A Novel Route Towards the Synthesis of Spirocyclic Bislactones

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Received 4 March 2008

Dedicated to Professor Manfred Reetz on the occasion of his 65th birthday

Abstract: A novel route towards the synthesis of 1,7-dioxaspiro[4.4]nonane-2,6-diones, based on the versatile reactivity of an acyclic trimethylenemethane dianion synthon, is presented.

Key words: trimethylenemethane, dianion synthon, lithiation, spirocyclization, bislactones

1,7-Dioxaspiro[4.4]nonanes[1] are abundant substructures present in a variety of natural products with diverse biological activities, some representative examples of these type of compounds being prehispanolone,[2] leopersin J,[3] and sphydrofuran.[4] 1,7-Dioxaspiro[4.4]nonanes can be also found in nature in the form of monolactones, such as longianone,[5] hyperolactone A,[6] and secosyrins 1 and 2,[7] as well as in the form of bislactones. Among the latter, it is worth mentioning forbic acid (**I**, from the leaves of *E. elegans*),[8] leudrin (**II**, present in some genera of *Proteaceae*),[9] dichotomain B (**III**, from the fronds of *Dicranopteris dichotoma*, which showed anti-HIV-1 activity)[10] or cinatrin A (**IV**, a potent inhibitor of rat platelet phospholipase A_2, from the fermentation broth of the microorganism *Circinotrichum falcatisporum*).[11] In addition, 1,7-dioxaspiro[4.4]nonane-2,6-diones, have also been used as valuable scaffolds in the synthesis of natural products (e.g. **V**, in zaragozic acid synthesis,[12] Figure 1).

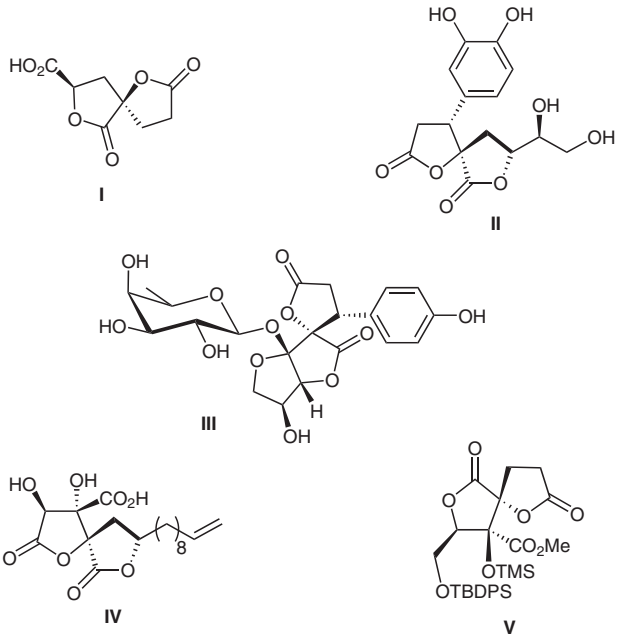
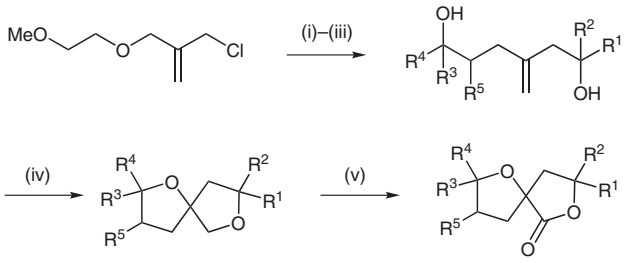


Figure 1 Examples of 1,7-dioxaspiro[4.4]nonane-2,6-diones

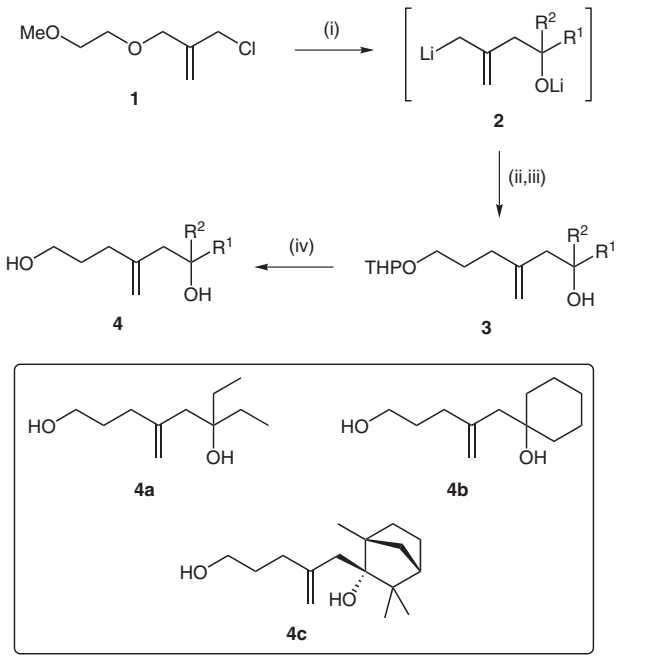
The unique structural nature of these spirobislactones has attracted the interest of synthetic organic chemists.[13] The methodologies described in the literature, however, normally involve intramolecular cyclizations on a preformed γ-lactone ring. The lactonization of 2-carboxy-2-hydroxyethyl-γ-lactones[14] and the iodolactonization of 2-allyl-2-carboxy-γ-lactones[15] are among the most general methods, whereas the ruthenium-catalyzed carbonylative cycloaddition of α-ketolactones with ethylene,[16] as well as the oxidation of 3-hydroxyethylcyclopentane-1,2-diones[17] are of more particular application. At any rate, and to the best of our knowledge, the synthesis of 1,7-dioxaspiro[4.4]nonane-2,6-diones through the double intramolecular cyclization of a complete acyclic precursor has never been reported.

On the other hand, in recent years we have shown an increasing interest in the synthesis of bicyclic[18] and spirocyclic[19] polyether skeletons as constituents of important biologically active compounds. In particular, we reported the two-step synthesis of 1,7-dioxaspiro[4.4]nonanes[19c,19d] from the versatile trimethylenemethane dianion synthon, 2-chloromethyl-3-(2-methoxyethoxy)propene (Scheme 1).[18b] The whole sequence involved selective initial lithiation in the presence of a carbonyl compound, second lithiation and reaction with an epoxide, and iodocyclization. Additionally, the compounds obtained could be oxidized to the corresponding 1,7-dioxaspiro[4.4]nonan-6-ones in excellent yields.



Scheme 1 *Reagents and conditions*: (i) Li, DTBB (cat.), R^1R^2CO, THF, –78 to 0 °C; (ii) $R^3R^4C(O)CHR^5$, 0–20 °C; (iii) H_2O; (iv) I_2, Ag_2O, THF or dioxane–H_2O, 20 °C; (v) RuO_2 (cat.), $NaIO_4$, CCl_4–H_2O, 20 °C.

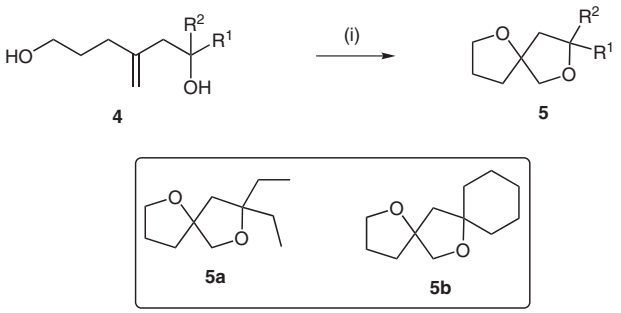
SYNLETT 2008, No. 11, pp 1627–1630
Advanced online publication: 11.06.2008
DOI: 10.1055/s-2008-1078489; Art ID: D06808ST



Scheme 2 *Reagents and conditions*: (i) Li, DTBB (2.5 mol%), R^1R^2CO, THF, –78 to 0 °C, 3.5 h; (ii) ICH_2CH_2OTHP, 0–20 °C, 3.5 h (**3a**, 43%; **3b**, 45%; **3c**, 42%); (iii) H_2O; (iv) PTSA, MeOH, 1 h (**4a–c**, quantitative yield).

This methodology, however, did not allow access to the corresponding 1,7-dioxaspiro[4.4]nonane-2,6-diones, due to the presence of one or two substituents at the 2-position. We wish to present herein our preliminary results on the synthesis of spirocyclic bislactones of the 1,7-dioxaspiro[4.4]nonane-2,6-dione type, using as the key step the selective arene-catalyzed lithiation[20] of 2-chloromethyl-3-(2-methoxyethoxy)propene in the presence of a carbonyl compound (Barbier conditions)[21] and subsequent reaction with protected 2-iodoethanol.

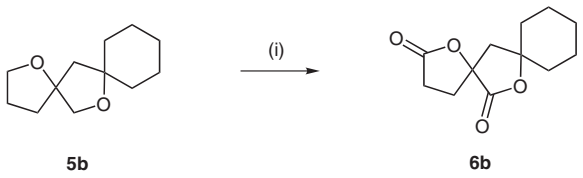
The reaction of 2-chloromethyl-3-(2-methoxyethoxy)propene (**1**) with an excess of lithium powder and a catalytic amount of DTBB (4,4′-di-*tert*-butylbiphenyl, 2.5 mol%), in the presence of a ketone in THF, at temperatures ranging from –78 °C to 0 °C, led to the organolithium intermediate **2**. Subsequent reaction of **2** with 2-iodoethanol, protected as the tetrahydro-2*H*-pyranyl derivative at 0–20 °C gave, after hydrolysis with water, the corresponding products **3** (Scheme 2).[22] This sequential incorporation of two different electrophilic fragments arises from the different reactivity of the carbon–chlorine and carbon–oxygen bonds in arene-catalyzed lithiations.[18,19] In spite of the fact that the yields of compounds **3** are modest, we must take into account that this process allows the introduction of two different electrophiles in one pot, the second electrophile being an alkyl iodide, which is prone to undergo side reactions under the reaction conditions. It is noteworthy that, in the case of using (–)-fenchone as the first electrophile, only one diastereoisomeric product was obtained.[23] Deprotection of compounds **3** was readily performed with a catalytic amount of PTSA in methanol, to furnish the corresponding methylidene diols **4** in quantitative yields.[24]



Scheme 3 *Reagents and conditions*: (i) I_2, Ag_2O, THF, 20 °C, 24 h (**5a**, 83%; **5b**, 89%).

The isolated diols **4a** and **4b** were subjected to double intramolecular cyclization by treatment with iodine and silver(I) oxide in THF at room temperature.[25] The corresponding 1,7-dioxaspiro[4.4]nonanes **5** were obtained in high yields and with such a high purity that they did not need any further purification (Scheme 3).

We believed that the spirocyclic compounds synthesized **5** could be used as adequate precursors of the 1,7-dioxaspiro[4.4]nonane-2,6-diones **6**. As an example, 1,7-dioxaspiro[4.4]nonane **5b** was successfully transformed into the corresponding spirocyclic bislactone **6b** by oxidation with a system composed of catalytic ruthenium(IV) oxide and sodium periodate.[26] The yield obtained for **6b** was high without the need of any further purification (Scheme 4). The structure of **6b** was unambiguously confirmed by X-ray crystallography (Figure 2).



Scheme 4 *Reagents and conditions*: (i) RuO_2 (15 mol%), $NaIO_4$, CCl_4–H_2O, 20 °C, 24 h (**6b**, 87%).

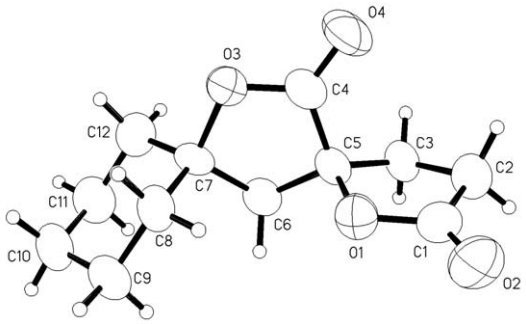


Figure 2 Plot showing the X-ray crystal structure and atomic numbering for compound **6b**

In conclusion, we have developed a novel synthesis of spirocyclic bislactones of the 1,7-dioxaspiro[4.4]nonane-2,6-dione type, starting for the first time from an acyclic precursor (a trimethylenemethane dianion synthon), through a selective arene-catalyzed lithiation (using a ketone and protected 2-iodoethanol as electrophiles), followed by double intramolecular iodocyclization, and final ruthenium-catalyzed oxidation. Further research to expand the scope of this methodology to the synthesis of spirocyclic bislactones with different substitution and ring sizes is under way.

Acknowledgment

This work was generously supported by the Spanish Ministerio de Educación y Ciencia (MEC; grants no. CTQ2004-01261 and CTQ2007-65218; Consolider Ingenio 2010-CSD2007-00006) and the Generalitat Valenciana (GV; grants no. GRUPOS03/135 and GV05/005). J.M. also thanks the GV for a predoctoral grant.

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(21) For a review, see: Alonso, F.; Yus, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 397.
(22) **General Procedure for the Preparation of Compounds 3** A solution of 2-chloromethyl-3-(2-methoxyethoxy)propene (164 mg, 1 mmol) and the corresponding ketone (0.95 mmol) in THF (2 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 neat 2-(2-iodoethoxy)tetrahydro-2*H*-pyran[27] (1.5 mmol) was added over 1.5 h continuing the stirring for 2 h at r.t. The reaction mixture was hydrolyzed with H_2O (5 mL), extracted with EtOAc (3 × 10 mL), and the organic phase was dried over anhyd $MgSO_4$. After removal of the solvent under reduced pressure ($2\cdot10^{-2}$ bar), the resulting residue was purified by column chromatography (SiO_2, hexane–EtOAc) to yield compounds **3**. **1-[2-Methylidene-5-(tetrahydro-2*H*-pyran-2-yloxy)pentyl]cyclohexanol (3b)** Colorless oil; R_f = 0.53 (hexane–EtOAc, 4:1). IR (neat): 3472 (OH), 3071, 1638 (C=CH), 1137, 1076, 1033 cm^{-1} (CO). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.90 [m, 19 H, OH, $(CH_2)_5$, $CH_2CH_2CH_2CH$, $CH_2CH_2C{=}CH_2$], 2.15–2.25 (m, 4 H, 2 × $CH_2C{=}CH_2$), 3.35–3.45, 3.45–3.55, 3.71–3.80, 3.83–3.90 (3 m, 4 H, 2 × CH_2O), 4.56 (t, *J* = 4.3 Hz, 1 H, 2 × CHO), 4.82, 4.95 (2 s, 2 H, CH_2=C). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6, 22.2, 25.4, 25.7, 28.0, 30.7 ($CH_2CH_2CH_2CH$, $CH_2CH_2C{=}CH_2$, $CH_2CH_2CH_2CH_2COH$), 34.4 ($CH_2CH_2C{=}CH_2$), 37.8 (2 × CH_2COH) 48.1 (CCH_2C), 62.3, 67.0 (2 × CH_2O), 71.0 (COH), 98.9 (CHO), 113.6 (CH_2=C), 146.0 (*C*=CH_2). MS (EI): *m/z* (%) = 282 (<1) [M^+], 99 (31), 85 (100), 81 (23), 67 (18), 55 (15). HRMS (EI): *m/z* calcd for $C_{17}H_{30}O_3$: 270.2195; found: 270.2201.
(23) The stereochemistry in **3c** and **4c** was established on the basis of the X-ray crystal structure of the methylidene diol resulting from the reaction of the analogue 3-methylidenepentane-1,5-dianion synthon with (–)-fenchone.[19g]
(24) **General Procedure for the Deprotection of Compounds 3** A flake of PTSA was added to a solution of the protected alcohol **3** (1 mmol) in MeOH (5 mL). After stirring for 1 h, the volatiles were removed under vacuum ($2\cdot10^{-2}$ bar), and H_2O (10 mL) was added to the residue followed by extraction with EtOAc (3 × 10 mL). The organic phase was

dried over anhyd $MgSO_4$ and the solvent evaporated under reduced pressure to give the pure product **4** which did not require further purification.

1-(5-Hydroxy-2-methylidenepentyl)cyclohexanol (4b)

Colorless oil; R_f = 0.40 (hexane–EtOAc, 4:1). IR (neat): 3373 (OH), 3072, 1638 (C=CH), 1146, 1059 cm^{-1} (CO). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.70 [m, 10 H, $(CH_2)_5$], 1.72–1.80 (m, 2 H, CH_2CH_2OH), 2.10–2.20 (m, 6 H, 2 × OH, 2 × $CH_2C{=}CH_2$), 3.65 (t, J = 6.2 Hz, 2 H, CH_2OH), 4.82, 4.94 (2 s, 2 H, $CH_2{=}C$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 25.7, 30.8, 33.8 (2 × CH_2CH_2CO, $CH_2CH_2CH_2CO$, CH_2CH_2O, $CH_2CH_2CH_2O$), 37.8 (2 × CH_2CO), 48.1 (CCH_2C), 62.1 (CH_2O), 71.3 (CO), 113.6 ($CH_2{=}C$), 146.0 ($C{=}CH_2$). MS (EI): *m/z* (%) = 180 (<1) [M^+ – 18], 99 (100), 81 (54), 55 (18). HRMS (EI): *m/z* calcd for $C_{12}H_{22}O_2$: 198.1620; [M^+ – H_2O]: 180.1514; found: 180.1515.

(25) **General Procedure for the Cyclization of Compounds 4**

Iodine (0.382 g, 1.5 mmol) was added to a solution of the corresponding diol **4** (1 mmol) in THF (5 mL). The mixture was stirred for 5 min at r.t. and then Ag_2O (0.346 g, 1.5 mmol) was added with additional stirring for 24 h. The resulting suspension was filtered and H_2O (10 mL) was added to the filtrate, followed by extraction with EtOAc (3 × 10 mL). The organic phase was successively washed with a sat. solution of Na_2SO_3 (2 × 10 mL) and H_2O (2 × 10 mL), and dried over anhyd $MgSO_4$. The solvent was removed under reduced pressure to furnish pure compounds **5**.

1,13-Dioxaspiro[4.1.5.2]tetradecane (5b)

Colorless oil; R_f = 0.69 (hexane–EtOAc, 4:1). IR (neat): 1058 cm^{-1} (CO). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30–1.95 [m, 14 H, $(CH_2)_5$, $CH_2CH_2CH_2O$], 1.73, 2.02 (AB system, J = 13.1 Hz, 2 H, CCH_2C), 3.35–3.50, 3.75–3.85 (2 m, 2 H, CH_2CH_2O), 3.63, 3.82 (AB system, J = 9.3 Hz, 2 H, CCH_2O). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 25.7, 29.4, 34.5, 37.7 (7 × CH_2), 49.0 (CCH_2C), 67.3 (CH_2CH_2O), 75.1 (CO), 82.9 (CCH_2O), 89.2 (OCH_2CO). MS (EI): *m/z* (%) = 196 (32) [M^+], 167 (13), 166 (17), 155 (100), 154 (18), 140 (21), 135 (10), 123 (36), 113 (10), 107 (11), 97 (15), 84 (19), 81 (14), 67 (13), 55 (29). HRMS (EI): *m/z* calcd for $C_{12}H_{20}O_2$: 196.1463; found: 196.1467.

(26) **1,13-Dioxaspiro[4.1.5.2]tetradecane-2,14-dione (6b)**

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 1,7-dioxaspiro[4.4]nonane **5b** (1.0 mmol) in CCl_4 (5 mL) at r.t.[28] After stirring the reaction for 24 h, *i*-PrOH (3 mL) was added, and the resulting mixture was extracted with CCl_4 (2 × 5 mL). The organic layer was dried over anhyd $MgSO_4$, 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 spirocyclic bislactone **6b**, which did not require any further purification.

Colorless solid; mp 138–140 °C; R_f = 0.50 (hexane–EtOAc, 4:1). IR (KBr): 1768 (C=O), 1139 cm^{-1} (CO). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30–2.65 (m, 16 H, 8 × CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3, 22.5, 24.6, 28.1, 31.3, 37.1, 38.0 (7 × CH_2), 45.4 (CCH_2C), 83.9, 85.0 (2 × CO), 173.7, 175.1 (2 × C=O). MS (EI): *m/z* (%) = 180 (29) [M^+ – CO_2], 139 (23), 138 (26), 137 (100), 124 (29), 120 (24), 111 (21), 109 (30), 99 (93), 98 (63), 96 (22), 95 (51), 82 (53), 81 (65), 80 (57), 79 (27), 70 (22), 69 (23), 67 (50), 56 (55), 55 (79), 54 (25), 53 (21). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19; O, 28.54. Found: C, 64.20; H, 7.23.

Selected X-ray Data: $C_{12}H_{16}O_4$, M = 224.25; monoclinic, a = 8.510(2) Å, b = 6.8849(16) Å, c = 9.445(2) Å, β = 95.993(4)°; V = 550.3(2) $Å^3$; space group $P2_1$; Z = 2; D_c = 1.353 Mg m^{-3}; λ = 0.71073 Å; μ = 0.101 mm^{-1}; F(000) = 240; T = 24 ± 1 °C; CCDC number 679641 contains the supplementary crystallographic data for compound **6b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.ac.uk/data_request/cif.

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