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SYNTHESES OF (±)-PYRENOPHORIN AND (±)-COLLETALLOL

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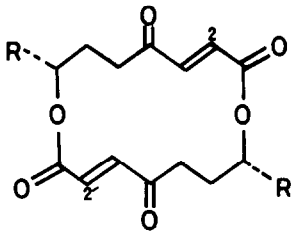
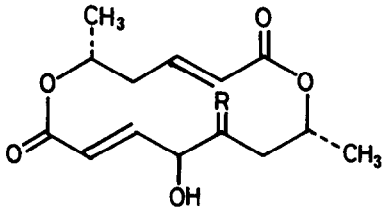
Summary: Pyrenophorin 1 and colletallol 3 were synthesized in their racemic forms from the corresponding hydroxycarboxylic acids 9 and 14 via stereoselective formation of the requisite trans double bonds after macrocyclization.

Naturally occurring antibiotic macrodiolides[1] can be devided into two classes of the C_2-symmetrical compounds 1 and 2 having 16-membered rings and the non-symmetrical compounds 3 and 4 having 14-membered rings. Extensive studies have been recently reported on the syntheses of these biologically active substances. Every method of lactonization of seco acids involving activation of the carboxyl group used hydroxy-α,β-unsaturated carboxylic acids.[2] However, use of these conjugated acids involves inherent problems such as a kinetically favored internal Michael addition[2c,3] of the hydroxy group across the conjugated double bond or tendency for elimination[1c] from the 4,5-position of the enoic acid moiety of macrodiolides. In order to overcome these difficulties, our attention has been focused on a new process that directly cyclizes hydroxy-α,β-saturated carboxylic acids via carboxyl activation, followed by stereoselective introduction of the two trans double bonds at the C-2 and C-2'.

We herein report the results of our detailed studies in applying this new method to the syntheses of pyrenophorin 1[4] and colletallol 3.[5]

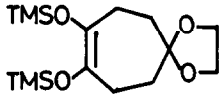


1 R=CH_3 Pyrenophorin
2 R=CH_2COCH_3 Vermiculine



3 R=H_2 Colletallol
4 R=O Colletoketol

The ketal bis(trimethylsilyl) enol ether 5[6] (79%, bp 110-120°C/1 mmHg) was easily prepared by the modified acyloin condensation of diester in the presence of chlorotrimethylsilane. Hydrolysis of 5 with refluxing aqueous tetrahydrofuran(THF) followed by treatment with methyllithium in THF afforded the vicinal diol 7 in 47% overall yield. Oxidative cleavage of compound 7 with lead tetraacetate in benzene at room temperature and subsequent reduction of the keto acid 8 with sodium borohydride in methanol gave hydroxycarboxylic acid 9 in 81% yield. Lactonization was best effected by using method of mixed phosphoric anhydride[7] of the corresponding hydroxycarboxylic acids. Thus, the saturated seco acid 9 (0.9 mmol) was treated with diethyl phosphorochloridate (1.1 mmol) and triethylamine (1.1 mmol) in dry acetonitrile (4 mL) at -15°C for 2 h under argon atmosphere. The reaction mixture was diluted with acetonitrile (30 mL). The resulting solution was added dropwise to a solution of refluxing acetonitrile (70 mL) containing 4-(dimethylamino)pyridine(DMAP) (4.5 mmol) over a period of 10 min and the whole reaction mixture was stirred at this temperature for 12 h. The diastereomeric diolide 10 was obtained in 60% yield after purification by chromatography on silica gel. Treatment of diolide 10 with lithium diisopropylamide(LDA) in THF at -78°C followed by the addition of phenylselenenyl bromide[8] gave the corresponding diselenide which in turn was subjected to oxidation with 30% hydrogen peroxide in aqueous acetic acid at 0°C for 2 h to give the desired trans bis-α,β-unsaturated diolide 11 in 46% yield. None of the stereoisomers other than this compound were observed among the reaction products. Thus, perfectly stereoselective formation of the trans double bonds took place under these conditions. Deprotection of ethylene acetal group of 11 with p-toluenesulfonic acid in acetone at room temperature gave (±)-pyrenophorin 1 (41%, mp 139-141°C) and meso-pyrenophorin (27%, mp 124-125°C), respectively. Spectral properties of the synthetic pyrenophorin 1 were identical with those of reported data.[3]



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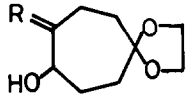
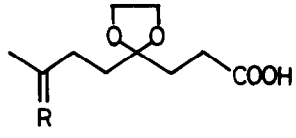


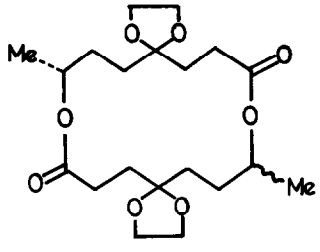
6 R=O

7 R=OH, Me



8 R=O

9 R=H, OH



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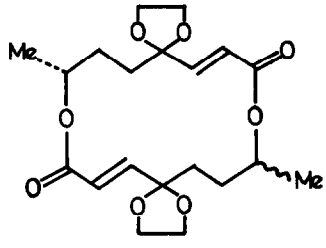

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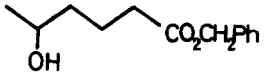
To establish the generality of this process, the method was further applied to the synthesis of the non-symmetric diolide colletallol 3. Treatment of the keto acid 8 and the hydroxybenzyl ester 12 with diethyl phosphorochloridate containing triethylamine in the presence of DMAP[9] in benzene at room temperature gave the keto ester 13 in 90% yield. Reduction of 13 with sodium borohydride in aqueous THF followed by debenzylation (H_2/5% Pd-C, AcOEt) offered the hydroxycarboxylic acid 14 in 72% yield which was immediately converted to diolide 15 in 90% yield under the same conditions as described for conversion of 9 to 10. The trans double bond formation of 15 was effectively performed (i PhSeBr, LDA, THF, -78°C. ii 30% H_2O_2, aq. AcOH, 0°C) to give rise to the desired diolide 16 in 50% yield. Deprotection of 16 with trifluoroacetic acid in methylenechloride at room temperature gave the keto lactone 17 and 18 in a ratio 3:2 in 82% yield. Reduction of the more polar 17 with sodium borohydride in the presence of cerium chloride[10] in methanol gave (±)-colletallol 3 and (±)-11-epi-colletallol in a ratio 1:2 in nearly quantitative yield. Spectral properties of the synthetic colletallol 3 were identical in all respects with those of authentic sample kindly provided by Professor MacMillan.



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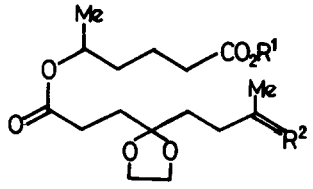
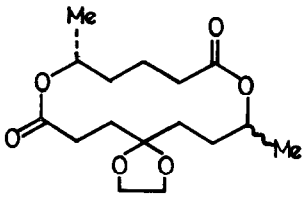


13 $R^1=CH_2Ph$, $R^2=O$

14 $R^1=H$, $R^2=H,OH$



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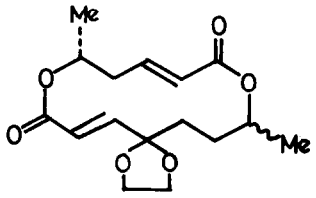

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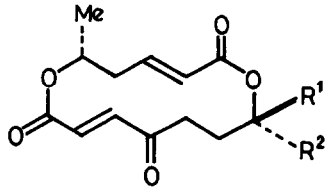

17 $R^1=H$, $R^2=Me$

18 $R^1=Me$, $R^2=H$

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