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Radical-Initiated, Skeletal Rearrangements of Bicyclo[2.2.2] Lactones

István E. Markó,* Stuart L. Warriner,† and Benoît Augustyns

Université catholique de Louvain, Département de Chimie, Bâtiment Lavoisier, Place Louis Pasteur 1, B-1348 Louvain-la-Neuve, Belgium

marko@chor.ucl.ac.be

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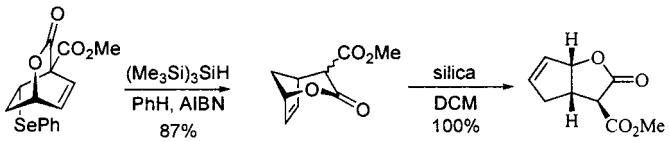
ABSTRACT



Treatment of bicyclic lactones derived from Diels–Alder reactions of 3-carbomethoxy-2-pyrone under radical conditions leads to a series of interesting skeletal rearrangements. The stereochemical and optical integrity of the starting material are maintained throughout the process.

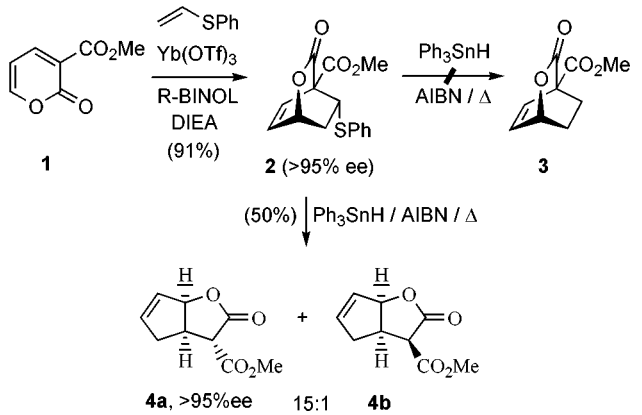
Inverse electron-demand Diels−Alder (IEDDA) reactions of 2-pyrones enable rapid access to a variety of bicyclic lactones which are valuable intermediates for natural product synthesis.[1] As part of our studies into asymmetric versions of these transformations,[2] we wished to explore new uses for the enantiomerically enriched lactones obtained from these cycloadditions.

Bicyclic sulfide (**2**) can be conveniently prepared with >95% ee and in excellent yield by the chiral lanthanide-catalyzed asymmetric IEDDA reaction between 3-carbomethoxy-2-pyrone (3-CMP) (**1**) and phenyl vinyl sulfide.[2a] We were intrigued by the possibility that the phenyl sulfide function in **2** could act as a radical precursor and generate the optically active bicyclic lactone (**3**), a useful synthetic intermediate inaccessible by the direct IEDDA cycloaddition of 3-CMP (Scheme 1).

However, in stark contrast to our expectation, treatment of **2** with triphenyltin hydride and AIBN in boiling toluene did not afford the expected compound (**3**) but generated instead the rearranged product (**4**) in 50% yield. Extensive spectroscopic investigations revealed this product to be the bicyclo[3.3.0] system (**4**) which was isolated as an inseparable 15:1 mixture of epimers (Scheme 1).

NOE experiments demonstrated that the methyl ester group of the major isomer (**4a**) was located on the *exo* face of the bicyclic system. Similarities with the spectra of the major isomer suggested that the minor component had the *endo*

Scheme 1



† Current address, School of Chemistry, University of Leeds, Leeds, U.K.

(1) For excellent reviews, see: (a) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111. (b) Woodward, B. T.; Posner, G. H. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press Inc., 1999; Vol. 5, p 47.

(2) (a) Markó, I. E.; Evans, G. R. *Tetrahedron Lett.* **1994**, *35*, 2771−2774. (b) Markó, I. E.; Evans, G. R. *Tetrahedron Lett.* **1994**, *35*, 2767−2770. (c) Markó, I. E.; Evans, G. R.; Declercq, J. P. *Tetrahedron* **1994**, *50*, 4557−4574. (d) Markó, I. E.; Evans, G. R.; Seres, P.; Chellé, I.; Janousek, Z. *Pure Appl. Chem.* **1996**, *68*, 113−122. (e) Markó, I. E.; Chellé-Regnaut, I.; Leroy, B.; Warriner, S. L. *Tetrahedron Lett.* **1997**, *38*, 4269−4272.

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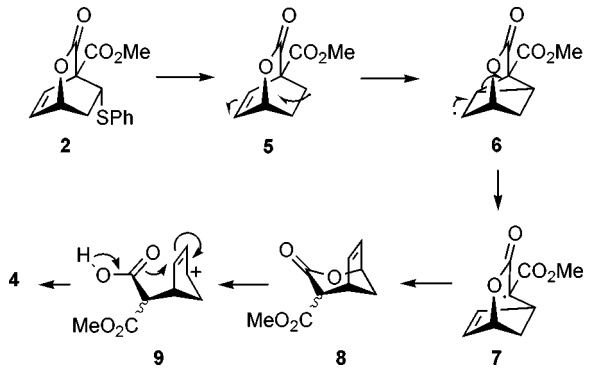
configuration of the methyl ester substituent. Interestingly, NMR experiments in the presence of the chiral shift reagent $Eu(hfc)_3$ also revealed that the optical purity of the starting material was maintained throughout the process.[3]

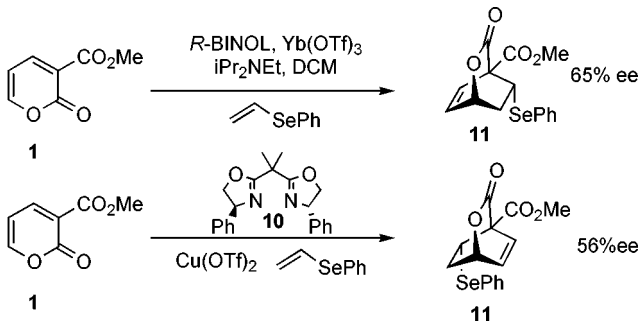
A plausible mechanism for the transformation of **2** into **4** is depicted in Scheme 2. Upon reaction of **2** with Ph_3SnH/AIBN, the radical **5** is generated which undergoes intramolecular capture by the proximal C−C double bond, generating the cyclopropylmethyl radical (**6**). Rapid ring opening of **6**, in the alternative direction, then leads to the stabilized radical (**7**) which is intercepted by Ph_3SnH, leading to a putative primary adduct (**8**). A subsequent [1,3]-shift of the carboxy function, probably mediated by some tin salts, results ultimately in the isolated, fused bicyclic lactones **4a**:**4b**. Similar [1,3] shifts have previously been noted in bicyclo-[2.2.1] systems.[4]

Scheme 2



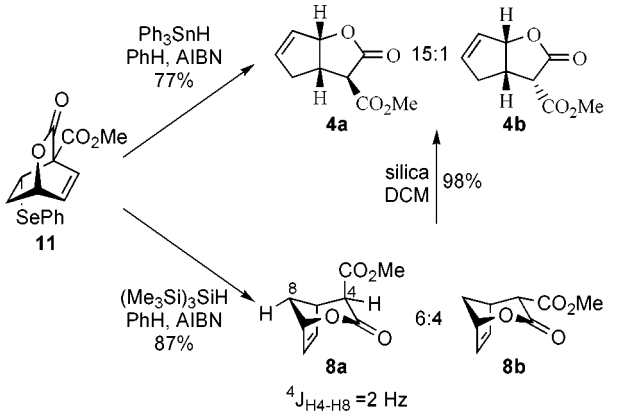
However, sulfide **2** proved unreactive toward other radical sources such as tris-trimethylsilylsilane (TTMSS) and it was decided to replace the SPh substituent with the SePh group in order to improve the initiation step of the rearrangement. Reaction of 3-CMP (**1**) with phenylvinyl selenide in the presence of $Yb(OTf)_3$, *R*-binaphthol, and Hünigs base gave the desired selenium substituted lactone (**11**) with an ee of 65% (Scheme 3). The diphenylbisoxazoline ligand (**10**)/copper (II) triflate combination proved to be an excellent catalyst for this cycloaddition, affording **11** in 90% isolated yield (56% ee) with catalyst loading as low as 3%.[5] Interestingly, product **11**, obtained by the copper-catalyzed IEDDA reaction possesses the opposite absolute configuration to the same adduct (**11**) prepared by the chiral lanthanide route. The ease of this transformation made it the method of choice for the preparation of **11**.

Scheme 3



Selenide **11** underwent initiation far more easily under radical conditions. Slow addition (over 1.5 h) of triphenyl tin hydride and AIBN to a boiling solution of **11** in benzene gave the rearranged product (**4**) in a pleasing 77% yield. Direct analysis of the crude mixture revealed that **4** had already been formed during the reaction and is not an artifact of the purification procedure (Scheme 4).

Scheme 4



To remove the requirement for slow addition of the hydride reagent, the triphenyltin hydride was replaced with tris-trimethylsilylsilane (TTMSS) which reacts more slowly with radicals.[5] Under these conditions, all the reducing agent could be added at the beginning of the reaction and the starting material was consumed in only 30 min. Furthermore, we were delighted to discover that TTMSS did not promote the allylic rearrangement into **4** and, for the first time, it was possible to isolate the putative intermediate bicycle (**8**) as a 6:4 mixture of isomers. We postulate that the shorter reaction time, combined with the lower Lewis acidity of the silane, prevents rearrangement of **8** into **4**. The configuration of the major isomer (**8a**) was based on the observation of a long range "w"-coupling between proton H-4 and H-8 in the NMR spectrum of this compound. Treatment of **8** with silica for 4 h quantitatively gave **4**, supporting our hypothesis that the second rearrangement is an acid-catalyzed process. Unsurprisingly, the exocyclic ester substituent rapidly epimerizes under silica gel treatment, affording an identical 15:1 ratio of **4a** and **4b**, demonstrating that the configuration observed in both **8** and **4** is under thermodynamic control.

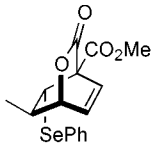
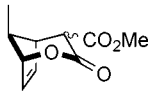
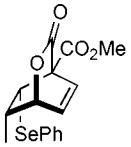
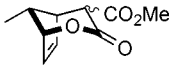
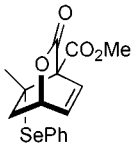
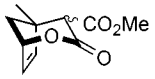
(3) Treatment of small quantity of racemic **2** under the radical conditions provided a reference sample of racemic **4** for validation of the chiral assay. Markó, I. E.; Evans, G. R. *Synlett* **1994**, 431−433.

(4) Kobayashi, T.; Ono, K.; Kato, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 61−65.

(5) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649 and references therein.

To widen the scope of this novel rearrangement, a series of bicyclic selenolactones (**11**), bearing a methyl substituent at various positions, were prepared by the IEDDA cycloaddition of 3-CMP with the corresponding vinyl selenides and submitted to the TTMSS-mediated radical rearrangement (Table 1).

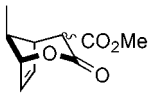
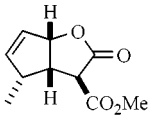
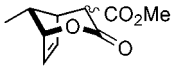
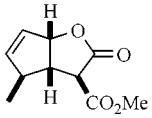
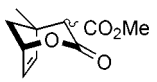
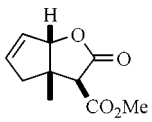
Table 1. TTMSS-Mediated Rearrangements of Lactones **11**

1	 **11a**	 **12a**	88%
2	 **11b**	 **12b**	89%
3	 **11c**	 **12c**	98%

[a] All yields are for pure isolated products (dr's ~2:1).

In all cases, the bridged lactones **12** were obtained in excellent yields and with complete control of the stereochemistry of the methyl substituent. It is noteworthy that the fused lactones could never be detected in these radical reactions.

Table 2. Acid-Catalyzed Rearrangements of Lactones **12**

1	 **12a**	 **4a**	80%[b]
2	 **12b**	 **4b**	79%[b]
3	 **12c**	 **4c**	90%[c]

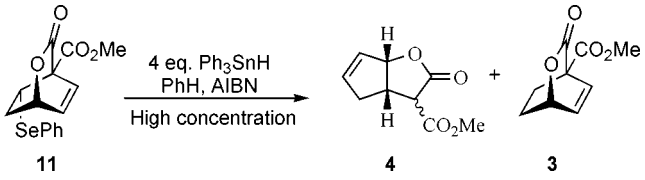
[a] All yields are for pure isolated products (dr's >15:1). [b] Full conversion was attained after 12 h stirring with silica. [c] 12 mol % PTSA was used in this case (13 h).

The subsequent, acid-catalyzed transformation of these bridged lactones into the corresponding [3.3.0] systems was then investigated (Table 2).

While lactones **12a** and **12b** rearranged smoothly upon stirring with silica gel, the time required for their transformation was considerably longer than for the unsubstituted analogue (**8**). Surprisingly, the α-methyl bicycle **12c** proved to be inert under silica gel treatment and recourse to a catalytic amount of a stronger acid (PTSA) proved to be mandatory. Under these conditions, good yields of the desired fused lactones **4c** were obtained. Again, in all cases, complete stereocontrol of the methyl substituent could be achieved.

Finally, we also undertook experiments to estimate the rate constant for the transannular cyclization process. Reaction of **11** with an excess of triphenyltin hydride at higher concentrations gave a mixture of **4** and reduced product **3** (Scheme 5). Using the rate constant for triphenyltin hydride defined by Newcomb,[6] the ratio of products obtained suggests a rate constant for the trans annular cyclization of ca. 1×10^6 s^{-1} at 80 °C. This is 10−100 times slower than that observed in bicyclo[2.2.1] systems.[7]

Scheme 5



In summary, we have developed a novel and high-yielding radical rearrangement of readily available bicyclo[2.2.2] lactones. The methodology possesses a number of important features, the most noteworthy one being the complete transfer of both the relative and absolute stereochemistry of the chiral centers present in the initial IEDDA adducts. Depending upon the conditions employed, the rearrangement yields bicyclo-[3.2.1] or bicyclo[3.3.0] products which have significant potential as building blocks for the synthesis of a variety of natural products.

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Supporting Information Available: Full experimental details and characterization for compounds **8**, **4**, **11**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151−1176.
(7) Wong, P. C.; Griller, D. *J. Org. Chem.* **1981**, *46*, 2327−2329.