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Regioselective synthesis of 1,7-dioxaspiro[4.4]nonanes from a trimethylenemethane dianion synthon

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Dedicated to the memory of Dr. Juan Carlos del Amo who died in the horrific terrorist attack of the 11th of March 2004 in Madrid.

Abstract—2-Chloromethyl-3-(2-methoxyethoxy)prop-1-ene behaves as a versatile trimethylenemethane dianion synthon, precursor of a variety of methylidenic diols obtained by DTBB-catalysed lithiation in the presence of a carbonyl compound ($E^1=R^1R^2CO$) in THF at −78 to 0 °C, followed by the addition of an epoxide [$E^2=R^3R^4C(O)CHR^5$] at 0 to 20 °C and final hydrolysis. These diols undergo double intramolecular iodoetherification in the presence of iodine and silver(I) oxide in THF or dioxane–water, to give the corresponding 1,7-dioxaspiro[4.4]nonanes, which can be easily oxidised to a variety of 1,7-dioxaspiro[4.4]nonan-6-ones. These skeletons are present in a wide series of natural products.

1. Introduction

1,7-Dioxaspiro[4.4]nonanes and its derived lactones are substructures present in a variety of natural products, some of them with important biological activities. These types of compounds are especially abundant within the family of the labdane diterpenoids, some representatives of which are prehispanolone (**I**) (a specific platelet activating factor receptor antagonist, isolated from the Chinese herbal medicine *Leonurus heterophyllus*),[1,2] leopersin J (**II**) (from *Leonurus persicus*),[3] otostegins (from *Otostegia fruticosa*),[4] or marrubiglobosin (from *Marrubium globosum*).[5] Some other naturally occurring compounds containing the mentioned skeletons are sphydrofuran (**III**) (a secondary metabolite produced by Actinomycetes),[6] cinatrin A (**IV**) (a potent inhibitor of rat platelet phospholipase A_2, from the fermentation broth of the microorganism *Circinotrichum falcatisporum*),[7] longianone (**V**) (from *Xylaria longiana*),[8,9] hyperolactone A (**VI**) (from *Hypericum chinense* L.),[10] or syringolides 1 and 2,[11] and secosyrins 1 and 2 (**VII**) (all from *Pseudomonas syringae*).[12] 1,7-Dioxaspiro[4.4]nonanes have also been used as valuable polycyclic scaffolds in the synthesis of natural products (e.g., **VIII**, in zaragozic acid synthesis)[13,14] or have been obtained as a result of carbohydrate modification (**IX**, **X**)[15–18] (Chart 1).

The unique structural nature of these spirocyclic compounds has attracted the interest of many synthetic organic chemists.[19–21] However, most of the research has focused on the synthesis of spirocyclic γ-mono- and bislactones, less attention being dedicated to the 1,7-dioxaspiro[4.4]nonane itself as a polycyclic ether. The methodologies described in the literature normally involve the intramolecular cyclisation of a moiety attached to a preformed γ-lactone or tetrahydrofuran ring. As representative examples we can mention: (a) the intramolecular Michael addition of a 3-hydroxyalkyl group to a 2-butenolide ring;[19] (b) Reformatsky-type reaction on a tetrahydrofuran-3-one, followed by lactonisation;[22] (c) lactonisation of 2-hydroxyalkyl-γ-lactone acids and related compounds;[23,24] (d) radical cyclisation of a 4-(3-butynyloxy)-2,5-dihydro-2-furanone;[25] or (e) intramolecular ketalisation from a 2,2-disubstituted tetrahydrofuran.[26]

On the other hand, in recent years we have shown an increasing interest in the synthesis of bicyclic[27–31] and spirocyclic[32,33] polyether skeletons as constituents of

Keywords: 1,7-Dioxaspiro[4.4]nonanes; Arene-catalysed lithiation; Spirolactones; Spirocyclisation.
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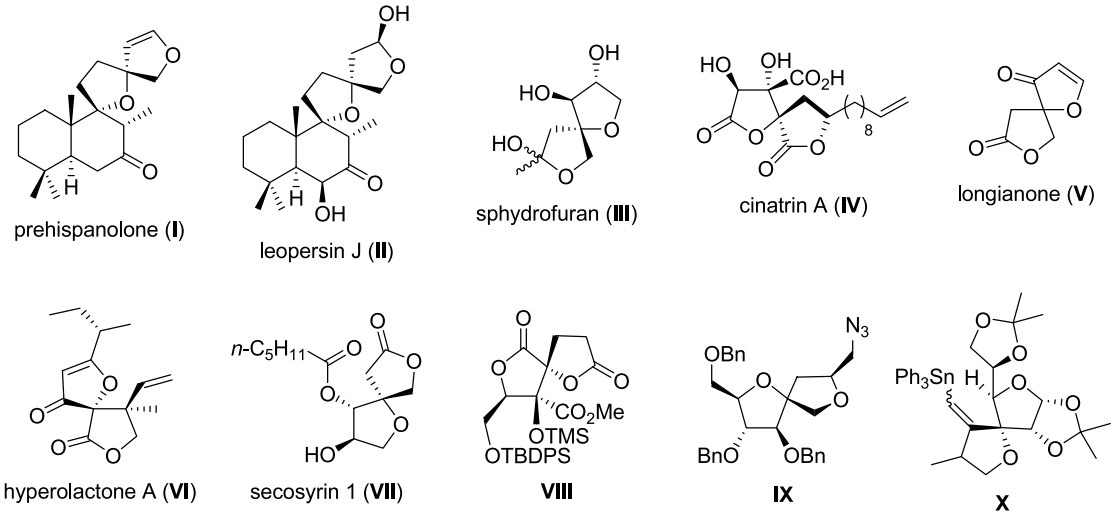
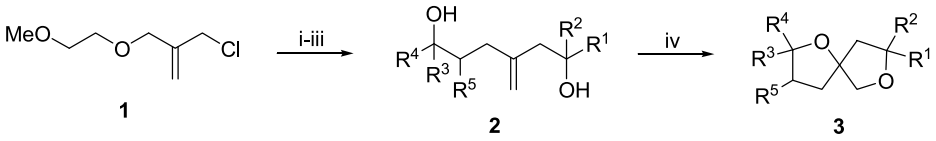


Chart 1.



Scheme 1. (i) Reagents and conditions: (i), Li, DTBB (2.5 mol%), R^1R^2CO, THF, −78 to 0 °C, 3.5 h; (ii), $R^3R^4C(O)CHR^5$, 0 to 20 °C, overnight; (iii), H_2O; (iv), I_2, Ag_2O, THF or dioxane–H_2O (7:1), 20 °C, overnight.

Table 1. Obtention of 1,7-dioxaspiro[4,4]nonanes from diols **2**

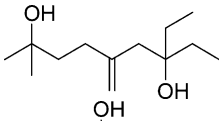
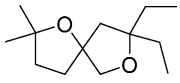
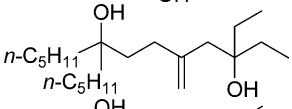
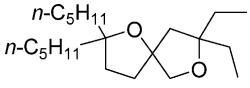
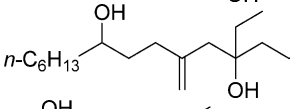
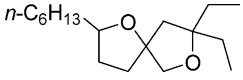
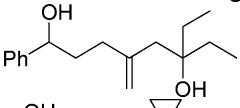
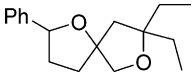
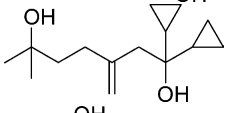
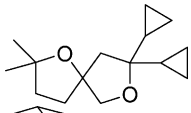
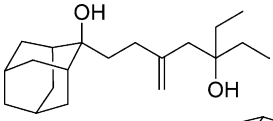
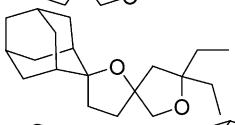
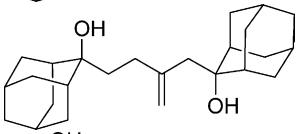
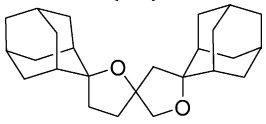
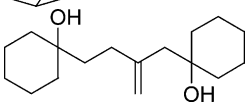
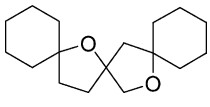
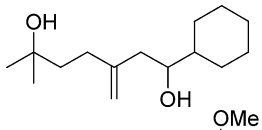
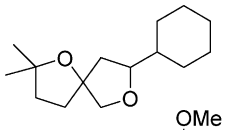
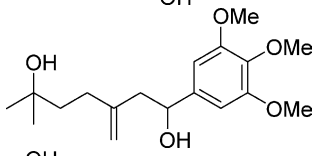
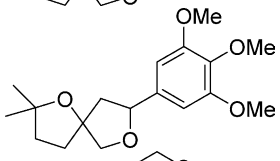
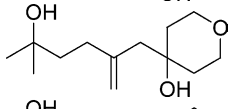
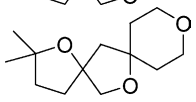
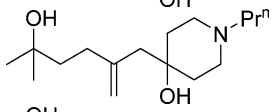
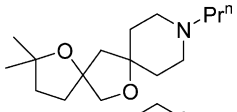
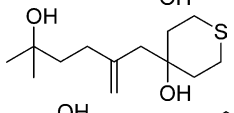
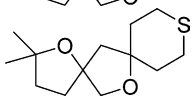
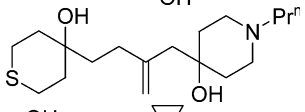
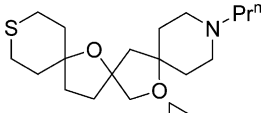
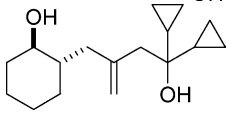
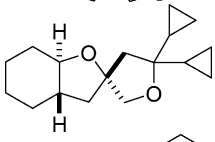
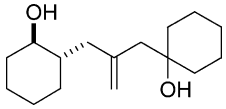
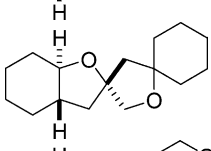
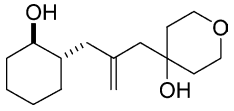
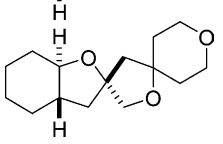
Entry	Product **2**[a]			Product **3**[a]		
	No.	Structure	Yield (%)[b]	No.	Structure	Yield (%)[c]
1	**2a**		70	**3a**		98
2	**2b**		43	**3b**		96
3	**2c**		55	**3c**		97[d]
4	**2d**		68	**3d**		88[e]
5	**2e**		57	**3e**		99
6	**2f**		41	**3f**		96
7	**2g**		33	**3g**		70[f]
8	**2h**		54	**3h**		92

Table 1 (*continued*)

Entry	Product **2**[a]			Product **3**[a]		
	No.	Structure	Yield (%)[b]	No.	Structure	Yield (%)[c]
9	**2i**		41	**3i**		–[g]
10	**2j**		30	**3j**		89[h]
11	**2k**		50	**3k**		91
12	**2l**		51	**3l**		89
13	**2m**		59	**3m**		90
14	**2n**		40	**3n**		92
15	**2o**		41	**3o**		90[i]
16	**2p**		43	**3p**		93[j]
17	**2q**		40	**3q**		92[k]

[a] All products were ≥95% pure (GLC and/or 300 MHz ^{1}H NMR).
[b] Isolated yield after column chromatography (silica gel, hexane/EtOAc or EtOAc/MeOH) based on the starting chloroether **1**.
[c] Yield of pure **3** from the reaction crude (unless stated otherwise) based on the starting diol **2**.
[d] Obtained as a 3.5:1 mixture of diastereoisomers (56% d.e.) (^{13}C NMR).
[e] Obtained as a 1:1 mixture of diastereoisomers (^{1}H and ^{13}C NMR).
[f] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the corresponding diol **2g**.
[g] Cyclisation of **2i** proved to be difficult and led to the corresponding iodohydrin **4i** in 97% yield, apparently, as a single diastereoisomer.
[h] Obtained as a 12:1 mixture of diastereoisomers (85% d.e.) (GLC).
[i] Obtained as a 3:1 mixture of diastereoisomers (50% d.e.) (^{1}H NMR), the major diastereoisomer is shown.
[j] Obtained as a 12:1 mixture of diastereoisomers (85% d.e.) (^{1}H NMR), the major diastereoisomer is shown.
[k] Obtained as a 13:1 mixture of diastereoisomers (86% d.e.) (GLC and ^{1}H NMR), the major diastereoisomer is shown.

important biologically active compounds. In particular, and in connection with the title topic, we reported the two-step synthesis of 1,6-dioxaspiro[3.4]octanes from 3-chloro-2-(chloromethyl)prop-1-ene[32] and 1,5-dioxaspiro[2.4]heptanes from 2,3-dichloroprop-1-ene.[33] In both cases an arene-catalysed lithiation[34–36] under Barbier conditions[37,38] and an iodine-mediated double intramolecular cyclisation were utilised as the key reaction steps. We want to demonstrate herein that the above mentioned methodology also allows a straight and ready access to the synthesis of 1,7-dioxaspiro[4.4]nonanes using 2-chloromethyl-3-(2-methoxyethoxy)prop-1-ene (**1**) as starting material. This compound undergoes a selective lithiation catalysed by DTBB (4,4′-di-*tert*-butylbiphenyl) with concomitant one-pot incorporation of two different electrophilic fragments, derived from a carbonyl compound and an epoxide, respectively. The resulting methylidenic diols (**2**) can be regioselectively cyclised in the presence of iodine and silver(I) oxide, affording the expected 1,7-dioxaspiro[4.4]nonanes (**3**) in high yields. In addition, these compounds can be easily oxidised to the corresponding 1,7-dioxaspiro[4.4]nonan-6-ones **6**.[39] The present study covers the scope and limitations of this methodology in the synthesis of the title compounds including a wide range of electrophiles and discusses in some detail the spirocyclisation reaction mechanism as well as the stereoselectivity

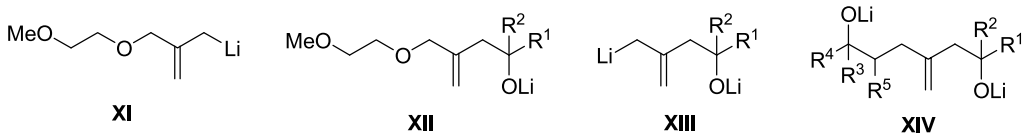


Chart 2.

observed. In addition, the structure of these compounds has been confirmed by X-ray diffraction analysis carried out for compound **3g**.

2. Results and discussion

The reaction of 2-chloromethyl-3-(2-methoxyethoxy)prop-1-ene (**1**) 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 ($E^1=R^1R^2CO$; 1:0.95 molar ratio) in THF, at temperatures ranging from −78 to 0 °C for ca. 3.5 h, led to a reaction mixture, which was treated with an excess of an epoxide as a second electrophile [$E^2=R^3R^4C(O)CHR^5$; 1:3 molar ratio] at 0 to 20 °C overnight giving, after hydrolysis with water, the corresponding methylidenic diols **2a–q** (Scheme 1 and Table 1). A wide variety of carbonyl compounds were utilised as the first electrophiles, including acyclic, cyclic, and heterocyclic ketones, as well as two aldehydes, whereas monosubstituted, 1,1-disubstituted, spirocyclic, and bicyclic oxiranes were used as the second electrophiles. In spite of the fact that the yields of diols **2** are moderate, this methodology is very advantageous since it allows the introduction of two different electrophiles in a one-pot sequence. It is noteworthy that even styrene oxide, which is prone to undergo reductive ring opening under the reaction conditions, could be introduced as a second electrophile in good yield (entry 4, Table 1). In the case of using cyclohexene oxide as the second electrophile, only the corresponding *trans*-diastereomeric products were obtained (entries 15–17, Table 1).

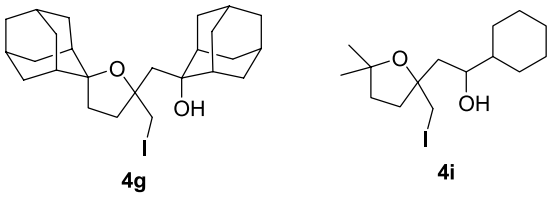
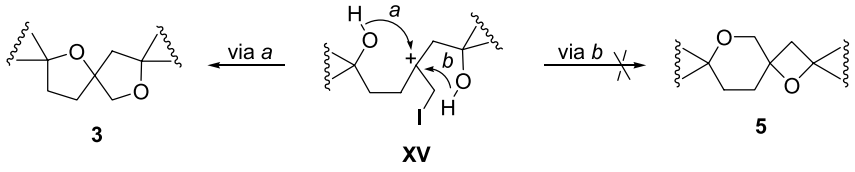
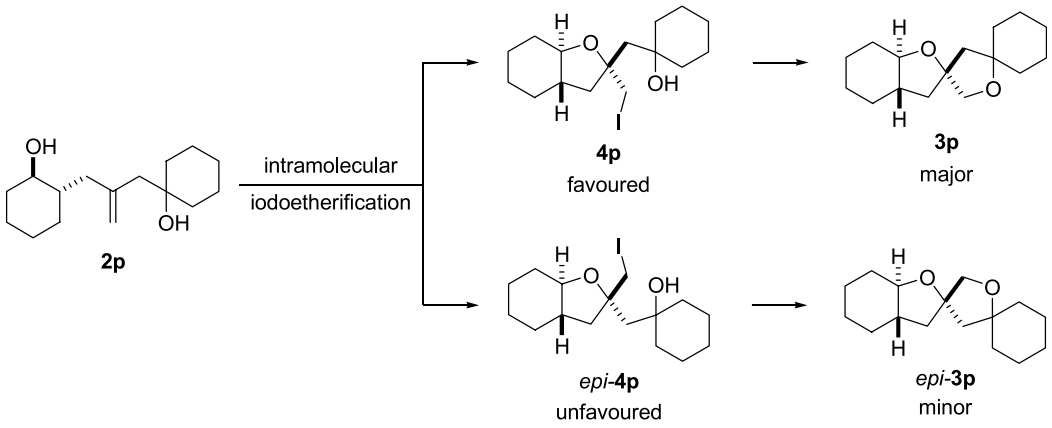


Chart 3.

This sequential incorporation of two electrophilic fragments arises from the different reactivity of the carbon–chlorine and carbon–oxygen bonds in arene-catalysed lithiations.[28–31] Thus, after the first chlorine–lithium exchange, a functionalised organolithium intermediate **XI** is formed,[40–42] which by reaction with a carbonyl compound (E^1) gives the expected alkoxide **XII**. This species can be lithiated at higher temperatures to yield a new dilithiated compound **XIII**, which by final reaction with an epoxide (E^2) affords the dialkoxide **XIV**, precursor of the diol formed **2** (Chart 2). The mediocre yield observed for some of the diols **2** (Table 1) was mainly due to competitive proton capture of carbanion **XIII** from the reaction medium instead of reaction with the corresponding epoxide.

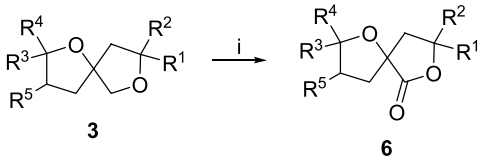


Scheme 2.



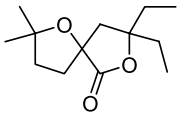
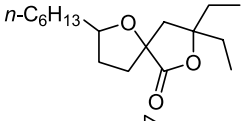
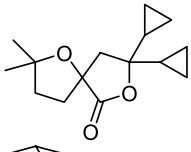
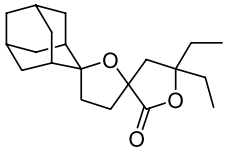
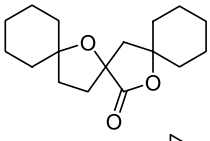
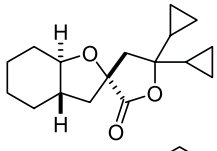
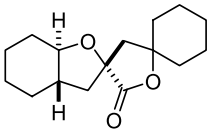
Scheme 3.

The isolated diols **2** were subjected to intramolecular cyclisation by treatment with iodine (1.5 equiv) and silver(I) oxide (1.5 equiv) in THF or a 7:1 mixture of dioxane–water at room temperature overnight, affording the corresponding 1,7-dioxaspiro[4.4]nonanes **3** in excellent yields and with such a high purity that they did not need any further purification (Scheme 1 and Table 1). Entries 1–5 in Table 1 show several monospirocyclic products. It is worth of note that chiral racemic diols where obtained when 1-octene and styrene oxides where used as second electrophiles (Table 1, entries 3 and 4), and consequently some asymmetric induction could be expected in the formation of the new spirocyclic stereocentre. Spirocyclisation of diol **2d** gave a disappointing 1:1 diastereomeric ratio, whereas a 3.5:1 ratio was observed for diol **2c**. Polyspirocyclic structures were easily obtained by the incorporation of cyclic ketones and spirocyclic epoxides in the starting diol (Table 1, entries 6–8). Symmetrically substituted dispirocyclic products **3g** and **3h** were readily prepared by using a cyclic carbonyl compound and its derived epoxide (Table 1, entries 7 and 8). In particular, compound **3g** was a solid and was subjected to X-ray diffraction analysis in order to provide more evidence about the presence of the 1,7-dioxaspiro[4.4]nonane skeleton in all products **3** (see Section 3). Unfortunately, cyclisation of diol **2i**, derived from cyclohexanecarboxaldehyde and isobutylene oxide, stopped at the iodohydrin stage, which however was apparently obtained as a single diastereoisomer (GLC, ^{1}H and ^{13}C NMR) (entry 9, Table 1). On the other hand, diol **2j** could be nicely cyclised to afford product **3j** as a 12:1 diastereomeric mixture. NOESY experiments carried out on compound **3j** did not provide any information about the relative stereochemistry of the major diasteroisomer. The heteroatom content in the whole structure of compounds **3** could be increased by choosing appropriate heteroatom-containing electrophiles. Thus,



Scheme 4. Reagents and conditions: (i) RuO_2 (0.15 equiv), $NaIO_4$ (4.88 equiv), CCl_4–H_2O 1:1, 20 °C.

Table 2. Oxidation of 1,7-dioxaspiro[4,4]nonanes **3** to lactones **6**

Entry	Starting compound	Product **6**[a]		
		No.	Structure	Yield (%)[b]
1	**3a**	**6a**		98
2	**3c**	**6c**		95
3	**3e**	**6e**		98
4	**3f**	**6f**		97
5	**3h**	**6h**		91
6	**3o**	**6o**		90[c]
7	**3p**	**6p**		93[d]

[a] All products were ≥95% pure (GLC and/or 300 MHz ^{1}H NMR).
[b] Yield of pure **6** from the reaction crude based on the starting compound **3**.
[c] Obtained as a 3.5:1 mixture of diastereoisomers (56% d.e.) (^{13}C NMR), the major diastereoisomer is shown.
[d] Obtained as a 12:1 mixture of diastereoisomers (85% d.e.) (^{13}C NMR), the major diastereoisomer is shown.

dispirocyclic compounds **3k–m** derived from tetrahydro-2*H*-pyran-4-one, *N*-propylpiperidin-4-one, and tetrahydrothio-2*H*-pyran-4-one with isobutylene oxide, were obtained in high yields (entries 11–13, Table 1). Even more interesting is the trispiro compound **3n**, derived from *N*-propylpiperidin-4-one and 1-oxa-6-thiaspiro[2.5]octane, which contains three different heteroatoms, oxygen, nitrogen and sulfur (entry 14, Table 1). The versatility of the methodology was also demonstrated in the synthesis of spirobicyclic ethers derived from an acyclic or cyclic ketone and cyclohexene oxide. In this case, cyclisation of the chiral racemic diols **2o–q** exhibited some diastereoselectivity, which was relatively high for compounds **3p** and **3q** [12:1 (85% d.e. and 13:1 (86% d.e.), respectively]. The structure of the major diasteroisomers of **3o–q** shown in Table 1 was determined by NOESY experiments (see Section 5). This result can be promising in the synthesis of chiral non-racemic 1,7-dioxaspiro[4.4]nonanes by utilising enantiomerically pure epoxides as second electrophiles.

It must be mentioned that spirocyclisation of the diol **2g** (entry 7, Table 1) could not be driven to completion, this explaines the lower yield observed in the formation of **3g** (70%) compared to the rest of compounds **3**. However, this reaction allowed the isolation of the corresponding iodohydrin intermediate **4g** (15%) (Chart 3). This fact, together with the isolation of the iodohydrin **4i** derived from diol **2i** gave us firm proofs about the mechanism of the spirocyclisation reaction (Chart 3). From compounds **4g**,**i** it can be inferred that the first cyclisation involves the nucleophilic attack of the epoxide derived hydroxylic moiety onto the iodonium ion (**XV**) in a 5-*exo* mode, followed by a nucleophilic displacement of iodide by the ketone derived hydroxylic moiety (Scheme 2, route a). The alternative cyclisation route involving 4-*exo* attack of the ketone derived hydroxylic moiety and nucleophilic displacement of iodide by the epoxide derived hydroxylic moiety did not occur at all (Scheme 2, route b). Therefore, the formation of 1,7-dioxaspiro[4.4]nonanes **3** is highly regioselective to the detriment of the less favoured 1,6-dioxaspiro[3.5]nonanes **5** (Scheme 2).

With a mechanism of spirocyclisation in hand, we tried to rationalize the diastereoselectivity observed in the cyclisation of compounds **2o–q** by using **2p** as a model compound. Thus, the geometry and the heats of formation of the diasteromeric intermediate iodohydrins were calculated and optimised with the semiempirical method PM3.[43] As a result, iodohydrin **4p** was found to be 4.7 kcal/mol more stable than the corresponding diastereoisomer *epi*-**4p**, which is in fair agreement with the 85% d.e. observed for compound **3p** (Scheme 3).

We believed that the spirocyclic compounds synthesized **3** could be used as adequate precursors of 1,7-dioxaspiro[4.4]nonan-6-ones **6**, which are also present as substructures in many natural products (see Chart 1). This transformation was successfully accomplished with the system composed of catalytic ruthenium(IV) oxide and sodium periodate,[44] leading to the corresponding lactones **6** in remarkable yields and without any further purification (Scheme 4, Table 2).

3. X-ray diffraction studies of compound 3g

Different attempts to crystallise compound **3g** led to very small and irregular crystals which were not good enough to be analysed by the single-crystal X-ray diffraction technique. On the other hand, the crystal structure determination of organic compounds by means of X-ray powder diffraction has been developed in recent years.[45] The data collected by this technique, in contrast to the single-crystal technique, have the inconvenience of peak overlapping. This limitation increases for most of the organic molecules composed of light atoms because of the decreasing of the peak intensity at high scattering angles. We used conventional X-ray powder diffractometers because, in contrast with the synchrotron radiation, are easily available and not expensive.

We could not use conventional direct methods for the structure solution because we were working with low quality data. However, we could work with initial organic structures as starting solutions and the support of other experimental techniques (IR, ^{1}H and ^{13}C NMR, MS and HRMS). We located such starting solutions on an indexed unit cell and refined it from the experimental diffraction data. We report herein the best solution found, which is in agreement with the structure proposed from other experimental techniques presented.

The samples were measured on a Siemens D5005 diffractometer with Bragg–Brentano geometry and with twin Göbel mirrors[46] as optical setup. A Cu sealed tube [λ(Kα1)=1.5406 Å] was used operating at 40 kV and 30 mA. The pattern was collected in the $4<2\theta<45$ range with a step size of 0.02° and counting time of 40 s per step. The sample was spun during the data acquisition in order to get the best peak profile and minimise the preferred orientation effect.

Once the data were collected with the greatest possible quality, the pattern was indexed using the program suite Crysfire.[47] The accepted solution was suggested by the programs *DICVOL91*[48] and *LZONv6.23b*,[49] based on the position of the 20 first peaks. The cell parameters, the zero point, the background and the peak shape (pseudo-Voigt function) were refined using the program Bruker AXS Topas.[50] The refined cell parameters were $a=6.4422(15)$, $b=10.9992(26)$, $c=28.3696(7)$, and $\beta=99.627(28)$. The systematic extinctions were consistent with the suggested monoclinic space group *P21/c*. This solution was also coherent with the expected values of density for the supposed molecule ($C_{25}H_{36}O_2$), since with

Table 3

	Cell refinement	Structural refinement
r_exp	3.00	3.75
r_exp_dash	2.94	3.46
r_wp	27.44	37.81
r_wp_dash	26.92	34.90
r_p	15.63	22.51
r_p_dash	15.45	21.87
weighted_Durbin_Watson	0.61	0.53
gof	9.15	10.07

$V=1981.92(10)$ Å^3 we obtained $Z=4$. In Table 3 it is shown the agreement factors of the cell refinement.

CHEM 3D[51] was used for the chemical modelling. We used different configurations in agreement with the other experimental analyses in order to test them with the diffraction data. Firstly, we located the different molecular solutions into the refined unit cell calculated with the F.O.X. program[52] from the experimental diffraction data. The best positioning obtained corresponds to the parameters Chi2=41534.562, GoF=26.78, RwP=0.54, Rp=0.36. The Rietveld method was used for the refinement of the positions of non H atoms with isotropic thermal factors using the Bruker AXS Topas program. Due to the low quality of the experimental data (because of the high overlapping and low intensity of the high angle peaks), we released the non hydrogen atomic positions within a box of 0.005 Å for each cycle. Once the new values of the atomic positions were calculated, the hydrogen positions were constrained to idealised positions with the WinGx program[53] at the end of each cycle. In the Figure 1 it is shown the variation of the atomic positions of the first cycle (F.O.X. solution) with respect to the last one (in green).

The agreement factors of the last cycle of the refinement are shown in Table 3, where 514 reflections were used. The experimental pattern (in black), calculated (in red) and the difference (in red) are shown in the Figure 2.

The resulting molecule was optimised by comparison with other models in which the oxygen atoms were located at different positions of the 1,7-dioxaspiro[4.4]nonane skeleton, a clear worsening of the obtained adjustments being observed. Therefore, it is possible to conclude that the technique of structural resolution by powder diffraction data is sensitive to changes of the atomic positions or the nature of atoms of the starting molecule, and that this technique has allowed the confirmation of the structure of compound **3g** (Fig. 3) as it was suggested by means of spectroscopic techniques.

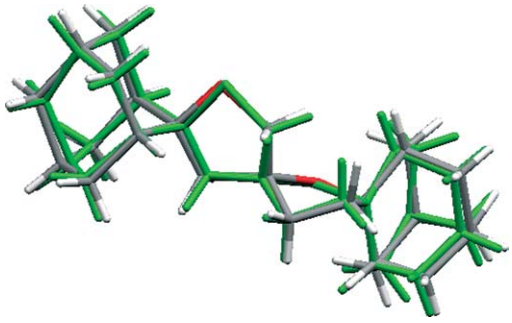


Figure 1.

4. Conclusions

We have described herein a methodology that gives a straight access to the synthesis of 1,7-dioxaspiro[4.4]-nonanes and 1,7-dioxaspiro[4.4]nonan-6-ones from 2-chloromethyl-3-(2-methoxyethoxy)prop-1-ene. This starting material behaves as a versatile trimethylenemethane dianion synthon under arene-catalyzed lithiation conditions,

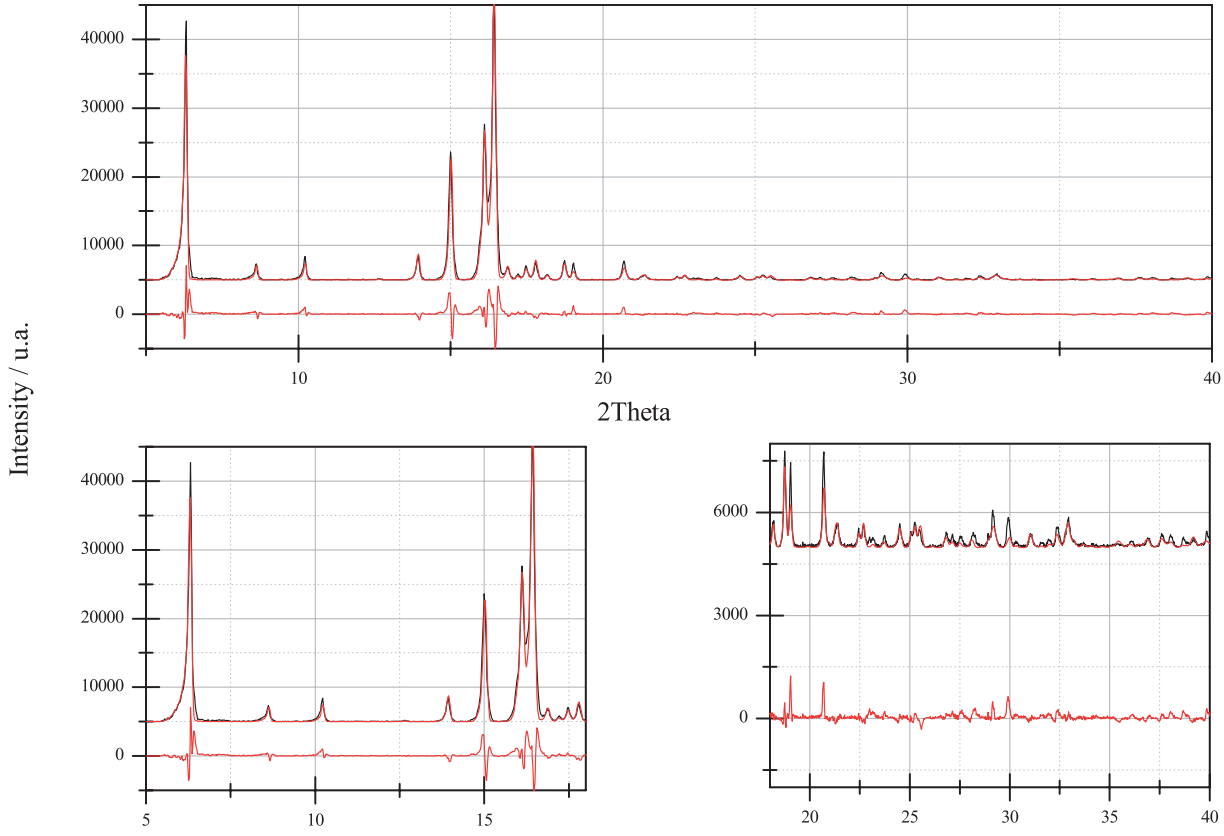


Figure 2.

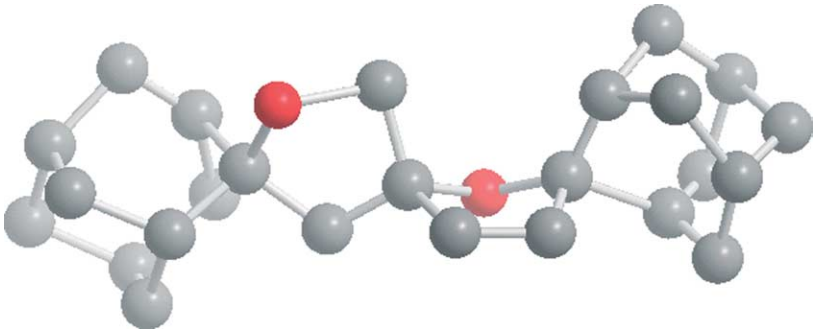


Figure 3.

allowing the one-pot incorporation of two different electrophilic fragments derived from a carbonyl compound and an epoxide. Iodine-promoted double intramolecular cyclisation of the resulting diols provides the expected spirocyclic ethers, which are easily oxidised to the corresponding lactones, all in excellent yields as well as in a regio- and stereoselective manner.

5. Experimental

5.1. General

Melting points were obtained with a Reichert Thermovar apparatus. NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) 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 ionization detector and a 12 m capillary column (0.2 mm diametre, 0.33 mm 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.). For the preparation of 2-chloromethyl-3-(2-methoxyethoxy)propene, see Ref. 30. Isobutylene, octene, styrene and cyclohexene oxides were commercially available. The other starting epoxides (α-methylstyrene, 2-pentylheptene, 2-methylideneadamantane, methylidenecyclohexane, 4-methylideneoxacyclohexane, and 4-methylidenethiacyclohexane oxides) were prepared from the corresponding ketones by reaction with the ylide derived from trimethylsulfoxonium iodide.[54]

5.2. General procedure for the preparation of diols 2

A solution of 2-chloromethyl-3-(2-methoxyethoxy)propene (164 mg, 1 mmol) and the corresponding carbonyl compound (0.95 mmol) in THF (3 ml), was added over 1.5 h to a green suspension of lithium powder (50 mg, 7 mmol) and DTBB (27 mg, 0.1 mmol) in THF (3 ml) at −78 °C. The mixture was allowed to reach 0 °C and then a solution of the corresponding epoxide (3 mmol) in THF (3 ml) was added over 1.5 h continuing the stirring for 8 h at room temperature. The reaction mixture was hydrolysed with water (5 ml), extracted with ethyl acetate (3×10 ml), and the organic phase was dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure (15 Torr), the resulting residue was purified by column chromatography (silica gel, hexane/EtOAc; EtOAc/MeOH was used for compounds **2k–n,q**) to yield compounds **2**. Compounds **2c,d,f,h,p** were previously described by us.[31] The physical and spectroscopic data of new compounds follow:

5.2.1. 7-Ethyl-2-methyl-5-methylenenonane-2,7-diol (2a). Colourless oil; t_r 11.04; R_f 0.33 (hexane/EtOAc 8:2); ν (film) 3388 (OH), 1639 (C=CH), 1133 cm^{-1} (CO); δ_H 0.87 (6H, t, J=7.4 Hz, 4×CH_3CH$_2$), 1.23 (6H, s, 2×CH$_3$C), 1.47 (4H, q, J=7.4 Hz, 2×CH_2CH$_3$), 1.60–1.66 (2H, m, CH$_2$CH_2COH), 1.97 (2H, s, 2×OH), 2.20–2.25 (4H, m, 2×CH_2C=CH$_2$), 4.79, 4.94 (2H, 2s, H$_2$C=C); δ_C 8.0 (2×CH$_3$CH$_2$), 29.2 (2×CH$_2$CH$_3$), 30.8 (2×CCH$_3$), 32.3 (CH$_2$CH$_2$COH), 42.0 (CH$_2$$CH_2$COH), 44.4 (C$CH_2$C), 70.8, 74.7, (2×COH), 113.4 (H$_2$$C$=C), 147.1 ($C$=CH$_2$); m/z 181 (M$^+$−33, 1%), 110 (13), 109 (16), 95 (74), 87 (85), 81 (14), 69 (21), 68 (27), 67 (14), 59 (25), 57 (88), 55 (19), 45 (98), 43 (100), 41 (41). HRMS calcd for $C_{13}H_{26}O_2$ 214.1933, (M$^+$−H$_2$O) 196.1827, found 196.1823.

5.2.2. 7-Ethyl-5-methylene-8-pentyltridecane-3,8-diol (2b). Colourless oil; t_r 15.76; R_f 0.38 (hexane/EtOAc 8:2); ν (film) 3361 (OH), 1640 (C=CH), 1030 cm^{-1} (CO); δ_H 0.75–0.95 (12H, m, 4×CH$_3$), 1.25–1.60 (24H, m, 11×CH_2CH$_2$, 2×OH), 2.05–2.20 (4H, m, 2×CH_2C=CH$_2$), 4.79, 4.94 (2H, 2s, H$_2$C=C); δ_C 7.9, 8.1 (4×CH$_3$), 29.3, 29.4, 29.7, 31.0, 31.6, 31.7, 44.5 (12×CH$_2$CH$_2$, CH$_2$C=CH$_2$), 74.4, 74.6 (2×COH), 113.4 (H$_2$$C$=C), 147.4 ($C$=CH$_2$); m/z 290 (M$^+$−36, 5%), 261 (24), 233 (15), 219 (48), 207 (43), 165 (15), 163 (16), 151 (18), 149 (20), 137 (22), 136 (11), 135 (54), 124 (21), 123 (52), 122 (13), 121 (26), 111 (11), 110 (20), 109 (45), 108 (11), 107 (56), 105 (14), 99 (13), 97 (17), 95 (62), 94 (12), 93 (52), 91 (29), 87 (47), 83 (23), 81 (68), 79 (38), 77 (18), 71 (20), 69 (53), 68 (12), 67 (51), 57 (48), 56 (11), 55 (100), 53 (15). HRMS calcd for $C_{21}H_{42}O_2$ 326.3185, found 326.3191.

5.2.3. 1,1-Dicyclopropyl-6-methyl-3-methyleneheptane-1,6-diol (2e). Colourless oil; t_r 12.82; R_f 0.23 (hexane/EtOAc 8:2); ν (film) 3355 (OH), 3051 (cyclopropyl C–H), 1642 (C=C), 1030 cm^{-1} (CO); δ_H 0.30–0.45 (8H, m, 4×CH_2CH), 0.75–0.85 (2H, m, 2×CH), 1.24 (6H, s, 2×CH_3), 1.62–1.68 (2H, m, CH_2CH_2COH), 2.29–2.35 (6H, m, 2×CH_2C=CH_2, 2×OH), 4.84, 4.93 (2H, 2s, H_2C=C); δ_C −0.3, 1.0 (4×CH_2CH), 19.1 (2×CH), 29.2 (2×CH_3), 32.3 (CH_2CH_2COH), 42.0 (CH_2CH_2COH), 48.2 (CCH_2C), 70.2, 71.0 (2×COH), 113.2 (H_2C=C), 147.2 (C=CH_2); *m/z* 220 (M^+−18, 1%), 117 (14), 111 (100), 105 (11), 95 (12), 91 (17), 69 (98), 59 (18), 55 (23), 53 (11), 43 (54), 41 (99). HRMS calcd for $C_{15}H_{26}O_2$ 238.1933, (M^+−H_2O) 220.1827, found 220.1804.

5.2.4. 2-[3-(2-Hydroxy-2-adamantylmethyl)-3-butenyl]-adamantan-2-ol (2g). Colourless solid; R_f 0.53 (hexane/EtOAc 8:2); mp 69–70 °C; ν (film) 3340 (OH), 1639 (C=CH), 1028 cm^{-1} (CO); δ_H 1.45–2.25 (34H, m, 8×CH, 13×CH_2), 2.47 (2H, s, 2×OH), 4.83, 4.97 (2H, 2s, H_2C=C); δ_C 27.0, 27.2, 27.4, 29.6, 36.9, 37.5, 38.4, 40.7 (8×CH), 30.6, 32.9, 33.1, 33.9, 34.6, 34.8, 35.0, 36.1, 37.0, 37.8, 38.3 (10×CH_2CH, CH_2CH_2CO), 41.1 (CH_2CH_2CO) 47.9 (CCH_2C), 74.3, 74.8 (2×CO), 114.0 (H_2C=C), 147.9 (C=CH_2); *m/z* 352 (M^+−18, >1%), 152 (11), 151 (100), 150 (36), 148 (16), 116 (11), 107 (13), 105 (10), 93 (17), 91 (27), 81 (25), 80 (28), 79 (42), 77 (15), 67 (14), 55 (18), 53 (10). Anal. calcd for $C_{25}H_{38}O_2$: C, 81.03; H, 10.34, found C, 80.95; H, 10.35.

5.2.5. 1-Cyclohexyl-6-methyl-3-methylideneheptane-1,6-diol (2i). Colourless oil; t_r 13.65; R_f 0.40 (hexane/EtOAc 8:2); ν (film) 3378 (OH), 1641 (C=CH), 1133 cm^{-1} (CO); δ_H 1.00–1.80 [13H, m, CHCHOH, $(CH_2)_5$, CH_2COH], 1.24 (6H, s, 2×CH_3), 1.85 (br s, 2×OH), 2.00–2.20 (3H, m, CH_2CH_2C=CH_2, CHC$H_A$$H_B$C), 2.31 (1H, d, J=12.0 Hz, CHC$H_A$$H_B$C), 3.48 (1H, ddd, J=10.2, 5.6, 2.8 Hz, CHO), 4.86, 4.93 (2H, 2s, H_2C=C); δ_C 26.2, 26.3, 26.5, 28.2, 29.1, 29.2 [$(CH_2)_5$, CH_2CH_2COH], 30.3 (2×CH_3), 41.5 (CH_2-CH_2COH), 41.6 (CHCOH), 43.5 (CCH_2CH), 70.9 (COH), 72.8 (CHOH), 112.2 (H_2C=C), 147.5 (C=CH_2); *m/z* 222 (M^+−18, <1%), 113 (11), 110 (21), 95 (100), 83 (12), 81 (15), 69 (14), 68 (29), 67 (21), 59 (30), 55 (48), 53 (11), 43 (48), 41 (64). HRMS calcd for $C_{15}H_{28}O_2$ 240.2089, (M^+−H_2O) 222.1984, found 222.1987.

5.2.6. 6-Methyl-3-methylene-1-(3,4,5-trimethoxyphenyl)heptane-1,6-diol (2j). Colourless oil; t_r 17.63; R_f 0.33 (MeOH/EtOAc 1:1); ν (film) 3394 (OH), 1595, 1507, 1630 (C=CH), 1127 cm^{-1} (CO); δ_H 1.25 (6H, s, 2×CH_3), 1.60–1.70 (2H, m, CH_2COH), 1.90–2.20 (6H, m, 2×OH, 2×CH_2C=CH_2), 3.83, 3.88 (9H, 2s, 3×CH_3O), 4.75–4.85 (1H, m, CHO), 4.94, 4.97 (2H, 2s, CH_2=C), 6.61 (2H, s, 2×ArH); δ_C 29.3 (2×CH_3), 30.4 (CH_2CH_2COH), 41.5 (CH_2CH), 46.9 (CH_2COH), 56.1, 60.8 (3×CH_3O), 70.9 (COH), 72.0 (CHOH), 102.7, 103.6 (2×ArCH), 112.7 (H_2C=C), 139.7, 139.8, 153.2 (4×ArC), 146.6 (C=CH_2); *m/z* 324 (M^+, <1%), 198 (11), 197 (100), 196 (25), 181 (10), 169 (44), 154 (16), 138 (17). HRMS calcd for $C_{18}H_{28}O_5$ 324.1937, found 324.1928.

5.2.7. 5-(4-Hydroxytetrahydro-2*H*-4-pyranylmethyl)-2-methyl-5-hexen-2-ol (2k). Colourless oil; t_r 12.65; R_f 0.43 (EtOAc); ν (film) 3396 (OH), 1639 (C=CH), 1097 cm^{-1} (CO); δ_H 1.23 (6H, m, 2×CH_3), 1.45–1.80 (6H, m, CH_2CH_2COH, 2×CH_2CH_2O), 2.03 (2H, br s, 2×OH), 2.18–2.25 (4H, m, 2×CH_2C=CH_2), 3.73–3.77 (4H, m, 2×CH_2CH_2O), 4.82, 4.98 (2H, 2s, H_2C=C); δ_C 29.3 (2×CH_3), 32.5 (CH_2CH_2COH), 38.0 (2×CH_2CH_2O), 41.7 (CH_2CH_2COH), 48.9 (CCH_2C), 63.8 (2×CH_2CH_2O), 68.5, 70.8 (2×COH), 114.1 (H_2C=C), 145.9 (C=CH_2); *m/z* 210 (M^+−18, <1%), 119 (12), 110 (32), 101 (46), 96 (10), 95 (100), 81 (13), 71 (28), 68 (23). HRMS calcd for $C_{13}H_{24}O_2$ 228.1725, found 228.1723.

5.2.8. 5-(4-Hydroxy-1-propyl-4-piperidylmethyl)-2-methyl-5-hexen-2-ol (2l). Colourless oil; t_r 14.55; R_f 0.30 (MeOH/EtOAc 1:1); ν (film) 3373 (OH), 1638 (C=CH), 1134 cm^{-1} (CO); δ_H 0.91 (3H, t, J=7.3 Hz, CH_3CH_2), 1.23 (6H, m, 2×CH_3C), 1.45–1.85 (8H, m, CH_2CH_2COH, 2×CH_2CH_2N, CH_2CH_3), 2.03 (2H, s, 2×OH), 2.15–2.23 (4H, m, 2×CH_2C=CH_2), 2.35–2.45, 2.75–2.85 (6H, 2m, 3×CH_2N), 4.82, 4.97 (2H, 2s, H_2C=C); δ_C 11.9 (CH_3CH_2), 19.5 (CH_2CH_3), 29.3 (2×CH_3), 32.5 (CH_2CH_2COH), 36.8 (2×CH_2CH_2N), 41.8 (CH_2CH_2OH), 49.1 (CCH_2C), 60.2 (3×CH_2N), 68.8, 70.8 (2×COH), 114.0 (H_2C=C), 146.2 (C=CH_2); *m/z* 269 (M^+, 2%), 240 (23), 222 (21), 142 (17), 140 (61), 124 (12), 112 (25), 98 (13), 72 (20), 70 (16), 59 (18), 57 (14), 56 (25), 55 (22), 44 (21), 43 (85), 42 (100), 41 (50). HRMS calcd for $C_{16}H_{31}NO_2$ 269.2355, found 269.2321.

5.2.9. 5-(4-Hydroxytetrahydro-2*H*-4-thiopyranylmethyl)-2-methyl-5-hexen-2-ol (2m). Colourless oil; t_r 14.53; R_f 0.45 (hexane/EtOAc 1:1); ν (film) 3385 (OH), 1637 (C=CH), 1127 cm^{-1} (CO); δ_H 1.24 (6H, m, 2×CH_3), 1.58–1.95 (6H, m, CH_2CH_2COH, 2×CH_2CH_2S), 1.95 (2H, br s, 2×OH), 2.18–2.22 (4H, m, 2×CH_2C=CH_2), 2.40, 2.44, (2H, 2m, 2×CH_2C$H_A$$H_B$S), 2.98 (2H, m, 2×$CH_2CH_A$$H_B$S), 4.80, 4.98 (2H, 2s, H_2C=C); δ_C 24.2 (2×CH_2S), 29.3 (2×CH_3), 32.7 (CH_2CH_2COH), 38.6 (2×CH_2CH_2S), 41.8 (CH_2CH_2COH), 49.2 (CCH_2C), 69.6, 70.9 (2×COH), 114.3 (H_2C=C), 145.8 (C=CH_2); *m/z* 244 (M^+, 1%), 110 (31), 99 (23), 95 (86), 88 (19), 87 (10), 83 (29), 81 (15), 79 (10), 71 (17), 69 (16), 68 (39), 67 (19), 61 (22), 60 (14), 59 (48), 55 (69), 53 (26), 47 (24), 46 (13), 45 (27), 44 (14), 43 (100), 42 (12), 41 (67), 40 (15). HRMS calcd for $C_{13}H_{24}O_2S$ 244.1497, found 244.1492.

5.2.10. 4-[2-(4-Hydroxytetrahydro-2*H*-4-thiopyranyl)-ethyl]allyl-1-propylpiperidin-4-ol (2n). Colourless oil; t_r 20.18; R_f 0.38 (MeOH/EtOAc 1:1); ν (film) 3385 (OH), 1638 cm^{-1} (C=CH); δ_H 0.90 (3H, t, J=7.3 Hz, CH_3CH_2,), 1.45–1.90 (12H, m, CH_2CH_2COH, 3×CH_2CH_2N, 2×CH_2CH_2S), 2.05 (2H, s, 2×OH), 2.18–2.23 (4H, m, 2×CH_2C=CH_2), 2.37–2.47 (2H, br dt, 2×C$H_A$$H_B$S), 2.25–2.35, 2.65–2.75 (6H, 2m, 3×CH_2N), 2.90–3.00 (2H, td, J=12.5, 2.8 Hz, 2×C$H_A$$H_B$S), 4.81, 4.96 (2H, 2s, H_2C=C); δ_C 12.0 (CH_3CH_2), 20.0 (CH_2CH_3), 24.3 (2×CH_2S), 30.6 (CCH_2CH_2COH), 37.2, 38.3 (2×CH_2CH_2N, 2×CH_2CH_2S), 41.4 (CCH_2CH_2COH), 49.5 (CCH_2C), 60.4, 60.7 (3×CH_2N), 69.3, 69.9 (2×COH), 114.3 (H_2C=C), 146.0 (C=CH_2); *m/z* 327 (M^+, 7%), 299 (20), 298 (99), 281 (37), 210 (10), 142 (20), 141 (15), 140 (100), 124 (12), 112 (27). HRMS calcd for $C_{18}H_{33}NO_2S$ 327.2232, found 327.2230.

5.2.11. 1,1-Dicyclopropyl-3-[(1*R,2*S**)-2-hydroxycyclohexylmethyl)]-3-buten-1-ol (2o).** Colourless oil; t_r 14.95; R_f 0.40 (hexane/EtOAc 8:2); ν (film) 3360 (OH), 3083 (cyclopropyl C–H), 1638 (C=CH), 1024 cm^{-1} (CO); δ_H 0.25–0.50 (8H, m, 4×cyclopropyl CH_2), 0.75–0.95 (2H, m, 2×cyclopropyl CH), 1.15–2.10 [12H, m, 2×OH, C*H*$_2$-CHCHOH, $(CH_2)_4$], 2.30, 2.39 (2H, AB system, J= 13.6 Hz, CCH_2C), 2.74 (1H, dd, J=13.9, 4.2 Hz, C*H*CHOH), 3.25 (1H, td, J=5.5, 4.2 Hz, CHOH), 4.87, 4.93 (2H, 2s, H_2C=C); δ_C −0.3, −0.2, 0.9, 1.0 (4× cyclopropyl CH_2), 18.9, 19.1 (2×cyclopropyl CH), 24.8, 25.5, 30.8, 35.5, 41.5 [$(CH_2)_4$, C*C*H$_2$CH], 43.7 (*C*HCOH), 47.6 (C*C*H$_2$C), 70.8 (COH), 75.2 (CHOH), 115.3 (H$_2$*C*=C), 146.1 (*C*=CH$_2$); *m/z* 246 (M^+−18, 1%), 160 (16), 145 (22), 120 (36), 119 (12), 117 (22), 111 (12), 105 (36), 92 (10), 91 (39), 79 (24), 77 (20), 69 (22), 67 (14), 65 (13), 57 (18), 55 (25), 53 (19), 51 (10), 43 (23), 41 (100), 40 (11). HRMS calcd for $C_{17}H_{28}O_2$ 264.2089, (M^+−H_2O) 246.1984, found 246.1980.

5.2.12. 4-[2-(1*R,2*S**)-(2-Hydroxycyclohexylmethyl)-allyl]tetrahydro-2*H*-pyran-4-ol (2q).** Colourless oil; t_r 15.68; R_f 0.30 (EtOAc); ν (film) 3441 (OH), 1641 (C=CH), 1106 cm^{-1} (CO); δ_H 1.15–2.05 (14H, m, $(CH_2)_4$, C*H*$_2$CHCHOH, 2×C*H*$_2$CH$_2$O), 2.22, 2.27 (2H, AB system, J=13.6 Hz, CC*H*$_2$C), 2.32 (2H, br s, 2×OH), 2.69 (1H, dd, J=13.9, 4.2 Hz, C*H*CHOH), 3.24 (1H, td, J= 5.5, 4.2 Hz, CHOH), 3.73–3.80 (4H, m, 2×CH_2O), 4.85–4.97 (2H, 2s, CH_2=C); δ_C 24.9, 25.5, 30.9, 35.7, 37.7, 38.6, 41.8 [C*C*H$_2$CH, 2×*C*H$_2$CH$_2$O, $(CH_2)_4$], 43.4 (*C*HCHOH), 48.3 (C*C*H$_2$C), 64.0 (2×CH_2O), 68.7 (COH), 75.3 (CHOH), 115.8 (H$_2$*C*=C), 144.7 (*C*=CH$_2$); *m/z* 236 (M^+−18, <1%), 136 (23), 121 (68), 107 (21), 101 (48), 99 (11), 98 (85), 95 (14), 94 (37), 93 (35), 91 (13), 83 (21), 81 (68), 80 (28), 79 (37), 77 (13), 71 (45), 69 (11), 68 (11), 67 (30), 57 (21), 55 (52), 54 (10), 53 (52), 43 (80), 42 (22), 41 (100). HRMS calcd for $C_{15}H_{26}O_3$ 254.1882, (M^+−H_2O) 236.1776, found 236.1786.

5.3. General procedure for the preparation of 1,7-dioxaspiro[4.4]nonanes 3. Isolation of iodohydrins 4g and 4i

Iodine (0.382 g, 1.5 mmol) was added to a solution of the corresponding diol **2** (1 mmol) in THF (20 ml) (dioxane/H_2O 7:1 was used for diols **2l**–**n**). The mixture was stirred for 5 min at room temperature and then Ag_2O (0.346 g, 1.5 mmol) was added with additional stirring for 24 h. The resulting suspension was filtered and water (10 ml) was added to the filtrate, followed by extraction with ethyl acetate (3×10 ml). The organic phase was successively washed with a saturated solution of Na_2SO_3 (2×10 ml) and water (2×10 ml), and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure (15 Torr) to furnish pure compounds **3**. Compound **3g** needed purification by column chromatography (silica gel, hexane/EtOAc).

5.3.1. 8,8-Diethyl-2,2-dimethyl-1,7-dioxaspiro[4.4]nonane (3a). Colourless oil; t_r 9.34; R_f 0.50 (hexane/EtOAc 8:2); ν (film) 1461, 1056 cm^{-1} (CO); δ_H 0.80–0.88 (6H, m, 2×C*H*$_3$CH$_2$), 1.20–1.30 (10H, m, 2×C*H*$_2$CH$_3$, 2×CCH$_3$), 1.35–2.15 (4H, CH_2CH_2), 1.75, 1.98 (2H, AB system, J= 13.2 Hz, CCH_2C), 3.64, 3.73 (2H, AB system, J=9.0 Hz, CH_2O); δ_C 8.4, 8.5 (2×*C*H$_3$CH$_2$), 28.9, 29.1, (2×*C*H$_3$C), 29.6, 30.0 (2×*C*H$_2$CH$_3$), 37.0, 38.8, (CH_2CH_2), 48.7 (C*C*H$_2$C), 76.6 (CH_2O), 80.7, 85.7, 89.5 (3×C); *m/z* 183 (M^+−29, 57%), 165 (10), 153 (32), 109 (57), 101 (12), 97 (17), 93 (25), 84 (15), 83 (21), 73 (18), 71 (11), 70 (29), 69 (43), 67 (12), 57 (100), 56 (29), 55 (66), 53 (13), 43 (81), 42 (15), 41 (85). HRMS calcd for $C_{13}H_{24}O_2$ 183.1385, found 183.1381.

5.3.2. 8,8-Diethyl-2,2-dipentyl-1,7-dioxaspiro[4.4]nonane (3b). Colourless oil; t_r 15.07; R_f 0.59 (hexane/EtOAc 8:2); ν (film) 1453, 1060 cm^{-1} (CO); δ_H 0.75–0.95 (12H, m, 4×CH_3), 1.20–2.10 (24H, m, 4×C*H*$_2$CH$_3$, 8×C*H*$_2$CH$_2$), 1.74, 1.99 (2H, AB system, J=13.1 Hz, CCH_2C), 3.61, 3.72 (2H, AB system, J=8.9 Hz, CH_2O); δ_C 8.5, 14.0 (4×CH_3), 22.6, 24.0, 24.1, 29.4, 29.6, 30.1, 32.5, 32.6, 35.5, 36.9, 39.2, 39.5 (4×*C*H$_2$CH$_3$, 8×*C*H$_2$CH$_2$), 48.4 (C*C*H$_2$C), 77.2 (CH_2O), 85.5, 85.7, 89.1 (3×C); *m/z* 295 (M^+−29, 22%), 253 (29), 139 (21), 121 (45), 109 (21), 101 (21), 99 (11), 97 (19), 95 (14), 83 (20), 81 (13), 71 (20), 69 (29), 67 (15), 57 (100), 56 (18), 55 (77), 43 (94), 42 (10), 41 (84). HRMS calcd for $C_{21}H_{40}O_2$ 324.3028, (M^+−C_2H_5) 295.2637, found 295.2638.

5.3.3. (2*R,5*R**) and (2*R**,5*S**)-8,8-Diethyl-2-hexyl-1,7-dioxaspiro[4.4]nonane (3c).** Colourless oil; t_r 13.38; R_f 0.50 (hexane/EtOAc 8:2); ν (film) 1459, 1060 cm^{-1} (CO); δ_H 0.75–1.00 (18H, m, 6×CH_3), 1.15–2.10 (40H, m, 6×C*H*$_2$CH$_3$, 12×C*H*$_2$CH$_2$, 2×CCH$_2$C), 3.40–3.45 (1H, m, CH minor diastereoisomer), 3.61, 3.76 (2H, AB system, J= 9.1 Hz, CH_2O minor diastereoisomer), 3.63, 3.80 (2H, AB system, J=9.1 Hz, CH_2O major diastereoisomer), 3.75–3.90 (1H, m, CH major diastereoisomer); δ_C 8.5, 13.4 (6×CH_3), 22.5, 26.0, 29.3, 29.4, 29.7, 29.8, 30.0, 31.3, 31.6, 31.7, 34.9, 36.2, 36.3 (6×*C*H$_2$CH$_3$, 12×*C*H$_2$CH$_2$), 47.4, 48.1 (2×C*C*H$_2$C), 76.0, 76.6 (2×CH), 78.8, 79.0 (2×CH_2O), 85.9, 86.0, 89.4 (4×C); *m/z* 239 (M^+−29, 33%), 221 (10), 109 (11), 83 (20), 69 (12), 57 (90), 55 (63), 43 (72), 41 (100). HRMS calcd for $C_{17}H_{32}O_2$ 268.2402, (M^+−C_2H_5) 239.2011, found 239.1992.

5.3.4. (2*R,5*R**) and (2*R**,5*S**)-8,8-Diethyl-2-phenyl-1,7-dioxaspiro[4.4]nonane (3d).** Colourless oil; t_r 14.08, 14.40; R_f 0.61, 0.63 (hexane/EtOAc 8:2); ν (film) 1459, 1060 cm^{-1} (CO); δ_H 0.75–0.95 (12H, m, 4×CH_3), 1.20–2.40 (20H, m, 4×C*H*$_2$CH$_3$, 2×CH_2CH_2, 2×CCH$_2$C), 3.70, 3.93 (2H, AB system, J=9.1 Hz, CH_2O), 3.75, 3.98 (2H, AB system, J= 9.5 Hz, CH_2O), 4.20, 4.93 (2H, 2t, J=8.9 Hz, CHPh), 7.20–7.40 (10H, m, 10×ArH); δ_C 8.5, 8.55, 8.6, 8.65 (4×CH_3), 29.7, 29.8, 29.9, 35.0, 35.1, 42.8, 45.0, 46.0 (4×*C*H$_2$CH$_3$, 2×CH_2CH_2), 48.4 (2×C*C*H$_2$C), 77.2 (2×CH_2O), 80.4 (2×CHO), 86.3, 86.7, 90.5, 90.8 (4×C); *m/z* (t_r 14.08) 231 (M^+−29, 52%), 129 (10), 109 (28), 105 (17), 104 (65), 91 (21), 77 (10), 57 (100), 55 (33), 53 (10), 43 (24), 41 (28), 40 (11); *m/z* (t_r 14.40) 231 (M^+−29, 30%), 91 (16), 83 (20), 57 (100), 55 (24), 43 (12), 41 (15). HRMS calcd for $C_{17}H_{24}O_2$ 260.1776, (M^+−C_2H_5) 231.3102, found 231.3100.

5.3.5. 8,8-Dicyclopropyl-2,2-dimethyl-1,7-dioxaspiro-[4.4]nonane (3e). Colourless oil; t_r 15.07; R_f 0.65 (hexane/EtOAc 8:2); ν (film) 3060 (cyclopropyl C–H), 1054 cm^{-1} (CO); δ_H 0.30–0.50 (8H, m, 4×C*H*$_2$CH), 0.80–0.95, 1.00–1.15 (2H, 2m, 2×CH), 1.20, 1.24 (6H, 2s,

2×CH_3), 1.70–1.85, 1.95–2.15 (4H, 2m, CH_2CH_2), 1.76, 1.98 (2H, AB system, J=13.3 Hz, CCH_2C), 3.60, 3.73 (2H, AB system, J=8.7 Hz, CH_2O); δ_C 0.5, 0.6, 1.3, 1.5 (4×CH_2CH), 18.8, 19.1 (2×CH), 28.9, 29.1 (2×CH_3), 36.7, 38.8 (CH_2CH_2), 48.1 (CCH_2C), 77.7 (CH_2O), 80.7, 83.4, 89.1 (3×C); *m/z* 236 (M^+, <1%), 195 (67), 121 (13), 109 (12), 93 (10), 79 (13), 69 (65), 67 (14), 55 (40), 43 (90), 41 (100). HRMS calcd for $C_{15}H_{24}O_2$ 236.1776, ($M^+-C_3H_5$) 195.1395, found 195.1404.

5.3.6. 2″,2‴-Diethyldispiro[adamantane-2,2′-tetrahydrofuran-5′,4‴-tetrahydrofuran] (3f). Colourless oil; t_r 16.28; R_f 0.75 (hexane/EtOAc 8:2); ν (film) 1460, 1061 cm^{-1} (CO); δ_H 0.70–0.85 (6H, m, 2×CH_3), 1.15–2.10 (24H, m, 2×CH_2CH_3, CCH_2C, CCH_2CH_2C, 4×C$H$$CH_2$, 5×C$H_2$CH), 3.62, 3.74 (2H, AB system, J=8.9 Hz, CH_2O); δ_C 8.6, 8.7 (2×CH_3), 27.2, 27.4, 36.1, 37.8, (4×CH), 31.3, 32.9, 33.2, 33.3, 34.4, 35.3, 35.9, 37.0, 37.7 (5×CH_2CH, CH_2CH_2, 2×CH_2CH_3), 49.5 (CCH_2C), 75.7 (CH_2O), 85.9, 86.2, 89.2 (3×C); *m/z* 304 (M^+, <1%), 276 (13), 275 (71), 203 (34), 190 (11), 175 (12), 166 (11), 135 (99), 151 (41), 149 (16), 148 (15), 135 (38), 133 (10), 121 (11), 105 (14), 97 (10), 95 (11), 93 (24), 92 (13), 91 (38), 81 (19), 80 (12), 79 (44), 77 (17), 69 (21), 67 (32), 65 (10), 57 (84), 55 (100), 53 (22), 43 (44), 42 (11), 41 (95). HRMS calcd for $C_{20}H_{32}O_2$ 304.2402, ($M^+-C_2H_5$) 275.2011, found 275.2015.

5.3.7. Dispiro[adamantane-2,2′-tetrahydrofuran-5′,4″-tetrahydrofuran-2″,2‴-adamantane] (3g). Colourless solid; R_f 0.67 (hexane/EtOAc 8:2); mp 48–49 °C; ν (film) 1469, 1065 cm^{-1} (CO); δ_H 1.40–2.28 (34H, m, 8×CH, 10×CH_2CH, CH_2CH_2, CCH_2C), 3.66, 3.77 (2H, AB system, J=8.9 Hz, CH_2O); δ_C 26.8, 27.1, 27.2, 27.3, 35.7, 38.0, 38.3, 38.8 (8×CH), 33.0, 33.4, 33.5, 33.7, 35.2, 35.5, 35.7, 35.8, 35.9, 36.3, 37.8, 37.9 (10×CH_2CH, CH_2CH_2), 49.7 (CCH_2C), 76.5 (CH_2O), 86.3, 86.6, 88.7 (3×C); *m/z* 368 (M^+, 2%), 338 (10), 206 (15), 205 (100), 204 (11), 165 (28), 151 (15), 91 (12), 79 (15). HRMS calcd for $C_{25}H_{36}O_2$ 368.2715, found 368.2711.

5.3.8. Trispiro[cyclohexane-1,2′-tetrahydrofuran-5′,4″-tetrahydrofuran-2″,1‴-cyclohexane] (3h). Colourless oil; t_r 14.45; R_f 0.45 (hexane/EtOAc 8:2); ν (film) 1459, 1061 cm^{-1} (CO); δ_H 1.20–2.10 (24H, m, 12×CH_2CH_2), 1.72, 2.01 (2H, AB system, J=12.8 Hz, CCH_2C), 3.65, 3.76 (2H, AB system, J=8.9 Hz, CH_2O); δ_C 23.5, 23.8, 23.9, 25.5, 25.6, 35.9, 36.1, 37.9, 38.3, 38.7 (12×CH_2CH_2), 50.3 (CCH_2C), 76.3 (CH_2O), 82.6, 82.8, 88.6 (3×C); *m/z* 264 (M^+, 14%), 221 (12), 165 (11), 155 (14), 152 (25), 151 (14), 133 (15), 125 (13), 113 (71), 109 (12), 97 (20), 96 (14), 95 (33), 94 (19), 91 (12), 81 (36), 79 (27), 69 (17), 67 (50), 57 (10), 55 (81), 54 (24), 53 (22), 43 (40), 42 (22), 41 (100), 40 (18). HRMS calcd for $C_{17}H_{28}O_2$ 264.2089, found 264.2122.

5.3.9. 2,2-Dimethyl-8-(3,4,5-trimethoxyphenyl)-1,7-dioxaspiro[4.4]nonane (3j) (major diastereoisomer). Colourless oil; t_r 17.21; R_f 0.55 (EtOAc); ν (film) 1591, 1506 (C=CH), 1127 cm^{-1} (CO); δ_H 1.27, 1.31 (6H, 2s, 2×CH_3), 1.70–2.20 (6H, m, CH_2CH_2, CH_2CH), 3.83, 3.86 (9H, 2s, 3×CH_3O), 3.84, 3.87 (2H, AB system, J=9.0 Hz, CH_2O), 5.04 (1H, dd, J=10.1, 5.9 Hz, CHO), 6.57 (2H, s, 2×ArH); δ_C 29.1 (2×CH_3), 35.0, 37.7 (CH_2CH_2), 48.8 (CH_2CH), 56.1, 60.8 (3×CH_3O), 77.2 (CH_2O), 79.5, 80.8 (2×C), 89.7 (CHO), 102.6 (2×ArCH), 138.1, 153.3 (4×ArC); *m/z* 322 (M^+, 85%), 251 (15), 221 (12), 211 (16), 195 (60), 194 (23), 182 (13), 181 (100), 179 (27). HRMS calcd for $C_{18}H_{26}O_5$ 322.1780, found 322.1767.

5.3.10. 2,2-Dimethyldispiro[tetrahydrofuran-5,4′-tetrahydrofuran-2′,4″-tetrahydro-2*H*-pyran] (3k). Colourless oil; t_r 11.48; R_f 0.34 (hexane/EtOAc 1:1); ν (film) 1051 cm^{-1} (CO); δ_H 1.22, 1.24 (6H, 2s, 2×CH_3), 1.60–2.10 (8H, m, 2×CH_2CH_2O, CCH_2CH_2C), 1.77, 2.08 (2H, AB system, J=13.0 Hz, CCH_2C), 3.56–3.65, 3.77–3.86 (4H, 2m, 2×CH_2CH_2O), 3.61, 3.72 (2H, AB system, J=9.2 Hz, CH_2O); δ_C 29.0, 29.1 (2×CH_3), 36.3, 37.2, 37.9, 38.7 (2×CH_2CH_2O, CCH_2CH_2C), 51.0 (CCH_2C), 65.1, 65.2 (2×CH_2CH_2O), 77.2 (CCH_2O), 79.4, 81.1, 89.2 (3×C); *m/z* 226 (M^+, 10%), 140 (15), 125 (14), 122 (28), 115 (52), 112 (17), 97 (12), 95 (13), 83 (53), 81 (13), 70 (40), 69 (25), 68 (16), 67 (22), 57 (14), 56 (33), 55 (45), 53 (27), 43 (100), 42 (27), 41 (91), 40 (23). HRMS calcd for $C_{13}H_{22}O_3$ 295.1569, found 226.1571.

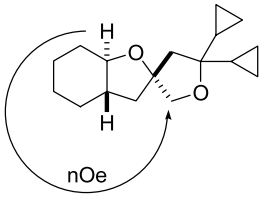
5.3.11. 2″,2‴-Dimethyl-1-propyldispiro[piperidine-4,2′-tetrahydrofuran-4′,5‴-tetrahydrofuran] (3l). Colourless oil; t_r 14.01; R_f 0.25 (EtOAc/MeOH 1:1); ν (film) 1057 (CO); δ_H 0.92 (3H, t, J=7.4 Hz, CH_3CH_2), 1.20, 1.22 (6H, 2s, 2×CCH_3), 1.40–2.10 (10H, m, CCH_2CH_2C, 2×CH_2CH_2N, CH_2CH_3), 1.73, 2.07 (2H, AB system, J=13.0 Hz, CCH_2C), 2.35–2.45, 2.70–2.80 (6H, 2m, 3×CH_2N), 3.63, 3.75 (2H, AB system, J=9.2 Hz, CH_2O); δ_C 12.1 (CH_3CH_2), 19.4 (CH_2CH_3), 28.7, 29.0 (2×CH_3C), 35.5, 36.1, 37.3, 37.5 (2×CH_2CH_2N, CCH_2CH_2C), 43.8 ($NCH_2CH_2CH_3$), 51.3 (CCH_2C), 60.1, 60.2 (2×NCH_2CH_2-C), 77.0 (CH_2O), 80.0, 81.1, 81.9 (3×C); *m/z* 267 (M^+, 3%), 239 (17), 238 (100), 110 (10). HRMS calcd for $C_{16}H_{29}NO_2$ 267.2198, found 267.2198.

5.3.12. 2,2-Dimethyldispiro[tetrahydrofuran-5,4′-tetrahydrofuran-2′,4″-tetrahydro-2*H*-thiopyran] (3m). Colourless oil; t_r 13.46; R_f 0.35 (hexane/EtOAc 7:3); ν (film) 1021 cm^{-1} (CO); δ_H 1.22, 1.26 (6H, 2s, 2×CH_3), 1.60–2.10 (8H, m, 2×CH_2CH_2S, CCH_2CH_2C), 1.78, 2.07 (2H, AB system, J=13.6 Hz, CCH_2C), 2.25–2.50, 2.75–2.90 (4H, 2m, 2×CH_2CH_2S), 3.69, 3.79 (2H, AB system, J=9.2 Hz, CH_2O); δ_C 25.4, 26.2 (2×CH_2CH_2S), 29.0, 29.1 (2×CH_3), 35.7, 38.7, 42.5, 42.6 (2×CH_2CH_2S, CCH_2CH_2-C), 52.5 (CCH_2C), 77.2 (CH_2O), 79.0, 81.4, 89.3 (3×C); *m/z* 242 (M^+, <1%), 227 (10), 209 (11), 140 (21), 125 (15), 110 (35), 99 (45), 98 (43), 97 (41), 83 (51), 81 (11), 70 (41), 67 (22), 57 (14), 53 (12), 44 (10), 43 (100), 42 (17). HRMS calcd for $C_{13}H_{22}O_2S$ 242.1341, (M^+-CH_3) 227.1106, found 227.1104.

5.3.13. 1-Propyltrispiro[piperidine-4,2′-tetrahydrofuran-4′,2″-tetrahydrofuran-5″,4‴-tetrahydro-2*H*-thyopyran] (3n). Colourless oil; t_r 18.51; R_f 0.10 (EtOAc); ν (film) 1045 cm^{-1} (CO); δ_H 0.87 (3H, t, J=7.4 Hz, CH_3CH_2), 1.40–2.10 (14H, m, CH_2CH_3, 2×CH_2CH_2N, 2×CH_2CH_2S, CCH_2CH_2C), 1.70, 2.05 (2H, AB system, J=12.8 Hz, CCH_2C) 2.20–2.75 (10H, 2×CH_2S, 3×CH_2N), 3.60, 3.73 (2H, AB system, J=9.3 Hz, CH_2O);δ_C 11.8 (CH_3CH_2), 22.5 (CH_2CH_3), 24.1, 24.3 (2×CH_2S), 33.3, 35.2, 37.1, 37.5, 38.0, 38.1 (CCH_2CH_2C, 2×CH_2CH_2N, 2×CH_2CH_2S), 49.9, 50.8 ($NCH_2CH_2CH_3$,

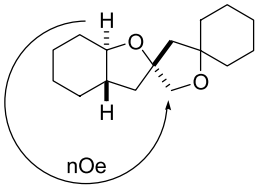
C*C*H$_2$C), 58.3, 59.0 (2×N*C*H$_2$CH$_2$C), 76.8 (CH$_2$O), 82.2, 82.4, 84.3 (3×C); *m/z* 325 (M$^+$, <1%), 296 (100), 282 (30), 142 (12), 141 (70), 140 (12), 124 (23), 123 (10), 112 (29), 44 (36), 43 (20), 42 (20), 41 (11). HRMS calcd for $C_{18}H_{31}NO_2S$ 325.2075, found 325.2070.

5.3.14. (2*R,3a*S**,7a*R**) and (2*R**,3a*R**,7a*S**)-2′,2′-Dicyclopropylspiro[perhydrobenzo[*b*]furan-2,4′-tetrahydrofuran] (3o).** Colourless oil; t_r 14.65; R_f 0.40 (hexane/EtOAc 8:2); *ν* (film) 3053 (cyclopropyl C–H), 1063 cm^{-1} (CO); δ_H 0.25–0.50 (16H, m, 8×cyclopropyl C*H*$_2$CH), 0.75–1.00 (4H, m, 4×cyclopropyl CH), 1.05–2.20 [26H, m, 2×(CH$_2$)$_4$, 2×CC*H*$_2$CH, 2×C*H*CHO, 2×CCH$_2$C], 3.00 (1H, td, *J*=10.0, 3.8 Hz, CHO major diastereoisomer), 3.05–3.15 (1H, m, CHO minor diastereoisomer), 3.48, 3.76 (2H, AB system, *J*=8.9 Hz, CH$_2$O minor diastereoisomer), 3.59, 3.87 (2H, AB system, *J*=9.2 Hz, CH$_2$O major diastereoisomer); δ_C −0.4, 0.1, 0.3, 0.6, 1.0, 1.2, 1.3, 1.4 (8×cyclopropyl *C*H$_2$CH), 18.5, 18.8, 19.0, 19.3 (4×cyclopropyl CH), 24.3, 25.4, 25.8, 28.8, 29.0, 29.4, 31.4, 31.5, 40.0, 40.6 [2×(CH$_2$)$_4$, 2×C*C*H$_2$CH], 45.4, 45.7 (2×*C*HCHO), 48.3, 48.9 (2×C*C*H$_2$C), 78.1, 78.4 (2×CH$_2$O), 82.8, 83.2 (2×CHO), 84.1, 84.3, 87.9, 88.2 (4×C); *m/z* 262 (M$^+$, <1%), 222 (15), 221 (100), 121 (11), 95 (10), 81 (11), 79 (13), 69 (14), 67 (11), 57 (17), 55 (55), 54 (25), 53 (35), 44 (10), 43 (79), 42 (27), 41 (100), 40 (27). HRMS calcd for $C_{17}H_{26}O_2$ 262.1933, found 262.1931.

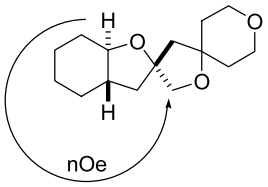


major diastereoisomer

5.3.15. (2″*R,3a″*S**,7a″*R**)-Dispiro[cyclohexane-1,2′-tetrahydrofuran-4′,2″-perhydrobenzo[*b*]furan] (3p).** Colourless oil; t_r 14.33; R_f 0.43 (hexane/EtOAc 8:2); *ν* (film) 1447, 1064 cm^{-1} (CO); δ_H 1.20–2.10 (21H, m, 9×C*H*$_2$CH$_2$, CC*H*$_2$CH, C*H*CHO), 1.76, 2.03 (2H, AB system, *J*=13.2 Hz, CCH$_2$C), 3.02 (1H, td, *J*=10.1, 3.6 Hz, CHO), 3.64, 3.90 (2H, AB system, *J*=9.4 Hz, CH$_2$O); δ_C 23.7, 23.8, 24.3, 25.4, 25.7, 29.0, 31.6, 37.3, 37.7, 40.6 (9×*C*H$_2$CH$_2$, C*C*H$_2$CH), 45.4 (*C*HCHO), 51.3 (C*C*H$_2$C), 76.2 (CH$_2$O), 83.1 (CHO), 83.2, 88.4 (2×C); *m/z* 250 (M$^+$, 16%), 221 (15), 207 (37), 155 (24), 154 (18), 152 (30), 119 (16), 113 (12), 107 (22), 96 (10), 95 (24), 82 (15), 81 (57), 80 (14), 79 (22), 69 (11), 68 (10), 67 (47), 57 (11), 55 (74), 54 (20), 53 (27), 43 (37), 42 (19), 41 (100), 40 (16). HRMS calcd for $C_{16}H_{26}O_2$ 250.1933, found 250.1963.



5.3.16. (2*R,3a*S**,7a*R**)-Dispiro[perhydrobenzo[*b*]-furan-2,4′-tetrahydrofuran-2′,4″-tetrahydro-2*H*-pyran] (3q).** Colourless oil; t_r 14.59; R_f 0.34 (hexane/EtOAc 1:1); *ν* (film) 1055 cm^{-1} (CO); δ_H 1.00–2.20 [15H, m, 2×C*H*$_2$CH$_2$CO, (CH$_2$)$_4$, CC*H*$_2$CH, C*H*CHO], 1.80, 2.07 (2H, AB system, *J*=13.3 Hz, CCH$_2$C), 3.04 (1H, td, *J*=10.1, 3.7 Hz, CHO), 3.60–3.90 (4H, m, 2×CH$_2$C*H*$_2$O), 3.67, 3.93 (2H, AB system, *J*=9.5 Hz, CH$_2$O); δ_C 24.2, 25.6, 28.9, 31.1, 31.5, 37.9, 40.0 [(CH$_2$)$_4$, C*C*H$_2$CH, *C*H$_2$CH$_2$O], 45.3 (*C*HCHO), 51.6 (C*C*H$_2$C), 65.1, 67.3 (CH$_2$*C*H$_2$O), 76.4 (CH$_2$O), 79.9, 88.2 (2×C), 83.3 (CHO); *m/z* (t_r 14.59) 252 (M$^+$, 4%), 208 (10), 155 (12), 154 (13), 122 (14), 107 (21), 115 (17), 108 (17), 99 (17), 98 (14), 97 (11), 96 (19), 95 (23), 94 (12), 83 (34), 82 (16), 81 (43), 80 (10), 79 (20), 70 (12), 69 (14), 68 (24), 67 (58), 57 (14), 55 (53), 54 (22), 53 (33), 43 (49), 42 (24), 41 (100), 40 (25). HRMS calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1724.



5.3.17. 5′-(2-Hydroxy-2-adamantylmethyl)-5′-iodomethylspiro[adamantane-2,2′-tetrahydrofuran] (4g). Colourless oil; R_f 0.60 (hexane/EtOAc 8:2); *ν* (film) 3444 (OH), 1100 cm^{-1} (CO); δ_H 1.20–2.20 (35H, m, 8×CH, 10×C*H*$_2$CH, OH, CCH$_2$CH$_2$C, CCH$_2$C), 3.33, 3.51 (2H, AB system, *J*=9.8 Hz, CH$_2$I); δ_C 15.1 (CH$_2$I), 26.2, 26.3, 27.3, 27.4, 29.4, 36.3, 37.4, 39.1 (8×CH), 31.0, 31.7, 31.8, 32.4, 32.9, 33.0, 33.3, 33.5, 34.4, 34.7, 38.4, 40.0, 42.5 (10×*C*H$_2$CH, C*C*H$_2$C, CC*H*$_2$*C*H$_2$C), 74.0, 78.1, 82.5 (3×C); *m/z* 368 (M$^+$−128, <1%), 338 (10), 206 (10), 205 (100), 151 (10), 79 (11), 127 (25), 126 (45), 43 (22), 42 (13). HRMS calcd for $C_{25}H_{37}IO_2$ 496.1838, (M$^+$−HI) 368.2715, found 368.2701.

5.3.18. 1-Cyclohexyl-2-(2-iodomethyl-5,5-dimethyltetrahydro-2-furanyl)ethan-1-ol (4i). Colourless oil; t_r 12.52; R_f 0.62 (hexane/EtOAc 8:2); *ν* (film) 3380 (OH), 1050 cm^{-1} (CO); δ_H 0.98–2.00 [16H, m, (CH$_2$)$_5$, CCH$_2$CH$_2$C, CHC*H*$_A$-H$_B$C, OH], 1.25, 1.28 (6H, 2s, 2×CH$_3$), 2.23–2.35 (2H, 2m, CHCH$_A$*H*$_B$C, C*H*CHOH), 3.19, 3.40 (2H, AB system, *J*=10.2 Hz, CH$_2$I,), 3.55–3.60 (1H, m, C*H*OH); δ_C 12.4 (CH$_2$I), 26.2, 26.3, 26.6, 28.4, 28.6 [(CH$_2$)$_5$], 29.0, 29.5 (2×CH$_3$), 37.5, 38.1 (CC*H*$_2$*C*H$_2$C), 41.1 (CH*C*H$_2$C), 44.0 (*C*HCHOH), 72.3 (CHOH), 84.3, 85.5 (2×C); *m/z* 238 (M$^+$−128, <1%), 155 (49), 127 (25), 126 (45), 125 (47), 113 (21), 97 (11), 95 (36), 93 (11), 83 (11), 81 (24), 70 (15), 69 (25), 67 (22), 57 (11), 56 (18), 55 (84), 54 (10), 53 (16), 43 (83), 42 (12), 41 (100). HRMS calcd for $C_{15}H_{27}IO_2$ 366.1056, (M$^+$−HI) 238.1933, found 238.1911.

5.4. General procedure for the oxidation of 1,7-dioxaspiro[4.4]nonanes 3 to lactones 6

A suspension of RuO_2 (21 mg, 0.16 mmol) and $NaIO_4$ (1.04 g, 4.88 mmol) in H_2O (5 ml) was added to a solution of the corresponding 1,7-dioxaspiro[4.4]nonane **3** (1.0 mmol) in CCl_4 (5 ml) at room temperature. After stirring the reaction for 24 h, Pr^{i}OH (3 ml) was added, the resulting mixture being extracted with CCl_4 (2×5 ml). The

organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The resulting residue was passed through a pad containing celite, in order to eliminate the remaining ruthenium compounds, yielding the corresponding pure lactones **6**, which did not require any further purification.

5.4.1. 8,8-Diethyl-2,2-dimethyl-1,7-dioxaspiro[4.4]nonan-6-one (6a). Colourless oil; t_r 11.05; R_f 0.31 (hexane/EtOAc 8:2); ν (film) 1770 (C=O), 1050 cm^{-1} (CO); δ_H 0.80–0.95 (6H, m, 2×CH_3CH$_2$), 1.21–1.29 (6H, m, 2×CH_3C), 1.35–1.40 (4H, m, 2×CH_2CH$_3$), 1.35–2.25 (4H, m, CH$_2$CH$_2$), 2.05, 2.24 (2H, AB system, J=13.7 Hz, CCH$_2$C); δ_C 7.7, 7.8 (2×CH$_3$CH$_2$), 28.3, 28.9 (2×CH$_2$CH$_3$), 30.6, 30.7 (2×CH$_3$C), 37.2, 38.5 (CH$_2$CH$_2$), 45.1 (CCH$_2$C), 83.8, 84.1, 86.4 (3×C), 178.0 (C=O); *m/z* 211 (M^+−15, 1%), 169 (34), 154 (10), 153 (71), 139 (16), 101 (12), 97 (35), 95 (10), 91 (11), 83 (37), 70 (31), 69 (47), 67 (10), 57 (78), 56 (41), 55 (50), 53 (15), 43 (100), 42 (18), 41 (76), 40 (12). HRMS calcd for $C_{13}H_{22}O_3$ 226.1569, (M^+−CH$_3$) 211.1334, found 211.1339.

5.4.2. (2*R,5*R**) and (2*R**,5*S**)-8,8-Diethyl-2-hexyl-1,7-dioxaspiro[4.4]nonan-6-one (6c).** Colourless oil; t_r 14.86; R_f 0.32 (hexane/EtOAc 8:2); ν (film) 1774 (C=O), 1030 cm^{-1} (CO); δ_H 0.80–1.00 (18H, m, 6×CH$_3$), 1.20–2.50 (36H, m, 12×CH_2CH$_2$, 6×CH_2CH$_3$) 2.07, 2.25 (4H, AB system, J=14.0 Hz, 2×CCH$_2$C), 3.50–3.83 (2H, 2m, 2×CH); δ_C 7.6, 7.7, 14.0, 14.05 (6×CH$_3$), 22.4, 22.5, 23.7, 28.1, 28.8, 30.5, 30.6, 31.4, 31.5, 31.7, 35.6, 35.7, 35.8, 37.7, 42.8 (12×CH$_2$CH$_2$, 6×CH$_2$CH$_3$), 44.3, 46.6 (2×CCH$_2$C), 80.9, 83.4, (2×CH), 86.7, 87.0 (4×C), 177.8, 177.9 (2×C=O); *m/z* 282 (M^+, 5%), 225 (19), 210 (12), 209 (77), 135 (10), 109 (11), 97 (10), 84 (11), 83 (80), 82 (10), 81 (15), 79 (13), 70 (10), 69 (39), 67 (21), 57 (87), 56 (15), 55 (100), 54 (16), 53 (17), 44 (18), 43 (90), 42 (22), 41 (94), 40 (23). HRMS calcd for $C_{17}H_{30}O_3$ 282.2195, found 282.2169.

5.4.3. 8,8-Dicyclopropyl-2,2-dimethyl-1,7-dioxaspiro-[4.4]nonan-6-one (6e). Colourless oil; t_r 16.00; R_f 1.29 (hexane/EtOAc 8:2); ν (film) 3048 (cyclopropyl C–H), 1773 cm^{-1} (C=O); δ_H 0.30–0.55 (8H, m, 4×CH_2CH), 0.85–1.15 (2H, 2m, 2×CH), 1.28, 1.35 (6H, 2s, 2×CH$_3$), 1.70–2.00 (4H, m, CH$_2$CH$_2$), 2.03, 2.26 (2H, AB system, J=13.9 Hz, CCH$_2$C); δ_C 0.6, 0.7, 1.3, 1.4 (4×CH$_2$CH), 19.2, 19.3 (2×CH), 28.2, 28.9 (2×CH$_3$), 37.6, 38.5 (CH$_2$CH$_2$), 49.2 (CCH$_2$C), 83.1, 83.8, 83.9 (3×C), 177.7 (C=O); *m/z* 250 (M^+, <1%), 191 (30), 181 (12), 177 (14), 163 (18), 151 (20), 150 (77), 149 (11), 139 (15), 138 (13), 137 (83), 136 (12), 135 (48), 133 (11), 132 (36), 125 (11), 123 (20), 122 (16), 121 (82), 119 (12), 117 (18), 112 (48), 109 (47), 108 (14), 107 (28), 105 (12), 97 (43), 96 (24), 95 (31), 93 (34), 91 (35), 83 (10), 82 (15), 81 (28), 80 (28), 79 (38), 77 (24), 70 (19), 69 (100), 67 (42), 65 (10), 56 (10), 53 (15). HRMS calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1572.

5.4.4. 5″,5″-Diethyldispiro[adamantane-2,2′-tetrahydrofuran-5′,3″-tetrahydrofuran-2″-one] (6f). Colourless oil; t_r 18.00; R_f 0.33 (hexane/EtOAc 8:2); ν (film) 1770 (C=O), 1050 cm^{-1} (CO); δ_H 0.80–0.95 (6H, m, 2×CH_3CH$_2$), 1.20–2.40 (24H, m, 2×CH_2CH$_3$, 4×CH, 5×CH_2CH, CH$_2$CH$_2$, CCH$_2$C); δ_C 8.6, 8.8 (2×CH$_3$), 26.5, 26.6, 37.4, 38.0 (4×CH), 29.8, 30.0, 30.6, 32.0, 32.8, 34.5, 36.2, 37.1, 37.5 (5×CH$_2$CH, CCH$_2$$CH_2$C, 2×$CH_2CH_3$), 46.1 (C$CH_2$C), 83.8, 87.4, 89.1 (3×C), 178.0 (C=O); *m/z* 289 (M^+−29, 18%), 274 (13), 246 (15), 245 (82), 177 (17), 175 (13), 149 (24), 107 (10), 105 (11), 98 (11), 97 (12), 95 (11), 93 (24), 92 (14), 91 (32), 84 (15), 81 (15), 80 (12), 79 (40), 77 (16), 69 (32), 67 (31), 57 (100), 56 (12), 55 (90), 54 (13), 53 (26), 44 (10), 43 (54), 42 (11), 41 (90), 40 (17). HRMS calcd for $C_{20}H_{30}O_3$ 318.2195 (M^+−CO_2) 274.2297, found 274.2303.

5.4.5. Trispiro[cyclohexane-1,2′-tetrahydrofuran-5′,3″-tetrahydrofuran-2′-one-5″,1‴-cyclohexane] (6h). Colourless oil; t_r 15.95; R_f 0.33 (hexane/EtOAc 8:2); ν (film) 1770 (C=O); δ_H 1.20–2.40 (24H, m, 12×CH_2CH$_2$), 2.02, 2.25 (2H, AB system, J=13.7 Hz, CH$_2$C); δ_C 22.5, 22.6, 23.7, 23.9, 24.9, 25.5, 35.8, 36.1, 37.5, 37.6, 37.8, 38.0 (12×CH$_2$), 47.6 (CCH$_2$C), 83.3, 83.9, 85.8, (3×C), 177.8 (C=O); *m/z* 234 (M^+−44, 20%), 191 (14), 152 (17), 137 (10), 125 (39), 97 (27), 96 (12), 95 (32), 94 (36), 93 (16), 82 (14), 81 (41), 79 (22), 69 (14), 68 (13), 67 (38), 55 (88), 54 (22), 53 (22), 44 (15), 43 (57), 42 (29), 41 (100), 40 (24). HRMS calcd for $C_{17}H_{26}O_3$ 278.1882, found 278.1879.

5.4.6. (2*R,3a*S**,7a*R**) and (2*R**,3a*R**,7a*S**)-4′,4′-Dicyclopropyldispiro[perhydrobenzo[*b*]furan-2,3′-tetrahydrofuran-2′-one] (6o).** Colourless oil; t_r 15.70; R_f 0.34 (hexane/EtOAc 8:2); ν (film) 3045 (cyclopropyl C–H), 1772 (C=O), 1030 cm^{-1} (CO); δ_H 0.20–0.50 (16H, m, 8× cyclopropyl CH_2CH), 0.75–1.00 (4H, m, 4×cyclopropyl CH), 1.05–2.25 [26H, m, 2×(CH$_2$)$_4$, 2×CCH_2CH, 2×CHCHO, 2×CCH$_2$C], 3.00–3.15 (2H, m, CHO); δ_C 0.0, 0.2, 0.3, 0.5, 0.9, 1.1, 1.2, 1.3 (8×cyclopropyl CH$_2$CH), 18.8, 18.9, 19.0, 19.1 (4×cyclopropyl CH), 24.2, 24.7, 25.3, 28.0, 29.1, 29.9, 31.3, 32.1, 40.0, 40.1 [2×(CH$_2$)$_4$, 2×CCH$_2$CH], 44.9 (2×CHCHO), 50.1, 51.3 (2×CCH$_2$C), 83.5, 85.8 (2×CHO), 83.7, 88.9, 89.0, 89.1 (4×C), 177.1 (2×C=O); *m/z* 276 (M^+, <1%), 121 (10), 95 (18), 82 (15), 81 (16), 79 (13), 67 (60), 57 (20), 55 (35), 54 (29), 44 (100). HRMS calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1731.

5.4.7. (2″*R,3a″*S**,7a″*R**)-Dispiro[cyclohexane-1,5′-tetrahydrofuran-2′-one-3′,2″-perhydrobenzo[*b*]furan] (6p).** Colourless oil; t_r 14.99; R_f 0.30 (hexane/EtOAc 8:2); ν (film) 1773 (C=O), 1025 cm^{-1} (CO); δ_H 1.20–2.10 (21H, m, 9×CH_2CH$_2$, CCH_2CH, CHCHO), 2.05, 2.21 (2H, AB system, J=14.0 Hz, CCH$_2$C), 3.00 (1H, td, J=10.1, 3.4 Hz, CHO); δ_C 23.6, 23.7, 24.9, 25.8, 25.9, 28.5, 30.2, 35.5, 37.1, 40.0 (9×CH$_2$CH$_2$, CCH$_2$CH), 46.0 (*C*HCHO), 51.6 (CCH$_2$C), 84.0, 87.9 (2×C), 86.2 (CHO), 177.5 (C=O); *m/z* 264 (M^+, 7%), 217 (16), 166 (12), 151 (12), 150 (35), 149 (12), 147 (11), 138 (48), 137 (70), 136 (24), 135 (22), 134 (17), 132 (36), 123 (28), 122 (19), 121 (100), 119 (15), 118 (10), 117 (25), 109 (25), 108 (46), 107 (31), 105 (17), 98 (12), 96 (17), 95 (74), 94 (29), 93 (84), 91 (51), 83 (10), 82 (19), 81 (67), 80 (41), 79 (81), 77 (35), 69 (46), 68 (14), 67 (61), 66 (12), 65 (15), 55 (35), 54 (17), 53 (20). HRMS calcd for $C_{16}H_{24}O_3$ 264.1725, (M^+−CO_2) 220.1827, found 220.1822.

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