Pergamon

Tetrahedron Letters 39 (1998) 1541–1544

TETRAHEDRON LETTERS

Preparation of Helioporin D from the *seco*-Pseudopterosin Aglycone: Revision of the Stereostructure of Helioporin D

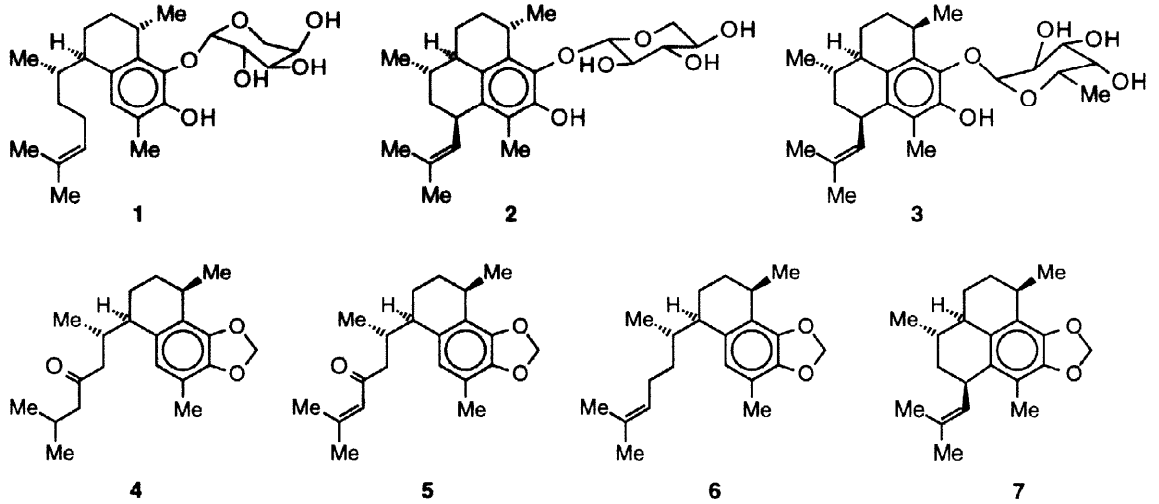
Thomas Geller, Jasmin Jakupovic and Hans-Günther Schmalz*

Institut für Organische Chemie der Technischen Universität, Straße des 17. Juni 135, D-10623 Berlin, Germany

Received 4 December 1997; accepted 23 December 1997

Abstract: A revised stereostructure for helioporin D was unequivocally established by its synthesis from the *seco*-pseudopterosin aglycone and by careful analysis of NMR data. As the corresponding benzodioxole derived from the pseudopterosin A aglycone was not identical with helioporin E, it was proven that helioporin D and E do not belong to the same stereochemical series. © 1998 Elsevier Science Ltd. All rights reserved.

The helioporins, an interesting class of bioactive diterpenes, were isolated from the blue coral *Heliopora coerulea* by T. Higa and coworkers in 1993.[1] In contrast to the structurally related anti-inflammatory *seco*-pseudopterosins (e.g. **1**)[2] and pseudopterosins (e.g. **2** and **3**),[3] the helioporins exhibit either antiviral or cytotoxic properties. The constitution of these compounds, which all share a characteristic benzodioxole substructure, became evident from the spectrocopic data (NMR, IR, HRMS). While the relative configuration of helioporin E (**7**) was judged by Higa after comparison of its NMR data with those of the pseudopterosins, the stereostructures of the tricyclic helioporins such as helioporin B (**4**), C (**5**) and D (**6**) were assigned based on chemical correlations which were, however, carried out on a rather small scale.[1] As a result of their correlation experiments Higa and coworkers considered all helioporins belonging to the same stereochemical series.



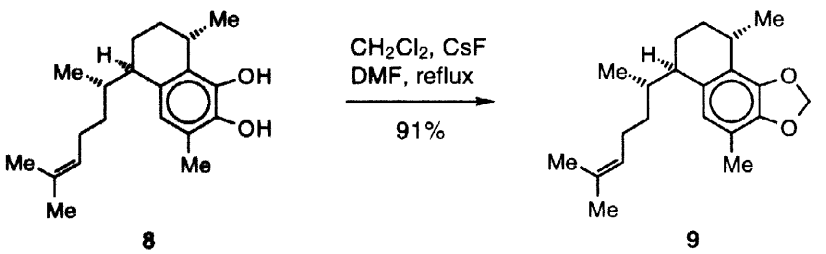
1 **2** **3**

4 **5** **6** **7**

PII: S0040-4039(98)00020-3

We recently completed an efficient diastereo- and enantioselective synthesis of compound **6** (putative helioporin D)[4] and were surprised to find that the data of this compound were similar but not identical with those of helioporin D (see Tables 1 and 2).[1,5] We suspected that an error in the stereostructural assignment was the cause for this contradiction. We here report a revised structure for helioporin D which was unequivocally established by its synthesis from the *seco*-pseudopterosin aglycone.

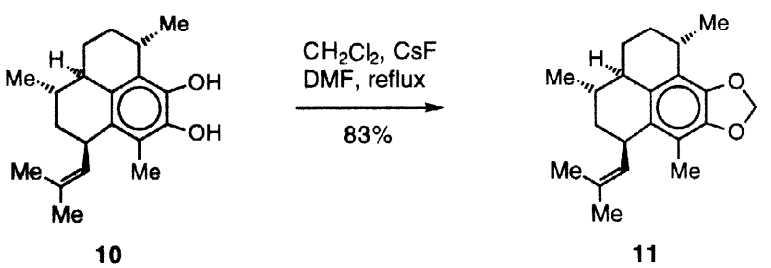
Since the pseudopterosins (which also are metabolites from a coral species) appear in two diastereomeric (epimeric) series differing only in the configuration at the methyl substituted benzylic center, and having in mind that a change of the relative configuration of the two adjacent chirality centers of **6** would result in distinct changes of the NMR spectrum[6], we suspected that helioporin D should have the same configuration as the *seco*-pseudopterosin aglycone (**8**). The latter had been independently prepared in this laboratory through a stereo-rational synthesis.[7] Therefore, we converted a sample of **8** to the corresponding benzodioxole **9** using the method of Clark et al. (CH_2Cl_2/CsF) (Scheme 1).[8] The comparison of the ^1H and ^{13}C NMR data[9] of **6** and **9** with those of natural helioporin D (Table 1 and Table 2) then unambiguously showed that formula **9** (and not **6**) represents the correct stereostructure of helioporin D. We would like to emphasize that the deviations (Δ) of the ^1H NMR data between the natural compound and synthetic **6** are rather small except for obvious differences in the pattern of the signals at ca. 2.7 and 2.9 ppm. The ^{13}C NMR data of natural helioporin D and **6**, however, differ to a significant extent. The almost perfect congruity of the NMR data of helioporin D and **9** needs no further comment. The comparison of the molecular rotation of synthetic **9** ($[\alpha]_D^{23}$ = +11.6°; c = 0.33 in $CHCl_3$) with the one reported for helioporin D ($[\alpha]_D^{23}$ = +6.3°; c = 0.36 in $CHCl_3$)[1] confirmed the presumed absolute configuration of the latter.



8 **9**

Scheme 1: Preparation of helioporin D (**9**) from the *seco*-pseudopterosin aglycone (**8**)

The possibility of the C-7-epimer of **7** being the correct structure for helioporin E was excluded by converting the pseudopterosin A aglycone **10**[7] to the methylenedioxy compound **11** (Scheme 2).[10] As the NMR data of this compound were not identical to those reported for helioporin E, we can at least exclude this structure for helioporin E.



10 **11**

Scheme 2: Preparation of an epimer of helioporin E (**11**) from the pseudopterosin A aglycone (**10**)

Table 1: Selected ^{1}H NMR data of natural helioporin D[1] and the synthetic compounds **6**[4] and **9**.

Position[a]	Helioporin D[b]	**6**[c]	Δ	**9**	Δ
1	2.93 (ψtq, J = 6.2, 6.9)	2.95 - 3.06 (m)	-0.08	2.93 (ψsext., J= 7.0)	0
4	2.66 (ψq, J = 5.6)	2.68 - 2.74 (m)	-0.05	2.66 (ψq, J= 5.5)	0
5	6.52 (s)	6.56 (s)	-0.04	6.52 (s)	0
14	5.15 (br t, J = 7.1)	5.17 (tt, J= 7.0, 1.5)	-0.02	5.15 (tt, J= 7.0, 1.5)	0
16	1.72 (s)	1.72 (s)	0	1.72 (s)	0
17	1.63 (s)	1.64 (s)	-0.01	1.64 (s)	-0.01
18	0.71 (d, J = 6.9)	0.70 (d, J = 7.0)	0.01	0.72 (d, J= 7.0)	-0.01
19	2.20 (s)	2.20 (s)	0	2.20 (s)	0
20	1.25 (d, J = 6.9)	1.22 (d, J= 7.0)	0.03	1.24 (d, J= 7.0)	0.01
OCH_2O	5.88 (d, J = 1.2)	5.90 (d, J= 1.0)	-0.02	5.88 (d, J= 1.0)	0
OCH_2O	5.94 (d, J = 1.2)	5.96 (d, J= 1.0)	-0.02	5.94 (d, J= 1.0)	0

a) Numbering according to Fenical[11]; b) assignments according to Higa[1]; c) assignments supported by spin-decoupling experiments.

Table 2: ^{13}C NMR data of natural helioporin D[1] and the synthetic compounds **6**[4] and **9**.

Position[a]	Helioporin D[b]	**6**[c]	Δ	**9**[b]	Δ
1	28.7 d	27.2 d	1.5	28.6 d	0.1
2	29.7 t	28.5 t	1.2	29.6 t	0.1
3	20.6 t	17.7 t	2.9	20.5 t	0.1
4	40.8 d	41.1 d	-0.3	40.7 d	0.1
5	122.5 d	121.6 d	0.9	122.3 d	0.2
6	116.0 s	116.2 s	-0.2	115.9 s	0.1
7	143.1 s	142.7 s	0.4	143.0 s	0.1
8	144.7 s	144.4 s	0.3	144.5 s	0.2
9	123.2 s	123.3 s	-0.1	123.1 s	0.1
10/15	131.3 s	131.3 s	0.0	131.2 s	0.1
10/15	133.9 s	133.3 s	0.6	133.8 s	0.1
11	37.4 d	35.7 d	1.7	37.3 d	0.1
12	35.6 t	35.1 t	0.5	35.5 t	0.1
13	26.4 t	26.3 t	0.1	26.3 t	0.1
14	125.0 d	124.8 d	0.2	124.9 d	0.1
16	25.9 q	25.8 q	0.1	25.8 q	0.1
17	17.8 q	17.7 q	0.1	17.7 q	0.1
18	15.7 q	14.7 q	1.0	15.6 q	0.1
19	14.8 q	14.4 q	0.4	14.7 q	0.1
20	21.2 q	20.5 q	0.7	21.0 q	0.2
OCH_2O	100.3 t	100.5 t	-0.2	100.2 t	0.1

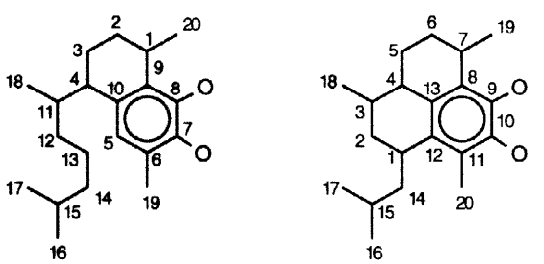
a) Numbering according to Fenical[11]; b) assignments according to Higa[1]; c) assignments supported by a C,H-COSY experiment.

In conclusion, we have revised the stereostructure of helioporin D by demonstrating its stereostructural relationship to the *seco*-pseudopterosin aglycone. In addition, we proved that helioporin D and helioporin E have a different configuration at the methyl-substituted benzylic position. The question, at which point the structural assignments reported by Higa and coworkers went wrong, remains open. We are currently about to address this question by synthesizing other (presumed) members of the helioporin/pseudopterosin group using our general, stereo-rational approach which is based on the exploitation of arene-$Cr(CO)_3$ chemistry.[4,7]

Acknowledgement. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We wish to thank the Chemetall GmbH and the Degussa AG for generous gifts of chemicals. T. G. acknowledges the Fonds der Chemischen Industrie for a graduate fellowship.

REFERENCES AND NOTES

1. Tanaka, J.-i.; Ogawa, N.; Liang, J.; Higa, T.; Gravalos, D.G. *Tetrahedron* **1993**, *49*, 811.
2. Look, S.A.; Fenical, W. *Tetrahedron* **1987**, *43*, 3363.
3. a) Look, S.A.; Fenical, W.; Jacobs, R.S.; Clardy, J. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 6238; b) Look, S.A.; Fenical, W.; Matsumoto; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5140; c) Roussis, V.; Wu, Z.; Fenical, W.; Strobel, S.A.; Van Duyne, G.; Clardy, J. *J. Org. Chem.* **1990**, *55*, 4916.
4. Geller, T.; Schmalz, H.-G.; Bats, J.W. *Tetrahedron Lett.* **1998**, *39*, 1537.
5. We are grateful to Prof. Higa, Nishihara, for providing us with copies of the original IR and ^{1}H NMR of the helioporins B-F.
6. We have independantly prepared analogeous compounds with an epimeric configuration at the sidechain chirality center (D. Hörstermann, H.-G. Schmalz, unpublished results).
7. Majdalani, A.; Schmalz, H.-G. *Synlett*, **1997**, 1303.
8. Clark, J.H.; Holland, H.L., Miller, J.M. *Tetrahedron Lett.* **1976**, 3361.
9. The given coupling constants for **6** and **9** have been rounded to a multiple of 0.5.
10. Data for **11**: M.p.: 102°C; IR (ATR): ν = 2951(s), 2920(s), 2870(s), 2857(s), 1457(s), 1422(s); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (d, 3H, *J* = 6.0 Hz), 1.07-1.23 (m, 1H), 1.23-1.32 (m, 1H), 1.29 (d, 3H, *J* = 7.0 Hz), 1.32-1.45 (m, 1H), 1.50-1.71 (m, 2H), 1.68 (s, 3H), 1.74 (s, 3H), 1.98-2.07 (m, 1H), 2.02 (s, 3H), 2.10-2.24 (m, 2H), 3.07 (ψsext., 1H, *J* = 7.5 Hz), 3.54-3.62 (m, 1H), 5.10 (d, br, 1H, *J* = 9.0 Hz), 5.84 (d, 1H, *J* = 1.5 Hz), 5.91 (d, 1H, *J* = 1.5 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 10.9 (q), 17.7 (q), 20.8 (q), 22.3 (q), 25.6 (q), 28.3 (t), 28.9 (d), 29.6 (d), 32.3 (t), 35.2 (d), 39.7 (t), 44.8 (d), 99.9 (t), 115.4 (s), 121.2 (s), 129.7 (s), 130.2 (d), 130.6 (s), 131.2 (s), 142.9 (s), 144.0 (s); optical rotation: $[\alpha]_D^{23}$ = -78.8°; c = 0.35 in $CHCl_3$).
11. The carbon atoms were numbered according to system used by Fenical for the *seco*-pseudopterosin[2] skeleton (**A**) and the pseudopterosin[3] skeleton (**B**).



A **B**