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Synthesis of Pinnaic acid; Asymmetric Construction of Spirocyclic Core

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Abstract:

An asymmetric synthesis of the spirocyclic core of pinnaic acid, a cPLA$_2$ inhibitor, is described. A key transformation in the sequence involves an asymmetric Michael-initiated ring closure.

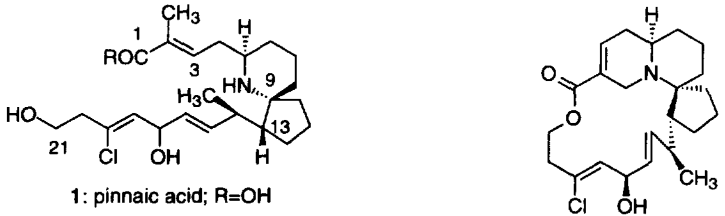
keywords: Alkaloids; Asymmetric synthesis; Marine metabolites; Spiro compounds

In our continuing search for biologically active substances from marine bivalves, we reported a potent PLA$_2$ inhibitor, pinnaic acid (**1**) and tauropinnaic acid (**2**), from *Pinna muricata*.[1] Since PLA$_2$ is involved in the initial step in the cascade of enzymatic reactions which lead to the generation of inflammatory mediators,[2,3,4] specific inhibitors have potential therapeutic value in the treatment of inflammation and other disease states. Pinnaic acid and tauropinnaic acid exhibited inhibitory activity with a cytosolic 85-kDa phospholipase(cPLA$_2$),[5,6] with IC$_{50}$ values of 0.2 mM and 0.09 mM, respectively. However, only several milligrams of **1** and **2** were obtained from the bivalves, which prevented further pharmacological studies.

In addition to their potency as anti-inflammatory agents, the biosynthetic origin of **1** and **2** is interesting due to their structural similarity to halichlorine(**3**), which was isolated from a marine sponge by our laboratory.[7]

Figure 1.

Structure of pinnaic acids(1, 2) and halichlorine(3)



1: pinnaic acid; R=OH
2: tauropinnaic acid;
R=NHCH$_2$CH$_2$SO$_3$H

3: halichlorine

We recently established the absolute stereochemistry of **3** by chemical degradation and synthesis.[8] Our current synthetic strategy toward **1** and **2** is based on our hypothesis that their absolute stereochemistry will match that of **3** as depicted in Figure 1.

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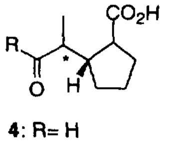
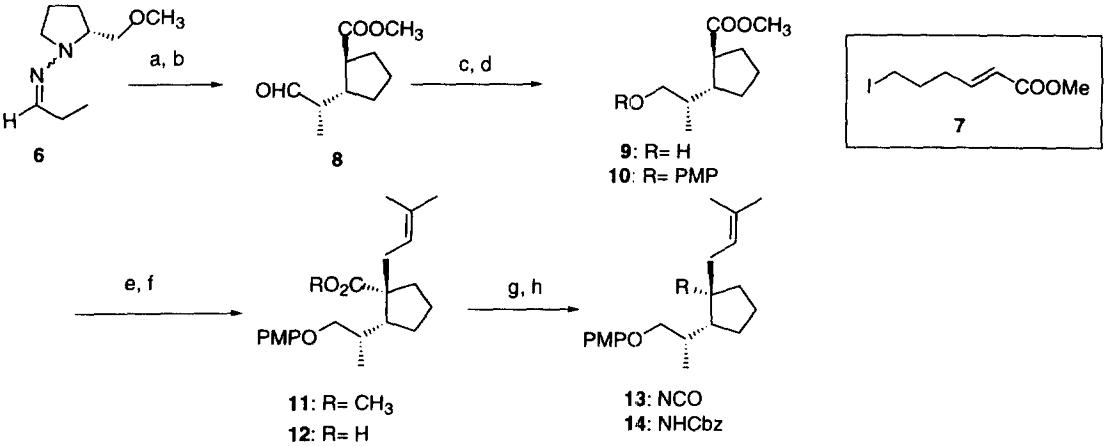


4: R= H
5: R= Alkyl or Aryl

A variety of strategies for the synthesis of aza-spiro compounds have been developed, most notably in approaches toward the frog toxins historionicotoxins.[9] Although related by the presence of a chiral quaternary spiro carbon and additional contiguous stereogenic centers, the differences of **1** and **2** from historionicotoxins in ring sizes and relative stereochemistry of the contiguous chiral centers were perceived as major synthetic challenges. We report here the asymmetric synthesis of the C3-C15 spirocyclic core of pinnaic acids, which contains four of the five total stereogenic centers.

Our strategy is based on a recent report of an asymmetric MIRC(Michael-initiated ring closure) reaction[10] by the Enders group.[11] Retrosynthetic disconnection at C8-C9 spirocyclic junction of **1**, followed by retro-Curtius transformation, yields aldehyde-carboxylic acid **4** as a key intermediate of pinnaic acid-halichlorine type alkaloids. Our initial targets were the known ketone derivatives **5**,[11] which are obtained from the MIRC reaction of ketone-derived SAMP or RAMP hydrazones. Subsequent conversion of **5** to **4** via regioselective Baeyer-Villiger oxidation was unsuccessful, however, prompting us to utilize the aldehyde-derived SAMP hydrazone as a more direct means to **4**. Treatment of the lithiated derivative of SAMP hydrazone **6** with Michael acceptor **7** provided the desired aldehyde **8** as a single isomer[12] following oxidative removal of the auxiliary by ozonolysis. A use of methyl iodide -hydrochloric acid conditions[14] gave lower yield with significant epimerization at C14. Reduction of **8** with sodium borohydride provided alcohol **9**, which was protected as a *p*-methoxyphenyl ether under the Mitsunobu conditions.

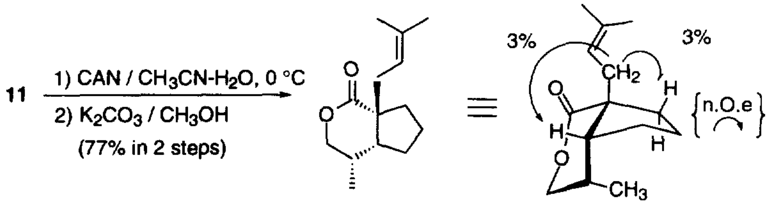
Scheme 1.



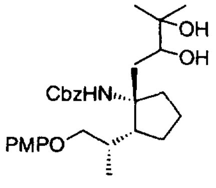
Reagents and conditions: (a) i) LDA, THF, 0°C, 4 hr, ii) TMEDA, -78°C, 0.5 hr, iii) 7, -78°C to room temp., 18 hr.(89%); (b) i) O_3/ CH_2Cl_2, -78°C, 0.5 hr, ii) $(CH_3)_2S$(50%); (c) $NaBH_4$, MeOH, 0°C, 1 hr (89 %); (d) *p*-methoxyphenol, PPh_3, diethyl azodicarboxylate, THF, 80°C, 2 hr (93%); (e) i) LDA, THF, -78°C, 2 hr, ii) prenyl bromide, -78°C to room temp., 20 hr (69%); (f) 2M KOHaq.-DMSO(1:1), 120°C, 7.5hr (89%); (g) DPPA, Et_3N, benzene, reflux, 2 hr; (h) BnOH, *i*-Pr_2NEt, benzene, reflux, 15 hr (86% in 2 steps).

Alkylation of ester enolate of **10** with prenyl bromide occured with complete facial selctivity from the β-side as expected, due to the shielding of α-side chain at C13. This was supported by the observance of n.O.e as shown in Scheme 2. Hydrolysis of the resultant methyl ester (**11**) required harsh conditions(KOH, DMSO, 120℃) due to steric hinderance, which also limited the use of conventional alcohol protective groups to *p*-methoxyphenyl ether. Treatment of carboxylic acid **12** under Curtius rearrangement conditions(diphenylphosphoryl azide, Et_3N, benzene, reflux) provided isocyanate **13**, which was fairly stable to aqueous workup. Addition of benzyl alcohol to **13** in the presence of an amine base, which provided the Cbz protected amine **14**.

Scheme 2.



Formation of the piperidine ring was then accomplished as shown in Scheme 3. Attempted oxidative cleavege of the double bond in **14** via Lemieux-Johnson oxidation(cat.OsO_4-$NaIO_4$/THF) yielded only diol **15** (57%). Attempts to cleave **15** failed either with $NaIO_4$(excess) or $Pb(OAc)_4$. Ozonolysis **14** in methanol proved more successful, affording an aldehyde in 83% yield. When the aldehyde was subjected to Horner-Wadsworth-Emmons olefination with **16** without isolation, **17** was obtained in 95% yield in two steps. Catalytic hydrogenation of **17** under neutral conditions, followed by sodium cyanoborohydride-acetic acid reduction, provided a complex mixture of products. Addition of small amount of acids was then examined, with catalytic amounts of acetic acid providing the best result. Thus, the saturation of the alkene in **17**, deprotection of the Cbz group, and reduction of intermediate imine **18** could be achieved simultaneously in excellent overall yield(93%). ^{1}H NMR of **19**[16] suggested that the hydrogenation proceeded exclusively from the desired α-face (supported by n.O.e experiments). We have been able to rationalize this selectivity by the presence of the substituent at C13 which hinders the approach of the palladium catalyst from the β-face.



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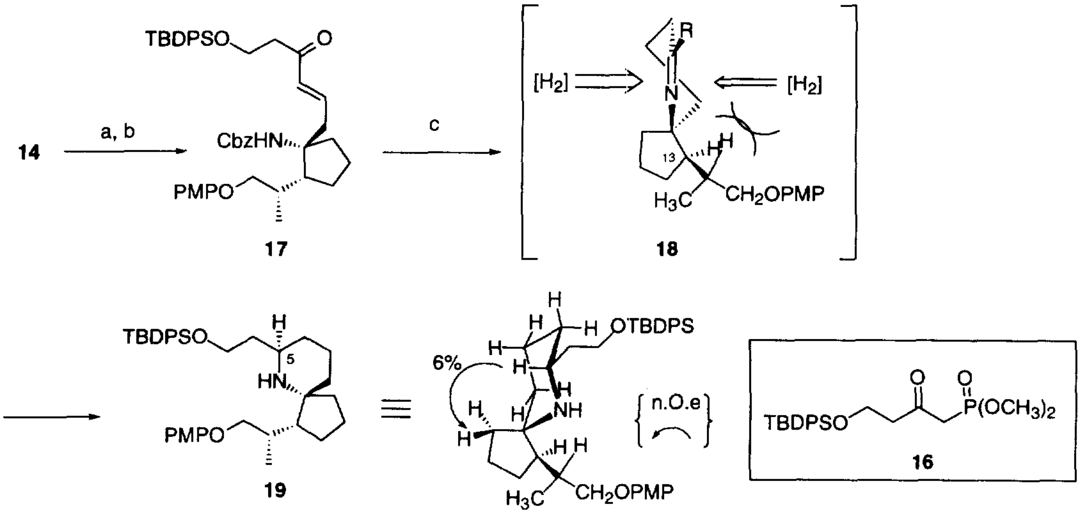
Scheme 3.



Reagents and conditions: (a) O_3, CH_3OH, -78°C, 5 min; (b) **16**, LiCl, Et_3N, THF, 0°C to room temp., 15 hr(95%); (c) $Pd(OH)_2$, H_2, CH_3COOH(cat.), EtOH(93%).

In conclusion, we have accomplished an efficient synthesis of the spirocyclic core of pinnaic acid in 11 steps in 17% overall yield. The synthesis is highlighted by an asymmetric MIRC reaction. Further effort toward the total synthesis of pinnaic acid is in progress.

Acknowledgments

The authors thank Prof. William Moser of IUPUI for helpful discussions and Dr. Kiyotake Suenaga of Nagoya University for some NMR experiments. This research was financially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

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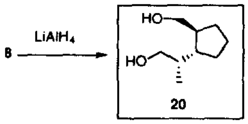
[12] The compound **8** could be reduced to diol **20** by lithium aluminum hydride. Racemic **20** and **21** could be prepared according to the procedure of Yamaguchi.[13] ^{1}H NMR spectra of epimers (**20**, **21**) were clearly distinguishable, which enabled the relative stereochemical assignment of **8** without ambiguity.



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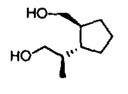

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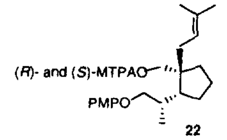
The absolute configurations were assigned by analogy of the results with ketone-derived hydrazone by Enders et al.[11] Ester **11** was reduced with lithium aluminum hydride to an alcohol, which was converted to its MTPA esters **22**. The enantiomeric excess of **22** was determined as 97% e.e. from ^{1}H NMR spectra.



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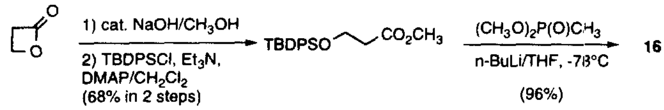
[15] Phosphonate **16** was prepared from cyclobutanone.



[16] Synthetic **19**: $[\alpha]_D^{24}$ +3° (*c* 0.48, $CHCl_3$); IR(film) 3430, 1720cm^{-1}; HRFABMS *m/z* 586.3689(M+H$^+$), calc. for $C_{37}H_{52}NO_3Si$ 586.3716; ^{1}H NMR(600MHz, C_6D_6) δ 1.03(1H, m; C6), 1.18(1H, m; C8), 1.22(9H, s; ^{t}Bu), 1.36(1H, m; C12), 1.37(1H, m; C11), 1.38(3H, d, *J*=6.6Hz; C22), 1.45(1H, m; C13), 1.48(2H, m; C6, C7), 1.59(1H, m; C7), 1.61(1H, m; C10), 1.63(2H, m; C4), 1.67(2H, m; C8, C11), 1.77(1H, m; C12), 1.85(1H, m; C10), 2.23(1H, m; C14), 2.90(1H, m; C5), 3.40(3H, s; OCH_3), 3.71(1H, dd, *J*=9.2, 7.0Hz; C15), 3.79(1H, ddd, *J*=10.3, 6.2, 6.2Hz; C3), 3.85(1H, ddd, *J*=10.3, 6.2, 6.2Hz; C3), 4.03(1H, dd, *J*=9.2, 3.7Hz; C15), 6.86(2H, d, *J* =9.2Hz; Ar; PMP), 6.98(2H, d, *J* =9.2Hz; Ar; PMP), 7.27(6H, m; Ph), 7.82(4H, m; Ph); ^{13}C NMR(100MHz, C_6D_6) δ 19.2(CH_3; C22), 19.4(C; ^{t}Bu), 22.8(CH_2; C11), 23.4(CH_2; C7), 27.2(CH_3; ^{t}Bu), 28.5(CH_2; C12), 33.1(CH; C14), 33.7(CH_2; C6), 36.6(CH_2; C10), 37.3(CH_2; C8), 41.0(CH_2; C4), 49.3(CH; C5), 54.2(CH; C13), 55.3(CH_3; OCH_3), 62.1(CH_2; C3), 63.2(C; C9), 73.6(CH_2; C15), 115.1(CH; Ar; PMP), 116.0(CH; Ar; PMP), 127.9(CH; Ar; Ph), 129.9(CH; Ph), 134.5(C; Ph), 136.0(CH; Ph), 154.2(C; Ar; PMP), 154.4(C; Ar; PMP).