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Towards colombiasin A

David C. Harrowven* and Melloney J. Tyte

Department of Chemistry, The University of Southampton, Southampton SO17 1BJ, UK

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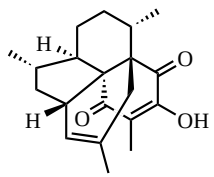
Abstract—A synthetic route to an unnatural diastereoisomer of colombiasin A is described. Key features are an arene alkylation with a γ-methylene-γ-butyrolactone and an intramolecular Diels–Alder cycloaddition.

Colombiasin A **1** is a structurally complex diterpene, recently isolated from the Caribbean sea whip *Pseudopterogorgia elisabethae*.[1] Though modest in size, its carbon frame contains three six-membered rings that share a common carbon to carbon bond. To this 'propellane' is fused a further cyclopentane ring. Six contiguous stereogenic centres are present within its unique tetracyclic skeleton, including two adjacent quaternary centres at its core (Fig. 1). Earlier this year, Nicolaou et al. reported the first total synthesis of colombiasin A.[2] Herein we report an alternative approach leading to an unnatural diastereoisomer of this challenging target.



Colombiasin A **1**

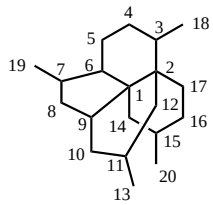


Figure 1. Colombiane numbering.

Our synthesis began with 2,6-dimethoxytoluene **2** which was converted into phenol **4** using a known sequence.[3] A Pechmann reaction with ethyl acetoacetate and mediated by triflic acid then gave coumarin **5**.[4] Reduction of the alkene and saponification of the lactone in the presence of dimethyl sulfate next furnished ester **7**, a precursor to aldehyde **9**. Union of aldehyde **9** and phosphonate **10** led to a separable 3:2 mixture of (*Z*)- and (*E*)-alkenes **11**.[5] Each of these materials underwent a diastereoselective aromatic alkylation on exposure to triflic acid giving spirolactone **12** as the major product. This was accompanied by traces of its diastereoisomeric partner and the cyclopentadienone **13** (Scheme 1).

At this juncture we attempted to effect a simultaneous alkene hydrogenation and ester hydrogenolysis under neutral conditions in order to establish the C-6 and C-7 stereogenic centres of colombiasin A. Unfortunately, even under forcing conditions we were unable to accomplish the second of these tasks, the product given being a single diastereoisomer of spirolactone **14** with the C-7 stereocentre installed with the correct relative stereochemistry. When the reaction was conducted in acidic media, reduction of the lactone was accomplished at room temperature and pressure, but proceeded with complete retention of configuration to give **16**! This was shown to be due to the formation of γ,δ-unsaturated ester **17** as an intermediate, with the pseudo-axial C-18 methyl group dictating the stereochemical course of the reduction (Scheme 2). Reduction of spirolactone **12** to **16** could also be effected in good yield using these conditions.

Though disappointed by our failure to establish the C-6 stereogenic centre correctly, we decided to progress ester **16** towards an unnatural colombiasin diastereoisomer. Thus, it was smoothly transformed into aldehyde

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* Corresponding author.

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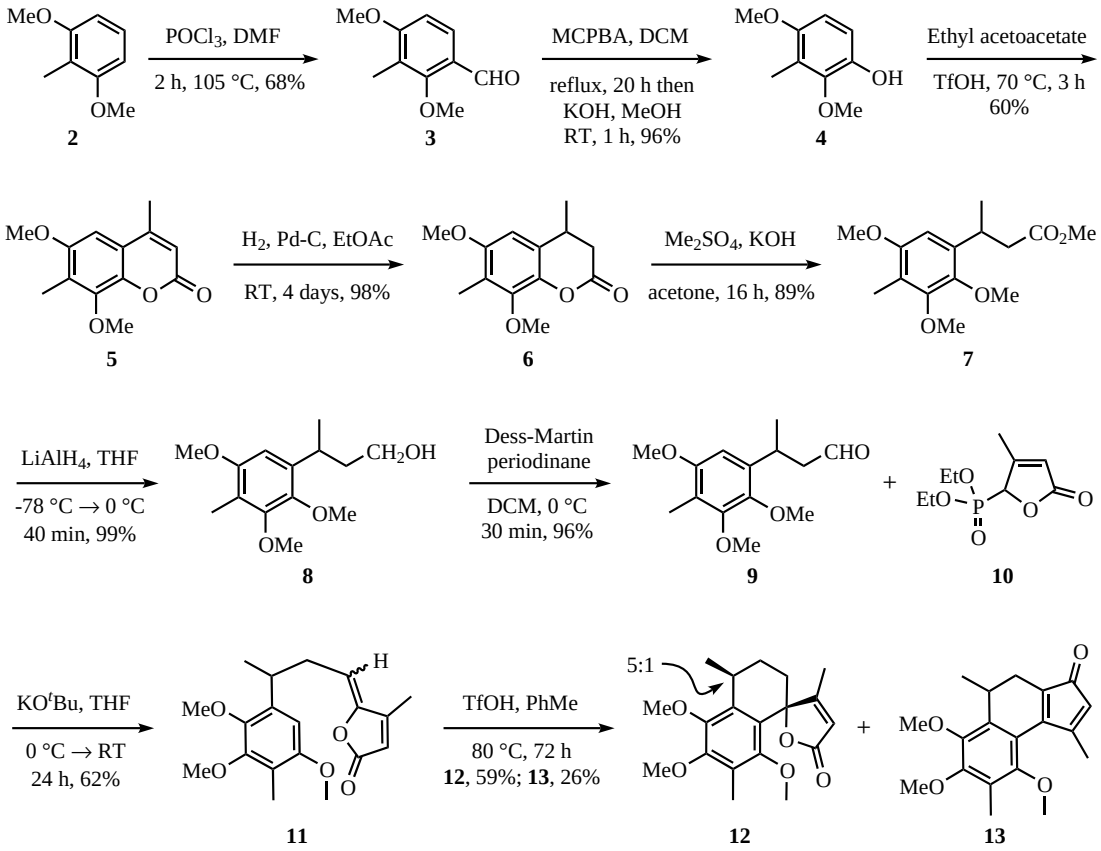
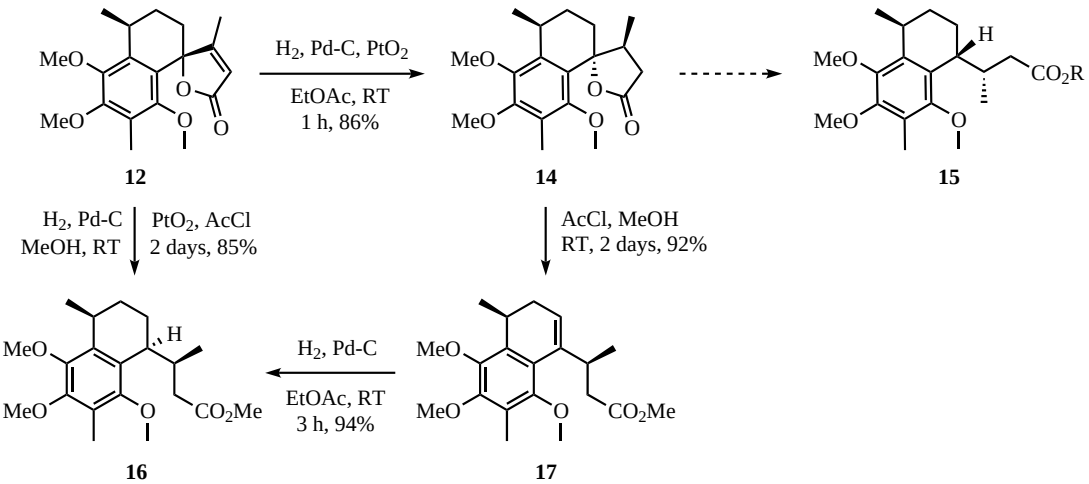


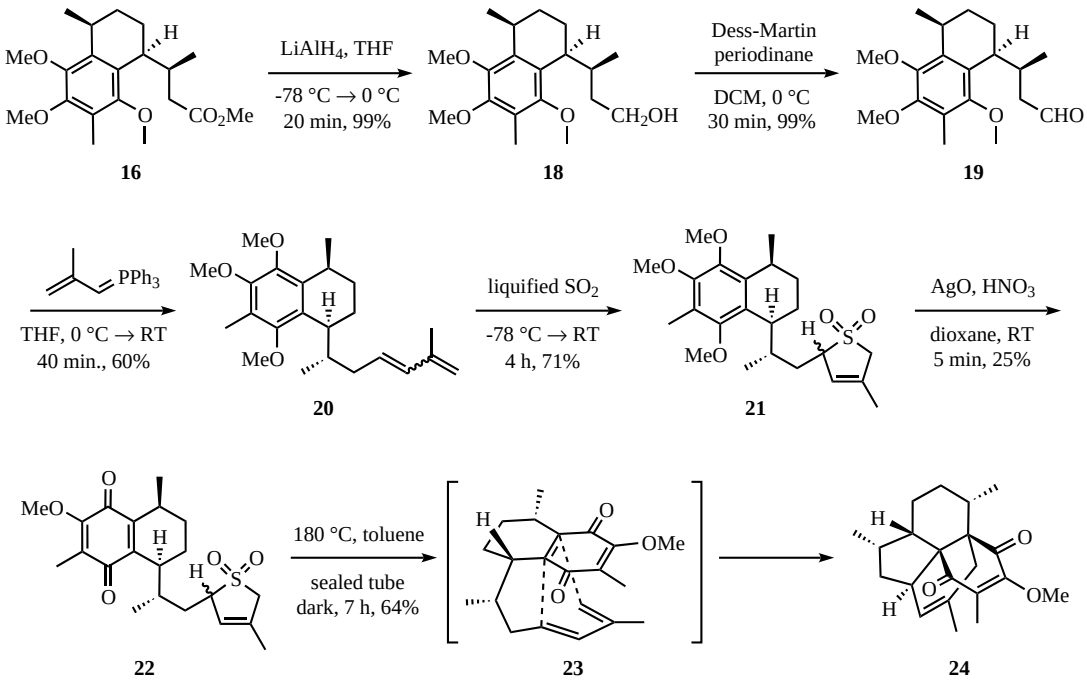
Scheme 1.

19 allowing a diene unit to be introduced by standard Wittig chemistry. Attempts to effect aromatic oxidation of **20** to a quinone led to a complex product mixture, many components seemingly derived from oxidation of the diene. Such a problem had been overcome by Nicolaou et al.,[2] through protection of the diene moiety as its sulfur dioxide adduct. Their tactic proved similarly effective in our hands, though oxidation of **21** to quinone **22** with silver oxide and nitric acid was still low yielding. Finally, heating a toluene solution of **22** in the dark at 180°C in a sealed tube induced the intramolecular Diels–Alder cycloaddition leading to a single diastereoisomer of dione **24** (Scheme 3).

At this time we must add a cautionary note on the stereochemistry of **24** as it has yet to be established with rigour. Our assignment is based on a knowledge of the stereochemistry of the precursor **22**, an assumption that no epimerisation of the transient diene **23** occurs and that the Diels–Alder cycloaddition to **24** proceeds though an *endo*-cyclic transition state. All concur with the findings of Nicolaou et al. Moreover, epimerisation



Scheme 2.



Scheme 3.

at the C-6 stereocentre in **23** would have provided us with the methyl ether of colombiasin A. Data reported for that material differs from that attained for **24**, again suggesting the outcome depicted.[6]

In conclusion, we have developed a route to an unnatural diastereoisomer of colombiasin A. Key features are the arene alkylation with a γ-methylene-γ-butyrolactone, viz. **11**→**12**, and the intramolecular Diels–Alder cycloaddition **23**→**24**. We are presently seeking a more efficient protocol for effecting the aromatic oxidation **21**→**22** and exploring other routes to **15**, from which the natural colombiasin A diastereoisomer should be accessible.

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6. Data for **24**: IR (film) ν_{max} 2931 m, 1673 s, 1626 w, 1457 m, 1230 w, 1127 s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 5.67 (1H, br. s, =C*H*), 3.89 (3H, s, OCH_3), 3.09 (1H, m, =CHC*H*), 2.99 (1H, m, CC*H*CH_3), 2.33–1.97 (7H, m), 1.97 (3H, s, CH_3C=C-C=O), 1.44 (3H, s, CH_3C=CH), 1.44–1.10 (3H, m), 1.10 (3H, d, *J* 7.7, CH_3CHC), 0.94 (3H, d, *J* 6.9, CH_3CHCH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 203.1 (s, C-14), 198.6 (s, C-17), 155.2 (s, C-16), 131.7 (s, C-11), 129.9 (s, C-15), 125.7 (d, C-10), 64.8 (s, C-1), 60.2 (q, OCH_3), 52.6 (s, C-2), 48.1 (d, C-7), 44.6 (d, C-6), 39.4 (t, C-12), 38.1 (d, C-9), 34.0 (d, C-3), 33.3 (t, C-8), 29.8 (t, C-5), 28.9 (t, C-4), 22.7 (q, C-13), 16.1 (q, C-19), 15.6 (q, C-18), 10.4 (q, C-20) assigned with reference to those data reported for **1** and colombiasin A methyl ether;[1,2] LRMS (CI) *m*/*z* 329 (100%, MH^+), 301 (18%, $[M-CO]^+$), 109 (42%); HRMS (EI) *m*/*z* Found M^+: 328.2038, $C_{21}H_{28}O_3$ requires 328.2038.