which, besides M^+ (m/e 364), includes diagnostically important peaks[5] for M^+-C_5H_9 (m/e 295), M^+-$C_3H_8O_3$ (m/e 272), M^+-$C_3H_8O_3$-CH_3 (m/e 257), M^+-$C_3H_8O_3$-C_3H_7 (m/e 229), M^+-$C_3H_8O_3$-C_5H_9 (m/e 203), M^+-$C_3H_8O_3$-$C_{10}H_{17}$ (m/e 135), $C_7H_9^+$ (m/e 93), $C_6H_9^+$ (m/e 81), $C_5H_9^+$ (base, m/e 69) and $C_3H_5^+$ (m/e 41).

The structure was confirmed by reduction with sodium in NH_3 and EtOH at -45 °C which afforded all-trans-2,6,10,14-tetramethylhexadeca-2,6,10,14-tetraene (M^+ m/e 274) as the main product, identified by chromatographic and spectroscopic comparison with an authentic specimen.

Since related, naturally occurring, higher glycerol 1-ethers (chimyl, batyl and selachyl alcohols), all possessing the S configuration, in dilute chloroform solution are slightly dextro-rotatory[6], the optical rotation of **1** suggested that this compound could possibly possess the opposite R configuration. This feature was confirmed by using the general method for the configurational correlation of alcohols described by Mislow[7]. Reaction of **1** with p-toluenesulfinyl chloride yielded a mixture of diastereomers which by reaction with methylmagnesium iodide gave a preponderance of (−)-(S)-methyl-p-tolyl sulfoxide.

Until now higher glycerol ethers with polyisoprenoidic hydrocarbon chains have been found only in extremely halophilic[8] and acidophilic bacteria[9]. It is interesting to note that all these lipids, as well as **1**, possess the 'unnatural' configuration of the glycerol moiety.

5 R. Ryhage and E. von Sidow, Acta chem. scand. *17*, 2025 (1963); E. von Sidow, Acta chem. scand. *17*, 2504 (1963).

6 Y. Toyama and T. Ishikawa, J. Chem. Soc. Japan *59*, 1367 (1938); E. Baer and H. O. L. Fischer, J. biol. Chem. *140*, 397 (1941); V. Prelog, L. Ruzicka and P. Stein, Helv. chim. Acta *26*, 2222 (1943); V. Prelog, L. Ruzicka and F. Steinmann, Helv. chim. Acta *27*, 674 (1944); E. Baer, L. J. Rubin and H. O. L. Fischer, J. biol. Chem. *155*, 447 (1944).

7 M. M. Green, M. Axelrod and K. Mislow, J. Am. Chem. Soc. *88*, 861 (1966); C. Fuganti and D. Ghiringhelli, Gazz. chim. ital. *99*, 316 (1969).

8 M. Kates, in: Ether Lipids. Chemistry and Biology, p. 351. Ed. F. Snyder. Academic Press 1972.

9 M. de Rosa, L. Minale and J. D. Bu' Lock, J. C. S. Chem. Commun. *1974*, 543.

Synthesis of (Glu-OMe)^2-litorin

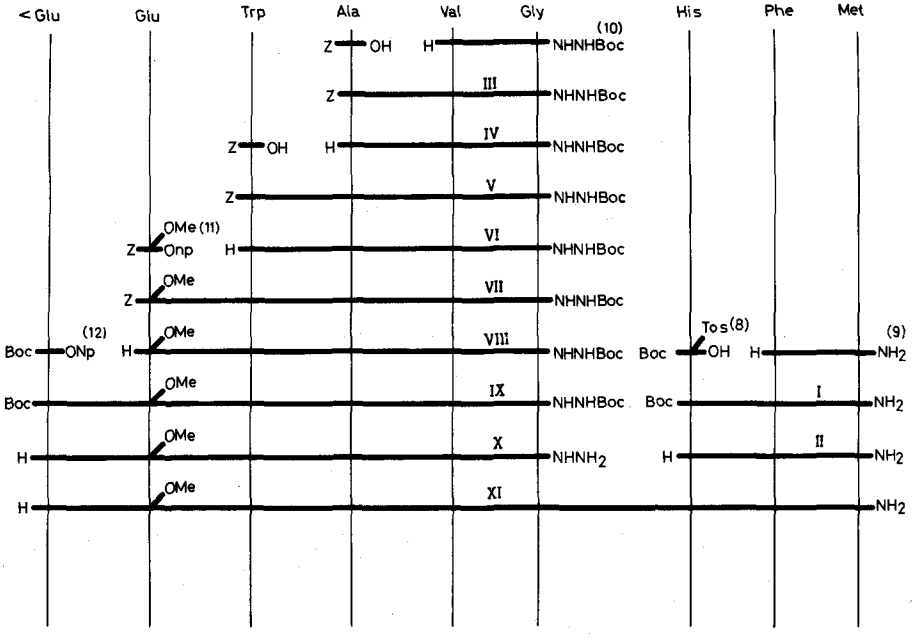
M. Mazzoli and R. de Castiglione

Laboratori Ricerche Farmitalia, I–20146 Milano (Italy), 4 February 1977

Summary. The synthesis of the nonapeptide <Glu-Glu(OMe)-Trp-Ala-Val-Gly-His-Phe-Met-NH_2, corresponding to the formula of the (Glu-OMe)^2-litorin, is described. The compound has the same chemical and biological properties of the second bombesin-like peptide extracted from the skin of the Australian frog Litoria aurea.

We briefly report the synthesis of a nonapeptide of formula <Glu-Glu(OMe)-Trp-Ala-Val-Gly-His-Phe-Met-NH_2[1] (XI), corresponding to the proposed sequence of the second bombesin-like peptide of the skin of the Australian frog Litoria aurea, i.e. Glu(OMe)^2-litorin[2]. Relevant information on the synthesis, accomplished by conventional solution methods, is summarized in the figure and the table.

The condensation of Boc-His(Tos) with Phe-Met-NH_2 via the Geiger procedure[3] (DCCI + HOBT) gave the detosylated[4] tripeptide I ($E_{1,2}$ = 0.32 His; $E_{5,8}$ = 0.45 His)[5]. The final coupling was carried out by the modified azide



Synthesis of Glu(OMe)^2-litorin.

Data on Glu(OMe)[2]-litorin and intermediates obtained during the synthesis*

Number	Formula	Method[a]	Reaction solvent[b]	Crystallization solvent[c]	Melting point[d]	Optical rotation[e]	TLC[f] Rf_A	Rf_B	Rf_C	Rf_D
I	$C_{25}H_{36}N_6O_5S$	DCCI + HOTB	DMF	MeOH-Et_2O	163 °C	− 11.5°	–	0.06	0.59	0.94
II	$C_{20}H_{28}N_6O_3S \cdot HCl$	HCl	AcOH	MeOH-Et_2O	~ 170 °C	− 2.3°	–	–	0.23	0.70
III	$C_{23}H_{35}N_5O_7$	MA	THF	AcOEt-Et_2O	140–141 °C	− 4.7°	0.46	0.71	0.91	0.96
IV	$C_{15}H_{29}N_5O_5$	H_2	MeOH	AcOEt-Et_2O	155 °C	− 18.8°	–	0.02	0.52	0.88
V	$C_{34}H_{45}N_7O_8$	MA	THF	MeOH-Et_2O	195 °C	− 14.7°	0.49	0.67	0.91	1.00
VI	$C_{26}H_{39}N_7O_6$	H_2	MeOH + DMF	DMF-Et_2O	105 °C	− 18.5°	–	0.03	0.72	0.84
VII	$C_{40}H_{54}N_8O_{11}$	ONp	DMF	–	–	–	–	0.33	–	–
VIII	$C_{32}H_{48}N_8O_9$	H_2	DMF	–	–	–	–	0.02	0.72	0.82
IX	$C_{42}H_{61}N_9O_{13}$	ONp	DMF	DMF-H_2O	195 °C	− 26.7°	–	0.12	0.77	0.87
X	$C_{32}H_{44}N_9O_9$	HCOOH	–	–	–	–	–	–	0.41	0.84
XI	$C_{52}H_{68}N_{13}O_{12}S$	N_3	DMF	–	–	–	–	–	0.12	0.77

Amino acid composition of acid hydrolizate of compound XI[g]: $Glu_{2.09}$, $Gly_{1.00}$, $Ala_{1.00}$, $Val_{1.05}$, $Met_{1.03}$, $Phe_{0.97}$, $His_{0.93}$

* All the products were checked for purity in TLC. Intermediates VII, VIII and X were not obtained homogeneous.
[a] DCCI + HOBT, activated ester prepared in situ from N,N′-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole; HCl, dry HCl (~ 1.3 N) for 30 min at room temperature; MA, mixed anhydride with N-methylmorfoline and ethylchlorocarbonate (activation time: 2 min at −15 °C); H_2, hydrogenation in the presence of 10% palladium-charcoal; ONp, p-nitrophenyl ester; HCOOH, 99% formic acid for 3.5 h in the presence of 2-mercapto-ethanol; N_3, azide prepared with n-butyl nitrite and dry HCl in tetrahydrofuran at −25 °C for 10 min. [b] DMF: dimethylformamide; AcOH: glacial acetic acid; THF: tetrahydrofuran; MeOH: methanol. [c] Et_2O: diethylether; AcOEt: ethyl acetate. [d] Capillary tube, uncorrected. [e] Optical rotations were measured at 22°, C = 1. The solvent used were MeOH for compound IV, and DMF for the others. [f] TLC on pre-coated silica gel plates (E. Merck) in the following solvent systems: A, benzene/ethyl acetate/acetic acid/water (100:100:20:10) (upper phase); B, benzene/ethyl acetate/acetic acid/water (100:100:40:15) (upper phase); C, n-butanol/acetic acid/water (40:10:10); D, chloroform/methanol/32% NH_4OH (65:45:20). [g] Trp in decomposed during acid hydrolysis (100 °C for 18 h).

procedure in anhydrous conditions[6]. The yield was very poor. The pure compound could be obtained by preparative chromatography on pre-coated silica gel plates 60 F_{254} (E. Merck, Darmstadt), using a mixture of n-butanol-acetic acid-water (4:1:1) as solvent. The synthetic peptide showed the same electrophoretic and chromatographic mobilities, the same degradative pattern and the same biological properties[7] as natural Glu(OMe)[2]-litorin[8–12].

1 The amino acids used, with the exception of glycine, have the L-configuration. Symbols and abbreviations are in accordance with the recommendations of the IUPAC-IUB Commission on Biochemical Nomenclature, Biochemistry *11*, 1726 (1972).
2 A. Anastasi, P. Montecucchi, F. Angelucci, V. Erspamer and R. Endean, Experientia, in press (1977).
3 W. König and R. Geiger, Chem. Ber. *103*, 788 (1970).
4 T. Fujii, T. Kimura and S. Sakakibara, Bull. chem. Soc. Japan *49*, 1595 (1976).
5 Paper electrophoretic mobilities in $HCOOH/CH_3COOH/H_2O$ (615:500:3885) and in CH_3COOH/pyridine/H_2O (50:450:4500), respectively, with histidine as standard.
6 J. Honzl and J. Rudinger, Coll. Czech. chem. Commun. *26*, 2333 (1961).
7 We are indebted to dr. A. Anastasi and to prof. V. Erspamer for these assays.
8 T. Fujii and S. Sakakibara, Bull. chem. Soc. Japan *47*, 3146 (1974).
9 F. Angelucci and R. de Castiglione, Experientia *31*, 507 (1975).
10 J. Beacham, G. Dupuis, F. M. Finn, H. T. Storey, C. Yanaihara, N. Yanaihara and K. Hoffmann, J. Am. chem. Soc. *93*, 5526 (1971).
11 G. Losse, H. Jesehkeit and W. Langenbeck, Chem. Ber. *96*, 204 (1963).
12 E. Schröder and E. Klieger, Justus Liebigs Ann. Chem. *673*, 196 (1964).

(−)-Dihydromylione A, a novel tetracyclic sesquiterpene ketone containing two conjugated cyclopropane rings, from Mylia taylorii (liverwort)

A. Matsuo, H. Nozaki, M. Shigemori, M. Nakayama and S. Hayashi

Department of Chemistry, Faculty of Science, Hiroshima University, Hiroshima 730 (Japan), 24 January 1977

Summary. A novel tetracyclic sesquiterpene ketone named (−)-dihydromylione A (**III**) was isolated from the liverwort, and the structure was determined together with the absolute configuration to be ent-5,10-cyclo-aromadendr-3-one by connecting the compound with co-occurring (−)-myliol (**II**).

In our investigation on constituents of the liverworts (Hepaticae), several enantiomeric sesquiterpenoids, which are antipodes of those from the higher plants, such as (−)-longiborneol, (−)-longifolene, (+)-α-himachalene, (−)-α-longipinene[1], (−)-maalioxide, (+)-cyclocolorenone[2], (−)-cuparene[3] and (−)-bicyclogermacrene[4] have been isolated. Recently, we have isolated a novel ent-1,10-seco-aromadendrene ketone, (−)-taylorione(**I**), from a leafy liverwort, Mylia taylorii (Hook.) Gray[5], and revised the structure of (−)-myliol, which had been isolated from the same plant, as ent-5,10-cyclo-aromadendrene

1 A. Matsuo, M. Nakayama and S. Hayashi, Chemistry Lett. 769 (1973).
2 A. Matsuo, M. Nakayama, S. Sato, T. Nakamoto, S. Uto and S. Hayashi, Experientia *30*, 321 (1974).
3 A. Matsuo, M. Nakayama, T. Maeda, Y. Noda and S. Hayashi, Phytochemistry *14*, 1037 (1975).
4 (−)-Bicyclogermacrene was isolated from the liverwort, Porella densifolia: S. Uto A. Matsuo, M. Nakayama and S. Hayashi, 20th TEAC, p. 45, Akita, 1976.
5 A. Matsuo, S. Sato, M. Nakayama and S. Hayashi, Tetrahedron Lett. 3681 (1974); A. Matsuo, S. Sato, M. Nakayama and S. Hayashi, 18th Symposium on the Chemistry of Natural Products, p. 69. Kyoto, 1974.