Total Synthesis of the CP Molecules CP-225,917 and CP-263,114— Part 2: Evolution of the Final Strategy**

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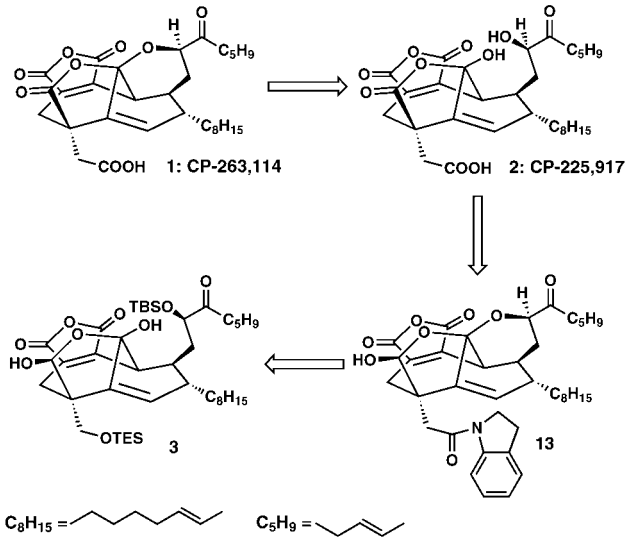
In the preceding communication[1] we described our findings from two unique strategies aimed at the total synthesis of the CP molecules **1** and **2**.[2, 3] The current retrosynthetic analysis (Scheme 1) is predicated on the basic strategic



Scheme 1. Final retrosynthetic analysis of the CP molecules **1** and **2**. TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

considerations and chemistry reported earlier from these laboratories.[1, 4, 8] In addition, extensive model studies, whose disclosure will have to await the full account of this work, led us to conclude that a plan that targeted CP-263,114 (**1**) first would be most prudent. The virtues of such a scheme would include a decreased reliance on protecting group chemistry, greater stability and ease of handling intermediates with the pyran motif,[5] and a rare opportunity to attempt the rather daring challenge of converting the seemingly robust CP-263,114 (**1**) into its hydrated counterpart CP-225,917 (**2**). Indoline amide **14** was targeted as an ideal precursor for the CP molecules by virtue of its facile accessibility from **3**[1] and because of the relative ease with which this special amide can be hydrolyzed in a two-step procedure.[6]

Thus, sequential treatment of **3** with aqueous TFA/CH_2Cl_2 to remove both silicon groups followed by exposure to CH_3SO_3H[2] in dry $CHCl_3$ led to pyranlactol **4** (Scheme 2; see Table 1 for selected physical data). A key observation was made during the selective oxidation of diol **4** to aldehyde **5**. When diol **4** was oxidized with DMP[7] in CH_2Cl_2 at ambient temperature the aldehyde lactol **5** was isolated as the major product along with significant quantities of lactone **6** (**5**:**6** approximate ratio 2:1, 85% combined yield). The fact that DMP was sufficient to effect this transformation, which was normally only possible using TEMPO,[1, 8] indicated to us that not only was the lactolpyran behaving as a normal lactol but also that it would be plausible to employ the simple DMP protocol to reach the amide **14** (see below). Over the course of this work we have taken notice of the ability to fine-tune the reactivity of DMP by mere solvent alteration. Thus, the undesired, yet highly informative, lactonealdehyde **6** could essentially be eliminated (**5**:**6** approximate ratio $>$20:1, 90% combined yield) by carrying out the oxidation in benzene at 25 °C.

The lactol **5** was shielded from the ensuing homologation procedure (potential ring closure) by protection as the TBS-ether **7** (TBSOTf, 2,6-lutidine, 85% yield). $NaClO_2$ oxidation of **7** proceeded smoothly to produce acid **8** in 90% yield. The intimidating task of converting the sterically congested (neopentyl, concave face) carboxylic acid **8** into diazoketone **10** was easily accomplished via the acyl mesylate **9** (prepared in situ with MsCl/ Et_3N at 0 °C) with excess CH_2N_2 at 0 °C.[1] The diazoketone so obtained was immediately dissolved in DMF:H_2O (2:1) and heated to 120 °C in the presence of excess Ag_2O for one minute to generate the homologated acid **11** in 35% overall yield from **8**. Combining carboxylic acid **11** and indoline in the presence of EDC and 4-DMAP provided amide **12** (85% yield). Removal of the pendant TBS group, assisted by TFA, revealed lactol **13** (95% yield), which could easily be oxidized to lactone **14** in 80% yield by using DMP for reasons alluded to above.

At this point in our synthesis it was critical to find reliable conditions for the counterintuitive[2] conversion of CP-263,114 (**1**) into CP-225,917 (**2**). By utilizing a small amount of natural **1** we were able to explore conditions to accomplish this conversion. We rationalized that LiOH might be efficaciously exploited for this purpose by virtue of its unique nucleophilicity and solubility profile.[10] In the event we were able to cleanly effect the desired transformation (**1** to **2**, Scheme 3) in over 90% yield with no significant decomposition or epimerization at C-7. A conceivable mechanistic rationale for this stunning cascade reaction sequence, which involves no less than four anions residing in the same molecule and a dizzying number of distinct steps occurring in the same reaction vessel,

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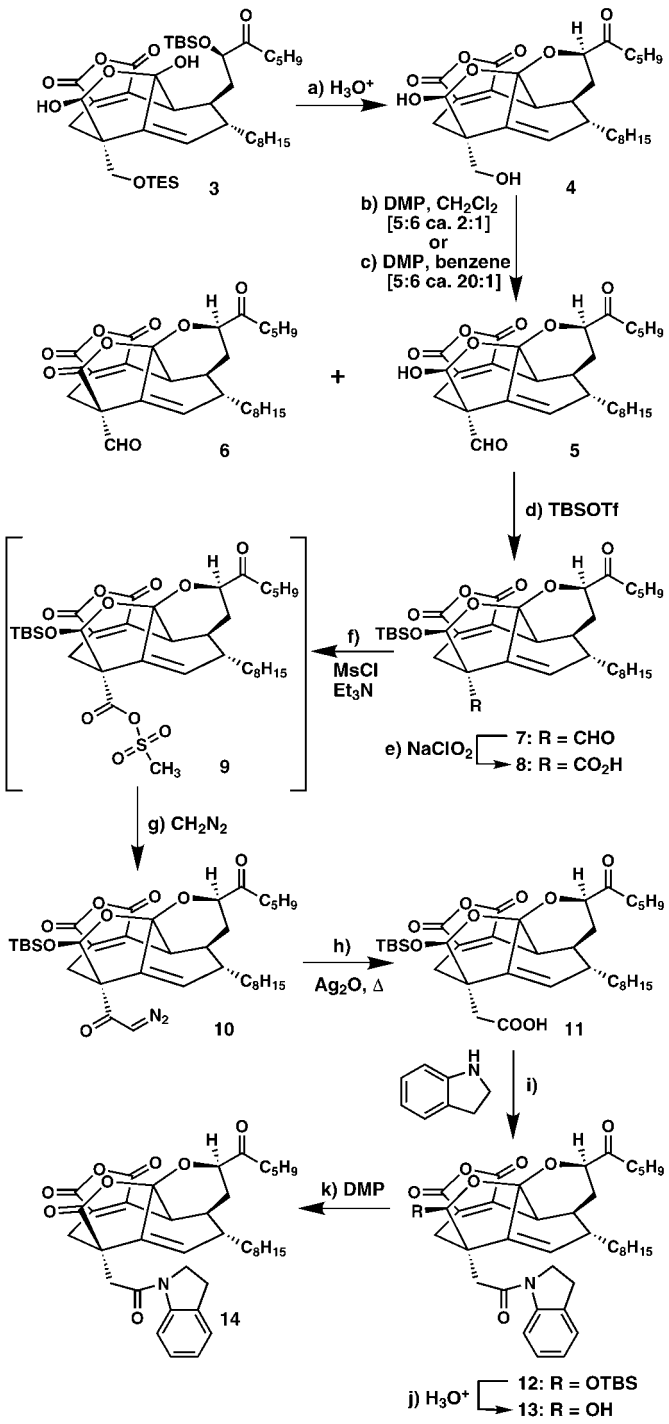


Scheme 2. Arrival at the key intermediate **14**. a) 1 CH_2Cl_2:TFA:H_2O (40:4:1), 25 °C, 2 h; 2 CH_3SO_3H (0.3 equiv), $CHCl_3$, 25 °C, 2 h, 83% overall; b) DMP (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 85%, **5**:**6** ca. 5:1 ratio; c) DMP (5.0 equiv), benzene, 25 °C, 2 h, 90%, **5**:**6** ca. >20:1 ratio; d) TBSOTf (20 equiv), 2,6-lutidine (50 equiv), CH_2Cl_2, 0 → 25 °C, 3 h, 85%; e) $NaClO_2$ (3.0 equiv), NaH_2PO_4 (1.5 equiv), 2-methyl-2-butene (50 equiv), *t*BuOH:H_2O (2:1), 25 °C, 10 min, 90%; f) MsCl (5.0 equiv), Et_3N (10 equiv), THF, 0 °C, 5 min; g) CH_2N_2 (100 equiv), Et_2O/THF, 0 °C, 45 min; h) Ag_2O (5.0 equiv), DMF:H_2O, (2:1) 120 °C, 1 min, 35% overall from **8**; i) indoline (1.5 equiv), EDC (3.0 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 1.0 h, 85%; j) CH_2Cl_2:TFA:H_2O (40:4:1), 25 °C, 1.5 h, 95%; k) DMP (20 equiv), $NaHCO_3$ (50 equiv), CH_2Cl_2, 25 °C, 24 h, 80%. TFA = trifluoroacetic acid, DMP = Dess–Martin periodinane, OTf = trifluoromethanesulfonate, Ms = methanesulfonyl, EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 4-DMAP = 4-*N*,*N*-dimethylaminopyridine.

Table 1. Selected physical properties of compounds **4**, **11**, and **14**.

4: $R_f = 0.36$ (silica gel, ethyl acetate:hexane 1:1); IR (film): $\tilde{\nu}_{max} = 3383$, 2973, 2916, 2847, 1762, 1716, 1648, 1508, 1630, 1517, 1464, 1374, 1260, 1100, 1018, 958, 804 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 5.55$ (d, $J = 1.5$ Hz, 1H), 5.45–5.28 (m, 5H), 4.40 (dd, $J = 7.7$, 4.2 Hz, 1H), 4.13 (d, $J = 11.2$ Hz, 1H), 4.00 (d, $J = 11.2$ Hz, 1H), 3.72–3.68 (brs, 2H), 3.16 (d, $J = 1.8$ Hz, 1H), 2.89 (d, $J = 21.4$ Hz, 1H), 2.70–2.57 (m, 2H), 2.51 (d, $J = 21.4$ Hz, 1H), 2.42–2.08 (m, 6H), 2.04–1.86 (m, 3H), 1.66–1.48 (m, 6H), 1.36–1.16 (m, 5H), 1.12–0.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 210.2$, 165.4, 165.0, 143.3, 141.5, 139.5, 131.1, 130.5, 129.5, 125.9, 124.9, 103.5, 99.5, 75.8, 62.8, 55.3, 43.0, 41.7, 38.9, 38.1, 36.5, 35.6, 32.3, 32.0, 29.3, 27.4, 26.3, 17.9 (2C); HRMS (FAB): calcd for $C_{30}H_{38}O_8Na$ (M+Na^+): 549.2464, found: 549.2474

11: $R_f = 0.47$ (silica gel, ethyl acetate:hexane 1:1); IR (film): $\tilde{\nu}_{max} = 3371$, 2973, 2917, 2846, 2672, 1764, 1714, 1648, 1618, 1461, 1440, 1385, 1258, 1227, 1101, 1076, 924, 838 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 5.53$ (s, 1H), 5.44–5.36 (m, 4H), 4.32 (dd, $J = 8.0$, 4.2 Hz, 1H), 3.35 (dd, $J = 21.8$, 1.5 Hz, 1H), 3.13 (s, 1H), 3.12 (d, $J = 17.8$ Hz, 1H), 3.06–2.99 (m, 1H), 2.74 (d, $J =$ 17.8 Hz, 1H), 2.55 (m, 2H), 2.42–2.35 (m, 1H), 2.32 (dd, $J = 21.8$, 2.0 Hz, 1H), 2.30–2.10 (m, 5H), 1.96–1.90 (m, 2H), 1.81–1.42 (m, 9H), 1.40–1.10 (m, 6H), 0.90 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 210.9$, 172.4, 165.6, 165.5, 143.2, 141.7, 135.2, 131.1, 129.8, 129.0, 125.9, 124.9, 109.3, 103.1, 75.0, 65.8, 52.2, 43.0, 41.4, 40.5, 38.1, 36.5, 35.7, 35.5, 32.3, 29.7, 29.3, 28.9, 27.5, 26.3, 25.6, 18.0, 17.9, 17.8, −4.2, −5.7 (2C); HRMS (FAB): calcd for $C_{37}H_{52}NO_9SiNa$ (M+Na^+): 892.2857, found: 892.2874

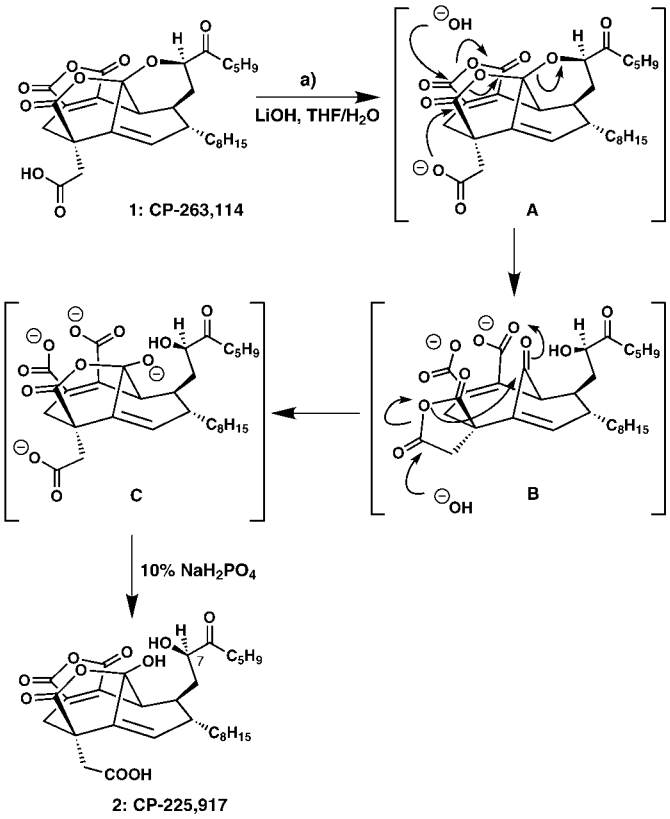
14: $R_f = 0.70$ (silica gel, ethyl acetate:hexane 1:1); IR (film): $\tilde{\nu}_{max} = 2971$, 2915, 2847, 1763, 1714, 1648, 1618, 1461, 1440, 1385, 1258, 1227, 1101, 1076, 924, 838 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.19$ (d, $J = 7.9$ Hz, 1H), 7.18 (d, $J = 7.4$ Hz, 1H), 7.15 (t, $J = 7.9$ Hz, 1H), 7.02 (t, $J = 7.4$ Hz, 1H), 5.59 (s, 1H), 5.53–5.32 (m, 4H), 4.57 (t, $J = 8.0$ Hz, 1H), 4.15–4.0 (m, 2H), 3.53 (s, 1H), 3.32 (d, $J = 16.8$ Hz, 1H), 3.30–3.20 (m, 1H), 3.06 (brd, $J =$ 19.4 Hz, 1H), 3.03 (d, $J = 16.8$ Hz, 1H), 2.89–2.75 (m, 2H), 2.55–2.45 (m, 1H), 2.40–2.10 (m, 4H), 1.97–1.86 (m, 1H), 1.69–1.51 (m, 13H), 1.35–1.15 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 208.8$, 175.8, 165.6, 164.6, 164.4, 142.3, 141.9, 140.7, 140.3, 131.1, 130.7, 129.5, 128.2, 127.5, 125.9, 125.0, 124.5, 124.2, 117.4, 104.7, 75.8, 47.9, 47.8, 43.5, 42.6, 40.3, 40.0, 38.3, 36.3, 35.6, 34.6, 32.3 (2C), 29.3, 28.9, 28.1, 26.9, 26.1, 17.9; HR-MS (FAB): calcd for $C_{39}H_{43}NO_8Cs$ (M + Cs^+): 786.204, found: 786.2068

appears in Scheme 3.[11] This cascade may have important implications in a general sense, including future total syntheses of the CP molecules, their possible biosynthetic origin, and their mechanism of action. In addition, it opens up new paths for the design and construction of analogues.

Since the danger of intramolecular attack by the newly installed hydroxyl group upon the electrophilic carbonyl group of the homologated carboxylic acid had now passed, amide **14** was transformed to indole **15** (Scheme 4) by the oxidative action of excess *p*-chloroanil[9] (toluene, △, 75% yield based on 50% conversion), thus regenerating the electrophilicity at the carbonyl center and rendering this moiety suceptible to mild base hydrolysis.

Application of the above unprecedented protocol to indole amide **15** (Scheme 4) succeeded in furnishing CP-225,917 (**2**, racemic, 72% yield),[12] thus verifying the relative configuration at C-7.[2] Furthermore, direct treatment with methanesulphonic acid in $CDCl_3$ over the course of 36 h resulted in an esentially quantitative conversion into CP-263,114 (**1**, 90% yield of isolated product, racemic).[12]

The journey to the CP molecules required an unrelenting quest through a synthetic labyrinth endowed with countless obstacles, yet filled with numerous hidden treasures. When taken together with the discovery of novel cascade reactions,



Scheme 3. Mechanistic analysis of the LiOH-induced cascade reaction. a) LiOH (10 equiv), THF:H_2O (4:1), 25 °C, 1 h, 90 %.

new synthetic technologies and unprecedented synthetic tactics, the current total syntheses are both a tribute to the innate complexity of these molecules and a triumph of modern organic synthesis over them. An asymmetric variant of the current synthesis, explorations to broaden the scope of newly discovered reactions, and the rational design of novel CP analogues for chemical biology studies are in progress.

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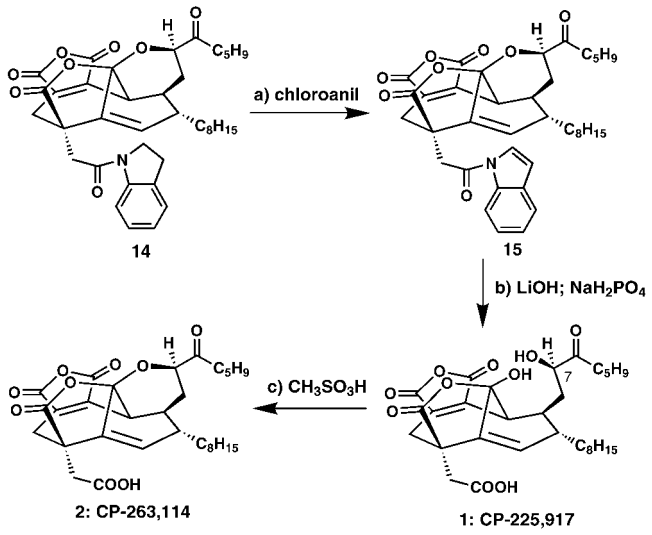

Scheme 4. Final stages of the total synthesis of CP-225,917 (**2**) and CP-263,114 (**1**). a) *p*-chloroanil (10 equiv), toluene, 110 °C, 2.5 h, 70 % based on 50 % conversion; b) LiOH (10 equiv), THF:H_2O (4:1), 25 °C, 3 h, then 10 % NaH_2PO4, 10 min, 72 %; c) CH_3SO_3H (1.0 equiv), $CDCl_3$, 25 °C, 36 h, 90 %.

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[5] Throughout the course of this work we found that intermediates with the pyran motif are much more stable and behave better on silica gel than their hydrated counterparts corresponding to the CP-225,917 structure (**2**).

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[9] Although reference [6] reports the use of DDQ to effect this transformation, only decomposition was observed under these conditions. After an extensive search, *p*-chloroanil was identified as the most suitable reagent to accomplish this conversion, presumably as a consequence of its milder nature.

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[11] Model studies on compounds with only the maleic anhydride moiety have shown that this delicate functionality is rapidly opened with LiOH; this seemingly detrimental outcome can be reversed simply by using mildly acidic conditions.

[12] Synthetic **1** and **2** exhibited identical chromatographic and spectroscopic data to those of authentic samples.

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