Carbon Atom Insertion: An Efficient Synthesis of Ishwarane[1]

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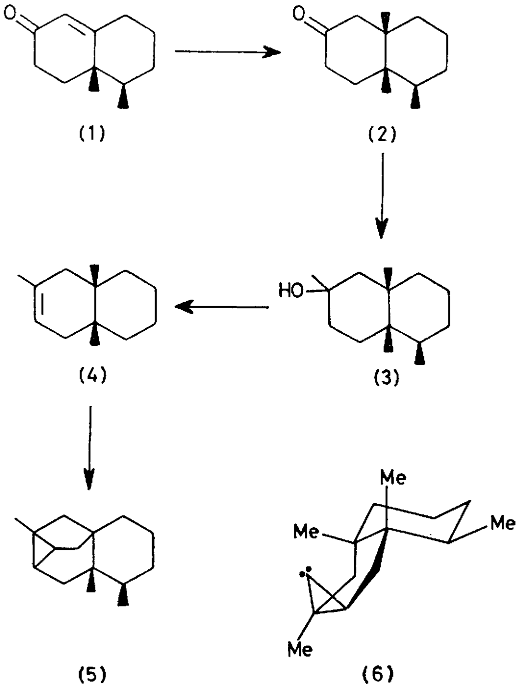
Summary A short total synthesis of the sesquiterpene ishwarane has been achieved using, as the key step, carbon atom insertion with carbon tetrabromide and methyl-lithium to form the tricyclo[3.2.1.$0^{2,7}$]octane ring system of the natural product.

Specific and efficient methods for insertion of a single carbon atom into an organic molecule would be synthetically important, but, with one exception, [2]known procedures involve at least two separate reactions. For example, the synthesis of bicyclobutanes discovered[3] by Moore and his co-workers consists of two steps; a cyclohexene is converted into a dibromocyclopropane by addition of dibromocarbene, followed by treatment of the isolated adduct with MeLi to give bicyclobutanes resulting from intramolecular insertion of the intermediate cyclopropylidene carbenoid into adjacent C-H bonds. In the one-step synthesis of allenes from alkenes discovered[2] by Untch and his co-workers, the reaction of MeLi with CBr$_4$ in the presence of an olefin gives a dibromocyclopropane, which, upon treatment *in situ* with a second equivalent of MeLi, provides the allene directly. We have found that a modification of this procedure can be used in place of Moore's method, so that a cyclohexene can be transformed into a bicyclobutane in a single operation without isolation of the dibromocyclopropane, and in a higher yield than with the old procedure.



While our work was in progress, Paquette and his coworkers, using Moore's (two-step) method, reported[4] that the *cis*-dibromocyclopropane resulting from addition of dibromocarbene (derived from CHBr$_3$) to 4-methylcyclohexene gives the tricyclo-octane formed by methyl C–H insertion rather than the expected ring C-H insertion products (bicyclobutanes). This observation led us to investigate the use of our procedure in a total synthesis of racemic ishwarane (**5**), the (−)-enantiomer of which (shown) occurs in *Aristolochia indica* Linn.[5] and other tropical plant species.[6] The synthesis of this sesquiterpene by Kelly and his coworkers[7] required 14 steps to convert the octalone (**1**) into ishwarane. By the use of carbon atom insertion, which results in the direct construction of a complex strained ring system from a simple precursor, our synthesis requires only four steps.

Three of these steps each results solely in the addition of one carbon atom to the framework of the preceding intermediate; only one step involves functional group modification, and protection of sensitive functional groups is not necessary. The octalone (**1**)[7] was first treated with lithium dimethylcuprate[8] to give a 77% yield of the *cis*-decalone (**2**)† (ν_{max} 1710 cm^{-1}) by conjugate addition. Direct addition of MeMgI to the carbonyl group of (**2**) then afforded an epimeric mixture of the tertiary alcohols (**3**) (ν_{max} 3610 and 3490 cm^{-1}) which, without purification, was dehydrated with 50% aqH$_2$SO$_4$.[9] The resulting octalin (**4**)†‡ [δ 1·60 (vinyl Me) and 5·14 (vinyl H)], formed in 74% yield from the decalone (**2**), was then treated as follows. To an ethereal solution of the octalin (**4**) and 2 mol. equiv. of CBr$_4$ at −75 °C was added 1 mol. equiv. (relative to CBr$_4$) of MeLi in ether. The resulting solution was warmed slowly to −30 °C, a second mol. equiv. of MeLi was added at that temperature, and the solution was allowed to warm to 0 °C. Upon aqueous work-up, racemic ishwarane (**5**) was isolated by preparative g.l.c. in 26% yield. This material was identical (^{1}H and ^{13}C n.m.r., mass spectroscopy, g.l.c., and t.l.c.) with an authentic sample of (−)-ishwarane from *A. indica*.

The final step is unique in being equivalent to insertion of a carbon atom by simultaneous addition to a double bond and insertion into a C–H bond. It is not immediately clear why insertion into the lower angular methyl group of (**4**) does not take place. However, conformation (**6**) of the intermediate carbenoid is expected to be largely predominant owing to the extremely unfavourable 1,3-diaxial methyl–methyl interaction in the other chair conformer. In conformation (**6**), the C–H bonds in closest proximity to the carbene centre are those of the methyl group into which insertion must occur in order for ishwarane to be formed. Also, addition of dibromocarbene to the double bond of (**4**) must occur mainly from the less hindered convex (*exo*) side, by analogy with previous results.[9,10] We are now investigating the total synthesis of the sesquiterpene ishwarone[11] by this method.§

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† Correct mass was determined by high resolution mass spectrometry.

‡ Contaminated with about 20% of the Δ^1-isomer (δ 4·91).

§ Professor Kelly has recently reported a shortened synthesis of ishwarane in which the number of steps is reduced to 10: R. B Kelly and S. J. Alward, *Canad. J. Chem.*, 1977, **55**, 1786.

[1] For the previous paper in the series 'Bicycloannulation,' see R. M. Cory and D. M. T. Chan, *Tetrahedron Letters*, 1975, 4441.
[2] K. G. Untch, D. J. Martin, and N. T. Castellucci, *J. Org. Chem.*, 1965, **30**, 8572.
[3] W. R. Moore, H. R. Ward, and R. F. Merritt, *J. Amer. Chem. Soc.*, 1961, **83**, 2019.
[4] L. A. Paquette, G. Zon, and R. T. Taylor, *J. Org. Chem.*, 1974, **39**, 2677.
[5] T. R. Govindachari, P. A. Mohamed, and P. C. Parthasarathy, *Tetrahedron*, 1970, **26**, 615.
[6] L. C. Teng and J. F. De Bardeleben, *Experientia*, 1971, **27**, 14; B. M. Lawrence and J. W. Hogg, *Phytochem.*, 1973, **12**, 2995.
[7] R. B. Kelly, J. Zamecnik, and B. A. Beckett, *Chem. Comm.*, 1971, 479; *Canad. J. Chem.*, 1972, **50**, 3455.
[8] H. O. House, C.-Y. Chu, J. M. Wilkins, and M. J. Umen, *J. Org. Chem.*, 1975, **40**, 1460.
[9] J. E. McMurry and S. J. Isser, *J. Amer. Chem. Soc.*, 1972, **94**, 7132.
[10] E. Piers, W. de Waal, and R. W. Britton, *J. Amer. Chem. Soc.*, 1971, **93**, 5113 and references therein.
[11] H. Fuhrer, A. K. Ganguly, K. W. Gopinath, T. R. Govindachari, K. Nagarajan, B. R. Pai, and P. C. Parthasarathy, *Tetrahedron*, 1970, **26**, 2371. Ishwarone has not yet been synthesized: for an unsuccessful attempted total synthesis, see D. L. Lickei, Ph.D. Thesis, Iowa State University, 1973.