

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

J. D. Harling and W. B. Motherwell*

Department of Chemistry, Imperial College of Science and Technology, South Kensington, London SW7 2AY, U.K.

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 radicals¹ have been coupled with intramolecular cyclisation reactions of predictable regio- and stereo-selectivity² 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.

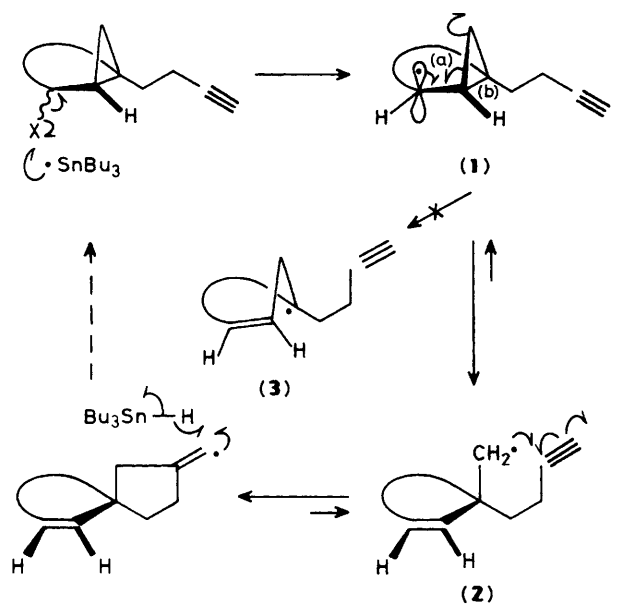
Consideration of the relative rates of ring opening and reclosure of cyclopropylcarbinyl radicals and of hex-5-ynyl radicals⁵ suggested to us that the elaboration of a tandem⁶ rearrangement–cyclisation strategy should prove possible under conditions of kinetic control without competing hydrogen abstraction 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

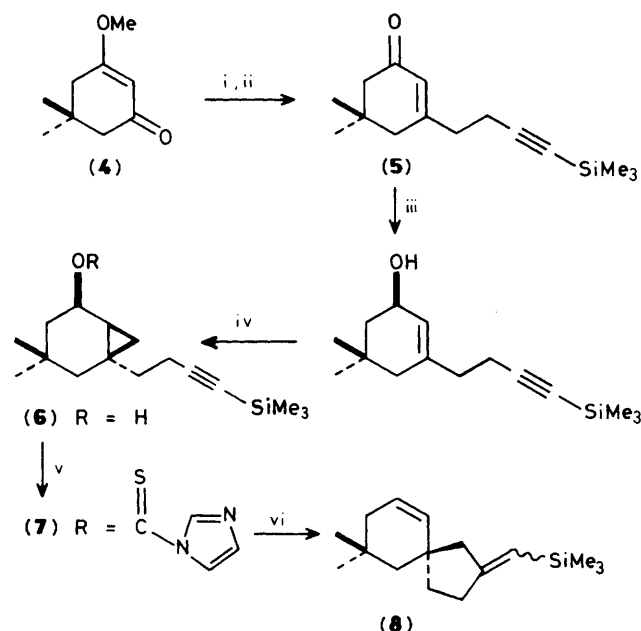
A second feature of the design, as illustrated for the particular case of the spiro-fused exomethylene cyclopentane, is that incorporation of the rearrangement in a rigid bicyclo-[x.1.0] system leads to a stereoelectronically controlled cleavage of bond (a) to produce the higher energy primary radical (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 followed⁸ by hydroxy-directed Simmons–Smith

† First presented at the Royal Society of Chemistry Autumn Meeting, Nottingham, 24th September, 1987.



Scheme 1

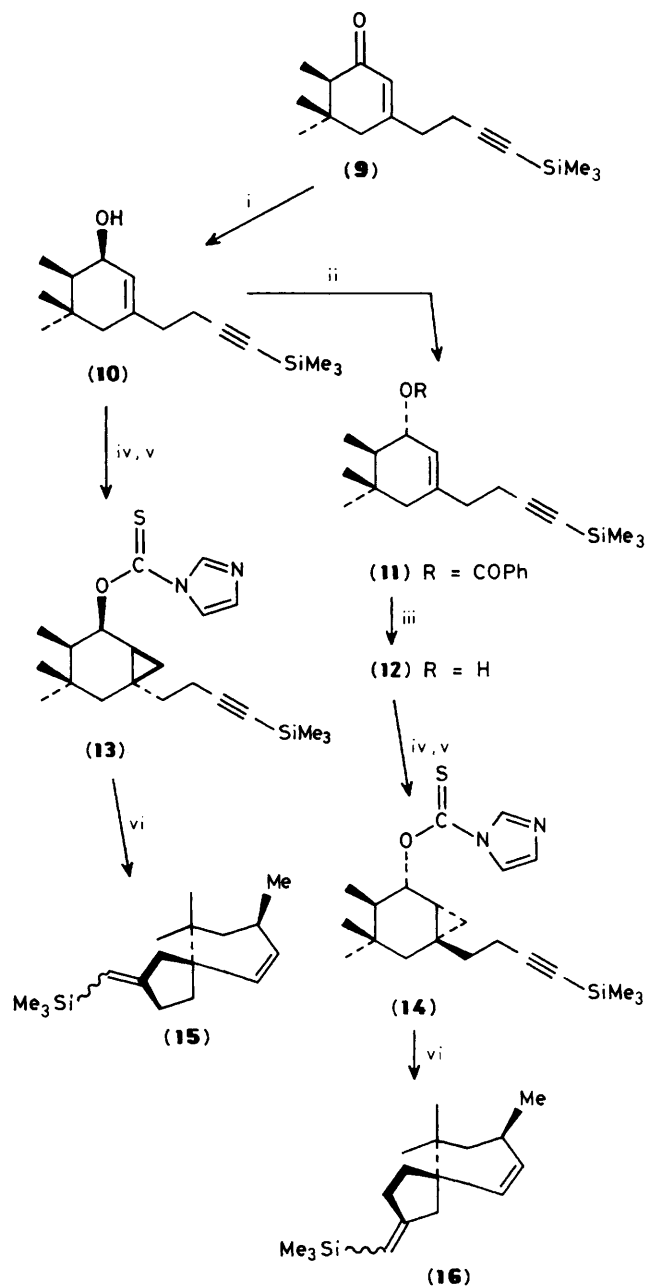


Scheme 2. Reagents: i, $\text{Me}_3\text{Si}-\text{CH}_2\text{CH}_2\text{Li}$; ii, H_3O^+ (Steps i and ii 80% yield); iii, di-isobutylaluminium hydride (88%); iv, CH_2I_2 , Zn/Ag couple (70%); v, thiocarbonyldi-imidazole, (100%); vi, tri-n-butyltin hydride, azobisisobutyronitrile, benzene, (71%).

cyclopropanation furnished the bicyclic cyclopropyl carbinol (6). Finally, quantitative conversion to the corresponding thiocarbonyl imidazole derivative (7) yielded a suitable precursor⁹ 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 regioselective 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



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, thiocarbonyldi-imidazole, (100%); vi, tri-n-butyltin hydride, azobisisobutyronitrile, benzene [from (13) 79% yield, from (14) 81% yield].

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 reaction¹⁰ followed by titanium(IV) isopropoxide¹¹ 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

We are grateful to the S.E.R.C., and to Quest International for the provision of a CASE studentship.

Received, 13th June 1988; Com. 8/02376J

References

- For recent reviews on the development of new free radical chain reactions see *inter alia*: D. H. R. Barton and W. B. Motherwell, *Pure Appl. Chem.*, 1981, **53**, 15; *Heterocycles*, 1984, **21**, 1; T. Ramaiah, *Tetrahedron*, 1987, **43**, 3541.
- A. L. J. Beckwith, *Tetrahedron*, 1981, **37**, 3073.
- For carbon-carbon bond forming radical chain reactions see *inter alia*: D. J. Hart, *Science (Washington D. C.)*, 1984, **223**, 883; G. Stork, 'Current Trends in Organic Synthesis,' Pergamon Press, Oxford, 1983, 359; B. Giese, 'Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds,' Pergamon Press, Oxford, 1986.
- For radical-induced epoxide cleavage see: D. H. R. Barton, R. S. Hay-Motherwell, and W. B. Motherwell, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2363; M. Cook, O. Hares, A. Johns, J. A. Murphy, and C. W. Patterson, *J. Chem. Soc., Chem. Commun.*, 1986, 1419.
- D. Griller and K. U. Ingold, *Acc. Chem. Res.*, 1980, **13**, 317.
- D. P. Curran and D. M. Rakiewicz, *J. Am. Chem. Soc.*, 1985, **107**, 1448 and references therein.
- J. W. Wilt, in 'Free Radicals,' ed. J. K. Kochi, Wiley-Interscience, New York, 1973, vol. 1, ch. 8, p. 399; E. C. Friedrich and R. L. Holmstead, *J. Org. Chem.*, 1971, **36**, 971.
- H. E. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, *Org. React. (N. Y.)* 1973, **20**, 1; R. E. Ireland and S. C. Welch, *J. Am. Chem. Soc.*, 1970, **92**, 7232.
- D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1574.
- O. Mitsunobu, *Synthesis*, 1981, 1.
- D. Seebach, E. Hungerbuhler, R. Naef, P. Schnurrenberger, B. Weidmann, and M. Zuger, *Synthesis*, 1982, 138.
- S. F. Martin, *Tetrahedron*, 1980, **36**, 419.