Synthesis of Substituted 1,5-Dioxaspiro[2.4]heptanes from 2,3-Dichloroprop-1-ene

by **Francisco Alonso**, **Jaisiel Meléndez**, and **Miguel Yus***

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, E-03080 Alicante
(phone: +34-965903548; fax: +34-965903549; e-mail: yus@ua.es)

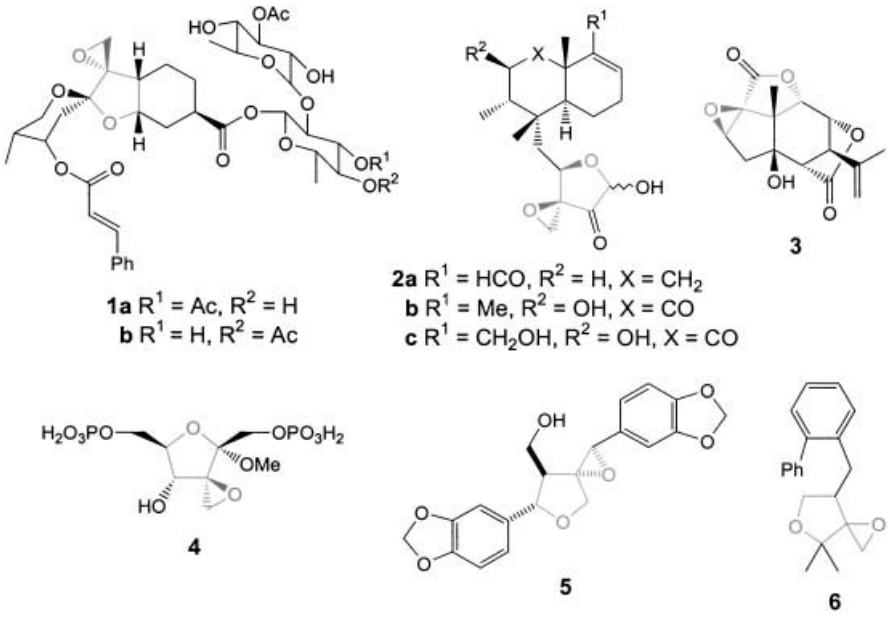
Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

The 4,4′-di(*tert*-butyl)biphenyl(DTBB)-catalyzed lithiation of 2,3-dichloroprop-1-ene (**10**) in THF at 0°, in the presence of symmetrically substituted ketones, led to the corresponding methylene-substituted diols **11** (*Scheme 2*), which, by treatment with NaH and I_2 in THF at room temperature, furnished a series of 1,5-dioxaspiro[2.4]heptanes **14** (*Scheme 4*). Oxidation of compounds **14** with RuO_4 gave the corresponding lactones **16**. Compounds **14** and **16** are structural units present in many biologically active natural compounds and in versatile intermediates in synthetic organic chemistry.

1. Introduction. – The 1,5-dioxaspiro[2.4]heptane unit is widespread in nature as the substructure of compounds with remarkable biological activities. This is the case in the antineoplastic glycosides phyllanthostatin 1 (**1a**) and phyllanthoside (**1b**) isolated from the Central American tree *Phyllanthus acuminatus* VAHL [1]. This unit is also present in the microbial diterpenoids clerocidin (**2a**) [2], terpentecin (**2b**) [3], and UCT4B (**2c**) [3c][4], which exhibit antitumor and antibiotic activities, and in picrotoxinin (**3**) [5] (one of the most toxic substances of plant origin known), as well as in many other natural products [6]. The attractive and complex structure of these compounds has challenged different research groups to undertake their total synthesis [7]. The 1,5-dioxaspiro[2.4]heptane moiety can be also found in intermediates or target compounds involved in both carbohydrate and nucleoside synthesis [8] (*e.g.*, **4**), as valuable precursors in the total synthesis of natural products and derivatives thereof [9] (*e.g.*, **5**), or as unnatural synthetic intermediates and products with biological activity [10] (*e.g.*, **6**).

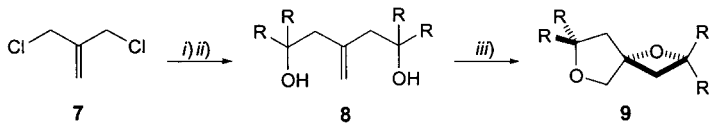
Some of the methodologies reported in the literature to generate the 1,5-dioxaspiro[2.4]heptane unit include the photochemical ring expansion of epoxycyclobutanones [11], *Darzens* condensation of α-halolactones [12], treatment of tetrahydrofuran-3-ones with dimethylsulfonium methylide [13], or epoxidation of 3-methyleneteterahydrofurans [14]. However, standard epoxidation of α-methylene-γ-lactones, although this appears to be the most direct route to the corresponding epoxylactones, proved to be difficult because the exocyclic C=C bond in these lactones showed very poor reactivity towards peracids, and nucleophilic epoxidation procedures led to polymeric materials [15].

On the other hand, in the recent years we have shown an increasing interest in the synthesis of bicyclic [16] and spirocyclic [17] polyether skeletons as constituents of



important biologically active compounds. In particular, and in connection with the title topic, we reported [17] the two-step synthesis of 1,6-dioxaspiro[3.4]octanes **9** from 3-chloro-2-(chloromethyl)prop-1-ene (**7**) using, as the key steps, an arene-catalyzed lithiation [18] under *Barbier* conditions [19] and an I_2-mediated double intramolecular cyclization (*Scheme 1*).

Scheme 1



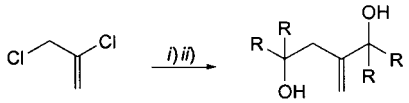
i) Li, $C_{10}H_8$ (5%), R_2CO (= Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, $O(CH_2CH_2)_2CO$, or adamantan-2-one), THF, $-78°$ to r.t. *ii*) H_2O. *iii*) I_2, Ag_2O, dioxane/H_2O 7:1, r.t.

We report herein an extension of the above described methodology to a straight and ready synthesis of the title compounds, using commercially available 2,3-dichloroprop-1-ene (**10**) as starting material, subjected in a first step to 4,4′-di(*tert*-butyl)biphenyl (DTBB)-catalyzed lithiation in the presence of a carbonyl compound, followed by a slightly modified method with respect to the final double iodoetherification published [17]. Moreover, the resulting 1,5-dioxaspiro[2.4]heptanes could be easily transformed into the corresponding 1,5-dioxaspiro[2.4]heptan-4-ones by using a simple oxidation method.

2. Results and Discussion. – The reaction of 2,3-dichloroprop-1-ene (**10**) with an excess of Li powder and a catalytic amount of DTBB (5 mol-%), in the presence of

different ketones in tetrahydrofuran (THF) at 0° led, after hydrolysis with H_2O, to the expected unsaturated 1,4-diols **11** in moderate yields (40–65%) (*Scheme 2* and *Table 1*) [20]. This step, which probably proceeds by sequential lithiation, has to be performed in the presence of the electrophile to prevent β-elimination from the intermediate 2-chloro-3-lithioprop-1-ene, which would lead to an allene. The reaction was applied to the alkyl ketones pentan-3-one and dicyclopropyl ketone (*Table 1*, *Entries 1* and *2*), the cyclic and heterocyclic ketones cyclohexanone, tetrahydro-4*H*-pyran-4-one, tetrahydro-4*H*-thiopyran-4-one, and 1-propylpiperidin-4-one (*Entries 3–6*), as well as to the tricyclic ketone adamantan-2-one (*Entry 7*).

Scheme 2

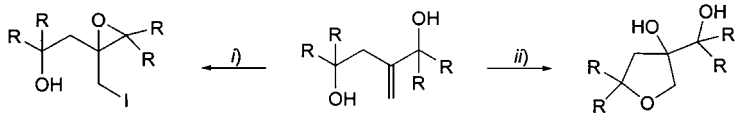


10 **11**

i) Li, DTBB (5%), R_2CO (= Et_2CO, (c-C_3H_5)$_2$CO, $(CH_2)_5CO$, $O(CH_2CH_2)_2CO$, $S(CH_2CH_2)_2CO$, $PrN(CH_2CH_2)_2CO$, or adamantan-2-one), THF, 0° to r.t, 2 h. *ii*) H_2O.

Initial attempts to cyclize methylene-substituted diols of type **11** to the corresponding 1,5-dioxaspiro[2.4]heptanes failed under the conditions reported [17], the corresponding intermediate iodohydrines **12** being the major compounds (*e.g.*, **12c** in the *Exper. Part*) (*Scheme 3*). On the other hand, at 80° ring opening of the epoxide moiety of the expected 1,5-dioxaspiro[2.4]heptanes, initiated by H_2O, occurred and furnished the undesired 1,2-diols **13** (*e.g.*, **13a** in the *Exper. Part*).

Scheme 3

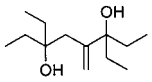
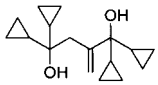
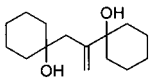
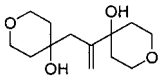
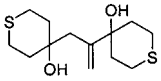
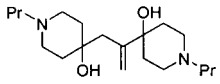
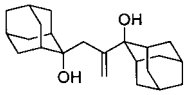


12 **11** **13**

i) I_2, Ag_2O, dioxane/H_2O 7:1, r.t. *ii*) I_2, Ag_2O, dioxane/H_2O 7:1, 80°.

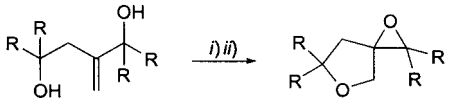
In spite of the different reagents and conditions tested to optimize the spirocyclization step, the best results were obtained by generation of the dialkoxide derived from **11** followed by the addition of I_2. Thus, when methylene-substituted diols **11** were treated with 2.2 equiv. of NaH in THF at 0° and 1.5 equiv. of I_2, a tandem double iodoetherification took place to form the corresponding and expected 1,5-dioxaspiro[2.4]heptanes **14** in high yield (78–99%) (*Scheme 4* and *Table 2*). Structurally very interesting dioxatrispiro compounds were also obtained, especially those possessing additional heteroatoms such as the polyether **14d** *(Entry 4)*, or the S- and N-containing analogues **14e** and **14f**, respectively (*Entries 5* and *6*).

Table 1. *Preparation of Methylene-Substituted Diols* **11**

Entry	Electrophile	Product[a])		Yield [%][b])
1	Et_2CO	**11a**		52 [20]
2	$(c\text{-}C_3H_5)_2CO$	**11b**		65
3	$(CH_2)_5CO$	**11c**		56 [20]
4	$O(CH_2CH_2)_2CO$	**11d**		40
5	$S(CH_2CH_2)_2CO$	**11e**		62[c])
6	$PrN(CH_2CH_2)_2CO$	**11f**		55[d])
7	Adamantan-2-one	**11g**		58[e])

[a]) All products **11** were >95% pure (GLC and 300-MHz ^{1}H-NMR) and were fully characterized by spectroscopic means (IR, ^{1}H- and ^{13}C-NMR, and MS). [b]) Yield after column chromatography (silica gel, hexane/AcOEt), unless otherwise stated. [c]) Reaction performed at −78°; yield after crystallization (AcOEt). [d]) Yield after column chromatography (silica gel, MeOH). [e]) Yield after crystallization (EtOH).

Scheme 4

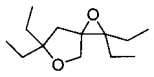
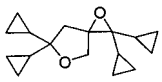
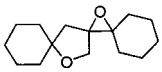
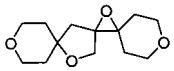
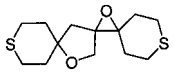
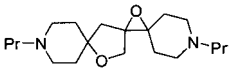
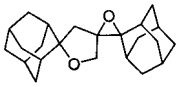


11 **14**

i) NaH, THF, 0°. *ii*) I_2, 0° to r.t.

The double cyclization reaction is interesting from a mechanistic point of view since only one out of all the theoretically possible cyclization pathways was involved. We were able to isolate the intermediate iodohydrin **12c** from diol **11c** with the system I_2/Ag_2O. From this result, we can infere that the reaction proceeds probably through carbocation **15** (or the precursor iodonium ion) and, as expected, intramolecular formation of the epoxide ring is preferred to formation of the oxetane ring. This gives

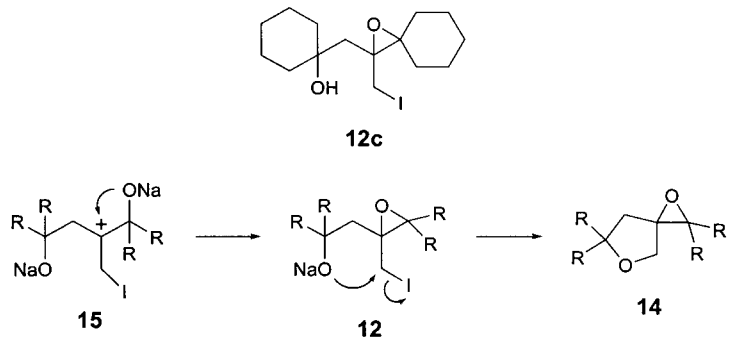
Table 2. *Preparation of 1,5-Dioxaspiro[2.4]heptanes* **14**

Entry	Diol	Product[a])		Yield (%)[b])
1	**11a**	**14a**		96[c])[d])
2	**11b**	**14b**		91[e])
3	**11c**	**14c**		99
4	**11d**	**14d**		97
5	**11e**	**14e**		78[c])
6	**11f**	**14f**		98[f])
7	**11g**	**14g**		91[c])

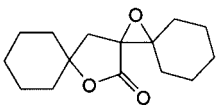
[a]) All products **14** were >95% pure (GLC and 300-MHz ^{1}H-NMR) and were fully characterized by spectroscopic means (IR, ^{1}H- and ^{13}C-NMR, and MS). [b]) Yield of crude **14** after 5 h (unless otherwise stated) based on starting diol **11**. [c]) Yield after column chromatography (silica gel, hexane/AcOEt). [d]) Reaction time 6 h. [e]) Reaction time 4 h. [f]) Reaction time 2 h.

rise to the iodohydrin salt **12**, which further undergoes S_N2 displacement of iodide to afford the 1,5-dioxaspiro[2.4]heptane skeleton **14** (*Scheme 5*).

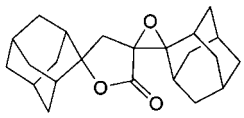
Scheme 5



Although 1,5-dioxaspiro[2.4]heptanes themselves are very interesting compounds, they can also be used as adequate precursors of 1,5-dioxaspiro[2.4]heptan-4-ones by oxidation adjacent to the tetrahydrofuran O-atom. Among the different methods available to carry out this transformation [21], the system composed of catalytic ruthenium(IV) oxide and sodium periodate gave excellent results (for some applications of this oxidation system, see, *e.g.*, [22]). Thus, by treating the 1,5-dioxaspiro[2.4]heptanes **14c** and **14g** derived from cyclohexanone and adamantan-2-one, respectively, with a catalytic amount (15 mol-%) of RuO_2 and an excess of $NaIO_4$ in CCl_4/H_2O at room temperature, the corresponding lactones **16c** and **16g** were obtained in remarkable yields.



16c (94%)



16g (96%)

3. Conclusions. – We have demostrated herein that the 1,5-dioxaspiro[2.4]heptane unit, present in many biologically active natural products, can be easily synthesized from 2,3-dichloroprop-1-ene in a two-step sequence that involves arene-catalyzed lithiation in the presence of a ketone followed by I_2-induced spirocyclization. Furthermore, the 1,5-dioxaspiro[2.4]heptanes synthesized can be used as versatile substrates that can be oxidized to the corresponding lactones. All reactions reported proceed under very mild conditions and in moderate to excellent yields. Therefore, this methodology is an interesting alternative to the previously reported ones.

Experimental Part

1. *General*. All solvents were treated prior to use by standard methods [23]. Gas-liquid chromatography (GLC): *Hewlett-Packard 5890* instrument, flame ionization detector; 30-m siloxane capillary column (0.25 mm i. d., 0.25 mm film thickness); N_2 (2 ml/min) as carrier gas; $T_{injector}$ 275°, T_{column} 60° (3 min) and 60–270° (15°/min); t_R in min. Column chromatography (CC): silica gel *60* (40–60 μm). M.p.: *Reichert-Thermovar* apparatus. IR Spectra (cm^{-1}): *Nicolet Impact-400D-FT* spectrophotometer. NMR Spectra: *Bruker AC-300* spectrometer; $CDCl_3$ as solvent and $SiMe_4$ as internal reference; chemical shifts δ in ppm and coupling constants J in Hz. MS: electron impact (EI) at 70 eV with a *Shimadzu GC/MS-QP-5000* spectrometer; in *m/z*, rel. intensity in %. High-resolution (HR) MS (*Finnigan MAT95S* apparatus) and elemental analyses (*Carlo-Erba EA-1108-(CHNSO)* elemental analyzer) were performed by the corresponding services at the University of Alicante.

2. *Diols* **11**: *General Procedure* [20]. A soln. of 2,3-dichloroprop-1-ene (0.19 ml, 2.0 mmol) and the corresponding ketone (4.0 mmol) in THF (5.0 ml) was added to a blue suspension of Li powder (100 mg, 14.0 mmol) and 4,4′-di(*tert*-butyl)biphenyl (DTBB) (26 mg, 0.1 mmol, 5 mol-%) in THF (5.0 ml) at 0°. After 2 h, the mixture was hydrolyzed with H_2O (5.0 ml), followed by addition of sat. $NaHCO_3$ soln. (5.0 ml), neutralization with 2M HCl, and extraction with AcOEt (3×10 ml). The org. layer was dried ($MgSO_4$) and evaporated at 10 Torr. The residue was purified by CC (SiO_2, hexane/AcOEt (**11a–d**), MeOH (**11f**)) or crystallization (AcOEt (**11e**), EtOH (**11g**)). Compounds **11a** and **11c** were fully characterized by comparison of their chromatographic and spectroscopic data with those reported in [20]. For data of new compounds, see below.

1,1,4,4-Tetracyclopropyl-2-methylenebutane-1,4-diol (**11b**): Colorless crystals. R_f 0.38 (hexane/AcOEt 8:2). t_R 14.90. M.p. 67–69°. IR (KBr): 3287, 3084, 3006, 1634, 1427, 1010, 912. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.29–0.56 (*m*, 8 CH_2CH); 0.80–0.95 (*m*, 4 CH); 2.57 (*s*, CH_2CO); 2.95 (br. *s*, 2 OH); 5.07, 5.39 (2*s*, CH_2=C). ^{13}C-NMR (75 MHz, $CDCl_3$): −1.0, −0.2, 0.1, 0.7 (8 CH_2CH); 18.2, 19.5 (4 CH); 44.2 (CH_2CO); 70.8, 72.8 (2 CO); 134.0

(CH_2=C); 150.0 (*C*=CH_2). MS: 244 (<1, $[M-18]^+$), 203 (47), 134 (26), 119 (13), 111 (30), 105 (12), 93 (17), 92 (11), 91 (38), 79 (18), 77 (15), 69 (100), 55 (21), 53 (11), 43 (12), 41 (99). Anal. calc. for $C_{17}H_{26}O_2$ (262.19): C 77.73, H 10.00; found: C 77.82, H 9.99.

*4,4′-(1-Methyleneethane-1,2-diyl)bis[tetrahydro-2*H*-pyran-4-ol]* (**11d**): Colorless crystals. R_f 0.35 (hexane/AcOEt 7:3). t_R 17.00. M.p. 111–113°. IR (KBr): 3212, 2950, 2861, 1644, 1475, 1432, 1090, 1017, 940, 847. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.54–1.91 (*m*, 4 C*H*$_2$CH$_2$O); 2.44 (*s*, CH_2C=C); 3.71–3.80 (*m*, 4 CH_2O); 4.03 (*s*, 2 OH); 4.94, 5.17 (2*s*, CH_2=C). ^{13}C-NMR (75 MHz, $CDCl_3$): 37.4, 38.1 (4 *C*H$_2$CH$_2$O); 44.8 (*C*H$_2$C=C); 63.7, 63.9 (4 CH_2O); 68.4, 70.0 (2 COH); 115.4 (*C*H$_2$=C); 149.5 (*C*=CH_2). MS: 224 (<1, $[M-18]^+$), 142 (12), 124 (71), 123 (15), 109 (91), 101 (29), 96 (17), 95 (33), 93 (18), 91 (20), 83 (32), 81 (33), 80 (27), 79 (96), 77 (31), 73 (17), 71 (61), 69 (20), 68 (22), 67 (26), 66 (12), 65 (14), 57 (13), 55 (47), 53 (51), 45 (13), 43 (100), 40 (62). Anal. calc. for $C_{13}H_{22}O_4$ (242.15): C 64.23, H 9.06; found: C 64.44, H 9.15.

*4,4′-(1-Methyleneethane-1,2-diyl)bis[tetrahydro-2*H*-thiopyran-4-ol]* (**11e**): Colorless crystals. R_f 0.26 (hexane/AcOEt 8:2). t_R 19.61. M.p. 148–149°. IR (KBr): 3231, 2940, 2917, 2833, 1633, 1427, 1275, 1065, 910. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.71–2.03 (*m*, 4 C*H*$_2$CH$_2$S); 2.38–2.52 (*m*, 2 CH_2S); 2.40 (*s*, CH_2C=C); 2.86, 3.05 (2*t*, *J* = 13.4, 2 CH_2S); 3.62 (*s*, 2 OH); 4.92, 5.14 (2*s*, CH_2=C). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.2, 24.4 (4 *C*H$_2$CH$_2$S); 38.7, 38.8 (4 CH_2S); 44.6 (*C*H$_2$C=C); 69.8, 71.7 (2 CO); 115.4 (*C*H$_2$=C); 151.0 (*C*=CH_2). MS: 274 (40, M^+), 256 (5, $[M-18]^+$), 228 (11), 158 (34), 157 (100), 155 (14), 140 (94), 125 (36), 118 (42), 116 (40), 112 (88), 99 (52), 97 (41), 93 (31), 91 (21), 82 (32), 79 (34), 71 (19), 61 (36), 55 (67), 54 (22). Anal. calc. for $C_{13}H_{20}O_2S_2$ (272.09): C 56.90, H 8.08, S 23.36; found: C 56.69, H 7.94, S 22.66.

4,4′-(1-Methyleneethane-1,2-diyl)bis[1-propylpiperidin-4-ol] (**11f**): Brown oil. R_f 0.31 (MeOH). t_R 20.01. IR (film): 3348, 2953, 2876, 1633, 1463, 1138, 1105. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.90 (*t*, *J* = 7.3, 2 Me); 1.48–1.86 (*m*, 6 C*H*$_2$CH$_2$N); 2.29–2.32, 2.60–2.73 (2*m*, 6 CH_2N); 2.43 (*s*, CH_2C=C); 3.45, 3.96 (2*s*, 2 OH); 4.88, 5.16 (2*s*, CH_2=C). ^{13}C-NMR (75 MHz, $CDCl_3$): 12.0, 12.1 (2 Me); 20.1, 20.2 (2 *C*H$_2$Me); 37.3, 37.5 (4 C*C*H$_2$CH$_2$N); 49.2, 49.5, 49.7 (4 CCH$_2$*C*H$_2$N, *C*H$_2$C=C); 60.8, 60.9 (2 *C*H$_2$CH$_2$Me); 69.3, 70.9 (2 CO); 114.7 (*C*H$_2$=C); 150.7 (*C*=CH_2). MS: 324 (1, M^+), 295 (12), 207 (10), 183 (12), 182 (37), 164 (22), 155 (16), 152 (13), 142 (26), 141 (10), 140 (66), 138 (10), 136 (25), 133 (27), 124 (41), 122 (14), 114 (31), 112 (31), 100 (15), 99 (15), 98 (100), 96 (12), 86 (15), 84 (27), 72 (27), 70 (38), 56 (14), 55 (13). HR-MS: 324.2796 ($C_{19}H_{36}N_2O_2^+$; calc. 324.2777).

2,2′-(1-Methyleneethane-1,2-diyl)bis[adamantan-2-ol] (**11g**): Colorless crystals. R_f 0.51 (hexane/AcOEt 8:2). M.p. 211–213°. IR (KBr): 3237, 3092, 2902, 2854, 1626, 1449, 1011. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.40–2.10 (*m*, 10 C*H*$_2$CH); 2.20–2.40 (*m*, 8 CH); 2.57 (*s*, CH_2C=C); 5.14, 5.35 (2*s*, CH_2=C). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.7, 27.3, 27.4, 31.0, 34.5, 34.6, 36.5, 36.9 (8 CH); 32.8, 32.9, 33.1, 34.5, 34.8, 35.0, 37.6, 37.7, 38.3, 38.5 (10 *C*H$_2$CH); 40.2 (*C*H$_2$C=C); 74.6, 75.7 (2 CO); 117.0 (*C*H$_2$=C); 146.7 (*C*=CH_2). MS: 324 (100, $[M-18]^+$), 203 (12), 189 (10), 176 (26), 175 (88), 174 (59), 161 (19), 159 (15), 151 (12), 149 (21), 148 (38), 147 (17), 145 (16), 135 (23), 133 (24), 132 (14), 131 (36), 121 (45), 120 (10), 119 (24), 117 (27), 115 (10), 107 (23), 106 (22), 105 (41), 96 (10), 95 (25), 94 (25), 93 (54), 92 (31), 91 (74), 81 (39), 79 (89), 77 (37), 67 (41), 65 (11), 55 (43), 53 (18). Anal. calc. for $C_{23}H_{34}O_2$ (342.26): C 80.65, H 9.94; found: C 79.75, H 10.01.

3. *Compounds* **12c** *and* **13a**. They were obtained following the general procedure described in [17] at 20 and 80°, resp.

1-{[2-(Iodomethyl)-1-oxaspiro[2.5]oct-2-yl]methyl}cyclohexan-1-ol (**12c**): Orange oil. R_f 0.43 (hexane/AcOEt 8:2). t_R 16.50. IR (film): 3502, 2929, 2855, 1445, 1161. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20–1.80 (*m*, 10 C*H*$_2$CH$_2$); 1.82, 2.13 (*AB*, *J* = 15.0, CCH$_2$C), 3.11, 3.61 (*AB*, *J* = 9.8, CH_2I), 3.25 (*s*, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 10.8 (CH_2I); 21.8, 22.0, 24.4, 24.9, 25.5, 25.8, 29.5, 30.3, 38.0, 38.9 (10 *C*H$_2$CH$_2$, C*C*H$_2$C); 67.4, 68.7, 72.5 (3 CO). MS: 364 (<1, M^+), 219 (14), 207 (14), 139 (38), 128 (13), 127 (10), 121 (21), 99 (95), 95 (19), 93 (23), 91 (15), 82 (10), 81 (100), 79 (36), 77 (12), 69 (35), 67 (19), 57 (18), 56 (12), 55 (75), 53 (18), 45 (10), 44 (95), 41 (66).

5,5-Diethyl-3-(1-ethyl-1-hydroxypropyl)tetrahydrofuran-3-ol (**13a**): Pale yellow oil. R_f 0.30 (hexane/AcOEt 8:2). t_R 16.02. IR (film): 3477, 2966, 2939, 2880, 1461, 1381, 1122, 1046, 954. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.75–1.05 (*m*, 4 Me); 1.40–1.70 (*m*, 4 C*H*$_2$Me, 1 H of CC*H*$_2$C); 2.02 (*d*, *J* = 14.0, 1 H of CCH$_2$C); 2.28 (br. *s*, 2 OH); 3.68, 3.96 (*AB*, *J* = 9.8, CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 8.5, 8.6 (4 Me); 27.1, 27.6, 29.4, 30.3 (4 *C*H$_2$Me); 44.8 (C*C*H$_2$C); 74.0 (CH_2O); 76.4, 85.9 (2 COH); 87.8 (THF-ring CH$_2$*C*O). MS: 201 (21, $[M-18]^+$), 97 (24), 87 (100), 83 (13), 69 (16), 57 (99), 55 (27), 45 (59), 43 (54), 41 (31).

4. *1,5-Dioxaspiro[2.4]heptanes* **14**: *General Procedure.* A soln. of diol **11** (1.0 mmol) in anh. THF (5.0 ml) was added to a suspension of 95% NaH (56 mg, 2.2 mmol) in THF (5.0 ml) at 0°. After 15 min, a soln. of I_2 (381 mg, 1.5 mmol) in THF (5.0 ml) was added, the stirring being maintained for 5 h. The resulting mixture was washed with sat. $NaHSO_3$ soln. (2 × 10 ml) and extracted with AcEOt (3 × 10 ml). The org. layer was dried

($MgSO_4$) and evaporated at 10 Torr, and the resulting residue was purified by CC (SiO_2, hexane/AcEOt) for compounds **14a**,**e**,**g**, whereas compounds **14b-d**,**f** did not require further purification.

2,2,6,6-Tetraethyl-1,5-dioxaspiro[2.4]heptane (**14a**): Pale yellow oil. R_f 0.57 (hexane/AcOEt 8:2). t_R 12.75. IR (film): 2964, 2928, 2878, 1605, 1459, 1118, 1058. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.80–1.20 (*m*, 4 Me); 1.40–1.80 (*m*, 4 C*H*$_2$Me); 1.71, 1.99 (*AB*, *J* = 14.0, CCH_2C); 3.72, 4.02 (*AB*, *J* = 10.4, CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 7.6, 8.2, 8.4, 9.1 (4 Me); 24.4, 24.5, 29.2, 29.3 (4 *C*H$_2$Me); 39.4 (C*C*H$_2$C); 66.1, 73.4 (2 oxirane ring C); 68.7 (CH_2O); 86.2 (THF-ring CH_2*C*O). MS: 194 (< 1, $[M-18]^+$), 183 (21), 115 (40), 97 (11), 87 (13), 69 (17), 57 (100), 55 (30), 43 (15), 41 (29). HR-MS: 194.1688 ($[C_{13}H_{24}O_2 - H_2O]^+$; calc. 194.1671).

2,2,6,6-Tetracyclopropyl-1,5-dioxaspiro[2.4]heptane (**14b**): Pale yellow oil. R_f 0.63 (hexane/AcOEt 8:2). t_R 13.81. IR (film): 3007, 2925, 2857, 1657, 1461, 1376, 1115, 1025. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.20–0.65 (*m*, 8 C*H*$_2$CH$_2$); 0.70–0.90, 0.90–1.10 (2*m*, 4 CH); 1.67, 2.05 (*AB*, *J* = 14.0, CCH_2C); 3.76, 4.09 (*AB*, *J* = 10.4, CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 0.3, 0.4, 0.8, 1.0, 1.1, 1.2, 2.1, 2.3 (8 *C*H$_2$CH$_2$); 12.2, 13.1, 18.7, 18.8 (4 CH); 37.6 (C*C*H$_2$C); 64.2, 73.5 (2 oxirane ring C); 69.0 (CH_2O); 83.7 (THF-ring CH_2*C*O). MS: 260 (< 1, M^+), 111 (100), 79 (10), 69 (55), 55(10). HR-MS: 260.1778 ($C_{17}H_{24}O_2$; calc. 260.1776).

15,17-Dioxatrispiro[5.0.1.5.2.1]heptadecane (**14c**): Pale yellow oil. R_f 0.59 (hexane/AcOEt 8:2). t_R 13.83. IR (film): 2930, 2856, 1448, 1054. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.26–1.80 (*m*, 10 C*H*$_2$CH$_2$, 1 H of CCH_2C); 1.94 (*d*, *J* = 14.0, 1 H of CCH_2C); 3.74, 4.02 (*AB*, *J* = 10.4, CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.3, 23.5, 24.8, 24.9, 25.5, 25.6, 32.2, 32.3, 35.1, 37.0 (10 *C*H$_2$CH$_2$); 40.9 (C*C*H$_2$C); 63.8, 72.9 (2 oxirane ring C); 67.7 (CH_2O); 83.1 (THF-ring CH_2*C*O). MS: 236 (5, M^+), 218 (4, $[M-18]^+$), 193 (17), 154, (24), 138 (27), 99 (30), 95 (26), 81 (58), 79 (23), 67 (50), 55 (100), 41 (86). HR-MS: 236.1768 ($C_{15}H_{24}O_2^+$; calc. 236.1776).

3,12,15,17-Tetraoxatrispiro[5.0.1.5.2.1]heptadecane (**14d**): Pale yellow oil. R_f 0.49 (hexane/AcOEt 7:3). t_R 13.72. IR (film): 2925, 2859, 1608, 1433, 1104, 1016. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20–1.60, 1.70–1.95 (2*m*, 4 C*H*$_2$CH$_2$O); 1.83, 2.00 (*AB*, *J* = 14.0, CCH_2C); 3.60–3.90 (*m*, 4 CH_2C*H*$_2$O); 3.77, 4.04 (*AB*, *J* = 11.0, CCH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 32.4, 33.6, 35.2, 36.8 (4 *C*H$_2$CH$_2$O); 41.0 (C*C*H$_2$C); 61.1, 72.2 (2 oxirane-ring C); 64.7, 64.8, 66.1, 67.5 (4 CH_2*C*H$_2$O, C*C*H$_2$O); 79.9 (THF-ring CH_2*C*O). MS: 240 (< 1, M^+), 196 (11), 156 (61), 144 (19), 140 (30), 125 (13), 123 (13), 122 (11), 113 (12), 112 (30), 111 (16), 110 (12), 109 (18), 101 (57), 99 (27), 98 (16), 97 (23), 96 (50), 95 (31), 93 (12), 91 (11), 85 (15), 84 (25), 83 (100), 82 (19), 81 (28), 79 (21), 77 (10), 73 (17), 71 (30), 70 (13), 69 (22), 68 (20), 67 (34), 59 (17), 57 (20), 56 (26), 55 (73), 54 (33), 53 (44). HR-MS: 240.1358 ($C_{13}H_{20}O_2^+$; calc. 240.1362).

15,17-Dioxa-3,12-dithiatrispiro[5.0.1.5.2.1]heptadecane (**14e**): Pale yellow oil. R_f 0.39 (hexane/AcOEt 8:2). t_R 16.63. IR (film): 2965, 2930, 1459, 1120, 1060. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20–2.00 (*m*, 4 C*H*$_2$CH$_2$S); 1.73, 1.93 (*AB*, *J* = 13.7, CCH_2C); 2.40–2.75, 2.80–3.10 (2*m*, 4 CH_2S); 3.72, 4.03 (*AB*, *J* = 11.0, CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 25.0, 25.2, 27.2, 29.4 (4 *C*H$_2$CH$_2$S); 33.8, 33.9, 35.8, 37.7 (4 CH_2S); 42.2 (CCH_2C); 61.9, 72.9 (2 oxirane-ring C); 67.7 (CH_2O); 80.9 (THF-ring CH_2*C*O). MS: 272 (36, M^+), 207 (21), 160 (29), 141 (22), 128 (17), 116 (18), 115 (17), 114 (16), 115 (18), 112 (100), 99 (95), 85 (20), 79 (11), 65 (13), 55 (52), 53 (43). HR-MS: 272.0909 ($C_{13}H_{20}O_2S_2^+$; calc. 272.0905).

3,12-Dipropyl-15,17-dioxa-3,12-diazatrispiro[5.0.1.5.2.1]heptadecane (**14f**): Dark brown oil. R_f 0.31 (MeOH). t_R 18.89. IR (film): 2954, 2927, 2870, 1646, 1456, 1114. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.75–1.00 (*m*, 2 Me); 1.10–1.35 (*m*, 2 MeC*H*$_2$); 1.40–2.05 (*m*, 4 CC*H*$_2$CH$_2$N, CCH_2C); 2.25–2.50 (*m*, 2 NC*H*$_2$CH$_2$Me); 2.59 (br. *s*, 4 CCH_2C*H*$_2$N); 3.73, 4.01 (*AB*, *J* = 10.7, CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 11.9, 12.0 (2 $MeCH_2$); 20.2, 19.7 (2 *C*H$_2$Me); 29.2, 29.4, 29.7, 30.2 (4 C*C*H$_2$CH$_2$N); 41.0 (C*C*H$_2$C); 50.1, 50.3, 51.7, 51.8 (4 CCH_2*C*H$_2$N), 60.4, 60.5 (2 NCH$_2$CH$_2$Me); 62.9, 72.2 (2 oxirane-ring C); 67.9 (C*C*H$_2$O); 80.4 (THF-ring CH_2*C*O). MS: 322 (3, M^+), 294 (20), 293 (100), 132 (24), 110 (15), 98 (23), 96 (10). HR-MS: 322.2601 ($C_{19}H_{34}N_2O_2^+$; calc. 322.2620).

*3′,5′-Dihydrotrispiro[adamantane-2,2′(4*H*′)-furan-4′,2″-oxirane-3″,2‴-adamantane]* (**14g**): Colorless crystals. R_f 0.63 (hexane/AcOEt 8:2). M.p. 129–131°. IR (KBr): 2905, 2850, 1449, 1113, 1073. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20–2.20 (*m*, 10 C*H*$_2$CH, 8 C*H*CH$_2$, CCH_2C); 3.76, 4.01 (*AB*, *J* = 10.7, CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.8, 26.9, 27.2, 27.4, 34.1, 37.2, (10 *C*H$_2$CH); 29.7, 32.7, 34.3, 34.7, 34.9, 35.5, 35.7, 36.4 (8 *C*HCH$_2$); 39.0 (C*C*H$_2$C); 66.9, 73.8 (2 oxirane-ring C); 68.7 (C*C*H$_2$O); 87.0 (THF-ring CH_2*C*O). MS: 340 (13, M^+), 206 (56), 191 (18), 190 (100), 175 (17), 163 (11), 162 (69), 161 (11), 151 (13), 150 (42), 149 (15), 148 (29), 135 (57), 134 (13), 133 (12), 121 (15), 119 (27), 107 (12), 106 (17), 105 (27), 93 (35), 92 (41), 91 (48), 81 (18), 80 (19), 79 (51), 77 (20), 67 (22), 55 (20). Anal. calc. for $C_{23}H_{32}O_2$ (340.24): C 81.13, H 9.47; found: C 80.99, H 9.45.

5. *Lactones* **16**: *General Procedure.* 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 soln. of the corresponding 1,5-dioxaspiro[2.4]heptane **14** (1.0 mmol) in CCl_4 (5 ml) at r.t. After stirring the mixture for 24 h, ^{i}PrOH (3 ml) was added, the resulting mixture being extracted with CCl_4 (2 × 5 ml). The org. layer was dried ($MgSO_4$), passed through a *Celite* pad to eliminate the

remaining ruthenium compounds and concentrated yielding the corresponding pure lactones **16**, which did not require further purification.

15,17-Dioxatrispiro[5.0.1.5.2.1]heptadecan-16-one (**16c**): Colorless oil. R_f 0.34 (hexane/AcOEt 8:2). t_R 16.88. IR (film): 2930, 2857, 1774, 1448, 1217, 1084, 1027. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.15–2.01 (*m*, 10 CH_2CH_2); 2.14, 2.26 (*AB*, $J = 14.0$, 2 CCH_2C). ^{13}C-NMR (75 MHz, $CDCl_3$): 22.2, 22.4, 24.6, 24.7, 24.9, 25.3, 28.2, 32.1, 37.4, 38.0 (10 CH_2CH_2); 36.6 (CCH_2C); 64.2, 82.2 (2 oxirane-ring C); 68.7 (lactone-ring CH_2); 172.7 (CO_2). MS: 250 (< 1, M^+), 169 (28), 124 (22), 110 (12), 109 (13), 99 (94), 97 (10), 96 (51), 95 (18), 82 (17), 81 (100), 80 (36), 79 (22), 68 (14), 67 (49), 55 (39), 54 (23), 53 (19). HR-MS: 250.1573 ($C_{15}H_{22}O_3^+$; calc. 250.1569).

*Trispiro[adamantane-2,2′(4′*H*)-furan-4′,2″-oxirane-3″,2‴-adamantan]-5′(2′*H*)-one* (**16g**): Colorless crystals. R_f 0.50 (hexane/AcOEt 8:2). M.p. 135–136°. IR (film): 2910, 2852, 1766, 1606, 1448, 1022. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20–2.40 (*m*, 10 CH_2CH, 8 $CHCH_2$); 2.11, 2.51 (*AB*, $J = 14.0$, CCH_2C). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.5, 26.6, 29.8, 34.1, 37.2 (10 CH_2CH); 32.6, 32.9, 33.8, 34.7, 34.9, 35.6, 36.4, 36.5 (8 $CHCH_2$); 39.0 (CCH_2C); 65.1, 86.4 (2 oxirane-ring C); 74.0 (lactone-ring CH_2); 172.6 (CO_2). MS: 338 (12, $[M-16]^+$), 280 (12), 208 (11), 207 (49), 189 (12), 188 (100), 176 (31), 175 (29), 162 (16), 161 (12), 160 (77), 151 (78), 150 (24), 149 (16), 148 (76), 135 (16), 134 (13), 133 (21), 119 (19), 117 (18), 107 (11), 106 (19), 105 (27), 93 (31), 92 (32), 91 (51), 81 (21), 80 (20), 79 (49), 77 (21), 67 (20), 55 (18), 53 (10). Anal. calc. for $C_{23}H_{30}O_3$ (354.22): C 77.93, H 8.53; found: C 75.55, H 8.51.

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