Enantioselective total synthesis of epoxyquinone natural products (−)-phyllostine, (+)-epoxydon, (+)-epiepoxydon and (−)-panepophenanthrin: access to versatile chiral building blocks through enzymatic kinetic resolution

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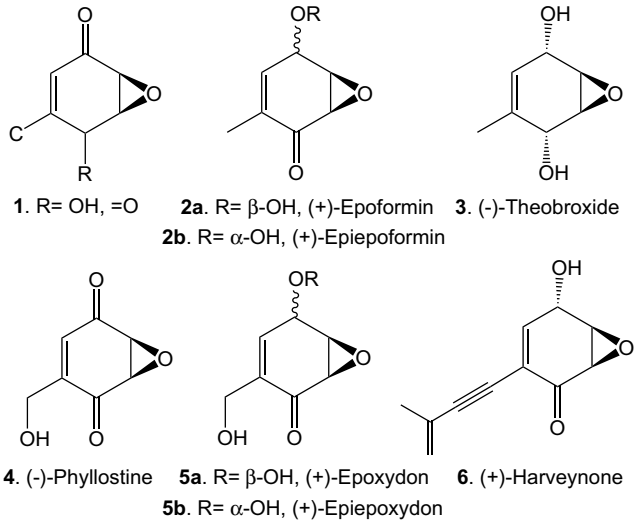
Abstract—A new enzyme mediated protocol to access versatile chiral building blocks for the synthesis of epoxyquinone natural products is delineated. Total syntheses of (−)-phyllostine, (+)-epoxydon, (+)-epiepoxydon and (−)-panepophenanthrin have been accomplished to demonstrate the efficacy of this approach.

A range of polyketide derived natural products, embodying a compact epoxyquinone derived motif **1**, as the core structure, have been encountered among diverse sources like bacteria, fungi, higher plants and mollusks.[1] Representative examples of such polyoxygenated cyclohexanoids are (+)-epoformin **2a**,[1a] (+)-epiepoformin **2b**,[1b] (−)-theobroxide **3**,[1c] (−)-phyllostine **4**,[1d](+)-epoxydon **5a**,[1e] (+)-epiepoxydon **5b**[1f] and (+)-harveynone **6**.[1g] These and related natural products have stimulated much synthetic activity due to their structural and stereochemical diversity and their wide ranging biological activity, from phytotoxicity, anti-fungal, anti-bacterial and anti-tumour to various kind of enzyme inhibition.[2]

More recently, a complex natural product (+)-panepophenanthrin **8**,[3] derived through a biosynthetic Diels–Alder reaction from a monomeric epoxyquinone precursor **7**, has been isolated from the fermentation broth of the mushroom strain *Panus rudis Fr.* IFO8994 and has aroused considerable current interest among synthetic chemists due to its unique activity in inhibiting the ubiquitin activating enzyme (E1), which is indispensable to the ubiquitin–proteosome pathway (UPP).[4]

As a part of our ongoing interest in the synthesis of epoxyquinone natural products,[4c,5] we further highlight



here the efficacy of the readily available Diels–Alder adduct **9**[6] of cyclopentadiene and *p*-benzoquinone and its epoxide **10** as versatile building blocks for the synthesis of natural products embodying the structural motif **1**. A notable feature of the efforts outlined here is the convenient and efficient enzyme mediated kinetic resolution of a derivative of **10** to provide access to both the enantiomeric forms of the core structure **1**. One of these

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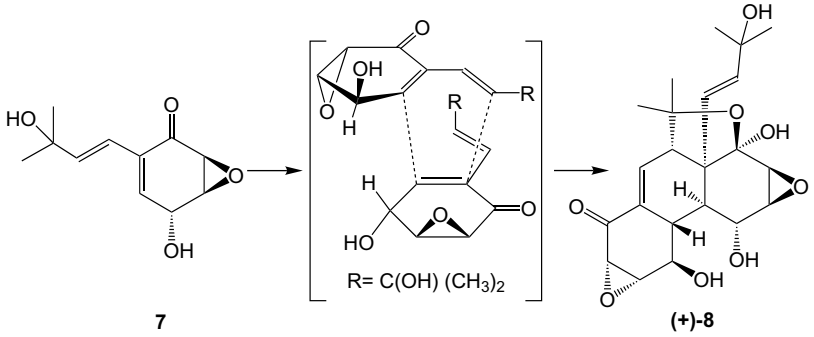
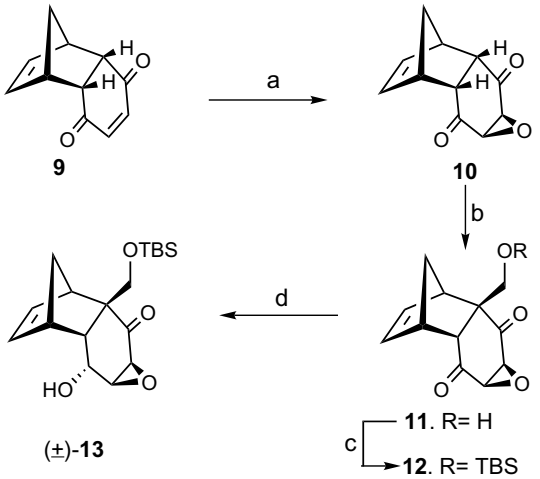
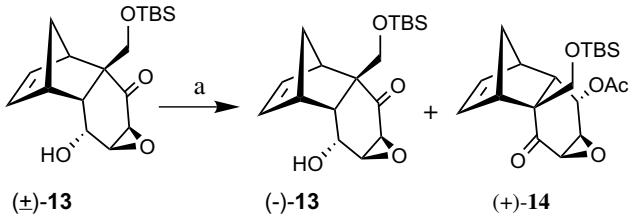


enantiomers has been elaborated to the natural products (−)-phyllostine **4**, (+)-epoxydon **5a** and (+)-epiepoxydon **5b** and also utilized for the total synthesis of (−)-panapophenanthrin **8**, the antipode of the biologically important natural product (+)-**8**. These endeavours towards the total synthesis of epoxyquinone natural products constitute the theme of this letter.

Readily available tricyclic *endo*-adduct **9** can be conveniently transformed to **10**[7] in high yield and further exposure to formalin solution in the presence of catalytic amounts of DBU under controlled conditions led stereoselectively to the α-hydroxymethylated product **11** in excellent yield (Scheme 1). TBS-protection of the hydroxyl group in **11** to yield **12** and sodium borohydride reduction stereoselectively furnished the *endo*-alcohol **13** (Scheme 1).[7] After some trial experimentation, it was found that **13** was amenable to efficient enzymatic kinetic resolution through transesterification.[8] Thus, exposure of (±)-**13** to lipase PS-D in vinyl acetate solvent and termination of the reaction at nearly 50% transesterification led to the isolation of hydroxy compound (−)-**13** (45% yield, ~99% ee)[8] and acetate (+)-**14** (46% yield, ~99% ee)[8] with high enantioselectivity and in preparatively useful yields (Scheme 2).[7,8] Both (−)-**13** and (+)-**14** are serviceable for the synthesis of



Scheme 1. Reagents and conditions: (a) 30% H_2O_2, 10% Na_2CO_3, acetone, 0 °C, 96%; (b) 0.1 equiv DBU, 40% formalin, THF, 0 °C, 95%; (c) TBSCl, imid. DMAP, DMF, rt, 92%; (d) $NaBH_4$, MeOH, −15 °C, 81%.

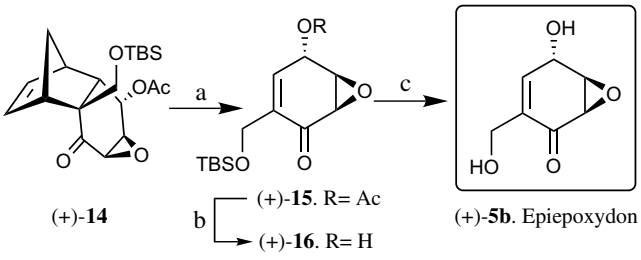


Scheme 2. Reagents and conditions: (a) Lipase PS-D (Amano), vinyl acetate, rt, 28 h. (−)-**13**, 45%, (+)-**14**, 46%.

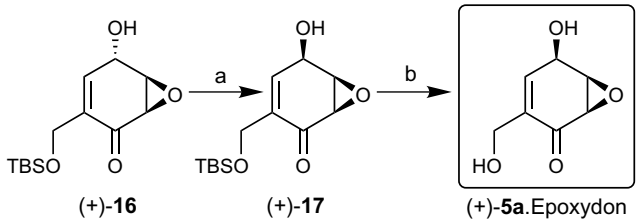
diverse natural products and herein we describe a few syntheses emanating from (+)-**14**.

Enantiopure tricyclic acetate (+)-**14** on thermal activation underwent facile retro-Diels–Alder reaction to eliminate cyclopentadiene and deliver epoxyquinone derivative (+)-**15** (Scheme 3).[7] Acetate hydrolysis in (+)-**15** gave (+)-**16** and further TBS deprotection furnished the natural product (+)-epiepoxydon **5b** ($[\alpha]_D$ +250, *c* 1.4, EtOH; lit.[1f,2k] $[\alpha]_D$ (+)-256, *c* 0.8, EtOH)[7] whose spectral data were found to be identical with those reported in the literature.[1f,2k]

Hydroxy-enone (+)-**16** was also suitable for the synthesis of the natural product (+)-epoxydon **5a** and this required stereochemical inversion of the secondary hydroxyl group. Consequently, (+)-**16** was directly subjected to the Mitsunobu protocol[9] to deliver the hydroxyl inverted product (+)-**17** after hydrolysis (Scheme 4).[7] TBS-deprotection in (+)-**17** led to (+)-epoxydon **5a** ($[\alpha]_D$ +98, *c* 1.0, EtOH; lit.[1e] $[\alpha]_D$ +102, *c* 1.0, EtOH) and its spectral characteristics were found to be identical to those reported[1e] for the natural product (Scheme 4).[7]



Scheme 3. Reagents and conditions: (a) diphenyl ether, 240 °C, 5 min, 93%; (b) LiOH, MeOH, 0 °C, 75%; (c) HF–pyridine, THF, 0 °C, 80%.

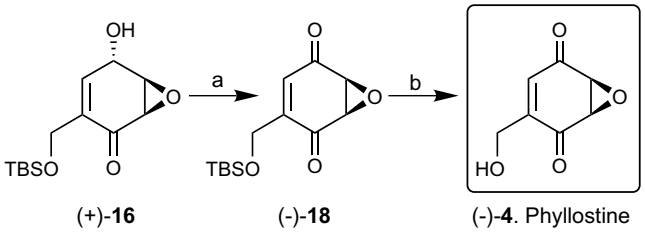


Scheme 4. Reagents and conditions: (a) (i) PPh_3, DIAD, PNBA, THF, −50 °C to rt; (ii) LiOH, MeOH, 0 °C, 65% (two steps). (b) HF–pyridine, THF, 0 °C, 76%.

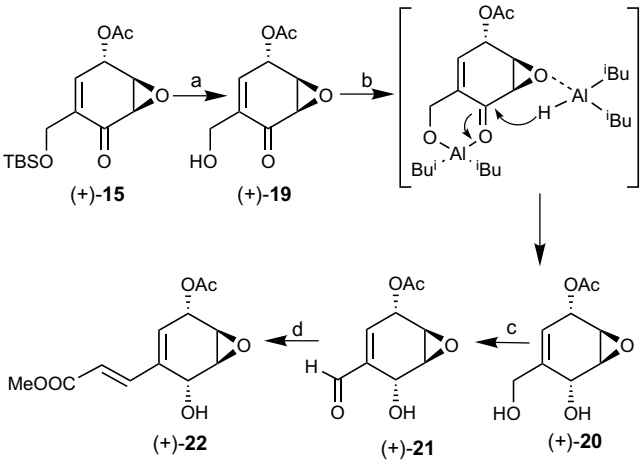
This synthesis, to our knowledge, is the first enantioselective synthesis of the natural product, (+)-epoxydon.[10]

For the synthesis of (−)-phyllostine, the hydroxyl group in (+)-**16** was subjected to oxidation with PDC to give (−)-**18** and further TBS-deprotection led to the epoxyquinone natural product (−)-**4** ($[\alpha]_D$ −108, *c* 1.61, EtOH; lit.[1d] $[\alpha]_D$ −105, *c* 1.0, EtOH), Scheme 5.[7] The spectral data for our synthetic (−)-phyllostine were found to be identical with those reported for the natural product.

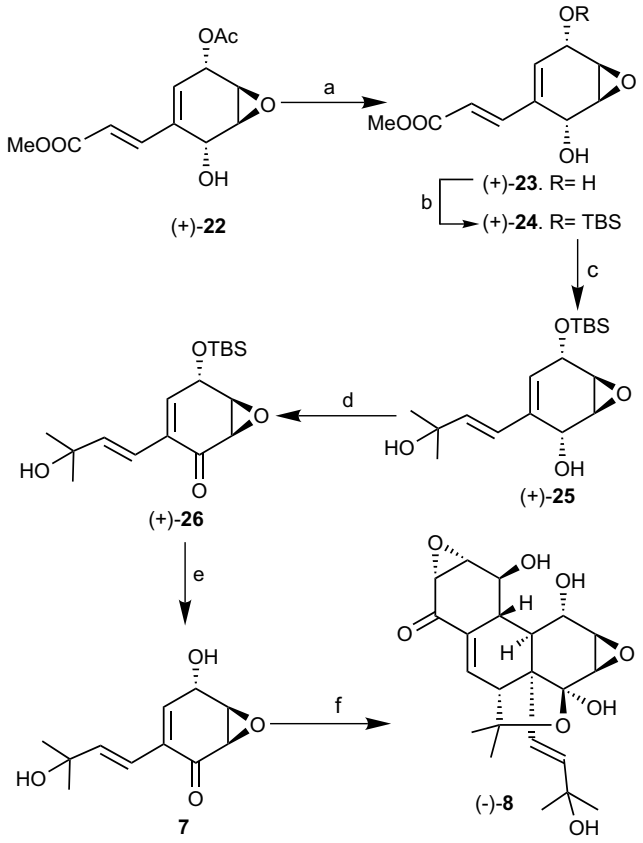
Monocyclic acetate (+)-**15** (Scheme 3) was considered as a suitable starting point for accessing the precursor **7** for a synthesis of (−)-panepophenanthrin **8**, the antipode of the natural product.[3] It has been shown by others[4a,b] and us[4c] that **7** undergoes spontaneous dimerization via a biomimetic Diels–Alder reaction to panepophenanthrin **8**. Thus, accessing **7** became our penultimate objective. TBS deprotection in (+)-**15** gave (+)-**19** and further DIBAL-H[11] reduction of the carbonyl group proceeded under chelation control to furnish diol (+)-**20** as a single diastereomer (Scheme 6).[7] The primary hydroxyl group in diol (+)-**20** was chemoselectively oxidized in the TEMPO–O_2–CuCl[12] milieu to furnish aldehyde (+)-**21**. Horner–Wittig olefination in the hydroxyaldehyde **21** proceeded smoothly to render the (*E*)-α,β-unsaturated ester (+)-**22** in good yield (Scheme 6).[7] At this stage, it was necessary to carry out a methyl lithium addition to the ester carbonyl group of (+)-**22** to deliver the desired side chain present in **7**. However, the presence of the acetate group in (+)-**22** made this manoeuvre extremely messy and difficult to execute and therefore a more circuitous approach at the expense of a few additional steps was adopted. Acetate hydrolysis in (+)-**22** was uneventful and led to the diol (+)-**23** in which one hydroxyl group was regioselectively protected as its TBS-derivative (+)-**24** (Scheme 7).[7] Addition of



Scheme 5. Reagents and conditions: (a) PDC, DCM, 0 °C, 89%; (b) HF–pyridine, THF, 0 °C, 72%.



Scheme 6. Reagents and conditions: (a) HF–pyridine, THF, 0 °C, 92%; (b) DIBAL-H, THF, −78 °C, 72%; (c) TEMPO, O_2, CuCl, DMF, rt, 81%; (d) $Ph_3P{=}CHCOOMe$, benzene, rt, 94%.



Scheme 7. Reagents and conditions: (a) LiOH, MeOH, 0 °C, 88%; (b) TBSOTf, imid. DMAP, DMF, rt, 71%; (c) MeLi, THF, 0 °C, 60%; (d) MnO_2, DCM, rt, 74%; (e) HF–pyridine, THF, 0 °C, 94%; (f) neat, 30 h, 82%.

methyllithium to (+)-**24** was now smooth and delivered (+)-**25**. Oxidation of the allylic hydroxyl group in (+)-**25** furnished the enone (+)-**26**[7] and TBS deprotection led to the monomeric precursor **7** of the natural product panepophenanthrin (Scheme 7). When **7** was left neat under ambient conditions (~26 °C) for 30 h, it began

to solidify and was transformed into a single dimeric product (−)-**8** through a stereospecific intermolecular Diels–Alder reaction.[13] The spectral data for (−)-**8** were identical with that of the natural product but had a rotation ($[\alpha]_D$ −147, *c* 1.0, MeOH) opposite in sign to that of the natural product (lit.[3] $[\alpha]_D$ +149.8, *c* 1.0, MeOH).[7] Thus, the first synthesis of the antipode of the biologically potent natural product panepophenanthrin has been achieved and its biological activity profile is being evaluated.

In short, we have devised a simple enzyme mediated strategy to access chiral building blocks for the synthesis of a range of biologically active epoxyquinone natural products from readily available starting materials. This versatile approach has resulted in the short syntheses of natural products (−)-phyllostine, (+)-epoxydon, (+)-epi-epoxydon and (−)-panepophenanthrin.

Acknowledgements

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7. All new compounds were fully characterised on the basis of IR, ^{1}H NMR, ^{13}C NMR, mass data. Spectral data of selected compounds: (−)-**13**: $[\alpha]_D^{24}$: −19.1 (*c* 1.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.22 (s, 2H), 4.62 (dt, 1H, *J* = 2.7, 9.9 Hz), 4.42 (d, 1H, *J* = 9.9 Hz), 3.57 (d, 1H, *J* = 9.9 Hz), 3.52 (dd, 1H, *J* = 3, 3.9 Hz), 3.26 (d, 1H, *J* = 3.9 Hz), 3.17 (s, 1H), 2.92 (s, 1H), 2.32 (dd, 1H, *J* = 3.3, 7.2), 1.44 (d, 1H, *J* = 9.3 Hz), 1.37 (d, 1H, *J* = 9.3 Hz), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.5, 136.9, 136.5, 69.4, 66.9, 62.7, 59.9, 54.6, 49.1, 46.1, 45.9, 44.9, 25.8 (3C), 18.2, −5.5, −5.6; HRMS (ES) *m/z* calcd for $C_{18}H_{27}O_4SiK[M+K]^+$: 375.1394, found: 375.1400. (+)-**14**: $[\alpha]_D^{24}$ +24 (*c* 1.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.16–6.13 (m, 1H), 5.94–5.91 (m, 1H), 5.80 (dd, 1H, *J* = 3.0, 7.5), 4.32 (d, 1H, *J* = 9.9 Hz), 3.60 (d, 1H, *J* = 9.6 Hz), 3.40 (dd, 1H, *J* = 2.7, 3.9 Hz), 3.26 (d, 1H, *J* = 3.6 Hz), 3.16 (s, 1H), 2.79 (s, 1H), 2.43 (dd, 1H, *J* = 3.3, 7.8 Hz), 2.10 (s, 3H), 1.42 (d, 1H, *J* = 9.3 Hz), 1.34 (d, 1H, *J* = 9.3 Hz), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.3, 169.9, 136.1, 135.9, 69.3, 66.7, 61.7, 57.2, 54.4, 46.9, 46.6, 45.7, 44.9, 25.8 (3C), 21.26, 18.2, −5.5, −5.6; HRMS (ES) *m/z* calcd for $C_{20}H_{30}O_5SiK[M+K]^+$: 417.1500, found: 417.1492. (+)-**5b**: $[\alpha]_D^{25}$ +250 (*c* 1.40, EtOH); ^{1}H NMR (300 MHz, CD_3COCD_3): δ 6.72–6.69 (m, 1H), 4.92 (d, 1H, *J* = 7.5 Hz), 4.66–4.63 (m, 1H), 4.30–4.10 (m, 3H), 3.78–3.76 (m, 1H), 3.40 (d, 1H, *J* = 3.6 Hz); ^{13}C NMR (75 MHz, CD_3COCD_3): δ 194.35, 139.30, 137.07, 63.25, 59.0, 58.79, 54.1; HRMS (ES) *m/z* calcd for $C_7H_8O_4Na[M+Na]^+$: 179.0320, found: 179.0314. (+)-**5a**: $[\alpha]_D^{25}$ +98.0 (*c* 1.0, EtOH); ^{1}H NMR (300 MHz, CD_3COCD_3): δ 6.50 (d, 1H, *J* = 1.8 Hz), 4.91 (d, 1H, *J* = 7.5 Hz), 4.80–4.77 (m, 1H), 4.24–4.06 (m, 3H), 3.80 (d, 1H, *J* = 3.0, 6.6 Hz), 3.34 (d,1H, *J* = 4.2 Hz); ^{13}C NMR (75 MHz, CD_3COCD_3): δ 194.5, 141.4, 135.2, 65.5, 59.1, 55.0, 54.0; HRMS (ES) *m/z* calcd for $C_7H_8O_4Na[M+Na]^+$: 179.0320, found: 179.0310. (−)-**4**: $[\alpha]_D^{24}$: −108 (*c* 1.61, EtOH); ^{1}H NMR (300 MHz,

$CDCl_3$): δ 6.67 (dd, 1H, J = 1.9, 3.8 Hz), 4.56 (d, 1H, J = 17.4 Hz), 4.38 (d, 1H, 17.4 Hz), 3.84–3.81 (m, 2H), 2.25 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.0, 191.3, 148.1, 131.0, 59.2, 54.0 (2C); HRMS (ES) *m/z* calcd for $C_7H_6O_4K[M+K]^+$: 192.9903, found: 102.9900. (−)-**8**: $[\alpha]_D^{24}$: −147.0 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 6.81 (dd, J = 5.0, 3.0 Hz, 1H), 5.99 (d, J = 16.2 Hz, 1H), 5.68 (d, J = 16.2 Hz, 1H), 4.55 (br s, 1H), 4.35 (br s, 1H), 3.84 (t, J = 3.4 Hz, 1H), 3.50 (t, J = 3.2 Hz, 1H), 3.42 (d, J = 4.0 Hz, 1H), 3.35 (dd, J = 5.0, 1.6 Hz, 1H), 3.31 (d, J = 4 Hz, 1H), 2.32 (br d, J = 10.0 Hz, 1H), 2.03 (br d, J = 9.7 Hz, 1H), 1.45 (s, 3H), 1.35 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 196.3, 143.0, 139.9, 138.8, 129.3, 102.7, 79.2, 71.8, 69.0, 66.2, 60.7, 57.4, 57.2, 57.1, 55.6, 55.1, 51.2, 50.0, 32.3, 30.3, 29.5, 26.2; HRMS (ES) *m/z* calcd for $C_{22}H_{28}O_8Na$ $[M+Na]^+$: 443.1682, found: 443.1698.

8. The enantiomeric excess (ee) was determined through ^{1}H NMR analyses based on the integration of the acetate methyl groups after the addition of chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato] europium (III). Procedure for enzymatic kinetic resolution: A mixture of racemic epoxy-alcohol **13** (1 g, 2.97 mmol), vinyl acetate (25 mL) and Amano lipase PS-D immobilized on celite (1 g) was stirred for 28 h at room temperature. The reaction mixture was monitored and after ~50% conversion it was filtered through a pad of celite and the filtrate was concentrated. The crude product was subjected to column chromatography on silica gel and eluted first with 10% ethyl acetate in hexane to furnish 516 mg (46%) of keto-acetate (+)-**14** ($[\alpha]_D$ +24, *c* 1.95 $CHCl_3$, ~99% ee). Further elution with 25% ethyl acetate in hexane gave 450 mg (45%) of (−)-**13** ($[\alpha]_D$ −19.1, *c* 1.15, $CHCl_3$, ~99% ee).
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13. The stereoselectivity in the Diels–Alder dimerisation of **7**, leading to the natural product (+)-**8** is quite remarkable and several explanations for it have been offered[4a,b] and elegantly probed both experimentally and computationally by the group of Porco.[4a]