A New and Versatile Allylic Alcohol Anion and Acyl β-Anion Equivalent for Three-Carbon Homologations

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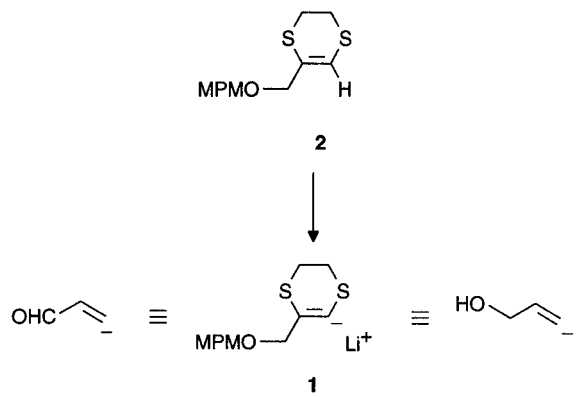
There are many reagents useful for the extension of organic molecules by three carbons with some functionality at the new terminus.[1] However, to the best of our knowledge, the possibility of introducing an allylic alcohol residue is restricted to only a few examples[2] despite its potential utility in the synthesis of complex organic molecules, like saccharides and related polyhydroxylated natural products, e.g., via asymmetric epoxidation[3] or dihydroxylation.[4] Therefore, we report herein the design, synthesis, and some examples of the synthetic versatility of 3-C-lithiated (5,6-dihydro-1,4-dithiin-2-yl)[(4-methoxybenzyl)oxy]methane (**1**) which can be utilized as an allylic alcohol anion equivalent and leads to elongations of various electrophiles by introduction of a fully protected hydroxypropenyl moiety. The latter contains a double bond, which can be unravelled with the cis configuration by diastereoselective removal of the dimethylene−disulfur bridge, as well as a protected primary hydroxyl group that, depending on the deprotection conditions used (DDQ/$NaBH_4$ or DDQ), may lead either to the free allylic alcohol or to an α,β-unsaturated aldehyde.

The parent compound of **1**, 2-[[*O*-(*p*-methoxybenzyl)-oxy]methyl]-5,6-dihydro-1,4-dithiin (**2**), can be easily prepared in four steps (overall yield 83%) from commercial methyl pyruvate via its 1,3-dithiolane and ring enlargement[5] of the latter. The choice of 4-methoxybenzyl ether (MPM)[6] as the hydroxyl-protecting group was crucial to the utilization of **2** as the intended allylic alcohol anion equivalent via its lithiation (Scheme 1). In addition, 4-methoxybenzyl ethers have the advantage of being selectively removed when in the presence of other common protecting groups including non-ring-substituted benzyl ethers.[7] The use of protecting groups such as *tert*-butyldimethylsilyl ethers (TBDMS) and tetrahydropyranyls (THP) was rather unsatisfactory and resulted in poor reactivity of the entire molecule under the C−C bond-forming reaction conditions.

The subsequent coupling reactions were effected by treatment of **2** with BuLi and then with miscellaneous

Scheme 1



electrophiles—namely, methyl iodide, benzyl bromide, (*R*)- and (*S*)-benzyl glycidyl ether, (*R*)-*O*-isopropylideneglyceral[8]—according to a standard procedure we already reported[9] for other 5,6-dihydro-1,4-dithiins. The results are shown in Table 1. The synthetic relevance of these coupling reactions resides on the fact that the products can be either deprotected, keeping the double bond tied up by the dimethylene−disulfur bridge (Table 2), or stereoselectively desulfurized affording a cis-configurated 4-methoxybenzyl propenyl ether (Scheme 2).

The cleavage of the 4-methoxybenzyl ether function was performed by treatment of the coupling products with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2/H_2O and then sodium borohydride in ethanol. The results are shown in Table 2. Sodium cyanoborohydride, reported[10] to be effective in the reductive cleavage of MPM ethers, led instead to only poor results. It is noteworthy that, if the above MPM ethers are cleaved by treatment with an equivalent amount of DDQ, a formyl function is quantitatively obtained rather than the expected[7] primary alcohol (Table 2) in the final product. Apparently, the aldehyde formation is not the result of the known oxidation[11] of the free allylic hydroxyl group by DDQ. As a matter of fact the MPM ether **4,** when treated with only 50% of the equivalent amount of DDQ, afforded aldehyde **14** and anisole (from the 4-methoxybenzyl ether moiety) in an approximately 1:1 ratio and 50% yield, in addition to a relevant amount (ca. 40%) of unreacted starting product. No traces of the hydroxyl-bearing compound **13** were detected. This is likely due to the preferential abstraction of a hydrogen atom from the vinylic rather than from the benzylic[12] methylene group and the consequent formation of a sulfur-stabilized carbocation.

Desulfurization of the above MPM ethers with Raney-Ni (W2) in glacial acetic acid at 0 °C led, as expected,[13] only to cis isomer formation (Scheme 2). Deprotection of the allyllic hydroxyl group and desulfurization of the double bond can be carried out independently, leading either to allylic alcohols or to their corresponding MPM ethers having a cis-configurated double bond. Two

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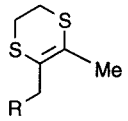
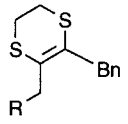
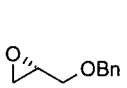
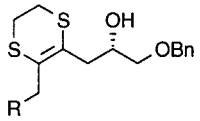
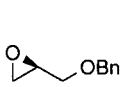
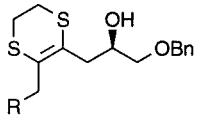
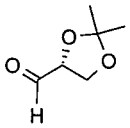
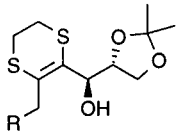
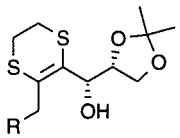
Table 1. Coupling Reactions of 2 with Miscellaneous Electrophiles

Electrophile	Product	Yield (%)	$[\alpha]_D^{25}$
MeI	 **3**	90	
BnBr	 **4**	92	
	 **5**	90	-8.0
	 **6**	88	+8.1
	 **7**	60	+32.0
	 **8**	24	+18.0

R = $OCH_2C_6H_4$-*p*-OMe; Bn = $CH_2C_6H_5$

examples reported in Scheme 2 illustrate the synthesis of polyhydroxylated substrates (**17**, **18**) with different protections of the hydroxyl groups.

In conclusion, we have disclosed the synthesis of **2** and its application in the three-carbon elongation, introducing in one step different functionalities such as a protected cis double bond with either a protected allylic primary hydroxyl group or a formyl group. Considering that the double bond can be further functionalized, even in a stereocontrolled manner, the utilization of **2** in the elongation of chiral substrates as (*R*)- and (*S*)-benzyl glycidyl ether and (*R*)-*O*-isopropylideneglyceral may represent an unprecedented and powerful tool for designing new synthetic strategies in the area of biologically relevant polyhydroxylated products.

Experimental Section

General. ^{1}H NMR spectra were recorded on $CDCl_3$ solutions; chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane (TMS), and *J* values are given in Hz. Optical rotations were measured on $CHCl_3$ solutions (1.0-dm cell). Thin-layer chromatography (TLC) analyses were performed on silica gel Merck 60 F_{254} plates (0.2-mm layer tickness). Column chromatography was carried out with Merck Kieselgel 60 (70−230 mesh). Dry solvents were distilled immediately before use (CH_2Cl_2 and $CHCl_3$ from P_2O_5; Et_2O from $LiAlH_4$).

(5,6-Dihydro-1,4-dithiin-2-yl)[(4-methoxybenzyl)oxy]-methane (2): prepared in four steps (a−d) from commercial methyl pyruvate in a 83% overall yield as follows.

(a)Methyl 2-Methyl-1,3-dithiolane-2-carboxylate. Methyl pyruvate (4.0 g, 39.2 mmol), freshly prepared PPh_3-I_2 complex[14] (39.2 mmol), and 1,2-ethanedithiol (3.2 mL, 39.2 mmol) dissolved in dry CH_2Cl_2 (60 mL) were stirred under N_2 atmosphere for 3 h (TLC monitoring). Usual workup[14] afforded the title compound (6.3 g, 90%). ^{1}H NMR (250 MHz): δ 1.95 (s, 3H), 3.38−3.48 (m, 2H), 3.49−3.60 (m, 2H), 3.75 (s, 3H). IR: 1735 cm^{-1}. MS: *m*/*z* 178 (M^+). Anal. Calcd for $C_6H_{10}O_2S_2$: C, 40.42; H, 5.65. Found: C, 40.55; H, 5.58.

(b)Methyl 5,6-Dihydro-1,4-dithiine-2-carboxylate. A solution of methyl 2-methyl-1,3-dithiolane-2-carboxylate (1.2 g, 6.6 mmol) and NBS (2.4 g, 13.2 mmol) in dry $CHCl_3$ (100 mL) was stirred at room temperature in the dark for 16 h. Workup[5] led to the title compound (1.1 g, 98%). ^{1}H NMR (200 MHz): δ 3.13−3.22 (m, 4H), 3.77 (s, 3H), 7.58 (s, 1H). IR: 1700 cm^{-1}. MS: *m*/*z* 176 (M^+). Anal. Calcd for $C_6H_8O_2S_2$: C, 40.89; H, 4.57. Found: C, 40.65; H, 4.66.

(c)(5,6-Dihydro-1,4-dithiin-2-yl)methanol (9). To a stirred solution of methyl 5,6-dihydro-1,4-dithiine-2-carboxylate (1.0 g, 5.7 mmol) in dry Et_2O (20 mL), at 0 °C and under N_2 atmosphere, was added a suspension of $LiAlH_4$ (0.8 g, 17.0 mmol) in the same solvent in small portions. After 30 min, AcOEt (a few drops) and aq 2 N HCl (10 mL) were added to the reaction mixture. The organic phase was washed with brine until neutral, then dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the crude residue on silica gel (light petroleum−AcOEt, 8:2) afforded pure **9** (0.8 g, 98%). ^{1}H NMR (200 MHz): δ 3.05−3.18 (m, 4H), 4.12 (s, 2H), 6.15 (s, 1H). IR: 3445 cm^{-1}. MS: *m*/*z* 148 (M^+). Anal. Calcd for $C_5H_8OS_2$: C, 40.51; H, 5.44. Found: C, 40.79; H, 5.38.

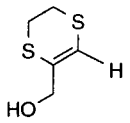
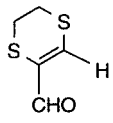
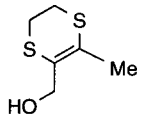
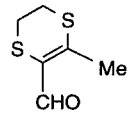
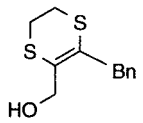
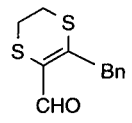
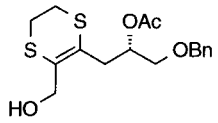
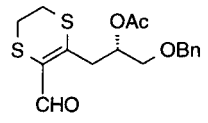
(d) 4-Methoxybenzyl chloride (1.3 g, 8.0 mmol) dissolved in dry DMF (20 mL) was added dropwise to a solution of pure **9** (1.0 g, 6.7 mmol) and NaH (0.2 g, 8.3 mmol) in the same solvent (20 mL) that had been kept under magnetic stirring and N_2 atmosphere for 30 min at room temperature. The stirring was continued for 15 h, and the reaction mixture was diluted with brine and extracted with Et_2O. The combined organic layers, after drying (Na_2SO_4) and evaporating under reduced pressure, gave a crude product which chromatography on silica gel (light petroleum−Et_2O, 9:1) and afforded the pure oily **2** (6.4 g, 96%). ^{1}H NMR (400 MHz): δ 3.13−3.23 (m, 4H), 3.83 (s, 3H), 4.00 (s, 2H), 4.43 (s, 2H), 6.20 (s, 1H), 6.88 (d, 2H, J = 8.5), 7.26 (d, 2H, J = 8.0). MS: *m*/*z* 268 (M^+). Anal. Calcd for $C_{13}H_{16}O_2S_2$: C, 58.18; H, 6.00. Found: C, 57.97; H, 6.08.

Coupling Reaction of 2 with Electrophiles. (2*S*)-1-(Benzyloxy)-3-(3-{[(4-methoxybenzyl)oxy]methyl}-5,6-dihydro-1,4-dithiin-2-yl)propan-2-ol (5). Typical Procedure. To a stirred solution of dithiin **2** (1.0 g, 3.7 mmol) in anhydrous THF (5 mL), at −78 °C and under argon atmosphere, was added 1.6 M BuLi in hexane (2.7 mL, 4.4 mmol) via cannula, dropwise over 10 min, followed by benzyl (*S*)-(+)-glycidyl ether (0.7 mL, 4.4 mmol) and $Ti(OPr^i)_4$ (0.2 mL, 0.9 mmol) dissolved in the same solvent (2 mL). The reaction mixture was kept for 1 h at −78 °C and for 3 h at −40 °C and then the reaction quenched carefully with 10% aq NH_4Cl (5 mL). Usual workup[9] and chromatography on silica gel (light petroleum−acetone, 8:2) of the crude residue finally afforded pure **5** (1.4 g, 90%). ^{1}H NMR (250 MHz): δ 2.39 (dd, 1H, J = 4.5, 15.0), 2.65 (dd, 1H, J = 8.4, 15.0), 3.19 (s, 4H), 3.44 (dd, 1H, J = 5.5, 10.0), 3.48 (dd, 1H, J = 4.6, 10.0), 3.80 (s, 3H), 3.93 (d, 1H, J = 11.5), 3.95−4.05 (m, 1H), 4.14 (d, 1H, J = 11.5), 4.48 (s, 2H), 4.55 (s, 2H), 6.87 (d, 2H, J = 8.0), 7.22 (d, 2H, J = 8.0), 7.28−7.40 (m, 5H). $[\alpha]^{25}_D$ = −8.0 (c = 2.0). IR: 3430 cm^{-1}. Anal. Calcd for $C_{23}H_{28}O_4S_2$: C, 63.86; H, 6.52. Found: C, 63.75; H, 6.55.

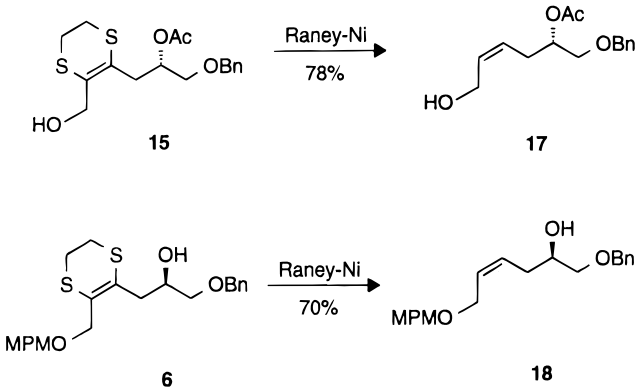
Reductive Cleavage of MPM Ether Derivatives. (3-Benzyl-5,6-dihydro-1,4-dithiin-2-yl)methanol (13). Typical

(14) Caputo, R.; Ferreri, C.; Palumbo, G. *Synthesis* **1987**, 386.

Table 2. Cleavage of the MPM Ether Derivatives under Reductive and Oxidative Conditions

DDQ/$NaBH_4$			DDQ		
Substrate	Product	Yield (%)	Substrate	Product	Yield (%)
2	 **9**	80	**2**	 **10**	83
3	 **11**	80	**3**	 **12**	88
4	 **13**	75	**4**	 **14**	89
Acetyl-**5**	 **15**	81	Acetyl-**5**	 **16**	85

Scheme 2



Procedure. To a stirred $CH_2Cl_2-H_2O$ (9:1) emulsion (50 mL) containing MPM ether **4** (0.5 g, 1.4 mmol) was added DDQ (0.4 g, 1.8 mmol) in one portion at room temperature. After 1 h, most of the solvent was evaporated under reduced pressure and replaced by EtOH (10 mL). To the resulting solution was added a suspension of $NaBH_4$ (0.05 g, 4.0 equiv) in a little amount of EtOH dropwise under stirring. After 10 min, the reaction mixture was diluted with brine and extracted with AcOEt. The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Chromatography of the crude product on silica gel (light petroleum−AcOEt, 8:2) gave the pure alcohol **13** (0.25 g, 75%). ^1H NMR (200 MHz): δ 3.18 (s, 4H), 3.68 (s, 2H), 4.23 (s, 2H), 7.20−7.32 (m, 5H). IR: 3430 cm^{-1}. Anal. Calcd for $C_{12}H_{14}OS_2$: C, 60.46; H, 5.92. Found: C, 60.70; H, 5.99.

Oxidative Cleavage of MPM Ether Derivatives. (3-Benzyl-5,6-dihydro-1,4-dithiine-2-carbaldehyde (14). Typical Procedure. To a stirred $CH_2Cl_2-H_2O$ (9:1) emulsion (50 mL) containing MPM ether **4** (0.5 g, 1.4 mmol) was added DDQ (0.4 g, 1.8 mmol) in one portion at room temperature. After 1 h, the suspension was filtered and the solid washed with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the crude product on silica gel (light petroleum−AcOEt, 8:2) gave the pure aldehyde **14** (0.25 g, 89%). Mp: 109−110 °C (benzene−hexane). ^1H NMR (200 MHz): δ 3.46−3.58 (m, 2H), 3.61−3.71 (m, 2H), 4.49 (s, 2H), 7.60−7.71 (m, 5H), 10.33 (s, 1H). Anal. Calcd for $C_{12}H_{12}OS_2$: C, 60.98; H, 5.12. Found: C, 61.15; H, 5.05.

Diastereoselective Desulfurization Reactions. (1*S*,3*Z*)-1-[(Benzyloxy)methyl]-5-hydroxy-3-pentenyl Acetate (17). Typical Procedure. A solution of dithiin **15** (0.1 g, 0.28 mmol) in glacial acetic acid (10 mL) was added in one portion to a stirred suspension of Raney-Ni (W2) (1.0 g, wet) in the same solvent (10 mL) at 0 °C and under dry argon (or nitrogen) stream. The resulting suspension was stirred for 5 min (TLC monitoring). Then the solid was filtered off and washed with glacial acetic acid, water, and Et_2O. The filtrate was neutralized with saturated aq Na_2CO_3 and extracted with Et_2O. The combined organic layers were washed with water until neutral, dried (Na_2SO_4), and evaporated under reduced pressure to afford a crude residue. Chromatography of the latter on silica gel (benzene−Et_2O, 9:1) gave the pure sulfur-free enyl acetate (**17**). ^1H NMR (250 MHz): δ 2.08 (s, 3H), 2.42−2.52 (m, 2H), 3.50−3.58 (m, 2H), 4.19 (d, 2H), 4.52−4.60 (m, 2H), 4.98−5.10 (m, 1H), 5.45−5.60 (m, 1H), 5.70−5.85 (m, 1H), 7.27−7.43 (m, 5H). $[\alpha]_{25D} = -7.6$ ($c = 1.2$). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.59; H, 6.95.

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