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HOMOSCALARANE SESTERTERPENES FROM *LENDENFELDIA FRONDOSA*

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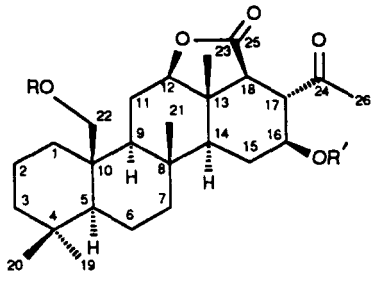
ABSTRACT.—The marine sponge *Lendenfeldia frondosa*, collected from the Solomon Islands, has yielded homoscalarane sesterterpenes. Two new metabolites, epihomoscalaralactone IIA [**5**] and homoscalarate II [**10**], were accompanied by two known metabolites, homoscalaralactone IIA [**1**] and homoscalaralactone IIB [**7**]. These structures were established by analysis of 2D nmr data, trends in ^{13}C-nmr shifts, and comparison of experimental with molecular-mechanics-calculated nmr J's. Each of the alcohols **1**, **2**, and **3** was converted to its corresponding acetate, **2**, **6**, and **8**, respectively. Compound **6** exhibited moderate anti-inflammatory activity.

Alkylated scalarane sesterterpenoids are notable from a biosynthetic perspective and also represent chemotaxonomic markers of the sponge order Dictyoceratida (1) or their nudibranch associants (2,3). Such alkylated scalaranes, sometimes called homoscalaranes, can be divided into four known skeletal types (Figure 1): the scalarane I skeleton with monomethylation II (4,5), dimethylation III, IV (1), or methylation accompanied by rearrangement V (6). Several years ago Kazlauskas *et al.* (4) reported five new II-type homoscalaranes from an Australian *Lendenfeldia* sp., and some were inhibitors of platelet aggregation. This prompted our collection of a Solomon Island *Lendenfeldia frondosa* (Bergquist) (family Spongiidae, order Dictyoceratida) because of the possibility of extending our ongoing evaluation of anti-inflammatory polycyclic sesterterpenoids (7–9). We now report additional II-category homoscalaranes, **1**, **5**, **7**, and **10**, along with several synthetic acetate derivatives. During the preparation of this manuscript Rao *et al.* (10) reported on similar metabolites including **1** and **7**. Interestingly, one of these homoscalaranes, **6**, is moderately potent in an anti-inflammatory assay.

RESULTS AND DISCUSSION

The semipure extract fractions of *L. frondosa* that contained sesterterpenes were rapidly identified by obtaining APT ^{13}C-nmr spectra on regular phase flash chromatography fractions of the crude extract. For example, chromatography fractions displayed ^{13}C-nmr resonances characteristic of polycyclic sesterterpenoids including: Me's at δ 16 (ca. 3 peaks), 20, 22, and 23, along with CH resonances as broad peaks centered at $\delta = 52$ and 56.

A homosesterterpene **1**, $C_{26}H_{40}O_5$ (hreims $[M]^+$ 432.2876), was isolated as an impure white solid (mp 280°). Prominent ^{1}H-nmr resonances consisted of five singlet methyls at δ 0.75 (3H), 0.82 (3H), 0.92 (3H), 0.96 (3H), and 2.13 (3H); an AB multiplet for anisochronous geminal protons at δ 3.93 (d, $J = 12.1$ Hz, 1H), 3.76 (d, $J = 12.1$ Hz, 1H); and two methine protons at δ 3.65 (dt, $J = 10.8$, 5.0 Hz, 1H) and 2.93 (dd, $J = 11.2$, 10.5 Hz, 1H). The features implied by these data could be accommodated by those of structure **1**, which has previously been reported (4,5,10). This alcohol, as well as the others isolated in our study, was sparingly soluble in most organic solvents. The straightforward conversion of **1** to the acetate derivative **2** was carried out, and the product was purified by hplc. The nmr and ms properties of diacetate **2** were as expected and generally analogous to data in the literature (4, 10) and are exemplified by the molecular formula of $C_{30}H_{44}O_7$ (eims $[M]^+$ 516) and ^{13}C-nmr APT formula of $C_{30}H_{44}$. An extensive 2D nmr study of **2** allowed unambiguous assignment of all of the



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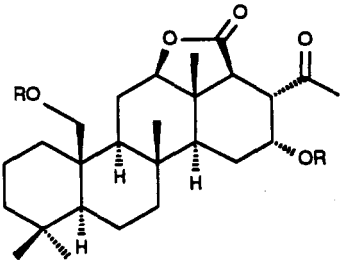
3 R=Ac, R′=H
4 R=H, R′=Ac



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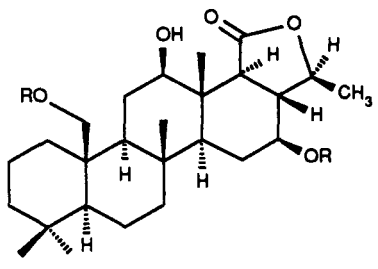

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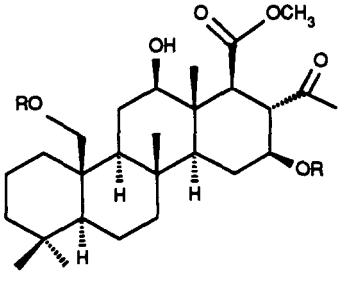
8 R=Ac



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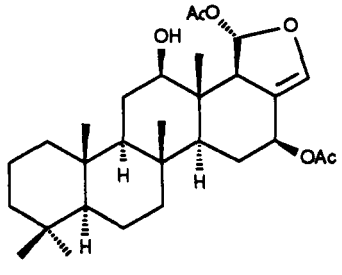
10 R=OAc



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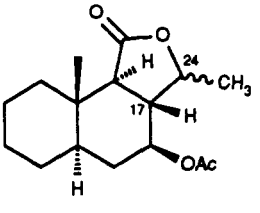

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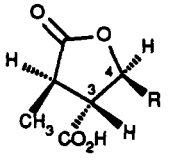

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^{13}C-nmr resonances. Our results show that past mis-assignments have been made for the ^{13}C-nmr data of **1**/**2** and for some nine other analogous homoscalaranes (1,4,10,11); these involved errors for the following carbon sets: C-12–C-16 [Table 1 versus Crews and Naylor (1) and Kazlauskas *et al.* (4)], and C-15–Me-26 [Table 1 versus Crews and Naylor (1) and Kazlauskas *et al.* (11)]. A specific illustration of this situation is provided by the most recent published data of **1** (10), in which five CH resonances were specified as interchangeable and the C-15–Me-26 resonances appear to be reversed. Our assignments are shown in Table 1 and are supported by a ^{1}H-^{1}H COSY nmr and the ^{1}H-^{13}C COSY (J = 140) nmr of **2** described in the experimental section. These assignments are also consistent with the ^{13}C-nmr resonances unequivocally assigned by us (9) for other polycyclic sesterterpenes. Finally, the all trans ABCD-ring-junction stereochemistry previously depicted for **2** was immediately recognized as consistent with the characteristic shifts at C-9, Me-21, and Me-23 (Table 1).

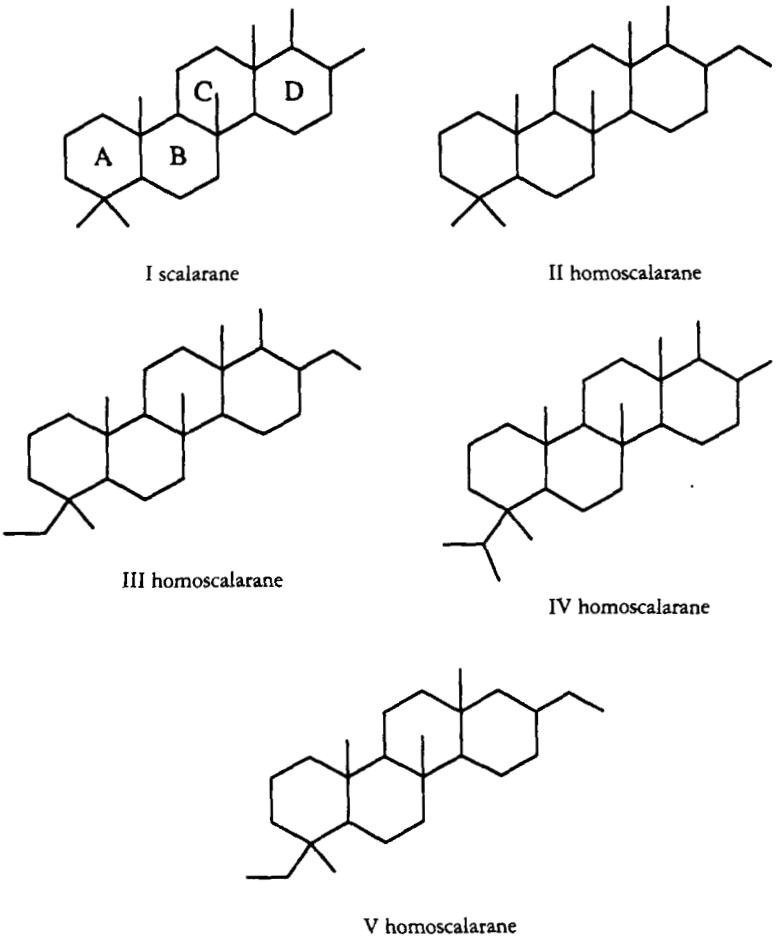

FIGURE 1. Skeletal types of homoscalaranes.

A new compound **5** was not directly isolated. Purification of the fraction containing this compound was complicated because, on standing, this oil became a solid which could not be redissolved in CH_2Cl_2 and was only slightly soluble in MeOH. Subsequent acetylation gave new solids which were fully soluble in these solvents. Hplc purification afforded the diacetate **6**, $C_{30}H_{44}O_7$ (hreims $[M]^+$ 516.3113), which is the C-16 epimer of **2** as indicated by key nmr data of **6** including the ^{1}H-nmr broad quartet at δ 5.67 ($J = 3$ Hz, H-16), the upfield shift at C-16 to δ 70.1, and the upfield shift at C-18 to δ 49.4. Shielding at C-18 in **6** versus **2** is expected due to a new 1,3-diaxial relationship that is introduced when the OAc switches from equatorial in **2** to axial in **6**. We assume that the natural product parent of this compound is **5**, because the ^{1}H-nmr of the original fraction before acetylation showed clearly resolved resonances for H-16 of **5** at δ 4.58 (t, $J = 3$ Hz), but these were accompanied by resonances of the other homosesterterpene alcohols.

A third lactone, **7**, was isolated as an impure (by ^{1}H nmr) white solid from a flash chromatography fraction (see Experimental). The upfield region of the ^{1}H-nmr spectra contained resonances for four singlet methyls (δ 0.92, 0.82, 0.80, and 0.76), and these were accompanied by a doublet methyl at δ 1.44 ($J = 6.1$ Hz); no OAc methyls could

TABLE 1. ^{13}C-nmr ($CDCl_3$, 75 MHz) Data.

Carbon	Compound			
	2[a]	**6**	**8**[a]	**10**
	δ	δ	δ	δ
C-1	35.3	35.3	34.8	34.8
C-2	18.4	18.3	18.4	18.4
C-3	41.4[b]	41.5	41.6	41.6
C-4	33.2	33.2	33.0	33.0
C-5	57.8	57.8	57.0	56.9
C-6	17.7	17.6	18.2	18.0
C-7	41.4[b]	41.3	42.2	41.8
C-8	38.4	37.8	37.5	37.8
C-9	52.0	51.9	49.0	52.1
C-10	42.9	42.6	42.0	44.1
C-11	23.8	23.8	28.3	29.9
C-12	90.3	90.3	79.3	79.1
C-13	41.8	41.8	40.6	40.6
C-14	61.2	61.0	56.5	58.4
C-15	25.8	26.5	26.7	26.0
C-16	75.9	70.1	73.6	75.2
C-17	48.8	49.1	58.5	55.4
C-18	56.7	49.4	58.4	56.0
C-19	21.9	21.8	21.9	21.9
C-20	33.8	33.8	33.8	33.7
C-21	17.8	17.6	16.2	16.5
C-22	64.7	64.8	64.6	64.7
C-23	14.3	13.5	12.4	10.3
C-24	207.9	204.7	80.7	210.7
C-25	174.3	175.6	177.1	174.0
C-26	32.7	29.4	19.7	32.7
OMe				52.3
Ac	170.7	170.9	171.3	171.0
	169.5	169.8	170.4	169.7
	21.2	21.2	21.4	21.3
	20.9	20.9	21.3	21.1

[a]Assignments based on ^{13}C-^{1}H COSY nmr data.
[b]Two resonances separated by 0.08 ppm.

be observed. Further purification was accomplished by acetylation followed by hplc, which afforded the diacetate alcohol **8**, $C_{30}H_{46}O_7$ (hreims $[M]^+$ 518.3239). Its ^{13}C nmr exhibited resonances for two acetates (δ 171.3 and 170.4) plus one lactone C=O (δ 177.1). The very recent publication by Rao *et al.* (10) described the structures and physical properties of both **7** and **8**, but remaining undescribed was the relative stereochemistry of Me-26. Our 2D heteronuclear COSY nmr data also indicated that some of the ^{13}C-nmr assignments needed revision (Table 1). We spent considerable time in deducing the lactone regiochemistry and assigning all the relative stereochemistries of **8**, whereas the discussion of these issues by Rao *et al.* was quite brief. Hence, it is relevant to discuss our strategies next. The shifts of Me-21, C-22, and Me-23 (Table 1) indicated that the carbocyclic ring junctions were all trans, while characteristic *J*'s to H-12, H-16, and H-17 established their axial stereochemistry as shown. An equatorial OH must be located at C-12 in view of the characteristic ^{1}H δ 3.40 along with the similarity of the chemical shift at C-12 between **8** (δ 79.3) and

heteronemin [**11**] (12) (δ 80.3) which is quite different from that of **2** (δ 90). A γ-lactone had to link C-18 and C-24 with trans D-ring annulation stereochemistry defined by the H-17β, as assigned above, and an H-18α deduced as follows. An equatorial *R*-group is indicated at C-18 based on the similarity of the δ 12.4 Me-23 shift in **8** to scalaranes with Me-23 flanked by two equatorial vicinal substituents: δ 8.8 of heteronemin [**11**], δ 9.9 of heteronemin acetate, and δ 10.3 of **10** versus the very different shift at Me-23 when it is flanked by one axial and one equatorial substituent: δ 16.3 of 12-*epi*-heteronemin acetate. Finally, a trans H-17/H-24 arrangement was deduced by comparing the observed coupling of $J_{17\text{-}24}=9.6$ (measured in a spectrum that included homonuclear spin decoupling at H_3-26) to values calculated from molecular-mechanics-energy-minimized structures of **12** where $J_{17\text{-}24}=10.7$, 168° (trans) and $J_{17\text{-}24}=6.9$, 34° (cis), and to the experimental literature data of $J_{3\text{-}4}=9$ for the trans protons of (+)-neodihydromurolic acid [**13**] (13) and $J_{17\text{-}24}=10$ Hz for the trans lactone protons of phyllofoloactone A (14).

The last homosesterterpenoid, **10**, $C_{31}H_{48}O_8$ (hreims $[M]^+$ 548.3348), was isolated from a nonpolar flash chromatography fraction. Its structure differed from that of **2** by addition of MeOH. The ^{13}C-nmr shifts of **2** varied from those of **10** only in the vicinity of the lactone, and these included that of C-12 at δ 90.3 in the former and 79.1 in the latter. The presence of **10** is intriguing, because its triol parent **9** could be in equilibrium with **1** and **7** in the biosynthetic mixture contained within the sponge tissue.

The homoscalaranes **6**, **8**, and **10** were evaluated by Glaser and Jacobs (15) in a model anti-inflammatory screen. An endogenous arachidonic acid release assay was utilized, with manoalide as the positive standard. The percentages for the inhibition of PLA2 activity are: manoalide (15) ca. 100% at 4 μM; **6** 35% at 8 μM; and **8** and **10** not active at 8 μM.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Nmr spectra were recorded at 250 MHz for ^{1}H and 62.5 MHz for ^{13}C or at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Multiplicities of ^{13}C-nmr peaks were determined from APT data and 2D heteronuclear COSY nmr experiments. Ms data were at low resolution on a quadripole apparatus at U.C.S.C. or at high reolution on a double focusing apparatus at U.C.B. Hplc was done using a 10 μ Si gel column (25 × 15 cm). All solvents were distilled and dried for hplc and were spectral grade for spectroscopy.

IDENTIFICATION.—The sponge (collection no. 89017) *L. frondosa* was collected from the Marovo lagoon region of the Solomon Islands in the summer of 1989; voucher specimens and underwater photos are available (from P.C.). Our voucher specimen no. 89017 was carefully examined by M.C. Diaz (U.C.S.C., Institute of Marine Sciences) and exhibits the following characteristics: *morphology*—(in life) flat encrusting tough sheets; *color*—iridescent purple in life, brown-reddish in spirit; *shape*—flabellate, profusely folded on itself (dried); *consistency*—fleshy; *surface*—elongated protuberances and shallow grooves; *ectosome*—organic skin; *choanosome*—fibrofascicles, primaries cored (70–100 μ) and uncored secondaries (30–70 μ). *Lendenfeldia* is a new genus defined by Bergquist (16) to include "lamellate sponges" of the genus *Phyllospongia* which possess cored primary fibers. This may be the same specimen of the name *Phyllospongia dendyi* var. *frondosa* (Lendenfeld) (16).

EXTRACTION.—The sponge (1.40 kg wet wt) was preserved and returned for workup consisting of soaking (48 h, room temperature) in MeOH × 3. Parallel concentration of this extract afforded viscous oils, and ^{13}C-nmr spectra revealed that each contained a mixture of lipids and terpenes. These combined extracts afforded a viscous oil (23.96 g) which was subjected to solvent partitioning in aqueous MeOH against hexane, CCl_4, CH_2Cl_2, with the percentage of H_2O adjusted to produce a biphase solution. Yields were hexane (18.78 g), CCl_4 (3.48 g), and CH_2Cl_2 (1.70 g). Flash chromatography of the CH_2Cl_2 solvent partition oil gave 24 fractions. Fraction 14 ws subjected to semi-preparative hplc [normal phase, 10 μm Si gl column, hexane-EtOAc (1:1)] to provide compound **10** (20 mg). Fractions 16–18 afforded pure compound **1** (100 mg). Fractions 19–22 were combined and subjected to acetylation followed by semi-preparative hplc [normal phase, 10 μm Si gel column, hexane-EtOAc (1:1)] to afford **6** (18 mg). Fraction 23 afforded **7** (45 mg).

16,22-Dihydroxyhomoscalaralactone IIA [**1**].—White solid: mp 280; hreims 432.2876 ($C_{26}H_{40}O_5$, Δ 0.0 mmu of calcd); lrcims *m/z* (rel. int.) $[M]^+$ 432 (2), 431 (3), 403 (6), 339 (7), 183 (20), 43 (100); ^{1}H-nmr ($CDCl_3$, 250 MHz) δ 3.93 (d, *J* = 12.1, H-22), 3.76 (d, *J* = 12.1, H-22′), 3.65 (dt, *J* = 10.8, 5.0, H-16), 2.93 (dd, *J* = 11.2, 10.5, H-17), 2.13 (s, Me-26), 0.96 (s, Me-23), 0.92 (s, Me-21), 0.82 (s, Me-20), 0.75 (s, Me-19).

16,22-Diacetylhomoscalaralactone IIA [**2**].—A solution of **1** (50 mg) in Ac_2O (10 ml) and pyridine (2 ml) was kept at room temperature overnight. The reaction mixture after usual workup yielded the diacetate **2**: white solid; mp 243–244°; [α]D +28° (*c* = 1 g/100 ml, $CHCl_3$); lreims *m/z* (rel. int.) $[M]^+$ 516 (2), 474 (4), 414 (5), 369 (30), 353 (10), 189 (100), 175 (30), 135 (60), 118 (68); ^{1}H-nmr ($CDCl_3$, 300 MHz) (assignments based on ^{1}H-^{1}H and ^{1}H-^{13}C COSY data) δ 4.93 (dt, *J* = 10.2, 10.2, 5.4, H-16), 4.60 (d, *J* = 12, H-22), 4.10 (d, *J* = 12, H-22′), 3.70 (dd, *J* = 12, 3, H-12), 3.04 (dd, *J* = 10.5, 11.4, H-17), 2.33 (s, Me-26), 2.27 (brd, *J* = 13, H-11eq), 2.23 (d, *J* = 12, H-18), 2.04 (s, Ac), 2.04 (m, H-1eq), 2.03 (m, H-11ax, H-15eq), 1.95 (m, H-1ax), 2.00 (s, Ac), 1.71 (m, H-3eq, H-7eq), 1.50 (m, H_2-2), 1.42 (q, *J* = 12, H-15ax), 1.25 (dd, *J* = 12.5, 3.3, H-9), 1.15 (m, H-3ax, H-7ax, H-14), 1.05 (m, H-5), 0.98 (s, Me-23), 0.93 (s, Me-21), 0.85 (s, Me-20), 0.80 (s, Me-19). The above COSY data enabled us to correct past assignment for C-12, C-16, C-15, and C-26 in **2** and in related sesterterpenes. The proton multiplet patterns and shifts of H-16 and H-12 allow them to be easily distinguished, which then enables straightforward assignments of their carbon shifts. The APT spectra pinpointed the position of Me-26, and the COSY correlations (both ^{1}H and ^{13}C) to H-15/15′ firmly identified the shift of C-15.

16,22-Diactyl-16-epi-*homoscalaralactone IIA* [**6**].—Amorphous solid: [α]D +12° (*c* = 1 g/100 ml, $CHCl_3$) hreims *m/z* 516.3113 ($C_{30}H_{44}O_7$, Δ 2.6 mmu of calcd); lrcims (isobutane) *m/z* (rel. int.) $[M+H]^+$ 517 (50), 457 (50), 397 (40), 379 (40), 238 (100), 169 (8), 128 (20); ir (CH_2Cl_2) 1785, 1740 cm^{-1}; ^{1}H nmr ($CDCl_3$, 300 MHz) (assignments based on ^{1}H-^{1}H COSY data) δ 5.67 (t, *J* = 3, H-16), 4.64/4.12 (AB, *J* = 12, H-22/H-22′), 3.85 (dd, *J* = 12.0, 3.6, H-12), 2.91 (dd, *J* = 12, 3, H-17), 2.78 (d, *J* = 11.7, H-18), 2.30 (m, H-11eq), 2.25 (s, Me-26), 2.07/2.00 (s, 2 Ac), 2.05 (m, H-11ax), 1.76 (dt, *J* = 9, 3, 3, H-15eq), 1.47 (m, H-14), 1.24 (m, H-9), 1.06 (m, H-15ax), 0.95 (s, Me-23), 0.92 (s, Me-21), 0.88 (s, Me-20), 0.83 (s, Me-19).

16,22-Dihydrohomoscalarelactone IIB [**7**].—White solid: reims *m/z* (rel. int.) $[M]^+$ 434 (1), 433 (2), 418 (20), 403 (3), 191 (4), 69 (20); ^{1}H nmr (MeOH-*d*, 250 MHz) δ 1.44 (d, *J* = 6.1), 0.92 (s), 0.82 (s), 0.80 (s), 0.76 (s).

16,22-Diacetylhomoscalarelactone IIB [**8**].—Colorless needles: mp 300°; [α]D +21° (*c* = 1 g/100 ml, $CHCl_3$); hreims *m/z* 518.3239 ($C_{30}H_{46}O_7$, Δ 0.3 mmu of calcd); lrcims *m/z* (rel. int.) $[M+H]^+$ 519 (50), 501 (2), 478 (8), 458 (30), 441 (40), 381 (30), 367 (48), 189 (34), 93 (100); ir (CH_2Cl_2) 3482 (br), 1745 (br) cm^{-1}; ^{1}H-nmr ($CDCl_3$, 300 MHz) (assignments based on ^{1}H-^{1}H and ^{13}C-^{1}H COSY data) δ 4.76 (dt, *J* = 10.2, 10.2, 5, H-16), 4.54/4.13 (AB, *J* = 12, H-22/H-22′), 4.32 (dq, *J* = 8, 6, H-24), 3.40 (dd, *J* = 10.8, 4.2, H-12), 2.24 (m, H-1eq), 2.17 (m, H-9), 2.14 (m, H-11eq, H-15eq, H-17), 2.11 (m, H-1eq), 2.08/2.07 (s, 2 Ac), 2.07 (m, H-15ax), 2.00 (m, H-11ax), 1.76 (m, H-7eq), 1.72 (m, H-7eq), 1.50 (m, H_2-2, H_2-6), 1.35 (m, H_2-3), 1.44 (d, *J* = 6.0, Me-26), 1.02 (m, H-18), 1.02 (s, Me-23), 0.99 (m, H-5), 0.94 (m, H-14), 0.88 (s, Me-21), 0.85 (s, Me-20), 0.81 (s, Me-19).

16,22-Diacetylhomoscalarate II [**10**].—Amorphous solid: [α]D +45° (*c* = 1 g/100 ml, $CHCl_3$); hreims *m/z* 548.3348 ($C_{30}H_{48}O_8$ Δ 0.9 mmu); lrcims *m/z* (rel. int.) $[M+H]^+$ 549 (1), 530 (5), 470 (50), 438 (70), 410 (100), 378 (80), 248 (40), 162 (40), 98 (60); ir (CH_2Cl_2) 3480 (br), 1760 (br) cm^{-1}; ^{1}H nmr ($CDCl_3$, 300 MHz) (assignments based on ^{1}H-^{1}H COSY) δ 4.99 (dt, *J* = 11.1, 11.1, 5.1, H-16), 4.64/4.04 (AB, *J* = 12, H-22/H-22′), 3.38 (s, OMe), 3.33 (dd, *J* = 12, 11, H-17), 3.10 (dd, *J* = 10, 4, H-12), 2.59 (d, *J* = 12, H-18), 2.15 (s, Me-26), 2.02 (bd, *J* = 12.6, H-15eq), 1.68 (s, OAc), 1.64 (m, H_2-11), 1.60 (s, OAc), 1.32 (m, H-15ax), 1.06 (s, Me-23), 1.0 (m, H-9), 0.84 (s, Me-21), 0.74 (s, Me-20), 0.68 (s, Me-19); selected signals from another $CDCl_3$ spectrum at a different concentration include 1.9 (dd, *J* = 13, 4, H-11eq), 1.75 (brd, *J* = 12, H-11ax).

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