to ~10% of its maximum intensity by 1.0 ns after excitation. In CH_3CN, a weak absorption band at 480 nm, which is assigned to $2^{\bullet}$,[9] and an absorption which extends from <400 nm are apparent at longer times when the promptly appearing absorption has decayed substantially (Figure 1i).

The 485-nm band shown in Figure 1 (parts f and g) agrees well with the sole band at 488 nm which was reported and assigned by Deno et al.[4a] to 2^+ generated from **2**-OH in sulfuric acid. We assign the longer wavelength absorption band ($\lambda_{max} \simeq 635$ nm) in Figure 1g to an $S_n \leftarrow S_1$ transition of **2**-OH. The shorter wavelength λ_{max} of 2^+ relative to 1^+ is consistent with the ground-state spectra of other 1,1-diarylethyl cations relative to the corresponding diarylmethyl cation.[4a,11] The intensities and decay kinetics of this 485-nm band in the several solvents relative to the 515-nm band observed after excitation of **1**-OH are consistent with the generation of 2^+ and the more reactive 1^+.[12,14] In view of the recent interest in the enhanced reactivities of electronically excited precursors to give cyclic $4n$ π-electron systems relative to $(4n + 2)$ π-electron analogues,[5,10,16] our spectroscopic studies do not provide any evidence for the intermediacy of excited-state 1^+ or 2^+.

It was suggested[4b] that, under the conditions of Deno et al.,[4a] the cation radical of **1**-OH may have been generated. The following data support this suggestion. We observed that 355-nm excitation of chloranil (**3**) in CH_3CN in the presence of 50 mM **1**-OH gives rise to the generation of $3^{\bullet-}$ (λ_{max} = 450 nm)[17] and an absorption band (λ_{max} = 635, ~590 nm; Figure 1j) that appears on the time scale of the conversion of $^3\mathbf{3}^*$ to $3^{\bullet-}$. This band, which we assign to $\mathbf{1}\text{-OH}^{\bullet+}$, exhibits a λ_{max} near the longer wavelength band reported and assigned by Deno et al.[4a] to 1^+. When **3** is excited in the presence of **2**-OH in CH_3CN, an absorption band (λ_{max} = 640, ~590 nm; Figure 1k), which we assign to $\mathbf{2}\text{-OH}^{\bullet+}$, is observed.[18]

Acknowledgment. We thank the National Science Foundation (Grants CHE-8605560 and CHE-8602678), Research Corporation (a Bristol-Myers Company Grant), the donors of The Petroleum Research Fund, administered by the American Chemical Society, and the Florida State University Council on Research and Creativity for support of this work. S.L.M. acknowledges financial support through the award of a Florida State University Fellowship.

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Enantiospecific Total Synthesis of Pseudopterosins A and E

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Although there has been an explosive growth in the number and variety of naturally occurring compounds identified from marine organisms in recent years, very few have shown therapeutically significant biological activity. A striking exception appears to be the case of the pseudopterosins, isolated from the sea plume *Pseudopterogorgia elizabethae*,[1,2] which have powerful antiinflammatory activity and which are not prostaglandin H_2 synthase inhibitors.[2] Most noteworthy with respect to biological activity are pseudopterosin A (**1**) and pseudopterosin E (**2**), the latter by far the most active known member of this series.[1d,3] In this communication we describe a useful route to **1** and **2** via the corresponding aglycone and new methodology for aromatic annulation, selective elaboration of catechols, and α-fucosylation.

The oxime **3**, readily available from (1*S*,2*R*,5*S*)-(+)-menthol nitrite ester by photolysis as a 5:1 mixture of *R* and *S* diastereomers at C(8),[4,5] was converted to a single γ-lactone (**4**), mp 35-36 °C (60% overall), by the following sequence: (1) oxime hydrolysis with 5 equiv of aqueous $NaHSO_3$[6] at 50 °C for 4 h; (2) lactol → lactone oxidation (Br_2 in $THF-H_2O-CaCO_3$ at 23 °C for 1.5 h); and (3) complete isomerization at C(8) to the *R* configuration (lithium diisopropylamide (LDA) in THF at 0 °C for 2 h, followed by quenching at 0 °C with aqueous NH_4Cl). The octalone **5** was synthesized from **4** in 40% overall yield by the following sequence: (1) reduction of **4** to the corresponding lactol with diisobutylaluminum hydride in CH_2Cl_2 at −78 °C for 2 h; (2) Wittig chain extension with $Ph_3P{=}C(CH_3)SEt$[7] in DMSO at 23 °C for 24 h; (3) Swern oxidation[8] with DMSO, $(CF_3CO)_2O$, and Et_3N in CH_2Cl_2 at −65 °C for 1 h; (4) thioether cleavage ($HgCl_2$, in CH_3CN-H_2O at 50 °C for 1 h);[9] and (5) aldol cyclization of the resulting 1,5-diketone with $NaOCH_3$ in CH_3OH at 23 °C for 12 h to give **5**.

Reaction of enone **5** with KH in THF-HMPA at 23 °C for 12 h followed by treatment with *tert*-butyldimethylsilyl chloride afforded the enol ether **6** (97%) which was transformed into diketone **7** in two steps (61% overall): (1) slow addition of **6** in CH_2Cl_2 (over 2 h) to a solution of 2-butynal and trimethylsilyl triflate in CH_2Cl_2 at −78 °C and quenching with water after an additional hour;[10] and (2) oxidation of the resulting propargylic alcohol by pyridinium chlorochromate in CH_2Cl_2 at 23 °C for 3 h in the presence of 4A molecular sieves. The tricyclic nucleus of the pseudopterosins was then constructed by a new aromatic annulation procedure which is related to a cyclization previously

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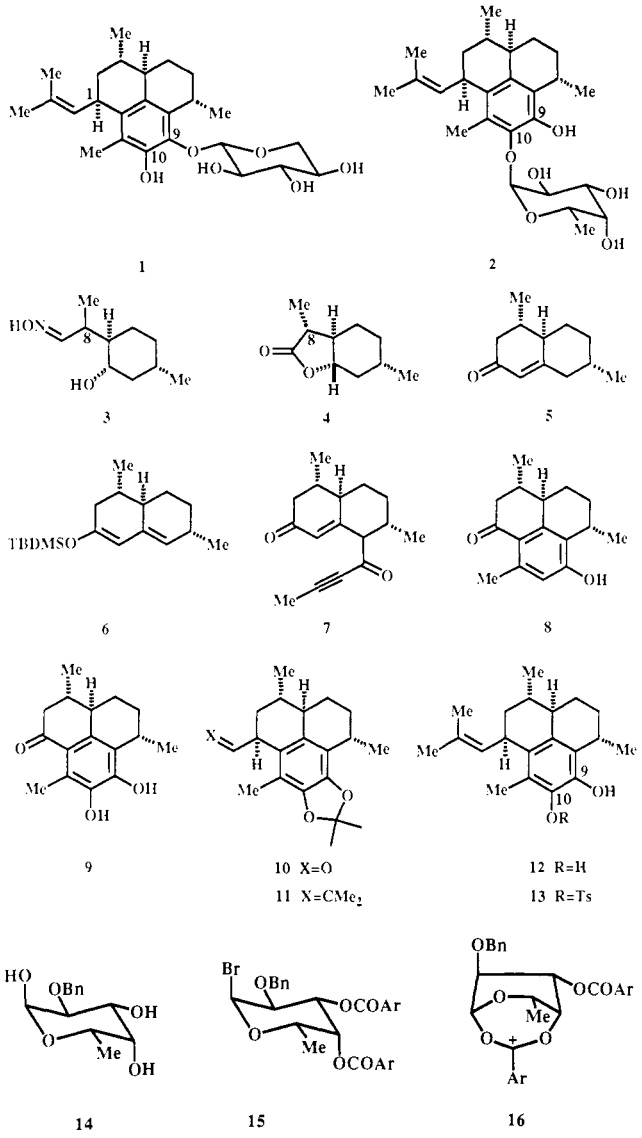
Chart I



used in this laboratory for the synthesis of bilobalide and which we believe will prove to be quite general.[11] Specifically, treatment of **7** with potassium hydride in THF at 23 °C for 24 h resulted in formation of the desired phenol **8**, mp 168–170 °C (70%). Ortho hydroxylation of **8** to form the corresponding catechol (**9**) was accomplished in two steps: (1) oxidation of **8** by benzeneselenic anhydride and hexamethyldisilazane (C_6H_6, 23 °C, 12 h) to form an *N*-(phenylselenyl)-*o*-quinone imine[12] (79%); and (2) treatment with aqueous acetic acid containing a little perchloric acid (23 °C, 2 h) to effect hydrolysis to the *o*-quinone followed by reduction with aqueous bisulfite to form **9**, mp 119 °C, in 71% yield.

The catechol unit was protected by the isopropylidene group (2,2-dimethoxypropane, pyridinium tosylate, $CHCl_3$, 70 °C, 12 h, 87%), and the resulting ketone was transformed into aldehyde **10** (76%) by methylenation with dimethylsulfonium methylide[13] (23 °C in THF) and rearrangement of the epoxide thus formed with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −30 °C to 23 °C over 1 h. Wittig reaction of aldehyde **10** with isopropylidenetriphenylphosphorane in THF at 0 °C for 1 h furnished **11** (81%) which upon exposure to 1:1:1 10% HCl–THF–MeOH at 70 °C for 12 h gave the oily catechol **12** in 71% yield, identical chromatographically and spectroscopically with the aglycone of the pseudopterosins, prepared by acid treatment of an authentic sample of **1**.[3]

Pseudopterosin E (**2**) was synthesized by the direct attachment of an L-fucose unit using a new method. The experience of Professor Fenical[3] and also our own is that the usual methods of making α-aryl glycosides do not result in a satisfactory conversion of **12** to **2**. The difficulty does not stem from reaction at the 9-hydroxyl rather than the 10-hydroxyl of **12**, as is indicated, for example, by the fact that **12** reacts with 1 equiv of tosyl chloride and Et_3N in CH_2Cl_2 at −30 °C to 23 °C (2 h) to afford selectively the 10-tosylate **13** (85% isolated yield). The known 2-benzyl ether of L-fucose (**14**) was converted by reaction with *p*-methoxybenzoyl chloride to the trianisoate ester ((dimethylamino)pyridine, CH_2Cl_2, 23 °C, 2 h) which upon treatment with gaseous HBr in CH_2Cl_2 at 23 °C for 30 min produced cleanly the protected α-bromofucose **15** (90%). Deprotonation of **12** with 2 equiv of *n*-butyllithium in THF and subsequent reaction with **15** at 23 °C proceeded stereo- and position-selectively to give the desired benzyl ether bisanisoate of pseudopterosin E along with some unreacted **12**. The gratifying stereoselectivity and position selectivity of this reaction (not realized with the bisbenzoate corresponding to **15**) is consistent with the intermediacy of cation **16** in the fucosidation. Sequential treatment of the benzyl ether bisanisoate of pseudopterosin E with (1) lithium hydroxide in THF–CH_3OH and (2) lithium–liquid ammonia–THF produced pseudopterosin E cleanly (53% overall from **12**). The synthetic and naturally derived samples[3] (solids, mp dec) were identical as shown by 500 MHz ^1H NMR, FT-IR, UV, reversed phase HPLC, TLC, and optical rotation measurements.[14]

Pseudopterosin A was synthesized from **13** by the following sequence: (1) deprotonation with NaH in CH_3CN at 23 °C and reaction with 2,3,4-triacetyl-α-D-xylopyranosyl bromide in situ to give the 9-triacetyl-β-D-xylopyranoside of **13** stereoselectively. Removal of acetyl (KOH, CH_3OH–H_2O, 23 °C, 1 h) and tosyl (6% NaHg in CH_3OH) protecting groups and chromatographic purification furnished pseudopterosin A (**1**) (solid, mp dec) which was indistinguishable from the natural product chromatographically, spectroscopically, and by optical rotation (54% overall).

The synthesis of pseudopterosins A and E described herein is noteworthy for its directness, the involvement of interesting and novel methodology, and the potential to provide numerous structural analogues. The last factor is of considerable interest in view of the apparent possibility that pseudopterosins A and E may be antiinflammatory because they can function as structural mimics of phosphatidylinositol and thus alter at a fundamental level the generation of eicosanoids, diacylglycerol, and inositol triphosphate.[15] The synthesis of various analogues of **1** and **2** may assist in both the testing of the above hypothesis and the development of potent new therapeutic agents.[16,17]

Registry No. 1, 104855-20-1; **2**, 121011-80-1; (8*R*)-**3**, 121011-81-2; (8*S*)-**3**, 121011-91-4; **4**, 121054-52-2; **5**, 121011-82-3; **6**, 121011-83-4; **7**, 121011-84-5; **8**, 121011-85-6; **8**[*N*-(phenylselenyl)-*o*-quinoneimine], 121011-93-6; **9**, 121011-86-7; **10**, 121011-87-8; **11**, 121011-88-9; **12**, 106671-54-9; **13**, 121011-89-0; **14**, 37776-55-9; **15**, 121011-90-3; $Ph_3P{=}C(CH_3)SEt$, 121011-92-5; $Ph_3P{=}C(CH_3)_2$, 16666-80-1.

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(17) This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.

Supplementary Material Available: Spectroscopic data (^{1}H NMR, IR, EIMS, and HRMS) are given for compounds **1-15** (4 pages). Ordering information is given on any current masthead page.

Accurate Measurements of Homonuclear H^N-H^α Coupling Constants in Polypeptides Using Heteronuclear 2D NMR Experiments†

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We have developed a heteronuclear 2D NMR method for accurate measurements of homonuclear H^N-H^α coupling constants from nonoverlapping cross peak components. This is achieved by separating along ω_1 the two multiplet components, which characterize the two orientations of the H^α spin, utilizing the large coupling $^1J(C^\alpha$-$H^\alpha)$. Protein structure determination in solution by NMR depends on collecting a large number of conformational parameters, most importantly NOE distance constraints. Vicinal coupling constants can provide local structural information complementary to NOE data. However, they are difficult to measure accurately with conventional techniques and have therefore been of less value in protein structure determinations. We have concentrated recently on developing new methods for measuring accurately conformation-dependent coupling constants in polypeptides.

Of special interest are $^3J(H^N$-$H^\alpha)$ coupling constants, which provide constraints on the backbone dihedral angle ϕ. Because these coupling constants are often small compared to protein ^{1}H line widths, the corresponding multiplet components of 2D NMR cross peaks overlap, and the apparent splittings are significantly smaller or larger than the true coupling constants when measured from inphase or antiphase cross peaks, respectively.[1] This overlap of multiplet components can sometimes be avoided by homonuclear ECOSY,[2] COSY-45,[3] or frequency-selective COSY[4] experiments, which provide cancellation of some multiplet components and simplify the cross peak pattern. This requires, however, that the two active coupling partners of the cross peak are each coupled to a third nucleus (passive spin). Accurate measurements of coupling constants from ECOSY-like experiments require also that at least one active coupling is significantly larger than the line width. In considering only proton-proton spin coupling, these requirements prohibit the application of such methods in measurements of $^3J(H^N$-$H^\alpha)$ coupling constants in all amino acid spin systems except for glycine. This restriction is overcome, however, when one considers heteronuclear H^N-^{15}N-H^α or H^N-$^{13}C^\alpha$-H^α spin systems in which heteronuclear ECOSY-like effects can be generated.

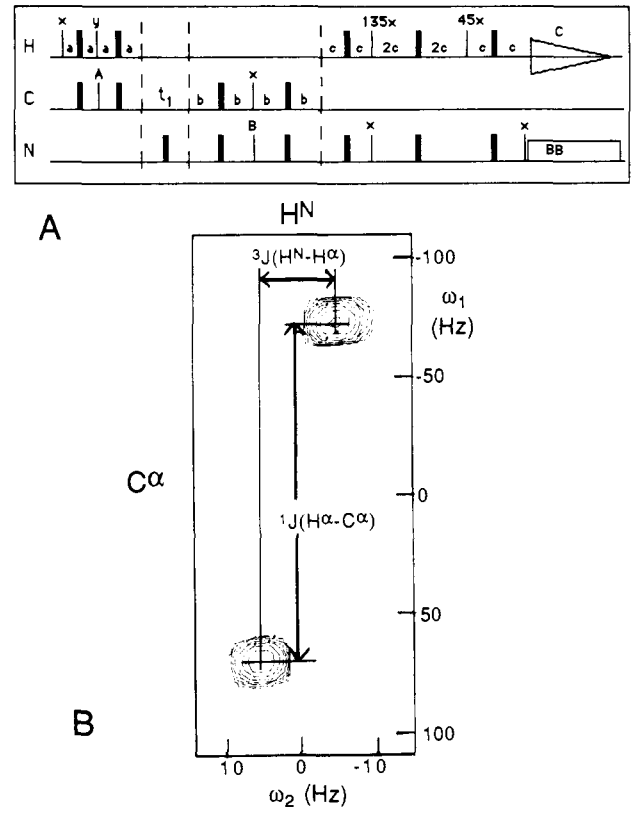

Figure 1. (A) Pulse sequence of the H^α-$C^\alpha(\omega_1)$-N-selective-$H^N(\omega_2)$ heteronuclear RELAY for measurements of homonuclear $^3J(H^\alpha$-$H^N)$ coupling constants. The delays are tuned in the following way: $a = (4^1J_{H_\alpha-C_\alpha})^{-1}$, $b = (4^1J_{N-C_\alpha})^{-1}$, and $c = (4^1J_{NH})^{-1}$. The phase cycles used were as follows: A, $x, -x$; B, $x, x, -x, -x$; C, $x, -x, -x, x$. Time-proportional 90° incrementation of phase A provided quadrature detection in ω_1. Water suppression can be performed by preirradiation of the solvent signal. (B) Intraresidue tyrosine heteronuclear RELAY cross peak of Ac-Asn-Pro-(^{15}N)Tyr-NHMe between C^α and H^N. The heteronuclear coupling $^1J(H^\alpha$-$C^\alpha)$ is along ω_1, and the homonuclear coupling constant $^3J(H^\alpha$-$H^N)$ can be measured along ω_2. The sample was prepared at 30 mM concentration in dimethyl-d_6-sulfoxide (Cambridge Isotopes). These data were recorded on a General Electric GN-500 spectrometer with a custom-built triple resonance probe and a modified transciever board (details available on request). Nine hundred t_1 values were recorded over 16 h. The final digital resolution after zero filling is 6.1 Hz/pt in ω_1 and 1.6 Hz/pt in ω_2.

Recently, we have described an approach which provides accurate measurements of long-range heteronuclear ^{15}N-^{1}H coupling constants from homonuclear 2D and 3D spectra of ^{15}N-enriched polypeptides.[5] These experiments rely on the analysis of homonuclear cross peak patterns between protons coupled to a common ^{15}N nucleus, which is not pulsed in the experiment. An analogous strategy can be used to measure $^3J(H^N$-$H^\alpha)$ coupling constants accurately in heteronuclear correlation experiments using pulse schemes which selectively excite either amide or α-proton resonances. One of several possible pulse sequences is described here. It can be denoted as H^α-$C^\alpha(\omega_1)$-N-selective-$H^N(\omega_2)$ heteronuclear RELAY. This is a short notation of the pulse sequence given in Figure 1A. It uses refocussed INEPT[6] polarization transfer from H^α to C^α. During the evolution period, the carbon coherence evolves decoupled from nitrogens but coupled to protons. This provides the desired large splitting ($^1J_{CH}$ = 140 Hz) of the cross peaks along the ω_1 axis which prevents an overlap of the two multiplet components. The remainder of the experiment

† Basic ideas leading to this experiment were presented at the UCLA symposium *Frontiers of NMR Molecular Biology*; Jan. 12-19, 1989; Park City, UT.

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