ORGANIC LETTERS

2004
Vol. 6, No. 18
3175−3177

Revision of the Structures Assigned to the Fungal Metabolites Boletunones A and B

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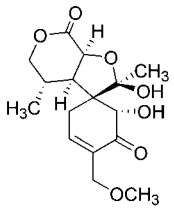
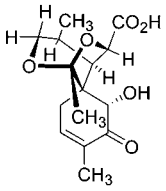
Received July 5, 2004

ABSTRACT



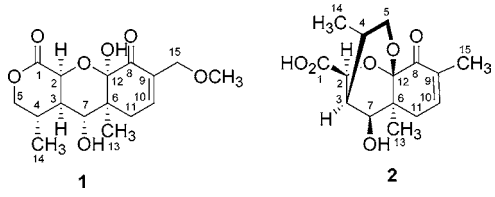
15-methoxycyclocalopin A (**5**)
(boletunone A)



isocyclocalopin A (**6**)
(boletunone B)

The structures recently assigned to the mushroom metabolites boletunones A (1) and B (2) are revised to those of 15-methoxycyclocalopin A (5) and isocyclocalopin A (6), respectively.

Recently, Kim et al.[1] reported the isolation and structural elucidation of two highly functionalized sesquiterpenoids from a Korean collection of *Boletus calopus*. On the basis of mainly NMR evidence, the authors proposed formulas **1** and **2** for boletunones A and B, respectively (Figure 1).

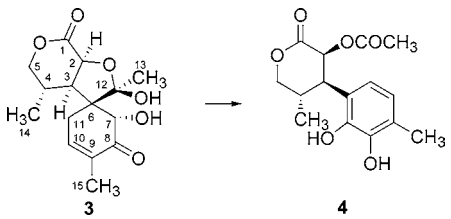


1 **2**

Figure 1. Structures for boletunones A (**1**) and B (**2**) as given in ref 1 (numbering refers to corresponding atoms in cyclocalopins[2]).

Unfortunately, the authors did not refer to our earlier work on the same topic,[2−5] in which the isolation and structural elucidation of a unique group of metabolites from *B. calopus* and related species were reported.[2] We proved the structure of cyclocalopin A (**3**), one of the major components, by extensive spectroscopic studies and a single-crystal X-ray analysis.[2] The oxidative transformation of sesquiterpene **3** into *O*-acetylcalopin A (**4**) of known absolute configuration[3,5] established the illustrated stereostucture for the natural product (Scheme 1).

Scheme 1. Stereochemical Correlation of Cyclocalopin A (**3**) with *O*-Acetylcalopin A (**4**)[2]



3 **4**

On the basis of such work, we have concluded that the structures proposed for boletunones A and B are wrong and

(1) Kim, W.-G.; Kim, J.-W.; Ryoo, I.-J.; Kim, J.-P.; Kim, Y.-H.; Yoo, I.-D. *Org. Lett.* **2004**, *6*, 823.

10.1021/ol048724t CCC: $27.50
Published on Web 08/13/2004

Table 1. Comparison of NMR Data for Boletunone A (BA)[1] and Cyclocalopin A (**3**) (CA)[2]

no.[c]	BA[a] δ_C	CA[b] δ_C	BA[a] δ_H (mult, J, Hz)	CA[b] δ_H (mult, J, Hz)
1	171.3	172.6		
2	73.2	73.7	4.49 (d, 9.6)	4.59 (d, 9.7)
3	45.9	46.2	2.14 (m)	2.21 (m)
4	29.8	30.6	2.01 (m)	2.21 (m)
5	71.5	72.2	5-H_α 3.88 (dd, 10.5, 10.5), 5-H_β 4.04 (dd, 10.5, 3.6)	3.83 (dd, 11.0, 11.0), 4.07 (dd, 11.0, 2.9)
6	56.0	56.3		
7	76.2	76.0	4.35 (s)	4.27 (s)
8	198.7	199.3		
9	133.1	133.0		
10	146.5	144.5	6.94 (m)	6.72 (m)
11	28.1	27.8	11-H_α 2.61 (dd, 20.8, 5.6), 11-H_β 2.50 (dd, 20.8, 2.3)	2.72 (ddm, 20.8, 5.7), 2.55 (dd, 20.8, 2.6)
12	106.3	107.6		
13	21.7	21.7	1.57 (s, 3H)	1.67 (s, 3H)
14	17.0	16.4	0.79 (d, 6.2, 3H)	0.77 (d, 6.4, 3H)
15	68.6	15.1	3.94/4.01 (2H)	1.85 (s, 3H)
OMe	58.4		3.36 (s, 3H)	

[a] In DMSO-d_6. [b] In $CDCl_3$. [c] Cyclocalopin numbering (see Figure 1). Assignments of H_α and H_β are opposite to those given in ref 1.

need to be revised to **5** and **6**, respectively (Figure 2). The identification of boletunone A as the hitherto undescribed

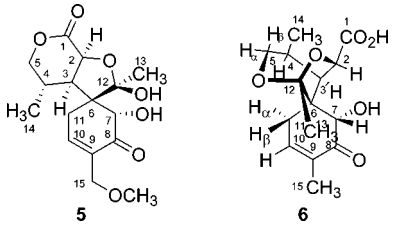


Figure 2. Revised structures for boletunones A (**5**) and B (**6**).

15-methoxy derivative of cyclocalopin A (**5**) follows, in a definite manner, from the excellent agreement between the NMR data sets for boletunone A[1] and cyclocalopin A (**3**)[2] (Table 1), the only variations arising from the expected changes caused by the additional methoxy group at C-15 in the former compound. The same can be said of the HMBC and NOE data. For example, Kim's group even described the important HMBC correlation of 7-H with C-8 but assigned it to a $^4J_{CH}$ coupling. In the case of cyclocalopin A (**3**), this correlation establishes that C-7 and C-8 are part of a common ring, which is further supported by the large downfield shift of the enone carbonyl ^{13}C NMR signal on formation of the 7-*O*-acetyl derivative.[2]

In the same manner, the NMR data given for boletunone B[1] are much better explained by structure **6** than by the original proposal **2**. Table 2 (Supporting Information) indicates the assignment of the NMR signals[1] to the new structure. Compound **6** may be derived from cyclocalopin A (**3**) by hydrolytic lactone ring opening, followed by participation of the resulting primary alcohol in the formation of the illustrated cyclic acetal substructure. The NMR signals of **6** are in general agreement with those of cyclocalopin A and show characteristic differences associated with the formation of the bridged structure. All NOEs and HMBC correlations mentioned in the original publication, especially the strong NOE between 11β-H and 4-H,[1] typical for cyclocalopin A and related compounds,[2] are accounted for by our proposal. To indicate the close relationship of **6** to cyclocalopin A, we propose the name isocyclocalopin A for this compound.

Compared to boletunone A (**5**), boletunone B suffers a high-field shift of the 13-CH_3 signal from δ 1.57 to 0.94.[1] This is nicely explained by structure **6**, in which the methyl group is situated directly above the enone system. This strong shielding is not accounted for by formula **2**. Another strong NMR argument against formulas **1** and **2** is that, in ref 1, neither $^3J_{H,H}$ couplings nor $^1H-^1H$ COSY correlations between the vicinal protons at C-3 and C-7 are reported. According to a geometry optimization at the B3LYP/6-31G** level of theory, the dihedral angles between these protons in structures **1**[6] and **2** are 156 and 41°, respectively. As predicted by the Karplus equation,[7] this should lead to

(2) Hellwig, V.; Dasenbrock, J.; Gräf, C.; Kahner, L.; Schumann, S.; Steglich, W. *Eur. J. Org. Chem.* **2002**, 2895 (including Supporting Information with a detailed description of NMR correlation signals from the HMBC and NOESY experiments).
(3) Ebel, H.; Polborn, K.; Steglich, W. *Eur. J. Org. Chem.* **2002**, 2905.
(4) Ebel, H.; Zeitler, K.; Steglich, W. *Synthesis* **2003**, 101.
(5) Ebel, H.; Knör, S.; Steglich, W. *Tetrahedron* **2003**, *59*, 123.

(6) The most stable conformation calculated for a compound with formula **1** indicates that it has not the "peculiar stereostructure of a U shape" of Figure 2 (ref 1), but a more open-shaped structure. Some of the NOE effects given in ref 1 are therefore not in accord with structure **1** (e.g., that between 4-H_β and 6-H (original numbering): calcd distance 5.19 Å).
(7) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.

visible coupling. This problem is avoided by structures **5** and **6**, in which the isolated carbinol group has no neighboring protons.

The cyclocalopin structures we have assigned to the boletunones are in accord with the biogenetic hypothesis proposed in our earlier publication.[2] In contrast, the carbon skeleton present in formulas **1** and **2** contradicts present theories on terpene biosynthesis.

(8) Boletunone A (**5**), $[\alpha]_D$ +50 (MeOH) (ref 1), and cyclocalopin A (**3**), $[\alpha]_D$ −34.5 ($CHCl_3$) (ref 2), exhibit opposite optical rotations. To exclude the unlikely possibility that these compounds are enantiomers occurring in the same fungal species, the CD curves of the two compounds should be compared in the same solvent. The CD spectra of **3** in CH_3CN and EtOH are reported in ref 2.

In conclusion, the structures proposed for boletunones A and B in ref 1 should be corrected to those of 15-methoxycyclocalopin A (**5**) and isocyclocalopin A (**6**), respectively.[8]

Acknowledgment. We thank Dr. Bernd Straub for stimulating discussions and the geometry optimizations.

Supporting Information Available: Assignment of the NMR signals given in ref 1 to revised structure **6**, as well as NOE and HMBC experiments given in ref 1 that confirm the revised structures **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048724T