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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 6519–6524

A new 3-methylidenepentane-1,5-dianion synthon: synthesis of perhydropyrano[2,3-*b*]pyrans and 1,7-dioxaspiro[4.5]decanes

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Received 7 June 2005; revised 8 July 2005; accepted 19 July 2005
Available online 3 August 2005

Abstract—4-Phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**2**) has proved to be an appropriate and new 3-methylidenepentane-1,5-dianion synthon. The reaction of **2** with an excess of lithium powder and a catalytic amount of DTBB (2.5%) in the presence of a carbonyl compound in THF at 0 °C, leads, after hydrolysis, to the expected methylidenic diols **3**. These diols when subjected to successive hydroboration–oxidation and final oxidation, undergo spontaneous cyclisation to furnish a series of *cis*-perhydropyrano[2,3-*b*]pyrans (**4**) in a highly diastereoselective manner (>99% de). Additionally, diols **3** also undergo double intramolecular iodoetherification promoted by a silver salt, to furnish the corresponding 1,7-dioxaspiro[4.5]decanes (**6**) in very high yields.

In the last decade a great interest has been devoted to study the design and reactivity of different methylidene dianion synthons. In particular, trimethylenemethane dianion synthons (**I**) have been the most studied ones because of their ready accessibility and because they allow the incorporation of two electrophilic fragments into both sides of a versatile methylidenic unit that can be subjected to further transformations.[1] However, very little attention has been paid to trimethylenemethane dianion homologue synthons such as 2-methylidenebutane-1,4- (**II**)[2] and 3-methylidenepentane-1,5-dianion (**III**) synthons (Chart 1). In fact, and to the best of our knowledge, a 3-methylidene-pentane-1,5-dianion synthon has never been reported.

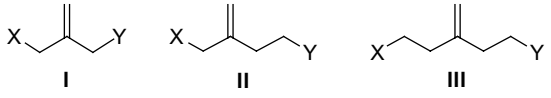

Chart 1.

On the other hand, the perhydropyrano[2,3-*b*]pyran moiety is present in a variety of natural products exhibiting interesting biological activities such as macralstonidine (**IV**, from *Alstonia* species, with antimalarial activity)[3] or sapogenin triterpene **V** (from *Emmenospermum pancherianum*),[4] as well as in dipyranosides like **VI** (key precursors for ansamycins) (Chart 2).[5] Most of the strategies developed to construct the perhydropyrano[2,3-*b*]pyran skeleton are related to carbohydrate modification.[6] At any rate, these and other methodologies normally involve intramolecular cyclisation over a preformed tetrahydropyran derivative under radical,[6a,c,7] acidic,[6b,8] Diels–Alder[6d,e] or Heck[9] conditions. More recently, different groups have focused on the synthesis of pyranobenzopyrans by Lewis-acid catalysed intermolecular cyclisation of 3,4-dihydro-2*H*-pyran and salicylaldehyde derivatives.[10]

The 1,7-dioxaspiro[4.5]decane moiety is very uncommon in Nature and has had little study at a methodological and synthetic level. Thus, it can be found, in its lactone form, in the structure of camelliatannin G (isolated from the leaves of *Camellia japonica* and belonging to a family of complex tannins that show anti-HIV activity)[11] or in stemotinine (**VII**) and isostemotinine (isolated from the roots of *Stemona tuberose* Lour., which are used in Chinese medicine as insecticides and anticough agents).[12] The mentioned unit is also present in the widely studied reduction products of artemisinin and its derivatives

Keywords: 1,5-Dianion synthon; DTBB-catalysed lithiation; Perhydropyranopyrans; Dioxaspirodecanes.
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doi:10.1016/j.tetlet.2005.07.077

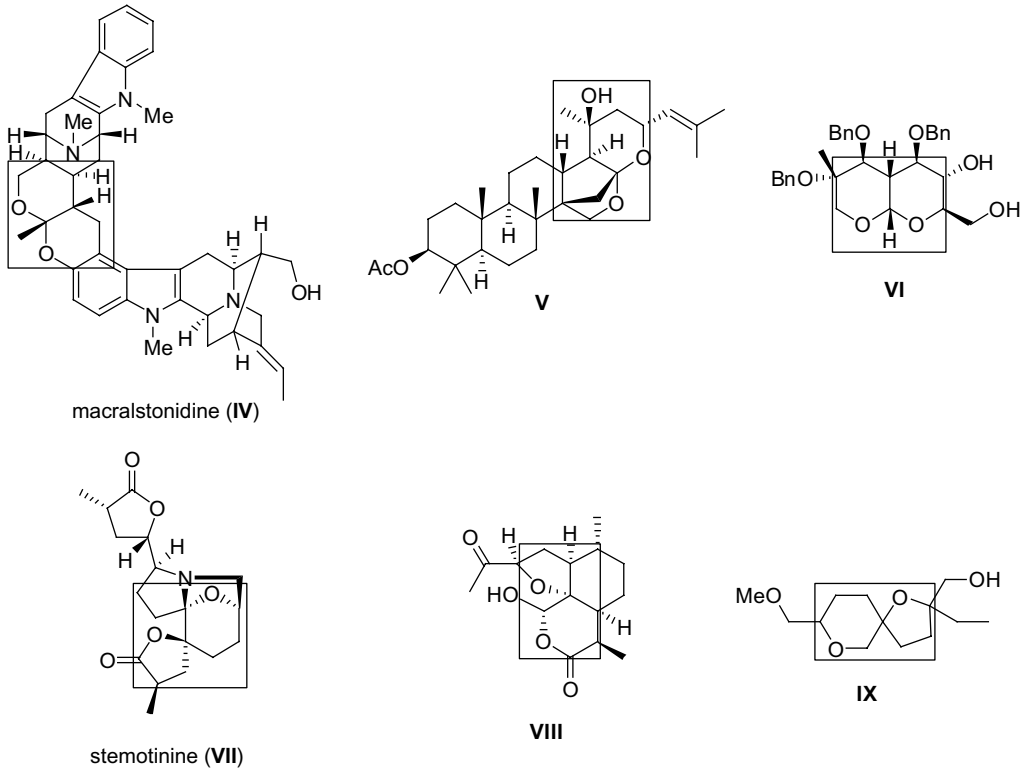


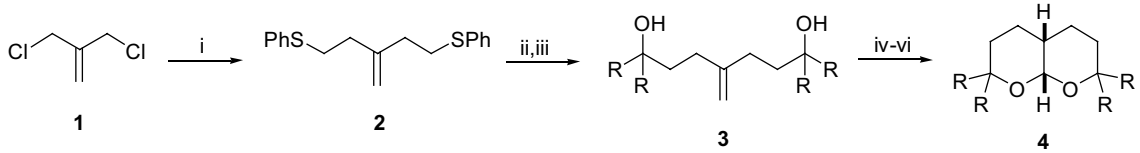
Chart 2.

(**VIII**)[13] as well as in a variety of compounds useful as plant growth regulators and herbicides (**IX**).[14]

In recent years, we have found out new methylidenic dianion synthons, which have been applied to the synthesis of fused bicyclic[15] and spirocyclic[16] polyether skeletons, as constituents of important biologically active compounds. In particular, 2-chloromethyl-3-chloroprop-1-ene (**I**, X = Y = Cl) and 2-chloromethyl-3-(2-methoxyethoxy)prop-1-ene (**I**, X = Cl, Y = OCH_2-CH_2OMe) showed to be versatile trimethylenemethane dianion synthons that allowed the incorporation of two equal or different electrophilic fragments, respectively, through a one-pot arene-catalysed lithiation.[17] In relation with the title topic, a series of perhydrofuro[2,3-*b*]furans and perhydrofuro[2,3-*b*]pyrans,[15] as well as a variety of spirocyclic ethers[16] could be synthesised in a straightforward manner from the above mentioned synthons.

We want to present herein 4-phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**III**, X = Y = SPh) as a new and the first 3-methylidenepentane-1,5-dianion synthon as well as its application to the straightforward and highly diastereoselective preparation of *cis*-perhydropyrano[2,3-*b*]pyrans and to the synthesis of 1,7-dioxaspiro[4.5]decanes. Some preliminary and promising isomerisation studies of the *cis*-perhydropyranopyrans directed to the obtention of the corresponding *trans* derivatives, and the oxidation of 1,7-dioxaspiro[4.5]decanes to the corresponding lactones are also reported.

An initial attempt to prepare 4-phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**2**) from 2-chloromethyl-3-chloroprop-1-ene (**1**) and phenylthiomethyllithium failed.[18] Instead, a modification of Corey's method, involving nucleophilic substitution with the organocuprate reagent derived from $PhSCH_2Li$ and CuCN, furnished **2** in 82% yield (Scheme 1). Compound **2** was subjected to reductive carbon–sulfur bond cleavage 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 ketones (Barbier conditions)[19] in THF, at 0 °C for 2 h, leading after hydrolysis with water, to the corresponding



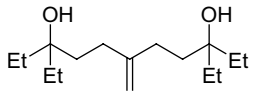
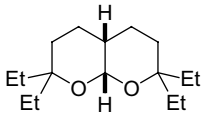
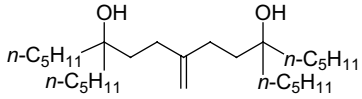
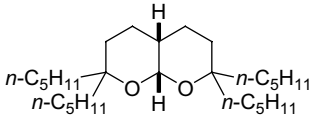
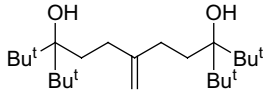
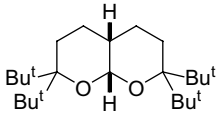
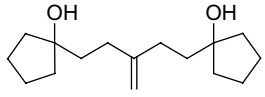
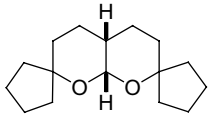
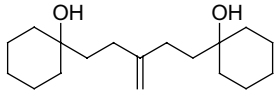
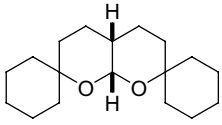
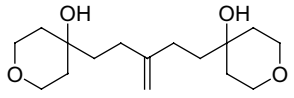
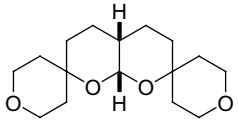
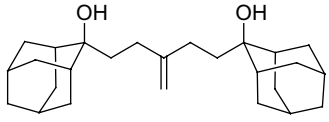
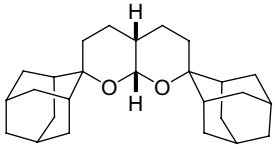
Scheme 1. Reagents and conditions: (i) $PhSCH_2Li$, CuCN, LiCl, 0 °C, 2 h; (ii) Li, DTBB (2.5 mol %), R_2CO, THF, 0 °C, 2 h; (iii) H_2O; (iv) BH_3·THF, 0 °C, 6 h; (v) 33% H_2O_2, 3 M NaOH, 0 °C, 8 h; (vi) PCC, CH_2Cl_2, rt, 8 h.

methylidenic diols **3** (Scheme 1 and Table 1).[20] Linear, branched, cyclic, polycyclic and heterocyclic ketones were used as electrophiles, the corresponding products **3** being obtained in modest yields after column chromatography.

The transformation of diols **3** into the corresponding perhydropyrano[2,3-*b*]pyrans **4** was effected by successive hydroboration–oxidation with borane–hydrogen peroxide, and final oxidation with PCC (Scheme 1 and Table 1).[15] Under the reaction conditions shown in Scheme 1 (step vi), the spontaneous intramolecular ketalisation occurred with exclusive formation of the *cis* diastereoisomers in high yields. Especially interesting from the structural point of view are the products derived from cyclic ketones (in particular polyether **4f**), which contain both spiro and fused bicyclic moieties. Compounds **4a** and **4d** showed to be in equilibrium with small amounts (~10%) of the corresponding precursor lactols. The *cis* stereochemistry in **4** was initially assigned by comparison of the ^{1}H NMR chemical shift of H_{8a} (acetal proton) and the J H_{8a},H_{4a} with the values appearing in the literature,[8] as well as by NOE experiments, and unambiguously established by X-ray crystallography of compound **4g** (Fig. 1).

To the best of our knowledge this is the first procedure that allows the straightforward preparation of perhydropyrano[2,3-*b*]pyrans from a completely acyclic precursor. Furthermore, this methodology is clearly advantageous with respect to those based on the acidic treatment of 2-alkoxy-3-(3-hydroxypropyl)tetrahydropyran derivatives and reported independently by the groups of Deslongchamps[8a] and Duhamel.[8b] In these studies, perhydropyrano[2,3-*b*]pyrans were obtained in 10–90% de, as a result that the acidic medium promoted

Table 1. Preparation of perhydropyrano[2,3-*b*]pyrans **4**

Product **3**[a]			Product **4**[a]		
No.	Structure	Yield (%)[b]	No.	Structure	Yield (%)[c]
3a		55	**4a**		82
3b		50	**4b**		91
3c		44	**4c**		91
3d		57	**4d**		84
3e		58	**4e**		87
3f		37[d]	**4f**		87
3g		33[e]	**4g**		76[f]

[a] All products were ⩾95% pure (GLC and/or 300 MHz ^{1}H NMR) and were fully characterised by spectroscopic means (IR, ^{1}H and ^{13}C NMR and MS).

[b] Isolated yield after column chromatography, unless otherwise stated (silica gel, hexane/EtOAc), based on the starting compound **2**.

[c] Yield of pure **4** from the reaction crude (unless otherwise stated) based on the starting diol **3**.

[d] Purification by column chromatography was carried out with EtOAc/MeOH as eluant.

[e] Isolated yield after recrystallisation with hexane.

[f] Isolated yield after column chromatography (silica gel, hexane), based on the corresponding diol **3g**.

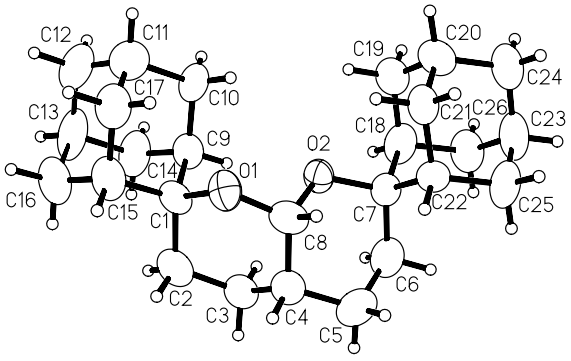
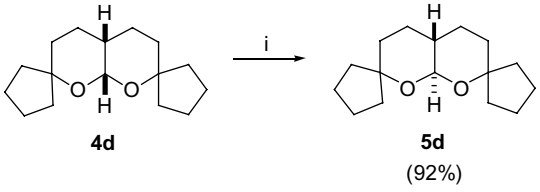


Figure 1. Plot showing the X-ray structure and atomic numbering for compound **4g**.

both intramolecular cyclisation and *cis–trans* isomerisation. In contrast, the methodology described herein, due to the mild and inert reaction conditions utilised, allowed a complete kinetically controlled ketalisation, leading to *cis*-perhydropyrano[2,3-*b*]pyrans (**4**) in >99% de.

We also devised the possibility to obtain stereoselectively *trans*-perhydropyrano[2,3-*b*]pyrans from the corresponding *cis* derivatives. In fact, and as a preliminary study, compound **4d** underwent progressive isomerisation by treatment with *p*-toluenesulfonic acid in $CHCl_3$ at room temperature, reaching a 8:92 *cis*/*trans* ratio after total equilibration (24 h) (Scheme 2 and Fig. 2). This isomerisation in favour of the thermodynamic *trans* product **5d** proved to be more stereoselective than those reported previously[8b] and expands the scope of the present methodology.



Scheme 2. Reagents and conditions: (i) *p*-TsOH (cat.), $CHCl_3$, rt.

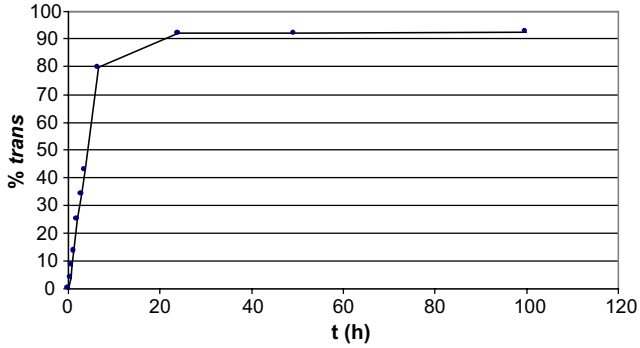
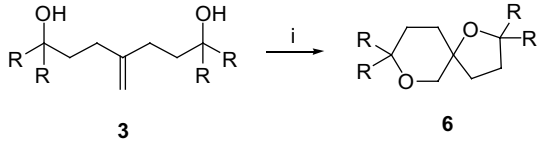


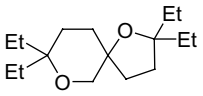
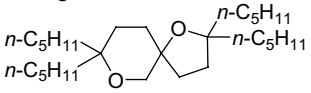
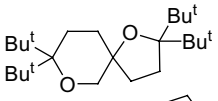
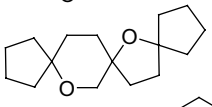
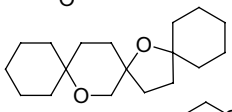
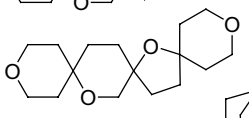
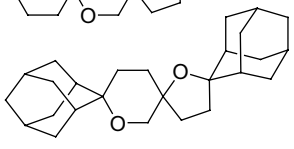
Figure 2. Graphic showing the *cis–trans* isomerisation of **4d** to **5d** versus time, under the conditions depicted in Scheme 2.

Concerning the synthesis of 1,7-dioxaspiro[4.5]decanes, we were very disappointed when initial attempts to cyclise the diols **3** under the previously experimented iodoetherification conditions failed.[16] Therefore, new reaction conditions had to be developed and optimised in which the base and silver source were the main variables. The best results were obtained using I_2, AgOTf and Na_2CO_3 in THF at rt.[21] Under those reaction conditions, diols **3** were transformed into the corresponding 1,7-dioxaspiro[4.5]decanes **6** in excellent isolated yields without any further purification (Scheme 3 and Table 2). It is noteworthy that this methodology allows the preparation of the structurally interesting trispiro compounds **6d–g**, and especially that of trispirocyclic polyether **6f**, in a very straightforward manner. The 1,7-dioxaspiro[4.5]decane nature of the core of compounds **6** was determined by spectroscopic means, and unequiv-



Scheme 3. Reagents and conditions: (i) I_2, AgOTf, Na_2CO_3, THF, rt, 24 h.

Table 2. Obtention of 1,7-dioxaspiro[4.5]decanes **6**

Product **3**[a]	Product **6**[b]		
No.	No.	Structure	Yield (%)[c]
3a	**6a**		95
3b	**6b**		96
3c	**6c**		94
3d	**6d**		95
3e	**6e**		99
3f	**6f**		94
3g	**6g**		98

[a] For yields and structure of compounds **3**, see Table 1.

[b] All products were ⩾95% pure (GLC and/or 300 MHz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR and MS).

[c] Isolated yield of pure **6** from the reaction crude based on the starting diol **3**.

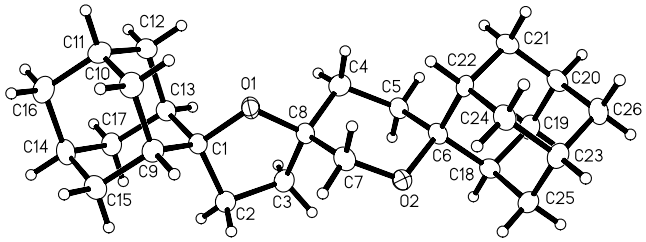
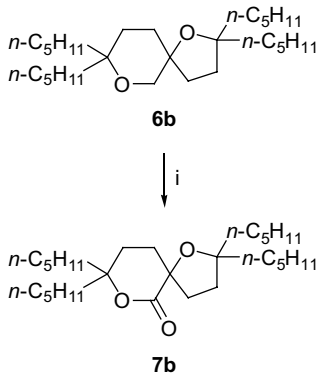


Figure 3. Plot showing the X-ray structure and atomic numbering for compound **6g**.

ocally established by X-ray crystallography of compound **6g** (Fig. 3).

We believed that the synthesised spirocyclic compound **6** could serve as an adequate precursor of the very rare 1,7-dioxaspiro[4.5]decan-6-ones by oxidation adjacent to the tetrahydropyran oxygen atom. To carry out this transformation, we used the ruthenium-catalysed oxidation under the conditions described in the literature[22] and applied by us to other homologue spirocyclic ethers.[16b–d] In a preliminary study, 1,7-dioxaspiro[4.5]decane **6b** was used as a model substrate and treated with a catalytic amount of RuO_2 (0.15 equiv) and an excess of $NaIO_4$ (4.88 equiv), in CCl_4–H_2O (1:1) at room temperature (Scheme 4). However, compound **6b** showed to be reluctant to oxidation under those conditions. Thus, only 29% conversion was obtained after the standard reaction time of 24 h. A moderate conversion of 61% was reached after one week, whereas the more desired 95% conversion was only achieved after a prohibitive reaction time of 36 days. The difficulty to oxidise the tetrahydropyran ring in **6b** might explain in part why dioxaspiro[4.5]decan-6-ones are so unusual. Nonetheless, we are dedicating our efforts in order to accelerate the rate of this transformation.

In conclusion, a new 3-methylidenepentane-1,5-dianion synthon has been introduced and successfully applied to the highly diastereoselective synthesis of both *cis*- and *trans*-perhydropyrano[2,3-*b*]pyrans, giving also a direct access to 1,7-dioxaspiro[4.5]decanes. Further research, including the use of other electrophiles, *cis*/*trans* isomerisation of other perhydropyranopyran derivatives, as well as the development of a more efficient methodology to convert 1,7-dioxaspiro[4.5]decanes into the corresponding lactones, is under way.



Scheme 4. Reagents and conditions: (i) RuO_2 (cat.), $NaIO_4$, CCl_4, H_2O, rt.

Acknowledgements

This work was generously supported by the Spanish Ministerio de Educación y Ciencia (MEC; Grant CTQ2004-01261) and the Generalitat Valenciana (GV; Grant no. GRUPOS03/135). J.M. also thanks the GV for a predoctoral grant.

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20. *In a typical procedure:* A solution of 4-phenylsulfanyl-2-(2-phenylsulfanylethyl)but-1-ene (**2**) (300 mg, 1 mmol) and the corresponding ketone (2 mmol) in THF (4 mL) was added to a green suspension of lithium powder (50 mg, 7 mmol) and DTBB (27 mg, 0.1 mmol) in THF (3 mL) at 0 °C. After stirring for 2 h at 0 °C, the resulting mixture was hydrolysed with water (5 mL), extracted with EtOAc (3×10 mL) and the organic phases dried over Na_2SO_4. The solvent was evaporated under reduced pressure (15 Torr) and the reaction crude purified by column chromatography [silica gel, hexane/EtOAc (compounds **3a**–**e**), hexane/MeOH (compound **3f**)] or recrystallisation with hexane (compound **3g**).
21. *In a typical procedure:* Iodine (382 mg, 1.5 mmol) was added to a solution of diol **3** (1 mmol) in THF (10 mL) and the mixture was stirred at room temperature for 5 min. After addition of Na_2CO_3 (159 mg, 1.5 mmol) and AgOTf (771 mg, 3 mmol) a white-yellow precipitate was rapidly formed. Additional stirring for 24 h was followed by filtration through a short column containing a layer of celite over silica gel and using hexane as eluant. Washing with a saturated solution of Na_2SO_3 is recommended if the filtrate is coloured. The resulting solution was dried over Na_2SO_4 and the solvents evaporated under reduced pressure (15 Torr), giving a reaction crude that contained pure compound **6** that did not require any further purification.
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