Stereocontrolled synthesis of complex polycycles using tetrathiafulvalene mediated radical-polar crossover reactions

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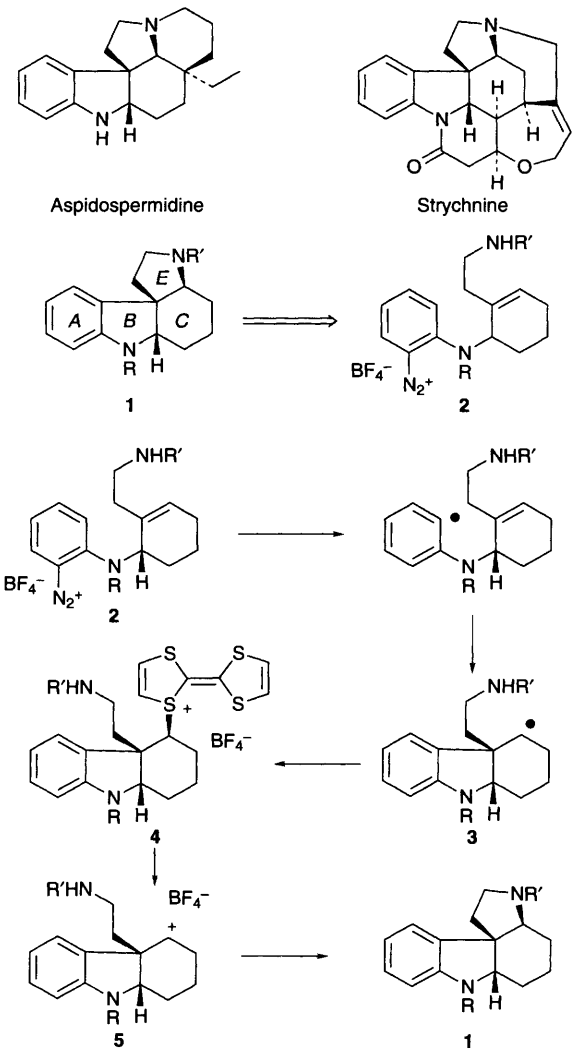
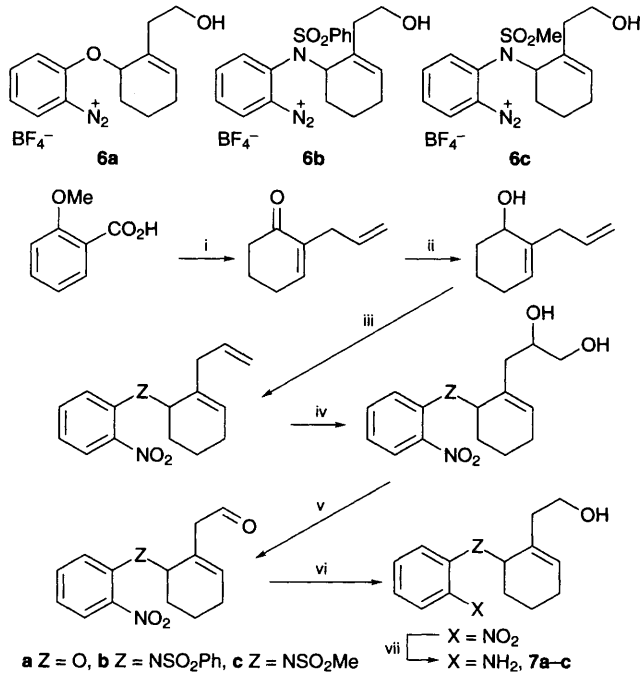
Tetracyclic heterocycles are prepared in a stereocontrolled manner using radical-polar crossover chemistry.

The preceding paper demonstrated that intramolecular nucleophiles can be used to terminate radical-polar crossover chemistry. The results were sufficiently encouraging to cause us to investigate whether this novel method could afford a direct, novel and stereoselective route to the *Aspidosperma* alkaloids.[1,2] Many members of this family, *e.g.* aspidospermidine and strychnine contain the ABCE tetracyclic substructure **1** which features defined stereochemistry at three contiguous centres. Our view was that cyclisation of the diazonium salt **2** should afford **1** with complete stereoselectivity. The initial cyclisation to form **3** must, from precedents in radical cyclisations, proceed with formation of a *cis* ring junction. The resulting radical is then predicted to trap the tetrathiafulvalene radical cation; from our experience,[3] this trapping is likely to occur from the less hindered face to give **4**. Loss of tetrathiafulvalene should then afford a secondary carbocation **5**, which should more easily afford attack by the nucleophile to give the product with all *cis*-stereochemistry. The radical-polar crossover method should be uniquely suited to the construction of this stereochemistry, by virtue of the intervening cation; if the displacement of TTF were to occur *via* a S_N2-type trajectory, a *trans* fusion should result.

This paper is concerned with establishing whether the stereochemistry of formation of tetracycles from diazonium salts such as **2** is as predicted. Compound **2** has not itself been prepared, but three of its analogues have, namely diazonium

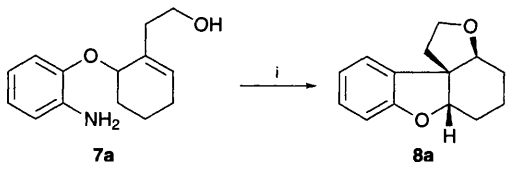




Scheme 1 *Reagents and conditions*: i, $NH_{3(l)}$, Na, −78 °C, 3-bromopropene, 1,2-dibromoethane, −78 °C to room temp., 48%; ii, $NaBH_4$, $Ce^{III}Cl_3{\cdot}7H_2O$, MeOH, 10 min., 71%; iii, **a**, 2-$NO_2C_6H_4OH$, DEAD, Ph_3P, THF, 0 °C to room temp., 2 h, 96%, **b**, 2-$NO_2C_6H_4NHSO_2Ph$, DEAD, Ph_3P, THF, 0 °C to room temp., 2 h, 97%, **c**, 2-$NO_2C_6H_4NHSO_2Me$, DEAD, Ph_3P, THF, 0 °C to room temp., 5 h, 97%; iv, OsO_4, NMO, H_2O, acetone, **a**, 15 h, 99%, **b**, 24 h, 72%, **c**, 20 h, 62%; v, $NaIO_4$, EtOH, H_2O, **a**, 17 h, 100%, **b**, 20 h, 91%, **c**, 4.5 h, 97%; vi, $NaBH_4$, EtOH, **a**, 5 min., 92%, **b**, 2 min, 86%, **c**, 10 min., 91%; vii, $NaBH_4$, $Cu^{II}(acac)_2$, EtOH, **a**, 1.5 h, 98%, **b**, 2.5 h, 24%, **c**, 2 h, 60%. DEAD = diethyl azodicarboxylate.

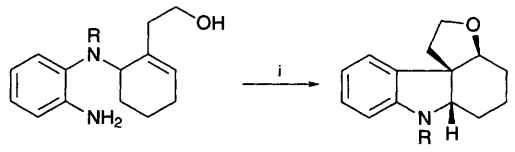
salts **6a–c**. (These diazonium salts were not isolated, but prepared *in situ* from the corresponding amines **7a–c**). The stereochemistry observed in the cyclisations of these compounds should parallel that formed with **1**.

Compounds **7a–c** were readily prepared by standard procedures, starting from 2-methoxybenzoic acid as shown in Scheme 1. Hence, Birch reduction and *in situ* allylation[4] followed by Luche reduction gave a 2-substituted cyclohex-2-enol. Mitsunobu coupling of this alcohol with either 2-nitrophenol (for **7a**) or a 2-nitrobenzenesulfonamide (for **7b,c**) gave a key bicyclic intermediate. Subsequent oxidation afforded the intermediate aldehyde, which was then subjected to sequential reduction, first with sodium boranuide (aldehyde to alcohol) and then sodium boranuide with copper(II) acetylacetonate (nitro to amine) affording the desired amines **7a–c**. Diazotisation of **7a–c** was followed by reaction *in situ* with TTF. As shown, the products were the tetracyclic compounds **8a–c**. The stereochemistry of the tetracycle **8b** was confirmed by single-crystal X-ray crystallographic analysis.



7a **8a**

Scheme 2 *Reagents and conditions*: i, $NOBF_4$, CH_2Cl_2 0 °C, 5 min followed by TTF, moist acetone, 30 min, room temp., 27%



7b,c **8b** R = SO_2Ph
c R = SO_2Me

Scheme 3 *Reagents and conditions*: i, $NOBF_4$, CH_2Cl_2, 0 °C, 1.5 h then TTF, acetone, 2 h, **b**, 68%, **c**, 75%

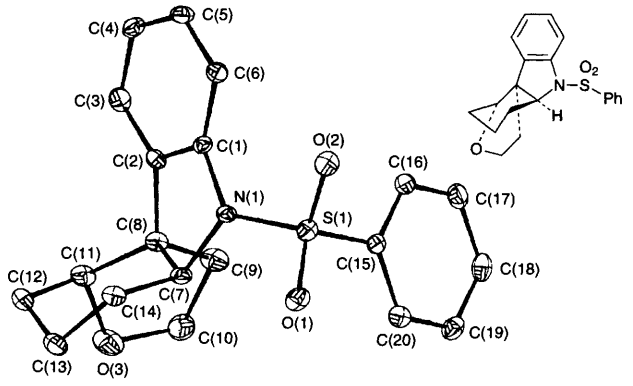


Fig. 1 X-Ray derived structure for **8b**

In conclusion, we have shown that our TTF mediated radical-polar crossover methodology can be applied to the synthesis of complex polycyclic molecules. In the case of the tetracyclic compounds discussed herein **8a–c**, the reaction proceeds stereoselectively, and suggests that this approach may be useful in the synthesis of the *Aspidosperma* alkaloids. This approach is complementary to our recently described tandem radical cyclisation chemistry.[5]

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