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Alkene protection against acid using a bromide substituent: application in a total synthesis of (−)-6,7-dideoxysqualestatin H5†

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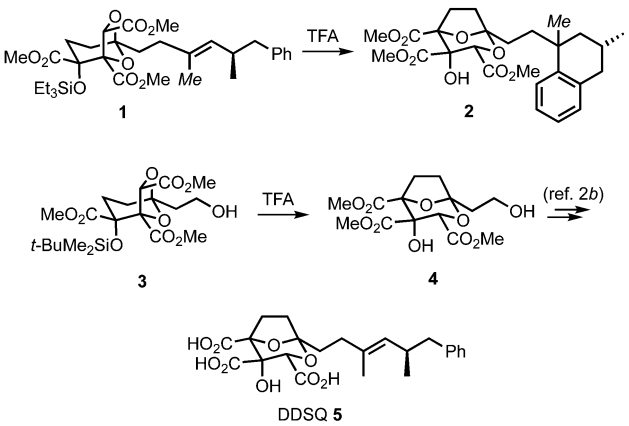
The presence of a bromide substituent, instead of a hydrogen or methyl group, on a carbon–carbon double bond, protects the alkene from addition reactions when exposed to trifluoroacetic acid. This concept is used to circumvent concomitant loss of unsaturation in a late-stage acid-catalysed 6,8- to 2,8-dioxabicyclo[3.2.1]octane rearrangement towards (−)-6,7-dideoxysqualestatin H5. The inertness of the alkenyl bromide functionality is demonstrated through several synthetic transformations in the assembly of the rearrangement substrate. Completion of the natural product synthesis is facilitated by post-rearrangement removal of the bromide substituent through stereoselective C–C cross-coupling in the presence of ester and hydroxyl functionalities.

(−)-6,7-Dideoxysqualestatin H5 (DDSQ) **5** (Scheme 1) is a member of the zaragozic acid/squalestatin family of natural products which display a variety of interesting bioactivities.[1,2] Structurally, DDSQ possesses a synthetically challenging 2,8-dioxabicyclo[3.2.1]octane core bearing a hydroxyl and three carboxylic acid groups and an unsaturated hydrocarbon side-chain at C-1. In an earlier study, we attempted to access DDSQ through acid-catalysed transketalisation of the advanced intermediate **1**.[3] Rearrangement to the desired core could be induced, however concomitant loss of the unsaturation in the side-chain by protonation/Friedel–Crafts cyclisation to give tetralin **2** could not be avoided. Although this problem could be solved by introducing the olefin after the rearrangement (**3** → **4** → **5**),[2b] we became intrigued by the issue of how to directly protect this type of electron-rich carbon–carbon double bond from such unwanted reactivity. While masking the alkene could potentially be achieved in numerous ways,[4] we were attracted to the idea of reducing its propensity to protonation through the presence of a temporary halide substituent. Here, we communicate the realisation of this concept, and its application in a synthesis of DDSQ **5** by halide replacement of the alkenyl methyl group in rearrangement substrate **1** (italicised Me).



Scheme 1 Transketalisation approaches to (−)-6,7-dideoxysqualestatin H5 **5**.

The *Z*-alkenyl halide functionality envisaged in the rearrangement substrate for DDSQ synthesis discussed above would not only have to remain inert during transketalisation. It would also be required to pass unscathed through several synthetic steps in the construction of the substrate (*vide infra*), and yet would need enough reactivity to undergo stereoretentive (and chemoselective – in the presence of ester functionality) cross-coupling with a methyl donor;[5] we therefore focused on bromide (rather than iodide or chloride) as the halide substituent. Before embarking on the target synthesis with this modification in place, the following observations provided initial support for the idea of alkene protection from an acid such as TFA, by a bromide substituent. 2-Methyl-1-octene (**6a**, Scheme 2) is known to be entirely converted to the corresponding tertiary

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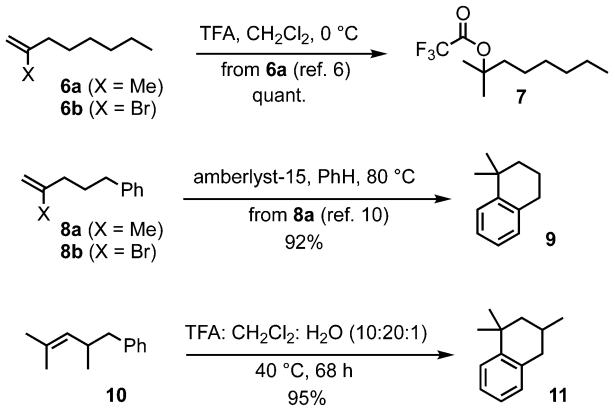
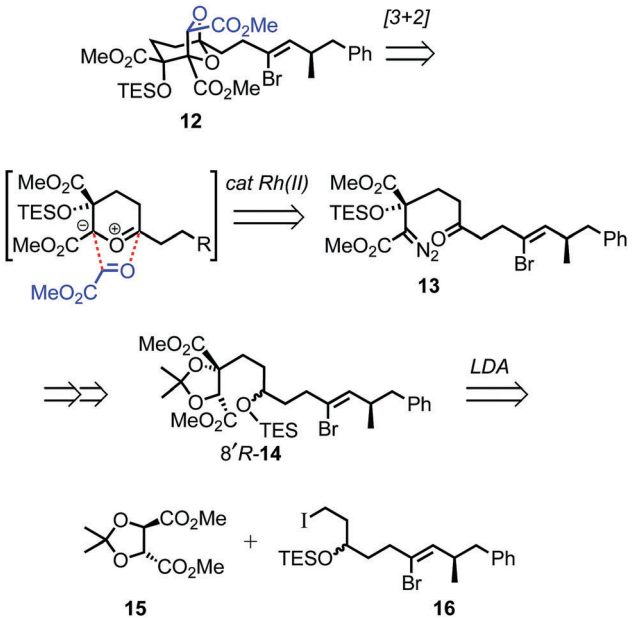


Scheme 2 Addition and cyclisation reactions of alkenes with acids.

trifluoroacetate **7** within 20 min using TFA (5 equiv.) in CH_2Cl_2 at 0 °C,[6,7] whereas 2-bromo-1-octene (**6b**)[8] was recovered unchanged from exposure to the acidic conditions typically necessary to induce the acid-catalysed 6,8- to 2,8-dioxabicyclo[3.2.1]octane rearrangement [TFA/CH_2Cl_2/H_2O (10 : 20 : 1), 40 °C, 48–68 h].[2b,9] Also, 2-methyl-5-phenylpentene (**8a**) is known to undergo Friedel–Crafts cyclisation to 1,1-dimethyltetralin (**9**) with acid,[10] and, similarly, we found 2,4-dimethyl-5-phenyl-2-pentene (**10**) with TFA gave the corresponding tetralin **11** in 95% yield (Scheme 2); in contrast, 2-bromo-5-phenylpentene (**8b**)[11] was recovered quantitatively from exposure to the standard TFA rearrangement conditions.

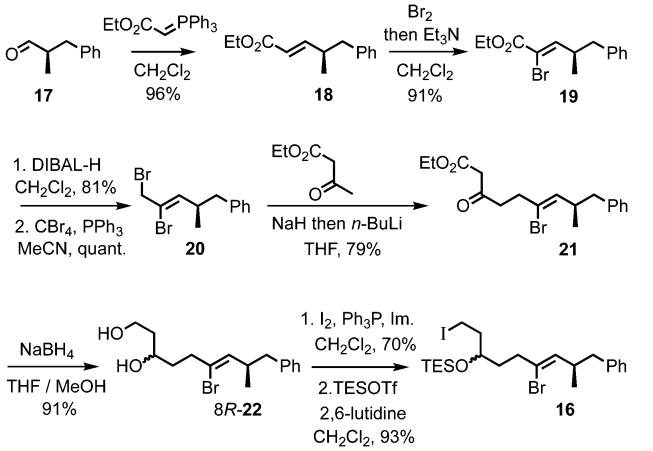
For the prospective synthesis of (−)-DDSQ **5**, the *Z*-alkenyl bromide-bearing rearrangement substrate **12** was anticipated to be available through a Rh(II)-catalysed tandem carbonyl ylide formation and cycloaddition of a diazoketone **13** with methyl glyoxylate (Scheme 3).[12] In turn, diazoketone **13** was considered as being accessible from substituted tartrate **14**, with the latter



Scheme 3 Outline of projected route to *Z*-alkenyl bromide-bearing rearrangement substrate **12**.

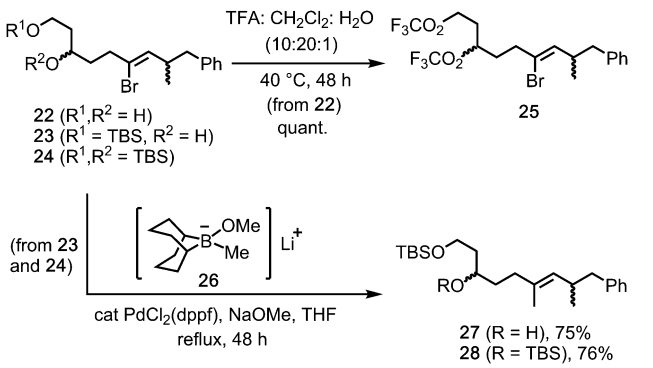
expected to arise through application of Seebach's tartrate alkylation methodology[2b,13] using the enolate of tartrate **15** and iodide **16**.

Access to the *Z*-alkenyl bromide-containing iodide **16** for tartrate alkylation was achieved from *R*-aldehyde **17**[14] (Scheme 4). Wittig olefination (known to proceed without erosion of enantiointegrity with such an ester-stabilised ylide on a related α-methyl aldehyde[15]) to give *E*-enoate **18**, was followed by bromination–dehydrobromination[15] to give the *Z*-α-bromoenoate **19**. The dianion of ethyl acetoacetate[16] was efficiently alkylated with the derived allylic bromide **20**, and the resulting β-ketoester **21** was reduced to the 1,3-diol **22** using $NaBH_4$ in MeOH/THF.[17] Iodination of the primary alcohol and TES protection of the secondary alcohol gave the iodide **16**.



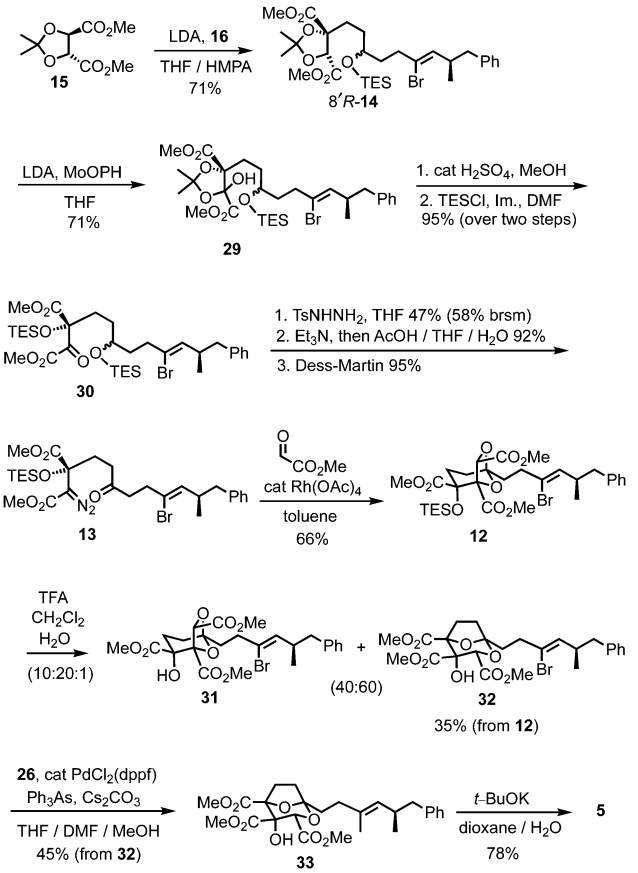
Scheme 4 Synthesis of iodide **16**.

Initial availability of the 1,3-diol **22** (from *rac*-**17**) provided an early opportunity to test the stability of the *Z*-alkenyl bromide motif under the TFA rearrangement conditions. Pleasingly, reaction of 1,3-diol **22** gave the bistrifluoroacetate **25** (quant., Scheme 5), in which the alkenyl bromide was unaffected. Moreover, stereoretentive Suzuki reactions between the 1,3-diol-derived mono- and bis-TBS ethers **23** and **24** and the borinate complex **26** (from MeLi and 9-MeO-9-BBN)[5] gave *E*-alkenes **27** and **28** in 75% and 76% yields, respectively.[18]



Scheme 5 Stability of alkenyl bromide functionality to TFA, and stereoretentive methylation.

The chemistry in Scheme 5 encouraged progression of iodide **16** towards (−)-DDSQ **5**. Thus, tartrate alkylation,[2b,13] followed by oxidation[19] of the resulting alkylated tartrate **14** gave hydroxy acetonide **29** (Scheme 6). The acidic conditions necessary to remove acetone from **29** resulted in concomitant desilylation, but the silyl group was reinstalled during formation of the bis-TES ether **30** from the intermediate lactol. This bis-TES ether **30** underwent condensation with tosylhydrazide, followed by Et_3N-induced generation of diazo functionality;[20] under the basic reaction conditions partial desilylation of the secondary TES ether occurred and this was completed by addition of aqueous acetic acid. The lability of the secondary TES ether under mild conditions was crucial, as it, along with mild Dess–Martin oxidation of the resulting intermediate secondary alcohol, allowed access to ketone **13** in which both the tertiary TES ether and the diazo functionality were retained.[9]



Scheme 6 Completion of the synthesis of (−)-6,7-dideoxysqualestatin H5 **5**.

Following cycloaddition of diazoketone **13** with methyl glyoxylate, we were pleased to observe that, in line with the model study (Scheme 5), rearrangement of the resulting cycloadduct **12** could be induced with preservation of the alkenyl bromide, to give the 2,8-dioxabicyclo[3.2.1]octane **32**.[21] Further Suzui methylation studies with alkylated tartrate **14** (from *rac*-**17**) as a closer (ester-containing) model system to **32**, led to the identification of Cs_2CO_3 (in MeOH) as the preferred base and Ph_3As as additive in DMF.†[22] Application of these conditions to alkenyl bromide **32** gave the squalestatin trimethyl ester **33**, which underwent global saponification using anhydrous KOH[23] to give **5**.[2]

The present work exemplifies prevention of electrophilic attack (protonation/Friedel–Crafts cyclisation) of an alkene by using a vinylic bromine substituent. Conceptually, this differs from earlier approaches, that mask a C=C bond by transient addition of elements across it, which are then subsequently eliminated.[4] During the sequence to prepare **5**, the alkenyl bromide functionality is also robust enough to survive a variety of other chemistry (Schemes 4 and 6), before being selectively replaced in a C–C bond-forming event at the penultimate step. The strategy should find application in other synthetic endeavours.

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Conflicts of interest

There are no conflicts to declare.

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