Total Synthesis of the CP Molecules CP-263,114 and CP-225,917— Part 1: Synthesis of Key Intermediates and Intelligence Gathering**

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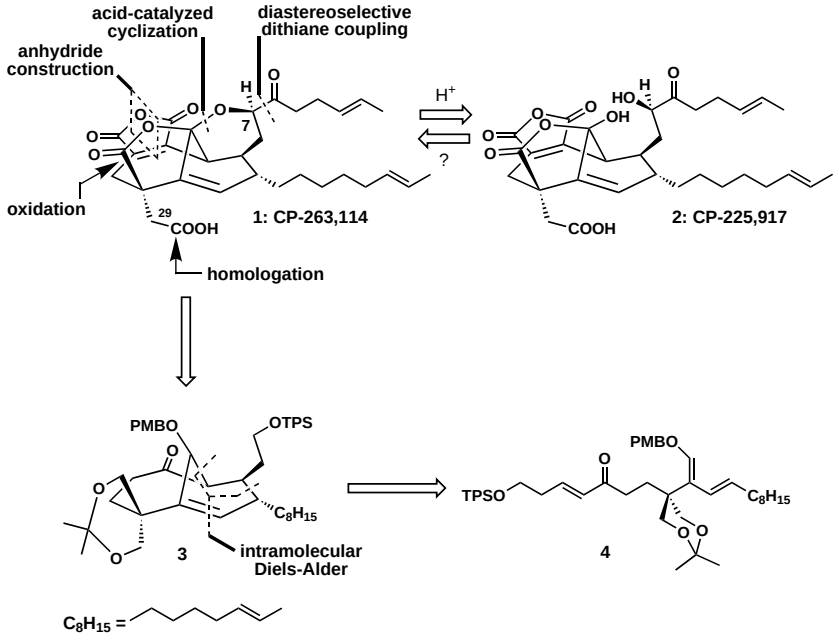
The CP molecules, CP-263,114 (**1**, Scheme 1) and CP-225,917 (**2**), exemplify architectures of unprecedented molecular connectivity and complexity and possess intriguing biological activities. Isolated from an unidentified fungal species by a group at Pfizer (Croton, USA),[1] these substances (absolute configuration unknown) exhibit impressive cholesterol-lowering properties through inhibition of squalene synthase.[1, 2] Furthermore, they inhibit farnesyl transferase, an enzyme implicated in cancer, and as such they stand as leads to potential drug candidates for cancer chemotherapy.[1, 3] The daunting molecular frameworks coupled with the array of sensitive functionalities present within these structures amount to a formidable synthetic challenge to which synthetic chemists have already begun to respond.[4] In this and the following communication[5] we recount our studies that led to the successful completion of the total synthesis of the CP molecules (**1** and **2**, racemic), in which a number of novel strategies and cascade reactions were discovered and developed. We begin here with the description of the overall strategy, the construction of a key intermediate (**27**, see Scheme 2), and of two unsuccessful, and yet highly useful in terms of intelligence gathering, attempts to reach the CP molecules **1** and **2**.



Scheme 1. Structures and retrosynthetic analysis of the CP molecules **1** and **2**. TPS = *tert*-butyldiphenylsilyl, PMB = *p*-methoxybenzyl.

The key strategic bond disconnections and retrosynthetic blueprint shown in Scheme 1 serve as a conceptual overview of our synthetic rationale. Because of the known conversion of **2** into **1** under anhydrous acid catalysis[1] and the inability of **1** to generate **2** under aqueous acidic conditions[1] it seemed more prudent to target **2**. However, the hope of transforming **1** to **2** under basic conditions (for a mechanistic rationale of this expectation see Scheme 2 in the following communication)[5] led us to accept that reaching either of the CP molecules was an opportunity to access the other as well. We soon discovered that seemingly logical routes to **1** or **2** from the intermediate compound **3** (Scheme 1) were plagued with countless unpredictable failures, which presumably arose from the unique peculiarities of the CP skeleton and its sensitive functionalities. Herein we report the lessons learned from two such expeditions. Proper implementation of novel chemistry harvested as a result of these synthetic blockades and explorations finally culminated in a fine-tuned synthetic stratagem capable of effectively addressing these issues.

Diverse model studies aimed at deconvoluting this synthetic maze pointed towards the use of key intermediate **27** as a beachhead from which all further synthetic tactics would diverge (Scheme 2). Notable among the envisioned operations of the forward sequence en route to compound **27** were: 1) the intramolecular Diels–Alder reaction of the prochiral precursor **4** casting the basic elements of the bicyclic core of the CP molecules,[6] 2) stereoselective fastening of the "upper" side chain by using substrate-directed dithiane chemistry,[7] 3) the installment of the anhydride moiety onto the periphery of the bicyclic CP skeleton by employing an unprecedented seven-step cascade reaction sequence.[8]

Scheme 3 summarizes the synthesis of the bicyclic core **17**. Thus, dimethyl malonate (**5**) was converted into aldehyde **6** by a five-step sequence involving: 1) anion formation with NaH and quenching with $I(CH_2)_3OTBS$ (90%), 2) a second alky-

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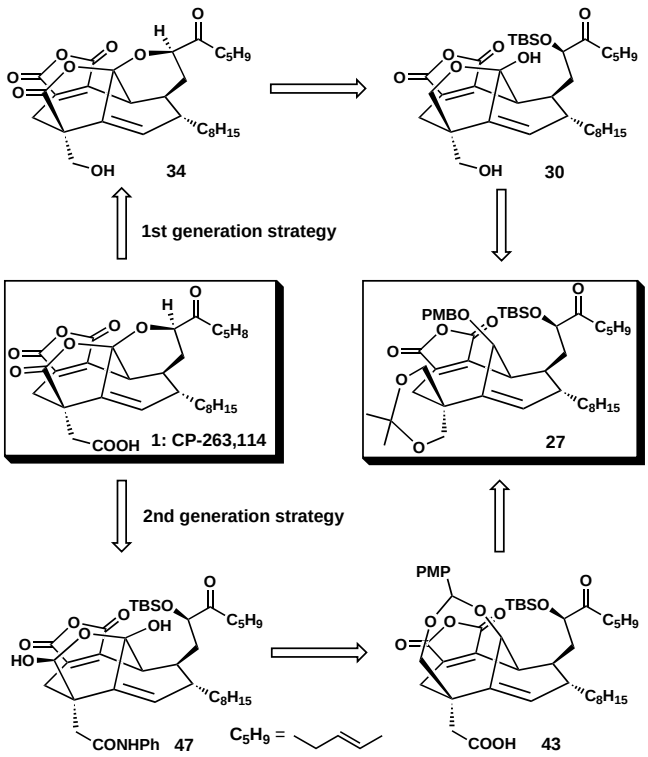
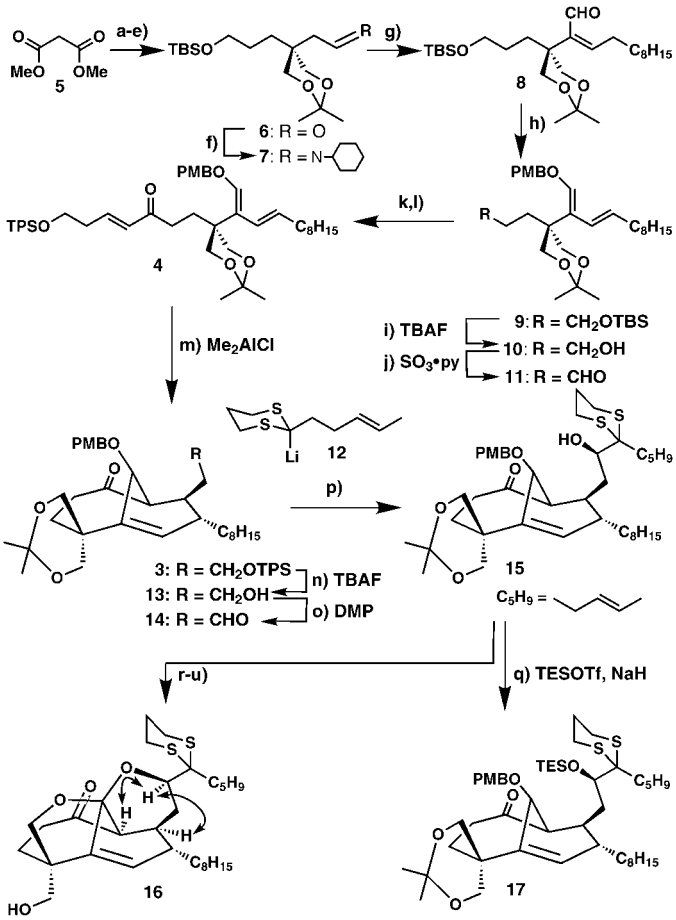


Scheme 2. Strategies for the first and second generation divergent from the key intermediate **27**. TBS = *tert*-butyldimethylsilyl, PMP = *p*-methoxyphenyl.



Scheme 3. Construction of the bicyclic CP core. a) NaH (1.3 equiv), $I(CH_2)_3OTBS$ (1.3 equiv), THF, 80 °C, 12 h, 90 %; b) allyl bromide (1.3 equiv), NaH (1.5 equiv), DME, 25 °C, 0.5 h, 95 %; c) $LiBH_4$ (2.0 equiv), THF, 0 → 25 °C, 12 h, 80 %; d) $Me_2C(OMe)_2$ (1.5 equiv), CSA (0.05 equiv), CH_2Cl_2, 25 °C, 0.5 h, 82 %; e) O_3, CH_2Cl_2, −20 °C, 1 h; then Ph_3P (1.0 equiv), −78 → 25 °C, 12 h, 95 %; f) cyclohexylamine (1.2 equiv), benzene, 80 °C, 1 h; g) LDA (1.1 equiv), Et_2O, −20 °C, 1 h; then $C_9H_{17}CHO$ (1.5 equiv) in Et_2O, −78 → −30 °C, 12 h; then oxalic acid (4.0 equiv), H_2O, 0 °C, 1 h, 60 % overall from **6**; h) KH (5.0 equiv), PMBCl (1.5 equiv), DME:HMPA (5:2), 0 °C, 4 h, 78 % (*E*,*E*,*Z*:*E*,*E*,*E* ca. 10:1); i) TBAF (2.0 equiv), THF, 0 °C, 3 h, 82 %; j) $SO_3 \cdot py$ (3.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2:DMSO (4:1), 25 °C, 0.5 h, 78 %; k) (*E*)-$TPSO(CH_2)_2CH{=}CHI$ (1.5 equiv), *n*BuLi (1.5 equiv), THF, −78 °C, 0.5 h; then **11** in THF, −78 °C, 0.5 h, 92 %; l) $SO_3 \cdot py$ (4.0 equiv), Et_3N (5 equiv), DMSO:CH_2Cl_2 (1:4), 25 °C, 3 h, 76 %; m) Me_2AlCl (0.15 equiv), CH_2Cl_2, −10 °C, 0.5 h, 90 %; n) TBAF (2.0 equiv), THF, 25 °C, 93 %; o) DMP, $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 92 %; p) **12** (1.3 equiv), THF, −78 °C, 8 min, 90 % (75 % conversion); q) NaH (6.0 equiv), TESOTf (2.0 equiv), THF, 0 → 25 °C, 2 h, 86 %; r) DDQ (3.0 equiv), CH_2Cl_2:H_2O (18:1), 25 °C, 0.5 h, 85 % (61 % conversion); s) PDC (5.0 equiv), CH_2Cl_2, 25 °C, 0.5 h, 88 %; t) 80 % aq AcOH, 25 °C, 5 h, 91 %; u) CH_3SO_3H (0.1 equiv), CH_2Cl_2, 25 °C, 0.5 h, 68 %. TES = triethylsilyl, DME = 1,2-dimethoxyethane, CSA = camphorsulfonic acid, LDA = lithium diisopropylamide, PMBCl = *p*-methoxybenzyl chloride; TBAF = tetra-*n*-butylammonium fluoride; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; PDC = pyridinium dichromate; OTf = trifluoromethanesulfonate; DMP = Dess–Martin periodinane.

lation with NaH and allyl bromide (95 %), 3) reduction of both ester groups with $LiBH_4$ (80 %), 4) acetonide formation (82 %), and 5) ozonolysis, followed by treatment with Ph_3P (95 %). Imine **7** was then formed by combining **6** and cyclohexylamine with the comcomittant azeotropic removal of water. Compound **7** was treated with LDA at −20 °C to attain its lithioderivative which was quenched with $C_8H_{15}CH_2CHO$[9] to furnish, after acidic workup, α,β-unsaturated aldehyde **8** in 60 % overall yield from **6**. Exposure of **8** to KH followed by addition of PMBCl led to **9** as the major product in an approximate 10:1 ratio with its *E*,*E* isomer and 78 % combined yield. Compound **9** was then desilylated by exposure to TBAF, and the resulting alcohol (**10**, 82 % yield) was oxidized with $SO_3 \cdot py$ in CH_2Cl_2:DMSO to give aldehyde **11** (78 % yield). Conversion of this aldehyde (**11**) into the targeted Diels–Alder precursor, enone **4**, required addition (92 % yield) of the lithioderivative derived from (*E*)-$TPSO(CH_2)_2CH{=}CHI$ and *n*BuLi, followed by $SO_3 \cdot py$ oxidation (76 % yield) of the resulting alcohol.

The intramolecular Diels–Alder reaction of **4** was facilitated by catalytic amounts of Me_2AlCl and ensued at −10 °C to afford the expected cycloadduct **3** in 90 % yield (selected spectroscopic data are given in Table 1). The high overall efficiency and facile scale-up of the preceding thirteen steps leading to **3** permitted multi-gram quantities of this key intermediate to be procured for extensive explorations (see below). The next task involved elongation of the "upper" side chain of the molecule, preferably with stereocontrol of the newly installed hydroxyl group, a problem whose solution was not obvious at first glance. To this end, aldehyde **14** was generated in two steps from **3** by a sequence entailing desilylation (TBAF, →**13**, 93 % yield) and oxidation of the primary alcohol (Dess–Martin periodinane,[10] 92 % yield). Treatment of **14** with lithiodithiane **12** (prepared from the corresponding dithiane and *n*BuLi) furnished the hydroxy

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Table 1. Selected physical properties of compounds **3**, **27**, **34**, and **48**.

3: $R_f = 0.61$ (silica gel, ethyl acetate:hexane 1:2); IR (film) $\tilde{\nu}_{max} = 2973$, 2931, 2843, 1704, 1614, 1515, 1455, 1418, 1372, 1303, 1250, 1200, 1111, 1035, 967, 823, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.68-7.64$ (m, 4H), 7.43–7.33 (m, 6H), 7.14 (d, $J = 8.5$ Hz, 1H), 6.82 (d, $J = 8.5$ Hz, 1H), 5.50–5.38 (m, 2H), 5.37–5.32 (m, 1H), 4.45 (d, $J = 11.0$ Hz, 1H), 4.27 (br d, $J = 11.5$ Hz, 1H), 4.17 (d, $J = 11.0$ Hz, 1H), 4.10–4.07 (m, 1H), 4.02 (d, $J = 12.0$ Hz, 1H), 4.00 (d, $J = 12.0$ Hz, 1H), 3.79–3.74 (m, 1H), 3.78 (s, 3H), 3.74–3.65 (m, 1H), 3.49 (br d, $J = 11.5$ Hz, 1H), 2.79 (br s, 1H), 2.31 (dd, $J = 13.0$, 11.5 Hz, 1H), 2.26–2.13 (m, 2H), 2.10–1.90 (m, 3H), 1.85–1.77 (m, 1H), 1.70–1.60 (m, 7H), 1.58–1.48 (m, 1H), 1.48–1.10 (m, 14H), 1.02 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 213.5$, 159.2, 142.1, 135.6 (2C), 135.5 (2C), 133.9, 133.7, 131.4, 129.8, 129.7 (4C), 129.3, 127.6 (4C), 124.8, 113.8 (2C), 97.6, 77.5, 71.0, 67.2, 65.1, 61.4, 58.7, 55.2, 41.5, 41.1, 39.9, 38.2, 36.5, 32.7, 32.6, 29.6, 29.3, 29.2, 27.6, 26.9, 26.8 (3C), 20.4, 19.1, 17.9; HRMS (FAB): calcd for $C_{49}H_{66}O_6SiNa^+$ (M+Na^+): 801.4526, found: 801.4539

27: $R_f = 0.49$ (silica gel, ethyl acetate:hexane 1:4); m.p. 77–78 °C (cyclohexane); IR (film) $\tilde{\nu}_{max} = 2991$, 2920, 2861, 1761, 1714, 1655, 1508, 1461, 1379, 1250, 1191, 1091, 1038, 968, 915, 838, 591 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.23$ (d, $J = 8.7$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 5.45–5.38 (m, 4H), 5.30 (br s, 1H), 4.65 (dd, $J = 9.5$, 2.5 Hz, 1H), 4.58 (d, $J = 11.0$ Hz, 1H), 4.39 (d, $J = 11.0$ Hz, 1H), 4.27 (br d, $J = 11.3$ Hz, 1H), 4.23 (br s, 1H), 4.00 (d, $J = 11.3$ Hz, 1H), 3.93 (d, $J = 11.0$ Hz, 1H), 3.80 (s, 3H), 3.29 (br d, $J = 11.0$ Hz, 1H), 3.26 (d, $J = 16.5$ Hz, 1H), 3.12 (br s, 1H), 2.90 (dd, $J = 16.5$, 3.1 Hz, 1H), 2.83 (dt, $J = 18.0$, 7.5 Hz, 1H), 2.60 (dt, $J = 18.0$, 7.0 Hz, 1H), 2.25 (m, 2H), 2.01–1.92 (m, 3H), 1.68–1.48 (m, 11H), 1.44 (s, 3H), 1.41 (s, 3H), 1.38–1.15 (m, 6H), 0.93 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 210.3$, 166.2, 165.9, 159.5, 145.6, 142.3, 142.1, 131.4, 129.9, 129.3 (2C), 129.1, 128.9, 125.5, 124.7, 114.1 (2C), 98.0, 77.1, 74.6, 71.3, 68.1, 66.0, 55.3, 46.0, 42.4, 42.3, 41.5, 38.7, 38.5, 32.9, 32.5, 29.6, 29.4, 29.1, 28.2, 26.3, 26.2, 25.8 (3C), 20.9, 17.9 (3C), −4.2, −4.5; HRMS (FAB): calcd for $C_{47}H_{68}O_9SiCs$ (M+Cs^+): 937.3687, found: 937.3669

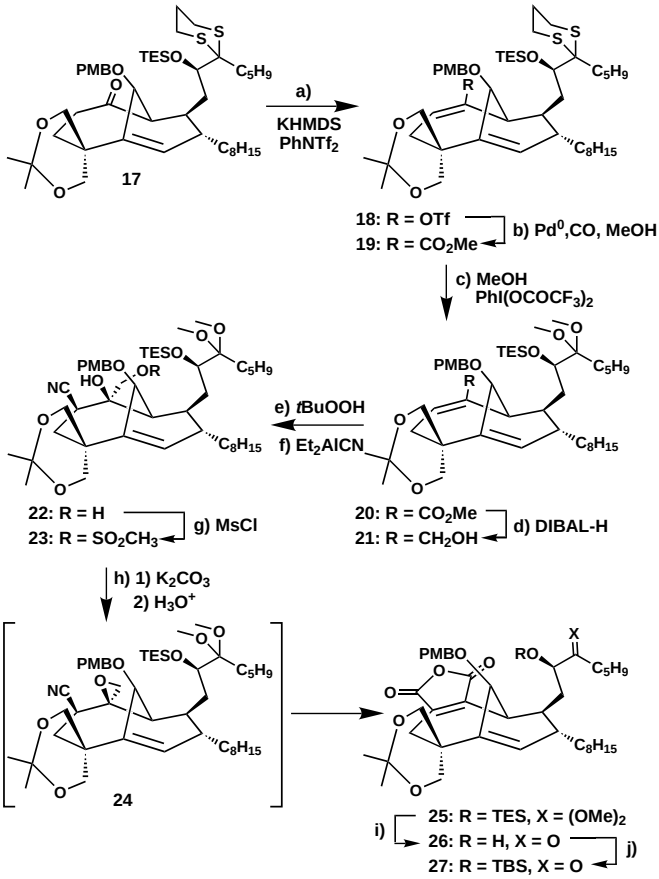
34: $R_f = 0.48$ (silica gel, ethyl acetate:hexane 1:2); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.79$ (d, $J = 1.6$ Hz, 1H), 5.50–5.30 (m, 4H), 4.53 (t, $J = 8.0$ Hz, 1H), 4.08 (s, 2H), 3.51 (s, 1H), 3.11 (br d, $J = 19.5$ Hz, 1H), 2.86 (dd, $J = 19.5$, 2.0 Hz, 1H), 2.71–2.60 (m, 2H), 2.56–2.51 (m, 1H), 2.38–2.21 (m, 5H), 2.06 (dd, $J = 14.0$, 10.0 Hz, 1H), 1.97–1.88 (m, 2H), 1.65–1.59 (m, 6H), 1.35–1.15 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 207.2$, 175.3, 164.4, 164.2, 141.1, 140.9, 138.0, 132.2, 131.0, 129.1, 126.3, 125.0, 105.3, 75.3, 62.5, 51.6, 43.6, 43.2, 38.5, 38.4, 36.0, 35.6, 35.2, 32.3, 29.7, 29.3, 28.9, 26.8, 25.9, 17.9; HRMS (FAB): calcd for $C_{30}H_{36}O_8Cs$ (M+Cs^+): 657.1465, found: 657.1448

48: $R_f = 0.47$ (silica gel, ethyl acetate:hexane 1:1); IR (film) $\tilde{\nu}_{max} = 3387$, 2975, 2915, 2847, 1768, 1713, 1661, 1607, 1484, 1437, 1161, 1092, 1072, 967, 932, 838 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.40$ (dd, $J = 7.6$, 1.3 Hz, 1H), 7.30 (td, $J = 6.8$, 1.3 Hz, 1H), 7.19 (t, $J = 7.6$ Hz, 1H), 7.01 (d, $J = 6.8$ Hz, 1H), 5.48–5.32 (m, 4H), 4.55 (dd, $J = 10.5$, 3.1 Hz, 1H), 4.39 (d, $J = 12.0$ Hz, 1H), 4.15 (br d, $J = 9.2$ Hz, 1H), 3.76 (d, $J = 9.2$ Hz, 1H), 3.18 (d, $J = 19.8$ Hz, 1H), 2.72 (s, 2H), 2.69–2.51 (m, 2H), 2.40–2.05 (m, 3H), 2.00–1.90 (m, 3H), 1.80–1.50 (m, 9H), 1.45–1.20 (m, 5H), 0.88 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 212.5$, 176.9, 164.9, 164.6, 150.0, 145.5, 136.2, 132.3, 131.3, 129.8, 128.6, 126.8, 125.5, 124.8, 124.1, 119.2, 108.6, 77.8, 76.0, 73.7, 48.0, 44.3, 41.7, 40.1, 37.6, 37.4, 35.7, 32.5, 30.4, 29.6, 29.3, 27.5, 26.1, 25.7 (3C), 23.0, 17.9 (3C), 14.2, −4.5, −4.9; HRMS (FAB): calcd for $C_{43}H_{57}NO_9SiCs$ (M+Cs^+): 892.2857, found: 892.2874

compound **15** (90% based on about 75% conversion) contaminated with small amounts of its C-7 diastereoisomer (approximate ratio 11:1).

The stereochemistry of the major component (namely **15**) of this mixture was deduced from NOE studies on the cyclized product **16** obtained from **15** through the sequence indicated in Scheme 3, and later confirmed by X-ray crystallographic analysis of a crystalline descendant (see Figure 1). This fortuitous selectivity may be a consequence of significant shielding of one face of the aldehyde by the neighboring CP skeleton. Not surprisingly, the sterically hindered ketone group in **14** did not interfere with the side-chain addition. Finally, silylation of **15** with TESOTf and NaH furnished the desired compound **17** in 86% yield.

Installation of the maleic anhydride moiety onto the bicyclic core **17** proceeded in accordance with our recently reported protocol.[8] Thus, enolate formation with KHMDS followed by quenching with $PhNTf_2$ converted **17** into enol triflate **18** (Scheme 4) in 95% yield. The carboxymethylation



Scheme 4. Installment of the maleic anhydride moiety: synthesis of key intermediate **27**. a) $PhNTf_2$ (1.5 equiv), KHMDS (2.0 equiv), THF, 0 °C, 10 min, 95%; b) $Pd(OAc)_2$ (0.06 equiv), Ph_3P (0.12 equiv), MeOH (40 equiv), Et_3N (2.0 equiv), DMF, CO (1 atm), 25 °C, 10 min, then **18**, 50 °C, 40 min, 78%; c) $PhI(OCOCF_3)_2$ (2.0 equiv), $CaCO_3$ (20 equiv), MeOH, 25 °C, 6 min, 81%; d) DIBAL-H (3.0 equiv), toluene, −78 °C, 95%; e) $[V(O)(acac)_2]$ (0.2 equiv), tBuOOH (1.4 equiv), benzene, 25 °C, 0.5 h, 83%, $\beta:\alpha$ ca. 10:1; f) Et_2AlCN, (5.0 equiv), toluene, 0 °C, 15 min; then 25 °C, 1 h, 73%; g) MsCl (3.0 equiv), Et_3N (10 equiv), THF, 0 °C, 5 min; h) 1) K_2CO_3 (20 equiv), MeOH, 1 h, 2) Et_2O, 10% aq oxalic acid, air, 0.5 h, 56% overall from **22**; i) 1) 90% aq AcOH, 25 °C, 1.5 h; 2) $Me_2C(OMe)_2$ (1.5 equiv), CSA (0.05 equiv), CH_2Cl_2, 25 °C, 30 min., 77% overall; j) TBSOTf (2.0 equiv), 2,6-lutidine (10 equiv), CH_2Cl_2, −20 → 0 °C, 1 h, 90%; Ms = methanesulfonyl, Tf = trifluoromethanesulfonyl; KHMDS = potassium bis(trimethylisily)amide; DIBAL-H = diisobutyl aluminum hydride.

of **18** with CO and methanol was catalyzed by $Pd(OAc)_2$ in the presence of Et_3N, and led to the α,β-unsaturated methyl ester **19** in 78% yield. Subsequent experiences, whose description will have to await the full account of this work, dictated the exchange of the dithiane group for a dimethoxy ketal at this

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stage. Thus, exposure of **19** to $PhI(OCOCF_3)_2$ and $CaCO_3$ in methanol according to the procedure of Stork and Zhao[11] led to compound **20** (81%), which was reduced with DIBAL-H to afford allylic alcohol **21** (95%). Vanadium-assisted epoxidation of **21**[12] led to the corresponding β-epoxide (83% yield, β:α approximately 10:1), whose opening with Et_2AlCN (Nagata reagent)[13] in toluene led smoothly to cyano diol **22** (73%). The anomalous stereochemical outcome of this opening (proven by NOE studies) may be attributed to the special environment of the epoxide moiety within the CP skeleton.[4l] Exposure of **22** to $MsCl/Et_3N$, followed by treatment of the resulting mesylate **23** with K_2CO_3 in methanol, and oxalic acid workup, gave maleic anhydride **25** via cyano epoxide **24** (56% overall yield from **22**). The synthesis of the desired synthetic intermediate **27** was brought about by the sequential use of aqueous acetic acid (to remove the TES group) and dimethoxypropane/camphorsulfonic acid (to protect the resulting 1,3-diol) to furnish the hydroxy ketone **26** (77% overall yield) whose silylation with TBSOTf proceeded smoothly in the presence of 2,6-lutidine (**27**, 90% yield). The X-ray crystallographic analysis of crystalline **27** (see ORTEP drawing in Figure 1) confirmed its structure and those of its predecessors.

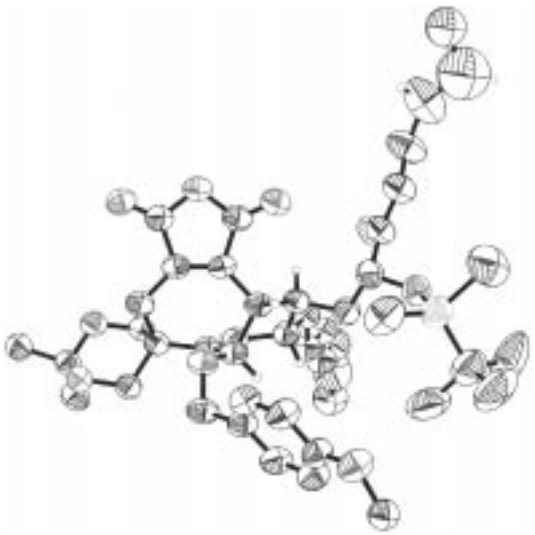
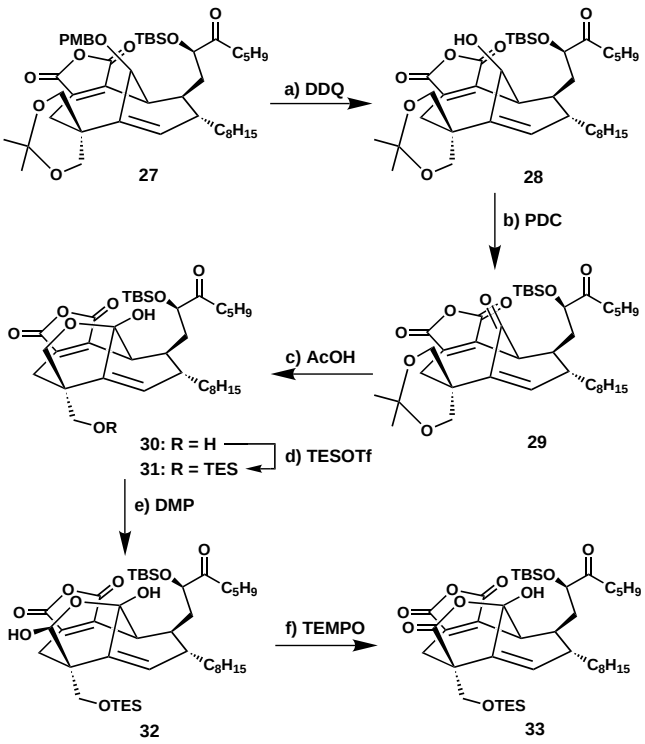


Figure 1. Structure of **27** in the crystal.

One of our first strategies towards the CP molecules was set forth on the notion that intermediate **34** (see Scheme 7) might be amenable to a late-stage one-carbon homologation to provide **1** directly. The synthesis of, and chemical explorations with intermediate **34** follow (Schemes 5 and 7).

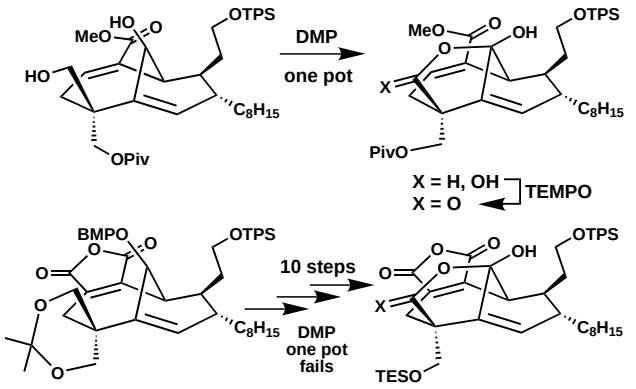
The construction of the γ-hydroxylactone functionality within the CP framework required a delicate balance of chemical manipulations and was finally accomplished through the sequence depicted in Scheme 5. The PMB group of **27** was cleaved by the action of DDQ (64% based on about 75% conversion) to afford hydroxy compound **28**, which was smoothly oxidized to enone **29** with PDC in 89% yield. Acetic acid induced removal of the acetonide group then liberated the hydroxymethyl groups, one of which immediately cyclized with the bridgehead carbonyl functionality by virtue of its proximity to it, leading to hemiketal **30** in 70% yield. The



Scheme 5. Construction of the γ-hydroxylactone functionality: synthesis of key intermediate **33**. Reagents and conditions: a) DDQ (2.0 equiv), CH_2Cl_2:H_2O (18:1), 25 °C, 1 h, 64% based on approximately 75% conversion; b) PDC (3.0 equiv), CH_2Cl_2, 25 °C, 2 h, 89%; c) 80% aq AcOH, 25 °C, 6 h, 82% based on 85% conversion; d) TESOTf (1.5 equiv), 2,6-lutidine (10 equiv), 0 °C, 2 h, 92%; e) DMP (5.0 equiv), benzene, 80 °C, 25 min, 63%; f) $PhI(OAc)_2$ (30 equiv), TEMPO (30 equiv), CH_3CN, 25 °C, 1.5 h, 74%. TEMPO = 2,2,6,6-tetramethyl-1-piperidinoxyl.

remaining hydroxyl group on the concave face of the molecule was then temporarily masked as a TES ether, furnishing **31** (92% yield).

At this juncture it is instructive to reflect on our previous encounters with the challenge of constructing the γ-hydroxylactone moiety of the CP molecules in the presence of the fused maleic anhydride system (Scheme 6). We reported recently our difficulties in dealing with this problem.[14] Utilizing a rather circuitous ten-step sequence based on careful protecting group manipulations we were indeed able to produce the γ-hydroxylactone moiety from a suitable 1,4-



Scheme 6. Summary of observations regarding the γ-hydroxylactone formation.[14]

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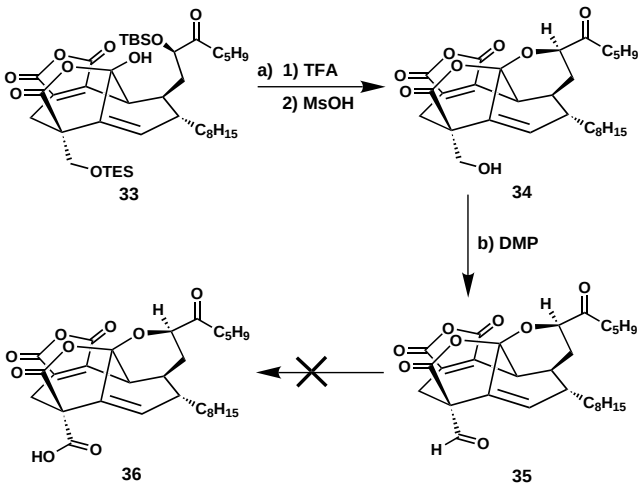
diol system. Only in certain model systems that did not contain the maleic anhydride functionality were we able to effect a four-step domino DMP oxidation reaction to create γ-hydroxylactols that could then be readily converted into the coveted γ-hydroxylactones. Thus, a distinguishing feature of the present strategy resides in the design and execution of a variant of this tandem DMP oxidation protocol, which triumphs even in the presence of the maleic anhydride moiety. Considering that the key step of this cascade is the ring-chain tautomerization[15] of a requisite hemiketal, logic dictated that temperature elevation in a suitable solvent may be sufficient to coax the hemiketal into baring the latent hydroxyketone long enough for the required additional oxidation step to take place. Subsequent hydration and ring closure of the resulting aldehyde functionality would complete the sequence and furnish the corresponding γ-hydroxylactol. In the event, we were pleased to observe formation of γ-hydroxylactol **32** (Scheme 5) in 63% yield and as a single stereoisomer upon oxidation of **31** with DMP in refluxing benzene. In accordance with our model studies,[14] TEMPO-mediated oxidation[16] of lactol **32** to the desired γ-hydroxylactone **33** proceeded smoothly and in 74% yield.

Two tasks remained for the success of this strategy, namely internal ketalization and a one-carbon homologation of the carboxylic acid side chain. Thus, treatment of **33** first with aqueous trfluoroacetic acid effected global deprotection, furnishing the corresponding triol, which upon exposure to CH_3SO_3H[1] in anhydrous $CHCl_3$ led to the desired hydroxy ketal **34** (50% overall yield from **33**; Scheme 7). Arrival at **34** brought us within one carbon atom and two oxidation states



Scheme 7. Synthesis of the labile aldehyde **35**: a dead end. a) 1) CH_2Cl_2:TFA:H_2O (40:4:1), 25 °C, 2 h; 2) CH_3SO_3H (1.0 equiv), $CHCl_3$, 25 °C, 24 h, 50% overall; b) DMP (5.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 2 h, 95%. TFA = trifluoroacetic acid.

away from the natural product CP-263,114 (**1**). Oxidation of **34** with DMP proceeded smoothly to provide aldehyde **35** (95%), which was now poised for further oxidation followed by an Arndt–Eistert homologation.[17] Unfortunately, however, our unrelenting efforts to effect this oxidation were thwarted by the fragile nature of aldehyde **35** coupled with the apparent extreme instability of the presumed carboxylic acid **36**. The unexpected instability of acid **36** may be a result of decarboxylative decomposition pathways (see Figure 2 for a mechanistic rationale) and has been confirmed to be a general phenomenon in such systems by relevant model studies.[18] Several other alternative maneuvers to utilize aldehyde **35** as a starting point for homologation also failed.

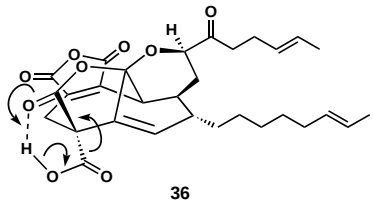


Figure 2. Possible explanation for the unstable nature of the elusive carboxylic acid **36** (intramolecularly assisted decarboxylation, decomposition).

After numerous attempts to alter this strategy so as to avoid these unstable species failed we were able to devise and pursue a novel second generation approach, results from which paved the way for the eventual total synthesis of the CP molecules. The reigning theme of this strategy (see Scheme 2) was the enlistment of an amide functionality to disguise and deactivate the electrophilic center of a homologated carboxylic acid. In doing so we could elude the problems associated with a late-stage homologation (see above) and, subsequently, be faced with what we perceived to be the comparably facile task of amide hydrolysis.

Our second generation approach to the CP molecules (Scheme 8) was launched from the key synthon **27** by removal of the isopropylidene group (aqueous acetic acid, 85%) to give diol **37** followed by DDQ-mediated[19] formation of the seven-membered benzylidine acetal **38** in 57% yield. The hydroxy compound **38** was then oxidized to the corresponding carboxylic acid **40** through the intermediacy of aldehyde **39** by the sequential action of DMP (90%) and $NaClO_2$ (80%). In order to execute the venerable Arndt–Eistert homologation protocol we required a mild method for the activation of hindered carboxylic acids such as **40**, since acid chloride formation with these systems was extremely inefficient or did not work at all. We rationalized that an acyl mesylate might provide a unique solution to the dilemma of activating sterically crowded acids for reasons illustrated in Scheme 9.

In the event carboxylic acid **40** was smoothly transformed into diazoketone **42** via the acyl mesylate **41** upon treatment with MsCl/Et_3N at 0 °C, followed by addition of excess CH_2N_2 as a dried ethereal solution.[20] To conclude the homologation a Wolff rearrangement took place at 120 °C in 1 minute in DMF:H_2O (2:1) in the presence of excess Ag_2O to furnish the homologated acid **43** in 38% overall yield from **40**. Amide bond formation between carboxylic acid **43** and aniline in the presence of EDC/4-DMAP proceeded smoothly to produce anilide **44** in 85% yield. Acid-induced hydrolysis of the bezylidine acetal **44** led to diol **45** (89%), which, as predicted, was found to be resistant to cyclization.[21]

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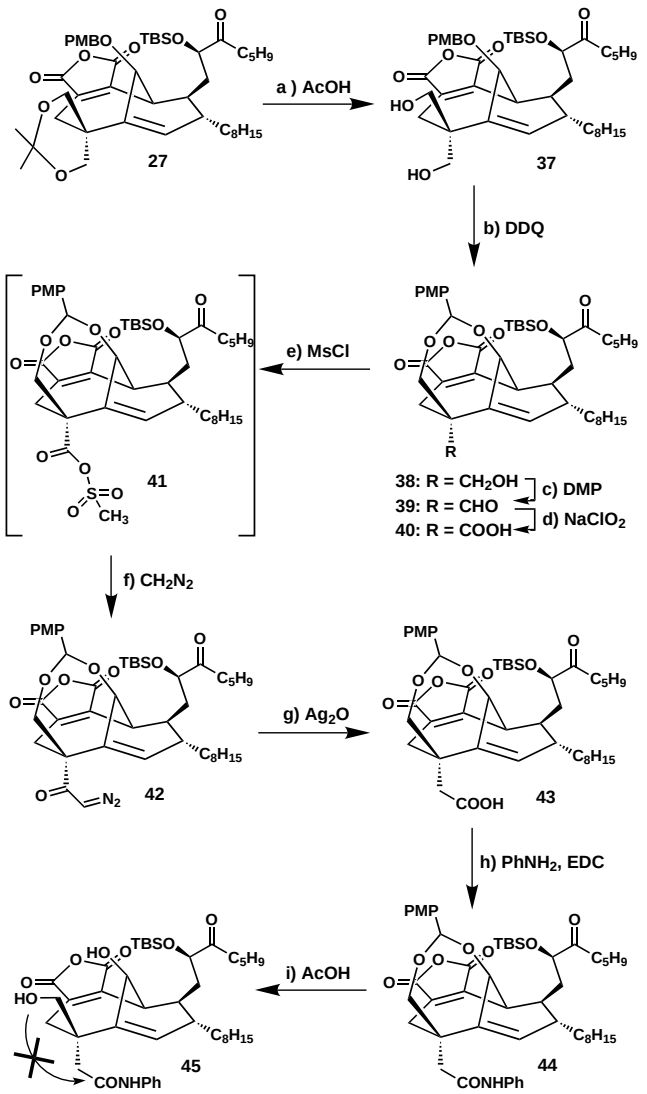
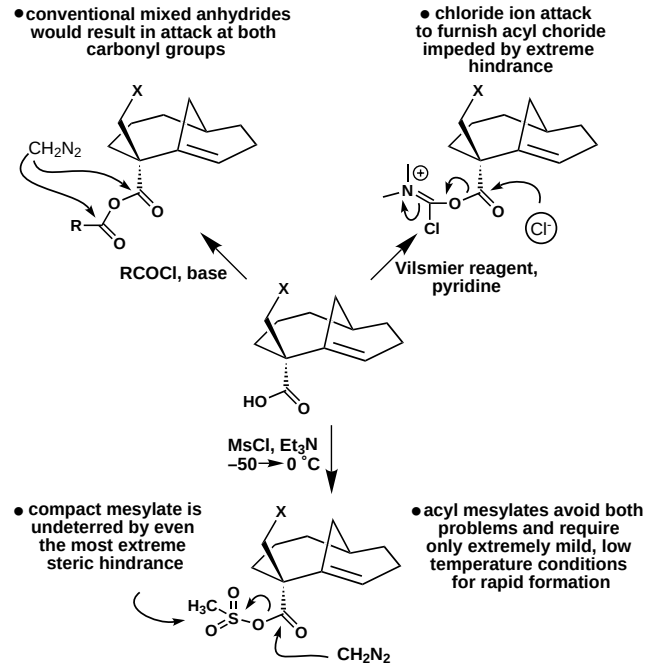
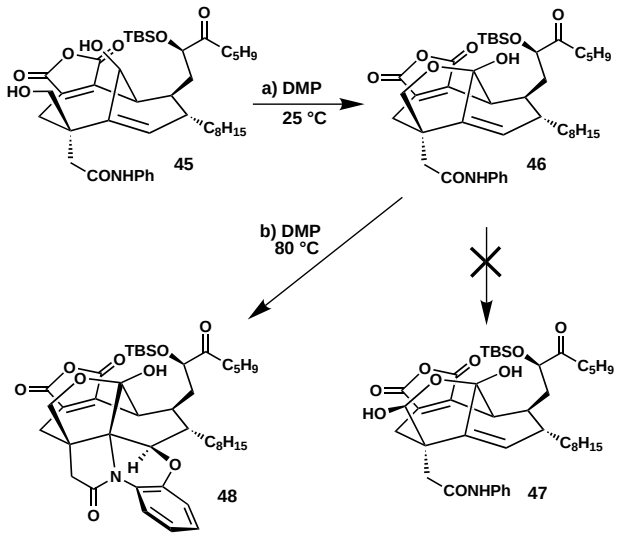


Scheme 8. Synthesis of diol-amide **45**: a stable intermediate resistant to intramolecular cyclization. a) 90% aq AcOH, 25°C, 5 h, 85%; b) DDQ (2.0 equiv), fluorobenzene, 25°C, 2.5 h, 57%; c) DMP (3.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25°C, 1 h, 90%; d) $NaClO_2$ (3.0 equiv), NaH_2PO_4 (1.5 equiv), 2-methyl-2-butene (50 equiv), *t*BuOH:H_2O (2:1), 25°C, 20 min, 80%; e) MsCl (5.0 equiv), Et_3N (10 equiv), THF, 0°C, 5 min; f) CH_2N_2 (excess), Et_2O/THF, 0→25°C, 1 h; g) Ag_2O (5.0 equiv), DMF:H_2O (2:1), 120°C, 1 min, 38% overall from **40**; h) $PhNH_2$ (1.5 equiv), EDC (3.0 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 25°C, 1 h, 85%; i) 80% aq AcOH, 25°C, 1.5 h, 89%. 4-DMAP = 4-*N*,*N*-dimethylaminopyridine, EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.



Scheme 9. Comparison of the use of acyl mesylates with conventional methods for activation of hindered acids.



Scheme 10. Serendipitous formation of polycycle **48**. a) Dess–Martin periodinane (2.0 equiv), benzene, 25°C, 40 min, 90%; b) Dess–Martin periodinane (5.0 equiv), benzene, 80°C, 20 min, 45%.

With diol **45** in hand, the stage was now set for the application of the DMP cascade oxidation sequence to install the γ-hydroxylactone functionality (Scheme 10). Admittingly, we had little, if any, intuition of the surprise that was soon awaiting us. When diol **45** was submitted to oxidation with DMP in benzene at room temperature, indeed rapid formation of hemiketal **46** was observed (90%). Further oxidation in refluxing benzene, however, furnished a compound which was clearly not the desired γ-hydroxylactol **47**. After rigorous spectroscopic analysis coupled with mechanistic reasoning (see Scheme 11) the structure was elucidated to be the novel polycycle **48**. With support from appropriate models, we offer the following speculative mechanism for the formation of **48** from **46**. Thus, the amide NH group of **46** engages the electrophilic DMP reagent to furnish intermediate **A** as shown in Scheme 11. *ortho*-Oxidation of **A** through intra- or intermolecular modes would furnish intermediate **B**, which is poised for an intramolecular [4+2] cycloaddition with the adjacent bridgehead double bond, thereby permitting rearomatization and resulting in fusion to the unprecedented structure **48**. The potential that this serendipitous discovery may hold in a general synthetic context is currently under investigation.

Although these strategies failed to deliver the targeted CP molecules, they provided enough reconnaissance information

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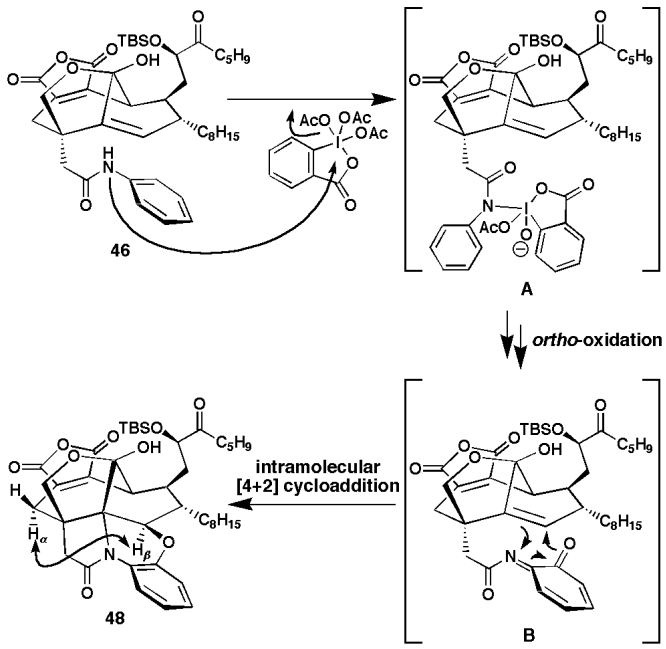

Scheme 11. Proposed mechanism for the formation of polycycle **48**. The NOE between H_α and H_β confirmed the indicated stereochemistry.

to form the foundation from which a revised synthetic strategy could be formulated. The coalescence of these two unique strategies into a final approach capable of addressing all of the aforementioned pitfalls and culminating in the total synthesis of the CP molecules (**1** and **2**) is reported in the following communication.[5]

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[22] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary publication no. CCDC-118962. Copies of the data can be obtained free of charge on application to CCDC, 12 Union road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033: e-mail: deposit@ccc.cam.ac.uk).