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Free radical reactions for heterocycle synthesis. Part 5: Formation of novel bridged spirolactones by double cyclizations

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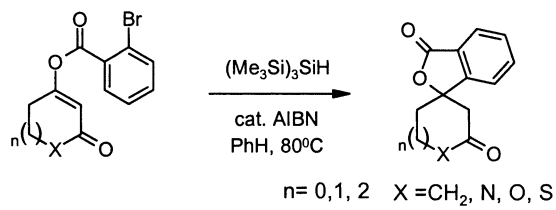
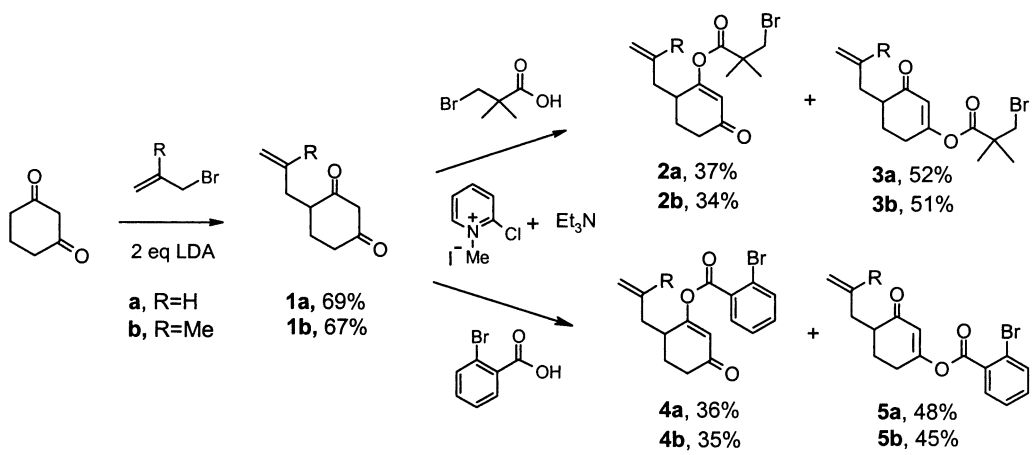
Abstract—Novel bridged spirolactones have been synthesized via double radical cyclization of enol ester radicals.

Free radical cyclizations can be designed to undergo a tandem (cascade) sequence.[1] This strategy has been widely used in the synthesis of fused polycyclic compounds[2] such as quinanes,[3] steroids,[4] and alkaloids.[5] Synthesis of bridged or spirocyclic systems by this approach, however, received relatively less attention.[1,6] We now report here a double cyclization sequence that leads to formation of novel tetracyclic systems containing both spiro and bridged rings.

In recent years, we have focused on the development of a general methodology to construct heterocyclic systems based on radical annulations of *o*-bromobenzoates.[7] One of its applications is the synthesis of spirolactones by intramolecular radical Michael additions (Eq. (1)).[7b,c] Extending the scope of this reaction by designing a double cyclization sequence allows us to access more complex heterocyclic systems. In order to undertake a systematic study, we purposely selected aryl and alkyl bromides that have allyl groups at two different positions of the α,β-unsaturated cyclic ketones. These compounds can be easily prepared by coupling of the allylated 1,3-cyclohexanediones with appropriate carboxylic acids followed by flash column chromatography to separate the different *O*-acylation products (Scheme 1).



(1)



Scheme 1.

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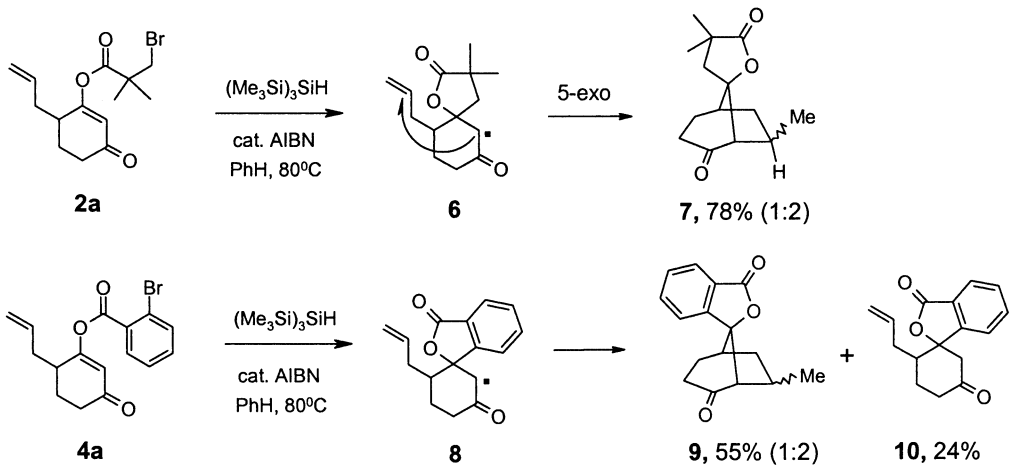
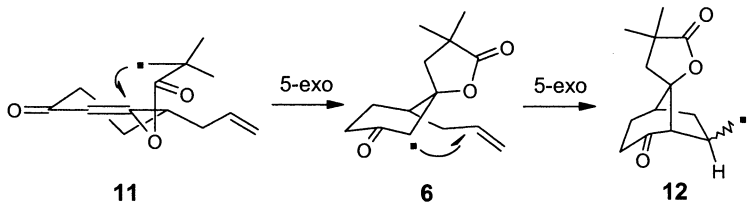
With these enol esters in hand, we carried out a series of $(Me_3Si)_3SiH$ mediated radical cyclizations. Using **2a** or **4a** as substrates, the initial radicals undergo double cyclizations, first by intramolecular Michael addition to form stabilized intermediate radicals **6** or **8**, followed by 5-*exo* cyclization onto the alkene to give bridged spirolactones **7** or **9** (Scheme 2). Reaction of **2a** generates **7** as a mixture of two diastereomers, whereas reaction of **4a** affords dicyclization product **9** along with monocyclization product **10**. Formation of **7** suggests that the spirocyclization (**11** to **6**) is stereoselective where the newly-formed C–C bond is *trans* to the vinyl group (Scheme 3). Subsequent 5-*exo* cyclization (**6** to **12**) is less selective probably due to free rotation around the allylic C–C single bond and gives a mixture of diastereomers. The structures of 7-*exo* and 7-*endo* are confirmed by X-ray structure analyses (Fig. 1).

Reactions using substrates **2b** or **4b** that both have a 2-methylallyl side chain also afford dicyclization products. In these two cases, the spirocyclization is followed by a cyclization of 6-*endo* instead of 5-*exo*. The bridged spirolactones **14**[8] and **15** are both single diastereomers (Scheme 4).



Scheme 2.



Scheme 3.

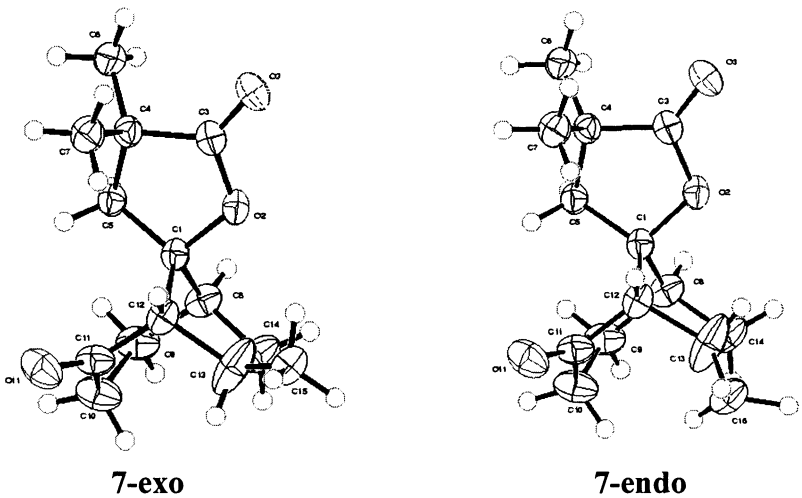
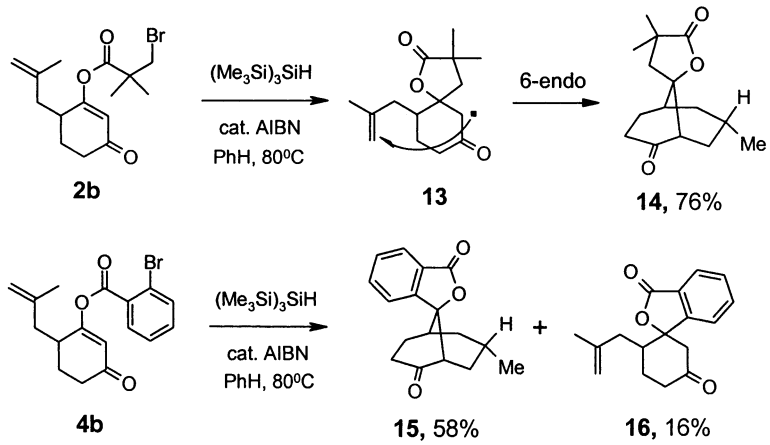


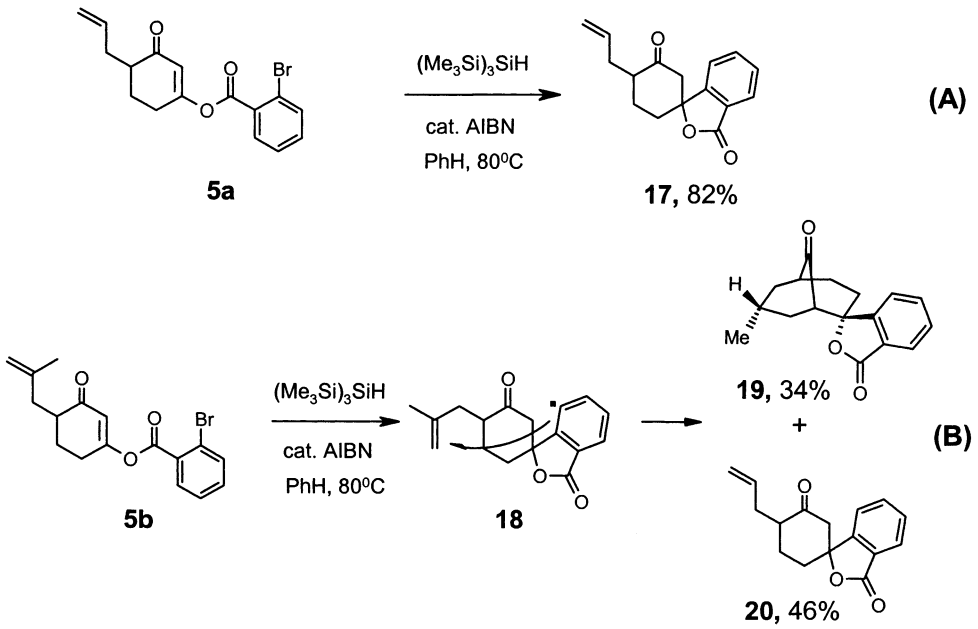
Figure 1. X-Ray structures of **7**-*exo* and **7**-*endo*.



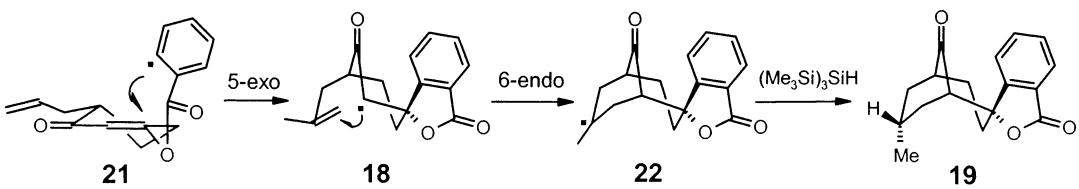
Scheme 4.

The reaction of enol esters **5a** produces only monocyclization products **17** (Scheme 5, A). Steric hindrance probably disfavors the second cyclization of 5-*exo*. This result is consistent with the report by Simpkins in the synthesis of spiroethers.[9] Addition of a methyl group to the allyl side chain (**5b**) induces the second cyclization of 6-*endo* (Scheme 5, B). In this case, adequate amount of dicyclization product **19**[10] is formed as a single diastereomer.[11] This result implies that spirocyclization of radical **21**, 6-*endo* cyclization of radical **18**, and subsequent H-atom transfer from $(Me_3Si)_3SiH$ to **22** go through a stereoselective pathway (Scheme 6). The structure of **19** is confirmed by X-ray structure analysis (Fig. 2).

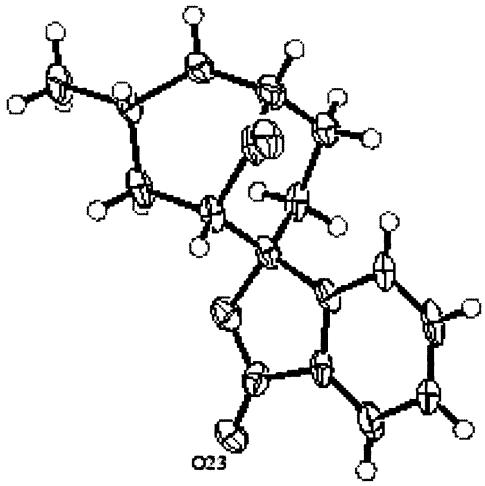
In conclusion, we have demonstrated that several novel bridged spirolactones can be prepared by tandem radical cyclizations of α,β-unsaturated cyclohexanone derivatives bearing an appropriate allyl side chain.



Scheme 5.



Scheme 6.



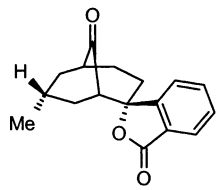


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Figure 2. X-Ray structure of compound **19**.

Acknowledgements

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8. Analytical data for **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, CH_3), 1.31 (s, $2CH_3$), 1.85 (d, 1H), 2.05 (d, 1H), 1.62–2.05 (8H), 2.40–2.50 (m, 2H), 2.68 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (q), 21.8 (t), 23.6 (d), 25.9 (q), 26.2 (q), 29.4 (s), 32.0 (t), 35.7 (t), 35.7 (t), 36.9 (d), 38.7 (s), 44.8 (t), 56.3 (d), 80.6 (s), 179.4 (s), 211.1 (s). IR (neat) 1769 (s, C=O), 1706 (s, C=O) cm^{-1}; MS m/e (rel. int.) 251 (M^++1, 100), 192 (72), 149 (43).
9. Middleton, D. S.; Simpkins, N. S. *Tetrahedron* **1996**, *46*, 545.
10. Analytical data for **19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, CH_3), 1.60–1.80 (m, 3H), 1.90–2.25 (m, 3H), 2.37 (m, 2H), 2.60 (m, 1H), 2.78 (m, 1H), 2.97 (td, 1H), 7.22 (d, 1H), 7.53 (t, 1H), 7.59 (t, 1H), 7.90 (d, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4 (q), 25.0 (t), 25.4 (d), 34.6 (t), 37.6 (t), 41.4 (d), 52.5 (d), 88.2 (s), 120.7 (d), 123.7 (s), 124.6 (d), 128.0 (d), 132.6 (d), 150.2 (s), 167.3 (s), 214.6 (s); IR (neat) 1766 (s, C=O), 1722 (m, C=O) cm^{-1}; MS m/e (rel. int.) 271 (M^++1, 100), 251 (60).
11. Reactions of **3a** and **3a** provide similar results as those of **5a** and **5b**.