HETEROCYCLES, Vol. 59, No. 2, 2003, pp. 441 - 444, Received, 1st August, 2002

SYNTHESIS OF (±)-PINNAIC ACID

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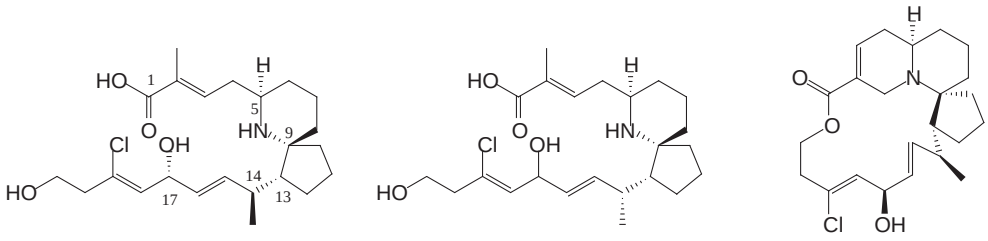
Abstract- (±)-Pinnaic acid (**1**) was synthesized *via* the catalytic hydrogenation of an α, β–unsaturated ketone (**12**) as the key step to construct an aza-spiro skeleton.

In our continuing search for biologically active substances from marine bivalves, we previously reported an isolation of potent $cPLA_2$ inhibitor, pinnaic acid (**1**), from *Pinna muricata*.[1] Interestingly, the structure of pinnaic acid is quite similar to that of halichlorine (**3**), which we previously isolated from a marine sponge.[2a] While the absolute stereochemistry of **3** has been fully established,[2b] the scarcity of **1** from natural sources has only allowed assignment of the relative stereochemical relationships between C5, C9, and C13. C14 has been proposed to be as depicted in structure (**2**). However, from a biogenetic point of view, this conclusion is open to question, when the configuration at C14 is compared to that of halichlorine.[3]

Figure 1.



1: pinnaic acid **2** **3**: halichlorine

These architecturally novel alkaloids have attracted the attention of synthetic chemists, and to date 14 research groups have published their synthetic studies.[4] The Danishefsky group has achieved the total synthesis of halichlorine[5] and pinnaic acid.[6] In the latter synthesis, it had been assumed that pinnaic acid had the same absolute configuration around the aza-spirocyclic moiety (C5, C9, C13), and all four possible diastereomers at C14 and C17 were synthesized. Comparison of the NMR spectra of these synthetic samples with the data[1] reported for the natural product made it possible to revise the relative structure for pinnaic acid as **1**.[6]

Pinnaic acid is a zwitterionic molecule, and thus the NMR spectrum is quite sensitive to the measurement

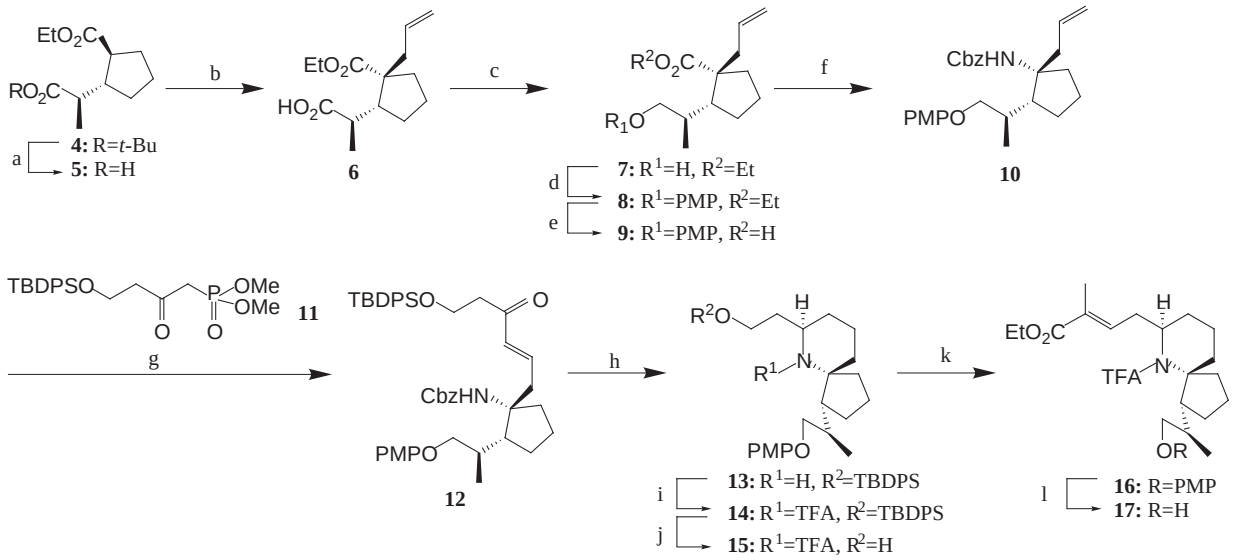
Dedicated to Prof. Y. Kanaoka on the occasion of his 75th birthday.

conditions. In view of the significant attention given to **1** in the synthetic community, we decided to prepare Danishefsky's pinnaic acid, and to support its proposed structure by direct comparison with our synthetic plan for Danishefsky's intermediate (**17**) based on our previously established approach:[7] **17** was transformed to pinnaic acid (**1**) according to his synthesis.[6]

Our synthesis started from known racemic diester (**4**).[8] After the selective removal of *t*-butyl ester of **4** with TFA, resultant **5** was treated with 2.1 eq. of potassium bistrimethylsilylamide to form dianion. Allylation of the ester enolate proceeded stereoselectively from the side opposite the adjacent carboxylate anion (**6** : C9 epimer = 5 : 1). Carboxyl group in **6** was reduced to a primary hydroxy group *via* a mixed anhydride, and then protected as a *p*-methoxyphenyl ether. Hydrolysis of ethyl ester part in **8** required rather harsh conditions (3M KOH aq.-DMSO, 1 : 1, 140$_o$C), presumably due to steric hindrance.

Treatment of carboxylic acid (**9**) under Curtius rearrangement conditions (diphenylphosphoryl azide,[9] Et_3N, benzene, reflux) provided an isocyanate, and subsequent addition of benzyl alcohol to the isocyanate gave the Cbz protected amine (**10**). The terminal alkene was cleaved by ozonolysis, and the resulting aldehyde was subjected to Horner-Wadsworth-Emmons olefination with phosphonate (**11**). Catalytic hydrogenation of **12** with a small amount of acetic acid achieved 1) saturation of the alkene, 2) deprotection of the Cbz group, 3) *in situ* formation of cyclic imine, and 4) stereoselective reduction of the imine in an excellent overall yield. ^{1}H-NMR spectrum of **13** showed no signs of the wrong diastereomer at the C5 stereocenter, as in our previous studies.[7] Protection of the secondary amino group as a trifluoroacetamide followed by deprotection of the *t*-butyldiphenylsilyl ether gave **15**. The alcohol (**15**) was oxidized to an aldehyde, and the C1-C2 unit of **1** was introduced by another Horner-Wadsworth-Emmons reaction. Deprotection of *p*-methoxyphenyl ether afforded alcohol (**17**), which was the key intermediate in Danishefsky's asymmetric total synthesis, in racemic form.[6]

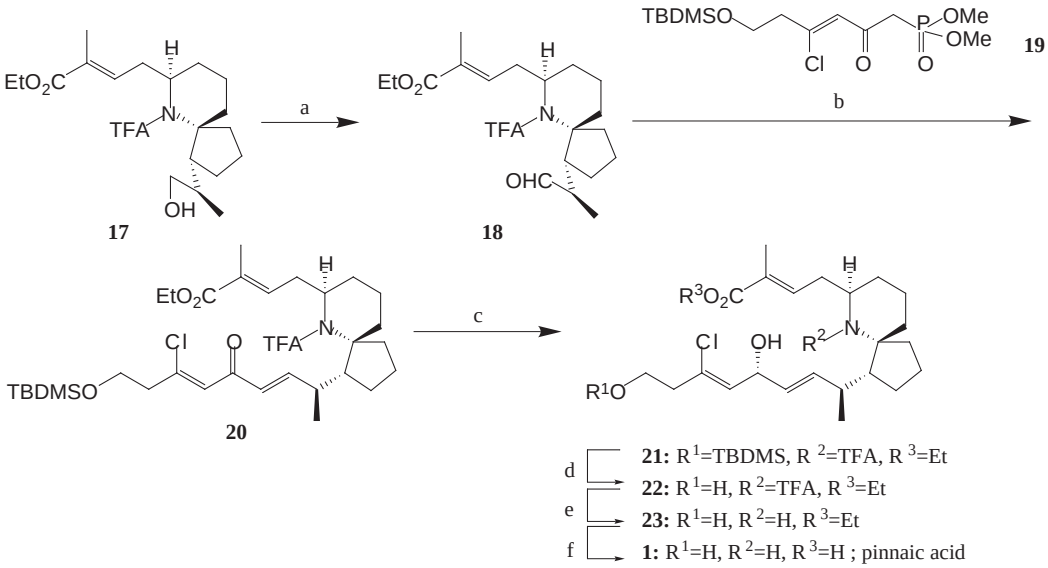
Scheme 1.



Reagents and Conditions: (a) TFA, CH_2Cl_2, rt, 97%; (b) i) KHMDS (2.1 eq.), -15^{o}C, 1 h, ii) allylbromide (3.0 eq.), THF, -15^{o}C, 3 h, 81%, ds=83%; (c) i) isobutyl chloroformate, Et_3N, THF, 0^{o}C; ii) $NaBH_4$, H_2O, 0^{o}C, 4 h, 91%; (d) *p*-methoxyphenol, DEAD, PPh_3, THF, reflux, 3hr, quant.; (e) 3M KOHaq.- DMSO (1:1), 140^{o}C, 98%; (f) DPPA, Et_3N, benzene, reflux, 2 h, then BnOH, *i*-Pr_2NEt, DMAP, reflux, 21 h, 88%; (g) i) O_3/MeOH then Me_2S, -78^{o}C, ii) **11**, LiCl, Et_3N, THF, rt, 3 h, 95% (in 2 steps); (h) H_2, 20% $Pd(OH)_2$/C, CH_3COOH (cat.), EtOH, rt, 93%; (i) TFAA (20 eq.), *i*-Pr_2NEt (21 eq.), 1,2-CH_2ClCH_2Cl, 0^{o}C, 15 min, 87%; (j) HF·pyr, THF, rt, 82%; (k) i) TPAP (14 mol%), NMO (2.7 eq.), MS4A, CH_2Cl_2, 0^{o}C; ii) Triethyl 2-phosphonopropionate, NaH, THF, rt, 80% (in 2 steps); (l) CAN, MeCN/H_2O, rt, 56%.

To convert **17** to (±) -**1**, we followed the reported procedure,[6] so that we would be certain to obtain the same diastereomer. Horner-Wadsworth-Emmons reaction with Weinreb's phosphonate (**19**)[4a] enabled us to construct the full carbon skeleton of pinnaic acid, but the yield was low (13%, lit.,[6b] 30%). Reduction of diene (**20**) by Luche conditions gave alcohol (**21**) as a predominant isomer.[6b] Due to the small reaction scale, we could not characterize the minor isomer. Deprotection of the *t*-butyldimethylsilyl group, reductive cleavage of trifluoroacetamide, and finally hydrolysis of ethyl ester furnished pinnaic acid (**1**).

Scheme 2.



Reagents and Conditions: (a) TPAP (12.5 mol%), NMO (2.7 eq.), MS4A, MeCN, 0°C, 74%; (b) **19** (2.1 eq.), LHMDS (2.0 eq.), THF/HMPA, rt.; (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, rt, 13% (in 2 steps); (d) HF·pyr, THF/pyr, 0°C, 80%; (e) $NaBH_4$, EtOH, rt, quant.; (f) LiOH, THF/MeOH/H_2O, 40°C, quant.

Table 1. ^{1}H-NMR spectral Data of Pinnaic Acid (600 MHz, in CD_3OD)

	Natural (carboxylate)	Synthetic (carboxylate)	Synthetic (free carboxylic acid)
Position	δ_H (*J* in Hz)	δ_H (*J* in Hz)	δ_H (*J* in Hz)
3	6.36 (t, 7.2)	6.35 (t, 7.2)	6.56 (m)
4	2.46 (br s)	2.49 (br s)	2.61 (br s)
14	2.32 (m)	2.32 (m)	2.37 (m)
15	5.74 (dd, 9.6, 15.6)	5.75 (dd, 9.6, 15.6)	5.83 (dd, 9.6, 15.6)
16	5.60 (dd, 6.6, 15.6)	5.60 (dd, 6.6, 15.6)	5.67 (dd, 6.6, 15.6)
17	4.96 (8.4)	4.96 (8.4)	5.01 (t, 7.8)
18	5.76 (d, 8.4)	5.76 (d, 8.4)	5.72 (d, 7.8)
20	2.56 (t, 6.0)	2.56 (t, 6.0)	2.55 (t, 6.0)
21	3.73 (m)	3.73 (m)	3.74 (m)
22	1.05 (d, 6.6)	1.06 (d, 6.6)	1.09 (d, 6.6)
23	1.87 (s)	1.86 (s)	1.87 (s)

Synthetic pinnaic acid was acidified with TFA and excess TFA was removed *in vacuo* to give free carboxylic acid. The ^{1}H-NMR spectrum of the free carboxylic acid was similar to that of the natural compound.[1] This synthetic sample was transformed to a sodium salt, and compared to **1** in carboxylate form. (Table 1) In carboxylate form, the chemical shifts of the side-chain protons (H3-H4, H15-H18) were quite different from those of the free carboxylic acid. The data for synthetic samples were in good agreement with those of the natural product.

In conclusion, we synthesized pinnaic acid in racemic form. Comparison of the ^{1}H-NMR spectra of synthetic and natural samples supported Danishefsky's revision of the configuration at C14. Efforts toward asymmetric synthesis are currently underway, and the results will be reported elsewhere.

ACKNOWLEDGMENT

This work was supported in part by Grant-in-Aid (Nos. 11558079, 12045235, and 12558076) for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and PRESTO, JST.

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