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Tropolonyl ethers of saccharides and cyclitol derivatives

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Abstract—Mitsunobu coupling between tropolones and saccharide or cyclitol derivatives featuring primary or secondary alcohol functions provides for the first time an easy, general and efficient access to the corresponding tropolonyl ethers. Selective deprotection of the carbohydrate or cyclitol units demonstrates that naked saccharides and cyclitols bearing a tropolonyl ether moiety may be prepared by this route.

The early suggestion by Dewar that natural products such as colchicine **1** and derivatives of puberulonic acid **2**, for instance, encompass the troponoid ring has generated a massive amount of work aiming at understanding and exploiting the chemistry of the cyclohepta-2,4,6-trienone cycle (tropone) (Fig. 1).[1] The belief that the tropone ring might be at least partly aromatic induced additional interest; this has however been largely refuted since then.[2]

Over a hundred natural compounds featuring the tropone moiety or its 2-hydroxyl derivative (**3**, tropolone) have been isolated in the past sixty years and shown to possess various bioactivities.[3]

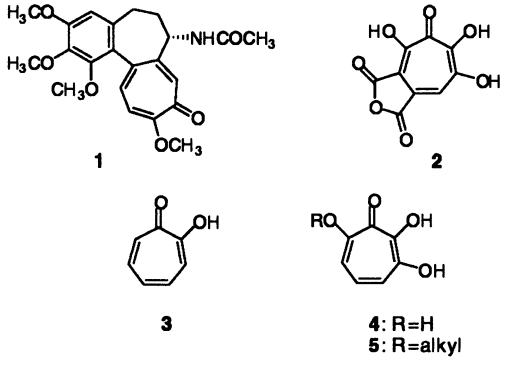

Figure 1. Troponoids **1**–**5**.

More recently, 3,7-dihydroxytropolone (**4**) has been reported to be a potent inhibitor of dimetallic enzymes via a novel mode of action linked to its ability to chelate metal ions.[4] Modeling studies have shown that in the case of inositol monophosphatase (IMPase), for example, **4** acts as a competitive inhibitor of the enzyme by efficiently replacing the phosphate group of the substrate in the chelation of the two magnesium ions present in the active site.[5] This suggests that the tropolone moiety (or its hydroxylated derivatives) might be used as an *organic analogue of the phosphate group* in the design of bioactive molecules.

Thus, developing a regiocontrolled access to ethers of the type **5** requires (i) an efficient method of synthesis of tropolonyl ethers, and (ii) a regiocontrolled protection of two of the three hydroxyl groups of dihydroxytropolone **4**. We herein report our results concerning the first part of this task.

Ethers of tropolones have traditionally been prepared (i) by alkylation of tropolones under basic conditions, (ii) by substitution reactions between halotropolones and alcoholates and (iii) through condensation reaction between alcohols and tropolones in the presence of dicyclohexylcarbodiimide (DCC) and catalytic amounts of cuprous chloride at 80°C.[6–8] Several drawbacks and limitations are associated with the two first methods; in particular, good yields were obtained only with simple or activated alcohols or halides. Takeshita reported the third method as being more general, albeit results are often erratic. For example, cyclopentanol furnished the expected ether in 90% yield, while cyclohexanol and cycloheptanol gave the desired products in only 15 and 8% yields, respectively. In this context and in view of the central roles played by inositol phosphates as well

Keywords: tropolone; Mitsunobu; ether; saccharide; cyclitol.

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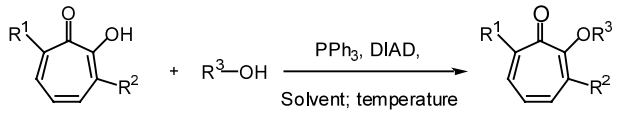
as phosphorylated saccharides, we have induced a search to develop an efficient and general synthetic route to compounds encompassing both a tropolonyl unit and either a saccharide or a cyclitol, linked by an ether function.

One of the most powerful methods available to date for the preparation of aryl ethers involves the interaction of two alcohols, a phosphine and a dialkyl azodicarboxylate.[9] The so-called Mitsunobu reaction has thus been largely exploited in organic chemistry. Surprisingly, however, and despite the acidic properties of tropolones, it has never been applied to the synthesis of tropolonyl ethers. When a mixture of tropolone **3**, triphenylphosphine (PPh_3 1.5 equiv.) and methanol (**9a**) (1.5 equiv.) in diethyl ether was treated at room temperature with di*iso*propylazodicarboxylate (DIAD) (1.5 equiv.), a rapid reaction ensued to produce 2-methoxytropone (**10a**), isolated in 72% yield (Scheme 1; Table 1, entry 1). *Iso*propyl alcohol reacted similarly, leading to a clean conversion of **3** into 2-*iso*propyloxytropone (**10b**) (60% isolated yield, entry 2). 2-Methoxyethanol furnished the first case of a more functionalized substrate, yielding the corresponding ether **10c** in 75% yield (entry 3).

A variety of protected furanosyl and pyranosyl carbohydrates were next tested. 3,7-Dibromotropolone **6** was chosen due to its ability to further undergo substitution, acetolysis and transition metal-catalyzed coupling reactions.[10] Saccharides featuring a primary alcohol cleanly produced the desired ethers **10e–h** in good to high yields (entries 4–8). Even the secondary alcohol function of diacetone allose (**9i**) furnished the expected ether under heating, albeit in lower yield (entry 9). Analysis of the ^1H NMR spectrum of **10i** indicated complete inversion of configuration at C_3.

The extensive studies of the past decades aiming at understanding and controlling the inositol cycle are due to its crucial importance in the metabolism of the cell. Thus, for instance, inositol-1,4,5-trisphosphate is a second messenger directing the release of intracellular stocks of calcium and it has been suggested that inhibition of inositol monophosphatase might lead to a treatment for bipolar disorders.[11] In this context, the hereabove described methodology may find application in the preparation of useful inositol phosphate analogues. Thus, both cyclohex-2-enol **9j** and cyclohex-3-enol **9k** reacted satisfactorily with tropolone **6** at room temperature to yield ethers **10j** and **10k** in 72 and 77% isolated yield, respectively (Table 2, entries 1–2).[12] Here again, the reaction proved to be somewhat sensitive to steric hindrance: interaction of *cis* or *trans* monoprotected cyclohexan-1,2-diols (**9l** or **9m**, respectively) with **6** required heating at 65°C to give the desired ethers **10l** and **10m** (Table 2, entries 3 and 4).[13] On the other hand, 4,5-protected cyclohex-2-en-1,4,5-triol **9n** and



3: $R^1=R^2=H$ **9** **10**
6: $R^1=R^2=Br$
7: $R^1=R^2=Cl$
8: $R^1=OH$; $R^2=H$

Scheme 1. Coupling reaction between tropolones and alcohols **9a–p**.

Table 1. Ethers **10a–i** from coupling reactions between **3** or **6** and alcohols (**9a–i**), including protected saccharide derivatives

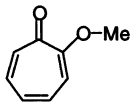
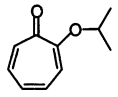
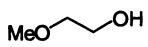
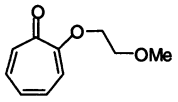
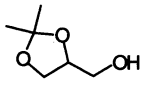
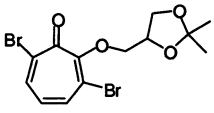
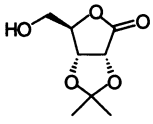
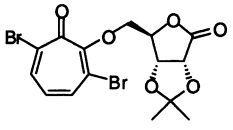
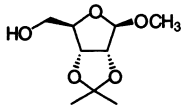
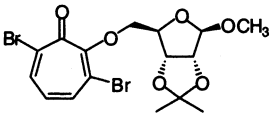
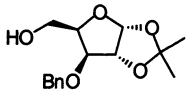
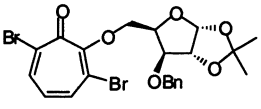
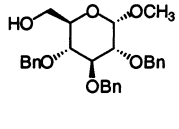
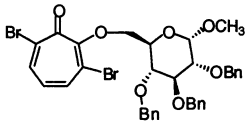
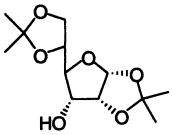
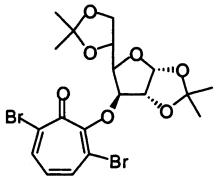
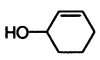
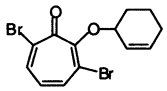
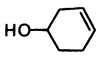
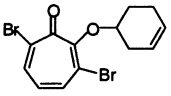
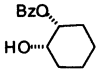
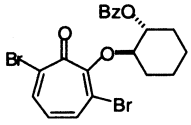
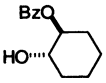
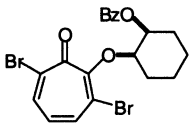
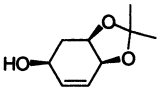
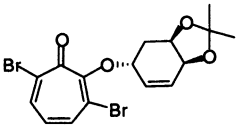
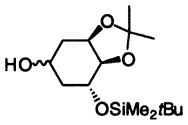
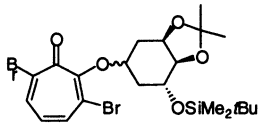
entry	substrate **9**	product **10**	yield (%)
1	CH_3OH **9a**	 **10a**	72
2	 **9b**	 **10b**	60
3	 **9c**	 **10c**	75
4	 **9d**	 **10d**	98
5	 **9e**	 **10e**	70
6	 **9f**	 **10f**	99
7	 **9g**	 **10g**	96
8	 **9h**	 **10h**	75
9	 **9i**	 **10i**	36

Table 2. Ethers **10j–o** from coupling reactions between **6** and protected carbosaccharide derivatives (**9j–o**)

entry	substrate **9**	product **10**	yield (%)
1	 **9j**	 **10j**	72
2	 **9k**	 **10k**	77
3	 **9l**	 **10l**	85
4	 **9m**	 **10m**	98
5	 **9n**	 **10n**	99
6	 **9o**	 **10o**	85[14]

4,5-protected-1,3,4,5-cyclohexantetraol **9o** (both obtained from quinic acid) furnished ether **10n** and **10o** at room temperature in very good isolated yields (Table 2, entries 5 and 6).

The procedure may also be applied to other substrates. Combining 3,7-dichlorotropolone (**7**) with *o*-iodobenzyl alcohol (**9p**) liberates compound **10p** (83% isolated yield) featuring different halogen atoms (Fig. 2); the possibility of conducting two different, sequential palladium-catalyzed cross-coupling reactions paves the way for the synthesis of various analogues and makes of ethers such as **10p** valuable scaffolds for the generation of libraries by parallel synthesis.

While application of this methodology still lies ahead, early glimpses of its potential in the context of the synthesis of bioactive molecules can already be defined at the present time. Thus, both tropolonyl ethers **10h** and **10n** are important intermediates *en route* to the synthesis of tropolonyl analogues of glucose-6-phosphate and D-inositol-3-phosphate, respectively. Competitive inhibitors of inositol-3-phosphate synthase and inositol monophosphatase may help modulate the inositol cycle. Deprotection of the products can easily be achieved by using standard procedures. For example, ethers **10d** and **10e** are quantitatively converted into compounds **11** and **12** by simply heating an aqueous acetic acid solution (60% v/v; **10d**: 45°C, 45 minutes; **10e**: 90°C, 4 hours) while sequentially subjecting cyclitol derivative **10o** to tetra-*n*-butylammonium fluoride (25°C, 18 hours) and aqueous acetic acid (60% v/v, 25°C, 2 hours) produces **13** (Fig. 2).

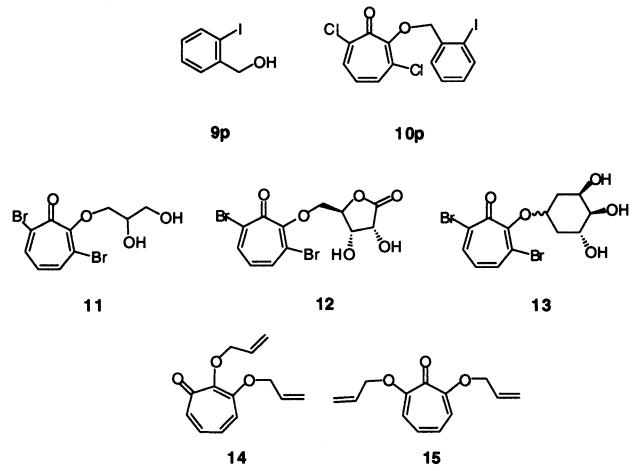


Figure 2. Additional tropolonyl ethers.

The possibility for (poly)hydroxytropolones to undergo multiple alkylations under the hereabove-described conditions was also investigated. Thus, reaction between 7-hydroxytropolone (**8**) and two equivalents of allyl alcohol quantitatively furnished a mixture of both isomeric 2,3- and 2,7-bis(allyloxy)tropones **14** and **15** (75:25 ratio).[15]

The methodology described in this communication efficiently leads to tropolonyl ethers of saccharides and cyclitols under mild conditions.[16] The procedure is simple to implement and may find direct applications in combinatorial chemistry and in the production of libraries of bioactive tropolonyl ethers as isosters of biological phosphates.

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12. In the case of **9j**, the reaction does not take place by a S_N2' mechanism. This was verified by reacting di*iso*propyl azodicarboxylate, triphenylphosphine, tropolone **6** and 1*D*-cyclohex-2-enol (synthesized from cyclohexenone, $NaBD_4$ and $CeCl_3$, see: Germal, A.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459), under the same conditions. The exclusive product was shown to possess both the deuterium atom and the ether group on the same carbon (^{1}H NMR spectrometry).
13. ^{1}H NMR spectra data fully support a complete inversion of configuration.
14. A 1:1 mixture of diastereomeric alcohols **9o** was converted into a 1:1 mixture of tropolonyl ethers **10o**.
15. Bis-*O*-alkylated (di)hydroxytropolones might thus also constitue useful analogues of *diesterified* phosphates.
16. Representative procedure for ether **10h**: pure di*iso*propyl azodicarboxylate (303 mg, 1.5 mmol) was added at room temperature to a stirring solution of tropolone **6a** (140 mg, 0.5 mmol), triphenylphosphine (393 mg, 1.5 mmol) and alcohol **9h** (697 mg, 1.5 mmol) in diethyl ether (10 mL). Stirring was continued for 1 h, after which period of time the mixture was diluted with dichloromethane (10 mL). The organic phase is washed with aqueous HCl (10 mL of a 1 M solution), dried over magnesium sulfate and filtered. Evaporation of the volatiles under reduced pressure leaves a residue which is purified by chromatography over silica and eluted with a mixture of ethyl acetate/heptane (30:70) to deliver the desired product **10h** as a yellowish solid (272 mg, 75%). Mp = 106–107°C. $[\alpha]_D$ = +47.6 (CH_2Cl_2, c = 2.1, 21°C). IR (KBr) ν 3455, 1608, 1590, 1559, 1554, 1450, 1358, 1330, 1294, 816 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.86 (dd, 1H, J = 0.8, 9.4 Hz), 7.41 (dd, 1H, J = 0.8, 11.7 Hz), 7.29–7.18 (m, 15H), 6.33 (dd, 1H, J = 9.4, 11.7 Hz), 4.91 (d, 1H, J = 10.5 Hz), 4.84 (d, 1H, J = 10.5 Hz), 4.76 (d, 1H, J = 10.5 Hz), 4.72 (d, 1H, J = 11.8 Hz), 4.61 (d, 1H, J = 10.5 Hz), 4.57 (d, 1H, J = 11.8 Hz), 4.56 (dd, 1H, J = 3.8, 12.0 Hz), 4.47 (d, 1H, J = 3.4 Hz), 4.40 (dd, 1H, J = 1.9, 12.0 Hz), 3.94 (dd, 1H, J = 8.7, 9.6 Hz), 3.77 (ddd, 1H, J = 1.9, 3.8, 9.8 Hz), 3.68 (dd, 1H, J = 8.7, 9.8 Hz), 3.27 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.8, 159.4, 139.0, 138.6, 138.5, 138.4, 138.3, 138.1, 129.8, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 125.9, 125.0, 98.5, 82.3, 80.2, 78.0, 70.8, 76.3, 75.6, 73.9, 71.3, 55.8 ppm. Anal. calcd for: $C_{35}H_{34}Br_2O_7$: C, 57.87; H, 4.72. Found C, 57.95; H, 4.68.