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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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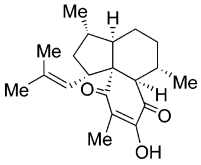
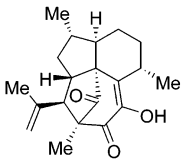
Over the past few years, Rodríguez and co-workers have reported the isolation of a series of structurally novel metabolites (e.g., **1**−**4**) from the gorgonian sea whip *Pseudopterogorgia elisabethae*, collected from the waters near San Andréas Island, Colombia.[1] The more intricate members of the 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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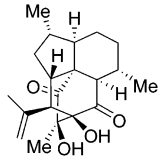
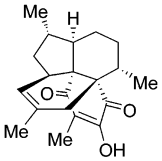
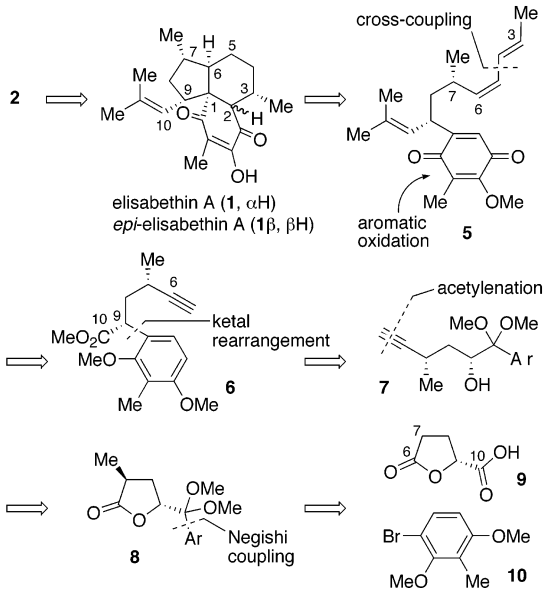

cumbiasin A (**3**)


colombiasin A (**4**)

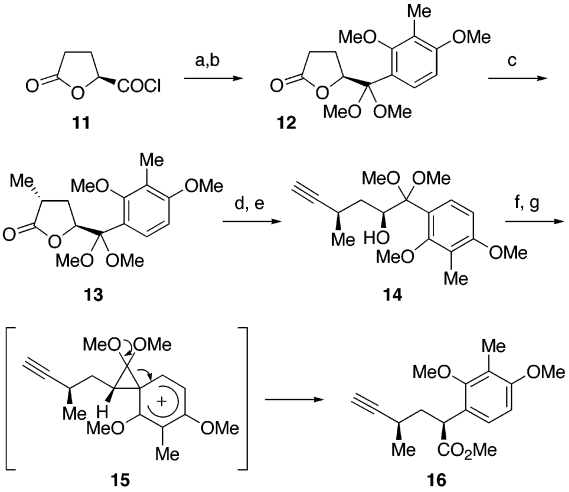
Our synthetic plan to elisabethin and elisapterosin B (Scheme 1) involves a series of diastereoselective reactions to set all of the stereocenters commencing with the single asymmetric center of 5-oxo-2-tetrahydrofurancarboxylic acid (**9**), both enantiomers of which are commercially available. The 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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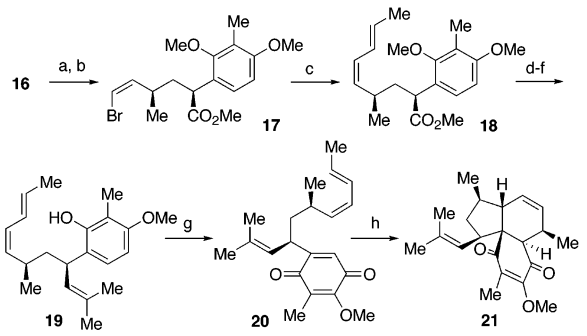
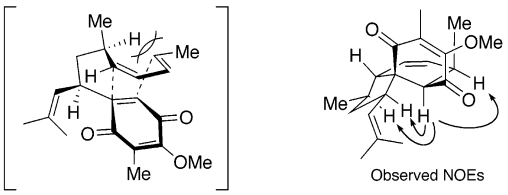
Scheme 3 [a]



[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%.

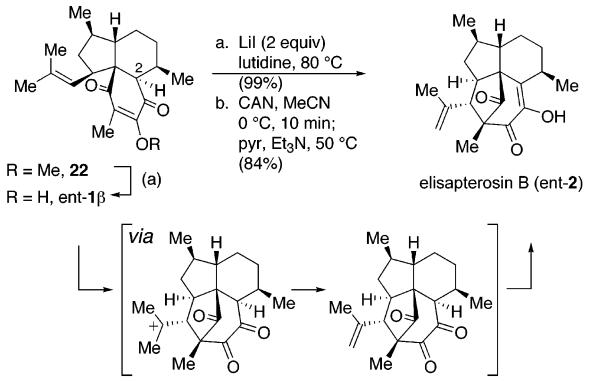
the lactone carbonyl to alkyne **14** was achieved through an efficient two-step sequence. Reduction of the lactone with DIBAL followed by treatment of the crude lactol intermediate with the Seyferth reagent[9] furnished acetylene **14**, poised for the pivotal pinacol-type rearrangement.[4] The aryl 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.

References

(1) (a) Rodríguez, A. D. *Tetrahedron* **1995**, *51*, 4571−618. (b) Rodríguez, A. D.; Gonzalez, E.; Huang, S. D. *J. Org. Chem.* **1998**, *63*, 7083−7091. (c) Rodríguez, A. D.; Ramirez, C. *Org. Lett.* **2000**, *2*, 507−510. (d) Rodríguez, A. D.; Ramirez, C.; Medina, V.; Shi, Y. P. *Tetrahedron Lett.* **2000**, *41*, 5177−5180. (e) Rodríguez, A. D.; Ramirez, C.; Rodríguez, I. I.; Barnes, C. L. *J. Org. Chem.* **2000**, *65*, 1390−1398. (f) Rodríguez, A. D.; Ramirez, C.; Shi, Y.-P. *J. Org. Chem.* **2000**, *65*, 6682−6687. (g) Rodríguez, A. D.; Shi, Y.-P. *Tetrahedron* **2000**, *56*, 9015−9023.

(2) Colombiasin: (a) Nicolaou, K. C.; Vassilikogiannakis, G.; Magerlein, W.; Kranich, R. *Chem. Eur. J.* **2001**, *7*, 5359−5371. (b) Nicolaou, K. C.; Vassilikogiannakis, G.; Magerlein, W.; Kranich, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2482−2486. (c) Harrowven, D. C.; Tyte, M. J. *Tetrahedron Lett.* **2001**, *42*, 8709−8711. See also ref 3b.

(3) While this manuscript was in preparation, the syntheses of two other elisabethane terpenes have appeared. (a) Elisabethin A: Heckrodt, T. J.; Mulzer, J. *J. Am. Chem. Soc.* **2003**, *125*, 4680−4681 and references therein. (b) Pseutopterosin B: Kim, A. I.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2003**, *42*, 1267−1270. This paper also describes the synthesis of colombiasin. (c) Miyaoka, H.; Honda, D.; Mitome, H.; Yamada, Y. *Tetrahedron Lett.* **2002**, *43*, 7773−7775.

(4) (a) Tsuchihashi, G., Kitajima, K., Mitamura, M. *Tetrahedron Lett.* **1981**, *22*, 4305−4308. (b) Honda, Y.; Ori, A.; Tsuchihashi, G. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1027−1036 and references therein.

(5) Gringore, O. H.; Rouessac, F. P. *Org. Synth.* **1985**, *63*, 99−102. We elected to use L-glutamic acid rather than D-glutamic acid, since the latter is considerably more costly (Aldrich: $31.80 for 1.0 kg vs $262.40 for 100 g).

(6) Acid chloride **11** is commercially available from Pfaltz & Bauer, Inc.

(7) (a) Schlegel, D. C.; Tipton, C. D.; Rinehart, K. L., Jr. *J. Org. Chem.* **1970**, *35*, 849−850. (b) Zhao, H.; Biehl, E. *J. Nat. Prod.* **1995**, *58*, 1970−1974.

(8) Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F. T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181−5184.

(9) (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379−1386. (b) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Chem. Commun.* **1973**, 151−152. (c) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 869−874. (d) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997−4998.

(10) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393−2401.

(11) (a) Review: Evers, M. *Chem. Scr.* **1986**, *26*, 585−597. (b) Ahmad, R.; Saá, J. M.; Cava, M. P. *J. Org. Chem.* **1977**, *42*, 1228−1230.

(12) (a) Van Dort, H. M.; Geursen, H. J. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 520−6. (b) Parker, K. A.; Petraitis, J. J. *Tetrahedron Lett.* **1981**, *22*, 397−400.

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