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RADICAL MACROCYCLISATIONS IN SYNTHESIS. A NEW APPROACH TO MUKULOL AND MARINE CEMBRANOLIDE LACTONES

Nicholas J.G. Cox and Gerald Pattenden*
Department of Chemistry, The University, Nottingham NG7 2RD.

Stuart D. Mills
ICI Pharmaceuticals Division, Mereside, Alderley Park,
Macclesfield, SK10 4TG.

Summary: Radical macrocyclisations, involving the allylic dienones (11b) and (16), are shown to lead to 14-membered precursors, i.e. (12) and (18), for the synthesis of the marine cembranolide lactone (6) and mukulol (5) respectively.

The wide ranging biological activities exhibited by members of the cembranoid family of marine diterpenes, e.g. desoxysarcophine (1),[1] lophotoxin (2),[2] sinularin (3),[3] asperdiol (4),[4] in combination with their diversity of structure[5] and the dearth of flexible synthetic methodology for the elaboration of 14-ring carbocycles, has made this family of natural product a particularly challenging area for the synthetic chemist. Methods that have been developed for macrocyclisation in the cembranoid field include: Ni°-mediated intramolecular coupling of bis-allylic bromides,[6] intramolecular Wadsworth-Emmons olefinations[7] together with sulphide/sulphone carbanion alkylations,[8] intramolecular Friedel-Crafts acylations,[9] additions of allyl organometallics to aldehydes,[10] [5,5]-sigmatropic ring expansion reactions,[11] and ring contraction by stereoselective Wittig rearrangements.[12,13] In connection with our interests in macrocyclic diterpenes,[14] together with radical cyclisation methods in synthesis,[15] and inspired by recent publications emanating from Porter's laboratory,[16] we have now examined the potential for intramolecular radical macrocyclisation as a strategem for synthesis in the cembranoid area. In this Letter, we describe a total synthesis of mukulol (5) found in Comiphora mukul[17] and also a new approach to the cembranolide lactone (6) isolated from soft cora Sinularia mayi.[18] Both syntheses are based on the facile 14-endo trigonal cyclisation, involving the novel allylic radical (7), shown in the Scheme.

Thus, treatment of farnesal (8) with vinylmagnesium bromide (THF-Et_2O, 0°C, 20 min) first led (92%) to the bis-allylic alcohol (9), which was then smoothly oxidised (MnO_2, CH_2Cl_2, 25°C, 18 h) to the corresponding tetraenone (10; 77%), b.p. 178-180°C at 7mm Hg, ν_{max} (film) 1680, 1670, 1630 $cm.^{-1}$, δ_H 6.52 (dd, J 18 and 11, COCH:CH_2), 6.35 (COCH:), 6.29 (dd, J 18 and 2 ,:CHH), 5.83 (dd, J 11 and 2, :CHH), 5.18 (br, 2 x :CH). Elaboration of (10) to the allylic alcohol (11a) was effected in a regio- and stereo-selective manner

using catalytic selenium dioxide in the presence of t-butylhydroperoxide (CH_2Cl_2, 0°→25°C, 2 h).[19,20] Treatment of (11a) with iodine in the presence of triphenylphosphine and imidazole[21] next gave an excellent 75% yield of the labile allylic iodide (11b). When a solution of the iodide (11b) in dry, deaerated benzene was heated under reflux for 3 h in the presence of tributyltin hydride and AIBN, work-up led to a 3 : 1 mixture of the 10-E-(12) and the 10-Z-(13) isomers of the anticipated tetradecatrienone, which were easily separated from each other by chromatography in a combined yield of 52%. The structure of the 10-E-isomer (12) followed from inspection and comparison of its spectral data with those reported by Kato et al[22] for the same compound prepared by an alternative route. The 10-Z stereochemistry (13) assigned to the minor product of the cyclisation followed from comparative cmr and pmr data with those of (12).[23] The isomer (13) is clearly the result of isomerisation, via allylic transposition, of the radical intermediate produced from (11b) prior to the observed 14-endo cyclisation.[24] The 10-E-enone (12) has been used by Kato et al in a synthesis of the cembranolide lactone (6) which is found in the soft coral Sinularia maji.[18] Our new synthesis of (12) therefore constitutes a formal synthesis of (6).

Using an identical sequence to that described above, we have also effected a new total synthesis of mukulol (5) a metabolite which was first isolated from the gum resin of the Indian tree Comiphora mukul.[17] Thus, elaboration of farnesal to the iodo-tetraeneone (16), via (14) and (15), followed by stannane-induced radical cyclisation led to a 1 : 4 mixture of (17) and (18) in a combined yield of 40%. After separation of (18) by chromatography, reduction in the presence of lithium aluminium hydride then gave (±)-mukulol (5) which showed spectral data identical with those reported for the natural product.[25]

The present studies have demonstrated conclusively the potential for radical macrocyclisation in the synthesis of 14-membered natural cembranoids. They have also highlighted the scope for allylic radical centres in natural product synthesis. Whether or not this approach to macrocyclisation via allylic radicals can accommodate more sensitive functionality in the substrates than we have examined, remains to be established. This feature is currently under investigation.[26]

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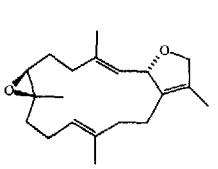

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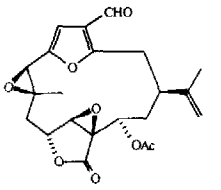

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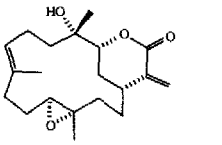

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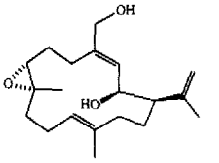

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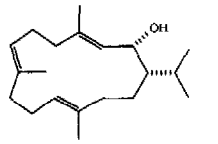

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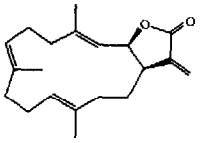

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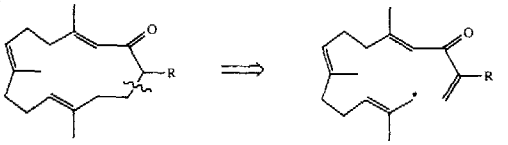
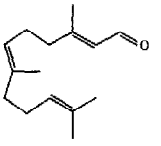


(7)

Scheme



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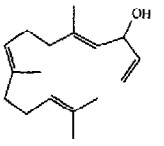

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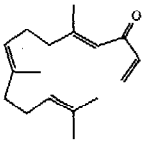

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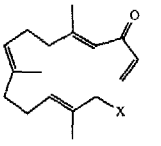
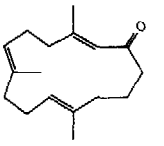


(11)

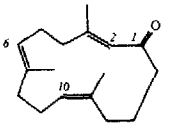
a X = OH
b X = I



(12)

steps

(6)



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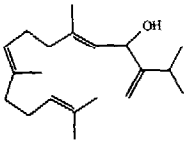

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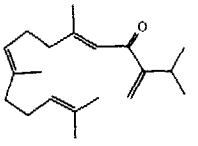

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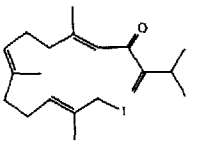

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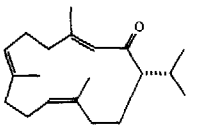

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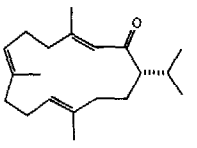

(18)

→ (5)

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20. Satisfactory spectroscopic data together with microanalytical and/or mass spectrometric data were obtained for all new compounds.
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23. Compound (13) showed: Ω_H 1.59 (C-7-Me), 1.66 (C-11-Me), 2.07 (C-3-Me), 4.92 (C-6-H), 5.96 (C-10-H), 5.98 (C-2-H); Ω_C 16.0 (C-7-Me), 19.0 (C-3-Me), 23.0 (C-11-Me), 135.0 (C-7), 138.0 (C-11), 157.0 (C-3), 202 (C-1) p.p.m.
24. No additional products, whose formation could be accounted for as a result of competitive 8-exo,10-exo or 12-endo cyclisation modes, were isolated and characterised.
25. cf T.Kato, T.Kobayashi, T.Kumagai, and Y.Kitahara, Synthetic Commun, 1976, 6, 365.
26. A range of alternative radical macrocyclisation approaches to cembranoids have been evaluated, and these will be discussed in a full publication.

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