A Practical Approach to *cis*-2,5-Disubstituted Tetrahydrofurans and O-Bridged Medium-Sized Carbocycles from [5 + 2] Pyrone−Alkene Cycloadducts

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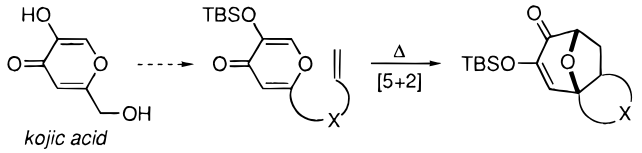
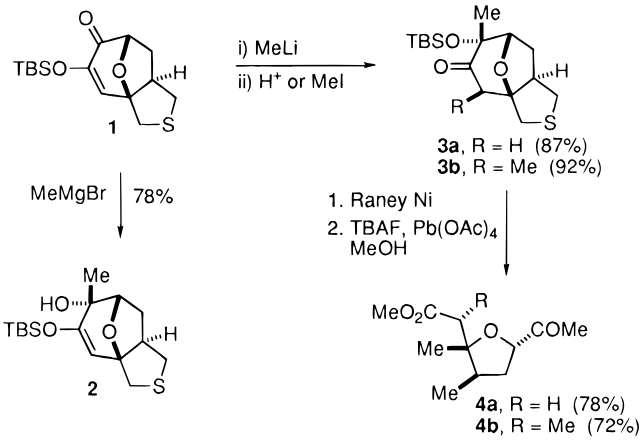
A major challenge in contemporary organic synthesis is to devise methods and strategies for the rapid and economic preparation of highly complex molecules from simple starting materials.[1] Among the alternative approaches to meet this challenge, those based on methods that allow the simultaneous creation of several bonds in a single operation, such as cycloaddition reactions,[2] are particularly appealing. Along these lines, we have recently developed a methodology for rapidly assembling stereochemically rich 8-oxabicyclo[3.2.1]octane systems by thermal [5C + 2C] cycloaddition of β-silyloxy-γ-pyrones to temporarily connected alkenes, substrates readily prepared from commercial pyrones such as kojic acid (Scheme 1).[3] In view of the dense and diverse functionalization of the resulting oxabicycles and the intrinsic stereochemical bias offered by their conformational rigidity, we felt that investigation of their stereoselective elaboration into advanced precursors of natural products was warranted.[4] Herein, we report a two-step protocol for the conversion of such cycloadducts into stereochemically rich *cis*-2,5-disubstituted tetrahydrofurans and an unprecedented strategy for acceding to 9- and 10-membered carbocycles based on a *ring closing metathesis−oxidative ring expansion* sequence.

As expected, treatment of enone **1**[3] with methylmagnesium bromide (THF, 0 °C) exclusively gave the *exo*-addition product **2**. Curiously, when the reaction was carried out with methyllithium instead of the Grignard reagent, the rearranged product **3a** was exclusively obtained, even at −78 °C.[5] This compound must arise from migration of the TBS group to the lithium alkoxide generated in the addition reaction, followed by protonation upon workup of the concomitantly formed enolate.[5] Interestingly, this enolate can be trapped in situ with an alkylating agent such as methyl iodide exclusively giving the *exo*-methylated product **3b** (92% yield). This *addition−migration−alkylation* sequence thus permits tandem stereocontrolled formation of two new C−C bonds in a single synthetic manipulation.

Scheme 1



Scheme 2



We envisaged that the α-silyloxy ketone generated in the above process might serve as a site for oxidative cleavage of the carbocycle, thus providing an entry to relatively complex *cis*-2,5-disubstituted tetrahydrofurans, which are substructures prominently displayed in a number of interesting and biologically important natural products.[6] Gratifyingly, after Raney nickel-promoted desulfuration of compounds **3a** and **3b**, room temperature treatment of the resulting oxabicycles with a mixture of tetrabutylammonium fluoride (3 equiv) and lead tetraacetate (1.5 equiv) in MeOH, cleanly provided the desired tetrahydrofuran derivatives **4a** and **4b** (96% and 92% yields for the oxidation step). Overall, the sequence establishes a new, succinct route to *cis*-2,5-disubstituted tetrahydrofurans with up to four stereocenters, from commercial inexpensive pyrones such as kojic acid.

Having established a one-step method for introducing two *exo*-alkyl groups into the oxabicyclic unit, we reasoned that if both alkyl chains were connected, subsequent oxidative fragmentation of the concomitantly formed α-silyloxy ketone would provide access to oxygen-bridged medium-sized carbocycles. This was of interest owing the well-known synthetic challenges associated to the construction of these sized rings.[7] The required tricyclic system **7** (Scheme 3) could in principle be prepared by an annulation reaction (route a) or a bis-alkylation followed by ring closure (route b). Assuming that introduction of chains bearing terminal alkenyl functionalities (X and Y equal to double bonds) would be straightforward, we decided initially to follow route b, using a ring closing metathesis C−C bond forming reaction (RCM) to link the two *exo*-alkenyl chains.[8]

The strategy was first evaluated for the synthesis of nine-membered carbocycles, a ring type present in a large number of naturally occurring terpenoids,[9] and for which

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(1) (a) Wender, P. A.; Miller, B. L. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: London, 1993; Vol 2, p 27. (b) Bertz, S. H.; Sommer, T. J. *Ibid.*, p 67.

(2) (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990.

(3) Rumbo, A.; Castedo, L.; Mouriño, A.; Mascareñas, J. L. *J. Org. Chem.* **1993**, *58*, 5585. As far as we know, this type of cycloaddition has only been used for an elegant synthesis of phorbol; see: Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990**, *112*, 4956.

(4) There are several precedents on the use of relatively unfunctionalized 8-oxabicyclo[3.2.1]octane systems as building blocks in organic synthesis. For reviews, see: (a) Lautens, M. *Pure Appl. Chem.* **1992**, *64*, 1873. (b) Lautens, M. *Synlett* **1993**, 177. See also: (c) Arjona, O.; De Dios, A.; Fernández de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 3906 and references therein.

(5) When the reaction with methyllithium is carried out in Et_2O, the TBS migration does not occur, not even at room temperature.

(6) (a) Robinson, J. A. *Prog. Chem. Org. Nat. Prod.* **1991**, *58*, 1. (b) Dutton, C. J.; Banks, B. J.; Cooper, C. B. *Nat. Prod. Rep.* **1995**, 166. For a review of approaches to *cis*-2,5-tetrahydrofurans, see: (c) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.

(7) (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res* **1981**, *14*, 95. (b) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1. (c) Kreiter, C. G.; Lehr, K.; Leyendecker, M.; Sheldrik, W. S.; Exner, R. *Chem. Ber.* **1991**, *124*, 3.

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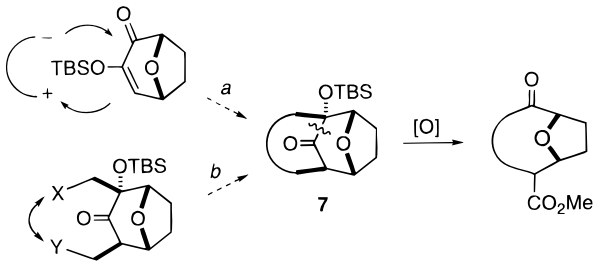
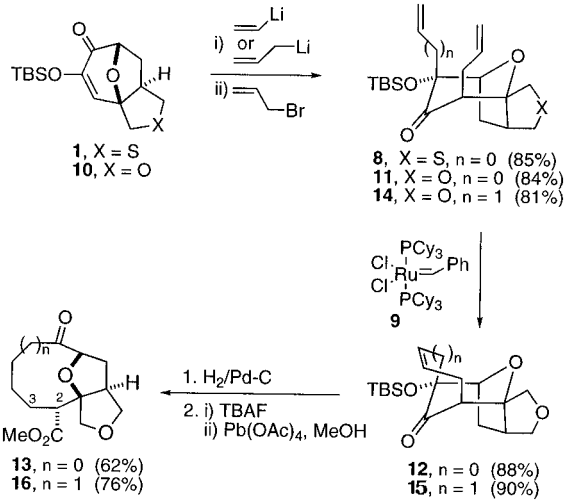
Scheme 3



Scheme 4



methods of assembly remain particularly scarce.[7c] As expected, addition of vinyllithium to adduct **1**, and alkylation of the resulting enolate with allyl bromide gave the expected α,α′-dialkylated ketone **8**. Since the conformational characteristics of the oxabicycle favors an axial disposition of alkyl substituents,[10] we predicted that this system would be particularly prone to the RCM.[11] However, attempts to induce the reaction using Grubbs ruthenium catalyst **9** failed, leading to recovery of the starting material. On the assumption that this failure could be due to poisoning of the catalyst by the sulfur atom,[12] and since removal of this atom with Raney Ni caused partial reduction of the alkenes, we decided to evaluate the reaction on the homologous adduct **11**.[13] Gratifyingly, refluxing **11** with the catalyst **9** (4 mol %) in CH_2Cl_2 gave the expected tetracycle **12** in 88% yield.

Preliminary experiments with **12** indicated that the oxidative ring-enlargement reaction was best executed after reducing the C−C double bond, and running separately the deprotection and the oxidation step. In any case, it required more severe conditions that those used previously for the fragmentation to tetrahydrofurans. Thus, after hydrogenation and desilylation of **12**, heating of a methanolic solution of the residue with 2 equiv of lead tetraacetate in a sealed tube (100 °C, 1 h) afforded the expected ring-enlarged product **13** as a single diastereoisomer.[14] The stereochemistry of C2 was established on the basis of NMR data at 500 MHz.[15]

To evaluate the power and versatility of this strategy we next targeted the homologous ten-membered carbocycle. This was specially appealing because the resultant 11-oxabicyclo[6.2.1] architecture is present in a large number of diterpenes of the eunicellin and cladiellane families.[16] This required just a slight change in the synthetic sequence, the use allyllithium instead vinyllithium in the addition reaction to **10**. Subsequent RCM of **14** gave tetracyclic product **15** in an excellent 90% yield. Hydrogenation and oxidative fragmentation of **15** gave the expected tricycle **16** in 76% yield.[17]

In summary, 3-(silyloxy)-8-oxabicyclo[3.2.1]oct-3-en-2-ones, which are easily assembled by thermal [5C + 2C] cycloaddition between β-(silyloxy)-γ-pyrones and tethered alkenes, can readily be transformed into stereochemically rich 2,5-*cis*-disubstituted tetrahydrofurans in a coupled, two-step process involving a stereoselective addition-alkylation sequence followed by oxidative C−C bond cleavage. Strategic inclusion of a RCM step prior to the oxidative step allowed extension of this synthetic protocol to the preparation of oxygen-bridged nine- and ten-membered carbocycles. Overall the strategies allowed for a rapid, atom economical increase in structural, functional and stereochemical complexity from simple commercially available compounds, and should prove versatile enough for introducing suitable modifications that might speed the access to natural products containing tetrahydrofurans and medium-sized carbocycles.

Acknowledgment. We are grateful to the Xunta de Galicia (XUGA 20901A94 and 20906B96) and the Spanish M.E.C. (SAF-95−0878) for financial support. A.R. thanks the Xunta de Galicia for a fellowship. We also thank Prof. M. Snapper for the generous gift of catalyst **9** and R. Gesto for running the NMR experiments.

Supporting Information Available: Experimental procedures, spectroscopic data (^{1}H, ^{13}C NMR, MS, HRMS, COSY, NOESY, and HMQC of selected products), and minimized conformation of **13** (9 pages).

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(8) For reviews on metathesis, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833.

(9) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall, 1991; Vol. 1, pp 290; Vol. 2, p 1058.

(10) This observation was confirmed by ^{1}H NMR NOE experiments.

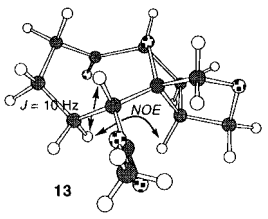
(11) It has been shown that ring-closing metathesis is accelerated if the substrate conformation constrains the olefins in close proximity. See ref 9 and: (a) Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Smith, D. W.; Schulz, G. R.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978. (b) Marsella, M. J.; Maynard, H. D.; Grubbs, R. G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1101.

(12) Shon, Y.-S.; Lee, T. R. *Tetrahedron Lett.* **1997**, *38*, 1997.

(13) The transformation of **10** to **11** was carried out using the same procedure as for the transformation of sulfide **1** to **8**. Compound **10** was obtained in 79% yield by keeping a toluene solution 2-[(allyloxy)methyl]-5-(*tert*-butyldimethylsilyl)-4-pyrone (see: Rumbo, A.; Castedo, L.; Mouriño, A.; Mascareñas, J. L. *J. Org. Chem.* **1996**, *61*, 6114) in a sealed tube at 180 °C for 12 h.

(14) There was NMR evidence for traces of the C2 epimer in the reaction residue, but it could not be isolated.

(15) Particularly enlightening were the ^{1}H NMR coupling pattern of H-2 and the presence of NOE between the axial H-3 and H-9. The NMR data were consistent with the lowest energy conformation obtained by molecular mechanics calculations; see the Supporting Information.



(16) (a) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall, 1991; Vol. 2, p 1005. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1996**, 106.

(17) The stereochemistry ascribed to the carbon α to the ester is in keeping with NMR data, particularly the ^{1}H NMR coupling pattern observed for H-2 (J = 12, 4 Hz), and with reasonable low energy conformations calculated for **16**. The conformation of the C2 epimer of **16** that would fit with the coupling pattern observed for H-2 is approximately 2 kcal/mol higher in energy than other minimal-energy conformers and cannot justify the ^{1}H NMR NOESY spectrum of the isolated compound.