(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].

[23] O. Kwon, D.-S. Su, D. Meng, W. Deng, D. D'Amico, S. J. Danishefsky, *Angew. Chemie.* **1998**, *110*, 1981–1983; *Angew. Chem. Int. Ed.* **1998**, *37*, 1880–1882.

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

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

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).

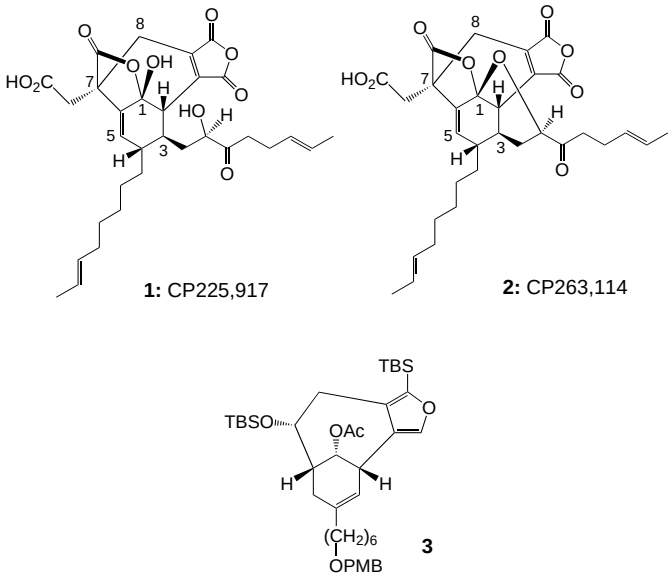
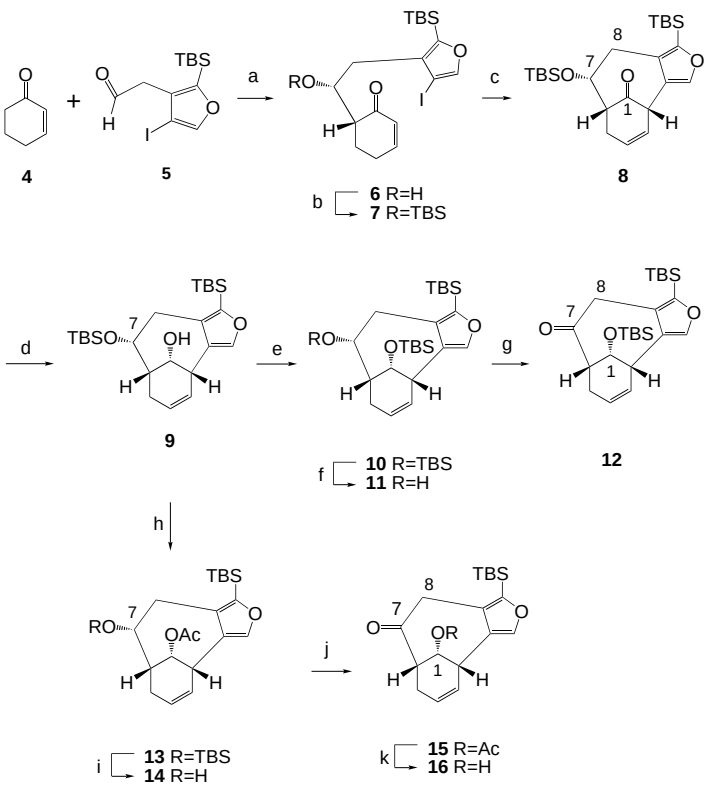


Figure 1. Structures of **1** and **2** as well as the central starting material **3**.

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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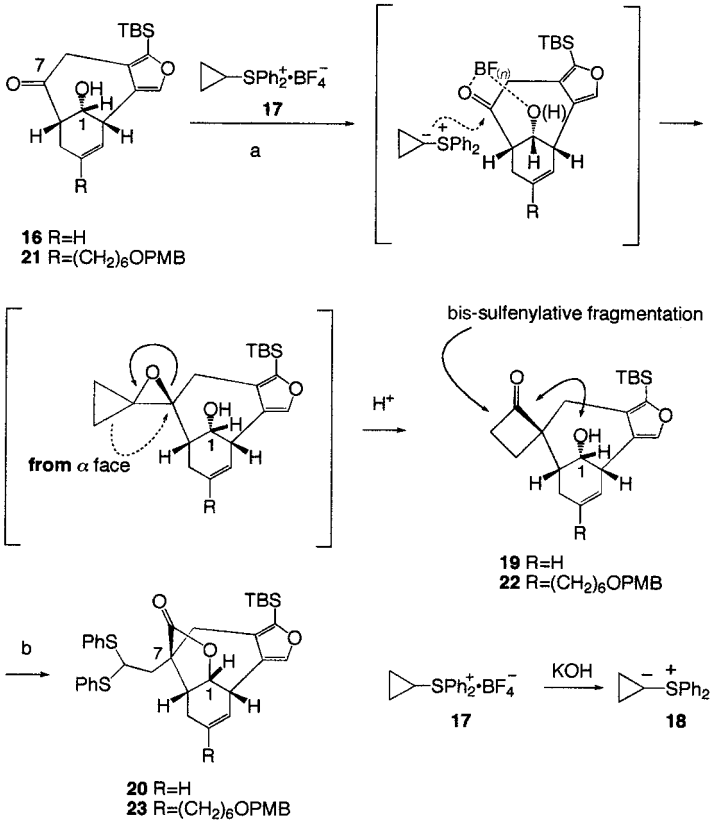
We next sought to generate a unique ketone group at C7 so that we could pursue some interesting possibilities for the installation of the quaternary center. Toward this end, compound **8** was reduced with diisobutylaluminum hydride, and the resultant carbinol **9** was silylated to give **10**. Selective desilylation at C7 (→**11**) could be achieved because, in fact, the C1 silyloxy group proved to be difficult to cleave. Oxidation of **11** provided ketone **12**.[5] In a parallel series of reactions, **9** was acetylated, giving rise to **13**. Desilylation of the latter led to **14**. Oxidation provided **15**, and, following deacetylation, keto alcohol **16** was then in hand. Many attempts were made to deliver various carbon-based nucleophiles to the C7 ketone group of **12**.[6] Only marginal success was realized toward this goal. It seemed that a significant complicating feature was enolization of the ketone by deprotonation at C8.

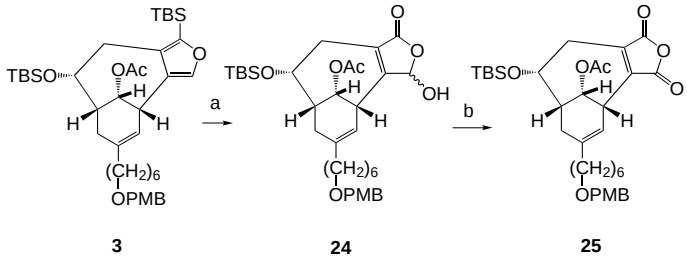
It was from this perspective that we turned to the use of the Trost sulfonium salt **17**.[7, 8] The hope was that the derived ylide **18**, being relatively nonbasic, would provide more favorable possibilities for C–C bond formation at C7 relative to enolization at C8 (Scheme 2). In practice, ketone **12** proved



Scheme 2. Synthesis of lactones **20** and **23**. a) **17**, KOH, DMSO, RT, 2.5 h, then aq HBF_4, Et_2O, RT, 56% for **19**, 46% for **22**; b) PhSSPh, NaOMe, MeOH, △, 5 d for **20**, 65 h for **23**, 81% for **20** based on 23% recovery of **19**, 35% for **23**. PMB = *p*-methoxybenzyl.

to be quite resistant to attack of **18** (generated from **17** through the action of potassium hydroxide).[8] We wondered about the possibility that the C7 ketone group of the hydroxyketone **16** might provide a more reactive electrophilic, site. Treatment of **16** with **18** occurred in a highly stereoselective fashion to provide, after acidic treatment, a spirocyclobutanone. From close analysis of the NMR spectrum, it seemed likely that **18** already had the stereochemistry indicated in **19**, wherein the spiroketone is on the β-face (i.e., *syn* to the C1 bridge). Such an outcome would be expected if formation of the carbon–carbon bond in the Trost reaction between **16** and **18** had occurred in the expected α sense (perhaps as a consequence of an emerging salt bridge between the oxido functions at C1 and C7). This surmise concerning the stereostructure of **19** was confirmed in a manner which itself augurs well for the synthesis of **1** and **2**: Under the Trost conditions[9] for bis-sulfenylation of the cyclobutanone, we obtained a cyclobutanone cleavage product in the form of lactone **20** in 62% yield.[10] In a similar way, **3** was converted into hydroxyketone **21**,[1] whose reaction with **18** and afforded **22** after workup with acid. Once again, under the conditions of bis-sulfenylative fragmentation of the cyclobutanone, compound **23** was obtained.

We next turned to validate the hypothesis concerning the use of the silylfuran as an entry to the maleic anhydride moiety. Encouragement toward this hope was secured upon photooxidation of **3** under the conditions shown in Scheme 3.



Scheme 3. Synthesis of anhydride **25**. a) O_2, rose bengal, $NEt(iPr)_2$, CH_2Cl_2, *hv*, 0 °C, 3.5 h, 93%; b) PCC, molecular sieves (4 Å), CH_2Cl_2, RT, 50 min, 83%. PCC = pyridinium chlorochromate.

This treatment gave rise to compound **24** as a mixture of diastereomers.[11, 12] Further oxidation with PCC afforded the anhydride **25**.[13]

Several problems await solution for the challenge of total syntheses of **1** and **2** to be surmounted. Foremost among these is the timing for introduction of the C5–C6 bridgehead double bond.[14] Nonetheless, the achievements accomplished, thus far in relatively few steps, encourage continued efforts directed at this goal.

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[4] The ratio varied between 8:1 to 10:1 in favor of **6**. The Heck closure of the unprotected **6** was also accomplished, but in much lower yield and with poor reproducibility.
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[6] Compound **12** was recovered after exposure to the conditions of the Wittig or Wadsworth–Emmons–Horner condensation. Similarly, it was unreactive toward the corresponding antimony ylide ($SbBu_3$, $N_2CH_2CO_2CH_3$, CuI (cat.), PhH, 50 °C). Addition of lithium ethoxyacetylide provided only a 21% yield of a tertiary alcohol (with 43% starting material recovered). The formation of the corresponding α,β-unsaturated ester from this product was not successful. A Peterson-type reaction with ethyl lithiotrimethylsilylacetate afforded only a 28% yield of the α,β-unsaturated ester (with 34% starting material recovered). By contrast, Reformatsky reaction provided almost complete transformation to a β-hydroxy ester. However, dehydration of this compound has thus far not been achieved. A modified Reformatsky reaction (with methyl dichloroacetate and Zn in the presence of diethylaluminum chloride: K. Takai, Y. Hotta, K. Oshima, H. Nozaki, *Bull. Chem. Soc. Jpn*. **1980**, *53*, 1698) produced the α,β-unsaturated ester in 73% yield. Early attempts to deliver a one-carbon fragment to the enoate have not been productive. Given our success in spirobutanone formation, these studies have not yet been pursued in detail.
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[13] Selected physical properties for **25**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.22 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 6.8$, 2.1 Hz, 2H), 5.34 (t, $J =$ 5.6 Hz, 1H), 5.12 (d, $J = 5.6$ Hz, 1H), 4.39 (s, 2H), 3.93 (dt, $J =$ 11.4 Hz, 1H), 3.77 (s, 3H), 3.58 (t, $J = 5.7$ Hz, 1H), 3.40 (t, $J =$ 6.5 Hz, 2H), 2.69 (dd, $J = 5.6$, 0.9 Hz, 1H), 2.53 (m, 3H), 2.31 (dd, $J = 10.2$ Hz, 1H), 2.02 (s, 3H), 1.58 (m, 4H), 1.28 (m, 6H), 0.85 (s, 9H), 0.039 (s, 3H), 0.007 (s, 3H); FT-IR (neat): 1771, 1698, 1558, 1508, 1248, 1091 cm^{-1}; LR-MS calcd for $C_{34}H_{48}O_8SiNa$: 635.3, found: 635.3 [M+Na].
[14] The construction of the C5–C6 bridgehead double bond has been accomplished recently: D. Meng, Columbia University, unpublished results.

Direct Observation of Fluid Mass Transfer Resistance in Porous Media by NMR Spectroscopy**

Ulrich Tallarek, Dagmar van Dusschoten, Henk Van As, Georges Guiochon, and Ernst Bayer*

In memory of John Calvin Giddings

The transport of solutes by dispersion, a combination of convection and hindered diffusion, through heterogeneous porous media is of fundamental importance in many areas such as liquid chromatography,[1, 2] catalysis,[3] the migration of pollutants in groundwater,[4] and petroleum recovery.[5] Most porous media exhibit bi- or multimodal pore-size distributions, which can result, for example, from the intraparticle and interparticle pores in beds of porous particles, as are used in chromatographic columns.[1, 6] Although the kinetics of mass transfer between the fluid percolating through the system and the stagnant fluid in the diffusional pores is known to be the rate-limiting step in numerous dynamic processes (e.g., the efficiency of chromatographic columns[2] or the amount of oil that can be economically recovered from a reservoir), no direct, quantitative measurement of these kinetics has been provided so far. Here we show how the pulsed field gradient (PFG) NMR method[7] allows the determination of these kinetics. A single series of measurements permits the identification of the stagnant fluid fraction, of the fractional volume exchanged as a function of time, and of the porosity and tortuosity of the porous medium.

Figure 1 illustrates the structure of a bed of porous particles as used in column chromatography or in heterogeneous catalysis. Permeable rocks have a more complex porous structure, with a multimodal pore-size distribution and interconnection of the pores.[8] However, water and oil bypass regions containing networks of finer pores by flowing through cracks. The fluid pools inside zones with fine pores are only accessible by diffusion. In chromatography, axial dispersion of a band arises from axial diffusion along the streamlines, eddy diffusion (resulting from the anastomosis of the porous space and the differences in the average velocity along streamlines), and the kinetics of mass transfer into and out of the particles.[2]

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