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- [8] **4** is prepared by combining 'C₄P₂' and [RuCl₂(bpy)₂] (1/2.2, with excess NH₄PF₆) in THF/ethylene glycol (2/1, 30 mL). After refluxing the mixture for 48 h, removing the THF, and adding the residue into saturated aqueous KPF₆ solution (50 mL), the yellow solid is collected by filtration (yield 85%, after column chromatography using basic alumina and acetonitrile/toluene as eluent). Analysis of this complex by CV and SWV shows one metal-based redox peak at +1.06 V. D. Xu, B. Hong, unpublished results.
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The Absolute Configuration and Asymmetric Total Synthesis of the CP Molecules (CP-263,114 and CP-225,917, Phomoidrides B and A)**

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The stunning molecular structures^[1] coupled with the promising biological activities of the CP compounds (pho-

moidrides,^[2] **1a** and **b**; Figure 1) have inspired numerous studies directed at their total synthesis.^[3] In 1999 we reported the first total synthesis of these molecules in their racemic form.^[4] Their absolute configuration, however, remained unknown despite the many attempts to prepare and analyze, through X-ray crystallography, a suitably crystalline derivative. After securing the overall structure and configuration at

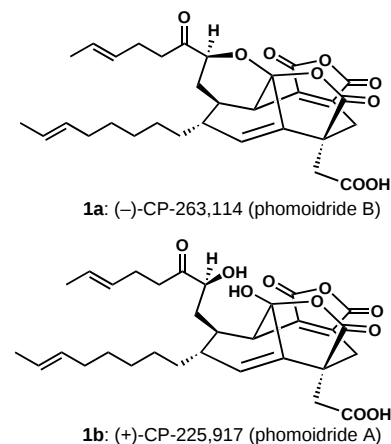
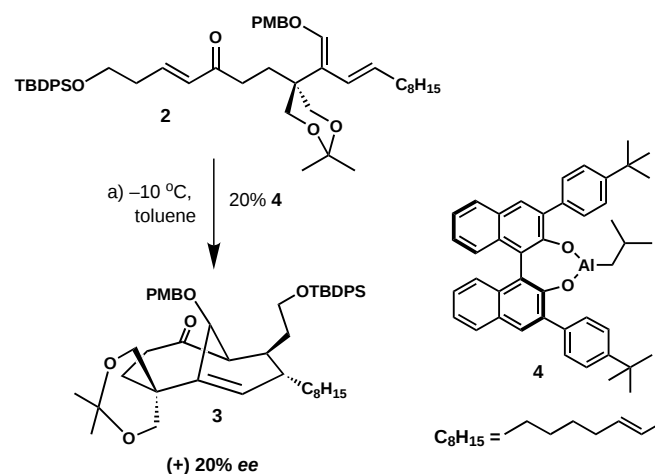


Figure 1. Absolute configuration of the CP compounds **1** and **2**.

C7^[5] of the CP molecules, admirably deduced by Kaneko and co-workers solely from NMR spectroscopic data, we were enticed by the challenge of establishing their absolute configuration. Such knowledge would provide an opportunity to explore modifications of our racemic synthesis and pave the way to optically active CP analogues and mimics, as well as guide future asymmetric total syntheses of these challenging target molecules. Here we report the absolute configuration of the CP molecules as unambiguously determined through chemical synthesis.

Our reported total synthesis of the CP compounds^[4] involved a type-II intramolecular Diels–Alder reaction^[6] as a key step to generate the core skeleton of their molecules. Logic dictated that this step (Scheme 1), which converts the



Scheme 1. Enantioselective Diels–Alder reaction of prochiral triene **2** to form the known CP precursor **3** (20% ee). PMB = *p*-methoxybenzyl; TBDPS = *tert*-butyldiphenylsilyl.

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prochiral triene **2** into the CP core **3**, would be a most appropriate stage for the introduction of asymmetry. Unfortunately, however, several reagent-based enantioselective approaches commencing with the known precursor **2**^[4] failed to deliver appreciable levels of enantiocontrol. A study of this intramolecular process with a number of optically active catalysts led to Lewis acid **4**^[7] as the optimum inducer of asymmetry, albeit delivering the CP core **3** in only 20% *ee*. We attributed the low levels of enantioselectivity in this reaction to the monodentate nature of the dienophile moiety and the flexibility of the aluminum–oxygen coordination bond of the initially formed complex between the substrate and the Lewis acid.

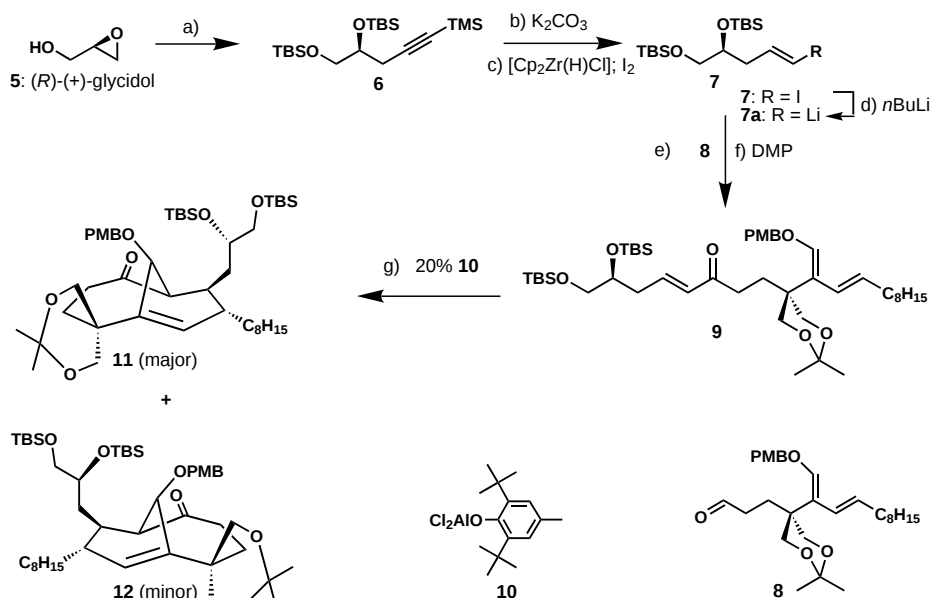
We then turned our attention to a strategy predicated on a substrate-based control of the diastereoselectivity of the intramolecular cycloaddition. Specifically, we envisaged modifying the triene **2** so as to introduce a bulky chiral moiety capable of influencing the facial selectivity of the intramolecular Diels–Alder reaction. Our goal was a smooth reentry into the previously chartered^[4] path to the CP molecules to complete the asymmetric total synthesis without additional steps.

The construction of the designed asymmetric Diels–Alder precursor **9** is outlined in Scheme 2. Thus, the *R* enantiomer of glycidol (**5**) was arbitrarily chosen and converted, in one step (epoxide opening with TMS-acetylide, followed by quenching with TBSOTf) to the *tri*-silyl acetylene **6**. Selective removal of the pendant TMS group, followed by exposure to the Schwartz reagent [Cp₂Zr(H)Cl]^[8] and addition of I₂ led to the vinyl iodide **7** in 54% overall yield from **5**. Metal–halogen exchange (*n*BuLi) facilitated the union of the vinyl iodide **7** with the aldehyde **8**^[4] furnishing, after oxidation with DMP,^[9] enone **9** via the lithio derivative **7a**.

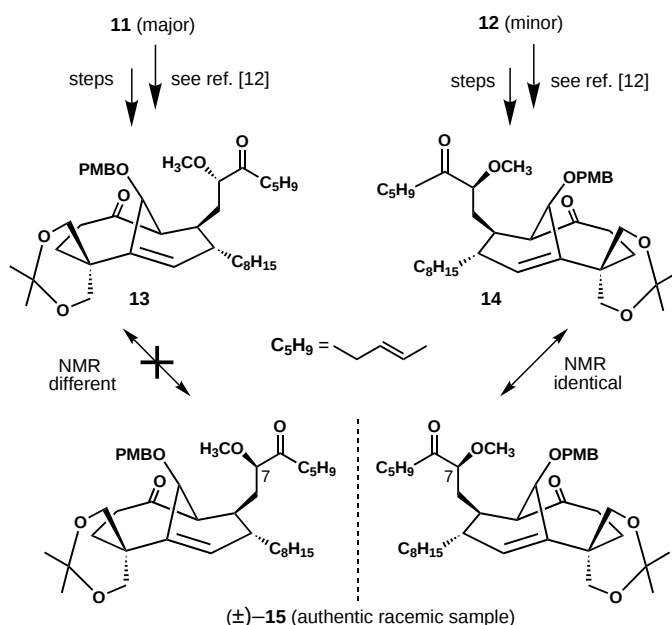
Initial Lewis acid induced cyclizations with **9** led to disappointingly low diastereomeric excesses. For instance, exposure of **9** to 20 mol% Et₂AlCl in CH₂Cl₂ at –10 °C afforded **11** and **12** as a 2:1 mixture (Scheme 2). Extensive experimentation, whose details will have to await the full account of this work, led us to catalyst **10**^[10] (Scheme 2). Thus, in the presence of 20 mol% of **10** at –80 °C in toluene, cycloaddition ensued to produce a 5.7:1 mixture (70% *de*) of **11** and **12** in 88% combined yield.

The relative configuration of these two diastereomers (**11** and **12**) was deduced by NMR correlation of downstream intermediates **13** and **14** with an authentic racemic sample **15**^[11] (Scheme 3).^[12]

In preparation for reentry into the previously developed route for the synthesis of the CP compounds, **11** and **12** were

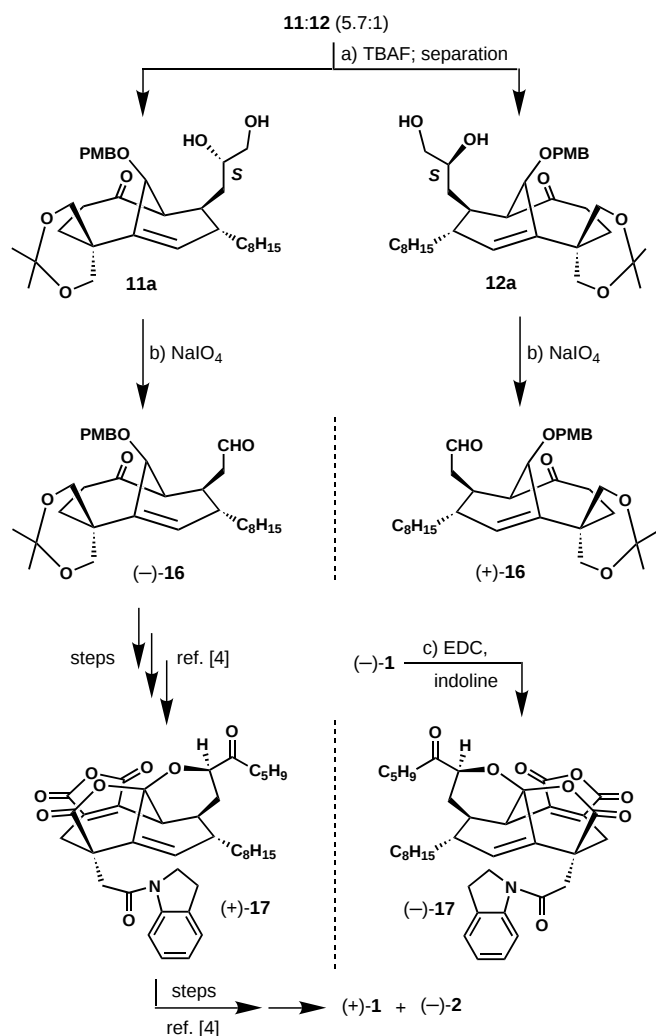


Scheme 2. Diastereoselective Diels–Alder reaction of triene **9** to form the CP precursors **11** and **12**. a) 1. TMSCH₂CH (1.5 equiv), *n*BuLi (1.4 equiv), THF, –78 °C, added to a solution of (*R*)-glycidol (**5**; 1.0 equiv), *n*BuLi (1.1 equiv), THF, –78 → 25 °C, 12 h; 2. TBSOTf (3.0 equiv), 2,6-lutidine (1.0 equiv), 0 → 25 °C; b) K₂CO₃ (2.0 equiv), MeOH, 25 °C, 12 h; c) [Cp₂Zr(H)Cl] (1.2 equiv), benzene, 25 °C, then I₂ (1.0 equiv), CCl₄, 25 °C, 54% overall yield (from **5**); d) **7** (1.5 equiv), *n*BuLi (1.5 equiv), THF, –78 °C, 30 min; e) **7a** added to **8** in THF, –78 °C, 30 min, 90%; f) DMP (1.3 equiv), NaHCO₃ (5.0 equiv), CH₂Cl₂, 25 °C, 10 min, 70%; g) **10** (0.2 equiv), toluene, –80 °C, 1 h, 88% (**11**:**12** = 5.7:1). DMP = Dess–Martin periodinane; TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonyl; TMS = *tert*-butyltrimethylsilyl.



Scheme 3. Determination of the relative configuration of intermediates **11** and **12** by NMR spectroscopic correlation with the authentic racemic sample **15** (relative configuration at C7 as depicted).

converted to the enantiomeric aldehydes (–)-**16** and (+)-**16**, respectively, (Scheme 4). Desilylation with TBAF followed by flash column chromatography (silica gel, hexanes/EtOAc (2:1)) of the diol mixture **11a/12a** allowed almost complete separation of the two diastereomers **11a** (major) and **12a** (minor) (Table 1). Sodium periodate induced oxidative cleav-



Scheme 4. Unambiguous proof of the absolute configuration of the CP compounds (–)-1 and (+)-2 and of the indoline derivative (–)-17 by asymmetric total synthesis of (+)-17, (+)-1, and (–)-2 from intermediate 11. a) TBAF (4.0 equiv), THF, 0–25 °C, 2 h, >95%; c) EDC (3.0 equiv), DMAP (3.0 equiv), indoline (1.5 equiv), CH₂Cl₂, 25 °C, 2.5 h; then 1N HCl, 25 °C, 5 min, 92%. EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; DMAP = 4-(dimethylamino)pyridine; TBAF = tetra-*n*-butylammonium fluoride.

age of diols 11a and 12a resulted in the formation of aldehydes (–)-16 and (+)-16, respectively. Based on the diastereomeric enrichment of 11a (ca. 15:1), the enantiomeric excess of (–)-16 was calculated to be ca. 87%.

The optically enriched aldehyde (–)-16, whose racemic form is a known intermediate in the total synthesis of racemic 1 and 2, was then efficiently converted to the indoline (–)-17 as previously described^[4] (Scheme 4). Due to the ease of purification and handling and the amplified optical rotation of the indoline derivatives, we made comparisons at this stage, and therefore, the naturally derived indoline (–)-17 was obtained by coupling 1^[13] with indoline in the presence of EDC (92%). Synthetic 17, derived from the major Diels–Alder product 11, was found to be identical to natural 17 according to NMR spectroscopy, TLC (three different solvent systems), HPLC, and IR spectroscopy. The optical rotation, however, was opposite in magnitude ($[\alpha]_D^{23} = +56.2$; $c = 0.08$;

Table 1. Selected physical and spectroscopic data of compounds 11a and 12a.

11a: $[\alpha]_D^{23} = -50.6$ ($c = 1.3$, CHCl₃); IR (neat): $\tilde{\nu} = 3388, 2991, 2928, 2857, 1692, 1613, 1514, 1452, 1376, 1303, 1252, 1199, 1160, 1094, 1035, 968, 875, 840$ cm^{–1}; ¹H NMR (CDCl₃, 500 MHz): $\delta = 7.19$ (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 5.44–5.35 (m, 3H), 4.49 (d, $J = 11.0$ Hz, 1H), 4.37 (d, $J = 11.0$ Hz, 1H), 4.30 (dd, $J = 11.4, 1.1$ Hz, 1H), 4.14 (q, $J = 2.2$ Hz, 1H), 4.06 (d, $J = 11.8$ Hz, 1H), 4.02 (d, $J = 11.4$ Hz, 1H), 3.90–3.85 (m, 1H), 3.79 (s, 3H), 3.56 (dd, $J = 11.4, 3.3$ Hz, 1H), 3.51 (dd, $J = 11.4, 1.5$ Hz, 1H), 3.44 (dd, $J = 11.4, 7.3$ Hz, 1H), 3.03 (s, 1H), 2.81 (s, 1H), 2.59 (s, 1H), 2.39 (q, $J = 7.3$ Hz, 1H), 2.33 (t, $J = 13.2$ Hz, 1H), 2.21 (td, $J = 13.2, 1.9$ Hz, 1H), 2.02–1.93 (m, 3H), 1.69–1.54 (m, 6H), 1.43 (s, 3H), 1.39 (s, 3H), 1.48–1.11 (m, 9H); ¹³C NMR (CDCl₃, 125 MHz): $\delta = 216.4, 159.4, 142.3, 131.4, 129.7, 129.5, 129.4, 124.8, 114.0, 97.9, 77.3, 71.6, 69.4, 67.3, 67.1, 64.5, 58.3, 55.3, 41.9, 41.8, 40.6, 38.9, 36.4, 32.7, 32.6, 29.6, 29.3, 28.7, 27.9, 27.0, 20.5, 18.0$; HR-MS (MALDI): calcd for C₃₄H₅₀O₇Na⁺ [$M + Na^+$]: 593.3449, found: 593.3457

12a: $[\alpha]_D^{23} = +43.4$ ($c = 2.0$, CHCl₃); IR (neat): $\tilde{\nu} = 3413, 2991, 2928, 2857, 1685, 1613, 1514, 1452, 1375, 1303, 1251, 1199, 1165, 1092, 1035, 968, 875, 839$ cm^{–1}; ¹H NMR (CDCl₃, 500 MHz): $\delta = 7.20$ (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 5.45–5.38 (m, 2H), 5.37–5.33 (m, 1H), 4.54 (d, $J = 11.0$ Hz, 1H), 4.36 (d, $J = 11.0$ Hz, 1H), 4.31 (dd, $J = 11.4, 1.4$ Hz, 1H), 4.13 (q, $J = 1.9$ Hz, 1H), 4.07 (d, $J = 11.8$ Hz, 1H), 4.03 (d, $J = 11.8$ Hz, 1H), 3.80 (s, 3H), 3.78–3.72 (m, 2H), 3.61–3.56 (m, 1H), 3.51 (dd, $J = 11.4, 1.5$ Hz, 1H), 3.46–3.40 (m, 1H), 3.30 (s, 1H), 2.43 (q, $J = 7.0$ Hz, 1H), 2.38 (t, $J = 13.6$ Hz, 1H), 2.24–2.18 (m, 2H), 2.03–1.94 (m, 3H), 1.71–1.52 (m, 6H), 1.43 (s, 3H), 1.40 (s, 3H), 1.48–1.13 (m, 9H); ¹³C NMR (CDCl₃, 125 MHz): $\delta = 217.3, 159.4, 142.3, 131.4, 129.6, 129.4, 128.7, 124.9, 114.0, 97.9, 77.1, 72.4, 71.5, 67.4, 66.5, 64.9, 58.5, 55.3, 45.2, 41.8, 40.6, 38.9, 37.0, 32.9, 32.6, 29.6, 29.3, 28.4, 27.9, 26.9, 20.6, 18.0$; HR-MS (MALDI): calcd for C₃₄H₅₀O₇Na⁺ [$M + Na^+$]: 593.3449, found: 593.3471

CH₂Cl₂) to that of the naturally derived 17 ($[\alpha]_D^{23} = -80.0$; $c = 0.1$; CH₂Cl₂). Circular dichroism (CD) spectroscopy verified the identity of synthetic 17 as the enantiomer of natural 17 by virtue of the pronounced antipodal Cotton effect observed (Figure 2).^[14] Synthetic 17 was also processed to give *ent*-1 and

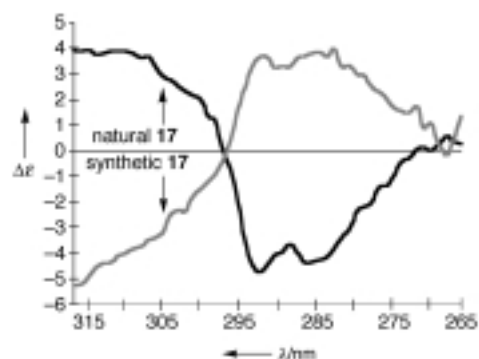


Figure 2. CD spectra (CH₂Cl₂, 25 °C, ca. 0.5 mm) of synthetic 17 (grey line) and natural 17 (black line).

ent-2. Therefore, the absolute configuration of the CP molecules can be confidently assigned as depicted in Figure 1. The asymmetric synthesis of *ent*-1 and *ent*-2 can obviously be employed to procure the natural enantiomers of the CP molecules simply by utilizing (*S*)-glycidol.

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- [10] Catalyst **10** was prepared by adding EtAlCl₂ (1 M in hexanes) to a solution of the corresponding phenol (1.1 equiv) in toluene at 0 °C and stirring the mixture at ambient temperature for 30 min.
- [11] Racemic **15** was prepared from the corresponding α -hydroxy dithiane^[4] by stirring with NaH (1.1 equiv) and MeI (1.1 equiv) at 0 °C (80% yield) followed by dithiane deprotection with PhI(O-COCF₃)₂ in aqueous methanol (71%).
- [12] Compounds **13** and **14** were prepared from **11** and **12** in 29 and 22% overall yield, respectively, by the following seven-step sequence: 1) TBAF (3.0 equiv), THF, 0 → 25 °C; 2) TBSCl (1 equiv), imidazole (1 equiv), CH₂Cl₂, 0 → 25 °C; 3) NaH (1.1 equiv), MeI (1.1 equiv), THF, 0 °C; 4) TBAF (1.5 equiv), THF, 25 °C; 5) DMP (1.2 equiv), CH₂Cl₂, 25 °C; 6) C₆H₅MgBr (1.1 equiv), THF, 0 °C; 7) DMP (1.2 equiv), CH₂Cl₂, 25 °C.
- [13] A sample of natural **1** was kindly provided to us by Dr. T. Kaneko, Pfizer (Groton, CT).
- [14] A similar effect was observed for (–)-**16** and (+)-**16**.