Conjugate Additions

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Uncatalyzed Mukaiyama–Michael Reaction: Rapid Access to Simple and Complex Enantiopure γ-Butenolides**

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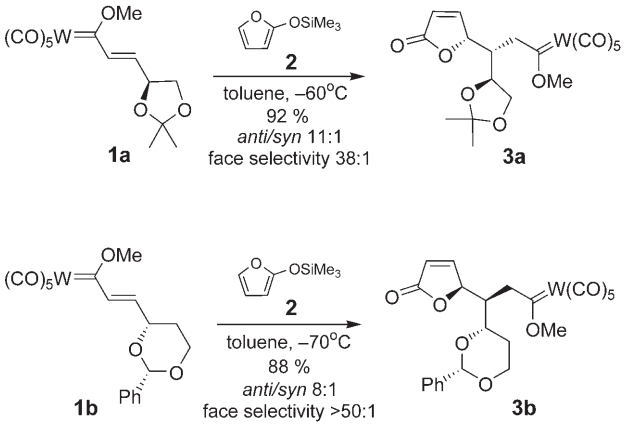
Access to enantiopure γ-butenolides currently represents a research area of great interest because of their presence as a subunit in many natural products and, particularly, in compounds with biological activity.[1] Elaboration of the commercial 2-trimethylsilyloxyfuran (TMSOF) reagent by means of an asymmetric Mukaiyama–aldol reaction has been, thus far, the most efficient method for the formation of substituted chiral γ-butenolides.[2] The Mukaiyama–Michael reaction is much less common and can be brought about through the use of either chiral metal catalysts and alkenoyl oxazolidinones[3] or chiral organocatalysts and enals, as was elegantly demonstrated by MacMillan and co-workers.[4] In looking for novel acceptor substrates, we focused on the suitability of enantiopure Fischer carbene complexes **1** as they are strongly electrophilic in nature,[5,6] and are readily accessible by condensation of methylcarbene complexes and chiral aldehydes.[7] Furthermore, the presence of both the acetal/ketal moiety and especially the metal carbene functionality in the Michael adduct permits further elaboration.[8]

We found that enantiopure tungsten carbene complexes **1** are reactive toward 2-trimethylsilyloxyfuran at low temperatures (Scheme 1). Thus, the treatment of carbene **1a** with TMSOF in toluene (−60 °C, 42 h) resulted in the formation of the carbene complex **3a** almost exclusively (92% yield). The high *anti*/*syn* ratio (11:1) and face selectivity (97:3 d.r.) is notable and allowed the isolation of pure **3a** in 81% yield after a single purification step by flash chromatography. Under similar reaction conditions (toluene, −70 °C, 48 h), the conjugate addition of TMSOF to the carbene complex **1b** afforded the adduct **3b** with high selectivity (*anti*/*syn* = 8:1, and > 98:2 d.r.) and yield (88% yield; 76% of pure **3b** after chromatographic purification). Both chiral subunits are reactive and complement each other in terms of stereoselective induction as the configuration of the stereogenic centers created in **3a** and **3b** each subunit are opposite.[9]



Scheme 1. Stereoselective Mukaiyama–Michael reaction of TMSOF (**2**) with carbene complexes **1**.

The stereoselectivity can be rationalized by assuming the model calculated for the [4+2] cycloaddition of the corresponding isolobal esters.[10] Thus, the less hindered approach of TMSOF to the C=C bond of **1a** from the minimum energy conformation **A** would lead to the major isomer **3a**. In the same way, the adduct **3b** would arise by the attack of TMSOF at **1b** through the conformation **B** (Figure 1).[11]

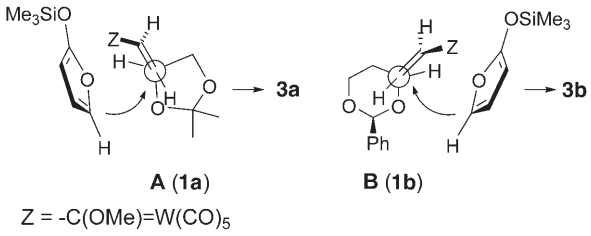


Figure 1. Proposed TMSOF–carbene complex approach.

The potential of this facile approach to γ-butenolides can be stressed by taking advantage of the broad chemistry of the metal carbene functionality. First, oxidative removal of the metal from **3a** through the action of pyridinium oxide yielded the corresponding ester derivative **4** in 93% yield ($[\alpha]_D^{20} = +74.7$ ($c = 0.17$, CH_2Cl_2); Scheme 2). In turn, methylenation of **3a** with diazomethane afforded the enol ether **5**, which was transformed into the methyl ketone **6** in situ by hydrolysis over silica gel (77% yield from **3a**; $[\alpha]_D^{20} = +70.2$ ($c = 0.55$, CH_2Cl_2)). These simple processes constitute efficient alternatives to the unknown Mukaiyama–Michael addition of TMSOF to both esters and ketones (75% and 62% overall yields of **4** and **6**, respectively, from carbene **1a**).[12,13]

The ease of synthesis of some complex enantiopure architectures containing the butenolide nucleus is exemplified in Scheme 3, which illustrates the transformation of **3a** into the fused lactone **8** (a process that formally involves an

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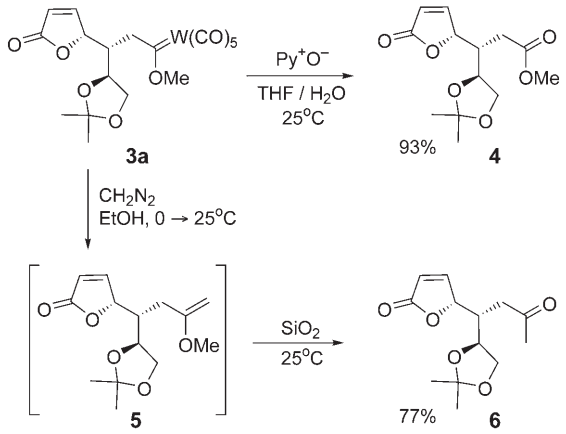
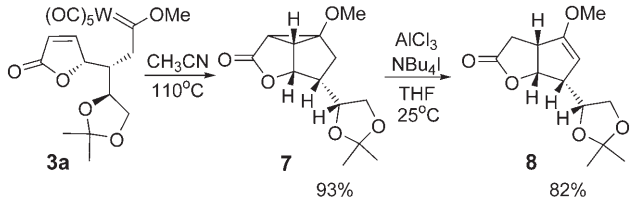


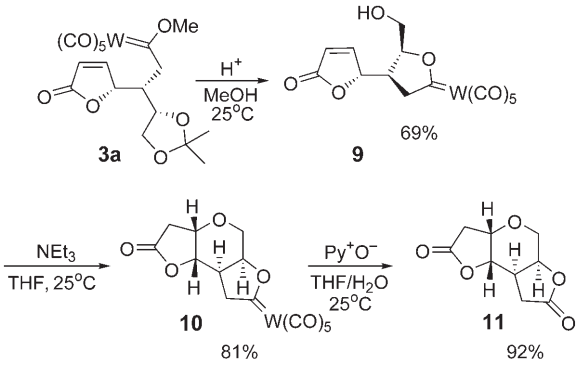
Scheme 2. Oxidation and methylenation of carbene complex **3a**.



Scheme 3. Transformation of complex **3a** into **7** and **8**: cyclopropanation and ring-opening reactions.

umpolung Michael addition reaction and therefore requires a metal catalyst). The intramolecular cyclopropanation of **3a** is carried out in acetonitrile (110 °C, 5 h, sealed tube) to furnish **7** as the sole stereoisomer (93 % yield; $[\alpha]_D^{20} = -58.8$ ($c = 0.34$, CH_2Cl_2)). The subsequent Lewis acid promoted cyclopropane ring opening of **7** gave the *cis*-fused γ-lactone **8** (82 % yield; $[\alpha]_D^{20} = -21.5$ ($c = 0.55$, CH_2Cl_2)).

The ketal chiral subunit is also useful for the formation of further complex enantiopure molecules (Scheme 4). As a result of the advantageous location of the protected diol functionality of **3a**, it might be possible, among other transformations, to assemble both γ-lactone and tetrahydropyran cores which would therefore give access to linearly fused furan–pyran–furan structures.[14] Simple deprotection of



Scheme 4. Diol deprotection of complex **3a**: Formation of bislactone **9** and enantiopure fused furan–pyran–furan compounds **10**–**11**. Py = pyridine.

the ketal functionality of **3a** with acid and subsequent intramolecular displacement of the methoxy group resulted in the regioselective formation of the cyclic metal carbene **9** (69 % yield). The carbene **9** was subsequently treated with base (Et_3N/CH_2Cl_2, 25 °C) to yield the enantiopure metal complex **10** (81 % yield) through a diastereoselective intramolecular Michael-type addition.[15,16] Notably, the metal carbene functionality does survive under acidic and basic conditions, thus allowing its reactivity to be exploited at any stage. The oxidative demetalation of **10** gave rise to the enantiopure bislactone **11** in 92 % yield ($[\alpha]_D^{20} = -94.2$ ($c = 0.48$, CH_2Cl_2), which features, two γ-lactone rings as well as a highly functionalized central pyran ring with four stereogenic carbon centers.

In conclusion, we reported herein the first uncatalyzed, diastereoselective Mukaiyama–Michael addition reaction and showed efficient access to a number of enantiopure butenolide-based structures. This sequence is a successful combination of two major features: 1) Fischer alkenyl carbenes that incorporate a chiral fragment at the β-carbon—readily available from the chiral pool—undergo very rapid diastereoselective Mukaiyama–Michael reaction with TMSOF, 2) these adducts can be transformed into valuable enantiopure molecules owing to the diverse reactivity of the metal carbene function, as well as to the conventional functional group transformations of the protected diol. Moreover, the synthetic utility of this strategy could be enhanced as a number of chiral pool derived aldehydes could provide structurally diverse alkenyl carbene complexes.

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[9] Both compounds **3a** and **3b** were crystallized from a hexane-CH_2Cl_2, and their structure was determined by X-ray crystalographic analysis.

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[11] In the case of carbene **1b**, a fixed conformation may result from π stacking between the phenyl and alkenyl moieties that would produce the same stereoisomer **3b** and therefore cannot be ruled out.

[12] At room temperature, TMSOF does not add to the methyl enoate that is structurally analogous to metal carbene **1a**, even in the presence of $BF_3{\cdot}OMe_2$.

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[16] The configuration of the new stereogenic center was determined by NMR COSY and NOESY experiments. Moreover, this stereochemical reaction pathway is in agreement with molecular modeling studies. The two possible cyclization approaches were analyzed with ab initio calculations by using the anionic Michael-type cyclization to the lactone **11** (replacing $W(CO)_5$ in **10** by O) as the model. At the MP2/6-31G*//HF/6-31G* level of theory, the transition state that gives rise to the isomer observed, is 17.4 kcal mol^{-1} more stable than the alternative transition state.

