Pergamon

Tetrahedron Letters 43 (2002) 3857–3861

TETRAHEDRON LETTERS

On the direct 2,3-hydroxyl-group differentiation of tartaric acid esters†

James McNulty* and Justin Mao

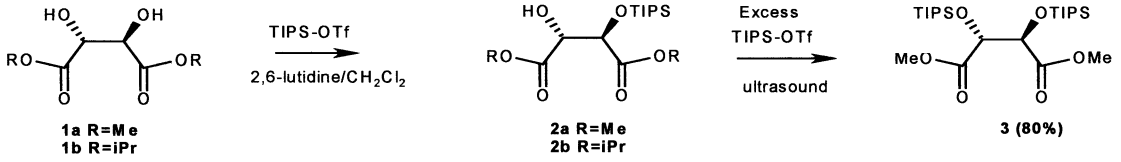
Institute of Molecular Catalysis, Department of Chemistry, Brock University, St. Catharines, Ontario, Canada L2S 3A1

Received 1 April 2002; accepted 4 April 2002

Abstract—Direct desymmetrization of tartaric acid esters with TIPS-triflate proceeds in up to 99% yield giving the useful intermediates **2a**–**b**. Selective reduction of the ester groups provides access to fully differentiated threonolactone derivatives while reduction of both esters of **2a** followed by periodate mediated diol cleavage allows access to 2-*O*-TIPS-protected L-glyceraldehyde.

The 1,2-diol subunit occurs in a large number of natural products of various classes including isoprenoids, alkaloids, polyketides and carbohydrate derivatives. Methods for the asymmetric synthesis of both *syn*- and *anti*-1,2-diols have received much attention including catalytic asymmetric routes to *syn*-1,2-diols via Sharpless asymmetric dihydroxylation[1] and more recently both *syn*- and *anti*-1,2-diols via catalytic asymmetric aldol reactions.[2] Tartaric acid **1** is a classic *chiral-pool* alternative for the rapid asymmetric synthesis of *syn*-1,2-diols. It is readily available in either enantiomeric form and possesses an innate *syn*-2,3-diol subunit. Tartaric acid has been used extensively as a chiral precursor in the asymmetric synthesis of natural and non-natural products[3a] as well as C_2-symmetrical molecules including chiral ligands.[4] One limitation of the *chiral-pool* approach from tartaric acid is that often several steps are necessary to desymmetrize (C_2 to C_1) the molecule through either differentiation of the 1,4-carbonyl groups or of the internal 2,3-diol. A similar problem exists for differentiation of the 1,2-diol functionality in non-symmetrical adducts produced through catalytic asymmetric processes.[2] We recently reported on a very successful and general method for the differentiation of the 1,4-carboxylate groups of tartaric acid via mono addition of Grignard reagents to the bis-Weinreb amide derivative.[5] This method allows rapid access to asymmetric extended linear fragments containing the internal 1,2-diol functionality. We next turned our attention to the problem of the 2,3-diol differentiation. A comprehensive literature survey revealed that essentially four methods have been utilized to achieve this transformation in the tartrate series. The 'statistical' approach (vide infra), conducted by employing 1 equiv. of reagent, is most simple and direct although unfortunately usually low yielding. The other general methods reported include conversion of the diol to a cyclic *O*-stannylene acetal followed by alkylation or acylation,[6] desymmetrization through reduction of a 2,3-diol derived benzilidene acetal,[7] and mono-acetylation of a cyclic orthoacetate derivative.[8] The latter three methods all require at least two steps to achieve the desired de-symmetrization.

Returning to the statistical approach, it is well known that the mono-functionalization of similar or homotopic 1,2-diols can be a challenging problem due to the similar reaction rates of the diol and intermediate mono



Scheme 1. TIPS protection of tartrate diesters.

* Corresponding author. Fax: 905 682 9020; e-mail: jmcnulty@chemiris.labs.brocku.ca

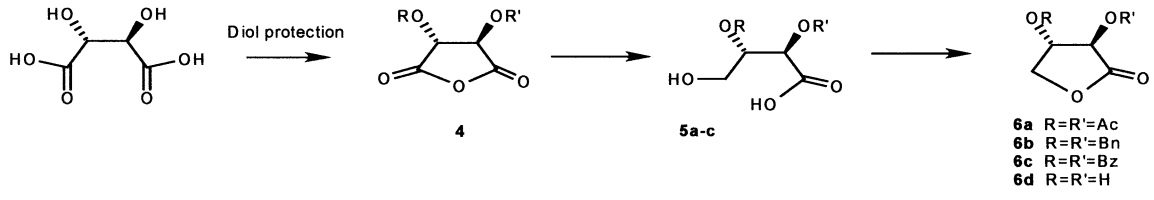
† Dedicated to Professor Ian W. J. Still on the occasion of his 65th birthday.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00662-7

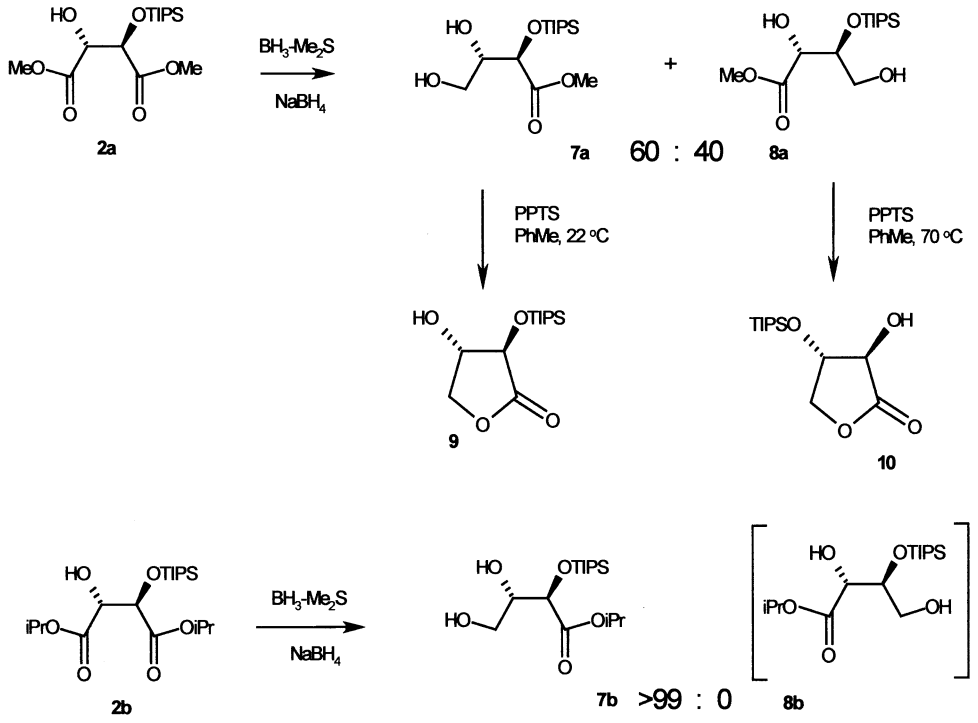
functionalized derivative with the alkylating or acylating agent.[9] Even when a stoichiometric amount of such an agent is employed, mixtures of diol, mono- and bis-protected product are formed. In the case of tartaric acid diesters, mono-functionalization of the internal 2,3-diol (acetylation, tosylation, benzylation etc.) generally proceeds in 30–60% yield[6] using the 'statistical' method. Additives such as silver oxide[10] and lanthanide chlorides[9] have been reported to assist mono-functionalization in some cases. A direct, high yielding mono-functionalization of tartaric acid diester did not appear to be a very rewarding venture. Notwithstanding this prognosis, we have observed (Scheme 1) that silyl-protection of dimethyltartrate **1a** with triisopropylsilyl (TIPS) triflate in either dichloromethane or dimethylformamide proceeds rapidly to the desymmetrized mono-TIPS **2a** derivative but *very slowly* to the bis-TIPS derivative **3**. We now report an optimized procedure for this simple and direct de-symmetrization proceeding routinely in 88–99% yield as well as some synthetic transformations of the useful desymmetrized product monoalcohols **2a** and **2b**.

Reaction of dimethyltartrate **1a** in dichloromethane with TIPS-OTf (1.2 equiv.) at 21°C in the presence of 2,6-lutidine (1.2 equiv.) provided alcohol **2a** in 88–99% yield.[11] Diisopropyl tartrate **1b** reacted somewhat slower under the same conditions to give the monoprotected non symmetrical alcohol **2b** in 80% yield. Under these conditions the TLC profile indicates only a trace of the bis-silylated product **3**. We were somewhat surprised at the high degree of selectivity shown in this transformation and wondered initially if this was not the result of some unexpected complexation (or precipitation) of an intermediate from which **2a**/**b** was obtained by hydrolysis. However, even when **2a** was treated with an excess TIPS-OTf and 2,6-lutidine (4.0 equiv. each) the second silylation was very slow. The bis-TIPS derivative **3** could only be obtained in good yield when this reaction was subjected to sonication (Branson 5510, 22°C, 4 h) giving **3** in 80% yield. The selectivity observed appears to be simply due to steric hindrance imposing a high activation barrier for the second silylation step. The reaction with *t*-butyldimethylsilyl (TBDMS) triflate was less selective under these conditions but still provided the mono-TBDMS derivative from **1a** in a useful 78% yield as well as the bis-TBDMS derivative corresponding to **3** (14.5%). Cyclic 2,3-bis-TBDMS protected tartrate derivatives have been previously reported in good yields through normal silylation protocols,[12] and a bis-TIPS protected tartaric acid derived cyclic imide derivative has been reported.[13] Steric factors are likely less important in these rigid cyclic *threo*-imides due to the lesser degree of rotational freedom allowing bis TIPS-silylation to proceed. The use of the bulky TIPS group then was key to the high selectivity observed in this kinetically controlled differentiation of the homotopic hydroxyl groups in the *acyclic* tartrate esters.

We have investigated several useful synthetic elaborations of the desymmetrized tartaric diesters **2a** and **2b**. Threonic acid **5** and threonolactone **6** derivatives are conveniently prepared by partial reduction and cyclization of 2,3-protected tartrates, sometimes via a cyclic anhydride **4** (Scheme 2) and have been utilized in several valuable synthetic transformations.[3a] The value of these intermediates is limited however as in almost all cases the 2,3-diol unit is not *differentially protected*.[3b] The mono-TIPS protected esters **2a** and **2b** potentially offer a rapid entry to fully differentiated threonolactones provided selective ester reductions can be carried out. The selective reduction of an α-hydroxy ester in the presence of a second ester fortunately is a well know transform typically achieved by the use of borane/sodium borohydride combinations.[8] In the present application, the desymmetrized dimethyl tartrate **2a** reacted with borane–dimethyl sulfide and sodium borohydride (Scheme 3) in THF to give a mixture of the two readily separable isomeric diols **7a** (58%) and **8a** (38%), 96% total isolated yield. The diol **7a** slowly cyclized of its own accord and readily so upon treatment with mild acid (pyridinium-4-toluene sulfonate (PPTS), toluene, 21°C, 4 h) to give lactone **9** quantitatively. The minor diol **8a** obtained from the reduction underwent cyclization under slightly more forcing conditions (PPTS, toluene, 70°C, 3 h) to give the isomeric lactone **10**, also in quantitative yield. Thus, in addition to achieving the selective reduction of the α-hydroxy ester, lactone formation proved to be a very convenient method to discriminate between the primary and secondary alcohol functions in **7a** and **8a**. Reduction of the 2,3-diol differentiated isopropyl ester **2b** under the same conditions proved to be highly regioselective, although more sluggish in comparison to **2a**. Starting diester still remained after 24 h, however the only reduction product was the diol **7b** (60% isolated yield from **2b**) with no trace of isomeric **8b** being observed. In contrast to methyl esters **7a** and **8a**, the isopropyl ester **7b** was more stable presumably due to the increased steric hindrance around the isopropoxy substituted acyl group. Threonolactone derivatives **9** and **10** are densely functionalized, fully differentiated chirons in contrast to the literature derivatives outlined in Scheme 2 (**6a**–**d**) and offer considerable promise for a variety of transformations towards linear *syn*-1,2-diol



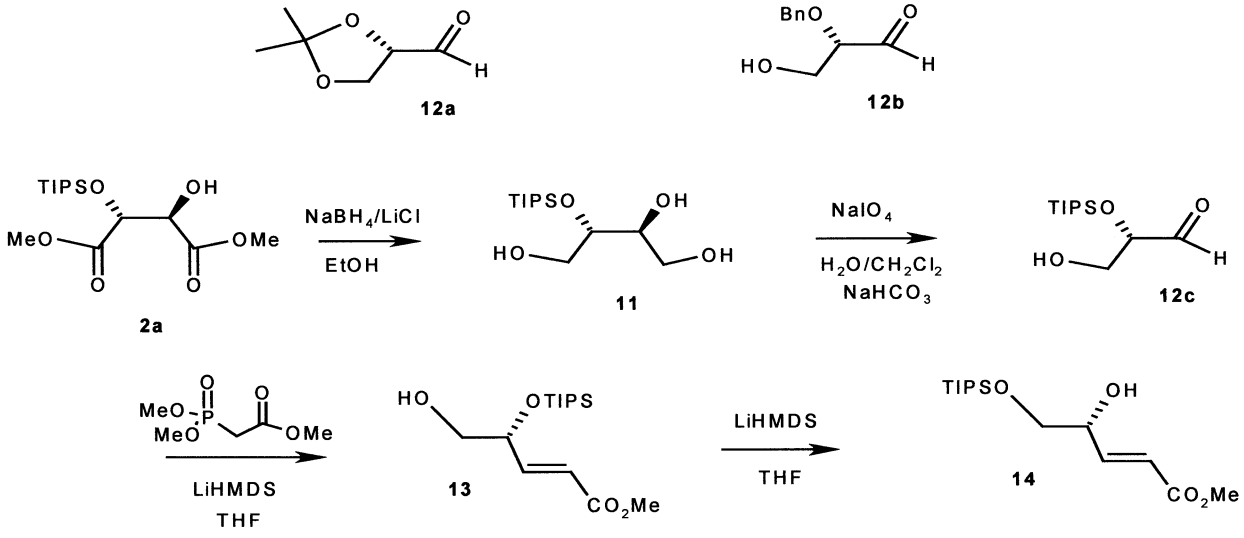
Scheme 2. Literature syntheses of 1,2-diol non-differentiated threonic acid and threonolactone derivatives.[3a]



Scheme 3. Synthesis of differentiated threonic acid and threonolactone derivatives.

containing fragments. The stability of **7b** offers an alternate route to open chain threonic ester derivatives.

Optically active, protected derivatives of D- and L-glyceraldehyde, such as the acetonide **12a** and the 2-*O*-benzyl derivative **12b** (Scheme 4), are valuable C3-building blocks and have been utilized extensively in organic synthesis.[14] While these two compounds are the most important members of protected chiral glyceraldehydes available, both suffer inherent limitations. For example in the acetonide **12a**, the primary and secondary diols are not differentiated and would require selective manipulations later on in a synthesis subsequent to acetonide hydrolysis. In derivative **12b**, the benzyl ether can lead to subsequent chemoselective incompatibilities also. For example Wittig or Horner–Wadsworth–Emmons olefination of **12b** gives an *O*-benzyl containing olefin[14] in which hydrogenolysis or hydrogenation could not be effected selectively. We felt that the 2-*O*-TIPS-L-glyceraldehyde **12c** would be an ideal C3 building block not subject to either of the limitations stated above. Reduction of both esters of the mono-*O*-TIPS protected tartaric acid **2a** was readily achieved using sodium borohydride/lithium chloride in ethanol to give the differentiated 2-*O*-TIPS protected L-threitol derivative **11** in 82% yield. Periodate cleavage of the 1,2-diol in **11** was carried out under standard conditions[14] giving the desired 2-*O*-TIPS protected L-glyceraldehyde



Scheme 4. Synthesis of differentiated allylic alcohols from 2-*O*-TIPS-L-glyceraldehyde.

12c as a colorless viscous oil. Reaction of the aldehyde with the Horner–Emmons reagent provided the (*E*)-olefin **13** in 72% yield from **11**. Olefin **13** is a C5 chiron incorporating five-differentially functionalized carbons and is available in only four steps from dimethyl tartrate. The ready access and presence of useful functionality, including a free primary alcohol, a protected allylic alcohol as well as an unsaturated ester, offers much potential for **13** as a useful synthetic intermediate.

Finally we made an interesting observation during the Horner–Wadsworth–Emmons reaction. If a slight excess of LiHMDS was employed during this reaction, a minor isomeric product could be isolated from the reaction. This compound was subsequently identified as the product of silyl migration to the less hindered primary position, **13** to **14**. The isomerization could be completely avoided employing a 1:1 ratio of phosphonate to base during the olefination reaction. In addition when a purified sample of **13** was treated independently with LiHMDS in dry THF, isomerization occurred readily giving **14** as the major product (82% yield). Compound **14** contains a free allylic alcohol as well as an unsaturated ester and further increases the versatility of this methodology from the differentiated glyceraldehyde **12c**. 1,2-Silyl migrations from one hydroxyl to another are well documented with less hindered silanes such as TBDMS[15a] and appear to be rare in the case of the TIPS group.[15b]

In conclusion, we report a simple one-step method for the direct 2,3-diol differentiation in tartaric diester derivatives. Selective reduction of the ester residues has been demonstrated leading to the potentially valuable fully differentiated threonolactone derivatives **9** and **10**. Complete reduction and periodate cleavage of the desymmetrized tartrate diester opens a route to a valuable differentiated glyceraldehyde derivative **12c**. This compound has been elaborated to the two highly functionalized linear C5 chirons **13** and **14**. Application of this methodology towards the preparation of biologically active compounds containing extended linear fragments is currently in progress in our laboratories.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada and Research Corporation (Cottrell Scholar Science Award to J.McN.) for financial support.

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11. Dimethyl-L-tartrate **1a** (50.0 mg, 0.281 mmol) was dissolved in dry CH_2Cl_2 (1.0 mL, dist. CaH_2) by stirring at rt for 15 min at which time triisopropylsilyltrifluoromethanesulfonate (0.337 mmol, 1.2 equiv.) was added slowly over 5 min. When the addition was completed, the mixture was stirred at rt for 10 min. before a solution of 2,6-lutidine (0.337 mmol, 1.2 equiv.) was added dropwise. The entire mixture was stirred at rt until starting material had disappeared; approx. 3 h (TLC:hexane:EtOAc, 50:50; compound (R_f): **1a** (0.12), **2a** (0.78), **3** (0.91)). The reaction was quenched with saturated ammonium chloride (0.5 mL), diluted with CH_2Cl_2, dried over Na_2SO_4 and evaporated under reduced pressure to give **2a** as a colourless oil. In most cases the material was pure enough for use in the next reaction. If desired, purification by flash chromatography, 1:4 ethyl acetate:hexane gave **2a** as a colourless oil. The yield ranged from 88 to 99% over 10 independent runs and may be scaled up to the gram level without incident (88–90% yield). When scaling up, it is important to maintain the same concentration as above. More concentrated solutions provided slightly higher yield of the bis-sililated product under otherwise identical conditions. **2a** had $[\alpha]_D^{22}$ +23.0° (*c* 2.87, MeOH); ^{1}H NMR 300 MHz ($CDCl_3$): δ 1.04–1.10 (m, 21H), 3.80 (s, 3H), 3.81 (s, 3H), 4.55 (br s, 1H), 4.83 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 172.2, 171.4, 74.50, 73.83, 52.93, 52.67, 18.21, 12.95; IR (KBr):

3559, 2868–2947, 1764, 1464, 1438, 1262, 1157, 1104, 883, 683; EIMS m/z (%) 291 (M^+–isopropyl, 100), 231 (44.2), 203 (77.8), 145 (75.5); HREIMS: calcd ($C_{12}H_{23}SiO_6$) 291.1264, found 291.1261.

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