Stereospecific Synthesis of the CP-263,114 Core Structure

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CP-263,114 (**1**) is a fungal metabolite that was isolated[1,2] as part of a program to identify inhibitors of Ras farnesyltransferase[3] and squalene synthase[4] (Figure 1). It has been proposed that **1** is a member of the nonadride class of natural products; in particular, its structural similarity to glaucanic acid (**2**) was noted.[1b,5] Inspection of the two structures suggests that transannular bond formation between C_{10} and C_{26} to generate the core skeleton of **1** may be feasible from a nine-membered-ring intermediate. This paper details a new bicyclic ring-forming reaction involving a transannular cyclization that has resulted in a rapid, stereospecific synthesis of the CP-263,114 core structure.

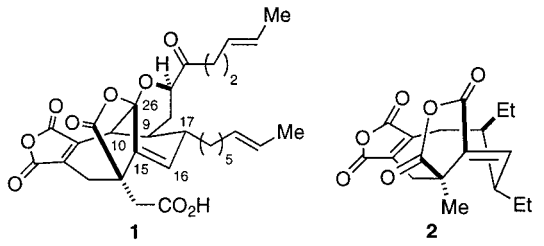
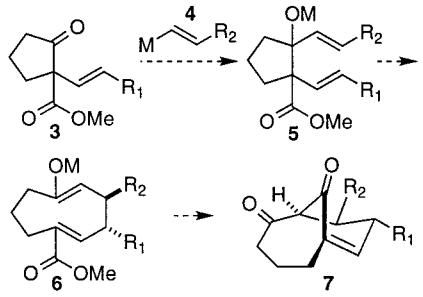


Figure 1.

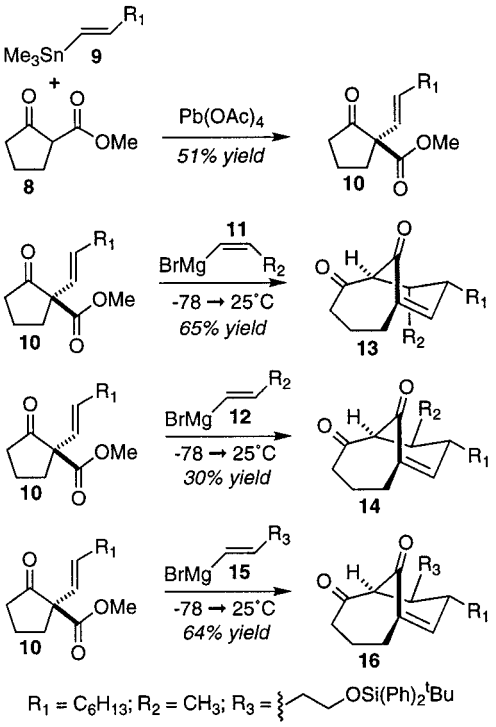
The synthetic plan for assembling the nine-membered-ring enolate and its transannular acylation is outlined in Scheme 1. It was envisaged that addition of a vinyl organometallic (**4**) to β-ketoester **3** would generate alkoxide **5** that, following an anion-accelerated oxy-Cope rearrangement, would lead to nine-membered-ring enolate **6**. Transannular enolate acylation of intermediate **6** to afford **7**, the core structure of **1**, would represent a reaction similar to the proposed $C_{10} \rightarrow C_{26}$ biosynthetic cyclization.[1b]

The synthesis was initiated (Scheme 2) by treatment of vinylstannane **9**[6] with $Pb(OAc)_4$ ($CHCl_3$, 25 °C) followed by exposure of the intermediate vinyllead reagent to β-ketoester **8**

Scheme 1



Scheme 2



($CHCl_3$, pyridine, 0−25 °C) to deliver ketone **10** in 51% yield as reported by Pinhey.[7] (*Z*)-1-Propenylmagnesium bromide (**11**) was added to ketone **10** at −78 °C (THF) and allowed to warm to room temperature. We were gratified to discover that compound **13**, the bicyclo[4.3.1]deca-1(9)-ene ring system of CP-263,114, could be isolated in 65% yield. Apparently the synthetic plan depicted in Scheme 1 had directly afforded the CP-263,114 core structure and only the cis (C_9-C_{17}) diastereomer was generated in this reaction.[8] Interestingly, only magnesium-based reagents result in the formation of the bicyclo[4.3.1]deca-1(9)-ene ring system. The analogous Li and Ce(III)-based nucleophiles afforded compounds containing a nine-membered ring;[9] however, products resulting from transannular acylation were not detected.

The stereospecificity of the bicyclization reaction was tested by exposure of ketone **10** to (*E*)-1-propenylmagnesium bromide

(1) (a) Dabrah, T. T.; Harwood, H. L.; 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. Antibiotics* **1997**, *50*, 1−7. (b) Dabrah, T. T.; Kaneko, T.; Massefski, W., Jr.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594−1598.

(2) Synthetic approaches to **1**: (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. Engl.* **1998**, *37*, 1877−1880. (g) Kwon, O.; Su, D.-S.; Meng, D.; Deng, W.; D'Amico, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1880−1882. (h) Waizumi, N.; Itoh, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 6015−6018.

(3) (a) Goldstein, J. L.; Brown, M. S. *Nature* **1990**, *343*, 425−430. (b) Buss, J. E.; Morsters, J. C. *Chem. Biol.* **1995**, *2*, 787−791.

(4) Watson, N. S.; Procopiou, P. A. *Prog. Med. Chem.* **1996**, *33*, 331−378.

(5) For seminal contributions describing the structure and biosynthesis of the nonadrides, especially glaucanic acid, see: (a) Barton, D. H. R.; Sutherland, J. K. *J. Chem. Soc.* **1965**, 1769−1771. (b) Barton, D. H. R.; Jackman, L. M.; Rodriguez-Hahn, L.; Sutherland, J. K. *J. Chem. Soc.* **1965**, 1772−1778. (c) Huff, R. K.; Moppett, C. E.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2584−2590.

(6) Vinylstannane **9** was constructed from 1-octyne employing a hydroalumination/stannylation protocol developed by Groh: Groh, B. L. *Tetrahedron Lett.* **1991**, *32*, 7647−7650.

(7) (a) Parkinson, C. J.; Pinhey, J. T.; Stoermer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1911−1915. (b) Moloney, M. G.; Pinhey, J. T.; Stoermer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2645−2655.

(8) The stereochemical assignments for **13**, **14**, and **16** were unambiguously determined by inspection of coupling constants and nOe experiments; see the Supporting Information for details.

(9) All compounds were fully characterized and their spectroscopic analysis is provided in the Supporting Information.

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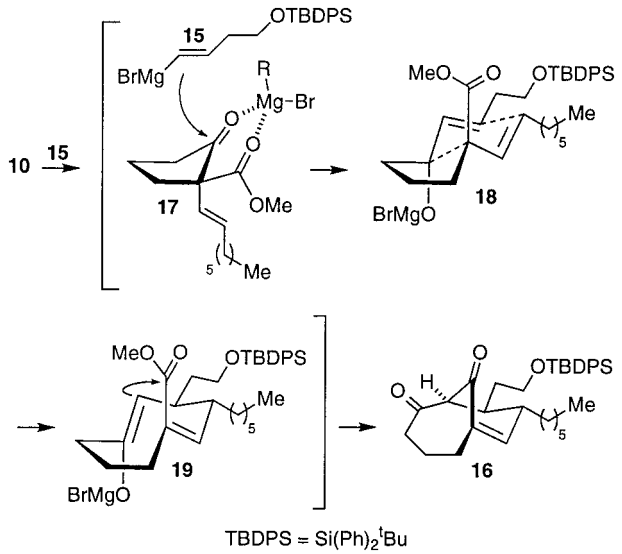
Scheme 3



(**12**) (THF−$PhCH_3$, −78 to 25 °C).[10] Again, the bicyclic core structure of **1** could be isolated. However, the major product (**14**) displayed a trans relationship between C_9 and C_{17}.[8] The relative stereochemistry of the C_9 and C_{17} substituents in **14** corresponds to the observed stereochemistry of the side chains of CP-263,114 (**1**). In addition to the major product (**14**) obtained with (*E*)-1-propenylmagnesium bromide (**12**), nine-membered-ring products were isolated.[9] To explore vinyl Grignard reagents which would deliver functionality suitable for construction of the fully elaborated C_9 side chain of **1**, cyclopentanone **10** was treated with (*E*)-vinyl Grignard **15**. The stereospecificity of the bicyclization reaction remained consistent as bicycle **16** was isolated in 64% yield displaying the natural stereochemistry at C_9 and C_{17}.

A mechanistic and stereochemical interpretation of this process is provided in Scheme 3. It has been demonstrated that 2-alkyl-β-ketoesters related to **10** undergo highly diastereoselective anti additions via chelated intermediates similar to **17**.[11] As a result, it is reasonable to assume anti addition of a vinyl Grignard reagent to **17** generating magnesium alkoxide **18**. An anion-accelerated oxy-Cope rearrangement of **18** through a chair transition state would afford the *trans,trans*-1,5-cyclononadiene intermediate **19** as a bromomagnesium enolate.[12,13] A chair transition state would explain the stereochemical outcome observed with (*Z*)-1-propenylmagnesium bromide (**11**), (*E*)-1-propenylmagnesium bromide (**12**), and (*E*)-vinyl Grignard **15** (Scheme 2). As portrayed in Scheme 3, addition of (*E*)-vinyl Grignard (**15**) to cyclopentanone **10** would place the silyloxyethyl group in a pseudoequatorial position throughout the sigmatropic rearrangement, resulting in direct formation of bicycle **16**. Addition of (*Z*)-1-propenylmagnesium bromide (**11**) to ketone **10** via a similar chelation-controlled anti addition would place the methyl group in a pseudoaxial position during the sigmatropic rearrangement, resulting in a cis relationship at C_9 and C_{17} (**10** → **13**).

Evans et al. have reported that anion-accelerated oxy-Cope rearrangements are further accelerated by appropriately positioned carbanion stabilizing groups that promote C−C bond ionization.[14] A similar effect, emanating from the methyl ester in **18**, may explain the facile rearrangement of **18** under conditions (0 °C, magnesium alkoxide)[15] that would not normally be expected to accelerate the [3,3]-sigmatropic rearrangement of a minimally strained ring system.[16,17] Following rearrangement, the nine-membered-ring bromomagnesium enolate **19** is well-positioned to undergo transannular acylation to provide **16**, the core structure of CP-263,114.[18] The chair (trans-hydrindane) transition state **18**, a critical feature in this process, provides control over four stereochemical issues during the reaction: (1) C_9 stereochemistry, (2) C_{17} stereochemistry, (3) C_{15}−C_{16} trisubstituted double bond stereochemistry, and (4) the (*Z*) enolate geometry of **19** that facilitates the transannular Dieckmann-related cyclization. Isolation of intermediates related to **18** and **19**[9] resulting from premature quenching of the reaction at −78 and 0 °C, respectively, supports the mechanism depicted in Scheme 3.[19]

In summary, a new bicyclic ring-forming process has been developed that results in direct construction of the CP-263,114 core system from readily available starting materials. In a single transformation, four stereochemical issues (C_9, C_{10}, C_{17}, and the C_{15}−C_{16} trisubstituted bridgehead double bond) have been addressed effectively while assembling the core system of **1**. The reaction described above also demonstrates the feasability of a C_{10}−C_{26} transannular cyclization that has been proposed for the biosynthesis of CP-263,114.[1b] Further utilization of this type of reaction in conjunction with mechanistic investigations will be conducted in efforts to synthesize CP-263,114 (**1**). This reaction is also being explored in the context of other bicyclic and polycyclic complex structures, beginning with readily available starting materials.

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Supporting Information Available: Details of experimental procedures and analytical data, including ^1H and ^{13}C NMR spectra (74 pages print/PDF). See any current masthead page for ordering information and Web access instructions.

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(10) (*E*)-1-Propenylmagnesium bromide (**12**) was synthesized in geometrically pure form from (*E*)-1-bromo-1-propene via lithium−halogen exchange (Seebach, D.; Neumann, H. *Tetrahedron Lett.* **1976**, *17*, 4839−4842) followed by exposure to freshly prepared $MgBr_2$.

(11) (a) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705−3716. (b) Eicher, T.; Servet, F.; Speicher, A. *Synthesis* **1996**, 863−870. (c) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 2944−2956.

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

(13) For a recent review detailing synthetic applications of anion accelerated oxy-Cope rearrangements, see: Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971−14020.

(14) Evans, D. A.; Baillargeon, D. J.; Nelson, J. V. *J. Am. Chem. Soc.* **1978**, *100*, 2242−2244.

(15) The conversion of **18** → **19** appears to take place at approximately 0 °C as observed by TLC and ^1H NMR.

(16) Attempts to induce anion-accelerated oxy-Cope rearrangements in acyclic systems bearing a carboalkoxy group adjacent to the alkoxide resulted in rapid retro-aldol dissociation: (a) Black, C. W.; Giroux, A.; Greidanus, G. *Tetrahedron Lett.* **1996**, *37*, 4471. (b) Schneider, C.; Rehfeuter, M. *Synlett* **1996**, 212−214. (c) Tomooka, K.; Nagasawa, A.; Wei, S.; Nakai, T. *Tetrahedron Lett.* **1996**, *37*, 8899−8900.

(17) Typical conditions required for anion-accelerated oxy-Cope rearrangements of unstrained systems involve a highly dissociated counterion (K, 18-Crown-6) and elevated temperatures (approximately 25−60 °C). See ref 13 for numerous examples.

(18) For examples of tandem anionic oxy-Cope rearrangements/transannular cyclizations, see: (a) Paquette, L. A.; Reagan, J.; Schreiber, S. L.; Teleha, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 2331−2332. (b) Reference 13.

(19) A cyclization resulting from an initial retro-aldol reaction followed by a 9-endo-trig conjugate addition (**18** → **19**) has not been disproven. Experiments to differentiate between this mechanism and the proposed sigmatropic rearrangement are currently underway.