Natural Product Synthesis

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Asymmetric Total Synthesis of Pinnaic Acid**

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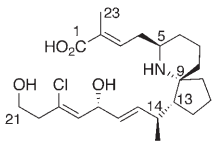
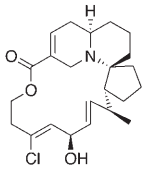
Phospholipase A_2 (PLA_2) is involved in the initial step of a cascade of enzymatic reactions which lead to the generation of inflammatory mediators.[1] A cytosolic 85 kDa phospholipase ($cPLA_2$) exhibits specificity for the release of arachidonic acid from membrane phospholipids.[2] Therefore, compounds that inhibit $cPLA_2$ activity are thought to be potential drugs for the treatment of inflammation and other disease states.

In 1996, a new class of marine natural products was isolated in our laboratory represented by pinnaic acid[3] (**1**)



1
Pinnaic acid

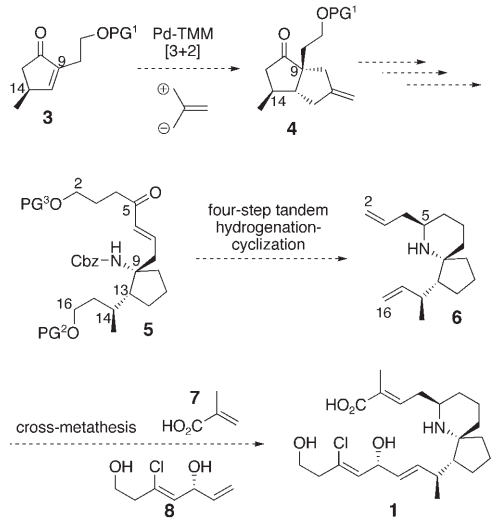


2
Halichlorine

and halichlorine[4] (**2**) from the bivalve *Pinna muricata*[5] and the black marine sponge *Halichondria okadai* Kadota, respectively. Pinnaic acid inhibits $cPLA_2$ in vitro at $IC_{50} = 0.2$ mM, whereas halichlorine blocks the induced expression of vascular cell adhesion molecule-1[6] (VCAM-1) in vitro at $IC_{50} = 7\ \mu g\,mL^{-1}$. Thus, both compounds are considered to be potential leads for anti-inflammatory drugs, despite their inhibiting different target proteins.

Even more impressive than their bioactivities are the architectural 6-aza-spiro[4.5]decane structures of these two molecules. They have attracted considerable attention in the synthetic chemistry community. They have been the topic of a specific review[7] and a large number[8] of reports describing efforts to synthesize them. However, as significant problems still exist, only one asymmetric total synthesis has been accomplished by Danishefsky and co-workers.[9] Asymmetric construction of the contiguous stereogenic centers at C9, C13, and C14 of **1** is a challenge, and thus most reported examples focus on the preparation of the spiro framework in racemic form. Another significant problem is the addition of side chains onto the spiro core. Regardless of extensive synthetic efforts, there is essentially only one protocol using a Wittig-type reaction available for the lower side-chain installation. The strategy was first used in Danishefsky's total synthesis[9b] and later modified by Heathcock's synthesis.[10] Installation of the C15–C21 side chain by this approach gave only a moderate yield.[9a–b]

Our efforts toward the total synthesis of pinnaic acid have taken the racemic route.[11a] Here, we describe the asymmetric total synthesis based on a new tactic employing a Pd-catalyzed trimethylenemethane [3+2] cyclization (Pd-TMM cyclization; Scheme 1).[12] We anticipated that Pd-TMM



Scheme 1. Synthetic plan for pinnaic acid. TMM = trimethylenemethane; Cbz = benzyloxycarbonyl; PG^1, PG^2, PG^3 = protecting groups.

cyclization with cyclopentenone **3** would occur from the opposite face of the adjacent methyl group to build up the three contiguous stereogenic centers diastereoselectively. Our tandem hydrogenation-cyclization protocol[11] can readily assemble the aza-spiro moiety, and cross-olefin-metathesis[13] reactions enable efficient installation of both the upper and lower chains.

Following the synthetic plan, the cyclopentane ring of pinnaic acid was constructed as shown in Scheme 2. Chiral

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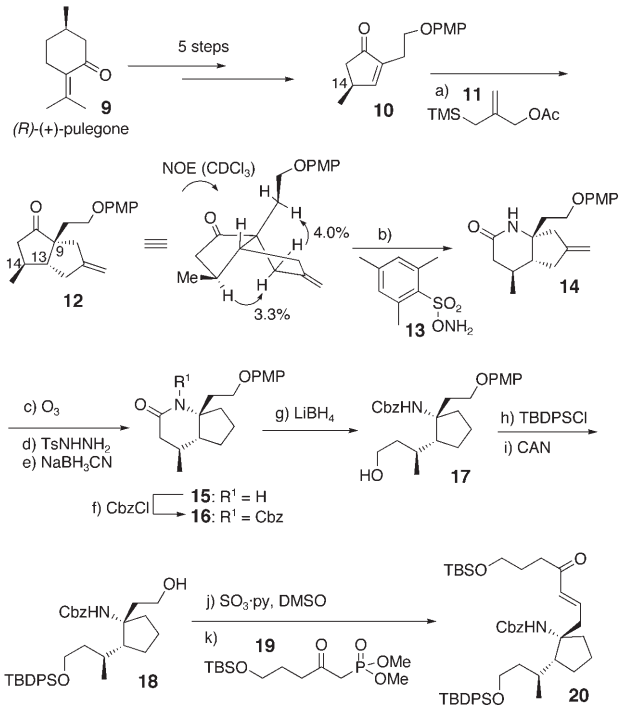
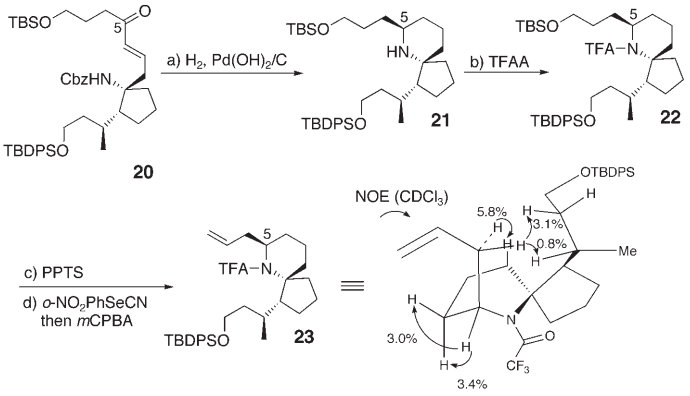


Scheme 2. Preparation of unsaturated ketone **20**. Reagents and conditions: a) **11**, $Pd(OAc)_2$, $(iPrO)_3P$, THF, reflux, 80%; b) MSH (**13**), 4-Å MS, alumina, CH_2Cl_2, RT, 43% (100% based on recovered starting material); c) O_3, MeOH, −78°C; then Me_2S, −78°C, 82%; d) $TsNHNH_2$, MeOH, 50°C; e) $NaBH_3CN$, TsOH, THF, reflux, 60% over two steps; f) NaH, CbzCl, THF, reflux, 87%; g) $NaBH_4$, LiBr, THF, 50°C, quant.; h) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, RT; i) CAN, MeCN/H_2O (1:1), 0°C, 76% over two steps; j) SO_3·py, Et_3N, DMSO, RT; k) **19**, Et_3N, LiCl, THF, 30°C, quant. in two steps. CAN = $(NH_4)_2Ce(NO_3)_6$, DMAP = 4-dimethylaminopyridine, DMSO = dimethyl sulfoxide, MS = molecular sieves, MSH = *O*-mesitylsulfonylhydroxylamine, PMP = *p*-methoxylphenyl, py = pyridine, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, Ts = *p*-toluenesulfonyl.

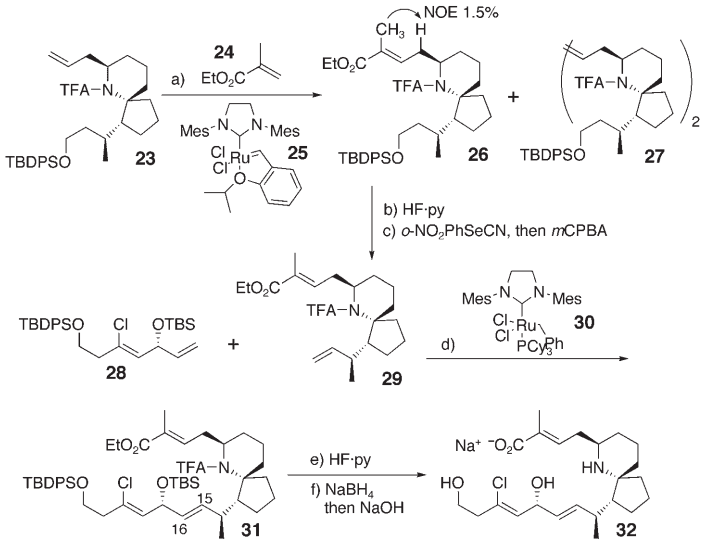
cyclopentenone **10** is a new chiral building block developed in this study.[14] It could be prepared easily from (*R*)-(+)-pulegone (**9**) in 41% yield over five steps on a 20-gram scale. As anticipated, the key Pd-TMM [3+2] cyclization proceeded with high stereoselectivity and only the *anti* adduct **12** could be isolated (80% yield). The configuration of the C9 and C13 asymmetric centers was verified by NOE experiments of **12**. Regioselective Beckmann rearrangement using a bulky hydroxylamine reagent **13** (MSH)[15] afforded the desired lactam **14** in 43% yield (quantitative yield based on the recovered starting material). Ozonolysis of the *exo* olefin, hydrazone formation of the resultant ketone, and deoxygenation with $NaBH_3CN$[16] provided **15**. Cbz protection of an amide nitrogen and $LiBH_4$ reductive opening of the lactam ring gave alcohol **17**. The enantiomeric purity of **17** was determined to be over 98% *ee*[17] by the modified Mosher's method.[18] It confirmed that no racemization had occurred during the above transformations from **10**. Silylation of the primary alcohol of **17** followed by oxidative removal of *p*-methoxyphenyl ether by CAN gave alcohol **18**. Oxidation (SO_3·Py, DMSO) to the aldehyde and Horner–Wadsworth–Emmons reaction with phosphonate **19** afforded the key precursor **20** of the tandem hydrogenation-cyclization as a single *E* isomer.

Our tandem hydrogenation-cyclization[11] (Scheme 3) is a powerful protocol for constructing the piperidine ring of **1** with the desired configuration at C5. It consists of four consecutive one-pot transformations: 1) saturation of the alkene, 2) removal of Cbz, 3) intramolecular cyclic imine and/or enamine formation, and 4) stereoselective reduction of the imine/enamine intermediate. Similar reductive cyclizations have been conducted lately by others.[8f,10] In our previous study,[11] this reaction was either carried out under neutral or acidic conditions with a catalytic amount of acetic acid. One remaining problem was the amount of Pd catalyst (50 mol%) required to obtain reproducible results. Careful re-examination of the reaction conditions revealed that the amino group of product **21** seemed to be deterring the Cbz hydrogenolysis step.[19] When a larger amount of acetic acid was used, as expected, only 20 mol% of Pd catalyst was sufficient to cleanly and reproducibly afford the desired diastereomer **21**. Protection of the amino group by TFAA and selective deprotection of the TBS group (PPTS)[20] followed by Grieco elimination[21] led to terminal olefin **23**, NOE correlations of which confirmed the stereochemistry of C5 to be that expected.

The stage was now set for installation of the side chains by cross-olefin-metathesis reactions (Scheme 4). Although olefin metathesis has become an indispensable tool, there is still a limited number of examples of the application of cross-metathesis strategy to the total synthesis of natural products.[13b] We first examined the upper side-chain connection, with the less reactive ethyl methacrylate **24** as solvent. Compound **26** was obtained in 74% yield by mixing compound **23** and 10 mol% Hoveyda–Grubbs second-generation catalyst **25**[22] under reflux for 13 h. The trisubstituted alkene of **26** was exclusively obtained in the desired *E* confi-



Scheme 3. Stereoselective construction of the aza-spiro ring. Reagents and conditions: a) H_2, $Pd(OH)_2$/C (20 mol%), HOAc (7 equiv), EtOH, 25°C; b) TFAA, $iPr_2NEt/ClCH_2CH_2Cl$ (1:5), 0°C, 81% over two steps; c) PPTS, EtOH, 25°C; d) *o*-$NO_2PhSeCN$, nBu_3P, THF, RT; then *m*CPBA, RT, 88% over two steps. *m*CPBA = *m*-chloroperbenzoic acid, PPTS = pyridium *p*-toluenesulfonate, TFAA = trifluroacetic anhydride.



Scheme 4. End game to pinnaic acid by cross-olefin-metathesis installation of the side chains. Reagents and conditions: a) ethyl methacrylate, **25** (10 mol%), neat, reflux, **26** (74%) + **27** (14%); b) HF·(py)$_x$/py (1:2), 45 °C; c) *o*-NO_2PhSeCN, *n*Bu_3P, THF, RT; then *m*CPBA, RT, 90% over two steps; d) **28** (5.5 equiv), **30** (80 mol%), toluene, 90 °C, 40% (69% based on the recovered starting material); e) HF·py/py (1:3), 25 °C; f) $NaBH_4$, EtOH, 25 °C; then NaOH (1.6 M in 1:2 EtOH/H_2O), 40 °C, 86% in two steps. Cy = cyclohexyl, Mes = mesityl.

guration. The homodimer of **23** was also formed in the above metathesis (14% yield). When the isolated dimer **27** was subjected again to the same reaction conditions, the dimer reached an equilibrium with **26**. TBDPS deprotection and Grieco elimination generated the terminal alkene **29**.

In the previous attempts toward pinnaic acid,[9–11] using the Wittig-based protocol, the configuration of the C17 alcohol was generated by a diastereoselective reduction of the Wittig products (dienones). Here we offer a second choice: In our cross-metathesis-based strategy, the C17 center of segment **28** was established (90% *ee*) before installation to the spirocyclic core **29**. Synthesis of the diene **28** from but-3-yn-1-ol consisted of a six-step transformation where the Corey–Bakshi–Shibata reduction[23] was a key step.[14] The next step was the cross-metathesis again. However, in the two precursors **28** and **29**, there are a total of four types of carbon–carbon double bonds which made the reaction even more challenging than the upper side-chain case. Fortunately, the two terminal double bonds proved to be more reactive, presumably for steric reasons, and led to the fully protected pinnaic acid **31** as a single *trans* isomer (C15–C16 bond) in 69% yield (based on 42% recovered starting material). Next, after successive deprotection of the two silyl protecting groups, the TFA amide, and the ethyl ester by the usual method,[9b] the chiral pinnaic acid was obtained in the sodium salt form, which is identical with the synthetic racemic pinnaic acid sodium salt on comparison of the ^{1}H NMR spectra.[10]

In conclusion, we have successfully completed the efficient asymmetric total synthesis of pinnaic acid through a strategy involving Pd-TMM [3+2] cyclization, four-step tandem hydrogenation-cyclization, and cross-olefin-metathesis reactions. Except for that of C17, all of the stereochemistry could be efficiently controlled from a single methyl group of cyclopentone **10**, which was originally obtained from the inexpensive *(R)*-pulegone. Further studies are underway in our laboratory toward the synthesis of halichlorine.

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