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An enantioselective double Diels–Alder approach to the tetracyclic framework of colombiasin A †

Jason H. Chaplin,‡[a] Alison J. Edwards[b] and Bernard L. Flynn*‡[a]

[a] *Department of Chemistry, The Faculties, Australian National University, Canberra, ACT, 0200, Australia*

[b] *Research School of Chemistry, Australian National University, Canberra, ACT, 0200, Australia*

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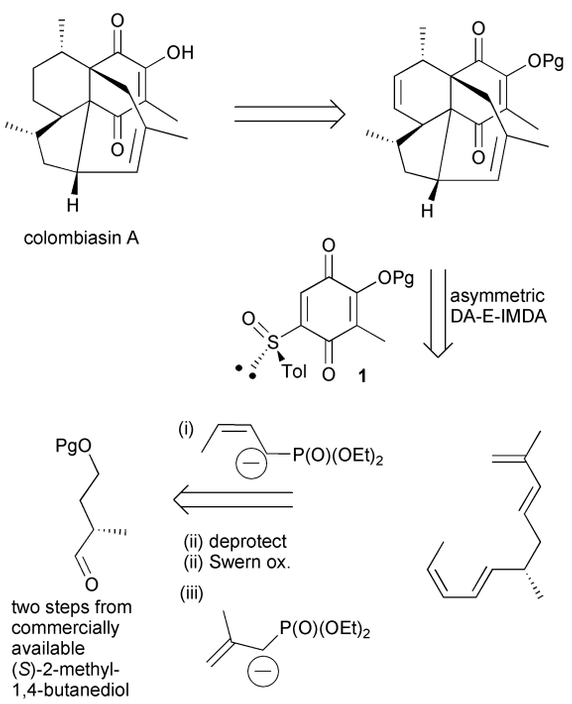
The complex tetracyclic carbon skeleton of colombiasin A is conveniently accessed through an enantioselective intermolecular Diels–Alder–sulfoxide elimination–intramolecular Diels–Alder (DA–E–IMDA) sequence.

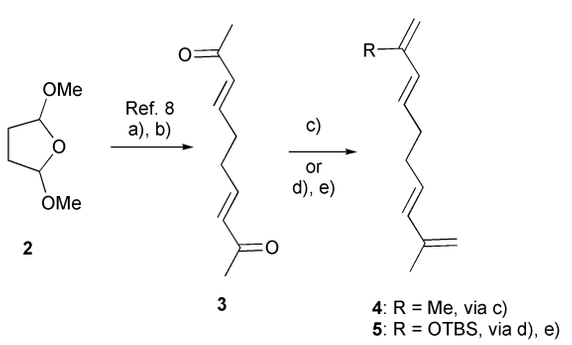
The tetracyclic core of the recently reported diterpene, colombiasin A, consists of an unprecedented dodecahydro-5a,8b-butanoacenaphthylene ring system bearing several oxygen and methyl substituents.[1–3] Our interest in this natural product stems from the notion that it might be readily accessed *via* a tandem enantioselective Diels–Alder–elimination–intramolecular Diels–Alder (DA–E–IMDA) sequence (Scheme 1).§[4–6] Furthermore, this DA–E–IMDA sequence may have additional applications, for example, in diversity-orientated synthesis based on structurally complex, natural product-like templates.[7] The sulfoxy group in **1** is the key component of our proposed approach to colombiasin A. It acts as a multifunctional substituent that controls both the regio and facial selectivity of the DA reaction and then eliminates to generate the dienophile for the IMDA (Scheme 1).[5] Herein, we report our initial investigations of this approach, in particular, the validation of the proposed enantioselective DA–E–IMDA sequence.

Two double-dienes **4** and **5**, each containing a two-carbon linker, were prepared *via* a concise synthetic pathway (Scheme 2). The common intermediate, deca-3,7-diene-2,9-dione (**3**), was prepared from 2,5-dimethoxytetrahydrofuran (**2**) as described by Klimko and Singleton.[8] Both carbonyls in **3** were methylenated using excess Wittig reagent to give the symmetrical double-diene 2,9-dimethyl-1,3,7,9-decatetraene (**4**) in a low but useful yield (44%). Monosilylation of **3** was achieved in a reasonable yield (52%, based on recovered starting material) and the product (not shown) mono-methylenated in high yield to give the unsymmetrical double-diene **5** (84%).

When the naphthoquinone sulfoxide **6**[9] (racemic) was reacted with the symmetrical double-diene **4** the DA reaction and sulfoxide elimination were achieved in one-pot, but only a low yield of the adduct **7** (29%) was obtained (Scheme 3). This low yield resulted in large part from competitive reduction of **6** to the dihydroquinone **9**, possibly in part by the phenylsulfenic acid (HOSPh) produced.[5f] The unsymmetrical double-diene **5** reacted with **6** to give a reasonable yield of the DA adduct **10** (55%). The yield improvement for **10** relative to **7** may result from the expected increase in DA reaction rate for the silyloxy substituted diene **5** relative to **4**, increasing the amount of DA adduct **10** produced relative to reduction product **9**. Both **7** and **10** were efficiently converted to the IMDA adducts **8** (81%) and



Scheme 1 Retrosynthetic analysis of colombiasin A based on a tandem enantioselective DA–E–IMDA sequence.



Scheme 2 *Reagents and conditions:* a) HCl(aq); b) $Ph_3P{=}CHC(O)CH_3$; c) 2 × $Ph_3P{=}CH_2$; d) TBSOTf, Et_3N, CH_2Cl_2 and e) $Ph_3P{=}CH_2$.

11 (71%), respectively, upon heating in toluene. A single crystal X-ray diffraction study of **11** was performed, confirming that the relative stereochemistry is as predicted for an *endo*-IMDA (Fig. 1).[10] This relative stereochemistry is also that contained within colombiasin A.

We next explored the possibility of preparing an enantiomerically enriched DA–E–IMDA product using unichiral sulfinylquinone **15**. This known material was prepared by a similar procedure to that described by Carreño *et al.* (Scheme 4).[5g] The bromophenol **12**[11] was doubly metalated and reacted

† Electronic supplementary information (ESI) available: Detailed procedures for the preparation of all compounds and their spectral data. See http://www.rsc.org/suppdata/ob/b3/b302522e/

‡ *New Address:* Department of Medicinal Chemistry, Victorian College of Pharmacy, Monash University, 381 Royal Pde, Parkville VIC 3052, Australia. E-mail: bernard.flynn@vcp.monash.edu.au

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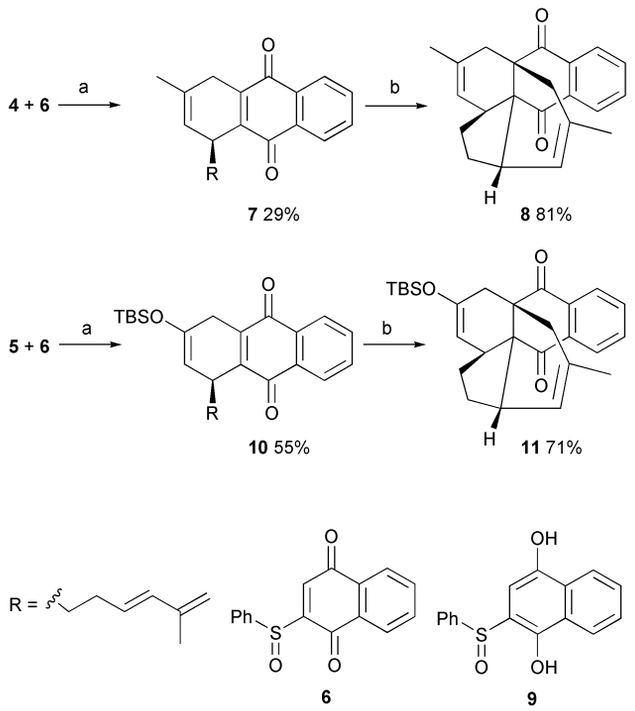


Scheme 3 *Reagents and conditions:* a) CH_2Cl_2, −15 °C to 18 °C; b) toluene, 160 °C (sealed tube).

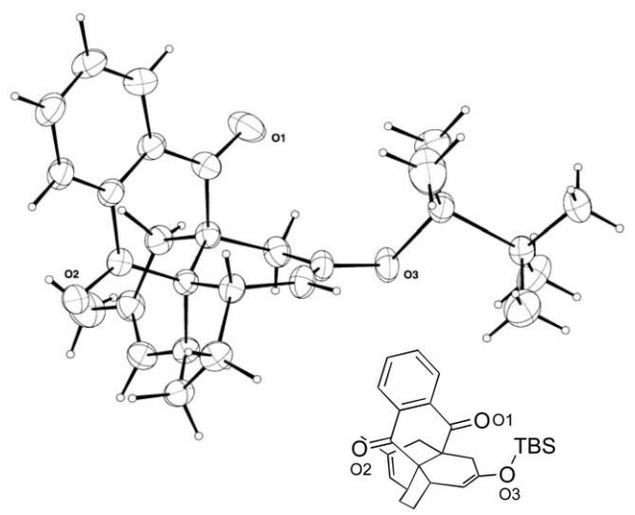
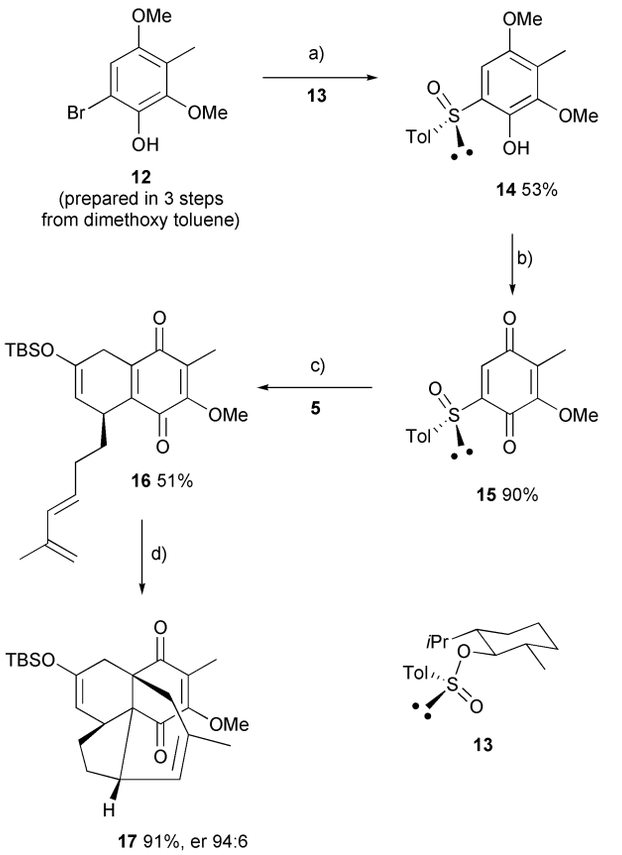


Fig. 1 Anisotropic displacement ellipsoid plot (50% probability) of a molecule of **11** derived from a crystallographic study.

with (S*S*)-menthyl *p*-toluenesulfinate **13** to give **14** (53%), which underwent efficient oxidation to give the sulfinylquinone **15** (90%). Diels–Alder reaction of double-diene **5** with dienophile **15** produced **16** in a reasonble yield (51%), which underwent the IMDA reaction upon heating to give the adduct **17** in an excellent yield and enantioselectivity (91% yield, er 94 : 6).[12] The major enantiomer of **17** has been tentatively assigned the absolute stereochemistry shown based on the mnemonic for asymmetric DA reactions involving sulfinylquinones proposed by Carreño *et. al.*, involving an *endo*-approach of **5** to the sterically less congested face (top-face) of the prefered s-*cis* conformation of **15** (as shown).[5h] The regioselectivty was confirmed by X-ray crystallography.[13]

Whilst it still remains to be seen if this DA–E–IMDA protocol can be used to synthesise the specific natural product, colombiasin A (Scheme 1), the capacity of this reaction sequence to provide convergent access to complex molecular cores with excellent relative and absolute stereochemical control should make it an attractive procedure for application



Scheme 4 *Reagents and conditions:* a) 2 × *n*BuLi, THF, −78°C then **13**; b) cerium ammoniumnitrate (CAN), CH_3CN, 18 °C; c) **5**, CH_2Cl_2, −15 °C to 18 °C; d) toluene, 160 °C (sealed tube).

to other areas, such as the diversity-orientated synthesis of natural product-like molecules.

Acknowledgements

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Notes and references

§ This year (2003) is the 75th anniversary of Diels' and Alder's first report on their [4 + 2]-cycloaddition reaction: O. Diels and K. Alder, *Justus Leibigs Ann. Chem.*, 1928, **460**, 98.

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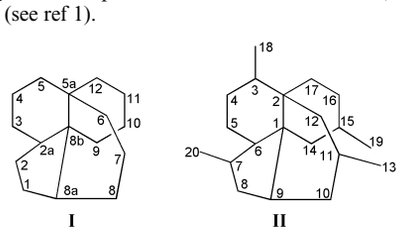
2 The name given to the core, dodecahydro-5a,8b-butanoaceanaphthylene **I**, is based on IUPAC nomenclature and has different numbering to the terpenoid colombiane skeleton **II**, identified by Rodriguez (see ref 1).



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10 Crystal structure analysis of **11**: data collection: KappaCCD diffractometer. Cell refinement: HKL Scalepack (Otwinowshi & Minor 1997). Data reduction: Denzo Scalepak (Otwinoowski & Minor, 1997). Program used to solve structure, *SIR*92 (Altomare *et al.*, 1994). Program used to refine structure: *CRYSTALS* (Watkin *et. al.*, 2001). T = 200 K, MoKα radiation, λ = 0.710373 Å, structure presentation: crystal dimensions 0.60 × 0.56 × 0.50 mm^3, colorless prism, space group $P2_1/a$ monoclinic, a = 12.9389 (2), b = 11.7515 (3), c = 16.9570 (4) Å, β = 111.054 (9)°, V = 2406.20 (9) Å^3, Z = 4, D_x = 1.200 Mg m^{-3}, θ = 3.08–27.45° μ = 0.123 mm^{-1}, 64739 measured, 5633 independent reflections, 3445 reflections with $I > 3.00\sigma(I)$, R_{int} = 0.064, R = 0.035, wR = 0.041, S = 1.053, $(\Delta/\sigma)_{max}$ = 0.0006, $\Delta\rho_{min}$ = −0.23, $\Delta\rho_{max}$ = 0.21 e Å^{-3}. CCDC reference number 199385. See http://www.rsc.org/suppdata/ob/b3/b302522e/ for crystallographic data in .cif or other electronic format.

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12 The er was determined using chiral HPLC, this involved the synthesis of racemic **17** using ethyl *p*-toluenesulfinate in place of **13** in Scheme 4 (see ESI for details †).

13 A single crystal X-ray diffraction experiment was undertaken for **17**. The initial structure solution and refinement clearly revealed the regiochemistry of the product, however, complex multi-site disorder of the TBS group led to abandonment of a full refinement of the structure (see ESI for an anisotropic displacement ellipsoid plot of **17** and unit cell dimensions †).