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Identification and Synthesis of New Bicyclic Acetals from the Mountain Pine Beetle, *Dendroctonus ponderosae* Hopkins (Col.: Scol.)

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Abstract—Head-space volatiles obtained from male mountain pine beetles, *Dendroctonus ponderosae*, were analyzed by coupled GC–MS and chiral gas chromatography. 5-Ethyl-7-methyl-6,8-dioxabicyclo[3.2.1]octane (**6**) was found as a new naturally occurring isomer of brevicomin (**1**). In addition, several stereoisomers of 7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octan-2-ol (**11**) and 1-(5-methyl-6,8-dioxabicyclo[3.2.1]octyl)ethanol (**12**) could be identified. Relative and absolute configurations of the compounds were determined by unambiguous syntheses, which are described. Copyright © 1996 Elsevier Science Ltd

Introduction

Alkylated 6,8-dioxabicyclo[3.2.1]octanes play a major role in the communication systems of several bark beetle species. Brevicomin, 7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (**1**)[1] was the first of these bicyclic acetals (Fig. 1), identified from the frass of females of the western pine beetle, *D. brevicomis*.[1] The compound is an important component in several *Dendroctonus* and *Dryocoetes* bark beetles. In some species it is produced by the males, in some by the females. Males of the mountain pine beetle, *D. ponderosae*, release (1*R*,5*S*,7*R*)-*exo*-brevicomin and (1*R*,5*S*,7*S*)-*endo*-brevicomin of high enantiomeric purity.[2] Another bicyclic acetal identified from *Dendroctonus* spp. is 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane, frontalin (**2**).[3] Females of the southern pine beetle, *Dendroctonus frontalis*, release a 85:15 mixture of the (1*S*,5*R*)- and (1*R*,5*S*)-enantiomers,[4] while almost pure (1*S*,5*R*)-frontalin is produced by *Dendroctonus simplex*.[5] Multistriatin, 5-ethyl-2,4-dimethyl-6,8-dioxabicyclo[3..1]-octane (**3**), is an important component of the aggregation pheromone of the smaller European elm bark beetle, *Scolytus multistriatus*,[6] the females of which produce the (1*S*,2*R*,4*S*,5*R*)-stereoisomer in high enantiomeric purity.[7] In the present paper we report on the identification and synthesis of a brevicomin isomer and of several hydroxylated brevicomins produced by males of *D. ponderosae*.

Results and Discussion

Using coupled GC–MS of head-space volatiles collected from emergent *D. ponderosae* males[8] (Fig. 2) revealed the presence of several trace compounds with the same molecular composition, $C_9H_{16}O_2$, as brevicomin (**1**). Two of these could be easily identified to be the known *endo*-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane (**4**)[9] and (*E*)-7-methyl-1,6-dioxaspiro[4.5]decane[10] (**5**). The mass spectrum (Fig. 3) of a third component (**D** in Fig. 2) showed a base peak at *m/z* 57 and another abundant fragment ion at *m/z* 100. According to the general fragmentation pattern of alkyl-6,8-dioxabicyclo[3.2.1]octanes,[11] this suggested 5-ethyl-7-methyl-6,8-dioxabicyclo[3.2.1]octane (**6**) to be the structure of the target compound, which we like to call 'isobrevicomin'. This was further corroborated by the presence of less intense signals at *m/z* 141 (M-CH_3), *m/z* 128 (M-C_2H_4) and *m/z* 112 (M-CH_3CHO). A reference sample obtained from cyclization of the epoxides of (*E*)- and (*Z*)-7-nonen-3-one according to Wassermann and Barber[12] proved the proposed structure to be correct. It became evident that both the *exo* and the *endo* isomer of **6** occurred in nature, however, the *exo* compound was far more abundant.

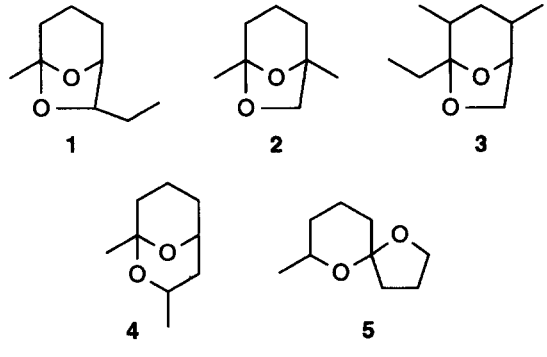


Figure 1. Bicyclic acetals identified from bark beetles.

Key words: Bicyclic acetals, 5-ethyl-7-methyl-6,8-dioxabicyclo[3.2.1]-octane, hydroxybrevicomin, *Dendroctonus ponderosae*.

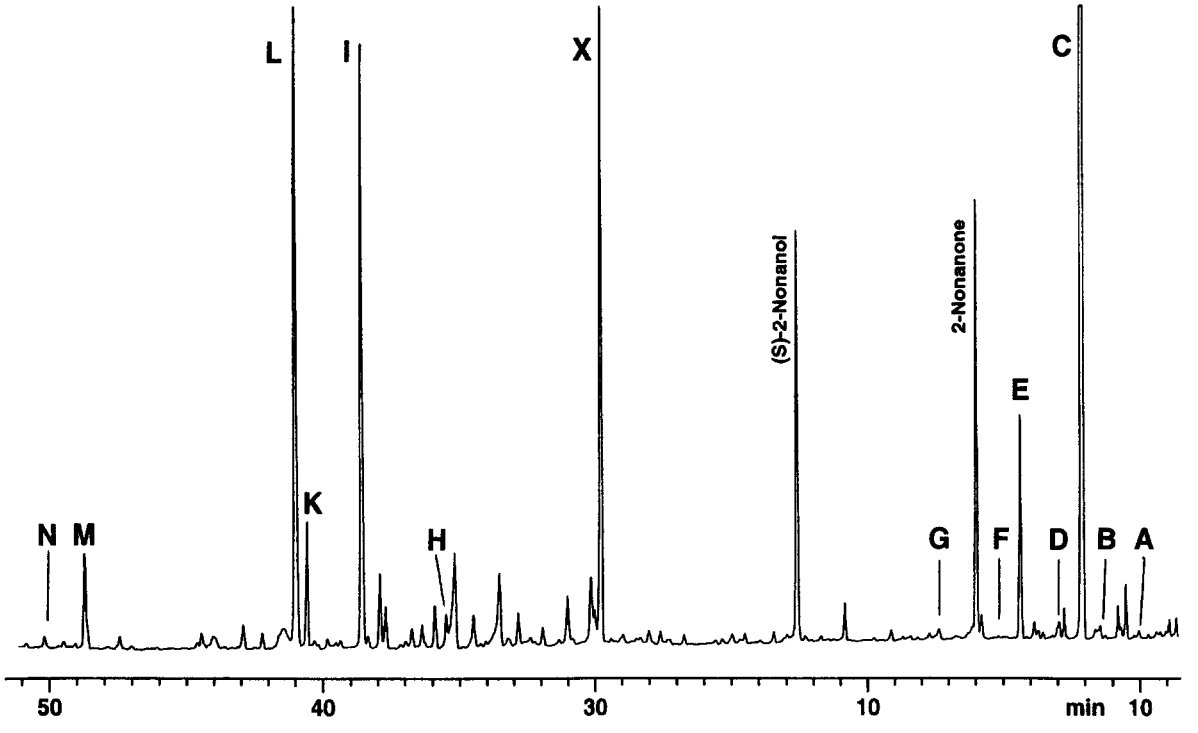


Figure 2. Gas chromatogram of head-space volatiles obtained from emergent *D. ponderosae* males, column: 50 m FS–FFAP; 3 min at 60 °C, then programmed to 220 °C at a rate of 3 °C/min.

For the determination of the absolute configuration of the natural *exo* isomer of isobrevicomin (**6**), an optically active sample was prepared following the strategy employed by Kotsuki et al.[13] for the synthesis of (+)-*exo*-brevicomin, **1** (Scheme 1). Tosyloxy-triflate (4′*S*,5′*S*)-**8**, prepared from (+)-diethyl tartrate [(2*R*,3*R*)-**7**],[13] was reacted with a Grignard reagent prepared from 2-(2-bromoethyl)-2-ethyl-5,5-dimethyl-1,3-dioxane **9**, derived from ethyl vinyl ketone,[14] to yield the tosylate (4′*S*,5′*S*)-**10**. Reduction and deprotection of (4′*S*,5′*S*)-**10** furnished (−)-*exo*-isobrevicomin (1*S*,5*R*,7*S*)-**6** in 98% ee and 98% de as determined by chiral GC.[15] Coinjection of natural and synthetic samples showed the natural *exo*-isobrevicomin to be the (−)-isomer (1*S*,5*R*,7*S*)-**6** of at least 90% ee.

The mass spectra of three late eluting components (**I**, **K** and **L** in Figure 2) of the head-space volatiles of *D. ponderosae* males are shown in Figure 4. The compounds could not be hydrogenated, but reacted upon silylation and trifluoroacetylation, which indicated the presence of a hydroxy group. High resolution GC–MS showed the parent ions to be *m/z* 172 = $C_9H_{16}O_3$, thus suggesting hydroxylated brevicomins. While the general fragmentation pattern of 6,8-dioxabicyclo[3.2.1]octanes[11] strongly indicated the first eluting compounds **I** and **K** to carry the hydroxyl group in position two, the later eluting component **L** clearly showed the presence of a 1-hydroxyethyl group

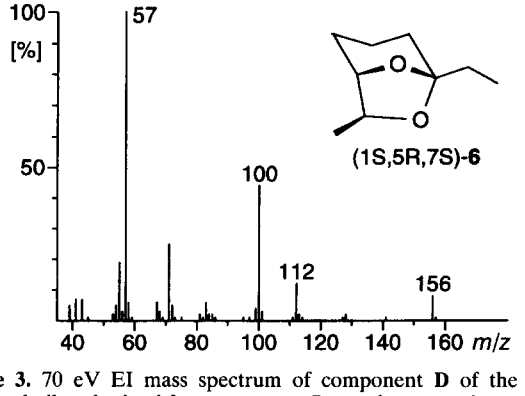
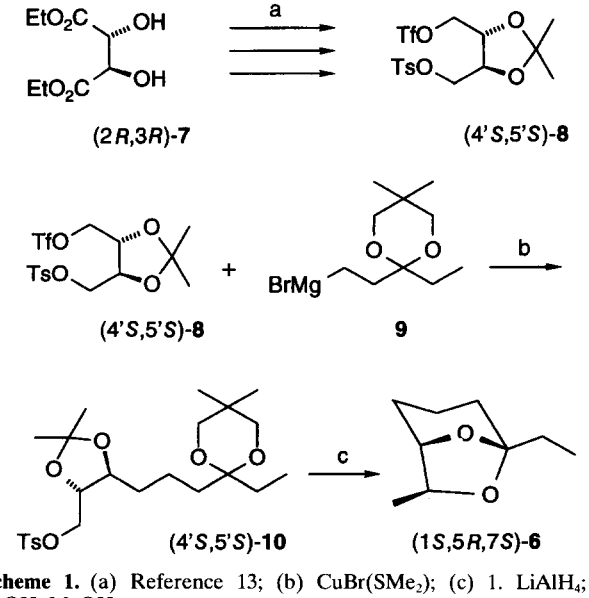


Figure 3. 70 eV EI mass spectrum of component **D** of the head-space volatiles obtained from emergent *D. ponderosae* males.



Scheme 1. (a) Reference 13; (b) $CuBr(SMe_2)$; (c) 1. $LiAlH_4$; 2. TsOH, MeOH.

as revealed by *m/z* 127 = [M-CH_3CHOH] and *m/z* 45 = $[CH_3CHOH]^+$. Thus, we regarded these compounds to be stereoisomers of 7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octan-2-ol (**11**) and 1-(5-methyl-6,8-dioxabicyclo[3.2.1]oct-7-yl)ethanol (**12**). Earlier, Prestwich[16] had described **12** to be produced by *D. ponderosae* along with two other hydroxybrevicomins with undetermined position of the hydroxy group. Structural proof and the determination of the relative stereochemistry of the new hydroxybrevicomins as well as assignments of absolute configurations were carried out by independent syntheses, which are described here.

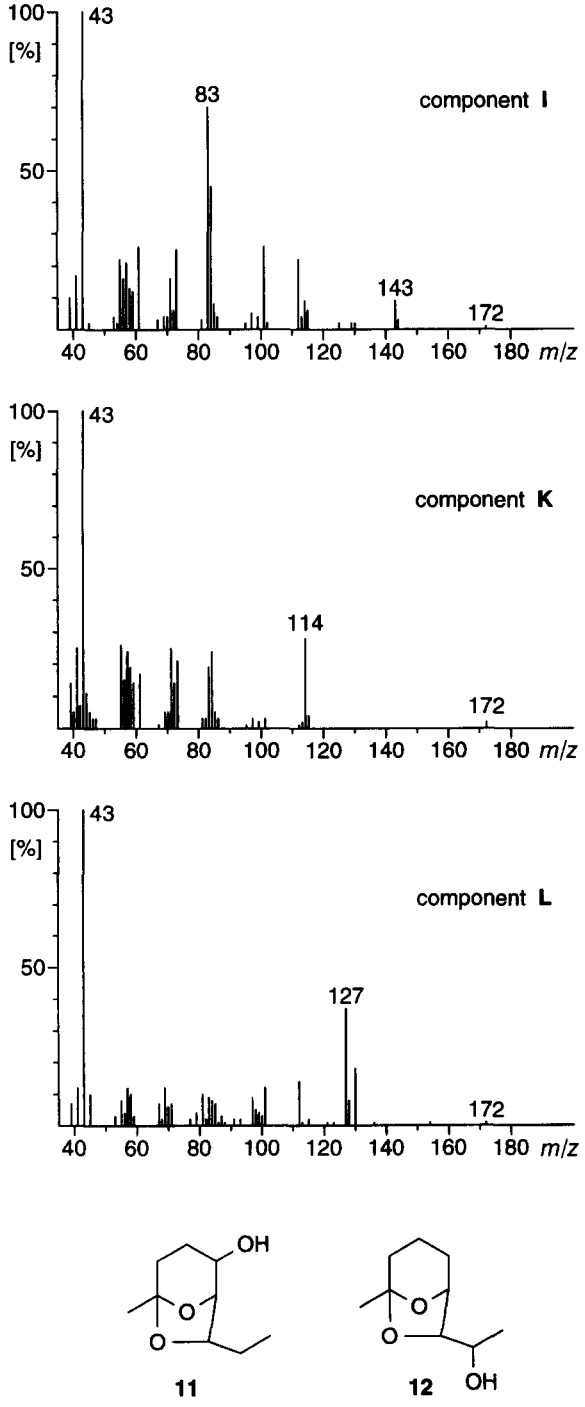
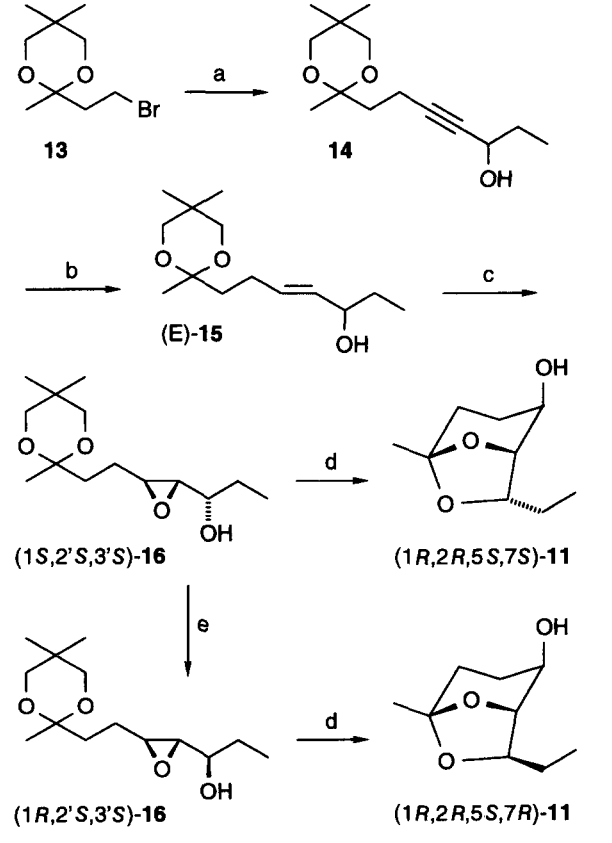


Figure 4. 70 eV EI–MS of components **I**, **K** and **L** of the head-space volatiles obtained from emergent *D. ponderosae* males and proposed structures.

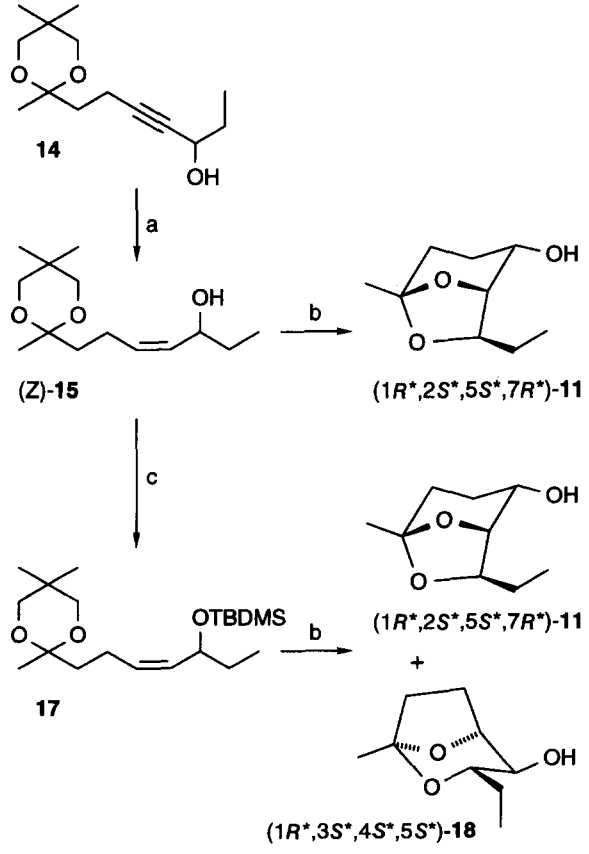
Since the natural stereoisomers of brevicomin (**1**) in *D. ponderosae* showed (1*R*,5*S*,7*R*)- and (1*R*,5*S*,7*S*)-configuration,[2] we started with the synthesis of the (1*R*,2*R*,5*S*,7*R*)- and (1*R*,2*R*,5*S*,7*S*)-stereoisomers of **11** as outlined in Scheme 2. The protected bromoketone **13**[14] was chain elongated with lithium acetylide ethylenediamine complex in DMSO. The resulting alkyne was reacted with propanal to yield the propargylic alcohol **14**. Reduction with lithium aluminium hydride in THF gave the allylic alcohol (*E*)-**15** in 98% geometric purity. Sharpless epoxidation[17] of (*E*)-**15** using (+)-diisopropyl tartrate gave (1*S*,2′*S*,3′*S*)-**16**, which after treatment with aqueous HF in acetonitrile cyclized to give (1*R*,2*R*,5*S*,7*S*)-**11** in 97% de and 96% ee, as determined by chiral GC.[15] The relative configuration was established via NMR experiments. As the coupling of the proton at C-2 (2-H) with the axial proton at C-3 (3-H_{ax}) is only ca. 4.4 Hz, the OH group at C-2 has to be in an axial position, which is corroborated by the observation of a significant positive NOE between the protons 7-CH_2 and 2-H. Furthermore, the *endo* configuration is indicated by an additional NOE observed between 7-CH_2 and 3-H_{ax}. To synthesize the corresponding *exo* isomer, (1*R*,2*R*,5*S*,7*R*)-**11**, the configuration of the OH-group



Scheme 2. (a) 1. LiC≡CH—EDA/DMSO; 2. *n*-BuLi, CH_3CH_2CHO/THF; (b) $LiAlH_4$/THF; (c) (+)-DIPT, ^{t}BuOOH, Ti(O^{i}Pr)$_4$; (d) HF/CH_3CN/H_2O; (e) 1. DNBCl, NEt_3/CH_2Cl_2; 2. aq KOH/MeOH/THF.

in (1*S*,2′*S*,3′*S*)-**16** was inverted according to Mitsunobu.[18] Cyclization of (1*R*,2′*S*,3′*S*)-**16** gave (1*R*,2*R*,5*S*,7*R*)-**11** in 98% de and 96% ee, the relative configuration of which was again derived from the coupling constants of 2-H and from the observation of a significant NOE between 7-H and 2-H and between 7-H and 3-H_{ax}. The fact that (1*S*,2′*S*,3′*S*)-**16** leads to the *endo* isomer (1*R*,2*R*,5*S*,7*S*)-**11** while (1*R*,2′*S*,3′*S*)-**16** yields (1*R*,2*R*,5*S*,7*R*)-**11**, strongly suggests a cyclization mechanism, where the epoxide is opened at position 3′ of **16**. Finally, comparison of natural and synthetic samples via chiral GC–MS showed the natural compounds **I** and **K** to be (1*R*,2*R*,5*S*,7*R*)- and (1*R*,2*R*,5*S*,7*S*)-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]-octan-2-ol (**11**) of more than 98% ee, respectively.

Additional GC–MS analysis of the head-space volatiles from *D. ponderosae* revealed the presence of a less abundant component (**M** in Fig. 2). Since its MS was almost identical to that obtained from (1*R*,2*R*,5*S*,7*R*)-**11**, the natural compound **M** was suggested to be an *exo* stereoisomer of **11** with an equatorial OH group. Scheme 3 shows our approach to the synthesis of stereoisomers of **11** with an equatorial OH group. Hydrogenation of **14** with Lindlar catalyst in the presence of quinoline gave the allylic alcohol (*Z*)-**15**, which after epoxidation with *m*-chloroperbenzoic acid and treatment with aqueous HF in acetonitrile furnished one single diastereomer of **11**. NMR experiments proved the product to show (1*R**,2*S**,5*S**,7*R**) configuration. The large coupling constant of 10 Hz between the axial proton at C-3 and the proton at C-2 as revealed by phase-sensitive (^{1}H,^{1}H) COSY spectra indicated the proton at C-2 to be in an axial position, thus leaving the equatorial position for the OH group. Furthermore, a significant positive NOE was observed between the axial proton at C-3 and the proton at C-7, indicating the *exo* configuration.

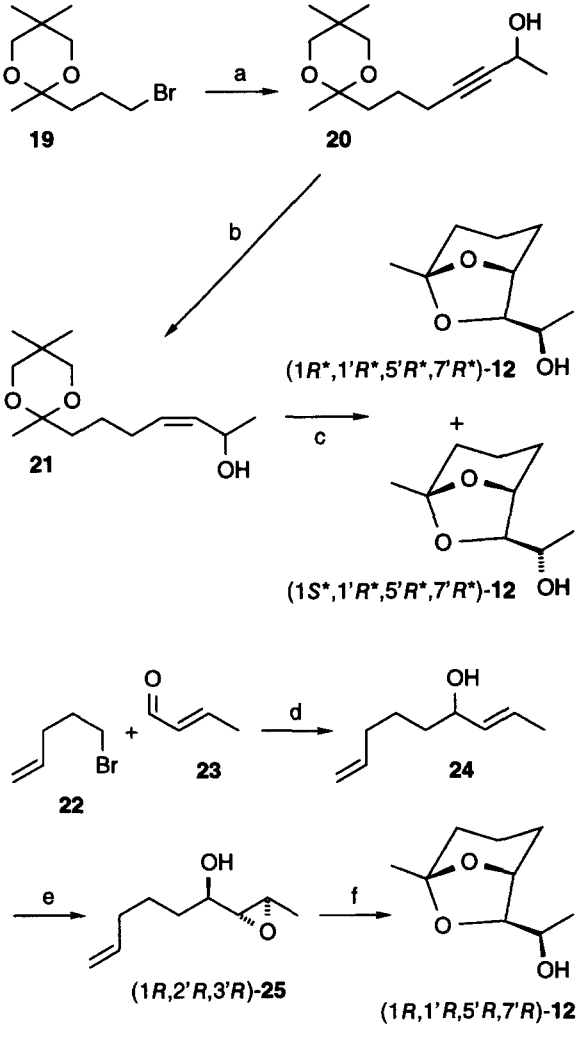


Scheme 3. (a) H_2, Lindlar catalyst, quinoline; (b) 1. *m*-CPBA/CH_2Cl_2; 2. HF/CH_3CN; (c) TBDMSCl, imidazole/DMF.

While the epoxidation of the nonprotected alcohol (*Z*)-**15** proceeded with very high diastereoselectivity, the epoxidation of the O-silylated compound **17** followed by deprotection and cyclization with HF yielded a mixture of two bicyclic acetals, (1*R**,2*S**,5*S**,7*R**)-**11** and (1*R**,3*S**,4*S**,5*S**)-3-ethyl-1-methyl-2,8-dioxabicyclo[3.2.1]octan-4-ol[(1*R**,3*S**,4*S**,5*S**)-**18**], which were separated by column chromatography. The relative configuration of **18** could be deduced from the large coupling observed between the protons at C-3 and C-4 and from the strong positive NOE observed between the proton at C-3 and the *exo* proton at C-6. The configurations at C-3, C-4 and C-5 of **18** are equivalent to the configuration of an hypothetical *endo* stereoisomer of **11** with an equatorial OH group, which could not be detected among the reaction products. Thus, of the two possible stereoisomers of **11** with an equatorial OH group, only the *exo* isomer seems to be stable. Chiral GC–MS showed the natural compound **M** to be the earlier eluting enantiomer of (1*R**,2*S**,5*S**,7*R**)-**11**. The absolute configuration of this natural product could not yet be determined.

As a next step we considered a synthesis to determine the absolute configuration of the natural stereoisomer **L** of 1-(5-methyl-6,8-dioxabicyclo[3.2.1]oct-7-yl)ethanol (**12**). Since the most abundant natural stereoisomer of brevicomin (**1**) shows *exo* configuration, we started with a synthesis of the *exo* stereoisomers of **12** (Scheme 4). The bromide **19**[19,20] was reacted with 3-butyn-2-ol to give the alkynol **20**. Subsequent hydrogenation using Lindlar catalyst, epoxidation and cyclization as described above for the preparation of (1*R**,2*S**,5*S**,7*R**)-**11** yielded the two *exo* stereoisomers (1*R**,1′*R**,5′*R**,7′*R**)-**12** and (1*S**,1′*R**,5′*R**,7′*R**)-**12**, one of which proved to show identical mass spectra and retention times as the natural compound **L**. Having established the *exo* configuration of **L**, we aimed at the elucidation of its absolute configuration via a stereoselective synthesis of a reference sample (Scheme 4). (*E*)-2-Butenal (**23**) was reacted with 4-pentenylmagnesium bromide to give (*E*)-2,8-nonadien-4-ol (**24**). Sharpless oxidation of **24**[17] furnished the epoxy alcohol (1*R*,2′*R*,3′*R*)-**25**, which was subjected to Wacker oxidation,[21] yielding (1*R*,1′*R*,5′*R*,7′*R*)-**12** in 96% de and 96% ee, as determined by chiral GC. The relative configuration of C-1 and C-7 in (1*R*,1′*R*,5′*R*,7′*R*)-**12** follows from comparison with the racemic *exo* stereoisomers and was corroborated via NMR experiments. A significant positive NOE is observed between 7-H and 3-H_{ax} compatible only with the *exo* configuration of the bicyclic acetal. Thus, the epoxy ring in (1*R*,2′*R*,3′*R*)-**25** is opened at position 2′ and the configuration at position 3′ is not affected. Coinjection

of natural and synthetic samples using chiral GC showed the natural compound **L** to be (1*R*,1′*R*,5′*R*,7′*R*)-1-(5-methyl-6,8-dioxabicyclo[3.2.1]oct-7-yl)-ethanol [(1*R*,1′*R*,5′*R*,7′*R*)-**12**] of more than 99% ee.



Scheme 4. (a) 3-Butyn-2-ol, $LiNH_2$/lq NH_3; (b) H_2, Lindlar catalyst, quinoline; (c) 1. *m*-CPBA/CH_2Cl_2; 2. HF/CH_3CN; (d) Mg/THF, −100 °C; (e) (−)-DIPT, ^tBuOOH, $Ti(O^iPr)_4$; (f) $PdCl_2$, CuCl, O_2/EtOH.

Furthermore, one of the trace components (**H**) in the natural extract proved to be the earlier eluting enantiomer of (1*S**,1′*R**,5′*R**,7′*R**)-**12**.

Conclusion

Our results on the identification of cryptical ketodiols and ketotriols from *D. ponderosae* are summarized in Table 1. *exo*-Isobrevicomin (**6**) is a new natural product, the biosynthesis of which may be closely related to that of brevicomin (**1**). It is interesting to note that the absolute configuration of natural *exo*-isobrevicomin (**6**) is opposite to the configuration of brevicomin (**1**) while that of the *exo*-hydroxybrevicomins (**11**, **12**) is the same. Due to the small amounts of *exo*-isobrevicomin (**6**) in the head-space volatiles of *D. ponderosae*, the enantiomeric purity of the natural product could only be estimated to exceed 90%. In addition, the *endo* isomer of **6** was found to be present in very small amounts. Its absolute configuration could, however, not be determined. So far, isobrevicomin (**6**) seems to show the same relative diastereomeric proportions as brevicomin (**1**), the *exo* isomer being much more abundant than the *endo* isomer. The same is true for the pair of 2-hydroxybrevicomins **11**, which carry the hydroxy group in axial position. Although the *exo*-2-hydroxybrevicomin with an equatorial hydroxy group [(1*R**,2*S**,5*S**,7*R**)-**11**] was also found in appreciable amounts, the corresponding *endo* isomer could not be detected. Instead, (1*R**,3*S**,4*S**,5*S**)-3-ethyl-1-methyl-2,8-dioxabicyclo-[3.2.1]octan-4-ol-[(1*R**,3*S**,4*S**,5*S**)-**18**], its possible rearrangement product, could be identified as a trace component. Analogously, (1*R**,2*S**,5*S**,7*R**)-**11** and (1*R**,3*S**,4*S**,5*S**)-**18** were formed during the acid-catalyzed cyclization of the epoxide of **17** (Scheme 3). The hydroxybrevicomin **12**, which is hydroxylated in the side chain, appears to occur as the *exo* isomer exclusively. This may be due to steric hindrance during enzymatic hydroxylation. Prestwich[16] showed that intact live beetles form hydroxybrevicomins from brevicomin.

The occurrence of hydroxybrevicomins in *D. ponderosae* parallels the presence of hydroxylated spiroacetals

Table 1. Bicyclic acetals identified from *D. ponderosae* head-space extracts

Peak in Fig. 1	Compound
A	1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octane (**2**)[a]
B	(*E*)-7-Methyl-1,6-dioxaspiro[4.5]decane (**5**)[a]
C	(1*R*,5*S*,7*R*)-*exo*-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane, (1*R*,5*S*,7*R*)-**1**
D	(1*S*,5*R*,7*S*)-*exo*-5-Ethyl-7-methyl-6,8-dioxabicyclo[3.2.1]octane, (1*S*,5*R*,7*S*)-**6**
E	(1*R*,5*S*,7*S*)-*endo*-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane, (1*R*,5*S*,7*S*)-**1**
F	*endo*-5-Ethyl-7-methyl-6,8-dioxabicyclo[3.2.1]octane, (**6**)[a]
G	*endo*-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (**4**)[a]
H	(1*S**,1′*R**,5′*R**,7′*R**)-*exo*-1-(5-Methyl-6,8-dioxabicyclo[3.2.1]oct-7-yl)ethanol, (1*S**,1′*R**,5′*R**,7′*R**)-**12**[a]
I	(1*R*,2*R*,5*S*,7*R*)-*exo*-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octan-2-ol, (1*R*,2*R*,5*S*,7*R*)-**11**
K	(1*R*,2*R*,5*S*,7*S*)-*endo*-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octan-2-ol, (1*R*,2*R*,5*S*,7S)-**11**
L	(1*R*,1′*R*,5′*R*,7′*R*)-*exo*-1-(5-Methyl-6,8-dioxabicyclo[3.2.1]oct-7-yl)ethanol, (1*R*,1′*R*,5′*R*,7′*R*)-**12**
M	(1*R**,2*S**,5*S**,7*R**)-*exo*-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octan-2-ol, (1*R**,2*S**,5*S**,7*R**)-**11**[a]
N	(1*R**,3*S**,4*S**,5*S**)-3-Ethyl-1-methyl-6,8-dioxabicyclo[3.2.1]octan-4-ol, (1*R**,3*S**,4*S**,5*S**)-**18**[a]

[a]The absolute configuration of this compound was not determined.

in fruit flies[22,23] and bees.[24] In these spiroacetals, also hydroxy groups are found as substituents both in the ring or in the side chain. To us it appears that those ketodiols which form spiroacetals such as **5** and bicyclic acetals like **1**, **4** and **6** share a common biogenetic precursor. The biological significance of isobrevicomin and the hydroxylated brevicomins in the communication system of the mountain pine beetle is presently under investigation.

Experimental

NMR: Bruker DRX 500 (500 MHz), Bruker AMX 400 (400 MHz) and Bruker AC 250-P (250 MHz) spectrometers, with TMS as the internal standard. The multiplicity of the ^{13}C NMR signals was determined by DEPT experiments. In case the multiplets in 1-D ^1H NMR experiments were not completely resolved, $^1H,^1H$ coupling constants were derived from phase-sensitive ($^1H,^1H$) COSY experiments. IR: Perkin–Elmer FT–IR spectrometer 1720 X. GC–MS: HP5890/VG70/250SE, 70 eV, and Fisons GC8008/MD 800, 70 eV; helium was used as the carrier gas. GC: Fisons GC 8008 with flame ionization detector and split injector; hydrogen was used as the carrier gas; columns: 50 m FS–FFAP, 0.32 mm i.d. (Macherey & Nagel); 30 m DB5, 0.32 mm i.d. (J&W). Chiral GC:[15] 25 m fused silica column, 0.25 mm i.d., coated with a 1:1 mixture of OV1701 and heptakis(2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin; temperature program: 3 min at 60 °C, then programmed to 170 °C at a rate of 5 °C/min. Column chromatography: flash chromatography on silica gel (Merck Kieselgel 60, 240–400 mesh). TLC: Merck Kieselgel 60 F_{254}. Optical rotations: Perkin–Elmer 243 polarimeter.

(4′*S*,5′*S*)-[2,2-Dimethyl-5-(3-{2-ethyl-5,5-dimethyl-1,3-dioxan-2-yl}propyl)-1,3-dioxolan-4-yl]methyl *p*-toluenesulfonate, (4′*S*,5′*S*)-10. A Grignard reagent prepared from **9**[14] (17.0 g, 68.7 mmol) in THF (150 mL) was added to a stirred suspension of $CuBr(SMe_2)$ (2.50 g, 12.2 mmol) in ethyl ether (100 mL) at −10 °C under argon. Subsequently, a solution of the triflate **8**[13] (9.00 g, 20.1 mmol) in ethyl ether (100 mL) was added dropwise over a period of 10 min. After stirring for 1 h at −5 to 0 °C the reaction mixture was poured into a beaker containing an ice-cold saturated aqueous NH_4Cl solution (200 mL) and concentrated aqueous ammonia (10 mL). The resulting mixture was vigorously stirred for 30 min. Then the organic layer was separated and the aqueous layer was extracted with two 50 mL portions of ethyl ether. The combined organic phases were washed with a saturated aqueous NaCl solution, dried with Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica [700 g, *n*-hexane:ethyl acetate:toluene (4:1:0.5)] yielding 7.4 g (15.8 mmol, 79 %) of (4*S*,5*S*)-**10** as a colorless oil; $[\alpha]_D^{25}$ −17.7 (*c* 3.12 in $CHCl_3$). ^1H NMR (C_6D_6, 400 MHz): δ 0.74 (s, 3H), 0.86 (s, 3H), 0.97 (t, J = 7.5 Hz, 3H), 1.23 (s, 3H), 1.29 (s, 3H), 1.31–1.47 (m, 2H), 1.51–1.62 (m, 1H), 1.69–1.79 (m, H), 1.86 (s, 3H), 3.32–3.36 (m, 4H), 3.64 (ddd, $J_{4,5}$ = 8.1, J_{4,CH_aH_bOTs} = 5.1, J_{4,CH_aH_bOTs} = 3.8 Hz, 1H, 4-H), 3.72 (td, $J_{4,5} = J_{5,1a'}$ = 8.1, $J_{5,1b'}$ = 3.9 Hz, 1H, 5-H), 3.97 (dd, J_{4,CH_aH_bOTs} = 10.7, $J_{4,CH_aH_bOTs,4}$ = 5.1 Hz, 1H, CH_aH_bOTs), 4.06 (dd, J_{4,CH_aH_bOTs} = 10.7, $J_{4,CH_aH_bOTs,4}$ = 3.8 Hz, 1H, CH_aH_bOTs), 6.71–6.75 (m, 2H), 7.74–7.78 (m, 2H) ppm. ^{13}C NMR (C_6D_6, 101 MHz): δ 8.00 (q), 20.2 (t), 21.1 (q), 22.6 (q), 22.9 (q), 26.0 (t), 26.8 (q), 27.5 (q), 29.6 (s), 33.5 (t), 34.1 (t), 69.4 (t), 70.0 (t, 2C), 78.0 (d), 78.7 (d), 100.4 (s), 109.2 (s), 128.2 (d, 2C), 129.8 (d, 2C), 134.0 (s), 144.4 (s) ppm. $C_{24}H_{38}O_7S$ (470.63): Calcd: C, 61.25, H, 8.14, S, 6.81. Found C, 61.37, H, 8.26, S, 6.64.

(4″*S*,5″*S*)-2-Ethyl-5,5-dimethyl-2-[3-(2,2,5-trimethyl-1,3-dioxolan-4-yl)propyl]-1,3-dioxane. A solution of (4*S*,5*S*)-**10** (6.6 g, 14.0 mmol) in ethyl ether (200 mL) was added dropwise over a period of 20 min to a stirred suspension of $LiAlH_4$ (1.06 g, 28 mmol) in ethyl ether (50 mL) at 0 °C under argon. The resulting mixture was refluxed for 4 h. Excess $LiAlH_4$ was destroyed by the dropwise addition of water (2 mL). After stirring for 5 min the mixture was treated with 2 mL of a 15% aqueous NaOH solution and after further 5 min of stirring with 2 mL of water. The precipitate was filtered off and the filtercake was extracted with three 50 mL portions of THF. The combined extracts were concentrated and the residue was chromatographed over silica [200 g, *n*-hexane:ethyl acetate 7:1] yielding 3.88 g (12.9 mmol, 92%) of (4″*S*,5″*S*)-2-ethyl-5,5-dimethyl-2-[3-(2,2,5-trimethyl-1,3-dioxolan-4-yl)propyl]-1,3-dioxane as a colorless oil; $[\alpha]_D^{28}$ −6.28 (*c* 3.25 in $CHCl_3$). ^1H NMR (C_6D_6, 400 MHz): δ 0.74 (s, 3H), 0.84 (s, 3H), 0.98 (t, J = 7.5 Hz, 3H, CH_3CH_2), 1.12 (d, $J_{5'',5''\text{-}CH_3}$ = 6.0 Hz, 3H, 5′-CH_3), 1.417 (s, 3H), 1.421 (s, 3H), 1.35–1.54 (m, 2H), 1.62–1.88 (m, 6H), 3.32–3.35 (m, 4H, CH_2O), 3.50 (td, $J_{4'',5''} = J_{4'',3a'}$ = 8.3, $J_{4'',3b'}$ = 3.8 Hz, 1H, 4″-H), 3.63 (dq, $J_{5'',4''}$ = 8.3, $J_{5'',5''CH_3}$ = 6.0 Hz, 1H, 5″-H) ppm. ^{13}C NMR (C_6D_6, 101 MHz): δ 8.1 (q), 17.8 (q), 20.6 (t), 22.7 (q), 22.9 (q), 26.2 (t), 27.68 (q), 27.71 (q), 29.7 (s), 33.0 (t), 34.4 (t), 70.1 (t, 2 C), 77.2 (d), 83.0 (d), 100.6 (s), 107.8 (s) ppm. $C_{17}H_{32}O_4$ (300.23): Calcd: C, 68.01; H, 10.74. Found: C, 67.72; H, 10.61.

(1*S*,5*R*,7*S*)-5-Ethyl-7-methyl-6,8-dioxabicyclo[3.2.1]-octane [(−)-*exo*-isobrevicomin], (1*S*,5*R*,7*S*)-6. A mixture of 1 N HCl (10 mL), (4″*S*,5″*S*)-2-ethyl-5,5-dimethyl-2-[3-(2,2,5-trimethyl-1,3-dioxolan-4-yl)propyl]-1,3-dioxane (3.2 g, 10.7 mmol) and methanol (30 mL) was stirred for 1.5 h at 20 °C and was then poured into a vigorously stirred mixture of a saturated aqueous $NaHCO_3$ solution (100 mL) and *n*-pentane (200 mL). The organic layer was separated and the aqueous layer was extracted with *n*-pentane (50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. Distillation of the residue yielded 1.31 g (8.39 mmol, 78%) of (1*S*,5*R*,7*S*)-**6** as a colorless oil; bp 74–76 °C/27 hPa; $[\alpha]_D^{24}$ −54.3 (*c* 1.34 in $CHCl_3$). On the chiral GC column, the enantiomers of (1*S**,5*R**,7*S**)-**6** were well separated: t_R = 6.7 min for (1*R*,5*S*,7*R*)-**6** and t_R = 7.9 min for (1*S*,5*R*,7*S*)-**6**. The ee of (1*S*,5*R*,7*S*)-**6** was estimated to be 98%. ^1H NMR

(C_6D_6, 500 MHz): δ 1.04–1.08 (m, 1H, 2-H_{eq}), 1.08 (t, 3H, 7-$CH_2C\underline{H}_3$), 1.085 (d, 3H, 7-CH_3), 1.34–1.40 (m, 1H, 3-H_{eq}), 1.46–1.59 (m, 2H, 4-H), 1.58 (ddt, J_t = 13.1, J_d = 5.4, J_d = 3.1 Hz, 1H, 2-H_{ax}), 1.66–1.84 (m, 3H, 5-$C\underline{H}_2CH_3$ and 3-H_{ax}), 3.74–3.76 (m, 1H, 1-H), 3.93 (q, 1H, 7-H) ppm; $J_{7,7\text{-}CH_3}$ = 6.2, $J_{7,1}$ < 1, $J_{1,2ax}$ = 3.2, $J_{1,2eq}$ = 3.1, $J_{2ax,2eq}$ = 13.1, $J_{2ax,3ax}$ = 13, $J_{2ax,3eq}$ = 5.6, $J_{3ax,2eq}$ = 12.5 Hz. ^{13}C NMR (C_6D_6, 126 MHz): δ 7.7 (q, 5-$CH_2\underline{C}H_3$), 17.6 (t, C-3), 21.8 (q, 7-CH_3), 28.4 (t, C-2), 31.1 (t, 5-$\underline{C}H_2CH_3$), 34.0 (t, C-4), 75.5 (d, C-7), 79.9 (d, C-1), 109.5 (s, C-5) ppm. MS *m/z* (%): 156 (6, M^+), 128 (1), 113 (1), 112 (11), 111 (1), 101 (2), 100 (32), 99 (3), 95 (2), 85 (3), 84 (2), 83 (6), 82 (2), 81 (3), 72 (5), 71 (23), 70 (2), 69 (11), 68 (3), 67 (6), 58 (7), 57 (100), 56 (6), 55 (25), 54 (6), 53 (3), 45 (3), 44 (4), 43 (15), 41 (15), 40 (3), 39 (10). $C_9H_{16}O_2$ (156.23): Calcd: C, 69.19; H, 10.32. Found: C, 69.02; H, 10.29.

(1*S,5*R**,7*R**)-5-Ethyl-7-methyl-6,8-dioxabicyclo[3.2.1]-octane [*endo*-isobrevicomin], (1*S**,5*R**,7*R**)-6.** A sample of racemic *endo*-isobrevicomin was prepared from (*E*)-7-nonen-3-one (150 mg, 1.1 mmol) according to Wassermann and Barber;[12] yield 40 mg (0.16 mmol, 24%). ^{1}H NMR (C_6D_6, 500 MHz): δ 1.06 (d, 3H, 7-CH_3), 1.095 (t, 3H, 5-$CH_2C\underline{H}_3$), 1.21–1.26 (m, 1H, 2-H_{eq}), 1.32–1.38 (m, 1H, 3-H_{eq}), 1.48–1.64 (m, 3H, 4-H_{ax}, 4-H_{eq} and 2-H_{ax}), 1.73–1.91 (m, 3H, 5-$C\underline{H}_2CH_3$ and 3-H_{ax}), 3.82–3.85 (m, 1H, 1-H), 4.07 (ddq, 1H, 7-H) ppm; $J_{7,7\text{-}CH_3}$ = 6.6, $J_{7,1}$ = 4.2, $J_{7,2ax}$ = 1.1, $J_{1,2ax}$ = 3.2, $J_{1,2eq}$ = 1.2, $J_{2ax,2eq}$ = 13.1, $J_{2ax,3ax}$ = 12.9, $J_{2ax,3eq}$ = 5.7, $J_{3ax,3eq}$ = 12.5 Hz. ^{13}C NMR (C_6D_6, 126 MHz): δ 7.5 (q, 5-$CH_2\underline{C}H_3$), 13.9 (q, 7-CH_3), 17.8 (t, C-3), 24.3 (t, C-2), 31.5 (t, 5-$\underline{C}H_2CH_3$), 33.0 (t, C-4), 76.0 (d, C-7), 77.2 (d, C-1), 108.7 (s, C-5) ppm. MS *m/z* (%): 156 (12, M^+), 128 (1), 112 (14), 113 (1), 100 (7), 99 (2), 97 (2), 95 (1), 84 (2), 83 (9), 82 (7), 81 (3), 72 (5), 71 (10), 70 (2), 69 (5), 68 (2), 67 (7), 58 (6), 57 (100), 56 (7), 55 (26), 54 (7), 53 (3), 45 (4), 44 (7), 43 (18), 42 (6), 41 (19), 40 (5), 39 (12). $C_9H_{16}O_2$ (156.23): Calcd: C, 69.19; H, 10.32. Found: C, 69.05; H, 10.13.

7-(2,5,5-Trimethyl-1,3-dioxan-2-yl)-4-heptyn-3-ol (14). 2-(2-Bromoethyl)-2,5,5-trimethyl-1,3-dioxane (**13**)[14] (10 g, 43.2 mmol) was added to a stirred suspension of lithium acetylide ethylendiamine complex (5.83 g, 63.3 mmol) in dry DMSO (50 mL) at +5 °C under argon. After stirring for 2 h at 20 °C, the reaction mixture was poured into 200 mL of ice-cold water and the mixture was extracted with two 100 mL portions of *n*-hexane. The combined extracts were washed with water, dried with Na_2SO_4 and concentrated to give 7.2 g of crude 2-(but-3-inyl)-2,5,5-trimethyl-1,3-dioxane, containing ca. 30% of 2,5,5-trimethyl-2-vinyl-1,3-dioxane. This material was employed in the next step without further purification. A solution of crude 2-(but-3-inyl)-2,5,5-trimethyl-1,3-dioxane (7.2 g) in THF (80 mL) was treated with *n*-BuLi (29 mmol, 18.7 mL of a 1.55 N solution in *n*-hexane) at −40 °C under argon. The mixture was allowed to warm to 0 °C and stirred for 30 min at this temperature. After cooling to −78 °C, a solution of freshly distilled propanal (1.7 g, 29 mmol) in THF (10 mL) was added within 5 min. The mixture was stirred for 5 min at −78 °C, warmed to 0 °C and then poured into ice-cold aqueous saturated NaCl solution (50 mL). After dilution with 50 mL of *n*-hexane, the organic layer was separated and the aqueous layer was extracted with three 50 mL portions of ethyl acetate. The combined organic phases were dried with Na_2SO_4 and concentrated. The residue was chromatographed over silica [400 g, *n*-hexane:ethyl acetate = (3:2)] to give 4.12 g (17.2 mmol, 41%, based on **13**) of **14** as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (s, 3H), 0.99 (t, $J_{1,2}$ = 7.5 Hz, 3H, 1-H), 1.01 (s, 3H), 1.37 (s, 3H), 1.61–1.76 (m, 2H, 2-H), 1.89 (d, $J_{OH,3}$ = 4.7 Hz, 1H, OH), 1.92–1.96 (m, 2H, 7-H), 2.34–2.39 (m, 2H, 6-H), 3.40–3.44 (m, 2H), 3.52–3.57 (m, 2H), 4.26–4.32 (m, 1H, 3-H) ppm. ^{13}C-NMR ($CDCl_3$, 63 MHz): δ 9.5 (q), 13.0 (t), 20.2 (q), 22.5 (q), 22.7 (q), 29.9 (s), 31.2 (t), 37.5 (t), 63.9 (d), 70.4 (t, 2 C), 80.8 (s), 85.4 (s), 98,0 (s) ppm. $C_{14}H_{24}O_3$ (240.34): Calcd: C, 69.96; H, 10.07. Found: C, 70.12; H, 10.09.

(4*E*)-7-(2,5,5-Trimethyl-1,3-dioxan-2-yl)-4-hepten-3-ol, (4*E*)-15. A solution of **14** (3.90 g, 16.3 mmol) in THF (20 mL) was added dropwise within 10 min to a stirred suspension of $LiAlH_4$ (1.25 g, 33 mmol) in THF (80 mL) at 0 °C under argon. After stirring for 24 h at 20 °C, excess $LiAlH_4$ was destroyed by the addition of water (2.2 mL). The mixture was stirred for 5 min and 2.2 mL of a 15% aqueous NaOH solution was added. After stirring for an additional 5 min, 2 mL of water was added. The white precipitate was filtered off and the filtercake was extracted with two 50 mL portions of THF. The combined filtrates were concentrated and the residue was filtered over a short column of silica [50 g, *n*-hexane:ethyl acetate (3:2)] yielding 3.84 g (15.9 mmol, 97%) of (4*E*)-**15**, containing less than 1% of the (4*Z*)-isomer (GC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (s, 3H), 0.90 (t, $J_{1,2}$ = 7.4 Hz, 3H, 1-H), 1.02 (s, 3H). 1.73 (s, 3H), 1.44–1.62 (m, 3H, OH and 2-H), 1.73–1.80 (m, 2H, 7-H), 2.15–2.22 (m, 2H, 6-H), 3.40–3.45 (m, 2H), 3.53–3.58 (m, 2 H), 3.93–4.00 (m, 1H, 3-H), 5.49 (ddt, $J_{4,5}$ = 15.3, $J_{4,3}$ = 7.0, $^4J_{4,6}$ = 1.4 Hz, 1H, 4-H), 5.68 (dt, $J_{5,4}$ = 15.3, $J_{5,6}$ = 6.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ 9.8 (q), 20.3 (q), 22.5 (q), 22.8 (q), 26.1 (t), 29.9 (s), 30.1 (t), 37.6 (t), 70.4 (t, 2 C), 74.5 (d), 98.7 (s), 131.9 (d), 132.8 (d) ppm. $C_{14}H_{26}O_3$ (242.36): Calcd: C, 69.38; H, 10.81. Found: C, 69.30; H, 10.86.

(1*R*,2′*R*,3′*R*)-1-(3-{2-[2,5,5-Trimethyl-1,3-dioxan-2-yl]-ethyl}oxiran-2-yl)propanol, (1*R*,2′*R*,3′*R*)-16.[17] Diisopropyl D-(−)-tartrate (1.41 g, 6.00 mmol) was added to a stirred suspension of molecular sieves (4 Å, 4 g) in dry CH_2Cl_2 (200 mL) under argon. After stirring for 15 min at room temperature, the mixture was cooled to −20 °C and 1.42 g (5.0 mmol) of $Ti(O^iPr)_4$ were added. Stirring was maintained for 1 h at −20 °C, followed by the addition of 21 mmol of *t*-butyl hydroperoxide (3.75 mL of a 5.6 N solution in CH_2Cl_2). After further 20 min at −20 °C, the mixture was cooled to −40 °C and a solution of (4*E*)-**15** (6.00 g, 24.8 mmol) in 20 mL of CH_2Cl_2 was added dropwise over a period of 10 min. The reaction mixture was

stirred for 15 h at −40 °C. It was then poured into an ice cold saturated NaCl solution (100 mL). Subsequently, the mixture was filtered through a pad of Celite to remove most of the emulsive titanium salts. The organic layer was separated and the aqueous layer was extracted with four 50 mL portions of CH_2Cl_2. The combined organic organic phases were washed with a saturated aqueous NaCl solution, dried with Na_2SO_4 and carefully concentrated. Column chromatography of the residue [200 g silica, *n*-hexane:ethyl ether (1:1)] yielded 3.1 g of crude (1*R*,2′*R*,3′*R*)-**16**, which was rechromatographed [300 g silica, *n*-hexane:ethyl acetate (3:2)] to give 2.7 g (10.5 mmol, 84%) of (1*R*,2′*R*,3′*R*)-**16** as a colorless oil; $[\alpha]_D^{22}$ +12.2 (*c* 1.58 in CH_2Cl_2). 1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (s, 3H), 1.01 (t, $J_{3,2}$ = 7.4 Hz, 3H, 3-H), 1.04 (s, 3H), 1.38 (s, 3H), 1.49–1.90 (m, 6H, 2-H and —CH_2CH_2—), 2.05 (d, $J_{OH,t}$ = 2.4 Hz, 1H, OH), 2.78 (dd, $J_{2',1}$ = 3.7, $J_{2',3'}$ = 2.3 Hz, 1H, 2′-H), 3.03 (dt, $J_{3',3'\text{-}CH_2}$ = 5.5, $J_{3',2'}$ = 2.3 Hz, 1H, 3′-H), 3.40–3.44 (m, 1H, 1-H) ppm. ^{13}C-NMR ($CDCl_3$, 101 MHz): δ 9.6 (q), 19.9 (q), 22.4 (q), 22.9 (q), 25.7 (t), 26.6 (t), 29.9 (s), 35.0 (t), 55.1 (d), 60.9 (d), 70.1 (d), 70.4 (t, 2 C), 98.5 (s) ppm. $C_{14}H_{26}O_4$ (258.36): Calcd: C, 65.09; H, 10.14. Found: C, 64.80; H, 10.21.

(1*S*,2′*S*,3′*S*)-1-(3-{2-[2,5,5-Trimethyl-1,3-dioxan-2-yl]-ethyl}oxiran-2-yl)propanol, (1*S*,2′*S*,3′*S*)-16. The epoxidation was performed as described for the preparation of the (1*R*,2′*R*,3′*R*)-isomer, in this case with 8.00 g (33.0 mmol) of (4*E*)-**15**, 1.99 g (8.5 mmol) of (+)-DIPT, 1.99 g (7.0 mmol) of $Ti(O^iPr)_4$ and 30 mmol. ^{t}BuOOH (5.4 mL of a 5.6 N solution) in 300 mL of CH_2Cl_2. Yield: 3.75 g (14.5 mmol, 88%) of (1*S*,2′*S*,3′*S*)-**16**; $[\alpha]_D^{22}$ −12.4 (*c* 1.75 in $CHCl_3$).

(1*R*,2*R*,5*S*,7*S*)-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]-octan-2-ol, (1*R*,2*R*,5*S*,7*S*)-11. Aqueous HF (40%, 0.3 mL) was added to a solution of (1*S*,2′*S*,3′*S*)-**16** (200 mg, 0.77 mmol) in a mixture of acetonitrile (5 mL) and water (5 mL) at 20 °C. After stirring for 1 h, the mixture was poured into a saturated aqueous $NaHCO_3$ solution (50 mL). The mixture was extracted with four 20 mL portions of ethyl acetate. The combined extracts were dried with Na_2SO_4 and concentrated. The residue was subjected to column chromatography [40 g silica, *n*-hexane:ethyl acetate (3:2)] yielding 110 mg (0.64 mmol, 83%) of (1*R*,2*R*,5*S*,7*S*)-**11** as a colorless oil; $[\alpha]_D^{23}$ +94.2 (*c* 1.62 in $CHCl_3$). A sample of the enantiomer (1*S*,2*S*,5*R*,7*R*)-**11** was prepared analogously.

Determination of the optical purity of (1*R*,2*R*,5*S*,7*S*)-**11** by chiral GC: On the chiral column, the stereoisomers of **11** were well separated: t_R = 15.02 min for (1*R*,2*R*,5*S*,7*R*)-**11**, t_R = 15.13 min for (1*R*,2*R*,5*S*,7*S*)-**11**, t_R = 15.82 min for (1*S*,2*S*,5*R*,7*R*)-**11** and t_R = 15.99 min for (1*S*,2*S*,5*R*,7*S*)-**11**. The enantiomers of the *exo* stereoisomer of **11** with an equatorial OH group [(1*R**,2*S**,5*S**,7*R**)-**11**] were also separated under these conditions: t_R = 17.51 and t_R = 17.97 min. The ee of (1*R*,2*R*,5*S*,7S)-**11** was estimated to be 96%, de 97%. ^{1}H NMR (C_6D_6, 500 MHz): δ 0.77 (t, 3H, 7-$CH_2C\underline{H}_3$), 1.12 (m, 1H, 7-$C\underline{H}_aH_bCH_3$), 1.35 (m, 1H, 4-H_{eq}), 1.47 (m, 1H, 7-$CH_a\underline{H}_bCH_3$), 1.55 (m, 1H, 3-H_{eq}), 1.63 (ddd, 1H, 4-H_{ax}), 1.88 (dddd, 1H, 3-H_{ax}), 2.55 (br. s, 1H, OH), 3.44 (m, 1H, 2-H), 3.83 (ddd, 1H, 7-H), 4.01 (m, 1H, 1-H) ppm; $J_{7\text{-}C\underline{H}_2CH_3}$ = 7.5, $J_{7,7\text{-}CH_a\underline{H}_b}$ = 6.1, $J_{7,7\text{-}CH_a\underline{H}_b}$ = 8.4, $J_{7,1}$ = 4.4, $J_{1,2}$ = 2.4, $^4J_{1,3eq}$ = 1.6, $J_{2,3ax}$ = 4.4, $J_{2,3eq}$ = 1.4, $J_{3ax,3eq}$ = 13.9, $J_{3ax,4ax}$ = 11.7, $J_{3ax,4eq}$ = 6.9, $J_{3eq,4ax}$ = 6.1, $J_{3eq,4eq}$ = 1.6, $J_{4ax,4eq}$ = 13.3 Hz. ^{13}C NMR (C_6D_6, 126 MHz): δ 11.3 (q, 7-$CH_2\underline{C}H_3$), 21.8 (t, 7-$\underline{C}H_2CH_3$), 25.2 (q, 5-CH_3), 26.6 (t, C-3), 31.7 (t, C-4), 64.1 (d, C-2), 80.3 (d, C-7), 81.3 (d, C-1), 107.5 (s, C-5) ppm. MS *m/z* (%): 172 (0.4, M^+), 115 (4), 114 (34), 101 (3), 99 (2), 97 (3), 95(1), 86 (3), 85 (5), 84 (24), 83 (19), 82 (3), 81 (3), 73 (21), 72 (14), 71 (25), 70 (5), 69 (5), 67 (1), 61 (17), 59 (14), 58 (19), 57 (24), 56 (15), 55 (26), 47 (3), 46 (3), 45 (5), 44 (11), 43 (100), 42 (7), 41 (24), 40 (5), 39 (14). $C_9H_{16}O_3$ (172.23): Calcd: C, 62.77, H 9.36. Found: C, 62.43, H, 9.40.

(1*R*,2′*S*,3′*S*)-1-(3-{2-[2,5,5-Trimethyl-1,3-dioxan-2-yl]-ethyl}oxiran-2-yl)propyl 3,5-dinitrobenzoate.[18] Diethyl azodicarboxylate (2.68 g, 2.4 mL, 15.4 mmol) dissolved in 40 mL of dry THF was added dropwise within 15 min to a mechanically stirred solution of triphenylphosphine (4.46 g, 17.0 mmol) in dry THF at −20 °C under argon. The resulting suspension was stirred for 20 min, then (1*S*,2′*S*,3′*S*)-**16** (3.60 g, 14.0 mmol) in 10 mL of THF was added dropwise within 10 min and stirring was continued for 15 min. Subsequently, 3,5-dinitrobenzoic acid (3.18 g, 15.0 mmol) was added and the mixture was allowed to warm to 20 °C. After stirring for 2 h at 20 °C, the mixture was concentrated in vacuo. The residue was chromatographed over silica [400 g, *n*-hexane: ethyl acetate (4:1)] yielding 5.3 g (11.7 mmol, 83%) of (1*R*,2′*S*,3′*S*)-1-(3-{2-[2,5,5-trimethyl-1,3-dioxan-2-yl]ethyl}-oxiran-2-yl)propyl 3,5-dinitrobenzoate as a pale yellow oil; $[\alpha]_D^{25}$ −20.1 (*c* 1.95 in $CHCl_3$). ^{1}H NMR (C_6D_6, 400 MHz): δ 0.53 (s, 3H), 0.76 (t, $J_{3,2}$ = 7.5 Hz, 3H, 3-H), 0.98 (s, 3H), 1.25 (s, 3H), 1.41–1.62 (m, 2H, 2-H), 1.75–1.92 (m, 4H, —CH_2CH_2—); 2.665 (dd, $J_{2',1}$ = 7.1, $J_{2',3'}$ = 2.0 Hz, 1H, 2′-H), 2.695–2.730 (m, 1H, 3′-H), 3.22–3.27 (m, 2H), 3.37–3.41 (m, 2H), 4.82 (q, $J_{1,2'} = J_{1,2}$ = 7.1 Hz, 1H, 1-H), 8.50 (t, *J* = 1.1 Hz, 1H), 8.71 (d, *J* = 1.1 Hz, 2H) ppm. ^{13}C NMR (C_6D_6, 400 MHz): δ 9.7 (q), 19.3 (q), 22.2 (q), 23.0 (q), 24.9 (t), 26.1 (t), 29.8 (s), 36.4 (t), 57.2 (d), 58.5 (d), 70.5 (t, 2 C), 79.3 (d), 98.5 (s), 122.0 (d), 128.8 (d, 2 C), 133.5 (s), 148.4 (s, 2 C), 162.1 (s) ppm. $C_{21}H_{18}N_2O_9$ (452.46): Calcd: C, 55.75; H, 6.24; N, 6.19. Found: C, 55.94; H, 6.27; N, 6.01.

(1*R*,2′*S*,3′*S*)-1-(3-{2-[2,5,5-Trimethyl-1,3-dioxan-2-yl]-ethyl}oxiran-2-yl)propanol, (1*R*,2′*S*,3′*S*)-16. A mixture of 1 N aqueous KOH (13.0 mL) and methanol (15 mL) was added dropwise within 15 min to a stirred solution of (1*R*,2′*S*,3′*S*)-1-(3-{2-[2,5,5-trimethyl-1,3-dioxan-2-yl]ethyl}oxiran-2-yl)propyl 3,5-dinitrobenzoate (5.81 g, 12.8 mmol) in THF (15 mL) at 0 °C. After stirring for 15 min at 0 °C, the mixture was poured into a saturated aqueous NaCl solution (100 mL). The

organic layer was separated and the aqueous layer was extracted with three 50 mL portions of ethyl ether. The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution, dried with Na_2SO_4 and concentrated. The residue was chromatographed over silica [200 g, *n*-hexane:ethyl acetate (2:1)] to give 3.18 g (12.3 mmol, 96%) of (1*R*,2′*S*,3′*S*)-**16** as a colorless oil; $[\alpha]_D^{24} -25.6$ (*c* 2.67 in $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (s, 3H), 0.99 (t, $J_{3,2} = 7.5$ Hz, 3H, 3-H), 1.03 (s, 3H), 1.37 (s, 3H), 1.57–1.90 (m, 6H, 2-H and —CH_2CH_2—), 2.09 (d, $J_{OH,1} = 5.6$ Hz, 1H, OH), 2.76 (dd, $J_{2',1} = 5.3$, $J_{2',3'} = 2.3$ Hz, 1H, 2′-H), 2.94–2.98 (m, 1H, 3′-H), 3.34–3.43 (m, 3H, 1-H and CH_2O), 3.55–3.59 (m, 2H, CH_2O) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ 9.7 (q), 19.9 (q), 22.4 (q), 22.9 (q), 25.7 (t), 27.4 (t), 29.9 (s), 34.8 (t), 56.8 (d), 61.7 (d), 70.4 (t, 2 C), 72.7 (d), 98.4 (s) ppm. $C_{14}H_{26}O_4$ (258.36): Calcd: C, 65.09; H, 10.14. Found: C, 64.91; H, 10.36.

(1*R*,2*R*,5*S*,7*R*)-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]-octan-2-ol, (1*R*,2*R*,5*S*,7*R*)-11. The cyclization was performed in the same manner as described for the preparation of the (1*S*,2*S*,5*R*,7*R*)-isomer, in this case with 1 mL of 40% aqueous HF and 2.9 g (11.2 mmol) of (1*R*,2′*S*,3′*S*)-**16** in a mixture of 40 mL of acetonitrile and 40 mL of water. Column chromatography [100 g silica, *n*-hexane:ethyl acetate (3:2)] yielded 1.46 g (8.48 mmol, 76%) of (1*R*,2*R*,5*S*,7*R*)-**11** as a colorless oil; $[\alpha]_D^{19} +81.0$ (*c* 1.91 in $CHCl_3$); ee 97% and de 97%, as determined by chiral GC [retention times: see preparation of (1*R*,2*R*,5*S*,7*S*)-**11**). A sample of the enantiomer (1*S*,2*S*,5*R*,7*S*)-**11** was prepared analogously. ^1H NMR (C_6D_6, 500 MHz): δ 0.79 (t, 3H, 7-$CH_2\underline{CH_3}$), 1.29 (m, 1H, 7-$C\underline{H_a}H_b$), 1.35 (m, 1H, 4-H_{eq}), 1.44 (m, 1H, 7-$CH_a\underline{H_b}$), 1.53 (ddq, 1H, 3-H_{eq}), 1.64 (m, 1H, 4-H_{ax}), 1.77 (dddd, 1H, 3-H_{ax}), 2.59 (br s, 1H, OH), 3.29 (m, 1H, 2-H), 3.48 (t, 1H, 7-H), 3.90 (m, 1H, 1-H) ppm; $J_{7\text{-}CH_2CH_3} = 7.5$, $J_{7,7\text{-}CH_a\underline{H}_b} = J_{7,7\text{-}CH_a\underline{H}_b} = 6.5$, $J_{7,1} < 1$, $J_{1,2} = 2.8$, $^4J_{1,3eq} = 1.6$, $J_{2,3ax} = 4.0$, $J_{2,3eq} = 1.4$, $J_{3ax,3eq} = 14.0$, $J_{3ax,4ax} = 12.5$, $J_{3ax,4eq} = 6.4$, $J_{3eq,4ax} = 5.6$, $J_{3eq,4eq} = 1.5$, $J_{4ax,4eq} = 13.8$ Hz. ^{13}C NMR (C_6D_6, 126 MHz): δ 9.9 (q, 7-$CH_2\underline{C}H_3$), 25.2 (q, 5-CH_3), 25.7 (t, C-3), 28.9 (t, 7-$\underline{C}H_2CH_3$), 31.8 (t, C-4), 66.2 (d, C-2), 79.5 (d, C-7), 83.7 (d, C-1), 108.0 (s, C-5) ppm. MS *m/z* (%): 172 (1, M^+), 157 (0.3), 155 (0.4), 143 (8), 129 (2), 115 (6), 114 (10), 113 (3), 112 (23), 101 (34), 98 (3), 97 (5), 95 (1), 86 (2), 85 (9), 84 (45), 83 (70), 82 (4), 81 (2), 73 (29), 72 (6), 71 (18), 70 (6), 69 (8), 67 (2), 61 (28), 59 (13), 58 (15), 57 (24), 56 (21), 55 (34), 54 (2), 53 (4), 45 (8), 44 (11), 43 (100), 42 (9), 41 (29), 40 (6), 39 (17). $C_9H_{16}O_3$ (172.23): Calcd: C, 62.77; H, 9.36. Found: C, 62.39, H, 9.44.

(4*Z*)-7-(2,5,5-Trimethyl-1,3-dioxan-2-yl)-4-hepten-3-ol, (4*Z*)-15. A mixture of **14** (380 mg, 1.6 mmol), 50 mg Lindlar catalyst (5% Pd on $CaCO_3$, deactivated with Pb, FLUKA) and 70 μL quinoline in 50 mL of *n*-heptane was hydrogenated for 4 h at 1 atm. After filtration, the mixture was concentrated and subjected to column chromatography [40 g silica, *n*-hexane:ethyl acetate (2:1)] to yield 372 mg (1.54 mmol. 96%) of (4*Z*)-**15**, containing 1% of the (4*E*)-isomer (GC). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.90 (s, 3H), 0.91 (t, $J_{1,2} = 7.5$ Hz, 3H, 1-H), 1.01 (s, 3H), 1.38 (s, 3H), 1.41–1.54 (m, 1H, 2-H_a), 1.57–1.68 (m, 1H, 2-H_b), 1.69–1.82 (m, 3H, OH and 7-H), 2.14–2.35 (m, 2H, 6-H), 3.41–3.45 (m, 2H). 3.52–3.57 (m, 2H), 4.36–4.42 (m, 1H, 3-H), 5.37 (ddt, $J_{4,5} = 10.9$, $J_{4,3} = 8.8$, $^4J_{4,6} = 1.4$ Hz, 1H, 4-H), 5.53 (dddd, $J_{5,4} = 10.9$, $J_{5,6a} = 7.0$, $J_{5,6b} = 8.0$, $^4J_{5,3} = 1.0$ Hz, 1H, 5-H) ppm. ^{13}C- NMR ($CDCl_3$, 101 MHz): δ 9.7 (q), 20.6 (q), 21.9 (t), 22.5 (q), 22.8 (q), 30.0 (s), 30.3 (t), 37.9 (t), 68.8 (d), 70.4 (t, 2 C), 98.7 (s), 132.1 (d), 132.6 (d) ppm. $C_{14}H_{26}O_3$ (242.36): Calcd:. C, 69.38; H, 10.81. Found: C, 69.24; H, 10.67.

(1*R,2*S**,5*S**,7*R**)-7-Ethyl-5-methyl-6,8-dioxabicyclo-[3.2.1]octan-2-ol, (1*R**,2*S**,5*S**,7*R**)-11.** A solution of (4*Z*)-**15** (50 mg, 0.21 mmol) and *m*-chloroperbenzoic acid (85%, 60 mg, 0.35 mmol) in 4 mL of CH_2Cl_2 was stirred for 2 h at 20 °C. The solvent was evaporated in vacuo and the mixture of epoxide and *m*-chlorobenzoic acid was taken in 2 mL of acetonitrile. Subsequently, 2 mL of water and 0.1 mL of 40% aqueous HF were added. After stirring for 2 h at 20 °C, the mixture was poured into a saturated aqueous $NaHCO_3$ solution (50 mL). The mixture was extracted with three 20 mL portions of ethyl acetate. The combined extracts were dried with Na_2SO_4 and concentrated. Column chromatography of the residue [40 g silica, *n*-hexane:ethyl acetate (3:2)] yielded 25 mg (0.15 mmol, 69%) of (1*R**,2*S**,5*S**,7*R**)-**11** as a colorless oil. ^1H NMR (CD_3CN, 500 MHz): δ 0.86 (t, 3H, 7-$CH_2\underline{CH_3}$), 1.33 (s, 3H, 5-CH_3), 1.34–1.51 (m, 2H, 7-$C\underline{H_2}CH_3$), 1.53 (m, 1H, 3-H_{ax}), 1.56–1.66 (m, 2H, 4-H_{ax} and 4-H_{eq}), 1.78 (m, 1H, 3-H_{eq}), 2.97 (d, 1H, OH), 3.72 (m, 1H, 2-H), 3.88 (dd, 1H, 1-H), 4.06 (t, 1H, 7-H) ppm; $J_{7,7\text{-}CH_2\underline{CH_3}} = 7.4$, $J_{7,7\text{-}CH_2} = 6.5$, $J_{7,1} < 1$, $J_{1,2} = 3.9$, $^4J_{1,3eq} = 1.5$, $J_{2,OH} = 4.4$, $J_{2,3eq} = 6.1$, $J_{2,3ax} = 10.1$, $J_{3ax,3eq} = 13$Hz. ^{13}C NMR (CD_3CN, 126 MHz): δ 10.0 (q, 7-$CH_2\underline{C}H_3$), 24.3 (q, 5-CH_3), 27.2 (t, C-3), 29.2 (t, 7-$\underline{C}H_2CH_3$), 35.7 (t, C-4), 66.4 (d, C-2), 77.8 (d, C-7), 81.5 (d, C-1), 107.5 (s, C-5) ppm. MS *m/z* (%): 172 (0.7, M^+), 155 (0.2), 143 (7), 129 (1), 115 (5), 114 (3), 113 (5), 112 (23), 102 (1), 101 (31), 99 (3), 97 (5), 95 (2), 86 (6), 85 (8), 84 (39), 83 (73), 82 (3), 81 (3), 73 (27), 72 (4), 71 (18), 70 (5), 69 (7), 67 (3), 61 (24), 59 (12), 58 (19), 57 (25), 56 (21), 55 (30), 54 (3), 53 (4), 45 (7), 44 (15), 43 (100), 42 (7), 41 (24), 40 (4), 39 (15).C (172.23): Calcd: C, 62.77, H 9.36. Found: C, 62.53, H, 9.42.

***t*-Butyldimethylsilyl (4*Z*)-7-(2,5,5-trimethyl-1,3-dioxan-2-yl)-4-hepten-3-yl ether, (4*Z*)-17.** *t*-Butyldimethylsilyl chloride (226 mg, 1.5 mmol) and imidazole (204 mg, 3 mmol) were added to a solution of (4*Z*)-**15** (350 mg, 1.45 mmol) in 5 mL of absolute DMF at 20 °C. The mixture was stirred for 2 h and then diluted with *n*-hexane (50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was separated and the aqueous layer was washed with 50 mL of *n*-hexane. The combined organic phases were washed with water (50 mL), dried with Na_2SO_4 and concentrated. The residue was chromatographed over silica [40 g, *n*-hexane:ethyl acetate (6:1)] yielding 500 mg (1.41 mmol, 97%)

of (4*Z*)-**17** as a colorless oil. ^{1}H NMR (C_6D_6, 400 MHz): δ 0.15 (s, 3H), 0.16 (s, 3H), 0.59 (s, 3H), 0.94 (t, $J_{1,2}$ = 7.5 Hz, 3H, 1-H), 0.96 (s, 3H), 1.02 [s, 9H, C(C$\underline{H}_3$)$_3$], 1.31 (s, 3H), 1.52 (ddq, $J_{2a,2b}$ = 13.4, $J_{2a,1}$ = 7.5, $J_{2a,3}$ = 6.0 Hz, 1H, 2-H$_a$), 1.67 (m, 1H, 2-H$_b$), 1.77–1.91 (m, 2H, 7-H), 2.33–2.51 (m, 2H, 6-H), 3.24–3.31 (m, 2H), 3.36–3.40 (m, 2H), 4.52–4.58 (m, 1H, 3-H), 5.38 (ddt, $J_{5,4}$ = 11.0, $J_{5,6}$ = 6.9, $^4J_{5,3}$ = 1.1Hz, 1H, 5-H), 5.51 (ddt, $J_{4,5}$ = 11.0, $J_{4,3}$ = 8.5, $^4J_{4,6}$ = 1.4 Hz, 1H, 4-H) ppm. ^{13}C NMR (C_6D_6, 101 MHz): δ −4.6 (q), -4.0 (q), 10.0 (q), 18.4 [s, $\underline{C}$(CH$_3$)$_3$], 19.9 (q), 22.3 (q), 22.4 (t), 22.9 (q), 26.2 [q, 3 C, C($\underline{C}$H$_3$)$_3$], 29.8 (s), 31.9 (t), 39.5 (t), 70.35 (t, 2 C), 70.42 (d, C-3), 98.6 (d), 129.3 (d), 134.4 (d) ppm. $C_{20}H_4O_3Si$ (356.63): Calcd: C, 67.36; H, 11.31. Found: C, 67.22; H, 11.45.

(1*R,3*S**,4*S**,5*S**)-3-Ethyl-1-methyl-2,8-dioxabicyclo-[3.2.1]octan-4-ol, (1*R**,3*S**,4*S**,5*S**)-18.** A solution of (4*Z*)-**17** (480 mg, 1.35 mmol) and *m*-chloroperbenzoic acid (85%, 325 mg, 1.6 mmol) in 30 mL of CH_2Cl_2 was stirred for 18 h at 20 °C. Subsequently, the solvent was evaporated in vacuo and the mixture of epoxide and *m*-chlorobenzoic acid was taken in 10 mL of acetonitrile. Water (10 mL) and 0.4 mL of 40% aqueous HF were added. After stirring for 4 h at 20 °C, the mixture was poured into a saturated aqueous $NaHCO_3$ solution (50 mL). The mixture was extracted with three 20 mL portions of ethyl acetate. The combined extracts were dried with Na_2SO_4 and concentrated. Column chromatography of the residue [100 g silica, *n*-hexane:ethyl acetate (3:2)] yielded 126 mg (0.73 mmol, 54%) of (1*R**,2*S**,5*S**,7*R**)-**11** and 28 mg (0.16 mmol, 12%) of (1*R**,3*S**,4*S**,5*S**)-**18** as colorless oils. ^{1}H NMR (C_6D_6, 500 MHz): δ 1.05 (t, 3H, 3-CH$_2$CH$_3$), 1.1 (br s, 1H, OH), 1.515 (m, 1H, 3-C$\underline{H}_a$H$_b$CH$_3$), 1.525 (s, 3H, 1-CH$_3$), 1.529 (m, 1H, 7-H$_{exo}$), 1.64 (ddt, 1H, 6-H$_{exo}$), 1.75 (m, 1H, 3-CH$_a\underline{H}_b$CH$_3$), 1.76 (m, 1H, 7-H$_{endo}$), 1.91 (ddd, 1H, 6-H$_{endo}$), 3.25 (dt, 1H, 3-H), 3.31 (dd, 1H, 4-H), 4.10 (dd, 1H, 5-H) ppm; $J_{3\text{-}CH_2CH_3}$ = 7.4, $J_{3,3\text{-}CH_a\underline{C}H_b}$ = 7.9, $J_{3,3\text{-}CH_a\underline{H}_b}$ = 3.0, $J_{3,4}$ = 7.8, $J_{4,5}$ = 3.9, $J_{5,6exo}$ = 7.0, $J_{5,6endo}$ < 0.5, $J_{6exo,6endo}$ = 12.5, $J_{6endo,7endo}$ = 9.6, $J_{6endo,7exo}$ = 4.3, $J_{exo,7exo}$ = 12.5, $J_{6exo,7endo}$ = 4.2 Hz. ^{13}C NMR (C_6D_6, 126 MHz): δ 10.1 (q, 3-CH$_2\underline{C}$H$_3$), 24.0 (t, C-6), 24.1 (q, 1-CH$_3$), 26.0 (t, 3-$\underline{C}$H$_2$CH$_3$), 34.3 (t, C-7), 68.6 (d, C-4), 75.3 (d, C-3), 83.0 (d, C-5), 105.4 (s, C-1) ppm. MS *m/z* (%): 172 (1, M$^+$), 144 (1), 143 (2), 130 (1), 129 (2), 125 (1), 115 (2), 114 (18), 113 (2), 112 (3), 102 (5), 101 (27), 100 (1), 99 (2), 97 (2), 96 (3), 95 (3), 89 (1), 88 (1), 87 (2), 86 (20), 85 (3), 84 (5), 83 (23), 82 (1), 81 (9), 73 (5), 72 (17), 71 (27), 70 (3), 69 (4), 61 (7), 60 (2), 59 (13), 58 (59), 57 (44), 56 (3), 55 (18), 54 (5), 53 (4), 45 (3), 44 (6), 43 (100), 42 (5), 41 (14), 39 (10). $C_9H_{16}O_3$ (172.23): Calcd: C, 62.77; H, 9.36. Found: C, 62.48; H 9.30.

7-(2,5,5-Trimethyl-1,3-dioxan-2-yl)-3-heptyn-2-ol (20). 3-Butyn-2-ol (280 mg, 4.0 mmol) dissolved in 5 mL of THF was added to a stirred suspension of $LiNH_2$ (200 mg, 8.8 mmol) in 30 mL of liquid ammonia. After stirring for 30 min at −33 °C, a solution of 2-(3-bromopropyl)-2,5,5-trimethyl-1,3-dioxane (**19**)[19,20] (500 mg, 2.0 mmol) in 5 mL of THF was added. The mixture was allowed to warm to 20 °C and was poured into a saturated NaCl solution (50 mL). The organic layer was separated and the aqueous layer was extracted with ether. The combined organic solutions were dried with Na_2SO_4 and concentrated. The residue was chromatographed over silica [50 g, *n*-hexane:ethyl acetate (2:1)] yielding 315 mg (13 mmol, 66%) of **20**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.90 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$), 1.37 (s, 3H, CH$_3$), 1.42 (d, $J_{1,2}$ = 6.6 Hz, 3H, 1-H), 1.60–1.68 (m, 2H, 6-H), 1.77–1.82 (m, 2H, 7-H), 2.24 (dt, $J_{5,6}$ = 6.8, $^4J_{5,2}$ = 1.8 Hz, 2H, 5-H), 3.43–3.47 (m, 2H), 3.53–3.57 (m, 2H), 4.50 (tq, $J_{2,1}$ = 6.6, $^4J_{2,5}$ = 1.8 Hz, 1H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ 18.9 (t, C-5), 20.5 (q), 22.5 (q), 22.6 (t, C-6), 22.8 (q), 24.8 (q, C-1), 29.9 (s), 37.7 (t, C-7), 58.6 (d, C-2), 70.4 (t, 2C), 82.6 (s), 84.4 (s), 98.8 (s) ppm. $C_{14}H_{24}O_3$ (240.34): Calcd: C, 69.96; H, 10.07. Found: C, 69.81; H, 10.32.

(1*R,1′*R**,5′*R**,7′*R**)-1-(5-Methyl-6,8-bicyclo[3.2.1]-oct-2-yl)ethanol, (1*R**,1′*R**,5′*R**,7′*R**)-12, and (1*S**,1′*R**,5′*R**,7′*R**)-1-(5-methyl-6,8-bicyclo[3.2.1]oct-2-yl)-ethanol, (1*S**,1′*R**,5′*R**,7′*R**)-12.** Hydrogenation of **20** (280 mg, 1.17 mmol) was performed as described for the preparation of (4*Z*)-**15**, using 20 mg of Lindlar catalyst and 40 μL of quinoline in 20 mL of *n*-heptane. Without purification, the resulting alcohol was submitted to epoxidation (325 mg 85% *m*-chloroperbenzoic acid, 1.6 mmol). Subsequent cyclization using a mixture of 0.1 mL 40% HF, acetonitrile (5 mL) and water (5 mL) followed by column chromatography [50 g silica, ethyl ether:*n*-pentane (2:1) afforded a mixture (ca. 1:1) of (1*S**,1′***R**,5′***R****,7′*R**)-**12** and (1*R**,1′*R**,5′*R**,7′*R**)-**12** (140 mg, 0.81 mmol, 69%).

(1*S,1′*R**,5′*R**,7′*R*)-1-(5-Methyl-6,8-bicyclo[3.2.1]-oct-2-yl)ethanol, (1*S**,1′*R**,5′*R**,7′*R**)-12.** ^{1}H NMR (CD_3CN, 500 MHz): δ 1.03 (d, 3H, 2′-H), 1.36 (s, 3H, 5′-CH$_3$), 1.44–1.48 (m, 1H, 2′-H$_{ax}$), 1.53–1.64 (m, 3H, 3′-H$_{eq}$, 4′-H$_{eq}$ and 4′-H$_{ax}$), 1.72 (dddd, 1H, 2′-H$_{ax}$), 1.79–1.87 (m, 1H, 3′-H$_{ax}$), 2.7 (br s, 1H, OH), 3.53 (quin, 1H, 1′-H), 3.76 (d, 1H, 7′-H), 4.23 (m, 1H, 1-H) ppm; $J_{1,2}$ = 6.4, $J_{1,7'}$ = 6.7, $J_{1',7'}$ = 0.5, $J_{1',2'ax}$ = 3.2, $J_{1',2'eq}$ = 3.1, $^4J_{1',3'eq}$ = 1.0, $J_{2'ax,2'eq}$ = 13.0, $J_{2'ax,3'ax}$ = 12.1, $J_{2'ax,3'eq}$ = 5.3Hz. ^{13}C NMR (CD_3CN, 126 MHz): δ 17.8 (t, C-3′), 18.6 (q, C-2), 25.0 (q, 5′-CH$_3$), 28.4 (t, C-2′), 35.5 (t, C-4′), 69.4 (d, C-1), 76.7 (d, C-1′), 84.3 (d, C-7′), 108.7 (s, C-5′) ppm. MS *m/z* (%): 172 (1), 157 (1), 143 (1), 131 (2), 130 (14), 129 (1), 128 (7), 127 (42), 126 (1), 121 (1), 115 (3), 113 (2), 112 (15), 111 (1), 109 (1), 101 (14), 100 (6), 99 (6), 98 (7), 97 (10), 95 (1), 94 (1), 93 (1), 88 (2), 87 (4), 86 (2), 85 (7), 84 (8), 83 (8), 82 (1), 81 (10), 79 (2), 71 (7), 70 (5), 69 (8), 68 (3), 67 (6), 61 (2), 59 (3), 58 (8), 57 (9), 56 (6), 55 (7), 53 (2), 45 (11), 44 (33), 43 (100), 42 (3), 41 (9), 39 (5).

(*E*)-2,8-Nonadien-4-ol (24). A solution of freshly distilled **23** (4.70 g, 67 mmol) in dry THF (80 mL) was added dropwise over a period of 30 min at −90 °C to a vigorously stirred Grignard-reagent prepared from 5-bromo-1-pentene (**22**) (10.0 g, 67 mmol) in THF (150

mL) under argon. After the addition was complete, the mixture was allowed to warm to 0 °C. It was then poured into a precooled saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with two 100 mL portions of ethyl ether. The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (50 mL), dried with Na_2SO_4 and concentrated in vacuo. The residue was distilled to yield 8.20 g (58.6 mmol, 87%) of **24** as a colorless oil; bp 97–89 °C/15 hPa. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.34–1.61 (m, 5 H, 5-H, 6-H and OH), 1.69 (ddd, $J_{1,2} = 6.5$, $^4J_{1,3} = 1.6$, $^5J_{1,4} = 0.6$ Hz, 3H, 1-H), 2.04–2.10 (m, 2H, 7-H), 4.00–4.06 (m, 1H, 4-H), 4.945 (ddt, $J_{9c,8} = 10.2$, $^2J_{9c,9t} = 2.0$, $^4J_{9c,7} = 1.2$Hz, 1H, 9-H_c), 5.015 (dq, $J_{9t,8} = 17.1$, $^2J_{9t,9c} = {}^4J_{9t,7} = 2.0$ Hz, 1H, 9-Ht), 5.48 (ddq, $J_{3,2} = 15.2$, $J_{3,4} = 7.1$, $^4J_{3,1} = 1.6$ Hz, 1H, 3-H), 5.65 (ddq, $J_{2,3} = 15.2$, $J_{2,1} = 6.5$, $^4J_{2,4} = 1.0$ Hz, 1H, 2-H), 5.80 (ddt, $J_{8,9t} = 17.1$, $J_{8,9c} = 10.2$, $J_{8,7} = 6.7$ Hz, 1H, 8-H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ 17.7 (q, C-1), 24.8 (t), 33.7 (t), 36.7 (t), 73.0 (d, C-4), 114.6 (t, C-9), 126.8 (d), 134.4 (d), 138.7 (d) ppm. $C_9H_{16}O$ (140.23): Calcd: C, 77.09; H, 11.50. Found: C, 76.88; H, 11.48.

(1*R*,2′*R*,3′*R*)-1-(3-Methyloxiran-2-yl)-5-hexen-1-ol, (1*R*, 2′*R*,3′*R*)-25.[17] Diisopropyl D-(−)-tartrate (2.67 g, 11.2 mmol) was added to a stirred suspension of molecular sieves (4 Å, 5 g) in dry CH_2Cl_2 (250 mL) under argon. After stirring for 15 min at room temperature, the mixture was cooled to −20 °C and 2.42 g (8.5 mmol) of $Ti(O^iPr)_4$ were added. Stirring was maintained for 1 h at −20 °C. Subsequently, 30 mmol of *t*-butyl hydroperoxide (5.4 mL of a 5.6 N solution in CH_2Cl_2) was added. After further 20 min at −20 °C, the mixture was cooled to −40 °C and a solution of freshly distilled **24** (6.2 g, 44.3 mmol) in 50 mL of CH_2Cl_2 was added dropwise over a period of 10 min. The reaction mixture was stirred for 20 h at −40 °C. It was then poured into an ice-cold solution of tartaric acid (4.5 g, 30 mmol) in water (100 mL). Work up was performed as described for the preparation of (1*S*,2′*S*,3′*S*)-**16**. Column chromatography [500 g silica, *n*-hexane:ethyl ether (1:1)] yielded 3.4 g of crude (1*R*,2′*R*,3′*R*)-**25**, which was rechromatographed [300 g silica, *n*-hexane:ethyl acetate (3:2)] to give 2.8 g (17.9 mmol, 81%) of (1*R*,2′*R*,3′*R*)-**25** as a colorless oil; $[\alpha]_D^{22} + 6.91$ (*c* 2.91 in $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 1.33 (d, $J_{3'\text{-}CH_3,3'} = 5.3$Hz, 3H, 3′-$CH_3$), 1.45–1.66 (m, 4H, 2-H and 3-H), 2.00–2.13 (m, 3H, OH and 4-H), 2.73 (dd, $J_{2',1} = 3.4$, $J_{2',3'} = 2.4$ Hz, 1H, 2′-H), 3.08 (dq, $J_{3',3'\text{-}CH_3} = 5.3$, $J_{3',2'} = 2.4$ Hz, 1H, 3′-H), 3.76–3.80 (m, 1H, 1-H), 4.97 (ddt, $J_{6c,5} = 10.2$, $J_{6c,6t} = 2.0$, $^4J_{6c,4} = 1.3$Hz, 1H, 6-H_c), 5.02 (dq, $J_{6t,5} = 17.1$, $J_{6t,6c} = {}^4J_{6t,4} = 2.0$ Hz, 1H, 6-H_t), 5.81 (ddt, $J_{5,6t} = 17.1$, $J_{5,6c} = 10.2$, $J_{5,4} = 6.6$ Hz, 1H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ 17.3 (q), 24.5 (t), 32.9 (t), 33.7 (t), 51.1 (d), 61.9 (d), 68.6 (d, C-1), 114.8 (t, C-6), 138.5 (d, C-5) ppm. $C_9H_{16}O_2$ (156.23): Calcd: C, 69.18; H, 10.32. Found: C, 69.00; H, 10.35.

(1*R*,1′*R*,5′*R*,7′*R*)-1-(5-Methyl-6,8-bicyclo[3.2.1]oct-2-yl)-ethanol, (1*R*,1′*R*,5′*R*,7′*R*)-12. A suspension of $PdCl_2$ (1.7 g, 9.6 mmol) and CuCl (4.95 g, 50 mmol) in 96% ethanol (40 mL) was vigorously stirred for 2 h at 50 °C under an oxygen atmosphere. The greenish solution was then cooled to 18 °C and a solution of (1*R*,2′*R*,3′*R*)-**25** (1.50 g, 9,6 mmol) in 20 mL of 96% ethanol was added dropwise within 10 min. After the addition was complete, stirring was maintained for 10 min. Subsequently, the mixture was poured into 200 mL of a saturated aqueous NaCl solution and the resulting mixture was extracted with three 100 mL portions of ethyl acetate. The combined extracts were washed with saturated NaCl solution (50 mL), dried with Na_2SO_4 and concentrated. The residue was dissolved in 50 mL of CH_2Cl_2 and 50 mg of *p*-toluenesulfonic acid was added. After stirring for 1 h at 20 °C, the mixture was washed with three 20 mL portions of a NaCl-saturated aqueous 5% K_2CO_3 solution. The aqueous phase was extracted with ether (50 mL) and the combined organic solutions were dried with Na_2SO_4 and concentrated. Column chromatography of the residue [80 g silica, *n*-hexane:ethyl acetate (5:2)] yielded 1.04 g (6.05 mmol, 63%) of (1*R*,1′*R*,5′*R*,7′*R*)-**12** as white needles; mp 29 °C; $[\alpha]_D^{21} + 56.7$ (*c* 0.8 in $CHCl_3$). When less than 1 equivalent $PdCl_2$ was used in this oxidation, a product of very low purity was obtained. This is probably due to double-bond isomerization in **25** catalyzed by Pd^0 species.

Determination of the optical purity of (1*R*, 1′*R*,5′R,7′*R*)-**12** by chiral GC: The four stereoisomers of *exo*-**12** were separated on the cyclodextrin column, providing $t_R = 15.61$ min for (1*R*,1′*R*,5′*R*,7′*R*)-**12**, $t_R = 15.70$ min for (1*S*,1′*S*,5′*S*,7′*S*)-**12**, $t_R = 13.64$ and $t_R = 14.20$ for the (1*S**,1′*R**,5′*R**,7′*R**)-pair. The ee of (1*R*,1′*R*,5′*R*,7′*R*)-**12** was estimated to be 96%. ^1H NMR (CD_3CN, 500 MHz): δ 1.11 (d, 3H, 2-H), 1.32 (s, 3H, 5′-CH_3), 1.45 (m, 1H, 2′-H_{eq}), 1.52–1.62 (m, 3H, 3′-H_{eq}, 4′-H_{eq} and 4′-H_{ax}), 1.73 (ddt, 1H, 2′-H_{ax}), 1.79–1.88 (m, 1H, 3′-H_{ax}), 2.69 (d, 1H, OH), 3.43 (m, 1H, 1-H), 3.66 (d, 1H, 7′-H), 4.36 (m, 1H, 1′-H) ppm; $J_{1,2} = 6.2$, $J_{7',1} = 7.2$, $J_{1,OH} = 5.3$, $J_{7',1'} < 1$, $J_{1',2'ax} = 3.2$, $J_{1',2'eq} = 3.1$, $^4J_{1',3'eq} = 1.1$, $J_{2'eq,2'ax} = 13.1$, $J_{2'ax,3'ax} = 12.8$, $J_{2'ax3'eq} = 4.6$, $J_{2'eq,3'ax} = 5.5$ Hz. ^{13}C NMR (CD_3CN, 101 MHz): δ 17.9 (t, C-3′), 19.7 (q, C-2), 25.0 (q, 5′-CH_3), 28.5 (t, C-2′), 35.5 (t, C-4′), 69.1 (d, C-1), 76.8 (d, C-1′), 84.5 (d, C-7′), 108.4 (s, C-5′) ppm. MS *m/z* (%): 172 (1), 157 (1), 143 (1), 131 (2), 130 (19), 129 (1), 128 (7), 127 (45), 126 (1), 121 (1), 115 (3), 113 (2), 112 (15), 111 (1), 109 (1), 101 (14), 100 (6), 99 (6), 98 (7), 97 (10), 95 (1), 94 (1), 93 (1), 88 (2), 87 (4), 86 (2), 85 (7), 84 (9), 83 (10), 82 (1), 81 (10), 79 (2), 71 (7), 70 (5), 69 (8), 68 (3), 67 (6), 61 (2), 59 (3), 58 (8), 57 (9), 56 (6), 55 (7), 53 (2), 45 (11), 44 (33), 43 (100), 42 (3), 41 (9), 39 (5). $C_9H_{16}O_3$ (172.23): Calcd: C, 62.77; H, 9.36. Found: C, 62.48; H, 9.35.

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