Guttiferone F, the First Prenylated Benzophenone from *Allanblackia stuhlmannii*[1]

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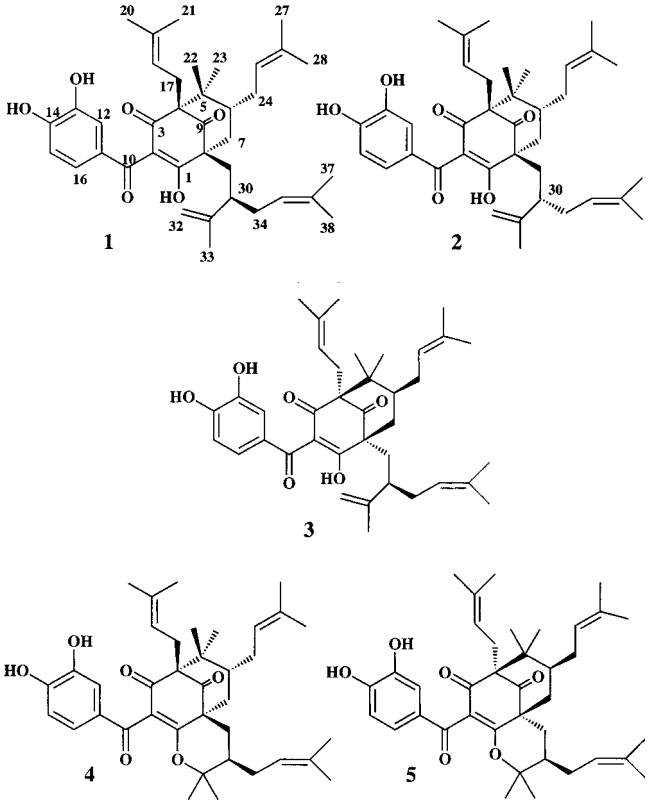
The HIV-inhibitory activity in extracts of *Allanblackia stuhlmannii* was tracked, via bioassay-guided fractionation, to a new member of the camboginol/guttiferone class of prenylated benzophenones, guttiferone F (**1**). The structure was solved by extensive NMR analyses and by acid-catalyzed conversion to 30-*epi*-cambogin (**4**). This is the first report of this compound type in the genus *Allanblackia*.

A series of HIV-inhibitory prenylated benzophenones, guttiferones A−E, was previously reported from extracts of three different genera (*Garcinia, Clusia,* and *Symphonia*) from the large plant family Guttiferae (Clusiaceae).[2] A dereplication effort[3] for this class of compounds has been extended to other genera in the family Guttiferae as the result of a somewhat larger than normal hit rate in the primary anti-HIV screen. Subsequently, we have isolated the first member of the camboginol[4]/guttiferone[2] class of polyprenylated benzophenones from the genus *Allanblackia*. Herein, we report the isolation and structure elucidation of guttiferone F (**1**) from *Allanblackia stuhlmannii* (Engl.) Engl.

An organic extract of one of three collections of the genus *Allanblackia, A. stuhlmannii,* gave a TLC response suggestive of the presence of guttiferones. Solvent−solvent partitioning and two gel permeation separations through Sephadex LH-20 (CH_2Cl_2−MeOH, 1:1, then hexane−CH_2Cl_2−MeOH, 2:5:1) gave **1** as the sole HIV-inhibitory constituent.

Guttiferone F (**1**), $C_{38}H_{50}O_6$ (MH^+, *m/z* 603.3696), had ^1H and ^{13}C NMR spectra (Table 1) virtually identical to those of camboginol (**2**)[4] and the antipodal guttiferone E (**3**),[2] except for resonances of protons on carbons in the C-29−C-32 region of the structure. All connectivities established by HMBC and COSY spectra (see Table 1) were identical to those shown previously for guttiferone E (**3**). These data suggested that guttiferone F was the C-30 epimer of camboginol or guttiferone E. The optical rotation of **1**, $[\alpha]_D$ −293°, suggested that its absolute stereochemistry was more like that of camboginol ($[\alpha]_D$ −125°) than guttiferone E ($[\alpha]_D$ +101°).

Verification of the epimeric configuration at C-30 was obtained by acid-catalyzed conversion of **1** to 30-*epi*-cambogin (**4**), which had ^1H and ^{13}C NMR spectra (Table 1) virtually identical to those of isoxanthochymol (**5**), except for proton and carbon resonances for C-7 and the C-29-C-32 region. The NOE interactions and $^3J_{HH}$ values recorded for **4** (Table 1) were consistent with a chair form for the tetrahydropyran ring, with C-7, C-33, H-29 (*pro-S*), and H-30 in axial dispositions. This would place the C-34 side chain in an equatorial configuration on the tetrahydropyran ring. This was in marked contrast to the conformation found previously for cambogin,[5] in which the tetrahydropyran ring occurred in a twist-boat arrangement, with the C-34 side chain equatorial to the tetrahydropyran ring. Molecular modeling supported the preference for a chair ring in **4** and a twist-boat conformation in **5**.



Typical of other guttiferones, **1** exhibited partial (not achieving 100%) cytoprotection against HIV-1 in vitro (EC_{50} 23 μg/mL), as well as direct cytotoxicity (IC_{50} of 82 μg/mL) to the host cells. This work extends further the distribution range of this class of compounds in the Guttiferae and suggests that these compounds may be even more widespread than previously known. In addition, a number of other research groups have reported unique and interesting variations in this biosynthetic class, including polyprenylated phloroglucinols,[6,7] an adamantyl phenyl ketone,[8] and differing levels of prenylation and/or carbocyclization.[9]

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Table 1. NMR Data for Guttiferone F (**1**) and 30-*epi*-Cambogin (**4**)[a]

	guttiferone F (**1**)				30-*epi*-cambogin (**4**)			
position	C	H	HMBC[b]	NOE	C	H	HMBC[b]	NOE
1	196.1				173.9			
2	117.9				110.2			
3	193.7				196.3			
4	69.4				69.6			
5	50.2				46.7			
6	47.9	1.49, m	5, 23, 24	7*R*, 22, 23, 24*RS*[c] 25, 27	47.5	1.50, m		7R*S*[c]18, 22, 23, 24*R*
7	43.8	2.04 *pro-S*, dd (13.5, 7.4)			40.0	2.02 *pro-S*, dd (14.5, 7.4)		
		2.24 *pro-R*, d (13.5)	1, 5, 6, 8, 9, 24, 29	6, 7*S*		2.28 *pro-R*, d (14)	1, 5, 6, 8, 9, 24	6, 7*S*
8	59.7				52.6			
9	210.6				208.0			
10	195.5				194.3			
11	129.5				131.2			
12	117.3	7.19, d (2)			116.3	7.24, d (2)	10, 13, 14, 16	
13	146.3				146.8			
14	152.5				152.5			
15	115.0	6.68, d (8)			115.6	6.73, d (8)	11, 13, 14	
16	125.3	6.96, dd (8, 2)			124.4	7.02, dd (8, 2)	10, 12, 14	
17	27.1	2.56 *pro-S*, dd (13, 3)	3, 4, 9, 18, 19		26.5	2.43 *pro-S*, dd (13.5, 5)	3, 4, 18, 19	
		2.71 *pro-R*, dd (13, 9)	4, 5, 9, 18, 19			2.63 *pro-R*, dd (13.8, 8)	4, 9, 18, 19	
18	121.3	5.03, m	20, 21		121.1	4.91, m		
19	135.9				135.3			
20	26.4	1.73, s	18, 19, 21		26.3	1.58, s	18, 19, 21	
21	18.3	1.69, s	18, 19, 20		18.2	1.57, s	18, 19, 20	
22	23.2	1.15, s	4, 5, 6, 23	6, 17*R*, 23, 24*RS*	22.8	1.14, s	4, 5, 6, 23	6, 23, 24*RS*
23	27.3	0.99, s	4, 5, 6, 22	6, 7*S*, 17*S*, 22	27.0	0.98, s	4, 5, 6, 22	6, 7*S*, 17*S*, 22
24	30.3	2.09, m	6, 7, 25, 26	6, 7*R*, 22	30.5	2.12 *pro-R*, m		6, 22, 24*S*, 25
		2.02, m				2.67 *pro-S*, m	6, 25, 26	24*R*, 25, 27
25	125.6	4.87, m	6, 24, 27, 28		126.2	4.91, m		
26	133.6				133.5			
27	25.9	1.65, s			26.1	1.68, s	25, 26, 28	
28	18.2	1.49, s	25, 26, 27	22, 23, 24*RS*, 25	18.5	1.66, s	25, 26, 27	
29	37.3	1.92 *pro-S*, dd (13.5, 4.5)	1, 7, 8, 9, 30, 31, 34	33	29.0	1.01 *pro-S*, dd (14, 14)	7, 8, 9, 30, 31	29*R*, 34*RS*
		1.98 *pro-R*, m				3.02 *pro-R*, dd (14, 3)	1, 8, 9, 30, 31	29*S*, 30, 35
30	45.2	2.62, m	29, 31, 32, 33, 34, 35	32, 33, 34, 35	44.7	1.36, m		29*R*, 32, 34*RS*
31	149.5				88.1			
32	113.0	4.45 (2H), s	30, 31, 33		29.0	0.90, s	30, 31, 33	30, 33, 34*S*
33	18.2	1.58, s	30, 31, 32		21.3	1.25, s	30, 31, 32	29*S*, 32, 34*RS*
34	33.5	2.01 (2H), m			30.5	1.83 *pro-R*, m	30, 32, 35, 36	29*S*, 33, 34*S*, 35
						2.05 *pro-S*, m		
35	124.1	5.03, m	30, 34, 37, 38		122.8	5.20, m	34, 37, 38	
36	132.7				134.6			
37	26.0	1.65, s			26.1	1.78, s	35, 36, 38	
38	18.2	1.57, s	35, 36, 37		17.8	1.63, s	35, 36, 37	

[a] Recorded in CD_3OD with 0.1% TFA at 500 MHz (^1H) and 125 MHz (^{13}C). [b] Carbons that correlate with the proton resonance. [c] *R* and *S* in this column refer to *pro-R* and *pro-S*.

These collective observations clearly increase the scope of the dereplication challenge in this family, since this compound class gives positive results in the primary screen but has not yet provided a candidate structure suitable for preclinical development.

The nomenclature of this class of compounds has a somewhat tortured history. The trivial name garcinol is frequently used for compound **2** (we used this name in our earlier work on this class of compounds[2]), but the names camboginol and cambogin (rather than isogarcinol) actually have precedence,[4] from both chronological and structural accuracy standpoints.[10] Subsequent authors have used the conflicting names garcinol and cambogin in the same paper.[11] The problem with the name garcinol is compounded further by its recent attribution to an unrelated (aryl benzofuran) *Garcinia* metabolite.[12]

We subsequently introduced the name guttiferone to avoid numerous trivial names based on genus or species and to emphasize the broader distribution of this compound class in the family Guttiferae.[2] However, we seem to have contributed to the confusion in naming compound **3** guttiferone E. As the enantiomer of the long known camboginol, it should more properly have been called (+)-camboginol.

Experimental Section

Plant Material. Rootwood of *A. stuhlmannii* was collected in the Iringe Region, Mufundi District, Tanzania, in December 1988 by R. Garcal and J. Lovell. A voucher specimen (RG2756) is maintained at the Missouri Botanical Garden.

Isolation of Gutteriferone F (1). A 5 g portion of the combined 1:1 CH_2Cl_2−MeOH and MeOH extracts was separated by solvent−solvent partitioning into hexane-, MeO-*t*-Bu-,

EtOAc-, and H_2O-soluble fractions. The antiviral MeO-*t*-Bu fraction (937 mg) was permeated through Sephadex LH-20 (2.5 × 100 cm) with CH_2Cl_2−MeOH (1:1). The second fraction (57 mg) was further separated on Sephadex LH-20 (2.5 × 50 cm) with hexane−CH_2Cl_2−MeOH (2:5:1) to give 12.5 mg (0.25% yield) of guttiferone F (**1**): $[\alpha_D]$ −293° (*c* 0.37, $CHCl_3$); λ_{max} (MeOH) 270 (ϵ 23 000) 230 (22 500) nm; IR ν_{max} (film) 3454, 2965, 1721, 1592, 1382, 1288, 1120 cm^{-1}; HRFABMS *m*/*z* 603.3696 (MH^+, calcd for $C_{38}H_{51}O_6$ 603.3607); LRFABMS *m*/*z* 603, 574, 465, 411, 307, 289, 231, 154; ^1H and ^{13}C NMR, see Table 1.

Conversion of 1 to 4. A solution of 5.6 mg of guttiferone F (**1**) in 5 mL of toluene and 30 μL of concentrated HCl was refluxed for 40 min. After cooling, the reaction mixture was washed with H_2O (2 × 5 mL) and evaporated to dryness to provide 3 mg of 30-*epi*-cambogin (**4**): $[\alpha]_D$ −125° (*c* 0.025, $CHCl_3$); λ_{max} (MeOH) 310 (ϵ 11 500), 277 (22 000), 230 (21 000) nm; HRFABMS *m*/*z* 603.3682 (MH^+, calcd for $C_{38}H_{51}O_6$ 603.3607); LRFABMS *m*/*z* 603, 574, 465, 411, 307, 289, 231, 154; ^1H and ^{13}C NMR, see Table 1.

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