Total Synthesis of (−)-CP-263,114 (Phomoidride B)

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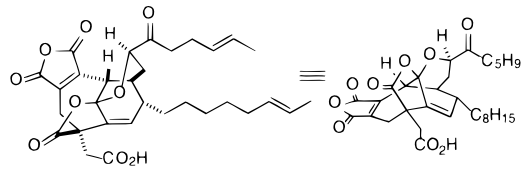
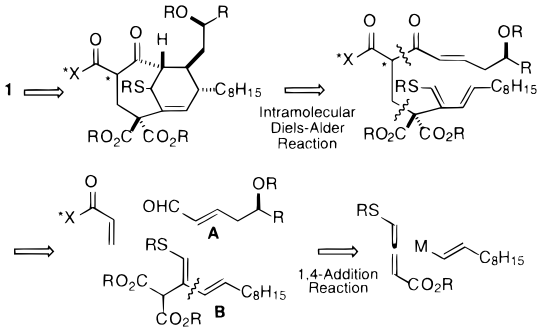
CP-263,114 (phomoidride B, **1**) was recently isolated from the culture broth of an unidentified fungus by a Pfizer group and shown to inhibit squalene synthase as well as Ras farnesyl transferase.[1] In addition to these interesting biological activities, CP-263,114 has a unique, densely functionalized polycyclic skeleton that consists of a bridgehead double bond, a γ-lactone-acetal, and a maleic anhydride moiety. These structural features and interesting bioactivities have attracted much interest from synthetic chemists. While a number of synthetic studies including ours[2] have been reported to date,[3] the only total synthesis of racemic **1** has recently been disclosed by Nicolaou.[4] However, the absolute configuration of **1** remains unknown.[5] Herein we report an enantioselective total synthesis of **1** and reveal its absolute configuration.



CP-263,114 (**1**)

Our retrosynthetic analysis of CP-263,114 features an intramolecular Diels−Alder reaction which is particularly well-suited for the preparation of strained bicyclic carbocycles (Scheme 1).[6] The precursor for the Diels−Alder reaction could be divided into three fragments **A**, **B**, and an acryloyl derivative. Fragment **A** would be derived from an appropriate chiral building block. To achieve a facile Diels−Alder reaction, a reliable procedure for stereoselective construction of an (*E*,*E*)-diene such as **B** must be established to secure the coplanarity of the diene. To this end, we opted to carry out a conjugate addition to a reactive allenic ester, in which nucleophilic attack is known to occur from the less hindered side.[7]

Scheme 1. Retrosynthetic Analysis



Conjugate addition of the alkenylcopper **4**[8] to the allenic ester **3**, prepared from **2**[8] by brief treatment with DBU, in the presence of TMSCl and HMPA[9] afforded the desired 1,3-diene **5** as the predominant product. After introduction of a second carbomethoxy group to **5**, Michael addition of the resultant malonate to *N*-acryloyl-(*S*)-4-benzyloxazolidinone[10] was performed to give **6** without appreciable isomerization of the double bonds. A boron-mediated diastereoselective aldol reaction[11] of **6** with aldehyde **7**,[8] which was prepared from (*S*)-epichlorohydrin,[12] yielded the adduct as a single diastereomer. The aldol product was then oxidized under Parikh−Doering conditions[13] to furnish enone **8**. Upon treatment with zinc chloride−ether complex in the presence of a small amount of pyridine,[14] **8** underwent a smooth intramolecular Diels−Alder reaction to give predominantly the desired bicyclic compound **9**. The relative configuration of **9** was determined by NOE studies.[15] This impressive stereoselectivity seems to be dictated by the stereochemistry at C-12 position. A similar type of diastereoselection has been reported in the literature.[16] However, this could be the first case where the adduct possesses a bridgehead olefin.

Construction of the maleic anhydride moiety on **9** presented formidable challenges. We could eventually solve the problem in the following manner. The Evans' chiral auxiliary was removed by lithium thiolate generated from allyl thioglycolate to give thiol ester **10**. Upon treatment with DBU, **10** underwent intramolecular aldol-type cyclization to provide **11** as a single diastereomer. After Pd-catalyzed deprotection of the allyl group, dehydration and concomitant decarboxylation were carried out by heating the resultant carboxylic acid in a mixture of acetic anhydride and pyridine at 100 °C to furnish directly the thiobutenolide **12**. This

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(2) Waizumi, N.; Itoh, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 6015.

(3) (a) Nicolaou, K. C.; Härter, M. W.; Boulton, L.; Jandeleit, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1194. (b) Nicolaou, K. C.; Postema, M. H. D.; Miller, N. D.; Yang, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2821. (c) Davies, H. M. L.; Calvo, R.; Ahmed, G. *Tetrahedron Lett.* **1997**, *38*, 1737. (d) Sgarbi, P. W. M.; Clive, D. L. J. *Chem. Commun.* **1997**, 2157. (e) Armstrong, A.; Critchley, T. J.; Mortlock, A. A. *Synlett* **1998**, 552. (f) Kwon, O.; Su, D.-S.; Meng, D.; Deng, W.; D'Amico, D. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.*. **1998**, *37*, 1877. (g) Kwon, O.; Su, D.-S.; Meng, D.; Deng, W.; D'Amico, D. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1880. (h) Chen, C.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **1998**, *120*, 10784. (i) Bio, M. M.; Leighton, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 890. (j) 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. (k) Clive, D. L. J.; Sun, S.; He, X.; Zhang, J.; Gagliardini, V. *Tetrahedron Lett.* **1999**, *40*, 4605. (l) Yoshimitsu, T.; Yanagiya, M.; Nagaoka, H. *Tetrahedron Lett.* **1999**, *40*, 5215. (m) Meng, D.; Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed*. **1999**, *38*, 3197. (n) Sulikowski, G. A.; Agnelli, F.; Corbett, R. M. *J. Org. Chem.* **2000**, *65*, 337. (o) For reviews: see ref 1c and Diederichsen, U. *Nachr. Chem. Technol. Lab.* **1999**, *47*, 1423; Starr, J. T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1415.

(4) (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Yoon, W. H.; He, Y.; Fong, K. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1669. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; He, Y.; Yoon, W. H.; Choi, H.-S. *Angew. Chem., Int. Ed.* **1999**, *38*, 1676.

(5) We have recently learned that Professor Nicolaou's group has determined the absolute configuration of **1** which is consistent with our own conclusion. Nicolaou, K. C.; Jung, J.-K.; Yoon, W. H.; He, Y.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1829.

(6) Gwaltney, S. L., II; Sakata, S. T.; Shea, K. J. *J. Org. Chem.* **1996**, *61*, 7438 and references therein.

(7) Bertrand, M.; Gil, G.; Viala, J. *Tetrahedron Lett.* **1977**, *18*, 1785.

(8) A detailed procedure for the preparation of this compound is described in Supporting Information.

(9) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029.

(10) Ho, G.-J.; Mathre, D. J.; *J. Org. Chem.* **1995**, *60*, 2271.

(11) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(12) In preliminary studies we found that the aldehyde **7b**, which was derived from L-malic acid (*S*-configuration), formed a matched pair with **6**.

(13) Parikh, J. R.; Döering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(14) In the absence of pyridine, an acid-catalyzed double bond isomerization occurred to give a small amount of the unreactive 1,3-diene isomer.

(15) NOEs between H-9 and H-12, H-12 and H-16, H-17 and H-26, respectively, were observed.

(16) Evans, D. A.; Ripin, D. H. B.; Johnson, J. S.; Shaughnessy, E. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2119 and references therein.

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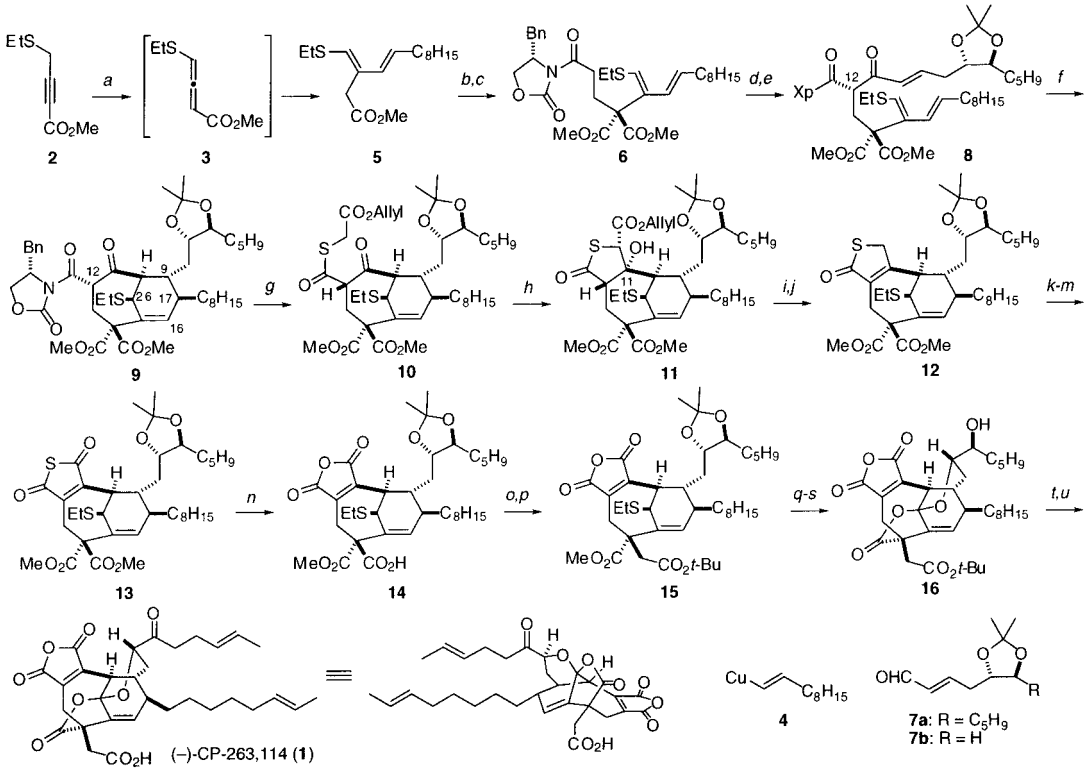
Scheme 2. Total Synthesis of (−)-CP-263,114[a]



[a] Reagents and yields: (a) cat. DBU, THF, 0 °C; then **4**, TMSCl, HMPA, Me_2S−THF, −78 °C to room temperature, 80%; (b) LHMDS, THF; $ClCO_2Me$, −78 °C, 84%; (c) *N*-acryloyl-(*S*)-4-benzyloxazolidinone, cat. Cs_2CO_3, CH_3CN, 50 °C, 82%; (d) Bu_2BOTf, Et_3N, CH_2Cl_2; **7a**, 0 °C, 1 h, 80%; (e) SO_3·Py, DMSO-*i*-Pr_2NEt, 1 h, 75%; (f) $ZnCl_2$·OEt_2, Py, CH_2Cl_2,1 h; (g) allyl thioglycolate, LHMDS, ether, 0 °C, 3 h, 53% (2 steps); (h) DBU, THF, rt, 1.5 h, 93%; (i) cat. $Pd(OAc)_2$, PPh_3, pyrrolidine, CH_3CN, rt, 15 min; (j) Py, Ac_2O, 100 °C, 1 h, 87% (2 steps); (k) TBSCl, DBU, CH_2Cl_2; (l) NIS, CH_2Cl_2, rt, 79% (2 steps); (m) $AgNO_3$, DMSO, 50 °C, 1 h, 74%; (n) LiOH·H_2O, MeOH, rt, 1 h; $Ba(OH)_2$·$8H_2O$, rt, 1 h; (o) $(COCl)_2$, CH_2Cl_2, rt; CH_2N_2, ether, −15 °C, 10 min; (p) $PhCO_2Ag$, *t*-BuOH, 50 °C, 1 h, 54% (3 steps); (q) mCPBA, CH_2Cl_2, −20 °C, 5 min; (r) TFAA, *i*-Pr_2NEt, toluene, 0 °C, 1 h; (s) 80% aq AcOH, 70 °C, 13 h, 51% (3 steps); (t) Jones oxidn, 0 °C, 20 min; (u) HCO_2H, rt, 1 h, 96% (2 steps).

process involves the formation of a somewhat unstable β-lactone intermediate. The thiobutenolide **12** thus formed was silylated to give 2-silyloxythiophene, which was subsequently oxidized with NIS to give 5-iodothiobutenolide. Upon heating with silver nitrate in DMSO, thiomaleic anhydride **13** was obtained in high yield. Successive treatment of **13** with lithium hydroxide and barium hydroxide in a one-pot process caused selective hydrolyses of the thiomaleic anhydride and the less hindered methyl ester, giving monocarboxylic acid **14** after acidic workup. The conventional Arndt−Eistert protocol was used to convert **14** into the homologated ester **15**. Careful oxidation of the sulfide in **15** with mCPBA followed by treatment with trifluoroacetic anhydride and *i*-Pr_2-NEt gave the desired ketone after aqueous workup. Hydrolysis of the acetonide with 80% aqueous acetic acid induced the concomitant cyclization to afford γ-lactone-acetal **16**. Finally, Jones oxidation of the secondary alcohol followed by deprotection of the *tert*-butyl ester with formic acid gave (−)-CP-263,114. The synthetic **1** was identical in all respects with natural CP-263,114 [^{1}H NMR, ^{13}C NMR and $[\alpha]^{27}_D$ −10° (c = 0.25, CH_2Cl_2) (lit. $[\alpha]_D$ −11° (c = 0.5, CH_2Cl_2))]. Since the specific rotation of the synthetic **1** is same as that of the natural **1**, we conclude that the absolute configuration of CP-263,114 is the one depicted in Scheme 2.

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Supporting Information Available: Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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