{-1} (comb.); δ_H 2.36 (4H, t, $J=6.9$ Hz, 2×CH_2CH_2S), 3.00 (4H, t, $J=6.9$ Hz, 2×CH_2S), 4.88 (2H,

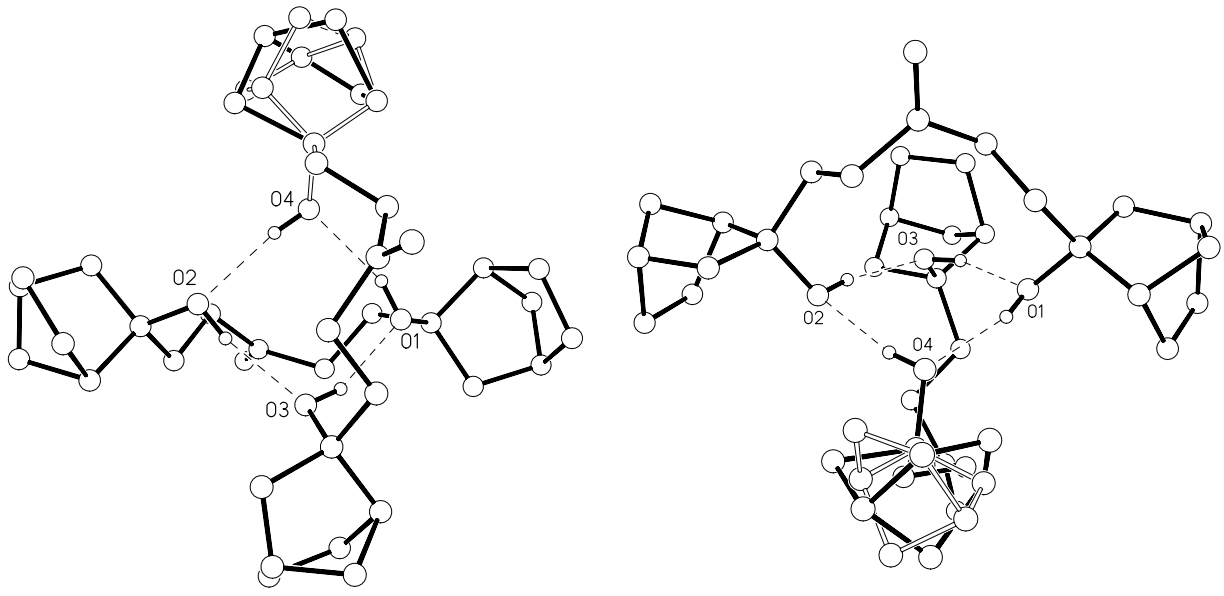


Figure 5. Two views of the hydrogen-bonding pattern between the hydroxyl groups of two molecules of the diol **3l** in the asymmetric part of the unit cell. The atoms are shown as spheres and the hydrogen atoms (except those involved in the hydrogen bonds) are omitted for clarity. Disorder components of the norbornyl moiety are shown with a different type of bond.

s, H_2C═C), 7.20–7.40 (10H, m, 10×ArH); δ_C 31.9 (2×CH_2S), 35.4 (2×CH_2CH_2S), 112.0 (H_2C═C), 126.0, 128.9, 129.2 (10×ArCH), 136.3 (2×ArC), 145.7 (C═CH_2); *m*/*z* 300 (M^+, 8%), 191 (34), 190 (46), 177 (10), 123 (100), 109 (10), 77 (10). HRMS calcd for $C_{18}H_{20}S_2$ 300.1006, found 300.0995.

5.3. General procedure for the preparation of diols 3

A solution of 4-phenylsulfanyl-2-(2-phenylsulfanylethyl)-but-1-ene (**2**) (300 mg, 1 mmol) and the corresponding carbonyl compound (2 mmol) in THF (4 mL) was added to a green suspension of lithium powder (50 mg, 7 mmol) and DTBB (27 mg, 0.1 mmol) in THF (3 mL) at 0 °C. After stirring for 2 h at 0 °C, the resulting mixture was hydrolysed with water (5 mL), extracted with EtOAc (3×10 mL), and the organic phases dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure (15 Torr) and the reaction crude purified by column chromatography [silica gel, hexane/EtOAc (compounds **3a**–**g**,**k**–**n**), EtOAc/MeOH (compounds **3h**,**i**)] or recrystallisation with hexane (compound **3j**).

5.3.1. 3,9-Diethyl-6-methyleneundecane-3,9-diol (3a). Colourless oil; t_r 14.08; R_f 0.38 (hexane/EtOAc 8:2); ν (film) 3384 (OH), 1644 cm^{-1} (C═CH); δ_H 0.87 (12H, t, J=7.5 Hz, 4×CH_3), 1.48 (8H, q, J=7.5 Hz, 4×CH_2CH_3), 1.52–1.65 (6H, m, 2×OH, 2×CH_2CH_2C═CH_2), 2.00–2.10 (4H, m, 2×CH_2C═CH_2), 4.75 (2H, s, H_2C═C); δ_C 7.8 (4×CH_3), 30.0, 30.9, 36.4 (4×CH_2CH_3, 2×CH_2CH_2), 74.6 (2×CO), 108.6 (H_2C═C), 150.7 (C═CH_2); *m*/*z* 238 (M^+-18, <1%), 209 (41), 191 (55), 149 (16), 141 (21), 138 (10), 137 (100), 136 (32), 135 (16), 125 (13), 124 (10), 123 (84), 121 (25), 109 (21), 107 (32), 96 (10), 95 (40), 93 (11), 87 (78), 85 (13), 83 (23), 81 (36), 69 (25), 67 (14), 57 (76), 55 (33). HRMS calcd for $C_{16}H_{32}O_2$ 256.2402, ($M^+-C_2H_5$) 227.2006, found 227.2007.

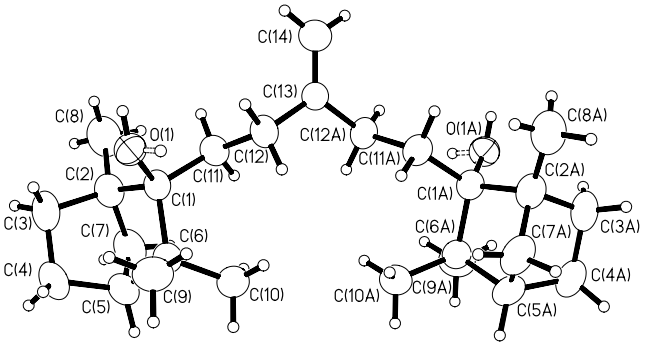


Figure 6. Plot showing the X-ray structure and atomic numbering for diol **3m**.

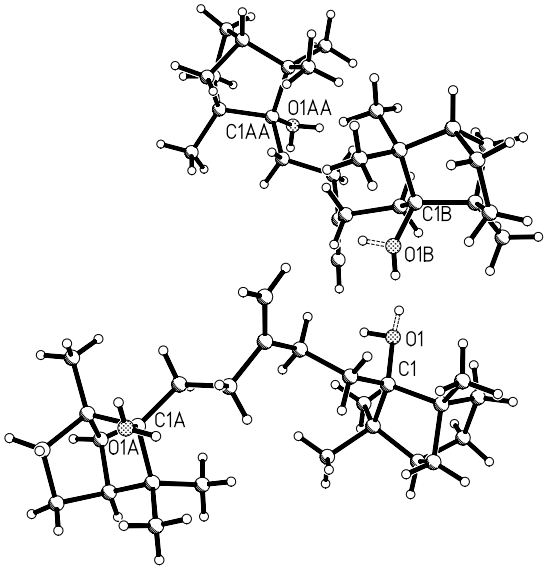


Figure 7. Plot showing the 50% disorder (hashed bonds) observed for the hydroxyl group hydrogen atoms in diol **3m**.

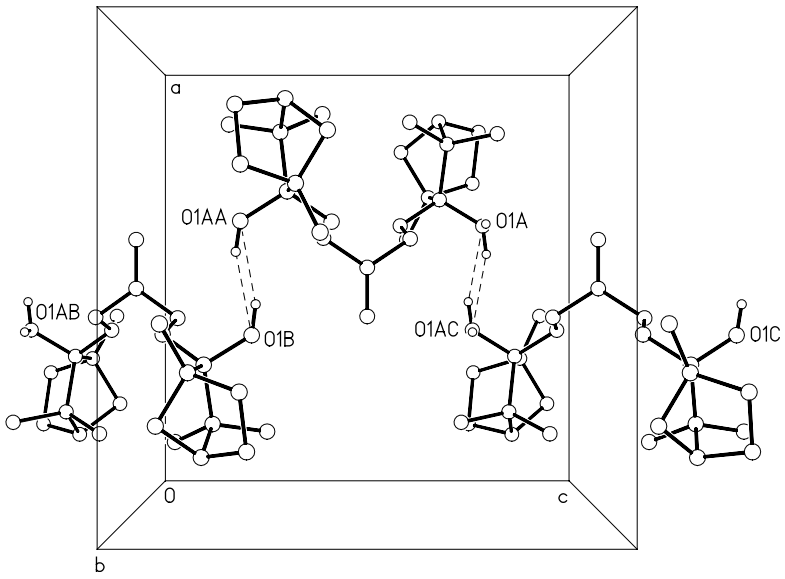


Figure 8. Unit cell plot showing the intermolecular hydrogen bonding between molecules of diol **3m** in the crystal. The hydrogen atoms, except the hydroxyl group hydrogen atoms, have been omitted for clarity.

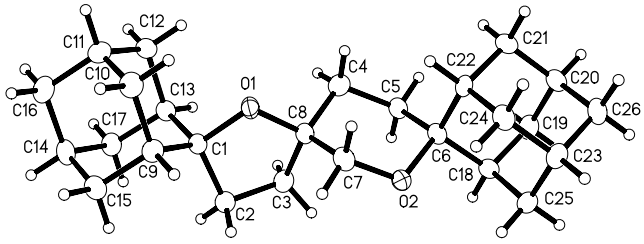


Figure 9. Plot showing the X-ray structure and atomic numbering for compound **4j**.

5.3.2. 9-Methylene-6,12-dipentylheptadecane-6,12-diol (3b). Colourless solid; t_r 23.75; R_f 0.45 (hexane/EtOAc 8:2); mp 65 °C; ν (KBr) 3426 (OH), 1022 cm^{-1} (CO); δ_H 0.89 (12H, t, $J=7.0$ Hz, 4×CH_3), 1.25–1.60 [38H, m, 4×$(CH_2)_4$, 2×C$H_2$$CH_2$C=$CH_2$, 2×OH], 2.00–2.10 (4H, m, 2×CH_2C=CH_2), 4.74 (2H, s, H_2C=C); δ_C 14.1 (4×CH_3), 22.6, 23.2, 30.0, 32.4, 37.4, 39.1 [4×$(CH_2)_4$, 2×CH_2CH_2], 74.4 (2×CO), 108.6 (H_2C=C), 150.7 (C=CH_2); *m/z* 388 (M^+-36, 10%), 336 (26), 335 (100), 331 (11), 318 (18), 317 (69), 236 (11), 225 (27), 222 (11), 221 (59), 220 (29), 207 (19), 179 (20), 172 (11), 171 (90), 167 (15), 165 (33), 163 (19), 151 (16), 149 (16), 137 (13), 127 (11), 123 (14), 111 (18), 110 (19), 109 (22), 99 (49), 97 (29), 95 (34), 93 (14), 83 (33), 81 (30), 71 (43), 69 (41), 67 (15), 57 (23), 55 (51). Anal. Calcd for $C_{28}H_{56}O_2$: C, 79.18; H, 13.29, found C, 79.29; H, 13.81.

5.3.3. 3,9-Diisopropyl-2,10-dimethyl-6-methyleneundecane-3,9-diol (3c). Colourless oil; t_r 16.09; R_f 0.52 (hexane/EtOAc 8:2); ν (film) 3463 (OH), 1645 (C=CH), 1380, 1365, 1020 cm^{-1}(CO); δ_H 0.90–1.00 (24H, m, 8×CH_3), 1.60–1.70, 1.85–1.95 (10H, 2m, 4×CH, 2×CH_2COH, 2×OH), 2.00–2.10 (4H, m, 2×CH_2C=CH_2), 4.74 (2H, s, H_2C=C); δ_C 17.3, 17.6 (8×CH_3), 30.7, 32.3 (2×CH_2CH_2), 34.0 (4×CH), 77.2 (2×CO), 108.4 (H_2C=C), 151.1 (C=CH_2); *m/z* 312 (M^+, <1%), 251 (46), 233 (33), 191 (10), 177 (22), 165 (20), 163 (20), 153 (37), 151 (11), 149 (12), 141 (10), 137 (26), 135 (19), 123 (25), 121 (21), 115 (26), 111 (57), 109 (48), 107 (14), 99 (14), 97 (17), 95 (45), 93 (11), 83 (21), 81 (23), 71 (100), 69 (51), 67 (13), 57 (13), 55 (28). HRMS calcd for $C_{20}H_{40}O_2$ 312.3028, found 312.3028.

5.3.4. 3,9-Di(*tert*-butyl)-2,2,10,10-tetramethyl-6-methyleneundecane-3,9-diol (3d). Colourless solid; t_r 18.43; R_f 0.80 (hexane/EtOAc 8:2); mp 40–42 °C; ν (KBr) 3367 (OH), 1647 cm^{-1} (C=CH); δ_H 1.06 (36H, s, 12×CH_3), 1.70–1.85 (4H, m, 2×CH_2CO), 2.00–2.15, 2.35–2.45 (6H, 2m, 2×OH, 2×CH_2C=CH_2), 4.76 (2H, s, H_2C=C); δ_C 28.6 (12×CH_3), 31.8, 33.0 (2×CH_2CH_2), 42.6 (4×$C$$CH_3$), 79.6 (2×CO), 108.6 ($H_2C$=C), 152.0 ($C$=$CH_2$); *m/z* 350 ($M^+-18$, <1%), 238 (10), 237 (59), 209 (12), 167 (34), 155 (10), 143 (10), 137 (31), 109 (17), 87 (21), 85 (14), 83 (40), 69 (10), 57 (100). Anal. Calcd for $C_{24}H_{48}O_2$: C, 78.20; H, 13.12, found C, 78.25; H, 12.99.

5.3.5. 1,1,7,7-Tetracyclopropyl-4-methyleneheptane-1,7-diol (3e). Colourless oil; t_r 17.26; R_f 0.42 (hexane/EtOAc 8:2); ν (film) 3483 (OH), 3084 (cyclopropyl CH), 1643 (C=CH), 1020 cm^{-1} (CO); δ_H 0.30–0.50 (16H, m, 8×CH_2CH), 0.75–0.95 (4H, m, 4×CH), 1.70–1.80 (4H, m, 2×C$H_2$$CH_2$C=$CH_2$), 2.20–2.35 (6H, m, 2×C$H_2$C=$CH_2$, 2×OH), 4.77 (2H, s, H_2C=C); δ_C −0.6, 0.8 (8×$C$$H_2$CH), 18.4 (4×CH), 30.4, 40.6 (2×CH_2CH_2CO), 70.8 (2×CO), 108.2 (H_2C=C), 151.0 (C=CH_2); *m/z* 286 (M^+-18, <1%), 245 (11), 147 (11), 145 (13), 133 (16), 131 (21), 120 (16), 119 (35), 117 (23), 111 (100), 108 (21), 107 (24), 106 (12), 105 (34), 95 (12), 93 (29), 92 (12), 91 (55), 81 (14), 79 (47), 77 (24), 69 (84), 67 (24), 55 (27). HRMS calcd for $C_{20}H_{32}O_2$ 304.2402, (M^+-H_2O) 286.2297, found 286.2301.

5.3.6. 1-{3-[2-(1-Hydroxycyclopentyl)ethyl]but-3-enyl}-cyclopentan-1-ol (3f). Colourless oil; t_r 15.50; R_f 0.50 (hexane/EtOAc 8:2); ν (film) 3384 (OH), 1643 cm^{-1} (C=CH); δ_H 1.40–2.00 [22H, m, 2×$(CH_2)_4$, 2×C$H_2$$CH_2$-C=$CH_2$, 2×OH], 2.10–2.25 (4H, m, 2×CH_2C=CH_2),

4.76 (2H, s, H_2C=C); δ_C 23.7, 31.3, 39.5, 39.7 (12×CH_2), 82.4 (2×CO), 108.6 (H_2C=C), 150.9 (C=CH_2); *m/z* 234 (M^+-18, <1%), 150 (11), 147 (32), 139 (45), 135 (69), 134 (100), 133 (13), 122 (11), 121 (58), 120 (13), 119 (43), 109 (10), 108 (21), 107 (21), 106 (20), 105 (32), 95 (20), 94 (17), 93 (41), 92 (13), 91 (22), 85 (48), 83 (10), 82 (10), 81 (48), 80 (22), 79 (41), 77 (11), 69 (15), 68 (12), 67 (51), 57 (19), 55 (40), 53 (12). HRMS calcd for $C_{16}H_{28}O_2$ 252.2089, found 252.2097.

5.3.7. 1-{3-[2-(1-Hydroxycyclohexyl)ethyl]but-3-enyl}-cyclohexan-1-ol (3g). Colourless oil; t_r 16.88; R_f 0.40 (hexane/EtOAc 8:2); ν (film) 3354 (OH), 1645 cm^{-1} (C=CH); δ_H 1.30–1.65 [24H, m, 2×$(CH_2)_5$, 2×C$H_2$$CH_2$-C=$CH_2$], 1.65 (2H, br s, 2×OH), 2.05–2.20 (4H, m, 2×CH_2C=CH_2), 4.73 (2H, s, H_2C=C); δ_C 22.2, 25.8, 29.3, 37.3, 40.5 (14×CH_2), 71.4 (2×CO), 108.6 (H_2C=C), 151.1 (C=CH_2); *m/z* 280 (M^+, <1%), 244 (18), 201 (14), 165 (11), 164 (24), 161 (26), 153 (44), 150 (10), 149 (74), 148 (100), 147 (11), 136 (15), 135 (87), 134 (16), 133 (26), 122 (11), 121 (14), 119 (13), 109 (13), 108 (15), 107 (22), 106 (22), 105 (20), 99 (80), 96 (10), 95 (42), 93 (27), 91 (15), 83 (10), 82 (10), 81 (82), 79 (30), 69 (20), 67 (32), 55 (44). HRMS calcd for $C_{18}H_{32}O_2$ 280.2402, found 280.2412.

5.3.8. 4-{3-[2-(4-Hydroxytetrahydro-2*H*-4-pyranyl)-ethyl]but-3-enyl}tetrahydro-2*H*-pyran-4-ol (3h). Colourless solid; t_r 17.59; R_f 0.51 (MeOH/EtOAc 1:9); mp 110 °C; ν (KBr) 3416 (OH), 1644 (C=CH), 1096 cm^{-1} (CO); δ_H 1.45–1.60 (12H, m, 2×CH_2CH_2C=CH_2, 2×C$H_2$$CH_2$-$OCH_2CH_2$), 2.10–2.30 (4H, m, 2×C$H_2$C=$CH_2$), 3.70–3.80 (10H, m, 2×OH, 4×CH_2O), 4.79 (2H, 2s, H_2C=C); δ_C 28.9, 37.6, 41.2 (2×CH_2CH_2C=CH_2, 2×C$H_2$$CH_2$-$OCH_2CH_2$), 63.8 (4×$CH_2O$), 69.0 (2×CO), 109.5 ($H_2C$=C), 149.9 (C=$CH_2$); *m/z* 266 ($M^+-18$, 2%), 167 (11), 166 (10), 155 (22), 151 (14), 150 (26), 138 (24), 137 (16), 122 (12), 121 (17), 120 (11), 119 (17), 110 (11), 109 (42), 107 (24), 106 (10), 105 (17), 101 (51), 99 (38), 97 (22), 96 (100), 95 (14), 94 (10), 93 (23), 91 (17), 83 (50), 81 (19), 79 (24), 73 (15), 71 (42), 69 (12), 68 (15), 67 (21), 55 (55), 53 (21). Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92, found C, 67.69; H, 10.01.

5.3.9. 4-{3-[2-(4-Hydroxy-1-propyl-4-piperidyl)ethyl]-but-3-enyl}-1-propylpiperidin-4-ol (3i). Colourless oil; t_r 21.71; R_f 0.20 (MeOH); ν (film) 3372 (OH), 1649 (C=CH), 1032 cm^{-1} (CO); δ_H 0.94 (6H, t, J=7.49 Hz, 2×C$H_3$$CH_2$), 1.55–2.20 (20H, m, 2×CH_2CH_2C=CH_2, 6×C$H_2$$CH_2$N), 2.50–2.70, 2.85–3.05 (14H, 2m, 2×OH, 6×CH_2N), 4.76 (2H, s, H_2C=C); δ_C 11.6 (2×CH_3), 18.9 (2×C$H_2$$CH_3$), 29.1, 35.3, 40.4 (2×C$H_2CH_2$C=$CH_2$, 4×COC$H_2$$CH_2$N), 49.1, 59.8 (6×$CH_2$N), 68.5 (2×CO), 109.7 ($H_2C$=C), 149.5 (C=$CH_2$); *m/z* 366 ($M^+$, 3%), 224 (25), 198 (32), 180 (16), 170 (12), 154 (25), 150 (10), 145 (11), 142 (11), 141 (10), 140 (100), 137 (10), 124 (11), 98 (34), 86 (13), 72 (16), 70 (16), 56 (14). HRMS calcd for $C_{22}H_{42}N_2O_2$ 366.3246, found 366.3257.

5.3.10. 2-{3-[2-(2-Hydroxy-2-adamantyl)ethyl]but-3-enyl}adamantan-2-ol (3j). Colourless solid; R_f 0.61 (hexane/EtOAc 8:2); mp 167 °C (sub.); ν (KBr) 3324 (OH), 1650 cm^{-1} (C=CH); δ_H 1.50–2.25 (36H, m, 8×CH, 14×CH_2), 2.50 (2H, br s, 2×OH), 4.75 (2H, s, H_2C=C); δ_C 27.2, 27.5, 34.8, 36.8 (8×CH), 28.5, 33.0, 34.5, 35.2, 35.5, 36.9, 38.3 (14×CH_2), 75.1 (2×CO), 108.8 (H_2C=C), 151.7 (C=CH_2); *m/z* 384 (M^+, <1%), 349 (15), 348 (51), 337 (17), 218 (14), 217 (62), 216 (21), 214 (10), 213 (26), 206 (10), 205 (62), 201 (11), 200 (21), 187 (30), 161 (12), 152 (12), 151 (100), 149 (14), 148 (22), 135 (17), 121 (12), 107 (14), 105 (15), 95 (11), 93 (18), 91 (24), 81 (20), 79 (27), 67 (18), 55 (15). Anal. Calcd for $C_{26}H_{40}O_2$: C, 81.20; H, 10.48, found C, 81.23; H, 10.48.

5.3.11. (1*S*,2*S*,5*R*)-1-(3-{2-[(1*S*,2*S*,5*R*)-1-Hydroxy-2-isopropyl-5-methylcyclohexyl]ethyl}but-3-enyl)-2-isopropyl-5-methylcyclohexan-1-ol (3k). Colourless oil; t_r 20.04; R_f 0.43 (hexane/EtOAc 8:2); $[\alpha]_D^{20}$ +4.7 (*c* 1.0, $CHCl_3$); ν (film) 3457 cm^{-1} (OH); δ_H 0.75–1.00 (18H, m, 6×CH_3), 1.05–1.85 (22H, m, 6×CH, 6×CH_2CH, 2×C$H_2$$CH_2$-C=$CH_2$), 1.95–2.10 (6H, m, 2×OH, 2×CH_2C=CH_2), 4.76 (2H, s, H_2C=C); δ_C 18.2, 22.5, 23.6, 25.6, 28.1, 47.9 (6×CH_3, 6×CH), 20.5, 30.5, 35.1, 39.4, 46.7 (10×CH_2), 75.1 (2×CO), 108.7 (H_2C=C), 150.3 (C=CH_2); *m/z* 392 (M^+, <1%), 209 (15), 204 (17), 191 (56), 189 (11), 177 (19), 175 (15), 163 (12), 162 (11), 161 (63), 155 (37), 151 (21), 150 (37), 149 (23), 147 (13), 138 (15), 137 (37), 135 (21), 123 (16), 121 (15), 119 (10), 111 (15), 109 (40), 108 (19), 107 (27), 105 (20), 97 (15), 95 (100), 93 (30), 91 (20), 83 (24), 82 (12), 81 (96), 79 (24), 71 (13), 69 (91), 67 (35), 57 (21), 55 (66). HRMS calcd for $C_{26}H_{48}O_2$ 392.3654, found 392.3649.

5.3.12. (1*R,2*S**,4*S**)-2-(3-{2-[(1*R**,2*S**,4*S**)-2-Hydroxybicyclo[2.2.1]hept-2-yl]ethyl}but-3-enyl)bicyclo[2.2.1]-heptan-2-ol (3l).** Colourless solid; t_r 18.17; R_f 0.41 (hexane/EtOAc 8:2); mp 100–102 °C; ν (KBr) 3383 (OH), 1644 cm^{-1} (C=CH); δ_H 1.05–1.15, 1.25–1.70, 1.85–2.00, 2.05–2.25 (30H, 4m, 4×$CH_2$$CH_2$, 4×$CH_2$CH, 2×OH), 4.76 (2H, s, H_2C=C); δ_C 22.1, 28.5, 30.0, 38.7, 40.3, 45.8 (4×$CH_2$$CH_2$, 4×C$H_2$CH), 37.1, 46.7 (4×CH), 79.6 (2×CO), 108.7 (H_2C=C), 151.2 (C=CH_2); *m/z* 304 (M^+, <1%), 268 (24), 176 (45), 175 (21), 166 (12), 165 (100), 161 (29), 160 (66), 148 (17), 147 (43), 133 (12), 132 (17), 131 (15), 121 (11), 119 (20), 111 (47), 109 (12), 108 (19), 107 (25), 106 (12), 105 (20), 95 (27), 94 (10), 93 (34), 92 (11), 91 (29), 83 (34), 81 (33), 80 (16), 79 (36), 77 (13), 69 (11), 68 (12), 67 (58), 66 (19), 55 (33). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59, found C, 78.99; H, 10.5.

5.3.13. (1*R*,2*S*,4*S*)-2-(3-{2-[(1*R*,2*S*,4*S*)-2-Hydroxy-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]ethyl}but-3-enyl)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (3m). Colourless solid; t_r 21.41; R_f 0.43 (hexane/EtOAc 8:2); mp 121–122 °C; $[\alpha]_D^{20}$ −20.1 (*c* 1.1, $CHCl_3$); ν (KBr) 3507 (OH), 1642 (C=CH), 1072 cm^{-1} (CO); δ_H 0.95–1.10 (18H, m, 6×CH_3), 1.30–1.50, 1.60–1.75, 1.85–2.30 (24H, 3m, 2×CH, 4×$CH_2$$CH_2$, 2×CC$H_2$CH, 2×OH), 4.76 (2H, s, H_2C=C); δ_C 18.1, 22.6, 27.7 (6×CH_3), 24.9, 30.7, 31.6, 34.0, 41.1 (4×$CH_2$$CH_2$, 2×C$CH_2$CH), 44.4, 52.8 (4×C$CH_3$), 50.2 (2×CH), 81.1 (2×CO), 108.3 (H_2C=C), 152.2 (C=CH_2); *m/z* 388 (M^+, <1%), 370 (26), 290 (10), 208 (10), 207 (60), 203 (12), 202 (16), 191 (10), 189 (20), 151 (12), 149 (21), 147 (20), 137 (11), 135 (14), 133 (18), 125 (41), 124 (12), 123 (74), 122 (13), 121 (18), 119 (10), 109 (22), 107 (37), 105 (15), 95 (19), 93 (17), 91 (10), 83 (14), 81 (100), 79 (16), 69 (48), 67

(22), 55 (19). Anal. Calcd for $C_{26}H_{44}O_2$: C, 80.35; H, 11.41, found C, 80.22; H, 11.29.

5.3.14. DL and *meso*-2,2,10,10-Tetramethyl-6-methyleneundecane-3,9-diol (3n). Colourless solid; t_r 13.52; R_f 0.50 (hexane/EtOAc 8:2); mp 65–67 °C; ν (KBr) 3395 (OH), 1639 (C=CH), 1018 cm^{-1} (CO); δ_H 0.90 (36H, s, 12×CH_3), 1.35–1.45, 1.60–1.80 (12H, 2m, 4×CH_2CH, 4×OH), 2.00–2.15, 2.25–2.35 (8H, 2m, 4×CH_2C=CH_2), 3.15–3.25 (4H, m, 4×CH), 4.79 (4H, s, H_2C=C); δ_C 25.7 (12×CH_3), 29.4, 29.5, 33.4, 33.6 (4×CH_2CH_2), 34.9 (4×$C$$CH_3$), 79.5, 79.6 (4×CH), 109.2, 109.3 (2×H_2C=C), 150.1, 150.2 (2×C=CH_2); *m/z* 238 (M^+-18, 1%), 181 (18), 163 (45), 137 (30), 135 (13), 123 (22), 121 (18), 111 (14), 109 (26), 107 (30), 100 (25), 97 (17), 96 (17), 95 (37), 93 (32), 87 (14), 85 (44), 84 (10), 83 (100), 82 (21), 81 (32), 79 (14), 71 (16), 70 (20), 69 (46), 67 (16), 57 (73), 55 (29). HRMS calcd for $C_{16}H_{32}O_2$ 256.2402, found 256.2402.

5.4. General procedure for the preparation of 1,7-dioxaspiro[4.5]decanes 4

Iodine (382 mg, 1.5 mmol) was added to a solution of the diol **3** (1 mmol) in THF (10 mL) and the mixture was stirred at rt for 5 min. After the addition of Na_2CO_3 (159 mg, 1.5 mmol) and AgOTf (771 mg, 3 mmol), a white-yellow precipitate was rapidly formed. Additional stirring for 24 h was followed by filtration through a short column containing a layer of Celite over silica gel, using hexane as eluant. Washing with a saturated solution of Na_2SO_3 is recommended if the filtrate is coloured. The resulting solution was dried over Na_2SO_4 and the solvents evaporated under reduced pressure (15 Torr), giving a reaction crude that contained the pure compound **4**, which did not require any further purification.

5.4.1. 2,2,8,8-Tetraethyl-1,7-dioxaspiro[4.5]decane (4a). Colourless oil; t_r 13.04; R_f 0.67 (hexane/EtOAc 8:2); ν (film) 1052 cm^{-1} (CO); δ_H 0.75–0.95 (12H, m, 4×CH_3), 1.25–2.05 (16H, m, 4×C$H_2$$CH_3$, 2×$CH_2CH_2$), 3.27, 3.38 [2H, AB system, J_{AB}=11.3, 3.27 Hz (C$H_{eq}H_{ax}$O, $^4J_{eq-eq}$=2.0 Hz), 3.38 (C$H_{ax}H_{eq}$O)]; δ_C 7.2, 7.7, 8.6, 8.7 (4×CH_3), 29.3, 30.1, 30.9, 31.3, 31.6, 32.8, 33.3, 33.4 (4×$C$$H_2CH_3$, 2×$CH_2CH_2$), 67.9 ($CH_2O$), 74.8, 79.8, 85.9 (3×C); *m/z* 254 (M^+, 1%), 225 (13), 189 (10), 154 (26), 153 (13), 140 (13), 135 (21), 133 (11), 111 (19), 101 (100), 98 (12), 97 (15), 57 (20), 55 (18). HRMS calcd for $C_{16}H_{30}O_2$ 254.2246, found 254.2229.

5.4.2. 2,2,8,8-Tetra(*n*-pentyl)-1,7-dioxaspiro[4.5]decane (4b). Colourless oil; t_r 19.50; R_f 0.68 (hexane/EtOAc 8:2); ν (film) 1067 cm^{-1} (CO); δ_H 0.85–0.90 (12H, m, 4×CH_3), 1.20–2.15 (40H, m, 10×CH_2CH_2), 3.24, 3.38 [2H, AB system, J_{AB}=11.2, 3.24 Hz (C$H_{eq}H_{ax}$O, $^4J_{eq-eq}$=1.2 Hz), 3.38 (C$H_{ax}H_{eq}$O)]; δ_C 14.1 (4×CH_3), 22.6, 22.7, 23.1, 23.9, 24.1, 31.8, 32.4, 32.5, 33.0, 33.5, 34.3, 38.7, 39.4, 39.7, 40.2, (10×CH_2CH_2), 67.9 (CH_2O), 74.6, 79.8, 85.4 (3×C); *m/z* 422 (M^+, <1%), 351 (19), 186 (13), 185 (100). HRMS calcd for $C_{28}H_{54}O_2$ 422.4124, found 422.4103.

5.4.3. 2,2,8,8-Tetraisopropyl-1,7-dioxaspiro[4.5]decane (4c). Colourless oil; t_r 15.33; R_f 0.66 (hexane/EtOAc 8:2); ν (film) 1382, 1365, 1065 cm^{-1} (CO); δ_H 0.80–0.95 (24H, m, 8×CH_3), 1.45–2.05 (10H, m, 2×CH_2CH_2, 2×C$H$$CH_3$), 2.45–2.55 (2H, m, 2×C$H$$CH_3$), 3.33, 3.44 (2H, AB system, J_{AB}=11.2 Hz); δ_C 18.3, 18.5, 18.6, 18.7, 18.8, 18.9 (6×CH_3), 23.6, 28.0, 31.9, 34.0 (2×CH_2CH_2), 27.6, 32.0, 33.4, 34.1 (4×CH), 67.9 (CH_2O), 77.2, 80.1, 90.4 (3×C); *m/z* 295 (M^+-15, <1%), 268 (19), 267 (100), 249 (24), 231 (12), 179 (10), 163 (44), 137 (13), 129 (36), 125 (32), 121 (12), 112 (14), 109 (12), 107 (19), 97 (10), 95 (14), 93 (11), 83 (13), 81 (12), 71 (34), 69 (30), 59 (12), 55 (16). HRMS calcd for $C_{20}H_{38}O_2$ 310.2872, ($M^+-C_3H_7$) 267.2319, found 267.2319.

5.4.4. 2,2,8,8-Tetra(*tert*-butyl)-1,7-dioxaspiro[4.5]decane (4d). Colourless oil; t_r 19.12; R_f 0.80 (hexane/EtOAc 9:1); ν (film) 1112 cm^{-1} (CO); δ_H 1.00–1.15 (36H, m, 12×CH_3), 1.20–2.00 (8H, m, 2×CH_2CH_2), 3.35, 3.41 [2H, AB system, J_{AB}=11.7, 3.35 Hz (C$H_{eq}H_{ax}$O, $^4J_{eq-eq}$=2.1 Hz), 3.41 (C$H_{ax}H_{eq}$O)]; δ_C 26.5, 27.7, 28.4, 28.6, 28.9, 29.2, 29.3, 29.5, 29.7, (12×CH_3), 29.3, 30.8, 31.6, 32.9, (2×CH_2CH_2), 42.9 (4×$C$$CH_3$) 67.4 ($CH_2O$), 76.6, 79.5, 85.3 (3×CO); *m/z* 309 (M^+-57, 27%), 253 (11), 235 (23), 135 (24), 109 (14), 57 (100). HRMS calcd for $C_{24}H_{46}O_2$ 366.3498, found 366.3486.

5.4.5. Trispiro[cyclopentane-1,2′-tetrahydrofuran-5′,3″-tetrahydro-2*H*-pyran-6″,1‴-cyclopentane] (4f). Colourless oil; t_r 14.17; R_f 0.61 (hexane/EtOAc 8:2); ν (film) 1073 cm^{-1} (CO); δ_H 1.30–2.15 (24H, m, 6×CH_2CH_2), 3.33, 3.39 [2H, AB system, J_{AB}=11.5, 3.33 Hz (C$H_{eq}H_{ax}$O, $^4J_{eq-eq}$=1.9 Hz), 3.39 (C$H_{ax}H_{eq}$O)]; δ_C 23.6, 23.9, 24.1, 33.5, 33.8, 33.9, 34.5, 36.4, 38.9, 39.3, 39.7 (6×CH_2CH_2), 69.5 (CH_2O), 79.4, 83.2, 91.2 (3×C); *m/z* 250 (M^+, 3%), 152 (55), 151 (13), 138 (27), 99 (100), 96 (11), 95 (29), 81 (10), 80 (16), 67 (12), 55 (10). HRMS calcd for $C_{16}H_{26}O_2$ 250.1933, found 250.1940.

5.4.6. Trispiro[cyclohexane-1,2′-tetrahydrofuran-5′,3″-tetrahydro-2*H*-pyran-6″,1‴-cyclohexane] (4g). Colourless oil; t_r 15.94; R_f 0.60 (hexane/EtOAc 8:2); ν (film) 1070 cm^{-1} (CO); δ_H 1.20–2.10 (28H, m, 14×CH_2CH_2), 3.29, 3.40 [2H, AB system, J_{AB}=11.4, 3.29 Hz (C$H_{eq}H_{ax}$O, $^4J_{eq-eq}$=1.9 Hz), 3.40 (C$H_{ax}H_{eq}$O)]; δ_C 21.6, 22.0, 24.1, 24.2, 25.6, 26.2, 30.7, 32.8, 33.3, 37.7, 38.7, 39.5 (14×$C$$H_2CH_2$), 67.8 ($CH_2O$), 71.5, 79.5, 83.0 (3×C); *m/z* 278 (M^+, 7%), 166 (42), 165 (13), 152 (15), 113 (100), 109 (14), 95 (12), 94 (26), 81 (12), 67 (13), 55 (12). HRMS calcd for $C_{18}H_{30}O_2$ 278.2246, found 278.2222.

5.4.7. Trispiro[oxacyclohexane-4,2′-tetrahydrofuran-5′,3″-tetrahydro-2*H*-pyran-6″,4‴-oxacyclohexane] (4h). Colourless oil; t_r 16.99; R_f 0.50 (hexane/EtOAc 1:1); ν (film) 1102 cm^{-1} (CO); δ_H 1.40–2.15 (16H, m, 4×CH_2CH_2O, 2×CCH_2CH_2C), 3.34, 3.41 [2H, AB system, J_{AB}=11.6, 3.34 Hz (C$H_{eq}H_{ax}$O, $^4J_{eq-eq}$=1.6 Hz), 3.41 (C$H_{ax}H_{eq}$O)], 3.55–3.90 (8H, m, 4×CH_2CH_2O); δ_C 32.0, 32.3, 33.0, 34.1, 35.4, 36.8, 38.9, 39.3 (4×$C$$H_2CH_2O$, 2×C$CH_2CH_2$C), 63.6, 63.7, 65.5, 65.6, 67.9 (5×CH_2O), 69.1, 77.2, 79.9 (3×CO); *m/z* 282 (M^+, 1%), 169 (13), 168 (43), 167 (10), 154 (11), 115 (100), 109 (10), 96 (30). HRMS calcd for $C_{16}H_{26}O_4$ 282.1831, found 282.1826.

5.4.8. Trispiro[adamantane-2,2′-tetrahydrofuran-5′,3″-tetrahydro-2*H*-pyran-6″,2‴-adamantane] (4j). Colourless solid; t_r 18.33; R_f 0.65 (hexane/EtOAc 8:2); mp 157–158 °C; ν (KBr) 1011 cm^{-1} (CO); δ_H 1.50–2.25 (36H, m, 8×CH, 2×CH_2CH_2, 10×CH_2CH), 3.27, 3.38 [2H, AB system, J_{AB}=11.6, 3.27 Hz ($CH_{eq}H_{ax}O$, $^4J_{eq-eq}$=1.7 Hz), 3.38 ($CH_{ax}H_{eq}O$)]; δ_C 27.1, 27.2, 27.5, 27.8, 29.3, 29.6, 38.3, 39.7 (8×CH), 30.4, 31.9, 32.8, 32.9, 33.4, 33.8, 33.9, 34.1, 34.2, 34.3, 35.8, 36.1, 37.9, 38.2 (10×CH_2CH, 2×CH_2CH_2), 67.4 (CH_2O), 75.4, 79.2, 86.1 (3×C); *m/z* 306 (M^+-76, 2%), 284 (10), 151 (19), 135 (38), 134 (100), 119 (16), 105 (15), 93 (29), 92 (44), 91 (27), 80 (10), 79 (24), 77 (14). Anal. Calcd for $C_{26}H_{38}O_2$: C, 81.62; H, 10.01, found C, 81.63; H, 9.89.

5.4.9. Trispiro[{(1*R*,2*S*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]-heptane}-2,2′-tetrahydrofuran-5′,3″-tetrahydro-2*H*-pyran-6″,2‴-{(1*R*,2*S*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]-heptane}] (4m). Mixture of diastereoisomers (63:37). Colourless oil; t_r 19.65 (major) and 19.72 (minor); R_f 0.65 and 0.68 (hexane/EtOAc 8:2); ν (film) 1069 cm^{-1} (CO); δ_H 0.80–2.10 (80H, m, 8×CH_2CH_2, 4×CH_2CH, 12×CH_3), 3.25–3.45 (4H, m, 2×CH_2O); δ_C (major) 17.8, 19.4, 23.1, 23.6, 28.0, 28.4 (6×CH_3), 25.7, 25.8, 26.5, 29.4, 29.6, 29.9, 33.3, 34.9, 41.2, 41.3 (2×CH_2CH, 4×CH_2CH_2), 44.6, 51.5, 53.1, 53.2 (4×CCH_3), 49.3, 51.0 (2×CH), 70.4 (CH_2O), 78.9, 81.5, 92.1 (3×C); δ_C (minor) 18.1, 21.9, 22.2, 24.2, 27.7, 27.9 (6×CH_3), 25.6, 25.9, 26.3, 28.6, 29.8, 30.3, 34.2, 34.9, 41.4, 43.2 (2×CH_2CH, 4×CH_2CH_2), 43.4, 46.2, 52.1, 53.3 (4×CCH_3), 49.3, 49.4 (2×CH), 70.9 (CH_2O), 78.2, 80.9, 92.1 (3×C); *m/z* (major) 386 (M^+, 7%), 305 (22), 304 (100), 222 (15), 219 (13), 218 (25), 206 (48), 125 (11), 124 (10), 123 (18), 107 (13), 81 (43), 79 (10), 69 (18), 67 (10), 55 (10). *m/z* (minor) 386 (M^+, 9%), 305 (22), 304 (100), 222 (14), 219 (15), 218 (28), 207 (10), 206 (55), 125 (12), 124 (12), 123 (20), 109 (11), 107 (14), 81 (49), 79 (11), 69 (20), 67 (11), 55 (12). HRMS calcd for $C_{26}H_{42}O_2$ 386.3185, found [386.3174 (major), 386.3186 (minor)].

5.5. General procedure for the oxidation of 1,7-dioxaspiro[4.5]decanes 4 to lactones 5

A solution of $NaIO_4$ (1.04 g, 4.88 mmol) and $RuCl_3 \cdot xH_2O$ (33 mg) in water (5 mL) was added in five portions at intervals of 1 h over a solution of compound **4** (1 mmol) and cetyltrimethylammonium bromide (CTAB) (10 mg, 0.027 mmol) in CCl_4 (5 mL) at reflux. The reaction mixture was stirred for an additional hour, extracted with CCl_4 (3×5 mL), and dried over anhydrous $MgSO_4$. After evaporation of the solvent at reduced pressure (15 Torr), the residue was purified by column chromatography (silica gel, hexane/EtOAc).

5.5.1. 2,2,8,8-Tetrapentyl-1,7-dioxaspiro[4.5]decan-6-one (5b). Colourless oil; t_r 20.99; R_f 0.39 (hexane/EtOAc 8:2); ν (film) 1735 (C=O), 1095 cm^{-1} (CO); δ_H 0.85–0.95 (12H, m, 4×CH_3), 1.20–2.15 (40H, m, 10×CH_2CH_2); δ_C 14.0, 14.1 (4×CH_3), 22.5, 22.6, 23.1, 24.0, 24.3, 28.4, 32.1, 32.2, 32.4, 35.4, 36.6, 38.2, 38.8, 38.9, 39.1 (20×CH_2), 80.8, 86.9, 88.5 (3×C), 173.8 (C=O); *m/z* 407 (M^+-29, <1%), 390 (23), 365 (18), 338 (24), 337 (100), 321 (10), 237 (14), 225 (12), 224 (27), 168 (17), 167 (11), 166 (13), 155 (10), 153 (47), 123 (15), 110 (50), 99 (10), 95 (12), 83 (10), 69 (16), 55 (20). HRMS calcd for $C_{28}H_{52}O_3$ 436.3916, found 436.3911.

5.5.2. 2,2,8,8-Tetraisopropyl-1,7-dioxaspiro[4.5]decan-6-one (5c). Colourless oil; t_r 16.35; R_f 0.38 (hexane/EtOAc 8:2); ν (film) 1736 (C=O), 1112 cm^{-1} (CO); δ_H 0.80–1.00 (24H, m, 8×CH_3), 1.50–2.15 (12H, m, 4×CH, 2×CH_2CH_2); δ_C 17.3, 17.4, 17.9, 18.1, 18.5, 18.8, 19.0 (8×CH_3), 27.6, 29.5, 32.6, 35.5 (4×CH_2), 33.6, 33.9, 35.0, 36.1 (4×CH), 91.2, 92.2, 93.6 (3×C), 172.6 (CO); *m/z* 282 (M^+-42, 11%), 281 (64), 278 (11), 263 (11), 253 (46), 235 (21), 217 (10), 168 (16), 155 (15), 153 (17), 149 (21), 125 (100), 111 (24), 107 (10), 69 (29), 55 (13). HRMS calcd for $C_{20}H_{36}O_3$ 324.2664, ($M^+-C_3H_7$) 281.2111, found 281.2122.

5.5.3. Trispiro[cyclopentane-1,2′-tetrahydrofuran-5′,3″-(tetrahydropyran-2-one)-6″,1‴-cyclopentane] (5f). Colourless oil; t_r 15.27; R_f 0.41 (hexane/EtOAc 8:2); ν (film) 1735 (C=O), 1090 cm^{-1} (CO); δ_H 1.30–2.10 (24H, m, 12×CH_2); δ_C 22.1, 22.6, 23.8, 24.1, 25.9, 28.1, 30.0, 32.2, 35.2, 35.7 (12×CH_2), 79.9, 83.7, 86.4 (3×C), 172.9 (C=O); *m/z* 236 (M^+-28, 19%), 218 (16), 151 (26), 141 (11), 139 (15), 138 (100), 109 (15), 96 (15), 95 (69), 94 (19), 81 (27), 80 (49), 79 (17), 67 (18), 55 (19). HRMS calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1721.

5.6. X-ray crystallography

All compounds studied were recrystallised from hexane. Data collection was performed on a Bruker Smart CCD diffractometer, based on three ω-scan runs (starting $\omega=-34°$) at the values of $\phi=0$, 120, 240° with the detector at $2\theta=-32°$. For each of these runs, 606 frames were collected at 0.3° intervals. An additional run at $\phi=0°$ of 100 frames was collected to improve redundancy. The diffraction frames were integrated using the SAINT[26] programme and the integrated intensities were corrected for Lorentz-polarisation effects with SADABS.[27]

X-ray data for **3l**. $C_{20}H_{32}O_2$, M=304.46; monoclinic, a=16.018(4) Å, b=11.695(3) Å, c=19.445(4) Å, β=94.389(6)°; V=3632.1(1) $Å^3$; space group P 2(1)/c; Z=8; D_c=1.114 Mg m^{-3}; λ=0.71073 Å; μ=0.069 mm^{-1}; $F(000)$=1344; T=21±1 °C. The structure was solved by direct methods[28] and refined to all 5707 unique F_o^2 by full matrix least squares (SHELX97).[29] All the hydrogen atoms were placed at idealised positions and refined as rigid atoms. Final $wR2$=0.3760 for all data and 409 parameters; R_1=0.1218 for 2826 $F_o>4\sigma(F_o)$.

X-ray data for **3m**. $C_{26}H_{44}O_2$, M=388.61; orthorhombic, a=12.4239(19) Å, b=15.247(2) Å, c=12.357(2) Å; V=2340.8(6) $Å^3$; space group $C222(1)$; Z=4; D_c=1.103 Mg m^{-3}; λ=0.71073 Å; μ=0.067 mm^{-1}; $F(000)$=864; T=23±1 °C. The structure was solved by direct methods[28] and refined to all 1188 unique F_o^2 by full matrix least squares (SHELX97).[29] All the hydrogen atoms were placed at idealised positions and refined as rigid atoms. Final $wR2$=0.1200 for all data and 140 parameters; R_1=0.0421 for 1000 $F_o>4\sigma(F_o)$.

X-ray data for **4j**. $C_{26}H_{38}O_2$, M=382.56; triclinic, a=6.4617(10) Å, b=11.1766(18) Å, c=14.176(2) Å, α=

99.041(3)°, $\beta = 96.642(3)°$, $\gamma = 90.790(3)°$; $V = 1003.7(3)$ Å^3; space group $P\bar{1}$; $Z = 2$; $D_c = 1.266$ Mg m^{-3}; $\lambda = 0.71073$ Å; $\mu = 0.077$ mm^{-1}; $F(000) = 420$; $T = -100 \pm 1$ °C. The structure was solved by direct methods[28] and refined to all 8481 unique F_o^2 by full matrix least squares (SHELX97).[29] All the hydrogen atoms were placed at idealised positions and refined as rigid atoms. Final $wR2 = 0.1489$ for all data and 254 parameters; $R_1 = 0.0606$ for 4486 $F_o > 4\sigma(F_o)$.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 288641-288643. 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; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/data_request/cif).

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