

The Total Synthesis of Frangulanine¹

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The reported preparation of the *p-ansa* compound frangulanine, previously isolated from *Rhamnus frangula* L., also constitutes the first total synthesis of a fourteen-membered cyclopeptide alkaloid.

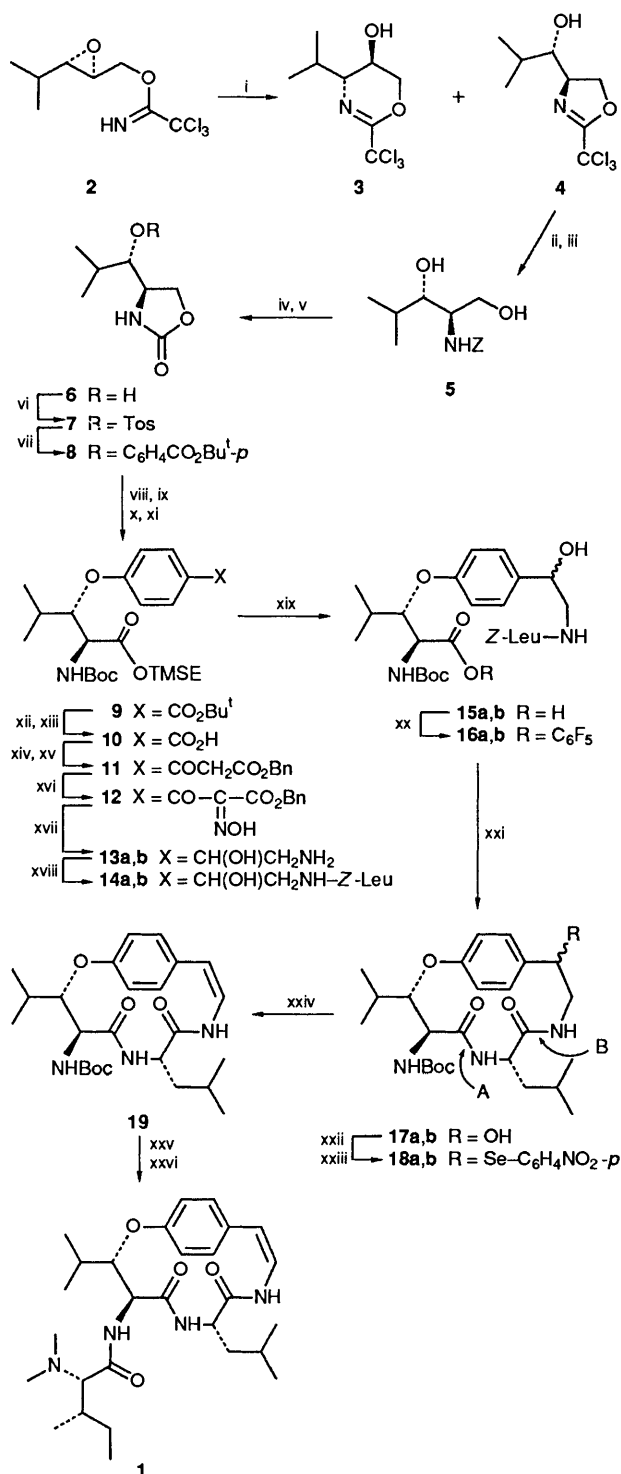
Since the structural elucidation of pandamine,² about 150 peptide alkaloids have been isolated and their structures clarified.³ Although numerous approaches for the synthesis of these compounds have been described practically all of them, including the most recent,^{4,5}† omit the characteristic but difficult to obtain structural unit of these natural products, namely the styrylamide double bond in the ring. Furthermore, the relevance of the total syntheses of a 13-membered and a 15-membered cyclic peptide alkaloid as well as of a linear peptide alkaloid reported by our group some years ago (*i.e.*, zizyphine A,⁶ mucronine B⁷ and hexaacetylcelenamide⁸) is frequently apparently overlooked. An exemplary synthesis of

a 14-membered peptide alkaloid having the *p-ansa* structure is still lacking; previously only dihydro derivatives of this series have been synthesized.^{4,5,9,10}

In the present communication, we describe the total synthesis of frangulanine¹¹ **1**, previously isolated from *Rhamnus frangula* L. (Rhamnaceae) which is endemic in Europe, North Africa, and Central Asia (black alder, berry-bearing alder, alder buckthorn, breaking buckthorn, butcher's prickwood). Frangulanine is the archetype of the 'frangulanine-type' to which the majority of the known peptide alkaloids belong.

The starting material for our synthesis was the easily accessible (2*S*,3*S*)-2-hydroxymethyl-3-isopropylloxirane¹² the trichloroacetimidic ester **2** of which, upon intramolecular ring opening under cobalt(II) chloride catalysis, yielded a mixture of the dihydrooxazine **3** and the dihydrooxazole **4**.¹² The five-membered ring product was hydrolysed to furnish the aminodiol **5** which, in turn, was transformed to the oxazolidinone **6**. For the subsequent conversion to the corresponding aryloxy compound, we have employed the reaction sequence **7** to **8** as developed by Pais¹³ which proceeds with retention of configuration *via* an aziridine. Ring cleavage, oxidation and

† The synthesis described in ref. 5 did not yield the 'fully functionalized skeleton' since the characteristic structural element of the peptide alkaloids, the enamide double bond, was missing. The described ring closure reaction *via* oxazolophanes can clearly only be performed with *N*-alkylated linear educts. The resultant cyclopeptides thus contain an *N*-alkylated β-hydroxy-α-amino acid as a constituent of the ring and this structural element is not a ring component of naturally occurring peptide alkaloids.



Abbreviations: Bn = benzyl; Boc = *tert*-butoxycarbonyl; Ts = *p*-Me₆H₄SO₂; Z = benzyloxycarbonyl; Succ = succinimido.

Scheme 1 Reagents and conditions: i, CoCl₂, MeCN, 20 °C, 14 h, 6% **3**, 86% **4**; ii, 2 mol dm⁻³ HCl, H₂O, 80 °C, 20 h; iii, ZCl, dioxane, NaHCO₃, 20 °C, 12 h, 90%; iv, TsCl, pyridine, -10 to 20 °C, 24 h, 86%; v, dioxane, 100 °C, 16 h, 78%; vi, TsCl, pyridine, -10 to 20 °C, 3 days, 71%; vii, Na⁺-OC₆H₄CO₂Bu^t-*p*, hexamethylphosphoric triamide (HMPT), 90 °C, 5 h, 93%; viii, (Boc)₂O, 4-dimethylaminopyridine (DMAP), Et₃N, tetrahydrofuran (THF), 20 °C, 4 h, 100%; ix, Cs₂CO₃, MeOH, 20 °C, 5 h, 87%; x, pyridinium dichromate (PDC), dimethylformamide (DMF), 20 °C, 40 h; xi, Me₃SiCH₂CH₂OH (TMSEOH), DMAP, dicyclohexylcarbodiimide (DCC), Et₂O, -20 to 20 °C, 20 h, x + xi 43%; xii, 6 mol dm⁻³ HCl-dioxane, 0 to 20 °C, 5 h, quant.; xiii, (Boc)₂O, NaHCO₃, dioxane, 20 °C, 14 h, 88%; xiv, carbonyldiimidazole (Im₂CO), THF, 20 °C, 4 h; xv, (-O₂CCH₂-CO₂Bn)₂ Mg²⁺, 50 °C, 4 h, 20 °C, 14 h, xiv + xv 98%; xvi, NaNO₂,

esterification then gave the 2-trimethylsilylethyl ester **9**.[‡] The aromatic carboxy group of **10** was then sequentially transformed to furnish an inseparable diastereoisomeric mixture of the amino alcohols **13a,b** by way of the β-keto ester **11**, § oxime formation (to **12**), and catalytic hydrogenation. Coupling of this mixture with (*Z*)-leucine gave **14a,b** and formation of the pentafluorophenyl esters **16a,b** provided the starting material for the ring closure reaction¹⁵ under the conditions of catalytic hydrogenation. By means of the high dilution technique (reaction time of 40 h at 90 °C), the ring compounds **17a,b** were obtained in 44% yield and could be separated readily by HPLC. ¶ The configurations of the epimers **17a/17b**, isolated in a molar ratio of 3:2, could not be determined. || Both isomers were transformed to the seleno ethers **18a** and **18b** by redox condensation;¹⁶ the reaction of **17b** proceeded only in poor yield and gave rise to numerous by-products. Oxidation of the selenium compound **18a** gave the unsaturated ring compound **19** in practically quantitative yield.** After cleavage of the Boc protecting group, reaction with the ester from (*S*)-*N,N*-dimethylisoleucine and 3-cyano-4,6-dimethylpyridine-2-thiol¹⁷ finally yielded frangulanin **1** which is identical in all respects with the natural product.

The rather low yield (20%) in the latter reaction reflects the shielding of the amino group bound to the rigid ring. The total yield of the last two reactions could not be improved by a reversed procedure; the Boc group of **18a** was split off and the amino group smoothly acylated with (*S*)-*N,N*-dimethylisoleucine. However, the oxidation-elimination of the seleno group from **18a** [(*S*)-*N,N*-dimethylisoleucine instead of Boc] yielded only 10% of **1**.

‡ This ester was chosen since the methyl esters **15a,b** (R = OMe) could not be saponified.

§ Prepared by the method of Masamune.¹⁴

¶ Attempts to realize ring closure at position B gave cyclic products in yields of less than 10%.

|| Selected NMR data for **17a** and **17b**. **17a**: ¹H NMR (250 MHz, CDCl₃-CD₃OD): δ 0.75 (d, *J* 6.4 Hz, 3H), 0.78 (d, *J* 6.2 Hz, 3H), 0.95 (d, *J* 6.7 Hz, 3H), 1.06 (d, *J* 6.8 Hz, 3H), 1.18–1.39 (m, 3H), 1.34 (s, 9H), 2.04–2.13 (m, 1H), 2.43 (s, br, 1H), 2.98 (d, *J* 14.1 Hz, 1H), 3.90 (dd, *J* 8.0, 6.3 Hz, 1H), 3.98 (d, *J* 8.8 Hz, 1H), 4.18 (dd, *J* 14.1, 4.1 Hz, 1H), 4.60 (dd, *J* 8.7, 1.2 Hz, 1H), 5.07 (d, *J* 3.4 Hz, 1H), 6.75 (dd, *J* 8.4, 2.4 Hz, 1H), 6.84 (dd, *J* 7.6, 2.4 Hz, 1H), 6.93 (dd, *J* 8.4, 2.1 Hz, 1H), 7.34 (dd, *J* 7.6, 2.1 Hz, 1H); **17b**: ¹H NMR (250 MHz, CDCl₃-CD₃OD): δ 0.70 (d, *J* 6.2 Hz, 3H), 0.73 (d, *J* 6.1 Hz, 3H), 0.93 (d, *J* 6.7 Hz, 3H), 1.07 (d, *J* 6.3 Hz, 3H), 1.14–1.37 (m, 3H), 1.34 (s, 9H), 1.95–2.11 (m, 1H), 3.14 (dd, *J* 13.3, 6.4 Hz, 1H), 3.81 (d, *J* 2.5 Hz, 1H), 3.82 (d, *J* 13.3 Hz, 1H), 3.95 (d, *J* 8.8 Hz, 1H), 4.55 (dd, *J* 8.8, 2.0 Hz, 1H), 4.62 (dd, *J* 8.5, 6.4 Hz, 1H), 6.72 (dd, *J* 8.4, 2.3 Hz, 1H), 6.80 (dd, *J* 7.8, 2.0 Hz, 1H), 6.84 (dd, *J* 7.8, 2.3 Hz, 1H), 7.31 (dd, *J* 8.4, 2.0 Hz, 1H).

** The reaction of **18b** proceeded only in poor yield; selected NMR data for **19**: ¹H NMR (300 MHz, CDCl₃): δ 0.74 (d, *J* 6.4 Hz, 3H), 0.83 (d, *J* 6.4 Hz, 3H), 1.02 (d, *J* 6.7 Hz, 3H), 1.26 (d, *J* 6.8 Hz, 3H), 1.32–1.42 (m, 11H), 1.71–1.79 (m, 1H), 2.01–2.06 (m, 1H), 4.10–4.19 (m, 2H), 4.89 (dd, *J* 7.1, 2.0 Hz, 1H), 4.99 (d, *J* 10.4 Hz, 1H), 5.64 (d, *J* 7.8 Hz, 1H), 6.39 (d, *J* 7.6 Hz, 1H), 6.48 (d, *J* 9.8 Hz, 1H), 6.65 (dd, *J* 9.8, 7.6 Hz, 1H), 7.03–7.07 (m, 2H), 7.10–7.13 (m, 1H), 7.15–7.19 (m, 1H).

AcOH, H₂O, 0 °C, 4 h, 79%; xvii, H₂, Pd/C, AcOH, 20 °C, 16 h; xviii, Z-Leu-OSucc, dioxane, KHCO₃, 20 °C, 14 h, xvii + xviii 84%; xix, Bu₄N⁺F⁻, DMF, 20 °C, 2 h, quant.; xx, C₆F₅OH, DCC, CH₂Cl₂, -20 to 20 °C, 14 h, 91%; xxi, dioxane, Bu^tOH, 4-pyrrolidinopyridine, H₂, Pd/C, 90 °C, 40 h, 44% **17a** + **17b**; xxii, preparative HPLC, hexane-ethyl acetate (20:80), 26% **17a** (first eluted), 18% **17b**; xxiii, NCS₂C₆H₄NO₂-*p*, Bu₃P, THF, 20 °C, 3 h, 91% **18a**, 16 h, 25% **18b**; xxiv, H₂O₂, CH₂Cl₂, pyridine, 20 °C, 1 h, 85% from **18a**, 43% from **18b**; xxv, CF₃CO₂H, *m*-C₆H₄(OMe)₂, 0 °C, 1 h; xxvi, ester of (*S*)-*N,N*-dimethylisoleucine and 3-cyano-4,6-dimethylpyridine-2-thiol, CH₂Cl₂, 20 °C, 14 h, xxv + xxvi 20%

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