A Versatile Chiral Pyrrolidine Aldehyde Building-Block for Synthesis and Formal Synthesis of *ent*-Nakadomarin A

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Dedicated to Prof. Gerry Pattenden on the occasion of his 70th birthday

Abstract: A stable, simple to synthesise and versatile chiral aldehyde building-block has been developed, its reactivity in Wittig, Horner–Wadsworth–Emmons and Grignard reactions investigated, and its use is demonstrated in a highly efficient synthesis of an intermediate in Dixon's synthesis of nakadomarin A.

Key words: aldehyde, building-block, nakadomarin, manzamine

Garner's aldehyde[1] is a very flexible chiral building-block that has seen use in over 200 publications since its debut in the literature in the mid 1980s.[2] Garner's aldehyde has been particularly useful in natural product synthesis, where it has been used to generate a wide range of chiral amine motifs.[3] Due to its nature, Garner's aldehyde functions as a three-carbon building-block and, therefore, if a chiral amine-containing ring is required in the synthesis, the ring will need to be synthesized from the functionality in place – often requiring several steps, protecting group manipulations and redox operations.

As there are a large number of natural products containing pyrrolidine rings with substituents at the 1-, 2-, 3- and 5-positions, we were attracted to the idea of developing a chiral building-block based on a pyrrolidine ring, such that this might serve as a versatile entry into many of these natural product systems. Figure 1 shows some representative natural products, manzamine A,[4] stemonine,[5] nirurine[6] and berkleyamide A.[7]

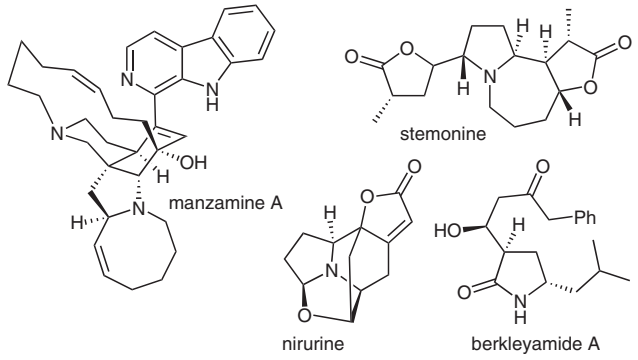
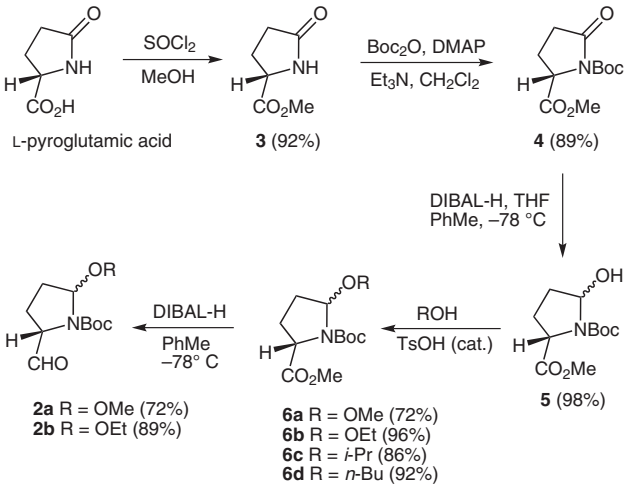


Figure 1

An inspection of the literature for pyroglutamate-derived chiral building-blocks provides three potential answers to the problem. Several reports of the use of pyroglutamic aldehyde have been disclosed.[8] In addition, several syntheses of *N*-Boc pyroglutamic aldehyde have been reported in the literature.[9] However, when we tried to use these materials in our own laboratories, we found them to be very unstable (too much so to purify), and both underwent epimerization upon isolation. A third, potentially less reactive building-block is that used by Clive in 1998 in a synthesis of epibatidine.[10] The pyroglutamic acid derived *N*-Boc hemiaminal aldehyde **2**, looked very interesting to us, because the aldehyde should be no more reactive or susceptible to epimerization than Garner's aldehyde, the nitrogen is protected with a reliable and simple to remove protecting group, and the lactam motif of the pyroglutamic acid has been transformed into a hemiaminal, which is a function that could be potentially transformed into either an enamine or an *N*-acyl iminium or can be reoxidised back to a lactone. We thus initially set out to investigate the range of pyroglutamate-derived hemiaminal aldehydes by synthesizing methyl, ethyl, isopropyl and *n*-butyl hemiaminals. The synthesis of these is outlined in Scheme 1.



Scheme 1

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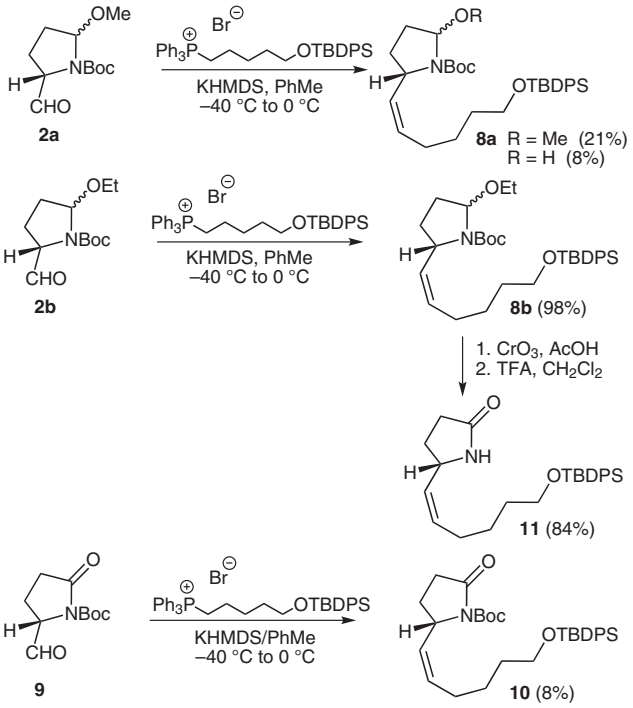
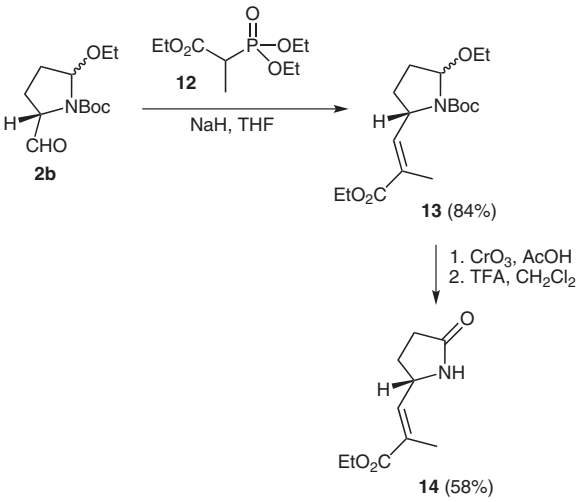
Both the methyl (**2a**) and ethyl (**2b**) building-blocks were easily formed and were stable at room temperature over a number of days; the isopropyl (**2c**) and *n*-butyl (**2d**) building-blocks did not undergo complete reduction in the final DIBAL-H step. In all cases, the ratio of diastereomers was 2:1.

We next looked at a typical Wittig reaction of aldehydes **2a** and **2b** using the protected alcohol-containing phosphonium salt **7** (Scheme 2). It was found that the methyl hemiaminal **2a** was relatively unstable under the reaction conditions, and thus only a very poor (21%) yield of the olefin product was obtained. In contrast, the ethyl hemiaminal **2b** was found to be an excellent substrate for the Wittig olefination, with alkene **8b** being formed in 98% yield. As a comparison, aldehyde **9**, which has previously been reported in the literature,[9] gave just 8% yield of the olefin product **10** when treated under the same reaction conditions. Indeed, this aldehyde proved to be very unstable even over a few hours, and is thus not a practical synthetic building-block. Having achieved olefination, we wished to discover whether the hemiaminal could be reoxidised to the lactam and found that reoxidation was, indeed, facile using chromium trioxide in acetic acid. If glacial acetic acid was used, the BOC protecting group was partially deprotected, and thus subsequent treatment of the resulting mixture with TFA gave lactam **11** in 84% yield over the two steps. On one occasion it was found that treatment of **8b** with chromium trioxide in a mixture of AcOH and H_2O (5:1) led directly to lactam **11** in 90% yield, however, this reaction proved to be unreliable, giving yields in the range 44–90%, so for further studies we decided to use the reliable two-step procedure.



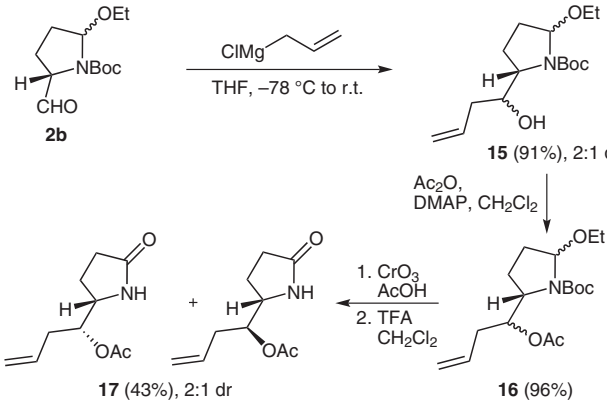
Scheme 2

With this excellent result, we decided to investigate a Horner–Wadsworth–Emmons reaction of **2b** (Scheme 3). Phosphonoacetate **12** was deprotonated with sodium hydride and reacted with aldehyde **2b**, giving the olefination product **13** in an excellent 84% yield as a single *E*-isomer. As before, it was found that the lactam functionality could be reintroduced by treatment of the hemiaminal **13** with chromium trioxide in acetic acid followed by treatment with TFA.



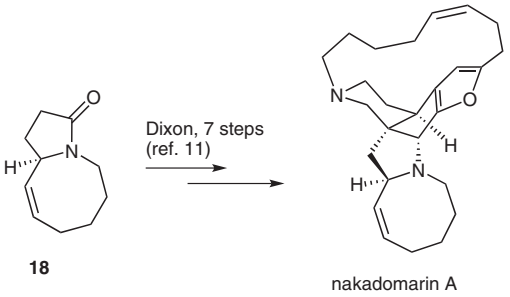
Scheme 3

As the aldehyde functionality of aldehyde **2b** was proving to be a good substrate for olefination chemistry, we decided to investigate its potential in Grignard addition chemistry (Scheme 4). Thus, aldehyde **2b** was treated with allyl magnesium chloride in THF at low temperatures. We found that Grignard addition proceeded smoothly to give a diastereomeric mixture of alcohols. To gauge the stereoselectivity of the reaction, we protected the alcohol functionality of **15** with an acetate group before oxidising **16** to the lactam. This procedure resulted in a 2:1 mixture of diastereomeric alcohols, suggesting that a reasonable degree of substrate control is afforded by the chiral aldehyde in the Grignard addition.



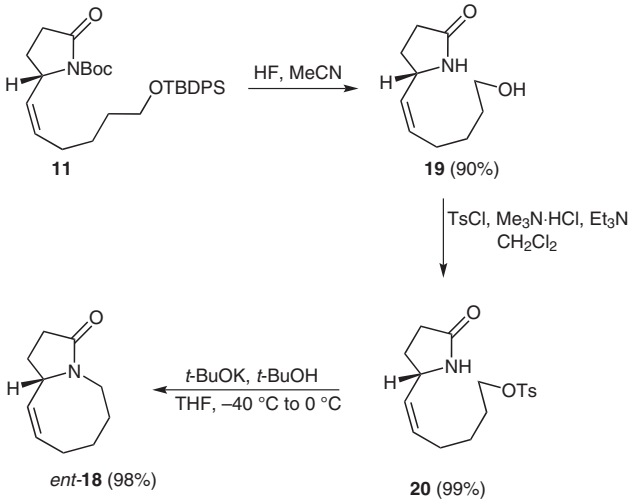
Scheme 4

Having investigated a number of reaction types for aldehyde substrate **2b**, we decided to investigate its suitability as a building-block for a synthesis of the manzamine alkaloids. Dixon used lactam **18** in his seminal recent synthesis of nakadomarin A,[11] which is a member of the manzamine family of alkaloids (Scheme 5).



Scheme 5

Thus, the lactam **11** was transformed in a three-step procedure into the 5/8 C/E ring system of the manzamine alkaloids, generating a potentially useful building-block for future synthetic efforts towards these topical natural products (Scheme 6). The first step of the three-step procedure involved deprotection of the alcohol functionality by treatment of **11** with HF in acetonitrile. Conversion of the revealed alcohol **19** into the tosylate **20** was found to proceed in near quantitative yield using Tanabe's procedure.[12] Eight-membered ring-closure to the 5,8-azabicycle *ent*-**18** was achieved[13] using potassium *tert*-butoxide in THF at –40 °C in two hours, followed by warming to room temperature overnight. The reaction proceeded in an outstanding 98% yield, giving an overall yield for the synthesis of *ent*-**18** of 49.2% from L-pyroglutamic acid. This compares well with Dixons synthesis of **18**, which proceeds in 29.2% yield from the tosylate of D-pyroglutamic alcohol (which also requires several synthetic steps from pyroglutamic acid). Thus, our synthesis could also be perceived as a formal synthesis of *ent*-nakadomarin A.



Scheme 6

In conclusion, we have developed a stable, easily synthesised chiral aldehyde building-block[13] for the synthesis of chiral 5-substituted pyrrolidin-2-ones.[14] We have also used this chiral aldehyde to prepare a useful intermediate for the synthesis of the manzamine family of alkaloids, including nakadomarin A, in very high yields. Further studies on the reactivity of chiral aldehyde **2b** are ongoing and will be reported in due course.

Acknowledgment

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(13) Compound **18** has also been reported previously in racemic form, see: Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Patzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7521.
Data for compound **20**: $R_f = 0.3$ (EtOAc); $[\alpha]_D^{22}$ +86.6 (*c* 1.0, $CHCl_3$); IR (thin film): 1683 (lactam), 1485 (olefin) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.80 (dt, *J* = 10.6, 8.5 Hz,

1 H), 5.41 (dd, *J* = 10.6, 6 Hz, 1 H), 4.26 (dt, *J* = 6.5, 6 Hz, 1 H), 3.42 (t, *J* = 5.4 Hz, 2 H), 2.50–2.05 (m, 6 H), 1.91–1.70 (m, 2 H), 1.68–1.49 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4, 131.9, 130.4, 56.8, 41.0, 30.9, 27.0, 26.4, 25.9, 25.2; MS (CI): *m*/*z* (%) = 166 (100) $[M + 1]^+$, 152 (23); HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{16}NO$: 166.1232; found: 166.1232. Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.82; H, 9.28; N, 8.51.

(14) Procedure for the synthesis of chiral aldehyde **2b**: A solution of pyroglutamic acid methyl ester (**3**; 25.7 g, 0.180 mol) in anhydrous CH_2Cl_2 (500 mL) was cooled to 0 °C under an atmosphere of argon. The reaction solution was treated with DMAP (2.19 g, 0.018 mol), Et_3N (27.0 mL, 0.198 mol) and $(Boc)_2O$ (41.2 g, 0.189 mol). The solution was allowed to warm to r.t. and stirred for 16 h. HCl (1 M, 300 mL) was added, and the organic layer was separated, washed with sat. $NaHCO_3$ (300 mL), dried over Na_2SO_4, and evaporated in vacuo. Recrystallisation from hexanes–EtOAc gave *N*-*tert*-butyloxycarbonylpyroglutamic acid methyl ester (**4**; 38.74 g, 89%) as colourless needles. Mp 58–65 °C; $[\alpha]_D^{20}$ –30 (*c* 2.06, $CHCl_3$); IR (nujol): 1763, 1703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.61 (dd, *J* = 9.4, 3 Hz, 1 H), 3.75–3.74 (m, 3 H), 2.65–2.55 (m, 1 H), 2.50–2.42 (m, 1 H), 2.34–2.23 (m, 1 H), 2.04–1.96 (m, 1 H), 1.45–1.41 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 172.1, 149.3, 83.8, 59.0, 52.8, 31.4, 28.1, 21.7; MS: *m*/*z* (%) = 261 (98) $[M + NH_4]^+$, 144 (100); Anal. Calcd for $C_{11}H_{17}NO_5$ $[M + NH_4]^+$: 261.1445. Found: 261.1443. A solution of *N*-*tert*-butyloxycarbonylpyroglutamic acid methyl ester (**4**; 34.12 g, 0.14 mol) in anhydrous THF (350 mL) was cooled to –78 °C under an atmosphere of argon. DIBAL-H (1 M in toluene, 150 mL) was added over a period of 1 h. The resulting solution was stirred at –78 °C for a further 2 h, before being quenched by the addition of anhydrous MeOH (30 mL). After warming to 0 °C, a 1 M aqueous solution of Rochelle's salt (600 mL) and EtOAc (300 mL) were added and the biphasic solution was stirred vigorously for 2 h. The organic layer was separated, dried over Na_2SO_4 and evaporated to give 1-(*tert*-butyloxycarbonyl)-5-(hydroxy)pyrrolidine-2-carboxylic acid methyl ester (**5**; 33.17 g, 98%) as a 2:1 mixture of diastereomers, as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.63–5.39 (m, 1 H), 4.60–4.17 (m, 1 H), 3.75–3.66 (m, 3 H), 2.64–1.83 (m, 4 H), 1.45–1.36 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 82.52–81.20, 70.71, 59.5, 52.5, 33.4, 28.5, 28.1, 27.3; MS: *m*/*z* (%) = 263 (5) $[M + NH_4]^+$, 245 (40), 128 (100); Anal. Calcd for $C_{11}H_{19}NO_5$ $[M + NH_4]^+$: 263.1601. Found: 263.1604. A solution of 1-(*tert*-butyloxycarbonyl)-5-(hydroxy)pyrrolidine-2-carboxylic acid methyl ester (**5**; 33.12 g, 0.135 mol) in EtOH (600 mL) was treated with PTSA·H_2O (1.85 g, 9.73 mmol), and the solution was allowed to stand for 18 h. The solvent was then removed under reduced pressure and the resulting residue was partitioned between EtOAc (300 mL) and sat. aq $NaHCO_3$ (300 mL). The organic layer was separated, dried over Na_2SO_4 and evaporated in vacuo to give 1-(*tert*-butyloxycarbonyl)-5-(ethoxy)pyrrolidine-2-carboxylic acid methyl ester (**6**; 35.90 g, 96%) as a 2:1 mixture of diastereomers, as a colourless oil. Bp 92°C (0.15 Torr); IR: 1755, 1703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.38–5.20 (m, 1 H), 4.37–4.22 (m, 1 H), 3.72 (s, 3 H), 3.66–3.49 (m, 2 H), 2.48–1.76 (m, 4 H), 1.41 (s, 9 H), 1.08 (t, *J* = 3.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 87.3, 64.0, 59.0, 52.07, 51.92, 32.5, 30.6, 27.5, 15.3; MS: *m*/*z* (%) = 273 (6) $[M + H]^+$, 228 (100); Anal. Calcd for $C_{13}H_{24}NO_5$ $[M + H]^+$: 274.1664. Found: 274.1654. A solution of 1-(*tert*-butyloxycarbonyl)-5-(ethoxy)pyrrolidine-2-carboxylic acid methyl ester (**6**; 16.3 g, 59.7 mmol) in anhydrous toluene (100 mL) was cooled to –78 °C under an atmosphere of argon. DIBAL-H (1 M in toluene, 71.6 mL) was added over a period of 30 min by cannula (dribbling down the inside of the flask). The resulting solution was stirred at –78 °C for a further 6 h before being quenched by the addition of anhydrous MeOH (10 mL). After warming to 0 °C, a 1 M aqueous solution of Rochelle's salt (300 mL) and EtOAc (100 mL) were added, and the biphasic solution was stirred vigorously for 2 h. The organic layer was separated, dried over Na_2SO_4, and evaporated in vacuo to give aldehyde **2b** (12.95 g, 89%) as a colourless oil after distillation (bp 96–98 °C, 0.2 Torr); IR: 1739, 1698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.55–9.36 (m, 1 H, 5-H), 5.39–5.18 (m, 1 H), 4.35–4.00 (m, 1 H), 3.72–3.48 (m, 2 H), 2.48–2.00 (m, 2 H), 1.98–1.63 (m, 2 H), 1.47–1.38 (m, 9 H), 1.09 (t, *J* = 7 Hz, 3 H); ^{13}C (100 MHz, $CDCl_3$): δ = 200.43, 200.31, 166.70, 88.0, 81.5, 81.2, 65.5, 64.4, 32.0, 28.4, 25.0, 15.5; MS: *m*/*z* (%) = 244 (10) $[M + H]^+$, 198 (62); Anal. Calcd for $C_{12}H_{22}NO_4$ $[M + H]^+$: 244.1549. Found: 244.1552.