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First Enantiospecific Total Synthesis of the Antitubercular Marine Natural Product Pseudopteroxazole. Revision of Assigned Stereochemistry

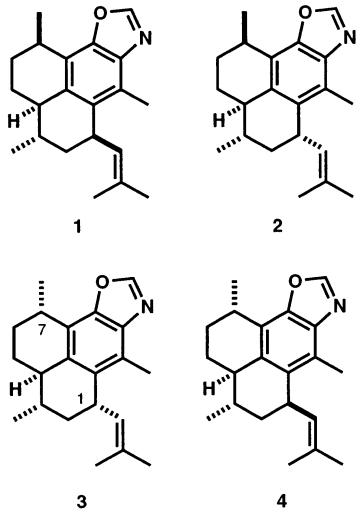
James P. Davidson and E. J. Corey*

Contribution from the Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Received August 12, 2003; E-mail: corey@chemistry.harvard.edu

Abstract: A concise, enantiospecific synthesis of pseudopteroxazole (**3**), which had originally been assigned structure **1**, has been accomplished starting from *S*-(−)-limonene. The known cyclohexanone **5** was converted in five steps to the α,β-enone **8** by a modified Robinson annulation. Transformation of **8** to the orthogonally protected amino phenol **11** was accomplished by a new modification of the Wolff−Semmler rearrangement. The synthesis was completed by cationic cyclization to form **14** diastereoselectively and subsequent introduction of the terminal oxazole subunit.

The report[1] by Rodriguez and co-workers of a novel tetracyclic oxazole, pseudopteroxazole, from the West Indian gorgonial coral *Pseudopteragorgia elisabethae* that exhibited strong inhibition of *Mycobacterium tuberculosis* in vitro further stimulated the interest of synthetic chemists in this class of compounds. As one of the world's leading pathogens, *Mycobacterium tuberculosis* infects an estimated 2 billion people and kills some 3 million a year. Currently, the standard treatment for *M. tuberculosis* infection is a 6-month regimen of antibiotics, consisting in some cases of more than 10 pills per day. Because of this demanding treatment schedule, patient compliance is low, and several different multi-drug-resistant strains have evolved. Thus, there is a clear need for new and efficacious therapeutic agents. We reported earlier three enantiospecific and stereocontrolled synthetic routes to the pseudopterosins,[2,3] and a variety of synthetic approaches have been developed in other laboratories.[4] Most recently, our synthetic and spectroscopic studies have allowed the revision of the structures originally proposed for several members of the pseudopterosin family.[5] This work also called into question the structure originally assigned to pseudopteroxazole (**1**).[1] An unambiguous total synthesis of **1** and its C(1)-diastereomer (**2**) later showed that pseudopteroxazole was neither of these and strengthened the case for structure **3**.[6] We describe herein an enantiospecific total synthesis of **3** which confirms this conclusion and unequivocally establishes this structure for pseudopteroxazole through comparison with the natural product. In addition, we have also synthesized the C(1)-diastereomer of pseudopteroxazole (**4**) by modifying final stages of the synthesis of **3**. Thus, all of the diastereomers **1**−**4** are available for studies of antimicrobial activity.



The pathway of the synthesis leading to **3**, which is outlined in Scheme 1, began with the known cyclohexanone **5**, available in three steps from inexpensive *S*-(−)-limonene.[3] Protection of the primary hydroxyl as the *tert*-butyl-diphenylsilyl ether (TBDPS) gave **6** in 96% yield. Kinetic deprotonation of the cyclohexanone **6** selectively at the α-methylene and trapping with chlorotrimethylsilane provided the required silyl enol ether, which, upon treatment with 1-benzyloxy-3-methyl-but-3-en-2-

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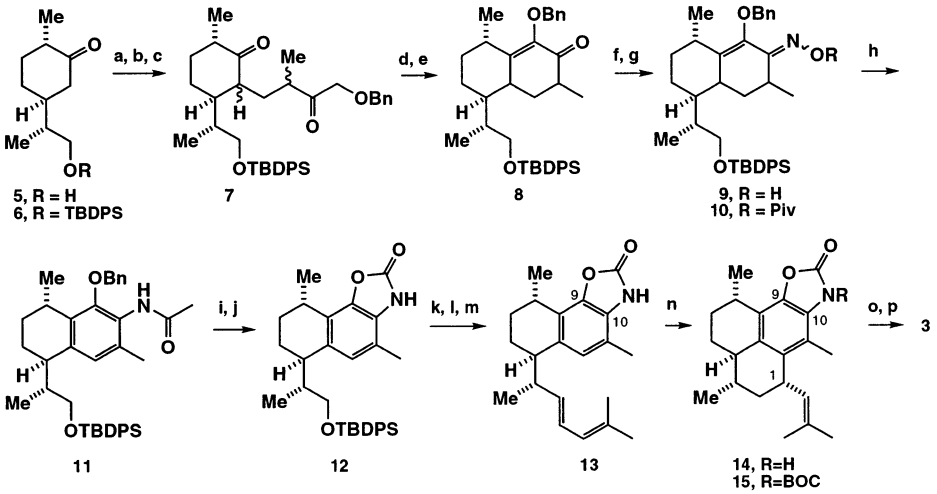
Scheme 1. Synthetic Pathway to Pseudopteroxazole **1**[a]



[a] (a) TBDPSCl, imidazole, DMF, 96%. (b) LDA, TMS−Cl, −78 °C, 100%. (c) 1-Benzyloxy-3-methyl-but-3-en-2-one, $SnCl_4$, CH_2Cl_2, −78 °C, 61%. (d) KOH, EtOH, −10 °C, 83%. (e) $SOCl_2$, pyridine, 83%. (f) NH_2OH−HCl, pyridine, 69%. (g) Pivaloyl chloride, pyridine, 96%. (h) Acetyl chloride, toluene, 80 °C, 64%. (i) H_2, $Pd(OH)_2$−C, EtOH, 99%. (j) Carbonyldiimidazole, Et_3N; then aqueous $NaHCO_3$, 94%. (k) HF−pyridine, 95%. (l) TPAP, NMO, 82%. (m) Wittig olefination, 81%. (n) $MeSO_3H$, acetic acid, 18 °C, 80%. (o) BOC_2O, DMAP, 96%. (p) MeMgBr, −78 to 23 °C; then TFA, $HC(OEt)_3$, 90%.

one and $SnCl_4$, gave the Mukaiyama−Michael adduct **7** in 61% yield (82% based on recovered **6**) as a mixture of diastereomers (approximate ratio 1:1). Cyclization of the 1,5-diketone **7** in dilute solution (0.01 M) using potassium hydroxide in ethanol (83%), and elimination of the tertiary hydroxyl group with thionyl chloride in pyridine, proceeded smoothly to give a mixture of diastereomeric α,β-enones **8** in 83% yield. Transformation of this diastereomeric mixture into the corresponding oximes **9** (65−70%)[7] followed by acylation with pivaloyl chloride provided the oxime pivalate **10** in 96% yield.

Next, we turned our attention to the aromatization of **10**. It was clear from the outset that conventional Wolff−Semmler conditions, which consist of heating with excess acetyl chloride and concentrated HCl in refluxing acetic anhydride,[8] would be far too harsh for this acid-sensitive substrate. We experimented extensively with different O-protected oximes, acylating agents, additives, and solvents (for discussion, see below). Ultimately, we found that 1 equiv of acetyl chloride in toluene at 80 °C in a tightly sealed reaction vessel effectively promoted the aromatization of the *O*-pivaloyl protected oxime **10** to give the orthogonally protected ortho aminophenol **11** reliably in 60−65% yield. It should be noted that both oxime diastereomers undergo aromatization equally well, regardless of whether they are subjected to the reaction conditions individually or as a mixture.

Hydrogenolysis of the benzyl ether (99%), followed by cyclization of the phenol with carbonyldiimidazole, gave the cyclic carbamate **12** in 94% yield after a mildly basic aqueous workup ($NaHCO_3$) to remove the *N*-acetyl group. Desilylation of **12** with hydrofluoric acid−pyridine complex (95%), followed by mild oxidation to the aldehyde with tetrapropylammonium perruthenate and 4-methylmorpholine-*N*-oxide (TPAP−NMO, 82%),[9] and Wittig−Vedejs *E*-selective olefination,[3,10] gave diene **13** (81%), the key intermediate for the formation of the third carbocyclic ring of **3** by cationic cyclization. Previous experience with this type of ring closure provided the insights for control of stereochemistry at C(1) by the relative electron donation of the substituents at C(9) and C(10) of the aromatic ring.[3] We speculated that the slightly superior electron-donating properties of the nitrogen atom at position 10 would direct the stereochemistry at C(1) to the desired *S* configuration. Surprisingly, it was found after experimentation that either C(1)-diastereomer of **14** could be accessed selectively by changing the reaction conditions for the cyclization. With acetic acid as solvent, treatment of **13** with 3 equiv of methanesulfonic acid at 19 °C for 72 h gave **14** in 80% yield as approximately a 4:1 ratio favoring the required *S* configuration at C(1). Alternatively, with CH_2Cl_2 as solvent and methanesulfonic acid at −30 °C for 6 h, the diastereomer of **14** at C(1) was obtained in 95% isolated yield with a 4:1 predominance over **14**. Tetracycle **14** and its C(1)-diastereomer were separated chromatographically on a Chiralcel OD column and converted individually by parallel processes to pseudopteroxazole (**3**) and the diastereomer **4**, respectively. This was accomplished by the sequence: (1) acylation of the free NH of **14** with di-*tert*-butyl dicarbonate (BOC_2O) to give **15** in 96% yield; (2) reaction with excess methylmagnesium bromide (MeMgBr) to cleave the cyclic carbamate; and (3) addition of the resulting dianion to a mixture of trifluoroacetic acid and triethylorthoformate to give **3** in 85−90% yield. Comparison of the spectral data for synthetic **3** with that originally reported for the natural material revealed identical rotation, IR, ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectra. The pseudopteroxazole diastereomer **4** was synthesized

(7) Under conventional oxime forming conditions (excess hydroxylamine hydrochloride in ethanol), no oxime was observed with **8**. Heating the reaction in ethanol with hydroxylamine resulted in a complex mixture containing only traces of the desired oxime. With excess hydroxylamine hydrochloride, at 50 °C, with pyridine as solvent the reaction proceeded to approximately 50% conversion after 4 h, leaving one diastereomer of **8** untouched (55% isolated yield of **9**, 84−89% based on recovered **8**). The remaining enone diastereomer was then isolated, and resubjected with excess hydroxylamine hydrochloride in refluxing pyridine to give predominantly a different oxime diastereomer in 50% yield (65−70% overall). If the initial mixture of enones **8** was subjected to excess hydroxylamine hydrochloride in refluxing pyridine, it was possible to force the reaction to completion. However, isolated yields of the resulting mixture of oximes were only about 55%. Curiously, the reaction was also not influenced by the addition of other amine bases or by the removal of water either azeotropically or with drying agents.

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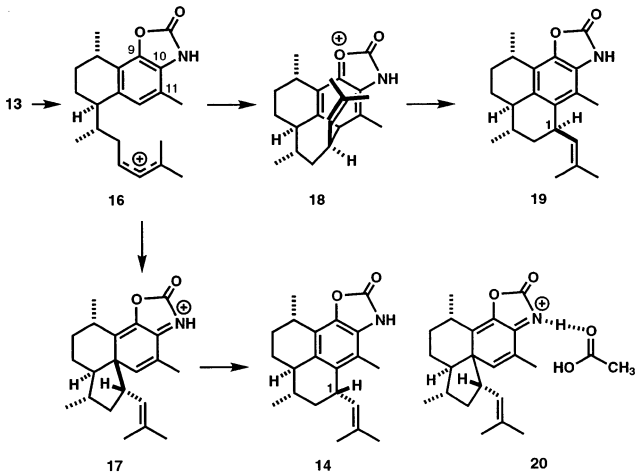
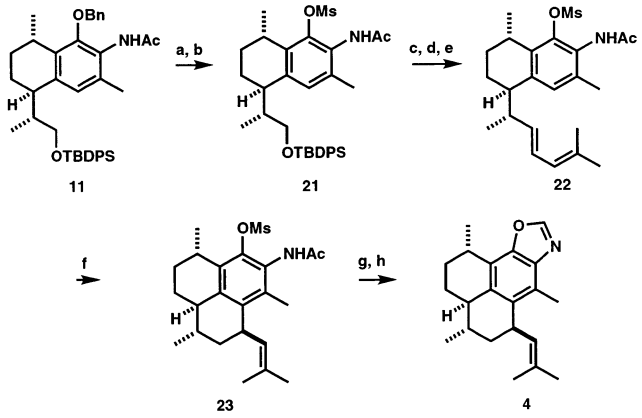
Scheme 2



Scheme 3 [a]



[a] (a) H_2, $Pd(OH)_2$−C, 99%. (b) MsCl, Et_3N, THF, 95%. (c) HF−pyridine, THF, 50 °C, 96%. (d) TPAP, NMO, 81%. (e) Wittig olefination, 90%. (f) $MeSO_3H$, CH_2Cl_2, 95%. (g) BOC_2O, Et_3N; then K_2CO_3, MeOH, 92%. (h) MeMgBr, −78 °C → 23 °C; then TFA, $HC(OEt)_3$, 42%.

using the analogous sequence from the C(1)-diastereomer of **14** and was demonstrated to be spectroscopically different from **3**.

Determination of the stereochemistry at C(1) was relatively straightforward. Our previous work on the pseudopterosin A−F aglycon, pseudopterosin G−J aglycon, helioporin E, as well as **1** and **2**, has demonstrated that the C(1)−H signal in the ^{1}H NMR spectrum is of significant diagnostic value.[3,5,6] In each case where the C(1) proton resides on the α (bottom) face of the molecule the peak width is smaller, and the signal appears nearly rectangular with no discernible splitting pattern. On the other hand, for each case where the C(1) proton resides on the β (top) face of the molecule the proton signal clearly appears as a quartet. Additionally, the proton signal for an α-oriented H at C(1) appears ∼0.1 ppm upfield from the βH of the C(1) diastereomer.[11]

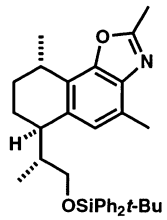
The stereocontrolled cyclization **13** → **14**, a key step in the synthesis of pseudopteroxazole, is of considerable mechanistic interest. Protonation of the 1,3-diene subunit of **13** by methanesulfonic acid initiates the cyclization by forming the stabilized allylic carbocation **16** (Scheme 2). Ring closure of **16** to form the spirocyclopentyl cation **17** was expected to be favored by two factors: (1) an intrinsic stereoelectronic effect leading to a preference for five-membered ring closure,[12] and (2) the greater electron-donating ability of the carbamate NH substituent on the benzenoid ring as compared with the carbamate O substituent. The *S* stereochemistry at C(1) of **17** is favored over the diastereomeric *R* arrangement because it involves less steric repulsion about the isobutenyl group. A 1,2-shift of C(1) in **17** to the next position on the benzenoid ring and subsequent deprotonation produces **14** stereoselectively when acetic acid is used as solvent. In methylene chloride as solvent with methanesulfonic acid as catalyst, the balance is shifted in favor of the alternative direct six-membered cyclization pathway **16** → **18** as shown in Scheme 2. In this ring closure, the *R* configuration at C(1) is clearly favored for steric reasons and so the final product is the C(1)-(*R*) diastereomer of **14**, compound **19** in Scheme 2. We believe that the reason for preferential formation of **14** with HOAc as solvent versus **19** with CH_2Cl_2 as solvent may simply be greater stabilization of the transition state for cyclization of **16** to **17** by hydrogen bonding of the carbamate NH to the solvent acetic acid, as depicted by **20** in Scheme 2. If this explanation is correct, it has significant implications with regard to synthetic planning for the use of benz-1,3-oxazol-2-one subunits in synthesis.

The use of the cyclic carbamate derivative **13** was critical to the successful cyclization to form **14**. One advantage of **13** is that the coplanarity of the oxygen and nitrogen substituents allows maximum electron supply from these groups into the aromatic ring as cationic cyclization is taking place. This aspect of the cyclization was probed further by the synthesis of the acetamide-mesylate **22**, and the corresponding triflate, from **11** via the intermediate **21**, as shown in Scheme 3. The methanesulfonyl substituent in **22** was chosen to provide strong attenuation of the electron-donating capabilities of oxygen into the aromatic ring during direct cationic attack at the para position. Methanesulfonic acid-catalyzed cyclization of **22** either in CH_2Cl_2 or in acetic acid produced **23** with at least 20:1 diastereoselectivity relative to **14**. A similar result was obtained even in the cyclization of the substrate having CF_3SO_2 instead of CH_3SO_2 of **22**. These data for **22** and the corresponding triflate make it clear that the acetamido substituent is a very poor electron donor in the cyclization of **22** as a consequence of its noncoplanarity with the aromatic ring due to ortho substitution.

The transformation of the α,β-enone **8** into the aromatic amino phenol derivative **11** (Scheme 1) presented a major challenge to the execution of the synthetic plan. As mentioned earlier, standard Wolff−Semmler conditions[8] were inappropriate. A number of exploratory experiments with oximes of model 2-cyclohexenones and with **8** provided the following useful information: (1) the best results were obtained with pivalate esters of the oximes, (2) the best reagent for the oxime pivalate aromatization was acetyl chloride in toluene at 80 °C, and (3) hydrogen chloride was an essential catalyst for the process. In the Wolff−Semmler transformation of the oxime pivalate **10** to the protected acetamide-phenol **11** (Scheme 1), a byproduct, identified as **24**, was isolated in yields of between 5% and 15%. Control experiments using HCl or triphosgene in toluene revealed that **24** could be derived from the aromatization product **11**, likely through an acid-catalyzed cleavage of the benzyl ether, and subsequent cyclization and dehydration of the *N*-acetyl. Efforts to remove excess hydrogen chloride from the reaction,

(11) For representative proton spectra, see Supporting Information and ref 5.
(12) See: Corey, E. J.; Sauers, C. K. *J. Am. Chem. Soc.* **1957**, *79*, 248.

designed to inhibit the formation of **24**, resulted in significantly depressed yields. The yield of **11** was maximized by limiting the temperature and duration of the reaction, and the conditions described herein for the conversion of **10** to the acetamido phenol ether **11** are superior to those previously recorded.



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The completion of the first synthesis of pseudopteroxazole as shown in Scheme 1 firmly establishes the structure of this interesting bioactive marine product as **3**. It also demonstrates a biomimetic cyclization which provides a basis for understanding the origin of the stereochemical diversity of the pseudopterosin family and how the natural diastereomeric structures are formed in nature.

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Supporting Information Available: Experimental procedures, and spectral data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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