THE STRUCTURES OF NEW LANOSTANE TRITERPENES FROM THE FRUITING BODIES OF *HEBELOMA SENESCENS*

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ABSTRACT.—Three new lanostane triterpenes, hebelomic acids B [4], E [5], and F [6], were isolated from the inedible mushroom *Hebeloma senescens*. The latter two compounds are acyl derivatives of the new triterpene senescensol (12-deoxycrustulinol) [12]. The structures of compounds 4–6, including the absolute configuration of the 3-hydroxy-3-methylglutaric acid moiety, were established on the basis of spectral and chemical evidence.

Despite their wide occurrence in nature, species belonging to the genus *Hebeloma* (Basidiomycetes, family Cortinariaceae), have been relatively poorly studied with respect to their secondary metabolites (1). A few years ago we isolated a cytotoxic triterpene, named hebelomic acid A [1], from *Hebeloma crustuliniforme* and *H. sinapizans* (2). Two closely related lanostane-type triterpene esters, named HS-B [2] and C [3] have been isolated recently from *H. spoliatum* (3). Intraperitoneal administration of 1, 2, or 3 caused death in mice, after paralysis of the limbs, at a dose of 100 mg/kg (3). Interestingly, numerous neurotoxic cucurbitane-type glycosides, called hebevinosides, have been found in the poisonous mushroom *H. vinosophyllum* (4). We recently reported the isolation of hebelomic acid A [1], and two new farnesane derivatives, from an EtOAc extract of the inedible mushroom *H. senescens* (Fr.) Berk. ex Br. (syn. *H. edurum* Metr. ex Bon) which exhibited moderate antibacterial activity (5). Herein we report the isolation, structural elucidation, and biological activity of the three new hebelomic acids B [4], E
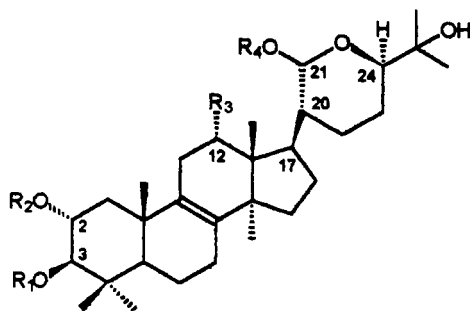
1 R_1=Ac, R_2=COCH$_2$C(Me)(OH)CH$_2$COOH, R_3=OH, R_4=H
2 R_1=R_4=Ac, R_2=COCH$_2$C(Me)(OH)CH$_2$COOH, R_3=OH
4 R_1=Ac, R_2=COCH$_2$C(Me)(OH)CH$_2$COOH, R_3=OAc, R_4=H
5 R_1=Ac, R_2=COCH$_2$C(Me)(OH)CH$_2$COOH, R_3=R_4=H
6 R_1=R_4=Ac, R_2=COCH$_2$C(Me)(OH)CH$_2$COOH, R_3=H
7 R_1=Ac, R_2=COCH$_2$C(Me)(OH)CH$_2$COOMe, R_3=OAc, R_4=H
9 R_1=R_2=R_4=H, R_3=OH
10 R_1=Ac, R_2=COCH$_2$C(Me)(OH)CH$_2$COOMe, R_3=R_4=H
12 R_1=R_2=R_3=R_4=H
24 R_1=Ac, R_2=COCH$_2$C(Me)(OH)CH$_2$CONHCH(Me)(1-naphthyl), R_3=OAc, R_4=H
25 R_1=Ac, R_2=COCH$_2$C(Me)(OH)CH$_2$CONHCH(Me)(1-naphthyl), R_3=R_4=H
26 R_1=R_4=Ac, R_2=COCH$_2$C(Me)(OH)CH$_2$CONHCH(Me)(1-naphthyl), R_3=H
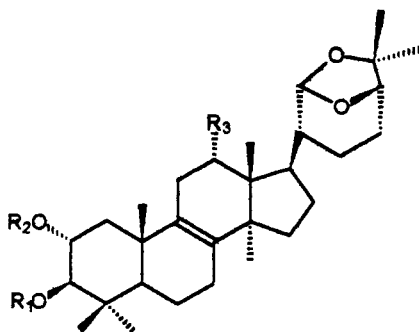
3 R₁=Ac, R₂=COCH₂C(Me)(OH)CH₂COOH, R₃=OH
8 R₁=Ac, R₂=COCH₂C(Me)(OH)CH₂COOMe, R₃=OAc
11 R₁=Ac, R₂=COCH₂C(Me)(OH)CH₂COOH, R₃=H

[**5**], and F [**6**] from this same mushroom. Compounds **1** and **4–6** are the main triterpene metabolites of *H. senescens*.

RESULTS AND DISCUSSION

Hebelomic acid B [**4**], obtained as a colorless powder, mp 160–163°, showed molecular ion peaks at m/z 734 [M]⁺ and 752 [M+NH₄]⁺ in the dcims (NH₃). These data, combined with elemental analysis and ¹H- and ¹³C-nmr spectral measurements (Table 1), indicated a molecular formula of $C_{40}H_{62}O_{12}$ for **4**. The ir bands at 3450 and 1725 cm⁻¹ were assigned to hydroxyl, ester, and/or carbonyl groups, respectively. The ¹³C-nmr signal at δ 174.6 and the formation of a monomethyl ester [**7**] with CH_2N_2 supported the presence in **4** of one carboxylic group, whereas three singlets at δ 170.5, 170.8, and 171.2 in the ¹³C-nmr spectrum could be attributed to two acetates (two methyl singlets at δ 2.04 and 2.06 ppm) and a third acyl group, which was identified as a 3-hydroxy-3-methylglutaryl moiety by the characteristic ¹H- and ¹³C-nmr signals (2). The other oxygenated carbons of compound **4** were assigned to one additional quaternary and four tertiary carbinyl groups, and to one hemiacetal methine group. The remaining ¹³C- and ¹H-nmr signals were attributed, with the aid of DEPT and ¹H-¹³C COSY nmr spectra, to seven tertiary methyls, eight methylenes, three methines, and six quaternary carbons, two of which were olefinic (see Table 1).

The above spectroscopic data, when compared with those of hebelomic acid A [**1**] (2), indicated the same pattern of oxygenated carbons for a lanostane-type triterpene aglycone including the characteristic hemiacetal pyran ring between C-21 and C-24. By analogy with **1** (2), exposure of methyl ester **7** to pyridine/TsOH (6) in CH_2Cl_2 afforded the anhydro derivative **8**. The structure of **8** was proven by the ¹H-nmr signal for H-24 which appeared as a characteristic narrow doublet (J=3.5 Hz). Hydrolysis of **4** with K_2CO_3 in MeOH afforded crustulinol [**9**] (2) and 3-hydroxy-3-methylglutaric acid (HMGA), identical with authentic samples. ¹H-Nmr acylation shifts indicated that **4** is a 2,3,12-triacylcrustulinol, namely, the 12-*O*-acetate of hebelomic acid A [**1**] (2).
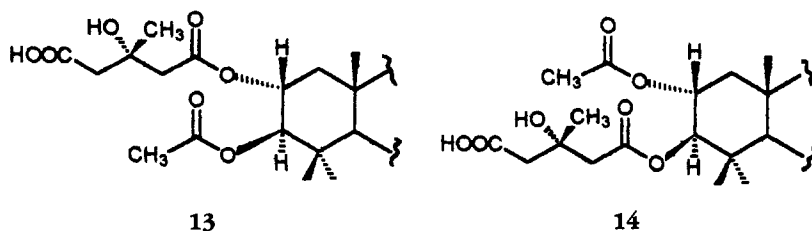
Hebelomic acid E [**5**] is a colorless amorphous solid, mp 170–172°. The ¹H- and ¹³C-nmr signals (see Table 1) of **5**, as well as the ions [M]⁺ and [M+NH₄]⁺ observed at m/z 676 and 694, respectively, in the dcims (NH₃), indicated a molecular formula of $C_{38}H_{60}O_{10}$. The ¹H- and ¹³C-nmr spectra of **5** included all signals of hebelomic acid A [**1**] (2), except those due to the 12-carbinyl group present in **1**. By analogy with the chemical behavior of hebelomic acids A [**1**] and B [**4**], **5** gave a monomethyl ester [**10**] on exposure to CH_2N_2 and afforded the corresponding 21,25-anhydro derivative [**11**] upon treatment with pyridine/TsOH (6). Hydrolysis of **5** with K_2CO_3 in MeOH afforded

TABLE 1.   ¹³C-Nmr Spectral Data for Compounds **4, 5, 6,** and **12.**[a,b]

Carbon	Compound			
	4[c]	**5**[d]	**6**[d]	**12**[c]
C-1	40.9 (t)	41.1 (t)	41.1 (t)	45.3 (t)
C-2	69.8 (d)	71.1 (d)	71.2 (d)	69.5 (d)
C-3	80.1 (d)	80.3 (d)	80.3 (d)	84.0 (d)
C-4	39.5 (s)	39.4 (s)	39.3 (s)	40.2 (s)
C-5	50.1 (d)	49.9 (d)	50.0 (d)	51.3 (d)
C-6	18.2 (t)	18.0 (t)	18.0 (t)	19.2 (t)
C-7	27.0 (t)[e]	27.0 (t)	27.1 (t)	27.8 (t)[e]
C-8	135.6 (s)	135.0 (s)	134.7 (s)	135.4 (s)
C-9	131.8 (s)	133.2 (s)	133.4 (s)	134.9 (s)
C-10	38.1 (s)	38.1 (s)	38.1 (s)	38.9 (s)
C-11	26.6 (t)[e]	21.3 (t)	21.2 (t)	22.0 (t)
C-12	73.8 (d)	26.2 (t)[e]	26.2 (t)[e]	27.1 (t)[e]
C-13	49.7 (s)	44.1 (s)	43.9 (s)	45.1 (s)
C-14	48.2 (s)	49.7 (s)	49.7 (s)	50.5 (s)
C-15	32.2 (t)	30.6 (t)[f]	30.6 (t)[f]	31.6 (t)[f]
C-16	31.4 (t)	30.5 (t)[f]	29.7 (t)[f]	31.5 (t)[f]
C-17	38.9 (d)	45.0 (d)[g]	45.0 (d)[g]	46.2 (d)
C-18	17.6 (q)[f]	16.6 (q)	16.5 (q)	17.4 (q)[g]
C-19	19.9 (q)	20.1 (q)	20.1 (q)	21.1 (q)
C-20	44.2 (d)	42.8 (d)[g]	41.2 (d)[g]	44.6 (d)
C-21	93.6 (d)	93.0 (d)	93.0 (d)	93.5 (d)
C-22	26.2 (t)	26.0 (t)[e]	25.3 (t)[e]	26.9 (t)[e]
C-23	23.6 (t)	23.2 (t)	23.8 (t)	24.8 (t)
C-24	74.5 (d)	74.2 (d)	76.6 (d)	75.1 (d)
C-25	71.3 (s)	72.2 (s)	71.6 (s)	71.8 (s)
C-26	26.2 (q)[g]	26.4 (q)[h]	25.6 (q)[h]	27.3 (q)[h]
C-27	26.6 (q)[g]	24.6 (q)[h]	24.4 (q)[h]	26.7 (q)[h]
C-28	25.4 (q)	23.8 (q)	23.8 (q)	25.1 (q)[h]
C-29	28.3 (q)	27.2 (q)	27.1 (q)	29.6 (q)
C-30	17.1 (q)[f]	17.5 (q)	17.5 (q)	17.9 (q)[g]
C-1'	170.8 (s)	171.5 (s)	171.4 (s)	
C-2'	46.4 (t)[h]	45.1 (t)	45.0 (t)[i]	
C-3'	69.8 (s)	69.9 (s)	69.6 (s)	
C-4'	46.3 (t)[h]	45.1 (t)	44.9 (t)[i]	
C-5'	174.6 (s)	174.7 (s)	174.0 (s)	
C-6'	28.3 (q)	28.2 (q)	28.2 (q)	
COMe	171.2 (s)	171.3 (s)	171.2 (s)	
	170.5 (s)		170.1 (s)	
COMe	21.1 (q)	21.1 (q)	21.0 (q)	
	21.7 (q)		21.1 (q)	

[a]75.5 MHz; δ_c values in ppm relative to TMS.
[b]The number of protons attached to each carbon was determined by DEPT experiments.
[c]C₅D₅N solution.
[d]CDCl₃ solution.
[e,f,g,h,i]Assignments in the same vertical column bearing the same superscript may be interchanged.

HMGA and a new triterpene alcohol, mp 222–224°, senescensol [**12**], whose dcims (NH₃) showed [M+NH₄]⁺ and [M]⁺ peaks at m/z 508 and 490, respectively, indicating a molecular formula of $C_{30}H_{50}O_5$. The nmr spectra confirmed that **12** is 12-deoxycrustulinol. Compared to the corresponding protons of hebelomic acid E [**5**], the characteristic ¹H-nmr signals for the 2α,3β-dihydroxy substituted ring A of **12** were shifted upfield, proving that compound **5** is a 2,3-diacylsenescensol containing either the partial structure **13** or the isomeric structure **14** (2).

13   **14**

Hebelomic acid F [6] was isolated as a colorless amorphous powder which could not be crystallized. The highest ms fragment ion for compound 6 occurred at m/z 658 in the eims and at m/z 676 in both the cims (NH_3) and the dcims (NH_3) spectra. These peaks correspond to $[M-AcOH]^+$ and $[M+NH_4-AcOH]^+$ ions, respectively, on the basis of the formula $C_{40}H_{62}O_{11}$, calculated from the elemental analysis and the ^1H- and ^{13}C-nmr spectral data (Table 1) of 6. All nmr signals of 6 resembled those of hebelomic acid E [5], except that the signal at δ 5.38 ppm in 5 was shifted to δ 6.1 ppm in 6 and the signals of one additional acetyl group were observed at δ 2.07 ppm in the ^1H-nmr spectrum and at δ 21.0 (CH_3) and 170.1 (CO) ppm in the ^{13}C-nmr spectrum of compound 6. Alkaline hydrolysis of 6 afforded HMGA and 12, whereas exposure of 6 to pyridine/TsOH afforded the 21,25-anhydro derivative 11, identical with the sample obtained from 5. Thus, hebelomic acid F [6] is 21-O-acetylhebelomic acid E.

In order to establish the pattern of the acyloxy substitutents at C-2 and C-3 for hebelomic acids E [5] and F [6] and also for 4 at C-12, the ^{13}C-nmr resonance positions of the ester carbonyl groups were correlated with the ^1H-nmr resonance positions of the proton signals at C-2 and C-3, and, in the cases of 4 and 6, also at C-12 and C-21, respectively. This experiment will be described in detail for hebelomic acid F [6]. The signals of the protons geminal to acyl groups in compound 6 were assigned unequivo-cally, since the acetal H-21 at δ 6.1 was a characteristic broad singlet (2) and H-3α at δ 4.78 formed a doublet (J=10.0 Hz) due to spin coupling to Hβ-2. The latter proton gives rise to a triplet of doublets at δ.517 due to additional coupling to the protons at C-1. Signals of the acyl carbonyl groups formed complicated multiplets in the gated-decoupled ^{13}C-nmr spectrum due to spin coupling with the protons within the acetate or glutaryl residue and to protons within the triterpene skeleton, where the $^3J_{C,H}$ coupling with the proton at the attached site will be predominant. In the 300 MHz ^1H-nmr spectrum of 6 the signals of protons H-2 and H-3 differ enough in shift to allow unambiguous selective-decoupling experiments. Removal of the coupling to H-3 revealed a quartet for the attached carbonyl signal at δ 171.2 ppm, whereas removal of the coupling to H-2 revealed a triplet as the remaining signal for the carbonyl group at δ 171.4 ppm. Similar results were obtained for selective ^1H-^{13}C decoupling experiments performed on hebelomic acids B [4] and E [5] and, for confirmation, also on hebelomic acid A [1], in accordance with the partial structure 13. In conclusion, the pattern of acyloxy substituents at C-2 and C-3 is the same for all known hebelomic acids A, B, E, and F, and the related compounds HS-B [2] and HS-C [3] (3).

The absolute configuration of the triterpene moiety of hebelomic acids 1–6 was established by chemical conversion to fasciculol C (2,3) and is supported by biosynthetic considerations, while the absolute configuration of the C-3' stereocenter of the HMGA moiety is as yet undetermined. However, in vivo esterification of hebelomic acids with HMGA should be assisted by enzymes and, therefore, the R- or S-configuration must be created at C-3 of HMGA. The chirality of the HMG acyl group found in several natural products such as terpenes, phenylpropanoids, and others (3,7,8) was determined to be R for most of these. Recently, however, Shirama *et al.* (7) suggested that these

assignments should be revised, and the chirality of the HMGA moiety of fasciculic acid A, related to hebelomic acids A, B, E, and F, was established by Nozoe *et al.* as S (8).

We now describe a general and reliable method for establishing the configuration of the stereocenter of HMGA in hebelomic acids A, B, E, and F. Initially, the more abundant hebelomic acid A [1] was used as a model compound. First, a selective reduction of the acid or ester group of the HMGA moiety in **1** was attempted in order to obtain either (R)-$(-)$- or (S)-$(+)$-mevalonolactone. However, reduction of **1** with selective reducing agents either for the free carboxylic group, like BH_3Me_2S (9) or $PhCH_2Et_3N^+BH_4^- + Me_3SiCl$ (10) or for the ester group, like $LiEt_3BH$ (11), $LiBH_4$ (12), or $Ca(BH_4)_2$ (13), led to intractable mixtures of products or gave ambiguous results (7). Equally unsatisfactory results were obtained from the reduction of simple derivatives of **1**.

Sassa and Nukina (14) reported the ^{1}H-nmr spectra and optical rotations of the diastereomeric $(3R,1'S)$- and $(3S,1'S)$-5-O-acetyl-N-[1-(napthyl)ethyl]-mevalonamides, **15** and **16**, respectively. The absolute configuration at C-3 in **15** and **16** was established by a separate hydrolysis of each amide to the corresponding optically active mevalono-lactone (14). Therefore, the configuration at C-3' in hebelomic acid A [1] could be inferred from that at C-3 of the 5-O-acetyl-N-[(S)-1-(naphthyl)ethyl]mevalonamide prepared from **1** through stereocontrolled reactions (Scheme 1).
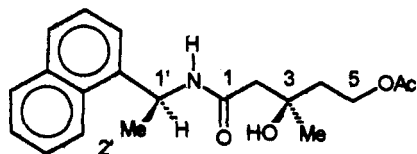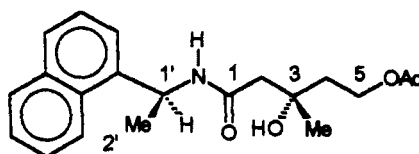

$(3R,1'S)$-**15** $(3S,1'S)$-**16**

Condensation of hebelomic acid A [1] with (S)-1-(1-naphthyl)ethylamine in the presence of the Castro reagent **17** (15) and 1-methylpiperidine proceeded unevent-fully, affording the amide **18** in 64% yield. Interestingly, this condensation reaction did not need a preliminary protection of the free hydroxyl groups of triterpene **1**. Mild alkaline hydrolysis of **18** followed by esterification with excess CH_2N_2, provided crustulinol [9] and the ester-amide **19** as a colorless viscous oil, $[\alpha]^{21}D$ $-16.9°$. Selective reduction of the ester group in **19** with $LiBH_4$ in THF followed by acetylation of the primary OH-5 group yielded the corresponding acetoxyamide, whose optical rotation data {$[\alpha]^{21}D$ $-14°$ ($c=0.5$, EtOH)} confirmed the $(3R,1'S)$ configuration [15] (14). Hydrolysis of this acetoxyamide under the conditions suggested by Hirai and Koshimizu (16) for the corresponding $(3R)$-5-O-acetyl-N-[(S)-phenylethyl]-mevalonamide, gave (R)-$(-)$-mevalonolactone [20], $[\alpha]^{21}D$ $-20.5°$ ($c=0.2$, EtOH) {lit. (18) $[\alpha]D$ $-21.8°$ ($c=1.1$, EtOH)}. Furthermore, amide **19** was identical with an authentic sample of the $(3S,1'S)$-stereoisomer, prepared from dimethyl 3-hydroxy-3-methylglutarate by enantiotopically selective hydrolysis (18) with PLE followed by condensation of the resulting $(3S)$-half ester with (S)-1-(1-naphthyl)ethylamine.

In searching for a simpler method for establishing the chirality of the HMG acyl group in compounds **4–6**, the ^{1}H-nmr spectrum of **19** was compared with that of a 1:1 mixture of diastereomeric amides $(3S,1'S)$-**19** and $(3R,1'S)$-**21**, which were synthesized from HMG anhydride **22** (20), as shown in Scheme 2. In this way signals for the methoxy and C-3 methyls and C-2 and C-4 methylene groups could be
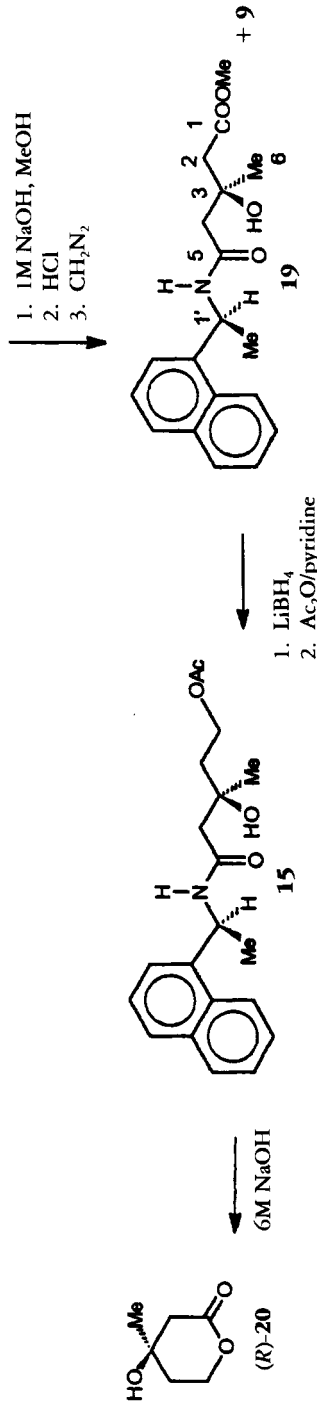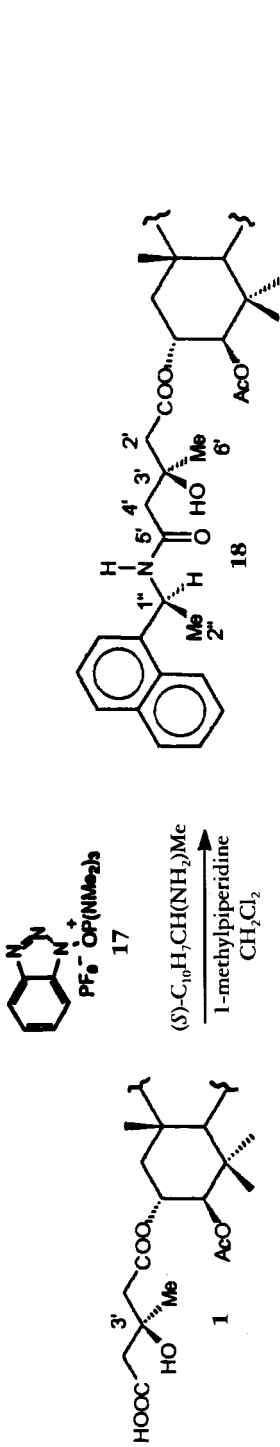
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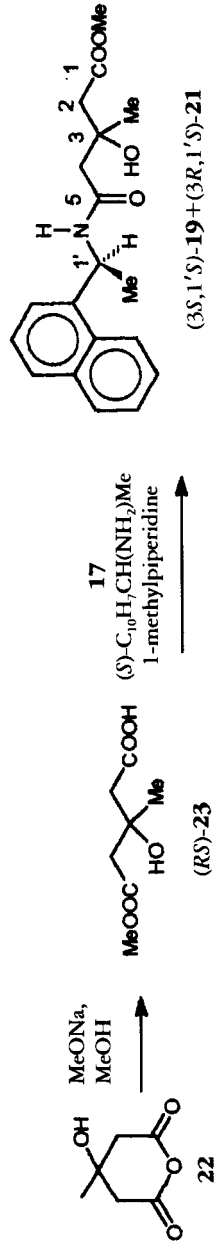
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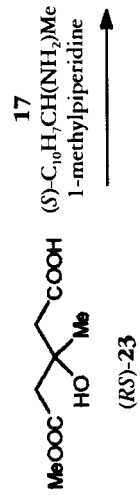
assigned unambiguously to amides **19** or **21**, allowing straightforward assignment of the absolute configuration to the HMGA moiety in each of the (S)-1-(1-naphthyl)ethylamides **24–26**, prepared separately from compounds **4–6**.

Hebelomic acids A [**1**], B [**4**], and F [**6**] showed moderate antibacterial activity in the Kirby-Bauer test against *Bacillus subtilis* and *Staphylococcus oxford*, but no activity against *Escherichia coli* or *Candida albicans*. The hebelomic acids were compared using *Artemia salina* (brine shrimp lethality assay) (19). The LD_{50} (μg/ml) values found for **1**, **4**, and **6** were 96.5, 386, and 19.7, respectively. These data show that a relationship exists between the toxicity and structure of hebelomic acids, and that an OH or OAc group at C-12 is detrimental to such activity.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps were determined on a Fisher-Johns hot-plate and are uncorrected. The ir spectra were recorded (film or KBr pellets) with a Perkin-Elmer model 881 spectrophotometer. ^{1}H- and ^{13}C-nmr spectra were recorded in CDCl$_3$ solution, unless otherwise indicated, using a Bruker 250 MHz or ACE 300 instrument. For 2D homonuclear and heteronuclear COSY, Bruker standard software was employed. Chemical shifts (δ) are reported in ppm with TMS as an internal standard. Coupling constants (J) are reported in Hz. In the ^{13}C-nmr spectra, the number of hydrogens attached to the corresponding carbon was determined from DEPT experiments. Ms were obtained on a Finnigan-MAT 8222 mass spectrometer. Specific optical rotations were determined with a Perkin-Elmer model 241 digital polarimeter. Cc was performed at atmospheric pressure on Kieselgel 60 (Merck), 0.040–0.063 mm, slurry packed. Analytical GF$_{254}$ tlc plates (0.25 mm) were obtained from Merck. The spots were visualized under uv light or by spraying the plates with 0.5% vanillin solution in H$_2$SO$_4$-EtOH (4:1) followed by heating at 120° for ca. 1 min, or with 0.04% bromocresol green solution in H$_2$O in the cold. All solvents were purified and dried by standard techniques just before use. (S)-(−)-1-(1-Naphthyl)ethylamine, 1-methylpiperidine, and benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) [**17**] (15) were purchased from Aldrich; 3-hydroxy-3-methylglutaric acid (HMGA) was obtained from Fluka; PLE was purchased from Sigma.

FUNGAL MATERIAL.—Collection and identification of fruiting bodies of *H. senescens* as described previously (5).

EXTRACTION AND ISOLATION.—The extraction of the fruiting bodies of *H. senescens* as well as the Si gel cc of the resultant extract have been described elsewhere (5). Sixteen groups (1–16) of fractions were collected. Farnesane sesquiterpenes were isolated from fractions 5 and 6 (5). In this investigation we have examined the more polar fractions containing metabolites showing a free carboxylic group (yellow spots with bromocresol green solution on tlc plates). Concentration of fraction 14 by rotary evaporation gave a white precipitate (3.2 g), which was crystallized from MeCN and found to be identical to hebelomic acid A [**1**] (2) ([α]D, mmp, ir, and nmr spectra). Concentration of fraction 12 gave a precipitate (17.1 g) consisting of a 1:1 mixture of hebelomic acids A [**1**] and B [**4**], which were then separated from one another. Fraction 11 (9.74 g) was further separated by Si gel (700 g) cc, using a CH$_2$Cl$_2$/Me$_2$CO/HOAc gradient, to provide, in order of elution, two novel triterpenes, hebelomic acids D (25 mg) and C (80 mg), along with additional quantities of **4** (5.1 g) and **1** (0.8 g). Fraction 10 (4.11 g) was further separated by Si gel (300 g) cc with CH$_2$Cl$_2$-Me$_2$CO-HOAc (75:25:2.5 and 70:30:2.5) to afford fractions A (0.28 g), B (1.04 g), C (0.146 g), D (0.097 g), E (0.152 g), F (1.15 g), G (0.275 g), and H (0.397 g). Fractions were monitored by Si gel tlc eluted with CH$_2$Cl$_2$-Me$_2$CO-HOAc (73:24.5:2.5). Crystallization of fraction B from Me$_2$CO/hexane afforded hebelomic acid F [**6**] (0.84 g). Fractions A, F, and H contained almost pure hebelomic acids D, B [**4**], and A [**1**], respectively. Fractions C, D, and E were pooled (395 mg) and separated by cc on different Si gel columns, eluted with hexane-Me$_2$CO-HOAc (48.7:48.7:2.5), C$_6$H$_6$-Me$_2$CO-MeOH (85:10:5), C$_6$H$_6$-MeOH-HOAc (93:5:2), CH$_2$Cl$_2$-MeOH-HOAc (94:4:2), C$_6$H$_6$-CH$_2$Cl$_2$-MeOH-HOAc (36:59:3:2), to afford hebelomic acid E [**5**] (61 mg).

Hebelomic acid B [**4**].—Amorphous powder, mp 160–163°; [α]^{21}D +27.7° (c=0.7, CHCl$_3$); tlc R_f 0.22 (Me$_2$CO-CH$_2$Cl$_2$-HOAc, 24.0:73.5:2.5); ir (KBr) ν max 3450 (OH), 1725 (C=O), 1375, 1235, 1073, 1030, 1000, 950, 897 cm^{-1}; ^{1}H nmr (250 MHz) δ 0.75, 0.91, 0.94, 1.11, 1.12, 1.15, 1.37 (24H overall, 7×s, H$_3$-18, -30, -29, -19, -28, -26, -27, -6′), 2.04 (3H, s, MeCOO-12), 2.06 (3H, s, MeCOO-3), 2.52, 2.69 (1H each, ABq, J=16.0 Hz, H$_2$-2′ or H$_2$-4′), 2.64, 2.69 (1H each, ABq, J=15.5 Hz, H$_2$-4′ or H$_2$-2′), 3.69 (1H, dd, J$_1$=11.5 Hz, J$_2$=2.0 Hz, H-24), 4.78 (1H, d, J$_{2,3}$=10.0 Hz, H-3), 4.93 (1H, br d, J=7.3 Hz, H-12), 5.18 (1H, td, J$_{2,3}$=J$_{2,1\alpha}$=11.0 Hz, J$_{2,1\beta}$=4.5 Hz, H-2), 5.28 (1H, br s, H-21); ^{1}H nmr (C$_5$D$_5$N, 250 MHz) δ 0.75, 0.95, 1.02, 1.31, 1.34, 1.74 (24H overall, 6×s, H$_3$-18, -30, -29, -19, -28, -26, -27, -6′), 2.10,

2.16 (3H each, 2×s, 2×MeCOO-), 3.11 (2H, ABq, H$_2$-2′ or H$_2$-4′), 3.18 (2H, ABq, H$_2$-4′ or H$_2$-2′), 4.20 (1H, dd, J_1=11.5 Hz, J_2=2.0 Hz, H-24), 5.08 (1H, d, $J_{2,3}$=10.0 Hz, H-3), 5.18 (1H, br d, J=7.5 Hz, H-12), 5.51 (1H, td, $J_{2\beta,3\alpha}$=$J_{1\alpha,2\beta}$=11.0 Hz, $J_{2,1\beta}$=4.5 Hz, H-2), 5.70 (1H, br s, H-21); ^{13}C-nmr data, see Table 1; cims (NH$_3$) *m/z* [M+NH$_4$-H$_2$O]$^+$ 734, [*m/z* 734-HOAc]$^+$ 674, [M+NH$_4$-2×HOAc]$^+$ 632; dcims (NH$_3$) *m/z* [M+NH$_4$]$^+$ 752, [M+NH$_4$-H$_2$O]$^+$ 734; eims (70 eV) *m/z* [M-H$_2$O-HOAc]$^+$ 656 (86), [*m/z* 656-Me]$^+$ 641 (77), 554 (25), 514 (20), 512 (46), 497 (24), 479 (32), 436 (21), 435 (43), 419 (28), 376 (23), 353 (22), 295 (30), 277 (23), 253 (31), 251 (25), 237 (23), 226 (20), 211 (29), 208 (33), 197 (20), 181 (100), 173 (25), 171 (30), 168 (64), 159 (33), 157 (29), 145 (44), 133 (35), 124 (42), 123 (38), 121 (30), 109 (24), 107 (33), 95 (41), 93 (21), 81 (21), 43 (29); *anal.*, calcd for C$_{40}$H$_{62}$O$_{12}$: C, 65.37, H, 8.50; found: C, 65.57, H, 8.38.

Hebelomic acid E [**5**].—Amorphous powder, mp 170–172°; [α]^{21}D −9.6° (*c*=0.6, CH$_2$Cl$_2$); tlc, R_f 0.29 (Me$_2$CO-CH$_2$Cl$_2$-HOAc, 24.0:73.5:2.5); ir (KBr) ν max 3424 (OH), 2948, 1742 (C=O), 1456, 1376, 1237, 1094, 1076, 1032, 951, 902, 803, 752, 730 cm^{-1}; ^{1}H nmr (250 MHz) δ 0.72, 0.88, 0.90, 0.94, 1.13, 1.15, 1.18, 1.36 (3H each, 8×s, H$_3$-18, -30, -29, -19, -28, -26, -27, -6′), 2.10 (3H, s, MeCOO-), 2.40–2.80 (4H, m, H$_2$-2′ and H$_2$-4′), 3.78 (1H, br d, J=11.0 Hz, H-24), 4.77 (1H, d, J=10.0 Hz, H-3), 5.17 (1H, br t, J=11.0 Hz, H-2), 5.38 (1H, br s, H-21); ^{13}C-nmr data, see Table 1; cims (NH$_3$+NH$_4$Cl) *m/z* [M+NH$_4$-H$_2$O]$^+$ 676, [*m/z* 676-H$_2$O]$^+$ 658, [M+NH$_4$-2×HOAc]$^+$ 574; dcims (NH$_3$) *m/z* [M+NH$_4$]$^+$ 694, [M+NH$_4$-H$_2$O]$^+$ 676; *anal.*, calcd for C$_{38}$H$_{60}$O$_{10}$: C, 67.43, H, 8.93; found: C, 67.66, H 8.76.

Hebelomic acid F [**6**].—Amorphous powder, [α]^{21}D −32.5° (*c*=0.8, CH$_2$Cl$_2$); tlc, R_f 0.47 (Me$_2$CO-CH$_2$Cl$_2$-HOAc, 24.0:73.5:2.5; ir (KBr) ν max 3464 (OH), 2953, 1743 (C=O), 1455, 1373, 1337, 1238, 1162, 1118, 1078, 1036, 1012, 959, 941, 928, 910, 866 cm^{-1}; ^{1}H nmr (250 MHz) δ 0.73, 0.86, 0.92, 0.95, 1.12, 1.13, 1.15, 1.38 (3H each, 8×s, H$_3$-18, -30, -29, -19, -28, -26, -27, -6′), 2.07, 2.10 (3H each, 2×s, 2×MeCOO-), 2.54, 2.64 (2H, ABq, J=15.0 Hz, H$_2$-2′ or H$_2$-4′), 2.61, 2.72 (2H, ABq, J=15.0 Hz, H$_2$-4′ or H$_2$-2′), 3.48 (1H, br d, J=11.5 Hz, H-24), 4.78 (1H, d, J=10.0 Hz, H-3), 5.17 (1H, td, $J_{2\beta,3\alpha}$=$J_{2\beta,1\alpha}$=11.0 Hz, $J_{2\beta,1\beta}$=4.2 Hz, H-2), 6.10 (1H, br s, H-21); ^{13}C-nmr data, see Table 1; cims (NH$_3$) *m/z* [M+NH$_4$-HOAc]$^+$ 676, [*m/z* 676-H$_2$O]$^+$ 658, 614 [M+NH$_4$-HMGA]$^+$ 574; dcims (NH$_3$) [M+NH$_4$-HOAc]$^+$ 676; eims (70 eV) *m/z* [M-HOAc]$^+$ 658 (2), [M-HMGA]$^+$ 556 (20), [*m/z* 556-Me]$^+$ 541 (13), [*m/z* 556-HOAc]$^+$ 496 (10), [*m/z* 496-Me]$^+$ 481 (3), [*m/z* 481-HOAc]$^+$ 421 (20), 294 (29), 168 (100), 125 (20), 119 (16), 107 (21), 95 (20), 69 (19), 43 (68); *anal.*, calcd for C$_{40}$H$_{62}$O$_{11}$: C, 66.83, H, 8.69; found: C, 66.71, H, 8.82.

METHYLATION OF HEBELOMIC ACID B [**4**].—An excess of CH$_2$N$_2$ in Et$_2$O was added to a solution of **4** (50 mg) in CH$_2$Cl$_2$ and the solution was left to stand at 0° for 15 min. The reaction mixture was taken to dryness and the residue was crystallized from CH$_2$Cl$_2$/hexane to afford methyl ester **7** (32 mg) as a colorless solid, mp 135–137°; ir (KBr) ν max 3450 (OH), 2940, 1725 (C=O), 1435, 1375, 1235, 1070, 1030, 950, 897 cm^{-1}; ^{1}H nmr (250 MHz) δ 0.75, 0.91, 0.93, 1.10, 1.11, 1.11, 1.15, 1.34 (3H each, 8×s, H$_3$-18, -30, -29, -19, -26, -27, -28, -6′), 2.04, 2.05 (3H each, 2×s, 2×MeCOO-), 2.53, 2.65 (2H, ABq, J=15.5 Hz, H$_2$-2′ or H$_2$-4′), 2.60, 2.71 (2H, ABq, J=15.0 Hz, H$_2$-4′ or H$_2$-2′), 3.67 (1H, dd, J_1=11.5 Hz, J_2=2.2 Hz, H-24), 3.70 (3H, s, OMe), 3.91 (1H, s, OH), 4.78 (1H, d, $J_{2,3}$=10.5 Hz, H-3), 4.96 (1H, br d, J=7.3 Hz, H-12), 5.16 (1H, ddd, $J_{2,3}$=10.5 Hz, $J_{2,1\alpha}$=11.5 Hz, $J_{2,1\beta}$=4.3 Hz, H-2), 5.28 (1H, br s, H-21); dcims (NH$_3$) *m/z* [M+NH$_4$]$^+$ 766, [M+NH$_4$-H$_2$O]$^+$ 748.

METHYLATION OF HEBELOMIC ACID E [**5**].—Methylation of **5** was carried out in the same manner as described for **4** to give the corresponding methyl ester **10** as an amorphous powder; ir (KBr) ν max 3450, 2945, 1730 (C=O) cm^{-1}; ^{1}H nmr (250 MHz) δ 0.71, 0.89, 0.92, 0.94, 1.13, 1.14, 1.18, 1.35 (3H each, 8×s, H$_3$-18, -30, -29, -19, -26, -27, -28, -6′), 2.07 (3H, s, MeCOO-), 2.54, 2.67 (2H, ABq, J=15.5 Hz, H$_2$-2′ or H$_2$-4′), 2.63, 2.70 (2H, ABq, J=15.0 Hz, H$_2$-4′ or H$_2$-2′), 3.70 (3H, s, OMe), 3.71 (1H, br d, J=11.0 Hz, H-24), 4.80 (1H, d, $J_{2,3}$=10.0 Hz, H-3), 5.16 (1H, br td, $J_{2,3}$=$J_{2,1\alpha}$=11.0 Hz, $J_{2,1\beta}$=4.3 Hz, H-2), 5.38 (1H, br s, H-21).

PREPARATION OF THE ANHYDRO DERIVATIVE **11** FROM HEBELOMIC ACID E [**5**] AND HEBELOMIC ACID F [**6**].—Compound **5** (18 mg) was dissolved in anhydrous THF (2 ml) to which solid pyridine/TsOH (6) (2 mg) was added. The solution was stirred at 60° for 24 h under a static Ar atmosphere, then taken to dryness. The residue was chromatographed on a Si gel column with CH$_2$Cl$_2$-Me$_2$CO-HOAc (85:15:1) to give **11** (7 mg) as an amorphous solid; ir (KBr) ν max 3480 (OH), 2966, 1740 (C=O), 1373, 1236, 1185, 1150, 1118, 1085, 1031, 929 cm^{-1}; ^{1}H nmr (250 MHz) δ 0.70, 0.92, 0.95, 0.96, 1.13, 1.27, 1.39, 1.43 (3H each, 8×s, H$_3$-18, -30, -29, -19, -26, -27, -28, -6′), 2.08 (3H, s, MeCOO-), 2.55, 2.69 (2H, ABq, J=16.0 Hz, H$_2$-2′ or H$_2$-4′), 2.63, 2.71 (2H, ABq, J=15.5 Hz, H$_2$-4′ or H$_2$-2′), 3.86 (1H, br d, J=3.0 Hz, H-24), 4.81 (1H, d, J=10.0 Hz, H-3), 5.20 (1H, br dt, $J_{2,3}$=$J_{2,1\alpha}$=11.0 Hz, $J_{2,1\beta}$=4.3 Hz, H-2), 5.59 (1H, br s, H-21); dcims (NH$_3$) *m/z* [M+NH$_4$]$^+$ 676, [M+NH$_4$-H$_2$O]$^-$ 658; eims (70 eV) *m/z* [M]$^+$ 658 (3), [M-HMGA]$^+$ 496 (15), [*m/z* 496-HOAc]$^-$ 436 (15), [*m/z* 436-Me]$^+$ 421 (25), 294 (70), 168 (100), 145 (25), 133 (21), 119 (35), 107 (28), 95 (35), 85 (20), 81 (20), 69 (30), 55 (20), 43 (67).

Compound **6** (42 mg) was exposed to pyridine/TsOH (6) in the same manner as described for **5** to afford the corresponding anhydro derivative (22 mg), which was identical (R_f, ir, and ^{1}H-nmr spectra) to compound **11** obtained from **5**.

HYDROLYSIS OF HEBELOMIC ACID B [**4**].—Solid K_2CO_3 (230 mg) was added to a solution of hebelomic acid B [**4**] (200 mg) in MeOH (15 ml). After stirring at room temperature overnight, the reaction mixture was diluted with MeOH (5 ml) and carefully neutralized by dropwise addition of 3% aqueous HCl at 0°. The mixture was diluted with H_2O (10 ml) and concentrated under reduced pressure to afford a white amorphous precipitate which was filtered off and washed with cold H_2O. This product (104 mg) was identical with crustulinol [9] (2) on the basis of mmp, $[\alpha]^{21}$D +19.1° ($c=0.8$, MeOH) [lit. (3) $[\alpha]^{18}$D +16.5° ($c=0.94$, MeOH)], and ir, ^{1}H-nmr, and ^{13}C-nmr spectral comparison with an authentic sample (2) and literature data (3). The above filtrate was adjusted to pH=3 by addition of HOAc and extracted with EtOAc (3×10 ml). The EtOAc layer was washed with brine, dried (MgSO$_4$), and taken to dryness. The residue was dissolved in CH_2Cl_2 and treated at 0° with excess CH_2N_2. After removal of the solvent, the crude residue was chromatographed on a Si gel column with CHCl$_3$ to give the dimethyl ester of HMGA as a colorless oil, identical with a sample prepared by methylation (CH_2N_2) of commercial HMGA; ir (film) ν max 3500 (OH), 2950, 1735 (C=O), 1435, 1375, 1345, 1200, 1180, 1150, 1120, 1095, 1010, 975 cm^{-1}; ^{1}H nmr (250 MHz) δ 1.37 (3H, s, Me), 2.67 (4H, s, H$_2$-2 and H$_2$-4), 3.72 (6H, s, 2×OMe).

HYDROLYSIS OF HEBELOMIC ACID E [**5**] AND F [**6**] TO AFFORD SENESCENSOL [**12**].—Hebelomic acids E [**5**] (20 mg) and F [**6**] (50 mg) were separately hydrolyzed following the same procedure as that described for the hydrolysis of **4**. The acid product was methylated (CH_2N_2) and identified as HMGA dimethyl ester (ir, nmr). The triterpene aglycone [**12**], precipitated during concentration of the reaction mixture (see above for crustulinol [9]), was crystallized from MeOH. The two samples (8 and 20 mg) obtained from **5** and **6**, respectively, were identical to each other (mmp, R_f, ir and nmr spectral comparison). Senescensol [**12**]: mp 222–224°, $[\alpha]^{21}$D −8.92° ($c=0.8$, C$_5$H$_5$N); ir (KBr) ν max 3378 (OH), 2947, 1470, 1372, 1270, 1130, 1107, 1071, 1030, 953, 900 cm^{-1}; ^{1}H nmr (C$_5$H$_5$N, 300 MHz) δ 0.92, 1.05, 1.17, 1.18, 1.32, 1.52, 1.52 (3H each, 7×s, H$_3$-18, -30, -29, -19, -26, -27, -28), 1.20–2.40 (21H, m, all CH$_2$ and CH protons but those indicated), 3.44 (1H, d, $J_{2,3}$=9.6 Hz, H-3), 4.18 (1H, ddd, $J_{2\beta,3\alpha}$=9.6 Hz, $J_{2\beta,1\alpha}$=11.5 Hz, $J_{2\beta,1\beta}$=4.5 Hz, H-2), 4.37 (1H, dd, J_1=11.5 Hz, J_2=2.0 Hz, H-24), 5.82 (1H, br s, H-21); ^{13}C-nmr data, see Table 1; dcims (NH$_3$) m/z [M+NH$_4$]$^+$ 508, [M+NH$_4$−H$_2$O]$^+$ 490; eims (70 eV) m/z [M]$^+$ 490 (50), [M−Me]$^+$ 475 (20), [M−H$_2$O]$^+$ 472 (26), [M−H$_2$O−Me]$^+$ 457 (100), [m/z 457−H$_2$O]$^+$ 439 (52), 431 (40), [m/z 439−H$_2$O]$^+$ 421 (28), 330 (20), 315 (55), 263 (15), 168 (21), 159 (19), 145 (19), 133 (20), 119 (25), 109 (20), 107 (30), 95 (32), 81 (21), 69 (24), 59 (28), 55 (25), 43 (35); *anal.*, calcd for C$_{30}$H$_{50}$O$_5$: C, 73.43, H, 10.27; found: C, 73.51, H, 10.33.

SYNTHESIS OF (S)-1-(1-NAPHTHYL)ETHYLAMIDES **18**, **24**, **25**, **26** FROM HEBELOMIC ACIDS A [**1**], B [**4**], E [**5**], AND F [**6**].—A representative procedure is described for the synthesis of amide **18** from hebelomic acid A [**1**]. BOP reagent [**17**] (15) (60 mg), 1-methylpiperidine (200 μl), and (S)-(−)-1-(1-naphthyl)ethylamine (20 μl) were successively added to a solution of **1** (90 mg) in anhydrous CH_2Cl_2 (3 ml) and the reaction mixture was stirred at room temperature for 3 h under a static Ar atmosphere. Volatiles were removed under reduced pressure and the residue was chromatographed on a Si gel column (10 g) with CH_2Cl_2-hexane-Me$_2$CO-MeOH (40:50:9:1) to afford amide **18** (70 mg) as a glassy solid. Following the same procedure, amides **24** (70 mg), **25** (21 mg), and **26** (52 mg) were prepared from hebelomic acids B [**4**] (100 mg), E [**5**] (29 mg), and F [**6**] (67 mg), respectively. Amide **18**: ir ν max 3413 (OH and NH), 3051, 2951, 1716 (ester C=O), 1639 (amide C=O), 1535, 1452, 1373, 1263, 1072, 1032, 991, 800, 779, 737 cm^{-1}; ^{1}H nmr (300 MHz) δ 0.51, 0.81, 0.85, 0.99, 1.00, 1.10, 1.11, 1.42 (3H each, 8×s, H$_3$-18, -30, -29, -19, -28, -26, -27, -6′), 1.62 (3H, d, J=7.0 Hz, H$_3$-2″), 2.02 (3H, s, MeCOO-), 2.3–2.6 (4H, 2 overlapped ABq, H$_2$-2′ and H$_2$-4′), 3.61 (1H, br d, J=11.5 Hz, H-24), 3.66 (1H, d, J=7.7 Hz, H-12), 4.67 (1H, d, $J_{2,3}$=10.0 Hz, H-3), 5.04 (1H, td, $J_{2,3}$=$J_{2\beta,1\alpha}$=11.0 Hz, $J_{2\beta,1\beta}$=4.5 Hz, H-2), 5.35 (1H, br s, H-21), 5.85 (1H, quint., J=7.5 Hz, H-1″), 7.12 (1H, d, J=7.5 Hz, NH), 7.3–8.15 (7H, m, Ar-H); dcims (NH$_3$) m/z [M+NH$_4$]$^+$ 863, [M+NH$_4$−H$_2$O]$^+$ 845. Amide **24**: ir ν max 3380 (OH and NH), 3030, 2975, 1730 (ester C=O), 1641 (amide C=O), 1520, 1452, 1374, 1238, 1030, 799, 770, 735 cm^{-1}; ^{1}H nmr (300 MHz) δ 0.73, 0.86, 0.88, 1.08, 1.10, 1.11, 1.15, 1.20 (3H each, 8×s, H$_3$-18, -30, -29, -19, -28, -26, -27, -6′), 1.68 (1H, d, J=7.0 Hz, H$_3$-2″), 1.63, 2.04 (3H each, 2×s, MeCOO-3 and MeCOO-12), 2.4–2.6 (4H, m, H$_2$-2′ and H$_2$-4′), 3.67 (1H, br d, J=11.0 Hz, H-24), 4.75 (1H, d, $J_{2,3}$=10.5 Hz, H-3), 4.96 (1H, br d, J=7.0 Hz, H-12), 5.10 (1H, ddd, $J_{2,3}$=10.5 Hz, $J_{2\beta,1\alpha}$=11.5 Hz, $J_{2\beta,1\beta}$=4.5 Hz, H-2), 5.25 (1H, br s, H-21), 6.0 (1H, br quint., J=7.0 Hz, H-1″), 6.88 (1H, d, J=8.0 Hz, NH), 7.4–8.2 (7H, m, Ar-H); dcims (NH$_3$) m/z [M+NH$_4$]$^+$ 905, [M+NH$_4$−H$_2$O]$^+$ 887, [m/z 887−H$_2$O]$^+$ 869. Amide **26**: ir ν max 3381 (OH and NH), 2974, 1742 (ester C=O), 1643 (amide C=O), 1539, 1451, 1370, 1273, 1113, 1034, 1011, 929, 798, 778 cm^{-1}; ^{1}H nmr (300 MHz) δ 0.72, 0.86, 0.87, 0.89, 1.07, 1.11, 1.13, 1.21 (3H each, 8×s, H$_3$-18,-30, -29, -19,-28, -26, -27, -6′), 1.68 (3H, d, J=7.0 Hz, H$_3$-2″), 2.00, 2.09 (3H each, 2×s, MeCOO-3 and MeCOO-

21), 2.45 (2H, ABq, $J=14.0$ Hz, H$_2$-2' or H$_2$-4'), 2.50 (2H, s, H$_2$-4' or H$_2$-2'), 3.46 (1H, dd, $J_1=11.0$ Hz, $J_2=2.0$ Hz, H-24), 4.74 (1H, d, $J_{2,3}=10.5$ Hz, H-3), 5.09 (1H, td, $J_{2,3}=J_{2\beta,1\alpha}=11.0$ Hz, $J_{2\beta,1\beta}=4.0$ Hz, H-2), 5.98 (1H, br quint., $J=7.5$ Hz, H-1''), 6.10 (1H, br s, H-21), 6.90 (1H, d, $J=7.5$ Hz, NH), 7.4–8.2 (7H, m, Ar-H); dcims (NH$_3$) *m/z* [M+NH$_4$]$^+$ 889, [M+NH$_4$–HOAc]$^+$ 829. The crude amide **25** was immediately converted to **19**.

SYNTHESIS OF METHYL (3S)-5-[(S)-1-(1-NAPHTHYL)ETHYLAMINO]-3-HYDROXY-3-METHYLGLUTARATE [**19**] FROM AMIDES **18, 24–26**.—A representative procedure is described for the synthesis of **19** from **18**. A stirred solution of naphthylamide **18** (85 mg) in MeOH (3 ml) was treated with 1 N NaOH aqueous solution (1 ml) at room temperature. Stirring was continued at room temperature for 2 h, monitoring the reaction on tlc with hexane-CH$_2$Cl$_2$-Me$_2$CO-MeOH (30:40:30:5), then the mixture was diluted with H$_2$O (5 ml) to precipitate crustulinol [**9**] (2) (35 mg), which was filtered off. The filtrate was concentrated under reduced pressure and the aqueous layer was acidified at 0° with 1 N HCl aqueous solution and extracted with CH$_2$Cl$_2$. After drying (MgSO$_4$) and removal of the solvents, the residue was dissolved in MeOH (1 ml) and treated with ethereal CH$_2$N$_2$ at 0°. The crude amide ester was chromatographed on a short Si gel column with hexane-CH$_2$Cl$_2$-Me$_2$CO-MeOH (60:30:8:2) to afford **19** (26 mg) as a colorless, viscous oil. Following the same procedure, amide **19** was also synthesized by separate hydrolysis of amides **24–26**. In addition to **19**, hydrolysis of amide **24** afforded **9**, while hydrolysis of amides **25** or **26** gave senescensol [**12**]. (3S,1'S)-**19** showed the following data: average value $[\alpha]^{21}$D $-17.7°\pm0.8°$ (c=0.3, CH$_2$Cl$_2$), ir (film) ν max 3318 (OH and NH), 3062, 1733 (ester C=O), 1635 (amide C=O), 1532, 1436, 1374, 1346, 1197, 1121, 1018, 916, 800, 779 cm^{-1}; ^{1}H nmr (300 MHz) δ 1.31 (3H, s, H$_3$-6), 1.67 (3H, d, $J=7.0$ Hz, H$_3$-2'), 2.40, 2.53 (2H, ABq, $J=14.0$ Hz, H$_2$-2 or H$_2$-4), 2.56 (2H, br s, H$_2$-4 or H$_2$-2), 3.66 (3H, s, OMe), 4.83 (1H, br s, OH), 5.95 (1H, quint., $J=7.0$ Hz, H-1'), 6.58 (1H, d, $J=7.0$ Hz, NH), 7.4–8.2 (7H, m, Ar-H); dcims (NH$_3$) *m/z* [M+NH$_4$]$^+$ 347.

An authentic sample of (3S,1'S)-**19** $[\alpha]^{21}$D $-17.83°$ (c=0.5, CH$_2$Cl$_2$), was prepared from methyl (S')-3-hydroxy-3-methylglutarate (18) by condensation with (S)-(−)-(1-naphthyl)ethylamine, following the same procedure as that described below for (±)-**23**.

SYNTHESIS OF (3R)-5-O-ACETYL-N-[(S)-1-(1-NAPHTHYL)ETHYL]MEVALONAMIDE [**15**].—1 M LiBH$_4$ solution (130 μl) in anhydrous THF was added by syringe to a magnetically stirred solution of amide **19** (19 mg) in THF (4 ml) and the mixture was refluxed for 90 min under a static Ar atmosphere. The reaction mixture was quenched by addition of Me$_2$CO (0.3 ml) and H$_2$O (1 ml) at 0°, then filtered through a pad of MgSO$_4$ and evaporated under reduced pressure. The residue was chromatographed on a Si gel column (4 g) with hexane-CH$_2$Cl$_2$-Me$_2$CO-MeOH (30:40:29:1) to afford the expected alcohol (ir ν max 3321, 1637, 1549, 778 cm^{-1}) which was immediately acetylated (Ac$_2$O/pyridine). After the usual work-up the residue was chromatographed on a Si gel column (4 g) with hexane-CH$_2$Cl$_2$-Me$_2$CO (60:30:10) to afford pure **15** (10.0 mg) as a colorless oil; $[\alpha]^{21}$D $-14°$ (c=0.5, EtOH) [lit. (14) $[\alpha]$D $-13°$ (c=1.5, EtOH)]; ir (film) ν max 3321 (OH), 3058, 2977, 2929, 1734 (ester C=O), 1637 (amide C=O), 1542, 1450, 1364, 1241, 1179, 1123, 1065, 1032, 973, 919, 801, 779, 735, 703 cm^{-1}; ^{1}H nmr (300 MHz) δ 1.19 (3H, s, H$_3$-6), 1.66 (3H, d, $J=7.0$ Hz, H$_3$-2'), 1.82 (2H, t, $J=7.0$ Hz, H$_2$-4), 2.00 (3H, s, MeCOO-), 2.20, 2.35 (2H, ABq, $J=14.5$ Hz, H$_2$-2), 4.18 (2H, t, $J=7.0$ Hz, H$_2$-5), 4.65 (1H, br s, OH), 5.92 (1H, quint., $J=7.0$ Hz, H-1'), 6.15 (1H, d, $J=7.0$ Hz, NH), 7.4–8.15 (7H, m, Ar-H); eims (70 eV) *m/z* [M]$^-$ 343 (18), 170 (100), 155 (53), 129 (18), 128 (15), 116 (16), 97 (25), 95 (22), 83 (30), 81 (25), 71 (46), 69 (41), 57 (62), 55 (49), 43 (51).

HYDROLYSIS OF MEVALONAMIDE **15**: SYNTHESIS OF (R)-(−)-MEVALONOLACTONE [**20**].—A solution of mevalonamide **15** (12 mg) in 6 M NaOH (2 ml) was refluxed for 2 h, then diluted with H$_2$O (5 ml), acidified with 6 M HCl, and extracted exhaustively with EtOAc. The EtOAc layer was washed with brine, dried (MgSO$_4$), and concentrated to give (R)-(−)-mevalonolactone [**20**] (4.4 mg); $[\alpha]^{21}$D $-20.5°$ (c=0.2, EtOH) [lit. (18) $[\alpha]$D $-21.8°$ (c=1.1, EtOH)]; ir (film) ν max 3425 (OH), 2975, 2928, 1728 (lactone C=O), 1473, 1403, 1266, 1244, 1131, 1071, 1025, 987, 969, 936, 882, 803 cm^{-1}; ^{1}H nmr (300 MHz) δ 1.37 (3H, s, H$_3$-3), 1.85–1.95 (2H, m, H$_2$-4), 2.50, 2.67 (2H, ABq, $J=17.0$ Hz, H$_2$-2), 4.35 (1H, dt, $J_1=11.0$ Hz, $J_2=4.5$ Hz, H-5), 4.61 (1H, dt, $J_1=11.0$ Hz, $J_2=7.5$ Hz, H-5'); eims (70 eV) *m/z* [M]$^+$ 130 (1), 103 (8), 102 (5), 87 (5), 85 (7), 71 (82), 58 (26), 53 (16), 43 (100).

SYNTHESIS OF METHYL 5-[(S)-1-(1-NAPHTHYL)ETHYLAMINO]-3-HYDROXY-3-METHYLGLUTARATES (3S)-**19** AND (3R)-**21**.—Anhydride **22** (20) (1 g) was dissolved in MeOH (25 ml) under an Ar atmosphere, and 1.95 ml of 1.54 M MeONa in MeOH was added. The solution was stirred at 50° for 1h, then filtered through Florisil and evaporated under reduced pressure. The crude residue was chromatographed on a Si gel column with C$_6$H$_6$-EtOAc-HOAc (59:39:2) to afford methyl ester **23** (0.95 g) as a pale yellow oil; ir (film) ν max 3600–2400 (OH), 2985, 1720 (C=O), 1439, 1379, 1351, 1203, 1035, 1012, 979, 896, 808, 736 cm^{-1}; ^{1}H nmr (300 MHz) δ 1.32 (3H, s, H$_3$-6), 2.62 (4H, 2 overlapped ABq, H$_2$-2 and H$_2$-4), 3.62 (3H, s, OMe), 3.95 (1H, br s, OH), 7.3 (1H, br, COO*H*). BOP Reagent [**17**] (15) (130 mg), 1-methylpiperidine (300 μl)

and (S)-(−)-1-(1-naphthyl)ethylamine (47 μl) were successively added to a solution of **23** (51 mg) in anhydrous CH_2Cl_2 (2 ml) and the reaction mixture was stirred at room temperature for 3 h under a static Ar atmosphere. Volatiles were removed under reduced pressure and the residue was chromatographed on a Si gel column (5 g) with CH_2Cl_2-hexane-Me_2CO-HOAc (50:40:8:2) to give a mixture of diastereomeric amides **19** and **21** (58 mg) as a glassy solid; ir (film) ν max 3304 (OH and NH), 3056, 2978, 1729 (ester C=O), 1640 (amide C=O), 1534, 1436, 1373, 1349, 1227, 1119, 1091, 1014, 973, 918, 800, 778, 736, 701 cm^{-1}; ^{1}H nmr (300 MHz) δ 1.25, 1.31 (3H each, 2×s, H_3-6), 1.66, 1.67 (3H each, d, J=7.0 Hz, H_3-2′), 2.35–2.64 (8H, m, 4 overlapped ABq, H_2-2 and H_2-4), 3.60, 3.66 (3H each, 2×s, OMe), 5.95 (2H, quint., J=7.0 Hz, H-1′), 6.57, 6.60 (1H each, 2 overlapped d, J=7 Hz, NH), 7.4–8.2 (14H, m, Ar-H); dcims (NH_3) m/z $[M+NH_4]^+$ 347.

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