Total Synthesis and Proof of Stereochemistry of Natural and Unnatural Pinnaic Acids: A Remarkable Long-Range Stereochemical Effect in the Reduction of 17-Oxo Precursors of the Pinnaic Acids**

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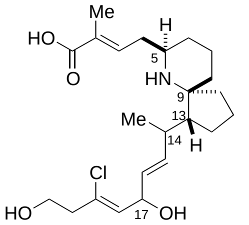
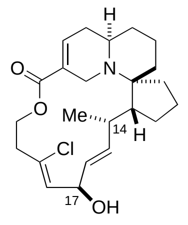
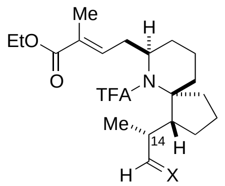
*This paper is dedicated to professor Uemura
for his discovery of many fascinating natural products*



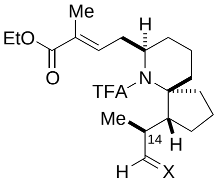
pinnaic acid
Proposed **1**: (14*R*, 17 (?))



halichlorine
2: (14*S*, 17*R*)



3: X = O
8: X = H, OH



4: X = O
12: X = H, OH

The extraordinary powers of spectroscopic methods and crystallography in elucidating structural, configurational, and conformational issues of small as well as larger (bio size) molecules are well appreciated by practicing chemists. It is rare that total synthesis contributes to the process of structural determination of natural products.[1]

The potentially important pinnaic acid (**1**), isolated in trace quantities from the Okinawan bivalve, *Pinna muricatta* appeared to be an exception.[2] The configuration at C14 of pinnaic acid was assigned to be *R* on grounds which were not rigorous.[2] Furthermore, the configuration at C17 was not assigned at all. We viewed the *R* designation of C14 in pinnaic acid with particular reservation. In the seemingly related halichlorine (**2**), isolated from the sponge *Halichondra okadain*, the configuration of this center was determined to be *S*,[3] which was corroborated by total synthesis.[4]

In the previous communication,[5] we charted a stereoselective route to aldehydes **3** and **4**, differing only in their configuration at C14. The thought was that a total synthesis from these intermediates would allow us to determine which C14 epimer would (following an appropriate outcome at C17) give rise to pinnaic acid. We were not confident that the configuration at C17 would be subject to stereocontrol. Furthermore, even if pinnaic acid were obtained from a particular C14 epimer, we would not necessarily be in a position to define its configuration at C17. It was only a combination of total synthesis and degradation that provided an unambiguous answer.

Herein we report: 1) the first total synthesis of pinnaic acid; 2) the rigorous deduction of the stereochemistry of natural pinnaic acid by a combination of total synthesis and chemical degradation; 3) the synthesis and rigorous assignments of the three C14, C17 stereocongeners of pinnaic acid by systematic permutation of the configurations at these carbons; and 4) the discovery of a remarkably stereospecific reduction at C17 en route to pinnaic acid and the dependency of this selectivity on the stereochemistry at C14.

As shown in Scheme 1, the opening step, that is, base-mediated reaction of aldehyde **3** with known phosphonate **5**,[6] turned out to be the most complicated element of the synthetic sequence.[7] The reaction did not go to completion, and separation of product **6** from starting material **3** was quite difficult. Instead, the mixture of **6** and **3** was carried forward. Remarkably, reduction of **6** with either (*R*)- or (*S*)-alpine hydride (lithium β-isopinocamphenyl-9-bora-bicyclo[3.3.1]-nonyl hydride)[8] gave a large excess of **7**. Compound **7** was obtained in approximately 30% yield (over two steps), after separation from **8** (the reduction product of **3**; ca. 50% recovery). Deprotection of the silyl group from **7** gave rise to **9**. Concurrent cleavage of the trifluoroacetyl and ethyl ester functions produced a compound whose high field NMR spectrum was quite similar to that reported by Uemura and co-workers.[2] The difficulty arose in that there was no sample of pinnaic acid available for a direct comparison of the synthetic and natural products.

We could not be sure if even the high field NMR spectra would distinguish stereocongeners that only differed at C17 (or C14, see below). Fortunately, the reduction of **6** with sodium borohydride gave useful amounts of **10** (Scheme 2). We used **10** to provide access to another pinnaic acid, which differed from the compound derived from **7** only with respect to the configuration at C17. Compound **10** was desilylated and the trifluoroacetyl and ethyl ester protecting groups were removed (Scheme 2) to afford a pinnaic acid congener. The high field NMR spectrum of this compound differed in rather

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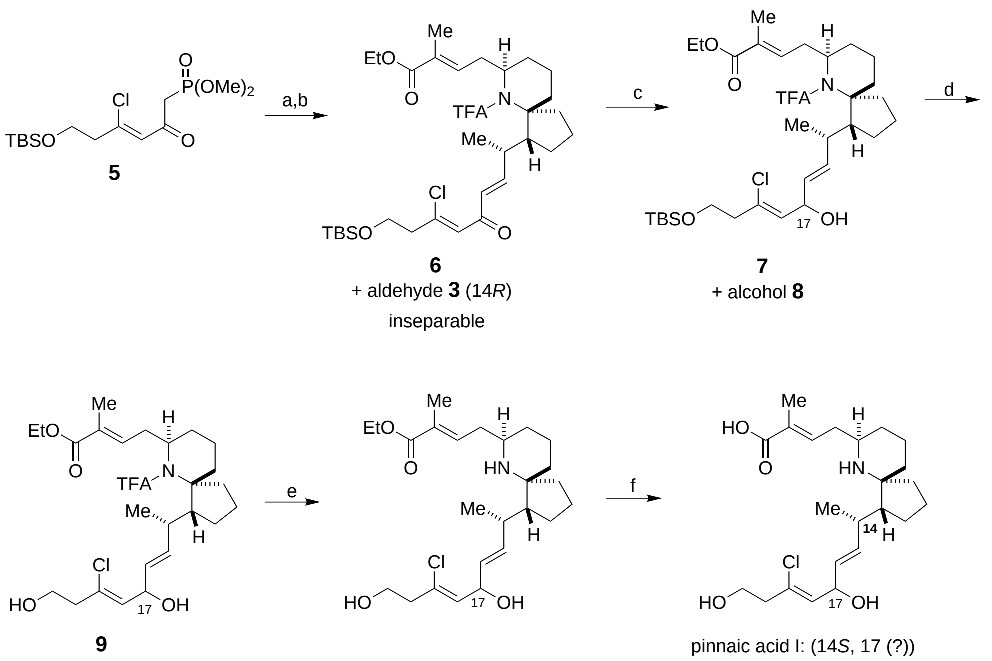
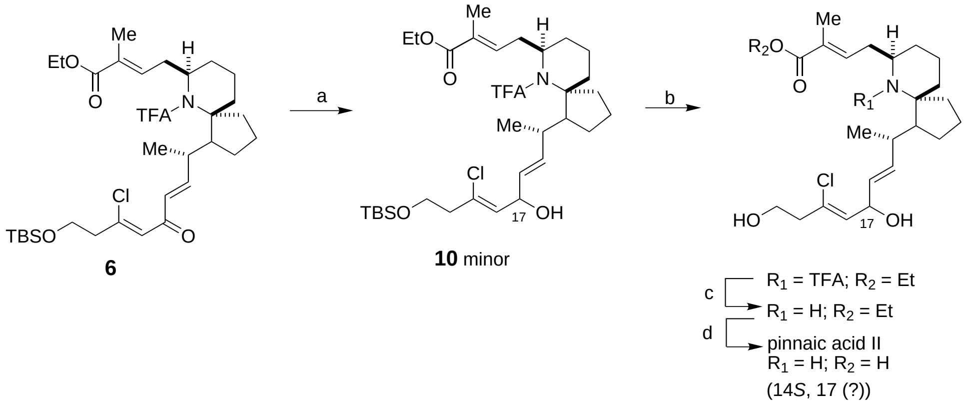
[**] This work was supported by the National Institutes of Health (Grant Numbers: CA28824). Postdoctoral Fellowship support is gratefully acknowledged by M.W.C. (U.S. Army BCRP, DAMD17-98-1-8154). We thank Dr. George Sukenick of the MSKCC NMR Core Facility for NMR and mass spectral analyses. We would like to thank professor Nakanishi for his supportive interest in the project.



Scheme 1. Reagents and Conditions: a) LiHMDS (1.1 equiv), THF, −78 °C, 0.5 h; b) **3**, THF/HMPA, −78 → 25 °C, 2 d; c) (*R*) or (*S*)-alpine hydride, 30 % over two steps; d) HF–pyridine, THF/pyridine, 0 °C, 1 h, 95 %; e) $NaBH_4$, EtOH, 25 °C, 18 h, 93 %; f) LiOH, THF/MeOH/H_2O, 4 h, 40 °C, 90 %. HMDS = 1,1,1,3,3,3-hexamethyldisilazane; HMPA = hexamethylphosphoramide; TFA = trifluoroacetic acid.



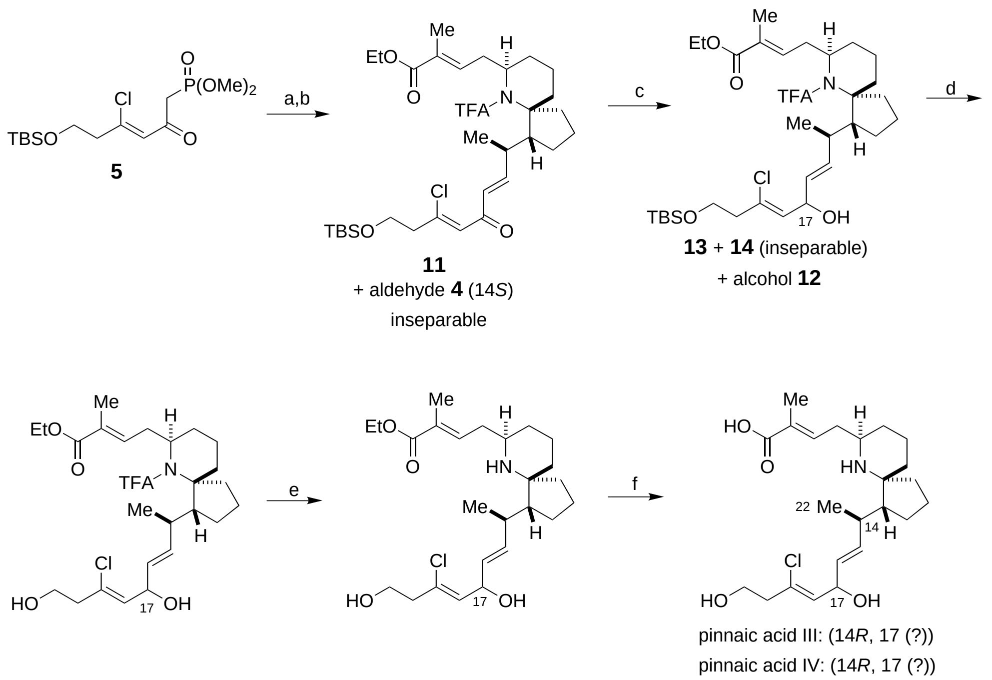
Scheme 2. Reagents and Conditions: a) $NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH, 25 °C, 0.5 h, 23 % (**7** + **10**) over two steps; b) HF–pyridine, THF/pyridine, 0 °C, 1 h, 71 %; c) $NaBH_4$, EtOH, 25 °C, 18 h, 90 %; d) LiOH, THF/MeOH/H_2O, 4 h, 40 °C, 97 %.

clear ways from the spectrum of natural pinnaic acid.[9] We refer to the final acid derived from **7** as pinnaic acid I and that from the less abundant **10** as pinnaic acid II; the former appeared more likely to be the natural structure.

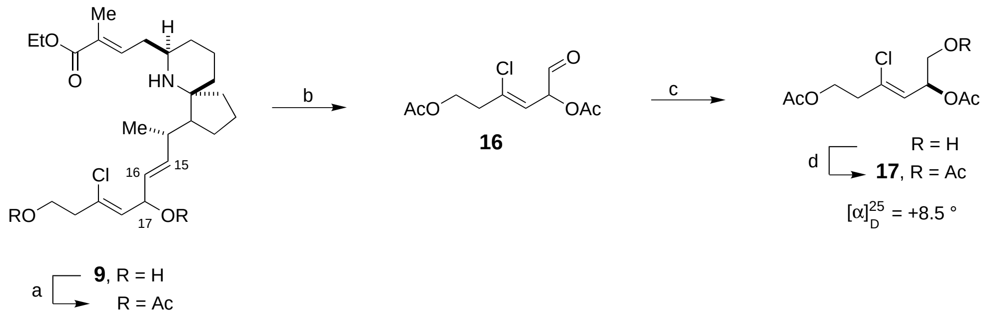
To use the spectra of the pinnaic acid I synthesized from aldehyde **3** as a basis for structural deduction, it is critical that the NMR spectra of neutral pinnaic acid and its C14 epimer be distinguishable, or else C14 of natural pinnaic acid could not be assigned the *S* configuration with any certainty. To this end, pinnaic acid-like congeners with established *R* configurations at C14 were prepared from aldehyde **4** (see below).[10]

Reaction of the lithium anion of **5** with **4** as above, gave rise to **11**, again mixed with unreacted **4** (Scheme 3).[7] Reduction of the mixture of unreacted **4** and **11** gave rise to a separable mixture of **13** and **14** (1.7:1) as well as alcohol **12**, the reduction product of **4**. These compounds were used individually to obtain pinnaic acids III and IV by methods comparable to those used in the synthesis of pinnaic acids I and II from their precursors, **7** and **10**, respectively. Once again, there were strong homologies in the high field NMR spectra of the end products, but there are clear differences in the readout of these compounds relative to pinnaic acids I and II.[11] At this point it was very clear that only in the case of pinnaic acid I, is there complete correspondence between the high field ^1H NMR spectrum of pure, synthetic product and that reported for the less than homogeneous natural acid.

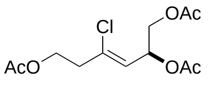
We had established that pinnaic acid I corresponds to the natural product, and that it has the *S* configuration at C14, since it had been derived from aldehyde **3**. We had not in fact determined rigorously the configuration at C17 of the synthetic material, and therefore of the natural product. Given the noncrystallinity of any of the intermediates, it was necessary for us to undertake an unusual course, that is, the degradation of our synthetic material. For this purpose, it would be necessary to manipulate the C15–C16 double bond in such a way that C17 remains intact in the degradation product. Diol **9** was exposed to acetic anhydride/pyridine in the presence of catalytic DMAP for two hours at room temperature. This treatment served to cap the hydroxy groups at C17 and C21. We hoped that ozonolysis of the C15=C16 bond would occur preferentially to a potentially competitive degradation at the C18=C19 bond containing the chlorine atom. Careful ozonolysis of the diacetate of **9** gave rise to the chloro aldehyde **16**. Reduction of the aldehyde and acetylation of the resultant alcohol produced **17** (Scheme 4). The two enantiomers, **17** and **18** had previously been synthesized by Uemura and coworkers.[3b, 12] It was clear that the degradation product derived from **9** is indeed **17**, which corresponds to the *R* configuration at C17 of pinnaic acid I. Thus the stereochemistry of pinnaic acids I and II (**19** and **20**, respectively) was fully assigned, and **19** corresponds to natural pinnaic acid.



Scheme 3. Reagents and Conditions: a) LiHMDS (1.1 equiv), THF, -78 °C, 0.5 h; b) **4**, THF/HMPA, $-78 \rightarrow 25$ °C, 2 d; c) (*R*)-or (*S*)-alpine hydride, 25% over two steps; d) HF–pyridine, THF/pyridine, 0 °C, 1 h, 99%, 3 steps; e) $NaBH_4$, EtOH, 25 °C, 18 h, 88%; f) LiOH, $THF/MeOH/H_2O$, 2.5 h, 40 °C, 91%.

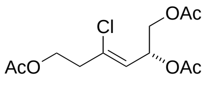


Scheme 4. Reagents and Conditions: a) Ac_2O, pyridine, cat. DMAP, 25 °C, 2 h, 80%; b) O_3, MeOH, -40 °C, then Me_2S; c) $NaBH_4$, $CeCl_3 \cdot H_2O$, MeOH; d) Ac_2O, NEt_3, 25 °C, 35% over three steps. DMAP = dimethylaminopyridine.



17

lit. [α]$_D^{25}$ = +7.3 °



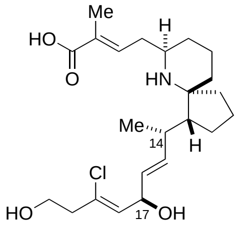
18

lit. [α]$_D^{25}$ = – 7.6 °

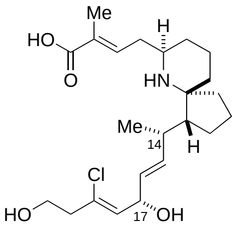
A similar degradation was conducted on pinnaic acid III (Scheme 5). After acetylation at C17, C21, and at the carboxy group, the resultant compound (presented as the mixed anhydride) underwent the procedure described above (cf. Scheme 4). Chiral-phase HPLC analysis showed that the degradation led once again to antipode **17**. Thus pinnaic acids III and IV correspond to **21** and **22**, respectively.

During this work, a remarkable case of long-range stereochemical transmission was discovered. Thus, the reduction of ketone **6** with large reducing agents (alpine boranes) is highly stereospecific towards the alcohol with the *R* configuration at C17. This stereospecificity is not dependent on the chirality of the two boranes. By contrast, the reduction of the C17 ketone moiety in **11** with the same boranes is not stereospecific and gave only a minor preference for **13**. It seems unlikely that the C14 substituent can influence the path of attack of the hydride donor.

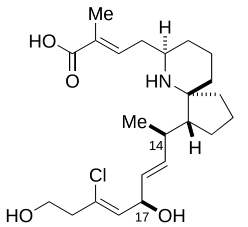
We propose that in the case of **6** there is a synergy between the directing influences of the methyl group at C14 and the total molecular environment of the spirocyclic ring system, which results in the control of the reactive conformation that brings with it a high selectivity in the sense of reduction. It seems likely that the configurations at C9 and C5 as well as the *E* C2–C3 side chain serve to dominate the presentation of the C1–C4 side chain. The nature of the C14–C19 side chain follows from the configurations at C13 and C14, and the *trans* double bonds at C15–C16 and C18–C19. An additional constraining factor could be the preference of the methyl group at C14 to be orthogonal to the plane of C15–C19 dienone linkage. This set of preferences coincides, in the case of **6**, with an *anti* relationship of the hydrogen atoms at C13 and C14. Such an *anti* preference of the corresponding hydrogens is

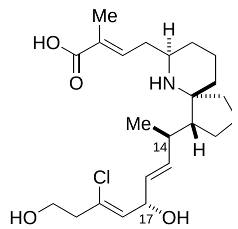


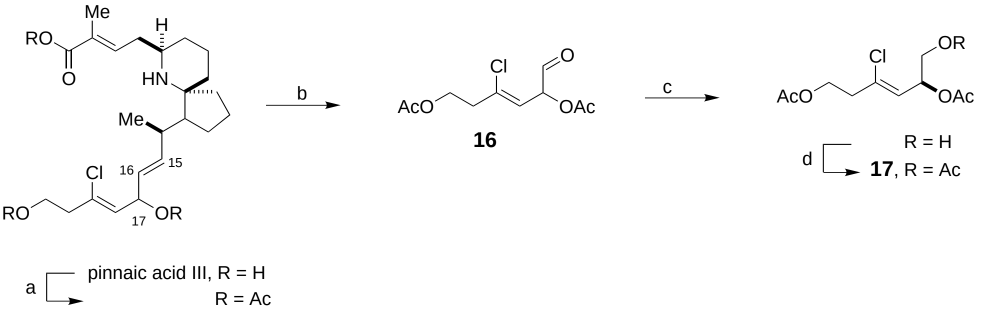
19: pinnaic acid I
(14*S*, 17*R*)



20: pinnaic acid II
(14*S*, 17*S*)







Scheme 5. Reagents and Conditions: a) Ac_2O, NEt_3, 25 °C, 2 h, 72 %; b) O_3, MeOH, −40 °C then Me_2S; c) $NaBH_4$, $CeCl_3 \cdot H_2O$, MeOH; d) Ac_2O, NEt_3, 25 °C, h, chiral-phase HPLC analysis.

seen in the one known X-ray crystal structure, currently available, of a *seco*-halichlorine.[4c] The synergy of these conformational preferences is suggested by the MM2 model depicted in Figure 1. In such a conformer, a strong preference for the delivery of the hydride from the pro-*R* face would be expected, and would lead to the observed product, pinnaic acid I (**19**).

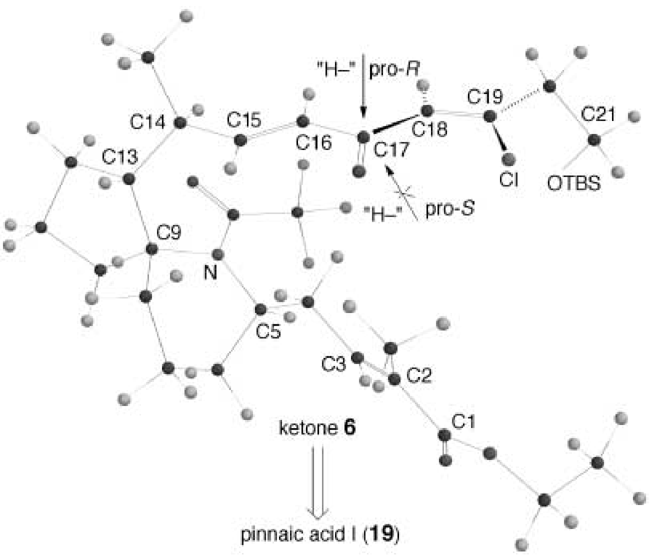


Figure 1. Calculated lowest energy conformer of ketone **6**. The calculations were performed with Macromodel V.6.5 (Monte Carlo simulation, MM2 force field).

By contrast, one (or more) of these preferences are not found in **11** (the C14 epimer of **6**). For instance, simple interchange of the methyl and H substituents at C14, leaving everything else intact, would create a potentially serious eclipsing interaction between the C14 methyl group and the C15–C16 double bond. Presumably, the point mutation at C14 in compound **11** brings with it a major conformational change in the C14–C19 moiety, in which the face preference for reduction of the C17 ketone is diminished. The concept that remote functional groups might profoundly influence a stereochemical outcome (such as face selectivity) by modulating the reacting (Curtin–Hammett[13]) conformer is a fascinating and little-probed aspect of stereochemical control.[14]

With the configurations of the pinnaic acids and halichlorine established by virtue of our synthesis program, we have a sound basis with which to evaluate their biological activity.[15]

Received: August 3, 2001 [Z17667]

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[1] The synthesis of himastatin is a recent example in which total synthesis was used to determine the stereochemical assignment of a natural product: T. M. Kamenecka, S. J. Danishefsky, *Angew. Chem.* **1998**, *110*, 3166; *Angew. Chem. Int. Ed.* **1998**, *37*, 2995.

[2] T. Chou, M. Kuramoto, Y. Otani, M. Shikano, K. Yazawa, D. Uemura, *Tetrahedron Lett.* **1996**, *37*, 3871.

[3] a) M. Kuramato, C. Tong, K. Yamada, T. Chiba, Y. Hayashi, D. Uemura, *Tetrahedron Lett.* **1996**, *37*, 3867; b) H. Arimoto, I. Hayakawa, M. Kuramoto, D. Uemura, *Tetrahedron Lett.* **1998**, *39*, 861.

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[6] S. P. Keen, S. M. Weinreb, *J. Org. Chem.* **1998**, *63*, 6739.

[7] Aldehyde **3** was recovered in good yield, even when excess reagent was used. It seems likely that the aldehyde function is co-opted during the reaction and recovered on workup. Several possible scenarios could be advanced to explain this phenomenon.

[8] a) S. Krishnamurthy, F. Vogel, H. C. Brown, *J. Org. Chem.* **1977**, *42*, 2534. For recent examples see: b) H.-C. Zhang, B. D. Harris, M. J. Costanzo, E. C. Lawson, C. A. Maryanoff, *J. Org. Chem.* **1998**, *63*, 7964; c) H.-C. Zhang, B. D. Harris, C. A. Maryanoff, B. E. Maryanoff, *Tetrahedron Lett.* **1996**, *37*, 7897; d) H.-C. Zhang, M. J. Costanzo, B. E. Maryanoff, *Tetrahedron Lett.* **1994**, *35*, 4891; e) G. L. Jeyaraj, W. R. Porter, *J. Heterocycl. Chem.* **1985**, *22*, 535.

[9] Inspection of the ^1H NMR spectra for pinnaic acid II and natural pinnaic acid revealed that the peaks in the ranges of 1.5–3.5 ppm (various azaspiro ring protons, as well as C20 and C21 side chain protons) and 5.6–5.8 ppm (C15, C16, and C18 vinyl protons) for pinnaic acid II display significantly different chemical shifts and couplings than the patterns displayed by natural pinnaic acid.

[10] We note that as a consequence of the *R* and *S* stereonomenclature systems, the priority rankings change at C14 in going from **3** and **4** to the various pinnaic acids.

[11] The C22 methyl ^1H NMR doublets in pinnaic acid III ($\delta = 1.13$, $J = 6.8$ Hz) and pinnaic IV ($\delta = 1.16$, $J = 6.8$ Hz) serve as diagnostic peaks and clearly show that neither pinnaic acid III nor pinnaic IV exist as natural pinnaic acid ($\delta = 1.08$, $J = 7.0$ Hz).

[12] We thank Professor Uemura for providing us with these compounds.

[13] a) F. A. Carey, R. J. Sunberg, *Advanced Organic Chemistry Part A: Structure and Mechanisms*, 3rd ed., Plenum, New York, **1990**, p. 215.

[14] For recent synthetic examples of remote stereochemical control from our group, see: a) D. Meng, S. J. Danishefsky, *Angew. Chem.* **1999**, *111*, 1582; *Angew. Chem. Int. Ed.* **1999**, *38*, 1485; b) D. Meng, Q. Tan, S. J. Danishefsky, *Angew Chem.* **1999**, *111*, 3393; *Angew Chem. Int. Ed.* **1999**, *38*, 3197; c) C. R. Harris, S. D. Kuduk, A. Balog, K. Savin, P. W. Glunz, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 7050.

[15] For a discussion of the biological background of these natural products and the proteins that they inhibit, see refs. [2–5], and references therein.