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STEREOSELECTIVE TOTAL SYNTHESIS OF (±)-ISOLOBOPHYTOLIDE, A MARINE CEMBRANOLIDE NATURAL PRODUCT

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Summary: The total synthesis of (±)-isolobophytolide (**20**) has been achieved via a route involving pi-allyl palladium initiated macrocyclization of sulfone ester **8** and subsequent carboxy inversion of the macrocyclic acid **11** to introduce the C-14 lactone oxygen. Lactone α-methylenation was effected by dehydration of the hydroxymethyl derivative **19** with 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate-$CuCl_2$.

The cembranoid diterpenes, a widespread class of natural products of plant and animal origin,[1] have been the focus of considerable recent synthetic effort.[2] Work to date has been largely confined to the relatively simple cembrenes and cembrenols while the more complex cembranolides have as yet received scant attention.[3] We recently described an efficient method for coupling lithiated allylic sulfides and sulfoxides with allylic alcohol epoxides via the magnesium alkoxide derivatives (*e.g.* I + II → III).[4] In the course of that study we prepared the sulfone diol 1, a potential cembranolide synthetic intermediate. We now describe the stereoselective conversion of that diol to isolobophytolide (**20**), a major terpenoid component of the soft coral *Lobophytum crassum*.[5]

Our plan entailed conversion of the coupling product III to the pentenolide IV via carboxylation and partial hydrogenation. Kinetically controlled 1,4-axial Michael addition of a phenylsulfonylacetate unit would introduce the first of the two additional stereo centers. Macrocyclization of the Michael adduct V would be achieved by using pi-allyl palladium methodology. Desulfonylation followed by equilibration was expected to afford acid VI as the more stable C14 epimer. Introduction of the C14 oxygen would be accomplished through carboxy inversion of acid VI with retention of stereochemistry. Following this, translactonization, internal epoxide formation and lactone α-methylenation would complete the synthesis.

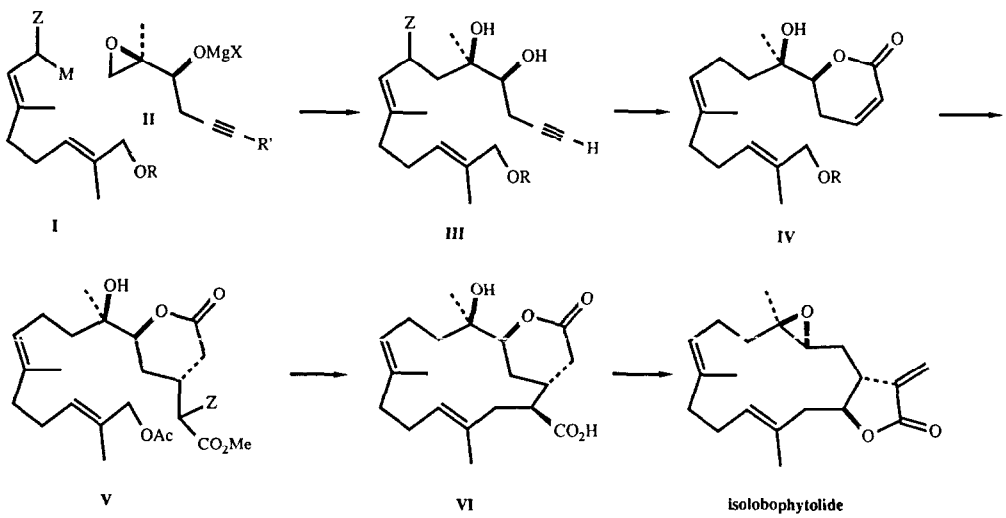
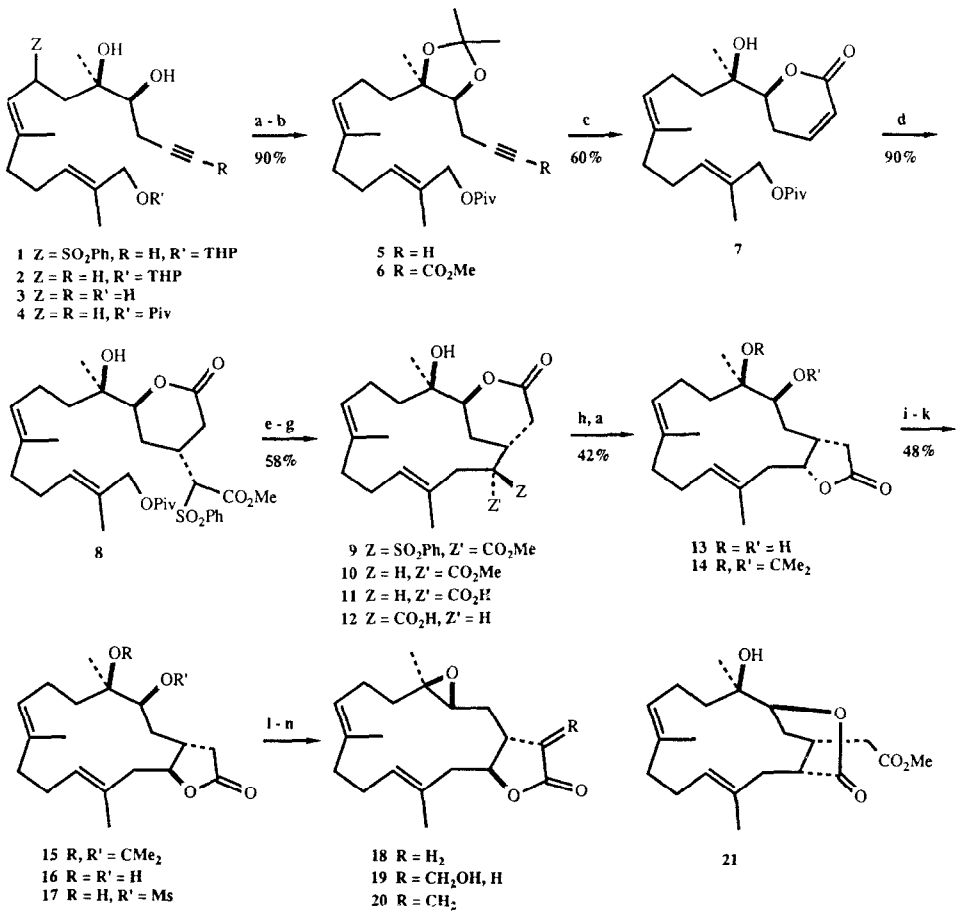


Figure 1. Synthetic plan for isolobophytolide

The key intermediate **4** was efficiently produced from sulfone diol **1** by desulfonylation with 6% Na(Hg) in MeOH at -78°C, hydrolysis of the THP ether in methanolic *p*-TsOH and esterification with pivaloyl chloride in pyridine-CH_2Cl_2. The acetonide **5** upon lithiation and treatment with methyl chloroformate afforded the acetylenic ester **6**. Hydrogenation of the derived diol over Pd-$BaSO_4$ followed by heating with 10-camphorsulfonic acid in THF gave the pentenolide **7**. As expected by analogy with related 1,4-additions of organocopper reagents,[6] Michael addition of methyl α-phenylsulfonylacetate to this conjugated ester led to the trans disubstituted valerolactone **8** in high yield and excellent stereoselectivity.

Scheme I



1 Z = SO_2Ph, R = H, R' = THP
2 Z = R = H, R' = THP
3 Z = R = R' = H
4 Z = R = H, R' = Piv

5 R = H
6 R = CO_2Me

7

8

9 Z = SO_2Ph, Z' = CO_2Me
10 Z = H, Z' = CO_2Me
11 Z = H, Z' = CO_2H
12 Z = CO_2H, Z' = H

13 R = R' = H
14 R, R' = CMe_2

15 R, R' = CMe_2
16 R = R' = H
17 R = H, R' = Ms

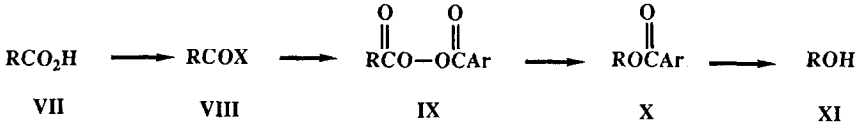
18 R = H_2
19 R = CH_2OH, H
20 R = CH_2

21

a) $CH_2=C(OCH_3)CH_3$, ppts, CH_2Cl_2; b) LDA, THF, -78°C; $ClCO_2Me$; c) MeOH, H_2O, H_2SO_4; H_2/Pd-$BaSO_4$, C_5H_5N; 10-camphorsulfonic acid, THF; d) $PhSO_2CH_2CO_2Me$, KO-*t*-Bu, *t*-BuOH, DMSO, 25°C; e) BSA, THF; Pd(PPh_3)$_4$, $Ph_3PCH_2CH_2PPh_2$; f) 6% Na(Hg), MeOH, THF, -78°C; g) NaOMe, MeOH; NaOH, THF, H_2O; HCl, H_2O, THF, Et_2O, 0°C, inverse addition; h) $ClCO_2Me$, Et_3N, THF, CH_2Cl_2, -78°C; *m*-$ClC_6H_4CO_3Na$, CH_2Cl_2, THF, -78°C; NH_4Cl, H_2O; EtOAc, Et_2O, 25°C, 2 da; NaOH, H_2O, THF; H_2O, HCl, 0° to 25°C; i) NaOH, H_2O, DME; H_2O, HCl, 0°C; CH_2N_2, CH_2Cl_2, Et_2O, -20°C; MsCl, C_5H_5N, CH_2Cl_2, 0°C; NaOH, H_2O, DME; H_2O, HCl; j) MeOH, Amberlite IR-120, 60°C, 4 h; k) MsCl, C_5H_5N, -20°C; l) Triton-B OH, MeOH, THF, -50°C; m) LDA, THF, -30°C; CH_2O (g); n) $O(CH_2CH_2)_2N^-MeCH_2CH_2N=C=NC_6H_{11}$, OTs^-, $CuCl_2$, CH_3CN, THF.

Cyclization of the sulfonyl ester pivalate **8** was readily achieved upon slow addition of the enol TMS derivative to $(Ph_3P)_4Pd$ in refluxing THF with added diphos, all at moderate dilution.[7] The product **9** was isolated as a single crystalline diastereoisomer.[8] Desulfonylation at -78°C with 6% Na(Hg) in methanol afforded the lactone ester **10** exclusively. Saponification of **10** followed by addition of the basic solution to excess aqueous HCl gave a 40:60 mixture of readily separable lactone acid **11** and a diacid. The latter, on heating in benzene, yielded the lactone acid **12**. Acid **11** could be esterified (CH_2N_2) and the epimerization-saponification repeated to give additional acid **12**. Pure acid **11** was best obtained by methanolysis of lactone ester **10** followed by saponification of the resulting "thermodynamic" lactone **21**.

Carboxylic acids undergo a Baeyer-Villiger type "carboxy inversion" with retention of stereochemistry upon conversion to mixed acylperoxides (*e.g.* IX) followed by heating.[9]



Accordingly, acids **11** and **12** should be convertible to lactones **13** and **16**, respectively.

Formation of the mixed acyl peroxides by treatment of **11** and **12** with oxalyl chloride in benzene followed by MCPBA and 2,6-lutidine[9] led to partial epimerization at C14 and decomposition, especially with **12**, a result attributable to the instability of the intermediate acid chlorides. The modification of Rosen using DCC as the condensing agent for acyl peroxide formation was unsuccessful.[9c] Therefore, a new procedure was devised employing the mixed ethyl carbonic anhydride (*e.g.* VIII, $X = OCO_2Et$) and subsequent treatment with sodium *m*-chloroperoxybenzoate. This led to reproducibly higher yields of cis lactone **13** from acid **11**. The yield of trans lactone **16** also increased but only to 10% or so. After numerous unsuccessful attempts to improve this step, we elected to complete the synthesis using cis lactone **13**.

The crystalline acetonide derivative **14**,[8] upon saponification followed by careful acidification and esterification with diazomethane, afforded the expected hydroxy ester. Conversion to the mesylate derivative followed by saponification led to the trans lactone **15**. The carbinyl proton of this lactone appeared at $\delta = 4.14$ ppm *vs.* $\delta = 4.82$ ppm for the cis lactone **14**. These chemical shifts are characteristic of cis and trans fused cembrane 1,14-γ-lactones.[10]

Diol **16** was converted to epoxide **18** via monomesylation and base treatment. A convenient two-step α-methylenation sequence was developed for lactone **18** consisting of hydroxymethylation with LDA and gaseous formaldehyde then dehydration of the hydroxymethyl lactone **19** with 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate[11]-$CuCl_2$.[12] Filtration of the reaction mixture through a column of silica gel to remove the highly polar urea by-product and unreacted diimide afforded (±)-isolobophytolide (**20**) whose high field ^1H NMR spectrum and TLC mobility matched those of the natural material.

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10. We have found the carbinyl (C14) proton of cis fused 1,14 lactones (8 examples) to appear at 4.7-4.8 ppm whereas the corresponding proton of trans fused lactones (3 examples) is seen a 3.9-4.1 ppm.

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