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Total Synthesis of the CP-Molecules (CP-263,114 and CP-225,917, Phomoidrides B and A). 2. Model Studies for the Construction of Key Structural Elements and First-Generation Strategy

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Abstract: Crucial model synthetic and mechanistic studies directed toward the development of methodology for the construction of the maleic anhydride moiety of the CP-molecules are described. Studies directed toward the stereoselective attachment of the upper side chain, culminating in the discovery of long-range stereochemical control, are also discussed. In addition, a first-generation strategy toward the CP-molecules, establishing key intermediate **5** as a "beachhead" from which all future operations would diverge, is also presented. Although this first-generation strategy failed to yield the target molecules, the endeavor laid the important groundwork for the next-generation drives toward the CP-molecules.

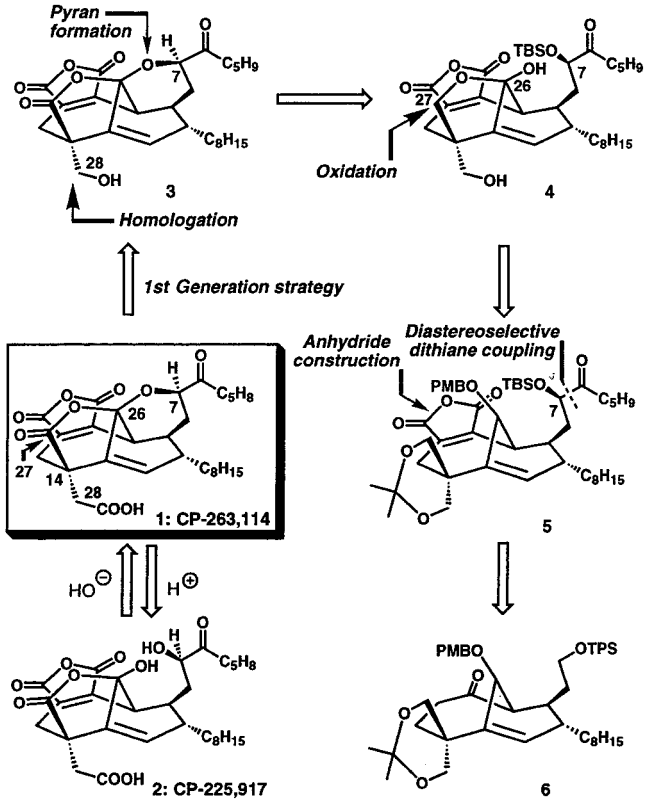
Introduction

In the preceding paper in this issue,[1] we described racemic and asymmetric modes of constructing the bicyclo[4.3.1] carbogenic framework of the CP-molecules (**1** and **2**, Scheme 1). These studies set the stage for a critical evaluation of modalities for appending the various moieties adorning the periphery of these novel molecular architectures. Upon casual inspection, the maleic anhydride, γ-hydroxylactonol, remote stereocenter at C-7, and quaternary center at C-14 appear to be only moderately challenging to construct. We soon found out, however, that classical routes to these seemingly innocent functionalities were plagued by numerous unpredictable events and failures. Compounding these challenges was the fickle nature of the CP skeleton, which required that the surrounding functionalities be incorporated in a certain order. But, as we shall see, it was this stream of obstacles which prompted the development of numerous new synthetic methods and the discovery of new chemistry. In this paper we address the problems posed by the fused maleic anhydride moiety, the γ-hydroxylactone system, and the remote stereocenter at C-7 in the context of a first-generation approach to the CP-molecules.

Results and Discussion

1. Retrosynthetic Analysis. We begin with the first-generation retrosynthetic analysis of the CP-molecules. A retrosynthetic overview of our key strategic bond disconnections is depicted in Scheme 1. Since the Pfizer group, which reported **1** and **2**, had already shown that **2** may be converted to **1** under anhydrous acid conditions and that **1** was stable in acidic aqueous media, it seemed logical to first target structure **2**.[2] Furthermore, and despite the array of base-sensitive functionalities present in **1**,

Scheme 1. First-Generation Retrosynthetic Analysis of **1** and **2**



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(1) 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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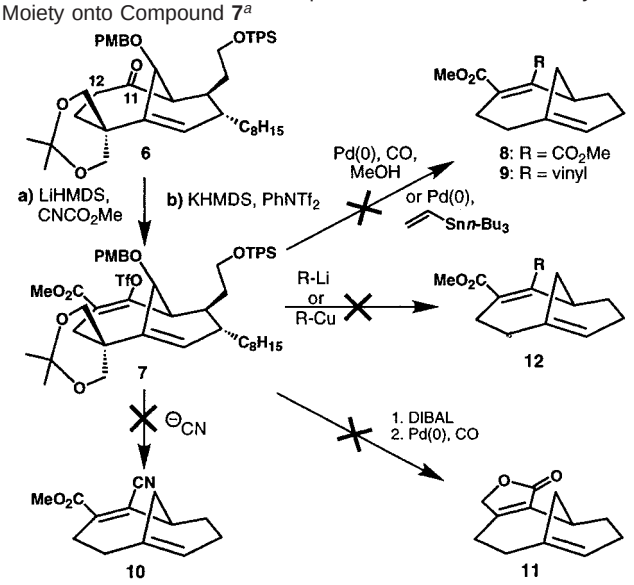
we hypothesized that the conversion of **1** to **2** might also be possible through the deployment of carefully controlled basic conditions. Thus, although we initially targeted **2**, we believed that reaching either **1** or **2** was an opportunity to access the other as well (Scheme 1).

As the first task in the retrosynthetic analysis and to shorten the potential synthesis through the introduction of symmetry elements, we decided to truncate the carboxylic acid chain by one carbon. Having identified the classic Arndt−Eistert reaction[3] as a potential method for a one-carbon homologation of the carboxylic acid terminus, we then converted retrosynthetically target **1** to primary alcohol **3**. Opening the pyran system of **3** and lowering the oxidation state of C-27 led to hydroxylactol **4** as a potential precursor to **3**. Protecting group manipulations and a further lowering of oxidation state, now at C-26, then unraveled advanced key intermediate **5**. Model studies and reactivity considerations pointed toward the use of key intermediate **5** as a beachhead from which all further synthetic maneuvers would diverge. Compound **5** was traced back to building block ketone **6**, which had already been secured through an intramolecular Diels−Alder reaction as described in the preceding paper.[1] To convert **6** to **5**, efficient methods for the installment of the fused anhydride moiety and stereoselective fastening of the "upper" side chain were envisaged. Although we predicted the former task to be considerably more challenging, we did not expect the stereoselective installation of the side chain to be trivial.

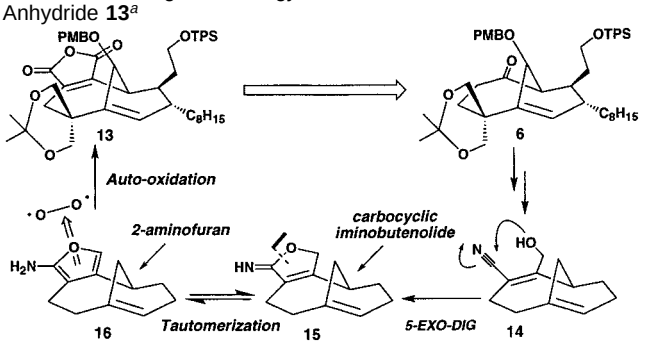
2. Studies toward the Maleic Anhydride Moiety. Having decided upon a reasonable plan of action as outlined above and with ample quantities of key intermediate **6** in hand, we proceeded to investigate the various methods for the fusion of the maleic anhydride moiety onto this intermediate using its carbonyl group as a handle. Our initial forays were met with disappointing results. A glimpse of the numerous failures encountered in attempting to build this moiety onto **6** may be gained by looking at Scheme 2. Thus, although conversion of ketone **6** to its carboxymethylated triflate **7** [(i) LiHMDS followed by quenching with Mander's reagent (CNCOOMe);[4] (ii) KHMDS followed by $PhNTf_2$, 26% overall yield, unoptimized] proceeded well, attempts to elaborate further the latter intermediate proved unsuccessful (see Scheme 2). Furthermore, attempts to construct the α-bromo triflate[5] via the corresponding α-bromo ketone were foiled due to our inability to introduce a bromine into the molecule without bromination of the neighboring olefins. It is now apparent that the precise structure of the employed intermediates is important for functionalization as desired since Shair and co-workers reported a successful Pd-mediated [$Pd(OAc)_2$, $P(OMe)_3$, CO (500 psi)] carboxymethylation on a related intermediate,[6] while we and others[7] experienced resistance in building the anhydride moiety employing conventional methods. Molecular models reveal substantial steric hindrance at C-11 when C-12 is substituted, and it is likely that substitution at both of these carbons blocks their access by most reagents.

Scheme 2. Unsuccessful Attempts To Install the Maleic Anhydride Moiety onto Compound **7**[a]



[a] Reagents and conditions: (a) LiHMDS (1.3 equiv), THF, −78 °C, 1 h; then $CNCO_2Me$ (1.2 equiv), −78 → 0 °C, 3 h; (b) KHMDS (1.5 equiv), $PhNTf_2$ (1.2 equiv), 0 °C, 1 h, 52% overall.

Scheme 3. Designed Strategy for the Conversion of Ketone **6** to Anhydride **13**[a]

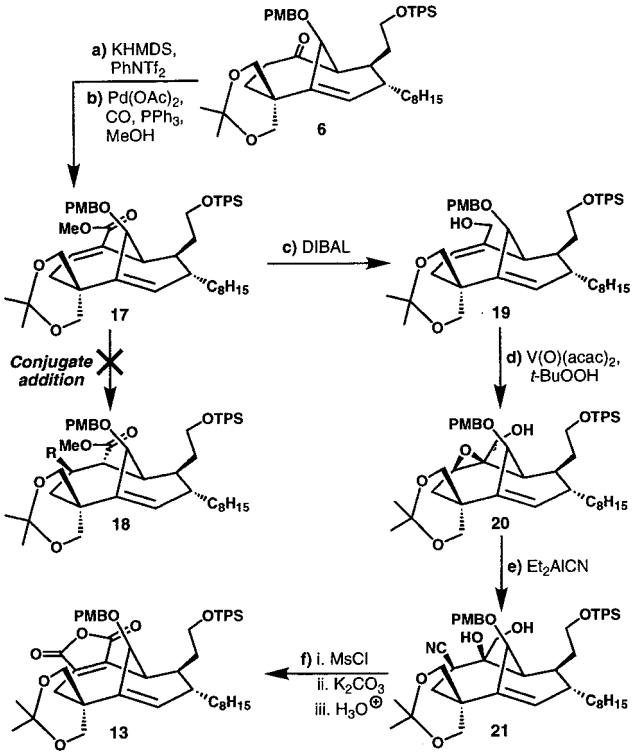


[a] Appendages in **14**−**16** have been deleted for clarity. PMB = *p*-methoxybenzyl; TPS = *tert*-butyldiphenylsilyl. For C_8H_{15}, see Figure 1.

The persistence of the maleic anhydride challenge inspired the development of a strategy which capitalized on the unique steric and electronic peculiarities present in the CP skeleton. The principal features of this strategy are outlined in Scheme 3. According to this approach, access to the recalcitrant anhydride moiety would rely on the autoxidation of an unprecedented carbocyclic 2-aminofuran[8] (i.e., **16**, Scheme 3). Thus, we reasoned that due to its highly electron-rich nature,[9] the 2-aminofuran **16** could serve as a novel masking device, revealing, upon facile oxidation in air, the desired anhydride **13**. Furthermore, from the extensive theoretical work of Dewar,[10] it was expected that the aminofuran **16** could be accessible from the tautomeric iminobutenolide system **15**, whose origin from hydroxynitrile **14** was obvious upon disconnection of the

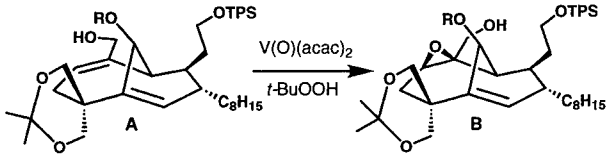
(2) Dabrah, T. T.; Kaneko, T.; Massefski, W., Jr.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594.
(3) Arndt, F.; Eistert, B. *Ber. Dtsch. Chem. Ges.* **1935**, *68B*, 200.
(4) Crabtree, S. R.; Mander, L. N.; Sethi, S. P. *Org. Synth.* **1991**, *70*, 256.
(5) Voigt, K.; Von Zezschwitz, P.; Rosauer, K.; Lansky, A.; Adams, A.; Reiser, O.; De Meijere, A. *Eur. J. Org. Chem.* **1998**, *8*, 1521.
(6) Chuo, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424.
(7) Clive, D. L. J.; Sun, S.; Gagliardini, V.; Sano, M. K. *Tetrahedron Lett.* **2000**, *41*, 6259. Nobuaki, W.; Itoh, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 7825.
(8) Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Heterocycl. Chem.* **1993**, *30*, 113. For the elegant use of amidofurans in synthesis, see: Padwa, A.; Dimitroff, M.; Liu, B. *Org. Lett.* **2000**, *2*, 3233 and references therein.
(9) Ito, K.; Yakushijin, K. *Heterocycles* **1978**, *9*, 1603. Yakushijin, K.; Kozuka, M.; Furukawa, H. *Chem. Pharm. Bull.* **1980**, *28*, 2178.
(10) Bodor; N.; Dewar, M. J. S.; Harget, A. J. *J. Am. Chem. Soc.* **1970**, *92*, 2929.

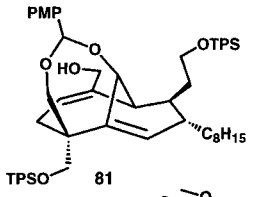
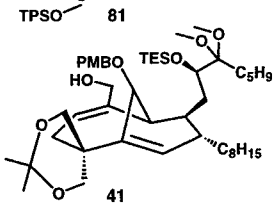
Scheme 4. Construction of Maleic Anhydride Derivative **13** from Ketone **6**[a]



[a] Reagents and conditions: (a) KHMDS (1.5 equiv), 0 °C; then $PhNTf_2$ (2.0 equiv), THF, 10 min, 95%; (b) $Pd(OAc)_2$ (0.06 equiv), PPh_3 (0.12 equiv), MeOH (40 equiv), Et_3N (2.0 equiv), DMF, CO, 25 °C, 10 min; then triflate, 50 °C, 20 min, 76%; (c) DIBAL (3.0 equiv), toluene, −78 °C, 95%; (d) $V(O)(acac)_2$ (0.2 equiv), *t*-BuOOH (1.4 equiv), benzene, 25 °C, 0.5 h, 85%, 3.7:1 β/α; (e) Et_2AlCN (5.0 equiv), toluene, 0 °C, 15 min; then 25 °C, 2.5 h, 68%; (f) (i) MsCl (3.0 equiv), Et_3N (10 equiv), THF, 0 °C, 5 min; (ii) K_2CO_3 (20 equiv), MeOH, 15 min; (iii) Et_2O, 10% oxalic acid (5% v/v), 0.5 h, 60%.

Table 1. Selectivity (α:β) in the Epoxidation of Allylic Bicyclo[4.3.1] Substrates **A** with $V(O)(acac)_2$/*t*-BuOOH[a]



Entry	Substrate	Yield (%)[b]	Ratio (α:β)[c]
1	R = Me (**79**)	83 (**79'**)	1:10
2	R = PMB (**19**)	86 (**20**)	1:3.7
3	R = H (**80**)	92 (**80'**)	1:80
4		71 (**81'**)	1:1
5		76 (**42**)	1:10.7

[a] Reagents and conditions: $V(O)(acac)_2$ (0.2 equiv), *t*-BuOOH (1.4 equiv), benzene (0.02 M), 25 °C. [b] Isolated yield of chromatographically pure products. [c] Determined by ^1H NMR spectroscopy.

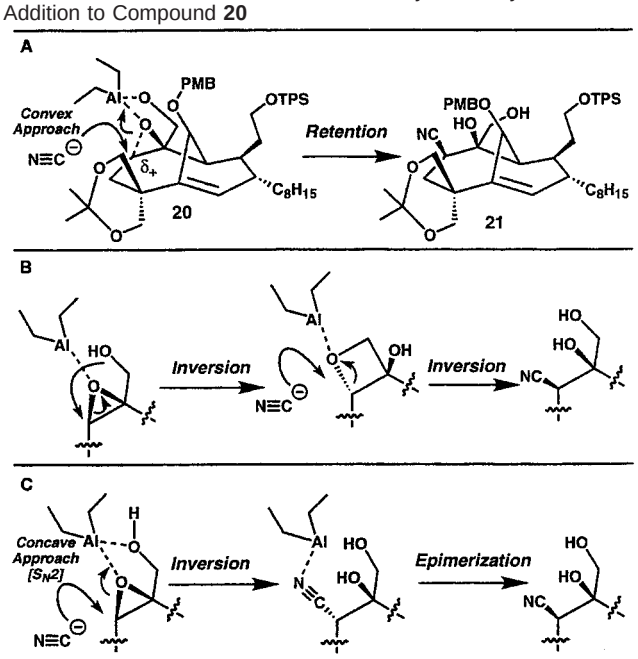
appropriate carbon−oxygen bond. Hydroxynitrile **14** was then traced back to ketone **6** via standard chemistry involving introduction of the two required carbon atoms.

The successful execution of this plan is summarized in Scheme 4. Thus, the Diels−Alder adduct **6** was efficiently converted to the α,β-unsaturated ester **17** via palladium-catalyzed carboxymethylation of the corresponding vinyl triflate in 72% overall yield. The efficiency and reproducibility of this reaction relied upon the mixing of all the required reagents [$Pd(OAc)_2$, Ph_3P, Et_3N] in methanol under a balloon of CO, followed by rapid addition of the vinyl triflate in DMF solution and immersion of the flask containing the reaction mixture into a preheated 50 °C oil bath. At this juncture, conjugate addition of various one-carbon nucleophiles to **17** to furnish structures of type **18** were evaluated but failed.[11] However, reduction of **17** with DIBAL provided allylic alcohol **19** in 95% yield. To allow for a possible means to introduce the required cyanide residue (see structure **14**, Scheme 3), the corresponding epoxide was formed from **19** by the chemoselective action of *t*-BuOOH in the presence of $V(O)(acac)_2$,[12] albeit in moderate stereoselectivity (85%, ca. 3.7:1 ratio in favor of β-epoxide **20**). A survey of the stereoselectivities achieved in this epoxidation reaction with various substrates is shown in Table 1. Insights gained from this study will be discussed in a later section. Incidentally, the ratios observed in the epoxidation with various substrates were completely substrate controlled and could not be improved by changing the solvent, temperature, or catalyst loading. In contemplating the next reaction, we reasoned that, regardless of the stereochemical outcome of the epoxide opening with a suitable cyanide carrier, access to the coveted iminobutenolide **15** (Scheme 3) would be possible, in principle. That is, if the cyanide were to be delivered *cis* to the hydroxymethyl group, a simple dehydration would lead to **15**, whereas *trans* delivery would permit a β-elimination-type pathway. In the event, treatment of epoxide **20** with Et_2AlCN (Nagata reagent)[13] led smoothly to the *cis*-cyano diol **21** in 68% yield. This observed, and seemingly unorthodox, stereochemical outcome (inversion was expected) may be rationalized in several ways, three of which are depicted in Scheme 5. The first scenario (A, Scheme 5) invokes a lengthening of the C−O bond (toward S_N1) with the concomitant approach of the incoming nucleophile from the convex face of the molecule, leading to a product with retention of stereochemistry. Alternatively, intramolecular attack of the neighboring hydroxyl group (upon activation with Et_2AlCN) to form a four-membered oxetane (B, Scheme 5) followed by S_N2 attack by cyanide anion to afford the product with overall retention cannot be ruled out. Finally, the reaction may indeed furnish the expected S_N2 product, which, under the reaction conditions, may epimerize to the thermodynamically more stable cyanide **21** (C, Scheme 5, overall retention).

With the cyano diol **21** in hand, we began to investigate its conversion to the targeted maleic anhydride **13** (see Scheme

(11) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.
(12) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.
(13) (a) Nagata, W.; Yoshioka, M.; Okumura, T. *Tetrahedron Lett.* **1966**, 847. (b) Liu, G.; Smith, T. C.; Pfander, H. *Tetrahedron Lett.* **1995**, *36*, 4979. Stereochemistry confirmed by ROESY and COESY experiments.

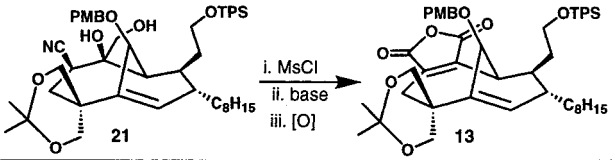
Scheme 5. Three Possible Mechanistic Explanations (A−C) for the Observed "Unorthodox" Stereoselectivity of the Cyanide Addition to Compound **20**



4). Through considerable experimentation (vide infra), it was found that diol **21** could be converted to anhydride **13** in essentially one operation and in ca. 60% overall yield. Thus, cyano diol **21** was selectively mesylated at the primary hydroxyl group, and the crude mesylate **28** (vide infra, Scheme 9) was treated with potassium carbonate in methanol; evaporation of the solvent, dissolution of the residue in ether, and addition of a 10% aqueous solution of oxalic acid resulted in the formation of maleic anhydride **13**. This remarkable cascade reaction involving several intermediates accomplished the following tasks: (a) selective mesylation of the primary alcohol; (b) epoxide formation via intramolecular expulsion of the mesylate group by the tertiary alcohol; (c) epoxide lysis via β-elimination; (d) 5-*exo*-dig cyclization of the resulting alkoxide upon the cyanide; (e) double oxidation; (f) hydrolytic loss of ammonia (>93% yield per step).

At first, we believed that the iminobutenolide **15** and 2-aminofuran **16** were much too labile to be isolated. In addition, the conditions originally reported (K_2CO_3/MeOH)[14] represent an optimized protocol arrived upon after careful experimentation (see Table 2). To demystify the inner workings of this cascade sequence, we attempted to identify and characterize as many stable intermediates and byproducts as possible. Thus, addition of KH (excess) to a solution of **21** (Scheme 4) in THF-d_8 containing approximately 5 equiv of water led to the nearly quantitative formation of iminobutenolide **15** as observed by ^{1}H, ^{13}C, ^{1}H−^{1}H COESY, and HMQC NMR spectra. Since this compound was unstable to the various matrixes used for high-resolution mass measurements, we obtained unit mass by using the sensitive electrospray ionization technique (ESI-MS). Iminobutenolide **15** was stable for several weeks at −78 °C and slowly decomposed upon standing at room temperature. Although we expected **15** to be only a fleeting intermediate, incapable of direct detection, its surprisingly stable nature may

Table 2. Optimization of Maleic Anhydride **13** Formation from Cyano Diol **21**



Entry	Base	[O]	Yield (%)[a]
1	KH/DME	air	32 - 48
2	K_2CO_3/MeOH	PDC (cat. AcOH), CH_2Cl_2	30 - 40
3	K_2CO_3/MeOH	DMP, air, CH_2Cl_2	7 - 10
4	DBU/CH_2Cl_2	DMP, air, CH_2Cl_2	trace
5	DBU/benzene	DMP, air, CH_2Cl_2	trace
6	K_2CO_3/MeOH	$PhI(O_2CCF_3)_2$, MeOH	N/R
7	K_2CO_3/MeOH	air/ silica gel	30
8	K_2CO_3/MeOH	PCC, CH_2Cl_2	31
9	K_2CO_3/MeOH	PCC, acetone, cat. PPTS	45
10	K_2CO_3/MeOH	10% oxalic acid, air, Et_2O	48 - 60
11	K_2CO_3/MeOH	10% oxalic acid, O_2, Et_2O	55 - 66

[a] Isolated, pure **13**. Ranges indicate maximum and minimum values obtained for several runs.

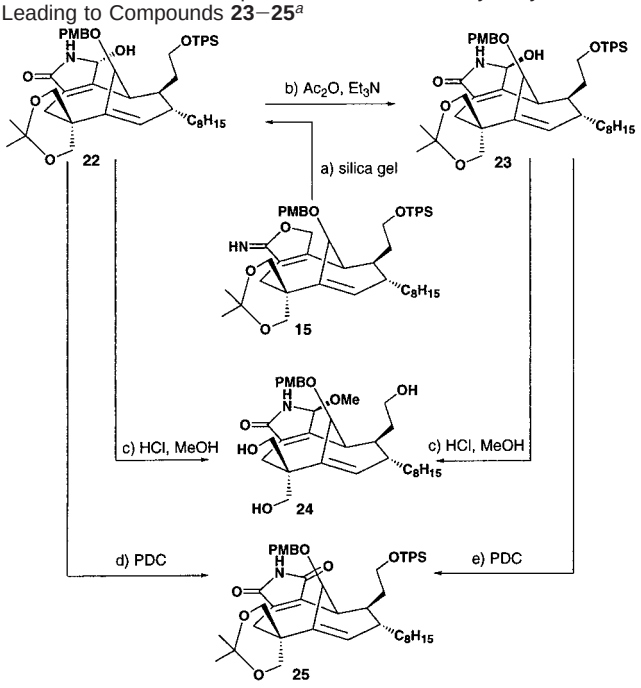
be due, in no small part, to the steric shielding granted by the CP skeleton. The optimized protocol used for the conversion of iminobutenolide **15** (see Scheme 3) to the anhydride **13** involved treatment of an ethereal solution of **15** with a 10% oxalic acid solution under an atmosphere of oxygen (entry 11, Table 2). Immediately upon addition of oxalic acid, under vigorous stirring, the solution turned a light brown color which slowly disappeared over a 5 min period. After an additional 25−35 min, the reaction was complete (as judged by TLC), and **13** was isolated in 66% yield along with traces of maleimide **25** (see Scheme 6). The remaining ca. 20% of the material consisted primarily of the hydroxyamide **22** (Scheme 6), which was always present in these reactions (Table 2).

Interestingly, we found that the ratio of hydroxyamide **22** to anhydride **13** formed from **15** differed as a function of the workup procedure employed. Adjusting the relative pH of the media allowed us to control completely the formation of either anhydride **13** or hydroxyamide **22** as the major product (Schemes 4 and 6). To verify the structure of the hydroxyamide **22**, we attempted to acetylate it under standard conditions (Ac_2O, Et_3N; see Scheme 6). Although the newly formed compound was dramatically less polar, suggesting that it was indeed acetylated, the epimeric hydroxyamide **23** was isolated (85%) instead. The fact that **22** and **23** were epimers followed from NMR studies and their reactivity. Thus, **22** and **23** were separately converted to methoxyamide **24** upon treatment with HCl in MeOH (75%).[15] In addition, **22** and **23** could both be oxidized to the novel maleimide **25** upon exposure to PDC; however, the latter epimer (**23**) reacted sluggishly. The efficient conversion of **22** to the maleimide **25** (90%) inspired the synthesis of novel CP-analogues, otherwise unaccessible (vide infra), containing the maleimide motif.[16]

(14) Nicolaou, K. C.; Baran, P. S.; Jautelat, R.; He, Y.; Fong, K. C.; Choi, H.-S.; Yoon, W. H.; Zhong, Y.-L. *Angew. Chem., Int. Ed.* **1999**, *38*, 549.

(15) Farina, F.; Martin, M. V.; Paredes, M. C. *Synthesis* **1973**, 167.

Scheme 6. Chemical Explorations of the Novel Hydroxyamide **22** Leading to Compounds **23**−**25**[a]

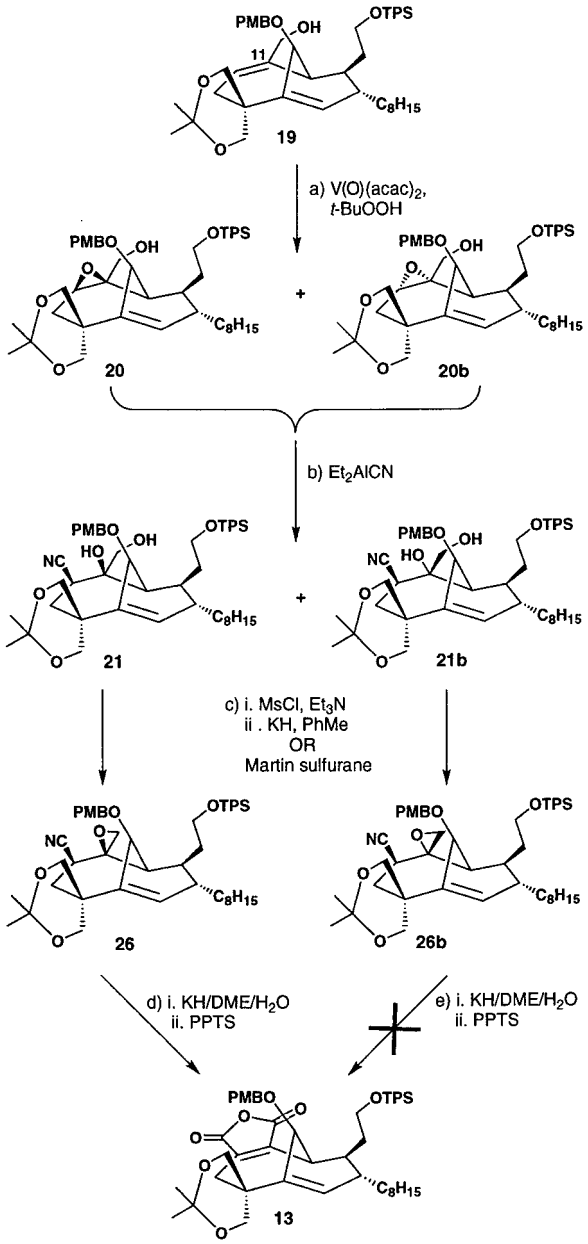


[a] Reagents and conditions: (a) silica gel, air, 25 °C, 10 min, 80%; (b) Ac_2O (10 equiv), Et_3N (20 equiv), CH_2Cl_2, 3 h, 85%; (c) HCl (5.0 equiv), MeOH, 12 h, 75%; (d) PDC, CH_2Cl_2, 10 min, 90%; (e) PDC, CH_2Cl_2, 48 h, 15%.

Before a final mechanistic rationale was put forth for the maleic anhydride cascade reaction, we sought to determine whether the β-elimination followed an E_2 or E_{1cb} mechanism en route to the iminobutenolide **15**.[17] Since an antiperiplanar geometry is necessary for the former mechanism (E_2) and merely an enolate for the latter (E_{1cb}), the epoxide **26b**, having the opposite configuration at C-11 (determined through NOE studies), was synthesized (Scheme 7). Indeed, treatment of **26** with potassium hydride in wet DME followed by addition of oxalic acid and stirring over air smoothly proceeded to furnish anhydride **13**, presumably via iminobutenolide **15** (for the structure of **15**, see Scheme 6). Whereas epoxide **26** reacted under these strong conditions in only 1 min, exposure of the isomeric epoxide **26b** to the same conditions for 4 h led only to recovered starting material and ca. 10% decomposition. The epoxides, synthesized from the corresponding mesylate by exposure to KH in dry toluene, could also be synthesized directly from cyano diols **21** and **21b** by treatment with the Martin sulfurane reagent.[18] To provide further support that the reaction proceeds through the cyano alkoxide derived from **14**, the cyano acetate **27** was targeted and synthesized as shown in Scheme 8. Thus, acetylation of **21** (Ac_2O, Et_3N) followed by exposure to Martin sulfurane led to **27** in 90% overall yield. As expected, treatment of this compound with potassium carbonate in methanol followed by addition of ether and oxalic acid led to the anhydride **13** (60% yield), presumably via **15** (Scheme 8).

On the basis of these studies, we propose the following mechanistic considerations to account for the formation of anhydride **13**, iminobutenolide **15**, hydroxyamide **22**, and

Scheme 7. Stereochemical Requirements for the Conversion of Epoxynitrile **26** to Maleic Anhydride **13**. Construction of *trans*-Epoxynitrile **26b**[a]

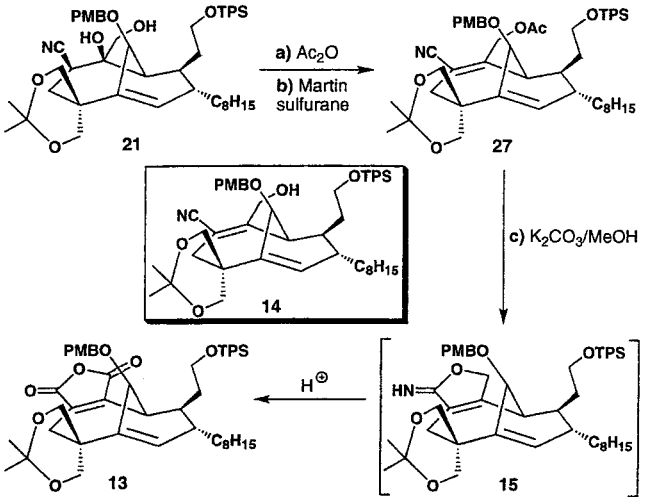


[a] Reagents and conditions: (a) $V(O)(acac)_2$ (0.2 equiv), *t*-BuOOH (1.4 equiv), benzene, 25 °C, 0.5 h, 85%, 3.7:1 **20**/**20b**; (b) Et_2AlCN (5.0 equiv), toluene, 0 °C, 15 min; then 25 °C, 2.5 h, 68% **21**, 16% **21b**; (c) KH (10 equiv), dry toluene, 1 h, 90% or Martin sulfurane (2.0 equiv), $CHCl_3$, 25 °C, 30 mins, 95%; (d) (i) KH (40 equiv), DME/0.1% H_2O, 30 s; (ii) H_2O/acetone, PPTS (1.0 equiv), 38−45%; (e) conditions as in (d), 4 h, ca. 90% recovered **26b**.

maleimide **25** from cyano alcohol **21** (Scheme 9). Thus, it is postulated that treatment of mesylate **28** with base leads to domino epoxide formation and β-elimination via an E_2 mechanism (vide supra) to furnish alkoxide derivative **14**. Spontaneous intramolecular attack of this alkoxide moiety onto the electrophilic locus of the cyanide residue leads to the iminobutenolide **15** via a 5-*exo*-dig cyclization. Slightly acidic conditions promote the energetically favored[10] tautomerization of **15** to the fleeting 2-aminofuran **16**, which may combine with triplet oxygen quite rapidly to afford hydroperoxide **C**. At this point, two pH-controlled divergent pathways likely originate

(16) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S.; Jung, J.; Choi, H.-S.; Yoon, W. H. *J. Am. Chem. Soc.* **2002**, *124*, 2202−2211.
(17) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; Wiley: New York, 1992; p 982.
(18) Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604.

Scheme 8. Indirect Evidence for the Intermediacy of Alkoxynitrile **14** in the Cascade Sequence Leading to Maleic Anhydride **13** from **21** via Iminobutenolide **15**[a]



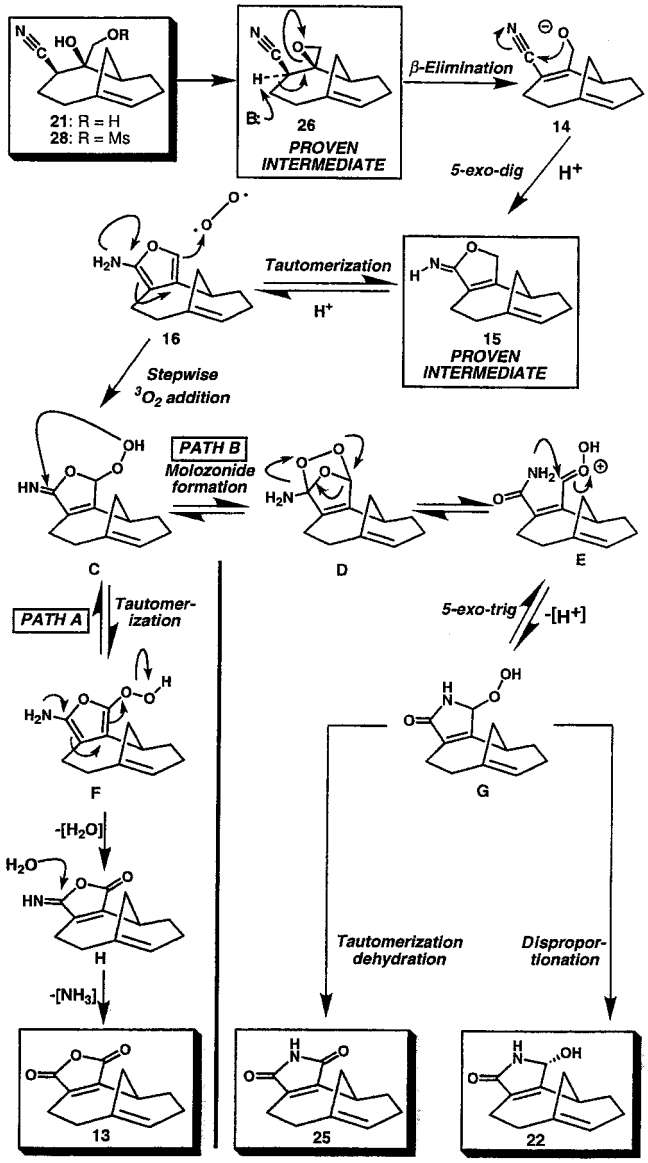
[a] Reagents and conditions: (a) Ac_2O (5.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 25 °C, 1 h; (b) Martin sulfurane (2.0 equiv), $CHCl_3$, 60 °C, 1 h, 90% from **21**; (c) K_2CO_3 (20 equiv), MeOH, 1 h; then ether, 10% aqueous oxalic acid, air, 0.5 h, 60%.

from intermediate **C**. Under acidic conditions (path A, Scheme 9), rapid tautomerization of **C** followed by loss of water furnishes anhydride surrogate **H**, via intermediate **F**, the former rapidly expelling ammonia facilitated by hydrolytic attack to generate the coveted anhydride **13**. However, under only weakly acidic conditions (decreased likelihood for tautomerization), path B (Scheme 9) may predominate with the formation of molozonide **D**, which may be followed by fragmentation to compound **E**, a cascade which is reminiscent of a classical ozonolysis[19] reaction. Rapid 5-*exo*-trig collapse of the amide functionality of the fleeting intermediate (**E**) upon the nearby electron sink furnishes intermediate **G**, which is actually an isomer of **C**, but which reacts quite differently at this point. Presumably due to the increase of pH (general conditions for path B) and the overall diminished tendency of intermediate **G** to tautomerize, the reaction mainly gives rise to hydroxyamide **22** by the well-precedented process of disproportionation[20] while, at the same time, affording maleimide **25** by a tautomerization−dehydration pathway only in trace amounts (see Scheme 9). Notable are the reproducibility and reliability with which these multistep cascade reactions can be performed.

Satisfied that we had identified a final solution to the issue of installing the maleic anhydride moiety, we then proceeded to investigate its unique reactivity (Scheme 10). Addition of $LiAlH_4$ to a solution of anhydride **13** in THF led to a deep brown color, presumably due to the anion **29**, which furnished butenolide **30**, in 90% yield, upon aqueous workup. The regiochemistry of the reduction, confirmed by 2D ROESY experiments, is logical if one considers the higher steric hindrance at the site of the remaining carbonyl group. Attempts to reoxidize butenolide **30** to the anhydride **13** were unsuccessful. Reduction of **13** using $NaBH_4$ in MeOH led to a 1:1:1 mixture of three lactols (74%) (two shown in structure **31**, stereochemistry and regiochemistry unassigned) which could be reconstituted back to the anhydride **13** via PCC oxidation

(19) Geletneky, C.; Berger, S. *Eur. J. Org. Chem.* **1998**, *1625*, 5.
(20) Smith, L. L.; Kulig, M. J. *J. Am. Chem. Soc.* **1976**, *98*, 1027.

Scheme 9. Proposed Mechanistic Underpinnings in the Conversion of Cyano Alcohol **21** to **13**, **15**, **22**, and **25**[a]

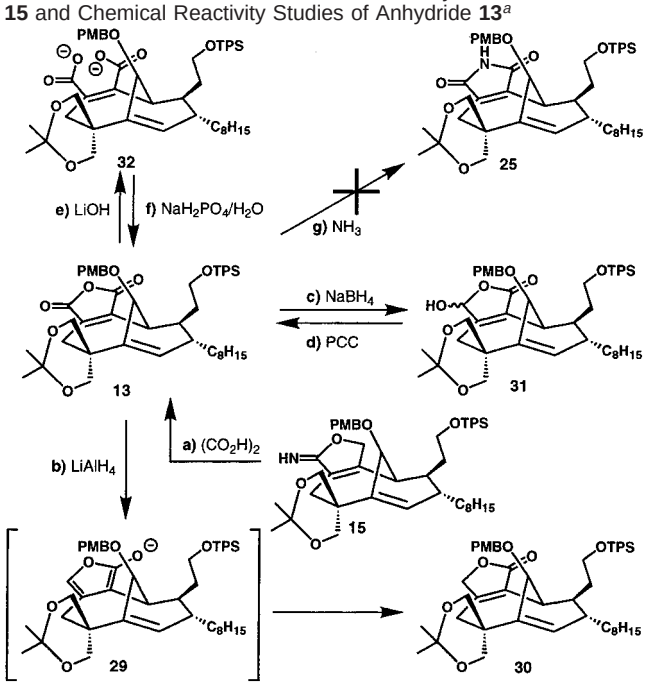


[a] Appendages have been deleted from the structures for clarity (see Schemes 4, 6, and 7 for complete structures).

(72%). Significantly, we found that addition of LiOH to anhydride **13** led to rapid "disappearance" as observed by TLC (all of the compound retreated to the baseline). This seemingly detrimental outcome could be reversed upon addition of NaH_2PO_4 buffer. We concluded from these results that generation of the bisanion **32** is both rapid and reversible; this piece of information was critical for the eventual completion of the total synthesis of the CP-molecules as it sustained our confidence in the counterintuitive conversion[16] of **1** to **2** (see Scheme 1). Finally, treatment of anhydride **13** with excess ammonia, in the hope of accessing the maleimide **25**, led only to recovered starting material. This result was of no consequence in terms of future analogue construction since the readily available hydroxyamide **22** could be efficiently converted to **25** (see Scheme 6).

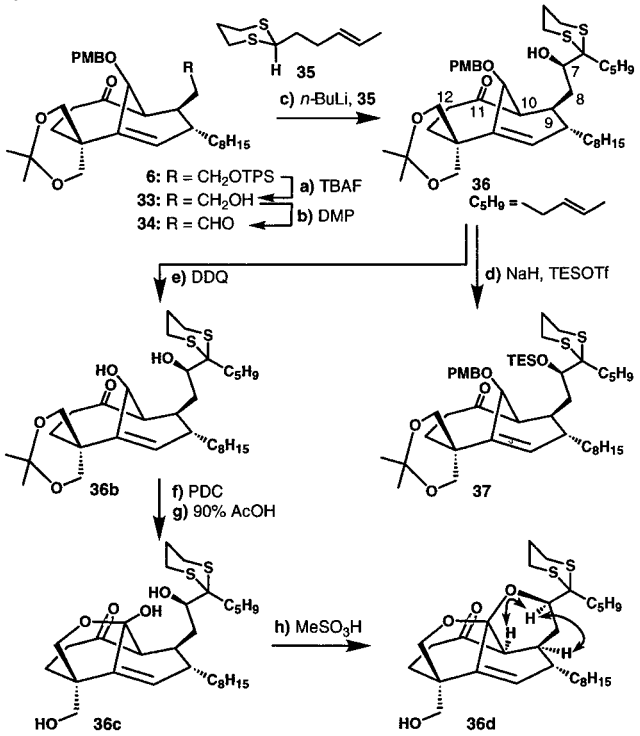
3. Studies Directed toward Construction of the Upper Side Chain. With the maleic anhydride studies providing a good foundation for pursuing that front, we then turned our attention

Scheme 10. Acid-Mediated Formation of Anhydride **13** from Imine **15** and Chemical Reactivity Studies of Anhydride **13**[a]



[a] Reagents and conditions: (a) Et_2O, 10% aqueous oxalic acid, air 0.5 h; (b) $LiAlH_4$ (8.3 equiv), THF, 25 °C, 10 min, 90%; (c) $NaBH_4$ (10 equiv.), CH_2Cl_2/MeOH (1:1), 25 °C, 30 min, 74%; (d) PCC (5.0 equiv), CH_2Cl_2, 25 °C, 12 h, 72%; (e) LiOH (10 equiv), THF/H_2O (4:1), 25 °C, 1 h; (f) 10% aqueous NaH_2PO_4, 95%; (g) NH_3, MeOH, 25 °C, 24 h, no reaction.

Scheme 11. Stereoselective Construction of the Upper Side Chain and Verification of Stereochemistry through the Synthesis of Pyran Derivative **36d**[a]



[a] Reagents and conditions: (a) TBAF (2.0 equiv), THF, 25 °C, 94%; (b) DMP, $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 92%; (c) **35** (1.3 equiv), *n*-BuLi (1.3 equiv), THF, −78 °C, 8 min, 70% **36** + 20% **34**; (d) NaH (6.0 equiv), TESOTf (2.0 equiv), THF, 0 → 25 °C, 2 h, 86%; (e) DDQ (3.0 equiv), CH_2Cl_2/H_2O (18:1), 25 °C, 0.5 h, 50% **36b** + 38% **36**; (f) PDC (5.0 equiv), CH_2Cl_2, 25 °C, 0.5 h, 88%; (g) 80% aqueous AcOH, 25 °C, 5 h, 91%; (h) $MeSO_3H$ (0.1 equiv), CH_2Cl_2, 25 °C, 0.5 h, 68%.

to the stereoselective fastening of the upper side chain harboring the remote stereocenter at C-7 (Scheme 11). The task constituted a challenge to introduce the missing chain of carbon atoms while securing the C-7 stereochemistry as well as the C-8 carbonyl functionality. Our first attempts at accomplishing this goal left the precise timing of the site construction undefined. To this end, the TBDPS group of the Diels−Alder product **6** was removed using TBAF (94% yield), and the resulting alcohol **33** was oxidized with DMP (92% yield) to afford aldehyde **34** (Scheme 11). Although the aldehyde group in **34** appeared distal from the remainder of the CP skeleton (and, therefore, undisturbed by its steric bulk), close inspection of molecular models revealed that the C-11 and C-12 substituents actually lie nearby and could conceivably influence its conformation and reactivity. A dithiane anion was chosen for attack on this aldehyde. In the event, the lithiated dithiane **35** smoothly engaged aldehyde **34**, furnishing an 11:1 mixture of diastereomers (70% plus 20% recovered starting material). Since we did not know whether the correct diastereomer was obtained until converting the product to a suitably rigid compound for NMR spectroscopic analysis, we probed the diastereoselectivity of other related aldehyde substrates as shown in Table 3.[21] As predicted, the substituents at C-11 and C-12 did indeed have a rather dramatic effect on the observed ratio of diastereomers, which ranged from ca. 11:1 to 1:7. Toward the end of rigidifying structure **36**, this compound was initially converted to diol **36b** via removal of its PMB group (DDQ, 50% plus 38% recovered starting material) and thence to pyran **36d** by selective PDC oxidation (88% yield), acid-induced removal of the acetonide group (**36c**, 91% yield), and exposure to $MeSO_3H$ (68% yield) (Scheme 11).

NOE studies on the latter compound (**36d**) revealed its stereochemistry (see the arrows on structure **36d**), and thus the stereochemical outcome of the addition of **35** to aldehyde **34**, which turned out to be in favor of the desired 7*R*-isomer. This result was later confirmed by X-ray crystallographic analysis of a crystalline descendant (i.e., **5**; see Figure 2). The high stereoselectivity in this reaction may be rationalized by assuming co-chelation to the lithium cation by both the aldehyde group and the proximate ketone moiety as modeled in Figure 1.[22] Such a scenario would explain the direction of attack in the desired fashion (*re*-face attack) in the case of **34** (see Figure 1), whereas aldehydes **82**−**84** do not enjoy this luxury, and thus lead to the undesired stereoselectivity (see Table 3).

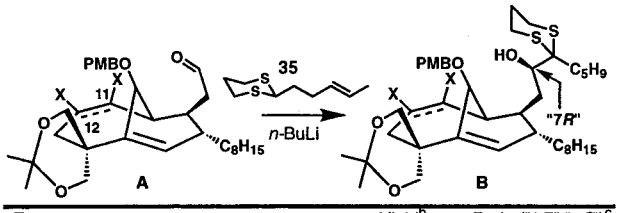
In preparation for the installation of the maleic anhydride moiety, alcohol **36** was protected as its TES ether derivative **37** by the action of NaH and TESOTf (86% yield, Scheme 11). Flash column chromatography of this latter intermediate also permitted the removal of the minor diastereomer formed in the dithiane coupling.

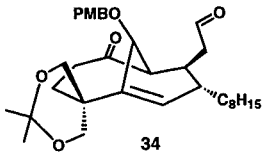
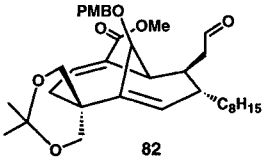
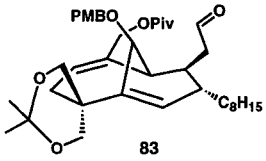
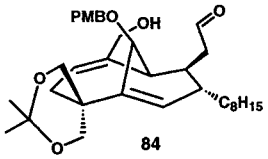
Scheme 12 illustrates the successful implementation of our protocol for the introduction of the maleic anhydride moiety onto ketone **37**. Thus, enolate formation with KHMDS followed by quenching with $PhNTf_2$ converted **37** into enol triflate **38** in 95% yield. Despite the presence of the dithiane moiety, carboxymethylation of **38** in the presence of Et_3N proceeded

(21) The Danishefsky group has recently reported similar observations; see: Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4509.

(22) MM3 calculations performed using ChemDraw 3D (version 4.5, Cambridge Software).

Table 3. Diastereoselectivity of Dithiane **35** Addition to Aldehyde Substrates **34** and **82**−**84**[a]



Entry	Substrate	Yield[b]	Ratio ("7*R*":"7*S*")[c]
1	 **34**	70 (**36**)	(11:1)
2	 **82**	49 (**82'**)	(3.5:1)
3	 **83**	91 (**83'**)	(1:2)
4	 **84**	78 (**84'**)	(1:7)

[a] For reagents and conditions, see Scheme 11. [b] Isolated yield of chromatographically pure products. [c] Determined by ^{1}H NMR spectroscopic comparison with compounds derived from **34** (see also Scheme 11).

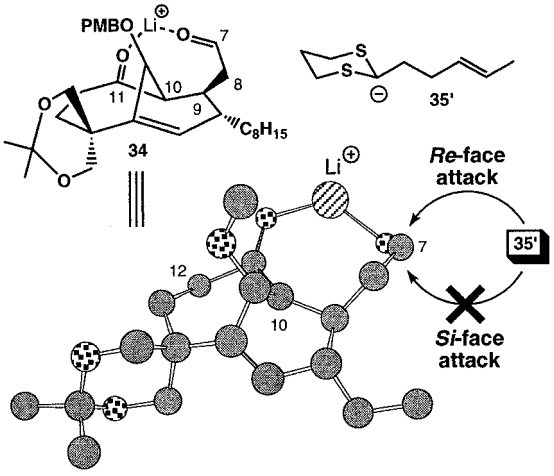
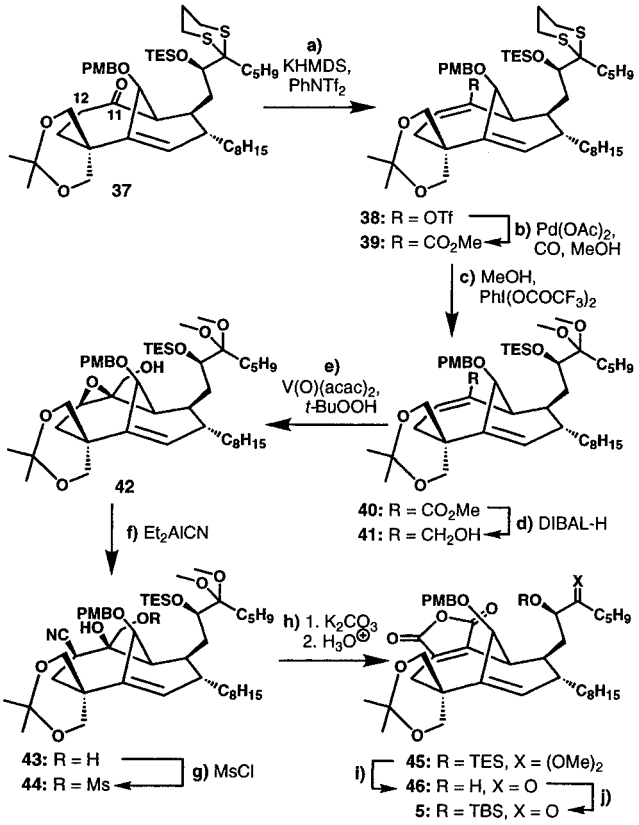


Figure 1. MM3-minimized structure of aldehyde **34** chelated to a lithium cation. Such an interaction explains why the *si*-face is blocked from attack of the incoming dithiane **35**.

smoothly, leading to the α,β-unsaturated methyl ester **39** in 78% yield. At this juncture and for compatibility reasons, the dithiane protecting group was exchanged for a dimethyl ketal using the Stork−Zhao protocol[23] [$PhI(OCCF_3)_2$, MeOH, 81% yield]. The resulting ketal **40** was then reduced with DIBAL to afford the

(23) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.

Scheme 12. Construction of Advanced Key Intermediate **5**[a]



[a] Reagents and conditions: (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 **38**, 50 °C, 40 min, 78%; (c) $PhI(OCCF_3)_2$ (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), *t*-BuOOH (1.4 equiv), benzene, 25 °C, 0.5 h, 83%, β:α = 10.7:1; (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% aqueous oxalic acid, air, 0.5 h, 56% overall from **43**; (i) (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, 30 min, 83% overall from **45**; (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(trimethylsilyl)amide; DIBAL-H = diisobutylaluminum hydride.

allylic alcohol **41** (95% yield). Vanadium-assisted epoxidation of **41** in benzene led smoothly to the epoxide **42** in a pleasing 10.7:1 ratio and 83% combined yield.

As alluded to earlier, the varying degrees of stereoselectivity in this epoxidation as a function of the neighboring functionalities did not escape our attention (see Table 1). In fact, the considerable increase in stereoselectivity in going from **19** to **41** (ca. 1:3.7 to 1:10.7), substrates differing only in the presence of the upper side chain, further attests to its close and influential proximity to the C-11 and C-12 carbons. It is worth noting again the importance of the strategic positioning of events in the CP-molecule synthesis. In this instance and to be sure, the ketone functionality in **34** (Scheme 11) ensured high stereoselectivity in the upper side chain fastening, which then served to bolster the stereoselectivity of the ensuing epoxidation (Scheme 12).

Continuing with the synthesis, Et_2AlCN-mediated rupture of the resulting epoxide **42** led smoothly to the cyano diol **43** (73% yield), just as in the model studies (vide supra). Transformation of **43** to the maleic anhydride **45** proceeded readily as with the

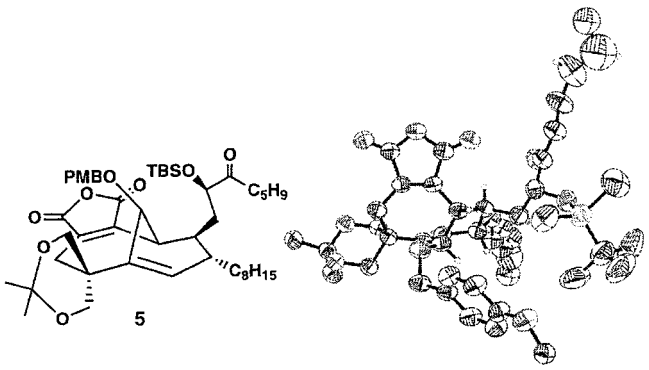
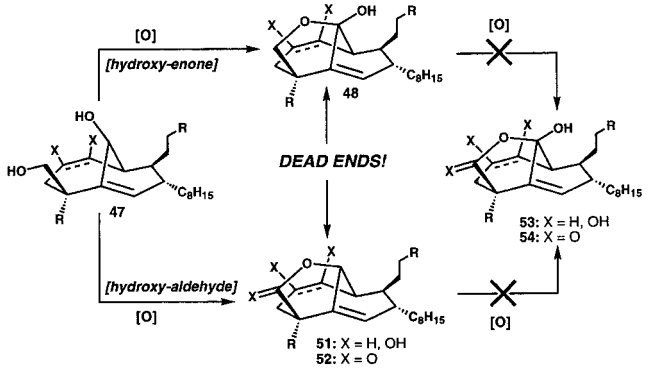


Figure 2. ORTEP drawing of compound **5** derived from X-ray crystallographic analysis.

Scheme 13. Initial Considerations for Construction of the γ-Hydroxylactone Moiety

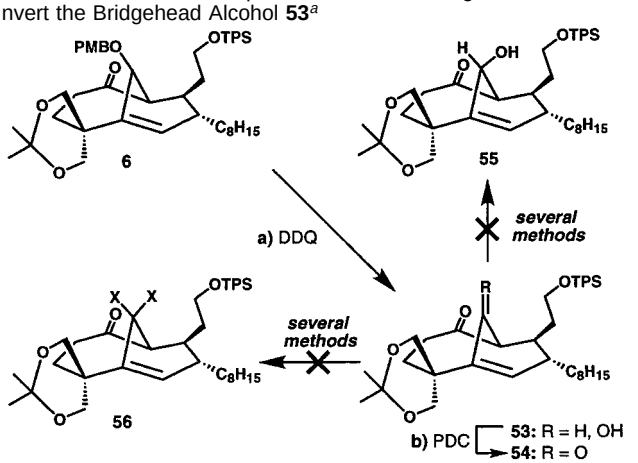


cyano diol **21** (Scheme 4) in 58% overall yield and through the intermediacy of mesylate **44**. The synthesis of the advanced key intermediate **5** (Schemes 1 and 12) was then accomplished by the sequential enlistment of aqueous acetic acid (to remove the TES group), dimethoxypropane/camphorsulfonic acid (to protect the resulting 1,3-diol), and TBSOTf/2,6-lutidine (to introduce a TBS group, 83% overall yield). The X-ray crystallographic analysis of crystalline **5** (see the ORTEP drawing in Figure 2) confirmed its structure and those of its predecessors. With this intermediate in hand, the time had come to address the next task, namely, the issue of the hydroxylactone moiety.

4. Studies Directed toward the γ-Hydroxylactone Moiety. As innocent as it looks, the γ-hydroxylactone (or its cyclic pyran equivalent) proved quite challenging to construct within the CP framework.[24] Indeed, we recognized rather early in these investigations that the construction of this system from the corresponding 1,4-diol (**47**) was not trivial (see Scheme 13). Oxidants selective for the bridge alcohol, such as PDC, DMP, and PCC, furnished the corresponding lactol, which resisted further oxidation with known reagents (to give a structure of type **48**, Scheme 13). Alternatively, oxidants capable of reacting selectively with the primary alcohol (of **47**, Scheme 13) such as Swern, TEMPO, and SO_3•py led only to lactol **51** or lactone **52**, both of which resisted further oxidative action by numerous reagents. In contemplating solutions to this problem, we reasoned that we could conceivably skirt these obstacles if one of the following objectives could be accomplished: (a) inversion of the bridge alcohol; (b) protection of the bridge enone; (c) use of a protecting group at the bridge position, which would

(24) Nicolaou, K. C.; He, Y.; Fong, K. C.; Yoon, W. H.; Choi, H.-S.; Zhong, Y.-L.; Baran, P. S. *Org. Lett.* **1999**, *1*, 63.

Scheme 14. Failed Attempts To Protect the Bridged Enone **54** or Invert the Bridgehead Alcohol **53**[a]



[a] Reagents and conditions: (a) DDQ (2.0 equiv), CH_2Cl_2/H_2O (18:1), 25 °C, 2 h, 40% plus 30% recovered starting material; (b) PDC (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 85%.

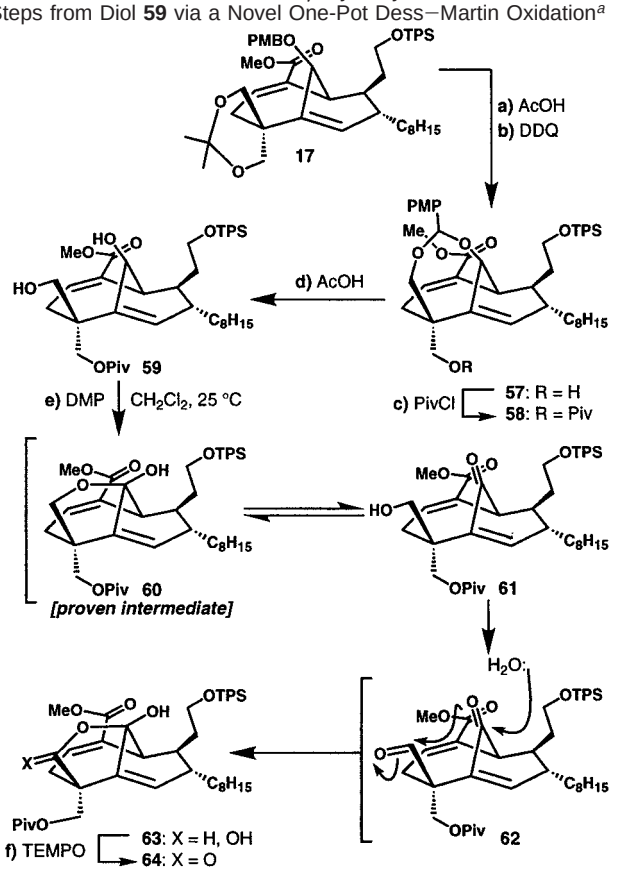
self-oxidize upon deprotection. It was envisioned that these strategies would prevent the lockup structures **48**, **51**, and **52** (Scheme 13) from forming and thus serve as effective means to overcome the problem of further oxidation. Our initial forays to explore such options utilized the model compound **6** (see Scheme 14). Attempts to mask the bridged alcohol **53**, derived from ketone **6** upon treatment with DDQ (40% plus 30% recovered starting material), either through inversion of stereochemistry or protection of the corresponding enone **54** (PDC, 85% yield, Scheme 14) failed. These failures were attributed to the extreme steric screening in the vicinity of the bridge alcohol. Specifically, steric congestion apparently prevented the bridge alcohol from becoming a leaving group (inversion) and protected the ketone group in **54** from nucleophilic attack from the required side (orbitals blocked). Attempts to employ Curran's elegant but rarely employed self-oxidizing protecting group[25] (*o*-bromobenzyl ether) yielded promising results in those model studies, but, unfortunately, ended up failing in more complex and relevant systems.

In the hope that a locked structure of type **48** (Scheme 13) could be coaxed into reacting, we turned our attention to a strategy predicated on the ring−open chain tautomerization of hydroxy ketones.[26] We surmised that extended reaction times with excess oxidant, such as DMP,[27] might trap the keto form to furnish a ketone−aldehyde, which upon hydration would furnish the γ-hydroxylactonol (i.e., **60** → **61** → **62** → **63**; see Scheme 15).

As a model system, we chose diol **59** to be derived from **17** (Scheme 15) and sought to develop a sequence which could ultimately involve construction of the γ-hydroxylactone after the maleic anhydride had been installed. Thus, the isopropylidene group of **17** was removed under acidic conditions (AcOH), and the resulting diol was subjected to the action of DDQ[28] with rigorous exclusion of water to furnish the seven-membered benzylidene acetal **57** in 85% overall yield. After protection of

(25) Curran, D. P.; Yu, H. *Synthesis* **1992**, 123.
(26) (a) Whiting, J. E.; Edward, J. T. *Can. J. Chem.* **1971**, *49*, 3799. (b) Hurd, C. D.; Saunder, W. *J. Am. Chem. Soc.* **1952**, *74*, 5324.
(27) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (c) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.
(28) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.

Scheme 15. Construction of the γ-Hydroxylactone **64** in Two Steps from Diol **59** via a Novel One-Pot Dess−Martin Oxidation[a]



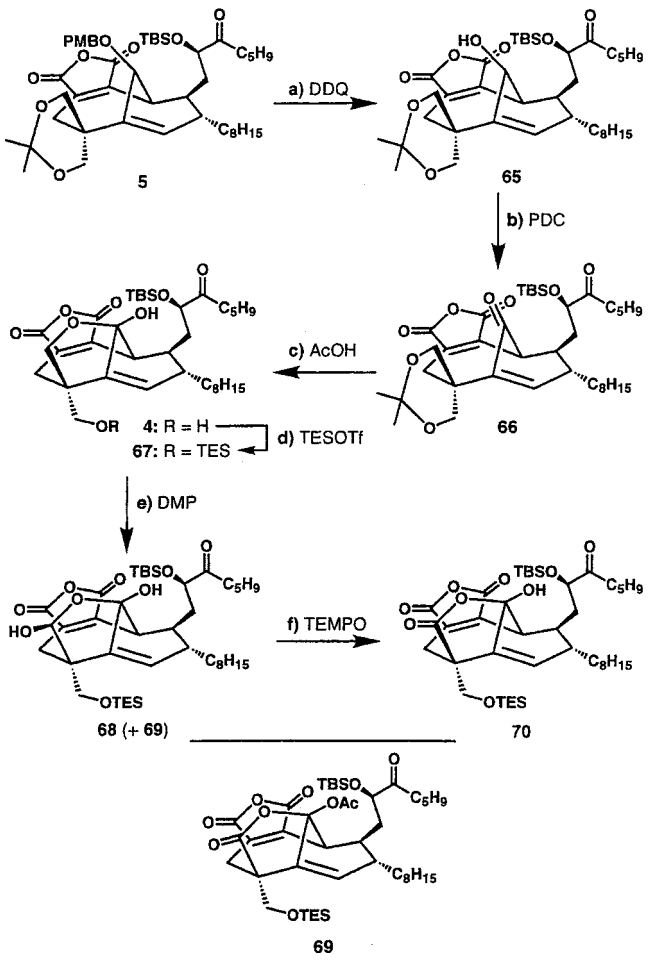
[a] Reagents and conditions: (a) 80% aqueous AcOH, 25 °C; (b) DDQ (2.0 equiv), fluorobenzene, 25 °C, 1.5 h, 85% from **17**; (c) PivCl (5.0 equiv), Et_3N (10 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2, 25 °C, 12 h, 99%; (d) 80% aqueous AcOH, 25 °C, 3.5 h, 98%; (e) DMP (10 equiv), CH_2Cl_2, 16 h, 82%; (f) TEMPO (20 equiv), KBr (0.1 equiv), cyclooctene (50 equiv), NaOCl (3.0 equiv), acetone/5% $NaHCO_3$ (2:1), 0 °C, 0.5 h, 68%. Piv = 2,2,2-trimethylacetyl, CSA = camphosulfonic acid, TEMPO = 2,2,6,6-tetramethylpiperidinyl-1-oxy, PMP = *p*-methoxyphenyl, 4-DMAP = (dimethylamino)pyridine.

the remaining primary alcohol as the pivaloate **58** (PivCl, Et_3N, 99% yield), benzylidene deprotection with AcOH proceeded smoothly to afford the targeted model 1,4-diol **59** (98% yield).

Upon exposure of **59** to DMP in methylene chloride at room temperature, we were pleased to observe formation of the γ-hydroxylactol **63** in 82% yield via the proven intermediate **60**. This tandem reaction sequence required the initial selective oxidation of the sterically hindered bridge alcohol (to furnish hydroxy ketone **61**) followed by ring closure to furnish the isolable hemiketal **60**. Further oxidation (10 equiv of DMP, CH_2Cl_2, ambient temperature, 16 h) funneled hemiketal **60** into ketoaldehyde **62** via the ring−open chain tautomer **61**. Trace amounts of water terminated the cascade, forming the stable γ-hydroxylactol **63**, which could not be oxidized further with DMP. Swern, SO_3•py, and chromium-based oxidants also failed to convert lactol **63** to the coveted γ-hydroxylactone **64**. It was finally found that the action of TEMPO could bring about the desired conversion of **63** to the γ-hydroxylactone **64** (68% yield).[29] With this success realized, we set out to probe the effects and compatibility of the maleic anhydride moiety on the course of these oxidation reactions.

(29) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.

Scheme 16. Construction of Key Intermediate **70** from Compound **5**[a]



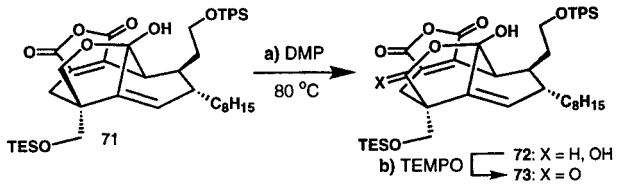
[a] Reagents and conditions: (a) DDQ (2.0 equiv), CH_2Cl_2/H_2O (18:1), 25 °C, 1 h, 48% **71** + 25% **5**; (b) PDC (3.0 equiv), CH_2Cl_2, 25 °C, 2 h, 89%; (c) 80% aqueous AcOH, 25 °C, 6 h, 82%; (d) TESOTf (1.5 equiv), 2,6-lutidine (10 equiv), 0 °C, 2 h, 92%; (e) DMP (5.0 equiv), benzene, 80 °C, 25 min, 49% **68** + 26% **67** + 9% **69**; (f) $PhI(OAc)_2$ (30 equiv), TEMPO (30 equiv), MeCN, 25 °C, 1.5 h, 74%.

Unfortunately, our success with the DMP-mediated oxidation of diol **59** could not be extended to similar systems containing the maleic anhydride moiety (cf. **71**, Scheme 17). Despite repeated attempts using a variety of oxidants, only conformationally locked structures (dead ends; see Scheme 13) were obtained.

To establish the relative stability of the γ-hydroxylactone in the presence of the maleic anhydride moiety, a stepwise route founded on careful protecting group manipulations was formulated and successfully executed.[23] Since this 10-step sequence was deemed untenable for the intended total synthesis, we decided to try oxidizing the real system (Scheme 16), starting with **5**, despite the ill-fated predictions of model studies. Our driving force for pushing forward was the belief (later shown to be incorrect) that the upper side chain could possibly encourage ring−open chain tautomerization of the conformationally locked hemiketal system (cf. **60**, Scheme 15). As discussed earlier, increased stereoselectivity encountered in the epoxidation reaction of various substrates (Scheme 11 and Table 1) attested to the long-range effects of this side chain.

Thus, the PMB group of **5** was cleaved by the action of DDQ (48% plus 25% recovered starting material) to afford hydroxy

Scheme 17. Conversion of Hemiketal **71** to the γ-Hydroxylactone **73** with DMP and TEMPO[a]



[a] Reagents and conditions: (a) DMP (5.0 equiv), benzene, 80 °C, 25 min, 70%; (b) $PhI(OAc)_2$ (20 equiv), TEMPO (20 equiv), MeCN, 25 °C, 2 h, 74%.

compound **65** (Scheme 16), which was smoothly oxidized to enone **66** with PDC in 89% yield. Acetic acid-induced removal of the acetonide group from the latter compound then liberated the hydroxy methyl groups, one of which spontaneously engaged the bridge carbonyl functionality as expected (vide supra), leading to hemiketal **4** in 82% yield. The remaining primary hydroxy group on the concave face of the molecule was then temporarily masked as a TES ether (TESOTf, 2,6-lutidine, 92% yield), furnishing compound **67**. Treatment of hemiketal **67** with excess DMP in CH_2Cl_2 at room temperature led to none of the desired product **68** despite prolonged reaction times. Reasoning that the rate-determining step of the desired cascade was the ring−open chain tautomerization of hemiketal **67**, we hypothesized that temperature elevation in a suitable solvent might be sufficient to coax the hemiketal into accommodating the latent hydroxy ketone long enough for further oxidation to take place. Despite the fact that we were aware of no reports of the DMP reagent being heated above room temperature, it seemed to us to be an ideal candidate for the desired transformation due to its mild and slightly acidic nature. In the event, we were pleased to observe, upon exposure of **67** to DMP in refluxing benzene, formation of γ-hydroxylactol **68** in 49% yield (in addition to 26% recovered starting material) and as a single stereoisomer. In accordance with our model studies (vide supra), TEMPO-mediated oxidation of lactol **68** to the desired γ-hydroxylactone **70** proceeded smoothly[30] and in 74% yield (Scheme 17). This DMP-mediated oxidation of **67** also provided small amounts of a nonpolar compound, later identified as the acetate-protected γ-hydroxylactone **69** (Scheme 17). This interesting byproduct presumably arose from attack by acetic acid, rather than hydration of the intermediate ketoaldehyde (cf. **62**, Scheme 15), and implied that a protected γ-hydroxylactol was easier to oxidize with DMP than the free lactol **68**, which required TEMPO oxidation to **70**.

Incidentally, a reinvestigation of the hemiketal **71** (Scheme 17) with the newly discovered oxidation conditions led smoothly to the corresponding γ-hydroxylactol **72** in 70% yield. Thus, the upper side chain had no influence on the reactivity of the distal hemiketal, although it served as an inspiration to try the high-temperature oxidation reaction in the first place, and despite the discouraging model studies (vide supra). On the basis of molecular models and these experiments, it appears that a decrease in conformational freedom at C11−C12 is directly proportional to the size of the angle θ (see Figure 3), which must reflect the ease with which the rate-determining, ring−open chain tautomerization takes place (e.g., room temperature was sufficient for **59**; 80 °C was required for **71**).

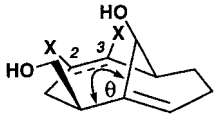
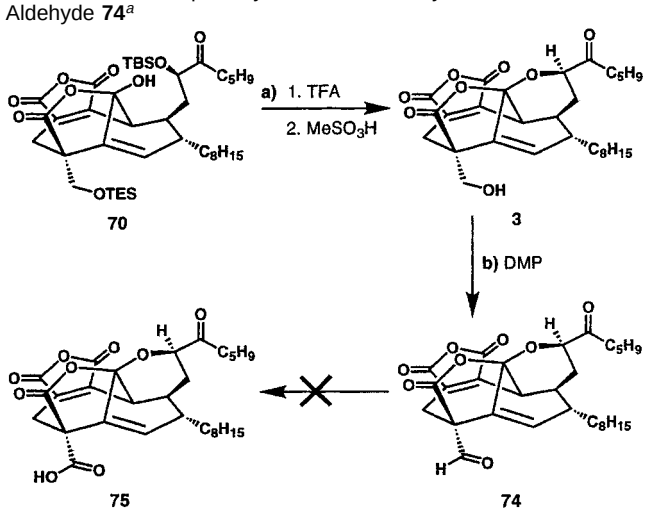


Figure 3. The angle θ appears to be a decisive factor in the formation of the lactone moiety within the bicyclo[4.3.1] system.

Scheme 18. Attempted Synthesis of Carboxylic Acid **75** from Aldehyde **74**[a]



[a] Reagents and conditions: (a) (1) CH_2Cl_2/TFA/H_2O (40:4:1), 25 °C, 2 h; (2) $MeSO_3H$ (10 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%.

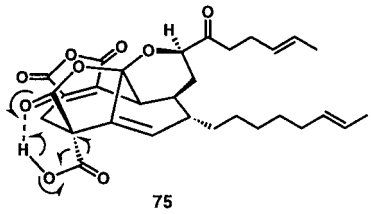


Figure 4. Proposed mechanism (most likely radical) for the rapid decomposition of the γ-hydroxylactonecarboxylic acid **75**.

5. Attempted Completion of the Synthesis. Two tasks remained for the success of our first-generation strategy toward the CP-molecules (Scheme 1), namely, (a) internal ketalization and (b) a one-carbon homologation of the remaining hydroxymethyl group. Thus, treatment of **70** (Scheme 18), first with aqueous trifluoroacetic acid, effected bis-deprotection of the silyl groups, furnishing the corresponding triol, which upon exposure to $MeSO_3H$ in anhydrous $CHCl_3$ led to the desired hydroxy ketal **3** (50% overall yield). Arrival at **3** brought us within one carbon atom and two oxidation states from the natural product CP-263,114 (**1**) (Scheme 18). However, we became concerned upon oxidation of **3** with DMP, which proceeded smoothly to generate the extremely fragile aldehyde **74** (95% yield). To implement the planned one-carbon homologation using the Arndt−Eistert protocol, the carboxylic acid **75** was required. Unfortunately, however, our unrelenting efforts to effect this oxidation were thwarted by the delicate nature of aldehyde **74** coupled with apparent extreme instability of the presumably formed carboxylic acid **75** (Figure 4).[31] A model compound (not shown) without the anhydride moiety, but containing a γ-hydroxylactone and a fully oxidized concave hydroxyl group, was also very unstable; but nevertheless, we were able to isolate it. On the basis of

(30) Mico, A. D.; Margarita, R.; Parlanti, L.; Vescoui, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

(31) The Shair group also observed pronounced instability in these types of systems; see ref 6.

model studies, we believe that the problem lies in the instability of the resulting acid rather than difficulties in oxidizing the aldehyde. The unexpected instability of carboxylic acid **75** may be a result of decarboxylative pathways (see Figure 4) which may be facilitated by the conformational and electronic changes brought about by the maleic anhydride moiety within the CP framework as depicted in these structures.

We then turned our attention to homologation strategies on the fragile aldehyde **74** (Scheme 18). Attempts to convert this aldehyde (**74**) directly to the acid chloride using *t*-BuOCl[32] also failed. Wittig reactions and other attempts at attacking aldehyde **74** also failed despite extensive experimentation. Finally, a strategy was developed for homologation via the corresponding cyanohydrin, but it, too, failed on this delicate substrate. Briefly, this attempt involved exposing aldehyde **74** to Et_2AlCN to generate the corresponding cyanohydrin, conversion of the resulting hydroxyl group of this moiety into the thionocarbonylimidazolide, and deoxygenation. Despite this failure, the challenge catalyzed the development of a general method for the homologation of hindered aldehydes in the presence of other electrophilic functionalities.[33]

Conclusion

In this paper we detailed our first-generation approaches toward the CP-molecules and described studies that laid the groundwork for a new generation of synthetic strategies which eventually led to the sought after total synthesis. Inspired by the difficulties encountered when crafting the maleic anhydride moiety, we devised a strategy which took advantage of the unique steric and electronic features of the CP skeleton. Aside from developing a highly efficient route to the fused maleic anhydride moiety, a number of fundamental observations regarding compact heterocyclic molecules and cascade reactions were made and capitalized upon. Also, a stereoselective installation of the upper side chain was accomplished using the CP skeleton as a novel, long-range stereocontroller. An efficient sequence was then devised to reach the advanced key intermediate **5** from which all further synthetic explorations would diverge. Efforts to unravel reactivity patterns that would lead to the γ-hydroxylactone system of the CP-molecules resulted in the development of another cascade reaction commencing from 1,4-diols and leading to the desired moiety in one pot. Application of this designed cascade, which was mediated by DMP, permitted the construction of the complex intermediate **3**, whose conversion to the final targets failed, challenging us even more severely. Despite the failures, we were confident that deconvolution of this synthetic maze would yield even more rewards in the form of novel chemistry. Indeed, and as will be described in the following paper in this issue,[16] such new synthetic strategies and technologies would lie ahead and together with the ones described herein would result in the successful total syntheses of **1** and **2**.

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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.

JA012011D

(32) Wilson, S. R.; Tofigh, S.; Misra, R. N. *J. Org. Chem.* **1982**, *47*, 1360.
(33) Nicolaou, K. C.; Vassilikogiannakis, G.; Kranich, R.; Baran, P. S.; Zhong, Y.-L.; Natarajan, S. *Org. Lett.* **2000**, *2*, 1895.