Stereospecific Sulfur-Mediated Cleavage of a Spirocyclobutanone: Synthesis of a Fully Functional Precursor to the CP Compounds**

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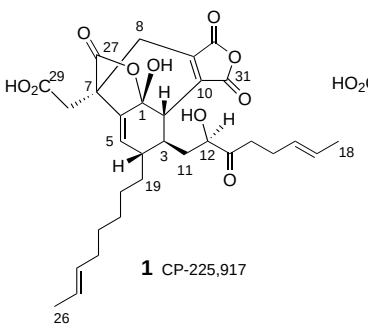
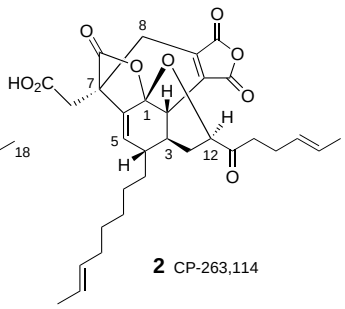
The screening of diverse sources of naturally occurring organic substances has many purposes. First, and no doubt foremost, is the hope that the activity profiles of some of the isolates may be of value for biomedical purposes. Compounds derived in this way may themselves become drugs, or may provide orienting leads for drug discovery. Indeed, some of the most important agents in the pharmaceutical industry began life in the context of natural products. Given major advances in separation sciences, structure determination by physical measurements, and the means for identifying specific cellular targets, the prospects for natural products as resources in drug discovery have never been better.[1, 2]

On rare occasion, compounds which arise from screening exercises are sufficiently striking that they emerge as milestone targets for the science of chemical synthesis. A mastery at the level of chemical synthesis of such systems may well result in analogue candidates for drug development. However, given enough architectural novelty, the milestone classification is not necessarily tied to any likely pharmaceutical advantage to be gained from chemical synthesis. Rather, the structure may pose an implicit challenge to the capabilities of synthesis. The vistas of synthesis grow from such confrontations, and the capacity of synthesis to contribute to projects with more likely benefit margins grows correspondingly.

Two recent compounds which well warrant the "milestone" designation are CP-225,917 and CP-263,114 (**1** and **2**, respectively) isolated at the Pfizer Laboratories.[3, 4] The derivations of these fascinating structures followed solely from spectroscopic measurements, and were not supported either by degradative or crystallographic validations. Although the compounds manifest two interesting forms of biological activity (inhibition of farnesyl transferase and squalene synthase), the great interest that they have engendered from the synthesis community can best be comprehended in terms of their novel molecular lattice work and the implicit challenge of such structures to chemists. Indeed, there is already a burgeoning literature describing highly imaginative approaches to assembling **1** and **2** in the laboratory.[5, 6] Clearly, any program which aspires to achieve a total synthesis of the CP compounds must transcend strictly regional issues and furnish provisions for all of the structural components of the natural products, including harmonization of competitive demands of various functional groups. Ideally, the synthesis program would be conducted with a view toward providing independent corroboration for the gross structure and configuration of **1** and **2**.



1 CP-225,917



2 CP-263,114

Recently, we disclosed an approach to the CP problem using an initial intermolecular α'-aldol condensation of a cyclohexenone with furylacetaldehyde derivative **3** (Scheme 1). This merger was followed by a bridging intramolecular Heck ring closure, leading to a consensus matrix structure (**4**) which either did or did not contain a functional group at C4 (**4a** and **4b**, respectively). In this context we could functionalize C5 by selenium dioxide mediated hydroxylation and exploit the resultant C5 β-hydroxyl group to introduce a potentially useful structural implement at C3 (**5**→**6**). Unfortunately, in the **4a** series, the selenium dioxide functionalization step lacks any regiochemical preference between C5 and the allylic methylene substituent on the C4 side chain. By contrast, if the aldol-Heck sequence was conducted on the C4-unsubstituted system (i.e., cyclohexenone itself), the resulting product **4b**, lacking the C4 side chain, suffers clean functionalization at C5, setting the stage for the Claisen transposition (→**7**). Unfortunately, with the C3 handle in place, we were unable to introduce the C4 substituent from any structure derived from **7** (e.g. **8**). Clearly, these problems required careful attention.

In our earlier report, we had reached systems of the type **9**. The oxo function in these structures could be exploited to create a quarternary center at C7, albeit with a suboptimal level of oxidation in its branches (see lactone **10**).[6] Also, the furan ring was exploited, as planned, to provide a straightforward pathway to the 2,3-fused maleic anhydride appendage (→**11**).[6] Neither of the most advanced compounds **10** or **11** had the bridgehead (C5–C6) olefin in place. While it seemed possible that some of our chemical implements could be channeled to gain access to the C5–C6 olefin, the point had not been demonstrated in practice. Also to be addressed was the potentially serious question as to the extent to which a bridgehead double bond would be restrictive of other required chemistry. Here we describe a program wherein these difficulties have been resolved, and all required elements for a global synthesis of the CP compounds or analogues appear to be in place.

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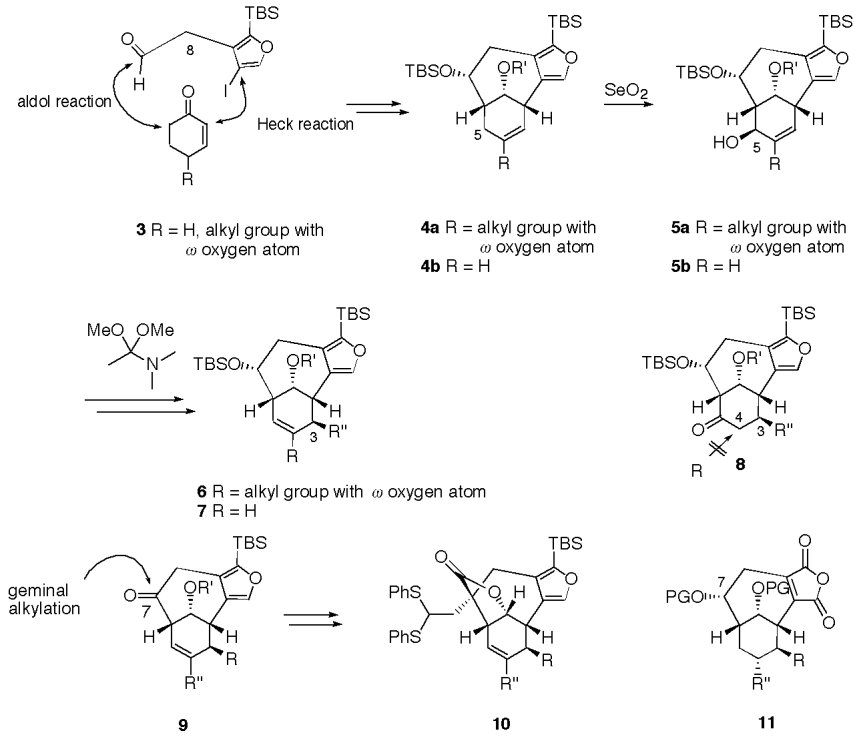
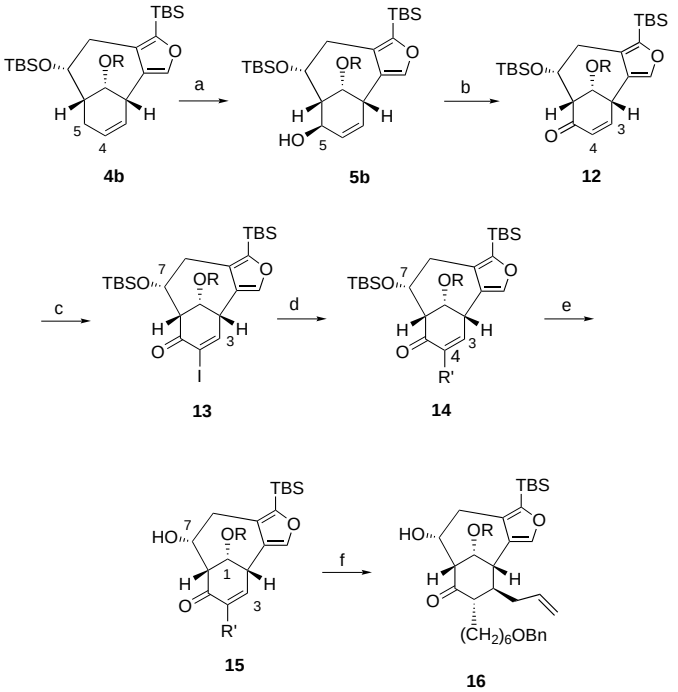


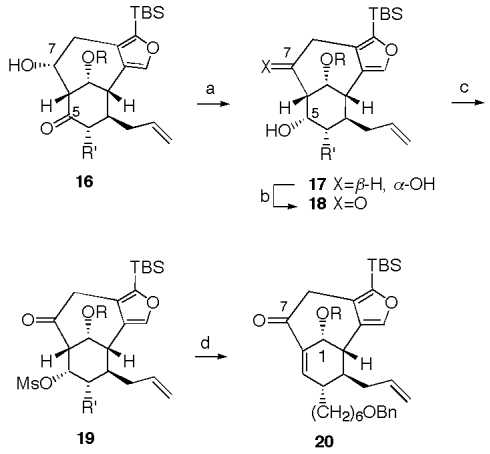
Scheme 1. Synthesis of the advanced CP precursors **10** and **11**.[6] TBS = *tert*-butyldimethylsilyl, PG = protecting group.

We returned to the previously described **4b**, which, upon oxidation with selenium dioxide and TPAP, afforded **12** (Scheme 2). The latter was converted into iodoenone **13** following the protocols of Johnson.[8] At this stage, we employed a *B*-alkyl Suzuki strategy[9, 10] to introduce the C4 side chain with the C5 oxo group already present (→**14**). In this way, the disastrous consequences of the regiorandom selenium-induced allylic dioxide hydroxylation of **4** were avoided. A variety of attempts to introduce a C3 substituent by conjugate addition to the enone linkage of **14** was to no avail. The logjam was broken as follows: A free alcohol functionality was exposed at C7 (→**15**). Presumably, this group plays a critical role in positioning the titanium tetrachloride derived Lewis acid moiety at the C5 oxo group. In the event, under these tightly defined circumstances, a Sakurai-type delivery of the β-oriented allyl group to C3 was accomplished.[12] Moreover, stereospecific β-protonation at C4 (either with HCl or on workup) afforded **16**. In this way, the stereochemical relationship assigned to the CP compounds at C3 and C4 had been simulated.

We turned next to installation of the C5–C6 double bond. Toward this end we could again exploit small but decisive differential reactivity margins. Thus, reduction of the C5 oxo group occurred from the β face (→**17**; Scheme 3). In a critical step, selective Swern



Scheme 2. Stereoselective introduction of side chains at C3 and C4 (R=TBS, R′ = $(CH_2)_6OBn$). a) SeO_2, 1,4-dioxane, 100 °C, 2 h, 90 %; b) TPAP, NMO, CH_2Cl_2, 85 %; c) I_2, pyridine, CH_2Cl_2, 95 %; d) [$PdCl_2$(dppf)], Cs_2CO_3, $AsPh_3$, H_2O; R'_3B, 70 %; e) HF·pyridine, 90 %; f) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, −78 °C, 75 %. TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, Bn = benzyl.



Scheme 3. Introduction of C5–C6 bridgehead double bond (R=TBS, R′ = $(CH_2)_6OBn$). a) $LiAlH_4$, Et_2O, 90 %; b) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C; c) DMAP, CH_2Cl_2, MsCl, then Et_3N, MsCl, 70 % for two steps; d) DBU, toluene, 80 °C, 90 %. MsCl = methanesufonyl chloride, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

oxidation occurs at C7 to give monoketone **18**. At this stage, mesylation at C5 could be conducted (→**19**). Elimination of the mesyloxy functionality was achieved by the reaction of **19** with DBU, providing **20** with the C5–C6 (bridgehead) double bond in place.

It then transpired that with the bridgehead olefin moiety in nominal conjugation to the C7 oxo group,[13] the geminal alkylation methodology which had previously been employed

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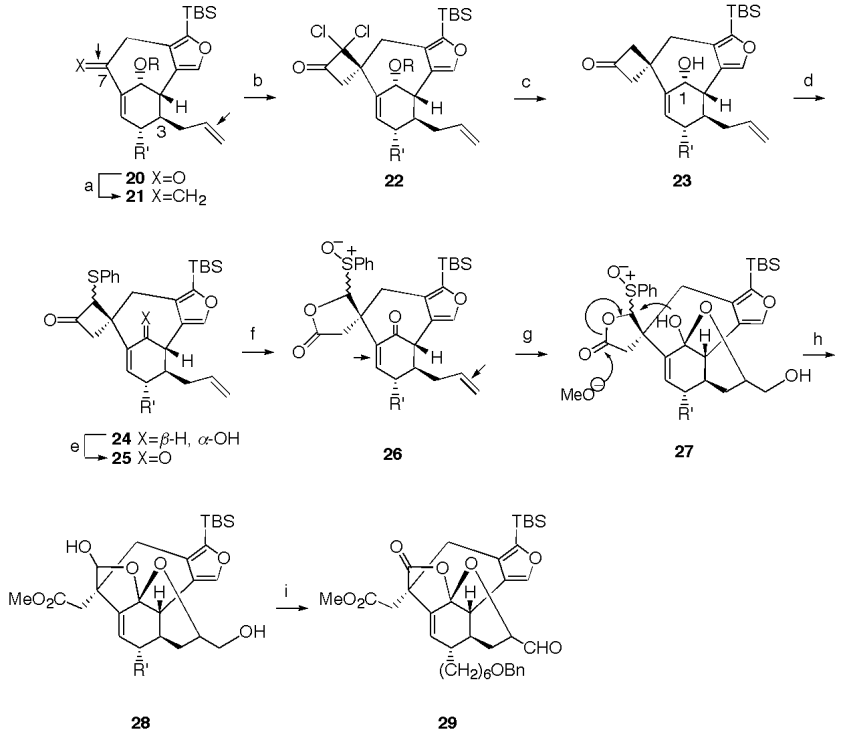
to produce **10**[7] broke down completely due to the base lability of the system. A new program was thus devised in response to the very restricted terrain available for feasible chemical elaboration (Scheme 4). Fortunately, it did prove possible to conduct a Tebbe olefination of **20** (→**21**).[14]



Scheme 4. Construction of the quaternary center at C7 and the CP-263,114 building array (R = TBS, R′ = $(CH_2)_6OBn$). a) Tebbe reagent, THF, −78 → −10 °C, 90%; b) trichloroacetyl chloride, Zn, Et_2O, DME, ultrasound, 85%; c) 1. Zn, NH_4Cl, MeOH, ultrasound, 80%; 2. TBAF, THF, 0 °C, 70%; d) PhSSPh, NaH/KH, THF, 80%; e) Dess–Martin periodinane, CH_2Cl_2, 90%; f) H_2O_2, MeOH, 70%; g) OsO_4,NMO, acetone/water, 70%; h) NaOMe, MeOH, 60%; i) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 70%. DME = dimethoxyethane, TBAF = tetrabutylammonium fluoride.

Remarkably, it was possible to realize a [2+2] cycloaddition of dichloroketene at the exocyclic double bond in the presence of the allyl group.[15] Moreover, and surprisingly, the reaction was highly stereoselective in the desired sense (→**22**). However, given the highly restricted menu of reactions feasible for the dichlorocyclobutanone functionality (it, too, is base labile), it was necessary to forgo the potential advantage of the geminal dichloro groups that are *syn* to the C1 bridge. Rather, both chlorine atoms were cleaved reductively and the C1 hydroxyl group was deprotected (→**23**). Possibly due to a directing effect of the free hydroxyl group, we could execute base-induced sulfenylation of **23** with diastereotopic specificity *syn* to the C1 bridge. At the kinetic level, it was possible to achieve stereoselectivity even within the required diastereotopic methylene group. However, in practice the configurational lability at this center was such that a diasterermeric mixture of **24** was employed in subsequent steps. Oxidation of **24** afforded **25**. While a regiospecific Baeyer–Villiger reaction, under the apparent control of the phenylsulfanyl group, could be conducted, the yield of the subsequent sequence of lactone cleavage and valence isomerization leading to **28** was rather low. This situation was much improved by further oxidation of the phenylsulfenyl lactone to the corresponding sulfoxide **26**. With the bridgehead double bond deactivated by its adjacency to the C1 oxo group, it proved possible to selectively dihydroxylate the terminal allyl group of **26**. Treatment of the crude hydroxylation product (see valence tautomer **27**)[16] with sodium methoxide in methanol afforded **28**, which on oxidation led to **29**.[17]

In various stages of these studies, we have demonstrated the viability of converting the furan moiety into the maleic anhydride unit. We have easily differentiated the aldehyde at C13 for relevant nucleophilic alkylation and, at an earlier stage, implemented the full CP side chain at C4. There remains now the still significant task of sequencing these capabilities in a fully harmonized program.

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[17] Analysis of the NMR spectrum of aldehyde **29** suggests that the formyl group at C12 is in the α position. The stereochemical assignment for **2** presented the C13 oxo group as being in the β position. The stereochemical relationships between the two CP natural products at C12 have not been rigorously defined. These matters, as well as the order of thermodynamic stabilities at C12, will require further research.

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