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Atom-Efficient Assembly of 1,5-Oxygen-Bridged Medium-Sized Carbocycles by Sequential Combination of a Ru-Catalyzed Alkyne−Alkene Coupling and a *Prins*-Type Cyclization

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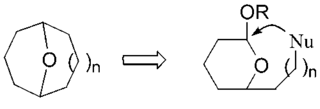
Received December 18, 2001

Medium-sized carbocycles, particularly eight- and nine-membered ones, form the structural cores of numerous biologically relevant natural products and are therefore important synthetic targets.[1] The well-known difficulty of their assembly by conventional cyclization routes, which is due to unfavorable entropic and enthalpic factors,[2] makes the development of new, practical approaches to these sized rings a major synthetic challenge.

We envisaged that the energy cost of the cyclization step might be considerably decreased if it is templated by the introduction of a temporary internal tether in the acyclic precursor. Thereby, a *Prins*-type cyclization of a mixed acetal such as **2** could lead to these sized carbocycles (**1**) because in effect the cyclization proceeds to form a six- or seven-membered oxacycle (eq 1). The oxygen bridge of **1** was thought particularly interesting because it imposes a high degree of conformational rigidity that might facilitate stereoselective manipulations at the carbocycle prior to untethering.[3]

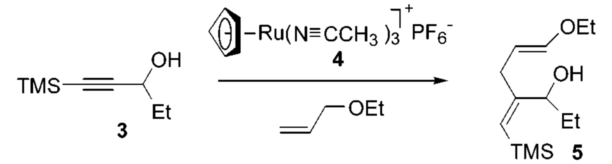


1 **2** (1)

Herein we demonstrate that a ruthenium-catalyzed coupling of 1-trimethylsilyl-1-alkyn-3-ols to commercially available allyl ethyl ether provides a rapid, atom-economical[4] and versatile method for preparing the required cyclization precursors. Lewis acid-induced closure of the resulting products leads to the expected oxabicycles, compounds that can be easily manipulated to unmask the underlying eight- and nine-membered carbocycles.

A key step in the genesis of the new procedure was the realization that 5-hydroxy-1-enol ethers susceptible to straightforward conversion to mixed acetals of type **2** might be obtained by using 1-trimethylsilyl-1-alkyn-3-ols and allyl ethers as reacting partners in the recently developed ruthenium-catalyzed alkyne−alkene coupling method.[5] However, reaction of alkyne **3** and allyl ethyl ether (1:1) with 10 mol % of catalyst **4**, in acetone (0.1 M) at room temperature,[5a] gave a quite complex mixture of products that included no more than traces of the desired alcohol **5**. In 5:1 THF/acetone the reaction proceeded with low conversion to give a 15% yield of **5**, with mostly unreacted starting material (Table 1, entry 2). Other alkenes such as allyl acetate or allyl alcohol gave mixtures of unwanted products in addition to unreacted starting material. We later found that using DMF as solvent the reaction is much more efficient,[6] and even more so when higher concentrations of the reactants were used (entry 4). Best results were obtained with 1.5 equiv of the allyl ether partner (entry 8). We have also observed that the order of addition is important (Table 1, footnote *a*): adding the allyl ether to a mixture of the catalyst and the alkynol in DMF gave a significantly lower yield (about 30%).[7]

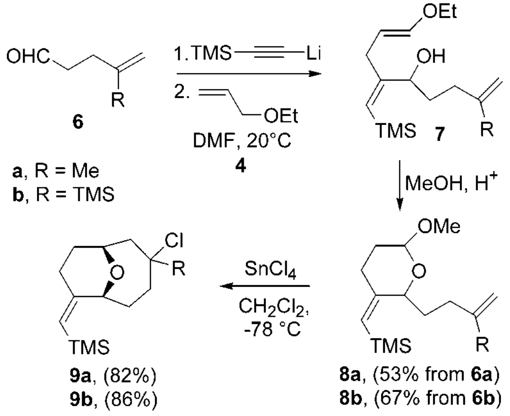
Table 1. Ruthenium-Catalyzed Coupling of **3** with Allyl Ethyl Ether[a]



entry	solvent	concn of **3** (M)	allyl ether (equiv)	**4** (%)	ratio **5**:**3**[b]	yield[c] (%)
1	acetone	0.1	1	10		
2	THF/acetone (10:1)	0.1	1	10	1:4	15 (50)[d]
3	DMF	0.2	1	10	1.6:1	48
4	DMF	1	1	10	2.3:1	66 (91)
5	DMF	1	1	1		8
6	DMF	1	1	5	1.5:1	48 (72)
7	DMF/H_2O (10:1)	1	1	10	2.3:1	60 (85)
8	DMF	1	1.5	10	2.7:1	73 (98)
9	DMF	1	3	10	1:1	49 (97)

[a] All reactions were carried out by adding catalyst **4** to a solution of **3** and allyl ethyl ether, and were stopped after 2 h at room temperature. [b] Calculated by ^{1}H NMR after workup. [c] Isolated yield. [d] Yield based on chromatographically recovered alkynol.

Scheme 1. Synthesis of 10-Oxabicyclo[4.3.1]decanes



Once the alkynol−alkene coupling had been optimized, its application to alkynols equipped with a nucleophilic alkene suitable for carrying out the planned *Prins* cyclization[8] was investigated. Gratifyingly, the enynol resulting from the addition of trimethylsilyllithium acetylide to aldehyde **6a** coupled efficiently with allyl ethyl ether, giving the expected enol ether **7a**. This product was

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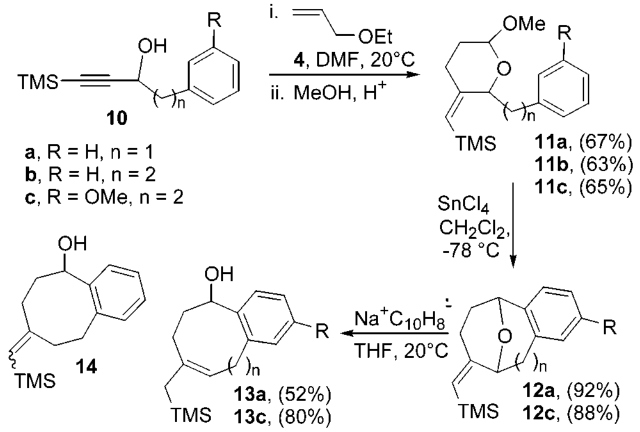
10.1021/ja017804e CCC: $22.00

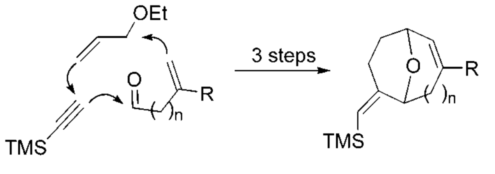
Scheme 2. Synthesis of 8−6 and 9−6 Fused Carbocyclic Systems



difficult to separate chromatographically from the starting alkynol, but addition of a 100:1 mixture of MeOH and 10% aqueous HCl to the reaction mixture smoothly converted it to acetal **8a** that can now be easily purified (58% yield from the alkynol, 77% based on recovered starting material). As far as we knew, there were no precedents for the assembly of 10-oxabicyclo[4.3.1]decane systems via *Prins*-like cyclizations;[9] however, we found that treatment of **8a** with 1.5 equiv of $SnCl_4$ at −78 °C gave a good yield (82%) of the desired bicycle **9a** as a 8:2 mixture of isomers at the tertiary center. Remarkably, the same reaction with the trimethylsilylalkene **8b**[10] produced only one stereoisomer in 86% yield.[11] This stereoselectivity confirms the potential of the bicyclic system for stereocontrol of substitution on the underlying carbocycle.

To investigate the extension of the above strategy to the construction of oxygen-bridged eight-membered carbocycles we preferred to use an aromatic system as the nucleophilic partner for the final cyclization, not only for practical reasons related to the handling of the starting alkenals, but also to find out whether the route allows the assembly of fused bicarbocyclic systems. The ruthenium-catalyzed coupling of alkynol **10a** with allyl ethyl ether, followed by in situ ketalization, gave the expected mixed acetal **11a** in 67% yield (86% based on recovered alkynol). Reaction of this compound with 1 equiv of $SnCl_4$ promoted the desired Friedel−Crafts reaction, affording tricycle **12a** in excellent yield.[12] When the same protocol was used to assemble the homologous oxygen-bridged 9−6 bicarbocyclic system, we found that compound **11b** failed to cyclize upon treatment with $SnCl_4$; however, the Friedel−Crafts reaction took place efficiently using the more electron-rich aromatic system **11c**[10] (Scheme 2). Importantly, the exocyclic double bond present in the tricyclic adducts **12**, functionality created in the Ru-catalyzed reaction, allows for facile reductive opening of the oxygen bridge under electron-transfer conditions to give the expected medium-sized carbocycles **13**. In the case of the eight-membered derivative, in addition to **13a** we obtained a 43% yield of a 1:1 isomeric mixture of vinylsilanes **14**.

In summary, we have developed a simple, versatile, and atom-economical protocol for rapidly assembling oxygen-bridged medium-sized carbocycles from inexpensive, readily available materials (eq 2).[13] The route involves a ruthenium-catalyzed alkyne−alkene C−C bond-forming reaction and a Lewis acid-promoted *Prins*-like cyclization. Since the oxygen bridge can be readily cleaved, and it is presumably easy to prepare the starting 1-alkyn-3-ols in enantiopure form, the new approach should provide for the straightforward synthesis of optically active medium-sized carbocycles. Work in this direction is currently underway.



(2)

Acknowledgment. We thank the Spanish M.E.C. (project PB97-0524) and the FEDER and MCyT (SAF2001-3120) for financial support. F.L. thanks the MEC for a predoctoral fellowship.

Supporting Information Available: Experimental procedures, including the preparation of the starting aldehydes when required, and spectroscopic data for selected compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA017804E