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A selective resin for *trans*-diequatorial-1,2-diols

Emilio Lence, Luis Castedo, Concepción González-Bello *

Laboratorio de Química Orgánica (CSIC) y Departamento de Química Orgánica, Facultad de Química, Universidad de Santiago de Compostela, Avenida de las Ciencias s/n, 15782 Santiago de Compostela, Spain

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ABSTRACT

A selective resin for linking *trans*-diequatorial-1,2-diols to solid support is described. This linking was carried out under mild and aprotic conditions involving the use of trimethylsilyl methyl ether in the presence of trimethylsilyl trifluoromethanesulfonate. Cleavage from the resin was also carried out under mild conditions by treatment with dichloromethane/trifluoroacetic acid/water (21:20:1). The usefulness of the described cyclohexane-1,2-diketone resin **7** in quinic acid chemistry was also studied.

Carbohydrates are cheap and widely used starting materials for the synthesis of very complex molecules. The use of these materials in synthetic chemistry usually requires the selective protection of their hydroxyl groups, for which a wide range of protecting groups have been developed. Several protecting groups have been developed for the selective protection of *cis*-1,2-diols, with acetals probably being the most widely used. On the contrary, only until a few years ago, the selective protection of cyclic *trans*-1,2-diols could only be achieved using disiloxanyl protecting groups, which are often incompatible with conventional transformations in carbohydrate chemistry. The solution was finally provided by Ley's group with the development of 1,2-diacetals.[1]

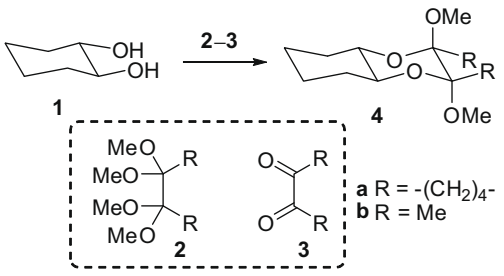
The use of 1,2-diacetals, which were initially developed as selective protecting groups for *trans*-diequatorial-1,2-diols, has been extended more recently to include other synthetic areas as a consequence of the excellent diastereoselectivity control.[2] This is the case of important hydroxylated chiral templates containing *trans*-1,2-diols, such as quinic and shikimic acids, and excellent building blocks, such as glycerate, glycolate, and tartrate diacetal derivatives. The protection of these diols as diacetals leads to a strong conformational rigidity that induces excellent diastereoselectivity control. Their integrity as protecting groups as well as the chemical properties derived from its conformational rigidity makes diacetals an extremely useful functional group. These important synthetic properties have successfully been exploited in the total synthesis of natural products, such as antascomicin B, (+)-aspicilin, herbarumin II, altenuene.[2]

Typical 1,2-diacetals are 1,1,2,2-tetramethoxycyclohexane (**2a**, TMC)[3] and 2,2,3,3-tetramethoxybutane (**2b**, TMB),[4] which provide cyclohexane-1,2-diacetals **4a** (CDA) and butane-2,3-diacetals **4b** (BDA), respectively, in good to excellent yields (Scheme 1). TMC (**2a**) and TMB (**2b**) are frequently replaced by their corresponding synthetic precursors, cyclohexane-1,2-dione (**3a**) and 2,3-butanedione (**3b**), in combination with methanol.[5]

The advantages of solid phase chemistry are well known.[6] Since the pioneering work of Merrifield in 1963,[7] solid phase chemistry has become an important tool for synthetic chemists. In this methodology, the selection of the solid support and the linker are two important factors that determine the type of reactions that can be employed. In this context, the integrity of 1,2-diacetals and the wide ranges of reactions that can be performed with them make them excellent candidates as solid phase linkers.

As part of our ongoing research into the synthesis of structurally diverse polyhydroxylated cyclohexane derivatives,[8] we investigated the synthesis of a solid support for the selective linkage of cyclic *trans*-diequatorial-1,2-diols. We synthesized 1,1,2,2-tetramethoxycyclohexane resins **5** and **6**, and cyclohexane-1,2-dione resin **7**, and explored their usefulness in the chemistry of quinic acid,[9] an optically active precursor for the synthesis of cyclohexane-substituted derivatives (Fig. 1).

The strategy for synthesizing resin **5** involved the initial preparation of hydroxyacetal **12** from commercially available cyclohex-3-enylmethanol (**8**) as it is outlined in Scheme 2.



Scheme 1. Protection of *trans*-diequatorial-1,2-diols as cyclohexane- and butane-1,2-diacetals.

* Corresponding author. Tel.: +34 981 563100; fax: +34 981 595012.
E-mail address: concepcion.gonzalez.bello@usc.es (C. González-Bello).

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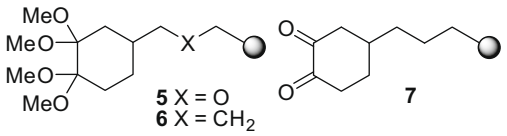
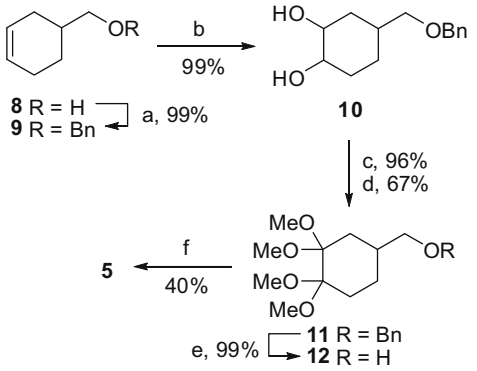
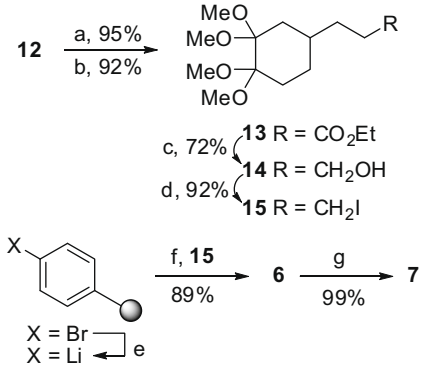


Figure 1. Functionalized polystyrene resins for the selective linkage of *trans*-1,2-diols.



Scheme 2. Reagents and conditions: (a) (1) NaH, THF, 0 °C; (2) BnBr, TBAI (cat). (b) OsO_4 (cat), NMO, $^tBuOH–THF–H_2O$, rt; (c) (1) DMSO, TFAA, DCM, −78 °C; (2) Et_3N, −78 °C; (d) $(MeO)_3CH$, MeOH, CSA (cat), Δ; (e) Pd/C (10%), MeOH, 80 psi; (f) (1) NaH, THF, 0 °C; (2) benzylbromide polystyrene, rt.

Linking of **12** to a solid support by treatment of Merrifield resin with the sodium alkoxide of alcohol **12** gave the ether resin **5**. Evidence for the formation of **5** was obtained by examining its gel phase ^{13}C NMR spectrum. Distinctive signals for the tetramethoxyacetal group were observed at 49.9 and 49.0 ppm (methoxy groups) and at 102.0 ppm (quaternary centers). Linking of cyclohexane-1,2-diol under standard conditions (i.e., heating of ether resin **5** in DMF/MeOH solution under reflux in the presence of a catalytic amount of sulfuric or camphorsulfonic acid) resulted in cleavage of the tetramethoxy moiety from the resin. Milder reaction conditions were also investigated, using trimethylsilyl methyl ether (TMSOMe) in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf). This method, which we had previously developed,[10] has been found to be a good alternative to the conventional protic method, providing high yields of the corresponding 1,2-diacetals even without reactive 1,2-diketones. However, cleavage of the linker **12** from the resin also occurred. Based on the assumption that the acid lability of resin **5** was due to the presence of a benzyl ether bond, we replaced this benzyl ether with a carbon–carbon bond. For this purpose, we carried out the synthesis of resins **6** and **7** (Scheme 3).

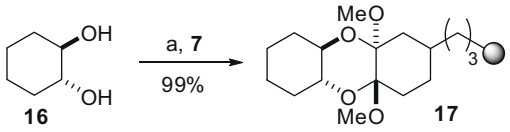


Scheme 3. Reagents and conditions: (a) (1) NMO, TPAP, DCM; (2) NaH, $(EtO)_2POCH_2CO_2Et$, THF; (b) H_2, $Pd(OH)_2/C$ (cat), EtOAc; (c) Dibal-H, THF, 0 °C; (d) I_2, PPh_3, Im, 0 °C to rt; (e) ^nBuLi, PhH, Δ; (f) TMEDA, THF, rt; (g) DCM/TFA/H_2O (21:20:1), rt.

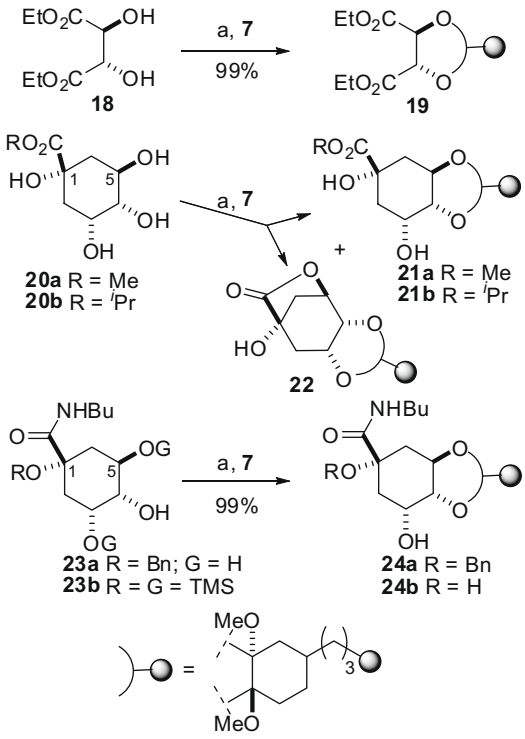
The strategy for the synthesis of resin **6** involved the linkage of the tetramethoxyacetal moiety by a nucleophilic substitution reaction between lithium polystyrene resin and iodide **15**, which was synthesized from **12**. Hydroxyacetal **12** was converted to **15** in a five-step reaction sequence. First, oxidation of primary alcohol **12** was followed by the Horner–Emmons reaction with triethyl phosphonoacetate, and hydrogenolysis gave saturated ester **13** in good yield. Hydride reduction of ester **13** followed by treatment of the corresponding alcohol **14** with iodine and triphenylphosphine gave the desired iodide **15** in 66% yield (two steps).

The next step involved linking of the tetramethoxyacetal moiety to the solid support. This was achieved by nucleophilic substitution of **15** by lithium polystyrene, which was obtained by halogen–metal exchange between bromopolystyrene and ^nBuLi.[11] Resin **6** was converted into the cyclohexane-1,2-diketone resin **7** by acid removal of the tetramethoxyacetal group. Gel phase FTIR spectroscopy of **7** confirmed the efficiency of the reaction, and revealed a strong band centered at 1720 cm^{-1}, corresponding to the 1,2-diketone group.

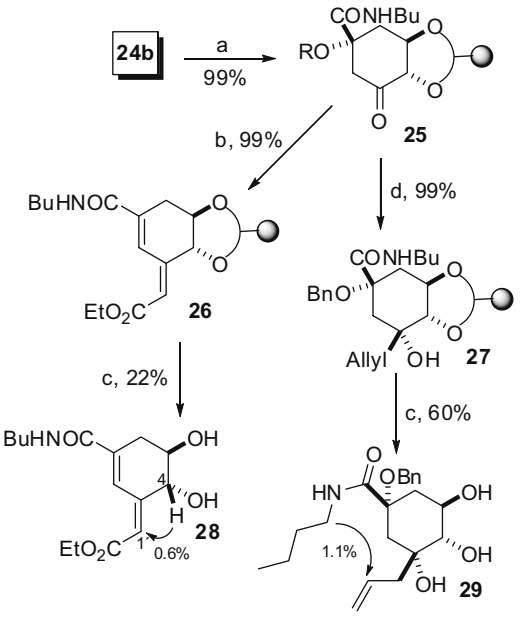
Attempts to link cyclohexane-1,2-diol (**17**) to resin **6** using either MeOH/H^+ or TMSOMe/TMSOTf conditions resulted in only low yields of the corresponding 1,2-diacetal. However, the reaction of resin **7** with TMSOMe in the presence of TMSOTf afforded the corresponding cyclohexane-1,2-diacetal **18** in good yield (Scheme 4).[12]



Scheme 4. Reagents and conditions: (a) TMSOMe, TMSOTf, 0 °C to rt.



Scheme 5. Reagents and conditions: (a) TMSOMe, TMSOTf, 0 °C to rt.



Scheme 6. Reagents and conditions: (a) $(COCl)_2$, DMSO, DCM, −78 °C then Et_3N; (b) NaH, $(EtO)_2OPCH_2CO_2Et$, THF, DCM, 0 °C; (c) DCM/TFA/H_2O (21:20:1), rt; (d) AllylMgBr, THF, −78 °C.

The linkage of other *trans*-1,2-diols including tartrate and quinic acid derivatives was investigated. Diethyl tartrate (**18**) was successfully linked to resin, affording the 1,2-diacetal **19** in good yield (Scheme 5).[13] However, attempts to link (−)-quinic acid methyl ester (**20a**) gave only low yields of the desired 1,2-diacetal **21a**. Gel phase FTIR showed a strong band typical of lactones at 1794 cm^{-1}, together with the expected band centered at 1730 cm^{-1} corresponding to the methyl ester. We reasoned that the former IR band should correspond to the cis-2,3-linked product **22**. The low loading obtained might be a consequence of the rapid lactonization of **20a**, prior to reaction with the solid support. The long reaction times usually required for solid phase reactions, as in this case, could favor this side reaction. Therefore, the use of a quinic acid derivative in which lactonization is less favored should provide better yields of the desired trans-junction. Indeed, replacement of the methyl ester in **20a** by an isopropyl ester **20b** resulted in an increased loading. It is worth highlighting that the low solubility of polyhydroxylated compounds of this type in the reaction solvent (dichloromethane) limits the loading success. However, this problem can be overcome by using more soluble quinic acid derivatives, such as the benzyl amide **23a** or the TMS protected amide **23b**. Indeed, treatment of **7** with an excess of **23a**, TMSOMe, and TMSOTf gave the corresponding 1,2-diacetal **24a** in excellent yield.[14]

The usefulness of resin **7** in solid phase organic synthesis of quinic acid derivatives was investigated, as shown for the conjugated ester **28** and the allyl derivative **29** (Scheme 6). Firstly, Swern oxidation of the secondary alcohol resin **24a** afforded ketone **25** in good yield.[15] Treatment of ketone **25** with triethylphosphonoacetate and sodium hydride produced the conjugated α,β-unsaturated ester resin **26**, resulting from a **β**-elimination and a Horner–Emmons reaction. Cleavage of resin **27** under mild conditions by treatment with DCM/TFA/H_2O (21:20:1) at room temperature afforded the unsaturated derivative **28**.[16] The *Z*/*E* stereochemistry of the unsaturated ester was studied by NOE experiments. Irradiation of H-4 led to a 0.6% enhancement of H-1′.

Ketone resin **25** underwent efficient nucleophilic addition of allyl magnesium bromide, giving the allyl derivative resin **27**.[17] Cleavage of resin **27** afforded the allyl derivative **28**.[18] The stereochemistry of the addition reaction was confirmed by NOE experiments. Irradiation of the methylene group in α to the amide nitrogen led to a 1.1% enhancement of H-2′ of the alkene.

In summary, the cyclohexane-1,2-diketone resin **7** can be used for the selective and efficient linking of *trans*-1,2-diols, such as cyclohexane-1,2-diol, tartrate or quinic acid derivatives, to a solid support. However, use of the corresponding tetramethoxydiacetal resin **6** is not efficient. In addition, replacement of the benzyl ether bond in resin **5** proved to be a good strategy for avoiding cleavage of the linker from the solid support. The linking of *trans*-1,2-diols to the cyclohexane-1,2-diketone resin **7** was carried out using mild and aprotic conditions involving the use of trimethylsilyl methyl ether and trimethylsilyl trifluoromethanesulfonate. The usefulness of cyclohexane-1,2-diketone resin **7** in solid phase organic synthesis of quinic acid derivatives, an attractive optically active precursors for the synthesis of a wide range of compounds, was demonstrated through the synthesis of derivatives **28** and **29**, whose cleavage from resin was carried out under mild conditions by treatment with DCM/TFA/H_2O (21:20:1). To our knowledge, this is the first example of a resin for linking *trans*-diequatorial-1,2-diols to solid support.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.157.

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11. Gel phase ^{13}C NMR spectrum of resin **6** showed distinctive signals at 49.7 and 49.0 ppm (OMe), and at 102.0 ppm (quaternary).
12. The extent of the reaction was monitored by gel phase FTIR spectroscopy, following the disappearance of the band at 1720 cm^{-1} corresponding to the 1,2-diketone group of resin **7**.
13. The gel phase FTIR spectrum of **19** showed a strong band centered at 1741 cm^{-1}, and its gel phase ^{13}C NMR data have a distinctive signal at 170.2 ppm corresponding to its ester groups.
14. The gel phase ^{13}C NMR spectrum of **24a** has distinctive signals at 98.6 (quaternary), 46.7 (OMe), and 13.6 (Me) ppm, and its gel phase FTIR spectrum has a strong band centered at 1673 cm^{-1} corresponding to the amide group.
15. The complete oxidation of the secondary hydroxyl group was confirmed in the gel phase FTIR spectra of **25**, which showed strong bands centered at 1724 cm^{-1}.

16. *Compound* **28**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.93 (d, J = 2.4 Hz, 1H), 6.24 (s, 1H), 6.17 (t, J = 5.2 Hz, 1H, NH), 4.20 (dq, J = 7.2 and 2.3 Hz, 2H), 4.17 (m, 1H), 3.76 (m, 1H), 3.32 (dq, J = 7.2 and 2.1 Hz, 2H), 3.03 (dd, J = 18.0 and 5.5 Hz, 1H), 2.41 (ddd, J = 18.0, 9.2, and 2.0 Hz, 1H), 1.53 (q, J = 7.4 Hz, 2H), 1.36 (h, J = 7.4 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H) and 0.93 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ: 167.4 (C), 166.5 (C), 150.5 (C), 138.0 (C), 124.6 (CH), 116.5 (CH), 73.9 (CH), 71.1 (CH), 60.4 (CH_2), 39.7 (CH_2), 31.5 (CH_2), 29.7 (CH_2), 20.1 (CH_2), 14.2 (CH_3) and 13.7 (CH_3) ppm. MS (CI) *m/z* (%) 298 (MH^+). HRMS calcd for $C_{15}H_{24}NO_5$ (MH^+): 298.1654; found, 298.1650.
17. A distinctive signal of the allyl group at 119.1 ppm in the gel phase ^{13}C NMR spectrum of **27** and the strong band centered at 3520 cm^{-1} in its gel FTIR spectrum confirmed the addition reaction.
18. *Compound* **29**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38 (m, 3H), 7.28 (m, 2H), 6.36 (t, J = 5.2 Hz, 1H), 5.80 (m, 1H), 5.12 (m, 2H), 4.59 (d, J = 11.0 Hz, 1H), 4.35 (d, J = 11.0 Hz, 1H), 3.86 (m, 1H), 3.76 (s, 1H), 3.34–3.19 (m, 3H), 2.60 (br s, 1H), 2.48 (dt, J = 15.0 and 3.5 Hz, 1H), 2.41 (dd, J = 14.0 and 7.0 Hz, 1H), 2.34 (br s, 1H), 2.26 (dd, J = 14.0 and 8.0 Hz, 1H), 2.17 (dd, J = 15.0 and 12.0 Hz, 1H), 2.01 (dd, J = 15.5 and 3.0 Hz, 1H), 1.92 (d, J = 15.5 Hz, 1H), 1.45 (m, 2H), 1.29 (m, 2H) and 0.89 (t, J = 7.4 Hz, 3H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ: 171.5 (C), 136.1 (C), 132.8 (CH), 129.0 (2 × CH), 128.6 (CH), 127.6 (2 × CH), 119.2 (CH_2), 83.2 (C), 78.3 (CH), 74.8 (C), 68.8 (CH), 67.2 (CH_2), 42.9 (CH_2), 42.0 (CH_2), 39.2 (CH_2), 33.3 (CH_2), 31.6 (CH_2), 20.0 (CH_2) and 13.7 (CH_3) ppm. MS (CI) *m/z* (%) 378 (MH^+). HRMS calcd for $C_{21}H_{32}NO_5$ (MH^+): 378.2280; found, 378.2274.