Concise Stereoselective Routes to Advanced Intermediates Related to Natural and Unnatural Pinnaic Acid**

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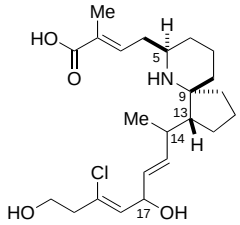
This paper is dedicated to Professor A. I. Meyers for his continuing accomplishments in organic chemistry.

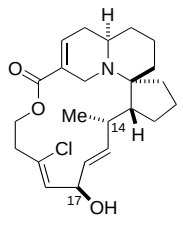
The phospholipase A_2 (PLA_2) family consists of lipolytic enzymes whose constituents catalyze the hydrolysis of intra- and extracellular membrane phospholipids.[1] Cytosolic 85-kDa phospholipase ($cPLA_2$)[2] is an important member of the PLA_2 family since it plays a significant role in the generation of free arachidonic acid from the *sn*-2 position of cellular phosholipids in most mammalian cells.[3] The released arachidonic acid can mediate the biosynthesis of eicosanoids, prostaglandins, leukotrienes, and thromboxanes.[4] These biological messengers govern critical phenomena such as cell proliferation and inflammatory responses. Accordingly, selective $cPLA_2$ inhibitors are promising targets for the development of novel anti-inflammatory drugs.

Two such agents were identified in 1996 when Uemura and co-workers isolated the structurally similar alkaloids pinnaic acid and halichlorine from the Okinawan bivalve *Pinna muricata* and the sponge *Halichondria okadai* Kadota, respectively.[5, 6] Both compounds mediate anti-inflammatory properties, albeit by different mechanisms. Thus, pinnaic acid inhibits $cPLA_2$ in vitro ($IC_{50} = 0.2$ mM) whereas halichlorine is a vascular cell-adhesion molecule-1 (VCAM-1) antagonist.[5, 6] Although pinnaic acid and halichlorine are reported to inhibit different target proteins, cursory inspection reveals that these alkaloids share a novel azaspiro core. Not surprisingly, these compounds have garnered much attention from the synthetic community.[7] Our group has recently reported the total synthesis of halichlorine[8] and suggested a conformational switch mediated by the macrolactone moiety to distinguish it from pinnaic acid.[9] To further our program, which seeks to gain access to natural product inspired non-steroidal privileged structures of potential interest with respect to inflammation, we embarked on the total synthesis of pinnaic acid (see **1**).



pinnaic acid

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

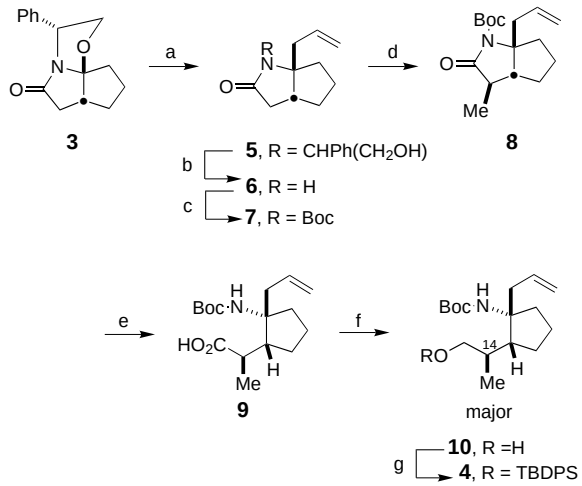


halichlorine

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

Uemura and co-workers had formulated the relative and absolute stereochemistry of halichlorine as shown in **2**.[6, 10] With only negligible quantities of pinnaic acid available through isolation, the relative stereochemistry at both C14 and C17 of this compound could not be assigned with complete confidence, even after extensive magnetic resonance experiments.[5] However, a preference for (14*R*)-**1** was expressed by Uemura and co-workers. The stereochemistry thus had to be verified by means of total synthesis.

Given the significant homology in the azaspiro core of halichlorine and pinnaic acid, it seemed at the outset that the hard-won lessons of the halichlorine campaign would simplify our objective.[8] In the end, although significant lessons were learned from the total synthesis of halichlorine, extensions to pinnaic acid were far from uneventful. Prior art demonstrated that the Meyers' lactam **3** could be readily converted into protected amino alcohol **4** (Scheme 1).[8, 11] The synthesis of



Scheme 1. Reagents and Conditions: a) $Me_3SiCH_2CH{=}CH_2$, $TiCl_4$, CH_2Cl_2, $-78 \rightarrow 25\,^{\circ}C$, 18 h, 98%; b) Na, EtOH, NH_3/THF, $-33\,^{\circ}C$, 1.0 h, 88%; c) Boc_2O, DMAP, THF, $25\,^{\circ}C$, 18 h, 93%; d) LiHMDS (1.1 equiv), hexanes/THF, $-78 \rightarrow -40\,^{\circ}C$, 1.5 h, then MeI (1.3 equiv), $-40\,^{\circ}C$, 1 h; e) LiOH, THF/H_2O, $25\,^{\circ}C$, 18 h; f) $ClCO_2Et$, NEt_3, THF, $-10\,^{\circ}C$, 1 h, then $NaBH_4$, MeOH, $0 \rightarrow 25\,^{\circ}C$, 1 h, 39% over three steps; g) TBDPSCl, NEt_3, DMAP (10 mol%), $0 \rightarrow 25\,^{\circ}C$, 96%. Boc = *tert*-butoxy carbonyl; DMAP = dimethylaminopyridine; HMDS = 1,1,1,3,3,3-hexamethyldisilazane; TBDPS = *tert*-butyldiphenylsilyl.

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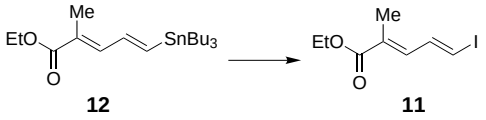
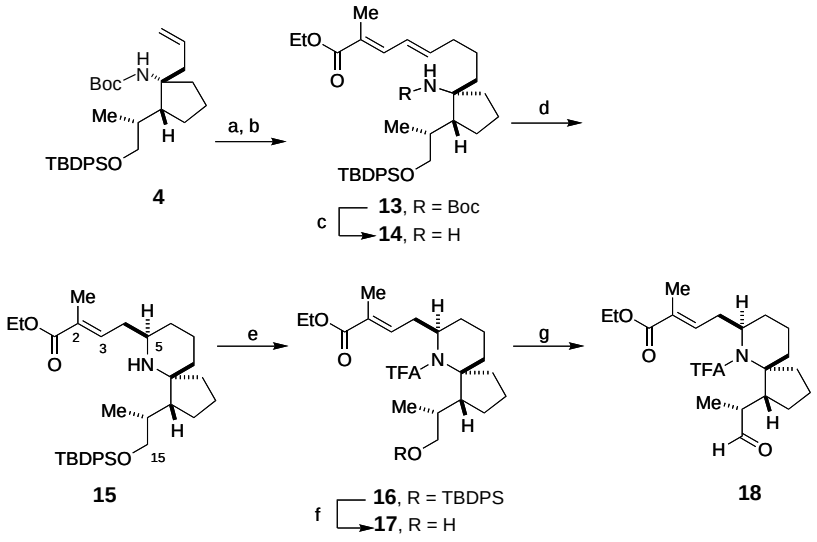
pinnaic acid commenced with the asymmetric allylation of lactam **3** to provide bicyclic lactam **5**. The nitrogen atom was protected, and subsequent highly stereoselective alkylation of the lithium enolate of **7** with methyl iodide led to **8**. Base-induced hydrolysis of **8** followed by reduction of the derived anhydride of **9** gave alcohol **10**.[12]

Given the less than rigorous grounds for assigning the *R* configuration at C14 in pinnaic acid (cf. **1**), we regarded it as unlikely that the two compounds, pinnaic acid and halichlorine, would differ at this center. Accordingly, we took compound **10** forward first. At the stage of **10**, the configuration of the secondary methyl center corresponds to the *S* configuration at C14 of **1**.[13] Protection of alcohol **10** delivered protected amino alcohol **4**, which contains chirality imprints that correspond to those suggested for C9, C13, and C14 of pinnaic acid (**1**).

Our attention was then directed at the azaspiro core of the target. We envisioned coupling an alkylborane derived from **4** with vinyl iodide **11**.[14] The latter was generated in a straightforward manner from known vinyl stannane **12** ([Eq. (1)]; I_2, CCl_4, 25 °C, 2 h).[15] Vinyl iodide **12** was coupled



successfully with the alkylborane of **4** to give **13** in 75% yield (Scheme 2). We then focused on the formation of the piperidine ring through an intramolecular vinylogous (1,6-addition) Michael reaction. Initial experiments showed that



Scheme 2. Reagents and Conditions: a) 9-BBN, THF, 25 °C, 1.5 h; b) **11**, Pd(dppf)$Cl_2 \cdot CH_2Cl_2$, $AsPh_3$, Cs_2CO_3, DMF/H_2O, 25 °C, 3 h, 75%; c) CF_3CO_2H, CH_2Cl_2, 25 °C, 1 h; d) DBU, 25 °C, 18 h, 81% over two steps; e) TFAA (20 equiv), Hünigs base (20 equiv), 1,2-CH_2ClCH_2Cl, 0 °C, 5 min, 88%; f) HF–pyridine, THF/pyridine, 0 → 25 °C, 18 h, 91%; g) TPAP (5 mol%), NMO (2.0 equiv), 3-Å molecular sieves, MeCN, 0.5 h, 84%. 9-BBN = 9-borabicyclo[3.3.1]nonane; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; dppf = 1,1′-bis(diphenylphosphinyl) ferrocene; Hünig's base = diisopropylethylamine; NMO = *N*-methylmorpholine *N*-oxide; TFAA = trifluoroacetic anhydride; TPAP = tetrapropylammonium perruthenate.

the lithium anion of **13** did not cyclize under a variety of conditions. We surmised that the bulk of the Boc protecting group may impede the N–C bond formation. Indeed, as shown in Scheme 2, upon removal of the Boc group, the resulting free amine **14** underwent smooth based-induced cyclization to afford piperidine **15** in good yield and with excellent diastereoselectivity. Equally important was the fact that the piperidine moiety **15** was generated exclusively as the correct *E* isomer at C2–C3.[16] Thus, in a few steps we were able to complete the bicyclic core of **1** by means of a Suzuki reaction and a stereoselective 1,6 Michael-type cyclization.

Continuing on the path toward pinnaic acid with the *S* configuration at C14 (natural or unnatural), the C15 alcohol of **15** was exposed by cleavage of the TBDPS group. At this point, considerable difficulties were encountered. The first of these was an inability to oxidize **15** to the corresponding aldehyde at C15. The situation here was clearly more complex than in the case of halichlorine, since the proximal nitrogen atom in pinnaic acid must emerge eventually as an NH group. This is in contrast to halichlorine in which the synthetic target mandates the tertiary character of the nitrogen atom at a comparable point. The choice of a proper protecting group for the NH group of **15** turned out to be critical. It would be necessary for this group to enable a diverse set of reactions and to be responsive to deprotection in a straightforward way at one of several stages. After many frustrations with various groups, we settled on the trifluoroacetyl derivative to form **16**. Deprotection of the TBDPS group gave **17**, which was oxidized to aldehyde **18**.

We then set out to form the C14 epimer (*S* configuration) building block of aldehyde **18**, anticipating a synthesis of the *R* version[5] of pinnaic acid. For this purpose, we returned to the methylated Meyers' lactam **8**. Deprotonation of **8** (LiHMDS) and kinetic quenching (2,6-di-*tert*-butyl-4-methylphenol) gave rise to **19** as the major product.[17] Forward processing of **19**, as shown in Scheme 3, afforded, after careful column chromatography, pure primary alcohol **20** (58%, 2 steps). Alcohol **20** was converted into **21**, the *S* version of the spirocyclization precursor. Indeed, deprotection of the Boc group of **21**, followed by treatment of the resultant **22** with DBU, provided **23**, which is the *S* epimer of **15** at C14. Progression of **23** as before afforded aldehyde **24**, the *S* epimer of **18** at C14.

In summary, we have secured the basis for synthesizing the C14 stereocongeners of pre-pinnaic acid building blocks by highly stereoselective sequences. In the following paper, we demonstrate how this chemistry set the stage for the total synthesis of natural and unnatural pinnaic acids in a fashion which elucidates their relative and absolute stereochemistry in rigorous detail.

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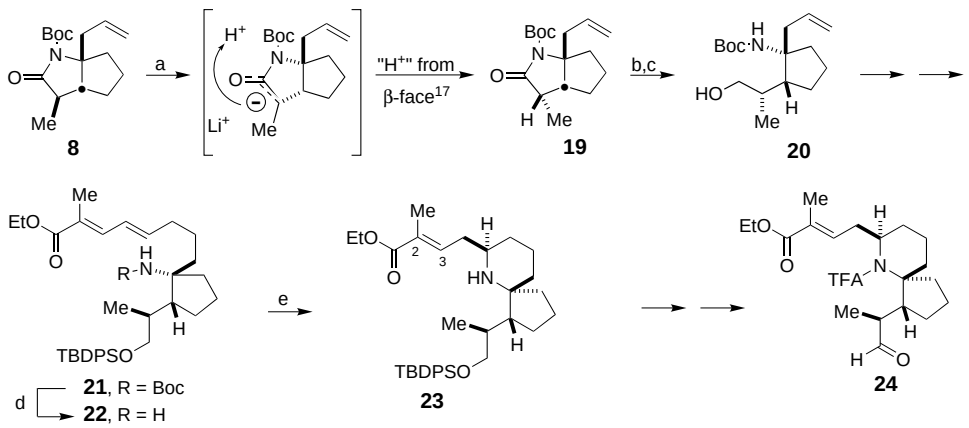

Scheme 3. Reagents and Conditions: a) LiHMDS (1.2 equiv), THF, −40 °C, 1.5 h, then BHT (1.2 equiv), −78 °C, 1.0 h, 82 %; b) LiOH, THF/H_2O, 25 °C, 18 h; c) $ClCO_2Et$, NEt_3, THF, −10 °C, 1 h, then $NaBH_4$, MeOH, 0 →25 °C, 1 h, 58 % over two steps; d) TFA, CH_2Cl_2, 25 °C, 1 h; e) DBU, 25 °C, 18 h, 76 % over two steps. BHT = 2,6-di-*tert*-butyl-4-methylphenol; TFA = trifluoroacetic acid.

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[12] A number of by-products were isolated, including an isomer of **10**, which is epimeric at the secondary methyl center (7 %, 3 steps). The minor stereoisomer was most likely generated by the partial epimerization of (14*R*)-Me-**9** during the basic hydrolysis, and nominally intersects in the synthesis of pinnaic acid (natural or unnatural) that has the *R* configuration at C14 (see below).

[13] As a consequence of the *R* and *S* stereonomenclature systems, the priority rankings change at the secondary methyl center from **10** to the putative pinnaic acid.

[14] For comprehensive reviews of the Suzuki reaction, see: a) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem./Angew. Chem. Int. Ed.*, in press; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; c) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147.

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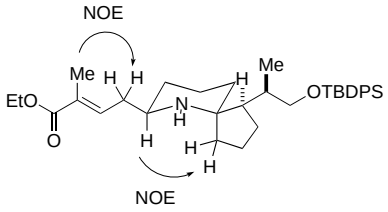
[16] The configurations at C5 and at the C2−C3 double bond were assigned as *R* and *E*, respectively, according to diagnostic NOESY cross peaks:



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[17] The kinetic quench resulted in a mixture of lactams **19** and **8** (>9:1).

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