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Pyrrolizidine alkaloids. A concise entry to (−)-pyrrolam A †

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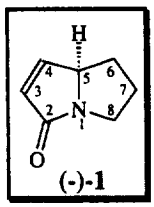
Abstract: The synthesis of (−)-pyrrolam A starting from (*R*)-prolinol is described. The key step is the dehydrative alkylation of a conveniently protected (*R*)-prolinol with triethyl methanetricarboxylate under the conditions of the Mitsunobu reaction. © 1997 Elsevier Science Ltd. All rights reserved.

The genus *Streptomyces* has been shown to produce a variety of interesting and biologically significant secondary metabolites. Chemical screening of the culture broth of the ascomycete *Streptomyces olivaceus* (strain Tü3082)[1] has since resulted in the isolation of pyrrolams, an hitherto unknown family of bicyclic lactams structurally related to the pyrrolizidine alkaloids.[2] In particular, unique among the pyrrolams, (−)-pyrrolam A **1** contains a double bond embodied in the γ-lactam ring.



(-)-1

Many pyrrolizidine alkaloids exhibit hepatotoxic, mutagenic and carcinogenic activities that appear to be related to the presence of the double bond.[3] Thus, pyrrolam A **1** may provide a lead for further chemical modification and serve as useful tool for structure–activity relationship (SAR) studies. We report herein a concise synthesis of (−)-**1** that is efficient, thus allowing good reproducibility and material throughput. In previous work we showed that triethyl methanetricarboxylate (TEMT) can act as an efficient protonated C-nucleophile (pK_{AH} 7.5) under Mitsunobu conditions[4] (eq. 1), thereby representing a suitable surrogate for diethyl malonate.[5]

$$R{-}OH + HC(COOEt)_3 \xrightarrow[DEAD]{TPP} R{-}C(COOEt)_3 \qquad \text{(Eq. 1)}$$

From this finding, we selected the two-carbon homologation of (*R*)-prolinol **2** as the pivotal step *en route* to (−)-**1**. This reaction should lead to our key intermediate **6**[6] which can be converted into the ultimate target by simple oxidation adjustment (Scheme 1).

After *N*-protection [2-(*tert*-butoxycarbonyloxymino)-2-phenylacetonitrile (BOC-ON)®, CH_2Cl_2, r.t.] of **2**, *N*-BOC-prolinol **3** was subjected to the Mitsunobu dehydrative alkylation protocol involving stirring with 1.5 equiv of TEMT and 2.0 equiv of TPP in Et_2O at r.t. for 10h in the presence of 2.0 equiv. of DEAD to form the *N*-BOC-triester **4** in 58% overall yield for the two steps. Protection of nitrogen was mandatory to avoid the formation of the 3,5-fused bicyclic compound(s) during the Mitsunobu reaction.[7]

With **4** in hand, we found it more convenient to carry out the triple sequence (**4**→**7**) in one vessel without isolating the intermediates **5** and **6**. Thus, **4** was first subjected to the TFA (4.5 equiv) in

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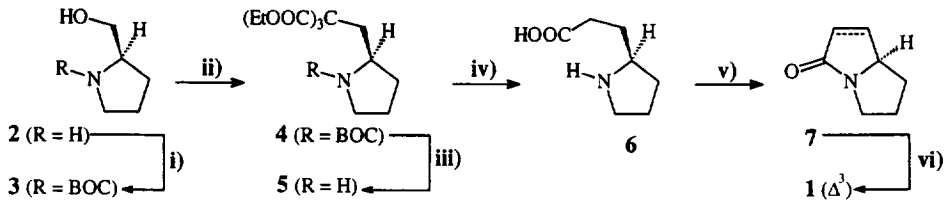

Scheme 1. *Reagents and conditions*: i) BOC-ON®, CH_2Cl_2, r.t.; ii) TEMT, TPP, DEAD, Et_2O, r.t.; iii) TFA, CH_2Cl_2, r.t.; iv) 12N HCl, reflux; v) HMDS, TMSCl (cat.), MeCN, reflux; vi) LDA, THF (−78°C), PhSeCl, then H_2O_2, THF, 0°C.

CH_2Cl_2 at r.t. followed by treatment of the crude reaction mixture (after removal of solvent and TFA) with an excess of 12 N HCl (reflux, 12 h). Simple evaporation of the reaction mixture allowed the recovery of the crystalline hydrochloride of **6** which could be used without further purification. Subsequent cycloamidation was accomplished by refluxing **6**·HCl in MeCN (8 h) in the presence of HMDS (10 equiv) and TMSCl (cat.).[8] By using this one-pot protocol, (*R*)-(+)-3,4-dihydropyrrolam A **7** $[\alpha]_D^{20}$ +31.5 (*c* 0.7; $CHCl_3$) [Lit.[1] +23.6; Lit.[9] −32.5 for *ent*-**7**] was obtained in 57% yield from **4**. Subsequently, all that remained to complete the synthesis was the installation of the double bond in a regioselective manner. The formation of the enolate of **7** with LDA (2 equiv) in THF (−78°C), followed by trapping with PhSeCl (1.5 equiv.) resulted in the phenylselenium intermediate that, without isolation, was oxidized with H_2O_2 at 0°C[10] to give (*R*)-(−)-pyrrolam A **1** $[\alpha]_D^{20}$ −26.3 (*c* 0.8; $CHCl_3$).[11] The sign of the specific rotation and absolute configuration of the synthetic molecule matched that of the natural product[1] $[\alpha]_D^{20}$ −29.3 *vs* +25.7 for *ent*-**1**.[9]

In conclusion, we have accomplished a novel synthesis of enantiomerically pure (−)-pyrrolam A **1** from (*R*)-prolinol in six steps and 30% overall yield. Furthermore, in only two steps was purification by column chromatography required, proving it to be a particularly efficient route to this alkaloid.

Typical procedure for Mitsunobu-type dehydrative alkylation

Compound **3** (1.0 mmol), triethyl methanetricarboxylate (1.5 mmol) and triphenylphosphine (2.0 mmol) are dissolved in 10 ml Et_2O (freshly distilled over sodium-benzophenone), and stirred under N_2 atmosphere at r.t. To this solution is slowly added (30 min) diethyl azodicarboxylate (2.0 mmol, dissolved in 3 ml Et_2O) and the reaction mixture is stirred for 10 h at r.t. The white precipitate is filtered off and washed with cold Et_2O. Filtrate and washings are combined and washed twice with 5% NaOH (to remove TEMT unreacted), twice with distilled water, and evaporated. The residue is submitted to flash chromatography (hexane/ethyl acetate 7/3) to give pure compound **4** (68%). Longer reaction times proved to be detrimental to the yield; treatment of compound **3** with a larger excess of the reagents didn't improve the yield of the reaction.

Selected data for compound **4–7**:

*(R)-2-[2-(*N*-tert-Butoxycarbonylpyrrolidinyl)]-1,1,1-tris(ethoxycarbonyl)ethane* **4**

Colourless thick oil, $[\alpha]_D^{20}$ +20.1 (*c* 1.49, CH_3OH); ^{1}H-NMR (400 MHz, $CDCl_3$) 4.24 (q[6H] J=7.1 Hz), 4.10 (m[1H]), 3.30 (m[2H]), 2.74 (dd[1H] J_1=14.3 Hz, J_2=3.8 Hz), 2.19 (dd[1H] J_1=14.3 Hz, J_2=10.4 Hz), 1.9–1.5 (m[4H]), 1.43 (s[9H]), 1.26 (t[9H] J=7.10 Hz); ^{13}C-NMR (100.3 MHz, $CDCl_3$) 167.0, 154.7, 79.8, 64.4, 62.5, 54.8, 46.1, 36.0, 30.3, 28.8, 23.4, 14.2. CI-MS *m/z* 416 (MH^+, Calc. for $C_{20}H_{33}NO_8$=415 a.m.u.); Elem. Anal. %Found (%Calc.) C 57.96% (57.81%), H 8.00% (8.01%), N 3.24% (3.37%).

(R)-2-(2-Pyrrolidinyl)-1,1,1-tris(ethoxycarbonyl)ethane **5**

Colourless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) 4.18 (q[6H] J=7.3 Hz), 3.7–3.2 (m[3H]), 2.2–1.4 (m[6H]), 1.28 (t[9H] J=7.4 Hz); CI-MS (isobutane) *m/z* 316 (Calc. for $C_{15}H_{25}NO_6$=315 a.m.u.); Elem. Anal. %Found (%Calc.) C 57.01% (57.13%), H 7.88% (7.99%), N 4.31% (4.44%).

(R)-3-(2-Pyrrolidinyl)propanoic acid hydrochloride **6**

Colourless needles, m.p. 123°C (dec., lit.[6c] 117–118°C (dec.)); $[\alpha]_D^{20}$ +6.8 (*c* 0.56, H_2O, lit.[6a] −7.5 for *ent*-**6**·HCl); ^{1}H-NMR (400 MHz, D_2O) 3.43 (q[1H] J=7.6 Hz), 3.16 (m[2H]), 2.38 (t[2H] J=6.3 Hz), 2.07 (m[1H]), 1.88 (m[4H]), 1.51 (m[2H]); ^{13}C-NMR (100.3 MHz, D_2O) 179.5, 62.6, 47.9, 33.4, 32.1, 29.2, 25.6. FAB$^+$-MS (glycerol) *m/z* 144 (Calc. for $C_7H_{13}NO_2$=143 a.m.u.); Elem. Anal. %Found (%Calc. per $C_7H_{13}NO_2$·HCl) C 46.98% (46.80%), H 7.77% (7.85%), N 7.69% (7.80%).

(R)-1-Azabicyclo[3.3.0]octan-2-one **7**

Pale yellow oil; $[\alpha]_D^{20}$ +31.5 (*c* 0.7, $CHCl_3$; Lit.[1] +23.6; Lit.[9] −32.5 for *ent*-**7**); ^{1}H-NMR (200 MHz, $CDCl_3$) 3.90 (m[1H]), 3.55 (dt[1H] J_1=11.5 Hz, J_2=7.5 Hz), 3.06 (m[1H]), 2.75 (dddt[1H] J_1=16.6 Hz, J_2=10.0 Hz, J_3=9.0 Hz, J_4=1.0 Hz), 2.45 (ddd[1H] J_1=16.6 Hz, J_2=9.4 Hz, J_3=2.1 Hz), 2.30 (dddd[1H] J_1=15.8 Hz, J_2=2.6 Hz, J_3=8.9 Hz, J_4=1.9 Hz), 2.18–1.99 (m[3H]), 1.73 (dddd[1H] J_1=20.5 Hz, J_2=12.7 Hz, J_3=9.4 Hz, J_4=7.7 Hz), 1.33 (m[1H]); ^{13}C-NMR (50.2 MHz, $CDCl_3$) 174.8, 62.0, 40.8, 35.3, 32.1, 27.0, 26.9; CI-MS *m/z* 126 (Calc. for $C_7H_{11}NO$=125 a.m.u.); Elem. Anal. %Found (%Calc.) C 66.99% (67.17%), H 8.86% (8.86%), N 11.25% (11.19%).

(R)-1-Azabicyclo[3.3.0]oct-3-ene-2-one **1**

Colourless solid, m.p. 59°C (lit.[1] 62°C); $[\alpha]_D^{20}$ −26.3 (*c* 0.8, $CHCl_3$; Lit.[1] −29.3; Lit.[9] +25.7 for *ent*-**1** (93.5% ee)); ^{1}H-NMR (200 MHz, $CDCl_3$); 7.19 (dd[1H] J_1=6.0 Hz, J_2=1.8 Hz), 6.06 (dd[1H] J_1=5.8 Hz, J_2=1.7 Hz), 4.28 (m[1H]), 3.62–3.18 (m[2H]), 2.45–2.20 (m[2H]), 2.13 (m[1H]), 1.25 (m[1H]); ^{13}C-NMR 175.6, 149.2, 128.5, 68.2, 42.0, 29.9, 29.1(50.2 MHz, $CDCl_3$); CI-MS *m/z* 124 (Calc. for C_7H_9NO=123 a.m.u.); Elem. Anal. %Found (%Calc.) C 68.40% (68.27%), H 7.29% (7.37%), N 11.06% (11.37%).

Acknowledgements

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11. The compound **1** was somewhat unstable; the characterization was made immediately after the preparation. The compound **1**, and to a minor extent the compound **7**, decomposed either at r.t. or at −20°C, giving rise to yellow mixtures, not analyzed.

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