ENANTIOSELECTIVE SYNTHESIS AND ABSOLUTE CONFIGURATION OF (-)-PULO'UPONE BY ASYMMETRIC INTRAMOLECULAR DIELS-ALDER REACTION ¹⁾

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<u>Abstract</u>: (-)-Pulo'upone (<u>1</u>) was synthesized via an asymmetric, bornane-10,2-sultam- directed, intramolecular Diels-Alder reaction ($\underline{3} \rightarrow \underline{2}$) and a 2-pyridylcuprate/allylacetate coupling ($\underline{18} \rightarrow \underline{1}$). The ($\delta'R$, 9'S, 13'R, 14'R)configuration of (-)-<u>1</u> follows from an X-ray diffraction analysis of the cycloaddition product <u>2</u>.

Pulo'upone, isolated in small quantity from the caphalaspidean mollusk *Philinopsis speciosa*, has been assigned structure <u>1</u> on the basis of spectral evidence ²). A very recent communication described a synthesis of racemic <u>1</u>³). Although the natural product was reported to be optically active ($[\alpha]_D = -10^\circ$, c = 0.2, hexane) its absolute configuration is unknown.

In connection with our work on asymmetric *inter-* and *intra*-molecular Diels-Alder reactions ⁴⁾ of N-enoylbornane-10,2-sultam dienophiles ^{4,5)} we present here an enantioselective synthesis of (-)-1 which establishes its absolute configuration.

Scheme 1



Disconnective analysis (Scheme 1) shows the crucial intramolecular Diels-Alder step $^{6)} \underline{3} \rightarrow \underline{2}$ where the simultaneous generation of the four stereogenic centers C-6', C-9', C-13', and C-14' was to be directed by the chiral sultam auxiliary X^* .

The realization of this plan is depicted in the Scheme 2.

Wittig-Horner reaction of aldehyde $4^{(7)}$ with phosphonate $5^{(8)}$ and chromatographic removal of the minor (2E, 4Z)- isomer gave pure (E,E)- dienoate $6^{(9)}$ (47%). Reduction of ester 6 with diisobutylaluminum hydride and acetylation of the crude dienol furnished $7^{(9)}$ in 94% overall yield. Li₂CuCl₄-catalyzed coupling ¹⁰⁾ of dienylacetate 2 with organomagnesium bromide 8 gave acetal $9^{(9)}$ which on acidic hydrolysis and resilylation of the crude alcohol furnished aldehyde $10^{(9)}$. To generate the dienophilic (E)- double bond directly from aldehyde 10 the chiral acylphosphonate $11^{(9)}$ was prepared by chloroacetylation of sultam 12 and subsequent Arbusov reaction with triethylphosphite. Lithium chloride- mediated Horner reaction ¹¹⁾ of phosphonate 11 with aldehyde 10 provided the pure (E,E,E)- trienoylsultam $2^{(9,12)}$ (oil, 89%).



(a) 5 (1.05 equiv), LDA (1.05 equiv), THF. -78° \rightarrow RT; add 4 (1.0 equiv), -40°, 10 min \rightarrow RT. (b) *i*Bu₂AlH (2.9 equiv), hexane/Et₂O-1:1, 0°, 2 h; RT, 1 h. (c) Ac₂O/pyridine (excess), RT, 2 h. (d) add $\frac{8}{2}$ (1.6 equiv) over 2 h to $\frac{7}{L_{12}CuCl_4}$ (0.035 equiv), -10°, then - 10°, 30 min. (e) 0.38 <u>N</u> HCl in acetone/H₂O 2:1, RT, 5 h. (f) TBDMS-Cl (2 equiv), NEt₃ (1.3 equiv), DMAP (0.15 equiv), RT, 2 h. (g) 12 (1 equiv), *n*-BuLi (1.1 equiv), THF -78°; ClCH₂COCl (1.1 equiv), -78° \rightarrow RT over 30 min; (h) P(OEt)₃, neat, 140°, 5 h. (i) <u>11</u> (1.5 equiv), DBU (1.0 equiv), <u>10</u> (1.0 equiv), LiCl (1.3 equiv), MeCN, RT, 2 h. (j) triene 3 (1 equiv), Me₂AlCl (2 equiv), CH₂Cl₂, -20°, 80 h; add Me₂AlCl (1 equiv), -10°, 50 h; sat aq. NaHCO₃, -10°. (k) BF₃.Et₂O (5 equiv), CH₂Cl₂, RT, 1 h. (l) LiH (4.4 equiv), DMF, RT, 16 h. (m) MeLi (1.5 equiv), lactone <u>13</u> (1 equiv), Et₂O, -78°, 30 min. (n) TsCl (3 equiv) in pyridine, 0°, 10 h, +10°, 5 h. (o) NaI (6 equiv), acetone, 35°, 3 h. (p) *n*-Bu₄N⁴CN⁻¹ (4 equiv), CH₂Cl₂, 40°, 2 h. (q) *i*-Bu₂AlH (3 equiv), Et₂O, 0°, then RT, 1 h, aq. workup. (r) Ph₃P=CHCOOMe (4 equiv), 60°, 6 h. (s) *i*-Bu₂AlH (4.3 equiv), -70°, CH₂Cl₂. (t) Ac₂O (1.5 equiv), pyridine (2.7 equiv), DMAP (cat.), 0°, 2 h, RT, 1 h. (u) 2-bromopyridine (19.6 equiv), *n*-BuLí (18.7 equiv), Et₂O, -60°, 1 h; CuL*n*-Bu₃P (9.3 equiv), Et₂O, -60°, 30 min; add cuprate solution to <u>18</u> (1 equiv), Et₂O, -40° \rightarrow 0° over 1.1 h. (v) oxalylchloride (16.7 equiv), DMSO (60 equiv), CH₂Cl₂, -60°, 2 min; sec. alcohol (1 equiv) $\rightarrow -50°$, 25 min; NEt₃ (38 equiv), -60°, 10 min; RT, 15 min, chromatography.

Proceeding to the crucial Diels-Alder step, we were pleased to find that treatment of triene 3 with the mild Lewis acid Me_2AlCl in CH_2Cl_2 at -20° to -10° afforded the crude *endo*-cycloaddition product 2 in 71% yield and in 93% d.e., conveniently raised to ~100% d.e. by crystallization (hexane/EtOAc 9:1) ¹³). No trace of the corresponding *exo*-adduct could be detected in the crude mixture or in the mother liquor (GC, ¹H-NMR).

Crystallized 2^{9} (m.p. 223 - 224°, 63% from 3) was unambigously assigned the expected ^{5b}) (6'R, 9'S, 13'R, 14'R)-configuration via an X-ray-diffraction analysis ¹⁴) considering the known configuration of the bornane moiety as well as a least-squares refinement of the absolute structure parameter x^{15} (Scheme 3).

Scheme 3



The conformation of $\underline{2}$ in the solid state shows *inter alia* the sterically encumbered carbonyl group which explains the relatively slow hydrolytic cleavage of the auxiliary group. However, the sultam moiety was readily removed by an intramolecular displacement, thus setting the stage for elaboration of the side-chains.

Desilylation ¹⁶⁾ of 2 gave a primary alcohol ⁹⁾ (m.p. 200°, 99%) which on treatment with LiH underwent smooth lactonization to afford, after chromatography, sultam <u>12</u> (90%) and lactone <u>13</u> ⁹⁾ (89%). Slow addition of methyllithium to lactone <u>13</u> at -78° and O-tosylation of the resulting ketoalcohol/lactol mixture furnished ketotosylate <u>14</u> ⁹⁾ (m.p. 74 - 75°, 80% from <u>13</u>) which was converted to iodide <u>15</u> ^{9,17)} (m.p. 52°, 91%).

For the remaining task, *i.e.* elaboration of the (E)-allyl-2-pyridine unit, we focussed our attention on the coupling of a 2-pyridyl cuprate with an (E)-allylacetate ¹⁸). To this end, iodide <u>15</u> was treated with n-Bu₄N⁺CN⁻¹⁹) to give nitrile <u>16</u>⁹ (m.p. 86°, 94%) which on reduction with *i*-Bu₂AlH afforded lactol <u>17</u>⁹) (stereoisomer mixture, 75%). Wittig reaction of <u>17</u> with carbomethoxymethylenetriphenylphosphorane ²⁰), reduction of the resulting enoate with *i*-Bu₂AlH followed by acetylation ²¹) gave allylacetate <u>18</u>⁹ (79% from <u>17</u>. E/Z = 94:6, C-15-epimers 3:1). Coupling of allylacetate <u>18</u> with di-(2-pyridyl)copperlithium ²²) proceeded smoothly with complete retention of the (E)-configuration to give, after Swern-oxidation ²³), pure (-)-pulo'upone (<u>1</u>)⁹ in 81% yield (from <u>18</u>). Synthetic (-)-<u>1</u> showed IR, ¹H-NMR and MS spectra identical to those of the natural product but an optical rotation of $[\alpha]_D = -156.2^\circ$ (c = 0.2, hexane, +20°C).

In summary, by achieving the total synthesis of pure (-)-pulo'upone (1) its absolute configuration and correct optical rotation have been determined. The strategic application of an intramolecular asymmetric Diels-Alder reaction highlights the practical and immensely versatile π -face differentiating bias of the bornane-10,2-sultam auxiliary ²⁴).

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- 12) No trace of the (2Z)-isomer of 3 could be detected by ¹H-NMR.
- 13) The diastereomeric excess (d.e.) of <u>2</u> was determined by capillary GC. The minor (6'S, 9'R, 13'S, 14'S)- isomer, m.p. 140 - 142°, isolated from the mother liquor was fully characterized ref 9).
- 14) Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre. Structure factors may be obtained from one of us (G.B.). The crystals (MeOH/CH₂Cl₂) are triclinic, space group Pl, a = 7.9342 (14), b = 8.2653 (6), c = 11.877 (2) A; α = 71.40 (1), β = 77.57 (1), γ = 87.97 (1)°; d_c = 1.203 g.cm⁻³; μ = 1.784 .cm⁻¹; F(000) = 284. Philips PW 1100 diffractometer (MoKα). The structure was solved by a direct method (Multan-80) and refined by a least squares analysis. R = 0,043 for 2959 observed reflections [|F₀| ≥ 4σ (F₀) and |F₀| ≥ 8.0]. The positions of the hydrogen atoms were calculated. The absolute configuration was also confirmed by a least squares refinement of the absolute-structure parameter x = 0.12 (13) ref. 15).
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