Synthesis of (+)-CP-263,114

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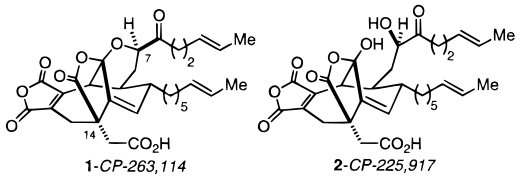
CP-263,114 (phomoidride B, **1**) and CP-225,917 (phomoidride A, **2**) are closely related fungal metabolites that were isolated as a consequence of their ability to inhibit squalene synthase and Ras farnesyltransferase (Scheme 1).[1] Both molecules present a dense array of diverse, highly oxygenated and sensitive functionality mounted upon an unusual bicyclo[4.3.1]deca-1(9)-ene ring system. These compounds have inspired many laboratories to develop approaches to the CP core ring system,[2] including studies by Danishefsky[3] and co-workers that raised the question of a possible new naturally occurring family member, and by Nicolaou[4] and co-workers that resulted in the first syntheses of (+)-**1** and (−)-**2**. We recently reported a fragment coupling/tandem cyclization reaction comprising a chelation-controlled alkylation, an anion accelerated oxy-Cope rearrangement, and a transannular cyclization that resulted in direct synthesis of the core structures of **1** and **2** from readily accessible starting materials.[5] This contribution describes a synthesis of (+)-**1** using a substantially more complex version of the same fragment coupling/tandem cyclization reaction.

Scheme 1



The synthesis commenced (Scheme 2) with Pd(0)-catalyzed cross-coupling between **3** and vinyl stannane **4**,[6] affording diene **5** in 80% yield. Compound **5** was converted to rac-**6** by a two-step procedure involving Cu(I)-mediated conjugate addition of a PMB-protected hydroxymethyl group followed by C-acylation of a subsequently generated lithium enolate using Mander's reagent ($NCCO_2Me$).[7] Exposure of rac-**6** to Corey's oxazaborolidine reduction catalyst[8] and catecholborane initiated an efficient kinetic resolution that directly generated (+)-**6** from rac-**6** in 90% ee and 31% yield (theoretical yield is 50%).[9]

The crucial fragment coupling/tandem cyclization was conducted by conversion of enantiomerically pure **7**[10] to Grignard reagent **8** followed by exposure to (+)-**6**. This stereospecific reaction directly afforded compound **9** in 53% yield. In a single transformation (Scheme 3), cyclopentanone (+)-**6** was alkylated with vinyl Grignard **8**, affording a bromomagnesium alkoxide that underwent anion-accelerated oxy-Cope rearrangement[11] followed by spontaneous transannular Dieckmann-like cyclization to deliver **9**. Compound **9** was transformed to β-ketoester **10** by deprotonation under thermodynamic control followed by C-acylation with $NCCO_2Me$.

To prepare for installation of the quaternary center at C_{14}, compound **10** was converted to enolcarbonate **11** by a five-step procedure that included removal of the PMB group, two-step oxidation to the carboxylic acid, protection of the acid as a MOM ester, and generation of the enol carbonate. Exposure of enol carbonate **11** to TMSOTf and $(MeO)_3CH$ initiated a multistep and multitask one-pot reaction that led directly to compound **14**. During this transformation, the quaternary center at C_{14} was installed, the pseudoester cage ring system was assembled, and a free acid at C_{14} was liberated for eventual homologation.

One plausible mechanism for the direct conversion of **11**→**14** is displayed in Scheme 4 and begins with TMSOTf-promoted ionization of the enol carbonate to liberate silylketene acetal **12** and a carbomethoxenium ion fragment. Recombination of **12** and the acyl cation at C_{14} affords intermediate **13**,[12] poised for TMSOTf-catalyzed ionization of the C_7 MOM group and cyclization to form the pseudoester cage ring system as shown. Following acyl-transfer and cyclization, TMSOTf catalyzes deprotection of the MOM ester at C_{14} to generate acid **14**.

One carbon homologation of the acid of **14** was greatly complicated by the surprising sensitivity of the γ-lactone functionality. A two-step sequence comprising diazoketone formation[4] and photolytic Wolff rearrangement accomplished the homologation in modest yield.[13] Following homologation, the β-ketoester was triflated using KN^iPr_2 and Tf_2O to afford **15** in 55% yield.

Attempts to carbonylate the enoltriflate of **15** using CO and catalysts derived from Pd complexed to phosphine ligands were unsuccessful due to the extreme steric hindrance surrounding the triflate. Following extensive experimentation, it was discovered

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(2) (a) Nicolaou, K. C.; Harter, M. W.; Boulton, L.; Jandeleit, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1194−1196. (b) Nicolaou, K. C.; Postema, M. H. D.; Miller, N. D.; Yang, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2821−2823. (c) Davies, H. M. L.; Calvo, R.; Ahmed, G. *Tetrahedron Lett.* **1997**, *38*, 1737−1740. (d) Sgarbi, P. W. M.; Clive, D. L. *Chem. Commun.* **1997**, 2158−2160. (e) Armstrong, A.; Critchley, T. J.; Mortlock, A. A. *Synlett* **1998**, 552−553. (f) Kwon, O.; Su, D.-S.; Meng, D.; Deng, W.; D'Amico, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1877−1880. (g) Kwon, O.; Su, D.-S.; Meng, D.; Deng, W.; D'Amico, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1880−1882. (h) Waizumi, N.; Itoh, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 6015−6018. (i) Bio, M. M.; Leighton, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 890−891. (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*, 549−552. (k) Clive, D. L. J.; Sun, S.; He, X.; Zhang, J.; Gagliardini, V. *Tetrahedron Lett.* **1999**, *40*, 4605−4609. (l) Yoshimitsu, T.; Yanagiya, M.; Nagaoka, H. *Tetrahedron Lett.* **1999**, *40*, 5215−5218. (m) Sulikowski, G. A.; Agnelli, F.; Corbett, M. A. *J. Org. Chem.* **2000**, *65*, 337−342. For recent reviews, see: (n) Hepworth, D. *Chem. Ind. (London)* **2000**, *2*, 59. (o) Starr, J. T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1415−1421.

(3) Meng, D.; Qiang, T.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3197−3201.

(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*, 1669−1675. (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*, 1676−1678. (c) Nicolaou, K. C.; Jung, J.-K.; Yoon, W. H.; He, Y.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1829−1832.

(5) Chen, C.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **1998**, *120*, 10784−10785.

(6) The synthesis of vinyl stannane **4** is described in the Supporting Information.

(7) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

(8) For a comprehensive review of the CBS catalyst, see: Corey, E. J. and Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.

(9) For examples of kinetic resolution using the oxazaborolidine-catalyzed reduction, see: (a) Kurosu, M.; Kishi, Y. *J. Org. Chem.* **1998**, *63*, 6100−6101. (b) Schmalz, H.; Jope, H. *Tetrahedron* **1998**, *54*, 3457−3464. (c) Bringmann, G.; Hinrichs, J.; Kraus, J.; Wuzik, A.; Schulz, T. *J. Org. Chem.* **2000**, *65*, 2517−2527.

(10) Compound **7** was synthesized in eight steps from *R*-glyceraldehyde acetonide. For details see the Supporting Information.

(11) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765−4766.

(12) $(MeO)_3CH$ is not required for this reaction, but it was discovered that the C_6 ketal resisted hydrolysis in the presence of $(MeO)_3CH$; most likely it is modulating the acidity of the reaction.

(13) The modest yield of the Arndt−Eistert homologation is more indicative of the extreme sensitivity of derivatives of **14** rather than the inefficiency of the reactions.

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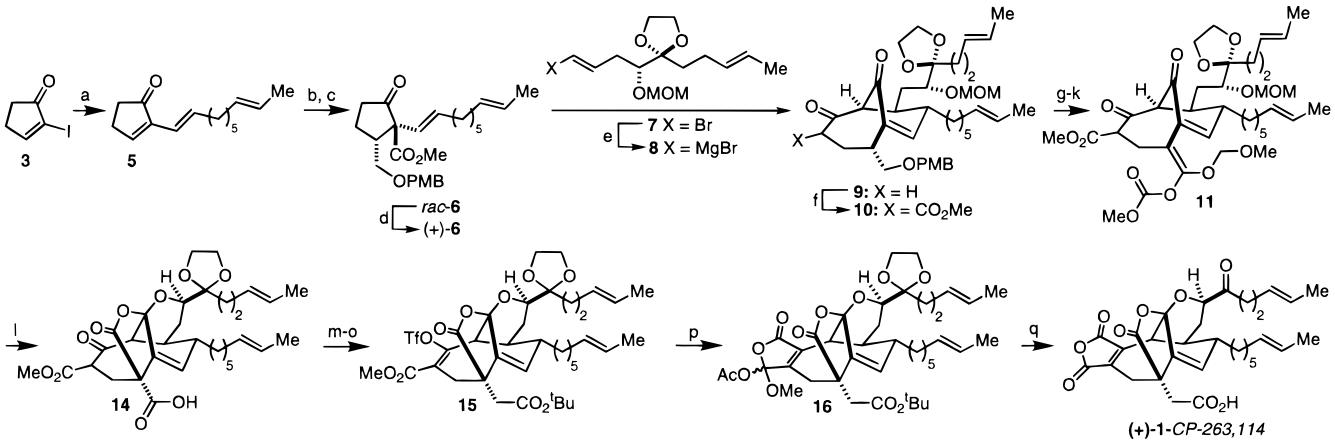
Scheme 2[a]

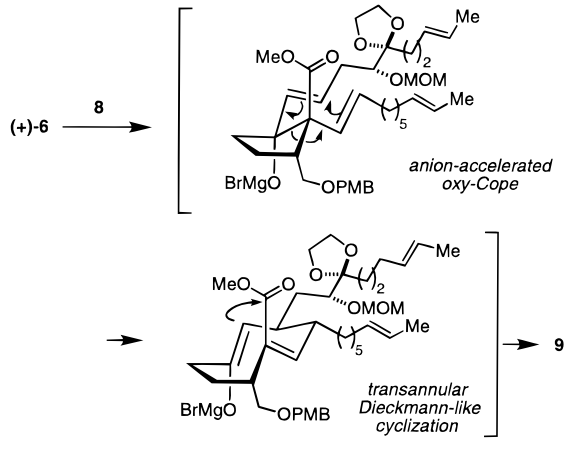


[a] Reagents: (a) (*E*,*E*)-$Me_3SnCH{=}CH(CH)Me$ (**4**), $Pd_2(dba)_3$, PPh_3, DMF, 65 °C, 80%. (b) $Li_2(PMBOCH_2)Cu$(thiophene)CN, TMSCl, THF, −78 °C. (c) ^{n}BuLi, Et_2O, −78 → 0 °C, $NCCO_2Me$, −78 → 0 °C, 62% over two steps. (d) (+)-Me−CBS, catecholborane, CH_2Cl_2, 23 °C, 90%, ee, 31%. (e) ^{t}BuLi, Et_2O, −78 °C, then $MgBr_2$ −78 → 23 °C, THF, then add (+)-**6** in toluene, −78 → 23 °C, dilute to 0.01 M, 53%. (f) KHMDS, THF, then $NCCO_2Me$, −78 → 0 °C, 51%. (g) BCl_3, −78 → −30 °C. (h) Dess−Martin periodinane, pyridine, $H_2O-CH_2Cl_2$, 23 °C. (i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, MeOH−H_2O, 23 °C. (j) MOMCl, Et_3N, CH_2Cl_2, 23 °C. (k) KHMDS, THF, then $NCCO_2Me$, −78 → 50 °C. (l) TMSOTf, $HC(OMe)_3$, CH_2Cl_2, −78 → 0 °C, 83−92% over six steps. (m) MsCl, Et_3N, THF, 0 °C, then CH_2N_2 −50 °C. (n) hν, ^{t}BuOH−Et_2O, 23 °C, 12% over two steps. (o) KN^iPr_2, Et_2O, then Tf_2O, −78 → 0 °C, 55%. (p) $Pd(OAc)_2$, $P(OMe)_3$, CO (500 psi), Et_3N, THF−MeCN, 23 °C, 70%. (q) HCO_2H, 23 °C, 79%.

that the crucial carbonylation could be accomplished by exposure of **15** to a catalyst derived from $Pd(OAc)_2$ and $P(OMe)_3$, affording anhydride ortho ester **16** in 70% yield.[14]

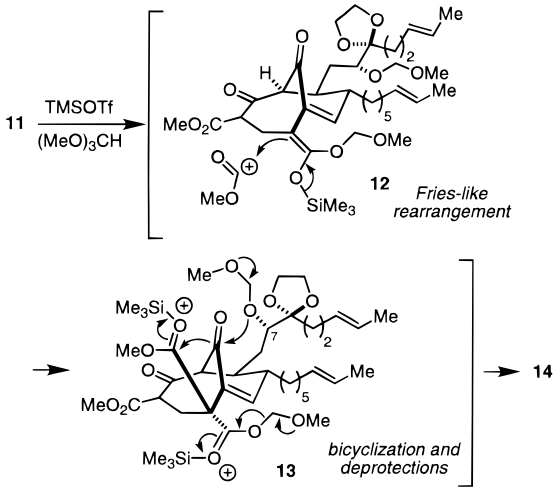
Global deprotection of **16** was accomplished upon treatment with neat HCO_2H to directly afford CP-263,114 (phomoidride B, **1**) in 79% yield. A synthetic sample of **1** was identical to authentic samples of the natural product as judged by ^{1}H NMR,[15] IR, HRMS, HPLC, and TLC analyses. The optical rotation measured for synthetic **1** was $[\alpha]_D$ +14° (c = 0.0033, CH_2Cl_2) while natural **1** is reported to have $[\alpha]_D$ −11° (c = 0.48, CH_2Cl_2).[1a] This assignment of the absolute configuration of **1** is in agreement with the recent assignment made by Nicolaou and coworkers.[4c]

Scheme 3



During the course of our synthesis of (+)-**1**, two new transformations were developed that may have applications beyond their use in this synthesis; a fragment coupling/tandem cyclization (**6** + **8** → **9**)[16] and a Lewis acid-catalyzed O → C acyl transfer reaction (**11** → **14**). In addition, the discovery of a Pd(0)−$P(OMe)_3$ complex that catalyzes the carbonylation of a highly hindered enol triflate where many other Pd catalysts fail may lead to future applications of Pd(0)−$P(OMe)_3$-catalyzed reactions involving hindered substrates.[17]

Scheme 4



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Supporting Information Available: Details of experimental procedures and analytical data are included (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA001958X

(14) For the use of $P(OMe)_3$ in a Pd-catalyzed carbonylation, see: Kayaki, Y.; Noguchi, Y.; Iwasa, S.; Ikariya, T.; Noyori, R. *Chem. Commun.* **1999**, 1235−1236.

(15) Although synthetic (+)-**1** was purified to a single HPLC peak and ^{1}H NMR analysis unequivocally proved its identitiy, it always contained a small amount of a proton-bearing compound unassociated with (+)-**1**.

(16) Sheehan, S. M.; Lalic, G.; Chen, J. Shair, M. D. *Angew. Chem., Int. Ed.* **2000**. In Press.

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