Bisabolane Derivatives from *Leontopodium alpinum*

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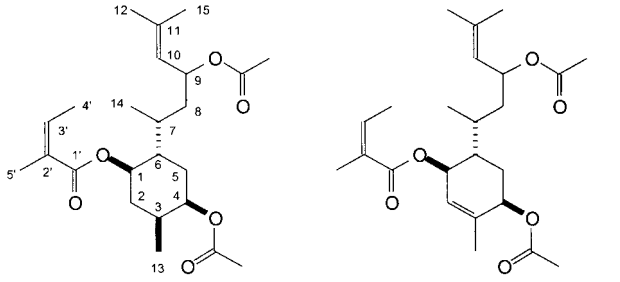
From the roots of *Leontopodium alpinum*, four new bisabolane sesquiterpenoids, (1*R**,2*S**,4*R**,5*S**)-4-(acetyloxy)-2-[3-(acetyloxy)-1,5-dimethylhex-4-enyl]-5-methylcyclohexyl (2*Z*)-2-methylbut-2-enoate (**1**), (1*R**,4*S**,6*R**)-4-(acetyloxy)-6-[3-(acetyloxy)-1,5-dimethylhex-4-enyl]-3-methylcyclohex-2-en-1-yl (2*Z*)-2-methylbut-2-enoate (**2**), and 3-methyl-1-{2-[(1*R**,2*R**,5*R**,6*S**)-2,5,6-tris(acetyloxy)-4-methylcyclohex-3-en-1-yl]propyl}but-2-enyl (2*Z*)-2-methylbut-2-enoate (**3** and **4**) have been isolated. The latter constituents differ from each other by the relative configurations of the chiral centers of the hexenyl side chain.

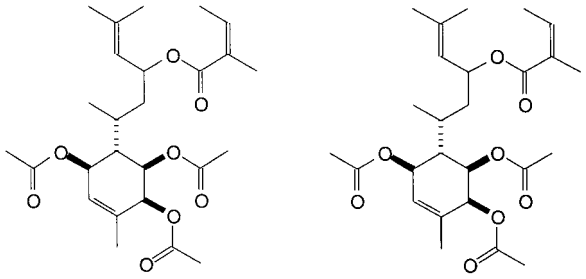
1. Introduction. – *L. alpinum* CASS. (Asteraceae), commonly known as 'Edelweiss', is a very ornamental and protected species. In the Alps, especially in Tyrol, this plant plays an important role in the commercial, cultural, and traditional life of people. It is pictured on uniforms, traditional clothing, flags, and emblems (*e.g.*, Austrian and German Alpine Clubs), and used in advertisement for promoting tourism. In traditional medicine, *L. alpinum* is used for the treatment of bronchitis, abdominal aches, and diarrhoea in people as well as in animals [1][2]. The use of *L. alpinum* against dysentery and for the therapy of cancer was reported by *Hoppe* [3] and *Hartwell* [4]. Considering how popular and well-known it is, it is surprising that phytochemical investigations of *L. alpinum* are very rare, and pharmacological studies are completely missing. Previous phytochemical investigations of this plant resulted in the isolation of flavonoids, phenolic acids, terpenes, and one chromane derivative [5–9]. This paper deals with the isolation and structure elucidation of bisabolane derivatives, which might be one pharmacological active principle of this plant.

2. Results and Discussion. – Powdered dried roots of *L. alpinum* were extracted with CH_2Cl_2, and the extract was fractionated on *Sephadex LH-20* (MeOH), silica gel (CH_2Cl_2/MeOH), and *RP-18* material to yield the bisabolane sesquiterpenoids **1**–**4**. Their structures were established by UV and NMR spectroscopy, and by mass spectrometry.

The molecular formula of **1** was determined as $C_{24}H_{38}O_6$ by high-resolution (HR) EI-MS (M^+ *m*/z 422.2615; calc. 422.2668). The UV spectrum exhibited an absorption maximum at 260 nm. The ^{1}H-NMR spectrum of **1** showed signals of five CH groups downfield shifted at δ 4.78 (*dt*, $J = 10.3, 4.3$), 5.00 (*d*, $J = 2.3$), 5.04 (br. *d*, $J = 9.3$), 5.49 (*m*), and 6.01 (*m*), as well as eight Me group resonances in the range of δ 0.6 and 2.1, which were partially overlapped by other signals.



1 **2**



3 **4**

Determination of the constitution of **1** and complete assignment of all signals was achieved by application of one- (1D) and two-dimensional (2D) NMR techniques (COSY, HMQC, HMBC, HSQC-TOCSY, NOESY, ROESY; *Figs. 1* and *2*, and *Tables 1* and *2*).[1])

Substitution of the bisabolane derivative was established by the HMBC experiment. The position of the butenoate moiety at C(1) was etablished by two bond couplings of the O-bearing CH group (δ(H) 4.78) with C(2) and C(6) of the cyclohexane ring, as well as three-bond couplings with C(7) of the hexenyl side chain, C(3) of the cyclohexane ring, and the C=O C-atom of the butenoate moiety. The (*Z*)-configuration of the butenoate moiety, *i.e.*, the presence of an angeloyl ester, was deduced from the NOESY experiment and the shift value of the olefinic H-atom (δ(H) 6.01) in comparison with literature data [10].

The second ester group, an acetate moiety, was positioned at C(9) of the hexenyl side chain. The HMBC experiment showed cross-peaks between the CH signal at δ(H) 5.49 (H–C(9)) and the signals of the C-atoms C(10) (δ(C) 124.0), C(11) (δ(C)

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[1]) As IUPAC Recommendations on Nomenclature of Organic Compounds provide changes in the numbering of corresponding positions due to changes in the substituents apart from the backbone, a numbering based on the bisabolane backbone as depicted in **1** is used throughout in the text and in the tables to ensure easier reading and comparison of these data.

Table 1. *^{1}H-NMR Data* (δ in ppm, J in Hz) *of Compounds* **1**–**4** ($CDCl_3$, 500 MHz)

H-atom	**1**	H-atom	**2**	H-atom	**3**	**4**
H−C(1)	4.78 (*dt*, *J* = 10.3, 4.3)	H−C(1)	5.31 (br. *d*, *J* = 9.7)	H−C(1)	5.36 (br. *d*, *J* = 9.7)	5.35 (br. *d*, *J* = 9.3)
H_{ax}−C(2)	1.43 (*m*)	H−C(2)	5.62 (br. *s*)	H−C(2)	5.62 (br. *s*)	5.62 (br. *s*)
H_{eq}−C(2)	1.88 (*m*)					
H−C(3)	1.76 (*m*)					
H−C(4)	5.00 (*d*, *J* = 2.3)	H−C(4)	5.22 (br. *s*)	H−C(4)	5.45 (*d*, *J* = 3.4)	5.46 (*d*, *J* = 3.4)
H_{ax}−C(5)	1.29 (*m*)	H−C(5)	1.56 (*s*)	H−C(5)	5.00 (*dd*, *J* = 12.2, 3.4)	5.00 (*dd*, *J* = 12.2, 3.4)
H_{eq}−C(5)	1.89 (*s*)	H−C(5)	1.85 (*s*)			
H−C(6)	1.86 (*s*)	H−C(6)	1.96 (*s*)	H−C(6)	2.34 (*m*)	2.33 (*m*)
H−C(7)	1.82 (*s*)	H−C(7)	1.75 (*s*)	H−C(7)	1.74 (*s*)	1.81 (*s*)
H_a−C(8)	1.32 (*m*)	H_a−C(8)	1.39 (*s*)	H_a−C(8)	1.58 (*m*)	1.49 (*m*)
H_b−C(8)	1.51 (*m*)	H_b−C(8)	1.61 (*s*)	H_b−C(8)	1.70 (*s*)	1.80 (*m*)
H−C(9)	5.49 (*m*)	H−C(9)	5.53 (*m*)	H−C(9)	5.52 (*m*)	5.58 (*m*)
H−C(10)	5.04 (br. *d*, *J* = 9.3)	H−C(10)	5.07 (br. *d*, *J* = 9.3)	H−C(10)	4.97 (br. *d*, *J* = 9.0)	5.08 (br. *d*, *J* = 8.8)
Me(12)	1.69 (*s*)	Me(12)	1.71 (*s*)	Me(12)	1.70 (*s*)	1.70 (*s*)
Me(13)	0.89 (*d*, *J* = 6.5)	Me(13)	1.71 (*s*)	Me(13)	1.72 (*s*)	1.72 (*s*)
Me(14)	0.76 (*d*, *J* = 6.9)	Me(14)	0.82 (*d*, *J* = 6.9)	Me(14)	0.92 (*d*, *J* = 6.9)	0.92 (*d*, *J* = 6.9)
Me(15)	1.72 (*s*)	Me(15)	1.74 (*s*)	Me(15)	1.73 (*s*)	1.73 (*s*)
$MeCO_2$−C(4)	2.11 (*s*)	$MeCO_2$−C(4)	2.13 (*s*)	$MeCO_2$−C(1)	1.98 (*s*)	1.97 (br. *s*)
$MeCO_2$−C(9)	1.97 (*s*)	$MeCO_2$−C(9)	1.97 (*s*)	$MeCO_2$−C(4)	2.14 (*s*)	2.16 (*s*)
				$MeCO_2$−C(5)	1.99 (*s*)	2.00 (*s*)
H−C(3′)	6.01 (*m*)	H−C(3′)	6.06 (*m*)	H−C(3′)	6.10 (*m*)	6.10 (*m*)
Me(4′)	1.97 (br. *s*)	Me(4′)	1.98 (br. *s*)	Me(4′)	2.01 (br. *s*)	2.01 (br. *s*)
Me(5′)	1.84 (br. *s*)	Me(5′)	1.87 (br. *s*)	Me(5′)	1.90 (br. *s*)	1.90 (br. *s*)

Table 2. *^{13}C-NMR Data* (δ in ppm) *of Compounds* **1**–**4** ($CDCl_3$, 125 MHz)

C-Atom	**1**	**2**	**3**	**4**
C(1)	72.5	70.4	70.0	70.0
C(2)	35.0	128.5	127.9	127.9
C(3)	33.9	134.7	133.2	133.4
C(4)	72.0	69.0	69.1	69.0
C(5)	28.1	26.0	69.3	69.2
C(6)	38.9	36.5	41.3	41.3
C(7)	26.8	27.3	27.5	27.3
C(8)	40.0	39.4	40.5	41.0
C(9)	69.4	68.9	70.3	69.8
C(10)	124.0	123.6	123.9	124.4
C(11)	137.4	137.9	137.8	137.4
C(12)	25.9	25.3	25.9	25.9
C(13)	17.6	20.4	20.3	20.3
C(14)	13.8	14.7	15.8	15.4
C(15)	18.5	18.2	18.6	18.6
MeCO_2–C(4)	21.3	20.7	21.1	21.4
MeCO_2–C(4)	170.9	171.3	169.9	170.8
MeCO_2–C(5)			21.1	21.1
MeCO_2–C(5)			169.5	170.2
MeCO_2–C(9)	21.4	20.7	21.1	21.1
MeCO_2–C(9)	170.3	170.4	170.4	171.4
C(1′)	167.6	167.9	167.6	168.0
C(2′)	128.2	128.1	127.7	127.9
C(3′)	137.6	138.3	138.9	139.0
C(4′)	15.8	15.5	15.9	16.0
C(5′)	20.6	20.3	20.6	20.6

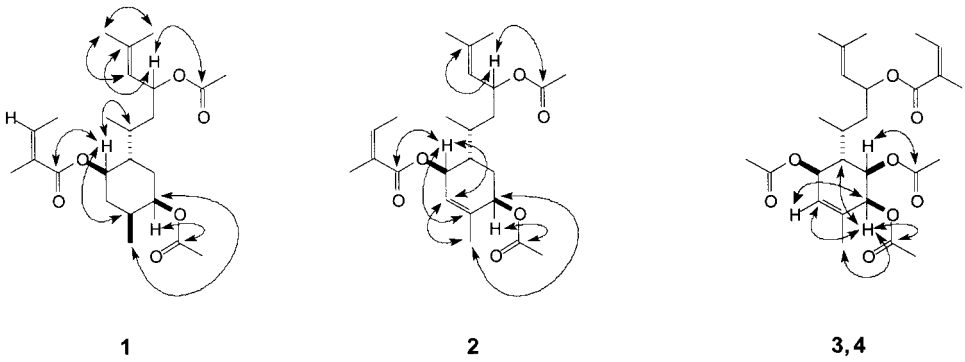

Fig. 1. *Selected HMBC interactions of compounds* **1**–**4**

137.4), C(8) (δ(C) 40.0), C(7) (δ(C) 26.8), and the AcO C=O resonance (δ(C) 170.3).

The vicinal position of the Me group at C(3) and the second AcO group at C(4) was established from HMBC long-range correlations between the highfield-shifted signal of the Me group at δ(H) 0.89 (H–C(13)) and the signals of the CH_2(2) group at δ(C) 35.0,

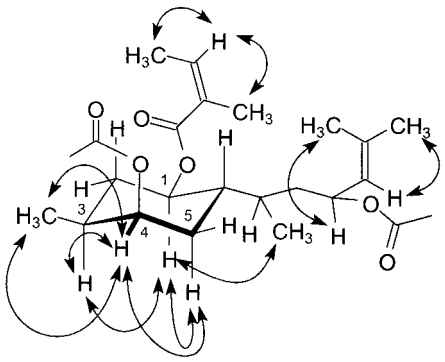

Fig. 2. *Selected NOE correlations of* **1**

and the CH C-atoms at δ(C) 33.9 (C(3)) and 72.0 (C(4)), as well as connectivities between the ^{1}H-NMR signal of the C(4) and the ^{13}C-NMR signals of C(3), the Me group at C(8), and the C=O group of the second AcO group (δ(C) 170.9).

The positions of the Me groups at C(7) and C(11) of the hexenyl side chain were in agreement with the isoprene rule. Thus, compound **1** is (1*R**,2*S**,4*R**,5*S**)-4-(acetyloxy)-2-[3-(acetyloxy)-1,5-dimethylhex-4-enyl]-5-methylcyclohexyl (2*Z*)-2-methylbut-2-enoate (=(1*R**,3*S**,4*R**,6*S**)-4,9-bis(acetyloxy)-1-{[(2*Z*)-2-methylbut-2-enoyl]oxy}-bisabol-10(11)-ene).

The relative configuration at C-atoms C(1)–C(6) of the cyclohexane ring is based on the coupling constants of H–C(1) (*dt* J = 10.3, 4.3 Hz), establishing an axial position, and the NOE experiments (*Fig. 2*): thus, the Me(13) group and the ester groups are in β-orientation, the 1,5 dimethyl-4-hexenyl side chain is in α-orientation.

The EI-MS of compound **2** displayed a signal at *m*/*z* 420.2516 (M^+; calc. 420.2512), which is congruent with a molecular formula of $C_{24}H_{36}O_6$. Except for differences due to a missing CH_2 and CH group, which are replaced by an CH group and a quaternary C-atom, respectively, in compound **2**, ^{1}H-NMR (*Table 1*) and ^{13}C-NMR (*Table 2*) data of **2** were almost identical with those of **1**. The C=C bond at C(2) of the cyclohexane ring was supported by the ^{13}C-NMR spectrum, which, instead of the C(3) and C(2) signals at δ 33.9 and 35.0, showed downfield-shifted signals at δ 134.7 and 128.5. Confirmation of the structure assignment was accomplished by HSQC and HMBC experiments (*Fig. 1*). Thus, **2** is (1*R**,4*S**,*6R**)-4-(acetyloxy)-6-[3-(acetyloxy)-1,5-dimethylhex-4-enyl]-3-methylcyclohex-2-en-1-yl (2*Z*)-2-methylbut-2-enoate (=(1*R**,4*S**,6*R**)-4,9-bis(acetyloxy)-1-{[(2*Z*)-2-methylbut-2-enoyl]oxy}-bisabo l-2(3),10(11)-diene).

Molecular formulae of **3** and **4** were determined as $C_{26}H_{38}O_8$ for both compounds by high-resolution EI-MS (*m*/*z* 478.2563, M^+; calc. 478.25667). ^{1}H- and ^{13}C-NMR spectra of **3** and **4** resemble each other very much, with nearly superimposible lines; only the signals resulting from C(7) to C(9) of a hexenyl side chain show remarkable differences in their chemical shifts (*Tables 1* and *2*). Further signals of a cyclohexene ring, three AcO, and one angeloyloxy groups were detected. Signal assignments in *Tables 1* and *2*, as well as the connectivity of the bisabolane part, were confirmed by 2D NMR spectroscopy. Localization of the ester groups only could partially be established

by HMBC and HSQCTOCSY experiments. The positions of two AcO groups at C(4) and C(5) were supported by long-range correlations between the CH H-atoms H–C(4) and H–C(5) and the C=O groups of two Ac moieties, but connectivities indicating the positions of the remaining two ester groups were missing. However, this problem could be solved by means of fragmentation patterns obtained by high-resolution EI-MS (*Scheme*), which showed that the butenoate group had to be placed at C(9) of the side chain and the third Ac group at C(1) of the cyclohexane ring.

Assignments of the relative configurations at C-atoms C(1)–C(6) of the cyclohexene rings of compounds **2**–**4** are based again on multiplicities and coupling constants of the corresponding H-atoms, indicating β-orientation for the ester groups and α-orientation of the side chain. Since no obvious differences in the constitution of the structure of the two compounds **3** and **4** could be detected, neither by mass spectrometry nor by NMR spectroscopy, and given the obviously identical configuration within the cyclohexane ring, a different configuration of at least one of the stereogenic centers of the hexenyl side chain (C(7) and C(9)) must be assumed.

Studies to evaluate pharmacological activities of these compounds are in progress.

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Experimental Part

General. Optical rotations: *Perkin-Elmer 341* polarimeter. NMR Spectra: *Varian UNITYPlus 500* spectrometer at 500 (^{1}H-NMR) and 125 MHz (^{13}C-NMR) in $CDCl_3$. MS: *Finnigan-MAT 95XL*; EI (70 eV), resolution 8000, *B* scan; the exact mass of **1** and **2** were obtained by peak matching and *E* scan.

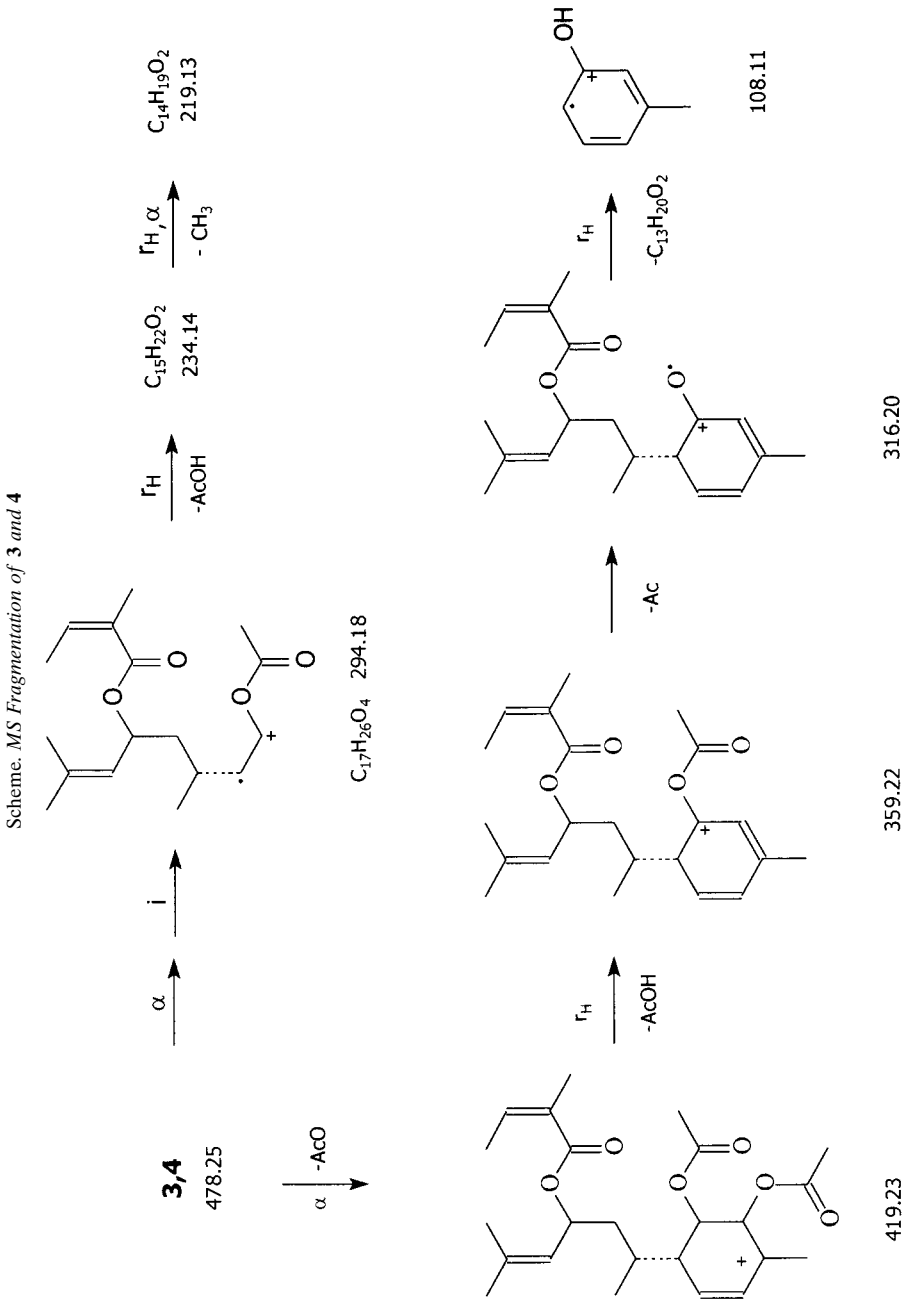
Plant Material. Leontopodium alpinum CASS. was cultivated in Natters near Innsbruck at 800 m of altitude by Mr. *G. Faulhammer* and harvested in July 1998. A voucher specimen is deposited in the herbarium of the Institute of Pharmacy.

Extraction and Isolation. The air-dried ground roots (499 g) of *L. alpinum* were exhaustively extracted with CH_2Cl_2 at r.t. by an *ultra turrax* ® extractor (*IKA Labortechnik*, D-Staufen). The extract was evaporated, and the residue (7.4 g) was subjected to silica-gel column chromatography (CC) with hexane/CH_2Cl_2 and CH_2Cl_2/MeOH. Fractions obtained with CH_2Cl_2/MeOH (9:1) were separated by silica-gel CC with CH_2Cl_2/acetone. Three subfractions obtained with CH_2Cl_2/acetone 10:0.1 were fractionated on *Sephadex LH-20* with MeOH. Final purification of the resulting compounds was achieved by semiprep. HPLC with H_2O/CH_3CN as mobile phase to yield pure compounds **1** (10 mg), **2** (5 mg), **3** (2 mg), and **4** (1 mg).

(1R,2S*,4R*,5S*)-4-(Acetyloxy)-2-[3-(acetyloxy)-1,5-dimethylhex-4-enyl]-5-methylcyclohexyl (2Z)-2-Methylbut-2-enoate* (=*(1R*,3S*,4R*,6S*)-4,9-bis(acetyloxy)-1-{[(2Z)-2-methylbut-2-enoyl]oxy}bisabol-10(11)-ene*; **1**). Colorless oil. $[\alpha]_D^{20} = +59.7$ ($c = 0.78$, MeCN); FT-IR (microspectrometry; ν_{max}^{ZnSe} [cm^{-1}]): 2932, 2877, 1737, 1649, 1584, 1453, 1372, 1245, 1162, 1103, 1044, 1018, 993, 945, 892, 849. MS: 422.26 (1.2, $C_{24}H_{38}O_6^+$), 379.23 (1.1, $C_{22}H_{35}O_5^+$), 362.24 (4.6, $C_{22}H_{35}O_5^+$), 323.22 (2.2, $C_{19}H_{31}O_4^+$), 302.22 (0.8, $C_{20}H_{30}O_2^+$), 279.19 (4.8, $C_{17}H_{27}O_3^+$), 262.19 (53.0, $C_{17}H_{26}O_2^+$), 220.18 (12.3, $C_{15}H_{24}O^+$), 202.17 (78.0, $C_{15}H_{22}^+$), 187.14 (20.5, $C_{14}H_{19}^+$), 159.11 (22.2, $C_{12}H_{15}^+$), 147.11 (21.07, $C_{11}H_{15}^+$), 121.10 (33.5, $C_9H_{13}^+$), 109.10 (41.5, $C_8H_{13}^+$), 85.06 (65.4, $C_5H_9O^+$), 83.05 (100.0, $C_5H_7O^+$), 55.05 (58.1, $C_4H_7^+$), 43.02 (49.0, $C_2H_3O^+$), 41.04 (11.9, $C_3H_5^+$).

(1R,4S*,6R*)-4-(Acetyloxy)-6-[3-(acetyloxy)-1,5-dimethylhex-4-enyl]-3-methylcyclohex-2-en-1-yl (2Z)-2-Methylbut-2-enoate* (=*(1R*,4S*,6R*)-4,9-Bis(acetyloxy)-1-{[(2Z)-2-methylbut-2-enoyl]oxy}bisabol-2(3),10(11)-diene*; **2**). Colorless oil. FT-IR (microspectrometry; ν_{max}^{ZnSe} [cm^{-1}]: 2932, 2359, 1736, 1446, 1371, 1245, 1159, 1019, 976, 912. MS: 420.30 (1.60, M^+), 361.3 (12.6, $C_{22}H_{33}O_4^+$), 278.2 (11.3, $C_{17}H_{26}O_2^+$), 262.2 (7.9, $C_{17}H_{26}O_2^+$), 236.2 (14.8), 218.2 (69.9), 200.2 (80.55), 185.1 (39.9), 161.1 (39.9), 146.1 (69.6), 135.1 (34.3), 119.1 (97.5), 109.1 (100.0, $C_8H_{13}^+$), 83.0 (97.1, $C_5H_7O^+$), 55,0 (41.2, $C_4H_7^+$), 43.0 (42.3, $C_2H_3O^+$).

Scheme. *MS Fragmentation of* **3** *and* **4**



3-Methyl-1-{2-[(1R,2R*,5R*,6S*)-2,5,6-tris(acetyloxy)-4-methylcyclohex-3-en-1-yl]propyl}but-2-enyl (2Z)-2-Methylbut-2-enoate* (*=(1R*,4R*,5R,6R*)-1,4,5-Tris(acetyloxy)-9-{[(2Z)-2-methylbut-2-enoyl]oxy}bisabol-2(3),10(11)-diene*; diastereoisomer A; **3**). Colorless oil. $[\alpha]_D^{20} = +8.2$ ($c = 0.39$, MeCN). FT-IR (microspectrometry; ν_{max}^{ZnSe} [cm^{-1}]): 2968, 2935, 2334, 1746, 1648, 1441, 1371, 1238, 1156, 1086, 1040, 951, 849, 756, 669. MS: 478.25 (4.6, $C_{26}H_{38}O_8^+$), 419.24 (7.4, $C_{24}H_{35}O_6^+$), 395.21 (1.8, $C_{21}H_{31}O_7^+$), 359.22 (1.5, $C_{22}H_{31}O_4^+$), 316.20 (2.1, $C_{20}H_{28}O_3^+$), 294.18 (5.5, $C_{17}H_{26}O_4^+$), 276.17 (8.7, $C_{17}H_{24}O_3^+$), 258.16 (9.4, $C_{17}H_{22}O_2^+$), 243.16 (43.1, $C_{15}H_{22}O_2^+$), 219.10 (25.9, $C_{14}H_{19}O_2^+$), 199.13 (33.6, $C_15H_{19}^+$), 193.08 (20.4, $C_{11}H_{13}O_3^+$), 177.09 (38.3, $C_{11}H_{13}O_2^+$), 162.10 (18.7, $C_{11}H_{14}O^+$), 151.07 (13.6, $C_9H_{11}O_2^+$), 135.08 (48.4, $C_9H_{11}O^+$), 119.08 (18.9, $C_9H_{11}^+$), 109.11 (84.6, $C_8H_{13}^+$), 108.09 (32.9, $C_7H_8O^+$), 93.06 (9.8, $C_7H_9^+$), 85.04 (24.9, $C_5H_9O^+$), 83.03 (100.00, $C_5H_7O^+$), 67.06 (9.1, $C_5H_7^+$), 55.05 (31.2, $C_4H_7^+$), 43.01 (39.7, $C_2H_3O^+$).

3-Methyl-1-{2-[(1R,2R*,5R*,6S*)-2,5,6-tris(acetyloxy)-4-methylcyclohex-3-en-1-yl]propyl}but-2-enyl (2Z)-2-Methylbut-2-enoate* (*=(1R*,4R*,5R,6R*)-1,4,5-Tris(acetyloxy)-9-{[(2Z)-2-methylbut-2-enoyl]oxy}bisabol-2(3),10(11)-diene*; diastereoisomer B; **4**). Colorless oil. $[\alpha]_D^{20} = 4.7$ ($c = 0.28$, MeCN). FT-IR (microspectrometry; ν_{max}^{ZnSe} [cm^{-1}]): 2968, 2935, 2334, 1746, 1648, 1441, 1371, 1238, 1156, 1086, 1040, 951, 849, 756, 669. MS: 478.25 (4.6, $C_{26}H_{38}O_8^+$), 419.24 (7.4, $C_{24}H_{35}O_6$), 395.21 (1.8, $C_{21}H_{31}O_7^+$), 359.22 (1.5, $C_{22}H_{31}O_4^+$), 316.20 (2.1, $C_{20}H_{28}O_3^+$), 294.18 (5.5, $C_{17}H_{26}O_4^+$), 276.17 (8.7, $C_{17}H_{24}O_3^+$), 258.16 (9.4, $C_{17}H_{22}O_2^+$), 243.16 (43.1, $C_{15}H_{22}O_2^+$), 219.10 (25.9, $C_{14}H_{19}O_2^+$), 199.13 (33.6, $C_15H_{19}^+$), 193.08 (20.4, $C_{11}H_{13}O_3^+$), 177.09 (38.3, $C_{11}H_{13}O_2^+$), 162.10 (18.7, $C_{11}H_{14}O^+$), 151.07 (13.6, $C_9H_{11}O_2^+$), 135.08 (48.4, $C_9H_{11}O^+$), 119.08 (18.9, $C_9H_{11}^+$), 109.11 (84.6, $C_8H_{13}^+$), 108.09 (32.9, $C_7H_8O^+$), 93.06 (9.8, $C_7H_9^+$), 85.04 (24.9, $C_5H_9O^+$), 83.03 (100.00, $C_5H_7O^+$), 67.06 (9.1, $C_5H_7^+$), 55.05 (31.2, $C_4H_7^+$), 43.01 (39.7, $C_2H_3O^+$).

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