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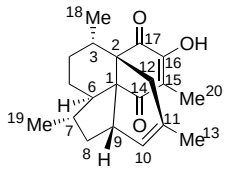
## Total Synthesis of Colombiasin A**

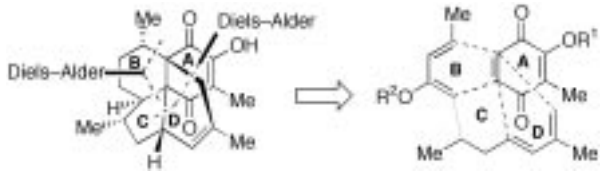
K. C. Nicolaou,* Georgios Vassilikogiannakis, Wolfgang Mägerlein, and Remo Kranich

Colombiasin A (**1**) is a novel diterpene recently isolated from a biologically active (against *Mycobacterium tuberculosis* H37Rv) extract obtained from the gorgonian octocoral, *Pseudopterogorgia elisabethae*, collected off San Andres Island, Colombia.[1] Its structure is characterized by a tetracyclic carbon framework whose periphery is decorated with four methyl groups, two carbonyl functions, two double bonds, and one hydroxy group. In addition, this unprecedented molecular architecture includes six stereogenic centers, two of which are adjacent quaternary carbon atoms. Despite the elegant spectroscopic studies that led to the structural elucidation of the colombiane skeleton, the absolute stereochemistry of colombiasin A (**1**) remains unassigned. The intrigue surrounding this natural product is heightened by a proposal suggesting elisabethin A (which was also found in *Pseudopterogorgia elisabethae*[2]) as a biogenetic precursor of **1**.[1] Here we report the total synthesis of colombiasin A (**1**) by a strategy which also delivered its C7 epimer as well as several other analogues.




**1:** colombiasin A

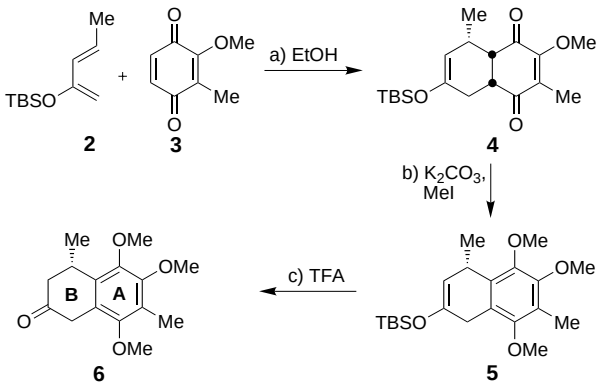
A brief retrosynthetic analysis of colombiasin A (**1**) is presented in Scheme 1. Inspection of the target's architecture suggested quinone **A** as the cornerstone of its construction.




Scheme 1. Retrosynthetic analysis of colombiasin A (**1**).

Two Diels – Alder reactions, first with diene **B** (intermolecular) and then with diene **D** (intramolecular), along the sequence of elaboration, were expected to complete the polycyclic skeleton of the molecule. According to this plan, the elaboration sequence between the two cycloadditions would require both tethering of domains **B** and **D** as well as reoxidation of ring **A** to a new quinone moiety after fusion of ring **B**. To facilitate tethering of segments **B** and **D** (i.e. forming the C6–C7 bond), an oxygen-based functional group ($R^2O$) was temporarily incorporated into diene **B** as shown in Scheme 1. As described below, two runs of the derived strategy were necessary to reach colombiasin A (**1**).

The construction of the first key intermediate, ketone **6**, starting with the first of the projected Diels – Alder reactions is summarized in Scheme 2. Thus, reaction of diene **2** with quinone **3**[3] (obtained by *ortho*-methylation of 1,2,4-trimethoxybenzene[4] followed by oxidative demethylation[5]




Scheme 2. Construction of **AB** ring system **6**. a) EtOH, 25 °C, 2 h, 83 %; b) $K_2CO_3$ (5.0 equiv), MeI (20 equiv), acetone, reflux, 48 h, 83 %; c) 2 % TFA in $CH_2Cl_2$, 25 °C, 2 h, 91 %. TFA = trifluoroacetic acid; TBS = *tert*-butyldimethylsilyl.

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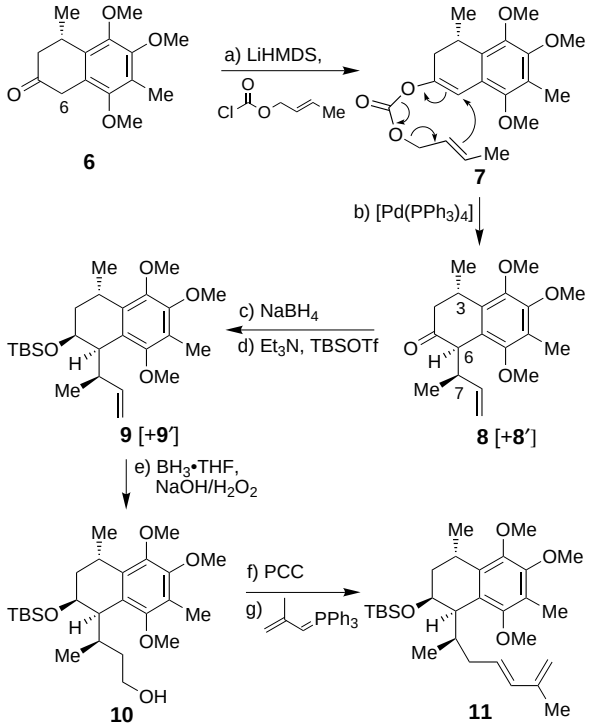
with $AgO/HNO_3$) in ethanol, at ambient temperature, resulted in the formation of the desired *endo* cycloadduct **4** as the sole product in 83% yield. The rather labile compound **4** was then masked as its aromatic derivative **5** by exposure to an excess of $K_2CO_3$ and MeI (83% yield) and the TBS group was then removed with TFA to afford the desired ketone **6** in 91% yield.

With the bicyclic **AB** system **6** in hand, the next objective was to introduce the requisite chain at C6 for the next planned cycloaddition reaction. After failing to accomplish this goal by direct alkylation, we next turned our attention to a sigmatropic rearrangement equivalent (structure **7**, Scheme 3) as a




Scheme 3. Construction of intramolecular Diels–Alder precursor **11**. a) LiHMDS (1.2 equiv), THF, −78 °C, 1 h; then crotyl chloroformate (1.4 equiv), 25 °C, 30 min, 94%; b) $[Pd(PPh_3)_4]$ (0.04 equiv), THF, 25 °C, 15 min, 58% plus 24% of isomeric *E*-disubstituted olefin **8′**; c) $NaBH_4$ (3.0 equiv), MeOH, 25 °C, 30 min, 96%; d) $Et_3N$ (2.0 equiv), TBSOTf (1.2 equiv), $CH_2Cl_2$, −78 °C, 1 h, 95%; e) $BH_3 \cdot THF$ (3 equiv), THF, 25 °C, 2 h; then 3 M NaOH and 30% $H_2O_2$, 25 °C, 1 h, 82%; f) PCC (1.5 equiv), $CH_2Cl_2$, 25 °C, 1.5 h, 91%; g) 2-methyl-2-propenyltriphenylphosphonium bromide (1.5 equiv), *n*BuLi (1.5 equiv), THF, 0 → 25 °C, 1 h; then aldehyde, 70 °C, 8 h, 70% plus 23% *Z* isomer. LiHMDS = lithium bis(trimethylsilyl)-amide; OTf = trifluoromethanesulfonate; PCC = pyridinium chlorochromate.

possible means to form the required C–C bond. A major issue shadowing this proposition, however, was the relative stereochemistry of the three stereogenic centers in the anticipated product, although initial molecular modeling studies appeared favorable for the required arrangement. In the event, a palladium(0)-induced intramolecular allylation[6] was employed to accomplish the desired goal. Thus, regioselective enolate formation from **6** (LiHMDS) followed by quenching with crotyl chloroformate[7] furnished the desired carbonate **7** (see Table 1) in 94% yield. Exposure of the latter compound

Table 1. Selected physical properties of compounds **7**, **16**, **18**, **23**, and **24**.[a]

**7**: Colorless syrup; $R_f = 0.51$ (silica gel, ethyl acetate/hexane 1/3); IR (film): $\tilde{\nu}_{max} = 2937, 1756, 1457, 1406, 1231, 1078, 966\ cm^{-1}$; $^1H$ NMR: $\delta = 6.50$ (d, $J = 2.9$ Hz, 1H), 5.89 (m, 1H), 5.66 (m, 1H), 4.62 (d, $J = 6.6$ Hz, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.67 (s, 3H), 3.43 (m, 1H), 2.88 (ddd, $J = 16.9$, 7.3, 2.9 Hz, 1H), 2.18 (m, 1H), 2.16 (s, 3H), 1.76 (dd, $J = 6.6$, 0.7 Hz, 3H), 1.18 (d, $J = 7.0$ Hz, 3H); $^{13}C$ NMR: $\delta = 152.9, 150.9, 150.8, 148.4, 146.2, 132.8, 130.1, 124.2, 123.3, 120.9, 108.1, 69.0, 61.3, 60.7, 60.0, 32.7, 27.6, 20.6, 17.8, 9.1$; HR-MS: calcd for $C_{20}H_{26}O_6Na$ $[M+Na^+]$: 385.1621, found: 385.1612

**16**: Colorless glass; $R_f = 0.47$ (silica gel, ethyl acetate/hexane 1/6); IR (film): $\tilde{\nu}_{max} = 2929, 1673, 1625, 1448, 1290, 1142, 1114\ cm^{-1}$; $^1H$ NMR: $\delta = 5.66$ (br s, 1H), 3.87 (s, 3H), 3.15 (br m, 1H), 2.37 (br d, $J = 18.1$ Hz, 1H), 2.27 (m, 1H), 2.07 (m, 1H), 1.99 (br d, $J = 18.1$ Hz, 1H), 1.90–2.00 (m, 2H), 1.85 (s, 3H), 1.67 (m, 1H), 1.59 (m, 1H), 1.55 (br s, 3H), 1.35–1.47 (m, 2H), 1.34 (d, $J = 7.0$ Hz, 3H), 1.28 (m, 1H), 0.90 (d, $J = 7.3$ Hz, 3H); $^{13}C$ NMR: $\delta =$ 202.1, 198.7, 156.2, 129.7, 129.2, 125.2, 66.8, 59.7, 51.7, 43.8, 36.7, 36.6, 34.2, 34.1, 33.3, 30.7, 24.3, 22.8, 17.3, 15.7, 9.9; HR-MS: calcd for $C_{21}H_{28}O_3$ $[M+H^+]$: 329.2111, found: 329.2103

**18**: Colorless syrup; $R_f = 0.50$ (silica gel, ethyl acetate/hexane 1/2); IR (film): $\tilde{\nu}_{max} = 2935, 1723, 1461, 1404, 1253, 1105, 1071, 1009, 880, 837, 777\ cm^{-1}$; $^1H$ NMR: $\delta = 9.50$ (d, $J = 1.1$ Hz, 1H), 4.31 (m, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 3.62 (br dd, $J = 6.2$, 3.3 Hz, 1H), 3.29 (m, 1H), 2.89 (m, 1H), 2.16 (s, 3H), 2.11 (m, 1H), 1.60 (dd, $J = 12.8$, 4.0 Hz, 1H), 1.24 (d, $J = 7.0$ Hz, 3H), 1.10 (d, $J = 7.0$ Hz, 3H), 0.92 (s, 9H), 0.11 (s, 6H); $^{13}C$ NMR: $\delta = 204.7, 152.2, 150.5, 147.2, 133.6, 125.2, 123.5, 67.6, 60.4, 60.3, 59.9, 47.9, 42.1, 35.5, 29.1, 25.9, 23.4, 18.2, 13.6, 9.5, -4.5, -4.8$; HR-MS: calcd for $C_{24}H_{40}O_5SiNa$ $[M+Na^+]$: 459.2537, found: 459.2554

**23**: Colorless glass; $R_f = 0.60$ (silica gel, ethyl acetate/hexane 1/1); IR (film): $\tilde{\nu}_{max} = 3488, 2930, 1672, 1628, 1446, 1294, 1115\ cm^{-1}$; $^1H$ NMR: $\delta = 5.67$ (br s, 1H), 3.98 (br m, 1H), 3.87 (s, 3H), 3.10 (br m, 1H), 2.38 (br d, $J = 18.4$ Hz, 1H), 2.34 (m, 2H), 2.06 (m, 1H), 1.95 (br d, $J = 18.4$ Hz, 1H), 1.93 (dd, $J =$ 5.5, 2.6 Hz, 1H), 1.86 (s, 3H), 1.74–1.83 (m, 2H), 1.65 (br s, 1H), 1.62 (m, 1H), 1.55 (br s, 3H), 1.33 (d, $J = 7.3$ Hz, 3H), 0.91 (d, $J = 7.3$ Hz, 3H); $^{13}C$ NMR: $\delta = 202.3, 198.5, 155.7, 131.5, 129.4, 124.9, 67.2, 63.7, 59.7, 52.7, 51.4, 41.3, 38.2, 37.0, 34.7, 33.4, 28.7, 22.7, 22.4, 17.7, 10.3$; HR-MS: calcd for $C_{21}H_{28}O_4$ $[M+H^+]$: 345.2060, found: 345.2058

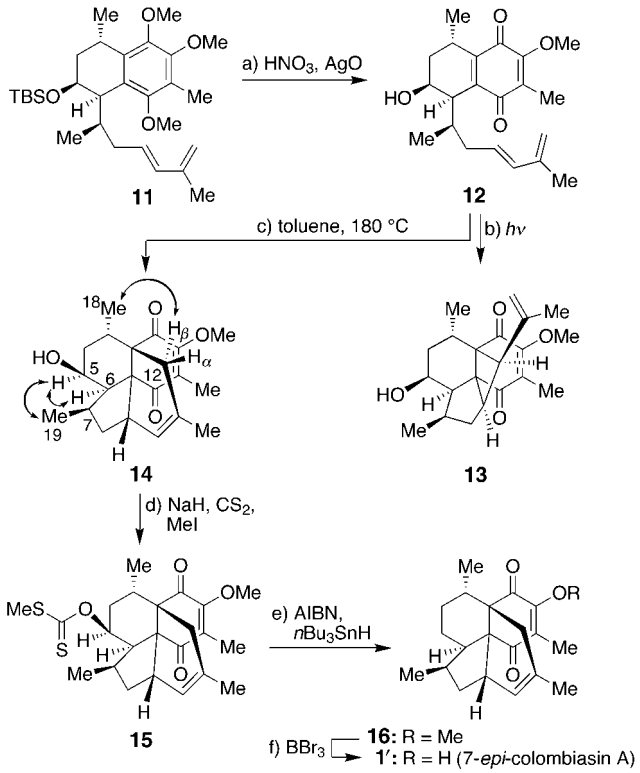
**24**: Colorless glass; $R_f = 0.47$ (silica gel, ethyl acetate/hexane 1/6); IR (film): $\tilde{\nu}_{max} = 2925, 1675, 1629, 1453, 1268, 1139, 1108\ cm^{-1}$; $^1H$ NMR: $\delta = 5.66$ (br s, 1H), 3.88 (s, 3H), 3.01 (br m, 1H), 2.41 (br d, $J = 19.0$ Hz, 1H), 2.12 (m, 1H), 1.91 (br d, $J = 19.0$ Hz, 1H), 1.89 (s, 3H), 1.78–1.89 (m, 5H), 1.57 (br s, 3H), 1.32 (d, $J = 7.0$ Hz, 3H), 1.29–1.36 (m, 3H), 0.82 (d, $J = 7.0$ Hz, 3H); $^{13}C$ NMR: $\delta = 203.1, 198.7, 155.1, 131.5, 129.5, 123.5, 63.5, 59.8, 51.6, 48.3, 39.6, 39.0, 36.6, 34.1, 33.6, 31.9, 31.1, 22.8, 22.2, 17.8, 10.4$; HR-MS: calcd for $C_{21}H_{28}O_3$ $[M+H^+]$: 329.2111, found: 329.2105

[a] $^1H$ NMR: 500 MHz, $CDCl_3$; $^{13}C$ NMR: 125 MHz, $CDCl_3$. HR-MS: matrix-assisted laser desorption/ionization.

to catalytic amounts of $[Pd(PPh_3)_4]$ in THF at ambient temperature led to terminal olefin **8** as the major product (58% yield) accompanied by its isomeric *E*-8,9-disubstituted olefin (**8′**, 24%, not shown). Although both regioisomers (**8** and **8′**) were formed as single diastereoisomers, it was difficult at this stage to assign the relative stereochemistry. It was decided, however, to push forward, hoping for full structural elucidation upon rigidification of the structure through the anticipated second cycloaddition. Toward this end, the inseparable mixture of **8** and **8′** was stereoselectively reduced with $NaBH_4$ and the resulting mixture of $\beta$-alcohols was protected as the TBS derivatives (**9** and **9′**), a mixture which was then subjected to hydroboration–oxidation to afford two hydroxy compounds, from which pure primary alcohol **10** was isolated by flash column chromatography. Finally, the requisite diene **11** was produced by PCC-mediated oxidation of **10** followed by Wittig reaction of the resulting aldehyde with the ylide derived from 2-methyl-2-propenyltriphenylphospho-

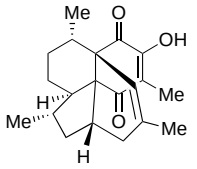
nium bromide and *n*BuLi. Diene **11** was formed as the major product and was accompanied by smaller amounts of its *Z* stereoisomer (*E*/*Z* ≈ 3/1, 93% total yield). This lack of stereochemical exclusivity in this reaction was inconsequential, since both geometrical isomers (the *Z* having first been converted to the *E* isomer) led to the same [4+2] cycloadduct (see below).

With diene **11** secured, the stage was now set for unveiling the quinone moiety to attempt the construction of the missing part of the targeted framework. As shown in Scheme 4, when **11** was treated with $AgO/HNO_3$ in dioxane[5] at ambient

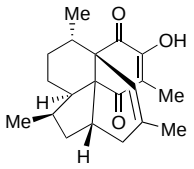



Scheme 4. Oxidation of aromatic diene **11** and synthesis of 7-*epi*-colombiasin A (**1′′**). a) Dioxane/6 M $HNO_3$ (10:1), 25 °C, 2 h; then AgO (5.0 equiv), 25 °C, 1 h, 27%; b) visible light, benzene, 25 °C, 15 min, 91%; c) toluene (sealed tube), in the dark, 180 °C, 5 h, 89%; d) NaH (5.0 equiv), $THF/CS_2/MeI$ (4/1/1), 50 °C, 5 h, 85%; e) AIBN (cat.), *n*$Bu_3SnH$ (5.0 equiv), toluene, careful deoxygenation, 110 °C, 30 min, 88%; f) $BBr_3$, (10 equiv), $CH_2Cl_2$, −78 °C, 20 min, 40% plus 20% of **1′′′**. AIBN = 2,2′-azobisisobutyronitrile.

temperature, quinone **12** was obtained in only 27% yield, with the remainder of the material being converted to numerous unidentified by-products. Despite the low yield in this step, however, we were encouraged to advance forward since we hoped to then be able to at least ascertain the pending stereochemical issues of our intermediates. Interestingly, our initial attempt to thermally induce the intramolecular cycloaddition reaction within structure **12** (toluene, 120 °C, sealed tube, ordinary room light) led to the exclusive formation of the [2+2] cycloadduct **13** in 80% yield. In an effort to confirm the suspected photochemically induced [2+2] cycloaddition process, we irradiated **12** with visible light (sunlamp) in benzene at ambient temperature and, indeed, observed its fast (15 min) and clean conversion to **13** (91% yield). Furthermore, and gratifyingly, when **12** was heated in toluene at 180 °C (sealed tube) in the dark, the desired [4+2] cycloadduct **14** was obtained in 89% yield (*endo*/*exo* ≈ 9/1). Analysis of the NMR spectra of the major (*endo*) isomer **14** and comparison to those of colombiasin A (**1**)[1] revealed its stereochemical structure. Particularly suggestive of the indicated C7-*epi* stereochemistry in **14** were the observed NOEs for Me18/H12$\beta$, H5/H6, and H5/Me19 (see arrows in structure **14**, Scheme 4). Having assembled the advanced intermediate **14**, and despite the incorrect stereochemistry at C7, we decided to transverse the remaining short sequence to 7-*epi*-colombiasin A (**1′**) with two objectives in mind. First, the exercise was expected to prepare the ground for the real intermediate to follow, and second, to render the final target (7-*epi*-colombiasin A, **1′**) available for biological evaluation. The two remaining tasks before reaching **1′** were deoxygenation at C5 and deprotection of the C16 hydroxy group. The former requirement was fulfilled upon conversion of **14** to its xanthate **15**[8] (NaH, $CS_2$, MeI, 85% yield) followed by treatment of the latter with *n*$Bu_3SnH$/AIBN[9] (toluene, 110 °C, 88% yield), while the second objective was accomplished by demethylation of the resulting compound **16** (see Table 1) with $BBr_3$ ($CH_2Cl_2$, −78 °C, 40% yield). A second product obtained in the last reaction (20% yield) was identified as the isomer of **1′** in which the double bond had shifted from the C10−C11 to the adjacent C11−C12 position (compound **1′′′**). While the chromatographic and spectroscopic data for both **1′** and **1′′′** were consistent with their assigned structures, they differed from those of colombiasin A (**1**).



**1′′**: $\Delta^{11,12}$-colombiasin A



**1′′′**: 7-*epi*-$\Delta^{11,12}$-colombiasin A

Refocusing on the original objective of reaching colombiasin A (**1**), we returned to terminal olefin **9**, whose C7 stereocenter now required inversion prior to its further processing (see Scheme 5). This was accomplished by epimerizing the corresponding aldehyde **17** (obtained by oxidative cleavage)[10] to the correct C7 epimer **18** (NaOMe/MeOH, **17**/**18** ≈ 2/1, chromatographic separation and recycling, 97% total recovery for each cycle, see Table 1) and reolefination of the latter compound ($Ph_3P{=}CH_2$, 97% yield). The resulting terminal olefin **19** was then converted to the desired diene system **20** by the three-step procedure developed earlier for the C7 epimeric series (see Scheme 5 for details).

The oxidation of the aromatic moiety of diene **20** proved to be even more challenging than that of its epimer **11**, leading only to traces of the desired quinone under the same $AgO/HNO_3$ conditions.[5] At this stage, the suspicion that the diene system was interfering with the oxidation of the aromatic nucleus led us to temporarily engage it with a molecule of $SO_2$ as a cyclic sulfone (see Scheme 6).[11] Thus, dissolution of **20** in

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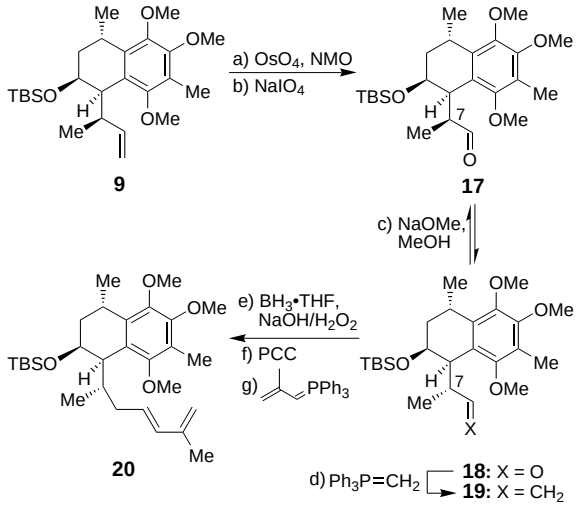
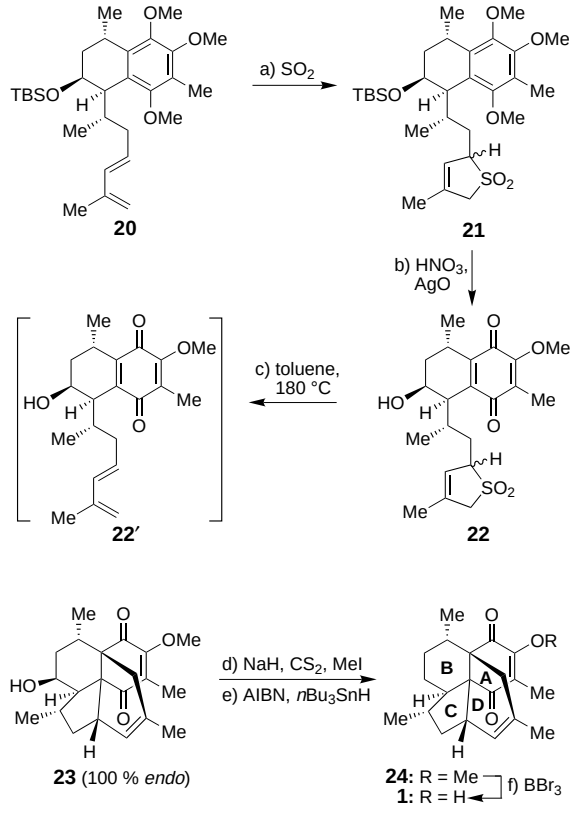



Scheme 5. Epimerization at C7 and synthesis of aromatic diene **20**. a) $OsO_4$ (0.05 equiv), NMO (2.0 equiv), acetone/$H_2O$ (10/1), 25 °C, 5 h, 89 %; b) $NaIO_4$ on silica gel, $CH_2Cl_2$, 25 °C, 30 min, 82 %; c) NaOMe (4 equiv), MeOH/THF (2:1), 25 °C, 12 h, 30 % of **18** and 67 % of **17**; d) methyltriphenylphosphonium bromide (1.5 equiv), KO*t*Bu (1.4 equiv), THF, 25 °C, 1 h; then **18**, 25 °C, 30 min, 97 %; e) $BH_3 \cdot$THF (3 equiv), THF, 25 °C, 1 h; then 3 M NaOH and 30 % $H_2O_2$, 25 °C, 1 h, 87 %; f) PCC (1.5 equiv), $CH_2Cl_2$, 25 °C, 1 h; 95 %; g) 2-methyl-2-propenyltriphenylphosphonium bromide (1.5 equiv), *n*BuLi (1.5 equiv), THF, 0 → 25 °C, 1 h; then aldehyde, 70 °C, 8 h, 70 % plus 19 % *Z* isomer. NMO = 4-methylmorpholine *N*-oxide.




Scheme 6. Completion of the synthesis of colombiasin A (**1**). a) $SO_2$, sealed tube, 25 °C, 30 min, 97 %; b) dioxane/6 M $HNO_3$ (10/1), 25 °C, 2 h; then AgO (6.0 equiv), 25 °C, 1 h, 85 %; c) toluene (sealed tube), 180 °C, 20 min, 89 %; d) NaH (5.0 equiv), THF/$CS_2$/MeI (4/1/1), 50 °C, 3 h, 91 %; e) AIBN (cat.), $nBu_3SnH$ (5.0 equiv), toluene, careful deoxygenation, 110 °C, 30 min, 88 %; f) $BBr_3$, (10 equiv), $CH_2Cl_2$, −78 °C, 30 min, 30 % plus 20 % of **1″**.

liquid $SO_2$ in a sealed tube at ambient temperature led to the formation of sulfone **21** in 97 % yield (≈1.2/1 mixture of diastereoisomers). Most gratifyingly, the AgO/$HNO_3$ oxidation of this sulfone (**21**) proceeded smoothly, furnishing the yellow quinone **22** in 85 % yield. Subsequent heating of a solution of **22** in toluene at 180 °C (in the dark, sealed tube) led to a single (*endo*) cycloadduct **23** (see Table 1) in 89 % yield, apparently through a sequence of cheletropic extrusion of $SO_2$, followed by [4+2] cycloaddition through the presumed intermediacy of the fleeting (under the reaction conditions) diene–quinone **22′** (see Scheme 6). Noteworthy features of this cascade sequence are not only the high-yielding oxidation of the aromatic nucleus to the corresponding quinone (**21** → **22**), but also the stereoselective manner (single isomer) in which the colombiasin A framework is formed (**22** → **23**). Finally, the extra oxygen in **23** was removed from C5 by the previously applied protocol involving xanthate formation followed by reductive cleavage of the C–O bond, leading to *O*-methyl colombiasin (**24**, see Table 1), from which colombiasin A (**1**) itself was generated upon treatment with $BBr_3$ (30 %) as described above for 7-*epi*-colombiasin A (**1′**). The final deprotection step was again accompanied by the formation of colombiasin A's $\Delta^{11,12}$ isomer (**1″**, 20 %). Synthetic colombiasin A (**1**) proved identical to an authentic sample[12] by the usual criteria (TLC, IR, $^1$H and $^{13}$C NMR, MS) except for the fact that it had no optical rotation, as expected based on its racemic synthesis.

To address the issue of the absolute stereochemistry and asymmetric synthesis of colombiasin A (**1**), the initial Diels–Alder reaction (**2** + **3** → **4**, Scheme 2) was carried out in the presence of a chiral catalyst ([(*S*)-BINOLTiCl$_2$],[13] toluene, −60 → −10 °C). The resulting product (**4**) was then elaborated according to Scheme 2 to ketone **6**, and the latter compound was analyzed by HPLC ($R_t$ = 6.1 and 6.7 min for the two enantiomers, 0 → 50 % *i*PrOH in hexane over 35 min, 1.5 mL min$^{-1}$, CHIRALCEL OD-H chiral column), revealing an *ee* of 94 % ($[\alpha]_D^{23} = -140°$, $c$ = 9.5 mg mL$^{-1}$, $CHCl_3$). Following this encouraging asymmetric induction (which was also demonstrated in the opposite sense in the presence of the other enantiomeric form of the catalyst), we anticipate both asymmetric synthesis of colombiasin A (**1**) and determination of its absolute stereochemistry.[14] The described chemistry is also expected to facilitate chemical biology studies with this new class of compounds.

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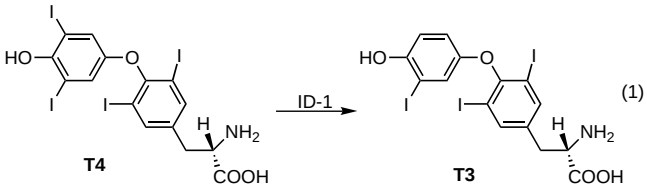
[14] Based on the chirality of the catalyst used to induce the asymmetry[13] in **4** and the rotation ($[\alpha]_D^{23} = -61°$, $c = 1\ mg\,mL^{-1}$, $CHCl_3$) of the synthetic natural product obtained from this intermediate, we tentatively assign the shown absolute stereochemistry of colombiasin A. Further studies to confirm this assignment are in progress.

## Reactions of Organoselenenyl Iodides with Thiouracil Drugs: An Enzyme Mimetic Study on the Inhibition of Iodothyronine Deiodinase**

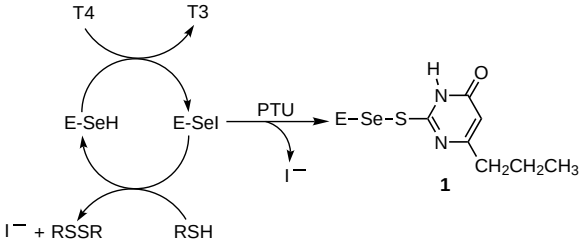
Wolf-Walther du Mont,* Govindasamy Mugesh, Cathleen Wismach, and Peter G. Jones

The monodeiodination of the prohormone thyroxine (**T4**) to the biologically active hormone 3,5,3′-triiodothyronine (**T3**) is the first step in thyroid hormone action and the type I iodothyronine deiodinase (ID-1), an enzyme containing selenocysteine in its active site, is responsible for most of this conversion [Eq. (1)].[1] ID-1 is an integral membrane




(1)

protein the highest amounts of which are found in the liver, kidney, and thyroid. The 5′-deiodination catalyzed by ID-1 is a ping-pong, bisubstrate reaction in which the selenol group of the enzyme (E-SeH) first reacts with thyroxine (**T4**) to form a enzyme selenenyl iodide (E-SeI) complex with release of deiodinated iodothyronine (**T3**). Subsequent reaction of the selenenyl iodide with an unidentified cytoplasmic thiol cofactor (possibly glutathione, GSH) releases $I^-$ ions and regenerates the E-SeH active site (Scheme 1).[2]




Scheme 1. Proposed mechanism for iodothyronine deiodination of thyroxin **T4** by ID-1 and the inhibition of ID-1 by PTU.

It was proposed that the drug 6-*n*-propyl-2-thiouracil (PTU), derived from thiourea, inhibits the activity of the enzyme, probably by reacting with the selenenyl iodide intermediate to form a stable selenenyl sulfide.[2] The selenenyl sulfide **1** is considered to be a dead-end product since this compound does not react with thiols under physiological conditions. Owing to this property, PTU is often used in the treatment of severely hyperthyroid (Graves disease) patients and is therefore well known as an antithyroid drug.

The formation of a mixed selenenyl sulfide adduct (**1**, Scheme 1) in the reaction of the selenenyl iodide with PTU has been proposed mainly on the basis of the following assumptions. 1) The PTU inhibition is noncompetitive with respect to thyroxine and competitive with respect to thiol cofactor, which suggests that PTU and cofactor react with the same enzyme intermediate.[1a] 2) The thiouracil derivatives are particularly reactive towards protein sulfenyl iodide (S–I) groups[1a] and presumably even more reactive towards selenenyl iodide (Se–I) groups. However, since the discovery that the ID-1 is a selenium-containing enzyme, the reactions of thiourea drugs with E-SeI and their mechanisms have never been experimentally verified. In contrast to ID-1, the other two deiodinases (ID-2 and ID-3) are insensitive to PTU.[1c] It is, therefore, still a matter of debate as to whether PTU reacts with a covalent Se–I species or if it reacts with the enzyme active site (E-SeH). Moreover, no reasons have been given for the insensitivity of ID-2 and ID-3 towards PTU.[1c] Herein, we report the first model studies on the reactivity of PTU towards selenenyl iodides as a basis for the deiodinase inhibition.

The reactions of organoselenenyl iodides as enzyme-mimetic substrates with thiourea derivatives have not been studied previously as areneselenenyl iodides such as PhSeI are themselves generally unstable and disproportionate in solution.[3a] Even the sterically hindered areneselenenyl iodides such as **2** have been found to exist in equilibrium with iodine and the corresponding diselenide in solution.[3b,c] The "non-existence" of stable binary Se–I compounds is associated with the very similar electronegativities of Se and I, that is, the lack of ionic contribution to the resonance energy in the covalent Se–I bond.[4] However, the recent observations that the

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