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A diastereoselective approach for an asymmetric synthesis in pinnaic acid series

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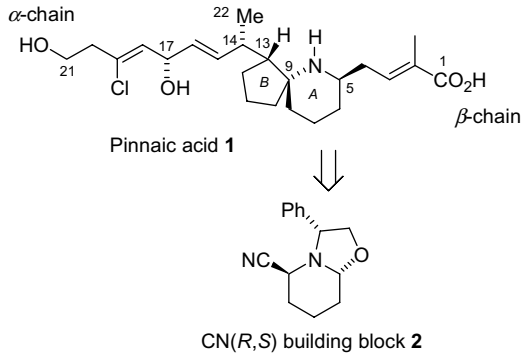
Abstract—An enantiopure spiran-bearing advanced intermediate in pinnaic acid series was obtained in 11 steps starting with CN(*R*,*S*) building block.

1. Introduction

In 1996, Uemura and co-workers[1] reported the isolation of pinnaic acid **1** from the bivalve *Pinna muricata*, an indigenous shell of the sea surrounding the Okinawa island. This alkaloid bears a unique spiranic skeleton and displays anti-inflammatory and immuno-suppressive properties mediated by the inhibition of phospholipase A_2. The potential medicinal importance of pinnaic acid provides an impetus for the research of an efficient asymmetric synthesis of azaspiro[3,5]decane system which is an integral feature of its remarkable structure.

The use of the CN(*R*,*S*) method[2] was envisaged as it provides access to enantiopure piperidines bearing a large array of possible substituents. Although only one total synthesis of pinnaic acid has been reported in the past decade,[3] other approaches[4] have provided useful insights (Scheme 1).



Scheme 1.

2. Results and discussion

The first step of our approach was the diastereoselective alkylation of the lithio anion of amino-nitrile **2** with a halogenated electrophile. The CN(*R*,*S*) strategy allowed us to control with confidence[2] the *S* absolute configuration of the C9 quaternary centre of pinnaic acid **1**. Indeed, a unique diastereomer **3**[5] was obtained by this means (Scheme 2). We then built the *B*-ring via the intramolecular attack on the nitrile function by an organo-lithium nucleophile **4** which was generated by a halogen/lithium exchange using lithium-naphthalenide at −78 °C.

This led to the quite unstable spiranic enamine derivative **6**[6] which arises from the opening of the postulated bicyclic imine intermediate **5**. We exploited the property of enamine **6** to be protonated as iminium salt **7** in order to introduce the β-chain, through nucleophilic attack of a silylenolether (Scheme 3). The reaction was performed using ytterbium triflate as a Lewis acid (10 mol%) in a

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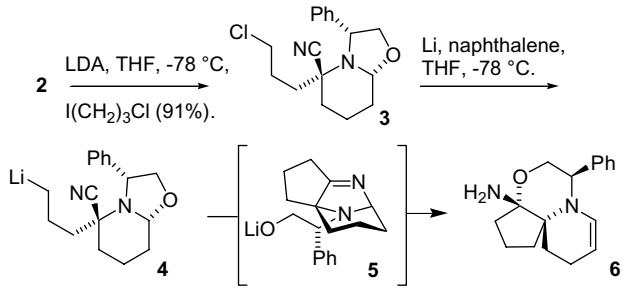
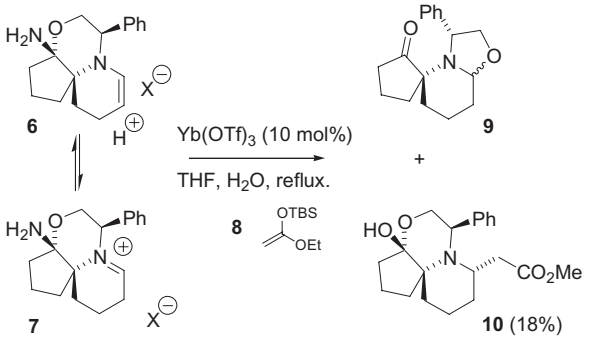


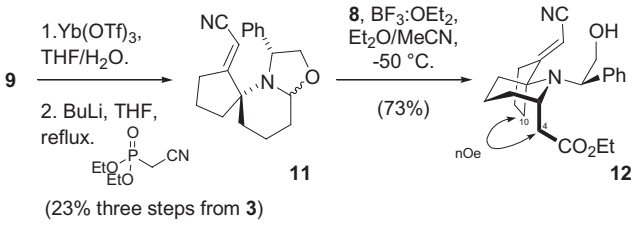
Scheme 2. Spiroannulation process by lithium/halogen exchange.



Scheme 3. Attack of silylenolether on iminium **7** and $Yb(OTf)_3$ catalysed hydrolysis of **6**.

9/1 THF/water mixture and *tert*-butyldimethylsilylenolether **8**[7] as a nucleophile. The expected ester **10** was obtained in poor yield only but as a unique diastereomer. However, we found that the main reaction product formed under these conditions was ketone **9**.[8] A more classical acidic hydrolysis of **6** (hydrochloric acid 1 N/THF, 1/1) only led to decomposition products. We decided to pursue this mild ytterbium triflate-mediated hydrolysis to obtain ketone **9** in an optimised yield; however, due to its acidic sensitivity, it could not be purified by column chromatography.

Thus, crude ketone **9** was used directly in a Horner–Emmons olefination step to introduce the α-chain (Scheme 4). Since the ketone function of **9** is very hindered, only



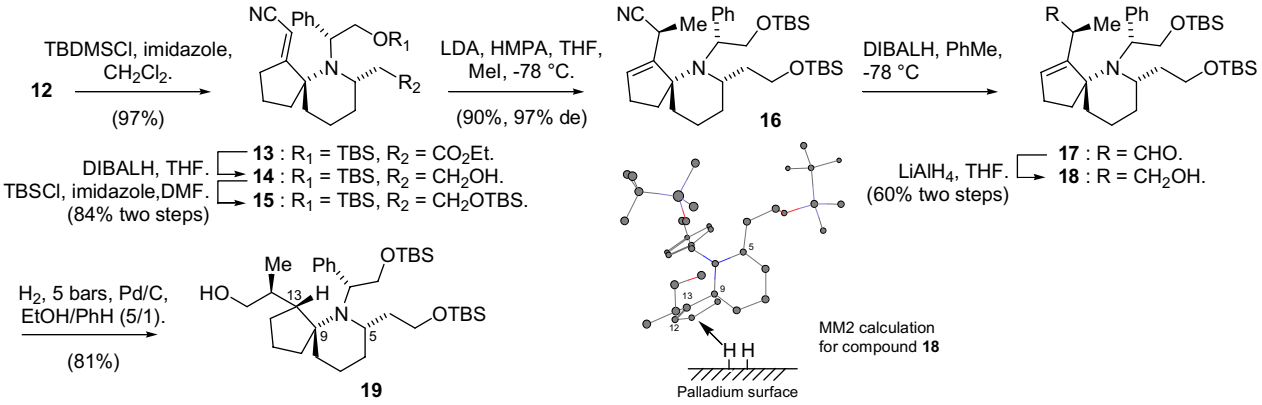
Scheme 4. Introduction of α- and β-chains.

the lithium anion of diethyl(cyanomethyl)-phosphonate in refluxing THF[9] gave the expected compound **11** (23% yield in three steps from amino-nitrile **3**) with exclusive *E*-configuration and partial racemisation at C5.

The β-chain was built at that point by reaction of silylenolether **8** with the iminium ion generated from the oxazolidine function[10] of **11**, leading to ester **12**.

The expected axial attack occurred and led exclusively to the unnatural stereochemistry at C5 as demonstrated by an NMR NOESY experiment on compound **12** (Scheme 4). Since an equatorial position for the β-chain is more thermodynamically favoured, we are planning to restore the correct stereochemistry at C5 in the course of a retro-Michael/Michael reaction sequence. This strategy is supported by the fact that Danishefsky et al.[3] built the piperidine *A*-ring of pinnaic acid **1** using a Michael reaction and obtained the correct stereochemistry at C5.

In the next step of our studies we hoped to reduce the C13–C14 double bond of the acrylonitrile function of **12** with control of the C13 stereochemistry. Unfortunately, none of the reducing reagents tried (Mg/MeOH,[11] hydrogenation H_2, Pd/C or $RhCl(PPh_3)_3$, dissolved metals (Li or Na)[12] or copper hydride[13]) led to the expected product; in most cases complex mixtures of over-reduced products were obtained. As a result, our strategy was modified and we decided to introduce the C22 methyl by alkylation of the acrylonitrile function. To achieve this we first needed to protect alcohol **12** as silyl ether **13** (Scheme 5). The ester function of



Scheme 5. Synthesis of advanced intermediate **19**. Conformation of minimum energy for compound **18** and most plausible explanation for its observed hydrogenation facial selectivity.

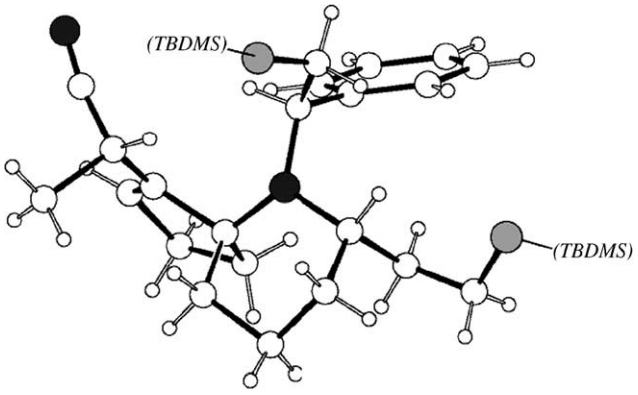


Figure 1. ORTEP drawing of **16**.

13 was selectively reduced into alcohol **14** and finally protected as a silyl ether **15**.

The alkylation of **15** in THF at −78 °C in the presence of 1.5 equiv of HMPA and LDA as a base gave compound **16**[14] with high control of the C14 stereochemistry (97% de). As expected, the alkylation of this α,β-unsaturated nitrile occurs α along with a double bond shift.[15] Unfortunately, we obtained the unnatural stereochemistry at C14 as demonstrated by X-ray analysis performed on compound **16**[16] (Fig. 1).

The nitrile function of **16** was reduced to alcohol **18** via aldehyde **17**. It was then possible to perform the planned hydrogenation of the cyclopentene ring of **18** without the over-reduction we encountered with the α,β-unsaturated nitrile **12**. Thus, a palladium-catalysed hydrogenation of the C12–C13 double bond, performed under pressure (5 bar), led to compound **19**[17] as the sole diastereomer. Despite NOESY ^{1}H NMR experiments, the C13 stereochemistry of compound **19** could not be determined. Nevertheless, the course of a heterogeneous phase hydrogenation reaction is predictable in the case of a space-congested molecule. Thus, the fact that no hydrogenation of the benzylic C–N bond took place and that the methylation of **15** at C14 specifically proceeds on one side, suggests a strong steric hindrance in this area of the molecule. This is plausible, as compound **18** bears two bulky TBS protective groups. This hindrance is probably at the origin of this face-selective hydrogenation of the cyclopentene *B*-cycle that leads to the correct stereochemistry at C13. Moreover, the MM2 calculation of the lowest energy conformation of compound **18** (Scheme 5) confirms that one face in ring-*B* is far less congested than the other.

3. Conclusion

This work demonstrates that the enantiopure spiranic core of pinnaic acid alkaloid **1** can be successfully built using the CN(*R*,*S*) strategy. Further progress in pinnaic acid total synthesis will focus on the stereochemical inversion of the C5 and C14 centres. At a final stage, the internal 1-6 retro-Michael/Michael equilibration[3] is envisaged to control C5 stereochemistry. A kinetic reprotonation of the enolate of nitrile **16** is planned for the inversion of the C14 stereochemistry.

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Dr. Yves Janin and Professor David Aitken are acknowledged for fruitful discussions.

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14. *Spectroscopic data for compound* **16**: colourless crystal recryst from hexane, mp: 139 °C, ^{1}H (400 MHz, $CDCl_3$) δ 0.04 (two s, 6H), 0.09 (two s, 6H), 0.93 (s, 18 H), 1.10–1.45 (m, 5H), 1.46 (d, 3H, J = 7.2 Hz), 1.59–1.88 (m, 5H), 2.20

(m, J = 7.0 Hz), 2.40 (m, 1H, J = 9.9 Hz), 3.40–3.58 (m, 4H, J = 4.9, 4.6 and 5.9 Hz), 3.75 (t, 1H, J = 6.1 Hz), 4.03 (m, 2H, J = 7.3, 4.5, 10.4 Hz), 4.24 (t, 1H, J = 10.3 Hz), 6.11 (s, 1H), 7.21 (m, 5H). ^{13}C (100 MHz, $CDCl_3$) δ −5.50, −5.41, −5.32, 17.00, 18.42, 23.16, 26.04, 26.11, 28.47, 29.54, 33.17, 34.02, 37.43, 46.62, 61.69, 62.33, 63.47, 74.28, 123.99, 127.14, 127.77, 129.55, 130.64, 141.48, 148.50. HRMS (CI^+, CH_4) calcd for $C_{34}H_{59}N_2O_2Si_2$ $(MH)^+$: 583.4115. Found: 583.4106.

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16. Despite many recrystallisation attempts on compound **16** to improve the crystal diffracting quality, the resolution of the best recorded full dataset did not exceed 2θ = 43 deg (for λ Cu Kα = 1.5418 Å). Only 28 non-H atoms out of 40, corresponding to the central core of compound **16**, could be solved by direct methods and refined isotropically by full-matrix least squares on F^2. Some carbon atoms of both TBS protective groups could be partially recognized in the successive difference Fourier maps but displayed very large displacement parameters explaining the very poor diffraction quality of these crystals. Therefore, refinement of the structure (excluding the 12 carbon atoms of TBS groups) was stopped at a poor convergence level (R = 0.24).
17. *Spectroscopic data for compound* **19**: colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 12H), 0.86 (s, 18H), 0.93 (d, 3H, J = 7.0 Hz), 1.27 (m, 3H), 1.42 (m, 1H), 1.55 (m, 1H, J = 6.8 Hz), 1.70 (m, 4H, J = 7.6 Hz), 1.92 (m, 1H), 1.99 (m, 1H, J = 6.8 Hz), 2.22 (m, 4H), 2.46 (m, 1H), 2.70 (m, 1H, J = 6.8 Hz), 3.40 (m, 2H, J = 10.1, 6.1 Hz), 3.56 (m, 1H, J = 10.4 Hz), 3.61 (m, 2H), 3.86 (m, 1H, J = 4.1 Hz), 7.29 (m, 5H). ^{13}C NMR, (100 MHz, $CDCl_3$) δ −5.40, −5.30, −5.19, 15.42, 18.35, 21.85, 24.54, 25.99, 26.05, 28.43, 29.80, 30.95, 35.23, 35.38, 36.03, 36.93, 51.91, 60.47, 62.41, 66.08, 68.49, 127.26, 128.07, 128.21, 135.81, 139.48, 142.06. HRMS (CI^+, CH_4) calcd for $C_{34}H_{64}NO_2Si_2$ $(MH)^+$: 590.4425. Found: 590.4417.