Temporary Tethering Strategies for [5 + 2] Pyrone-Alkene Cycloadditions[1]

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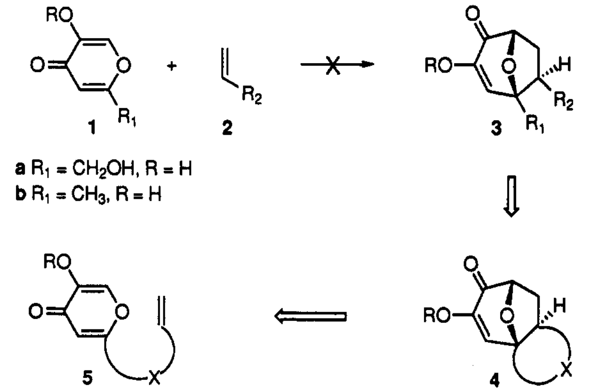
Summary: Temporary connection of alkenes to 3-alkoxy-4-pyrones via sulfur or silicon tethers allows their thermal [5 + 2] cycloaddition and ensures complete regio- and stereochemical control.

Efforts to develop efficient, expeditious approaches to stereodefined seven-membered rings have been stimulated by increasing awareness of the occurrence of these substructures in a wide variety of bioactive natural products, including guiane and pseudoguiane sesquiterpenes,[2] troponoids,[3] and tumor-promoting diterpenes.[4] Among the strategies developed for synthesis of these rings, those based on annulation protocols are particularly attractive since they allow simultaneous formation of several bonds in a single operation.[5] Several years ago, Garst reported that thermolysis of 2-(w-alkenyl)-5-hydroxy-4-pyrones provides products that are formally the result of internal [5 + 2] cycloaddition.[6] Although this transformation proved successful for intramolecular cases,[7] its intermolecular counterpart, exemplified by the reaction between commercially available kojic acid (**1a**) or its derivatives (e.g., **1b**) and electron-deficient alkenes (**2**, R_2 = electron-withdrawing group), fails to produce the expected cycloadducts (**3**, Scheme I).[8] This limitation was recently overcome by conversion of the pyrone into a highly reactive 4-methoxy-3-oxidopyrylium ylide.[9] Unfortunately, this method leads to mixtures of stereoisomeric cycloadducts, and its success is restricted to electron-deficient alkenes.

Scheme I



a $R_1 = CH_2OH$, R = H
b $R_1 = CH_3$, R = H

In view of the potential of this kind of [5 + 2] cycloaddition for the synthesis of highly oxygenated seven-membered carbocycles from readily available starting materials, we sought to develop alternative strategies for overcoming the problems associated with the bimolecular process. In this paper we demonstrate that unreactive alkenes can be induced to participate in the thermal cycloaddition by their temporary attachment to the pyrone through a readily removable connector (X, Scheme I). Furthermore, the conformational constraints inherent to the intramolecularity of the process allow complete control of the stereochemistry of the reaction products.

Chloride **6**, prepared by reaction of commercially available kojic acid (**1a**) with thionyl chloride followed by O-5 silylation (82% yield over the two steps),[10] was efficiently transformed into the thioether **7** by treatment with allyl mercaptan and triethylamine (88% yield). Heating a solution of **7** in toluene (145 °C, sealed tube, 40 h) gave the expected *exo* cycloadduct **8** in 71% yield. Treatment of this thioether with Raney nickel in THF at room temperature induced very slow conversion to the expected oxabicycle **9**. Heating the reaction mixture under reflux provided a new desulfurized compound that was identified as the ketone **10** (70% yield).[11,12] The formation of **10** can tentatively be attributed to Raney nickel-induced reduction of the carbonyl group and subsequent O-3 → O-2 migration of the silyl group, although alternative mechanisms cannot be ruled out.[13] Overall, the process achieves a formal *inter*molecular cycloaddition between a nonactivated alkene (propene) and α-deoxykojic acid (**1b**), a transformation that cannot be carried out in a

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[1] Preliminary results of this work were presented at the 203rd National Meeting of the American Chemical Society, San Francisco, CA, 1992; ORGN 403.

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[11] Structural assignment was based on NMR experiments. The stereochemistry of the carbon bearing the *tert*-butyldimethylsilyl ether substituent was deduced from the characteristic coupling constant of 5 Hz for the C-2 *exo*-H observed in the ^{1}H NMR spectrum. See: Murray, D. M.; Albizati, K. M. *Tetrahedron Lett.* **1990**, *31*, 4109.

[12] All new compounds were characterized by ^{1}H and ^{13}C NMR and high-resolution mass spectroscopy.

[13] It is known that activated Raney nickel may reduce ketones, see: (a) Caubère, P.; Coutrut, P. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds; Pergamon: New York, 1991; Vol. 8, Chapter 4.3 and references cited therein. (b) Takahashi, T.; Kitano, K.; Hagi, T.; Nihomantsu, H. *Chem. Lett.* **1989**, 597.

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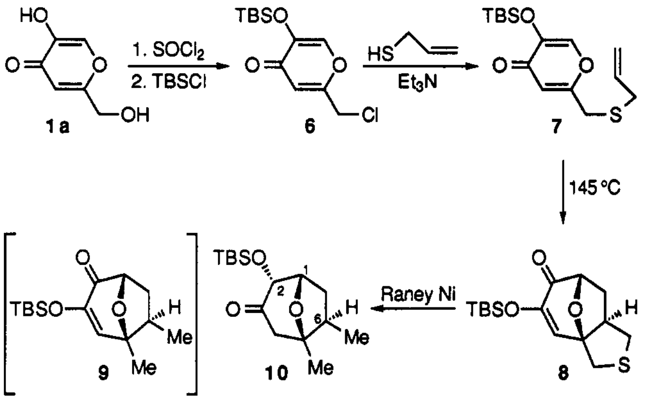
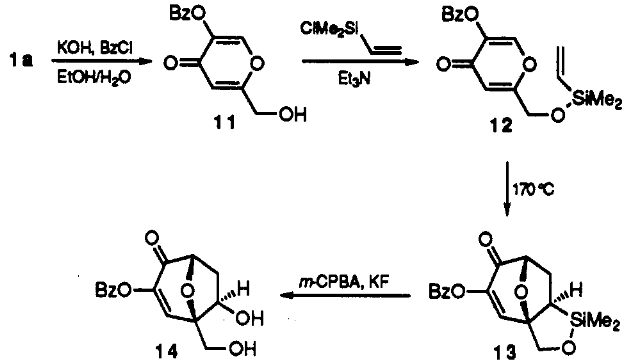
Scheme II



Scheme III

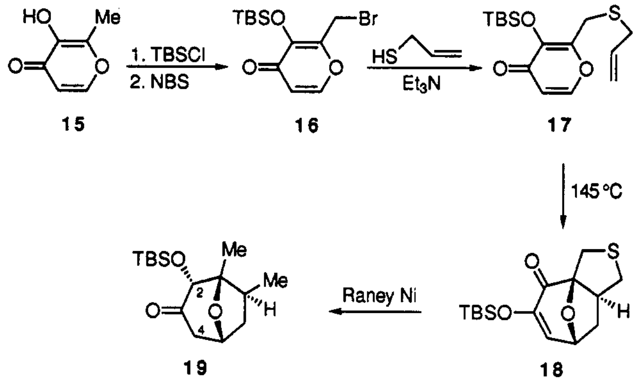


*bi*molecular mode. Note that the method allows complete control of the stereochemistry of the product at four centers.

We next envisaged that the use of silicon instead of sulfur linkages might provide a route to a wider variety of cycloadducts, in part as a consequence of the greater versatility of the carbon–silicon bond. Temporary silicon connections have been increasingly used to control stereochemistry in a variety of processes such as radical cyclizations,[14] hydrosilylations,[15] Diels–Alder cycloadditions,[16] and electrochemical reactions.[17] Application of this device to the pyrone–alkene cycloaddition demanded the use of an O-5 protecting group that would not interfere with subsequent removal of the silicon tether. We found that the benzoyl group fulfills the necessary requirements as protecting-activating group.

Treatment of benzoate **11**, readily prepared from kojic acid (**1a**),[18] with dimethylvinylchlorosilane and triethylamine in CH_2Cl_2 afforded the required siloxane **12** (Scheme III). The lability of this vinylsilyl ether to moisture and silica gel led us to carry out the entire cycloaddition sequence, including workup of the carbon–silicon bond of the cycloadduct, in a single operation.[19] A typical "one-pot" protocol, exemplified for the case in which the silicon is replaced by a hydroxyl group, involved the following: (i) formation of the silyl ether **12** as indicated above; (ii) removal of solvents under vacuum and heating of a solution of the residue in toluene (170 °C, sealed tube, 80 h); and (iii) elimination of toluene under vacuum and treatment of the residue with potassium fluoride and *m*-chloroperbenzoic acid in DMF at room temperature.[20] This procedure gave the oxabicycle diol **14** in 78% yield from benzoate **11**.[12] The overall transformation **11** → **14** constitutes a completely regio- and stereoselective formal *inter*molecular [5 + 2] cycloaddition between kojic acid and the enolic tautomer of acetaldehyde.

Scheme IV



The feasibility of using the above tethering strategies to obtain cycloadducts with complementary regiochemistry, and therefore of expanding the range of ring substitution patterns attainable, was demonstrated for the case of the thioether tether (Scheme IV). The required starting bromide **16** was readily prepared in 85% yield by silylation and subsequent allylic bromination of commercially available maltol (**15**). A sequence similar to that described for the synthesis of **10** led to the expected bicyclic compound **19** in 52% overall yield.[12,21]

In conclusion, thermal [5 + 2] cycloaddition between unactivated alkenes and 3-alkoxy-4-pyrones can be efficiently performed by means of temporary attachment of the reacting partners via sulfur or silicon links. This approach allows complete control of the regio- and stereochemistry of the adducts, which by virtue of their rich substitution pattern and rigid structure may serve as building blocks for the stereoselective synthesis of a wide variety of products containing seven-membered rings or tetrahydrofurans. To the best of our knowledge, the work described here is the first application of temporary tethering strategies to higher order cycloadditions. We are currently exploring the chemistry of the cycloadducts and studying the facial selectivity achievable by introduction of stereogenic centers in the tether.[22]

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Supplementary Material Available: Experimental details, spectroscopic data (^1H, ^{13}C NMR, MS, and HRMS), and ^1H and ^{13}C NMR spectra (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[21] The stereochemistry of the carbon bearing the *tert*-butyldimethylsilyl ether group (C-2) was deduced from the NOE effect (4%) observed for the proton at C-2 upon irradiation of the C-4 *exo*-H.

[22] We have observed that the presence of a sulfoxide group in the chain induces remarkable facial selectivity (unpublished results).