Pergamon

Tetrahedron Letters 40 (1999) 41–44

TETRAHEDRON LETTERS

Convergent Synthesis of a Polyol Chain with 4-Acetoxy-1,3-dioxanes Using a 1,1-Bis((trimethylsilyl)methyl)ethene Linchpin

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Received 16 September 1998; revised 13 October 1998; accepted 15 October 1998

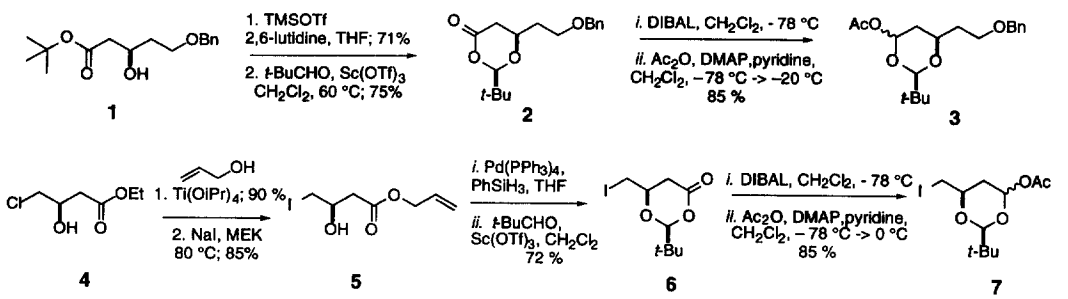
Abstract: The symmetric dinucleophile, 1,1-bis((trimethylsilyl)methyl)ethene, was used as a linchpin to join two different 4-acetoxy-1,3-dioxanes. These couplings produce *anti*-diols, and were used to prepare a segment of the roflamycoin polyol. The *anti*-diol selectivity normally observed on coupling 4-acetoxy-1,3-dioxanes was found to be a function of the C2 acetal substituent, and *tert*-butyl was superior to methyl.

Convergent strategies for polyol chain assembly have played an important role in the syntheses of complex natural products. Couplings based on cyanohydrin acetonide intermediates have featured prominently in our own work, and are particularly effective for the synthesis of *syn*-diols.[1] The use of dinucleophiles as linchpins has been developed by a number groups. In this strategy two different electrophiles are coupled sequentially with a bis nucleophile to form a carbon chain. Dithane, the most widely used linchpin, has been used to assemble spiroacetals,[2] and both Nakata[3] and Lipshutz[4] have used this approach to synthesize polyol chains. Smith recently developed an improved dithiane coupling using a solvent-induced Brook rearrangement to generate the second anion.[5] Acetone has also been used as a linchpin, using sequential enantioselective aldol reactions with aldehydes to assemble a chain.[6] Described herein is the use of 1,1-bis((trimethylsilyl)-methyl)ethene[7] (**9**) as a linchpin for the coupling of two 4-acetoxy-1,3-dioxanes to give protected *anti*-diols.[8] An intermediate in the synthesis of roflamycoin was prepared to validate this approach.[9]

A segment coupling strategy requires enantiomerically pure building blocks, and syntheses of the necessary enantiopure 4-acetoxy-1,3-dioxanes are outlined in Scheme 1. Both of the 3-hydroxy esters, **1** and **4**, were prepared in $\geq$ 94% ee by Noyori's enantioselective reduction.[10] Hydrolysis of the *tert*-butyl ester of **1**, followed by acetal formation with $Sc(OTf)_3$ catalysis, gave the 1,3-dioxan-4-one **2**.[11] Reduction and *in situ* acetylation[12] gave the 4-acetoxy-1,3-dioxane **3** as a mixture of epimers, which were used without further purification. The corresponding methyl acetal **8** was prepared in an analogous sequence using acetaldehyde instead of pivaldehyde. The 4-acetoxy-1,3-dioxane **7** was prepared from the chloro ester **4**. Since basic hydrolysis of the ester **4** lead to decomposition, the carboxylic acid was prepared by ester exchange with allyl alcohol, followed by Pd catalyzed deprotection. The iodide was introduced in a Finkelstein reaction with the hydroxy ester. Finkelstein reaction after protection of the adjacent alcohol

PII: S0040-4039(98)02260-6

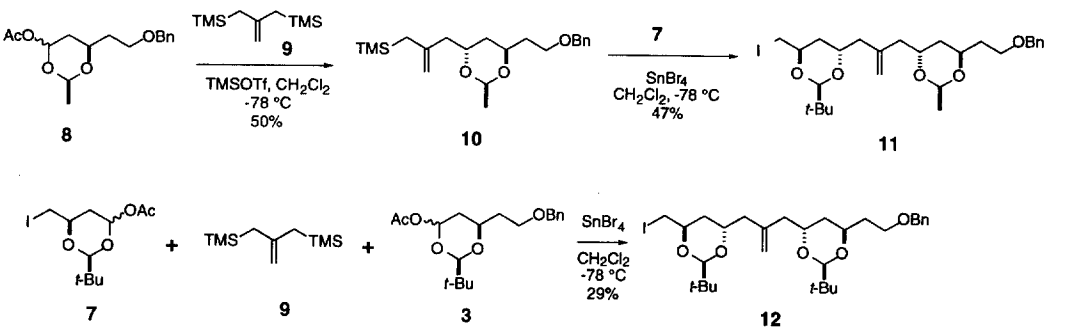
Scheme 1



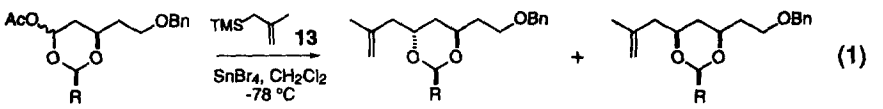
requires much harsher conditions.[13] Pd catalyzed deprotection of the allyl ester of **5**, followed by *in situ* acetal formation and reductive acetylation gave the 4-acetoxy-1,3-dioxane **7** in good overall yield. Compounds **3** and **7** were prepared in ≥ 94% ee from readily available materials.

The segment coupling reactions are shown in Scheme 2. A stepwise coupling was carried out beginning with **8** and the disilane linchpin **9**.[7] Combining the two components with TMSOTf as a promoter in CH_2Cl_2 at –78 °C gave allylsilane **10** in 50% yield. Reaction of allylsilane **10** with the 4-acetoxy-1,3-dioxane **7** and using $SnBr_4$ as a promoter gave coupled segment **11** in 47% yield. On further investigation, it was found that formation of the allylsilane **10** was accompanied by significant amounts of the syn isomer. The low anti selectivity observed in the coupling of 2-methyl dioxane **8** with **9** in Scheme 2 has little impact on the sequence because **10** and its syn isomer were separated by chromatography.

Scheme 2



Isolation of the syn isomer was unexpected, as previous couplings of allylsilanes with 4-acetoxy-1,3-dioxanes had always resulted in high anti selectivity. Reaction of **8** with the allyltrimethylsilane using $SnBr_4$ as a promoter led to the anti isomer exclusively in 92% yield. Reaction with the branched 3-(2-methylpropenyl)trimethylsilane (**13**), however, gave significant amounts of the syn isomers as shown in Eq. 1. The 2-methyl dioxane **8** produced a 3.6:1 mixture of anti to syn isomers. We have found that 2-*t*-butyl dioxanes often show better anti selectivity than 2-methyl dioxanes in dialkylzinc additions.[14] Switching to the 2-*t*-butyl dioxane **3** gave a 12:1 ratio of anti to syn isomers. Unbranched allylsilanes add

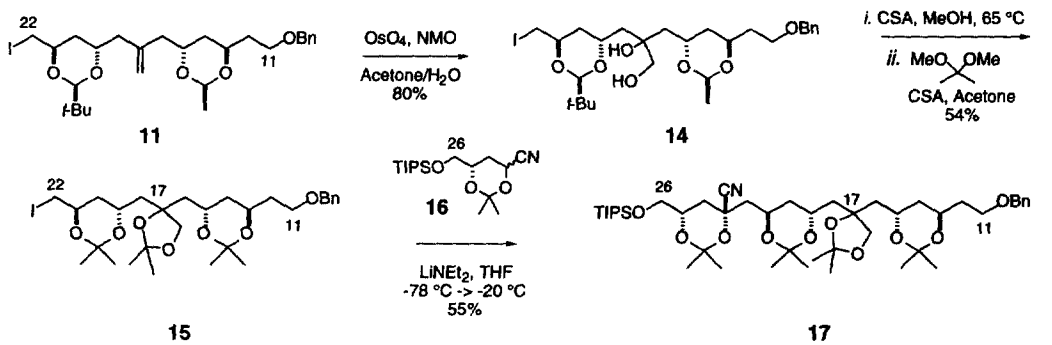


8: R = Me	3.6 : 1	90%
3: R = *t*-Bu	12 : 1	99%

to 4-acetoxy-1,3-dioxanes with high anti selectivity, but branched allylsilanes should be coupled with the more selective 2-*t*-butyl dioxane substrates.

The roflamycoin polyol segment could also be assembled in a one-pot, three-component coupling, Scheme 2. Compounds **7** and **9** were combined with the $SnBr_4$ promoter, followed by the addition of **3** to give the complete segment **12** in modest yield. In this case, reaction of the 2-*t*-butyl dioxane **3** leads to higher stereoselectivity and reduces the amount of unwanted syn isomer in the product.

Scheme 3



Either **11** or **12** would be a viable intermediate for the synthesis of roflamycoin, but chemical correlation required a change of protecting groups. The reprotection and correlation of segment **11** with roflamycoin intermediate **17** is illustrated in Scheme 3. Osmium tetraoxide oxidation of alkene **11** gave a 3:2 mixture of diastereomeric diols **14**. The quaternary center will be converted into the C17 ketone of roflamycoin, so the both diastereomers could be used in the synthesis. Deprotection of **14** followed by reprotection with 2,2-dimethoxypropane produced the triacetonide **15.** For the purposes of correlation, both diastereomers were carried on independently to **17** and its known epimer. The bromide corresponding to **15** was an intermediate in the synthesis of roflamycoin, and the ^1H NMR spectra of iodide **15** and the corresponding bromide were very similar. Alkylation with cyanohydrin acetonide **16** gave the correlation compound **17**. Compound **17** incorporates the C11 through C26 atoms of roflamycoin, and was identical to the previously synthesized authentic material by TLC, ^1H NMR and MS evaluation.

The 4-acetoxy-1,3-dioxanes **7** and **8** were coupled with the disilane linchpin **9** to give protected polyol **11**. Anti to syn ratios are lower with branched allylsilanes, but reaction with 2-*t*-butyl-1,3-dioxanes gave synthetically useful selectivities. Polyol **11** was converted to **17**, a previously reported intermediate in

the synthesis of roflamycoin. Stereoselective coupling of 4-acetoxy-1,3-dioxanes with the disilane linchpin **9** is a highly convergent route to polyol chains.

One-pot coupling to form 12. To a stirred solution of acetate **7** (34 mg, 0.1 mmol, 2 equiv) and silane **9** (24 mg, 0.12 mmol, 1.2 equiv) in 1.0 mL of methylene chloride at -78 °C under argon was added a 1 *M* solution of tin(IV)bromide (109 μL, 0.11 mmol, 1.1 equiv). After ten minutes, a solution of benzyloxy acetate **3** (47 mg, 0.14 mmol, 1.4 equiv) in 0.5 mL of methylene chloride was added via cannula, followed by a second addition of the 1 *M* solution of tin(IV)bromide (149 μL, 0.15 mmol, 1.5 eq). The mixture was stirred for 20 minutes, the reaction quenched with 0.3 mL of 1:1 triethylamine/methanol, and the solution was allowed to warm to room temperature. The mixture was partitioned between CH_2Cl_2 and water, and the organic layer was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to pale yellow oil. Purification by chromatography (SiO_2, 5% ethyl acetate/hexanes) provided 16 mg (29%) of **12** as a colorless oil: IR (neat) 2975, 2954, 2926, 2867, 1482, 1360, 1239, 1125, 1046, 992 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ, 7.32 (m, 5 H), 4.88 (m, 2 H), 4.51 (dd, J = 14.1, 12.0 Hz, 2 H), 4.39 (s, 1 H), 4.37 (s, 1 H), 4.26 (m, 2 H), 3.95 (m, 1 H), 3.83 (m, 1 H), 3.63 (m, 1 H), 3.55 (m, 1 H), 3.16 (m, 2 H), 2.50 (m, 2 H), 2.30 (m, 2 H), 1.75 (m, 5 H), 1.13 (m, 1 H), 0.88 (s, 9 H), 0.83 (s, 9 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ, 142.4, 138.5, 128.4, 127.7, 127.5, 114.8, 100.2, 100.0, 73.1, 71.5, 69.8, 69.7, 68.4, 66.2, 37.0, 36.8, 36.5, 34.9, 34.8, 33.7, 33.4, 24.7, 24.6, 9.2 ppm. HRMS (FAB) calcd. for $(M+H)^+$, $[C_{30}H_{48}IO_5]^+$ 615.2548, found 615.2542.

Acknowledgments. Financial support was provided by National Institutes of Health (GM-43854) and the University of California, Irvine.

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