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Note

Monoesterification of di-*O*-isopropylidene and di-*O*-cyclohexylidene *chiro*-inositols

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Abstract

Monoesterification of D- or L-*chiro*-inositols protected as diacetals proceeds in excellent selectivity and yields. The metal-catalyzed, one-step reaction proceeds at room temperature under an air atmosphere and has been developed using a range of examples. © 2003 Elsevier Science Ltd. All rights reserved.

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Selective protection of the *cis*-diols of D- and L-*chiro*-inositols as the di-*O*-isopropylidene[1] (**1**) or di-*O*-cyclohexylidene[2,3] (**2**) derivatives is a facile, high-yielding procedure (87 and 77%, respectively, Scheme 1). However, further selective differentiation of the resulting diol as unsymmetrical diesters or diethers, or monoprotected esters and ethers is usually a difficult process. Given the wide use of C_2 symmetric ligands in asymmetric synthesis and that **1** and **2** are C_2 symmetric, the ability to differentiate these alcohols would in theory lead to the use of D- and L-*chiro*-inositol in a host of asymmetric processes.[4] These processes could include conversion to amino alcohols for use as asymmetric ligands or formation of unsaturated esters for use in Diels–Alder cycloadditions or Michael additions.[5]

Examples of inositols as monofunctionalized diisopropylidene acetals do exist, for instance 3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-*myo*-inositol[6] and 3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol[1b] have been reported, although benzylation of **1** gives only modest and irreproducible yields in our hands. The kinetic resolution of 1,2:5,6-di-*O*-isopropylidene-*myo*-inositol by lipase-catalysed acetylation has also been achieved.[7] Etherification of **2** as a silyl-, benzyl- or methoxymethyl-ether in yields from 77 to 89% has also been reported and appears to be assisted by the increased size of the cyclohexylidene protecting groups.[3] Because of the difficulty in differentiating the diols of **1** and forming monoesters of **2**, other methods of obtaining selectively protected inositols have been used. These include starting with the naturally occurring methyl ethers, such as L-quebrachitol,[8] and performing multiple protection–deprotections steps; or enzymatic conversion of benzene derivatives using *E. coli* to chiral *cis*-dienediols, followed by multiple chemical steps.[9] Although diols **1** and **2** have proven moderately useful as chiral auxiliaries,[3,10] building blocks for unnatural saccharide mimics[11] and glycosyl inositols,[12] we felt that the further development of *chiro*-inositols in these areas required an improved method for the monoesterification of both **1** and **2**.

Partial acetylation has been used in carbohydrate chemistry,[13] although only a few reliable methods have been developed for the monoacetylation of diols.[14] Recently, however, a method for the one-step monoesterification of symmetrical 1,2-diols was reported by Clarke and co-workers.[15] We have used this methodology for the synthesis of a variety of monoester diacetal protected *chiro*-inositols with good success. Clarke and co-worker's procedure uses 10 mol% of a lanthanide(III) salt with 10 equivalents of an anhydride in

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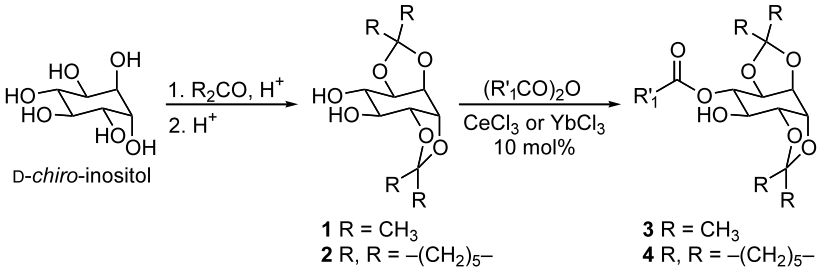
THF at room temperature. We applied these conditions to diol **1**, initially with Ac_2O and either $CeCl_3 \cdot 7\ H_2O$ or $YbCl_3 \cdot 6\ H_2O$, to give **3b** in good yield with no evidence of the diester. Subsequently, we found that the amount of the anhydride could be reduced to five equivalents with no loss in yield. We also found that THF was the optimal solvent, as dichloromethane gave lower yields and longer reaction times (Clarke reported that CH_2Cl_2 gave improved results in some instances). Absence of the catalyst gave complex mixtures of starting material and the diester, with no appearance of the desired monoester.

Using this modified procedure, we have prepared the monoesters listed in Table 1. Although some improvement of yields were observed using the Yb salt in entries 1 and 4, products of reactions using the cerium salt tended to be easier to purify, and thus the cerium catalyst was used for a multigram reaction. Gratifyingly, we observed no loss of yield in the preparation of **3d** on the two-gram scale. Of significant disappointment was the poor yield using benzoic anhydride, entry 5, in which no improvement was observed using a variety of conditions. As expected, monoesterification of the L enantiomer of **1** occurs equally well (entry 6) as does esterification of di-*O*-cyclohexylidene (**2**) (entries 7 and 8).

A further advantage of this method is that in all cases the reactions need no special conditions. All reactions were carried out at room temperature under air with the hydrated lanthanide salt and undried solvents. Finally, given the success and ease of these reactions, we attempted using triflic, mesyl and tosyl anhydrides; however, these gave intractable black oils.

We have synthesised a range of previously unreported di-*O*-isopropylidene and di-*O*-cyclohexylidene monoester-protected *chiro*-inositols. With these new substrates in hand, we have been further developing these D- and L-*chiro*-inositols for use in asymmetric synthesis. These results will be reported in due course.



Scheme 1.

Table 1
Monoprotection of *chiro*-inositol derivatives **1** and **2** [a]

Entry	Anhydride	Reaction time (h)	Product ($R^1 =$)	Catalyst (isolated yield)
1	Chloroacetic	3 3	**3a** $ClCH_2$	Yb (95%) Ce (48%)
2	Acetic	4 2.5	**3b** Me	Yb (78%) Ce (83%)
3	Propionic	6 8	**3c** Et	Yb (76%) Ce (74%)
4	Crotonic	6 7	**3d** (*E*)MeCH=CH	Yb (65%) Ce (60%)
5	Benzoic	24 24	**3e** Ph	Yb (11%) Ce (24%)
6	Chloroacetic	3	**3f** $ClCH_2$	Yb (90%)
7	Chloroacetic	4 5	**4a** $ClCH_2$	Yb (73%) Ce (85%)
8	Acetic	6 8	**4b** Me	Yb (65%) Ce (65%)

[a] All trials were done on the D isomer except entry 6, for which the L-*chiro* derivative was used.

1. Experimental

1.1. General

All melting points are uncorrected. Optical rotations were measured in a 10-cm cell at ambient temperature in CH_2Cl_2. Reaction progress was monitored using aluminum-backed thin-layer chromatography (TLC) plates pre-coated with silica gel UV254 and visualised by either UV radiation (254 nm) or ceric ammonium molybdate dip. Column chromatography was performed using Silica Gel 60 (E. Merck, 220–240 mesh) with the solvent systems as indicated. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova at 300 and 75 MHz, respectively and referenced to solvent peaks (^1H, residual $CHCl_3$; ^{13}C, $CDCl_3$). Accurate masses (HRMS) were recorded on a Mariner time-of-flight spectrometer. Pinitol was obtained from New Zealand Pharmaceuticals and demethylated according to literature procedures.[1]

1.2. Preparation of 1D-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol (1)

To a solution of 1D-*chiro*-inositol (2.00 g, 11.1 mmol) in DMF (11 mL), acetone (12.0 mL, 166.5 mmol) and 2,2-dimethoxypropane (10.0 mL, 77.7 mmol) was added *p*-TsOH (200 mg, 10 mol%). The mixture was stirred overnight at room temperature (rt) under air, then neutralized with Et_3N and concentrated. Filtration of the resulting syrup through silica gel using 1:1 hexanes–EtOAc gave the tris-acetonide (3.17 g, 95%) as a white solid. Selective hydrolysis following the procedure of Paulsen and co-workers[1b] gives **1** in 88–93% yield.

1.3. General procedure for the $YbCl_3$ and $CeCl_3$ catalysed monoesterification of 1 and 2 with anhydrides

The anhydride (5 mmol) was added to a stirred solution of diol **1** or **2** (1 mmol) and metal salt ($YbCl_3 \cdot 6\ H_2O$ or $CeCl_3 \cdot 7\ H_2O$) (0.1 mmol, 10 mol%) in THF (5 mL). The reaction was stirred at rt and monitored by TLC (5:1 hexanes–EtOAc). Upon completion, EtOAc (10 mL) was added, the organic layer was washed with satd aq $NaHCO_3$ (3×10 mL), once with brine (10 mL) and dried over $MgSO_4$. Filtration, concentration and purification via flash column chromatography (hexanes–EtOAc mixtures) gave pure **3** or **4**.

1.4. 1D-3-*O*-Chloroacetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol (3a)

Eluted with 5:1 hexanes–EtOAc (R_f 0.15) to give a white solid, mp 109 °C, $[\alpha]_D^{21}$ +50.2° (c 1.86×10^{-2}, CH_2Cl_2). ^1H NMR (300 MHz $CDCl_3$): δ 1.37 (s, 3 H, CMe_2), 1.39 (s, 3 H, CMe_2), 1.53 (s, 6 H, CMe_2), 2.24 (brs, 1 H, OH), 3.64 (dd, 1 H, J 8.1, 11.5 Hz, H-4), 4.19 (s, 2 H, CH_2Cl), 4.24 (m, 2 H, H-2, H-5), 4.5 (m, 2 H, H-1, H-6), 5.03 (dd, 1 H, J 8.3, 11.5 Hz, H-3); ^{13}C NMR (75 MHz $CDCl_3$): 25.7, 25.8, 27.8, 28.1, 41.1, 71.6, 75.2, 75.3, 75.5, 76.2, 79.0, 109.1, 110.0, 167.4; IR (neat): 3463, 2987, 1764 cm^{-1}; HRMS Calcd for $C_{14}H_{22}{}^{35}ClO_7$, m/z 337.1054 [M + H]; Found: m/z 337.1049.

1.5. 1D-3-*O*-Acetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol (3b)

Eluted with 5:1 hexanes–EtOAc (R_f 0.10) to give a colourless oil $[\alpha]_D^{21}$ +41.1° (c 1.97×10^{-2}, CH_2Cl_2); ^1H NMR (300 MHz $CDCl_3$): δ 1.36 (s, 3 H, CMe_2), 1.38 (s, 3 H, CMe_2), 1.51 (s, 6 H, CMe_2), 2.17 (s, 3 H, Ac), 2.60 (brs, 1 H, OH), 3.6 (dd, 1 H, J 8.1, 11.2 Hz, H-4), 4.24 (m, 2 H, H-2, H-5), 4.46 (m, 2 H, H-1, H-6) 4.95 (dd, 1 H, J 8.3, 11.5 Hz, H-3); ^{13}C NMR (75 MHz $CDCl_3$): δ 21.3, 25.6, 25.8, 27.8, 28.1, 71.9, 75.5, 75.4, 75.7, 76.5, 79.2, 109.1, 109.5, 170.9; IR (neat) 3468, 2987, 1749 cm^{-1}; HRMS calcd for $C_{14}H_{23}O_7$, m/z 303.1440 [M + H]; Found m/z 303.1438.

1.6. 1D-3-*O*-Propanoyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol (3c)

Eluted with 5:1 hexanes–EtOAc (R_f 0.18) to give a colourless oil $[\alpha]_D^{21}$ +44.9° (c 9.0×10^{-3}, CH_2Cl_2); ^1H NMR (300 MHz $CDCl_3$): δ 1.18 (t, 3 H, J 7.5 Hz, CH_3), 1.35 (s, 3 H, CMe_2), 1.37 (s, 3 H, CMe_2), 1.51 (s, 6 H, CMe_2), 2.45 (q, 2 H, J 7.5 Hz, CH_2), 3.41 (bs, 1 H, OH), 3.59 (dd, 1 H, J 8.1, 11.4 Hz, H-4), 4.23 (m, 2 H, H-2, H-5) 4.45 (m, 2 H, H-1, H-6), 4.96 (dd, 1 H, J 8.2, 11.4 Hz, H-3); ^{13}C NMR (75 MHz $CDCl_3$): δ 9.4, 25.7, 25.9, 27.9 (2C), 28.2, 72.1, 72.8, 73.6, 75.9, 76.7, 79.4, 109.9, 110.0, 174.8; IR (neat) 3466, 2987, 1741 cm^{-1}; HRMS: Calcd for $C_{15}H_{25}O_7$, m/z 317.1597 [M + H]; Found, m/z 317.1595.

1.7. 1D-3-*O*-[(*E*)-But-2-enoyl]-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol (3d)

Eluted with 5:1 hexanes–EtOAc (R_f 0.21) to give a colourless oil $[\alpha]_D^{21}$ +58.1° (c 7.3×10^{-3}, CH_2Cl_2); ^1H NMR (300 MHz $CDCl_3$): δ 1.35 (s, 3 H, CMe_2), 1.37 (s, 3 H, CMe_2), 1.52 (s, 6 H, CMe_2), 1.91 (dd, 3 H, J 1.7, 6.9 Hz, CH_3), 3.64 (dd, 1 H, J 8.0, 11.3 Hz, H-4), 4.27 (m, 2 H, H-2, H-5), 4.46 (m, 2 H, H-1, H-6) 5.01 (dd, 1 H, J 8.2, 11.4 Hz, H-3), 5.93 (dd, 1 H, J 1.7, 15.6 Hz, vinylCH) 7.06 (m, 1 H, vinylCH); ^{13}C NMR (75 MHz $CDCl_3$): δ 18.4, 25.7, 25.9, 27.9, 28.2, 31.2, 72.2, 73.6, 75.8, 76.0, 76.8, 79.4, 109.9, 110.0, 122.5, 146.6, 166.7; IR (neat) 3469, 2989, 1724 cm^{-1}; HRMS: Calcd for $C_{16}H_{25}O_7$, m/z 329.1600 [M + H]; Found, m/z 329.1595.

1.8. 1D-3-*O*-Benzoyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol (3e)

Eluted with 5:1 hexanes–EtOAc (R_f 0.25) to give a white solid mp 81 °C $[\alpha]_D^{21}$ +47.4° (c 1.4×10^{-2}, CH_2Cl_2); ^{1}H NMR (300 MHz $CDCl_3$): δ 1.36 (s, 3 H, CMe_2), 1.38 (s, 3 H, CMe_2), 1.54 (s, 6 H, CMe_2), 3.6 (dd, 1 H, J 8.1, 11.5 Hz, H-4), 4.31 (dd, 1 H, J 6.1, 8.1 Hz, H-5), 4.4 (dd, 1 H, J 5.7, 8.1 Hz, H-2) 4.5 (m, 2 H, H-1, H-6), 5.24 (dd, 1 H, J 8.1, 11.5 Hz, H-3) 7.45 (m, 2 H, Bz) 7.55(m, 1 H, Bz) 8.08 (m, 2 H, Bz); ^{13}C NMR (75 MHz $CDCl_3$): δ 25.7, 25.9, 27.9, 28.1, 72.1, 74.2, 75.6, 75.9, 76.7, 79.3, 109.8, 109.9, 128.6, 130.2, 133.6, 166.7; IR (neat) 3465, 2987, 1723 cm^{-1}; HRMS: Calcd for $C_{19}H_{25}O_7$, m/z 365.1558 [M + H]; Found, m/z 365.1595. Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63; H, 6.64. Found: C, 62.80; H, 6.61.

1.9. 1L-3-Chloroacetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol (3f)

Eluted with 5:1 hexanes–EtOAc (R_f 0.15) to give a white solid, mp 108.5 °C $[\alpha]_D^{21}$ −51.5° (c 1.3×10^{-2}, CH_2Cl_2) HRMS: Calcd for $C_{14}H_{22}{}^{35}ClO_7$, m/z 337.1054 [M + H]; Found, m/z 337.1049.

1.10. 1D-3-*O*-Chloroacetyl-1,2:5,6-di-*O*-cyclohexylidene-*chiro*-inositol (4a)

Eluted with 10:1 hexanes–EtOAc (R_f 0.21) to give a colourless oil, $[\alpha]_D^{21}$ +25.9° (c 9.7×10^{-3}, CH_2Cl_2); ^{1}H NMR (300 MHz $CDCl_3$): δ 1.39–1.68 (m, 20 H, Cy), 3.61 (dd, 1 H, J 8.3, 11.2 Hz, H-4), 4.14 (s, 2 H, CH_2Cl), 4.24 (m, 2 H, H-2, H-5), 4.53 (m, 2 H, H-1, H-6), 4.99 (dd, 1 H, J 8.5, 11.5 Hz, H-3) 6.07 (brs, 1 H, OH); ^{13}C NMR (75 MHz $CDCl_3$): δ 22.6, 23.6, 23.8, 23.9, 24.8, 34.6, 34.8, 37.3, 37.7, 40.9, 71.6, 74.5, 74.8, 75.4, 75.4, 78.3, 110.2, 110.4, 167.2; IR (neat) 3437, 2937, 1732 cm^{-1}; HRMS: Calcd for $C_{20}H_{30}{}^{35}ClO_7$, m/z 417.1680 [M + H]; Found, m/z 417.1675.

1.11. 1D-3-*O*-Acetyl-1,2:5,6-di-*O*-cyclohexylidene-*chiro*-inositol (4b)

Eluted with 5:1 hexanes–EtOAc (R_f 0.16) to give a colourless oil, $[\alpha]_D^{21}$ +27.0° (c 1.49×10^{-2}, CH_2Cl_2); ^{1}H NMR (300 MHz $CDCl_3$): δ 1.36–1.56 (m, 20 H, Cy), 2.14 (s, 3 H, Ac), 2.62 (brs, 1 H, OH), 3.54 (dd, 1 H, J 8.3, 11.2 Hz, H-3), 4.20 (m, 2 H, H-2, H-5), 4.49 (m, 2 H, H-1, H-6), 4.91 (dd, 1 H, J 8.5, 11.5 Hz, H-3); ^{13}C NMR (75 MHz $CDCl_3$): δ 21.3, 23.8, 23.9, 24.1, 24.2, 25.1, 25.2, 34.9, 35.1, 37.6, 38.0, 72.1, 73.8, 75.0, 75.3, 76.0, 78.8, 110.2, 110.3, 171.2; IR (neat) 3466, 2934, 2859, 1749 cm^{-1}; HRMS: Calcd for $C_{20}H_{31}O_7$, m/z 383.2070 [M + H]; Found, m/z 383.2064.

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