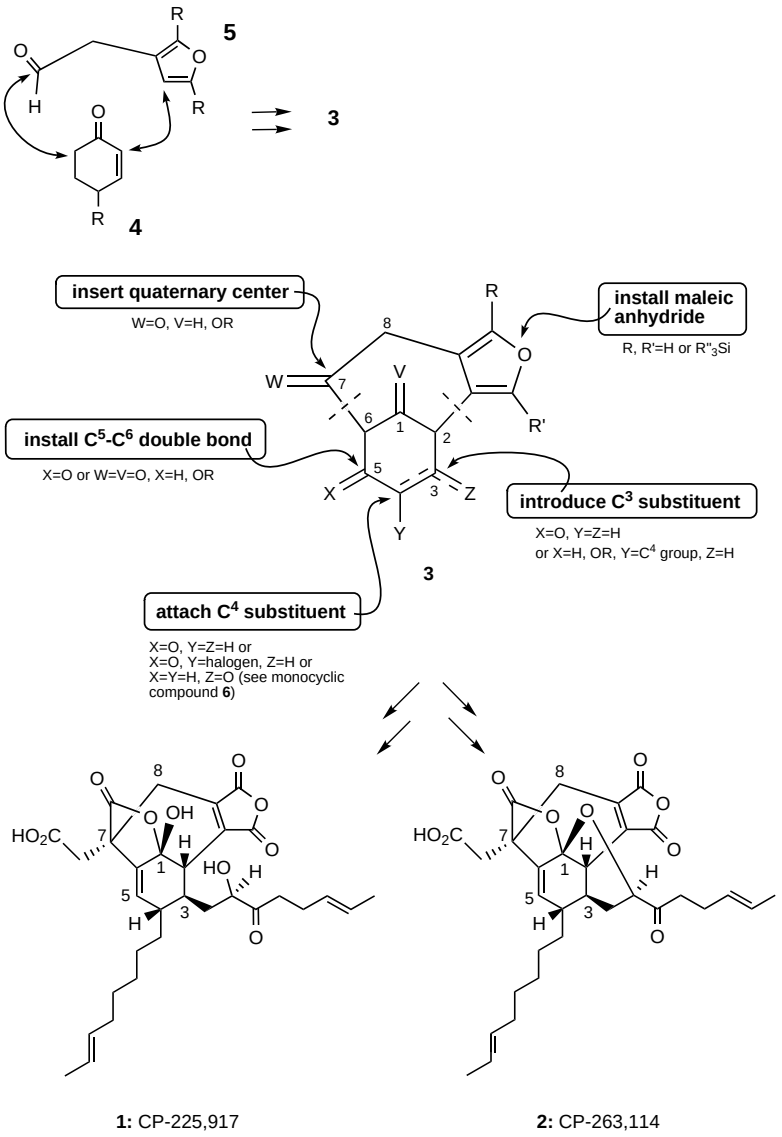
Total Syntheses of CP-225,917 and CP-263,114: Creation of a Matrix Structure By Sequential Aldol Condensation and Intramolecular Heck Ring Closure**

Ohyun Kwon, Dai-Shi Su, Dongfang Meng, Wei Deng, Derin C. D'Amico, and Samuel J. Danishefsky*

Recently Kaneko and co-workers at the Charles Pfizer laboratories described the isolation and structure elucidation of compounds **1** and **2** (see Scheme 1).[1, 2] Apart from the curiosity provoked by their novel structures, these metabolites warrant additional attention as they are potent inhibitors of squalene synthase and farnesyl transferase. The potentialities of modulating the pathways regulated by these enzymes are of great interest to the pharmaceutical industry, though no agents operating through such mechanisms are in current usage.[3] Our notice of the Pfizer compounds arose from the inherent summons their syntheses pose to the ingenuity and capacities of organic chemistry.

Given the multifaceted problems which would have to be surmounted to complete such a goal in the case of **1** and **2**, it seems unlikely that achieving a total synthesis would impact on the availability of these natural products for detailed evaluation, let alone clinical application. However, since the structure – activity profiles of such compounds are not known, it is not inconceivable that useful biological function could be realized from rather simpler structures which might, in fact, be available in acceptable amounts through purely synthetic means. An exploration of the total syntheses of **1** and **2** might provide a valuable perspective to study these issues.



Scheme 1. Strategies for a matrix structure **3** in the total synthesis of **1** and **2**.

Several early and interesting initiatives directed to the synthesis of **1** and **2** have been reported by Nicolaou,[4] Davies,[5] Clive,[6] and Armstrong.[7] These previous thrusts directly addressed the introduction of the C5 – C6 bridgehead double bond, which is present in both compounds. Progress toward this end was accomplished through bond-reorganization strategies (cycloadditions[8] or sigmatropic rearrangements).

The route we are exploring herein reflects a different view of the problem. Its main focus is on gaining rapid access to a 5,6-dihydro ring system, with provisions (albeit in less than mature form) for the introduction of all the functional groups needed to obtain **1** and **2**. The scheme provides for properly placed carbonyl groups and double bonds to serve these ends. Central to the plan is the presence of a furan moiety that contributes two carbon atoms to the four-carbon spanning element of coupling agent **5** (Scheme 1). The furan ring provides an annulation handle (see below) and, furthermore, is a locus of reasonable stability in the resultant cyclization product. Moreover, appropriate oxidation of the furan would lead to the maleic anhydride.[9] The optimal timing of this event would be ascertained as matters unfold. As for the introduction of the C5 – C6 bridgehead double bond, we envisioned reliance on functionalities derivable from one or more keto groups at C7 and C1, where C5 is equipped with a leaving group.

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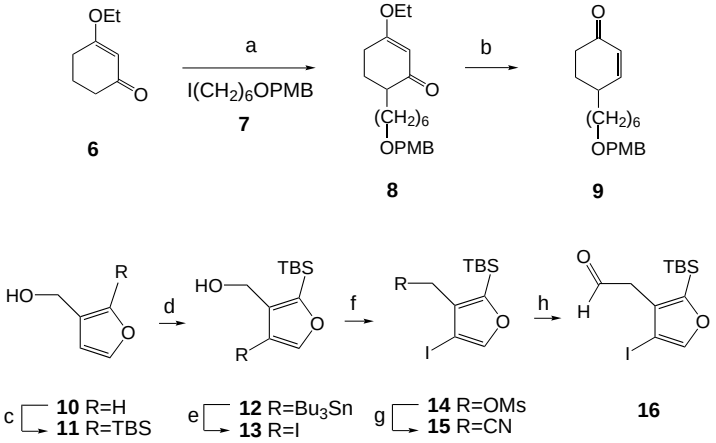
Our general thought process is summarized in formula **3** (Scheme 1). We emphasize that this picture is not intended to represent a specific compound. Rather, it conveys a perspective by which required functional groups are introduced through potential implementation sites in a matrix system. Left unaddressed in such a presentation are important subtleties of timing and orchestration.

Seeking proof of principle, we studied the feasibility of melding systems of types **4** and **5** as a route to the matrix entity **3**. In the particular variation we report here, the future substituent at C4 in **3** is introduced already in the monocyclic precursor **4**. In other constructions, we have introduced this substituent after formation of **3**.

The alkylation of **6** with **7** afforded **8** in 78% yield (Scheme 2).[10] Reduction of the vinylogous ester **8** and acidic

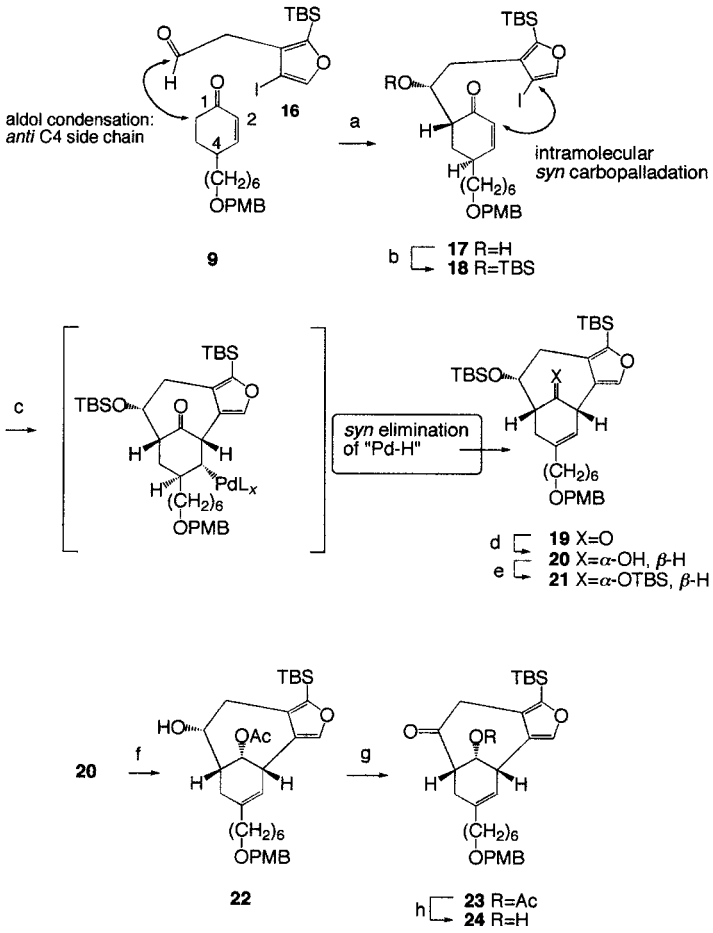


Scheme 2. Synthesis of monocycles **9** and **16**. a) LDA, HMPA, THF, $-78\,^{\circ}C$, then **7**, $-78\,^{\circ}C \rightarrow RT$ (room temperature), 16 h, 78%; b) $LiAlH_4$, Et_2O, $0\,^{\circ}C$, 40 min, then 4 N HCl, RT, 0.5 h, 93%; c) 1. TBSCl, $NEt(iPr)_2$, CH_2Cl_2, RT, 1 h, 98%; 2. *n*BuLi, HMPA, THF, $-78\,^{\circ}C \rightarrow RT$, 16 h, 89%; d) *n*BuLi, DME, $-78 \rightarrow 0\,^{\circ}C$, 15 min, then Bu_3SnCl, $0\,^{\circ}C$, 1 h, 80%; e) 1. I_2, CH_2Cl_2; 2. KF, Et_2O, RT, 16 h, 96%; f) MsCl, NEt_3, CH_2Cl_2, $-78\,^{\circ}C$, 2 h; g) KCN, DMF, RT, 16 h, 98% over two steps; h) DIBAlH, toluene, RT, 1 h, 92%. DIBAlH = diisobutyl aluminum hydride, DME = dimethoxyethane, HMPA = hexamethyl phosporamide, LDA = lithium diisopropylamide, Ms = methanesulfonyl, PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl.

hydrolysis led, as anticipated,[11] to enone **9**, a specific example of the monocyclic precursor **4**. The synthesis of a furan of type **5** commenced with the commercially available **10**, which was converted into the corresponding *tert*-butyldimethylsilyl ether. Silyloxy-directed metalation at C2 followed by $O \rightarrow C$ migration of the silyl group afforded **11**. Next, we made use of hydroxyl-directed metalation at C3 to introduce a stannyl group (**12**). Destannylative iodination in the *ipso* sense provided **13**,[12,13] which was homologated (via mesylate **14**) to the furanylacetonitrile derivative **15**. Finally, controlled reduction of the nitrile functionality and careful hydrolysis afforded the somewhat labile aldehyde **16**.

With both coupling components in hand, we directed our attention to construction of a prototype corresponding to **3**. The plan involved an initial merger of the two components at the future C6–C7 bond through an aldol condensation. Formation of the bridging carbon–carbon bond would occur by an intramolecular Heck vinylation reaction.[14, 15] Aldol reaction of the α'-enolate[16] derived from **9** with aldehyde **16** afforded with high stereoselectivity[17] **17** in 91% yield. At this point, it was prudent to protect the C7 alcohol in the form of its TBS derivative **18**.[18] The stage was now set for the critical intramolecular Heck reaction. In practice, cyclization occurred smoothly to afford **19**. Thus, a credible matrix compound for the projected synthesis is assembled in a remarkably straightforward way. The key to the successful Heck reaction on a side chain at C4 of cyclohexenone is that the aldol reaction at C6 occurs *anti* to the side chain. Thus, following protection and *syn* carbopalladation, *syn* elimination of palladium hydride is possible, which is central to the success of the enterprise.

Once we had compound **19**, we began to explore some possible functional-group modifications which could be helpful in reaching structures **1** or **2**. We found that reduction of **19** with diisobutyl aluminum hydride provides a single alcohol, **20** (Scheme 3). Silylation of **20** gives rise to **21**. Alternatively,



Scheme 3. Synthesis of tricycles **21** and **24**. a) **9**, LDA, THF, $-78\,^{\circ}C$, 1 h, then **16**, THF, $-78\,^{\circ}C$, 2 h, 91%; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT, 1 h, 63%; c) $[Pd(OAc)_2(PPh_3)_2]$, NEt_3, THF, $\triangle$, 3 d, 85% or $[Pd(OAc)_2(PPh_3)_2]$, NEt_3, dioxane, $\triangle$, 24 h, 77%; d) DIBAlH, CH_2Cl_2, $-78 \rightarrow -30\,^{\circ}C$, 96%; e) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT, 16 h, 94%; f) 1. Ac_2O, NEt_3, DMAP, CH_2Cl_2, 16 h, 98%; 2. TBAF, THF, $45\,^{\circ}C$, 2 h; g) TPAP, NMO, CH_2Cl_2, molecular sieves (4 Å), RT, 10 min; h) K_2CO_3, MeOH, RT, 1.25 h, 77% over three steps. DMAP = 4-(dimethylamino)-pyridine, NMO = *N*-methylmorpholin-*N*-oxide, TBAF = tetrabutylammonium fluoride, Tf = trifluoromethanesulfonyl, TPAP = tetrapropylammonium perruthenate.

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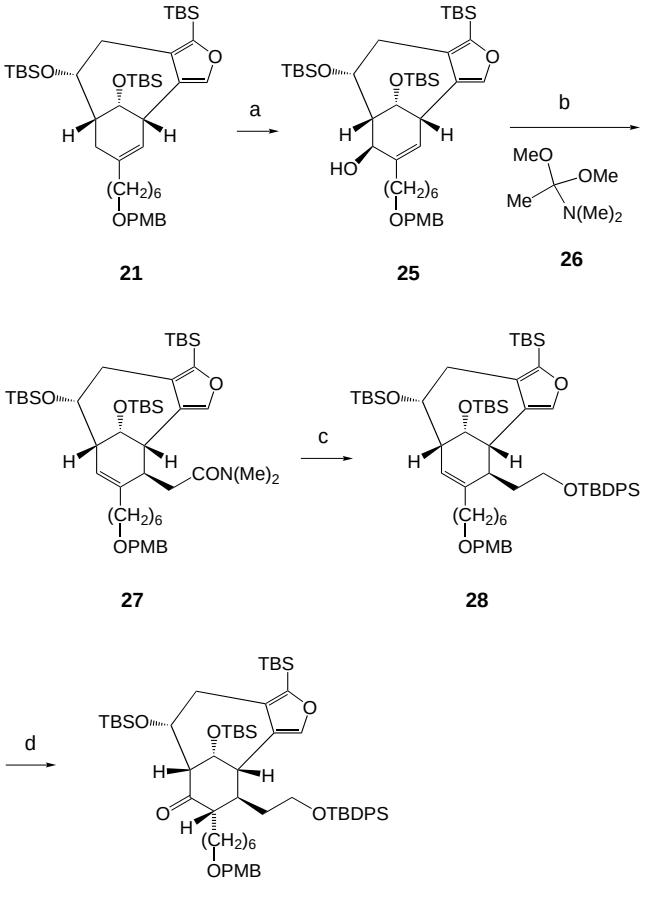
acetylation of **20** followed by cleavage of the C7 silyl group led to **22**, which upon oxidation provided ketone **23**. The latter can be deprotected at C1 (**24**).

Another milestone was reached, albeit in a manner that currently[19] lacks tight regiochemical control,[20] through the action of selenium dioxide on **21**. This process produced **25** as well as a somewhat smaller amount of side chain oxidation products (Scheme 4). Reaction of **25** with **26** gave, upon [3,3] sigmatropic rearrangement, the γ,δ unsaturated amide **27**.[21] Reduction of the amide linkage and protection of the resulting primary alcohol led to **28**, which on hydroboration and oxidation provided **29**.[22]



21 **25** **26** **27** **28** **29**

Scheme 4. Synthesis of **29**. a) SeO_2, pyridine, 70 °C, 20 min, 31 % (+21 % side chain oxidation product); b) **26**, xylenes, 150 °C, 18 h, 91 %; c) 1. $LiEt_3BH$, THF, 0 °C→RT, 2 h, then 1N NaOH, H_2O_2, RT, 1.75 h, 91 %; 2. TBDPSCl, imidazole, DMAP, THF, RT, 2 h, 91 %; d) 1. $BH_3\cdot$THF, 0 °C→RT, 16 h, then 1N NaOH, H_2O_2, RT, 1 h, 68 %; 2. Dess–Martin periodinane, CH_2Cl_2, RT, 2 h, 92 %. TBDPS = *tert*-butyldiphenylsilyl.

In principle, several compounds in this series contain promising functionality implements required to reach CP-225,917 and CP-263,114. This theme will be amplified in the following contribution.[23]

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[18] In parallel experiments, the Heck reaction of the unprotected alcohol was also accomplished, but in much lower yield and with poor reproducibility. For another instance of the power of the sequential Heck–Aldol logic, see reference [15].
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(m, 1H), 1.50 (m, 4H), 1.18 (m, 8H), 0.90 (s, 9H), 0.86 (s, 9H), 0.79 (s, 9H), 0.64 (s, 9H), 0.16 (2s, 6H), −0.03 (s, 3H), −0.07 (s, 3H), −0.09 (s, 3H), −0.13 (s, 3H); FT-IR (neat): $\tilde{\nu}$ = 1714, 1512, 1470, 1250, 1104 cm^{-1}; MS: calcd for $C_{62}H_{98}O_7Si_4Na$: 1089.6, found: 1089.6 [M+Na].

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A Stereospecific Geminal Alkylation Scheme En Route To CP-225, 917 and CP-263,114**

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Dedicated to Professor Barry M. Trost

In the previous contribution[1] we outlined a conceptual framework and encouraging results for assembling the ring systems of CP-225,917 (**1**) and CP-263,114 (**2**)[2, 3] (Figure 1).

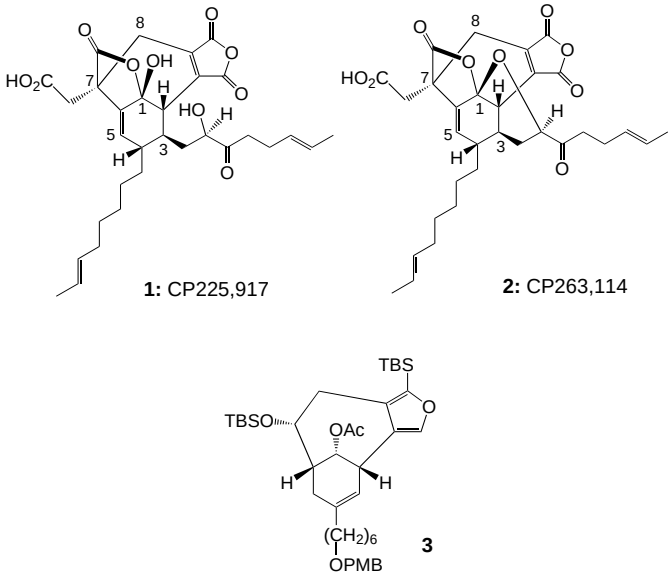
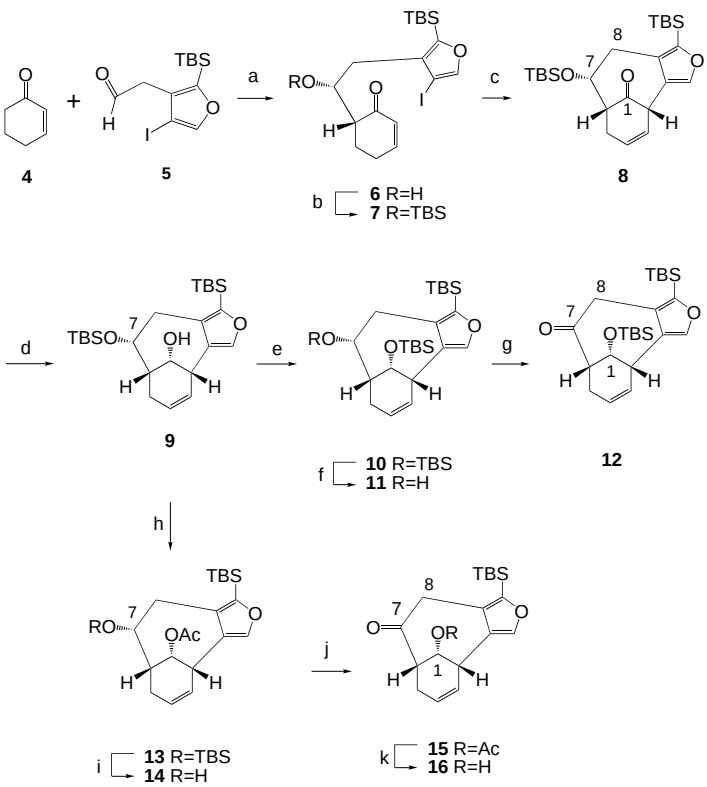


Figure 1. Structures of **1** and **2** as well as the central starting material **3**.

The key element of our synthetic program is the rapid construction of an intermediate lacking the C5–C6 bridgehead double bond (**3**) through the proper sequencing of aldol and intramolecular Heck-type bond formations using a 2,3,4-trisubstituted furan as a connecting device. We demonstrated how the resultant product of this sequence provides implementation sites through which the requisite functionality for the six-membered ring can be emplaced.[1]

Herein, we turn our attention to the more complex functionality found in the seven-membered ring of **1** and **2**. To explore our ideas concerning this sector of the natural products, we utilized the previously described **3**[1] as well as compound **8**, which lacks the substituent of C4 of the cyclohexenone ring (Scheme 1). Compound **8** was assembled through aldol condensation of cyclohexenone **4** with aldehyde **5**, which was also described in the previous article.[1] In this case, the stereospecificity was somewhat diminished relative to that encountered en route to **3**. The reaction provided **6** in 79% yield (as well an apparent diastereoisomer in 10% yield).[4] Protection of the secondary alcohol group gave rise to **7**. Intramolecular Heck vinlylation, as earlier,[1] provided **8** in 92% yield.



Scheme 1. Synthesis of ketones **12** and **16**. a) **4**, LDA, THF, −78 °C, 1 h, then **5**, THF, −78 °C, 2 h, 79% plus 10% diasteromer; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→RT (room temperature), 1 h, 85%; c) $[Pd(OAc)_2(PPh_3)_2]$, NEt_3, THF, △, 4 d, 92%; d) DIBAlH, CH_2Cl_2, −78→−30 °C; e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→RT, 16 h, 61% over two steps; f) EtOH/10% H_2SO_4 (10/1), RT, 31 h; g) Dess–Martin periodinane, CH_2Cl_2, RT, 0.5 h, 85% over two steps; h) Ac_2O, pyridine, DMAP; i) TBAF, AcOH, THF, RT; j) Dess–Martin periodinane, CH_2Cl_2, 93% over three steps; k) K_2CO_3, MeOH, RT, 88%. DIBAlH = diisobutylaluminum hydride, DMAP = 4-(dimethylamino)pyridine, LDA = ithium diisopropylamide, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

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