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Short Note

Bis(3-(((4-methoxybenzyl)oxy)methyl)-5,6-dihydro-1,4-dithiin-2-yl)methanol

Anna Esposito [1,*] and Annalisa Guaragna [2]

[1] Department of Chemical, Materials and Production Engineering, University of Naples Federico II, I-80125 Naples, Italy
[2] Department of Chemical Sciences, University of Naples Federico II, I-80126 Naples, Italy; annalisa.guaragna@unina.it
* Correspondence: anna.esposito5@unina.it

Abstract: An organolithium reagent containing a 5,6-dihydro-1,4-dithiin moiety has been herein used as homologating agent to build up a fully protected divinylcarbinol by two different synthetic procedures, respectively, based on a step-by-step approach or a tandem process. The resulting molecule contains two double bonds masked by two dithiodimethylene bridges that can be stereoselectively removed to give a *E*,*E*- or *Z*,*Z*-configured divinylcarbinol. These products could then be conveniently functionalized, for example, with hydroxyl or amino functions, for the construction of the skeleton of more complex systems.

Keywords: homologating agent; dithiins; divinylcarbinol; tandem process; organolithium compounds

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1. Introduction

Carbon–carbon chain construction has been of constant and increasing interest for researchers during the last decades, mainly for those interested in the building of key molecular scaffolds to be further functionalized and employed in the synthesis of more complex organic molecules.

Homologation reactions [1–5] are the most fundamental and attractive methods by which the substrates, thanks to the insertion of one or more methylene groups, are converted into their corresponding homologs. In particular, organometallic reagents play a crucial role in the reaction forming carbon–carbon bonds for the construction of organic molecular systems [6–9]. Within this context, the negatively polarized site of the carbon–metal bond represents a suitable reactive center to be coupled with a plethora of electrophilic species. Generally, the efficacy of an organometallic reagent is determined by the ionic percentage of the carbon–metal bond, which in turn depends on the difference in electronegativity between the two atoms. Therefore, reactants containing C-Li, C-Ti, C-Mg, and C-Al bonds are more reactive than those containing C-Z, C-Sn, C-Cu, and C-B bonds, for which the bond character is essentially covalent [10–13].

Thanks to their high reactivity toward most functional groups, even under mild conditions, the most popular organometallics in contemporary organic chemistry are organolithium compounds [14–18]. Their preparation is mainly obtained by deprotonation with lithiated bases [19], halogen–Li exchange, carbon–heteroatom bond cleavage, carbolithiations, and by reactions of transmetalation, mainly by Sn–Li exchange [20].

In the past years, within the scope of our interest in the preparation of bioactive compounds [21–24], we devised the synthesis of a new organolithium reagent, based on the 5,6-dihydro-1,4-dithiin heterocyclic system **1** (Figure 1), a three-carbon homologating agent, which represents an allylic alcohol anion equivalent, useful for the homologation of various electrophiles by introduction of a fully protected hydroxypropenyl moiety.

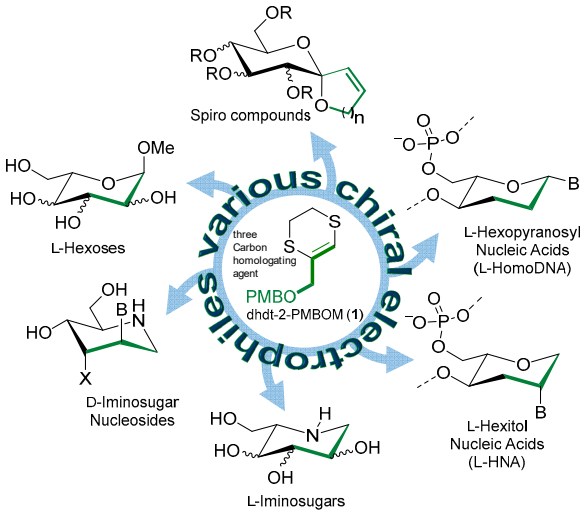
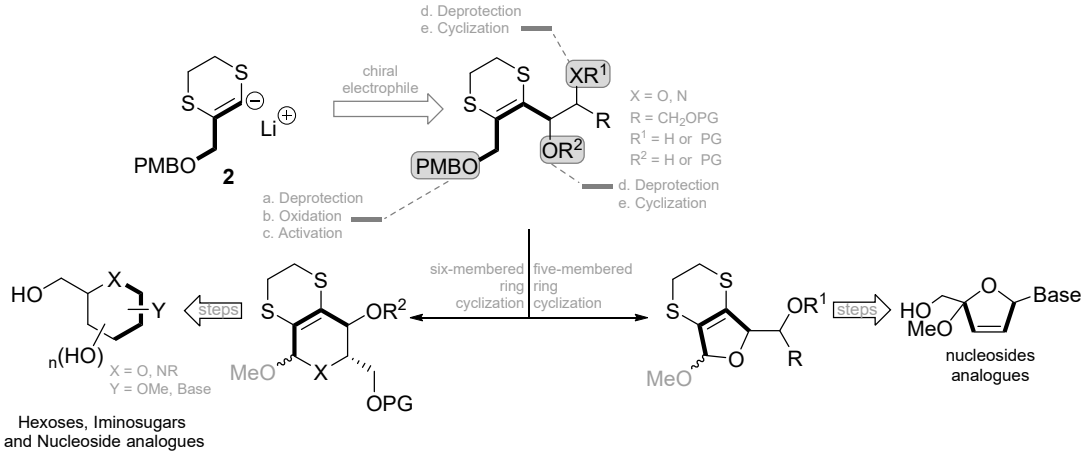


Figure 1. Synthetic applications of dhdt-2-PMBOM (**1**) in the construction of bio- and glycomimetics.

The *O*-protected (5,6-dihydro-1,4-dithiin-2-yl)methanol (**1**, dhdt-2-PMBOM) was easily prepared in a few steps from methyl pyruvate and has been successfully employed for the construction of biologically relevant molecules by a convergent approach. In particular, **1** has been used for the three-carbon homologation of various electrophiles by the introduction of a fully protected allylic alcohol moiety, allowing the preparation of nucleoside analogues, unnatural oligonucleotides, and several polyhydroxylated compounds, such as hexoses and iminosugars [25,26]. As highlighted in Scheme 1, the three-carbon chain present in **1** has been used to build up the saccharide or pseudo-saccharide skeleton, or to be conjugated to a sugar moiety. Indeed, the masked double bond, after the removal of the dithiodimethylene bridge, has been further functionalized in a stereoselective manner to add the desired residues [27]. Our results have been extensively discussed in an excellent review by J.M. Winne and coauthors [28].



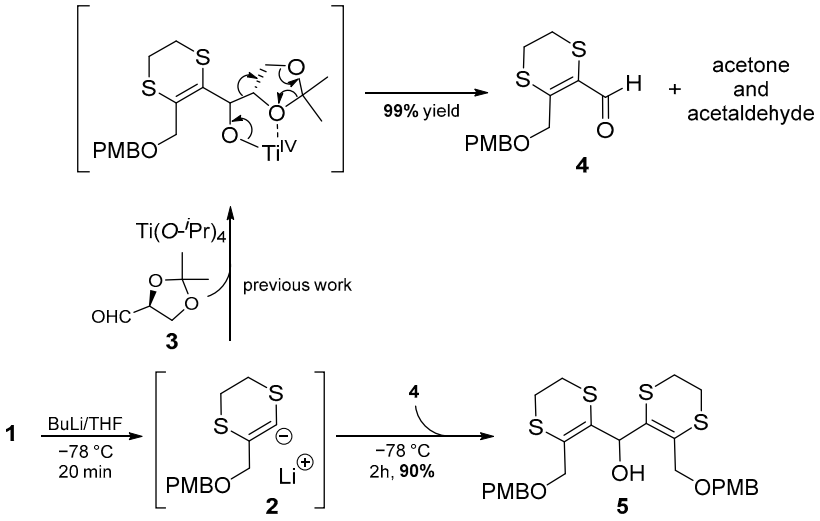
Scheme 1. Simplified representation of the synthetic path for the construction of five- and six-member rings, starting from the coupling products obtained by homologation of lithiated carbanion **2** with different electrophiles.

As an example, a coupling reaction of lithiated **1** with oxygen or nitrogen-containing chiral electrophiles (Scheme 1), such as the Garner aldehyde [29] or 2,3-*O*-isopropylidene-D- or L-glyceraldehyde [30,31], allowed for the elongation of the carbon chain to a six-carbon intermediate, that, after a suitable cyclization reaction, led to five or six-membered ring skeletons. Thanks to the removal of the dithiodimethylene sulfur bridge, the exposed

double bond was stereoselectively functionalized, by *cis*- or *trans* dihydroxylation [27,32] or by nucleobase insertion [33], to afford different classes of bio- and glycomimetics.

2. Results and Discussion

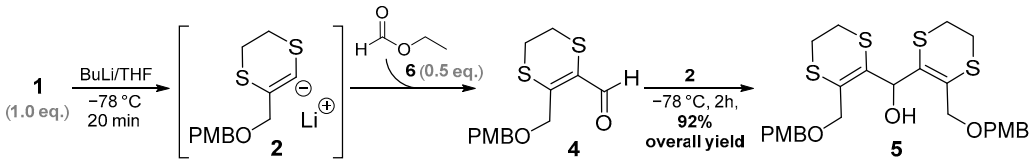
Herein, the homologating agent **1** (dhdt-2-PMBOM, Scheme 2) was used to build up a polycarbon chain, as system **5**, representing a fully protected divinylcarbinol which, after the unmasking of the double bonds, can be used as a substrate for further functionalization to synthesize more complex compounds of biological interest.



Scheme 2. Synthetic path to *O*-protected divinylcarbinol **5** by a two-step procedure.

In the first approach, the synthesis of **5** (Scheme 2) started by adding a 2.5 M solution of butyllithium (BuLi) in hexane to **1**, solved in THF, at −78 °C to generate the corresponding lithiated carbanion **2** after 20 min. Then, aldehyde **4** was added, leading to the complete consumption of the substrates and the formation of divinylcarbinol **5** as the sole reaction product, in an almost quantitative yield, after 2 h. Overall, the procedure involved two reaction steps with the preparation of the appropriate electrophile **4**. It should be noted that the aldehyde **4** has been previously obtained by us through a Ti(*O*-^{i}Pr)$_4$-mediated retroaldol reaction in the pathway toward the synthesis of L-hexoses, when **2** was reacted with 2,3-*O*-isopropylidene-L-glyceraldehyde (**3**) as the chiral electrophile.

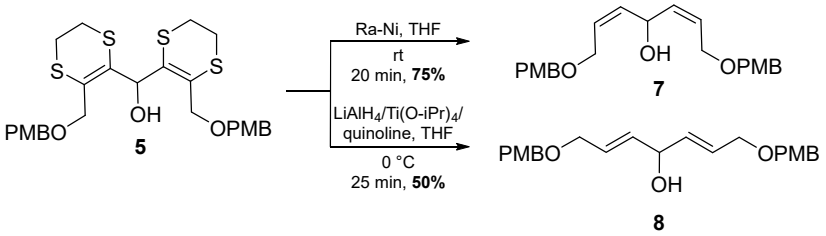
Alternatively, the target divinylcarbinol **5** was obtained through the tandem process depicted in Scheme 3. Starting from **1**, the electrophilic aldehyde **4,** was easily prepared in situ by reacting the lithiated carbanion **2**, obtained under the same conditions described above (BuLi/THF, −78 °C), with a substechiometric amount (0.5 eq) of commercially available ethylformate (**6**). Thus, the unreacted homologating system **2** left in the solution could, in turn, promptly act again as nucleophile on the newly formed aldehyde **4** to generate, after 2 h at −78 °C, the desired product **5** using a single reaction vessel and, even in this case, with an excellent overall yield (92%). NMR analysis confirmed the formation of target divinylcarbinol **5** as indicated by the appearance of a downfield proton (5.93 ppm).



Scheme 3. Synthetic path to *O*-protected divinylcarbinol **5** by a tandem process.

Eventually, the removal of sulfur bridges was performed to demonstrate the synthetic utility of the prepared divinylcarbinol **5.** Accordingly, the fully protected **5** was

subjected to a chemoselective and stereospecific mild desulfurization (Scheme 4) with Raney nickel [34–36] in THF to give rise to the already known [37–40] bis(*cis*-configured) *O*-protected divinylcarbinol **7** in a satisfactory overall yield (75%). On the other hand, the use of the $LiAlH_4/Ti(O\text{-}^iPr)_4$/quinoline system [36] (Scheme 4), instead of Raney nickel, promoted the dithiodimethylene bridge removal in a chemo- and stereoselective manner, even if in a lower reaction yield (50%), leading to the formation of the already known [39] bis(*trans*-configured) carbinol **8**. The *cis*/*trans* configuration of divinylcarbinols **7** and **8** was assigned by comparison of the NMR data with those reported in the literature [37,39] and by observing the large J value (15.7 Hz) related to the interaction of the *trans*-configured H nuclei (see Supplementary Materials for details).



Scheme 4. Desulfurization reaction to bis(*cis*- and *trans*-configured) *O*-protected divinylcarbinols **7** and **8**.

Divinylcarbinols **7** and **8** represent useful substrates for various functionalization, for instance, by inserting hydroxyl or amino functions to give polyhydroxylated chains or amino hydroxylated compounds, suitable intermediates in the synthesis of sugar analogues, iminosugar moiety, and aminosugars [41,42].

3. Materials and Methods

3.1. General Information

All moisture-sensitive reactions were carried out under Ar atmosphere using pre-dried glassware. Reactions were monitored by TLC (silica gel plates F254, Merk Life Science S.r.l., Milan, Italy) and by exposing the plates to UV radiation, iodine vapor, and spraying with 5% EtOH solution of sulfuric acid. Column chromatography (Merck Kieselgel 60, 70–230 mesh) was employed for compound purification. The Thermo Scientific Flash Smart V elemental analyzer was used for combustion analyses. The IR spectrum was recorded with a Fourier transform spectrophotometer, PerkinElmer FT-IR Spectrum 100 (Perkin Elmer, Waltham, MA, USA). The HRESI-MS spectrum was acquired on a Thermo Orbitrap XL mass spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). The NMR spectra were recorded on NMR spectrometers operating at 400 MHz (Bruker AVANCE, Billerica, MA, USA) and using C_6D_6 solutions.

3.2. Bis(3-(((4-methoxybenzyl)oxy)methyl)-5,6-dihydro-1,4-dithiin-2-yl)methanol (**5**)

3.2.1. Method A (Two-Step Procedure)

n-BuLi (2.5 M in hexane, 0.32 mL, 0.79 mmol) was added dropwise to a stirred solution of **1** (0.20 g, 0.75 mmol) in anhydrous THF (5.0 mL) at −78 °C under argon atmosphere. After 20 min, a solution of aldehyde **4** (0.24 g, 0.82 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred for 2 h at −78 °C and then carefully quenched with 10% aq NH_4Cl. The mixture was extracted with Et_2O, and the combined organic phases washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the residue (hexane/acetone = 7:3) gave the pure **5** (0.38 g, 90% yield) as follows: oily. ^1H NMR (C_6D_6, 400 MHz), δ: 2.49–2.57 (*m*, 4H, CH_2S), 2.59–2.66 (*m*, 4H, CH_2S), 3.27 (*s*, 6H, OCH_3– PMB), 3.63 (*d*, 1H, J = 5.1 Hz, OH), 4.12 (*d*, 2H, J = 12.3 Hz, H-1a), 4.35 (*d*, 4H, J = 12.3 Hz, H-1b, Ha-PMB), 4.38 (*d*, 2H, J = 12.3 Hz, Hb-PMB), 5.93 (*d*, 1H, J = 5.1 Hz, H-4), 6.75 (*d*, 4H, J = 8.7 Hz, H_{meta}-PMB), 7.23 (*d*, 4H, J = 8.7 Hz, H_{orto}– PMB). ^{13}C NMR (C_6D_6, 100 MHz): ppm 27.5, 29.7, 54.4, 70.5, 71.6, 71.7, 113.8, 125.7, 129.5, 130.1, 130.8, 159.5. HRMESI-MS calcd for $C_{27}H_{31}O_4S_4^+$: 547.1100; found 547.1093. FT-IR υ (cm^{-1}): 3408.08,

2923.62, 2853.47, 1610.52, 1583.98, 1511.85, 1462.58, 1246.18, 1173.05, 1062.90, 1031.13, 817.95. Anal. Calcd (%) for $C_{27}H_{32}O_5S_4$: C 57.42; H 5.71; S 22.71. Found: C 57.63; H 5.59; S 23.01.

3.2.2. Method B (Tandem Procedure)

n-BuLi (2.5 M in hexane, 0.36 mL, 0.91 mmol) was added dropwise to a stirred solution of **1** (0.19 g, 0.71 mmol) in anhydrous THF (10 mL) at −78 °C under argon atmosphere. After 2 h, ethyl formate (**6**; 29.0 µL, 0.35 mmol) was added dropwise. The reaction mixture was stirred for 3 h at −78 °C and then carefully quenched with 10% aq NH_4Cl. The mixture was extracted with Et_2O, and the combined organic phases washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the residue (hexane/acetone = 7:3) gave the pure **5** (0.18 g, 92% yield) described as follows: oily.

*3.3. (2Z,5Z)-1,7-Bis[(4-methoxybenzyl)oxy]hepta-2,5-dien-4-ol (**7**)*

A suspension of Raney Ni (W2, 0.6 g wet) was added to a solution of **5** (60 mg, 0.11 mmol) in THF (2 mL) at room temperature. The resulting suspension was stirred for 20 min and then the solid was filtered off and washed with Et_2O. The filtrate was evaporated under reduced pressure. Chromatography of the crude residue over silica gel (hexane/Et_2O = 1:1) gave the pure **7** (32 mg, 75% yield) described as follows: oily. NMR data were fully in agreement with those reported elsewhere [40].

*3.4. (2E,5E)-1,7-Bis[(4-methoxybenzyl)oxy]hepta-2,5-dien-4-ol (**8**)*

To a solution of Ti(*O*Pr*i*)$_4$ (0.28 mL, 0.96 mmol) in anhydrous THF (2 mL) at 0 °C and under argon atmosphere, a suspension of $LiAlH_4$ (73 mg, 1.92 mmol) in the same solvent (2.0 mL) was added dropwise. The solution was stirred at 0 °C for 1 h, and then a solution of **5** (68 mg, 0.12 mmol) and quinoline (2 µL, 0.02 mmol) in anhydrous THF (2.0 mL) was added dropwise to the suspension. After 25 min (TLC monitoring), the reaction mixture was treated with brine and 1M aqHCl and extracted with Et_2O. The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give a crude residue which chromatography over silica gel (hexane/Et_2O = 1:1), resulting in the pure **8** (23 mg, 50% yield), oily. NMR data were fully in agreement with those reported elsewhere [40].

4. Conclusions

The synthetic paths herein described allowed for the preparation of the dithiin system **5**, starting from the homologating agent **1,** by two different synthetic methodologies, the second of which (Scheme 3) has the evident advantage with respect to the first one (Scheme 2), with an easier in situ preparation of the key intermediate aldehyde **4**. Through this tandem process, that involved the in situ generation of both the electrophile and the nucleophile, the desired **5** could be obtained with high reaction yield, avoiding the necessary isolation and purification steps. Divinylcarbinol **5** represents a key scaffold to synthesize, after sulfur bridge removal and further functionalization of the double bonds, more complex compounds, including those of biological interest.

Supplementary Materials: Figure S1. Copy of ^{1}H spectra of compound **5**; Figure S2. Copy of ^{13}C NMR spectra of compound **5**; Figure S3. Copy of HRESI-MS spectrum of compound **5**; Figure S4. Copy of FT-IR spectrum of compound **5**.

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Conflicts of Interest: The authors declare no conflicts of interest.

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