The Total Synthesis of Frangulanine[1]

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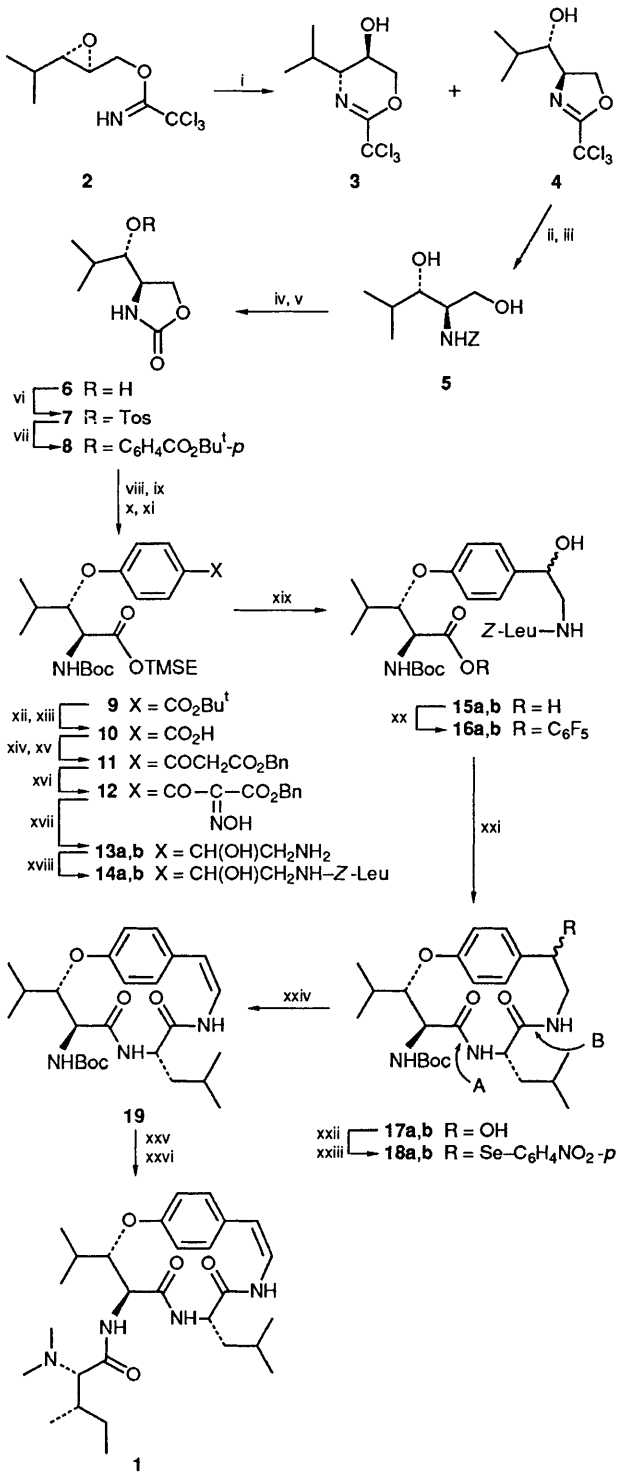
The reported preparation of the *p-ansa* compound frangulanine, previously isolated from *Rhamnus frangula L.*, also constitutes the first total synthesis of a fourteen-membered cyclopeptide alkaloid.

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 B[7] and hexaacetylcelenamide[8]) 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 frangulanine[11] **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-isopropyloxirane[12] 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 Pais[13] 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*-$Me_6H_4SO_2$; Z = benzyloxycarbonyl; Succ = succinimido.

Scheme 1 *Reagents and conditions*: i, $CoCl_2$, MeCN, 20 °C, 14 h, 6% **3**, 86% **4**; ii, 2 mol dm^{-3} HCl, H_2O, 80 °C, 20 h; iii, ZCl, dioxane, $NaHCO_3$, 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, $Na^{+-}OC_6H_4CO_2Bu^t$-*p*, hexamethylphosphoric triamide (HMPT), 90 °C, 5 h, 93%; viii, $(Boc)_2O$, 4-dimethylaminopyridine (DMAP), Et_3N, tetrahydrofuran (THF), 20 °C, 4 h, 100%; ix, Cs_2CO_3, MeOH, 20 °C, 5 h, 87%; x, pyridinium dichromate (PDC), dimethylformamide (DMF), 20 °C, 40 h; xi, $Me_3SiCH_2CH_2OH$ (TMSEOH), DMAP, dicyclohexylcarbodiimide (DCC), Et_2O, −20 to 20 °C, 20 h, x + xi 43%; xii, 6 mol dm^{-3} HCl–dioxane, 0 to 20 °C, 5 h, quant.; xiii, $(Boc)_2O$, $NaHCO_3$, dioxane, 20 °C, 14 h, 88%; xiv, carbonyldiimidazole (Im_2CO), THF, 20 °C, 4 h; xv, $(^-O_2CCH_2CO_2Bn)_2$ Mg^{2+}, 50 °C, 4 h, 20 °C, 14 h, xiv + xv 98%; xvi, $NaNO_2$, AcOH, H_2O, 0 °C, 4 h, 79%; xvii, H_2, Pd/C, AcOH, 20 °C, 16 h; xviii, Z-Leu-OSucc, dioxane, $KHCO_3$, 20 °C, 14 h, xvii + xviii 84%; xix, $Bu_4N^+F^-$, DMF, 20 °C, 2 h, quant.; xx, C_6F_5OH, DCC, CH_2Cl_2, −20 to 20 °C, 14 h, 91%; xxi, dioxane, Bu^tOH, 4-pyrrolidinopyridine, H_2, Pd/C, 90 °C, 40 h, 44% **17a** + **17b**; xxii, preparative HPLC, hexane–ethyl acetate (20:80), 26% **17a** (first eluated), 18% **17b**; xxiii, $NCSeC_6H_4NO_2$-*p*, Bu_3P, THF, 20 °C, 3 h, 91% **18a**, 16 h, 25% **18b**; xxiv, H_2O_2, CH_2Cl_2, pyridine, 20 °C, 1 h, 85% from **18a**, 43% from **18b**; xxv, CF_3CO_2H, *m*-$C_6H_4(OMe)_2$, 0 °C, 1 h; xxvi, ester of (*S*)-*N*,*N*-dimethylisoleucine and 3-cyano-4,6-dimethylpyridine-2-thiol, CH_2Cl_2, 20 °C, 14 h, xxv + xxvi 20%

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 reaction[15] 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-thiol[17] finally yielded frangulanine **i** which was 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**: ^{1}H NMR (250 MHz, $CDCl_3$–CD_3OD): 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**: ^{1}H NMR (250 MHz, $CDCl_3$–CD_3OD): 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**: ^{1}H NMR (300 MHz, $CDCl_3$): 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).

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References

1 For Part 78 of the series Amino Acids and Peptides, and Part 21 of the series Cyclopeptides, see U. Schmidt, R. Meyer, V. Leitenberger, F. Stäbler and A. Lieberknecht, *Synthesis*, 1991, 409.
2 M. Pais, F.-X. Jarreau, X. Lusinchi and R. Goutarel, *Ann. Chim. (Paris)*, 1966, 83.
3 For recent reviews, see: U. Schmidt, A. Lieberknecht and E. Haslinger, in the *The Alkaloids*, vol. 26, ed. A. Brossi, Academic Press, New York, 1985, pp. 299–326; M. M. Joullié and R. Nutt, in *Alkaloids: Chemical and Biological Perspectives*, vol. 3, ed. S. W. Pelletier, Wiley, New York, 1985, pp. 113–168.
4 R. J. Heffner and M. M. Joullié, *Tetrahedron Lett.*, 1989, **30**, 7021.
5 B. H. Lipshutz, B. E. Huff, K. E. McCarthy, T. A. Miller, S. M. Jaweed Mukarram, T. J. Siahaan, W. D. Vaccaro, H. Webb and A. M. Falick, *J. Am. Chem. Soc.*, 1990, **112**, 7032.
6 U. Schmidt, A. Lieberknecht, H. Bökens and H. Griesser, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 1026; *J. Org. Chem.*, 1983, **48**, 2680.
7 U. Schmidt and U. Schanbacher, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 152; *Liebigs Ann. Chem.*, 1984, 1205.
8 U. Schmidt and J. Wild, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 991; *Liebigs Ann. Chem.*, 1985, 1882.
9 R. F. Nutt, K. N. Chen and M. M. Joullié, *J. Org. Chem.*, 1984, **49**, 1013.
10 U. Schmidt, A. Lieberknecht, H. Griesser and J. Häusler, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 281; *Liebigs Ann. Chem.*, 1982, 2153.
11 Isolation and structural elucidation: R. Tschesche, H. Last and H.-W. Fehlhaber, *Chem. Ber.*, 1967, **100**, 3937; X-ray analysis: M. Takai, Y. Ogihara, Y. Itaka and S. Shibata, *Chem. Pharm. Bull.*, 1976, **24**, 2181; NMR analysis: E. Haslinger, *Tetrahedron*, 1978, **34**, 685; *Monatsh. Chem.*, 1978, **109**, 523; E. Haslinger and W. Robien, *Monatsh. Chem.*, 1979, **110**, 1011; 1983, **113**, 95.
12 U. Schmidt, M. Respondek, A. Lieberknecht, J. Werner, and P. Fischer, *Synthesis*, 1989, 256.
13 F. Rocchiccioli, F.-X. Jarreau and M. Pais, *Tetrahedron*, 1978, **34**, 2917.
14 D. W. Brooks, L. D.-L. Lu and S. Masamune, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 72.
15 U. Schmidt, A. Lieberknecht, H. Griesser and J. Talbiersky, *J. Org. Chem.*, 1982, **47**, 3261.
16 P. A. Grieco, S. Gilman and M. Nishizawa, *J. Org. Chem.*, 1976, **41**, 1485.
17 U. Schmidt and K. Schefenacker, *Liebigs Ann. Chem.*, 1985, 1254.