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FURANOCEMBRANOLIDE INTERCONVERSIONS. TRANSFORMATION OF PSEUDOPTEROLIDE INTO TOBAGOLIDE AND ITS REVERSAL

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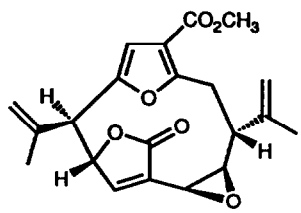
Summary: Pseudopterolide is efficiently transformed into tobagolide by reaction with dimethylamine. Sequential treatment of tobagolide with methyl iodide and sodium hydride results in intramolecular S_N' displacement with reconstruction of pseudopterolide.

The gorgonian corals of the genus *Pseudopterogorgia* have become recognized as important sources of a small class of structurally complex 12-membered furanocembranolides valued for their cytotoxic and anti-inflammatory properties. Following the original characterization of pseudopterolide (1) in 1982,[1] Fenical subsequently identified kallolide A (2a) and kallolide B (2b) as lesser oxygenated analogues.[2] More recently, Chan, McLean, and their co-workers reported on the isolation of tobagolide (3a), the first nitrogenous pseudopterane, from *P. acerosa* in the month of July.[3] The presence of 3a



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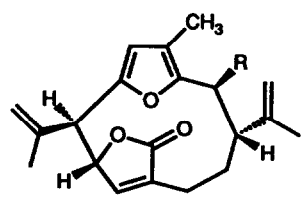
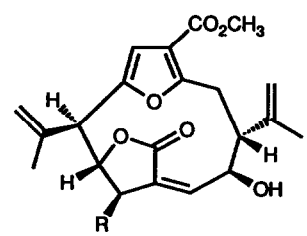
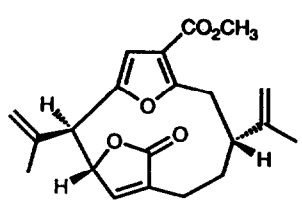


2a, R = OH
2b, R = H



3a, R = $N(CH_3)_2$
3b, R = OCH_3



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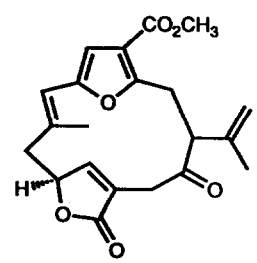

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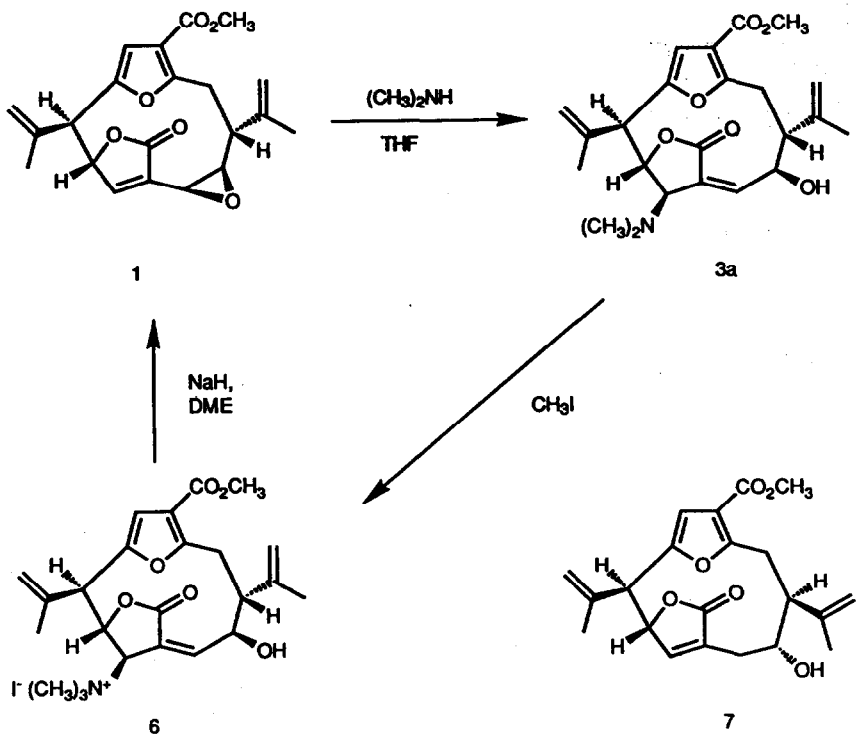
appears to be a function of the season, for collection in March has provided desoxypseudopterolide (4) and the cembranoid acerosolide (5) instead as major metabolites.[4]

The development of suitable means for setting the unusual array of functionality present in the southeast sector of 1 is relevant to our synthetic interest in pseudopterolide.[5] Central to the existing approach is a threo-selective Cr(II)-mediated cyclization that delivers a product more akin to 3a than to 1. For this reason, we have sought to interconvert these pseudopteranes and herein report that such can be readily accomplished.

Fenical has previously noted that the storage of 1 in methanol eventuates in the formation of a methanol adduct shown to be 3b.[1] This conversion is accelerated by acid catalysis. We reasoned that analogous addition of dimethylamine to pseudopterolide should yield tobagolide. Indeed, exposure of 1 to a THF solution of anhydrous dimethylamine afforded 3a in 90% yield. The susceptibility of 1 to nucleophilic attack is noteworthy for reasons other than its possible biosynthetic relevance. This reactivity is not shared by molecules such as 7[6] which lack the vinyl epoxide moiety that presumably serves as the

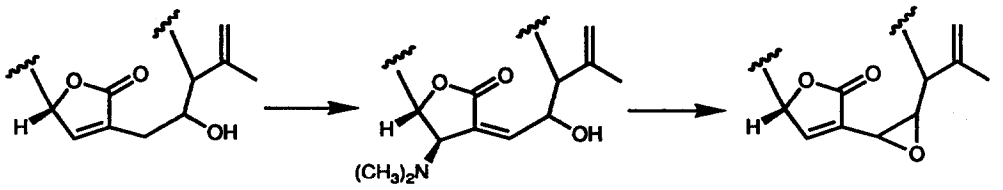


activating subunit since oxirane ring strain is concomitantly released. The impressively high stereoselectivity of these additions owes its origin to the cylindrical shape of the

pseudopterane framework which relegates nucleophilic approach from the much less hindered outer periphery.

If the earlier assumption regarding ring strain release is correct, then any chance to return from tobagolide to 1 should require that some means of chemical activation first be implemented. This is easily accomplished by neat reaction of 3a with methyl iodide to give 6. Molecular models of this quaternary ammonium salt show the -OH and $(CH_3)_3N^+$ groups to be predisposed in a synclinal manner well suited to intramolecular S_N' displacement.[7,8] In agreement with this analysis, direct treatment of unpurified 6 with excess sodium hydride in 1,2-dimethoxyethane at room temperature gave pseudopterolide in 90% overall yield.

In light of these developments, there now exists a direct link between hydroxylated pseudopteranes represented by B and chemically activated epoxides of the C type. Since the possibility of accessing pseudopterane systems of general formula A has been documented, it now remains to accomplish a workable A → B conversion to complete the *de novo* acquisition of these intricate marine diterpenoids. We hope to report on developments along these lines in the future.



From Pseudopterolide to Tobagolide. Five drops of dimethylamine was condensed into 500 μL of dry THF cooled to 0 °C. A solution of 1 (10 mg) in the same solvent (100 μL) was introduced and the reaction mixture was stirred at 0 °C for 1 h. The THF was removed under a stream of nitrogen and the residue was chromatographed on silica gel (elution with petroleum ether-ether-isopropyl alcohol 1:1:1) to give a colorless oil, crystallization of which from petroleum ether-acetone afforded 3a as colorless crystals (10 mg, 90%), mp 163-165 °C (lit[3] mp 165-166 °C); $[\alpha]_D^{23}$ -138° (*c* 0.3, $CHCl_3$) [lit[3] $[\alpha]_D$ -130.5° (*c* 0.22, $CHCl_3$)]. This material was identical by ^1H NMR, ^{13}C NMR, and TLC to an authentic sample of 3a.

From Tobagolide to Pseudopterolide. Tobagolide (10 mg) was dissolved in methyl iodide (500 μL) and this solution was kept at room temperature for 12 h. Solvent evaporation left a colorless solid (13 mg) which was taken up in 1,2-dimethoxyethane (1 mL) and

treated with an excess (0.3 mmol) of NaH. The reaction mixture was stirred at room temperature for 20 min, diluted with water (0.5 mL), and extracted with ether (3 x 3 mL). The combined organic phases were dried and concentrated to leave a residue that was purified by silica gel chromatography. Elution with petroleum ether-acetone 4:1 gave pseudopterolide as a colorless oil (8 mg, 90%), $[\alpha]_D^{23}$ +97° (*c* 2.0, $CHCl_3$) [lit[1] $[\alpha]_D^{26}$ +96.3° (*c* 1.9, $CHCl_3$)], identical to authentic 1 by the same criteria as used above.

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References and Notes

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(5) Paquette, L. A.; Rayner, C. M.; Doherty, A. M. *J. Am. Chem. Soc.* 1990, *112*, 4078.

(6) The (1*R**,12*S**) assignment originally accorded to 7[5] requires revision to (1*S**,12*R**) by virtue of a single crystal X-ray analysis (Astles, P. C.; Gallucci, J. C.). Therefore, stereochemical inversion of these stereogenic centers is made necessary prior to advancing on 1. The precise factors that underlie the remarkable stereoselectivity of Cr(II)-promoted ring closures (four options are possible) is under investigation.

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