

## Studies on Bifunctional Annulating Reagents: a Combined Annulation–Ring Cleavage Approach to the Synthesis of Eight- and Nine-membered Rings

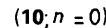
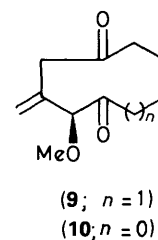
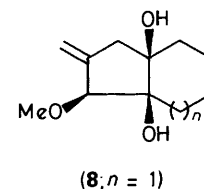
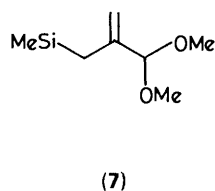
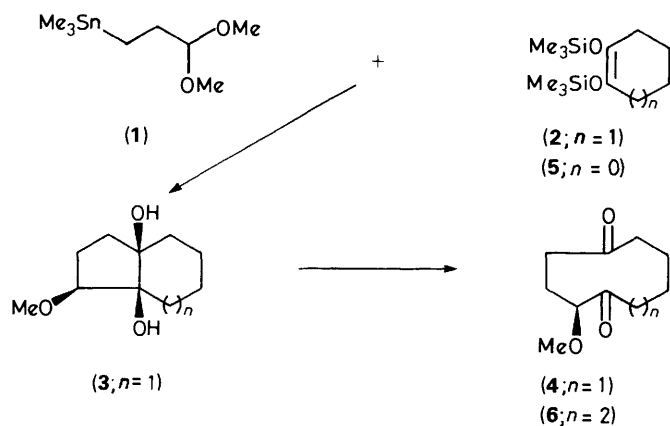
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Eight- and nine-membered rings are available by using a combined annulation–ring cleavage strategy which utilises the reaction of the stannane (1) or the allylsilane (7) with silylated enediols and ring opening of the thus formed bicyclic diols.

The synthesis of medium sized rings continues to pose a major challenge, especially if attempted *via* a direct annulation strategy. One of the more successful routes to these compounds is by ring cleavage of a suitably substituted bicyclic diol<sup>1</sup> but such methods are often unattractive owing to the lack of a direct route to the bicyclic precursors. We now describe a new synthesis of eight- and nine-membered rings which by combining a direct annulation process with ring cleavage gives improved access to these compounds.

During our studies on the use of chemoselective bifunctional acceptor-donor annulating reagents, it became apparent that the ease with which acetals such as (1)<sup>2</sup> and (7)<sup>3</sup> allow the preparation of cyclopentanes in a one-pot process, could provide considerable advantages in addressing the problems of medium-sized ring synthesis. Thus, reaction of (1) with the acyloin reaction-derived<sup>4</sup> silylated enediol (2), using a catalytic amount of trimethylsilyl trifluoromethanesulphonate (TMSOTf), followed by TiCl<sub>4</sub>, all at –78 °C, afforded the bicyclic diol (3) in 33% yield. Previous syntheses of such diols normally involved a multi-step procedure and thus the ability of the acetalstannane to undergo this direct annulation reaction offers appreciable promise.

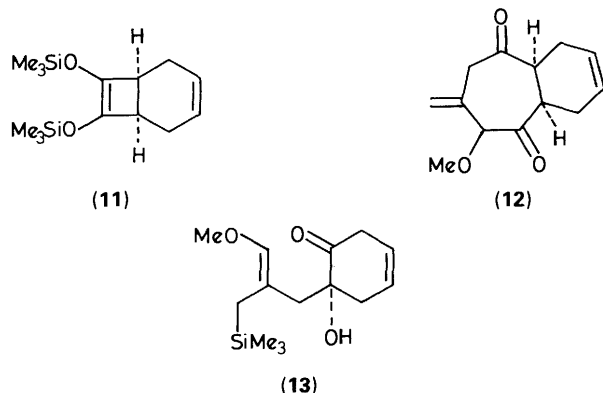
A similar reaction sequence with the acetal allylsilane (7)<sup>5</sup> gave much improved yields (67%) of the related diol (8), which



in conjunction with the fact that (8) possesses additional useful functionality makes the use of the allylsilane preferable. Both (3) and (8) react with Pb(OAc)<sub>4</sub> in a ring cleavage process to form the nine-membered ring diketones (4) and (9)<sup>†</sup> in essentially quantitative yield. The fact that each of the two ketones of (4) and (9) can be chemodifferentiated is an important additional feature of this chemistry which enhances and contrasts it with other similar ring cleavages for which the two ketones are often chemically indistinguishable.<sup>1</sup> Repeating both the reaction of (1) and (7) with the smaller silylated enediol (5) leads to a new synthesis of the eight-membered rings (6) and (10) in overall yields of 35 and 30% respectively. The lower yields in this overall process reflect a slower reaction in the first two-bond-forming process, during which some decomposition of the acetals occur. However, since there is no necessity to purify the intermediate diol the new chemistry does constitute an efficient way to synthesize eight-membered rings and more notably nine-membered rings, which are the most difficult to synthesize *via*

<sup>†</sup> All new compounds were characterised by high field n.m.r. (270 and 400 MHz) and by high-resolution mass spectrometry and/or elemental analysis.

an annulation strategy. Furthermore, an additional example of this strategy is the reaction of the enediol derivative (**11**) with (**2**) giving in 51% yield the diketone (**12**), so illustrating an alternative way of preparing fused seven-membered rings.



In previous studies of (**7**) we showed that the initial bond-forming reaction, which occurs by nucleophilic attack of an enol ether at an unsymmetrical carbocation, displays a dependence upon the structure of the enol ether with  $S_N1$  attack being highly favoured in some cases.<sup>3</sup> In the present examples we can isolate, by using a catalytic amount of TMSOTf, intermediates such as (**13**) in 67% yield, indicating that a similar mode of reaction has occurred. These intermediates then cyclize to the observed diols which, due to their symmetry, mask any indication of the inherent initial regioselectivity of this process.

The combination of a direct annulation strategy and a ring cleavage strategy does, therefore, potentially offer advantages for the synthesis of ring sizes of this type. The method will be especially useful in reactions with bicyclic enediols such as (**11**) to give access to fused medium sized rings.

### Experimental

**3-Methoxy-4-methylenebicyclo[5.4.0]undec-8-ene-2,6-dione (12).**—The enediol (**11**) (0.284 g, 1.00 mmol) and the allylsilane (**7**) (0.188 g, 1.00 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (15 ml), under nitrogen at  $-78^\circ\text{C}$ , were treated with TMSOTf (0.01 mmol). After 1 h  $\text{TiCl}_4$  (2.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 ml) was added at  $-78^\circ\text{C}$  and the resulting reddish brown solution was stirred for 1.5 h. Addition of water (7 ml) at  $-78^\circ\text{C}$  and warming to ambient temperature was followed by washing with  $\text{CH}_2\text{Cl}_2$  ( $4 \times 5$  ml). The combined organic layers were washed with water (10 ml) and saturated aqueous  $\text{NaHCO}_3$  (10 ml) and dried ( $\text{MgSO}_4$ ) to

give on evaporation a green oil (0.21 g, 97%) which could either be used directly or be purified by chromatography on silica gel [elution, light petroleum–diethyl ether (1:1)] to give the intermediate tricyclic diol as a colourless oil (0.11 g, 51%) (Found:  $M^+$ , 222.1247.  $\text{C}_{13}\text{H}_{18}\text{O}_3$  requires 222.1256);  $\nu_{\text{max}}(\text{CCl}_4)$  3 420, 1 719, 1 673, 1 262, 1 125, and 906  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CDCl}_3)$  1.86–2.64 (10 H, m,  $\text{CH}_2$ ), 3.47 (3 H, s, OMe), 4.06 (1 H, s, CHOMe), 5.05 (1 H, m, vinyl H), 5.18 (1 H, m, vinyl H), and 6.11 (2 H, br t,  $J$  3.5 Hz,  $\text{CH}=\text{CH}$ );  $\delta_{\text{C}}(\text{CDCl}_3)$  20.7, 20.9, 31.6, 39.6, 43.4, 58.2, 80.7, 87.75, 108.3, 129.65, 130.3, and 144.3;  $m/z$  223 ( $M^+ + 1$ , 2.4%), 222 ( $M^+$ , 14%), 204 ( $M^+ - 18$ , 57%), 190 ( $M^+ - 32$ , 45%), and 110 (100%).

A solution of the above diol (0.052 g, 0.23 mmol) in benzene (3 ml) was treated with anhydrous  $\text{Pb}(\text{OAc})_4$  (0.114 g, 0.26 mmol) and stirred at room temperature for 18 h. The pale yellow suspension was then filtered off and the filtrate evaporated under reduced pressure to afford an oil which after chromatography on silica gel [elution, light petroleum–diethyl ether (1:1)] gave the dione (**12**) as a colourless oil (0.049 g, 98%) (Found:  $M^+$ , 220.1089.  $\text{C}_{13}\text{H}_{16}\text{O}_3$  requires 220.1099);  $\nu_{\text{max}}(\text{CCl}_4)$  3 033, 1 707, 1 426, 1 231, 1 091, and 915  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CDCl}_3)$  2.04–2.42 (4 H, m, allylic  $\text{CH}_2$ ), 3.05 (1 H, m, CH), 3.21 (1 H, dd,  $J$  16.3, 0.7, CH), 3.34 (3 H, s, OMe), 3.48–3.61 (2 H, m), 4.25 (1 H, s, CHOMe), 5.27 (1 H, m, vinyl H), 5.41 (1 H, m, vinyl H), and 5.67 (2 H, m,  $\text{CH}=\text{CH}$ );  $\delta_{\text{C}}(\text{CDCl}_3)$  24.9, 25.4, 42.3, 46.1, 48.8, 56.8, 91.05, 120.45, 124.1, 125.1, 137.1, 206.4, and 208.5;  $m/z$  221 ( $M^+ + 1$ , 4%), 220 ( $M^+$ , 24%), 192 (18), 117 (26%), and 84 (100%).

### Acknowledgements

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