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Efficient and convergent stereocontrolled spiroannulation of ketones

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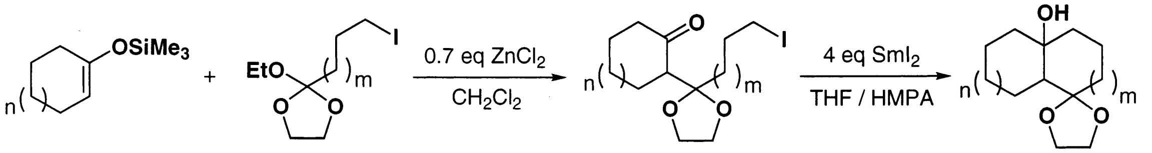
Abstract—Upon treatment with tBuOK/H_2O, a variety of ω-halo-β-keto-ketals undergo smooth cyclisation, affording in excellent yields mono-protected [n,m] spiro bicyclic diketones. This transformation is highly stereoselective producing, in all cases, the diastereoisomerically pure spiro derivatives. © 2003 Elsevier Science Ltd. All rights reserved.

A wide variety of biologically active natural products contain embedded in their complex architectural frameworks, a spiro-bicyclic motif. The ubiquitous presence of this subunit has impelled the development of a range of elegant methodologies for their efficient assembly.[1] During the course of the total synthesis of natural products possessing diversely substituted hydrindane and decalin core structures, we had the opportunity to establish a novel strategy for the rapid construction of fused bicyclic systems of various ring sizes (Fig. 1).[2]

Our approach involved the initial condensation between cyclic silyl enol ethers **1** and the dioxolane-containing orthoesters **2**,[3] affording in good yield the corresponding β-keto-ketals **3**. Reductive cyclisation with SmI_2 proceeded smoothly,[4] generating the polysubstituted, fused, bicyclic derivatives **4**. This last step required a large excess of SmI_2 and HMPA and proved to be difficult to scale-up. The pursuit for alternative and cheaper reductants thus became necessary. During one of these experiments, substrate **5** was reacted with a suspension of Li metal in THF, under sonication. Whilst no trace of the desired decalin **4** could be detected, we were pleasantly surprised to observe the formation of the spiro-bicycle **6** which was isolated in 61% yield (Fig. 2).

Unfortunately, this reaction displayed erratic behavior and no cyclisation occurred in rigorously dried THF (entry 1), indicating that some serendipitous moisture had been responsible for the initially successful ring closure.[5] In order to promote this spiroannulation reproducibly, a variety of bases were then screened, alas to no avail (entries 2–4). At last, it was discovered that the combination tBuOK (1.5 equiv.)/H_2O (1 equiv.), in anhydrous THF, repeatedly afforded the desired spirocycle **6** in 95% yield (entry 5).[6] These optimised conditions were then applied to the intramolecular cyclisation of a range of β-keto-ketal derivatives. Some representative examples are collected in Table 1.



1 **2** **3** **4**

n = 0, 1, 2; m = 1, 2; X = Cl, I; overall yields: 46 - 79%.

Figure 1.

Keywords: annulation; orthoesters; spirobicycle; alkylation; stereocontrol.

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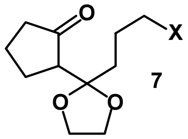
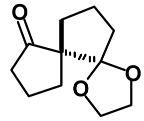
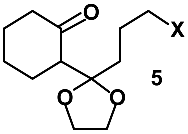
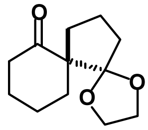
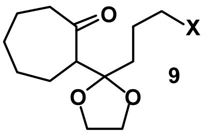
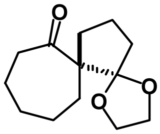
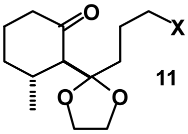
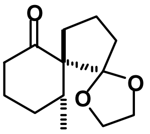
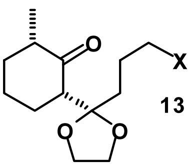
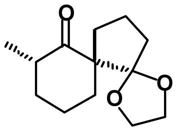
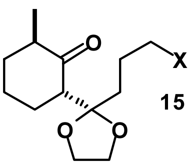
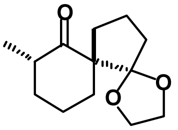
As can be seen from Table 1, [4,4], [5,4] and [6,4] spiro-bicycles can be obtained in good to excellent yields using this protocol (Table 1, entries 1–3). This ring-closure is also highly stereoselective. For example, base-promoted annulation of the C_3-substituted cyclohexanone **11** provided keto-ketal **12** as a single diastereoisomer (entry 4, Table 1). The structure and relative stereochemistry of **12** were unambiguously established by a single-crystal X-ray diffraction analysis (Fig. 3).[7]

The cyclisation of epimers **13** and **15** (Table 1, entries 5 and 6) proceeds smoothly under these base-catalysed conditions and provides a stereoconvergent preparation of spiro-bicycle **14**. In both cases, the same enolate is generated and intramolecular alkylation occurs *anti* to the C_6-methyl substituent. It is noteworthy that the more readily available chloro-substituted β-keto-ketals react with equal efficiency—in some cases even better—than the corresponding iodo-derivatives.[8]

The formation of isomer **12** can be rationalised by invoking a transition state such as **16** in which the ring system adopts a half-chair conformation and the electrophilic center of the annulating agent approaches the enolate along an axial trajectory. The C_3-substituent occupies an axial position in order to minimise repulsive *gauche* interactions with the dioxolane moiety (Fig. 4).[9]

Table 1. Spirocyclisation of iodo- and chloro-keto ketals

Entry	Substrate	X	Product	Yield[(a)]
1		Cl I	 8	89% 85%
2		Cl I	 6	82% 95%
3		Cl I	 10	78% 88%
4		Cl	 12	85%
5		Cl I	 14	89% 78%
6		Cl I	 14	92% 89%

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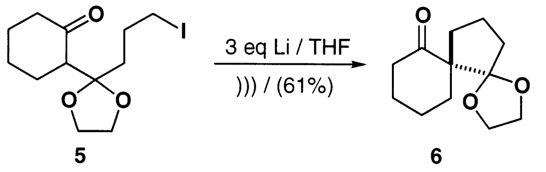
[a] All yields are for pure, isolated products. All these reactions were performed in anhydrous THF using 1.5 equiv. of *t*BuOK and 1 equiv. of H_2O, at room temperature (Ref. 10).



Entry	conditions	yield of **6**
1	Li / anhydrous THF	0%
2	LDA / THF / -78°C	0%
3	KOH / THF	0%
4	*t*BuOK / THF	0%
5	***t*BuOK / H_2O / THF**	**95%**

Figure 2.

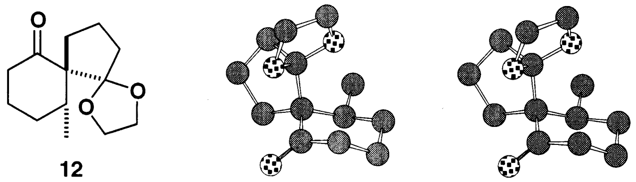


Figure 3. Cross-eyed stereoview of ketone **12**.

Furthermore, base-catalysed cyclisation of adducts **17**, **19** and **21**, possessing a one carbon longer tether, also proceeded smoothly under these conditions, affording the [4,5], [5,5] and [6,5] spiro-bicycles **18**, **20** and **22**, respectively (Table 2).

It is interesting to note that the judicious choice of annulating agent and starting ketone can lead in some cases to chemoselectively protected spirocycles (Fig. 5).

Thus, condensation of cyclopentanone derived silyl enol ether **23** with the C_5-orthoester **2** (X = Cl, *n* = 2), followed by spiro-annulation, afforded adduct **18** in which the 6-membered ring ketone is protected as a dioxolane. In contrast, coupling of **24** with the C_4-orthoester **2** (X = Cl, *n* = 1), followed by base-catalysed cyclisation, produced derivative **6** in which the ketal substituent is now located on the five-membered ring.

In summary, we have developed a novel, efficient and stereoselective methodology for the rapid construction of spirobicycles of varied ring sizes and substitution pattern from readily available ketones and ω-halo-orthoesters.[10] Current efforts are directed towards delineating the full scope of this connective approach, installing an enantioselective version and applying this strategy to the total synthesis of relevant natural products.

Acknowledgements

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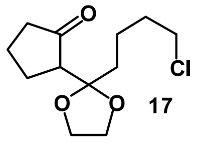
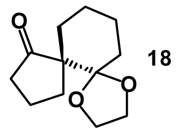
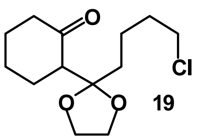
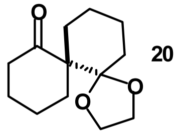
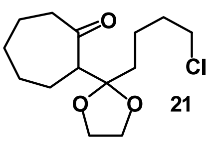
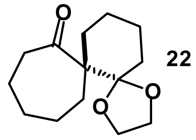
Table 2. Six-membered ring spirocyclisations

Entry	Substrate	Product	Yield[a]
1			65%
2			58%
3			59%

[a] All yields are for isolated, pure products. All these reactions have been performed according to the standard protocol, in anhydrous THF, using 1.5 equiv. of *t*BuOK and 1 equiv. of H_2O, at room temperature (Ref. 10).

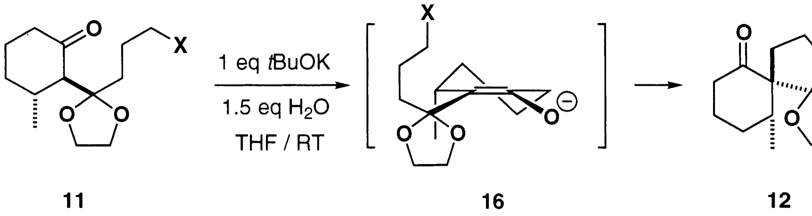


Figure 4.

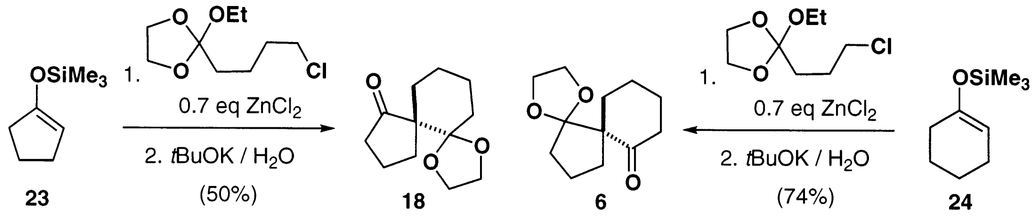


Figure 5.

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1. (a) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007; (b) Heathcock, C. H.; Gaham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1983; Vol. 5, p. 264; (c) Marshall, J. A.; Brady, S. F.; Andersen, N. H. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 283.
2. Markó, I. E.; Ates, A. *Synlett* **1999**, 1033.
3. For the elegant development of related orthoesters as cyclopentannulation reagents, see: (a) Ding, P.; Ghosez, L. *Tetrahedron* **2002**, *58*, 1565; (b) Huart, C.; Ghosez, L. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 634. For the use of related acetals, see: Lee, T. V.; Boucher, R. J.; Porter, J. R.; Taylor, D. A. *Tetrahedron* **1988**, *44*, 4233.
4. For excellent reviews on SmI_2, see: (a) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745; (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29; (c) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573.
5. Repeating the reaction under identical conditions but adding small aliquots of water indeed led to some of the spiro derivative **6**. However, the results were irreproducible from one experiment to another.
6. It is quite plausible that under these conditions, a soluble complex base, akin to the Gassman system is generated; Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918. For pertinent references concerning other complex bases, see: (a) Carre, M. C.; Ndebeka, G.; Riondel, A.; Bourgasser, P.; Caubere, P. *Tetrahedron Lett.* **1984**, *25*, 1551; (b) Pearson, D. E.; Buehler, C. A. *Chem. Rev.* **1974**, *74*, 45. For the X-ray structure analysis of potassium enolates generated using ^{t}BuOK, see: Williard, P. G.; MacEwan, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 7671.
7. Crystal data: $C_{13}H_{20}O_3$, Mr = 224.29, triclinic, *P*-1, $a = 8.252$ (3), $b = 11.130(4)$, $c = 14.436(5)$ Å, $\alpha = 100.70(2)$, $\beta = 90.10(2)$, $\gamma = 108.93$ (2)°; $V = 1229.6(8)$ Å^3, $Z = 4$. 5239 reflections were collected with a MAR image plate using monochromatized MoKα radiation ($\lambda = 0.71069$ Å). The structure was solved and refined with SHELXS and SHELXL-97. (Sheldrick, G. M. (1997) University of Göttingen, Germany). The *R* indices converge to 0.0627 for 2636 observed reflections and to 0.0746 for all 3241 independent data.
8. Indeed, the iodo-substituted β-keto-ketals are obtained by condensation between the corresponding silyl enol ethers and the iodine-containing orthoester **2**. This annulating agent is, in turn, generated by Finkelstein exchange from the initially prepared chloro-derivative (Ref. 2).
9. (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841; (b) Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 6867; (c) Stork, G.; Danheiser, R.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 3414; (d) For an alternative explanation, see: Asaoka, M.; Takenouchi, K.; Takei, H. *Chem. Lett.* **1988**, 1225.
10. *Typical experimental procedure. Preparation of spirobicycle **8**.*

    Solid potassium *tert*-butoxide (700 mg, 6.2 mmol) was added to a stirred solution of 2-[2-(3-chloropropyl)-[1,3]dioxolan-2-yl]-cyclopentanone **7** (1 g, 4.3 mmol) in anhydrous THF (30 ml) containing H_2O (77 mg, 4.3 mmol). The resulting yellow solution was stirred for 1 h at room temperature. The reaction mixture was treated with water (20 ml) and the organic layer was separated. The aqueous phase was extracted with ether (2×30 ml). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure to afford the crude product which was further purified by chromatography on silica gel (eluant: petroleum ether/EtOAc: 7/3). The pure spiro compound **8** was isolated in 85% yield. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 3.97$–3.89 (m, 4H), 2.33–2.22 (m, 3H), 2.05–1.60 (m, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 219.9$, 118.4, 65.1, 64.3, 59.6, 38.7, 34.7, 33.3, 31.9, 19.6, 19.4; IR (film): $\nu = 2961$, 1736, 1326 cm^{-1}; MS (70 eV): *m*/*z* (%): 197 (16) [M^++1], 196 (50) [M^+]. Anal. calcd for $C_{11}H_{16}O_3$: C, 68.55; H, 8.63. Found: C, 68.29; H, 8.53.