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A REGIOSELECTIVE ROUTE TO 2,3,4-TRISUBSTITUTED FURANS‡

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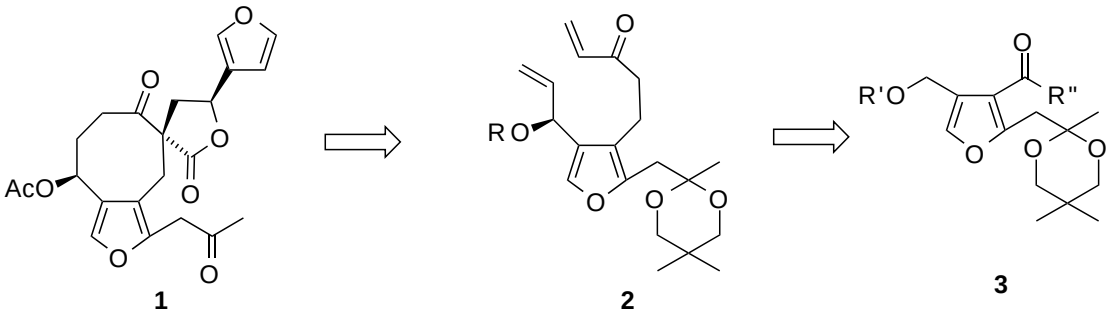
Abstract - Several potential routes to furans substituted with C-C bonds at the 2-, 3-, and 4- positions have been evaluated.

We have undertaken the goal of a total synthesis of the rearranged *neo*-clerodane diterpenoid teubrevin G (**1**).[2] The presence of a medium-sized ring and the pattern of connectivity of its stereogenic centers were considered to provide a proper setting for the implementation of ring closing metathesis involving **2**.[3] This stratagem prompted consideration in turn of an efficient means for producing **3**. The complexities associated with the generation of monocyclic 2,3,4-trisubstituted furans are well known[4-6] and are not to be taken lightly. Of the four potential synthetic pathways examined here, only one proved to be practical and amenable to scale-up. Knowledge of the potential awkwardness awaiting certain approaches should preclude redundancy regarding their possible future application in related contexts.

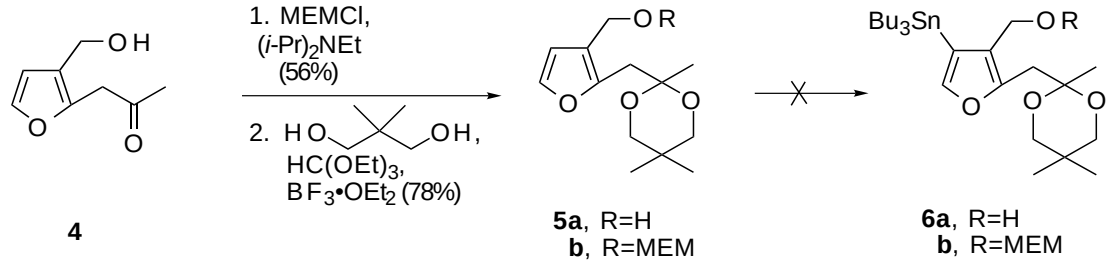


1 **2** **3**

The first route began with the known hydroxy ketone (**4**).[7] Formation of the MEM derivative (**5b**) was followed by ketalization with neopentyl glycol (Scheme 1). After numerous attempts to introduce a tributyltin substituent at C-4 as in **6a** or **6b** were to no avail,[8] the focus was shifted to the possibility of C-2 stannylation, which was expected to occur more readily.[5] To this end, aldehyde (**8**) was prepared by $O \rightarrow C$ silyl migration performed on the previously reported **7**[9] (Scheme 2). Treatment of **8** with vinylmagnesium bromide delivered the carbinol in 77% yield and set into motion two functional group modification steps leading efficiently to **9**. This alcohol reacted with 2.2 equiv of *n*-butyllithium in THF at 0 ˚C followed by

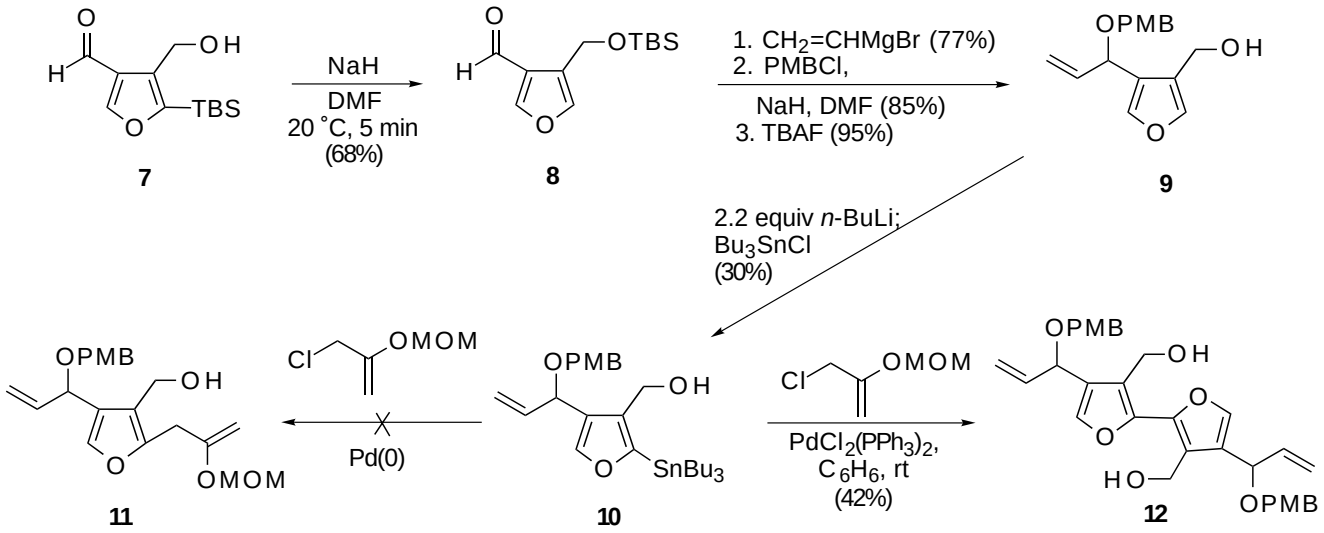
‡This paper is dedicated to Professor James Kutney as we celebrate his 70th birthday and his many substantive contributions to synthetic and bioorganic chemistry.

Scheme 1



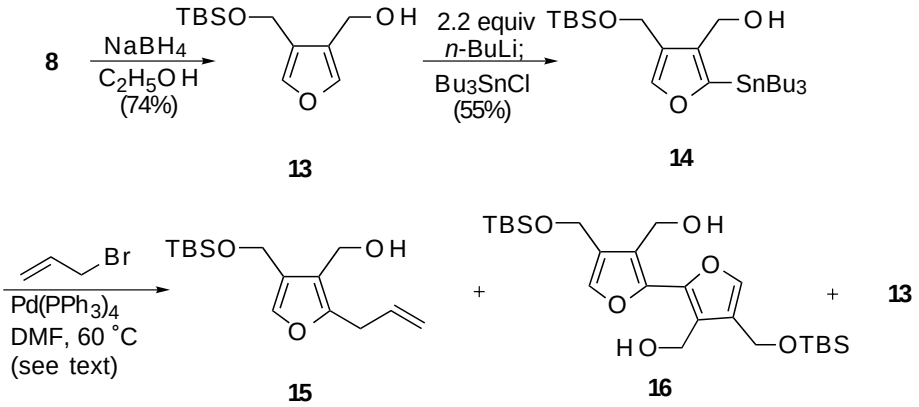
tri-*n*-butyltin chloride to afford **10**, but only in low (30%) yield. The difficulty in this instance conforms to the reported instability of 2-stannylated furans[5] and manifests itself in the readiness with which **9** is regenerated upon the attempted purification of **10**. Beyond this, attempts to effect the palladium(0)-catalyzed coupling of **10** to 2-chloromethyl-3,5-dioxahex-1-ene gave rise not to the desired **11** but to the dimeric furan **12**.

Scheme 2



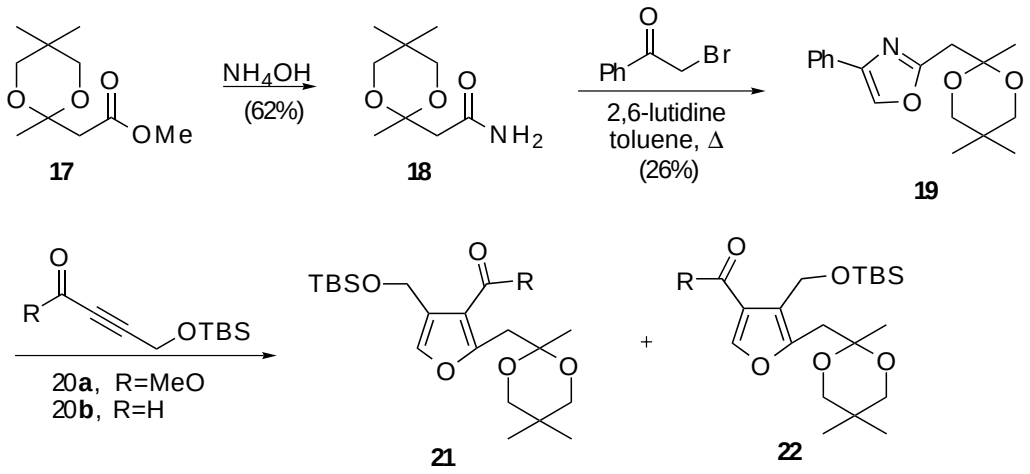
A comparable observation was made following the generation of **14** from **8**, and its palladium-mediated coupling to allyl bromide (Scheme 3). Although more elevated temperatures and the use of a polar aprotic solvent did serve to induce the formation of **15** (47%), simple destannylation (30% of **13**) and reductive coupling to give **16** (17%) were also operational.

Scheme 3

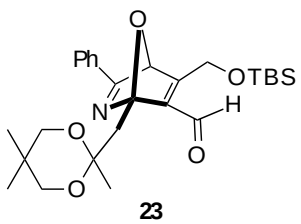


At this point consideration was given to the possibility of achieving appropriate thermal Diels-Alder cycloaddition-retrograde fragmentation between functionalized oxazoles and disubstituted alkynes. This ploy has seen extensive use when alkyne-tethered oxazoles are involved because structural constraints rule out the possible operation of competing regioselective pathways.[10] Intermolecular [4+2] cycloadditions to unsymmetrical alkynes have been accorded much less attention[11] and potentially useful directive effects have not been elucidated.[12] Despite these concerns, we proceeded to transform methyl ester (**17**)[13] into its amide in a step preliminary to formation of oxazole (**19**) (Scheme 4). Although formation of this heterocycle proceeded only with modest efficiency, the sequence proved easily scalable and the only chromatographic purification needed was readily accomplished. Heating ester (**20a**) with **19** in tetralin produced a 5.3:1 mixture of **21a** and **22a**. Yet more impressive and useful was the discovery that the involvement of aldehyde (**20b)** gave rise only to **21b** within our limits of detection.

Scheme 4



The substantial kinetic preference for formation of adduct (**23)** is noteworthy and suggests that steric and electronic effects are exploitable for the one-step regiocontrolled elaboration of 2,3,4-trisubstituted furans from oxazole precursors. The ease of access to **21** in this manner has proven to be particularly well suited to the expedient construction of **1**.[3]



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