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LETTERS

Synthetic Studies on CP-225,917 and CP-263,114

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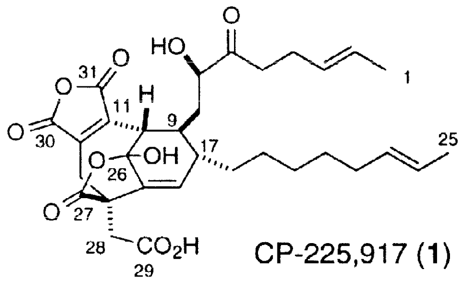
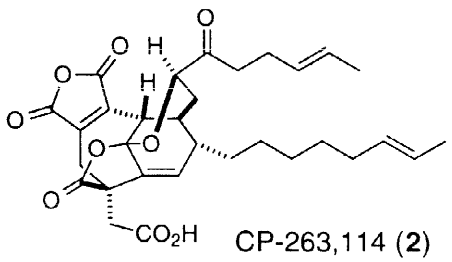
Abstract: An efficient synthesis of bicyclic diketone **3**, possessing most of the functional groups and stereogenic centers required for construction of the unique skeletons of CP-225,917 (**1**) and CP-263,114 (**2**), was achieved by utilizing an intramolecular Diels-Alder reaction and Pummerer rearrangement.

Keywords: Diels-Alder reactions; Pummerer reactions

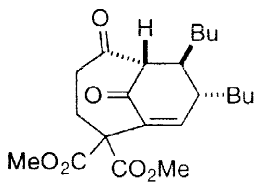
CP-225,917 (**1**) and CP-263,114 (**2**) were recently isolated from an unidentified fungus, and have been shown to inhibit squalene synthase and Ras farnesyl transferase by a Pfizer research group.[1] Inhibition of these enzymes suggests that they may serve as leads in the design of cholesterol-lowering and anticancer drugs. These compounds have a unique polycyclic skeleton, which consists of a bridgehead double bond,[2] a γ-lactone acetal or a hemiacetal, and a maleic anhydride moiety. Because of the unique skeletal complexity and interesting biological activities, these compounds have attracted much interest among synthetic chemists.[3] We report herein an efficient synthesis of the bicyclic model compound **3** which possesses most of the functional groups and the stereogenic centers required for the total syntheses of **1** and **2**.



CP-225,917 (**1**)



CP-263,114 (**2**)



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Our synthetic strategy is based on the construction of the basic skeleton possessing a bridgehead olefin by means of an intramolecular Diels-Alder reaction, which is known to be particularly suited for the construction of the strained bicyclic carbocycles.[3a,4] In order to perform a facile Diels-Alder reaction, a reliable procedure for a stereoselective construction of an (*E*, *E*)-diene such as **6** needs to be established to secure the coplanarity of the diene. Toward this end, we opted to carry out a Michael reaction with a very reactive allenic ester where a γ-substituent is known to direct the attack of nucleophiles from the less hindered, opposite side.[5]

Upon treatment with a catalytic amount of DBU in THF at room temperature, methyl 4-ethylthio-2-butynoate **4** underwent smooth isomerization to allene **5**, which was immediately used for the next reaction without isolation (Scheme 1). Unfortunately, 1,4-addition of the dialkenylcuprate to allenic ester **5** resulted in the formation of a 1:1 mixture of the desired diene **6** and a byproduct, which arose from the addition of the incipient anion of adduct **6** to allene **5**. As a result of a great deal of experimentation, we found that the addition of a mixture of allenic ester **5** and phenol to a solution of monoalkenylcopper was effective in suppressing the formation of the undesired byproduct (PhOH, (*E*)-CuCH=CHBu, Me_2S-THF, -23 °C, 58% yield).[6] As expected, this addition reaction proceeded with high stereoselectivity, giving exclusively the desired (*E*, *E*)-diene **6**. A second methoxycarbonyl group was then introduced to ester **6** under conventional conditions to give malonate **7**. Subsequent Michael addition of malonate **7** to acrolein afforded aldehyde **8** in 79% yield (cat. Cs_2CO_3, acrolein). It should be noted that the geometry of the 1,3-diene was completely retained throughout these reactions.[7] Addition of an alkenylaluminum reagent,[8] prepared from 1-hexyne and DIBAL, to aldehyde **8** afforded allylic alcohol **9**. Swern oxidation[9] of alcohol **9** furnished enone **10**, a requisite substrate for our planned intramolecular Diels-Alder reaction.

Upon treatment of **10** with $EtAlCl_2$ at 0 °C, the critical, intramolecular Diels-Alder reaction proceeded to give the desired bicyclic compound **11** as a single diastereomer along with an isomer of **10** with respect to the geometry of the olefin attached by the ethylthio group. Suppression of this undesired, proton-catalyzed isomerization of the enol sulfide was accomplished by addition of a small amount of pyridine, resulting in the increased yield of **11** (63%). The structure of the Diels-Alder product **11** was fully characterized spectroscopically[10] and by an X-ray crystal analysis as shown in Figure 1. The sulfide **11** was oxidized with mCPBA to afford a diastereomeric mixture of the sulfoxides, which was subjected to the Pummerer rearrangement[11] conditions without purification. Thus, treatment of the sulfoxides with TFAA and Et_3N in THF followed by aqueous workup successfully introduced the C-26 carbonyl group (CP-225,917 numbering), giving diketone **3**[12] in 67% yield based on sulfide **11**. It is worth noting that the Pummerer rearrangement occurred only at C-26 and none at the ethyl group. This selectivity is probably attributable to the stability of the transient sulfonium ylide in conjugation with the nearby bridgehead double bond. With these results in hand, total synthesis of CP-263,114 is currently under way in our laboratories.

Scheme 1

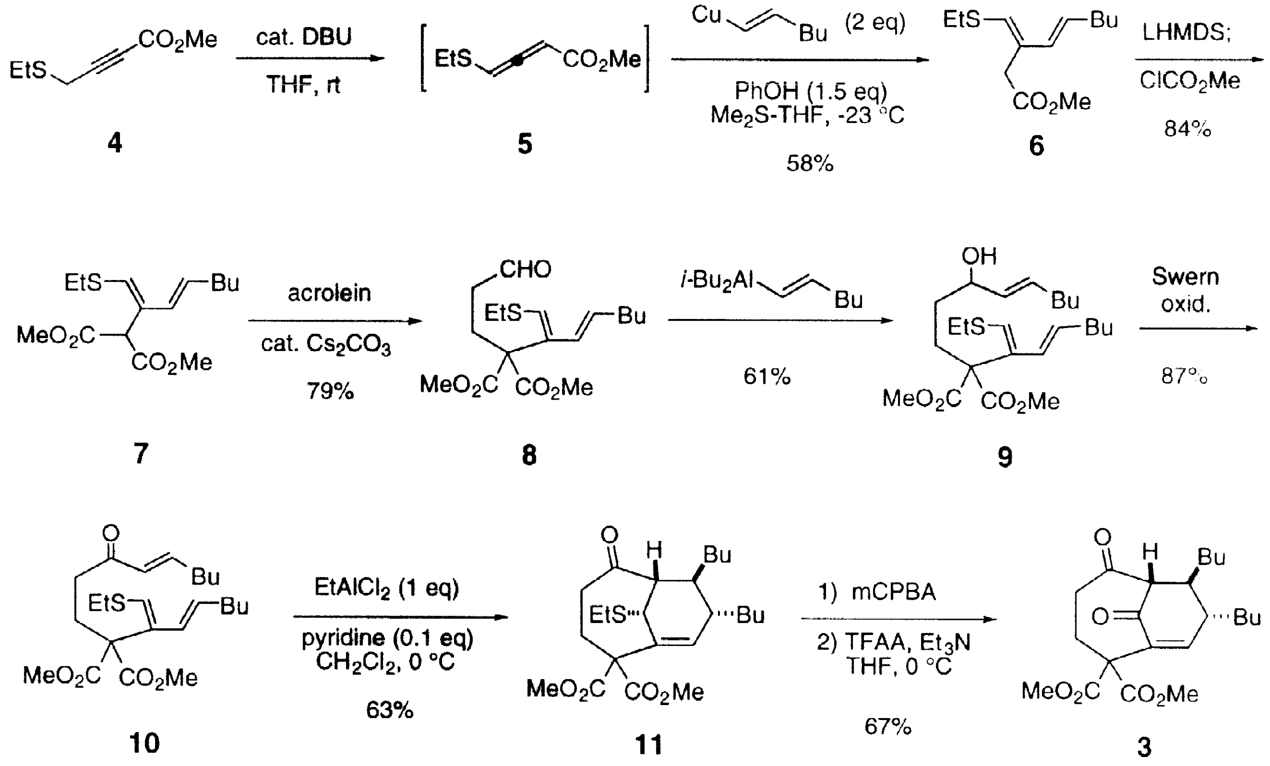
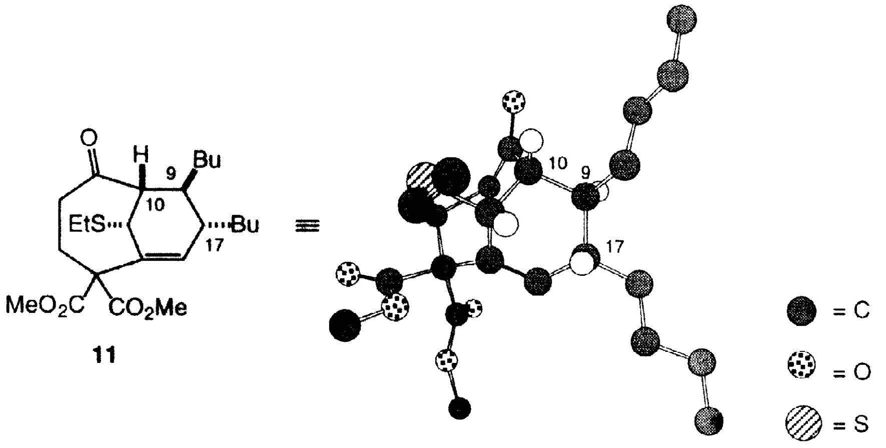


Figure 1: Structure of **11** deteremined by X-ray crystallography.



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References and Notes

1. (a) Dabrah, T. T.; Harwood, H. J.; Huang, L. H.; Jankovich, N. D.; Kaneko, T.; Li, J.-C.; Lindsey, S.; Moshier, P. M.; Subashi, T. A.; Therrien, M.; Watts, P. C. *J. Antibiot.*

1997, *50*, 1. (b) Dabrah, T. T.; Kaneko, T.; Massefski, W. Jr.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594.

2. For a review, see: Warner P. M. *Chem. Rev.* **1989**, *89*, 1067.
3. (a) Nicolaou, K. C.; Härter, M. W.; Boulton, L.; Jandeleit, B. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1194. (b) Sgarbi, P. W. M.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1997**, 2157. (c) Nicolaou, K. C.; Postema, M. H. D.; Miller, N. D.; Yang, G. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2821.
4. Gwaltney, S. L., II; Sakata, S. T.; Shea, K. J. *J. Org. Chem.* **1996**, *61*, 7438 and references cited therein.
5. Schuster, H. F.; Coppola, G. M. In *Allenes in Organic Synthesis*; John Wiley: New York, 1984; p. 179.
6. Kanda,Y.; Fukuyama T. *J. Am. Chem. Soc.*, **1993**, *115*, 8451.
7. Under more harsh conditions (cat. Triton B, DMSO, 80 °C), however, formation of the geometrical isomer at the ethylthio group was observed.
8. Bernady, K. F.; Floyd, M. B.; Poletto, J. F.; Weiss, M. *J. Org. Chem.*, **1979**, *44*, 1438.
9. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
10. Spectral data for **11**: FTIR (film, cm^{-1}) 2956, 2930, 1739, 1691, 1446, 1271, 1221, 1172, 1096; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.85-0.95 (m, 6H), 1.15-1.40 (m, 15H), 1.90 (m, 1H), 2.30-2.65 (m, 7H), 2.80 (brs, 1H), 3.34 (dd, J=3.4, 1.6 Hz, 1H), 3.78 (s, 3H), 3.82 (s, 3H), 5.55 (dd, J=4.0, 1.6 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 13.96, 14.01, 14.19, 22.77, 22.82, 28.72, 29.09, 29.16, 29.85, 32.23, 33.47, 39.82, 40.69, 44.54, 46.49, 52.85, 53.05, 64.13, 135.00, 137.68, 170.60, 170.90, 212.48.
11. Lucchi, O. D.; Miotti, U.; Modena, G. In *Organic Reactions*; Paquette, L. A.; Beak, P.; Overman, L. E.; Ciganek, E.; Reich, H. J.; Hanessian, S.; Sih, C.; Hegedus, L.; Smith, A. B., III; Kelly, R. C.; Uskokovic, M.; Ley, S. V., Eds.; John Wiley: New York, 1991; Vol. 40, p. 157.
12. Spectral data for **3**: FTIR (film, cm^{-1}) 2956, 2930, 2859, 1743, 1706, 1434, 1280, 1230, 1208, 1175; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.82–0.95 (m, 6H), 1.17–1.65 (m, 12H), 1.74–1.81 (m, 1H), 2.03 (ddd, J = 13.7, 12.5, 2.7 Hz, 1H), 2.25 (m, 1H), 2.48 (ddd, J = 13.3, 6.7, 2.8 Hz, 1H), 2.76 (ddd, J = 13.7, 6.6, 2.7 Hz, 1H), 2.88 (ddd, J = 13.3, 12.5, 2.7 Hz, 1H), 3.01 (s, 1H), 3.78 (s, 3H), 3.88 (s, 3H), 6.59 (d, 2.7 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 13.94, 13.96, 22.57, 22.68, 28.96, 29.46, 33.76, 34.38, 38.37, 39.15, 40.01, 40.60, 53.05, 53.20, 59.44, 67.90, 139.12, 139.51, 168.40, 168.79, 203.55, 206.96.