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An expeditious construction of 9-membered rings †

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Abstract

9-Membered rings are readily constructed through a radical addition–cyclisation sequence on a 1,6-dien-3-ol system followed by a Grob-type fragmentation.

With a few notable exceptions (e.g. the rapidly emerging metathesis reaction[1a]), cyclisation processes generally fail when applied to the construction of medium-sized rings.[1b] Indirect routes such as ionic and radical based ring expansions and fragmentations are, thus, often needed to access such structures.[2] The base induced Grob fragmentation occupies, in this respect, a prominent position having been used in several historical total syntheses.[3] Its importance has not diminished with time, as shown by its very recent application by Paquette and his co-workers in an approach to jatrophatrione, a 9-membered ring containing triterpene.[4] The main limitation of the Grob fragmentation is the difficulty in building the appropriate precursor: several steps are often required, causing a sharp decline in the overall efficiency of the synthetic scheme.[5] As part of our work on the chemistry of xanthates,[6] we now wish to report a simple solution to this problem.

Our approach relies on the use of an inter- and an intramolecular radical addition sequence to put together in essentially one step all the elements necessary for a Grob fragmentation. The principle, outlined in Scheme 1, is straightforward. Thus, a dienol of general structure **1** should undergo an intermolecular addition at the least hindered olefin by a radical derived from a xanthate **2**, followed by a fast 5-*exo* ring closure and transfer of a xanthate group to give finally bicyclic product **3**.[6] If the xanthate in **3** is cleaved into the corresponding thiol **4** which is then converted into a sulfonium leaving group by the action of 1,4-dibromobutane for example, then a Grob-type fragmentation should ensue, leading to the expanded monocyclic structure **6**.

This conception was readily reduced to practice, as shown by the examples displayed in Scheme 2. Ultrasound assisted addition of 3-butenyllithium to 4,4-dimethyl-2-cyclohexenone under Barbier-type conditions gave the requisite dienol **1a** in 64% yield. Lauroyl peroxide induced radical addition of

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† Dedicated with respect to the memory of Paul Dowd.

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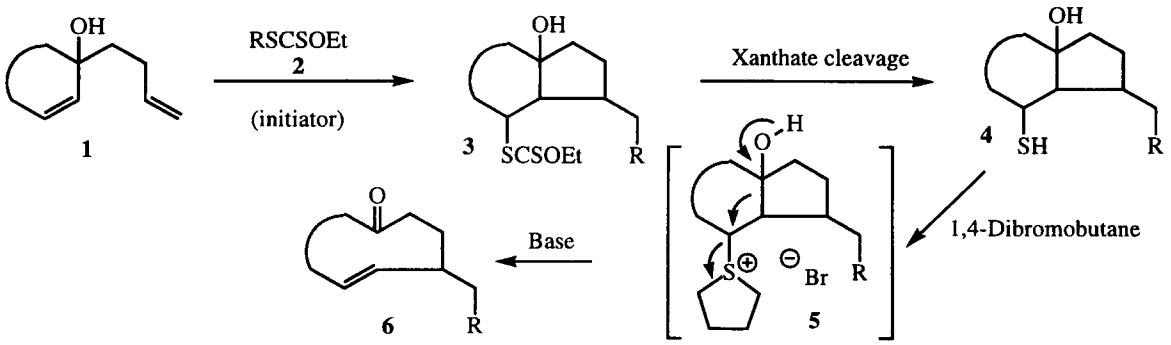
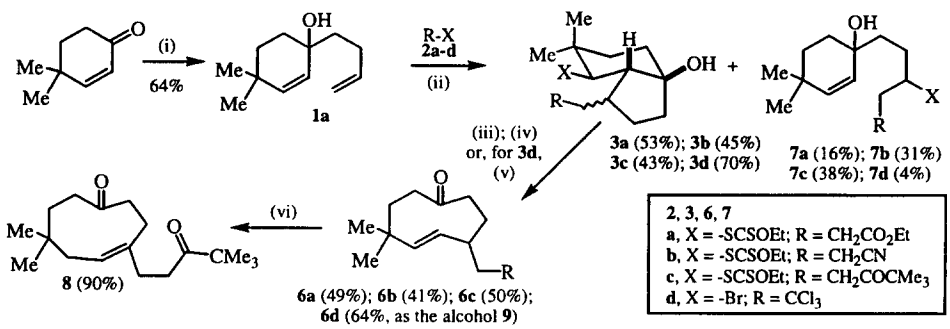


Scheme 1.

xanthate **2a**, easily made from ethyl bromoacetate by a simple substitution reaction with *O*-ethyl potassium xanthate, produced the desired bicyclic derivative **3a** in 53% yield, together with a small amount of monocyclic adduct **7a** (16%). We found that addition of some hexamethyldisiloxane to the reaction mixture had a beneficial effect since it protected **1a** against dehydration induced by any adventitious lauric acid. Compound **3a** was obtained as one major isomer (*exo*:*endo* ca. 85:15) with the xanthate group occupying an equatorial position as shown by NMR. Selective cleavage of the xanthate group was accomplished by exposure to ethylenediamine in ethanol at room temperature. Finally, we were delighted to find that heating the crude thiol with 1,4-dibromobutane in refluxing acetonitrile gave the desired 9-membered ring product **6a** in 49% overall yield. This derivative exists as two diastereomers (in a 90:10 ratio) due to an atropisomerism caused by the presence of a *trans*-double bond in a medium-sized ring.



Scheme 2. Conditions: (i) 4-Bromobutene/Li/THF/0°C (sonication); (ii) lauroyl peroxide (0.1–0.25 equiv.)/cyclohexane–$Me_3SiOSiMe_3$ (4:1)/reflux; (iii) 1,2-ethylenediamine/ethanol/rt; (iv) 1,4-dibromobutane (4 equiv.)/K_2CO_3/MeCN/reflux; (v) K_2CO_3/MeCN/reflux; (vi) H_2/Pd/C

A similar sequence was performed, in a comparable overall yield, using xanthates **2b** and **2c**, derived, respectively, from chloroacetonitrile and chloropinacolone. Not unexpectedly, compounds **6a–c** turned out to be somewhat unstable because of the strained *trans*-olefin which probably explains the modest (albeit unoptimised) yield. Interestingly, when in the case of **6c**, we attempted a catalytic hydrogenation in order to eliminate the atropoisomerism and obtain a more stable substance, we observed no reduction but rather an efficient palladium-induced 1,2-shift of the olefinic bond to give isomeric structure **8**. The olefin is now trisubstituted and more difficult to reduce.

This preliminary work demonstrates the possibility of combining a radical process with a Grob fragmentation to swiftly access 9-membered ring structures decorated with a variety of substituents. Moreover, this strategy is not limited to the use of xanthates but can be extended to halogen atom transfers

(Kharasch reactions) as demonstrated by the obtention of **6d**. The fragmentation can be directly applied to adduct **3d** since a bromide is a suitable leaving group. In this case the crude ketone, **6d**, was immediately reduced into alcohol **9** (64% overall yield from **3d**). Further work aimed at exploring the scope of this approach is under way, especially in terms of building other ring sizes and extending it to macrolactones.

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References

1. (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–452. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95–102.
2. (a) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, 1991. (b) Stach, H.; Hesse, M. *Tetrahedron* **1988**, *44*, 1573–1590. (c) Wovkulich, P. M. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds; Pergamon Press: Oxford, 1991; Vol. 1, pp. 843–899. (d) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881–930. (e) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757–5821. (f) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091–2115.
3. (a) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535–546. (b) Ho, T.-L. *Heterolytic Fragmentation of Organic Molecules*; Wiley: New York, 1993. (c) Weyerstahl, P.; Marschall, H. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds; Pergamon Press: Oxford, 1991; Vol. 6, pp. 1041–1070. (d) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989.
4. Paquette, L. A.; Edmonson, S. D.; Monck, N.; Rogers, R. D. G. *J. Org. Chem.* **1999**, *64*, 3255–3256.
5. Amann, C. M.; Fisher, P. V.; Pugh, M. L.; West, F. G. *J. Org. Chem.* **1998**, *63*, 2806–2807 and references cited therein.
6. For a review, see: Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 3001–3013.