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Synthesis of spiroketals under neutral conditions *via* a type III ring-rearrangement metathesis strategy†

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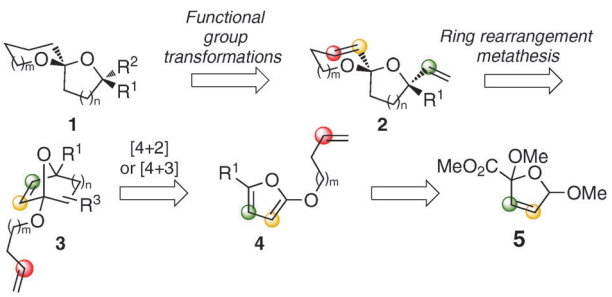
A conceptually novel approach to spiro- and dispiroketals of various ring-sizes under *neutral conditions* has been designed which complements the classical thermodynamically driven tactic. Key steps involved the formation of α-alkoxyfurans, their [4 + 2] or [4 + 3] cycloaddition reactions and the ring-rearrangement metathesis of the resulting oxabicycles.

For the past few years, we have been interested in the ring rearrangement metathesis[1] (RRM) of strained heterobicycles as an efficient strategy to access complex molecular scaffolds in a single step.[2] In connection with a total synthesis project ongoing in our laboratories, we recently became interested in developing an efficient strategy for the elaboration of spiroketal moieties **1** *via* the RRM of oxabicyclic derivatives **3** (Scheme 1). This type III-RRM tactic[3] would proceed under *neutral conditions* thereby complementing the classical and well-established thermodynamically-driven acid-catalyzed condensation of dihydroxyketones.[4] In addition, the potential for the rapid increase in molecular complexity and diversity combined with the general functional group tolerance exhibited by metathesis catalysts would be of high value to the synthetic chemist.

Quite surprisingly however, such an approach has not been reported to the best of our knowledge,[5] certainly due to the lack of practical and general access to 1-alkoxy oxabicyclic derivatives **3**. We wish to report herein a general access to a diversity of oxabicyclic derivatives **3** and their use in an efficient RRM sequence. Spiroketals of various ring-sizes have been synthesized in high yield and the method is amenable to RCM-ROM-RCM as exemplified with the straightforward elaboration of 1,7-dioxadispiroalkane derivatives.



Scheme 1 A type III-RRM tactic for spiroketal synthesis.

It was envisaged that 1-alkoxy oxabicyclic derivatives **3** could be accessed through a [4 + 2] or [4 + 3] cycloaddition reaction of the corresponding α-alkoxyfuran **4** (Scheme 1). The latter species has been scarcely reported in the literature. Indeed, the few reported syntheses rely on thermal rearrangement of strained rings,[6] trapping of a transient γ-crotonolactone enolate,[7] oxidation of 2-lithiofuran,[8] elimination of 2-substituted 2,5-dialkoxy-2,5-dihydrofuran,[9] or nucleophilic aromatic substitution of activated α-bromofurans with aliphatic sodium alkoxide or phenoxide under pressure at 100 °C.[10] These methods suffered from either low yields or narrow scope thereby affording a unique opportunity to develop a general methodology for the construction of these seemingly trivial heterocycles.

An efficient synthetic strategy of α-alkoxyfurans **4** was found, based on the acid-catalysed transformation of commercially available methyl 2,5-dimethoxy-2,5-dihydrofuranoate **6** (Scheme 2). At reflux in heptane with 5 mol% of *p*-TsOH, **6** is converted to a separable mixture of the desired α-alkoxyfurans **7** and **8a–j** in 50–98% yield.[11] Primary, secondary and neopentylic alcohols were found to be excellent partners, with secondary alcohols leading exclusively to α-alkoxyfurans **7** (see **7b**, **7h** and **7j**, Scheme 2). Interestingly, unsaturated alcohols such as but-3-enol or cyclopent-3-enol were also tolerated which was of central importance in the context of our RRM-based approach to spiroketals.[12]

Having in hand a straightforward synthesis of α-alkoxyfurans, we investigated their reactivity in [4 + 2] and [4 + 3] cycloaddition reactions (Scheme 3). [4 + 2] cycloaddition of furan derivatives with vinylcyanoacetate **11a** has a long standing history with the seminal work of Katsuki and Nishizawa[13] and Vogel and Vieira[14] who demonstrated that high pressure (15 kbars, 8 h) or an external Lewis acid (ZnI_2, 96 h) was required. In sharp contrast, the cycloaddition reaction of dienophile **11a** with the electron rich α-alkoxyfuran **9** (obtained in two steps from **7i**—or even from the 1 : 1 mixture of **7i** and **8i**—in 87% yield) proceeded quite smoothly at 60 °C in the absence of solvent.[15] A unique regioisomer was obtained in 80% yield.[16] However, the diastereoselectivity of this reaction was only moderate

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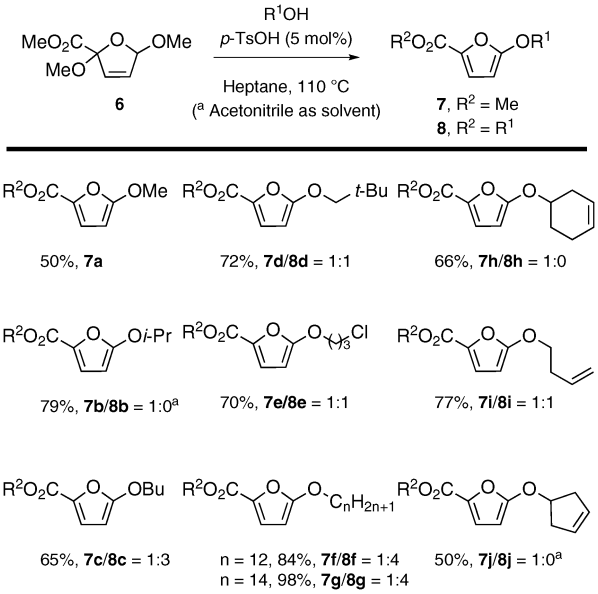


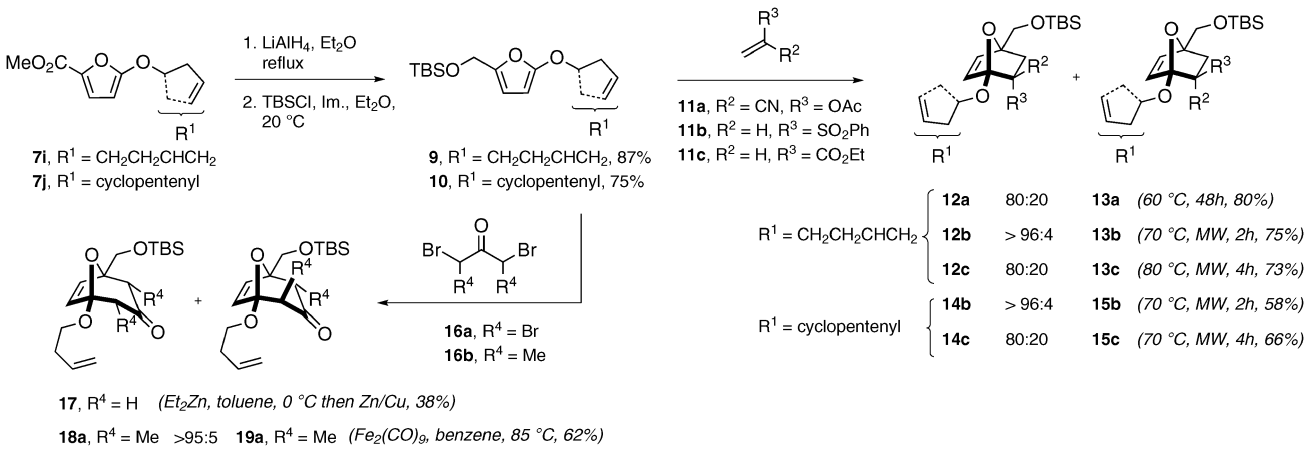
Scheme 2 A general synthesis of α-alkoxyfurans.

(**12a**/**13a** = 80 : 20) in agreement with related cycloaddition reactions of 2-alkyl substituted furans.[13,14a] Two other dienophiles were evaluated in this [4 + 2] cycloaddition reaction, phenylvinylsulfone **11b** and ethyl acrylate **11c**. In these two cases, microwave irradiation proved beneficial to the rate and yield of the reaction. Bicyclic adduct **12b** was isolated as single regio- and diastereomer in 75% yield.[16b,c] On the other hand, two diastereomers were obtained in the cycloaddition reaction of **9** with ethyl acrylate **11c** (**12c**/**13c** = 80 : 20, 73% yield). We next focused on α-alkoxyfuran **10** bearing a cyclopentenyloxy motif (Scheme 3). [4 + 2] cycloaddition reactions with phenylvinyl sulfone **11b** and ethyl acrylate **11c** proceeded in moderate yield under microwave irradiation (2–4 h, 70 °C, 58 and 66% yield respectively). Cycloadduct **14b** was obtained as a single regio- and diastereomer whereas the cycloaddition with **11c** led to two diastereomers in a **14c**/**15c** = 80 : 20 ratio.[16b,c]

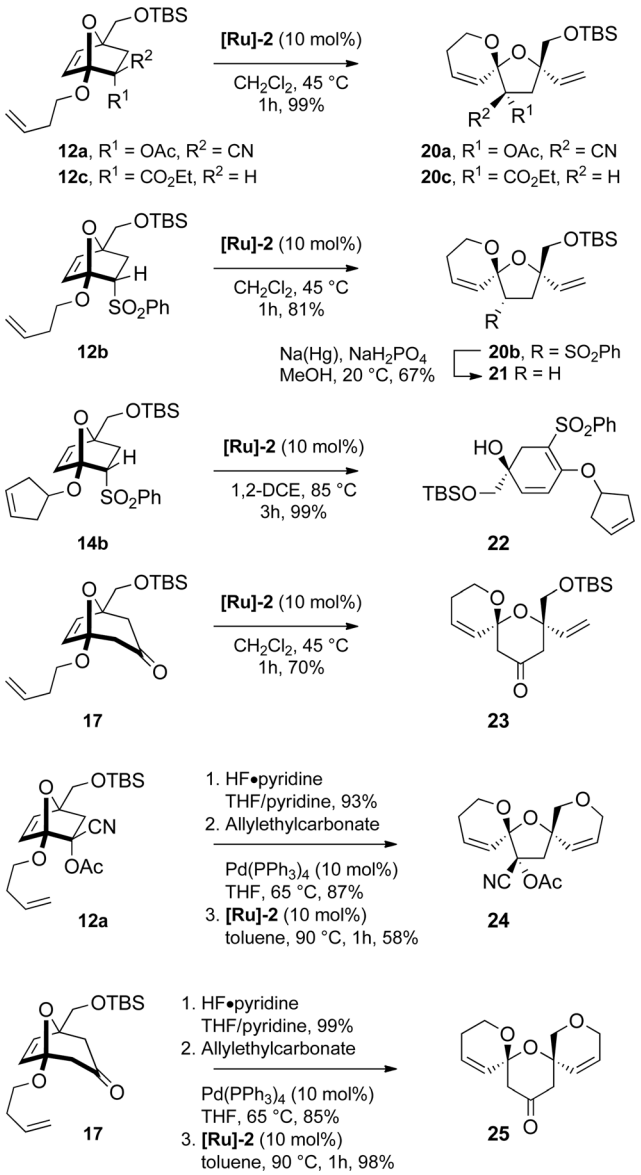
In the context of a RRM-based approach to spiroketal motifs, a metathetic rearrangement of 1-alkoxy-1-oxabicylo[3.2.1]heptenes **3** (n = 2) (Scheme 1) would be of high interest, giving access to (6,6)-spiroketals **2**. Actually, we found that α-alkoxyfuran **9** is a reactive partner in [4 + 3] cycloaddition[17] under Noyori's[18] and Mann's[19] conditions leading to RRM precursors **17**–**19**, the structure of the latter being confirmed by X-ray diffraction studies of the corresponding *p*-nitrobenzoate.[16c]

The reactivity of the [2.2.1] and [3.2.1]-oxabicycles **12**, **14** and **17** in a RRM sequence was then evaluated (Scheme 4). Much to our delight, a complete conversion of **12a** to the desired (5,6)-spiroketal **20a** was observed under mild conditions (Grubbs second generation catalyst **[Ru]-2** 10 mol%, CH_2Cl_2, 45 °C, 1 h). The RRM of the corresponding sulfone- or ester substituted [2.2.1]-oxabicycles **12b** and **12c** proceeded equally well delivering (5,6)-spiroketal derivatives **20b** and **20c** in 87 and 99% yield. It is of note that spiroketal **20b** can be smoothly desulfonylated to compound **21** by treatment with sodium amalgam. Replacement of the butenyloxy moiety of **12a–c** with a cyclopentenyloxy moiety as in oxabicycles **14b** or **14c** prevents any RRM sequence under the standard reaction conditions or under an ethylene atmosphere. Only the ring opening of the oxa-bridge of **14b** was observed under forcing conditions (1,2-DCE, 85 °C, 3 h), delivering cyclohexadienylsulfone **22** in quantitative yield. Finally, the RRM of [3.2.1]-oxabicycle **17** was studied. A good yield of the desired (6,6)-spiroketal **23** could be obtained in 1 h under mild conditions thus validating this straightforward strategy for the rapid elaboration of polyfunctional spiroketal units.

A plausible sequence of events in this RRM approach to spiroketals is a favorable initiation at the mono-substituted exo-olefin of **12** followed by a RCM/ROM reaction. We thus wondered whether the trapping of the last ruthenium alkylidene by an internal olefin (instead of a bimolecular event with a second [2.2.1]-oxabicycle) would generate the 1,7-dioxadispiropentadecane tricyclic motif, a fascinating structural subunit shared by several biologically relevant natural products such as the aculeatins and aculeatols.[20] To this end, [2.2.1]- and [3.2.1]-oxabicycles **12a** and **17** were converted to the corresponding bis(alkenyl)ether through a high-yielding two-step sequence involving silyl ether deprotection followed by a palladium-catalyzed allylation reaction (Scheme 4).[21] Under optimized reaction conditions (**[Ru]-2** 10 mol%, toluene, 90 °C, 1 h), the desired (6,5,6)- and (6,6,6)-dispiroketals **24** and **25** were prepared in excellent yield demonstrating that a RCM/ROM/RCM sequence is indeed possible for the elaboration of complex spiroketals.



Scheme 3 [4 + 2] and [4 + 3] cycloaddition reactions of α-alkoxyfurans.



Scheme 4 Synthesis of di- and trispiroketals under neutral conditions.

In conclusion, we have devised a conceptually novel approach to spiro- and dispiroketals of various ring-sizes under neutral conditions, which complements the classical thermodynamically driven tactic. During this endeavour, a general access to α-alkoxyfurans, versatile electron-rich heterocycles, has been established and their use as dienophiles in [4 + 2] and [4 + 3] cycloaddition reactions has been demonstrated.

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