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Total Synthesis of Pseudopterosin A and E Aglycon

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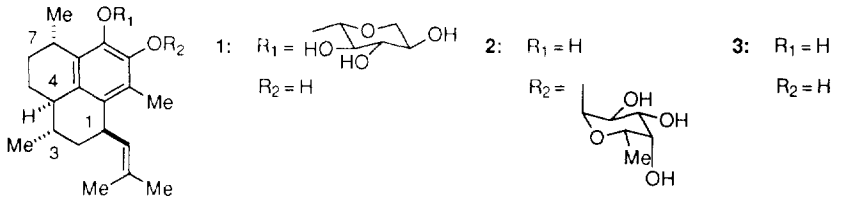
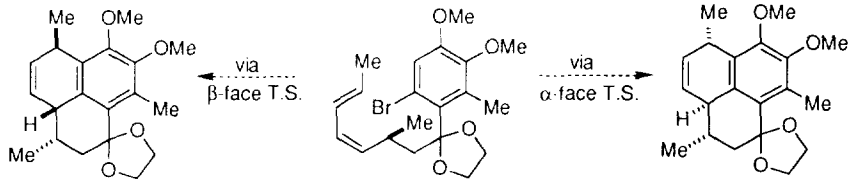
Abstract: A total synthesis of the pseudopterosin A and E aglycon **3** has been achieved through a novel intramolecular benzyne Diels-Alder cycloaddition with a substituted cyclohexadiene.

The pseudopterosins represent a new class of extremely potent antiinflammatory tricyclic diterpenes recently isolated by Fenical from the sea whip *Pseudopterogorgia elisabethae* in tropical Atlantic waters.[1] Pseudopterosin A (**1**) and E (**2**)[2] in particular have attracted special attention because they possess superior



antiinflammatory properties, are relatively nontoxic, and have an unknown mode of action. We have been investigating the unprecedented use of both acyclic and nonaromatic cyclic dienes in the intramolecular benzyne Diels-Alder reaction (IMBDA) as part of a program to gauge the scope and limitations of such a process and to establish a comprehensive reaction profile for this type of chemistry.[3] In this paper we describe the total synthesis of the aglycon **3** of pseudopterosin A and E by means of a novel IMBDA cycloaddition with a tethered cyclohexadiene.

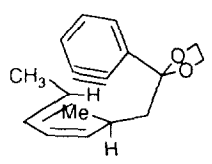
Our original strategy projected the synthesis of the key E,Z-diene **4**. The anticipated IMBDA cycloaddition via the lower energy α-face transition state would then establish the required stereochemistry at



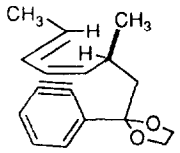
5 **4** **6**

C.4 and C.7 in the product **6**. MM2 calculations revealed that such a transition state would be favored by at approximately 5 kcal/mol over the alternative β-face approach, which suffers severe non-bonded steric interactions between the stereogenic methyl group at C.3 and the terminal diene hydrogen. Previous work from this laboratory, however, demonstrated that the course of such cycloadditions is dependent on the diene

geometry.[3] Specifically, E,Z-dienes and others that cannot adopt an unstrained transition state leading to the [4+2] cycloadducts will instead proceed along alternative reaction manifolds to give either initial [2+2] cycloadditions followed by further rearrangement, or intramolecular ene processes. The use of cyclic dienes



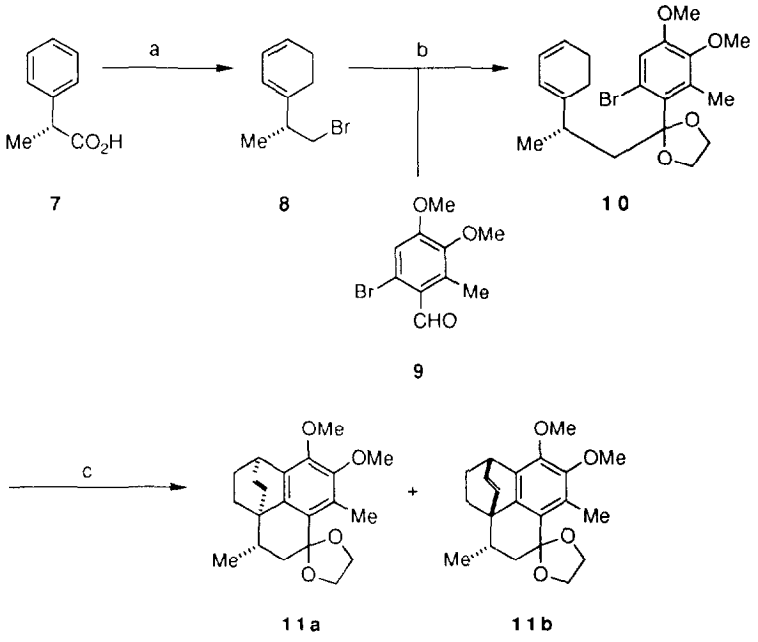
β-face approach



α-face approach

provided an attractive solution to this problem. The enforced s-cis conformation of cyclohexadiene allows for an unexceptional transition state leading to facile [4+2] cycloadducts. Oxidative cleavage of the resulting ethylene bridge then would afford differentiated functional groups that can be elaborated into the pseudopterosin aglycon framework.[4]

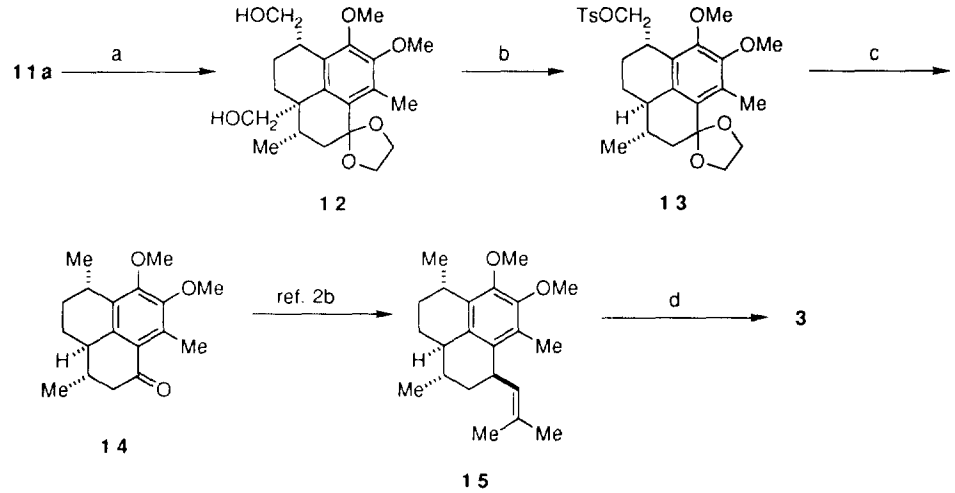
The synthesis started with commercially available (*R*)-(-)-2-phenylpropionic acid **7** (Scheme 1). Reduction of the carboxylic acid with excess lithium aluminum hydride in THF at 65°C for 12 h afforded the corresponding alcohol. Birch reduction[5] followed by base-induced isomerization gave the 1-substituted



Scheme 1. Reagents and Reaction Conditions
(a) 1. $LiAlH_4$/THF/65°C/12 h. 2. Na/NH_3/EtOH/-78°C/6 h. 3. *t*-BuOK/DMSO/65°C ---> RT/2 h. 4. PPh_3/NBS/cat. pyridine/CH_2Cl_2/RT/1 h. (b) 1. Mg/THF/RT ---> 0°C/0.5 h, then add to **9** in THF at 0°C. 2. $(COCl)_2$/DMSO/Et_3N/CH_2Cl_2/-78° ---> RT/1 h. 3. $TMSOCH_2CH_2OTMS$/cat. $TMSOTf/CH_2Cl_2$/-78°C/4 h. (c) 1. LDA/THF/-78°C/2 h, then slow warming to RT over 12 h.

cyclohexadiene in 56% overall yield for three steps. Among the various methods attempted for the conjugation of the 1,4-diene, the use of powdered *t*-BuOK in warm DMSO proved the most practical. Finally, the alcohol was brominated (86%) with PPh_3/NBS[6] in CH_2Cl_2 to furnish **8** (48% overall yield for the four steps) which was used immediately in subsequent operations.[7]

The Grignard reagent derived from **8** was added to the aldehyde **9**[8] in THF at 0° C to give in 78% yield a mixture of benzylic alcohols. The key benyzne precursor was prepared as follows. Swern oxidation[9] gave the corresponding ketone which was protected as its 1,3-dioxolane ketal **10** under Noyori conditions (81% for two steps).[10] Surprisingly, the use of Dess-Martin periodinane[11] as the oxidant resulted in concomitant aromatization of the cyclohexadiene. The reactive benzyne was generated[12] by the slow addition of 0.1 M LDA to a solution of the aryl bromide in THF at -78° and slowly warming the reaction mixture to room temperature over 12 h, after which time a 58:42 mixture of diastereomers **11a:11b** was obtained in 63-71% yield.[13] The more polar diastereomer **11a**,[14] identified on the basis of NOE difference NMR experiments, was chromatographically separated. Oxidative cleavage of the ethylene bridge afforded in 85% yield a differentiated pair of primary alcohols **12** (Scheme 2). Selective protection of the less hindered alcohol at C.19 as the *p*-toluenesulfonate (83%) was followed by oxidation of the remaining neopentyl-like alcohol to the aldehyde with Dess-Martin periodinane. Stereospecific decarbonylation with Wilkinson's catalyst by brief exposure to hot benzonitrile gave **13** in 76% yield as a single diastereomer.[15] Nucleophilic hydride displacement of the tosylate with excess LAH in refluxing THF then established the C.19 methyl group in 68% yield. Deketalization with PPTS in warm acetone/H_2O quantitatively afforded the key hexahydrophenalen-1-one **14**. Introduction of the isobutenyl side chain was carried out according to the method of Corey.[2b] Finally, deprotection of the methyl ethers with TMSI[16] gave the aglycon **3**, which exhibited the same physical and spectroscopic properties as that derived from the authentic material.[17]



Scheme 2. Reagents and Reaction Conditions
(a) 1. NMO/cat. 10% OsO_4 in toluene/acetone-H_2O (9:1, v/v)/RT/2.5 h. 2. $NaIO_4$/THF-H_2O (1:1, v/v)/RT/ 4 h, then $NaBH_4$. (b) 1. TsCl/pyridine/0°C ---> RT/ 6 h. 2. Dess-Martin periodinane/CH_2Cl_2/RT/2 h. 3. $(PPh_3)_3RhCl$/PhCN/RT ---> 160°C/0.5 h. (c) 1. $LiAlH_4$/THF/65°C/18 h. 2. PPTS/acetone/H_2O/12 h. (d) 1. TMSI/$CHCl_3$/35°C/48 h.

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References and Notes.

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3. See preceding paper.
4. For a related strategy, see: Taschner, M. J.; Cyr, P. T. *Tetrahedron Lett.* **1990**, *31*, 5297.
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7. Satisfactory spectroscopic data was obtained for all new compounds reported in this paper.
8. Prepared in 47% overall yield from 2-methylpiperonal (Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564) in seven steps: (i) BCl_3•SMe_2/$ClCH_2CH_2Cl$/83°C; (ii) Me_2SO_4/NaOH/H_2O/100°C; (iii) $LiAlH_4$/Et_2O/RT; (iv) Ac_2O/pyridine/DMAP/CH_2Cl_2/RT; (v) Br_2/HOAc/RT; (vi) K_2CO_3/MeOH-THF (2.5:1, v/v)/RT; (vii) Dess-Martin periodinane/CH_2Cl_2/RT.
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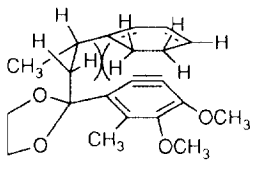
13. Transition states that expose either the α- or β- face of the diene to the aryne in order to avoid unfavorable steric interactions are possible. For example, one can consider a 180-degree rotation of the 1,3-cyclohexadiene in the β-face transition state **17**:



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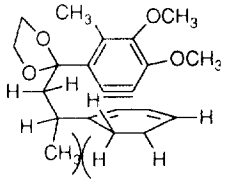

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The issue of relative asymmetric induction in this class of cycloaddition is under investigation.
14. ^1H NMR ($CDCl_3$) of **11a**: δ 1.14 (3 H, d, *J* = 6.4 Hz), 1.45-2.40 (7 H, m), 2.25 (3 H, s), 3.82-4.11 (5 H, m), 3.80 (3 H, s), 3.86 (3 H, s), 6.55 (1 H, d, *J* = 5.6 Hz), 6.71 (1 H, dd, *J* = 2.9, 5.6 Hz).
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17. We are grateful to Professor William Fenical, Scripps Institution of Oceanography, University of California, San Diego, for providing us with generous samples of authentic pseudopterosin A and E.

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