Generation of Spirocyclic Quaternary Centres *via* a Tandem Free Radical Cyclopropylcarbinyl Rearrangement–Cyclisation Strategy†

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Regio- and stereo-specific construction of spirocyclic quaternary centres may be achieved by hydroxy-directed Simmons–Smith cyclopropanation of an allylic alcohol followed by a tandem free radical cyclopropylcarbinyl rearrangement–cyclisation reaction; generation of the spiro-fused systems is subject to stereoelectronic and kinetic control.

Within the last decade, new methods for the controlled production of carbon-centred free radicals[1] have been coupled with intramolecular cyclisation reactions of predictable regio- and stereo-selectivity[2] to provide a powerful technique for carbon–carbon bond formation in organic synthesis.[3] Although such substitution and addition reactions have been extensively studied, preparative sequences incorporating an intermediate free radical rearrangement as part of the chain are much less common,[4] particularly in all-carbon systems.

Consideration of the relative rates of ring opening and reclosure of cyclopropylcarbinyl radicals and of hex-5-ynyl radicals[5] suggested to us that the elaboration of a tandem[6] rearrangement-cyclisation strategy should prove possible under conditions of kinetic control without competing hydrogen abstraction from stannane by intermediate carbon centred radicals (**1**) or (**2**) (Scheme 1). The rapidity of cyclopropane ring opening by an adjacent carbon-centred radical has proved to be an extremely useful mechanistic probe.[7]

A second feature of the design, as illustrated for the particular case of the spiro-fused exomethylene cyclopentane, is that incorporation of the rearrangement in a rigid bicyclo-[*x*.1.0] system leads to a stereoelectronically controlled cleavage of bond (a) to produce the higher energy primary radical (**2**), as opposed to the thermodynamically favoured species (**3**) [bond (b)]. We now describe our preliminary results on the construction of spiro[4.5]decanes which support the foregoing analysis.

A suitable bicyclic precursor was readily assembled as shown in Scheme 2. 1,2-Addition of 4-lithio-1-trimethylsilylbut-1-yne to the methyl enol ether (**4**) of dimedone gave, after aqueous acidic work-up, enone (**5**). Reduction of the enone with di-isobutylaluminium hydride followed[8] by hydroxy-directed Simmons–Smith

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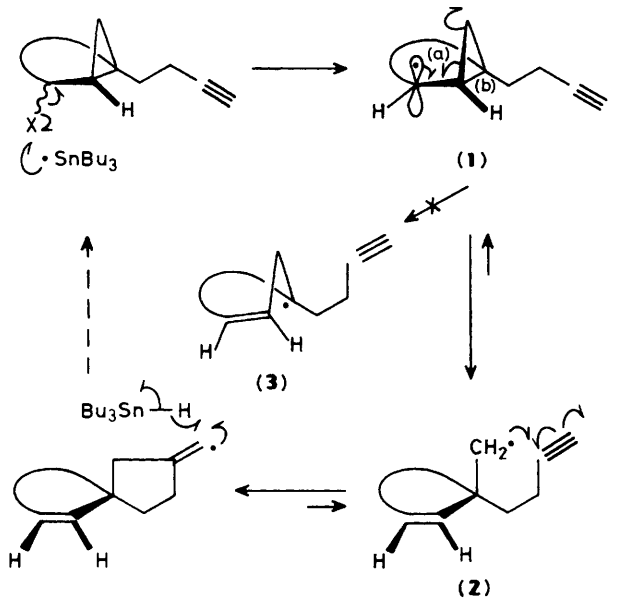
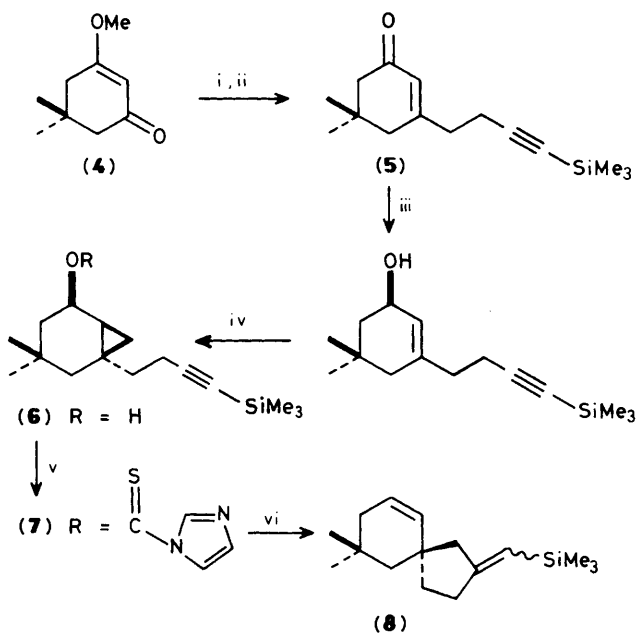
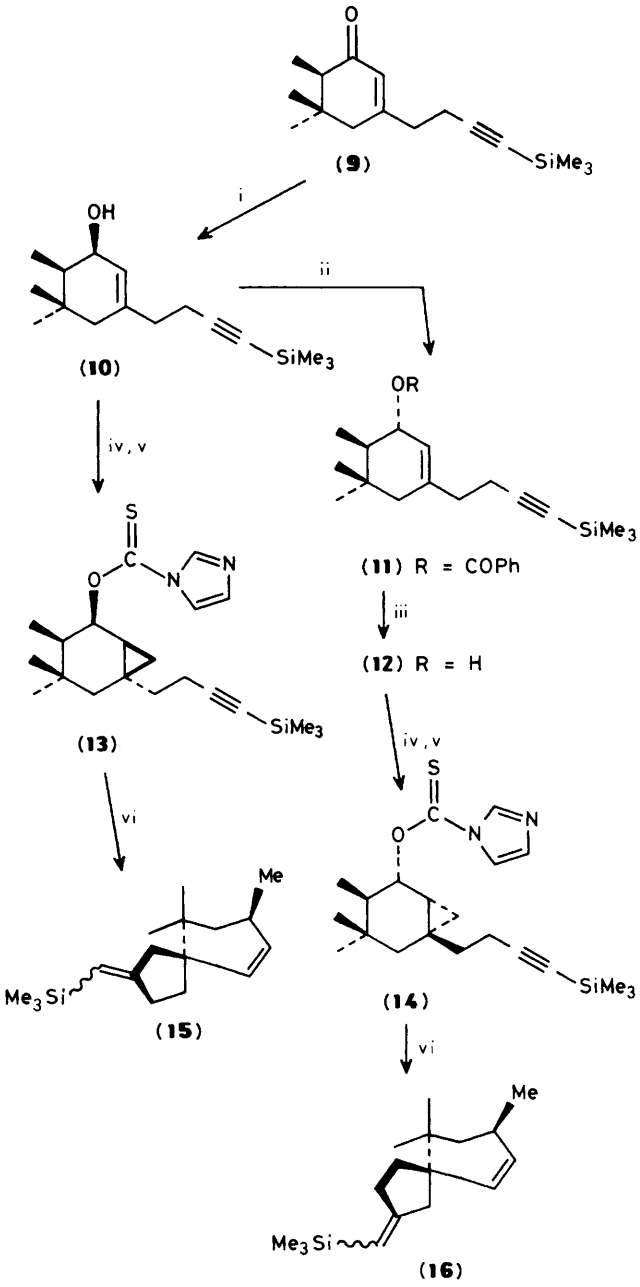


Scheme 1



Scheme 2. *Reagents*: i, $Me_3Si{-}\equiv{-}CH_2CH_2Li$; ii, H_3O^+ (Steps i and ii 80% yield); iii, di-isobutylaluminium hydride (88%); iv, CH_2I_2, Zn/Ag couple (70%); v, thiocarbonyldi-imidazole, (100%); vi, tri-n-butyltin hydride, azobisisobutyronitrile, benzene, (71%).



Scheme 3. *Reagents*: i, L-Selectride, aqueous work-up (65%); ii, diethylazodicarboxylate, triphenylphosphine, benzoic acid (65%); iii, titanium tetraisopropoxide, propan-2-ol (60%); iv, Zn/Ag couple, CH_2I_2 [from (**10**) 74% yield from (**12**) 84% yield]; v, thiocarbonyldiimidazole, (100%); vi, tri-n-butyltin hydride, azobisisobutyronitrile, benzene [from (**13**) 79% yield, from (**14**) 81% yield].

cyclopropanation furnished the bicyclic cyclopropyl carbinol (**6**). Finally, quantitative conversion to the corresponding thiocarbonyl imidazolide derivative (**7**) yielded a suitable precursor[9] for carbon-centred radical generation.

Dropwise addition of tri-n-butylstannane to a refluxing solution of (**7**) with addition of azobisisobutyronitrile (AIBN) as initiator led smoothly to the desired spirocyclic system (**8**) (71%), thus confirming the regiospecific nature and the kinetic and stereoelectronic features of the proposed sequence.

It was also of interest to demonstrate that this method can be used in a stereospecific manner. Accordingly, alkylation of the kinetic lithium enolate of enone (**5**) with methyl iodide gave the trimethyl analogue (**9**) (77%) containing the necessary stereochemical marker (Scheme 3). Efficient chemo- and stereo-selective reduction was achieved through use of L-Selectride, a feature of interest being that the major allylic alcohol (**10**) was readily separated in pure form from epimer (**12**) by simple aqueous work-up involving kinetically controlled hydrolysis of the intermediate borate esters. Inversion of configuration at the hydroxy centre of (**10**) was accomplished *via* Mitsunobu reaction[10] followed by titanium(IV) isopropoxide[11] mediated solvolysis of the intermediate benzoate ester (**11**). The power and effectiveness of the stereospecific hydroxy directed Simmons–Smith

cyclopropanation sequence was demonstrated by the consistently high yields of cyclopropyl carbinols (**13**) [74% yield from (**10**)] and (**14**) [84% yield from (**11**)]. Transformation *via* reductive deoxygenation of their derived thiocarbonyl imidazolides (**13**) and (**14**) with tri-n-butyl tin hydride as described above, generated spirocycles (**15**) (79%) and (**16**) (81%) respectively which differ only in their relative orientation of the vinyl silane moiety with respect to the methyl group marker.

Although a variety of connectivity patterns may be envisaged for the tandem rearrangement-cyclisation strategy, the above examples in the spiro-mode are of particular interest inasmuch as they present a solution to the challenging problem of stereospecific elaboration of a quaternary centre.[12]

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