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Total Synthesis of the CP-Molecules (CP-263,114 and CP-225,917, Phomoidrides B and A). 3. Completion and Synthesis of Advanced Analogues

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Abstract: The completion of the total syntheses of the CP-molecules is reported. Several strategies and tactics, including the use of amide-based protecting groups for the homologated C-29 carboxylic acid and the use of an internal pyran protecting group scheme, are discussed. The endeavors leading to the design of new methods for the homologation of hindered aldehydes and to the isolation of a polycyclic byproduct (**23**), which inspired the development of a new series of reactions based on iodine(V) reagents, are described. In addition, the discovery and development of the LiOH-mediated conversion of CP-263,114 (**1**) to CP-225,917 (**2**) is described, and a mechanistic rationale is presented. Finally, a synthetic route to complex analogues of the CP-molecules harboring a maleimide moiety in place of the maleic anhydride is presented.

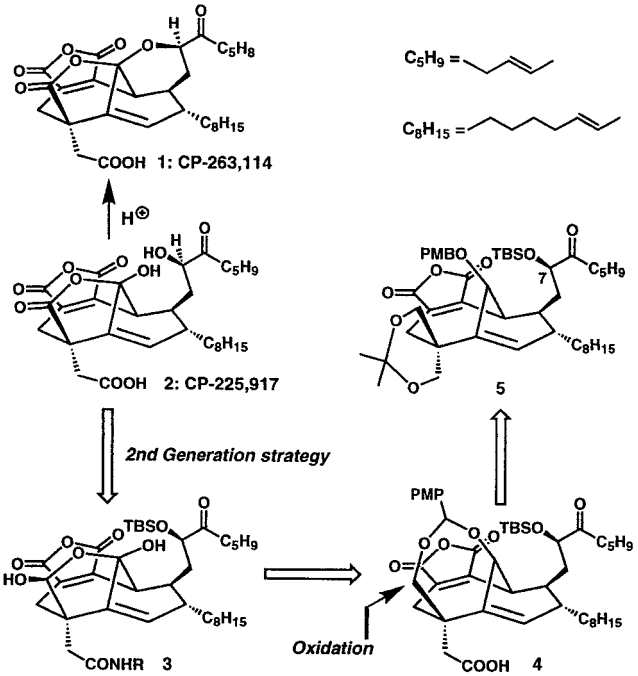
Introduction

In the preceding paper in this issue,[1] basic strategies for the installation of the maleic anhydride, γ-hydroxylactone, and remote stereocenter at C-7 ("upper" side chain) of the CP-molecules (**1** and **2**, Scheme 1) were devised and carried out. In addition, a first generation synthetic route to the natural products was tested employing these new methodologies. Central to our synthetic plan was the premise that the advanced key intermediate **5** (Scheme 1) would eventually lead to the target structures. Arrival at this "checkpoint" in the synthetic "labyrinth" permitted a systematic investigation of the timing of the individual steps in the final stages. Specifically, the correct order for the installation of the γ-hydroxylactone and the one-carbon homologation of the "lower" side chain (C-28 → C-29) remained to be addressed. Whether to first target CP-263,114 (**1**) or CP-225,917 (**2**) was also a lingering question in our minds. In this paper, second- and third-generation strategies toward the CP-molecules are delineated. Most importantly, the design and discovery of new cascade reactions and synthetic technologies en route to **1** and **2**, and designed analogues thereof, are described.

Results and Discussion

1. Second-Generation Retrosynthetic Analysis. During our first-generation[1] approach to **1** and **2**, we attempted to install the C-29 carbon after the construction of the γ-hydroxylactone and failed, due to the frailty of the precursors. The only dilemma associated with inverting the order of these events is shown in Scheme 2. Thus, if we were to perform the one-carbon homologation of C-28 prior to the γ-hydroxylactone formation, the latter operation would require the presence of a free 1,4-diol such as the one generated from **7** upon hydrolysis of the acetal protecting group. In the event, the primary alcohol of that diol, when generated by acid catalysis, spontaneously cyclized onto the proximate ester to furnish lactone **8** (see Scheme 2), a stop that proved to be a dead end. Due to the

Scheme 1. Second-Generation Strategy for the Total Synthesis of **1** and **2**



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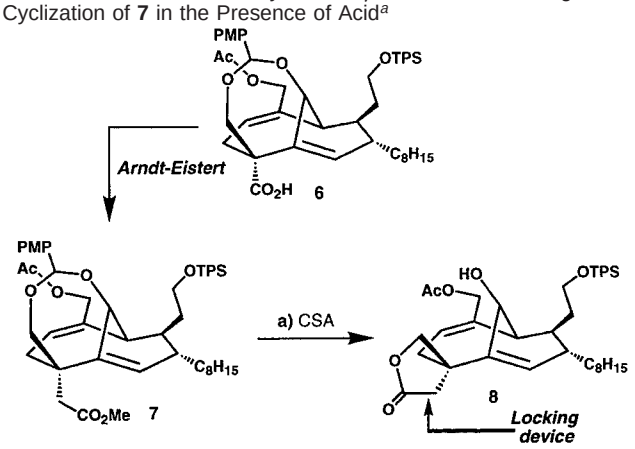
(1) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; Choi, H.-S. *J. Am. Chem. Soc.* **2002**, *124*, 2190−2201.

10.1021/ja0120126 CCC: $22.00

Scheme 2. Conformationally Locked γ-Lactone **8** Resulting from Cyclization of **7** in the Presence of Acid[a]



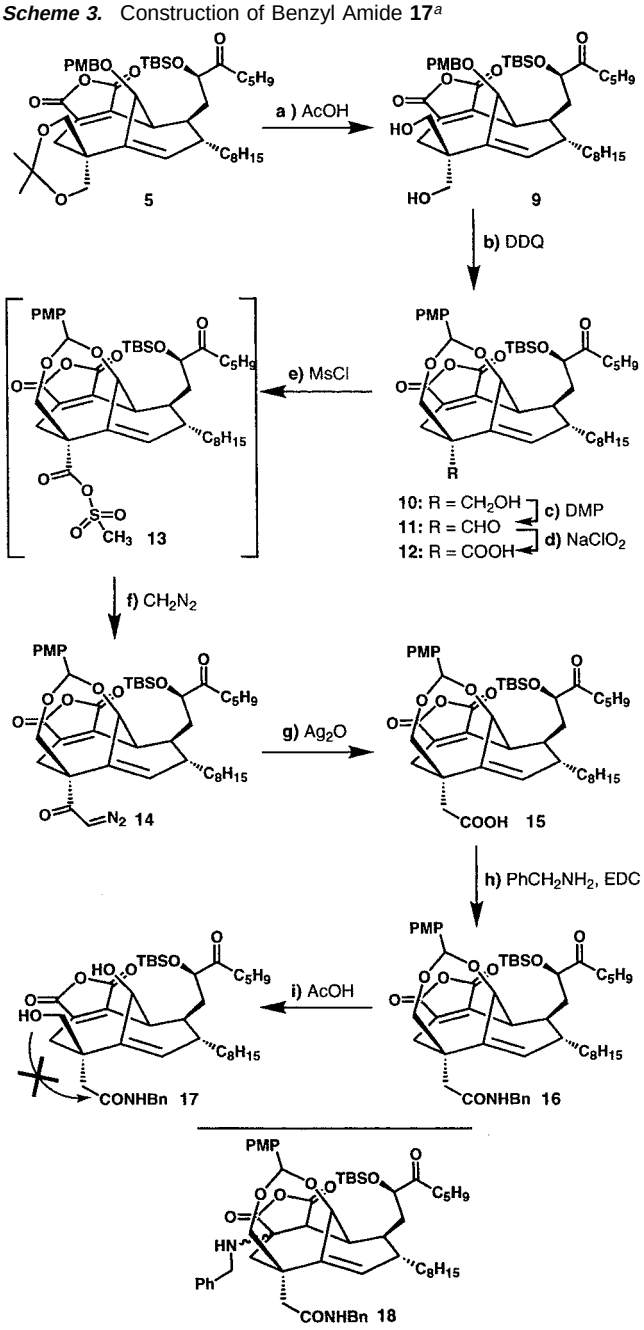
[a] Reagents and conditions: (a) CSA (0.2 equiv), MeOH, 25 °C, 1 h, 90%.

conformational rigidity in this system, and the sensitivity of neighboring functionalities, we were unable to open lactone **8**. Efforts to reduce the C-29 carbon to the alcohol stage were complicated by protecting group incompatibilities. To circumvent this problem, the reigning theme of our second-generation strategy (Scheme 1), which provided a potential solution to this roadblock, involved the enlistment of an amide functionality to disguise and deactivate the electrophilic center at C-29. In doing so, we could avoid the problems associated with the late-stage homologation of the first-generation strategy,[1] lockup structures, and, subsequently, only face what we perceived to be the comparably facile task of amide hydrolysis. As shown in the retrosynthetic blueprint in Scheme 1, an intermediate of type **3** was targeted as a potential precursor to **2**. Intermediate **3** was envisioned to arise from homologated intermediate **4** by employing the DMP-mediated cascade for γ-hydroxylactol construction described in the preceding paper.[1] Retrohomologation and protecting group manipulations led to the previously synthesized advanced key intermediate **5**.

2. Explorations To Implement the Second-Generation Strategy. The attempted execution of the newly designed second-generation strategy toward the CP-molecules began with the advanced key intermediate **5** as shown in Scheme 3. Thus, removal of the isopropylidene group from **5** using aqueous AcOH furnished the diol **9** in 85% yield. DDQ-mediated formation[2] of the seven-membered benzylidene acetal **10** (57% yield) followed by stepwise oxidation of the remaining hydroxyl group with DMP (90% yield) and then $NaClO_2$ led to carboxylic acid **12** in 78% yield via the intermediate aldehyde **11**. Optimization studies of the DDQ-mediated cyclization (see Table 1) led to the identification of fluorobenzene as a superior solvent for this transformation.

To execute the planned Arndt−Eistert homologation protocol[3] on carboxylic acid **12**, we required a mild method for the activation of hindered carboxylic acids since acid chloride formation with this system and others related to it was extremely inefficient or did not work at all. As we had done with the maleic anhydride construction, we designed a method which responded

Scheme 3. Construction of Benzyl Amide **17**[a]



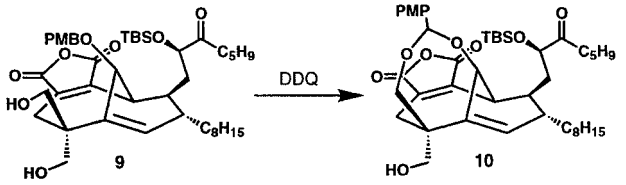
[a] Reagents and conditions: (a) 90% aqueous AcOH, 25 °C, 5 h, 85%; (b) DDQ (2.0 equiv), fluorobenzene, 25 °C, 2.5 h, 57%; (c) DMP (3.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 1 h, 90%; (d) $NaClO_2$ (3.0 equiv), NaH_2PO_4 (1.5 equiv), 2-methyl-2-butene (50 equiv), *t*-BuOH/H_2O (2:1), 25 ° C, 20 min, 78%; (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, 43% overall from **12**; (h) $PhCH_2NH_2$ (1.5 equiv), EDC (3.0 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 1 h, 85%; (i) 80% aqueous AcOH, 25 °C, 1.5 h, 77%. TFA = trifluoroacetic acid; 4-DMAP = 4-(*N*,*N*-dimethylamino)pyridine; EDC = 1-(3-(dimethylamino)-propyl)-3-ethylcarbodiimide hydrochloride; PMP = *p*-methoxyphenyl.

to the highly hindered nature of the CP-skeleton. Specifically, we took advantage of the reactive and compact nature of the acyl mesylate species to activate these sterically blocked systems for attack by diazomethane, a small reagent itself. The developed method[4] is extremely mild, requiring only low temperatures

(2) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.
(3) (a) Arndt, F.; Eistert, B.; Partale, W. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1364. (b) Arndt, F.; Amende, J. *Ber. Dtsch. Chem. Ges.* **1928**, *61*, 1122. (c) Arndt, F.; Eistert, B. *Ber. Dtsch. Chem. Ges.* **1935**, *68B*, 200. See also: Smith, A. B., III; Toder, B. H.; Branca, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 3995.

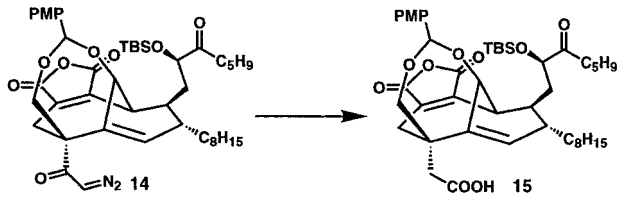
(4) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Fong, K. C.; He, Y.; Yoon, W. H. *Org. Lett.* **1999**, *1*, 883.

Table 1. Optimization of the DDQ-Mediated Benzylidene Formation



Entry	Conditions	Yield (%)[a]
1	CH_2Cl_2, 4A M.S., 25 °C, 2.5 h	41
2	CH_2Cl_2, 25 °C, 2.5 h	40
3	benzene, 25 °C, 3.0 h	50
4	fluorobenzene, 25 °C, 2.5 h	57
5	benzotrifluoride, 25 °C, 2.5 h	45
6	1,2-dichloroethane, 25 °C, 3.0 h	40

Table 2. Optimization of the Wolff Rearrangement Leading to Carboxylic Acid **15**

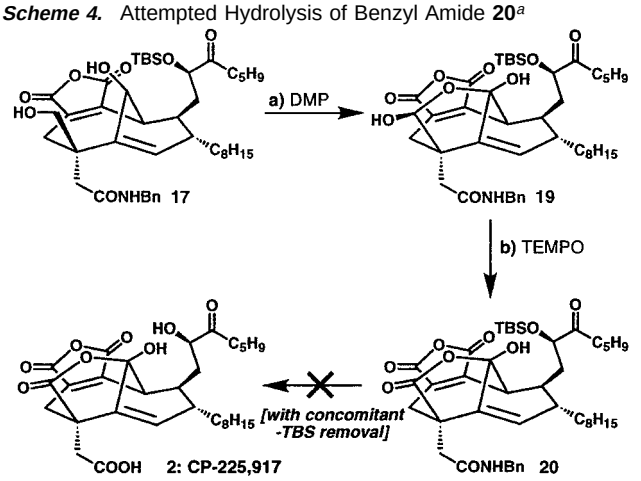


Entry	Conditions	Yield (%)[a]
1	THF/H_2O (5:1), hv, 10 min	5
2	THF/H_2O (2:1), reflux, Ag_2O, 12 min	10
3	Dioxane/H_2O (1:1), Ag_2O, reflux, 15 min	8
4	DMF/H_2O (3:1), Ag_2O, Et_3N (1 equiv), 80 °C, 10 min	15
5	DMF/H_2O (2:1), Ag_2O, 120 °C, 1 min	38
6	DMF/H_2O (1:1), Ag_2O, 110 °C, 2 min	43

for rapid activation. Thus, carboxylic acid **12** was smoothly transformed into diazo ketone **14** via the acyl mesylate **13** upon treatment with MsCl/Et_3N at 0 °C followed by addition of excess CH_2N_2 as a dried ethereal solution. The generality of this protocol and relevant mechanistic studies have been reported elsewhere.[4] To conclude the homologation, a Wolff rearrangement was required, an event that took place at 120 °C in 1 min in DMF/water (2:1) in the presence of ca. 5 equiv of Ag_2O. For the success and reproducibility of this reaction, it was critical to purify the Ag_2O immediately prior to its use.[5] Optimization of this step (see Table 2) led to a small (ca. 5%) improvement in the yield of **15** (43%, entry 6).

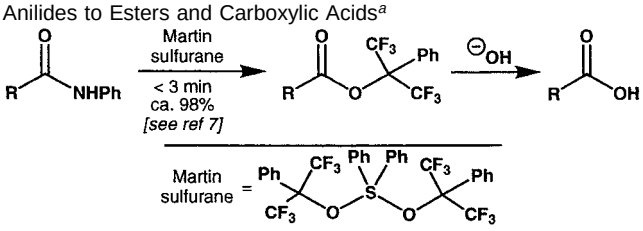
The planned protection of the carboxylic acid was the next task. Amide bond formation between carboxylic acid **15** and benzylamine was facilitated by EDC/4-DMAP, furnishing amide **16** in 85% yield (Scheme 3). Interestingly, when more than 1.5 equiv of benzylamine was employed, Michael addition to the maleic anhydride was observed, producing varying amounts of compound **18**. This was of no consequence, however, since acid-induced hydrolysis of the benzylidene acetal in **16**, as required for the next step, also caused a retro-Michael reaction on **18**,

Scheme 4. Attempted Hydrolysis of Benzyl Amide **20**[a]



[a] Reagents and conditions: (a) DMP (5.0 equiv), benzene, 80 °C, 8 min, 35%; (b) TEMPO (10 equiv), $PhI(OAc)_2$ (10 equiv), CH_3CN, 25 °C, 2 h, 70%.

Scheme 5. Use of the Martin Sulfurane for the Conversion of Anilides to Esters and Carboxylic Acids[a]



[a] See ref 7.

leading to diol **17**. The latter compound was found to be resistant to cyclization as predicted.

With diol **17** in hand, the stage was now set for the application of the DMP cascade oxidation sequence to install the γ-hydroxylactone functionality (Scheme 4). Thus, treatment of **17** with DMP in refluxing benzene led to the γ-hydroxylactol **19** in 35% yield. TEMPO-mediated conversion of **19** to the lactone **20** proceeded smoothly in 70% yield. However, and despite encouraging model studies,[6] amide **20** resisted hydrolysis under conditions required for the survival of the parent structures. This time, we had successfully constructed the entire CP skeleton with correct oxidation states at all centers only to be frustrated by one protecting group which refused to dismantle as expected.

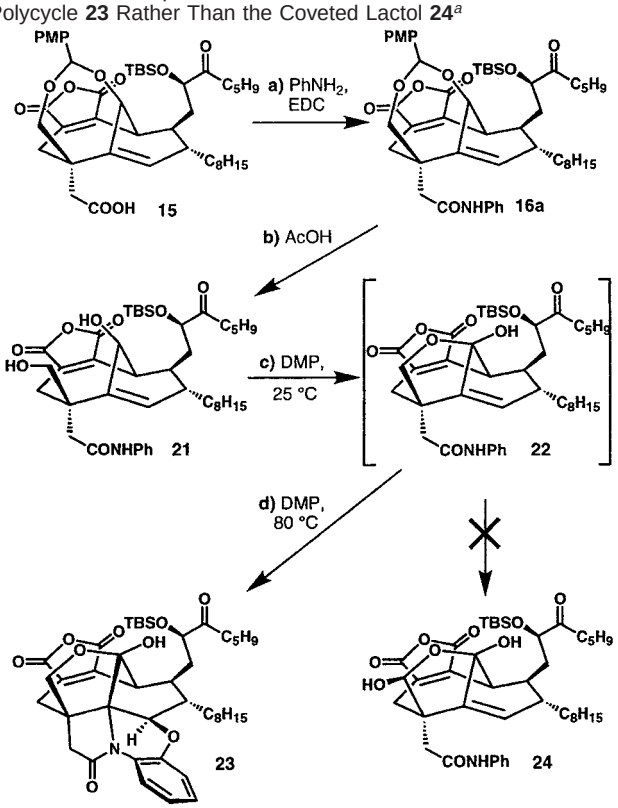
A search of the literature led us to a report by J. C. Martin and co-workers on the use of sulfuranes as a mild method for anilide deprotection (see Scheme 5).[7] Thus, after a promising model study, we began the construction of intermediate **21** (see Scheme 6) following a path similar to that used for **17** (Scheme 3). Coupling of aniline with the carboxylic acid **15** led to anilide **16a** (83% yield). This event was followed by hydrolysis of the benzylidine group from **16a** with aqueous AcOH to furnish 1,4-diol **21** in 89% yield. Admittedly, we had little if any intuition of the surprise that was soon awaiting us. When diol **21** was submitted to oxidation with DMP in benzene at room temperature, rapid formation of hemiketal **22** was observed. Further oxidation in refluxing benzene, however, furnished a compound

(5) Armarego, W. L. F.; Perrin, D. D. *Purification of Organic Compounds*; Butterworth-Heinemann: Oxford, 1996; p 421.

(6) Successful removal of the benzylamide on model substrates was realized using protocols described in the following papers: Evans, D. A.; Carter, P. H.; Dinsmore, C. J.; Barrow, J. C.; Katz, J. L.; Kung, D. W. *Tetrahedron Lett.* **1997**, *38*, 4535. Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.

(7) Martin, J. C.; Franz, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 6137.

Scheme 6. Attempted Oxidation of 1,4-Diol **21** Leads to the Novel Polycycle **23** Rather Than the Coveted Lactol **24**[a]

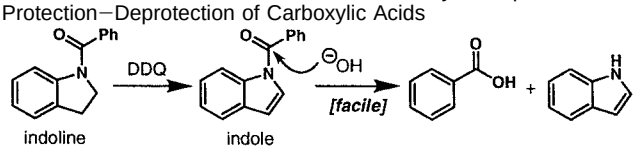


[a] Reagents and conditions: (a) $PhNH_2$ (1.5 equiv), EDC (3.0 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 1 h, 83%; (i) 80% aqueous AcOH, 25 °C, 1.5 h, 89%; (c) Dess−Martin periodinane (2.0 equiv), benzene, 25 °C, 40 min; (d) Dess−Martin periodinane (5.0 equiv), benzene, 80 °C, 20 min, 45%.

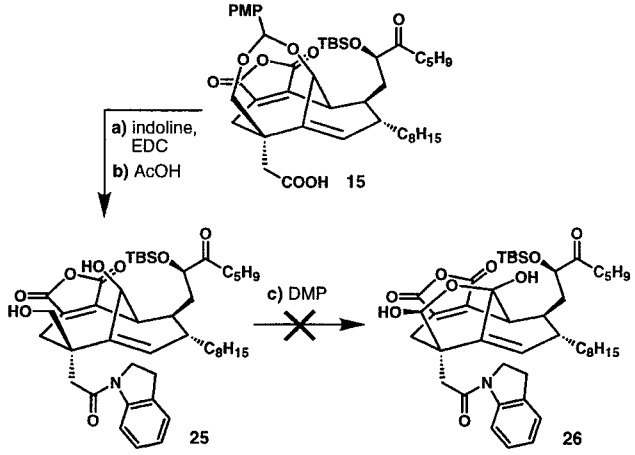
which was clearly not the desired γ-hydroxylactol **24**. After extensive spectroscopic analysis and mechanistic reasoning, the new structure was elucidated as the novel polycycle **23** (Scheme 6). Although disappointing at the time, this serendipitous discovery opened new horizons and led to a number of new synthetic technologies employing hypervalent iodine reagents.[8] A clear mechanistic picture of this remarkable DMP-mediated polycyclization reaction since emerged[9] and will be discussed in more detail elsewhere, as will its scope and generality.

Confronted with this latest failure, we searched for an alternative approach. During the course of synthetic studies on the penicillins, Barton and co-workers developed the novel concept of masked heteroaromaticity and its application to a mild protection method of carboxylic acids (see Scheme 7).[10] A decision was made to try this tactic. The indoline amide was thus chosen due to its predicted stability during the DMP oxidation (the side reaction mentioned above required a free

Scheme 7. Barton's "Latent" Heteroaromaticity Principle for the Protection−Deprotection of Carboxylic Acids



Scheme 8. Failure To Oxidize the Indoline Amide **25** to Lactol **26**[a]



[a] Reagents and conditions: (a) indoline (1.5 equiv), EDC (3.0 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 1 h, 86%; (b) 80% AcOH, 25 °C, 1.5 h, 70%.

NH bond; see ref 9) and because its oxidation to the corresponding indole appeared feasible in the presence of the delicate functionalities which surrounded it. To this end, and as shown in Scheme 8, we synthesized indoline amide **25** (starting with **15**, by coupling with indoline and acid-induced deprotection, 60% overall yield), which was now poised for oxidation with DMP. We were, once again, to be disappointed. For still unknown reasons, indoline amide **25** resisted oxidation past the hemiketal stage, decomposing slowly over the course of several hours (as observed by TLC). This last failure led to a conjecture that the DMP oxidation would have to precede homologation. Although this sequence seemed similar to that of our first-generation strategy, it was rather distinguished in that it would now entail protection of the intermediate γ-hydroxylactol rather than construction of the lactone moiety and subsequent employment of an indoline amide group to shield the C-29 carbonyl from internal attack. Before a third-generation retrosynthesis could be finalized, however, we first decided to investigate possible protection strategies for the γ-hydroxylactol as shown in Scheme 9. Thus, we explored a number of protecting groups for the γ-hydroxylactol such as in the bisacetate **27c** and protected aldehyde lactols **27d**. However, the first scheme involving bisacetate **27c** was frustrated by our inability to remove the acetate groups once the final compound was reached, while suitable protecting groups R^1 and R^2 could not be defined[11] for **27d**. It was at this juncture that we came to the realization that we might use the pyran motif itself as the ideal protection scheme. During these investigations we had also found that the pyran-containing compounds were much more stable and behaved better on silica gel than their hydrated counterparts corresponding to **2**. In brief, the virtues of such a scheme included a decreased reliance on protecting group chemistry (only one protecting group versus three would be

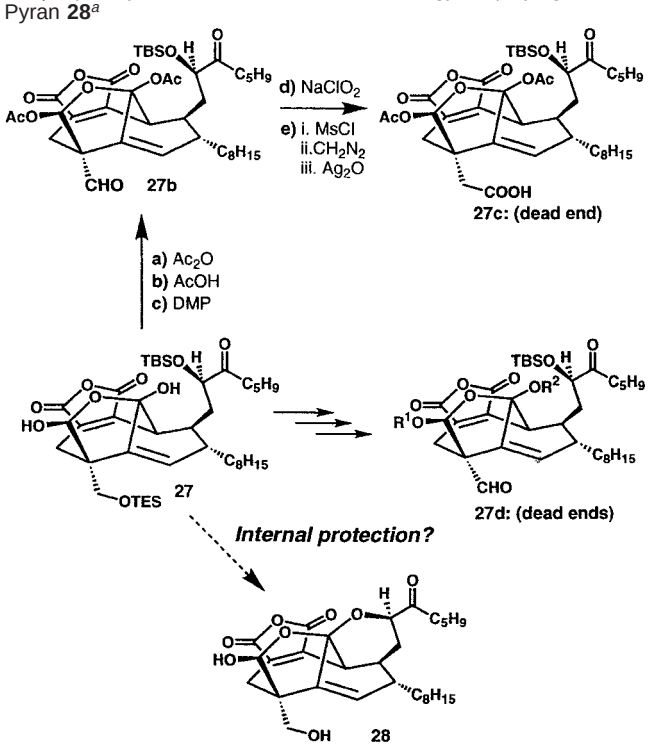
(8) (a) Nicolaou, K. C.; Zhong, Y.-L. Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 622. (b) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 625. (c) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Vega, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2525. (d) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596. (e) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y.-L. *Angew. Chem., Int. Ed.* **2001**, *40*, 207. (f) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2001**, *123*, 3183. (g) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S.; Sugita, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 2145.

(9) Nicolaou, K. C.; Baran, P. S.; Kranich, R.; Zhong, Y.-L.; Sugita, K.; Zou, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 202.

(10) De Oliveira Baptista, M. J. V.; Barrett, A. G. M.; Barton, D. H. R.; Girijavallabhan, M.; Jennings, R. C.; Kelly, J.; Papadimitriou, V. J.; Turner, J. V.; Usher, N. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1477.

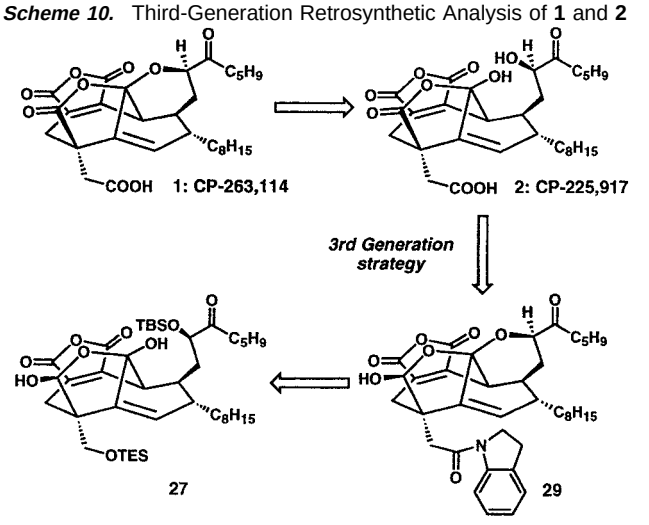
(11) For instance, the use of TES, TMS, and Alloc groups in several different combinations led to difficulties during the oxidation step with $NaClO_2$.

Scheme 9. Model Studies with Various Protection Schemes for the γ-Hydroxylactol Lead to a Revised Strategy Employing the Pyran **28**[a]



[a] Reagents and conditions: (a) Ac_2O (8.0 equiv), Et_3N (10 equiv), 4-DMAP (0.2 equiv), 25 °C, 3 h; (b) 80% aqueous AcOH, 25 °C, 1 h; (c) DMP (2.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 1 h, 57% overall; (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; (e) (i) MsCl (5.0 equiv), Et_3N (10 equiv), THF, 0 °C, 5 min; (ii) CH_2N_2 (excess), Et_2O/THF, 0 → 25 °C, 1 h; (iii) Ag_2O (5.0 equiv), DMF/H_2O (2:1), 120 °C, 1 min, 30% overall from **27b**.

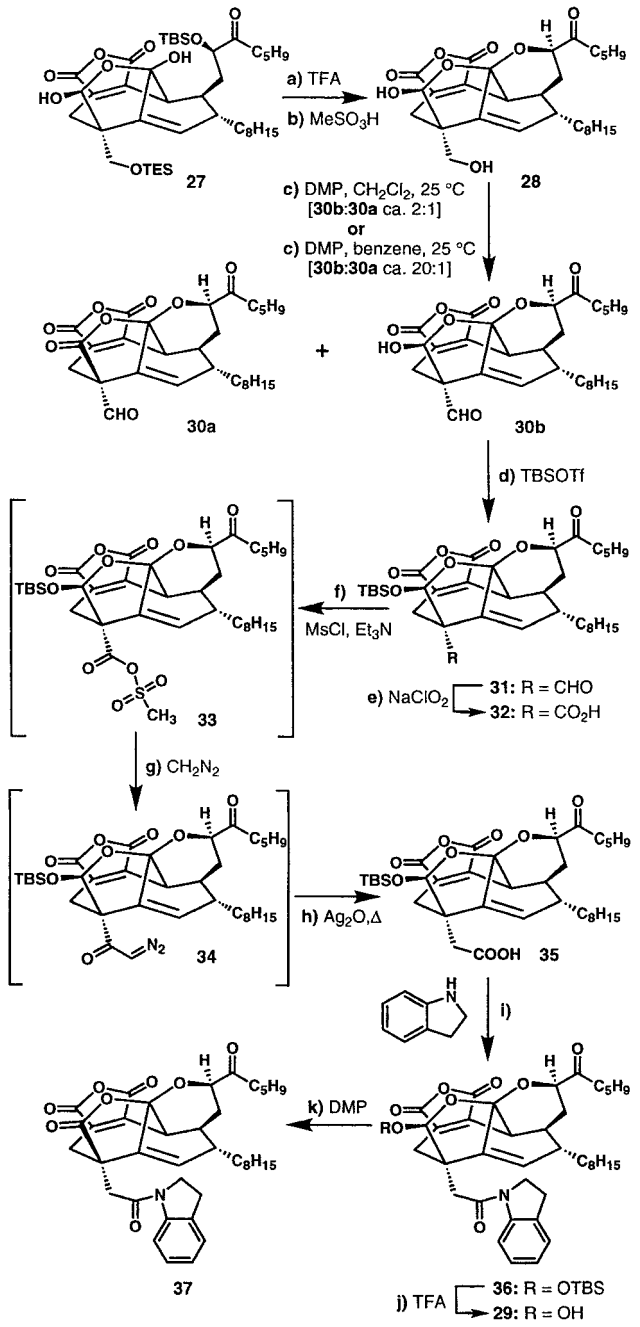
Scheme 10. Third-Generation Retrosynthetic Analysis of **1** and **2**



necessary) and greater stability and ease of handling for the pyran-containing intermediates.

With these considerations in mind, a new plan that targeted **1** via **2** was devised as shown retrosynthetically in Scheme 10. Since the conversion of **2** to **1** was already known,[12] the challenge was to procure **29** from the previously synthesized **27** and convert it to **2**. The feasibility of converting the pyran-containing intermediate **29** into **2** will be addressed later (vide infra). The implementation of the new strategy is shown in Scheme 11. Thus, sequential treatment of **27** with aqueous TFA/CH_2Cl_2 to remove both silicon groups followed by exposure to $MeSO_3H$ in dry $CHCl_3$ led to pyran−lactol **28** in 83% overall yield. A key observation was made during the selective oxidation of diol **28** to aldehyde **30b**. When diol **28** was oxidized using

Scheme 11. Arrival at the Indoline Amide **37**[a]



[a] Reagents and conditions: (a) (1) CH_2Cl_2/TFA/H_2O (40:4:1), 25 °C, 2 h; (b) $MeSO_3H$ (0.3 equiv), $CHCl_3$, 25 °C, 2 h, 83% overall; (c) DMP (5.0 equiv), CH_2Cl_2, 25 °C, 1 H, 85%, **30b**:**30a** = 2:1, or DMP (5.0 equiv), benzene, 25 °C, 2 h, 90%, **30b**:**30a** = ca. >20:1; (d) TBSOTf (20 equiv), 2,6-lutidine (50 equiv), CH_2Cl_2, 0 → 25 °C, 3 h, 80%; (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, 83%; (f) MsCl (5.0 equiv), Et_3N (10 equiv), THF, 0 °C, 5 min; (g) CH_2N_2 (excess), Et_2O/THF, 0 → 25 °C, 45 min; (h) Ag_2O (5.0 equiv), DMF/H_2O, (2:1), 120 °C, 1 min, 35% overall from **32**; (i) indoline (1.5 equiv), EDC (3.0 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 1.0 h, 87%; (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, 35 h, 90%.

(12) Dabrah, T. T.; Kaneko, T.; Massefski, W., Jr.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594.

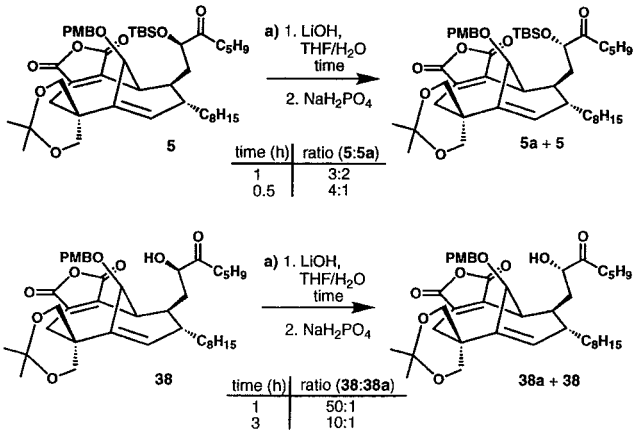
DMP in CH_2Cl_2 at ambient temperature, the aldehyde lactol **30b** was isolated as the major product along with significant amounts of lactone **30a** (**30b**:**30a** = ca. 2:1, 85% combined yield). The implication was that DMP rather than TEMPO (as required before)[1] would be sufficient to convert the γ-hydroxylactol to the corresponding lactone. Although the TEMPO protocol accomplished this task, it required excess reagents and flash chromatography for purification and removal of excess reagent. Consistent with observations reported in the previous paper,[1] when protected, the reactivity of the hydroxyl group of the γ-hydroxylactol became comparable to that of a simple lactol.

Over the course of this work we had also learned that it is possible to modulate the reactivity of DMP simply by altering the solvent of the reaction. Thus, the undesired, yet highly informative, lactone aldehyde **30a** could essentially be eliminated (**30b**:**30a** > 20:1, 90% combined yield) by carrying out the DMP oxidation in benzene at 25 °C rather than CH_2Cl_2. The resulting lactol **30b** was shielded from the ensuing homologation conditions by protection as the TBS ether **31** (TBSOTf, 2,6-lutidine, 80% yield). Oxidation of the latter compound (**31**) with $NaClO_2$ proceeded smoothly to produce carboxylic acid **32** in 83% yield. The challenging task of converting the sterically congested carboxylic acid **32** into diazo ketone **34** was easily accomplished by the technology described above and via the acyl mesylate **33** (prepared in situ with MsCl/Et_3N at 0 °C).[4] The diazo ketone so obtained was immediately dissolved in DMF/water (2:1) and heated to 120 °C in the presence of freshly purified Ag_2O for 1 min to generate the homologated carboxylic acid **35** in 35% overall yield from **32**. The union of carboxylic acid **35** with indoline proceeded smoothly in the presence of EDC and 4-DMAP to provide amide **36** (87% yield). Removal of the pendant TBS group from **36** was assisted by TFA and revealed lactol **29** (95% yield), which could easily be oxidized to lactone **37** in 90% yield by the action of DMP (5.0 equiv, CH_2Cl_2, 25 °C, 28 h).

At this juncture, it became necessary to find reliable conditions for the counterintuitive conversion of **1** into **2**. From our studies regarding the general stability of the maleic anhydride moiety, we were confident of the ability to open and reclose the anhydride ring through exposure to base (LiOH) and acid, respectively.[1] We then tested the stability of the advanced key intermediate **5** toward basic treatment to probe the ease with which the suspected epimerization at C-7 might take place (Scheme 12). To our dismay we found that treatment of **5** with LiOH (10 equiv) in THF/water followed by workup with NaH_2PO_4 led to a 3:2 mixture of epimers (**5**/**5a**) as observed by ^{1}H NMR after only 1 h. Halting the reaction after 30 min afforded a 4:1 mixture of epimers, the major of which was still **5**. As troubling as this was, in the real system we would also be faced with the potentially destructive isomerization of the α-hydroxy ketone system. With these issues in mind, we submitted the hydroxy ketone **38** to the same conditions (LiOH, 10 equiv, THF/water; then workup with NaH_2PO_4) and much to our delight found that the α-hydroxy ketone system was still intact with almost no epimerization (>50:1 **38**/**38a** by ^{1}H NMR) after 1 h. After 3 h the ratio was still a remarkable 10:1 in favor of **38**.

On the basis of these promising model studies and armed with a small amount of natural **1**, supplied by Pfizer,[13] we proceeded to test the conversion in the real system. All along

Scheme 12. Epimerization Studies with the Advanced Key Intermediates **5** and **38**[a]



[a] Reagents and conditions: (a) LiOH (10 equiv), THF/H_2O (4:1), 25 °C, time indicated above; then 10% NaH_2PO_4, 10 min, analysis by ^{1}H NMR spectroscopy.

we had rationalized that LiOH could serve as an excellent candidate for the planned transformation of **1** to **2** by virtue of its unique nucleophilicity and solubility profile.[14] Gratifyingly, we were able to cleanly effect this conversion (**1** to **2**, Scheme 13) in over 90% yield and with no significant decomposition or epimerization at C-7. Since this operation, commencing with **1**, accomplished masking of the maleic anhydride (as its dianion), basic opening of the γ-hydroxylactone, deprotonation of the C-29 carboxylic acid, and reconstitution to **2** upon acidic workup, this represents a unique cascade reaction sequence (Scheme 13). In the case of the free acid **1**, the initially formed carboxylate anion **A** has the option of either attacking, intramolecularly, the γ-lactone via a 5-*exo*-trig cyclization, forming **B** and **C** (in equilibrium) (path A, Scheme 13), which then may suffer external hydroxide attack, leading to **D**−**F** (in equilibrium), or directly experiencing attack by hydroxide to form the same intermediates (**D**−**F**, path B, Scheme 13). This tandem hydrolysis obviously involves a mechanism analogous to path B (Scheme 13) in the case where C-29 is protected with a more robust group than the delicate γ-hydroxylactone (vide infra). After our initial report, the Danishefsky group utilized similar conditions to study the C-7 epimers of the CP-molecules,[15] and observed a similar "epimerization-free" result in the conversion of **1** to **2**.

Equipped with this crucial information regarding the interconversion of **1** and **2**, we returned to the total synthesis efforts. Specifically, we set out to convert the indoline **37** to the indole **39** (Scheme 14) in preparation for the key cascade hydrolysis. Although DDQ was reported[10] to effect this transformation, only decomposition was observed with **37** under these conditions. After an array of oxidants were scanned, *p*-chloroanil was identified as the most suitable reagent to accomplish this conversion, presumably due to its milder nature. Thus, treatment of **37** with excess *p*-chloroanil (toluene, Δ) led to the indole **39** (67% yield plus 30% recovered **37**), thus regenerating the electrophilicity at the carbonyl center and rendering this moiety

(13) Samples of **1** and **2** were kindly provided by Dr. T. Kaneko of Pfizer (Groton, CT).
(14) West, F. G.; Bender, J. A. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, U.K., 1995; Vol. 5, p 3132.
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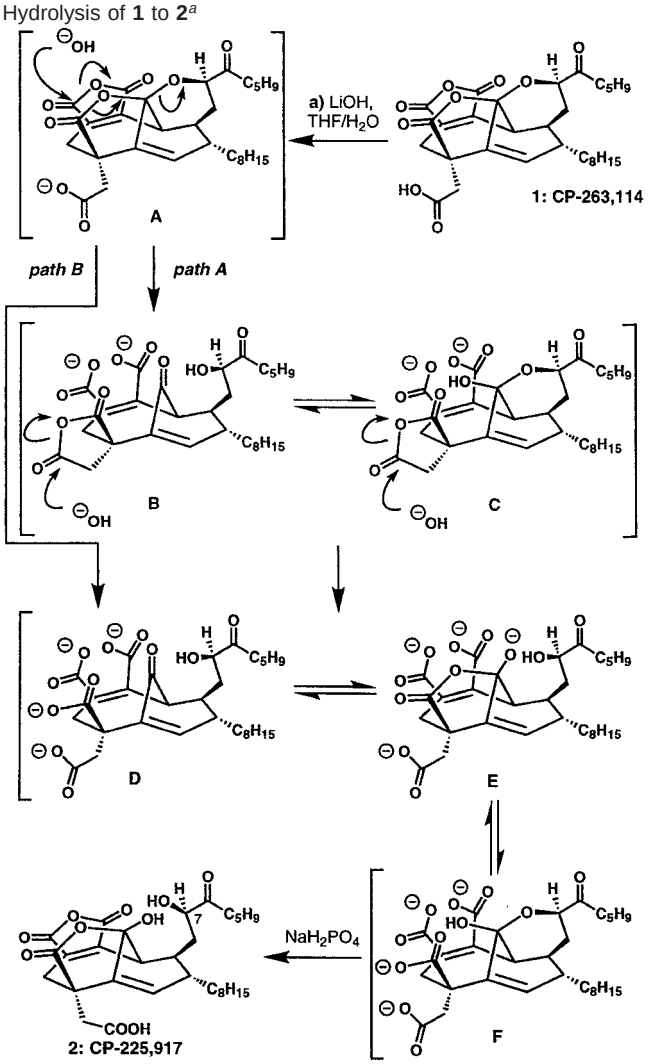
Scheme 13. Mechanistic Considerations for the Cascade Hydrolysis of **1** to **2**[a]

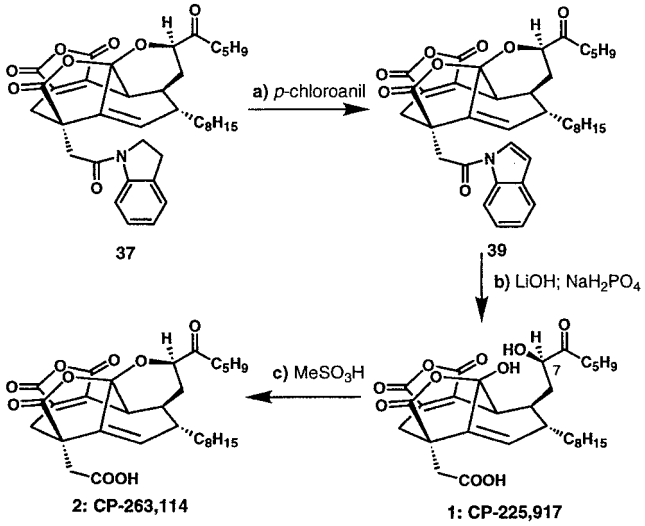


[a] Reagents and conditions: (a) LiOH (10 equiv), THF/H_2O (4:1), 25 °C, 30 min, then 10% NaH_2PO_4, 10 min, 90%.

susceptible to mild, base-induced hydrolysis (Scheme 14). Enlistment of our LiOH-based cascade hydrolysis succeeded in furnishing **2** (72% yield), thus verifying the relative configuration at C-7. Furthermore, direct treatment with methanesulfonic acid in $CDCl_3$ over the course of 36 h resulted in an essentially quantitative conversion of **2** into **1** (72% yield of isolated product). The spectroscopic and chromatographic properties of both synthetic **1** and **2** matched those of authentic samples.[12,13]

Scheme 15 summarizes our asymmetric total synthesis of **1** and **2**, which also served to establish, for the first time, their absolute configuration.[16] Having already described the asymmetric synthesis of intermediates **40** and **41** (Scheme 15) in the first paper[17] of this series, we will now detail the conversion of the major one to the natural products **1** and **2**, a process that revealed their absolute stereochemistry. Thus, compounds **40** and **41** (5.7:1 mixture) were desilylated with TBAF, and the resulting mixture of diols (**42** and **43**, respectively) was subjected to flash chromatography [silica gel, hexanes/EtOAc (2:1)], which allowed almost complete separation of the two diastereomers

Scheme 14. Completion of the Total Synthesis of **1** and **2**[a]



[a] Reagents and conditions: (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_2PO_4, 10 min, 72%; (c) $MeSO_3H$ (1.0 equiv), $CDCl_3$, 25 °C, 24 h, 90%.

42 (major) and **43** (minor). Sodium periodate-induced oxidative cleavage of these diols (**42** and **43**) resulted in the formation of aldehydes (−)-**44** and (+)-**44**, respectively (95% yield); on the basis of the diastereomeric enrichment of **42** (ca. 15:1), the enantiomeric excess of (−)-**44** was calculated to be ca. 87%. The optically enriched aldehyde (−)-**44**, whose racemic form is a known intermediate in the total synthesis of racemic **1** and **2**, was then converted to the indoline (+)-**37** as described above. Due to the ease of purification and handling and the amplified optical rotation of the indoline derivatives, we chose to make comparisons at this stage (**37**, Scheme 15). Thus, synthetic (+)-**37**, derived from the major Diels−Alder product **40**,[17] was found to be identical to natural (−)-**37** according to ^1H and ^{13}C NMR spectroscopy, TLC (three different solvent systems), HPLC, and IR spectroscopy. The optical rotation, however, was opposite in magnitude ($[\alpha]_D^{23} = +56.2°$, $c = 0.08$, CH_2Cl_2) to that of the naturally derived (−)-**37** ($[\alpha]_D^{23} = -80.0°$, $c = 0.1$, CH_2Cl_2). Circular dichroism (CD) spectroscopy verified the identity of synthetic (+)-**37** as the enantiomer of natural (−)-**37** by virtue of the pronounced antipodal Cotton effect observed (see the Supporting Information). Synthetic (+)-**37** could also be processed in the same manner as racemic **37** (vide supra) to give *ent*-**1** and *ent*-**2**. Since the absolute configuration of **40** and **41** is certain,[17] the absolute configuration of the CP-molecules can be confidently assigned as shown in Scheme 15 (structures **1a** and **1b**). Subsequent asymmetric syntheses of the CP-molecules by Shair[18] and Fukuyama[19] confirmed this assignment.

3. Generation of Complex CP-Analogues. The anhydride domain is perhaps the most important area of the CP skeleton in terms of its biological activity. Our synthetic studies on the CP-molecules revealed the paradox of the maleic anhydride moiety: possessing a fragile and reactive nature yet exhibiting admirable robustness under certain conditions. Treatment with

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(17) Nicolaou, K. C.; Jung, J.; Yoon, W. H.; Fong, K. C.; Choi, H.-S.; He, Y.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 2183−2189.

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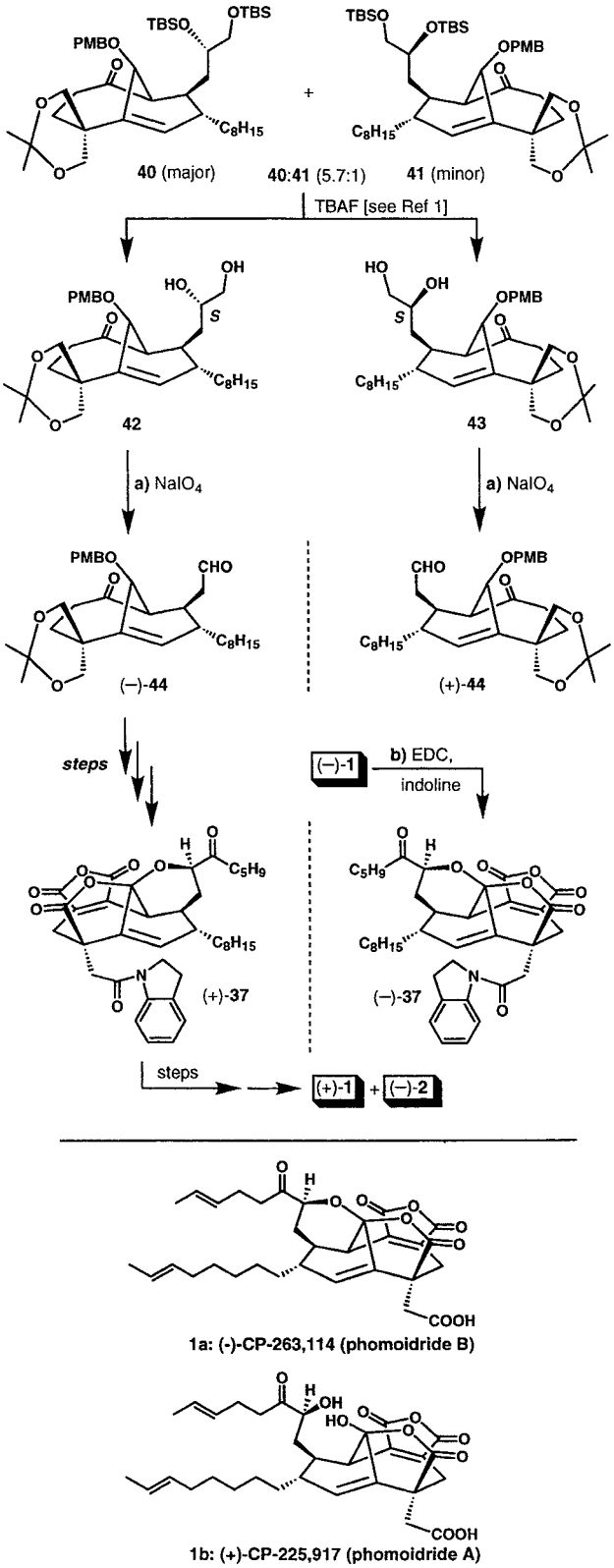
Scheme 15. Completion of the Asymmetric Total Synthesis of the CP-Molecules and Assignment of Their Absolute Configuration (**1a** and **1b**)[a]



1a: (-)-CP-263,114 (phomoidride B)

1b: (+)-CP-225,917 (phomoidride A)

[a] Reagents and conditions: (a) $NaIO_4$ (1.5 equiv), NaOH, EtOH, 0 → 25 °C, 2 h, >95%; (b) indoline (1.5 equiv), EDC (3.0 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 1.0 h, 85%.

hydroxide ion rapidly leads to rupture of this moiety to the corresponding dicarboxylate. Reclosure is quite rapid upon addition of acid. Most significantly, this cycle can be accomplished without epimerization or isomerization (vide supra) of the α-hydroxy ketone (C-7). It is interesting to note the resemblance of the structures of the highly oxygenated CP-molecules with those of the squalestatins (zaragozic acids), especially under basic conditions.[20] Not surprisingly, both classes of molecules display inhibition of squalene synthase although the CP-molecules are also highly selective inhibitors of farnesyl transferase.[12] Analogues of the CP-molecules equipped with a maleimide functionality instead of the maleic anhydride moiety may serve as unique tools to investigate the role of the latter group in the mechanism of action of these natural products.

Our progress toward the first complex analogue of the CP-molecules, "NH"-CP-225,917 (**62**), is shown in Scheme 16. Thus, starting from the hydroxyamide **45** (whose synthesis has been described in the preceding paper[1]), PDC-mediated oxidation led to the maleimide **46** (90% yield).[1] Removal of the TES and dimethoxy ketal groups from **46** under acidic conditions led to the corresponding α-hydroxy ketone **47** (upon reinstallment of the acetonide which was cleaved under the reaction conditions). Masking of both the free hydroxyl and maleimide NH group with TBSOTf/2,6-lutidine in CH_2Cl_2 furnished the maleimide analogue of **5** (Scheme 1), compound **48** (72% overall). Intermediate **48** was then processed in a manner similar to that of **5** (Scheme 1; see also ref 1), leading to indole **60** as summarized in Scheme 16. The overall yield of this sequence was slightly higher than that for the corresponding anhydride-containing intermediates due to the higher stability of the protected maleimide moiety. Notably, the homologation of acid **57** proceeded to furnish the corresponding carboxylic acid in an admirable 67% yield. TBAF-mediated removal of the *N*-TBS group from **60** led to indole **61** (95% yield). Preliminary results indicated that the maleimide functionality was rather labile under basic conditions, giving rise to a mixture of products upon exposure to LiOH. To circumvent this problem, the acid-labile *tert*-butyl ester **63** was targeted from **57** and synthesized as shown in Scheme 16 (after Arndt−Eistert homologation with *t*-BuOH, 39% yield). Assuming that the lactol can be deprotected without cyclization, ester **63** offers the opportunity for an acid-mediated final deprotection en route to **62** (Scheme 16). The methyl ester **64** was also prepared from **57** (exposure to diazomethane followed by TBAF-induced desilylation, 36% overall yield).

Conclusion

By virtue of their stunning molecular architecture, the CP-molecules presented us a myriad of synthetic challenges and required a relentless quest through a synthetic labyrinth showered with unforeseen obstacles, yet filled with numerous hidden "treasures". The blend of novel cascade reactions, new synthetic methods, and unprecedented synthetic strategies and tactics arising from these total synthesis endeavors stand as a tribute to the innate complexity and yet rewarding nature of these molecules and a triumph of modern organic synthesis over them. Most significantly, this highly fruitful experience underscores the importance of total synthesis in catalyzing the invention, discovery, and development of new and enabling technologies for organic synthesis, biology, and medicine.[21] Among them

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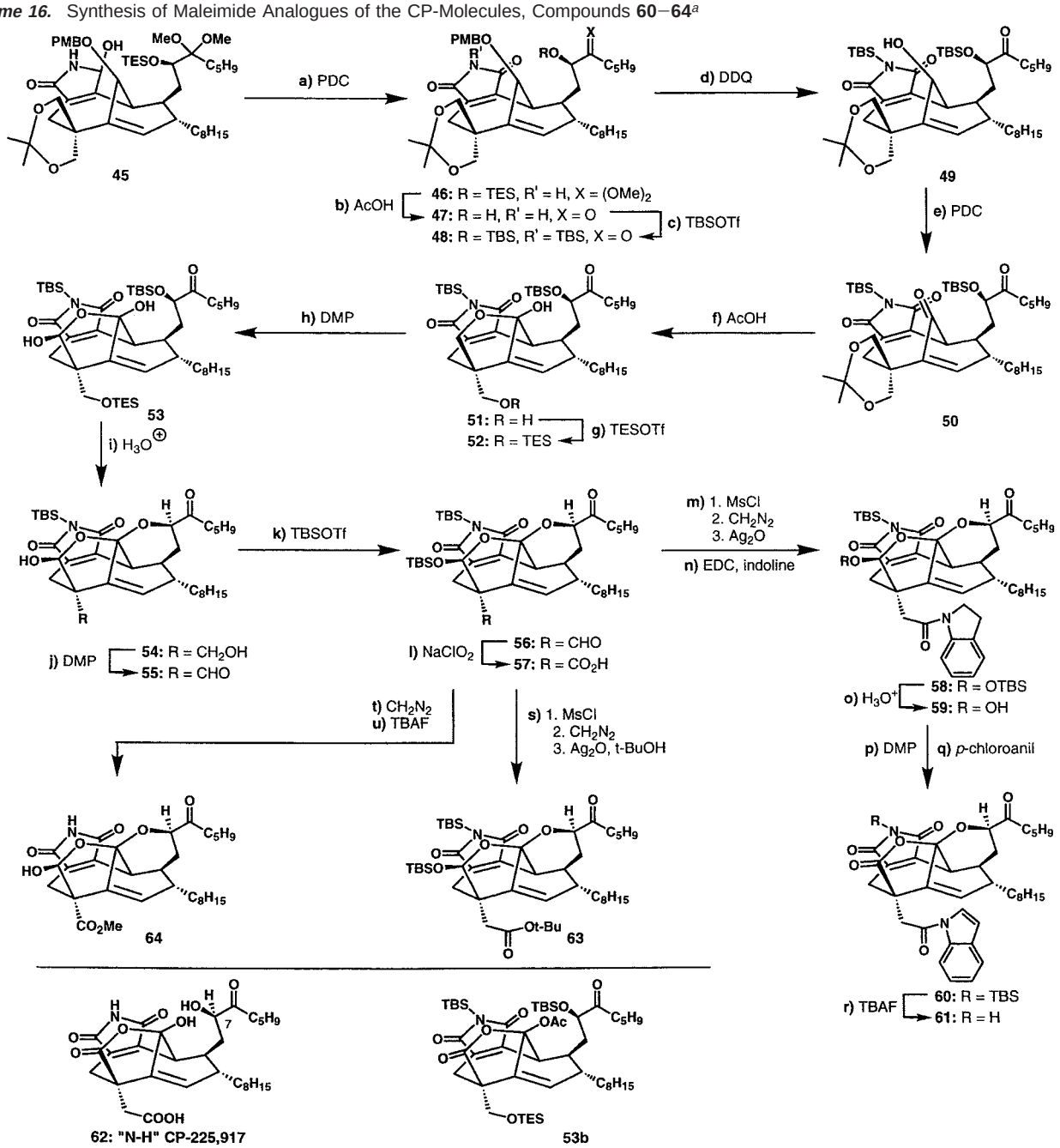
Scheme 16. Synthesis of Maleimide Analogues of the CP-Molecules, Compounds **60**−**64**[a]



[a] Reagents and conditions: (a) PDC (5.0 equiv), AcOH (cat.), 4A molecular sieves, CH_2Cl_2, 25 °C, 2 h, 90%; (b) (1) 90% aqueous AcOH, 25 °C, 1.5 h; (2) $Me_2C(OMe)_2$ (1.5 equiv), CSA (0.05 equiv), CH_2Cl_2, 25 °C, 1 h; (c) TBSOTf (3.0 equiv), 2,6-lutidine (15 equiv), 25 °C, 2 h, 72% overall; (d) DDQ (2.0 equiv), CH_2Cl_2/H_2O (18:1), 25 °C, 40 min, 60% **49** + 11% **48**; (e) PDC (3.2 equiv), CH_2Cl_2, 25 °C, 1 h, 91%; (f) 80% aqueous AcOH, 25 °C, 6 h, 75%; (g) TESOTf (1.3 equiv), 2,6-lutidine (10 equiv), CH_2Cl_2, −30 °C, 30 min; then 0 °C, 30 min, 88%; (h) DMP (3.0 equiv), H_2O (3.0 equiv), benzene, 80 °C, 15 min, 58% **53** + 10% **52** + 8% **53b**; (i) (1) CH_2Cl_2/TFA/H_2O (40:4:1), 0 → 25 °C, 1.3 h; (2) CH_3SO_3H (0.1 equiv), CH_2Cl_2, 25 °C, 12 h, 73% overall; (j) DMP (2.0 equiv), benzene, 25 °C, 1 h, 84%; (k) TBSOTf (10 equiv), 2,6-lutidine (50 equiv), CH_2Cl_2, 0 → 25 °C, 2 h, 83%; (l) $NaClO_2$ (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, 80%; (m) (1) MsCl (5.0 equiv), Et_3N (10 equiv), THF, 0 °C, 5 min; (2) CH_2N_2 (100 equiv), Et_2O/THF, 0 → 25 °C, 45 min; (3) Ag_2O (5.0 equiv), DMF/H_2O (2:1) 120 °C, 1 min, 35% overall from **57**; (n) indoline (1.5 equiv), EDC (3.0 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 1.0 h, 85%; (o) CH_2Cl_2/TFA/H_2O (40:4:1), 0 → 25 °C, 1.3 h, 8 h, 75% **60** + 14% starting material; (r) TBAF (10 equiv), THF, 25 °C, 15 min, 95%; (s) (1) MsCl (5.0 equiv), Et_3N (10 equiv), THF, 0 °C, 5 min; (2) CH_2N_2 (100 equiv), Et_2O/THF, 0 → 25 °C, 45 min; (3) Ag_2O (5.0 equiv), Et_3N (10 equiv), *t*-BuOH, 120 °C, 10 min, 39% overall from **57**; (t) CH_2N_2 (excess), Et_2O, 0 °C; (u) TBAF (4.0 equiv), THF, 0 °C, 1 min, 36%.

are methods for the chemoselective homologation of hindered systems,[4,22] DMP-mediated synthesis of unique heterocycles[8a] and quinones[8e] via *o*-azaquinones,[8g] IBX-mediated heterocycle synthesis,[8b,c] SET-based oxidations,[8d,f,9] and new routes to ubiquitous heterocycles using α-sulfonated ketones.[23] Some of

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these new reactions and enabling synthetic technologies are described in detail in the following papers.[24−27]

Acknowledgment. We thank Dr. T. Kaneko of Pfizer for kindly providing us with samples of **1** and **2**. We also thank Drs. D. H. Huang and G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. This work was financially supported by the National Institutes of Health, The Skaggs Institute for Chemical Biology, doctoral fellowships from the National Science Foundation (to P.S.B.), a postdoctoral fellowship from the Korea Science and Engineering Foundation (to H.-S.C.), and grants from Abbott, Amgen, ArrayBiopharma, Boehringer Ingelheim, DuPont, Glaxo, Hoffmann-La Roche, Merck, Pfizer, and Schering Plough.

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Supporting Information Available: Experimental procedures and compound characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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