Total Synthesis of *cis*-Maneonenes-A and -B

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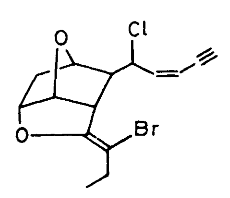
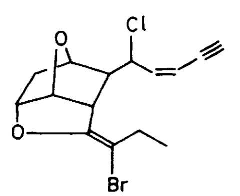
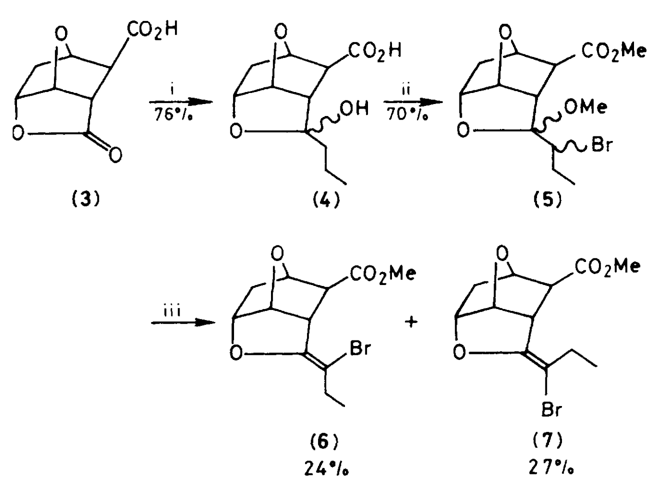
The first syntheses of *Laurencia*-derived cyclic ethers containing terminal *cis*-enyne side chains are reported which employ (for the first time in complex natural product synthesis) a recently developed partial catalytic hydrogenation of a silylated butadiyne derivative which, in turn, is derived from bis(trimethylsilyl)butadiyne.

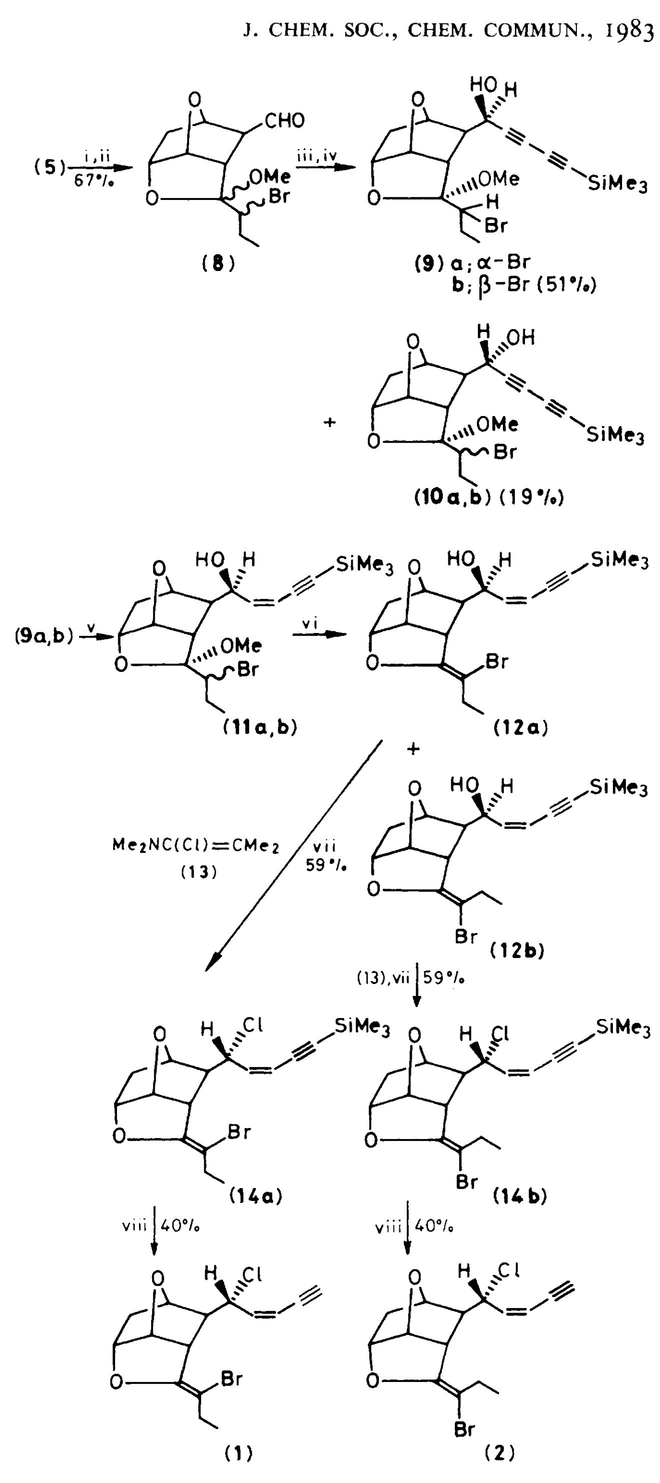
The genus *Laurencia* has proven to be a rich source of various C-15 halogenated cyclic ethers containing conjugated enyne or halogeno-allene side chains.[1] We report the first synthesis of the *cis*-maneonenes-A (**1**) and -B (**2**) which were isolated by Erickson and co-workers from the green variety of the Hawaiian alga, *Laurencia nidifica*.[2] Other related *Laurencia*-


(1)


(2)



Scheme 1. i, PrMgBr, $Me_2NCH_2CH_2NMe_2$, tetrahydrofuran (THF), −78 °C; ii, Br_2, MeOH, room temp.; iii, *N*,*N*-dimethylacetamide, reflux, 1 h.



Scheme 2. i, $LiBH_4$, THF, reflux, 4 h; ii, pyridinium chlorochromate, CH_2Cl_2, room temp., 4 h; iii, $MgBr_2$, Li–C≡C–C≡C–$SiMe_3$, Et_2O, −78 °C to room temp., 1 h; iv, flash chromatography; v, H_2, 5% Lindlar catalyst, hexane–methanol–ethyl acetate; vi, 200 °C, 0.1 mmHg, 30 min; vii, CH_2Cl_2, 0 °C, 0.5 h; viii, $Bu_4N^+F^-$, THF, room temp., 30 min.

derived metabolites to have been synthesised recently are laurencin,[3] laurencenyne,[4] and panacene.[5]

The readily available lactone (**3**)[6] gave the hemiacetal (**4**) after reaction with an excess of propylmagnesium bromide. Bromination with bromine in methanol introduced a bromine atom adjacent to the masked carbonyl group[7] with concomitant ester and acetal formation to give the oily bromo-acetal ester (**5**) as a mixture of isomers.† Pyrolysis of this mixture resulted in elimination of methanol to give the bromo-enol ethers (**6**)† (24%) and (**7**)† (27%) corresponding, respectively, to the A and B series of maneonenes (Scheme 1).

The introduction of the top side chain and the final stages of the synthesis are shown in Scheme 2. The ester (**5**) was converted into aldehyde (**8**)† (mixture of isomers) by standard methods. The aldehyde (**8**), in the presence of magnesium bromide in ether, was treated with 4-lithio-1-trimethylsilylbutadiyne (generated from the reaction of MeLi–LiBr with $Me_3Si–C≡C–C≡C–SiMe_3$[8]) to give four crystalline silylated diacetylenic alcohols (**9a,b**)† and (**10a,b**)†. The structure of isomer (**9a**) was firmly established by *X*-ray analysis. Isomers (**9a,b**) were shown to have the identical relative configuration at the propargylic carbon C-5 whereas isomers (**10a,b**) were C-5 epimers of (**9a,b**), since pyrolysis of (**9a**) and (**9b**) gave an identical pair of enol ethers, whereas pyrolysis of (**10a**) and (**10b**) gave an epimeric pair of enol ethers. Selective partial catalytic hydrogenation[9] of the individual isomers (**9a,b**) and (**10a,b**) in the presence of 5% Lindlar catalyst (type A)‡ gave the corresponding *cis*-enynes in 30—40% yield, with 50% recovery of starting material. Isomers (**11a,b**)† derived from (**9a,b**), respectively, proved to be the required *cis*-maneonene precursors. Pyrolysis of either (**11a**) or (**11b**) gave a mixture of enol ethers (**12a**)† (20%) and (**12b**)† (30%) corresponding, respectively, to the maneonenes-A and -B. A variety of methods were investigated for the preparation of the allylic chloro-compounds. The Mitsunobu[10] reagent caused desilylation. Modest yields were achieved with triphenylphosphine–*N*-chlorosuccinimide and with mesyl chloride–lithium chloride.[11] However the most effective reagent was the tetramethyl-α-

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† Satisfactory spectroscopic and analytical data were obtained for this compound.

‡ Lindlar catalyst was generously supplied by Dr. H. Maag, Hoffmann-La Roche, Basel.

chloro-enamine (**13**)[12] which converted the alcohols (**12a**) and (**12b**) in good yield into the corresponding chloro-compounds (**14a**)† and (**14b**)†. Desilylation[13] of (**14a**) gave (±)-*cis*-maneonene-A (**1**), identical in all respects except rotation with the data reported.[2] Similarly (**14b**) gave (±)-*cis*-maneonene-B (**2**) identical in all respects with an authentic sample. Although the relative stereochemistry of the chloro-substituent at C-5 was not established in the original studies of the maneonenes,[2] the stereochemistry depicted for (**1**) and (**2**) in Scheme 2 has been deduced in this synthesis from the proven structure of the diyne (**9a**) and the reasonable assumption that inversion of stereochemistry occurs in the reactions of (**12a**) and (**12b**) with (**13**) as has been shown for other chloro-enamines.[14]

We thank the S.E.R.C. for the award of studentships (to C. L. D. J.-W. and D. A. K.) and for the allocation of the 400 MHz proton n.m.r. facility at the University of Sheffield (spectra kindly recorded by Dr. B. Mann). We thank Professor K. L. Erickson for supplying spectra of (**1**) and (**2**) and an authentic sample of (**2**). We thank Dr. P. R. Raithby for carrying out *X*-ray determinations, and Professor L. Ghosez for a generous sample of (**13**).

Received, 7th January 1983; Com. 036

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