

Stereoselective Bakkane Synthesis: (\pm)-Palmosalide C

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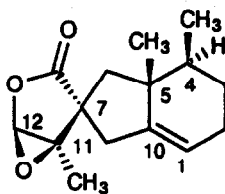
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Abstract: Palmosalide C, a spiro β,γ -epoxy- γ -butyrolactone sesquiterpene from the soft coral *Coelogorgia palmosa*, has been stereoselectively prepared in racemic form from 1,6-dimethylcyclohexene.

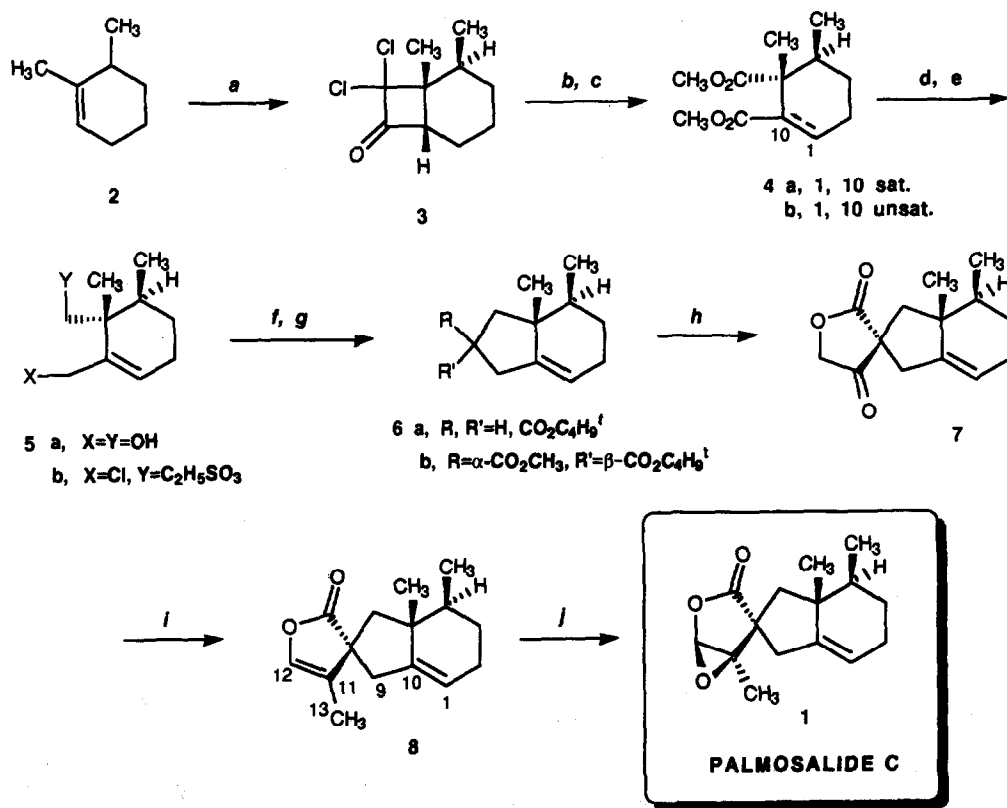
Palmosalide C was isolated by Fenical and co-workers from the telestacean octocoral *Coelogorgia palmosa*, a rare gorgonian-like soft coral found in the Indian Ocean, and was shown through X-ray analysis to have the novel structure and relative stereochemistry depicted in 1.¹ While bearing considerable resemblance to the terrestrial bakkanes,^{2,3} this sesquiterpene differs by the presence of the unusual spiro β,γ -epoxy- γ -butyrolactone function, which is found in only a few other sesquiterpenes such as dysetherin,^{4a} ptychanolide,^{4b} spiro tubipolide,^{4c} and spirodensifolins A and B^{4d} (none synthesized to date), and through its relative configuration at the C-7 spiro center and unsaturation at C-1-C-10. In this communication the first synthesis of palmosalide C is reported.



PALMOSALIDE C

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Scheme



a CCl₃COCl, POCl₃, Zn-Cu, ether, 20 °C. b *n*-C₄H₉Li, THF, -78 °C, then (CH₃CO)₂O, -78 → 20 °C; RuCl₃, NaIO₄, CCl₄-CH₃CN-H₂O, 20 °C; CH₂N₂, ether. c LDA, THF, HMPA -78 °C, then C₆H₅SeCl; O₃, CH₂Cl₂, -78 °C, then (C₃H₇)₂NH, -78 → 20 °C. d DIBAL-H, C₆H₅CH₃, 0 °C. e C₂H₅SO₂Cl, collidine, CH₂Cl₂, 20 °C. f (CH₃)₃CO₂CCH₂CO₂CH₃, NaH, HMPA, 0 → 20 °C, then NaCN, 110 °C. g LDA, NCCO₂CH₃, -78 → 20 °C. h CF₃CO₂H, CH₂Cl₂, 20 °C, then evaporation, SOCl₂, DMF, 60 °C, then evaporation, CH₂N₂, ether, 0 °C, then evaporation, aq HCl-CH₃OH, 0 °C. i CH₃MgBr, ether, 0 °C; SOCl₂, C₅H₅N, C₆H₅CH₃, 60 °C, separation (Δ¹¹⁽¹²⁾/Δ¹¹⁽¹³⁾ = 1/1.5).¹⁴ j SO₂Cl₂, C₆H₅CH₃, 20 °C; *m*-ClC₆H₄CO₃H, CH₂Cl₂, 20 °C, separation (nat/iso = 1.2/1); Zn, CH₃CO₂H-ether.

Vicinal dicarboxylation⁵ of 1,6-dimethylcyclohexene through dichloroketene cycloaddition^{3a,6} followed by oxidative cleavage of the resulting cyclobutanone **3** produced highly stereoselectively the succinate **4a**⁷ after esterification in 67 % overall yield. It was found that the introduction of unsaturation in **4a** to give **4b**⁷ could best be accomplished through a phenylselenenylation–oxidative elimination tandem⁸ (62 %), although iodination–elimination could also be successfully used for this purpose. The diester **4b** on treatment with diisobutylaluminum hydride in toluene solution at 0 °C then furnish in 90 % yield the diol **5a**⁷, mp 58 °C, which was converted directly to the bis-electrophile **5b** (65 %) with ethanesulfonyl chloride in the presence of collidine in dichloromethane.⁹

It had initially been hoped that the dienolate derived from 3-methylbut-2-enolide¹⁰ would provide a means of obtaining lactone **8** directly from **5b**, but this proved impossible to translate into practice, and therefore a longer, but more stereochemically rational, approach was developed. One-pot treatment of **5b** in hexamethylphosphoric triamide with *tert*-butyl methyl malonate in the presence of 2 equiv of sodium hydride and then with excess sodium cyanide¹¹ cleanly delivered in 55 % yield the hydrindane ester **6a**⁷, from which lactone **7**⁷, mp 117-118 °C, could be produced via **6b**⁷ as indicated in 60 % overall yield and *with total stereochemical control*.¹² The conversion of **7** to the key intermediate, diene **8**⁷, was next accomplished through successive treatment with methylmagnesium bromide in ether and thionyl chloride–pyridine in warm toluene.^{13,14}

After considerable experimentation, a novel protocol was found for effecting the desired regioselective epoxidation of **8** at the less reactive of the two olefinic double bonds. Allylic chlorination of the diene with sulfuryl chloride¹⁵ cleanly introduced in 75 % yield a C-1 β -chloro substituent, which nicely served to deactivate¹⁶ the hydrindane double bond (now Δ^9) toward epoxidation. The epoxidation, carried out with *m*-chloroperbenzoic acid in dichloromethane, generated regioselectively as desired in 84 % yield a separable 1.2:1 mixture of stereoisomers. The more abundant epoxide stereoisomer^{7,17} on exposure to zinc dust in acetic acid-ether underwent reduction with concomitant double bond retransposition to produce in 93 % yield racemic pamosalide C, mp 129-130 °C, identified by direct spectroscopic and chromatographic comparison with the naturally derived material.

Work directed toward the preparation of several related sesquiterpenes through the use of this potentially general synthetic approach is currently being carried out in our laboratory.

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