Asymmetric catalysis

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Efficient Total Syntheses of (−)-Colombiasin A and (−)-Elisapterosin B: Application of the Cr-Catalyzed Asymmetric Quinone Diels–Alder Reaction**

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The gorgonian corals are notable as sources of many diverse pharmacological agents,[1] and substantial effort has been directed toward isolation of natural products from these organisms. One species from this family, the soft coral *Pseudopterogorgia elisabethae*, has provided compounds with antiinflamatory, analgesic, cytotoxic, antiviral, antibacterial, antituberculosis and antimalarial activity.[2] Members of the pseudopterosin family of diterpene glycosides (Scheme 1) were isolated from this organism and have subsequently been found to be potent antiinflamatory and analgesic agents.[3] This class of natural products, which contains more than 15 variants, has been shown to be derived from a common biosynthetic precursor, erogorgiaene.[4] More recently, other secondary metabolites that appear to originate from a related biosynthetic pathway have been recovered from extracts of this species.[5] These compounds, such as colombiasin A, elisapterosin B, and elisabethin A, have attracted considerable interest from the synthetic community, due in significant part to the challenge presented by their interesting molecular architectures.[6–8] It has been proposed that these natural products could be derived from a common intermediate such as **1** by different cyclization pathways.[9]

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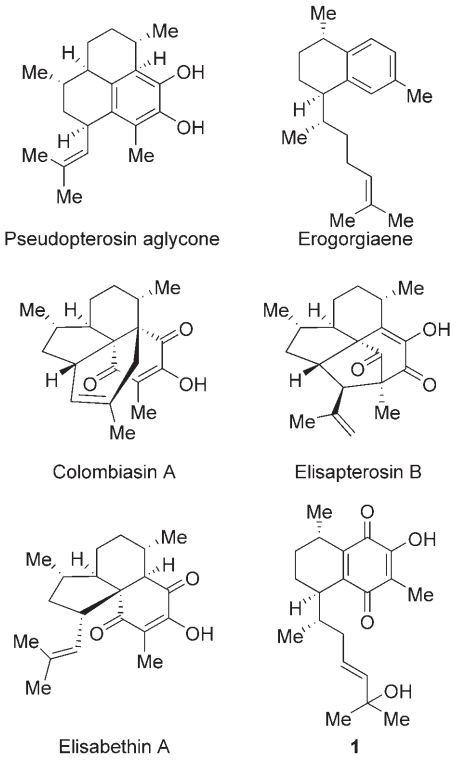
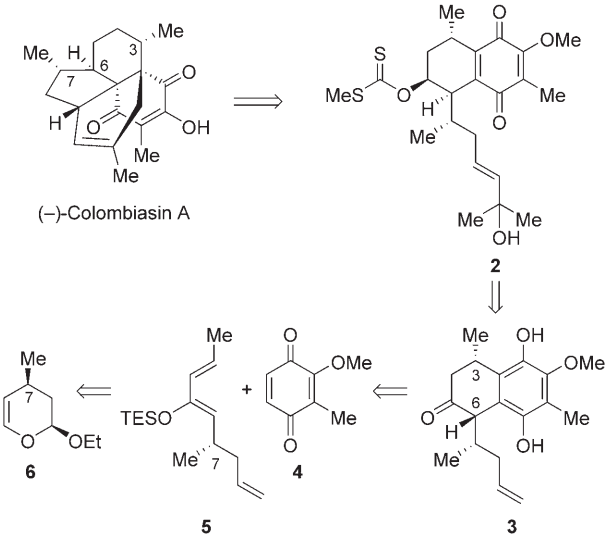
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Representative secondary metabolites isolated from *Pseudopterogorgia elisabethae*.

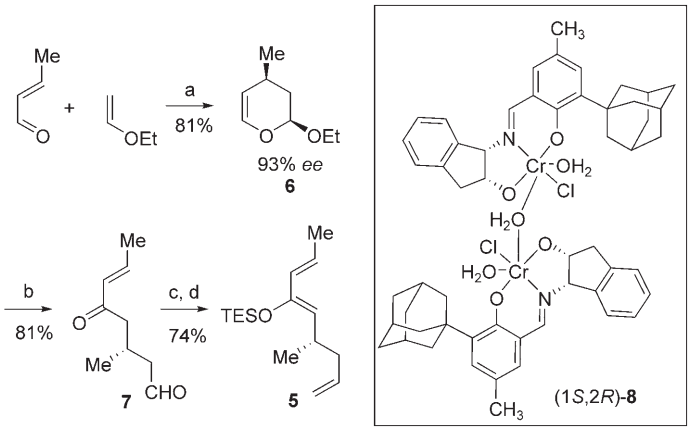
Such diversity-oriented synthesis practiced on a biosynthetic level would allow the organism to generate an array of compounds for chemical defence, and is supported by the observation of **1** in extracts from *P. elisabethae*.[10]

We were intrigued by the versatility of putative biosynthetic intermediate **1**, and became interested in developing a synthetic route to (−)-colombiasin A that would proceed through a similar advanced intermediate, such as alcohol **2** (Scheme 2). We envisioned preparation of **2** by a diastereo- and regioselective quinone Diels–Alder (qDA) reaction. This strategy would require a method to adjust the stereochemistry at C6 (colombiane numbering) in a subsequent step. Indeed, while several elegant syntheses of colombiasin A have been reported, control over all stereochemical elements of the molecule has proven to be a most significant challenge.[6] To insure high selectivity in the qDA reaction, we undertook an effort to develop new catalysts for this reaction as an integral part of our synthetic plan. The details of those studies are presented in the preceding communication in this issue.[11] To address the stereochemistry at C6, we chose to employ silyl enol ether **5** as the diene component, with the thought that the ketone **3** could undergo epimerization to afford the desired diastereomer. The silyl enol ether would also serve to differentiate the diene termini, and thus allow high regioselectivity in the qDA reaction.



Scheme 2. Retrosynthetic analysis applied to colombiasin.

Our synthesis of diene **5** began with an inverse electron demand hetero-Diels–Alder (HDA) reaction catalyzed by dimeric chromium complex **8**, a reaction that was developed in our group for the preparation of optically pure dihydropyrans.[12,13] Reaction of ethyl vinyl ether with *trans*-crotonaldehyde afforded cycloadduct **6** in good yield (81%) and high enantioselectivity (93% *ee*) on multigram scale, thereby introducing the requisite stereochemistry of the methyl-bearing stereocenter at C7 (Scheme 3). Palladium-catalyzed



Scheme 3. Synthesis of diene **5**. a) (1*S*,2*R*)-**8** (5 mol%), MS 4 Å, 20 h; b) 1. *t*BuLi, THF, −78 to 0°C, 0.5 h; 2. $ZnCl_2$, THF, 0°C to RT, 0.5 h; 3. [Pd(PPh_3)$_4$] (2.5 mol%), 1-bromopropene (2 equiv, *cis*/*trans* 1:1), THF, 2 h; 4. HCl (aq.) (0.5 M), 1 h; c) 1. $BrCH_3PPh_3$, KHMDS, PhMe, 0°C, 1 h; 2. **7**, −78 to 0°C, 82%; d) 1. KHMDS, THF, −78°C, 0.5 h; 2. TESCl, −78°C, 0.5 h, 90% (90% isomerically pure). HMDS = bis(trimethylsilyl)amide, TES = triethylsilyl.

Negishi coupling with 1-bromopropene (1:1 *E*/*Z* mixture) was performed after lithiation of **6** with *t*BuLi and transmetalation with $ZnCl_2$.[14] The isomerically pure cross-coupled product was hydrolyzed directly to afford ketoaldehyde **7** in 81% yield. Selective olefination of the aldehyde in the presence of the enone was achieved by a standard Wittig olefination. The enone was then treated with KHMDS and the resultant enolate was quenched with TESCl to provide diene **5**.[15]

With diene **5** in hand, catalysis of the key qDA reaction was investigated (Table 1). Reactions of simpler model dienes

suggested that monomeric chromium complex **12** might be a suitable catalyst (see previous paper for a detailed discussion).[11,16] The inherent substrate-induced diastereoselectivity, as measured by catalysis with achiral catalyst **11**, was low (1.8:1 d.r., 3:1 regioselectivity; Table 1, entry 1), though the diastereomer required for the synthesis was obtained as the major product.[17] Gratifyingly, chiral catalyst **12** was found to exert high levels of stereocontrol over the reaction. In the matched case, catalyst (1*R*,2*S*)-**12** provided the desired product in high diastereoselectivity (17:1) and regioselectivity (10:1; Table 1, entry 2). The mismatched catalyst, (1*S*,2*R*)-**12**, though less selective overall, induced a reversal in diastereoselectivity (1:6.5 d.r., 4.6:1 regioselectivity; Table 1, entry 3).

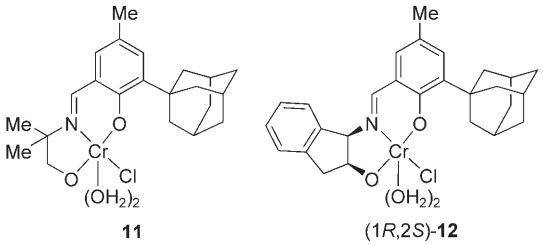
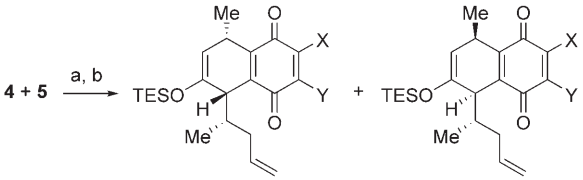


Table 1: Diels–Alder reaction of quinone **4** and diene **5**.



Entry	Catalyst	d.r. (**9a**:**9b**)	Regioselectivity (**9**:**10**)
1	achiral **11**	1.8:1	3:1
2	(1*R*,2*S*)-**12**	17:1	10:1
3	(1*S*,2*R*)-**12**	1:6.5	4.6:1

[a] Catalyst (10 mol%), MS 5 Å, PhMe, 0°C; b) salcomine (10 mol%), DBU, O_2, 0°C, 0.5 h.

Having demonstrated the highly stereoselective qDA reaction, we next investigated the crucial epimerization of the C6 stereocenter (Figure 1). The qDA reaction of **4** and **5** afforded silyl enol ether **13**, along with an olefin isomer **13′**, in 86% yield.[18] These isomers were not separated as both led to the desired ketone upon hydrolysis. Treatment with a 1:1 mixture of concentrated HCl and methanol effected deprotection of the silyl enol ether, tautomerization of the enedione to the hydroquinone, and epimerization to the desired diastereomer (> 10:1 d.r. as measured by ^{1}H NMR spectroscopy).[19] The relative stereochemistry of ketone **14** was confirmed by X-ray crystallography (Figure 1).[20] A highly diastereoselective reduction followed by in situ aerobic oxidation furnished quinone alcohol **15** in 75% yield (over two steps from **13** + **13′**).[21]

We planned to install the tertiary allylic alcohol by a cross-metathesis reaction catalyzed by the Grubbs second-generation ruthenium catalyst **18** (Scheme 4).[22] Preliminary studies suggested that the free secondary alcohol of **15** could interfere with the subsequent dehydration reaction to the requisite diene, so we chose to block this group first. As deoxygenation at C5 would ultimately be required, xanthate was chosen as a functional protecting group.[23,24] The cross-metathesis reaction of quinone **16** with 2-methyl-3-buten-2-ol catalyzed by **18** (10 mol%) proceeded smoothly at room temperature (87% yield).[25] Warming a solution of tertiary alcohol **2** in benzene to reflux in the presence of $MgSO_4$ resulted in a tandem dehydration-intramolecular qDA reaction to assemble the tetracyclic colombiane framework (77% yield). The ^{1}H and ^{13}C NMR spectra of xanthate **17** matched those reported by Nicolaou and co-workers for this intermediate in their synthesis of colombiasin A.[6a] Completion of the synthesis proceeded in a straightforward fashion. Deoxygenation and demethylation were performed by using modifications of the literature conditions,[6a,c] affording the natural product, (−)-colombiasin A in 67% yield for the two-step sequence. Spectral data (NMR, HRMS, IR) of synthetic material and natural (−)-colombiasin A were in complete accord.[26]

During the course of investigations into alternate deprotection conditions for methyl colombiasin A, we discovered that treatment of (−)-colombiasin A with superstoichiometric quantities of $BF_3{\cdot}Et_2O$ resulted in smooth conversion to (−)-elisapterosin B (Scheme 5). This reaction may proceed by a fragmentation reaction, affording an allylic cation that undergoes subsequent cyclization, or by a retro [4+2] cycloaddition followed by a [5+2] cycloaddition. While the mechanism of this reaction has yet to be determined, it is stereoselective and

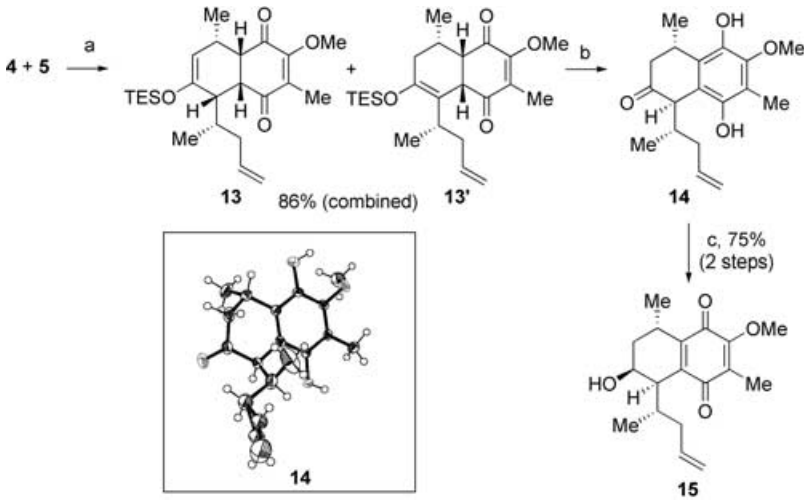
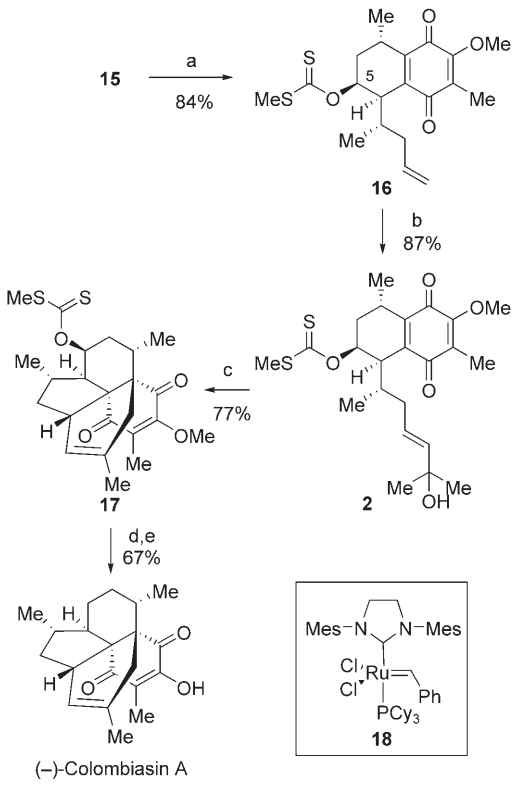
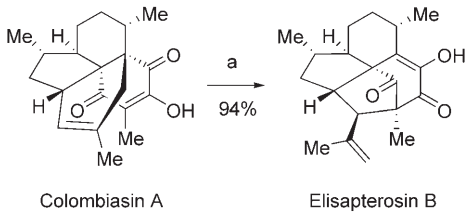


Figure 1. Synthesis of alcohol **15** and the X-ray crystal structure of 14. Ellipsoids are drawn at the 50% probability level. a) (1*R*,2*S*)-**12** (10 mol%), 5 Å MS, PhMe, 0°C, 24 h; b) HCl (conc.), MeOH, 0°C to RT, 10 h; c) 1. $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78°C, 1 h; 2. air, RT, 2 h.



Scheme 4. Completion of the synthesis. a) 1. NaH, THF, 0 °C to RT, 0.5 h; 2. CS_2; 3. MeI, 9 h; b) 1. 2-methyl-3-buten-2-ol, catalyst **18** (10 mol%), CH_2Cl_2, 24 h; c) $MgSO_4$, PhH, reflux, 3 h; d) AIBN, nBu_3SnH, PhMe, 110 °C, 0.5 h; e) $AlCl_3$, $PhNMe_2$, CH_2Cl_2, 0 °C to RT, 0.5 h. AIBN = 2,2′-azobisisobutyronitrile.



Scheme 5. Conversion of colombiasin A to elisapterosin B. a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, RT, 4 h

high-yielding (94%), and underlines the close structural relationship between these natural products.

The enantioselective synthesis of (−)-colombiasin A was accomplished in 12 steps and 11.5% overall yield from ethyl vinyl ether and *trans*-crotonaldehyde. A stereoselective qDA reaction catalyzed by a [(Schiff base)Cr^{III}] complex developed expressly for this purpose allowed control of diastereo- and regioselectivity in one of the key steps of the sequence. Other key steps included highly selective installation of the C6 stereocenter under thermodynamic control, and a tandem dehydration-qDA reaction to assemble the tetracyclic framework of the molecule. The use of protecting groups was minimized by careful synthetic design. (−)-Elisapterosin B was prepared by a remarkably facile Lewis acid-mediated rearrangement of colombiasin A. Current studies focus on biomimetic syntheses of other natural products isolated from *Pseudopterogorgia elisabethae* by way of intermediates such as tertiary alcohol **2**.

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[16] Although not required for the synthetic sequence, in situ oxidation of the cycloadduct to quinones **9** and **10** was performed to facilitate determination of the diastereo- and regioselectivity of the reaction by HPLC.
[17] This would be predicted by reaction of a ground state conformation of diene **5** wherein allylic strain is minimized.
[18] Formation of isomer **13′**, wherein the olefin has isomerized to the tetrasubstituted silyl enol ether, presumably occurs during chromatographic purification. Analogous isomerizations are not observed with less hindered cycloadducts. See Supporting Information for details. For an example of isomerization of a silyl enol ether upon exposure to silica gel, see: P. Magnus, I. S. Mitchell, *Tetrahedron Lett.* **1998**, *39*, 9131 – 9134.
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[20] Details of the crystal structure analysis are provided as Supporting Information. CCDC-263118 (**14**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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[24] Attempts to effect deoxygenation of this intermediate led only to complex decomposition mixtures.
[25] Access to tertiary alcohol **2** could prove interesting in synthetic routes toward other related natural products, such as elizabethin A. However, cross metathesis of quinone **16** with isoprene would serve as a shorter route to colombiasin A. Tandem cross-metathesis/qDA reactions did provide the desired product, but in consistently lower yields than the two-step cross-metathesis/dehydration/qDA sequence. For examples of cross-metathesis reactions of conjugated dienes, see: T. W. Funk, J. Efskind, R. H. Grubbs, *Org. Lett.* **2005**, *7*, 187 – 190.
[26] We are grateful to Professor A. D. Rodríguez of the University of Puerto Rico for kindly supplying a sample of natural colombiasin A.

