Furanose Synthesis via Regioselective Dihydroxylation of 1-Silyloxy-1,3-dienes: Application to the Furanose Unit of 4-*epi*-Hygromycin A

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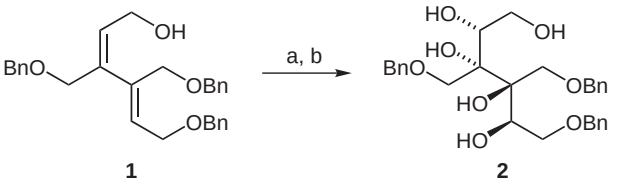
Abstract: Asymmetric dihydroxylation of a 1-silyloxy-1,3-diene is shown to occur regioselectively on the non-oxygenated alkene. Second dihydroxylation is complicated by over-oxidation to the dione and epimerisation of reaction products. However, subsequent manipulations including selective oxidation of a primary alcohol allow synthesis of a protected furanose corresponding to that present in C4-*epi*-hygromycin.

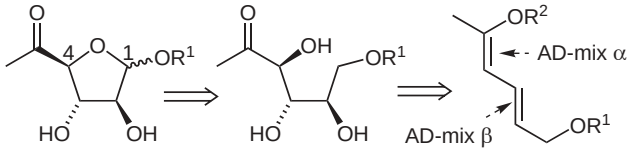
Key words: alkenes, dihydroxylation, osmium, regioselective, oxidations

The use of chiral-pool materials is a well established approach to the synthesis of complex polyhydroxylated natural products. Whilst this strategy conveniently provides enantiomerically pure compounds, the excision of unwanted functionality can lead to lengthy synthetic routes. Additionally, the unnatural enantiomeric series can be difficult to access. In our total synthesis of (+)-zaragozic acid C, we utilised an alternative approach which involved preparation of a stereodefined 1,3-diene unit **1** containing the required carbon framework, followed by double asymmetric dihydroxylation (AD)[1] to introduce the hydroxyl functionality in **2** with a high degree of stereocontrol (Scheme 1).[2] The first dihydroxylation step gave a mixture of regioisomers, which was inconsequential in the context of this total synthesis but would preclude the use of a different functionalisation reaction (such as the enantiomeric chiral ligand series) in the second step. In order to make this synthetic strategy more general and flexible, we sought to discover dienes where initial dihydroxylation could be achieved regioselectively. 1,3-Dienes with an ester substituent in the 1-position have been reported by Sharpless to undergo AD reaction at the more electron rich 3,4-alkene.[3] We wondered whether 1-oxygenated-1,3-dienes would also undergo regioselective AD, allowing a flexible route to substituted polyol derivatives. A particular target was the furanose unit **3** of the important antibiotic hygromycin,[4] previous syntheses of which have required multi-step routes from carbohydrate precursors.[5] Our retrosynthetic approach to this furanose **3** is outlined in Scheme 2, where the key requirements are the regioselective dihydroxylation of diene **5** – predicted on the basis of the Sharpless AD mnemonic[1] to require opposite chiral ligand series in the two dihydroxylation steps – as well as selective oxidation of the terminal, primary hydroxyl group in **4**. In this paper we report successful regioselective dihydroxylation of a 1-silyloxy-1,3-diene and synthetic manipulations leading to **16**, corresponding to the C4-epimer of **3**.



1 **2**

Scheme 1 *Reagents and conditions:* (a) AD-mix β, *tert*-BuOH/H_2O, 78%; (b) $(DHQD)_2PHAL$, OsO_4, acetone/H_2O, 58%, >80% de, 76% ee.



3 **4** **5**

Scheme 2

The first requirement was a synthetic route to the substituted silyloxy diene **8**. This was accomplished as shown in Scheme 3. Deprotonation of propargyl alcohol benzyl ether **6** and reaction with formaldehyde was followed by stereoselective reduction to the *E*-allylic alcohol with RED-AL,[6] conversion to the bromide, displacement with 2-lithio-2-methyl-1,3-dithiane and subsequent removal of the 1,3-dithiane unit to afford **7**. Thermodynamic silyl enol ether formation was then readily accomplished, providing the desired 1,3-diene **8** as a 2.5:1 *Z*:*E* mixture. We were now able to test the dihydroxylation of diene **8**. Interestingly, when **8** was subjected to AD conditions,[7] dihydroxylation proceeded with apparently complete regiocontrol, with reaction taking place on the non-silyloxy-substituted olefin (Scheme 3). The two silyl enol ether isomers (*Z*)-**9** and (*E*)-**9** proved separable by flash chromatography, and the enantiomeric excess of (*Z*)-**9** was shown to be 84% by chiral HPLC.[7] The regiochemical outcome of this reaction was perhaps surprising, since it is the same as that observed for 1,3-dienes with an electron withdrawing ester group in the 1-position.[3] In order

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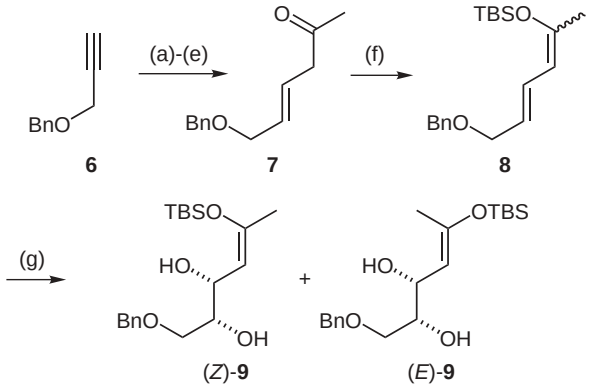
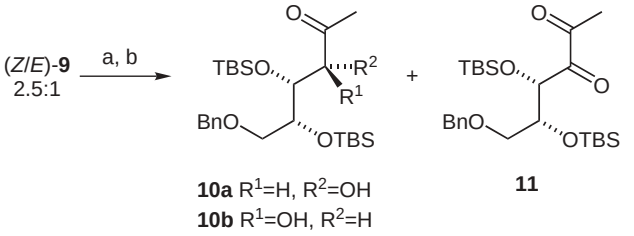
to rule out the influence of alkene substitution pattern, we also tested 1-*tert*-butyldimethylsilyloxy-1,3-pentadiene, where both alkenes are disubstituted. Interestingly, analysis of the reaction mixture at low conversion indicated that this diene also reacted regioselectively on the 3,4-alkene, suggesting that the differing substitution pattern between the two alkenes in **8** is not responsible for the AD-regioselectivity.



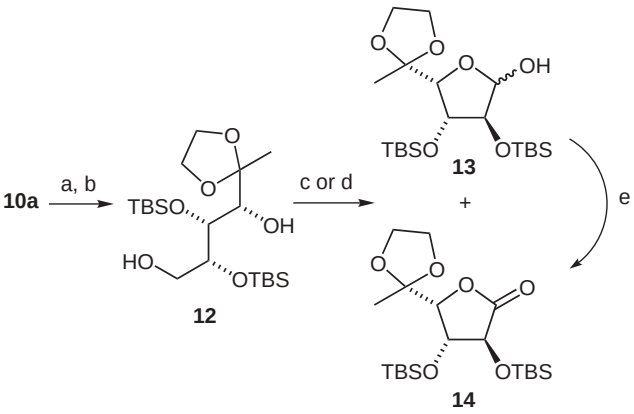
Scheme 3 *Reagents and conditions:* (a) *n*-BuLi, THF, –78 °C, then $(CH_2O)_n$, 69%; (b) REDAL, –20 °C, THF, 79%; (c) NBS, PPh_3, –40 °C, THF, 79%; (d) 2-lithio-2-methyl-1,3-dithiane, DMPU, –78 °C, THF, 75%; (e) $AgNO_3$, NCS, $MeCN/H_2O$, 78%: (f) KH, TBSCl, THF, 76%; (g) super AD-mix β, *tert*-$BuOH/H_2O$, 4 d, 0 °C, 41% (*Z*)-**9**, 21% (*E*)-**9**.

The second dihydroxylation step was now examined. Sharpless and co-workers have previously reported the efficient AD of silyl enol ethers.[8] Importantly, their studies indicated that *E*- and *Z*-isomers of trisubstituted enol ethers afforded the same product enantiomer, indicating that an *E*/*Z*-mixture could be employed. Accordingly, the (*E*/*Z*)-**9** mixture was taken on through the synthesis. These diols were protected as their *bis*-TBS ethers in order to facilitate product analysis and to allow efficient hydroxyl differentiation later in the synthesis. AD reaction using the AD-mix-α ligand series, which was predicted to lead ultimately to the required C4-stereochemistry, afforded recovered starting material (10%) along with three products: two diastereomeric α-hydroxy ketones **10a** and **10b**, along with the dione **11**.[9] Dione **11** presumably arises from conversion of **10** to the ene-diol tautomer and subsequent dihydroxylation. Indeed, resubmission of **10a**/**10b** to the AD conditions led to formation of **11**. This side-reaction has been reported once before, in the AD of silyl ketene acetals,[10] but to the best of our knowledge has not been reported previously in the AD of silyl enol ethers. Subsequent manipulations suggest that the major α-hydroxyketone **10a** has the unexpected and undesired configuration α- to the ketone (vide infra). However, control experiments suggest that **10a** and **10b** undergo epimerisation and over-oxidation under the AD conditions at different rates, which means that the observed ratio of **10a**/**b** may not reflect the outcome of the initial AD step. Despite experimentation with the AD-reaction conditions, we were not able to prevent the formation of dione **11** or to make **10b** the major product. Use of AD-mix β again afforded predominantly **10a**.



Scheme 4 *Reagents and conditions:* (a) TBSCl, imidazole, DMF, 94%; (b) (i) super AD mix-α, *tert*-$BuOH/H_2O$, r.t., 120 h,: **10a**: 34%, **10b**: 6%; **11**: 13%.

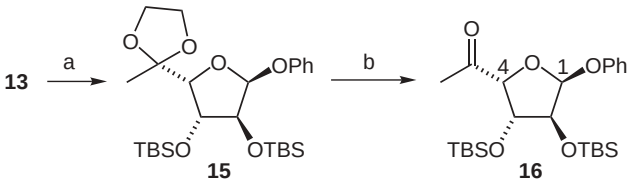
With **10a** in hand, we investigated the manipulations needed for furanose formation (Scheme 5). Protection of the ketone as a dioxolane and removal of the benzyl group led to **12**. Mosher's ester analysis of this material indicated that it had >95% ee. We now required selective oxidation of the primary alcohol in the presence of the secondary one. We were aware of recent progress in the selective oxidation of primary alcohols using TEMPO-based oxidation systems.[11a] Use of TEMPO with NCS as co-oxidant[11b] afforded a mixture of the lactone **14** (45%) and the lactol **13** (36%), which could be oxidised to **14** using PCC. Interestingly, the recently reported TEMPO/isocyanuric acid system[11c] led directly to the lactone **14** in good yield. This selective primary oxidation therefore allowed realisation of our aim of using 1,3-dienes as precursors to furanoses.



Scheme 5 *Reagents and conditions:* (a) Ethylene glycol, triethyl orthoformate, PPTS, 30 h, 79%; (b) H_2, Pd/C, MeOH; (c) 5 mol% TEMPO, 2 equiv isocyanuric acid, CH_2Cl_2, 79% **14**; (d) TEMPO, NCS, Bu_4NCl, CH_2Cl_2/H_2O, pH 8.6, 45% **14**, 36% **13**; (e) PCC, CH_2Cl_2, 4Å ms, 4 h, 78%.

Since NOE studies on **14** proved inconclusive, we opted to assign relative configuration by correlation of lactol **13** with known literature compounds. Thus, coupling of **13** with phenol afforded a 3:1 mixture of anomers with the major assigned structure **15**.[12] Deketalisation of the major anomer gave **16** (Scheme 6), silyl deprotection of which gave a product whose ^1H NMR spectrum did not match

that of the correct hygromycin C4-epimer reported by Buchanan.[5b] NOE measurements on **16** gave firm evidence that it was the C4-epimer. A 14% enhancement of H4 upon irradiation of H3 was particularly diagnostic. Assuming that complete epimerisation did not occur in any of the transformations employed,[13] this suggests that the major product **10a** in the second AD step has the configuration depicted in Scheme 4.



Scheme 6 *Reagents and conditions:* (a) Phenol (1.1 equiv), PPh_3 (1.2 equiv), THF, then DEAD (1.2 equiv), 2.5 h, 98% (3:1 **15**:*C1-epi*-**15**); (b) TFA, THF, H_2O, 79%.

In conclusion, we have demonstrated that 1-silyloxy-1,3-dienes can be regioselectively dihydroxylated on the 3,4-alkene. In the second dihydroxylation step, we have noted an unusual side-reaction, namely over-oxidation to the dione. We have shown that the double dihydroxylation products may be manipulated via selective oxidation of a primary alcohol to allow the synthesis of furanose derivatives, including compounds related to the C4-epimer of the furanose contained in the antibiotic hygromycin. Efforts to refine this strategy by improving the yield and selectivity of the second alkene functionalisation step are currently under investigation.

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(7) 'Super AD-mix' refers to commercial AD-mix supplemented with 1 mol% $K_2OsO_2(OH)_4$, 5 mol% ligand and 1 equiv $MeSO_2NH_2$. The absolute configuration of **9** is assigned based upon the Sharpless mnemonic.[1] The ee of (*Z*)-**9** was determined using HPLC (Chiralcel OD, 1 mL per min, 5% IPA/hexane, detection at 210 nm, retention times: 11.8 min (minor enantiomer), 27.8 min (major enantiomer). We have been unable to determine the ee of (*E*)-**9**.
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(9) R_f values (20% Et_2O-petroleum Et_2O): **11**, 0.85; **10a**, 0.21; **10b**, 0.14. Characteristic data for dione **11** include carbonyl stretches in the IR spectrum at 1716 and 1675 cm^{-1}, and ^{13}C NMR resonances at δ = 201 and 200 ppm.
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(12) H1 in the major anomer appeared as a singlet, while that in the minor was d, *J* = 3.6 Hz. Comparison to ref.[5a,b] and to various pentafuranoses then suggests the anomeric configuration indicated. Stevens, J. D.; Fletcher, H. G. J. *J. Org. Chem.* **1968**, *33*, 1799.
(13) We have demonstrated that deketalisation of the benzyl ether of **12** regenerates **10a**, suggesting that epimerisation has not occurred here. We cannot rule out epimerisation at C4 in the deprotection of **15**. However, molecular mechanics (MMFF) indicate that the **16** is 7.7 kcal/mol less stable than its C4-epimer, suggesting that epimerisation is unlikely.
Data for **16**: white amorphous solid; mp 79–81 °C; $[\alpha]_D^{20}$ –37.5 (*c* 0.1, CH_2Cl_2). IR (film): ν_{max} = 2949, 2928, 2857, 1718, 1587, 1490, 1254, 1254 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ = 7.35–7.01 (5 H, m, Ph), 5.82 (1 H, d, *J* = 3.1 Hz, 2-H), 4.72 (1 H, d, *J* = 4.4 Hz, 5-H), 4.42 (1 H, dd, *J* = 2.6 and 4.4 Hz, 4-H), 4.16 (1 H, app. t, *J* = 3.0 Hz, 3-H), 2.28 (3 H, s, 6-CH_3), 0.95 [9 H, s, $SiC(CH_3)_3$], 0.86 [9 H, s, $SiC(CH_3)_3$], 0.15 [3 H, s, $Si(CH_3)_2$], 0.13 [3 H, s, $ROSi(CH_3)_2$], 0.10 [3 H, s, $Si(CH_3)_2$], 0.05 [3 H, s, $Si(CH_3)_2$]. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 209.0 (C), 157.3 (C), 129.5 (CH), 122.2 (CH), 116.3 (CH), 102.2 (CH), 85.7 (CH), 79.2 (CH), 77.9 (CH), 28.6 (CH_3), 25.7 (CH_3), 25.6 (CH_3), 18.2 (C), 17.8 (C), –4.4 (C), –4.7 (C), –5.1 (C), –5.2 (C). MS (CI): *m/z* = 484 (100) $[M + NH_4]^+$, 390 (5), 201 (31), 132 (24). Anal. Calcd for $C_{24}H_{42}Si_2O_5$ $[M+NH_4]^+$ requires 484.2915. Found: 484.2919.