A Concise and Flexible Synthesis of the Core Structure of Pinnaic Acid

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Abstract: An efficient and flexible approach to the core structure of pinnaic acid has been developed that centres on the microwave-induced 1,3-dipolar cycloaddition of a novel spirocyclic nitrone **5** with alkene **7**. The application of this nitrone to the synthesis of a diverse set of C5-substituted analogues of pinnaic acid is also demonstrated.

Key words: pinnaic acid, nitrones, cycloadditions, isoxazolidine, oxidative ring opening

Pinnaic acid **1** is a spirobicyclic alkaloid extracted, along with tauropinnaic acid (**2**), from the Okinawan bivalve *Pinna muricata* by Uemura and co-workers in 1996.[1] The unusual 6-azaspiro[4.5]undecane core of this alkaloid is also present in the spiroquinolizidine alkaloid halichlorine (**3**), isolated by the same research group from the black marine sponge *Halichondria okadai* (Figure 1).[2] Pinnaic acid is an inhibitor of cytosolic phospholipase A_2 (cPLA_2; IC_{50} 0.2 mM), an enzyme that plays a key role in the biosynthesis of inflammatory mediators and as such is an interesting lead in the search for novel anti-inflammatory treatments.[3]

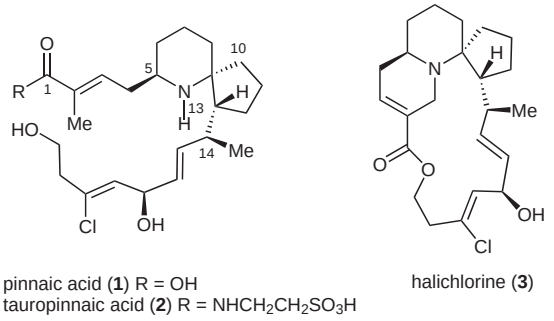

Figure 1

The intriguing core structure and therapeutic potential of pinnaic acid has stimulated the development of a number of total syntheses of this target and synthetic routes to the azaspirodecane core structure.[4,5] In an effort to develop a synthetic strategy that could be applied to the synthesis of all members of the 6-azaspiro[4.5]decane family of alkaloids and analogues, in racemic fashion, we have investigated an approach to core structure **4** that centres on the use of spirocyclic nitrone **5** as a key intermediate.

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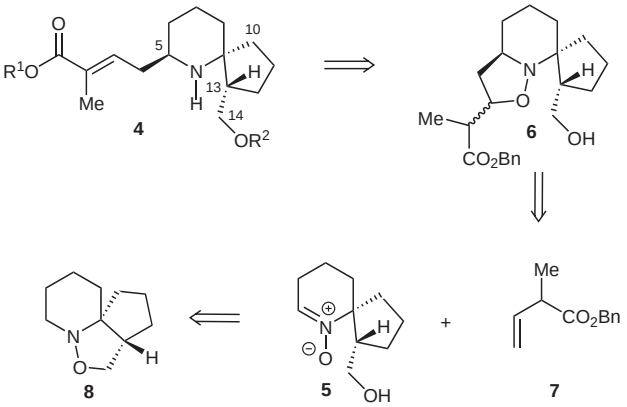
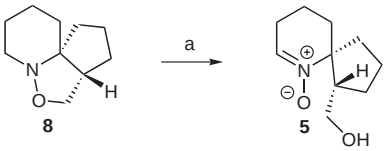
Nitrones exhibit a diverse reactivity profile[6,7] and we envisioned that **5** could be used to provide access to both the core structure of halichlorine and a diverse set of C5-substituted analogues of compounds **1**–**3**. It was planned to access core structure **4** by reductive cleavage of cycloadduct **6** formed by 1,3-dipolar cycloaddition of alkene **7** with nitrone **5**. We envisioned that **5** could be accessed by oxidative cleavage of known isoxazolidine **8** (Scheme 1).[8]



Scheme 1

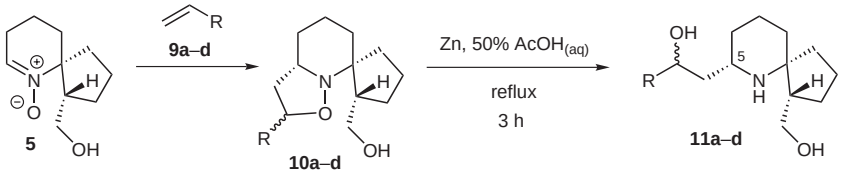
Multigram quantities of isoxazolidine **8** were synthesised in five steps from 1,5-dibromopentane utilizing the synthetic route developed by Gossinger et al.[8] After some experimentation it was discovered that oxidative cleavage of **8** to give nitrone **5** could be effected in high yield by dropwise addition of a solution of MCPBA in dichloromethane at 0 °C over a period of seven hours (Equation 1).[9,10] While nitrone **5** decomposes over a period of two days at room temperature it may be stored for up to five months in a freezer.



Equation 1 *Reagents and conditions*: (a) MCPBA, dropwise, CH_2Cl_2, 0 °C to r.t., 20 h, 89%.

The reactivity and synthetic utility of nitrone **5** was probed by investigating the 1,3-dipolar cycloaddition of this molecule with a small number of diverse dipolarophiles and attempted reductive ring opening of the resulting cycloadducts. The results of this study are summarised

Table 1 1,3-Dipolar Cycloadditions of Nitrone **5** with Dipolarophiles **9a–d** and Reductive Cleavage of the Resulting Cycloadducts **10a–d**

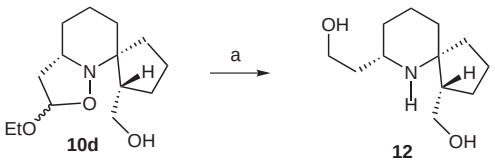


Entry	Alkene **9**[a]	R	Solvent	Temp (°C)	Time (h)	**10**[c]	Yield (%)[d]	**11**[c]	Yield (%)[d]
1	**9a**	Ph	PhMe	110	13	**10a**	62	**11a**	76
2	**9b**	CO_2Et	CH_2Cl_2	25	48	**10b**	90	**11b**	70
3	**9c**	CH_2CH_2OBz	PhMe	110	14	**10c**	60	**11c**	81
4	**9d**[b]	OEt	EtOH	40	55	**10d**	80	**11d**	0

[a] Unless otherwise stated, cycloadditions were carried out using 3 equiv of dipolarophile.
[b] Cycloaddition was carried out using 17 equiv of dipolarophile.
[c] Relative stereochemistry determined by 2D-NOESY studies performed on azaspirodecanes **11a–d**.
[d] Isolated and chromatographically pure products.

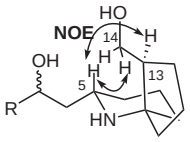
in Table 1. The reaction conditions specified for the cycloadditions are those resulting in optimum yields of products. Nitrone **5** undergoes regio- and stereoselective 1,3-dipolar cycloaddition with a range of dipolarophiles and compounds **10a–d** were the sole products isolated as single diastereomers in good to high yield. Nitrone **5** is reactive towards both electron-poor and electron-rich alkenes and undergoes cycloaddition with ethyl acrylate (**9b**) and ethyl vinyl ether (**9d**) at relatively low temperature.

Reductive cleavage of the cycloadducts **10a–c** proceeded under standard conditions, utilizing zinc powder in acetic acid under reflux, to give the C5-substituted azaspiro[4.5]decanes **11a–c**. Isoxazolidine **10d** decomposed under these reaction conditions and the expected aldehyde, arising from hydrolysis of hemiacetal **11d**, was not isolated. Reductive cleavage of isoxazolidine **10d** could only be effected by hydrogenation in the presence of $Pd(OH)_2$ in methanol[11] and, under these conditions, overreduction occurred to give the diol **12** in moderate yield (Equation 2).



Equation 2 *Reagents and conditions*: (a) H_2, 20 mol% $Pd(OH)_2$, MeOH, r.t., 48 h, 44%.

The stereochemistry of cycloaddition was most conveniently determined by NOE studies performed on the reduction products **11a–c** and **12** owing to overlapping of crucial signals in the ^1H NMR spectra of isoxazolidines **10a–d**. Unfortunately, these studies did not allow us to assign *exo*/*endo*-stereochemistry to the cycloadducts. Strong NOE's observed between the C5-proton and those at C13 and C14 indicated that cycloaddition occurred from the α-face of nitrone **5** to ultimately yield azaspiro[4.5]decanes **11a–c** and **12** with unnatural stereochemistry at C5 (Figure 2). This stereoselectivity is similar to that obtained during the nucleophilic addition of silyl enol ethers[5a] and allylsilanes[12] to spirocyclic iminium species comparable in structure to **5**. While the relative stereochemistry of the azaspiro[4.5]decanes obtained is not that desired this short study reveals that nitrone **5** has the potential to act as the synthetic gateway to a diverse set of C5-substituted, azaspirodecane-based analogues of pinnaic acid and halichlorine.

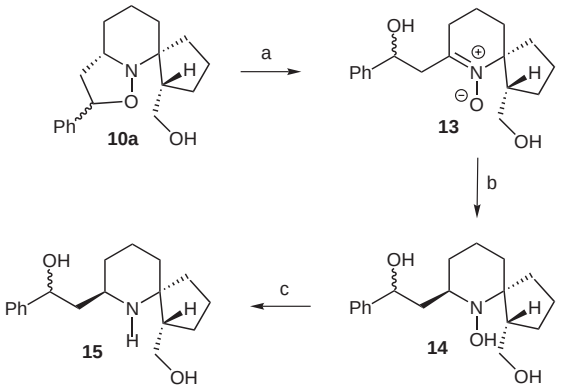


11a; R = Ph
11b; R = CO_2Et
11c; R = CH_2CH_2OBz
12; R = H

Figure 2 Selected NOE observed in azaspiro[4.5]decanes **11a–c** and **12**.

The reduction of imines/iminium ions[13] and spiro-2,3,4,5-tetrahydropyridine *N*-oxides,[14] similar to **5** proceeds via hydride delivery from the α-face and we reasoned that oxidative cleavage of cycloadducts **10a–d** followed by reduction of the resulting nitrones would yield 5-substituted azaspirodecanes with the desired relative stereochemistry. The strategy was initially attempted on isoxazolidine **10a**. Oxidation of **10a** with MCPBA gave nitrone **13** which underwent stereoselective reduction with $NaBH_4$[14,15] to give hydroxylamine **14** as a single diastereomer. Further reduction, with aqueous $TiCl_3$ in MeOH[16] gave the C5-epimer of **11a**; azaspiro[4.5]decane **15** (Scheme 2).

Epimerisation was confirmed by analysis of the 2D-NOESY spectrum of **14**. While NOE cross-peaks between the C5-proton and those at C13/C14 were absent, strong NOE were observed between the axial proton at C5, the C10-protons and the axial C7-proton (Figure 3).



Scheme 2 *Reagents and conditions*: (a) MCPBA, CH_2Cl_2, 0 °C, 1 h, 90%; (b) $NaBH_4$, MeOH, 0 °C, 20 min, 90%; (c) 20% $TiCl_{3(aq)}$, H_2O, MeOH, r.t., 2 h, 95%.

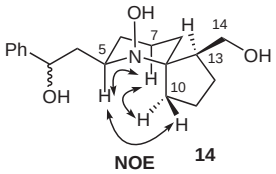
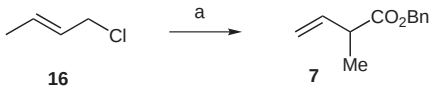


Figure 3 Selected NOE observed in azaspiro[4.5]decane **14**.

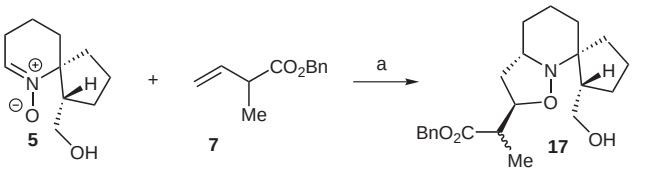
With multigram quantities of nitrone **5** in hand and proven methodology for the synthesis of 5-substituted azaspirodecanes in place we next embarked on a synthesis of core structure **4** utilising key dipolarophile **7**.[17] Alkene **7** was synthesised by quenching of the Grignard reagent derived from crotyl chloride (**16**) with carbon dioxide[18] followed by esterification of the resulting acid (Equation 3).



Equation 3 *Reagents and conditions*: (a) (i) Mg, THF, r.t. to reflux, 3 h; (ii) CO_2, THF, 51%; (iii) BnOH, DCC, DMAP, r.t., 12 h, 98%.

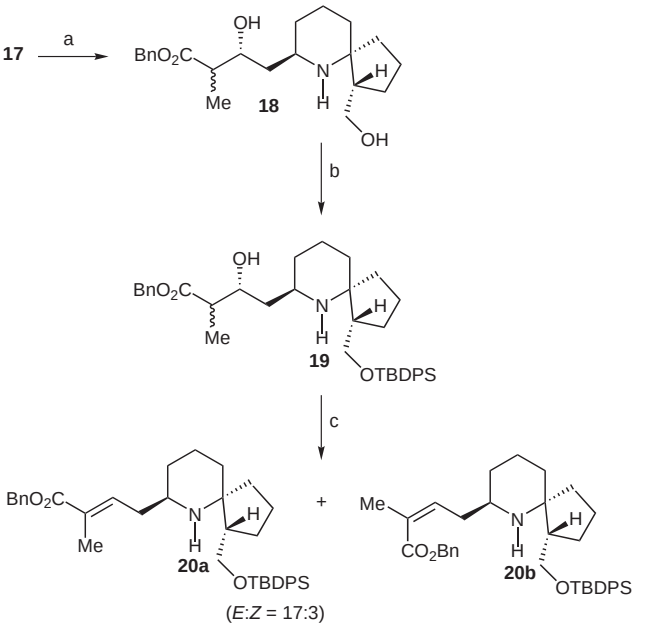
1,3-Dipolar cycloaddition of alkene **7** with nitrone **5** proceeded poorly under conventional thermal conditions using a variety of solvents and temperatures. It has been shown that the rate and yield of nitrone cycloadditions can be much enhanced under microwave irradiation[19] and irradiation of a mixture of a three-fold excess of **7** and **5** in a microwave reactor for one hour resulted in clean cycloaddition to give isoxazolidine **17** as a separable mixture of two diastereomers in 80% yield (Equation 4).[20] In this case NOE data obtained for these diastereomers confirmed that cycloaddition occurred from the α-face of nitrone **5** and proceeded with complete *exo*-selectivity.

The diastereomeric mixture **17** was then further elaborated to the pinnaic acid core structure (Scheme 3). Oxidative ring opening of **17** followed by reduction of the



Equation 4 *Reagents and conditions*: (a) MW, toluene, 165 °C, 1 h, 80%.

resulting nitrone gave azaspirodecane **18**. Selective protection of the primary hydroxy group in **18** and treatment of the resulting silyl ether **19** with two equivalents of MsCl in triethylamine led to the formation of a readily seperable 17:3 mixture of the desired *E*-α,β-unsaturated ester **20a** and the *Z*-isomer **20b**.



Scheme 3 *Reagents and conditions*: (a) (i) MCPBA, CH_2Cl_2, 0 °C to r.t., 1 h, 83%; (ii) $NaBH_4$, MeOH, 0 °C, 20 min, 68%; (iii) 20% $TiCl_{3(aq)}$, MeOH, r.t., 2 h, 94%; (b) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, r.t., 3 h, quant.; (c) 2 equiv MsCl, Et_3N, CH_2Cl_2, r.t., 2 h, 60%.

In conclusion, a concise stereoselective synthesis of the core structure of pinnaic acid has been developed utilising a novel, spirocyclic nitrone **5**. Furthermore, we have demonstrated the use of this nitrone to access a small but diverse array of C5-substituted analogues of pinnaic acid/halichlorine with both natural and unnatural stereochemistry at this position. Current efforts are directed towards the further elaboration of **20a** and the application of our synthetic strategy to the synthesis of the more challenging spiroquinolizidine core of halichlorine.

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(10) A solution of MCPBA (70%, 5.70 g, 33.0 mmol) in CH_2Cl_2 (130 mL) was added to a solution of isoxazolidine **8** (3.80 g, 22.7 mmol) in CH_2Cl_2 at 0 °C over 7 h. After the addition was complete the mixture was warmed to r.t. and stirred for a further 20 h. Then, sat. aq $Na_2S_2O_3$ (60 mL) and sat. $NaHCO_3$ (60 mL) were added and the mixture extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over anhyd $MgSO_4$, concentrated and purified by column chromatography on silica gel using CH_2Cl_2–MeOH (9.5:0.5) as eluent to give nitrone **5** as a yellow solid (3.72 g, 89%); mp 70–73 °C. IR (neat): 3410, 2961, 1642 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30–2.10 (m, 10 H), 2.45–2.52 (m, 2 H), 2.70–2.85 (m, 1 H), 3.65–3.80 (m, 2 H), 7.34 (t, 1 H, *J* = 4.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4, 24.0, 26.3, 28.3, 37.0, 38.5, 52.7, 61.1, 76.5, 142.0. HRMS (EI): *m*/*z* calcd for $[C_{10}H_{17}NO_2]^+$: 183.1253; found: 183.1259.

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(20) A 10 mL microwave reaction vessel was charged with ester **7** (0.62 g, 3.27 mmol), nitrone **5** (0.30 g, 1.63 mmol) and toluene (5 mL). The vial was sealed with a cap containing a silicon septum, loaded into the cavity of a focussed microwave oven (Discover® CEM, 250 W) and heated for 1 h at 165 °C. The reaction mixture was cooled to r.t., concentrated and purified by column chromatography on silica gel using EtOAc–hexane (3:7) as eluent to give isoxazolidine **17** as two diastereomers as colourless oils (0.48 g, 80%; dr = 1:1; diastereomers unassigned).
Diastereomer A: IR (neat): 3443, 2958, 1728 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, 3 H, *J* = 7.1 Hz), 1.30–1.63 (m, 8 H), 1.64–1.93 (m, 3 H), 1.94–2.08 (m, 2 H), 2.09–2.12 (m, 2 H), 2.66 (dq, 1 H, *J* = 7.9, 7.1 Hz), 3.45 (d, 1 H, *J* = 5.8 Hz), 3.56–3.65 (m, 2 H), 4.12 (td, 1 H, *J* = 7.9, 5.7 Hz), 5.11 (d, 2 H, *J* = 7.4 Hz), 7.30–7.38 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 19.2, 21.2, 26.4, 27.8, 30.2, 38.2, 40.0, 45.3, 45.4, 57.8, 65.4, 66.1, 69.2, 76.0, 128.0, 128.1, 128.5, 135.9, 174.3. HRMS (EI): *m*/*z* = calcd for $[C_{22}H_{31}NO_4]^+$: 373.2253; found: 373.2253.
Diastereomer B: IR (neat): 3448, 2958, 2931, 1727 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.11 (d, 3 H, *J* = 7.0 Hz), 1.23–1.68 (m, 10 H), 1.69–1.96 (m, 2 H), 1.97–2.08 (m, 2 H), 2.09–2.15 (m, 2 H), 2.70 (dq, 1 H, *J* = 8.5, 7.1 Hz), 3.45 (d, 1 H, *J* = 6.3 Hz), 3.54–3.64 (m, 2 H), 4.20 (td, 1 H, *J* = 8.5, 6.0 Hz), 5.14 (d, 2 H, *J* = 4.9 Hz), 7.29–7.36 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7, 19.2, 21.1, 26.4, 27.7, 29.6, 38.0, 39.1, 45.2, 45.4, 57.9, 65.4, 66.0, 69.1, 76.3, 127.9, 128.0, 128.4, 136.1, 174.5. HRMS (EI): *m*/*z* calcd for $[C_{22}H_{31}NO_4]^+$: 373.2253; found: 373.2256.