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Benzothiazines in Synthesis: Studies Directed toward the Synthesis of Erogorgiaene

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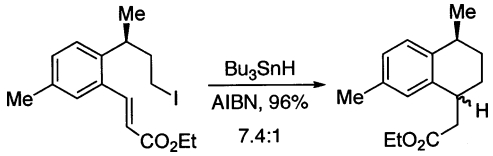

The use of benzothiazenes for the formal total synthesis of erogorgiaene and stereoselective total syntheses of two diastereomers of this natural product is described. In particular, the stereochemical course of a radical cyclization anticipated to give the correct relative stereochemistry for the synthesis of erogorgiaene is discussed utilizing both experimental and computational data.

Introduction

Since the late 1990s, a very large number of structurally interesting natural products have been discovered from the West Indian Sea Whip, *Pseudopterogorgia elisabethae* (Bayer).[1] The evaluation of the pharmacologically active metabolites of this marine organism revealed a wide variety of promising bioactivities including antitubercular, anticancer, anti-inflammatory, and antibacterial. Some representatives of these metabolites are shown in Figure 1. Their unique structures, limited availability from natural sources, and potential importance in medicinal chemistry have provided the impetus for the development of total synthetic routes to these natural products in the recent past.[2] Highlighted in red in Figure 1 are the stereochemical and structural features shared by these compounds. This suggests that a single strategy to construct this array of stereocenters might be sufficient for the synthesis of all of the compounds shown.

As part of our program involving the study of the synthesis and chemistry of benzothiazines, and in conjunction with our interest in the synthesis of compounds possessing antitubercular activity, we have been interested in the preparation of a number of the compounds shown in Figure 1. We recently reported the synthesis of pseudopteroxazole (**2a**)[3] and formal total syntheses of (+)-curcuphenol, (+)-curcumene,[4] and (+)-erogorgiaene (**1**).[2e]

Our basic approach involves the application of the intramolecular addition of a sulfoximine carbanion to an α,β-unsaturated ester (Scheme 1).[5] As far as we can tell, this reaction is completely diastereoselective. Enantiomerically pure starting material is converted to enantiomerically pure product with complete stereochemical fidelity. Establishing the benzylic

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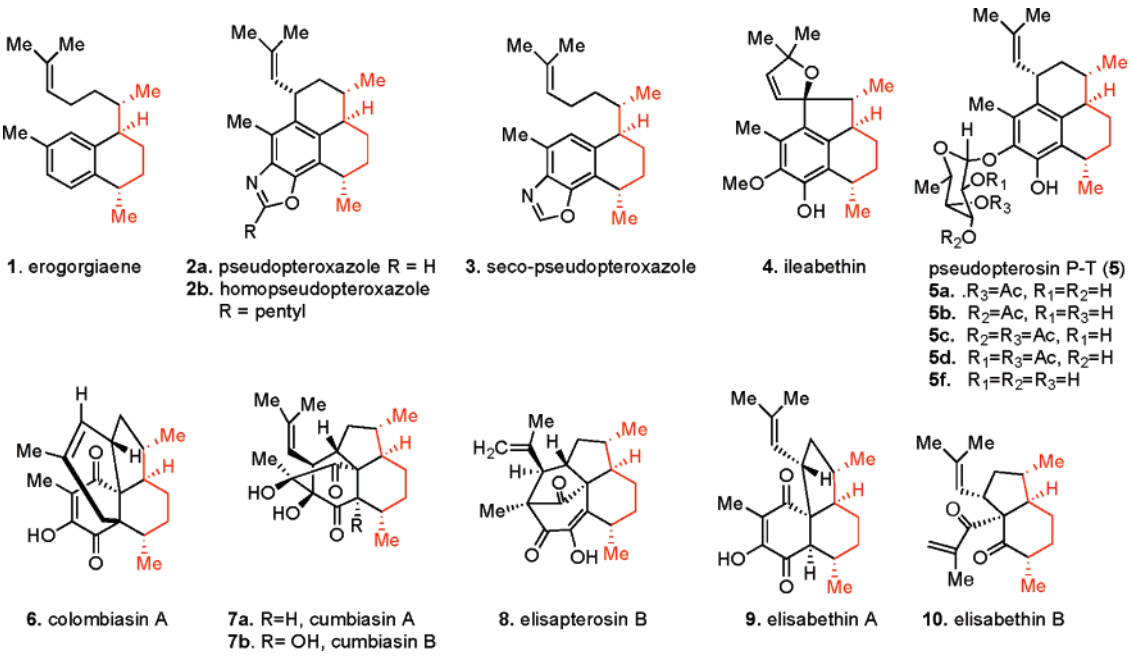
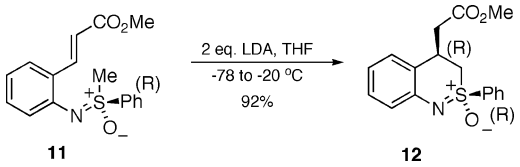


FIGURE 1. Natural products from *Pseudopterogorgia elisabethae*.

SCHEME 1. Stereoselective Synthesis of Benzothiazines



stereocenter then serves as a basis for studying chemistry that can establish the remaining stereocenters in various targets, largely through substrate control of stereoselecitivity.

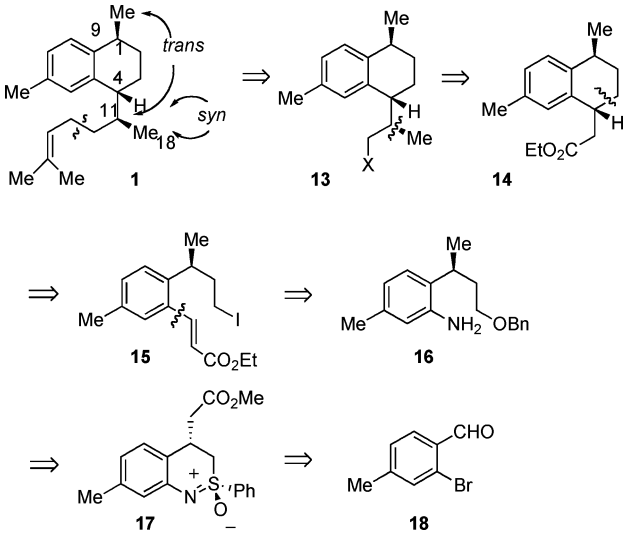
Erogorgiaene (**1**), a novel anti-mycobacterial serrulatane diterpene, was first isolated from the West Indian Sea Whip *Pseudopterogorgia elisabethae* and showed activity against *Mycobacterium tuberculosis* $H_{37}Rv$. The promising biological activity of erogorgiaene has aroused attention due to interest in the development of new chemotherapeutics for tuberculosis. Organic chemists have devised several synthetic approaches to **1**. The first asymmetric total synthesis of (+)-erogorgiaene was accomplished in 2004 by Hoveyda and co-workers.[2f] It utilized catalytic, asymmetric conjugate addition chemistry to install a key benzylic stereogenic center. A second synthetic route involved a carbene insertion and Cope rearrangement strategy that rapidly established all of the stereocenters of the natural product and provided a somewhat more efficient route to erogorgiaene.[2d] As mentioned above, a formal synthesis of erogorgiaene was reported from our group using benzothiazine chemistry.[2e]

We decided to use our methodology toward the synthesis of (+)-erogorgiaene and indeed completed a formal total synthesis. We also pursued a different approach to this compound based on the retrosynthetic analysis shown in Scheme 2. This effort ended in the synthesis of two diastereomers of (+)-erogorgiaene.

Results and Discussion

To facilitate our presentation, we use a nomenclature that is based on the relative stereochemistry of the methyl group at C-1 and the alkyl chain at C-4 of (+)-erogorgiaene. They are

SCHEME 2. Retrosynthetic Analysis of 1



either *cis* or *trans*. More subtle is the relationship between the hydrogen at C-4 and the methyl group at C-11. When erogorgiaene is *drawn as shown* in Scheme 2, these two groups are denoted as being *syn*. Thus, we would refer to erogorgiaene as *trans*/*syn*.

Our efforts toward realizing the plan depicted in Scheme 2 began with a Horner−Wadsworth−Emmons reaction of commercially available *o*-bromobenzaldehyde (**18**). This was then coupled with (*S*)-*S*-methyl-*S*-phenylsulfoximine using the Buchwald−Hartwig reaction as modified by Bolm[6] to give the corresponding sulfoximine in 89% yield. This compound was treated with an amide base (LDA or LiHMDS) to afford benzothiazine **17** with complete diastereoselectivity in 85% yield.[4] The aniline **16** was obtained in 65% yield over three steps by reduction, protection, and reductive desulfurization (Scheme 3).[7]

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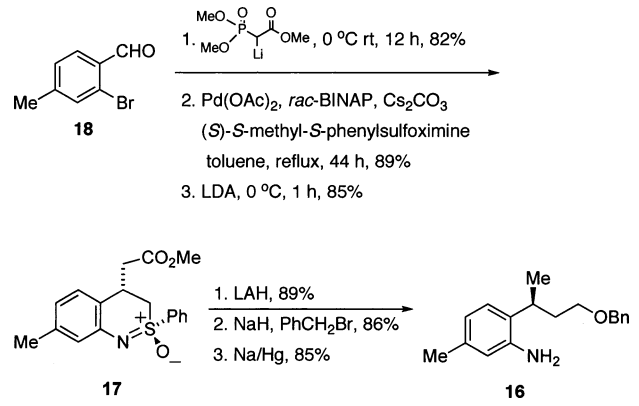
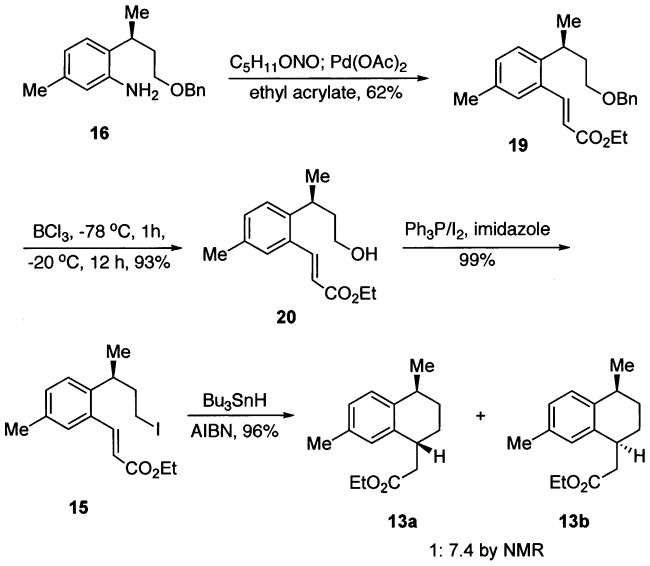
SCHEME 3. Synthesis of Aniline 16



SCHEME 4. Intramolecular Radical Cyclization of 15



The elaboration of aniline **16** (Scheme 4) into erogorgiaene started with the construction of the *trans* ring system. This began with a Heck coupling reaction of an aromatic diazonium salt with ethyl acrylate in the presence of $Pd(OAc)_2$ to yield the ester **19**. During the course of the diazotization we utilized isoamyl nitrite and 2.1 equiv of trifluoroacetic acid (TFA) in CH_2Cl_2 to furnish the soluble diazonium trifluoroacetate salt. In the same pot, a diazotization−Heck reaction was carried out in ethanol delivering **19** in 62% yield (two steps).[8] The benzyl group of **19** was removed by treatment with BCl_3 at −78 °C for 1 h, then at −20 °C for 12 h to afford alcohol **20** in 93% yield. The reaction of alcohol **20** with triphenylphosphine, imidazole, and iodine resulted in the formation of iodide **15** in quantitative yield.[9] The next step was an intramolecular radical cyclization with carbon−carbon bond formation to give a tetrahydronaphthalene, which was anticipated to occur with the desired diastereoselectivity. The radical cyclization reaction was performed via a standard procedure to give a mixture of the compounds **13a** and **13b** in a ratio of 1:7.4 by NMR. At this stage we did not actually know the stereochemistry of what we had produced. The assignment, based on later results, is given here to make the presentation simpler (Scheme 4).

To rationalize the stereochemical outcome of this reaction, we computed the cyclization paths from radical intermediate **15r** (i.e., **15** minus iodine) to the respective cyclic radicals **13ar** and **13br** utilizing density functional theory at the B3PW91[10] level in conjunction with a cc-pVDZ[11] basis set. This approach has shown to be reasonably accurate for reproducing the heats of formations of polycyclic hydrocarbons.[12] We used the Gaussian program suite for all computations.[13] In agreement with the experimental findings the formation of **13b** is also preferred computationally (Figure 2, Table 1). The reaction apparently is kinetically controlled as the radical products have virtually the same energies. The chairlike transition structures are markedly different in their orientation of the 1,4 substituents: while the preferred $\mathbf{TS_{13br}}$ places these groups both in approximately equatorial orientations, the methyl group is axial in $\mathbf{TS_{13ar}}$. This conformational preference (we also evaluated other transition state conformations but all of these are higher in energy) ultimately leads to a sizable energy difference for the two cyclization paths of 3.5 kcal/mol. Hence, the product prefence should therefore even be larger for groups larger than methyl.

Though at this stage we did not experimentally know the stereochemistry of the products, we pushed forward. Installation of the C-11 stereogenic center was easily accomplished by alkylation of the lithium enolate of esters **13** with methyl iodide. The reaction was conducted at −45 °C. Subsequently, reduction of the corresponding inseparable alkylated esters with lithium aluminum hydride delivered four alcohols in 86% overall yield in the ratio of 7.2:1.0:0.6:0.1 (Scheme 5). We could not separate the alcohols **21a**−**d** but we were able to use HPLC to get two fractions, each enriched in one component. The first sample contained **21a** and **21b** in a ratio of 13:1. The second sample contained **21c** and **21d** in a ratio of 11:1. The stereochemistry of alkylation reaction can be rationalized using a model introduced by Kocienski to predict the stereochemical outcome of related enolate alkylations (Figure 3).[14] The desired (*R*)-stereochemistry is a consequence of alkylation taking place selectively from the less hindered *re*-face of the enolates of **13a** and **13b**, the favored conformation of which the carbon 11−H bond resides in the plane of the enolate in order to minimize $A^{1,3}$-strain.[15]

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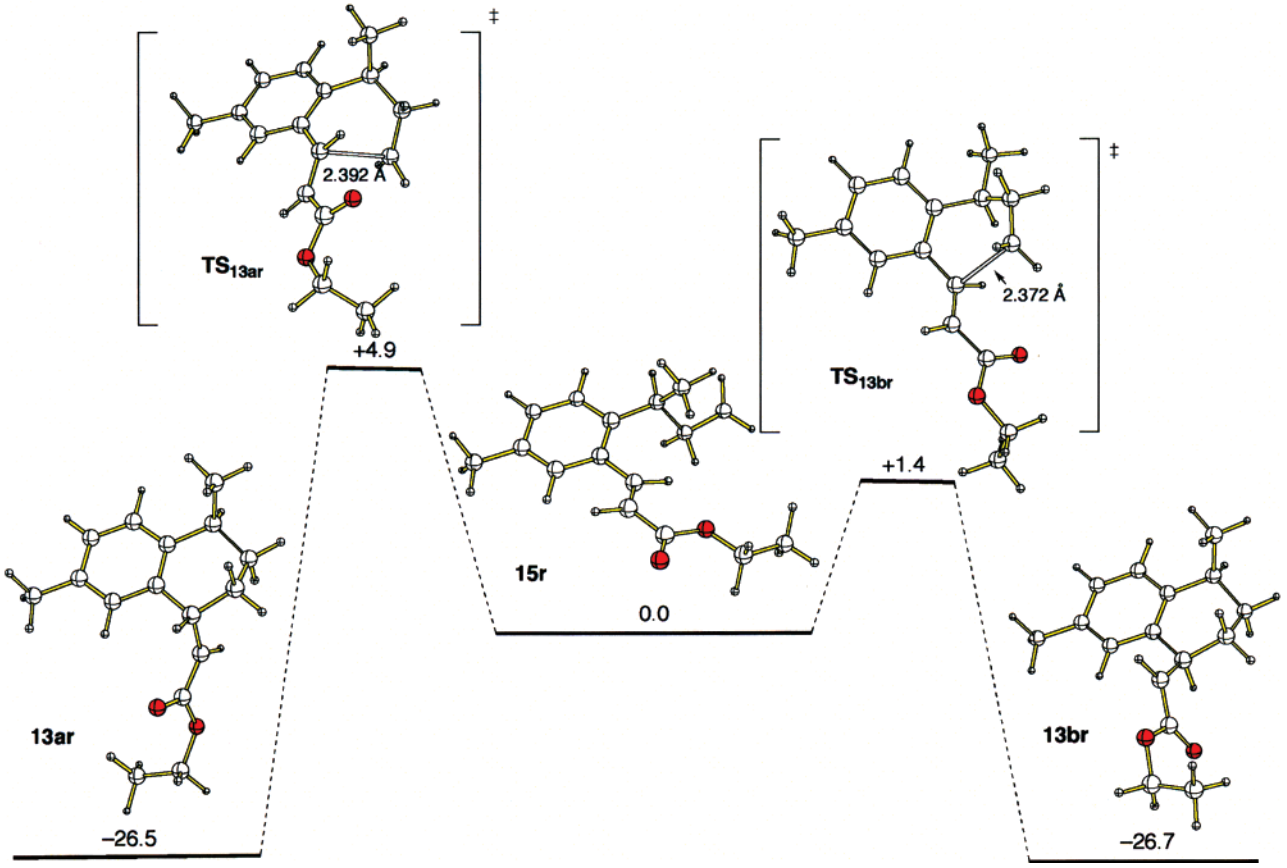
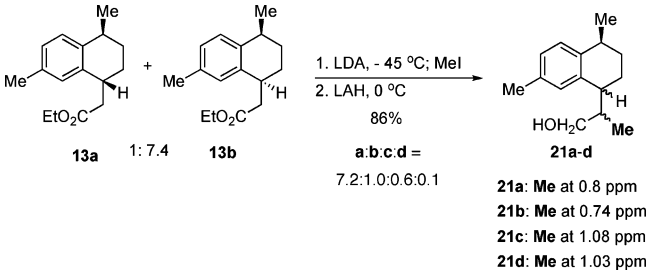


FIGURE 2. Computed reaction path for the cyclization of radical intermediate **15r** to bicyclic radicals **13ar** and **13br**; relative energies at B3PW91/cc-pVDZ+ZPVE (in kcal/mol).

TABLE 1. Absolute (in au) and Relative Energies (in kcal/mol) for the Optimized Radicals and Transition Structures Depicted in Figure 2

	B3PW91/cc-pVDZ	ZPVE	ΔH_0
15r	772.49987	206.7	0.0
TS$_{13ar}$	772.49312	207.4	+4.9
TS$_{13br}$	772.49906	207.6	+1.4
13ar	772.54767	210.2	−26.5
13br	772.54765	210.0	−26.7

SCHEME 5. Alkylation and Reduction of Ester 13



NMR data suggested that the pairs **21a**/**21b** and **21c**/**21d** had the same stereochemical relationship between carbons 4 and 11 (erogorgiaene numbering) as the chemical shift for the newly introduced methyl group was approximately the same for each member of the group. It should be noted that all compounds have the same configuration at carbon 1. So the pairs **21a**/**21b** and **21c**/**21d** are either both *syn* or both *anti*, as shown in Figure 4. However, at this stage we did not know which set was which.

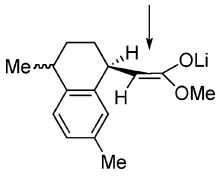


FIGURE 3. Rationalization for the stereoselective alkylation of enolates of **13a** and **13b**.

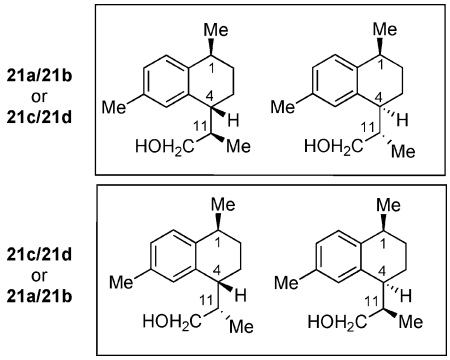


FIGURE 4. Preliminary structural assignments for the pairs **21a/b** and **21c/d**.

Kocienski and co-workers reported the synthesis of compounds **22** and **23** in 2001.[14] Compound **22** is *cis*/*syn*, and the methyl group appears at 0.72 ppm in the ^{1}H NMR whereas the corresponding signal for *cis*/*anti* **23** appears at 1.12 ppm (Figure 5). On the basis of these data, we made an initial stereochemical

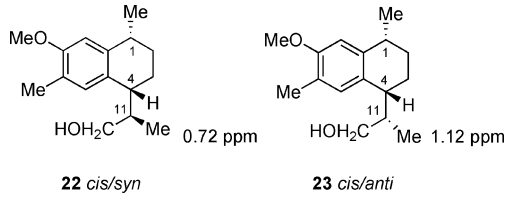


FIGURE 5. C-11 methyl shifts (erogorgiaene numbering) for two model compounds.

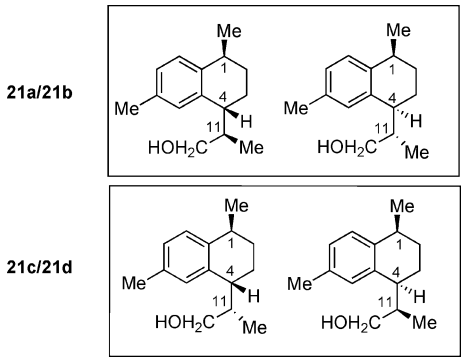
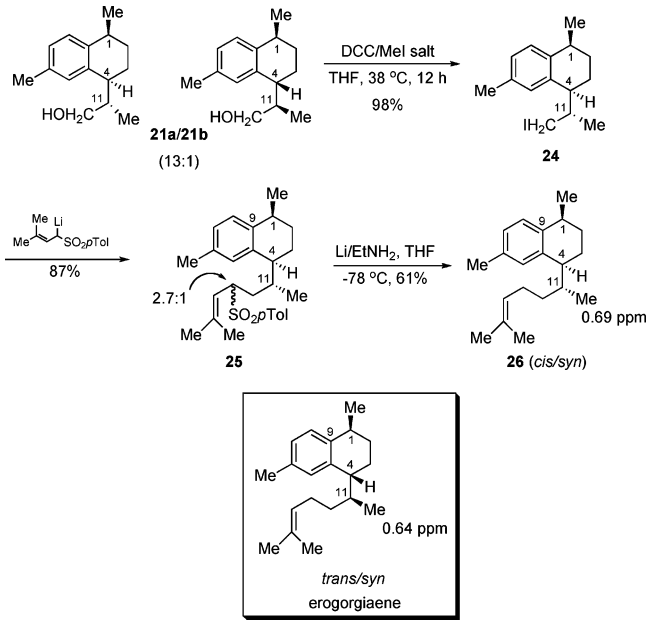


FIGURE 6. Assignment of C-4/C-11 relative stereochemistry in **21a/b** and **21c/d** pairs.

SCHEME 6. Synthesis of an Isomer (26) of Erogorgiaene



assignment. We assigned the H and the C-11 methyl group as *syn* in **21a**/**b** and *anti* in **21c**/**d** (Figure 6).

To verify this assignment and complete the synthesis, **21a**/**21b** was treated with DCC−MeI in THF at 37 °C to give iodide **24** in almost quantitative yield (Scheme 6).[16] It was anticipated that the iodide product **24** would be derived from **21a** since the **21a**/**21b** mixture was enriched in **21a** (13:1).[17] Nucleophilic displacement of the iodide **24** with the lithium derivative 3,3-dimethylallyl *p*-tolyl sulfone gave an 87% yield of the alkylation product **25** as a 2.7:1 mixture of diastereoisomers. The lack of

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(17) The amount of material obtained demanded that the product was derived from the major component of the mixture, **21a**.

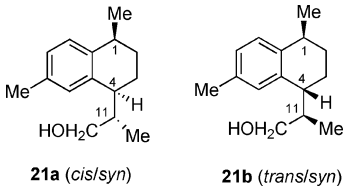


FIGURE 7. Stereochemical assignments of **21a** and **21b**.

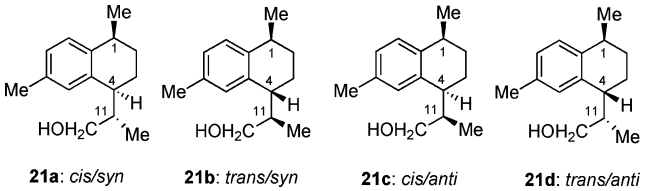
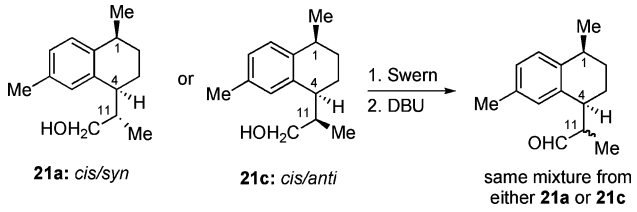


FIGURE 8. Complete stereochemical assignments of **21a**−**d**.

SCHEME 7. Establishing Stereochemical Relationships through Oxidation and Epimerization

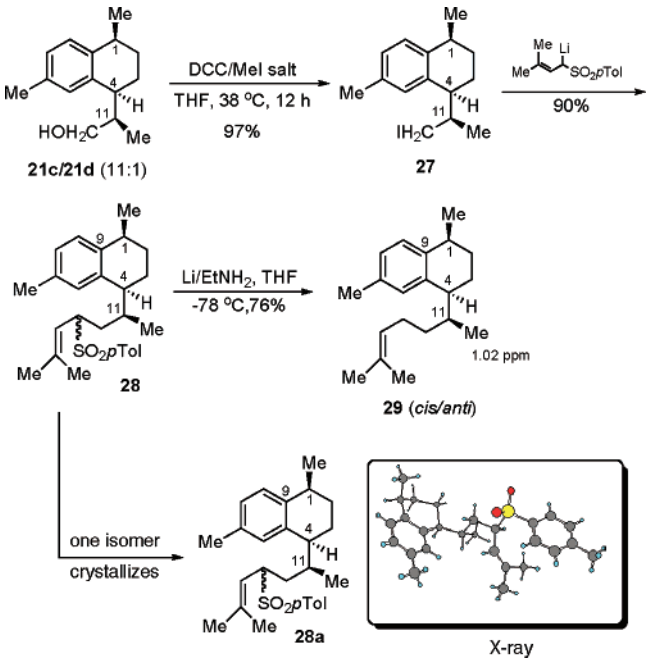


stereocontrol in the alkylation was of no practical consequence, since treatment of the mixture with lithium and ethylamine at −78 °C resulted in rapid and clean reduction of **25** to produce compound **26** in 61% yield. The ^{1}H NMR spectroscopic data for erogorgiaene and compound **24** are very similar with the exception of the signals for the methyl group on carbon 11. Erogorgiaene displays a signal at 0.64 ppm, whereas the compound **24** signal appears at 0.69 ppm. Moreover, ^{13}C NMR chemical shifts of compound **26** are significantly different from that of erogorgiaene. On the basis of these data, we assigned the stereochemistry of compound **26** as *cis/syn* (erogorgiaene is *trans/syn*). We thus also predicted that **21b** was *trans/syn* (Figure 7).

The configurations of the remaining diastereoisomers were established completely by a chemical correlation of the two samples **21a**/**21b** and **21c**/**21d**. Swern oxidation of the mixtures **21a**/**21b** or **21c**/**21d** and then epimerization of the corresponding aldehydes with 10 equiv of DBU gave mixtures of two aldehydes for both reactions (Scheme 7). These samples were the essentially *the same* by ^{1}H NMR. This suggested that **21a** and **21c** were epimeric at carbon 11. Since **21c**/**21d** was enriched in **21c**, and **21a** was indeed *cis*/*syn*, then **21c** had to be *cis*/*anti*. Since we could conclude that **21b** was *trans*/*syn*, then **21d** had to be *trans*/*anti* (Figure 8).

To further confirm our assignment, the same reaction sequence for the **21a**/**21b** mixture shown in Scheme 6 was repeated on the **21c**/**21d** mixture (Scheme 8). Iodination of **21c**/**21d** with DCC−MeI in THF at 37 °C led to iodide **27** in 97% yield. The product isolated was derived from **21c** since **21c**/**21d** mixture is enriched in **21c** (11:1). Nucleophilic displacement of the iodide **27** with the lithium derivative 3,3-dimethylallyl *p*-tolyl sulfone gave a 90% yield of the alkylation product **28** as a mixture of diastereoisomers. One of the stereoisomers was crystallized and the X-ray structure of **28a** confirmed that the

SCHEME 8. Synthesis of an Isomer (29) of Erogorgiaene



stereochemistry of **21c** was indeed *cis*/*anti*.[18] Reduction of compound **28** with lithium and ethylamine at −78 °C resulted in the formation of compound **29** in 76% yield. This is the *cis*/*anti* diastereoisomer of (+)-erogorgiaene.

At this point, we knew we had prepared two diastereoisomers of erogorgiaene in enantiomerically pure form. Both of them were submitted to the Tuberculosis Antimicrobial Acquistion and Coordinating Facility (TAACF) for biological testing. The *cis*/*syn* diastereomer **26** showed 94% growth inhibition at 12.5 μg/mL, whereas the *cis*/*anti* diastereomer **29** showed no inhibition at all, compared to 96% inhibition for (+)-erogorgiaene (against *Mycobacterium tuberculosis* $H_{37}Rv$).[19] These results are interesting. They suggest that there is specificity in activity based on stereochemistry and not something more general like simple hydrophobicity. The conformation of the side chain is likely important to activity. Further studies will be required to provide more support for this idea.

Since our radical cyclization approach to erogorgiaene was not successful, we explored a new approach to its synthesis.

Aniline **30** was converted to 1-aryl-3,3-diethyltriazene in 90% yield at 0−5 °C, in an Et_2O/THF/CH_3CN/H_2O solvent system, in the presence of potassium carbonate. Subsequently, upon treatment with iodomethane in a sealed tube at 130 °C for 30 min, triazene was smoothly converted to aryl iodide **31** in 80% yield. Sonogashira coupling reaction of iodide **31** with (trimethylsilyl)acetylene in the presence of $PdCl_2$, PPh_3, CuI, and triethylamine afforded compound **32** in 90% yield. Swern oxidation of **32** provided aldehyde **33** in 96% yield. Finally, aldehyde **33** was converted to compound **34** in 98% yield via a Wittig reaction. Hoveyda and co-workers reported that this compound could be converted to erogorgiaene in 12 steps. The proton and carbon NMR data as well as rotation value for compound **34** matched those reported by Hoveyda.[2f] We obtained **34** in 10 steps in an overall yield of 27% (Scheme 9), while Hoveyda required 6 steps with an overall yield of 48%. We required more functional group manipulations and this situation must be reckoned with as other applications of our methodology are considered.

In conclusion, we have accomplished a formal synthesis of the serrulatane diterpene, (+)-erogorgiaene (**1**), and two of its diastereoisomers (**26** and **29**) using our benzothiazine methodology as a key step. The antitubercular activity of **26** and **29** differ dramatically, suggesting a specific interaction based on conformation is responsible for the activity. Future studies including an independent approach to erogorgiaene as well as the synthesis of pseudopteroxazole and related compounds will be reported in due course.

(18) The amount of material obtained demanded that the product was derived from the major component of the mixture, **21c**.

(19) TAACF, http://www.taacf.org/.

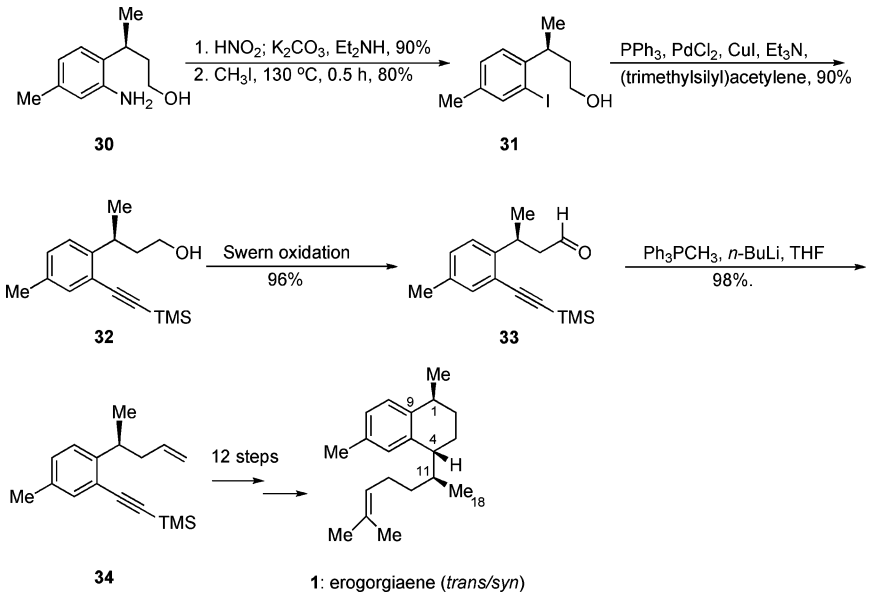
Experimental Section

A few representative reactions are listed here. Full experimental details for all reactions and characterization data for all compounds can be found in the Supporting Information, which also contains the *xyz* coordinates of the structures depicted in Figure 2.

(*S*,*E*)-Ethyl 3-(2-(4-(Benzyloxy)butan-2-yl)-5-methylphenyl)-acrylate (19). The aniline (**16**) (538 mg, 2 mmol) was dissolved in 5 mL of CH_2Cl_2 at room temperature under Argon. Under vigorous stirring, 323 μL (4.2 mmol) of TFA was then added dropwise. The mixture was cooled at 0 °C for 10 min, and isoamyl nitrite (322 μL, 2.4 mmol) was added to the well-stirred reaction mixture over a period of 10 min dropwise at 0 °C. The reaction was stirred for 1 h at 0 °C. Then solvent was removed at reduced pressure under no light. The resulting diazonium trifluoroacetate was dissolved in 5 mL of ethanol under Ar and with protection from light. The ethyl acrylate (260 μL, 2.4 mmol) was then added to the stirred solution, followed by the $Pd(OAc)_2$ catalyst (22.4 mg, 0.1 mmol). After 1 h, the reaction was stopped simply by filtration through Celite. The filtrate was concentrated in vacuo, the residue was redissolved in diethyl ether, and the resulting solution was washed twice with water and brine. After drying over $MgSO_4$ purification of the product by flash chromatography (5% EtOAc/Hexanes) afforded compound **19** as a colorless oil (439 mg, 62%); IR 2921, 2855, 1711, 1634, 1311, 1176, 1098 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.14 (d, J = 15.7 Hz, 1H), 7.33−7.15 (m, 8H), 6.32 (d, J = 15.7 Hz, 1H), 4.39 (dd, J = 19.3, 11.9 Hz, 2H), 4.22 (q, J = 7.2 Hz, 2H), 3.41−3.26 (m, 3H), 2.30 (s, 3H), 1.94−1.86 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.8, 143.3, 142.5, 138.4, 135.4, 132.9, 131.0, 128.1, 127.4, 127.3, 127.2, 126.0, 119.8, 72.8, 68.2, 60.2, 37.7, 30.7, 22.2, 20.8, 14.2; HRMS calcd for $C_{23}H_{28}O_3Na$ $[M + Na]^+$ 375.1930, found 375.1929; $[\alpha]^{25}_D$ −10.4 (c 1.0, $CHCl_3$).

(*S*,*E*)-Ethyl 3-(2-(4-Iodobutan-2-yl)-5-methylphenyl)acrylate (15). Triphenylphosphine (285 mg, 1.09 mmol), imidazole (74 mg, 1.09 mmol), and iodine (275 mg, 1.09 mmol) were successively added to **20** (151 mg, 0.543 mmol) in a mixture of diethyl ether/acetonitrile (16 mL/4 mL). The reaction mixture was stirred for 2 h at rt. Diethyl ether (15 mL) was added, and the mixture was filtered on Celite and washed with diethyl ether (10 mL). The yellow solution recovered was washed with a saturated sodium thiosulfate solution (2 × 15 mL) and brine (20 mL), dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude oil was purified by flash chromatography on silica gel using 2% EtOAc/hexanes to yield **15** (210.7 mg, 99%) as a colorless oil. IR 2962, 2921, 1711, 1629, 1311, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 15.7 Hz, 1H), 7.34 (s, 1H), 7.16−7.12 (m, 2H), 6.32 (d, J = 15.7 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 3.30−3.25 (m, 1H), 3.10−2.96 (m, 2H), 2.32 (s, 3H), 2.21−2.03(m, 1H), 1.34 (t, J = 7.1 Hz, 2H), 1.23 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 142.2, 141.7, 135.9, 133.1, 131.1, 127.5, 125.9, 120.2, 60.4, 41.5, 35.0, 21.4, 20.8, 14.3, 4.0; HRMS calcd for $C_{16}H_{21}IO_2Na$ $[M + Na]^+$ 395.0478, found 395.0504; $[\alpha]^{25}_D$ −36.3 (*c* 3.31, $CHCl_3$).

SCHEME 9. Formal Synthesis of Erogorgiaene



Ethyl 2-((1*S*,4*S*)-4,7-Dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)acetate (13b). To a solution of iodide **15** (150 mg, 0.387 mmol) in benzene (20 mL) was added Bu_3SnH (0.167 mL, 0.62 mmol) in 10 mL of benzene and AIBN (0.01 g, 0.058 mmol) in 10 mL of benzene dropwise via syringe pumps under refluxing. The reaction was stirred overnight. After the reaction mixture was cooled, a concentrated KF (3 mL) was added, and then the reaction was stirred again overnight. The reaction mixture was extracted with Et_2O (3 × 15 mL) and washed with brine. After drying over $MgSO_4$, the solvent was removed under reduced pressure. The crude product was subjected to flash chromatography on silica gel (4% Et_2O/Hexanes) to afford a colorless oil, two diastereoisomers in a ratio of 7.4:1 by NMR (95.1 mg, 96%). Major **13b**: IR 2953, 2917, 2859, 1732, 1605, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.13−7.11 (m, 1H), 6.98−6.95 (m, 2H), 4.17 (q, J = 7.2 Hz, 2H), 3.29−3.26 (m, 1H), 2.83−2.79 (m, 1H), 2.71 (dd, J = 15.1, 4.7 Hz, 1H), 2.52 (dd, J = 15.1, 10.5 Hz, 1H), 2.28 (s, 3H), 1.88−1.83 (m, 2H), 1.75−1.70 (m, 1H), 1.56−1.50 (m, 1H), 1.30−1.20 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 139.0, 138.9, 135.1, 128.6, 127.7, 127.0, 60.3, 41.9, 35.0, 32.3, 28.2, 26.1, 22.3, 20.9, 14.2; HRMS calcd for $C_{16}H_{22}O_2Na$ $[M + Na]^+$ 269.1512, found 269.1524; $[\alpha]^{25}_D$ +9.12 (*c* 1.71, $CHCl_3$).

(−)-1-(*epi*)-*ent*-Erogorgiaene (26). A 50-mL round-bottomed flask was charged with 0.5 mL of anhydrous THF and sulfone **25** (10 mg, 0.024 mmol). The solution was cooled to −78 °C and $EtNH_2$ (5 mL) was added. The lithium wire (1.7 mg, 0.24 mmol) was added and the solution sustained a blue color. The reaction was stirred for 15 min then quenched by EtOH at −78 °C. The resulting solution was warmed to room temperature for a while. Removal the solvents gave the crude residue, which was purified by column chromatography (pentanes) to afford (−)-1-(*epi*)-*ent*-erogorgiaene **26** as a colorless oil (4.0 mg, 61%). IR 2958, 2921, 2855, 1499, 1454, 1372 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.04 (s, 1H), 7.01 (d, J = 7.7 Hz, 1H), 6.92 (d, J = 7.0 Hz, 1H), 5.18−5.15 (m, 1H), 2.86−2.84 (m, 1H), 2.80−2.76 (m, 1H), 2.30 (s, 3H), 2.22−2.16 (m, 1H), 2.10−2.04 (m, 2H), 1.85−1.77 (m, 1H), 1.72 (s, 3H), 1.68−1.57 (m, 2H), 1.63 (s, 3H), 1.49−1.21 (m, 3H), 1.22 (d, J = 7.2 Hz, 3H), 0.69 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 139.9, 134.7, 131.3, 128.6, 127.8, 126.0, 124.8, 41.1, 35.8, 35.3, 32.5, 29.0, 26.3, 25.8, 23.2, 21.2, 18.0, 17.7, 14.7; HRMS calcd for $C_{20}H_{30}$ 270.2348, found 270.2327; $[\alpha]^{25}_D$ −18.5 (*c* 0.5, $CHCl_3$).

(−)-4-(*epi*)-Erogorgiaene (29). The procedure was similar to the above yielding a colorless oil (76%). IR: 2962, 2921, 2847, 1499, 1458, 1372 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.04−6.90 (m, 3H), 5.02−4.98 (m, 1H), 2.88−2.83 (m, 1H), 2.67−2.62 (m, 1H), 2.29 (s, 3H), 2.17−2.12 (m, 1H), 2.10−1.91 (m, 1H), 1.88−1.64 (m, 4H), 1.67 (s, 3H), 1.57 (s, 3H), 1.25−1.09 (m, 3H), 1.22 (d, J = 7.2 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.1, 139.4, 134.5, 131.2, 128.6, 128.3, 126.1, 125.0, 43.6, 35.2, 32.5, 31.6, 29.0, 26.2, 25.7, 23.4, 21.2, 19.6, 18.1, 17.7; HRMS calcd for $C_{20}H_{30}$ 270.2348, found 270.2309; $[\alpha]^{25}_D$ −20.0 (*c* 0.28, $CHCl_3$).

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Supporting Information Available: Spectroscopic data and experimental procedures for the reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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