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Skeletal rearrangements of bicyclo[2.2.2]lactones: a short and efficient route towards Corey's lactone

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Abstract—The application of a unique tandem radical-initiated, Brönsted acid-catalysed, skeletal rearrangement of bicyclo[2.2.2]-lactones provides a novel route towards Corey's lactone **2**. The strategy also features a high-pressure promoted inverse electron-demand Diels–Alder (IEDDA) reaction of 3-carbomethoxy-2-pyrone (3-CMP), which proceeds with complete regio- and diastereocontrol.

The prostaglandins (represented by $PGF_{2\alpha}$ **1**) belong to a class of natural products that has been extensively studied.[1] Indeed, few other families of compounds have generated such a wealth of elegant research and creativity, culminating in a plethora of total syntheses and formal approaches.[2] Among these, the strategy developed by Corey in the late 1960's remains a milestone in synthetic organic chemistry, both for its conciseness and its versatility.[3] Particularly appealing is the possibility of generating the entire prostaglandin family from a single, common precursor, which conceals all the required functionalities within a bicyclo[3.3.0]lactone moiety. Such a versatile compound is suitably referred to as 'Corey's Lactone' **2** (Fig. 1).[4]

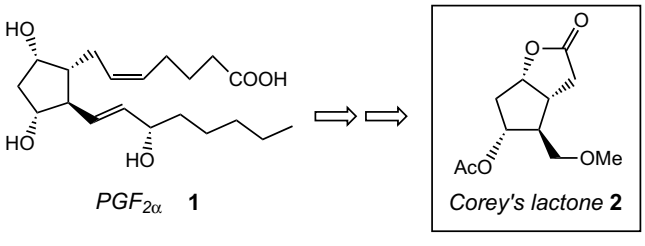
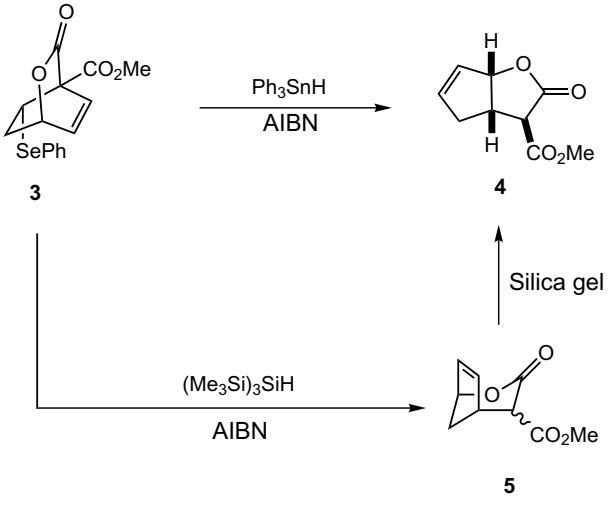


Figure 1. Corey's retrosynthetic analysis.

Recently, we have described a novel tandem radical-initiated, Brönsted acid-catalysed, skeletal translocation of bicyclo[2.2.2]lactones (Scheme 1).[5] This rearrangement proceeds with complete transfer of relative and absolute stereochemistry and, depending upon the conditions employed, yields either the isomeric bicyclo[3.2.1]- or the bicyclo[3.3.0]lactones, respectively. Thus, treatment of the IEDDA adduct **3** with Ph_3SnH, under standard radical conditions, affords the rearranged bicyclo[3.3.0]-lactone **4** whereas reaction of **3** in the presence of tris(trimethylsilyl)silane generates the unprecedented,



Scheme 1. Skeletal rearrangements of bicyclo[2.2.2]lactones.

Keywords: Lactones; Bicyclic; Radical; Rearrangement; Corey's lactone; 3-CMP; Diels–Alder.
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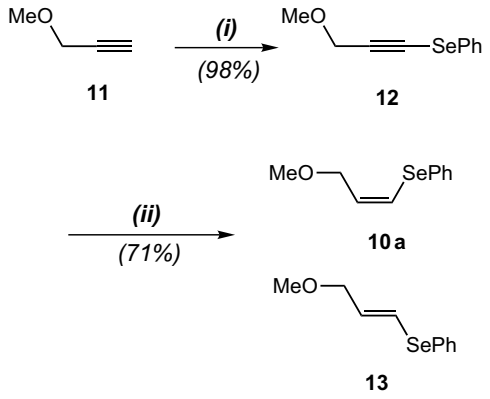
bridged lactone **5**, which could be smoothly converted to the aforementioned isomer **4** by simple stirring with silica gel in dichloromethane.[5]

We were intrigued by the possibility of preparing Corey's lactone **2** via the rearrangement of a suitable bicyclo[2.2.2]lactone precursor. In this communication, we wish to report our results on the successful implementation of this methodology and its application to a short and efficient assembly of racemic **2**. Our proposed antithetic analysis is presented in Scheme 2. The fused lactone **6** was selected as an advanced precursor, easily convertible into Corey's intermediate **2**.[6] Applying our rearrangement protocol in a retrosynthetic sense leads, via the bicyclic lactone **7**, to the Diels–Alder adduct **8a**. Compound **8a** would, in turn, derive from 3-carbomethoxy-2-pyrone **9** (3-CMP) and vinylselenide **10a** by an inverse electron-demand [4+2] cycloaddition reaction (vide infra). In this novel approach, the requisite stereochemical relationships will be implemented at an early stage (cycloaddition step) and will be preserved throughout the subsequent stereospecific operations.

This convergent approach requires the preparation of vinylselenide **10a**, 3-CMP **9** being nowadays commercially available. It was anticipated that **10a** could be readily accessed by a host of different routes. In practice, however, the path presented in Scheme 3 proved to be the most successful one.

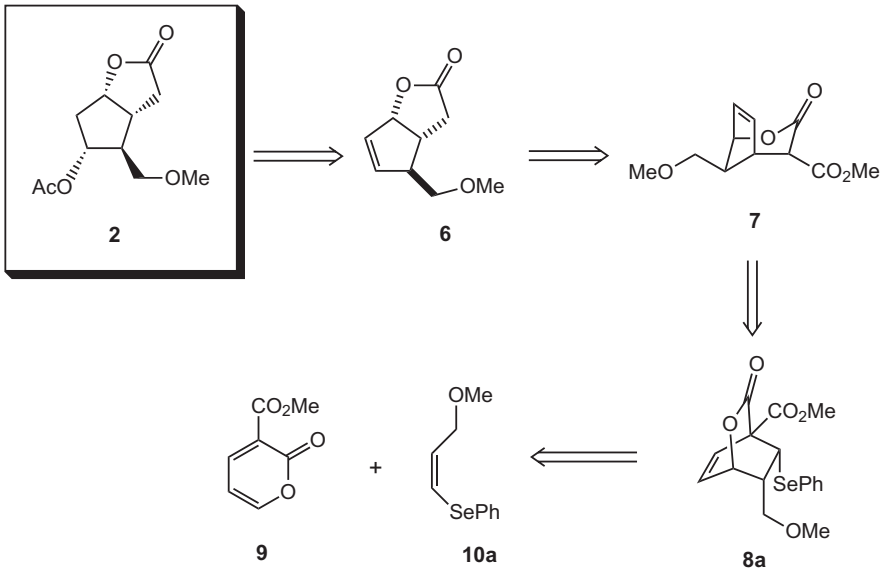
Commercially available methylpropargyl ether **11** was treated with *n*-butyllithium, in THF, at −78 °C. The resulting anion was then slowly added to 1.1 equiv of freshly prepared PhSeBr or PhSeCl, affording selenoalkyne **12** in 98% isolated yield. The success of this reaction appears to be highly dependent upon both the rate of addition and the source of electrophilic selenium. Indeed, the use of diphenyldiselenide and/or prolonged addition times led to the formation of several unidentified by-products.



Scheme 3. Preparation of vinyl selenide **10a**. Reagents and conditions: (i) *n*-BuLi, THF, −78 °C then PhSeBr or PhSeCl, −78 °C to rt; (ii) $Cp_2Zr(H)Cl$, THF, rt then NH_4Cl (aq).

Partial reduction of the C≡C of **12** proved to be a challenge in its own right. Initial attempts at hydrogenation under conventional Lindlar conditions (Pd/C, $BaSO_4$, quinoline)[7] or using palladium on charcoal resulted in recovery of the starting material, most likely due to irreversible poisoning of the catalyst by the selenium atom. Although effective for similar substrates, DiBAL-H resulted mainly in cleavage of the carbon–selenium bond, affording mostly alkyne **11**.[8] The use of diimide (HN=NH) as the reducing agent delivered for the first time alkene **10a**.[9] Unfortunately, this procedure was plagued by the formation of considerable amounts of over-reduced material.

Inspired by a recent report describing the successful hydrozirconation of related chalcogenides,[10] alkyne **12** was treated with Schwartz's reagent, $Cp_2Zr(H)Cl$, followed by an aqueous quench. Gratifyingly, the *cis*-alkene **10a** was obtained in pure form (71% yield). It is noteworthy that olefin **10a** is prone to light-induced isomerisation, eventually providing a 1:1 mixture of



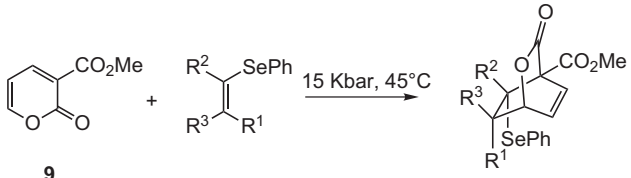
Scheme 2. Antithetic analysis of Corey's lactone **2**.

the *E*/*Z* isomers **13** and **10a** after extended periods of time.[11] Therefore, the hydrozirconation protocol was best performed in the dark and alkene **10a** directly engaged in the subsequent step.

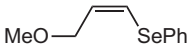
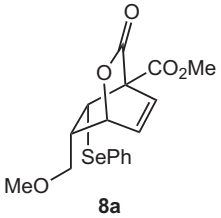
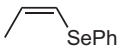
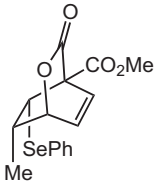
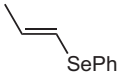
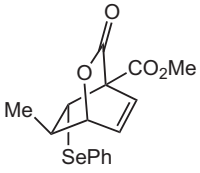
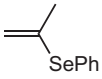
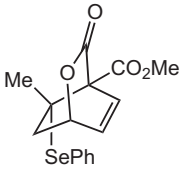
With a ready access to the desired dienophile **10a** finally secured, we next turned our attention to the assembly of the key intermediate: bicyclo[2.2.2]lactone **8a**, by employing an inverse electron-demand Diels–Alder (IEDDA) cycloaddition with 3-CMP.[12] It was anticipated that the presence of a selenium atom on the dienophile would considerably hamper the reaction, mainly due to the weaker electron-donating ability of selenium, as compared to sulfur- and oxygen-containing analogues.[13] To our delight, reaction of 3-CMP **9** with **10a**, at 15 kbar and 45 °C, for 3 days, provided the desired IEDDA-adduct **8a**, in quantitative yield. Only the *endo*-isomer, possessing the correct regiochemistry, was produced under these conditions (Table 1, entry 1). Other selenium-containing dienophiles could also be added to 3-CMP **9** in good to excellent yields (Table 1), testifying to the substrate generality and efficiency of these high-pressure conditions.

With large quantities of the suitably functionalised cycloadduct **8a** in hand, the stage was now set for the application of our tandem radical rearrangement/acid-catalysed translocation methodology. In the event (Scheme 4), sequential treatment of bicyclo[2.2.2]lactone **8a** with tris(trimethylsilyl)silane (TTMSS) and AIBN, in boiling benzene, generated quantitatively the bridged lactone **7**, which upon stirring overnight with silica gel

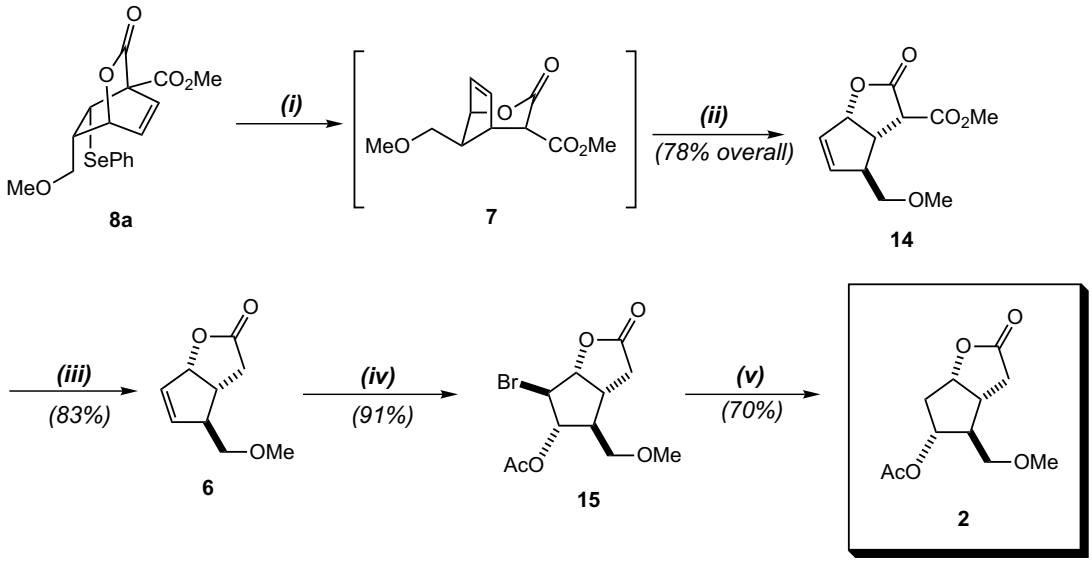
Table 1. High-pressure cycloadditions of 3-CMP **9**



9 **10a-d** **8a-d**

Entry	Dienophile	Adduct	Yield[a] (%)
1	 **10a**	 **8a**	94
2	 **10b**	 **8b**	60
3	 **10c**	 **8c**	60
4	 **10d**	 **8d**	80

[a] All yields are for pure, isolated products.



Scheme 4. Tandem rearrangement/translocation of **8** and completion of the synthesis. Reagents and conditions: (i) $(Me_3Si)_3SiH$, AIBN, benzene, reflux; (ii) silica gel, CH_2Cl_2, rt; (iii) LiCl, DMSO/H_2O, 110 °C; (iv) (a) NBA, acetone/H_2O, rt; (b) AcCl, py, CH_2Cl_2, 0 °C to rt; (v) Bu_3SnH, AIBN, benzene, reflux.

in dichloromethane, smoothly afforded the fused adduct **14**. This cascade of rearrangements took place in an impressive 78% overall yield, providing the advanced intermediate **14** in diastereomerically pure form. The striking simplicity of this protocol, as opposed to the remarkable structural changes it imposes on the starting cycloadduct, bodes well for future applications to more heavily functionalised substrates.

At this juncture, removal of the excedentary methyl ester appendage of **14** could be achieved in a straightforward manner by using the decarboxylation protocol developed by Krapcho and subsequently modified by Anderson and Villhauer.[14] Accordingly (Scheme 4), heating lactone **14** with LiCl in wet DMSO provided, in 83% yield, the decarbomethoxylated intermediate **6**. This intermediate could be readily converted to Corey's lactone **2** by a simple three-step procedure involving bromohydrin formation, acetylation and reductive cleavage of the bromine atom to afford, in 56% overall yield (three steps), the desired prostaglandin precursor **2**.

In summary, we have shown that the tandem radical-initiated, acid-catalysed skeletal rearrangement of bicyclo[2.2.2]lactones provides an efficient access to Corey's lactone **2** and its derivatives. Using this methodology, the highly functionalised intermediate **6** was assembled in only five steps and in 25% overall yield, from commercially available products. Moreover, the entire sequence proceeds with complete diastereocontrol and further exemplifies the usefulness of high-pressure conditions in promoting resilient IEDDA cycloadditions. Current efforts are now directed towards the establishment of an enantioselective version of this synthetic route and towards broadening the scope and applications of this novel tandem rearrangement/translocation methodology. The results of these investigations will be reported in due course.

Acknowledgements

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11. For a similar case, see: Fryzuk, M. D.; Bates, G. S.; Stone, C. *J. Org. Chem.* **1991**, *56*, 7201.
12. (a) See, for example: Markó, I. E.; Evans, G. R. *Tetrahedron Lett.* **1993**, *34*, 7309; (b) Markó, I. E.; Evans, G. R. *Synlett* **1994**, *6*, 431; (c) Markó, I. E.; Evans, G. R.; Seres, P.; Chellé-Regnault, I.; Leroy, B.; Warriner, S. L. *Tetrahedron Lett.* **1997**, *38*, 4269; (d) Markó, I. E.; Evans, G. R.; Declercq, J.-P. *Tetrahedron* **1994**, *50*, 4557; For other leading references in this field, see, for example: (e) Posner, G. H.; Johnson, N. *J. Org. Chem.* **1994**, *59*, 7855; For a review on Diels–Alder cycloadditions of 2-pyrones, see: (f) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111.
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