New Routes to Tetracycline Analogues: an Intramolecular Diels–Alder Approach

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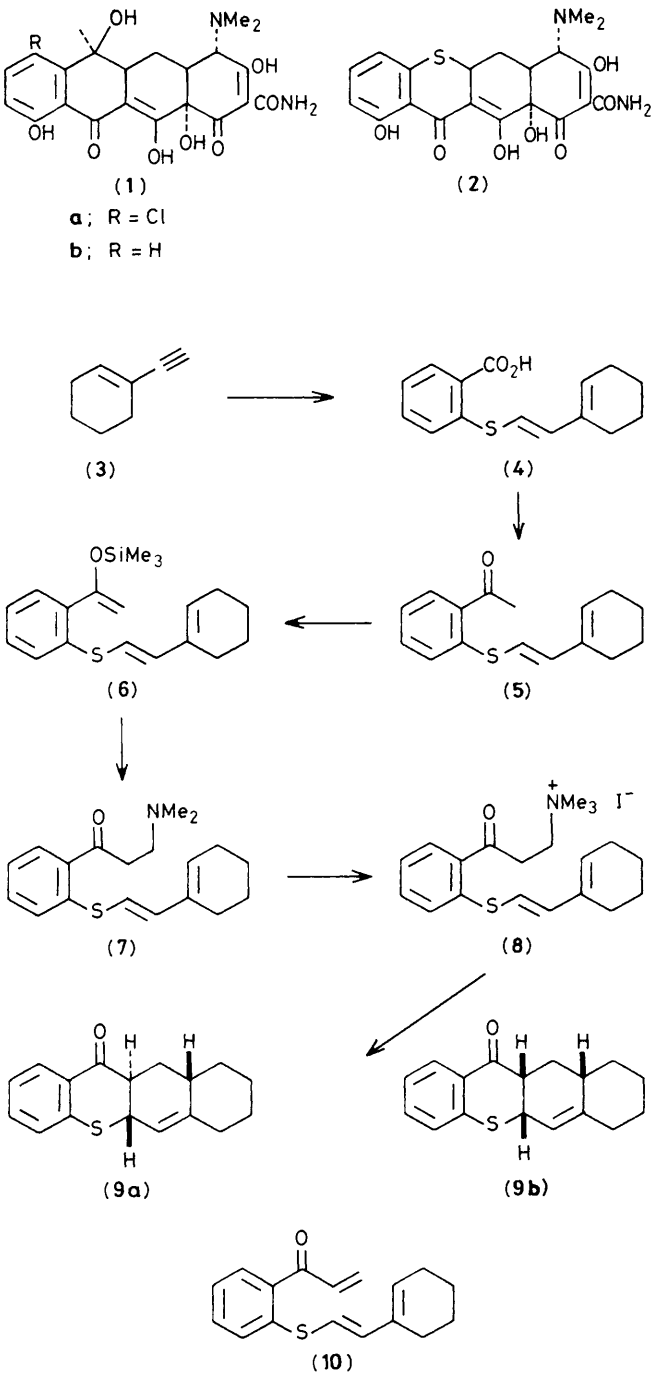
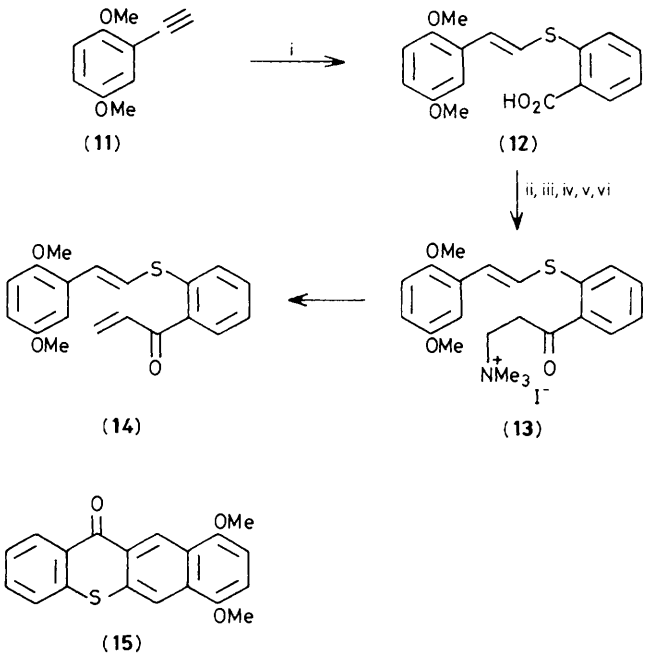
A new and short approach to tetracycline analogues is presented using an intramolecular Diels–Alder approach.

The tetracyclines are a family of broad-spectrum antibiotics which have a common perhydronaphthacene skeleton.[1] Since the discovery of chlorotetracycline[2] (**1a**), which was the first member of the family to be isolated, they have been extensively used by the medical and veterinary professions, being active against both Gram positive and negative bacteria. The fermentation-derived natural tetracyclines, the parent substance of which is tetracycline (**1b**), have been supplemented by numerous products of partial synthesis. The Merck group have recently reported a total synthesis of 6-thiatetracycline (**2**) by a procedure which followed the earlier Muxfeldt strategy for (**1**).[3] This compound has shown activity against



Scheme 1



Scheme 2. *Reagents:* i, *o*-$HSC_6H_4CO_2H$, AIBN, xylene (70%); ii, MeLi, Et_2O (76%); iii, Me_3SiCl, NaI, MeCN, Et_3N (65%); iv, $CH_2{=}\overset{+}{N}Me_2Cl^-$; v, K_2CO_3, H_2O; vi, MeI; vii, H_2O (82% from stage iv).

tetracycline-resistant organisms. In this communication we present a new approach to thiatetracycline analogues, that is flexible and would allow the construction of modified tetracyclic structures for biological screening.

Treatment of 1-ethynylcyclohexene (**3**)[4] with thiosalicyclic acid in hot xylene containing a catalytic amount of azoisobutyronitrile (AIBN) gave the sulphide (**4**) in 98% yield as a stable crystalline solid (Scheme 1). Addition of methyl-lithium (2 equiv.) to (**4**) gave the methyl ketone (**5**) (85%) which was converted into the silyl enol ether (**6**) (83%).[5] Conversion of (**6**) into (**7**) (92%) was achieved using *N,N*-dimethylmethyleneammonium chloride in acetonitrile at room temperature, followed by work-up with aqueous potassium carbonate. Methyl iodide reacted smoothly with (**7**) yielding a quaternary ammonium salt (**8**) (92%) which on suspension in boiling water[6] gave the desired tetracyclic compounds (**9a**) and (**9b**) in a combined yield of 70%. The cyclisation proceeds by way of the triene (**10**). The sequence from (**4**) to (**8**) was employed because, in our hands, vinyl-lithium failed to react with the acid (**4**).

A similar scheme was adopted for the construction of the A-ring functionalised thiatetracycline (**15**) (Scheme 2). The conditions used for the preparation of (**8**) were found to be suitable for the synthesis of (**13**). When (**13**) was heated in water no cyclisation took place but the enone (**14**) was obtained in high yield. After much experimentation, we found that (**14**) cyclised smoothly in boiling *o*-dichlorobenzene giving the tetracyclic system (**15**) as a yellow solid in 66% yield. We are now using this strategy to construct other tetracycline analogues.

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