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Straightforward synthesis of 1,6-dioxaspiro[4.4]nonanes

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Abstract—Diols **2**, easily prepared by a DTBB-catalysed lithiation of the dithioether **1** in the presence of different carbonyl compounds, react with ozone in dichloromethane at −78 °C leading, after treatment with thiourea at 20 °C, to the corresponding substituted 1,6-dioxaspiro[4.4]nonanes **3**.

Among organolithium compounds,[1] those possessing two lithium atoms[2] offer the possibility of introducing two electrophilic fragments at once by reaction with electrophiles, giving polyfunctionalised organic molecules in one single synthetic operation. One important problem associated with the preparation of dilithiated intermediates has to do with their instability and, therefore, their preparation has to be usually performed under Barbier-type reaction conditions (lithiation in the presence of the electrophile)[3] in order to avoid decomposition of the lithiated intermediate species, above all after the first lithiation step. The functionalised character of the intermediates[4] involved in these reactions makes these species rather unstable, undergoing easily either elimination processes or proton abstraction from the reaction medium, and therefore provoking their decomposition. Due to this fact, it is necessary to work generally at low temperatures. In our research group, we have developed in the last few years a practical way to perform lithiation reactions under very mild reaction conditions using lithium metal and a catalytic amount of an arene [usually naphthalene or 4,4′-di-*tert*-butylbiphenyl (DTBB)].[5] By this procedure, we have generated in situ aliphatic (**I**[6]), olefinic (**II**[7] and **III**[8]) or aromatic (**IV**[9] and **V**[10]) dianionic synthons by a chlorine–lithium exchange and explored their applications in organic synthesis (Chart 1).

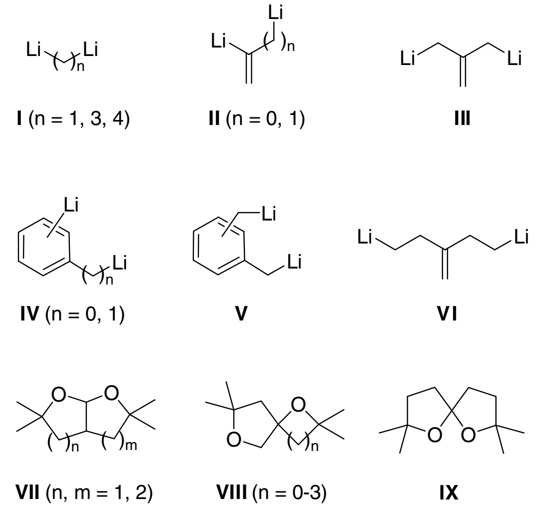

Chart 1.

Particularly, synthons of the type **II** and especially **III** have been successfully applied to the preparation of polycyclic ethers (**VII**[11]) and dioxaspiro compounds (**VIII**[12]), structural units that are present in many interesting naturally occurring compounds with biological activity. In this letter, we report about the use of the dianionic synthons **VI** for the straightforward preparation of substituted 1,6-dioxaspiro[4.4]nonanes of the type **IX** by a successive reaction with carbonyl compounds and ozonolysis. This type of heterocyclic moiety is present in many natural products from different sources including insects, microbes, plants, fungi and marine organisms.[13] Among them one can find simple structures, such as the volatile insect pheromone chalcogran (**X**; an aggregation pheromone of *Pityiogenes chalcographus*)[14] or more complex molecules, such as

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Keywords: Unsaturated 1,7-diols; 1,6-Dioxaspiro[4.4]nonanes; Spiroketals; Ozonolysis; Cyclization.

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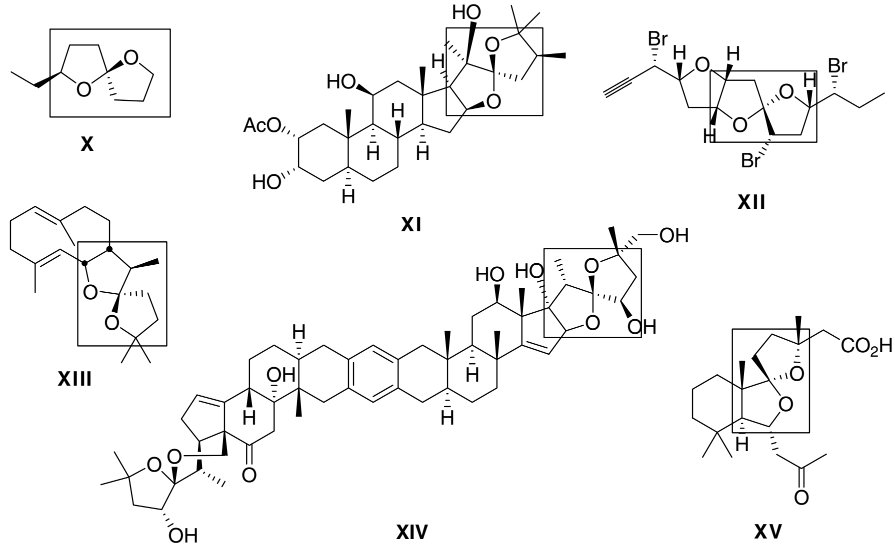
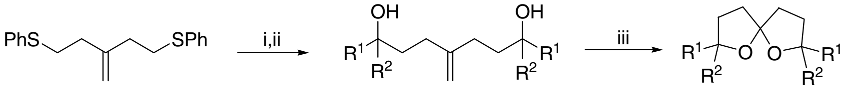
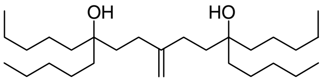
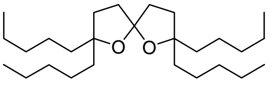
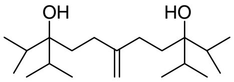
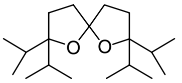
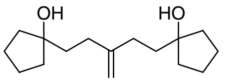
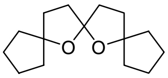
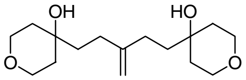
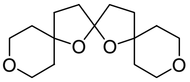
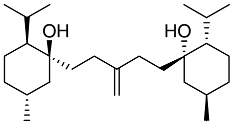
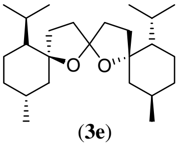
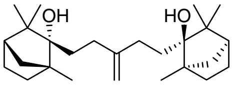
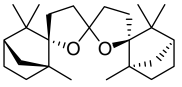


Chart 2.



Scheme 1. Reagents and conditions: (i) Li, DTBB (2.5 mol %), R^1R^2CO, THF, 0 °C, 2 h; (ii) H_2O; (iii) O_3, CH_2Cl_2, −78 °C, then $SC(NH_2)_2$, rt.

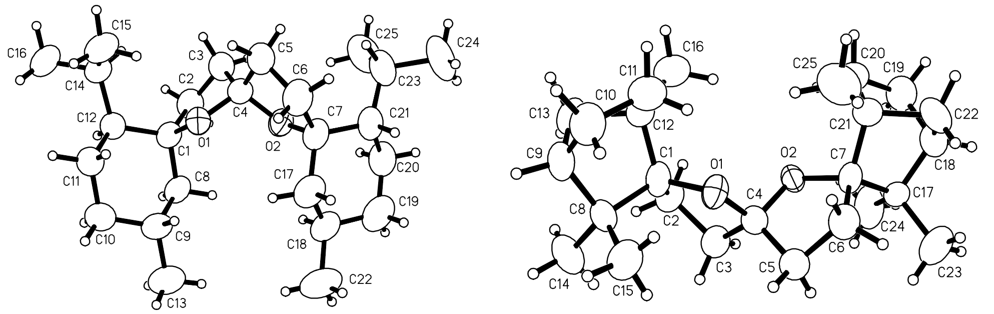
Table 1. Preparation of 1,6-dioxaspiro[4.4]nonanes **3**

Entry	Starting diol **2**	Product **3**	Yield[a] (%)
1	 (**2a**)	 (**3a**)	94
2	 (**2b**)	 (**3b**)	80
3	 (**2c**)	 (**3c**)	81
4	 (**2d**)	 (**3d**)	85
5	 (**2e**)	 (**3e**)	83[b]
6	 (**2f**)	 (**3f**)	95[c]

[a] Isolated crude yields of >95% pure compounds **3** (GLC and/or 300 MHz ^1H NMR).

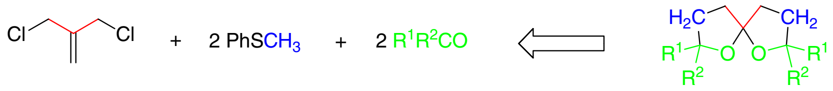
[b] Obtained as a 93.5:6.5 mixture of diastereomers (GLC; 87% de).

[c] Obtained as a 86.5:13.5 mixture of diastereomers (GLC; 73% de).



3e **3f**

Figure 1. X-ray structures of the major diastereomers of compounds **3e** and **3f**.



Scheme 2.

hippurin-1 (**XI**; isolated from the gorgonian *Isis hippuris*),[15] obtusin (**XII**; isolated from the red seaweed *Laurrecia obtusa*),[16] asperketal D (**XIII**; isolated from the Caribbean sea whip *Eunicea asperula*),[17] cephalostatin 1 (**XIV**; isolated from the marine worm *Cephalodiscus gilchristi*)[18] or chrisothane (**XV**; isolated from the Compositae *Crisothamnus paniculatus*)[19] (Chart 2).

Unsaturated 1,7-diols **2** were prepared by reaction of the dithioether **1**[20] with lithium and a catalytic amount of DTBB (2.5 mol %) in the presence of a carbonyl compound R^1R^2CO in THF at 0 °C, followed by hydrolysis.[11f] Isolated diols **2** were then reacted with ozone in dichloromethane at −78 °C giving the expected 1,6-dioxaspiro[4.4]nonanes **3** in pure form without any need of further purification (Scheme 1 and Table 1).[21]

In the case of enantiopure diols **2e** and **2f**[12f] an enriched diastereomeric mixture (87% and 73% de, respectively) was obtained (Table 1, entries 5 and 6 and footnotes b and c, respectively). In both cases, the major diastereomer was analysed by X-ray crystallography, the corresponding structures being shown in the Figure 1.[22]

In conclusion, we have reported here an easy and straightforward preparation of 1,6-dioxaspiro[4.4]nonanes **3**, which given a way of preparing unsaturated diols **2** [from commercially available 3-chloro-2-(chloromethyl)propene, thioanisol and a carbonyl compound], are generated from very simple materials and through easily performed procedures (Scheme 2).

Acknowledgements

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20. This compound is easily prepared from commercially available 3-chloro-2-(chloromethyl)propene by reaction with phenylsulfanylmethyllithium in the presence of equimolar amounts of copper(I) cyanide and lithium chloride. See Ref. 11f.

21. *Typical procedure for compounds* **3** *and their characterization.*[23] Through a solution of the corresponding diol **2** (1 mmol) in dichloromethane (10 mL) at −78 °C, ozone was bubbled until the mixture became blue (ca. 4 h). Then the temperature was allowed to rise up to room temperature and thiourea (38 mg, 0.5 mmol) was added and the mixture was stirred for 6 h. The resulting mixture was filtered through a small column with silica gel and the solvent was evaporated at reduced pressure to give the corresponding pure crude product **3** (>95%). Yields are given in Table 1; physical, spectroscopic and analytical data follow:

    Compound **3a**: Colourless oil; t_R 17.55; R_f 0.70 (hexane/EtOAc 8:2); ν (film) 1007 cm^{-1} (CO); δ_H 0.88 (12H, t, $J = 7.0$ Hz, $4 \times CH_3$), 1.15–2.00 (40H, m, $20 \times CH_2$); δ_C 14.0, 14.1 ($4 \times CH_3$), 22.7, 22.8, 24.0, 24.3, 32.5, 32.6, 34.4, 36.3, 38.6, 41.5 ($20 \times CH_2$), 86.1 ($2 \times$ *C*OCO), 114.7 (OCO); *m*/*z* 408 (M$^+$, <1%), 337 (100). HRMS calcd for $C_{27}H_{52}O_2$ 408.3967, found 408.3957.

    Compound **3b**: Colourless oil; t_R 14.97; R_f 0.79 (hexane/EtOAc 8:2); ν (film) 1383, 1368, 1045 cm^{-1} (CO); δ_H 0.80–1.05 (24H, m, $8 \times CH_3$), 1.45–2.60 (12H, m, $2 \times CH_2CH_2$, $4 \times CH$); δ_C 18.0, 18.2, 18.3, 18.4, 18.7, 18.75, 18.8, 18.9 ($8 \times CH_3$), 33.5, 34.0, 35.2, 35.8 ($4 \times CH$), 35.9, 37.6 ($2 \times CH_2CH_2$), 89.2 ($2 \times$ *C*CH), 112.3 (OCO); *m*/*z* 270 (M$^+$−26, 18%), 269 (100). HRMS calcd for $C_{19}H_{36}O_2$ 296.2715, found 296.2715.

    Compound **3c**: Colourless oil; t_R 12.23; R_f 0.65 (hexane/EtOAc 8:2); ν (film) 1041 cm^{-1} (CO); δ_H 1.20–2.05 (24H, m, $12 \times CH_2$); δ_C 23.6, 29.7, 36.1, 36.8, 39.1, 39.7 ($12 \times CH_2$), 91.2 ($2 \times$ *C*OCO), 111.0 (OCO); *m*/*z* 237 (M$^+$+1, 13%), 236 (M$^+$, 77), 151 (100). HRMS calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1778.

    Compound **3d**: Colourless oil; t_R 14.68; R_f 0.25 (hexane/EtOAc 8:2); ν (film) 1103, 1037 cm^{-1} (CO); δ_H 1.50–2.10 (20H, m, $8 \times CH_2C$, $4 \times$ C*H*HO), 3.55–3.65, 3.70–3.80 (4H, 2m, $4 \times$ CH*H*O); δ_C 35.4, 35.8, 38.3, 39.5 ($8 \times$ *C*H$_2$C), 65.5 ($4 \times CH_2O$), 80.0 ($2 \times$ *C*OCO), 114.3 (OCO); *m*/*z* 269 (M$^+$+1, 16%), 268 (M$^+$, 100). HRMS calcd for $C_{15}H_{24}O_4$ 268.1675, found 268.1683.

    Compound **3e** (major diastereomer): Colourless solid; t_R 17.10 (t_R 17.15 for the minor diastereomer); mp 99–101 °C; R_f 0.57 (hexane/EtOAc 8:2); $[\alpha]_D^{20}$ −36.0 (*c* 0.7, CHCl$_3$); ν (KBr) 1017 cm^{-1} (CO); δ_H 0.80–1.05 (18H, m, $6 \times CH_3$), 1.25–2.10 (26H, m, $6 \times CH$, $10 \times CH_2$); δ_C 18.0, 22.6, 24.0, 26.3, 29.1, 50.7 ($6 \times CH_3$, $6 \times CH$), 21.8, 35.3, 36.0, 36.3, 50.6 ($10 \times CH_2$), 86.1 ($2 \times$ *C*CH), 115.4 (OCO); *m*/*z* 377 (M$^+$+1, 29%), 376 (M$^+$, 100). Anal. Calcd for

$C_{25}H_{44}O_2$: C, 79.73; H, 11.78, found C, 79.70; H, 11.85.
Compound **3f** (major diastereomer): Colourless solid; t_R 17.89 (t_R 17.99 for the minor diastereomer); mp 151–153 °C (dec.); R_f 0.61 (hexane/EtOAc 8:2); $[\alpha]_D^{20}$ −11.9 (*c* 1.0, $CHCl_3$); ν (KBr) 1036 cm^{-1} (CO); δ_H 0.80–1.15 (18H, m, $6 \times CH_3$), 1.25–2.10 (22H, m, $2 \times CH$, $10 \times CH_2$); δ_C 18.2, 24.1, 27.8 ($6 \times CH_3$), 25.9, 28.5, 30.6, 37.1, 41.5 ($10 \times CH_2$), 43.2, 51.1 ($4 \times CCH_3$), 49.3 ($2 \times CH$), 92.7 ($2 \times COCO$), 111.6 (OCO); *m/z* 373 (M^++1, 23%), 372 (M^+, 88), 219 (100). Anal. Calcd for $C_{25}H_{40}O_2$: C, 80.59; H, 10.82, found C, 80.68; H, 10.78.

22. For general information on X-ray analysis, see Ref. 24. X-ray data for compounds **3e** and **3f** (major diastereomers) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 290099 and CCDC 290098, respectively. Selected data follow:
Compound **3e**: $C_{25}H_{44}O_2$, $M = 376.60$; monoclinic, $a = 10.2478(9)$ Å, $b = 10.2604(9)$ Å, $c = 23.130(6)$ Å, $\alpha = 90°$, $\beta = 114.304(2)°$, $\gamma = 90°$; $V = 1190.14(18)$ Å^3; space group $P2(1)$; $Z = 2$; $D_c = 1.051$ Mg/m^{-3}; $\lambda = 0.71073$ Å; $\mu = 0.064$ mm^{-1}; $F(000) = 420$; $T = 295(1)$ K.
Compound **3f**: $C_{25}H_{40}O_2$, $M = 37257$; orthorhombic, $a = 6.5142(18)$ Å, $b = 14.394(4)$ Å, $c = 12.4196(11)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$; $V = 2168.9(10)$ Å^3; space group $P21\ 21\ 21$; $Z = 4$; $D_c = 1.141$ Mg/m^{-3}; $\lambda = 0.71073$ Å; $\mu = 0.070$ mm^{-1}; $F(000) = 824$; $T = 297(1)$ K.

23. For detailed information on instrumentation (mp's, microanalysis, IR, NMR and MS equipments) and GLC (for t_R data) conditions, see Ref. 12d. Specific rotations were determined with a Perkin–Elmer 341 digital polarimeter.

24. Foubelo, F.; Moreno, B.; Soler, T.; Yus, M. *Tetrahedron* **2005**, *61*, 9082–9096.