*Diterpene Anti-tuberculosis Agents*

# Unified Strategy for the Synthesis of (−)-Elisapterosin B and (−)-Colombiasin A**

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Elisapterosin B (**1**) is a polycyclic diterpene isolated and characterized by Rodriguez and co-workers from the West Indian sea whip *Pseudopterogorgia elisabethae* (Bayer).[1] Among its cogeners, it showed the most potent inhibitory activity against *Mycobacterium tuberculosis* H37Rv. Rodriguez and co-workers proposed that the uncommon cagelike skeleton of **1** might arise by cyclization of a serrulatane diterpene such as **2**, which was isolated from the same organism (Scheme 1).[2] An alternative biosynthetic cyclization of a serrulatane core leads to colombiasin A (**3**), another unusual structure isolated from the *P. elisabethae*.[3] We became interested in the possible [5+2] and [4+2] cyclizations of a serrulatane skeleton as biomimetic routes to elisapterosin B (**1**) and colombiasin A (**3**), respectively. Nicolaou and co-workers recently reported the synthesis of **3** by an intramolecular Diels–Alder cyclization of a serrulatane diene.[4,5] The [5+2] cycloaddition was discovered by Joseph-Nathan many years ago[6] but has only rarely found use in synthesis.[7,8] Herein we outline the first synthesis of elisapterosin B (**1**) using an intramolecular [5+2] cycloaddition as well as an efficient route to colombiasin A (**3**).

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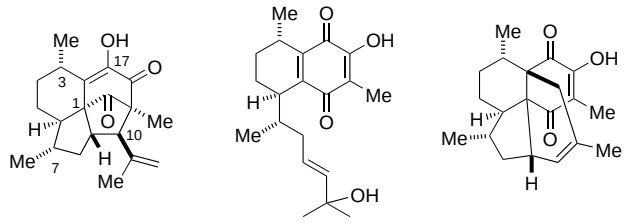
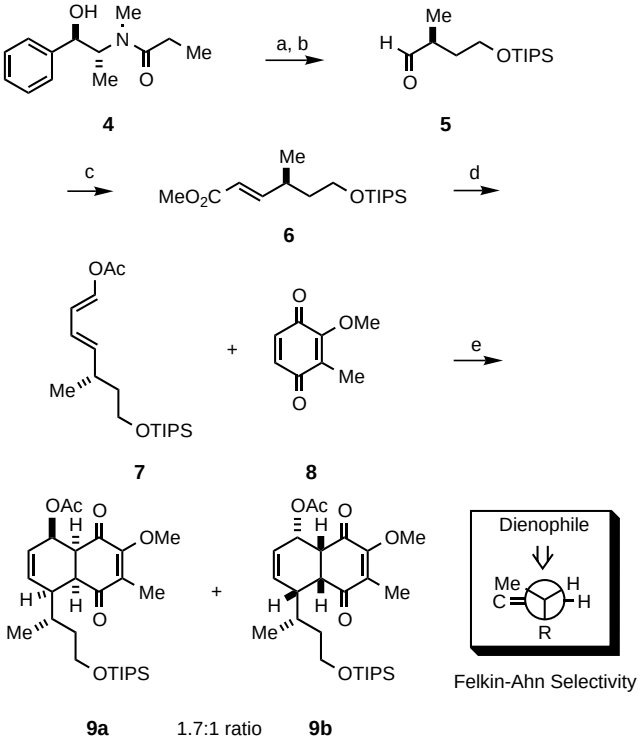



***Scheme 1.*** The structures of (−)-elisapterosin B (**1**), (−)-colombiasin A (**3**), and a serrulatane diterpene **2**, which were each isolated from the sea whip *Pseudopterogorgia elisabethae*.

Synthesis of the *cis*-decaline serrulatane skeleton was based on a Diels–Alder addition (Scheme 2). The chiral diene **7** was prepared beginning with Myers' pseudoephedrine auxiliary.[9] Alkylation of **4**, followed by reduction and hydrolysis produced the enantiomerically pure aldehyde **5**.

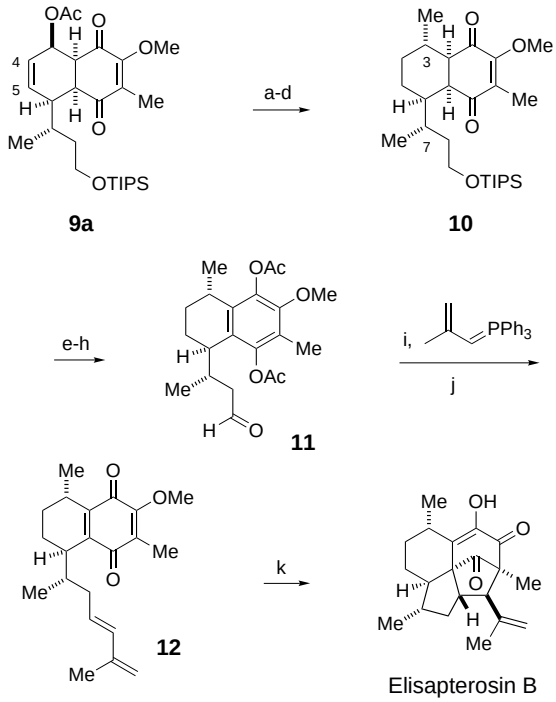



**4** **5** **6** **7** **8** **9a** **9b**

***Scheme 2.*** Synthesis of the decaline **9**. a) LDA, LiCl, $ICH_2CH_2OTIPS$, 94%, >97% *de*; b) $LiAlH(OEt)_3$, then $H^+$, 77%; c) $Ph_3P{=}CHCO_2Me$, $CH_3CN$, reflux, 85%; d) 1. $LiCH_2Br$, THF, −78 °C; 2. *n*BuLi, −78 to 23 °C; 3. LiH, reflux; 4. $Ac_2O$, 79%; e) 5 M $LiClO_4$, $Et_2O$, 24 h, 75%, 1.7:1 ratio. LDA = lithium diisopropylamide, TIPS = triisopropylsilyl.

Wittig olefination of **5** gave the ester **6**. Conversion of **6** into the diene **7** followed precedent from Kowalski's group.[10] Homologation to the lithium ynolate followed by treatment with LiH and acetylation produced the acetoxy diene **7** as a single isomer in 79% yield. The dienophile **8** was prepared by using the strategy developed by Knolker and co-workers.[11] The key Diels–Alder reaction between **7** and **8** was unsuccessful under thermal conditions, and use of Lewis acids such as $ZnBr_2$ led to very low yields. Lithium perchlorate in diethyl ether was uniquely effective in promoting this cycloaddition.[12] Treatment of the diene and dienophile for one day at ambient temperature generated the desired adduct **9** in 75% yield. The Diels–Alder adduct **9** was a 1.7:1 mixture of inseparable diastereomers. Attempts to improve the diastereoselectivity using chiral Lewis acids were unsuccessful,[13,14] and so the mixture of diastereomers was carried on through the synthesis. Ultimately the major isomer was shown to have the configuration **9a** by correlation with the natural product. The minor isomer was shown to have the structure **9b** by correlation with a previously synthesized compound.[15] The stereoselectivity arises from a Felkin–Ahn like approach of the dienophile to the diene as shown in Scheme 2. Thus, overall, decaline **9** was prepared in only five steps from the pseudoephedrine amide **4**.

The acetate substituent on diene **7** controlled the regioselectivity in the cycloaddition to **9** but must be replaced by a methyl group. Several strategies were considered, but a simple dimethylcuprate displacement turned out to be the best approach (Scheme 3). Reduction of the ketone group at C17 with $NaBH_4$ prevented aromatization in the subsequent steps. Treatment with lithium dimethylcuprate cleanly replaced the acetate group with a methyl group. COSY experiments suggested that the position of the C4–C5 alkene had not changed in the reaction, and correlation with the




**9a** **10** **11** **12**

***Scheme 3.*** Synthesis of elisapterosin B (**1**). a) $NaBH_4$, $CeCl_3$, MeOH, 93%; b) $LiCuMe_2$, $Et_2O$, 0 to 23 °C, 89%; c) $H_2$, Pd/C, EtOH, 95%; d) Dess–Martin, $CH_2Cl_2$, 92%; e) DBU, $CH_2Cl_2$, (air), 70%; f) Zn, $Ac_2O$, NaOAc, then $Ac_2O$, pyridine, 96%; g) HF–pyridine, THF, 94%; h) Dess–Martin, $CH_2Cl_2$, 99%; i) Wittig reagent, THF, 78% 3:1 *E*/*Z*; j) $K_2CO_3$, MeOH (air), 79%, k) 25 equiv $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, −78 °C, 41%. All the intermediates in this scheme are a 1.7:1 diastereomeric ratio derived from the mixture **9a** and **9b**. The diastereomers were separated after the final step in the sequence to produce pure (−)-elisapterosin B (**1**). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

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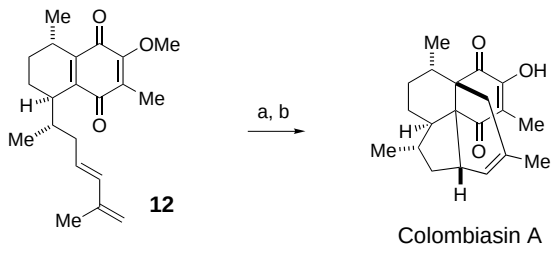
natural product confirmed that $S_N2$ rather than $S_N2'$ displacement of the acetate had taken place. This felicitous outcome was unexpected.[16] Hydrogenation and Dess–Martin oxidation returned enedione **10** in excellent yield. Treatment of **10** with DBU and air gave the corresponding quinone. Zinc reduction and acetylation produced the hydroquinone diacetate. In theory, deprotonation and acetylation of **10** would give the same product, but all such attempts to effect this transformation produced only the quinone. Deprotection, oxidation, and Wittig reaction generated the diene side chain as a 3:1 mixture of *E* and *Z* isomers. Treatment of the hydroquinone diacetate with $K_2CO_3$ in methanol led directly to the quinone **12** by a facile air oxidation. Diene **12** is set up to test the key [5+2] cycloaddition.

The proposed [5+2] cycloaddition had good precedent from work of Joseph-Nathan's group, who showed that Lewis acid catalysis promoted intramolecular [5+2] additions.[6] Grieco's group also reported several [5+2] cycloadditions catalyzed by $LiClO_4$.[8] We found that treatment of diene **12** with a modest excess of $BF_3{\cdot}OEt_2$ at 0 °C did not promote the cyclization efficiently, but a large excess of $BF_3{\cdot}OEt_2$ at lower temperature produced the [5+2] cycloadduct. The best conditions involved the use of 25 equivalents of $BF_3{\cdot}OEt_2$ at −78 °C for one hour. Elisapterosin B (**1**) was isolated as a 1.7:1 mixture of diastereomers (from **9a** and **9b**) in 41% yield. The product was accompanied by 22% of *O*-methyl colombiasin A. Attempted cyclization with trimethylsilyl trifluoromethanesulfonate (TMSOTf) led to decomposition, and addition of 2,6-di-*tert*-butylpyridine lowered the yield in the $BF_3{\cdot}OEt_2$ cyclization. Presumably, the [5+2] cycloaddition proceeded from a conformation of **12** with an axial diene side chain that was reinforced by a peri interaction in the alternative chair conformation. The [5+2] cycloaddition is favored by Lewis acid coordination to the quinone, which polarizes the carbonyl π bond. The resulting complex contains a five-carbon, four-electron π system that can undergo a thermally allowed cycloaddition with the pendant alkene. This analysis is related to the explanation for Lewis acid catalysis of a Nazarov cyclization.[17] The synthesis of elisapterosin B was completed by chromatographic separation of the C7 methyl epimers to provide pure (−)-elisapterosin B, which was identical to the natural product by $^1$H NMR and $^{13}$C NMR spectroscopy, high-resolution mass spectrometry (HRMS), and optical rotation.[1,18] Elisapterosin B (**1**) was synthesized from pseudoephedrine amide **4** in 16 steps and 2.6% overall yield.

Colombiasin A methyl ether was isolated as a minor side product in the Lewis acid promoted cyclization of diene **12**. Nicolaou and co-workers had previously shown that the intramolecular Diels–Alder route to colombiasin A (**3**) was viable under thermal conditions.[4] When diene **12** was heated to 180 °C in toluene, the colombiasin A methyl ether was isolated in 83% yield (Scheme 4). The diene **12** was a 3:1 *E*/*Z* mixture, which suggested that *E*/*Z* isomerization was taking place under the reaction conditions and that the (*E*)-diene cyclized preferentially. Synthesis of colombiasin A (**3**) was completed by demethylation using $AlCl_3$ buffered with *N*,*N*-dimethylaniline.[19] Synthetic colombiasin A was isolated in 73% yield as a 1.7:1 mixture of diastereomers (from **9a** and **9b**). Chromatographic separation gave pure (−)-colombiasin A, which was identical to the natural product by $^1$H NMR and $^{13}$C NMR spectroscopy, and HRMS.[3,4] Colombiasin A was prepared in 17 steps and 3.9% yield from pseudoephedrine amide **4**.




***Scheme 4.*** Synthesis of colombiasin A (**3**). a) 180 °C, toluene, 83%; b) $AlCl_3$, $PhNMe_2$, $CH_2Cl_2$, 0 to 23 °C, 73%.

We have developed an efficient route to the elisapterosin and colombiasin natural products based on [5+2] and [4+2] intramolecular cyclizations of a common serrulatane diene. These syntheses provide support for biosynthetic proposal developed by Rodriguez's group and provide access to these interesting anti-tuberculosis agents.

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**Keywords:** cycloaddition · natural products · total synthesis

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[15] Compound **9b** was carried through the remainder of the syntheses, and the epimeric mixture was only separated at the final step. The structure of **9b** was confirmed at the penultimate step of the colombiasin A synthesis, where the minor isomer present in the mixture was compared with the (±)-7-*epi*-*O*-methyl colombiasin A prepared by Nicolaou and co-workers.[4] The two compounds showed identical $^1$H and $^{13}$C NMR data, confirming the structure of our minor component as *ent*-7-*epi*-*O*-methyl colombiasin A.
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[18] Synthetic elisapterosin B had a rotation of $[\alpha]_D^{23} = -31.5$ ($c$ = 0.16, $CHCl_3$). The natural product had a reported rotation of $[\alpha]_D^{25} = -3.0$ ($c$ = 4.4, $CHCl_3$).[1] Professor Rodriguez was able to resolve the discrepancy by finding an error in the original calculation. The correct rotation for the natural product is $[\alpha]_D^{25} = -29.8$ ($c$ = 0.44, $CHCl_3$). We thank Professor Rodriguez for his prompt assistance in this matter.
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