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The Synthesis of (±)-Pyrenolide C Using the Oxazole-Singlet Oxygen Reaction. Assignment of Stereochemistry.

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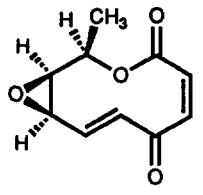
Key Words: macrolides; singlet oxygen; oxazoles; triamides; antifungal agents

Abstract: Pyrenolide C has been synthesized for the first time using an oxazole template to construct the framework of the ten-membered unsaturated lactone system. The stereochemical assignment, based on the mode of synthesis, has been confirmed by NMR studies.

The morphogenic substances recently isolated by Nukina from *Pyrenophora teres*, pyrenolides A (**1**), B (**2**) and C,(**3**) are highly functionalized unsaturated lactones which are of special interest as antifungal agents.[1] These systems have a secondary methyl group in the (R) configuration at C-9, and the-2,3-Z, 5,6-E-dienedione unsaturated grouping in common, and differ only in the pattern of substitution at the C_7-C_8 positions.



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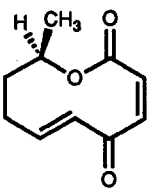

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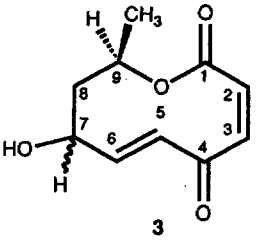

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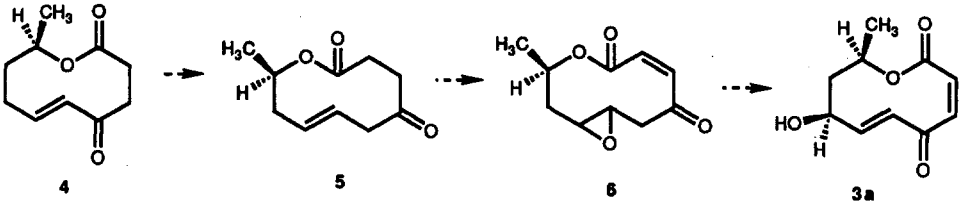
We have previously studied the use of oxazoles as protecting groups for carboxylic acids which may be regenerated in activated (triamide) form by singlet oxygen oxidation,[2] and have now explored the application of this methodology to the synthesis of the pyrenolides. In this paper, we report the first total synthesis of (±)-pyrenolide C by a route which resolves the stereochemical ambiguity at C-7.

The initial objective in our synthesis was the α,β-unsaturated macrolide **4**. We hoped to convert **4** to the β,γ–isomer **5** which could then be transformed to a trans-epoxide **6** for subsequent ring opening to the allylic-alcohol system in the product **3a**, (Scheme 1) which, as will be shown, contains the desired stereochemistry corresponding to the natural product.

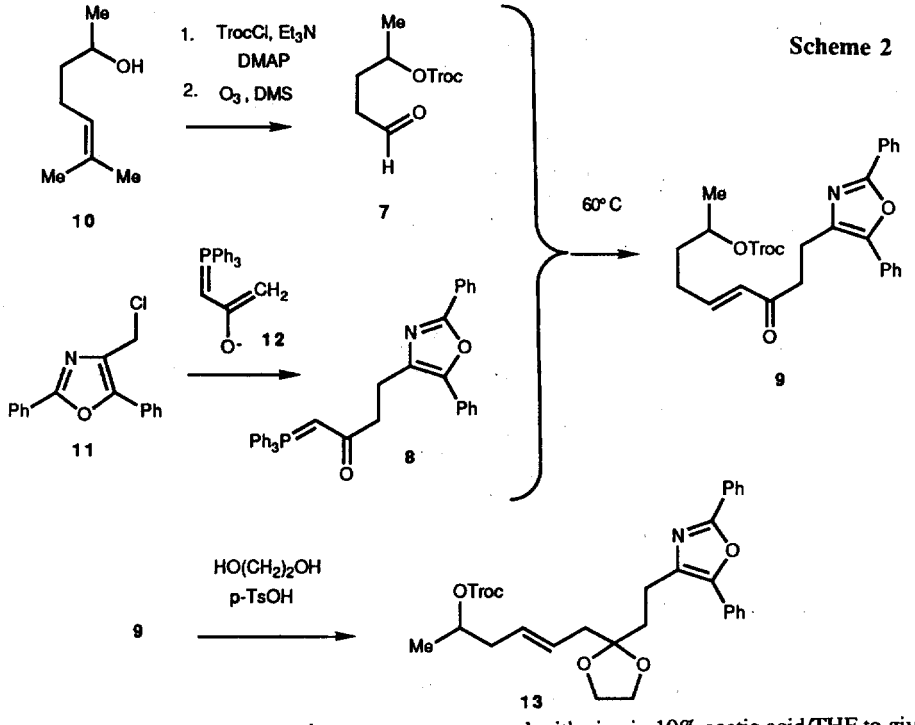


4 **5** **6** **3a**

Scheme 1

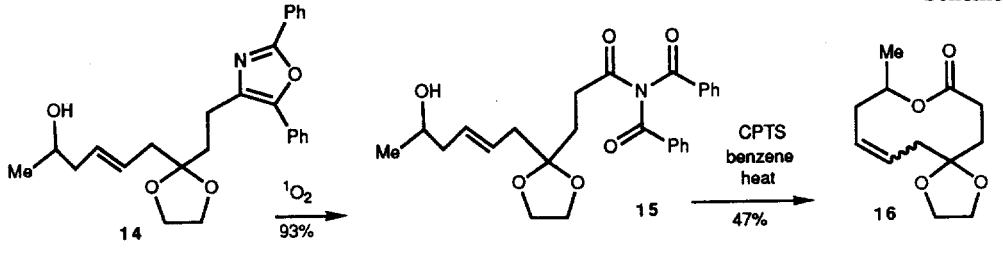
We began our synthesis of **4** using a Wittig coupling of the aldehyde **7** with the ylide partner **8** to form the E enone **9** (95%) incorporating the complete framework of the macrolide target. Compound **7** was efficiently formed from commercially available 6-methyl-5-heptene-2-ol **10,** and the ylide component **8** was prepared by the reaction of 4-chloromethyloxazole **11**[3] with the enolate **12** (Scheme 2).[4] We found it advantageous to protect the ketone **9** by converting it to the ethylene ketal **13** with ethylene glycol in the presence of p-TsOH. Under these conditions, the double bond shifted into the favorable β,γ–position (4:1/ β,γ: α,β) with respect to the ketal .

Scheme 2

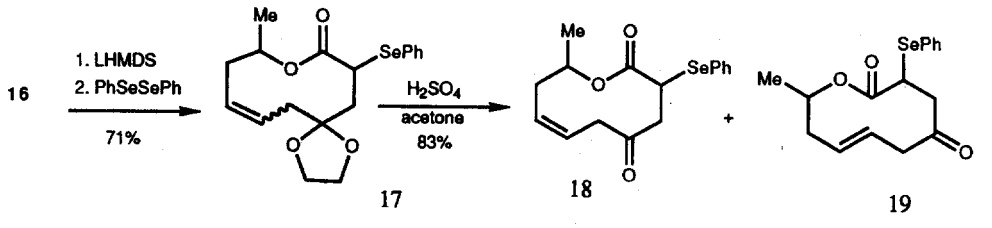


In the next phase, the Troc protecting group was removed with zinc in 10% acetic acid/THF to give the alcohol **14** (89%). Dye-sensitized photooxidation (Sensitox, sensitizer) then transformed **14** to the triamide **15** (93%) which was slowly added to refluxing benzene in the presence of collidine p-toluenesulfonate, under modified high dilution, to yield the ten membered lactone **16** (47%) as a mixture of *cis* and *trans* isomers[5] (Scheme 3). Treatment of **16** with lithium bis-trimethylsilylamide and diphenyldiselenide yielded α-selenolactones **17** (71%) as a mixture of isomers, which, on removal of the ketal protecting group, (acetone/H_2SO_4, 60°, 2 days) yielded two isolable products: the *cis* selenium derivative **18** (43%) and the *trans* isomer **19** (57%).

Scheme 3

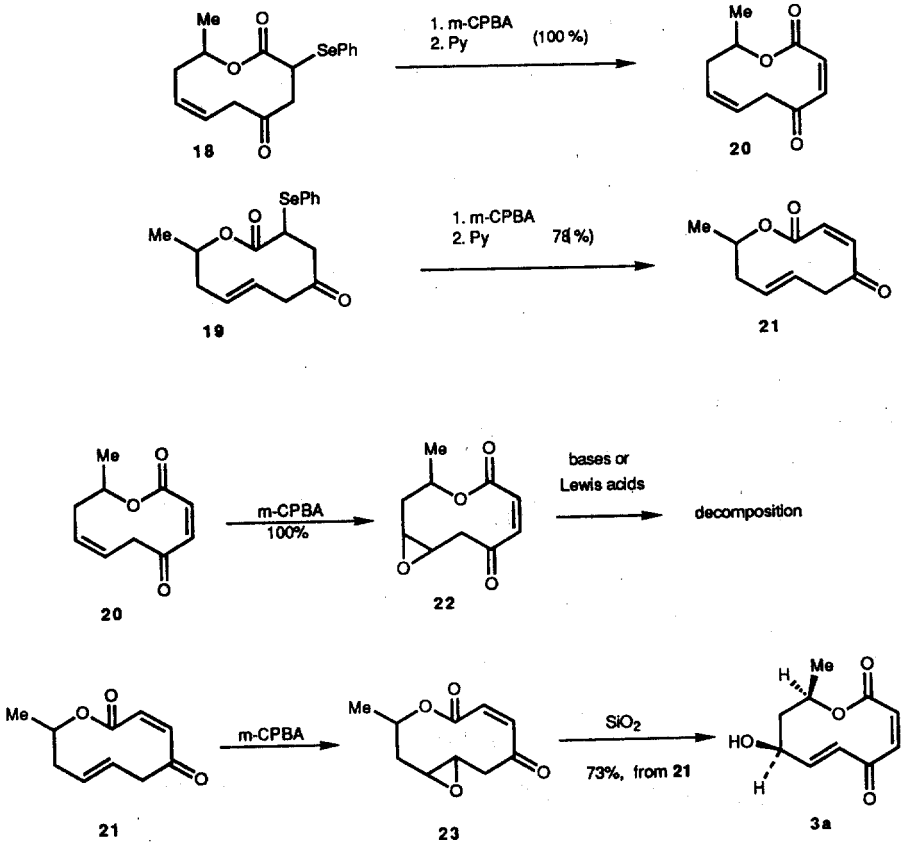


Scheme 4



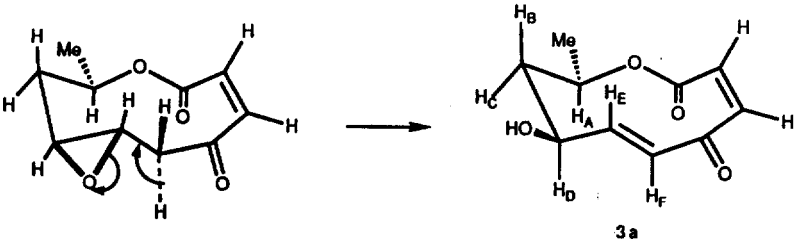
Oxidation of each isomer with m-CPBA followed by treatment with pyridine, yielded the two Z-enediones **20** and **21**[6] (Scheme 4). Both *cis* and *trans* alkenes (**20** and **21**) were oxidized with m-CPBA to give the corresponding epoxides (**22** and **23**) in essentially quantitative yields. On treatment with base (NaOt-Bu) or Lewis acids ($FeCl_3$-SiO_2), the *cis* epoxide **21** gave only products of decomposition. By contrast, the *trans* epoxide **23** was readily transformed by silica gel to an allylic alcohol (Scheme 5) which was identical (TLC, IR, ^1H MNR, MS spectrum) with natural pyrenolide C.[7]

Scheme 5



Assignment of the syn-relationship between the allylic hydroxyl and the secondary methyl group in **3a** followed from the mode of generating the allyl alcohol in the last step. Thus, in the opening of the epoxide by a β-elimination[8] as shown in Scheme 6, a *trans*-enone system would be formed in which the newly formed hydroxyl group would bear a syn orientation with respect to the methyl group. This stereochemical feature was confirmed by decoupling experiments in which the pair of protons, H_B and H_D, as well as the pair, H_A and H_B were shown to be 160-180° apart. The geometrical assignment was based on examination of coupling constants and the corresponding angles estimated from a Karplus diagram for vicinal protons.[9] Finally, in NOE experiments, irradiation of protons D and A gave enhancements in complete accord with the stereochemistry shown in **3a**.

Scheme 6



3a

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4. In initial work, we found that with **12**, the reaction of the 2-chloromethyl isomer yielded side-products resulting from o-alkylation and lithium-halogen exchange.

5. Deketalization of this mixture by exchange with acetone (H_2SO_4, catalyst) permitted separation into the *cis* product (30%) and the *trans* isomer (62%).

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7. We thank Professor M.Nukina for generously proving us with samples of natural pyrenolides A, B, and C.

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