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Efficient access to functionalised medium-ring systems by radical fragmentation/radical addition to α-iodoketones

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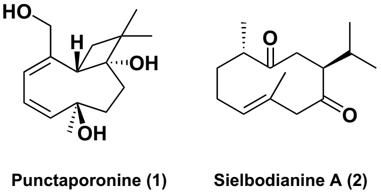
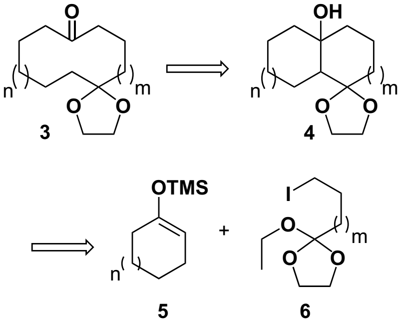
Abstract—Functionalised medium-ring systems of various sizes can be efficiently prepared by a novel approach that embodies a radical-induced fragmentation of bicyclic β-hydroxy ketones, followed by a second radical-coupling reaction. The unexpected reactivity of α-keto radicals is also discussed.

Compounds possessing a medium-ring fragment embedded in their structure, for example, punctaporonine **1** or sielbodianine A **2** (Scheme 1), have historically[1] attracted much attention because of their biological activities and the synthetic challenge imposed by the formation of the ring itself.[2] Numerous methods, involving ring expansion, have been employed to access such subunits.[3] Among these, oxy-Cope rearrangements,[4] Wharton/Grob fragmentations[5] and SmI_2-mediated sequential condensations[6] have been successfully applied to the synthesis of medium-sized rings.

As part of a project aimed at the rapid and versatile assembly of a variety of natural products containing a medium-ring system, the approach outlined in Scheme 2 was investigated. It was thought that Grob–Wharton fragmentation of bicycle **4**, readily available by the condensation of silylenol ethers **5** with the orthoesters **6**, would lead to the ketoketals **3**, in which one of the carbonyl functions has been selectively protected.



Scheme 1. Medium-sized ring containing natural products.



Scheme 2. Retrosynthesis of medium-sized rings.

The presence of the ketone function in adduct **3** raises also the interesting possibility of subsequently iterating the process, and therefore, obtaining not only medium but also functionalised macrocyclic structures.

In this letter, we wish to report the successful implementation of this strategy as well as describe some aspects of the reactivity of α-keto radicals.

Accordingly, a variety of bicyclic alcohols **4** have been prepared by the two step sequence depicted in Scheme 3.[7] Thus, condensation of the iodo-orthoester **6** with the silyl enol ethers **5**, catalysed by $ZnCl_2$,[8] afforded the corresponding β-ketoketals **7**. Cyclisation of **7** was

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Keywords: Medium-sized ring; Radical fragmentation; Intermolecular radical reaction; α-Ketoradicals; Orthoesters; α-Iodoketones.

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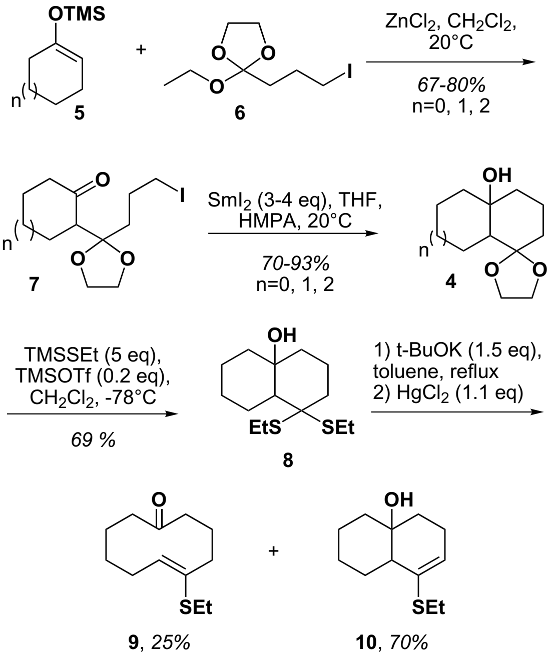
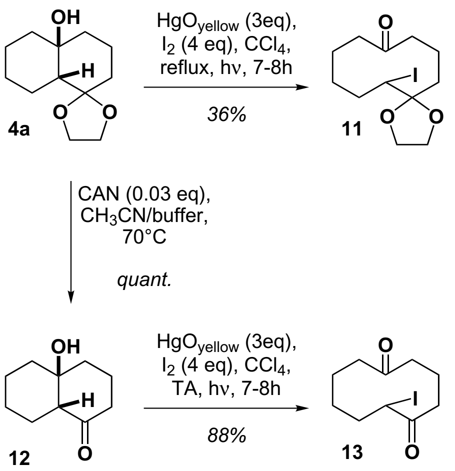


Scheme 3. Synthesis of bicyclic precursors.

found to proceed best in the presence of an excess of SmI_2, leading to the desired substrates **4** in good to excellent yields.

With a rapid access to a range of bicycles **4** in hand, attention was then devoted to the crucial Grob–Wharton fragmentation step. Unfortunately, numerous attempts at promoting this transformation failed to provide the desired ring-enlarged product. It transpires that the ketal functionality refuses to act as a leaving group, despite the proper antiperiplanar alignment of all the bonds implicated in the fragmentation. In order to favour the ring-opening process, adduct **4** ($n = 1$) was transformed into the corresponding dithioketal **8**, using TMSSEt in the presence of catalytic amounts of TMSOTf.[9]

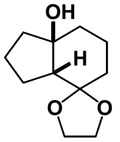
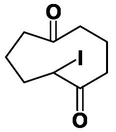
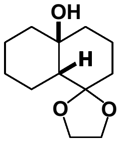
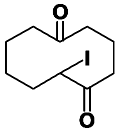
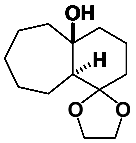
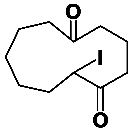
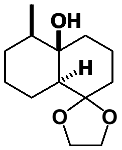
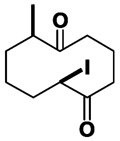
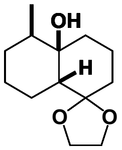
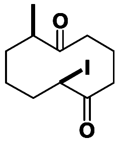
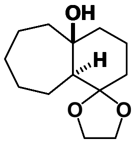
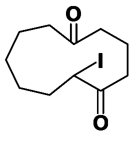
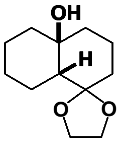
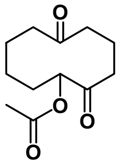


Scheme 4. Radical fragmentation of bicyclic precursors.

Disappointingly, most of the conditions examined led either to recovered starting material or to the elimination product **10**. The thought-after vinyl sulfide **9** could be obtained when a thiophilic Lewis acid, combined with a hard base, was employed, though in a mediocre 25% yield. The sulfoxide and sulfone analogues of **8** did not behave any better.

In desperation, we turned our attention to the radical-induced fragmentation of bicycle **4a** (Scheme 4). Recently, Suginome reported that tertiary alcohols underwent ring opening when reacted with yellow HgO and iodine.[10] Under these conditions, **4a** afforded the cyclodecanone derivative **11** in a modest 36% yield, accompanied by various products resulting from the cleavage of

Table 1. Synthesis of medium-sized ring by deprotection/radical fragmentation

Entry	Substrate	Products	Yield[a] (%)
1			87
2			88
3			86
4			75
5			65
6[b]			70
7[c]			48

[a] Yields over two steps (deprotection/fragmentation).

[b] (1) Deprotection, (2) $PhI(OAc)_2$, I_2.

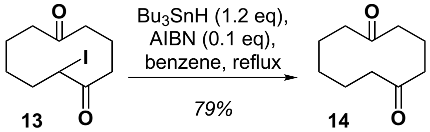
[c] (1) Deprotection, (2) $Pb(OAc)_4$ (2 equiv), AIBN, benzene.

the other C–C bonds connected to the tertiary alcohol function. Varying the conditions (IBDA/I_2,[11] NIS/Li_2CO_3,[12]...) neither improved the yields nor the product distribution.

In order to control the regioselectivity of the fragmentation, the ketal protecting group was removed. Using our CAN-catalysed procedure,[13] the acid and base sensitive aldol product **12** could be obtained quantitatively. Gratifyingly, ring opening of **12** proceeded smoothly, at room temperature, affording the desired α-iodoketone **13** in 88% isolated yield. This method proved to be rather general and a selection of pertinent results are displayed in Table 1.

As can be seen from Table 1, the HgO/I_2 induced fragmentation provides the corresponding 9-, 10- and 11-membered ring iodo-diketones in excellent yield (entries 1–3). Moreover, the process appears to be independent of the stereochemistry of the ring junction of the initial bicyclic adduct (entries 4 and 5). In both cases, a single diastereoisomer is obtained, as depicted in Table 1. It is noteworthy that the reaction proceeds under very mild conditions. Interestingly, HgO can be replaced by $PhI(OAc)_2$, though the yields are somewhat lower and the purification can be more tedious (entry 6). Finally, lead tetraacetate also induces the cleavage of **12**, affording the α-acetoxy diketone in moderate yield, accompanied by substantial amounts of the corresponding bicyclic enone (entry 7).

Having devised a simple and efficient route towards these medium-ring systems, we then turned our attention to their selective functionalisation. At the onset, it was thought that the presence of the iodine substituent would provide an easy discrimination between the two carbonyl functions. Unfortunately, this assumption proved to be invalid in these cases. Indeed, under a wide variety of conditions,[14] only the ring-closed bicycle **12** was observed, implying that transannular cyclisation far exceeds any intermolecular process.



Scheme 5. Reduction of α-iodoketone.

A solution to this problem surfaced when the iodocyclodecane-dione **13** was treated with Bu_3SnH/AIBN and afforded the reduced product **14** in excellent yield (Scheme 5).

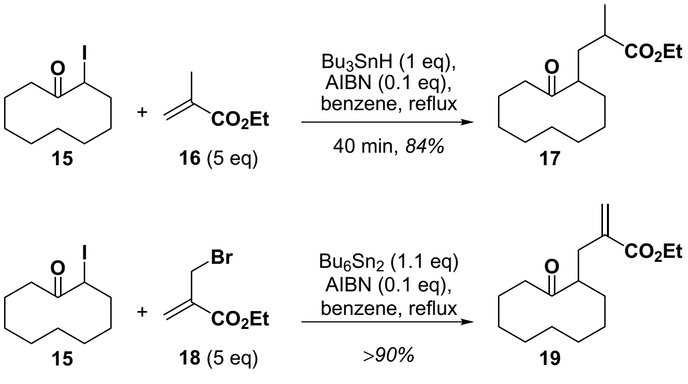
Alas, attempted capture of the in situ generated α-keto radical by a variety of radicophilic trapping agents (tetraallyltin, Bu_3Snallyl, butylvinylether), in the presence of AIBN or light, resulted either in the formation of the reduced product **14** or the bicycle **12**. It thus transpires that, in contrast to our expectation, the α-ketoradical does not appear to possess an electrophilic character but rather might display nucleophilic properties.

To test this hypothesis, α-iodocyclodecanone **15** was reacted with methyl methacrylate, in the presence of Bu_3SnH and AIBN. Gratifyingly, the desired adduct **17** was obtained in 84% yield. It is noteworthy that the time of addition is crucial to the success of this reaction, with 40 min being the optimum. Longer or shorter addition times lead to decreased yields. More interestingly, the radical-mediated coupling of **15** with α-bromomethyl ethyl acrylate **18** produced the α,β-unsaturated ester **19** in essentially quantitative yield (Scheme 6).

In order to expand the scope of this allylation reaction, a range of α-iodoketones were treated with **18** in the presence of AIBN. A selection of pertinent examples are displayed in Table 2.

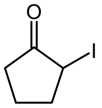
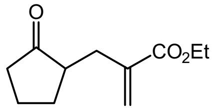
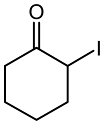
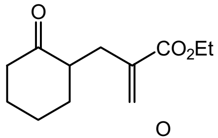
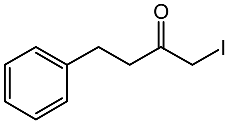
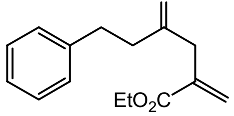
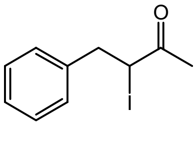
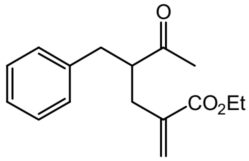
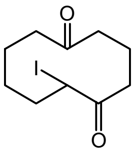
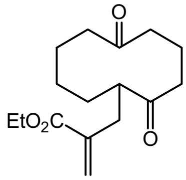
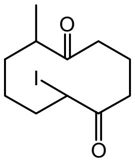
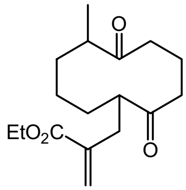
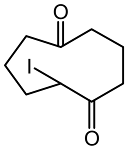
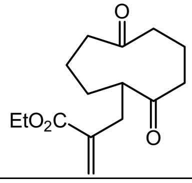
In general, good to excellent yields of the keto-acrylate adducts are obtained, regardless of the ring size of the substrate (entries 1, 2, 5 and 7) or the degree of substitution of the radical (primary or secondary; entries 3 and 4). The medium-ring iodo diketones afforded the desired coupling product in good yields. It is noteworthy that no reduction or transannular ring closure was observed in these cases (entries 5–7). To the best of our knowledge, this is the first general method for the intermolecular capture of a α-keto radical.[15,16]

The keto enoates, obtained by the union of the α-iodoketones with the allylic bromide **18**, are useful synthetic



Scheme 6. α-Keto radical addition to activated olefins.

Table 2. Addition of α-iodoketones to ethyl α-bromomethyl acrylate

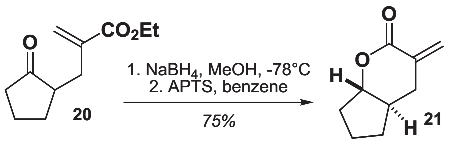
Entry	substrate	Products	Yield[a] (%)
1			90
2			85
3[b]			80
4			76
5			55
6			60 (*syn*:*anti* 3:1)
7			70

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

[b] All the reactions were completed within 4 h except in this case (1 h).

intermediates. For example, chemoselective reduction of the ketone function of **20**, followed by acid-catalysed cyclisation, leads to the corresponding α,β-unsaturated valerolactone **21**,[17] a motif, which is ubiquitous in a wide range of natural products (Scheme 7).

In summary, a simple and efficient protocol has been devised for the transformation of bicyclic tertiary hydroxyketals into medium-ring-containing α-iodo diketones.[18] Subsequent radical-mediated functionalisation afforded useful intermediates, which can be easily and chemoselectively converted into the corresponding unsaturated valerolactones. Further work is now directed towards expanding the scope of this novel methodology, exploring the unique reactivity of α-keto radicals and applying this approach to the total synthesis of relevant natural products. The results of these investigations will be reported in due course.



Scheme 7. α-Methylene lactone formation.

Acknowledgements

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References and notes

1. (a) Ruzicka, L.; Stoll, M.; Schinz, H. *Helv. Chim. Acta* **1926**, *9*, 249; (b) Ruzicka, L. *Bull. Soc. Chim. Belg.* **1932**, *41*, 565.
2. Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.
3. (a) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881; (b) Boivin, J.; Pothier, J.; Ramos, L.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 9239; (c) Yet, L. *Tetrahedron* **1999**, *55*, 9349; (d) Yet, L. *Chem. Rev.* **2000**, *100*, 2963; (e) Ivkovic, A.; Matovic, R.; Saicic, R. N. *Org. Lett.* **2004**, *6*, 1221.
4. (a) Bluthe, N.; Malacria, M.; Gore, J. *Tetrahedron* **1984**, *40*, 3277–3284; (b) Janardhanam, S.; Rajagopalan, K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2727; (c) Janardhanam, S.; Shanmugam, P.; Rajagopalan, K. *Synth. Commun.* **1993**, *23*, 311–323.
5. (a) Wharton, P. S.; Hiegel, G. A. *J. Org. Chem.* **1965**, *30*, 3254; (b) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535–622; (c) Tietze, L.-F.; Reichert, U. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 830–831; (d) Patel, H. A.; Dev, S. *Tetrahedron* **1981**, *37*, 1577–1581; (e) Grast, M. E.; Roberts, V. A.; Prussin, C. *J. Org. Chem.* **1982**, *47*, 3969–3971; (f) Caine, D.; McCloskey, C. J.; Derveer, D. V. *J. Org. Chem.* **1985**, *50*, 175–179; (g) Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1996**, *37*, 957–960; (h) Amann, C. M.; Fisher, P. V.; Pugh, M. L.; West, F. G. *J. Org. Chem.* **1998**, *63*, 3806–3807.
6. (a) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321–3354; (b) Molander, G. A.; Huérou, Y. L.; Brown, G. A. *J. Org. Chem.* **2001**, *66*, 4511–4516.
7. (a) Tinant, B.; Feneau-Dupont, J.; Declercq, J.-P.; Ates, A.; Marko, I. E. *Bull. Soc. Chim. Belg.* **1997**, *106*, 297; (b) Marko, I. E.; Ates, A. *Synlett* **1999**, *7*, 1033.
8. (a) Akgun, E.; Pindur, U. *Synthesis* **1984**, 227–228; (b) Pindur, U.; Muller, J.; Flo, C.; Witzel, H. *Chem. Soc. Rev.* **1987**, *16*, 75–87.
9. Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.
10. Suginome, H.; Kondoh, T.; Gogonea, C.; Singh, V.; Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 69–81.
11. Conception, J. I.; Francisco, C. G.; Hernandes, R.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett.* **1984**, *25*, 1953–1955.
12. McDonald, C. E.; Holcomb, H.; Leathers, T.; Ampadu-Nyarko, F.; Frommer, J. *Tetrahedron Lett.* **1990**, *31*, 6283–6286.
13. (a) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Marko, I. E. *Tetrahedron Lett.* **1999**, *40*, 1799–1802; (b) Marko, I. E.; Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C. *Angew. Chem., Int. Ed.* **1999**, *38*, 3207–3209; (c) Dalpozzo, R.; Nino, A. D.; Maiuolo, L.; Procopio, A.; Tagarelli, A.; Sindona, G.; Bartoli, G. *J. Org. Chem.* **2002**, *67*, 9093–9095; (d) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C.; Marko, I. E. *Tetrahedron* **2003**, *59*, 8989–8999.
14. (a) Lee, K.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 5590; (b) Usugi, S.-I.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2049.
15. (a) Lee, K.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 5590; (b) Usugi, S.-I.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2049.
16. For intramolecular examples: (a) Snider, B. B.; Buckman, B. O. *J. Org. Chem.* **1992**, *57*, 4883–4888; (b) Sha, C.-K.; Chiu, R.-T.; Yang, C.-F.; Yao, N.-T.; Tseng, W.-H.; Liao, F.-L.; Wang, S.-L. *J. Am. Chem. Soc.* **1997**, *119*, 4130–4135; (c) Sha, C.-K.; Santhosh, K. C.; Lih, S.-H. *J. Org. Chem.* **1998**, *63*, 2699–2704; (d) Sha, C.-K.; Lee, F.-K.; Chang, C.-J. *J. Am. Chem. Soc.* **1999**, *121*, 9875–9876; (e) Sha, C.-K.; Liao, H.-W.; Cheng, P.-C.; Yen, S.-C. *J. Org. Chem.* **2003**, *68*, 8704–8707; (f) Lin, H.-H.; Chang, W.-S.; Luo, S.-Y.; Sha, C.-K. *Org. Lett.* **2004**, *6*, 3289–3292.
17. Ghera, E.; Yechezkel, T.; Hassner, A. *J. Org. Chem.* **1990**, *55*, 5977–5982.
18. *Typical experimental procedure*: Synthesis of α-iodocyclodecane-2,6-dione **13**: A solution of HgO_{yellow} (4.5 mmol, 960 mg), I_2 (4.0 mmol, 1020 mg) and **13** (1.49 mmol, 250 mg) in 50 mL of CCl_4 was irradiated by 500 W tungsten lamp and stirred at 0 °C for 2 h. The reaction mixture was filtered over *Celite*® and the filter cake was washed with CH_2Cl_2 (2 × 20 mL). Filtrates were combined and washed with satd $Na_2S_2O_3$ (3 × 20 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The compound **13** was obtained as yellow oil (400 mg) in 93% yield. *Experimental data*: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.31–1.43 (m, 1H), 1.60–1.76 (m, 3H), 1.75–2.06 (m, 1H), 2.07–2.16 (m, 2H), 2.24 (dddd, 1H, $^2J = 15.4$, $^3J = 11.5$, $^3J = 6.7$, $^3J = 4.7$ Hz), 2.34 (ddd, 1H, $^2J = 14.4$, $^3J = 5.8$, $^3J = 5.8$ Hz), 2.44 (ddd, 1H, $^2J = 14.4$, $^3J = 7.0$, $^3J = 7.0$ Hz), 2.58 (ddd, 1H, $^2J = 16.4$, $^3J = 9.7$, $^3J = 4.4$ Hz), 2.57 (m, 2H), 4.43 (dd, 1H, $^3J = 11.5$, $^3J = 3.3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 19.70 (CH_2), 22.30 (CH_2), 27.22 (CH_2), 31.81 (CH), 34.69 (CH_2), 34.98 (CH_2), 40.32 (CH_2), 43.78 (CH_2), 206.64 (C=O), 213.23 (C=O). EI-MS (70 eV), *m/z* (%): 294 (4) [M^+], 167 (100) [M^+–I], 149 (58), 139 (26), 125 (37), 121 (44), 97 (60), 55 (57).