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Total Synthesis of Elisabethin A: Intramolecular Diels−Alder Reaction under Biomimetic Conditions

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The marine diterpenoid elisabethin A (**1**) was isolated, along with its structurally related isomers elisapterosin B **(2)** and colombiasin A **(3)**, from the chemically rich Caribbean gorgonian *Pseudopterogorgia elisabethae* (Octocorallia) in the late 1990s (Figure 1).[1] Detailed pharmacological properties of **1**−**3** have not yet been communicated; however, some members of the elisabethane class do show significant activity against *Mycobacterium tuberculosis*, as well as in vitro cancer cell cytotoxicity.[1] Moreover, **1** has attracted particular attention as a potential biosynthetic intermediate of **2** and **3**.

The complex molecular architecture and rich functionalization of these molecules make them interesting and attractive synthetic targets.[2] We now report the first total synthesis of **1**.[3]

According to our retrosynthetic plan (Scheme 1) the elisabethane carbon skeleton should be assembled via an intramolecular Diels−Alder (IMDA) cyclization[4] of quinone **5** which should be generated by oxidation of the corresponding hydroquinoid precursor.

The synthesis of the benzenoid fragment (Scheme 2) started from commercially available aldehyde **6** which was converted to phenol **7**. Selective 4-O-demethylation was achieved via an oxidation/reduction sequence to give hydroquinone **8**.[5] O-Silylation and regioselective bromination with NBS led to aryl bromide **9**, which was subsequently converted to aryl acetic ester **11a** using a palladium-catalyzed Negishi−Reformatsky coupling with stannane **10**.[6] To obtain the Evans' oxazolidinone **11b**, ester **11a** was transformed into acid **12** in a three-step reduction/oxidation sequence which was necessary because ester **11a** remained unchanged even after refluxing it in concentrated NaOH/EtOH for 14 h. Acid **12** was converted to the desired imide **11b** via the mixed anhydride because the corresponding acid chloride did not react, probably due to formation of the ketene.[7]

The dienyl iodide **18** was synthesized from known aldehyde **13** (Scheme 3).[8] Olefination with phosphonate **14** furnished the desired (*E*)-Weinreb-enamide **15**, which was reduced to the α,*β*-unsaturated aldehyde **16**. The *Z*-geometry of the second double bond was installed by a "salt-free" Wittig reaction (NaHMDS, Ph_3PEtBr) to give isomerically pure diene **17**, which was converted into iodide **18** by two additional steps.

The alkylation of ester **11a** with iodide **18** (Scheme 4) proceeded smoothly to **19a** but with a moderate de of 42%. In contrast, oxazolidinone **11b** gave a significantly higher de (86%); however, the reaction required recycling of unreacted starting material to furnish **19b** in an overall yield of 69%. Reduction of **19a/b** to the alcohol with $LiBH_4$ allowed separation of diastereoisomers by column chromatography. Swern oxidation delivered aldehyde **20** which was converted to the desired Diels−Alder precursor **21** by a Wittig reaction. The choice of the hydroquinone 1,4-OH-protecting groups turned out to be a very crucial issue. An earlier attempt to accomplish an oxidative 1,4-O-di-demethylation under various conditions such as CAN, AgO/HNO_3, and so forth had totally failed to produce any of the desired quinone.[3] A complex

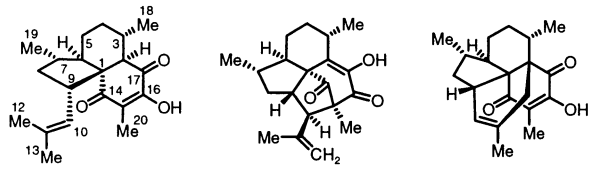
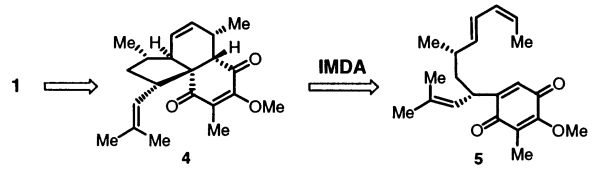
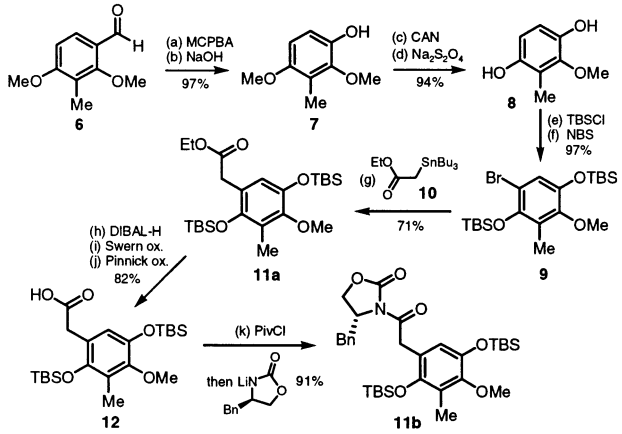


Figure 1. Marine natural products from *Pseudopterogorgia elisabethae*.

Scheme 1. Retrosynthetic Analysis of Elisabethin A (**1**)



Scheme 2. Synthesis of the Aryl Acetic Acid Derivatives **11a/b**[a]



[a] Reagents and conditions: (a) MCPBA (1.5 equiv), CH_2Cl_2, rt, 5 h; (b) NaOH (3.0 equiv), $MeOH/H_2O$, rt, 4 h; (c) CAN (2.5 equiv), $MeCN/H_2O$, rt, 1 h; (d) $Na_2S_2O_4$ (5.0 equiv), $MeCN/H_2O$, 4 h, rt; (e) TBSCl (3.0 equiv), im (4.0 equiv), DMF, rt, 20 h; (f) NBS (1.0 equiv), MeCN, rt, 6 h; (g) $ZnBr_2$ (1.4 equiv), **10** (1.4 equiv), $PdCl_2(o\text{-}tol_3P)_2$ (0.08 equiv), DMF, 80 °C, 12 h; (h) DIBAL-H (3.0 equiv), CH_2Cl_2, −78 → 0 °C, 6 h; (i) $(COCl)_2$ (2.0 equiv), DMSO (4.0 equiv), Et_3N (6.0 equiv), CH_2Cl_2, −78 °C → rt; (j) $NaClO_2$ (5.0 equiv), KH_2PO_4 (5.0 equiv), $H_2O/^tBuOH/Me_2C{=}CMe_2$, rt, 12 h; (k) PivCl (1.1 equiv), Et_3N (1.3 equiv), then deprotonated Evans' oxazolidinone (1.2 equiv), THF, 14 h, −78 °C→ rt, (MCPBA = *m*-chloroperbenzoic acid, im = imidazole, PivCl = pivaloyl chloride).

mixture of products was formed, probably due to the decomposition of the diene under the strongly acidic conditions. However, the OTBS-modified precursor **21** was easily deprotected with TBAF and oxidized[9] with aqueous $FeCl_3$ to form quinone **5** (detectable by TLC and NMR) which cyclized in situ to adduct **4**.

The significance of this IMDA reaction lies in (1) the use of of a terminal (*Z*)-olefin—to our knowledge the first case that has been successfully developed, (2) the unusually mild and virtually biomimetic conditions (aqueous medium, ambient temperature), and

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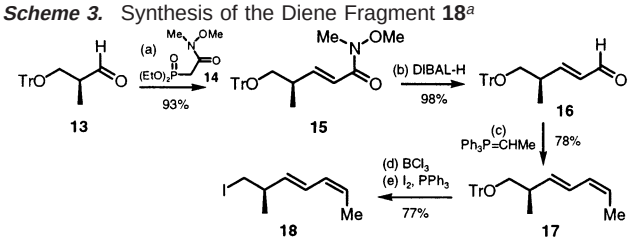
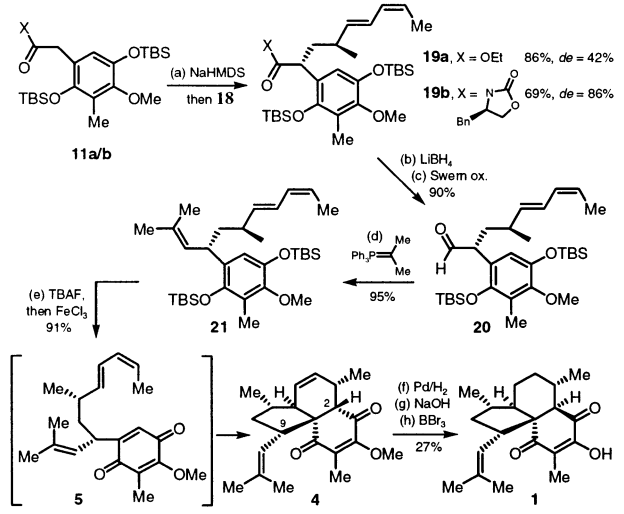
Scheme 3. Synthesis of the Diene Fragment **18**[a]



[a] Reagents and conditions: (a) **14** (1.02 equiv), NaH (1.02 equiv), THF, 5 h, 0 °C → rt; (b) DIBAL-H (3.0 equiv), THF, 2 h, −78 °C; (c) Ph_3PEtBr (1.5 equiv), NaHMDS (1.5 equiv), THF, 12 h, −78 °C → rt; (d) BCl_3 (1.4 equiv), CH_2Cl_2, 1 h, −40 → −10 °C; (e) Im (2.0 equiv), Ph_3P (2.0 equiv), I_2 (2.0 equiv), benzene, 2 h, rt (NaHMDS = sodium bis(trimethylsilyl)amide).

Scheme 4. Completion of the Total Synthesis[a]



[a] Reagents and conditions: (a) NaHMDS (1.1 equiv), then **18** (1.5 equiv), HMPA (10 equiv), THF, 4 h, −78 → −40 °C; for **19b**: 30 equiv HMPA, −78 °C → rt; (b) $LiBH_4$ (1.1 equiv), H_2O (1.1 equiv), Et_2O, 2 h, 0 °C; (c) $(COCl)_2$ (2.0 equiv), DMSO (4.0 equiv), Et_3N (6.0 equiv), CH_2Cl_2, −78 °C → rt; (d) $(CH_3)_2CHPPh_3I$ (2.0 equiv), *n*-BuLi (2.0 equiv), THF, 4 h, 0 °C; (e) TBAF (2.4 equiv), THF, 1 h, rt, then $FeCl_3$ (10 equiv), H_2O, 6 h, rt; (f) Pd/C (0.1 equiv), H_2 (1 atm), EtOAc, 1 h, rt; (g) NaOH (5 equiv), $MeOH/H_2O$, 5 h, 80 °C; (h) BBr_3 (6 equiv), THF, 0.5 h, −100 °C. (HMPA = hexamethylphosphoramide).

(3) the high yield and stereoselectivity (^{1}H NMR: no isomers detectable, HPLC: less than 3%).

The relative configuration of **4** was confirmed by extensive NOESY experiments. The observed stereochemical course of the IMDA reaction can be rationalized in terms of the endo transition-state geometry shown in Figure 2. The facial selectivity of the diene−quinone attack is controlled by a minimization of allylic strain between the substituents at C9 and the quinoid carbonyl functionality. Selective hydrogenation of the disubstituted olefin **4** followed by base-catalyzed epimerization at C2 and cleavage of the methyl ether with BBr_3 led to compound **1**, whose NMR, MS, and IR data were in agreement with those reported for the natural elisabethin A. The optical rotation of **1** compared well to the literature value (synthetic **1**: $[\alpha]^{25}_D$ +129.7 (c = 0.05, $CHCl_3$),

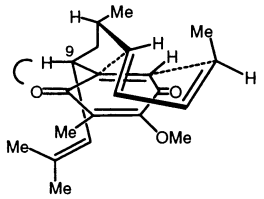


Figure 2. Endo transition state of the IMDA cyclization.

natural **1**[1a]: $[\alpha]^{25}_D$ +133.0 (c = 0.45, $CHCl_3$). This means that we have synthesized the natural enantiomer of **1** on a stereochemically unambiguous route and have thus proven its absolute configuration.

In conclusion we have accomplished a convergent and highly stereocontrolled total synthesis of elisabethin A (**1**) in 17−20 steps and 7% overall yield along the longest linear sequence. The synthesis is flexible and potentially allows the introduction of a variety of nonnatural substituents. The preparation of such analogues and the evaluation of the bioprofile of **1** is currently underway in our laboratory.

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Supporting Information Available: Detailed experimental procedures and characterization data for **4**, **11a/b**, **18**, **19a/b**; copies of ^{1}H and ^{13}C NMR spectra of Diels−Alder adduct **4** and synthetic elisabethin A (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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