

Medium ring synthesis by radical *ipso*-substitutionDavid C. Harrowven,^{*a} Nathalie L'Helias,^a Jonathan D. Moseley,^b Nigel J. Blumire^a and Stuart R. Flanagan^a^a Department of Chemistry, The University of Southampton, Southampton, UK SO17 1BJ.

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A new approach to eight and nine membered ring synthesis is described in which a radical *ipso*-substitution reaction features as a key step.

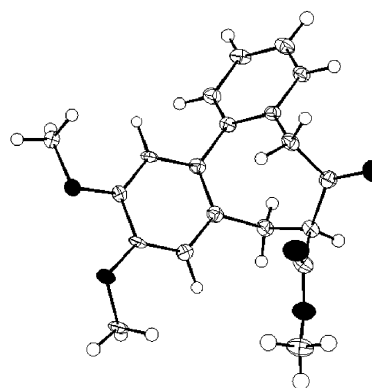
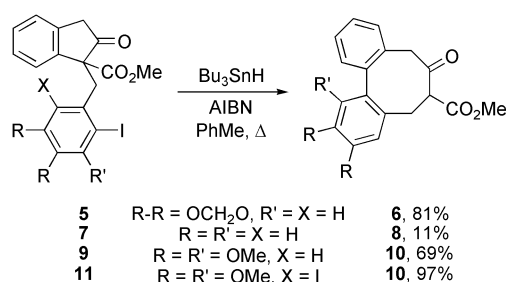
The widely held view that intramolecular radical additions to arenes were unruly processes of little synthetic utility has largely been dispelled by the discovery in recent years of many high yielding *ortho*-cyclisation and *ipso*-substitution reactions. Indeed, current interest in the area has led to many useful developments including new approaches to poly-aromatics,¹ biaryls,^{2,3} triaryls,³ helicenes,⁴ and a host of other aromatic and heterocyclic ring systems.^{5–7} Our interest in this area and in lignan total synthesis⁸ led us to consider an approach to the stegane family of natural products based on the ring expansion protocol outlined in Scheme 1. We hoped that generation of an aryl radical from **1** would initiate a 5-*exo-trig* cyclisation leading to **3**. Collapse of **3** with scission of the cyclopentane ring might then be favourable, as it would lead to rearomatisation of the acceptor ring and to the generation of a highly stabilised radical intermediate **4**. Hydrogen atom abstraction from tributyltin hydride would complete the sequence giving dihydro-5*H*-dibenzo[*a,c*]cyclooctenone **2**, the tricyclic core of the steganes.

Pleasingly, when **1** was exposed to tributyltin hydride under standard radical forming conditions (1.1 equiv. Bu₃SnH, 0.2 equiv. AIBN, PhMe, 85 °C), dihydro-5*H*-dibenzo[*a,c*]cyclooctenone **2** was afforded in 74% yield as a white solid (Scheme 1). X-Ray crystallographic and NMR analysis showed that a single diastereoisomer of **2** (Fig. 1) was given after recrystallisation (ether/petrol).

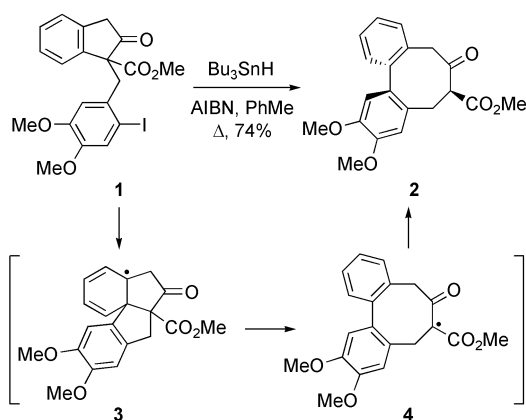
A series of related cyclisation reactions was then examined. Most gave the expected dihydro-5*H*-dibenzo[*a,c*]cyclooctenone in high yield (Scheme 2). One exception was the unsubstituted example **7** which provided **8** in a disappointing 11% yield. In this case the product was found to be incompatible with the reaction conditions, decomposing to baseline material on prolonged heating.

The method was next extended to tetralones. Our initial results were discouraging, with **12** giving the product of *ortho*-cyclisation **17** (Fig. 2), rather than the anticipated dihydro-5*H*-

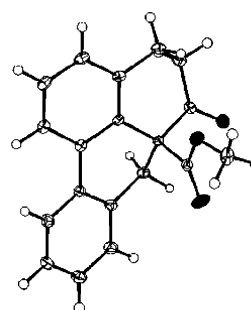
dibenzo[*a,c*]cyclooctenone **16**. In other cases, however, *ipso*-substitution and *ortho*-cyclisation pathways were competitive leading to product mixtures comprised of the respective dibenzo[*a,c*]cyclooctenones (Fig. 3) and tetrahydrobenzo[*de*]anthracenes (Scheme 3). The influence of substituents on the course of aryl radical additions to arenes has yet to be studied in detail, though the available evidence indicates that ether groups on the donor aryl radical accelerate 5-*exo-trig* pathways.⁷ The different behaviour observed in the indanone and tetralone series presumably reflects the relative ease of the 6-*exo/endo-trig* cyclisation mode. In the indanone series, the energy needed to bring the aryl radical and the *ortho*-carbon of the acceptor ring into close proximity is considerable. By

Fig. 1 ORTEP diagram of **2**.

Scheme 2



Scheme 1

Fig. 2 ORTEP diagram of **17**.

contrast, that transition state is easy to accommodate within the more flexible tetralone series.

We have also shown that vinyl radicals may be used to trigger the ring expansion reaction. Thus, vinyl bromides **24** and **25** were transformed into benzocyclooctenone **26** and benzocyclononone **28** respectively on treatment with tributyltin hydride (Scheme 4).

In conclusion, a new approach to medium sized carbocycles has been developed involving the expansion of indanones and tetralones by means of a radical *ipso*-substitution reaction. We are presently seeking to apply the methodology in target oriented synthesis and to gain some further insight into the factors that influence *ortho*- and *ipso*-cyclisation modes.

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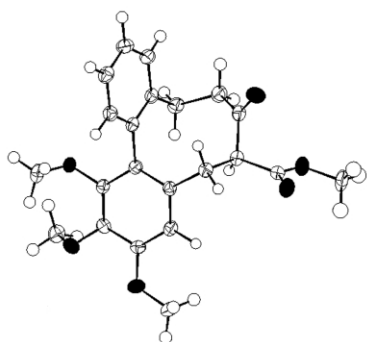
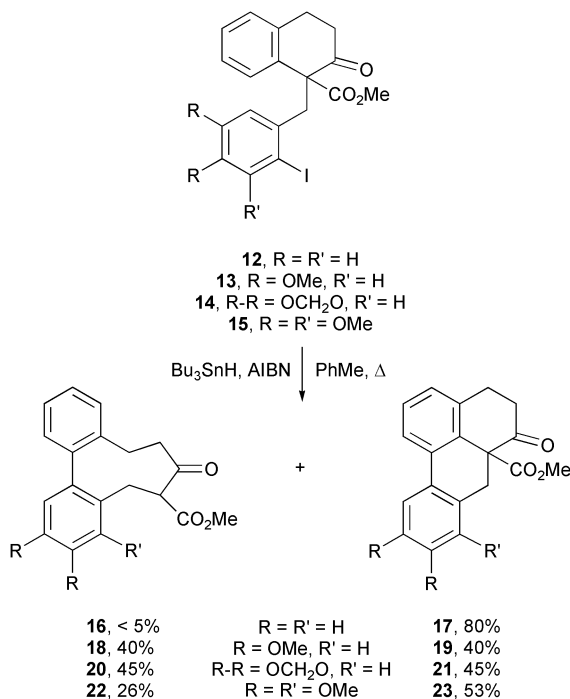
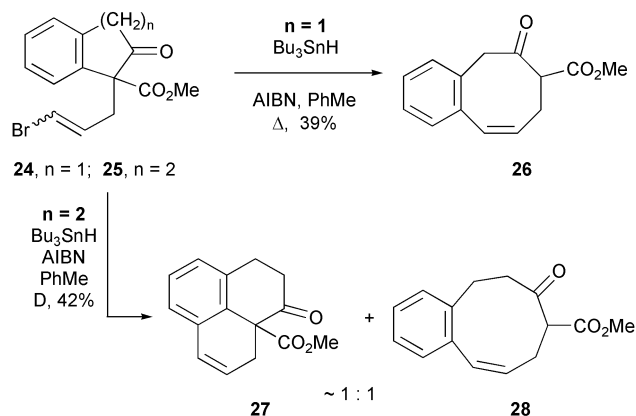


Fig. 3 ORTEP diagram of **22**.



Scheme 3



Scheme 4

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