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Lanostane and Hopane Triterpenes from the Entomopathogenic Fungus *Hypocrella* sp. BCC 14524

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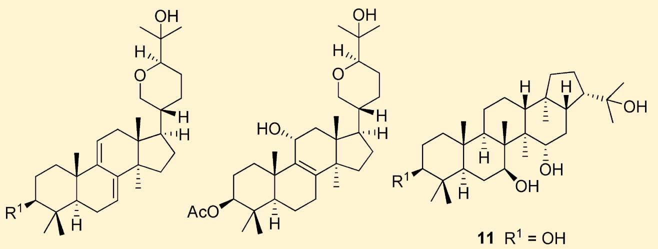
Supporting Information

ABSTRACT: Seven new lanostane-type triterpenes, hypocrellols A–G (**1–7**), and six new hopane-type triterpenes, 7β,15α-dihydroxy-22(29)-hopene (**8**), 3β,7β-dihydroxy-22(29)-hopene (**9**), 3β-acetoxy-15α-hydroxy-22(29)-hopene (**10**), 3β,7β,15α,22-tetrahydroxyhopane (**11**), 3β-acetoxy-7β,15α,22-trihydroxyhopane (**12**), and 7β,15α,22-trihydroxyhopane (**13**), were isolated from the scale insect pathogenic fungus *Hypocrella* sp. BCC 14524. The structures of the new compounds were elucidated by analyses of the NMR spectroscopic and mass spectrometry data. The structure of **1** was confirmed by X-ray crystallography.



1 R^1 = OH
2 R^1 = OAc

4

11 R^1 = OH
12 R^1 = OAc
13 R^1 = H

Entomopathogenic fungi have recently proved to be potent sources of structurally unique and biologically active compounds.[1,2] As part of our research program on secondary metabolites from this group of fungi,[3] we recently reported that *Hypocrella* and *Moelleriella* species and their anamorph, *Aschersonia* species, are common producers of three hopane-type triterpenes, 6α,22-dihydroxyhopane (zeorin), 15α,22-dihydroxyhopane (dustanin), and 3β-acetoxy-15α,22-dihydroxyhopane, and these hopanoids may be useful as chemotaxonomic markers.[4] In this study, we examined ^{1}H NMR spectroscopic data profiles of the extracts from 98 strains of these fungi. *Hypocrella* sp. strain BCC 14524 showed a unique profile, suggesting the presence of a complex mixture of many terpenoids, and this strain was selected for large-scale fermentation and further chemical analysis. We report here the isolation of seven new lanostane-type triterpenes, hypocrellols A–G (**1–7**), and six new hopane-type triterpenes, 7β,15α-dihydroxy-22(29)-hopene (**8**), 3β,7β-dihydroxy-22(29)-hopene (**9**), 3β-acetoxy-15α-hydroxy-22(29)-hopene (**10**), 3β,7β,15α,22-tetrahydroxyhopane (**11**), 3β-acetoxy-7β,15α,22-trihydroxyhopane (**12**), and 7β,15α,22-trihydroxyhopane (**13**), along with the known 3β,15α,22-trihydroxyhopane (**14**),[5] 3β-acetoxy-15α,22-dihydroxyhopane (**15**),[6] and 15α,22-dihydroxyhopane (**16**, dustanin).[7] Compounds obtained in high yield were evaluated for biological activities.

■ RESULTS AND DISCUSSION

Hypocrellol A (**1**) was isolated as a colorless solid, and the molecular formula was determined as $C_{30}H_{48}O_3$, from the sodiated quasimolecular ion peak in the HRESIMS. The IR spectrum exhibited a broad absorption band at ν_{max} 3483 cm^{-1}, which indicated the presence of hydroxy groups. The ^{1}H and ^{13}C NMR data recorded in $CDCl_3$ strongly suggested that **1** was a triterpenoid, but the resonance patterns differed from the known hopane-type cometabolites **14–16**. The ^{1}H and ^{13}C NMR, DEPT135, and HMQC data for **1** indicated the presence of two olefinic quaternary carbons at δ_C 146.1 and 142.3, two olefinic methines at δ_C 120.6 (δ_H 5.48) and 115.8 (δ_H 5.29), an oxygenated quaternary carbon at δ_C 71.8, two oxymethines at δ_C 78.9 (δ_H 3.23) and 84.0 (δ_H 3.00), an oxymethylene at δ_C 72.9 (δ_H 4.18 and 3.06), four sp^3 quaternary carbons, three methines, eight methylenes, and seven methyl groups (Tables 1 and 2). The planar structure of **1** was deduced by analyses of COSY and HMBC data as a lanosta-7,9(11)-diene (Figure 1). Key HMBC correlations were observed from seven methyl groups (H_3-18, H_3-19, H_3-26, H_3-27, H_3-28, H_3-29, and H_3-30) attached to quaternary sp^3 carbons C-13, C-10, C-25, C-4, C-4, and C-14, respectively. A tetrahydropyran ring was indicated by HMBC correlations from H_2-21 (δ_H 4.18 and 3.06) to C-24. The relative configuration of **1** was addressed on the basis of *J*-values and NOESY correlations (Figure 1). NOESY correlations for protons and methyl protons at axial positions demonstrated the lanostane-type relative configuration of the ABCD-ring system. An axial orientation of H-3 was evident from its coupling constants (dd, *J* = 11.4, 4.3 Hz), and this proton showed NOESY correlations to H_α-1 and H-5. The

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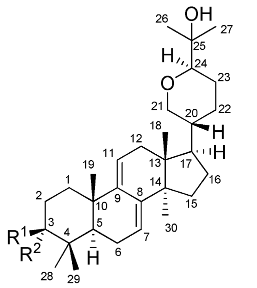
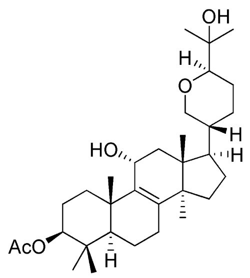
Chart 1



1 R^1 = OH, R^2 = H
2 R^1 = OAc, R^2 = H
3 R^1,R^2 = O



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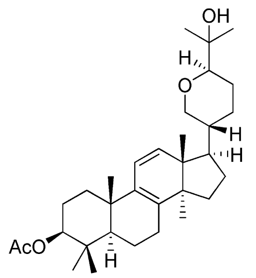

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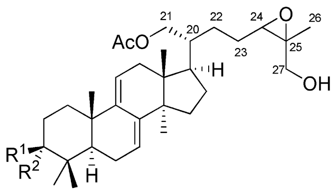
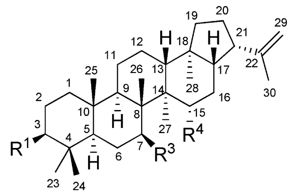
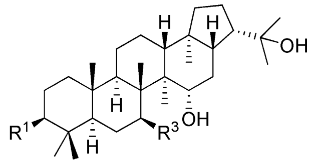


6 R^1 = OAc, R^2 = H
7 R^1,R^2 = O



8 R^1 = H, R^3 = OH, R^4 = OH
9 R^1 = OH, R^3 = OH, R^4 = H
10 R^1 = OAc, R^3 = H, R^4 = OH



11 R^1 = OH, R^3 = OH
12 R^1 = OAc, R^3 = OH
13 R^1 = H, R^3 = OH
14 R^1 = OH, R^3 = H
15 R^1 = OAc, R^3 = H
16 R^1 = H, R^3 = H

coupling constants for H_α-21 (t, J = 10.8 Hz) and H-24 (dd, J = 11.4, 1.7 Hz) and NOESY correlations from these protons to H_α-22 (δ_H 1.09) demonstrated that the tetrahydropyran adopted a chair conformation and axial positions and coplanar relation of H_α-21, H_α-22, and H-23. NOESY correlations from H_β-21 (δ_H 4.18) to H_β-12 (δ_H 2.13, br d, J = 17.4 Hz) and H_3-18 suggested the 17R*,20R* configuration. Finally, the structure of **1** was confirmed by X-ray crystallographic analysis (Figure 2). The absolute configuration was determined by application of the modified Mosher's method.[8] The $\Delta\delta$ values of the (S)- and (R)-MTPA esters, **17a** and **17b**, indicated the 3S-configuration (Figure 3).

Hypocrellol B (**2**) possessed the molecular formula $C_{32}H_{50}O_4$ (HRESIMS). The ^{1}H and ^{13}C NMR spectroscopic data were similar to those of **1**. Significant differences were the presence of an acetyl group (δ_C 170.9; δ_C 21.3/δ_H 2.06) and the downfield shift of H-3 (δ_H 4.50, dd, J = 11.4, 4.6 Hz), which showed an HMBC correlation to the carbonyl carbon of the acetyl group (δ_C 170.9). Therefore, compound **2** was assigned as the 3-O-acetyl derivative of **1**. Acetylation of **1** (Ac_2O/pyridine, rt, 15 h) gave a sole product whose ^{1}H NMR ($CDCl_3$) and ESIMS data were identical to those of **2**.

The molecular formula of hypocrellol C (**3**) was determined by HRESIMS as $C_{30}H_{46}O_3$, containing two less hydrogen atoms than **1**. The ^{1}H and ^{13}C NMR spectroscopic data were similar to those of **1** except for the presence of an aliphatic ketone at δ_C 216.6 and absence of the hydroxylated methine (CH-3). The location of the ketone (C-3) was confirmed by the HMBC correlations from H_β-1 (δ_H 2.28), H_α-2 (δ_H 2.34), H_β-2 (δ_H 2.78), H_3-28 (δ_H 1.08), and H_3-29 (δ_H 1.12) to this carbon (δ_C 216.6).

The NMR spectroscopic data of hypocrellol D (**4**) suggested that it was a lanostanoid similar to **2**, possessing a 3β-acetoxy group (Table 3). The differences were the absence of two olefinic methines (CH-7 and CH-11 in **2**) and the presence of an additional sp^3 methylene (CH_2-7) and a hydroxylated methine (CH-11) at δ_C 65.1 (δ_H 4.33). The location of the tetrasubstituted olefin was assigned to position C-8/C-9 on the basis of the HMBC correlations from H-5, H-11, and H_3-19 to C-9 (δ_C 136.2) and from H-11 and H_3-30 to C-8 (δ_C 141.5). NOESY correlations from H-11 to H_3-19 and H_3-18 indicated the β-face orientation of H-11. Presumably, either hypocrellol B (**2**) or D (**4**) could be the biosynthetic precursor of the other.

Hypocrellol E (**5**) possessed the same molecular formula as **2**, $C_{32}H_{50}O_4$ (HRESIMS). The ^{1}H and ^{13}C NMR spectroscopic data differed from those of **2** at the B and C ring. Two olefinic methine protons at δ_H 5.78 (H-11) and 5.76 (H-12) were coupled with a J value of 10.0 Hz. The following HMBC correlations demonstrated that the location of the conjugated diene shifted to lanosta-8,11-diene: from H-11 and H_3-30 to C-8 (δ_C 138.4), from H-11, H-12, and H_3-19 to C-9 (δ_C 135.8), and from H_3-18 to C-12 (δ_C 135.1). This compound was probably produced by dehydration of **4**.

The side chain (C-20−C-27) structure of hypocrellols A−E (**1**−**5**) shows resemblance to those of some lanostanes isolated from mushrooms, but differs in the oxidation state of C-21. Crustulinol[9] and its derivatives,[10] isolated from *Hebeloma* species, possess a six-membered hemiacetal instead of the tetrahydropyran of hypocrellols. Inonotsulides A−C, isolated from the sclerotia of *Inonotus obliquus*, form a δ-lactone.[11]

The HRESIMS of hypocrellol F (**6**) showed a sodiated molecular ion peak consistent with an elemental formula of $C_{34}H_{52}O_6Na$. The ^{1}H and ^{13}C NMR spectroscopic data were similar to **2** for the ABCD ring moiety, but different from those of **1**−**3** at the C-20−C-27 side chain. The side chain structure was addressed on the basis of COSY and HMBC data. The attachment of an acetoxy group to C-21 was evident from the HMBC correlations from the nonequivalent oxymethylene

Table 1. ^{13}C NMR ($CDCl_3$, 125 MHz) Data for Hypocrellols A–G (1–7)

position	1	2	3	4	5	6	7
1	35.7, CH_2	35.4, CH_2	36.6, CH_2	35.4, CH_2	35.2, CH_2	35.4, CH_2	36.6, CH_2
2	27.8, CH_2	24.2, CH_2	34.8, CH_2	24.1,[b] CH_2	24.1, CH_2	24.3, CH_2	34.8, CH_2
3	78.9, CH	80.8, CH	216.6, qC	80.7, CH	80.7, CH	80.8, CH	216.6, qC
4	38.7, qC	37.6, qC	47.5, qC	37.9, qC	37.7, qC	37.6, qC	47.5, qC
5	49.1, CH	49.3, CH	50.7, CH	50.1, CH	50.4, CH	49.2, CH	50.7, CH
6	23.0, CH_2	22.83, CH_2	23.7, CH_2	18.1, CH_2	17.9, CH_2	22.83, CH_2	23.7, CH_2
7	120.6, CH	120.3, CH	120.3, CH	26.12,[c] CH_2	28.2, CH_2	120.4, CH	120.4, CH
8	142.3, qC	142.4, qC	142.6, qC	141.5, qC	138.4, qC	142.4, qC	142.5qC
9	146.1, qC	145.8, qC	144.7, qC	136.2, qC	135.8, qC	145.8, qC	144.7, qC
10	37.4, qC	37.3, qC	37.2, qC	37.7, qC	35.8, qC	37.3, qC	37.2, qC
11	115.8, CH	116.1, CH	116.8, CH	65.1, CH	122.9, CH	116.2, CH	116.9, CH
12	37.3, CH_2	37.4, CH_2	37.3, CH_2	44.6, CH_2	135.1, CH	36.9, CH_2	36.9, CH_2
13	43.6, qC	43.6, qC	43.6, qC	47.8, qC	47.6, qC	43.5, qC	43.5, qC
14	50.2, qC	50.2, qC	50.2, qC	50.3, qC	50.0, qC	50.4, qC	50.4, qC
15	31.4, CH_2	31.4, CH_2	31.4, CH_2	31.5, CH_2	27.8, CH_2	31.4, CH_2	31.4, CH_2
16	26.0, CH_2	26.0, CH_2	26.0, CH_2	26.0,[c] CH_2	26.0, CH_2	27.6, CH_2	27.6, CH_2
17	48.0, CH	48.0, CH	48.0, CH	48.2, CH	42.2, CH	45.4, CH	45.4CH
18	16.0, CH_3	16.0, CH_3	16.1, CH_3	17.4, CH_3	14.1, CH_3	15.9, CH_3	15.9, CH_3
19	22.7, CH_3	22.76, CH_3	22.0, CH_3	20.8, CH_3	21.3, CH_3	22.87, CH_3	22.0, CH_3
20	39.3, CH	39.3, CH	39.3, CH	39.3, CH	39.9, CH	40.2, CH	40.1, CH
21	72.9, CH_2	72.9, CH_2	72.8, CH_2	72.8, CH_2	72.9, CH_2	64.3, CH_2	64.3, CH_2
22	30.1, CH_2	30.1, CH_2	30.1, CH_2	30.1, CH_2	30.0, CH_2	27.4, CH_2	27.4, CH_2
23	26.7, CH_2	26.7, CH_2	26.7, CH_2	26.4,[c] CH_2	26.8, CH_2	25.2, CH_2	25.2, CH_2
24	84.0, CH	84.0, CH	84.1, CH	84.0, CH	84.0, CH	65.0, CH	65.0, CH
25	71.8, qC	71.8, qC	71.8, qC	71.8, qC	71.8, qC	60.7, qC	60.7, qC
26	26.1, CH_3	26.1, CH_3	26.1, CH_3	26.14, CH_3	26.2, CH_3	20.2, CH_3	20.2, CH_3
27	24.0, CH_3	24.1, CH_3	24.1, CH_3	24.1,[b] CH_3	24.0, CH_3	63.9, CH_2	63.9, CH_2
28	28.1, CH_3	28.1, CH_3	25.4,[a] CH_3	27.9, CH_3	27.9, CH_3	28.1, CH_3	25.3, CH_3
29	15.8, CH_3	16.9, CH_3	22.5, CH_3	16.4, CH_3	16.4, CH_3	16.9, CH_3	22.5, CH_3
30	25.6, CH_3	25.5, CH_3	25.4,[a] CH_3	24.8, CH_3	20.4, CH_3	25.5, CH_3	25.4, CH_3
3-$OCOCH_3$		170.9, qC		170.9, qC	171.0, qC	171.0, qC	
3-$OCOCH_3$		21.3, CH_3		21.3, CH_3	21.4, CH_3	21.3, CH_3	
21-$OCOCH_3$						171.4, qC	171.4, qC
21-$OCOCH_3$						21.0, CH_3	21.0, CH_3

[a,b]The carbon resonances were superimposed. [c]The assignment of these carbons can be interchanged.

protons at δ_H 4.26 and 3.97 to the ester carbonyl at δ_C 171.4. One of the terminal methyl groups was hydroxylated (δ_C 63.9; δ_H 3.68–3.66, CH_2-27). The presence of an epoxide (C-24/C-25) was demonstrated by the HMBC correlations from H_3-26 and H_2-27 to the oxygenated methine at δ_C 65.0 (C-24; δ_H 2.82) and the oxygenated quaternary carbon at δ_C 60.7 (C-25). An intense NOESY cross-peak of H-24 and H_3-26 and a weak correlation of H_a-23 and H_2-27 indicated the *cis*-relationship of H-24 and CH_3-26. Therefore, the relative configuration of the epoxide should be 24*R**,25*S**. The relative configuration of C-13/C-17/C-20 was suggested by the NOESY correlations from H_3-18 to H-20 and H_β-12 and from H_β-12 to H_b-21 (δ_H 3.97), which was consistent with the co-occurrence with **1–3**.

Hypocrellol G (**7**), with the molecular formula $C_{32}H_{48}O_5$ (HRESIMS), was assigned as the 3-keto derivative of **6**. The NMR spectroscopic data were very similar to those of **3** for ring A and those of **6** for the C-20–C-27 side chain. The NOESY correlations from H-20 to H_3-18 and H_β-12 (δ_H 1.98) and from H_β-12 to H_b-21 (δ_H 3.96) demonstrated the relative configuration of C-13/C-17/C-20.

The molecular formula of compound **8** was established as $C_{30}H_{50}O_2$ by HRESIMS. The ^1H and ^{13}C NMR data suggested that **8** was a hopane-type triterpene related to the known co-metabolites **14–16**. The ^1H and ^{13}C NMR, DEPT135, and HMQC data for **8** indicated the presence of an exomethylene group at δ_C 148.0 (qC) and 110.5 (CH_2; δ_H 4.80 and 4.78), two oxygenated methines at δ_C 72.1 (δ_H 3.87) and 73.1 (δ_H 3.86), five sp^3 quaternary carbons, five methines, nine methylenes, and seven methyl groups (Table 4). The planar structure of **8** was deduced by analyses of COSY and HMBC data (Figure 4). Key HMBC correlations were observed from seven methyl groups (H_3-23, H_3-24, H_3-25, H_3-26, H_3-27, H_3-28, and H_3-30) to their attached quaternary carbons (^2J), C-4, C-4, C-10, C-8, C-14, C-18, and C-22, respectively, and the ^3J correlations. The exomethylene group was assigned to positions C-21/C-29 on the basis of the following HMBC correlations: from H-21 to C-22 and C-30, from H_2-29 to C-21, C-22, and C-30, and from H_3-30 to C-21, C-22, and C-29. The locations of two secondary alcohols, CH-7 and CH-15, were revealed by the HMBC correlations from H-5 (δ_H 0.76), H_α-6 (δ_H 1.73), H_β-6 (δ_H 1.45), and H_3-26 (δ_H 1.01) to C-7 (δ_C 72.1) and from H_α-16 (δ_H 1.59), H_β-16 (δ_H 1.95), and H_3-27 (δ_H 1.00) to C-15 (δ_C 73.1). The relative configuration of **8** was assigned by analyses of *J* values and NOESY correlations to be a hopane-type triterpene (Figure 4). The axial orientations of the oxymethine protons were evident from the observed coupling constants. Compound **8** was therefore assigned as 7β,15α-dihydroxy-22(29)-hopene.

Table 2. ^{1}H (500 MHz, $CDCl_3$) NMR Data for Hypocrellols A−C (1−3)

position	1	2	3
1	α 1.42, m; β 1.99, m	α 1.52, m β 1.99, dt (13.4, 3.5)	α 1.74, dt (4.3, 13.8) β 2.28, ddd (13.3, 5.6, 2.4)
2	α 1.71, m; β 1.63, m	α 1.74, m; β 1.70, m	α 2.34, ddd (14.4, 4.3, 2.4) β 2.78, dt (5.6, 13.8)
3	3.23, dd (11.4, 4.3)	4.50, dd (11.4, 4.6)	
5	1.08, dd (11.2, 4.8)	1.18, m	1.51, m
6	α 2.09, m; β 2.07, m	α 2.08, m; β 2.06, m	α 2.05, m; β 2.20, m
7	5.48, br d (5.8)	5.47, m	5.52, d (6.7)
11	5.29, br d (6.2)	5.29, br d (6.2)	5.37, d (6.4)
12	α 2.13, br d (17.4) β 1.90, dd (17.4, 6.4)	α 2.14, br d (17.5) β 1.90, dd (17.5, 6.5)	α 2.15, br d (17.7) β 1.92, m
15	α 1.41, m; β 1.65, m	α 1.40, m; β 1.65, m	α 1.40, m; β 1.64, m
16	1.95, m; 1.36, m	1.95, m; 1.36, m	1.97, m; 1.36, m
17	1.48, m	1.48, m	1.50, m
18	0.60, s	0.60, s	0.62, s
19	0.97, s	1.00, s	1.20, s
20	1.51, m	1.50, m	1.52, m
21	4.18, m; 3.06, t (10.8)	4.18, dq (10.8, 1.6); 3.07, t (10.8)	4.18, ddd (10.8, 4.0, 2.0); 3.07, t (10.8)
22	α 1.09, m; β 1.92, m	α 1.10, m; β 1.92, m	α 1.10, m; β 1.93, m
23	α 1.61, m; β 1.34, m	α 1.62, m; β 1.34, m	α 1.62, m; β 1.34, m
24	3.00, dd (11.4, 1.7)	3.01, dd (11.4, 1.6)	3.01, dd (11.4, 1.8)
26	1.16, s	1.17, s	1.17, s
27	1.12, s	1.13, s	1.12, s
28	1.00, s	0.88, s	1.08, s
29	0.88, s	0.95, s	1.12, s
30	0.86, s	0.86, s	0.86, s
3-OAc		2.06, s	

The molecular formula of compound **9** was the same as that of **8** ($C_{30}H_{50}O_2$, HRESIMS). The NMR spectroscopic data were similar to those of **8**, possessing an isopropenyl group (C-22/C-29/C-30). Detailed analysis of COSY, HMQC, and HMBC data revealed the location of two hydroxy groups at 3*β* and 7*β*; therefore, compound **9** was identified as 3*β*,7*β*-dihydroxy-22(29)-hopene.

The ^{1}H and ^{13}C NMR spectroscopic data for compound **10** suggested that it was a 22(29)-hopene, possessing acetoxy and a hydroxy functionalities. HMBC correlation from H-3 (δ_H 4.47) to the ester carbonyl carbon at δ_C 171.0 indicated the position of the acetoxy group at 3*β*. NOESY correlations from H-15 (δ_H 3.86) to H_3-26, H_β-16, and H-17 revealed the *β*-face (axial) orientation of this oxymethine proton. Compound **10** was therefore assigned as 3*β*-acetoxy-15*α*-hydroxy-22(29)-hopene, a dehydrated analogue of **15**.

The molecular formula of compound **11** was determined to be $C_{30}H_{52}O_4$ by HRESIMS. The ^{1}H and ^{13}C NMR spectroscopic data were similar to those of the known 22-hydroxyhopanes **14**, **15**, and **16**. It possessed three secondary alcohol functionalities, whose locations were assigned to 3*β*, 7*β*, and 15*α* positions. Compound **12**, $C_{32}H_{54}O_5$ (HRESIMS), was identified as 3*β*-acetoxy-7*β*,15*α*,22-trihydroxyhopane, the 3-*O*-acetyl derivative of **11**. Similarly, the structure of compound **13** was determined by analyses of HRESIMS and 2D NMR spectroscopic data as 7*β*,15*α*,22-trihydroxyhopane.

Compounds **1**, **2**, **4**, **8**, **10**, **11**, and **12** were subjected to our bioassay protocols: antimalarial activity against *Plasmodium falciparum* K1, antimycobacterial activity against *Mycobacterium tuberculosis* H37Ra, and cytotoxicity to three cancer cell lines, KB, MCF-7, and NCI-H187, and nonmalignant Vero cells. Compounds **1**, **2**, **8**, and **10** were inactive in these assays. Lanostane **4** and hopanes **11** and **12** exhibited antimalarial activity (**4**, IC_{50} 8.0 μM; **11**, IC_{50} 12 μM; **12**, IC_{50} 5.2 μM), antimycobacterial activity (**4**, MIC 50 μg/mL; **11**, MIC 50 μg/mL; **12**, MIC 6.25 μg/mL), and cytotoxicity to KB cells (**4**, IC_{50} 15 μM; **11**, IC_{50} 28 μM; **12**, IC_{50} 56 μM), MCF-7 cells (**4**, IC_{50} 38 μM; **11**, IC_{50} >105 μM; **12**, IC_{50} >96 μM), NCI-H187 cells (**4**, IC_{50} 18 μM; **11**, IC_{50} 12 μM; **12**, IC_{50} 11 μM), and Vero cells (**4**, IC_{50} 30 μM; **11**, IC_{50} 47 μM; **12**, IC_{50} 13 μM). Antimycobacterial activity of hopanoids **14** (MIC >50 μg/mL), **15** (MIC 12.5 μg/mL), and **16** (MIC 12.5 μg/mL) was previously reported, and **14−16** were not cytotoxic to Vero cells.[6]

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were measured with an Electrothermal IA9100 digital melting point apparatus. Optical rotations were measured with a JASCO P-1030 digital polarimeter. UV spectra were recorded on a GBS Cintra 404 spectrophotometer. FTIR spectra were taken on Bruker VECTOR 22 and ALPHA spectrometers. NMR spectra were recorded on Bruker DRX400 and AV500D spectrometers. ESITOF mass spectra were measured with a Bruker micrOTOF mass spectrometer.

Fungal Material. The fungus used in this study was isolated from a scale insect collected in Nam Nao National Park, Phetcha Bun Province, Thailand. This fungus was deposited in the BIOTEC Culture Collection (BCC) on February 16, 2004, as BCC 14524. On the basis of the sequence data of the ITS rDNA, we performed a BLAST search and found the specimen within the family Clavicipitaceae close to *Aschersonia hypocreoidea* (teleomorph *Hypocrella*) with a similarity of 97% (maximum identity).

Fermentation and Isolation. The fungus BCC 14524 was maintained on potato dextrose agar at 25 °C. The agar was cut into small plugs and inoculated into 6 × 250 mL Erlenmeyer flasks containing 25 mL of potato dextrose broth (PDB; potato starch 4.0 g/L, dextrose 20.0 g/L). After incubation at 25 °C for 13 days on a rotary shaker (200 rpm), each primary culture was transferred into a

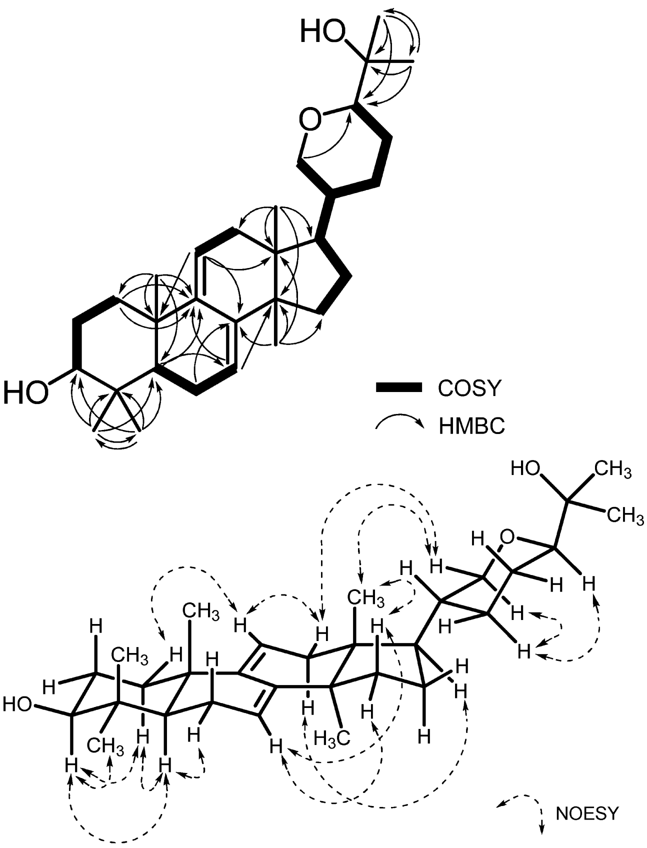


Figure 1. Selected COSY, HMBC, and NOESY correlations for **1**.

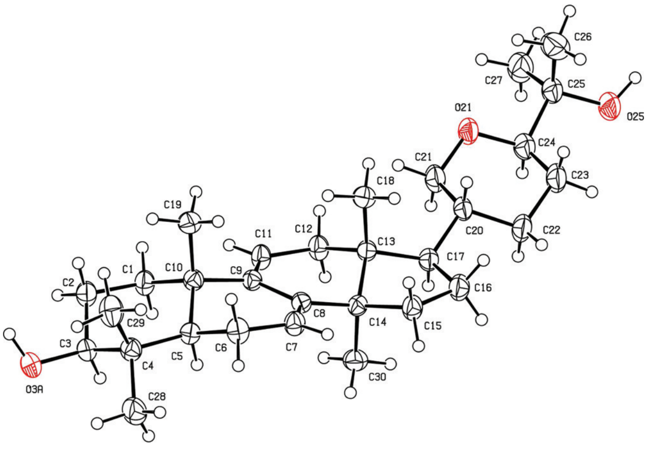
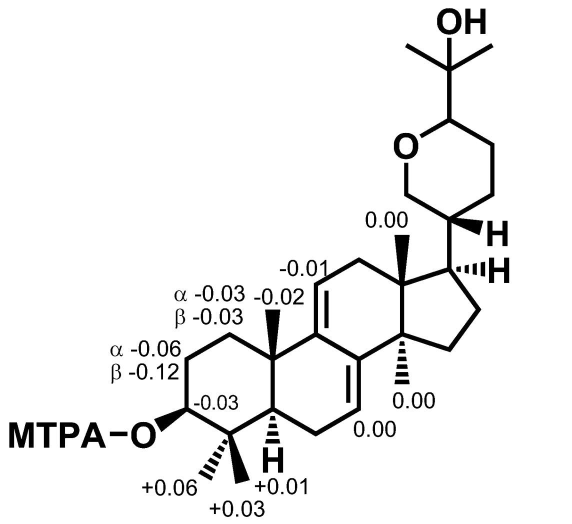


Figure 2. ORTEP plot of hypocrellol A (**1**).

1 L Erlenmeyer flask containing 250 mL of the same liquid medium (PDB) and incubated at 25 °C for 13 days on a rotary shaker (200 rpm). These secondary cultures were pooled, and each 25 mL portion was transferred into 60 × 1 L Erlenmeyer flasks containing 250 mL of PDB. The final fermentation was carried out at 25 °C for 34 days under static conditions. The culture was filtered to separate broth (filtrate) and mycelia (residue). The EtOAc extract from broth did not contain any new or unique compounds. The wet mycelia were macerated in MeOH (2 L, rt, 2 days) and filtered. This extraction was repeated once again. To the first extract (2 L MeOH solution) was added hexanes (2 L), and the layers were separated. The MeOH layer was concentrated by evaporation, and H_2O was added to the residue, which was then extracted with EtOAc (1.5 L). The EtOAc solution was concentrated under reduced pressure to obtain a brown gum (2.7 g, extract A1). The hexane layer was concentrated under reduced



17a (*S*)-MTPA ester
17b (*R*)-MTPA ester

Figure 3. $\Delta\delta$ values ($\delta_S - \delta_R$) of the Mosher esters **17a** and **17b**.

pressure, leaving a pale yellow gum (2.4 g, extract B1). The second MeOH solution was also treated with the same procedure to obtain extracts A2 (2.3 g) and B2 (2.0 g). Extracts A1 and A2 were separately subjected to fractionation by column chromatography (CC) on silica gel (4.7 × 13 cm, step gradient elution with EtOAc/CH_2Cl_2), and the fractions were repeatedly fractionated by CC on silica gel (EtOAc/hexanes) to furnish pure compounds: **1** (28 mg), **2** (36 mg), **3** (1.2 mg), **4** (2.0 mg), **5** (1.4 mg), **6** (5 mg), **7** (6 mg), **8** (8 mg), **10** (4 mg), **12** (12 mg), **15** (300 mg), **16** (694 mg), and ergosterol (100 mg). The hexane portions (extracts B1 and B2) were also repeatedly fractionated by CC on silica gel (EtOAc/CH_2Cl_2 and EtOAc/hexanes) to obtain **1** (12 mg), **2** (73 mg), **3** (2.0 mg), **4** (6 mg), **5** (2.7 mg), **8** (9 mg), **9** (6 mg), **10** (6 mg), **12** (8 mg), **13** (4 mg), **15** (600 mg), **16** (130 mg), and ergosterol (21 mg). A Preliminary study on another fermentation batch (28 × 250 mL, same culturing conditions) led to the isolation of **1** (9 mg), **2** (8 mg), **11** (9 mg), **12** (9 mg), **14** (45 mg), **15** (251 mg), **16** (291 mg), and ergosterol (30 mg).

Hypocrellol A (1): colorless solid; mp 253−254 °C; $[\alpha]^{25}_{D}$ +53 (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ε) 217 (4.24), 243 (4.31), 251 (4.13) nm; IR (KBr disk) ν_{max} 3483, 2962, 1389, 1090, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) data, see Table 2; ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 1; HRMS (ESI-TOF) *m/z* 479.3500 [M + Na]$^+$ (calcd for $C_{30}H_{48}O_3Na$, 479.3496).

Hypocrellol B (2): colorless solid; mp 201−203 °C; $[\alpha]^{25}_{D}$ +51 (*c* 0.20, MeOH); UV (MeOH) λ_{max} (log ε) 236 (3.96), 242 (4.03), 252 (3.86) nm; IR (KBr disk) ν_{max} 3513, 2965, 1713, 1373, 1269, 1091, 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) data, see Table 2; ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 1; HRMS (ESI-TOF) *m/z* 521.3609 [M + Na]$^+$ (calcd for $C_{32}H_{50}O_4Na$, 521.3601).

Hypocrellol C (3): colorless solid; mp 204−205 °C; $[\alpha]^{24}_{D}$ +27 (*c* 0.065, MeOH); UV (MeOH) λ_{max} (log ε) 236 (3.96), 243 (4.03), 252 (3.85) nm; IR (ATR) ν_{max} 3479, 2960, 1705, 1372, 1177, 1090, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) data, see Table 2; ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 1; HRMS (ESI-TOF) *m/z* 477.3337 [M + Na]$^+$ (calcd for $C_{30}H_{46}O_3Na$, 477.3339).

Hypocrellol D (4): colorless solid; mp 124−125 °C; $[\alpha]^{26}_{D}$ +42 (*c* 0.11, MeOH); UV (MeOH) λ_{max} (log ε) 213 (3.68) nm; IR (ATR) ν_{max} 3439, 2943, 1730, 1372, 1244, 1087 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) data, see Table 3; ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 1; HRMS (ESI-TOF) *m/z* 539.3701 [M + Na]$^+$ (calcd for $C_{32}H_{52}O_5Na$, 539.3707).

Hypocrellol E (5): colorless, amorphous solid; $[\alpha]^{25}_{D}$ +14 (*c* 0.055, MeOH); UV (MeOH) λ_{max} (log ε) 273 (3.52) nm; IR (ATR) ν_{max} 3505, 2953, 1735, 1368, 1246, 1087, 1035 cm^{-1}; ^1H NMR

Table 3. ^{1}H (500 MHz, $CDCl_3$) NMR Data for Hypocrellols D−G (4−7)

position	4	5	6	7
1	α 1.71, m; β 1.83, m	α 1.32, m; β 1.88, m	α 1.52, m; β 1.98, m	α 1.73, m; β 2.27, m
2	α 1.74, m; β 1.64, m	α 1.72, m; β 1.65, m	α 1.74, m; β 1.70, m	α 2.34, m; β 2.78, m
3	4.52, dd (11.7, 4.1)	4.51, dd (11.8, 4.6)	4.51, dd (11.4, 4.6)	
5	1.30, dd (12.8, 2.3)	1.08, dd (12.3, 1.6)	1.18, dd (10.7, 5.2)	1.52, dd (12.3, 3.8)
6	α 1.71, m; β 1.57, m	α 1.70, m; β 1.50, m	2.10−2.05, m	α 2.06, m; β 2.19, m
7	α 2.14, m; β 2.10, m	α 2.00, m; β 2.15, m	5.48, m	5.52, br d (6.5)
11	4.33, dd (9.0, 3.4)	5.78, d (10.0)	5.30, br d (6.0)	5.37, br d (6.1)
12	α 1.73, m; β 2.13, m	5.76, d (10.0)	α 2.18, br d (17.6)	α 2.20, br d (17.2)
			β 1.95, m	β 2.27, dd (17.2, 6.1)
15	α 1.25, m; β 1.65, m	α 1.39, m; β 1.62, m	α 1.41, m; β 1.65, m	α 1.42, m; β 1.65, m
16	1.91, m; 1.33, m	1.98, m; 1.63, m	2.03, m; 1.39, m	2.04, m; 1.40, m
17	1.50, m	1.66, m	1.91, m	1.90, m
18	0.68, s	0.87, s	0.59, s	0.61, s
19	1.02, s	0.98, s	0.99, s	1.19, s
20	1.49, m	1.52, m	1.66, m	1.67, m
21	4.18, br d (10.7)	4.21, ddd (10.9, 3.9, 1.9)	4.26, dd (11.5, 2.4)	4.25, dd (11.5, 2.4)
	3.04, t (10.7)	3.18, t (10.9)	3.97, dd (11.5, 5.2)	3.96, dd (11.5, 5.2)
22	α 1.10, m; β 1.90, m	α 1.10, m; β 1.90, m	1.71, m; 1.64, m	1.70, m; 1.63, m
23	α 1.62, m; β 1.33, m	α 1.63, m; β 1.34, m	1.69, m; 1.52, m	1.68, m; 1.53, m
24	3.00, dd (11.4, 1.5)	3.02, dd (11.4, 1.7)	2.82, m	2.81, m
26	1.17, s	1.17, s	1.39, s	1.39, s
27	1.12, s	1.13, s	3.68−3.66, m	3.68−3.66, m
28	0.89,[a] s	0.88,[b] s	0.88,[c] s	1.08, s
29	0.89,[a] s	0.88,[b] s	0.95, s	1.12, s
30	1.06, s	0.88,[b] s	0.88,[c] s	0.88, s
3-OAc	2.05, s	2.06, s	2.06, s	
21-OAc			2.08, s	2.08, s

[a−c]The proton resonances were superimposed.

(500 MHz, $CDCl_3$) data, see Table 3; ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 1; HRMS (ESI-TOF) *m/z* 521.3606 $[M + Na]^+$ (calcd for $C_{32}H_{50}O_4Na$, 521.3601).

Hypocrellol F (6): colorless, amorphous; $[\alpha]^{25}_{D}$ +43 (*c* 0.125, MeOH); UV (MeOH) λ_{max} (log ε) 236 (4.01), 243 (4.08), 252 (3.90) nm; IR (ATR) ν_{max} 3423, 2943, 1728, 1371, 1234, 1032 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) data, see Table 3; ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 1; HRMS (ESI-TOF) *m/z* 579.3651 $[M + Na]^+$ (calcd for $C_{34}H_{52}O_6Na$, 579.3656).

Hypocrellol G (7): colorless, amorphous; $[\alpha]^{24}_{D}$ +22 (*c* 0.30, MeOH); UV (MeOH) λ_{max} (log ε) 236 (3.89), 243 (3.94), 251 (3.79) nm; IR (ATR) ν_{max} 3401, 2924, 1731, 1705, 1376, 1234, 1031 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) data, see Table 3; ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 1; HRMS (ESI-TOF) *m/z* 513.3576 $[M + H]^+$ (calcd for $C_{32}H_{49}O_5$, 513.3575).

7β,15α-Dihydroxy-22(29)-hopene (8): colorless solid; mp 228−229 °C; $[\alpha]^{24}_{D}$ +50 (*c* 0.095, MeOH); IR (ATR) ν_{max} 3305, 2942, 1460, 1375, 1038, 884 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) data, see Supporting Information; ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 4; HRMS (ESI-TOF) *m/z* 465.3697 $[M + Na]^+$ (calcd for $C_{30}H_{50}O_2Na$, 465.3703).

3β,7β-Dihydroxy-22(29)-hopene (9): colorless solid; mp 228−230 °C; $[\alpha]^{27}_{D}$ +32 (*c* 0.11, MeOH); IR (ATR) ν_{max} 3316, 2921, 1386, 1042, 1019, 879 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) data, see Supporting Information; ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 4; HRMS (ESI-TOF) *m/z* 465.3709 $[M + Na]^+$ (calcd for $C_{30}H_{50}O_2Na$, 465.3703).

3β-Acetoxy-15α-hydroxy-22(29)-hopene (10): colorless solid; mp 238−239 °C; $[\alpha]^{24}_{D}$ +35 (*c* 0.15, MeOH); IR (ATR) ν_{max} 2943, 1726, 1373, 1250, 980, 885 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) data, see Supporting Information; ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 4; HRMS (ESI-TOF) *m/z* 507.3804 $[M + Na]^+$ (calcd for $C_{32}H_{52}O_3Na$, 507.3809).

3β,7β,15α,22-Tetrahydroxyhopane (11): colorless solid; mp 130−131 °C; $[\alpha]^{24}_{D}$ +16 (*c* 0.11, MeOH); IR (ATR) ν_{max} 3361, 2925, 1377, 1040 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) data, see Supporting Information; ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 4; HRMS (ESI-TOF) *m/z* 499.3756 $[M + Na]^+$ (calcd for $C_{30}H_{52}O_4Na$, 499.3758).

3β-Acetoxy-7β,15α,22-trihydroxyhopane (12): colorless solid; mp 266−268 °C; $[\alpha]^{24}_{D}$ +21 (*c* 0.105, MeOH); IR (ATR) ν_{max} 3206, 29441720, 1370, 1244 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) data, see Supporting Information; ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 4; HRMS (ESI-TOF) *m/z* 541.3868 $[M + Na]^+$ (calcd for $C_{32}H_{54}O_5Na$, 541.3863).

7β,15α,22-Trihydroxyhopane (13): colorless, amorphous solid; $[\alpha]^{25}_{D}$ +24 (*c* 0.09, MeOH); IR (ATR) ν_{max} 3336, 3208, 2925, 1460, 1387, 1155, 1037, 1004 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) data, see Supporting Information; ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 4; HRMS (ESI-TOF) *m/z* 483.3802 $[M + Na]^+$ (calcd for $C_{30}H_{52}O_3Na$, 483.3809).

X-ray Crystallographic Data of Hypocrellol A (1): colorless needles ($MeOH−CH_2Cl_2$); $C_{30}H_{48}O_3\cdot CH_4O$, MW = 488.75, triclinic, *P*1, *a* = 6.1987(3) Å, *b* = 6.9755(4) Å, *c* = 17.8242(12) Å, α = 93.032(3)°, β = 94.147(4)°, γ = 111.351(4)°, *V* = 713.32(7) $Å^3$, D_x = 1.138 g/cm^3, *Z* = 1, F_{000} = 270. A total of 5214 reflections, of which 4229 unique reflections (3829 observed, $|F_o| > 4\sigma|F_o|$), were measured at 298(2) K from a 0.20 × 0.10 × 0.10 mm^3 colorless crystal using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) on a Bruker-Nonius kappaCCD diffractometer. The crystal structure was solved by the direct method using SIR-97,[12] and then all atoms except hydrogen atoms were refined anisotropically by full-matrix least-squares methods on F^2 using SHELXL-97 to give a final *R* factor of 0.0480 (R_w = 0.1269 for all data).[13] Crystallographic data of compound **1** have been deposited at the Cambridge Crystallographic Data Centre under the reference number CCDC-822477. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

Table 4. ^{13}C NMR ($CDCl_3$, 125 MHz) Data for Hopanes 8−13

position	8	9	10	11	12	13
1	40.4, CH_2	38.60, CH_2	38.6, CH_2	38.7, CH_2	38.4, CH_2	40.3, CH_2
2	18.7, CH_2	27.4, CH_2	23.7,[b] CH_2	27.4, CH_2	23.7, CH_2	18.7, CH_2
3	41.7[a], CH_2	78.8, CH	80.9, CH	78.7, CH	80.6, CH	41.7, CH_2
4	33.0, qC	38.63, qC	37.2, qC	38.6, qC	37.5, qC	33.0, qC
5	53.0, CH	52.2, CH	54.9, CH	52.1, CH	52.2, CH	53.0, CH
6	28.7, CH_2	29.2, CH_2	18.5, CH_2	28.2, CH_2	27.90, CH_2	28.8,[e] CH_2
7	72.1, CH	73.5, CH	36.7, CH_2	72.0, CH	71.8, CH	72.1, CH
8	48.6, qC	43.6, qC	43.3, qC	48.4, qC	48.5, qC	48.6, qC
9	50.5, CH	50.3, CH	50.5, CH	50.3,[d] CH	50.3,[c] CH	50.5,[f] CH
10	37.5, qC	37.2, qC	37.7, qC	37.3, qC	37.2, qC	37.5, qC
11	20.7, CH_2	20.9, CH_2	21.0, CH_2	20.8, CH_2	20.9, CH_2	20.6, CH_2
12	23.8, CH_2	23.9, CH_2	23.9,[b] CH_2	23.9, CH_2	23.9, CH_2	23.9, CH_2
13	48.5, CH	49.7, CH	48.7, CH	49.0, CH	49.0, CH	48.9, CH
14	48.3, qC	47.4, qC	47.3, qC	48.0, qC	48.0, qC	48.1, qC
15	73.1, CH	37.6, CH_2	74.6, CH	73.5, CH	73.5, CH	73.4, CH
16	31.5, CH_2	22.0, CH_2	32.6, CH_2	31.6, CH_2	31.6, CH_2	31.7, CH_2
17	51.4, CH	54.4, CH	51.6, CH	50.3,[d] CH	50.2,[c] CH	50.3, CH
18	44.9, qC	44.8, qC	44.8, qC	44.3, qC	44.3, qC	44.3, qC
19	41.6,[a] CH_2	42.1, CH_2	41.5, CH_2	41.0, CH_2	41.0, CH_2	41.0, CH_2
20	27.5, CH_2	27.2, CH_2	27.6, CH_2	26.9, CH_2	26.9, CH_2	26.8, CH_2
21	45.8, CH	46.4, CH	45.8, CH	50.4, CH	50.4, CH	50.5,[f] CH
22	148.0, qC	148.6, qC	148.0, qC	73.7, qC	73.7, qC	73.6, qC
23	33.2, CH_3	28.0, CH_3	27.9, CH_3	28.0, CH_3	27.94, CH_3	33.2, CH_3
24	21.5, CH_3	15.3, CH_3	16.5, CH_3	15.3, CH_3	16.4, CH_3	21.5, CH_3
25	15.4, CH_3	15.5, CH_3	15.9, CH_3	15.5, CH_3	15.5, CH_3	15.4, CH_3
26	11.8, CH_3	11.1, CH_3	17.3, CH_3	11.8, CH_3	11.8, CH_3	11.8, CH_3
27	12.1, CH_3	17.4, CH_3	11.4, CH_3	12.3, CH_3	12.2, CH_3	12.3, CH_3
28	15.6, CH_3	16.1, CH_3	15.7, CH_3	15.7, CH_3	15.7, CH_3	15.7, CH_3
29	110.5, CH_2	110.1, CH_2	110.6, CH_2	28.5, CH_3	28.3, CH_3	28.8,[e] CH_3
30	24.9, CH_3	25.1, CH_3	24.9, CH_3	31.1, CH_3	31.2, CH_3	30.9, CH_3
3-$OCOCH_3$			171.0, qC		171.0, qC	
3-$OCOCH_3$			21.3, CH_3		21.3, CH_3	

[a−c]The carbon assignment may be interchanged. [d−f]The carbon resonances were superimposed.

Synthesis of the Mosher Ester Derivatives 17a and 17b. Compound **1** (2.0 mg) was treated with (−)-(*R*)-MTPACl (12 μL) in pyridine (0.4 mL) at room temperature for 18 h. The mixture was diluted with EtOAc and washed with H_2O and 1 M $NaHCO_3$, and the organic layer was concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2) to furnish the (*S*)-MTPA ester **17a** (1.9 mg). Similarly, (*R*)-MTPA ester derivative **17b** (2.0 mg) was prepared from **1** (2.1 mg) and (+)-(*S*)-MTPACl. Assignments of protons of the Mosher ester derivatives **17a** and **17b** were accomplished on the basis of COSY and NOESY data (^{1}H NMR data, see Supporting Information).

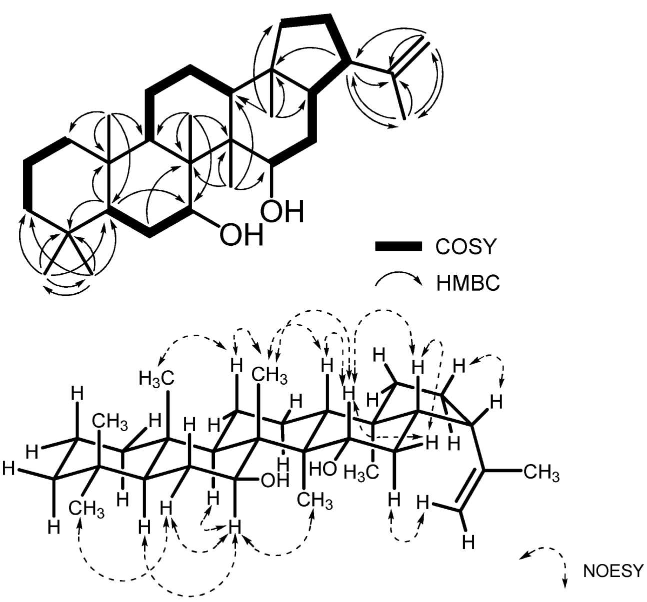


Figure 4. Selected COSY, HMBC, and NOESY correlations for **8**.

Biological Assays. Assay for activity against *Plasmodium falciparum* (K1, multi-drug-resistant strain) was performed in duplicate using the microculture radioisotope technique.[14] Standard antimalarial compounds, dihidroartemisinin and mefloquine hydrochloride showed IC_{50} values of 1.1 nM and 0.040 μM, respectively. Growth inhibitory activity against *Mycobacterium tuberculosis* H37Ra and cytotoxicity to Vero cells (African green monkey kidney fibroblasts) were performed in triplicate using the green fluorescent protein microplate assay.[15] The standard anti-TB drug isoniazid showed MIC values of 0.0234−0.0468 μg/mL. Ellipticine was used as a standard compound for the cytotoxicity to Vero cells (IC_{50} 9.8 μM). Cytotoxic activities against human cancer cell lines were evaluated using the resazurin microplate assay (4 replicates).[16] The IC_{50} values of a standard compound, doxorubicin hydrochloride, against KB (oral epidermoid carcinoma), NCI-H187 (small-cell lung cancer), and MCF-7 (breast cancer) cells were 1.2, 0.25, and 15 μM, respectively.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of **1**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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