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STEREOSELECTIVE TOTAL SYNTHESIS OF CEMBRANOLIDES THROUGH CYCLIZATION OF A HOMOCHIRAL (α-ALKOXYALLYL)STANNANE PRECURSOR

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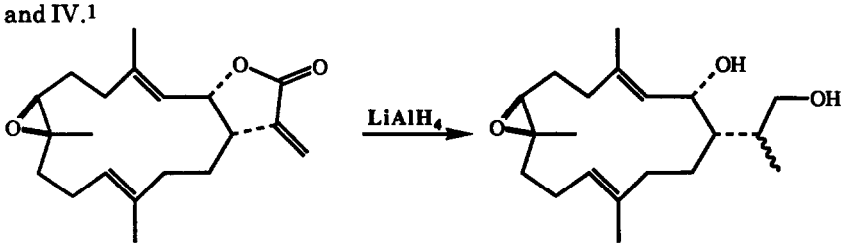
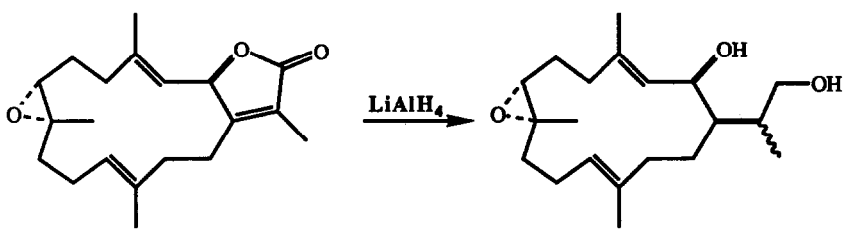
Summary: The homochiral hydroxy enol ether **2**, secured through BF_3-promoted cyclization of alkoxy stannane **1**, was elaborated to the unnamed cembranolide **V**, a constituent of a soft coral inhabitant of the Great Barrier Reef. The synthesis confirms the absolute stereochemistry of the natural product.

In a recent report on cembranolide constituents of the Great Barrier Reef, Coll and co-workers described a chemical correlation of epoxy lactone I, from the soft coral *Efflatounaria variabilis*, with *ent*-sarcophine III, a cembranolide of known configuration, through comparison of the reduction products II and IV.[1]

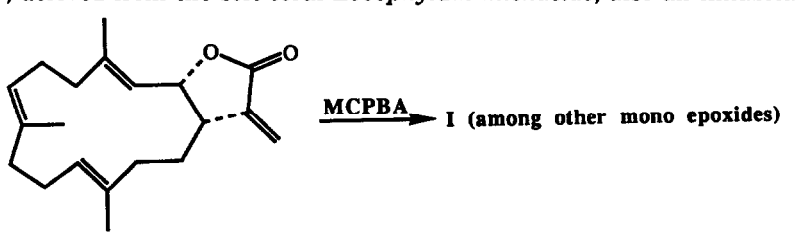


I II $[\alpha]_D$ -46°



III IV $[\alpha]_D$ +45°

They also noted that I was produced along with other epoxides upon monoepoxidation of an unnamed cembranolide V, derived from the soft coral *Lobophytum michaelae*, also an inhabitant of the Great Barrier Reef.[2]



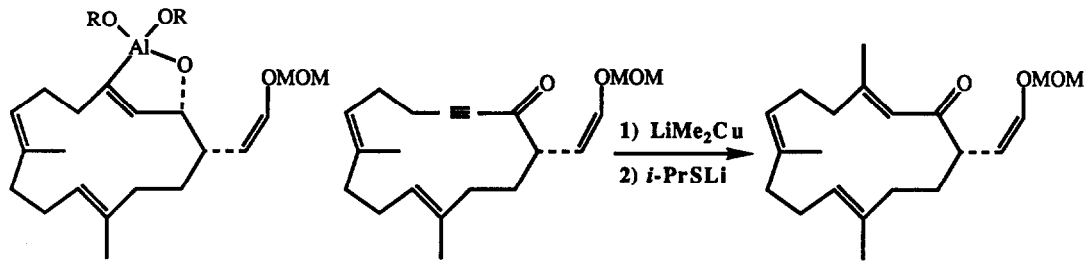
V

This correlation of V with I and I with III was used to assign absolute stereochemistry to V and I.

We recently completed a total synthesis of the racemic form of cembranolide V by a stereoselective route featuring a highly efficient cyclization of an (α-alkoxyallyl)stannane precursor.[3] We subse-

quently showed that through use of the homochiral alkoxystannane 1, this cyclization could be employed to produce a cembranoid precursor 2 of the indicated absolute stereochemistry in 90% ee.[4] It was of interest to examine the conversion of this homochiral cyclization product to the unnamed cembranolide V in order to confirm the configurational assignment and to further explore methodology for cembranolide synthesis.

In our earlier synthesis of (±)-V we were unable to efficiently iodinate the vinylalanate VI owing to competing reactions with the enol ether double bond.[3] Consequently an alternative sequence for methylation of the alkyne was developed through methylcuprate addition to alkynone VII followed by equilibration.[3]



VI VII VIII

For the present application we were concerned that the requisite equilibration step leading to the (*E*)-enone VIII would cause racemization of the C-1 side chain. We therefore pursued the methodology outlined in Scheme I. Accordingly, the interfering enol ether was removed through hydrolysis and reduction to the diol 3. This diol was smoothly converted to an 88:12 mixture of the crystalline vinyl iodide 4 and the protonolysis product 5 in 77% yield.[5] Iodide 4 was methylated by prolonged treatment with $LiMe_2Cu$[6] at 0°C affording the crystalline cembranoid 6 in 85% yield. This result stands in sharp contrast to our previous unsuccessful efforts to methylate the analogous vinylic iodide obtained in low yield from alanate VI.[3]

Several attempts at direct oxidation of diol 6 to lactone 11 were unpromising[7] so a multistep sequence was employed as shown. Methylenation[8] of lactone 11 afforded the cembranolide V, $[\alpha]_D^{25}$ +78° (lit.[2] $[\alpha]_D$ +77.9°), whose ^1H and ^{13}C NMR spectra proved identical to those of the natural product.

These findings support the assignments of absolute stereochemistry proposed for V and I and demonstrate the applicability of the Corey iodination-methylation sequence in macrocyclic propargylic alcohols such as 3.[6] Furthermore, the present synthesis of V is the first recorded for a nonracemic cembranolide.[9]

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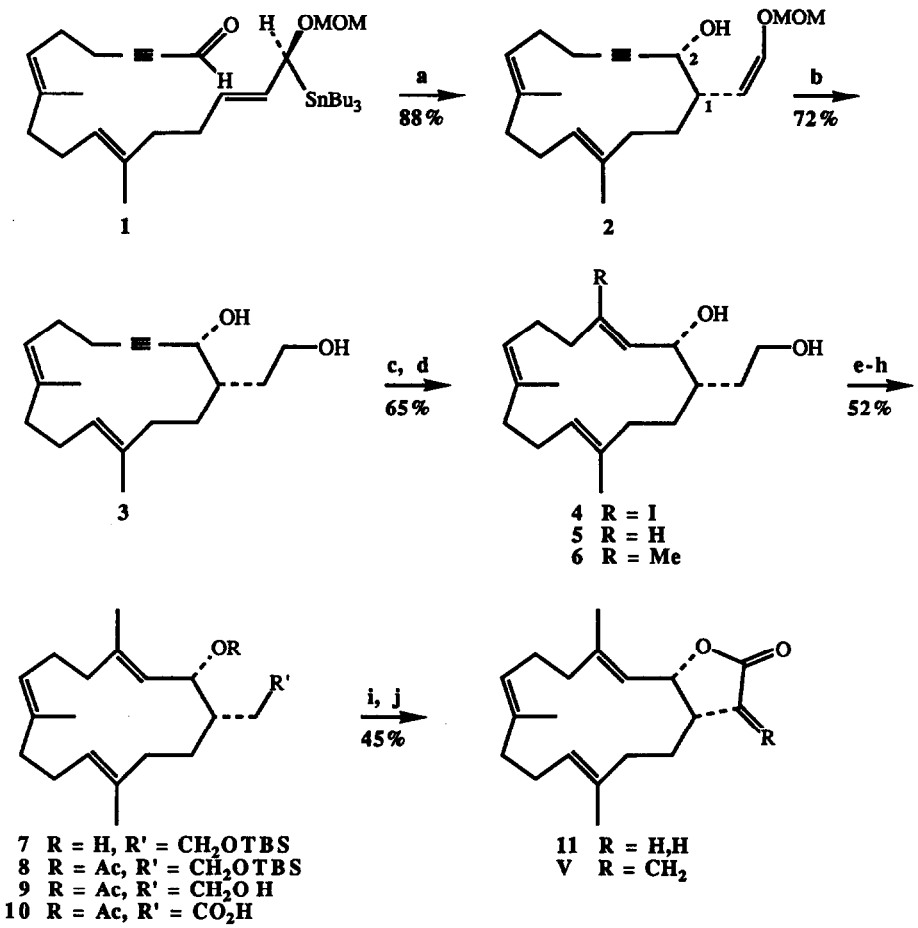
Scheme I[a, b]



[a](a) $BF_3 \cdot Et_2O$, CH_2Cl_2, -78°C; (b) 10% HCl, THF; $NaBH_4$, EtOH; (c) Red-Al, THF; I_2, THF; (d) $LiMe_2Cu$, THF, 0°C, 4 da; (e) TBSCl, Et_3N, CH_2Cl_2; (f) AcCl, C_5H_5N, 0°C; (g) TBAF, HOAc, THF; (h) PDC, DMF, 25°C; (i) K_2CO_3, MeOH; DCC, DMAP, CH_2Cl_2; (j) LDA, THF, $(CH_2O)g$; MsCl, Et_3N; DBU, C_6H_6, 0°C.

[b]Abbreviations: ADD = azodicarbonyl dipiperidide; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC = 1,3-dicyclohexylcarbodiimide; DMAP = 4-(*N*,*N*-dimethyl)aminopyridine; DMF = Me_2NCHO; LDA = $LiN(i\text{-}Pr)_2$; MCPBA = *m*-$ClC_6H_4CO_3H$; MOM = $MeOCH_2$; Ms = $MeSO_2$; PCC = pyridinium chlorochromate; PDC = pyridinium dichromate; Red-Al = $(MeOCH_2CH_2O)_2AlH_2Li$; TBAF = $(n\text{-}Bu)_4NF$; TBS = *t*-$Bu(Me)_2Si$-; THF = tetrahydrofuran.

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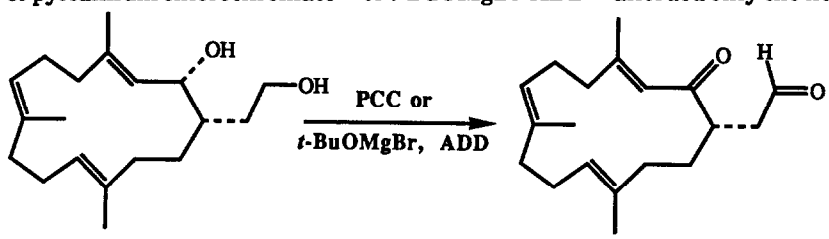
7. The use of pyridinium chlorochromate[10] or *t*-BuOMgBr-ADD[11] afforded only the keto aldehyde i.



6 i

Swern oxidation[12] or Ag_2CO_3[13] caused decomposition of the starting material.

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