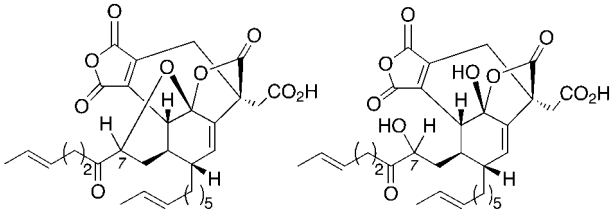
The Synthesis of CP-263,114 and CP-225,917: Striking Long-Range Stereocontrol in the Fashioning of C7**

Qiang Tan and Samuel J. Danishefsky*

During a screening exercise which was designed to target inhibitors of Ras farnesyl transferase and squalene synthase, Pfizer scientists reported the isolation of two natural products CP-263,114 (**1**) and CP-225,917 (**2**) as fungal metabolites extracted from juniper twigs in Texas.[1] These compounds have fostered a great deal of creative research from synthetic organic chemists. The interest accrues from the novel and challenging structures of the CP metabolites rather than from compelling biological imperatives. Three total syntheses of **1** and **2** have been described.[2] The first of these was reported by Nicolaou and co-workers.[2a–c] When appropriately modified, their synthesis revealed the configuration of **1** and **2**. These compounds are now known to correspond to the absolute stereostructures shown. This finding was independently confirmed by the groups of Shair[2d] and Fukuyama.[2e]



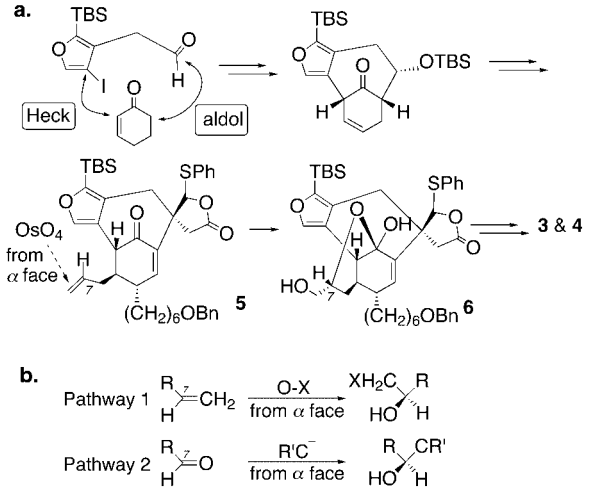
1: 7-H= α (CP-263,114)
3: 7-H= β (7-*epi*-CP-263,114)

2: 7-H= α (CP-225, 917)
4: 7-H= β (7-*epi*-CP-225, 917)

In our earlier report[3] we disclosed the total synthesis of the 7-*epi* series of the CP compounds (**3** and **4**). We are now confident that these 7-*epi* compounds are themselves less abundant natural products, found in the fermentation broth.[4] Nonetheless, since the goal structures of our synthetic venture were compounds **1** and **2**, we undertook the challenge of reaching these natural products. In the course of this study, we encountered some remarkable instances of stereochemical guidance by remote functional groups arising from the novel architectures of the pre-CP intermediates. These findings, as well as the attainment of our synthesis goals in reaching **1** and **2**, are described herein.

On casual inspection it would appear that the synthetic problem could readily be solved by equilibration of **3** or **4**, or their precursors, at C7. However, as was detailed in our total synthesis report,[3d] epimerization at C7 under apparent thermodynamic control only proceeds in the direction of the 7-*epi* diastereomer. Hoped for solutions based on kinetic quenching of enolates derived from deprotonation at C7 under irreversible conditions were unsuccessful. Complicating both of these strategies for inverting the C7 configuration was the general instability of the CP systems to several intended deprotonation protocols. Hence it was necessary to retreat to earlier stages of the synthesis to accomplish our objective of reaching **1** and **2** through our total synthesis.

The reaction that established the eventual 7-*epi* stereochemistry arose from the action of osmium tetroxide on the side-chain allyl group of compound **5** (Scheme 1a). This oxidation resulted in a hemiacetal bearing a hydroxymethyl



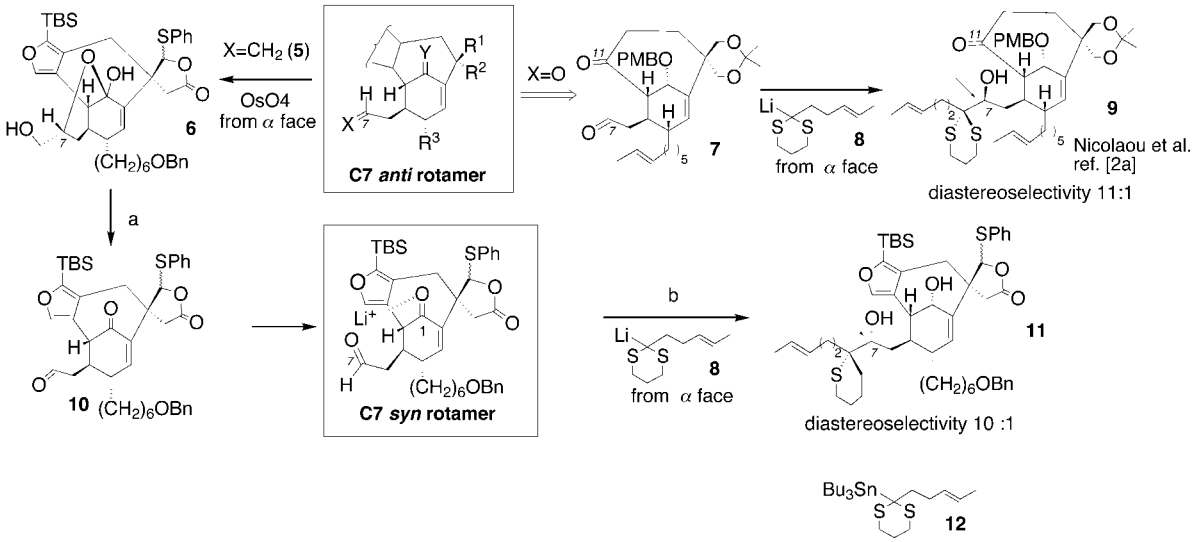
Scheme 1. TBS = *tert*-butyldimethylsilyl, Bn = benzyl.

group at C7. The dihydroxylation was essentially stereospecific. The hemiacetal was shown to have the stereochemistry of **6** by its eventual conversion into **3** and **4**. In retrospect this result can be explained by α-face attack of the oxidant upon an "extended *anti*" conformation as proposed for **5** (Scheme 1a). While this was a disappointing result at the time, a seemingly workable solution virtually suggested itself. The thought was to gain access to the required C7 side-chain stereochemistry by inverting the order of element linkage to the achiral C7 sp^2 precursor (Scheme 1b). Thus, in the dihydroxylation reaction (Pathway 1) an oxygen atom had been added to the C7 methane carbon of a terminal methylene group. Now we hoped to reverse the stereochemical outcome by adding a carbanion equivalent to a C=O linkage (Pathway 2).

Specifically we sought to add lithio dithiane **8** to aldehyde **10**. Of course the successful realization of the scheme

[*] Prof. S. J. Danishefsky, Q. Tan
Laboratory for Bioorganic Chemistry
Sloan–Kettering Institute for Cancer Research
1275 York Avenue, New York, NY 10021 (USA)
Fax: (+1) 212-772-8691
E-mail: s-danishefsky@ski.mskcc.org
Prof. S. J. Danishefsky
Department of Chemistry
Columbia University
Havemeyer Hall, 3000 Broadway, New York, NY 10027 (USA)

[**] Financial support was provided by the National Institutes of Health (Grant nos. CA-28824 and HL-25848 for S.J.D., CA-08748 for the Sloan–Kettering Institute Core Facility). Q.T. gratefully acknowledges the US Department of Defense for a postdoctoral fellowship (U.S. Army grant no. DAMD-17-99-1-9373). We thank the Pfizer Corporation, particularly Dr. T. Kaneko and Dr. T. T. Dabrah for discussions and for providing valuable CP samples from fermentation broth. We are grateful to Dr. Dongfang Meng for his major contributions to this work. We also thank George Sukenick of the Sloan–Kettering Institute Core Facility for mass spectral analyses and assistance in NMR spectroscopic and HPLC analyses, and Sylvi Rusli for mass spectral analyses.

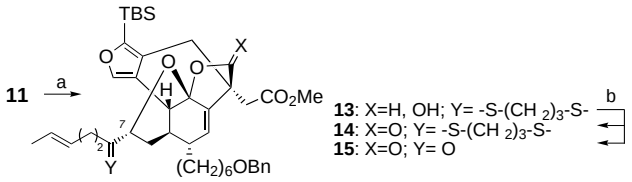


Scheme 2. a) $Pb(OAc)_4$, PhMe, 0 °C, 20–45 min, 90 %; b) **12**, MeLi/LiBr, THF, −78 °C, then add aldehyde at −200 °C, warm to −78 °C, 15 min, 70 % total. PMB = *para*-methoxybenzyl.

presumed that the conformation of the reacting formyl group of **10** would also be "extended *anti*" and that the nucleophile would again (as with the osmium tetroxide reaction) attack from the α-face. Indeed as we were preparing for this very experiment, Nicolaou and co-workers reported that the addition of lithio dithiane **8** to aldehyde **7** produced **9** in an approximately 11:1 ratio relative to the C7 epimer (Scheme 2).[2a] The result from the Nicolaou group was consistent with our dihydroxylation result in that opposite diastereomers had been produced at C7 following the opposite linkage orders.

Notwithstanding its dominantly hemiacetal character, **6** reacted with lead tetraacetate to afford **10** (Scheme 2). The latter reacted smoothly with **8** (generated in situ from its *n*-butylstannyl derivative **12**) to afford substantially a single carbinol in a 10:1 ratio with the C7 diastereomer. Our satisfaction with the result was short-lived when it was learned that the carbinol was **11**. This realization followed a two step conversion of **11** into **13** followed by oxidation of the γ-lactol and the deprotection of the dithioketal (Scheme 3). The resultant **15** had been previously encountered in our synthesis of the 7-*epi* systems **3** and **4**.

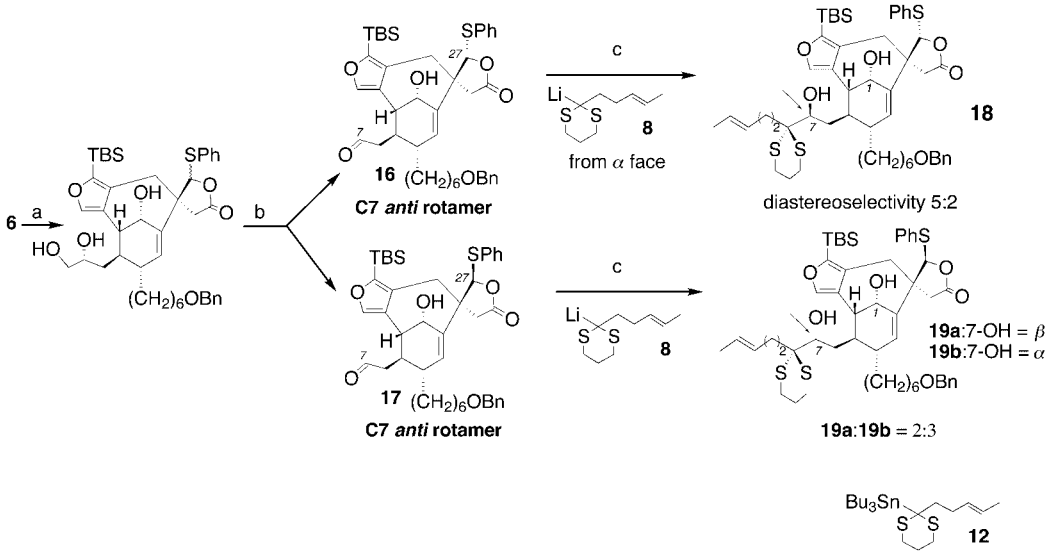
It seemed that a factor to explain the massive difference (11:1 versus 1:10) between our case and that of Nicolaou and co-workers was the absence or existence of the C1 ketone. Perhaps the presence of this ketone in our substrate **10** occasioned a shift in either



Scheme 3. a) 1. LiOH, THF, 36 h; 2. CH_2N_2, 60 %; b) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 75 %, **14**:**15** = 1:1.

the nature of the reactive aldehyde rotamer or the sense of attack on the corresponding rotamer. For instance, formation of a local "lithio channel", by the C1 ketone and the C7 aldehyde, would favor an otherwise unfavorable *syn*-like rotamer as shown in Scheme 2.

This argument was evaluated following conversion of **6** into **16** and **17** as shown in Scheme 4. While not productive with respect to our goal, these studies provided striking instances



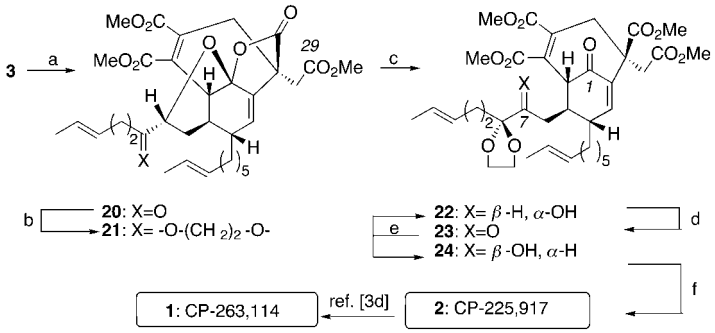
Scheme 4. a) $NaBH_4$, PhMe/*i*PrOH, 6.5 h, 70 %; b) $Pb(OAc)_4$, PhMe, 0 °C, 20–45 min, 90 %; c) **12**, MeLi/LiBr, THF, −78 °C, then add aldehyde at −200 °C, warm to −78 °C, 15 min, 70 % total.

  0044-8249/00/11224-4684 $ 17.50+.50/0

of long-range effects. Indeed, even the two C27 epimeric thiophenyl compounds reacted quite differently with **8**. In the case of **16**, the ratio of **18** and its C7 epimer was 5:2, whereas with **17**, the ratio of **19a**:**19b** was 2:3.[5]

Qualitatively at least, removal of the C1 ketone did markedly shift the sense of addition of anion **8** in the predicted sense. Failure to achieve the very high selectivity described by the Nicolaou and co-workers[2a] may be a consequence of the presence of the C11 ketone in their substrate **7**. This ketone could well provide additional guidance for α-face attack by the nucleophile on the rotamer shown.

While **18** and **19a** are potentially valuable precursors toward the CP systems **1** and **2**, a more rapid progress was registered. This involved the reduction of a C7 ketone to reach our goal (Scheme 5). Here too neighboring group influences



Scheme 5. a) $TMSCHN_2$, 15 min, >90%; b) $(TMSOCH_2)_2$, TMSOTf, CH_2Cl_2, 5 h, 90%;[6] c) 1. LiOH, THF/H_2O, 1.2 h; 2. $TMSCHN_2$, 0.5 h, 70% overall; d) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 4 h, 90%; e) $LiAlH(OtBu)_3$, toluene, $-10\,^{\circ}C$, 5 min, 70%, **22**:**24** = 1:1; f) 1. LiOH, THF–H_2O, 24 h; 2. TFA/CH_2Cl_2/H_2O (54/4/1), 30 min, 70% overall.

are pivotal. The sequence started with the interesting reaction of trimethylsilyldiazomethane with **3** to afford **20** and thence **21**. The latter reacted with lithium hydroxide and then trimethylsilyldiazomethane to give **22**, which following oxidation yielded **23**. Treatment of this compound with lithium tri(*tert*-butoxide) hydride provided **22** and **24**. We note again[3d] that, in the case of **21**, a "cascade"[2b] driven by carboxylate participation can not be invoked, since the lactone saponification occurs with the C29 methylester intact.

It is also likely that the regiospecific reduction of the C7 ketone relative to that at C1 is orchestrated by the proximal dioxolane protecting group. For instance, the corresponding ketodithiane analogue undergoes more rapid reduction at the C1 ketone relative to that at C7. The reduction of **23** as shown affords **24** as well as the separable and recyclable **22**. The four methyl esters are cleaved through long-term treatment of **24** with lithium hydroxide and reconstruction of the system was accomplished through the action of TFA (see structure **2**). The conversion of **2** into **1** has been reported.[3d]

The contrathermodynamic conversion of the **3**, **4** minor series of metabolites into the more prevalent **1**, **2** family has been accomplished, which thus completes our file on all the known components of the fermentation mixture. Clearly the densely funtionalized architectures of these four compounds and their synthetic precursors give rise to quite striking intramolecular signaling which invites further experimentation and elucidation.

Received: August 22, 2000 [Z15679]

[1] a) T. T. Dabrah, T. Kaneko, W. Massefski, Jr., E. B. Whipple, *J. Am. Chem. Soc.* **1997**, *119*, 1594; b) T. T. Dabrah, H. J. Harwood, Jr., L. H. Huang, N. D. Jankovich, T. Kaneko, J.-C. Li, S. Lindsey, P. M. Moshier, T. A. Subashi, M. Therrien, P. C. Watts, *J. Antibiot.* **1997**, *50*, 1.

[2] For total syntheses, see: a) K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, H.-S. Choi, W. H. Yoon, Y. He, K. C. Fong, *Angew. Chem.* **1999**, *111*, 1774; *Angew. Chem. Int. Ed.* **1999**, *38*, 1669; b) K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, K. C. Fong, Y. He, W. H. Yoon, H.-S. Choi, *Angew. Chem.* **1999**, *111*, 1781; *Angew. Chem. Int. Ed.* **1999**, *38*, 1676; c) K. C. Nicolaou, J. K. Jung, W. H. Yoon, Y. He, Y.-L. Zhong, P. S. Baran, *Angew. Chem.* **2000**, *112*, 1899; *Angew. Chem. Int. Ed.* **2000**, *39*, 1829; d) C. Chen, M. E. Layton, S. M. Sheehan, M. D. Shair, *J. Am. Chem. Soc.* **2000**, *122*, 7424; e) N. Waizumi, T. Itoh, T. Fukuyama, *J. Am. Chem. Soc.* **2000**, *122*, 7825. For synthetic approaches, see: f) K. C. Nicolaou, M. W. Harter, L. Boulton, B. Jandeleit, *Angew. Chem.* **1997**, *109*, 1243; *Angew. Chem. Int. Ed.* **1997**, *36*, 1194; g) K. C. Nicolaou, M. H. D. Postema, N. D. Miller, G. Yang, *Angew. Chem.* **1997**, *109*, 2922; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2821; h) H. M. L. Davies, R. Calvo, G. Ahmed, *Tetrahedron Lett.* **1997**, *38*, 1737; i) P. W. M. Sgarbi, D. L. J. Clive, *Chem. Commun.* **1997**, 2157; j) A. Armstrong, T. J. Critchley, A. A. Mortlook, *Synlett* **1998**, 552; k) N. I. Waizumi, T. Ito, T. Fukuyama, *Tetrahedron Lett.* **1998**, *39*, 6015; l) C. Chen, M. E. Layton, M. D. Shair, *J. Am. Chem. Soc.* **1998**, *120*, 10784; m) M. M. Bio, J. L. Leighton, *J. Am. Chem. Soc.* **1999**, *121*, 890; n) K. C. Nicolaou, P. S. Baran, R. Jautelat, Y. He, K. C. Fong, H.-S. Choi, W. H. Yoon, Y.-L. Zhong, *Angew. Chem.* **1999**, *111*, 532; *Angew. Chem. Int. Ed.* **1999**, *38*, 549; o) T. Yoshimitsu, M. Yanagiya, H. Nagaoka, *Tetrahedron Lett.* **1999**, *40*, 5215; p) D. L. J. Clive, S. Y. Sun, X. He, J. Zhang, V. Gagliardini, *Tetrahedron Lett.* **1999**, *40*, 4605; q) G. A Sulikowski, F. Agnelli, R. M. Corbett, *J Org. Chem.* **2000**, *65*, 337; r) J. T. Starr, E. M. Carreira, *Angew. Chem.* **2000**, *112*, 1473; *Angew. Chem. Int. Ed.* **2000**, *39*, 1415.

[3] a) O. Kwon, D.-S. Su, D. Meng, W. Deng, D. D'Amico, S. J. Danishefsky, *Angew. Chem.* **1998**, *110*, 1978; *Angew. Chem. Int. Ed.* **1998**, *37*, 1877; b) O. Kwon, D.-S. Su, D. Meng, W. Deng, D. D'Amico, S. J. Danishefsky, *Angew. Chem.* **1998**, *37*, 1981; *Angew. Chem. Int. Ed.* **1998**, *37*, 1880; c) D. Meng, S. J. Danishefsky, *Angew. Chem.* **1999**, *111*, 1582; *Angew. Chem. Int. Ed.* **1999**, *38*, 1485; d) D. Meng, Q. Tan, S. J. Danishefsky, *Angew. Chem.* **1999**, *111*, 3393; *Angew. Chem. Int. Ed.* **1999**, *38*, 3197. Previously we had referred to the 7-*epi* compounds as 7*S* based on the particular antipod arbitrarily selected to describe the synthesis of the racemate. In fact, the structures we employed were antipodal to the natural series, which thus necessitated a reversal of the designation at C7.

[4] These compounds have now been identified directly in the fermentation mixture as will be described in detail.

[5] The ratios were determined by oxidizing the C1 alcohol of the dithiane adducts (PDC, PhMe, approximately 80%), and comparing the NMR spectra of the resultant ketones with those of **11**. PDC = pyridinium dichromate.

[6] T. Tsunoda, M. Suzuki, R. Noyori, *Tetrahedron Lett.* **1978**, *21*, 1357.