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THE SYNTHESIS OF PACIFIGORGIOL

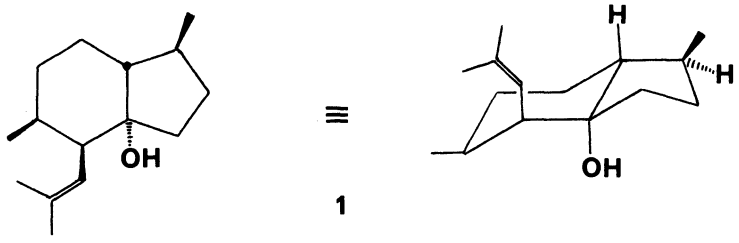
Michael Martin and Jon Clardy*

Department of Chemistry, Cornell University, Ithaca, NY 14853, USA

Abstract - Pacifigorgiol is a new irregular sesquiterpene isolated from the Pacific gorgonian coral Pacifigoria adamsii. It has modest biological activity as a fish toxin. An 11 step synthesis of racemic pacifigorgiol from commercially available starting material is presented. The ultimately successful route is patterned on a biogenetic speculation. Our current progress toward the synthesis of optically active pacifigorgiol is also described.

INTRODUCTION

For the last several years Bill Fenical's group has been actively exploring the natural products chemistry of the gorgonian soft corals found along the subtropical Pacific coast of Mexico (Ref. 1). These animals have produced a fascinating array of natural products with high levels of biological activity. Since these animals lack the endosymbiotic algae frequently found in gorgonians, the isolated secondary metabolites must come from animal metabolism. One interesting new compound, pacifigorgiol, was recently isolated from the sea fan Pacifigorgia cf. adamsii (Ref. 2). The isolation was guided by toxicity toward the reef-dwelling fish Eupomacentrus leucostictus and pacifigorgiol is toxic at the 1 μg/mℓ level. The structure of pacifigorgiol was elucidated by chemical, spectral and crystallographic techniques and is shown below as 1.



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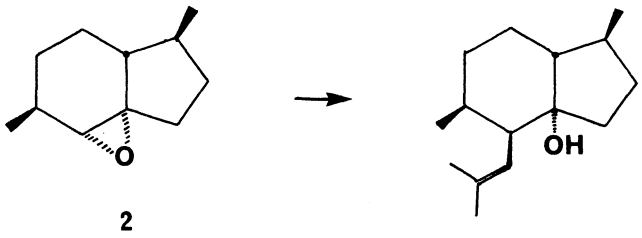
This work did not define the absolute stereochemistry of pacifigorgiol and the enantiomer shown is an arbitrary choice. The basic structure is a trans-perhydroindane with five contiguous asymmetric centers. The cyclohexane ring is in a chair conformation and the isobutenyl and hydroxy substituents are axial. Pacifigorgiol is the first example of this irregular sesquiterpene skeleton and the biogenesis of pacifigorgiol is not clear at this time. We were interested in the synthesis of pacifigorgiol in part because of its biological activity but in greater measure because of the challenge of constructing this new skeleton in an efficient manner. In our original analysis we decided that if epoxide 2 could be made, a trans-diaxial opening by a suitable isobutenyl nucleophile would yield pacifigorgiol.



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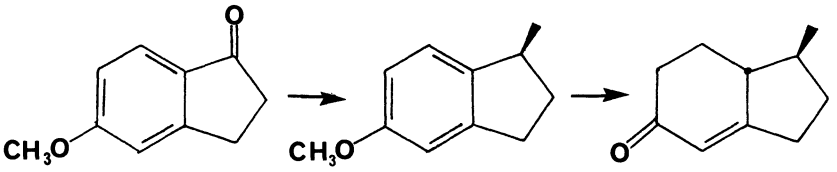
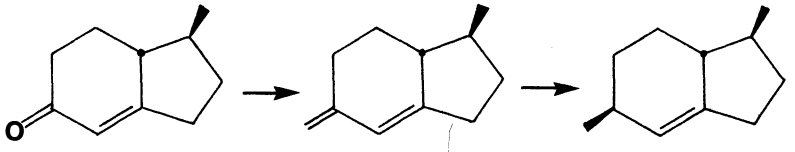
THE EPOXIDE ROUTE

The synthesis of epoxide 2 began with the commercially available methoxyindanone 3 which we converted to methylindane 4. Treatment of 3 with $(C_6H_5)_3P{=}CH_2$ or CH_3Li yielded mostly



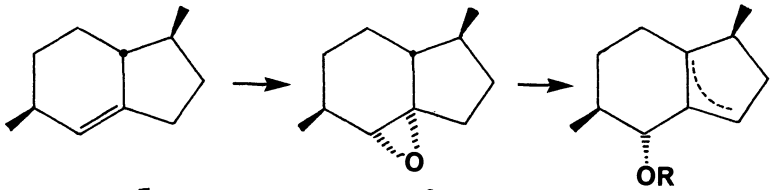
3 4 5

starting material after workup. Rapid proton exchange limited the applicability of these reagents. Addition of 3 to a twenty-fold molar excess of refluxing CH_3MgBr gave a good yield of the adduct. Attempted acid catalyzed dehydration of this adduct did not give the desired olefin but rather a dimeric product. Hydrogenolysis of the alcohol using Pd-C/H_2 in benzene gave methylindane 4. Birch reduction followed by an aqueous acid workup gave enone 5. The yield of 5 from starting material 3 was 80%. The trans stereochemistry of the hydrogens was expected from conformational analysis and from the work of Das Tushar et al. (Ref. 3). The conversion of enone 5 into diene 6 was first attempted with $(C_6H_5)_3P{=}CH_2$ but the yield was disappointingly low. Use of Tebbe's reagent,



5 6 7

$Cp_2TiCH_2C\ell A\ell(CH_3)_2$, gave a 65% yield of 6 (Ref. 4). It was important to use a benzene-hexane solvent system to simplify the isolation of the rather volatile diene 6. The next step was the selective reduction of 6 to 7. This could be done regioselectively using Wilkinson's catalyst but the stereoselectivity was only 3:2, β:α. Better stereoselectivity could be achieved using $(i\text{-}C_5H_9)_2BH$ but the protonolysis of the carbon-boron bond led to rearrangement of the olefin. The isomers of 7 were not separated at this point. We next converted 7 into 8. Epoxidation using m-chloroperbenzoic acid gave only the undesired β-epoxide but epoxidation using N-bromosuccinimide in aqueous dimethyl sulfoxide buffered with $NaHCO_3$ gave a mixture of α-epoxides. The 3:2 mixture of α-epoxides represented the mixture of methyl isomers generated in the reduction and could be easily separated by chromatography. While the yields of the last few steps were not good, we had arrived at crucial intermediate 8 and began to explore the epoxide opening.



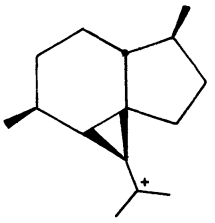
7 8 9

Epoxide 8 could not open in the desired manner! Reaction of 8 with $(i\text{-butenyl})_2CuLi$ gave no reaction up to the decomposition point of the cuprate. We selected cyanide as a better nucleophile but prolonged treatement of 8 with KCN in dimethyl sulfoxide at room temperature led to no reaction. Upon heating this mixture to 80° we were disappointed to find that an elimination took place to give the mixture of olefins shown as 9. Trimethylsilyl cyanide failed to open the epoxide while a mixture of trimethylsilyl cyanide and trimethylsilyl

triflate gave only elimination products even at -78°. At this point we sadly concluded that the epoxide route was not viable.

THE CYCLOPROPENE ROUTE

Pacifgorgiol is an irregular sesquiterpene of uncertain biogenetic origin. While considering possible biogenetic schemes for pacifigorgiol we entertained carbonium ion 10 as a plausible precursor. While the transformation shown is not well precedented, we



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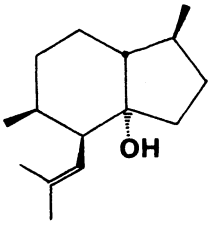
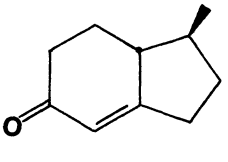


decided to attempt a chemical synthesis along these lines. To do this we returned to enone 5. The conversion of 5 to 11 required three steps and went in an overall yield of 70%. We first reduced enone 5 to the allyl alcohol (97%) using $LiAlH_4$. The dibromo-



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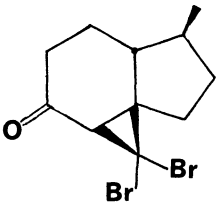

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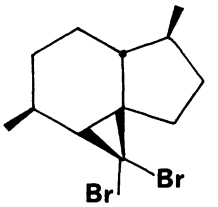

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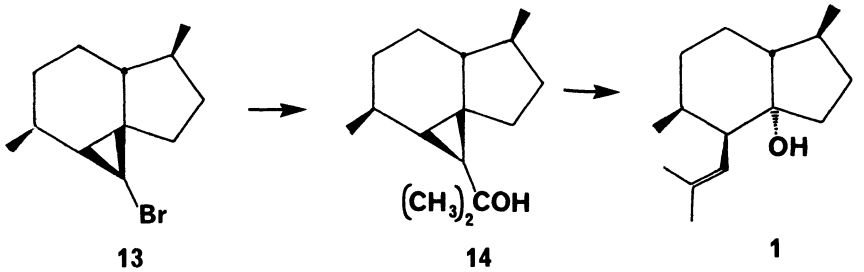
cyclopropanation went smoothly using $CHBr_3/NaOAc/CH_2Cl_2$ and a phase transfer catalyst (75%). The oxidation of the resulting alcohol to 11 required nonacidic conditions and $RuO_2/NaIO_4$ oxidation, as described by Sharpless, gave a 96% yield of 11 (Ref. 5). The conversion of 11 to 12 required two steps and the combined yield was 70%. The ketone was converted to an exocyclic methylene using Tebbe's reagent (73%) and this was reduced using Wilkinson's catalyst (95%). This time the stereoselectivity of the reduction was excellent. The β:α ratio was at least 20:1; a result which is not surprising in view of the bulky dibromocyclopropane substituent hindering access of the reducing agent to the β-face. Dibromide 12 was converted to a mixture of monobromocyclopropanes using $(n\text{-}C_4H_9)_3SnH$ (95%). This gave a 1:1 mixture of exo:endo bromides, a surprising but eventually insignificant result. Monobromide (13) was converted to the penultimate target 14. Treatment of 13 with t-butyllithium caused complete halogen-metal exchange in 10 minutes at -78°. Treatment of the lithio derivative with



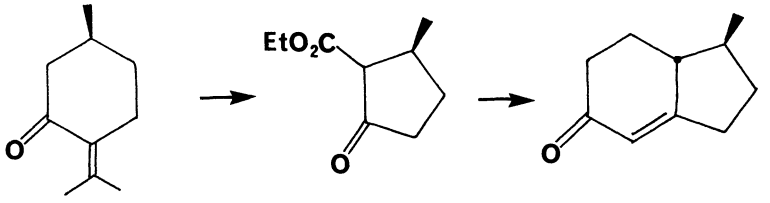
13 14 1

acetone gave a dismal yield of 14. This could be improved by converting the lithio derivative to the Grignard reagent using anhydrous $MgBr_2$. The Grignard was allowed to warm to -20° and quenched with acetone. This gave a 50% yield of 14. Of course 14 was produced as a mixture of stereoisomers with the exo isomer predominating. This stereochemical mixture is also of no consequence for the eventual product. We were now set to try the crucial conversion of 14 to pacifigorgiol. Treatment of 14 with a pH 4.5

phosphate buffer solution at 95° for several hours resulted in the complete disappearance of starting material. The reaction mixture is 50% pacifigorgiol and 50% dehydropacifigorgiols. This completed an eleven step synthesis of racemic pacifigorgiol in an overall yield of 9.3%. The modest yield can be traced to the last two steps and these are still under active investigation. We then turned our attention to the preparation of optically active pacifigorgiol in order to determine its absolute configuration.

OPTICALLY ACTIVE ROUTE

It appeared most efficient to prepare intermediate enone 5 from chiral starting materials. The plan was to convert pulegone (15), which is in principle available in both enantiomeric forms, into 5. This involved a five step procedure. Following Marx and Norman (Ref. 6)



15 16 5

pulegone was brominated and treated with sodium ethoxide to carry out a Favorsky rearrangement. Ozonolysis of this product gave chiral ethyl-3-methyl-2-cyclopentanonecarboxylate (16). This β-ketoester was condensed with methylvinylketone and then refluxed with 6N HCl. The acid treatment caused hydrolysis, decarboxylation and ring closure to give 5 in good yield.

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