Tandem radical rearrangement/Pd-catalysed translocation of bicyclo[2.2.2]lactones. An efficient access to the oxa-triquinane core structure†

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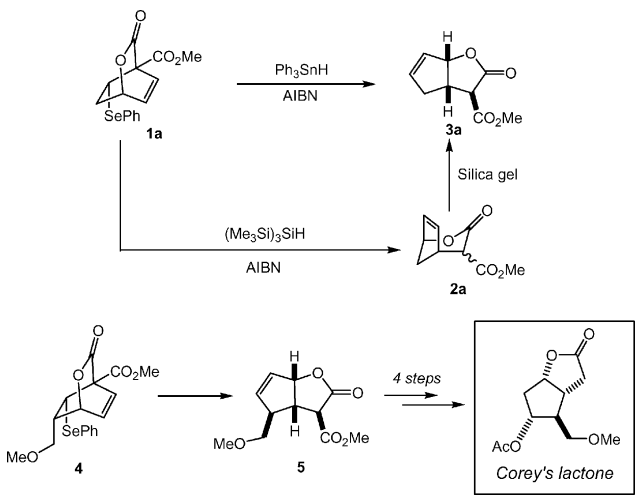
Received 21st December 2005, Accepted 26th February 2006
First published as an Advance Article on the web 8th March 2006
DOI: 10.1039/b518121f

The skeletal rearrangement of bicyclo[2.2.2]lactones, involving a mild and chemoselective palladium-catalysed translocation key-step, provides an efficient and diastereoselective access to synthetically useful bicyclo[3.3.0]lactones.

The advent of transition metal-mediated transformations considerably enhanced the ability of synthetic chemists to assemble complex molecular structures. In particular, the generalised use of palladium complexes as mediators or catalysts for carbon–carbon and carbon–heteroatom bond forming reactions has clearly revolutionised the field of organic chemistry.[1] Most importantly, these palladium-based transformations often occur with high levels of selectivity and under exceptionally mild conditions.

We have recently reported a novel tandem radical-initiated Brønsted-acid catalysed skeletal rearrangement of bicyclo[2.2.2]-lactones **1a** (Scheme 1).[2] This rearrangement proceeds with complete transfer of relative and absolute stereochemistry and yields, depending upon the conditions employed, either the bicyclo[3.2.1]-lactone **2a** or its isomer **3a**. The synthetic usefulness of this sequence was demonstrated by the ready conversion of derivative **4** into Corey's lactone (Scheme 1).[3]



Scheme 1 Previously reported skeletal rearrangement and application to a short synthesis of Corey's lactone.

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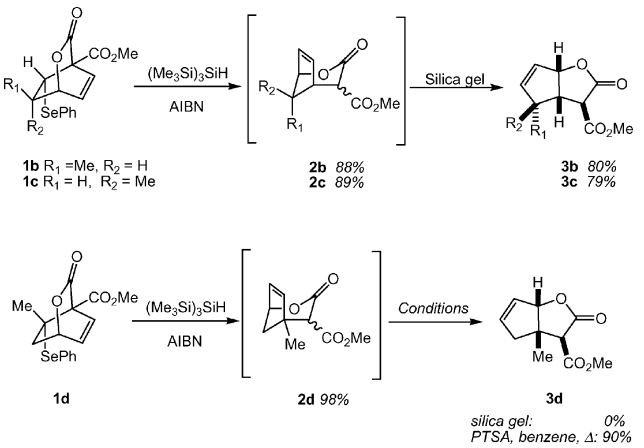
† Electronic supplementary information (ESI) available: Instrumentation and procedures. See DOI: 10.1039/b518121f

Whilst seeking to extend the scope of this methodology, we became aware of a potential limitation in our two-step protocol (Scheme 2). Indeed, whereas skeletal rearrangement of lactones **1b** and **1c** took place smoothly under the "standard" conditions (TTMSS–AIBN in boiling benzene, followed by stirring with silica gel in dichloromethane), the translocation of bridged bicyclo[3.2.1]lactone **2d** (formed by radical rearrangement of α-substituted selenide **1d**) to its fused counterpart **3d**, required more vigorous conditions (PTSA, refluxing benzene).[2a] It appears that the strain induced by the additional bridgehead substituent considerably raised the energetic barrier for the acid-catalysed reorganisation of the allylic lactone moiety in **2d**.

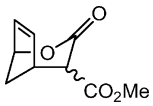
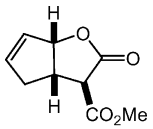
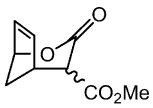
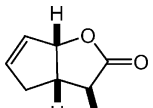
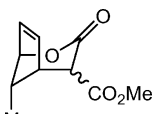
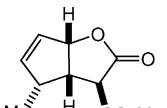
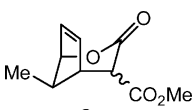
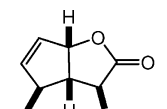
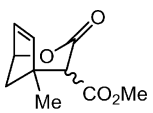
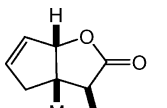


Scheme 2 Skeletal rearrangement of substituted bicyclo[2.2.2]lactones.

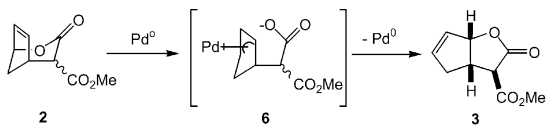
Recognising that the compatibility of these strongly acidic conditions with potentially sensitive functional groups, present in more elaborated substrates, would significantly impair the scope of our methodology, we became interested in the possibility of effecting this crucial cationic rearrangement under neutral conditions. The palladium-catalysed allylic alkylation reaction (also known as the Tsuji–Trost reaction) has received considerable attention and ranks amongst the most reliable transition metal-mediated carbon–carbon bond forming reactions.[4] Since allylic lactones react with Pd(0) complexes,[5] we envisioned that the treatment of **2** with a suitable palladium(0) catalyst could lead to the π-allyl complex **6**, which could be driven to cyclise to the thermodynamically more stable fused lactone **3**, under neutral conditions (Scheme 3).

Our preliminary experiment involved the addition of 10 mol% palladium(II) acetate and triphenylphosphine to a THF solution of racemic, bridged bicyclo[3.2.1]lactone **2a** (Table 1, Entry 1). Pleasingly, smooth isomerisation of **2a** ensued and fused lactone **3a**

Table 1 Pd-catalysed translocation of lactones **2**[a]

Entry	Substrate	Product	Catalyst	Yield (%)
1	 **2a**	 **3a**	$Pd(OAc)_2$–PPh_3	90
2	 **2a**	 **3a**	$Pd(PPh_3)_4$	90
3	 **2b**	 **3b**	$Pd(PPh_3)_4$	92
4	 **2c**	 **3c**	$Pd(PPh_3)_4$	91
5	 **2d**	 **3d**	$Pd(PPh_3)_4$	90

[a] All reactions performed in THF from 0 °C to rt. For the synthesis of lactones **2**, see ref. 6.

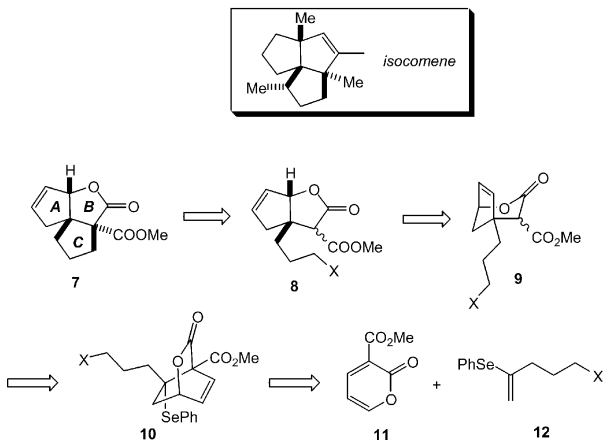


Scheme 3 Proposed palladium-catalysed translocation of bicyclo[3.2.1]-lactones.

was isolated in high yield. In order to rule out a possible mediation by traces of acetic acid formed *in situ*, this experiment was repeated using palladium *tetrakis*(triphenylphospine). A similar result was obtained, clearly establishing the viability of the allylic rearrangement under non-acidic conditions (Table 1, Entry 2).

These conditions were then applied to the rearrangement of a selection of other bridged bicyclic lactones (Table 1). Thus, bicyclo[3.2.1]lactones **2b** and **2c**[6] smoothly reacted in the presence of the palladium catalyst affording the desired, fused lactones **3b** and **3c** in 92 and 91% yields, respectively. The crucial test came with the more resilient bicyclo[3.2.1]lactone **2d**[6] (Table 1, Entry 5). In the event, this bridged lactone also underwent clean rearrangement into its fused isomer **3d**.

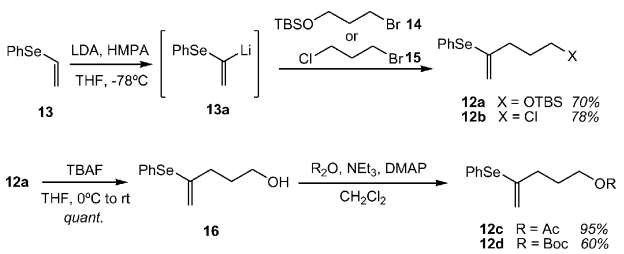
Having established that these neutral conditions were broadly applicable, we next sought to apply this novel radical-mediated/palladium-catalysed skeletal rearrangement sequence to a short synthesis of the angular triquinane core structure, in racemic form. Triquinanes are a well-known family of biologically relevant, naturally occurring substances, and numerous approaches towards their synthesis have been described.[7] Angular triquinanes typically possess an intricate tricyclic structure, featuring two to three all-carbon quaternary centres, as in the case of isocomene (Scheme 4).



Scheme 4 Antithetic analysis of angular oxa-triquinane core structure **7**.

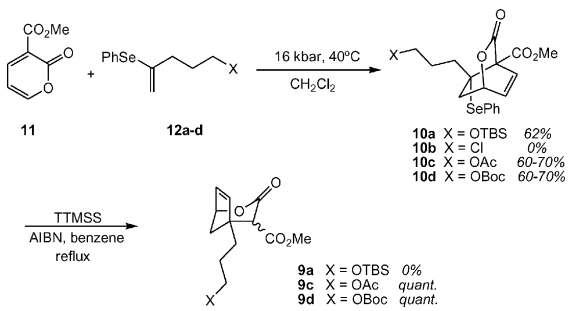
Our proposed retrosynthetic analysis of the angular oxatriquinane core **7** is depicted in Scheme 4. Intramolecular alkylation of α-carbomethoxylactone derivative **8** (X = leaving group) should lead to the desired tricyclic system **7** by generating ring *C*. Application of the Pd-catalysed retron to **8** reveals lactone **9** as the bridged intermediate. Retro-radical rearrangement ultimately produces bicyclic lactone **10**. Finally, straightforward IEDDA (Inverse Electron-Demand Diels–Alder) disconnection of bicyclo[2.2.2]lactone **10** reveals 3-carbomethoxy-2-pyrone (3-CMP) **11** and the α-substituted vinyl selenide **12**, bearing on the terminal carbon, either a protected alcohol or a suitable leaving group.

The synthesis of **7** begins with the preparation of suitably functionalised dienophiles **12a**–**d** (Scheme 5). Lithiation of readily available vinylphenyl selenide **13** by LDA,[8] followed by reaction of the *in situ* generated alkenyllithium species **13a** with TBS-protected 3-bromopropanol **14**, afforded selenide **12a** in 70% yield. Analogously, alkylation of **13a** with 3-chloro-1-bromo-propane **15** provided the corresponding dienophile **12b** in similar yields. Fluoride-induced deprotection of the TBS ether in **12a**, followed by acylation of the alcohol function under standard conditions, then provided the Ac- or Boc-protected dienophiles **12c** and **d** in high overall yields.



Scheme 5 Synthesis of dienophiles **12a**–**d**.

These four diversely decorated dienophiles were then submitted to the IEDDA reaction with 3-CMP **11**, under our typical high-pressure conditions (CH_2Cl_2 as solvent, 16 kbar, 40 °C, 3 d).[3,9] The results are depicted in Scheme 6.

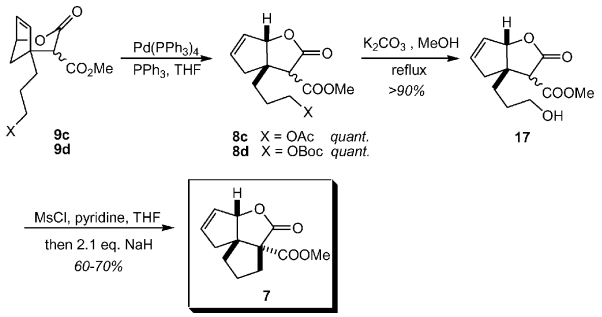


Scheme 6 IEDDA reaction and radical-initiated rearrangement.

Whilst the ω-chloro selenide **12b** afforded only a complex mixture of products, from which no lactone **10b** could be isolated, all the hydroxy-protected dienophiles underwent smoothly the IEDDA cycloaddition with 3-CMP **11**, providing the bicyclo[2.2.2]lactones **10a**, **10c** and **10d** in good yields. Interestingly, adduct **10a** was obtained as a 10 : 1 *endo–exo* (relative to the selenide substituent) mixture of bicyclic lactones, as opposed to the exclusive *endo*-selectivity in the case of the acetate- and Boc-protected derivatives **10c** and **10d**. The generation of a mixture of epimers is, however, inconsequential as this stereogenic centre will be destroyed upon the subsequent radical-initiated rearrangement.

These bicyclo[2.2.2]lactones were then subjected to the action of TTMSS and AIBN, in boiling benzene (Scheme 6). Gratifyingly, lactones **10c** and **10d** underwent clean skeletal reorganisation, affording adducts **9c** and **9d** in quantitative yields, following purification. Much to our surprise, the TBS-protected derivative **10a** failed to provide the desired, bridged lactone **9a**. Although complete consumption of the starting material **10a** was observed by TLC, only a complex mixture of products was obtained.[10]

The stage was now set for the application of our palladium-catalysed allylic translocation on these functionalised substrates (Scheme 7). In the event, the conversion of lactones **9c** and **9d** to their fused bicyclo[3.3.0] counterparts **8c** and **8d** smoothly took place under our newly-developed conditions, providing the desired adducts in essentially quantitative yields. It thus transpires that this neutral palladium-catalysed rearrangement protocol is a mild, highly chemoselective and reliable alternative to our previously reported acid–based procedure.



Scheme 7 Palladium-catalysed allylic rearrangement and completion of the synthesis of **7**.

To complete our preparation of **7**, all that remained was a deprotection step, followed by the conversion of the hydroxyl function into a suitable leaving group and intramolecular cyclisation to deliver ring C.

This sequence of events could be attained in only two synthetic operations (Scheme 7). Thus, chemoselective deprotection of **8c** and **8d**, using potassium carbonate in refluxing methanol, led to the same alcohol **17**. Mesylation of this compound, followed by addition of NaH to the reaction mixture, finally afforded the desired tricyclic compound **7**, possessing the oxatriquinane core structure and featuring two contiguous quaternary centres built with complete diastereocontrol.

In summary, a novel tandem sequence, featuring a radical rearrangement–palladium-catalysed translocation of bicyclo[2.2.2]lactones, provides an efficient and versatile access to a variety of fused, bicyclo[3.3.0]lactones. The scope of this procedure has been evaluated and its synthetic utility demonstrated by the expeditious assembly of the tricyclic lactone **7**, bearing the angular triquinane core structure, in a small number of steps and good overall yields. Current efforts are now directed towards expanding the scope of this unique methodology and applying it to the synthesis of triquinanes, as well as other relevant natural products. The results of these investigations will be reported in due course.

Acknowledgements

Financial support for this work by the Université catholique de Louvain, the National Science Council of Taiwan (post-doctoral fellowship to J.-H.L.), the Fonds pour la Recherche dans l'Industrie et l'Agriculture (F.R.I.A., studentship to N.M.), Merck, Sharp and Dohme (Merck Academic Development Award to I.E.M.) and SHIMADZU Benelux (financial support for the acquisition of a FTIR-8400S spectrometer) is gratefully acknowledged. N.M. is grateful to the Fond National de la Recherche Scientifique (F.N.R.S.) for receiving an "Aspirant F.N.R.S." fellowship.

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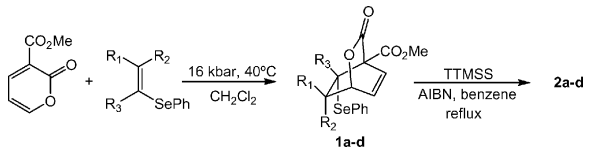
2 (*a*) I. E. Markó, S. L. Warriner and B. Augustyns, *Org. Lett.*, 2000, **2**, 3123. For a conceptually similar strategy employed in the construction of azabicyclic compounds, see: (*b*) D. M. Hodgson, S. Hachisu and M. D. Andrews, *Org. Lett.*, 2005, **7**, 815 and references therein.

3 B. Augustyns, N. Maulide and I. E. Markó, *Tetrahedron Lett.*, 2005, **46**, 3895.

4 For early reviews on the Tsuji–Trost reaction, see: (*a*) B. M. Trost, *Acc. Chem. Res.*, 1980, **13**, 385; (*b*) J. Tsuji, *Tetrahedron*, 1986, **42**, 4361. For recent reviews on the asymmetric allylic alkylation reaction, see: (*c*) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921; (*d*) B. M. Trost, *J. Org. Chem.*, 2004, **69**, 5813. See also ref. 1*e*.

5 For examples, see: (*a*) H. F. Olivo and J. Yu, *Tetrahedron: Asymmetry*, 1997, **8**, 3785; (*b*) S. Maki, K. Toyoda, T. Mori, S. Kosemura and S. Yamamura, *Tetrahedron Lett.*, 1994, **35**, 4817; (*c*) E. J. Bergner and G. Helmchen, *J. Org. Chem.*, 2000, **65**, 5072.

6 Prepared in racemic form from the Inverse Electron-Demand Diels–Alder (IEDDA) adducts **1a**–**d** by radical rearrangement, as shown below. Products **1a**–**d** can be obtained in enantioenriched form by using chiral Lewis acid catalysts. See ref 2*a*.



7 For a review on the synthesis of poliquinane natural products, see: (*a*) G. Mehta and A. Srikrishna, *Chem. Rev.*, 1997, **97**, 671. For a recent example of the synthesis of dioxatriquinanes, see: (*b*) K. P. Kaliappan and R. S. Nandurdikar, *Chem. Commun.*, 2004, **21**, 2506.

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10 At this stage it is not clear whether the silyl substituent acts as a radical quencher by favoring intramolecular radical translocation.