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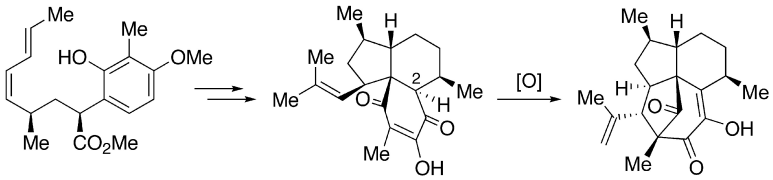

C_2-epi-elisabethin A elisapterosin B (ent-**2**)

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A General Strategy to Elisabethane Diterpenes: Stereocontrolled Synthesis of Elisapterosin B via Oxidative Cyclization of an Elisabethin Precursor

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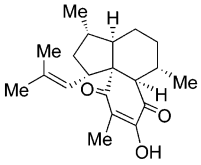
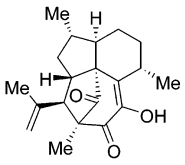
Over the past few years, Rodríguez and co-workers have reported the isolation of a series of structurally novel metabolites (e.g., **1**−**4**) from the gorgonian sea whip *Pseudopterogorgia elisabethae*, collected from the waters near San Andréas Island, Colombia.[1] The more intricate members of the family were suggested to be biosynthesized from elisabethin A, which in turn arises from geranylgeranyl pyrophosphate via a serrulatane precursor. The confluence of structural complexity and interesting biological activity has made these terpenes attractive targets for chemical synthesis.[2] In connection with the development of a general strategy to these natural products, we describe here the stereocontrolled asymmetric synthesis of the elisabethin skeleton and its oxidative cyclization to elisapterosin B (**2**),[3] a potent in vitro inhibitor of *Mycobacterium tuberculosis* H37Rb.[1]


elisabethin A (**1**)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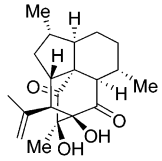
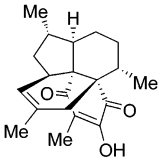
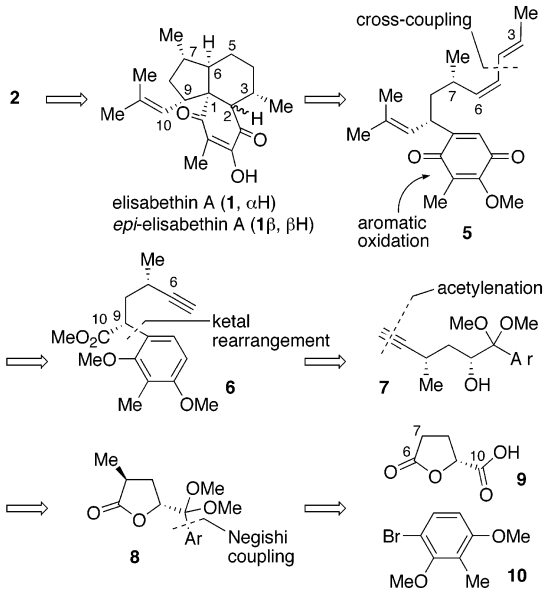

cumbiasin A (**3**)


colombiasin A (**4**)

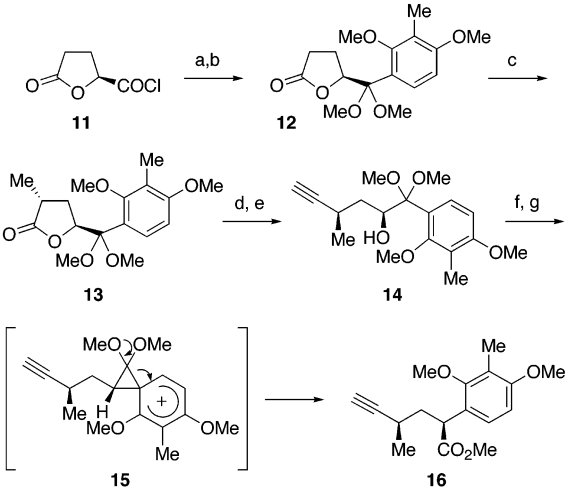
Our synthetic plan to elisabethin and elisapterosin B (Scheme 1) involves a series of diastereoselective reactions to set all of the stereocenters commencing with the single asymmetric center of 5-oxo-2-tetrahydrofurancarboxylic acid (**9**), both enantiomers of which are commercially available. The latent quinone functionality as well as the required "anti" relative stereochemistry in aryl acetic ester **6** would be introduced by a pinacol-type ketal rearrangement, a highly stereocontrolled process that has seen few applications in complex molecule synthesis.[4] The tricyclic elisabethin framework would be constructed by an intramolecular Diels−Alder (IMDA) reaction of an *E*,*Z*-diene unit with quinone portion of **5**, a transformation that was expected to create three of the remaining five chiral centers of elisapterosin B. The final two stereocenters would be installed through a biosynthesis-inspired oxidative cyclization.

The desired rearrangement product, alkyne-ester **16** (Scheme 2), was synthesized starting with *S*-(+)-tetrahydro-5-oxo-2-furancarboxylic acid, which was prepared from the inexpensive L-enantiomer of glutamic acid.[5] The selection of the simple dimethoxyaryl precursor was predicated on the expectation that it could be oxidized selectively at a later stage to the required methoxy-*p*-quinone. The coupling of acid chloride **11**[6] to the Grignard reagent of aryl bromide (**10**)[7] was mediated by $ZnCl_2$ and a palladium catalyst,[8] and the resulting ketone was subjected to ketal-forming conditions. The expected methyl ketal was accompanied by the lactone methanolysis product, so that the crude product was treated with *t*-BuOK to yield lactone **12** in 83% overall yield. Methylation of the lithium enolate of lactone **12** afforded the desired trans product (**13**) with 8:1 diastereoselectivity. The required one-carbon homologation of

Scheme 1



Scheme 2 [a]



[a] (a) ArMgBr, $ZnCl_2$, cat. $PdCl_2(PPh_3)_2$, THF (75%); (b) cat. TsOH, $HC(OMe)_3$, MeOH; *t*-BuOK, THF, (83%); (c) NaHMDS, MeI, THF, (86%); (d) DIBAL, toluene; (e) $(MeO)_2P(O)CHN_2$, *t*-BuOK, THF (70% overall); (f) MsCl, 2,6-lutidine, 50 °C; (g) $CaCO_3$, wet MeOH, 50 °C (72%, 2 steps).

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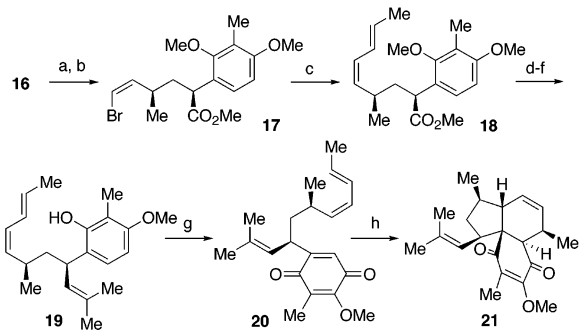
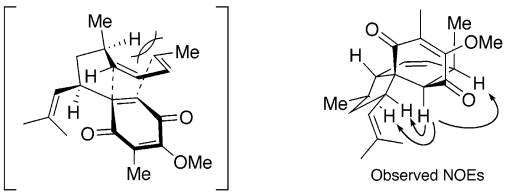
Scheme 3 [a]



[a] (a) cat. $AgNO_3$, NBS (1.0 equiv), acetone, rt; (b) H_2NNHTs (6 equiv), AcONa (7 equiv), MeOH, Δ, 65% 2 steps; (c) *E*-1-bromopropene (1.2 equiv), *t*-BuLi (2.4 equiv), −78 °C; $ZnCl_2$ (1.2 equiv), $PdCl_2$(dppf) (0.01 equiv), THF, rt, 70%; (d) DIBAL, −95 °C; (e) Wittig, 62% for 2 steps; (f) NaSEt (10 equiv), DMF, 90 °C, 67%; (g) O_2, cat. Salcomine, DMF, rt, 49%; (h) toluene, 80 °C, 67%.

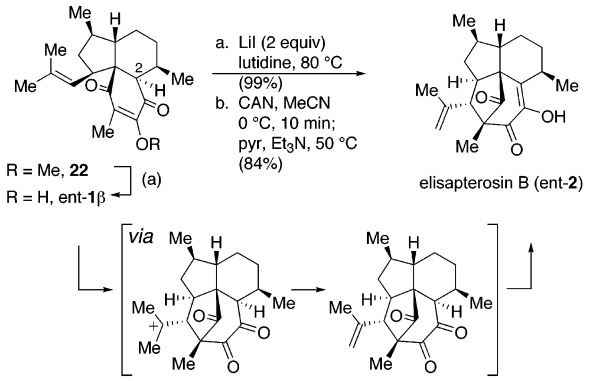
the lactone carbonyl to alkyne **14** was achieved through an efficient two-step sequence. Reduction of the lactone with DIBAL followed by treatment of the crude lactol intermediate with the Seyferth reagent[9] furnished acetylene **14**, poised for the pivotal pinacol-type rearrangement.[4] The aryl group migration was triggered upon heating the mesylate of **14** in methanol in the presence of excess calcium carbonate as an acid scavenger to furnish methyl ester **16** in 72% yield.

In preparation for the IMDA reaction (Scheme 3), the acetylene was converted to the *Z*-bromoalkene (**17**), cross-coupling of which with *E*-bromopropene afforded diene **18**.[10] The ester functionality was transformed into the 2-methylpropenyl side chain via DIBAL reduction followed by Wittig olefination. Regioselective demethylation[11] of the more hindered methyl ether provided phenol **19**, which upon subjection to Salcomine-catalyzed oxidation[12] yielded quinone **20**, required for the IMDA reaction. Upon heating in toluene, compound **20** underwent a clean cycloaddition to afford the expected *endo* adduct as a single diastereomer. Of the two *endo* transition states, the one shown below avoids potentially severe allylic strain between the C7-Me group and propenyl unit on the *cis*-double bond. The assigned relative stereochemistry is consistent with NOE results as well as with the further conversion of **21** to elisapterosin B (vide infra).



Selective hydrogenation of the Diels−Alder product (**21**), accomplished in quantitative yield with Wilkinson's catalyst, gave **22**, which is just an epimerization and O-demethylation away from *ent*-elisabethin A. Contrary to expectations, however, ene-dione **22** proved recalcitrant to deprotonation at C2: no epimerization was evident even with sodium ethoxide in refluxing ethanol. On the other hand, the elisabethin skeleton of **22** was primed for testing the biosynthesis-based cyclization to the elisapterosins. The methyl ether was smoothly cleaved upon heating with LiI in 2,6-lutidine to furnish enol *ent*-**1**β in quantitative yield. The oxidative cyclization of *ent*-**1**β to elisapterosin B (*ent*-**2**) took place smoothly and in high yield upon treatment with $Ce(NH_4)_2(NO_3)_6$, followed by addition of pyridine and triethylamine, to enolize the presumed diketone intermediate. The ^{1}H and ^{13}C NMR spectra of our synthetic sample perfectly matched those of natural elisapterosin B.

Scheme 4



In summary, we have completed a stereocontrolled asymmetric synthesis of the enantiomer of elisapterosin B, by a route that features (a) a pinacol-type ketal rearrangement to transfer chirality, (b) an IMDA reaction of an *E*,*Z*-diene to construct the elisabethin skeleton, and (c) a biosynthesis-inspired oxidative cyclization of the elisabethin precursor to elisapterosin B (Scheme 4).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra (PDF) of all key intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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