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SYNTHESIS OF THE ELEUTHESIDE CORE FROM (+)-δ-CADINOL: CONSTRUCTION OF SIDE CHAINS ON THE MENTHANE RING

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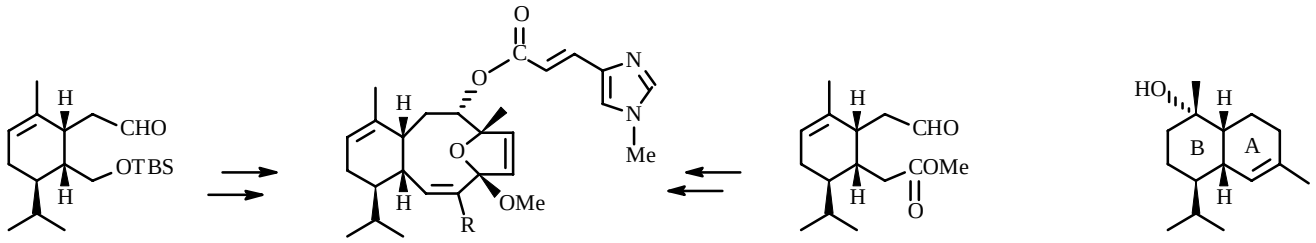
Methods for allylic oxygenation of (+)-δ-cadinol by SeO_2 have been developed to study approaches to the formation of the eleutheside core from it. Diasteromeric alcohols and the product of their 1,4-oxacyclization, which is transformed into a bicyclic derivative containing the required functional groups to study the final cyclization into the eleutheside core, were prepared. The α-hydroxy derivative was converted after benzylation and ozonolysis into a mixed acetal, a convenient compound for performing the synthesis via an alternate route.

Key words: sesquiterpenoids, (+)-δ-cadinol, allylic oxidation, acetal, ozonolysis, chelate control, Knoevenagel reaction.

Eleutherobin, a glycosylated diterpenoid with an unusual structure, was isolated from the extract of soft coral (*Eleutherobia* sp.), which possesses extraordinary cytotoxic activity [1]. This compound is one of the closest taxol analogs with respect to mechanism, activity, and selectivity of biological action [2]. Eleutherobin together with the recently discovered sarcodictyins [3] and valdivones [4] form the new structurally related group of eleuthesides **1**, which characteristically have the 4,7-oxaeunicellane tricyclic core [5]. The scarcity of eleuthesides in nature prompted studies of their chemical synthesis. Schemes for preparing eleutherobin and sarcodictyins are based on the use of chiral matrices **2** and **3**, which are prepared from the monoterpenoids (+)-carvone [6] and (-)-α-phellandrene [7] in nine and five steps, respectively. They differ in the order of glycosylation and the method of generating the tricyclic core.



Eleutherobin: R = –CH$_2$–O, OAc, OH, O, OH

Sarcodictyins:
A, R = COOMe
B, R = COOEt

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TABLE 1. Allylic Oxidation of (+)-δ-Cadinol (**4**) by SeO_2

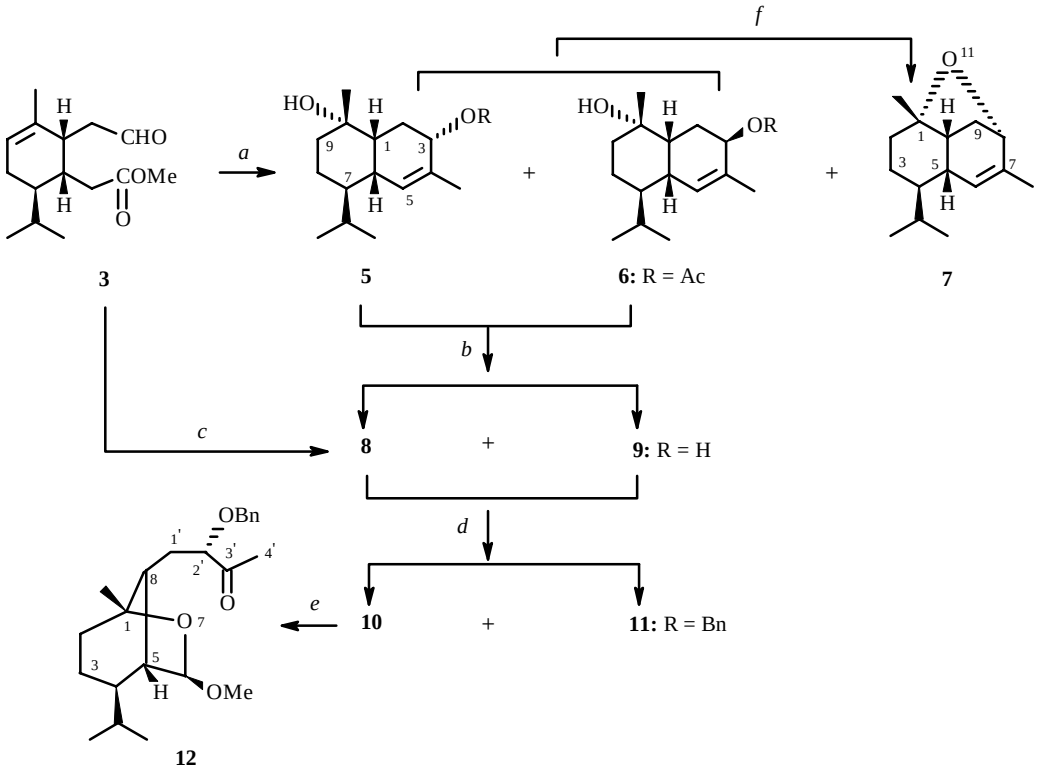
Solvent	T, °C	**8** + **9**, %	**7**, %	**8** : **9***, %	
DMSO	100	74	-	5	95
t-BuOH	80	77	-	-	>99
Ac_2O	0	55**	30	20	80
Ac_2O	70	71**	13	43	57

*According to ^1H NMR.

**Overall yield, including hydrolysis of acetates by MeONa—MeOH

We selected another higher homolog, (+)-δ-cadinol (**4**), in attempts to form the central core [8]. The structure of this sesquiterpenoid, which is isolated from resin of Siberian pine (*Pinus sibirica* R. Mayr), is very well known and firmly established [9]. (+)-δ-Cadinol contains a menthane ring that is *cis*-fused to a cyclohexene ring. The absolute configurations of the asymmetric centers correspond to the stereochemical structure of the eleutheside C-1, C-10, and C-14 atoms. The route for the transformation into the chiral molecule is obvious. Allylic hydroxylation and opening of ring A by cleavage of the double bond with differentiation of the resulting functional groups. It should be noted that a double bond can be easily generated in the menthane ring [10]. Thus, the synthetic scheme consists of two steps. These are construction of the side chains on the menthane ring and final cyclization into the 4,7-oxaeunicellane core.

Information on the stereochemistry of addition to the double bond of (+)-δ-cadinol is inconclusive. However, it seems certain that the steroselectivity of the side reactions is controlled by its bicyclic structure, which directs attack primarily from the *exo*-side [10, 11]. An analogous result, i.e., preferential formation of the β-isomer, should probably be expected for generation of the asymmetric center in the diastereotopic allylic position. Nevertheless, the use of transformations occurring under conditions that minimize steric control (including by changing the conformation) or that rearrange the initially formed intermediates provides some hope that the stereoselectivity of the process can be influenced to a certain extent [12].



a. SeO_2, Ac_2O, 70°C; *b*. MeONa - MeOH; *c*. DMSO (or *t*-BuOH), SeO_2; *d*. DMSO/NaH, BnCl; *e*. O_3, MeOH, –78° C, Me_2S, *p*-TsOH; *f*. C_6H_6, *p*-TsOH, boiling.

Allylic oxygenation of olefins by SeO_2 is one of the transformations that includes rearrangement of the initial intermediates. As it turned out, the reaction proceeds stereoselectively relative to the β-alcohol **9**. Nevertheless, we were able to obtain a mixture containing acetates **5** and **6** by varying the reaction conditions. Separation of ether **7** and hydrolysis of the acetates gave a mixture of α- and β-alcohols **8** and **9** (Table 1).

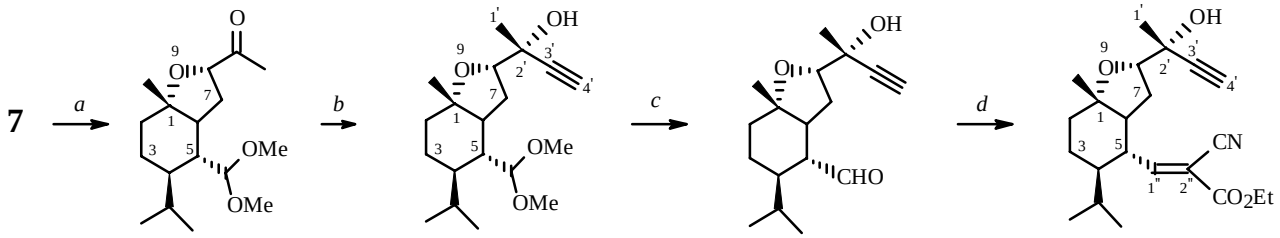
The alcohols **8** and **9** can be isolated as a crystalline mixture or by chromatography after blocking the hydroxyls as benzylates **10** and **11**.

A strong-field shift of the signals for β-isomer **9** in the ^{13}C NMR spectra owing to *syn*-coupling with C-3 and C-1 provides a criterion for distinguishing epimeric **8** and **9**. The equatorial orientation of H-3 in the ^1H NMR spectrum of this isomer is confirmed by the small spin—spin coupling constant (SSCC) $J_{2\text{-}3}$ = 4.4 Hz at 3.94 ppm, in contrast with the axial location of this proton with $J_{2\text{-}3}$ = 7.5 Hz at 4.03 ppm in the α-isomer **8**. It should be noted that the chemical shift of H-7 in the β-isomer is 1.82 ppm. Comparison with the α-isomer (1.37 ppm) indicates that the equilibrium shifts toward the conformer with an axial isopropyl group.

Ozonolysis of the double bond of α-benzyloxy derivative **10** formed only one of the possible ethers, the mixed acetal **12**. The configuration of the new asymmetric center of **12** was established using ^1H NMR spectra. Thus, the singlet for H-6 at 4.70 ppm indicates that the torsion angle H-5—C-5—C-6—H-6 is close to 90°. This occurs only if this center has the R-configuration.

A side "self-protected" product of allylic oxidation is ether **7**, which is a convenient model for studying the conditions for forming the tricyclic system of the eleutheside core. Furthermore, it could be a key intermediate for resolving the problem of opening the tetrahydrofuran ring. Our efforts in this direction were to optimize its production. Thus, boiling the product mixture from allylic oxygenation in benzene containing catalytic amounts of *p*-TsOH produced **7** in 73% yield. The formation of **7** from both isomers indicates that the process occurs with generation of the allyl cation. The transformation of diols **8** and **9** into **7** is accompanied by locking of the $^9H_{10}$ conformation in a rigid tricyclic system. The torsion angle H-8—C-8—C-9—H^{ax}-9 becomes close to 90°. This is evident in the ^1H NMR spectrum from the coalescence of H-8 into a doublet at 3.94 ppm with $J_{8\text{-}9}^{eq}$ = 5.4 Hz. In the ^{13}C NMR spectra, the reaction is accompanied by a weak-field shift of the C-1 and C-8 signals to 81.6 and 76.6.

Ozonolysis of the double bond of **7** and reduction of the ozonide with simultaneous exposure of the mixture to acid-catalysis conditions at tempertures below -10°C led to selective formation of the acetal of the aldehyde to give chiral **13**.



13 **14** **15** **16**

a. O_3, MeOH, -78°C, Me_2S, *p*-TsOH; *b*. CH≡CMgBr, THF, 0° C;
c. H^+; *i*-PrOH-$CHCl_3$, SiO_2; *d*. $CNCH_2CO_2Et$, EtOH, β-alanine.

1,2-Addition of ethynylmagnesium bromide to **13** occurs stereospecifically becuase of α-chelate control and produces α-hydroxy derivative **14**. Hydrolysis of the dimethoxyacetal protecting group and addition of cyanoacetic ester in a Knoevenagel reaction give enyne **16** in 46% yield in two steps. It should be noted that a doublet characteristic of H-1″ appears in the ^1H NMR spectra of **13-16**. The significant increase in the SSCC to ~11.0 Hz at 7.51 ppm in the spectrum of **16** indicates that the torsion angle H-1″—C-1″—C-5—H-5 is close to 180°. This occurs if the position of the terminal substituents of the double bond is perpendicular to the plane of the drawing.

Thus, the stable compound **16** that is transformed from (+)-δ-cadinol has the required functional groups to proceed to the next step in which the conditions for cyclization into the 4,7-oxaeunicellane core will be studied.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were taken on a Bruker AM 300 instrument at working frequencies 300.13 for ^{1}H and 75.47 MHz for ^{13}C in $CDCl_3$. Signals of protons and the corresponding C atoms were assigned based on C—H correlation spectra (CH-corr.). Mass spectra were taken in an MX-1320 instrument (EI, 70 eV). Optical rotation angles were measured on a Perkin—Elmer 141 polarimeter. Analytical TLC was performed on Sorbfil PTSKh-AF-A plates (ZAO Sorbpolimer, Krasnodar). Compounds were detected by spraying with ethanolic phosphomolybdic acid (25%) with subsequent heating for 5 min at 100-110°C. Synthesis products were isolated by column chromatography over L40/100 (Chemapol, Czech. Rep.) silica gel using 30-100 g per gram of compound and solvent systems with R_f values given in each instance. We used (+)-δ-cadinol with mp 137.8°C and optical rotation $[\alpha]_D^{20}$ +100.3° (*c* 1.0, $CHCl_3$). Solutions of ethyl- and ethynylmagnesium bromide were prepared according to the literature methods [13, 14].

Analytical data for **6**, **7**, **8**, **10**, **12**, and **13** corresponded to those calculated.

Allylic Oxidation of (+)-δ-Cadinol by SeO_2.

a. In Acetic Anhydride

A solution of (+)-δ-cadinol (**4**, 1 g, 4.5 mmole) in Ac_2O (25 mL) at 70°C was treated with a solution of SeO_2 (0.45 g, 4.5 mmole) in H_2O (0.5 mL). When the reaction was finished (TLC monitoring), the reaction mixture was diluted with EtOAc (20 mL), poured onto ice, and filtered. The aqueous layer was extracted with EtOAc (3×10 mL). The extracts were washed with saturated $NaHCO_3$ solution (5×10 mL) and dried over $MgSO_4$. The solvent was distilled in a rotary evaporator. The solid was chromatographed to give a mixture of acetates **5** and **6** (0.29 g), β-acetate **6** (0.31 g, overall yield 74%), and 1,4-epoxide **7** (0.13 g, 13%).

1R,3R,6S,7R,10S-3-Acetyloxy-7-isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-en-10-ol (6). Mp 134-136°C (Et_2O), R_f 0.35 (petroleum ether—EtOAc, 3:1), $C_{17}H_{28}O_3$, $[\alpha]_D^{26}$ +138.1° (*c* 1.0, $CHCl_3$).

PMR spectrum (δ, ppm, J/Hz): 0.81 [3H, d, J = 6.9, $CH_3(C\underline{H}_3)CH$], 0.88 [3H, d, J = 6.9, $C\underline{H}_3(CH_3)CH$], 1.10 (1H, m, H^{ax}-8), 1.30 (1H, m, H-7), 1.30 (3H, s, CH_3C-10), 1.50 (3H, m, H^{eq}-8 and CH_2-9), 1.68 (3H, s, CH_3C-4), 1.72 (1H, dd, $J_{2\text{-}3}^{ax}$ = 3.4, J_{gem} = 14.9, H^{ax}-2), 1.83 (1H, m, H-1), 1.94 (1H, dqq, $J_{Me2CH\text{-}7}$ = 3.4, $J_{Me2CH\text{-}Me}$ = 6.9, $Me_2C\underline{H}$), 2.05-2.18 (2H, m, H^{eq}-2, H-6), 2.10 (3H, s, CH_3), 5.20 (1H, d, $J_{3\text{-}2}^{ax}$ = 3.4, $J_{3\text{-}2}^{eq}$ = 0, H-3), 5.69 (1H, d, $J_{5\text{-}6}$ = 5.3, H-5). ^{13}C NMR spectrum (δ, ppm): 18.99 (CH_3), 21.03 (CH_3), 21.22 (CH_3), 21.40 (C-8), 21.50 (CH_3), 23.70 (C-2), 26.37 ($Me_2\underline{C}$), 27.37 (CH_3), 34.24 (C-9), 37.50 (C-6), 38.66 (C-1), 44.22 (C-7), 71.45 (C-10), 73.83 (C-3), 127.40 (C-5), 133.04 (C-4), 170.81 (C=O).

1R,3S,6S,7R,10S-3-Acetyloxy-7-isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-en-10-ol (5). PMR spectrum (δ, ppm, J/Hz): chemical shifts of protons coincide with those of the 3R-epimer with the exception of 5.30 (1H, dd, $J_{3\text{-}2}^{ax}$ = 9.2, $J_{3\text{-}2}^{eq}$ = 4.6, H-3) and 5.82 (1H, d, $J_{5\text{-}6}$ = 5.6, H-5).

^{13}C NMR spectrum (δ, ppm): 15.25 (CH_3), 20.70 (CH_3), 21.29 (C-8), 21.41 (CH_3), 21.52 (CH_3), 25.33 (C-2), 27.82 (CH_3), 26.73 ($Me_2\underline{C}$), 34.93 (C-9), 36.63 (C-6), 40.09 (C-1), 42.54 (C-7), 70.34 (C-3), 71.68 (C-10), 131.17 (C-5), 131.66 (C-4).

1S,4R,5S,8S,10R-4-Isopropyl-1,7-dimethyl-11-oxatricyclo[6.2.1.0^{5,10}]undec-6-ene (7). Oil, R_f 0.87 (petroleum ether—EtOAc, 3:1), $C_{15}H_{24}O$, $[\alpha]_D^{26}$ -58.0° (*c* 1.0, $CHCl_3$).

PMR spectrum (δ, ppm, J/Hz): 0.83 [3H, d, J = 6.5, $C\underline{H}_3(CH_3)CH$], 0.86 [3H, d, J = 6.5, $CH_3(C\underline{H}_3)CH$], 1.02 (1H, m, H-4), 1.08 (3H, s, CH_3C-1), 1.28 (1H, m, H^{ax}-3), 1.40 (1H, m, H^{ax}-2), 1.53 (1H, m, H^{eq}-3), 1.62 (2H, m, H^{ax}-9, $Me_2C\underline{H}$), 1.65 (3H, d, $J_{Me\text{-}6}$ = 1.7, CH_3C-7), 1.72 (1H, m, H^{eq}-2), 1.90 (1H, ddd, $J_{9\text{-}10}^{eq}$ = 5.0, $J_{10\text{-}5}$ = 5.4, and $J_{10\text{-}9}^{ax}$ = 8.0, H-10), 2.25 (1H, ddd, $J_{9\text{-}10}^{eq}$ = 5.0, $J_{9\text{-}8}^{eq}$ = 5.4, and J_{gem} = 10.8, H^{eq}-9), 2.50 (1H, m, H-5), 3.94 (1H, d, J = 5.4, H-8), 4.88 (1H, m, H-6). ^{13}C NMR spectrum (δ, ppm): 19.33 (C-3), 20.83 ($2CH_3$), 20.92 (CH_3), 25.42 $Me_2\underline{C}$), 30.19 (CH_3), 30.51 (C-2), 35.42 (C-9), 38.50 (C-10), 38.90 (C-5), 44.98 (C-4), 76.58 (C-8), 81.60 (C-1), 127.26 (C-6), 140.19 (C-7). Mass spectrum (EI), *m/z* (I_{rel}, %): 220 (M^+, 25).

Hydrolysis of Acetates 5 and 6. A solution of the mixed acetates **5** and **6** (0.26 g, 0.91 mmole) that were obtained by the above method and from which ether **7** had been removed in MeOH (5 mL) was treated with NaOMe (0.05 g, 1 mmole) in MeOH (10 mL). After the reaction was finished (TLC monitoring) the mixture was neutralized by adding HCl (3% solution). The MeOH was removed at reduced pressure. The solid was extracted with EtOAc (3×10 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated in a rotary evaporator. The solid was chromatographed to produce a mixture of diastereomers **8** and **9** (0.18 g, 85%). The α-epimer was isolated from the mixture by crystallization (diethylether—pentane, 5:1) or, like the β-epimer, by chromatography.

1R,3S,6S,7R,10S-7-Isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-en-3,10-diol (8). Mp 102-103°C (Et_2O), R_f 0.28 (EtOAc), $C_{15}H_{26}O_2$, $[\alpha]_C^{26}$ +49.1° (*c* 1.0, $CHCl_3$).

PMR spectrum (δ, ppm, J/Hz): 0.81 [3H, d, J = 7.0, C<u>H</u>$_3$(CH$_3$)CH], 0.88 [3H, d, J = 7.0, CH$_3$(C<u>H</u>$_3$)CH], 1.20 (1H, m, H^{ax}-9), 1.25 (3H, s, CH_3C-10), 1.37 (1H, m, H-7), 1.50 (3H, m, CH_3-8 and H^{eq}-9), 1.67 (1H, dd, J_{gem} = 9.5, $J_{2\text{-}3}^{eq}$ = 5.0, $J_{2\text{-}1}^{eq}$ was not determined*, H^{eq}-2), 1.73 (1H, m, H-1), 1.75 (3H, s, CH_3C-4), 1.88 (1H, dqq, $J_{Me2CH\text{-}7}$ = 4.5, $J_{Me2CH\text{-}Me}$ = 7.0, Me_2C<u>H</u>), 2.05 (1H, m, $J_{6\text{-}5}$ = 5.0, H-6), 2.24 (1H, dd, J_{gem} = 9.5, $J_{2\text{-}3}^{ax}$ = 7.5, H^{ax}-2), 2.50 (1H, br.s, OH), 2.56 (1H, br.s, OH), 4.03 (1H, dd, $J_{3\text{-}2}^{eq}$ = 5.0, $J_{3\text{-}2}^{ax}$ = 7.5, H-3), 5.54 (1H, qd, $J_{5\text{-}Me}$ = 1.5, $J_{5\text{-}6}$ = 5.0, H-5). ^{13}C NMR spectrum (δ, ppm): 16.22 (CH_3), 19.62 (CH_3), 21.15 (C-8), 21.70 (CH_3), 26.47 (Me_2<u>C</u>), 27.74 (CH_3), 29.80 (C-2), 35.13 (C-9), 37.18 (C-6), 43.32 (C-7), 44.40 (C-1), 70.72 (C-3), 72.07 (C-10), 128.37 (C-5), 137.29 (C-4).

1R,3R,6S,7R,10S-7-Isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-en-3,10-diol (9). Mp 69-71°C (Et_2O), R_f 0.26 (EtOAc), $[\alpha]_D^{22}$ +93° (*c* 1.0, $CHCl_3$).

PMR spectrum (δ, ppm, J/Hz): 0.78 [3H, d, J = 7.0, C<u>H</u>$_3$(CH$_3$)CH], 0.82 [3H, d, J = 7.0, CH$_3$(C<u>H</u>$_3$)CH], 1.05 (1H, m, H-9), 1.22 (3H, s, CH_3C-10), 1.27 (1H, m, H^{ax}-8), 1.42 (1H, m, H^{eq}-9), 1.47 (1H, m, H^{eq}-8), 1.68 (1H, td, $J_{2\text{-}3}^{ax}$ = 4.4, $J_{2\text{-}1}^{ax}$ = 4.4, J_{gem} = 10.1, H_{ax}-2), 1.72 (1H, d, $J_{Me\text{-}5}$ = 1.5, CH_3C-4), 1.78 (1H, m, $J_{2\text{-}3}^{eq}$ = 1.7, $J_{2\text{-}1}^{eq}$ was not determined, J_{gem} = 10.1, H^{eq}-2), 1.82 (1H, m, H-7), 1.87 (1H, dqq, $J_{Me2CH\text{-}7}$ = 3.2, $J_{Me2CH\text{-}Me}$ = 7.0, Me_2C<u>H</u>), 1.95 (1H, m, H-1), 2.0 (1H, m, H-6), 3.94 (1H, dd, $J_{3\text{-}2}^{eq}$ = 1.7, $J_{3\text{-}2}^{ax}$ = 4.4, H-3), 5.65 (1H, qd, $J_{5\text{-}Me}$ = 1.5, $J_{5\text{-}6}$ = 5.6, H-5). ^{13}C NMR spectrum (δ, ppm): 15.36 (CH_3), 21.02 (CH_3), 21.33 (C-8), 21.53 (CH_3), 26.80 (C-13), 28.01 (C-2), 28.06 (CH_3), 34.59 (C-9), 36.97 (C-6), 39.62 (C-7), 42.56 (C-1), 68.36 (C-3), 71.77 (C-10), 129.02 (C-5), 134.70 (C-4).

b. In DMSO

(+)-*δ*-Cadinol was oxidized at 100°C by a procedure analogous to that above using DMSO as the solvent. After the reaction was finished (TLC monitoring), the reaction mixture was diluted with saturated NaCl solution (5 mL) and extracted with EtOAc (3×5 mL). The extracts were dried over $MgSO_4$. The solvent was removed in a rotary evaporator. The solid was chromatographed to give a mixture of diastereomeric **8** and **9** in 74% yield and a 5:95 ratio.

c. In *t*-butanol

(+)-*δ*-Cadinol was oxidized at 80°C by a procedure analogous to that above using *t*-BuOH as the solvent to give **9** in 77% yield.

1R,3S,6S,7R,10S-3-Benzyloxy-7-isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-en-10-ol (10) and 1R,3R,6S,7R,10S-3-benzyloxy-7-isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-en-10-ol (11). A solution of dimsyl sodium that was prepared by adding NaH (0.05 g, 1.1 mmole) to DMSO (5 mL) under Ar was added dropwise to a solution of a mixture of **8** and **9** (0.13 g, 0.54 mmole, 43:57 ratio) in DMSO (5 mL). The reaction mixture was stirred at room temperature for 30 min and treated with BnCl (0.13 mL, 1.1 mmole). After the reaction was finished (TLC monitoring), the mixture was poured into icewater (10 mL) and extracted with EtOAc (3×10 mL). The extracts were combined, dried over $MgSO_4$, and evaporated in a rotary evaporator. The solid was chromatographed to give **10** (0.07 g, 40%) and **11** (0.1 g, 54%).

***α*-Epimer 10.** Mp 97-99°C (Et_2O), R_f 0.30 (hexane—EtOAc, 7:1), $C_{22}H_{32}O_2$, $[\alpha]_D^{22}$ +54.6° (*c* 1.0, $CHCl_3$).

PMR spectrum (δ, ppm, J/Hz): 0.82 [3H, d, J = 6.9, C<u>H</u>$_3$(CH$_3$)CH], 0.9 [3H, d, J = 6.9, CH$_3$(C<u>H</u>$_3$)CH], 1.15 (1H, ddd, J = 3.4, J = 4.0, and J = 11.2, H-8), 1.28 (3H, s, CH_3C-10), 1.48 (1H, m, J = 3.0, H-7), 1.50 (3H, m, CH_2-9, H-8), 1.68 (1H, m, H-1), 1.78 (3H, s, CH_3C-4), 1.98 (1H, dqq, J = 3.0 and J = 6.9, <u>H</u>CMe_2), 2.05 (1H, m, H-6), 2.30 (1H, m, J_{gem} = 10.0, H-2), 2.46 (1H, ddd, J = 1.0, J = 6.3, and J_{gem} = 10.0, H-2), 3.96 (1H, dd, J = 6.3 and J = 8.4, H-3), 4.51 (1H, d, J = 11.5, OC<u>H</u>$_2$Ph), 4.70 (1H, dd, J_{gem} = 11.5 and J = 10.4, OC<u>H</u>$_2$Ph), 5.67 (1H, d, J = 5.4, H-5), 7.38 (5H, m, Ph). ^{13}C NMR spectrum (δ, ppm): 15.24 (CH_3), 19.76 (CH_3), 21.32 (C-8), 21.46 (CH_3), 24.80 (C-2), 26.32 (CH_3), 27.68 (H<u>C</u>Me_2), 35.06 (C-9), 36.88 (C-6), 43.68 (C-7), 44.10 (C-1), 70.42 (O<u>C</u>H$_2$Ph), 71.83 (C-10), 78.22 (C-3), 128.80 (C-5), 135.48 (C-4), 127.35, 127.66, 128.33, 138.69 (Ph).

***β*-Epimer 11.** Oil, R_f 0.28 (hexane—EtOAc, 7:1), $[\alpha]_D^{20}$ +42.3° (*c* 1.0, $CHCl_3$).

PMR spectrum (δ, ppm, J/Hz): 0.82 [3H, d, J = 6.9, C<u>H</u>$_3$(CH$_3$)CH], 0.90 [3H, d, J = 6.9, CH$_3$(C<u>H</u>$_3$)CH], 1.10 (1H, m, H-8), 1.28 (3H, s, CH_3C-10), 1.48 (1H, m, H-7), 1.50 (3H, m, CH_2-9, H-8), 1.58 (1H, m, H-1), 1.78 (3H, s, CH_3C-4), 1.92 (1H, m, <u>H</u>CMe_2), 1.94 (1H, dd, J = 2.9, J_{gem} = 14.1, H^{ax}-2), 2.05 (1H, m, H-6), 2.28 (1H, d, J_{gem} = 14.1, H^{eq}-2), 3.72 (1H, d, J = 2.9, H-3), 4.51 (1H, d, J = 12.0, OC<u>H</u>$_2$Ph), 4.70 (1H, d, J = 12.0, OC<u>H</u>$_2$Ph), 5.75 (1H, d, J = 5.1, H-5), 7.38 (5H, m, Ph). ^{13}C NMR spectrum (δ, ppm): 15.39 (CH_3), 21.26 (CH_3), 21.39 (C-8), 24.63 (CH_3), 23.08 (C-2), 26.80 (CH_3), 28.16 (H<u>C</u>Me_2), 34.68

*$J_{2\text{-}1}^{eq}$ could not be determined by double resonance because of signal overlap.

(C-9), 36.92 (C-6), 39.82 (C-7), 42.69 (C-1), 71.26 (O<u>C</u>H_2Ph), 71.86 (C-10), 75.61 (C-3), 129.71 (C-5), 127.50, 127.66, 128.09, 128.28, 133.52 (Ph), 139.22 (C-4).

1R,2′S,4R,5R,6R,8R-8-(2′-Benzyloxy-3′-oxobutyl)-4-isopropyl-1-methyl-6-methoxy-7-oxabicyclo[3.2.1^{1,5}]octane (12). An ozone-oxygen mixture was passed through a solution of **10** (0.25 g, 0.71 mmole) in MeOH (20 mL) at -78°C until the starting material disappeared (TLC monitoring). The solution was purged with Ar, treated with Me_2S (0.07 g, 0.9 mmole) and *p*-TsOH (0.01 g) and held at -10°C for 72 h. The solid was removed. The solid was chromatographed to give **12** (0.21 g, 72%). Oil, R_f 0.39 (petroleum ether—EtOAc, 3:1), $C_{23}H_{34}O_4$, $[\alpha]_D^{20}$ -55.0° (*c* 1.0, $CHCl_3$).

PMR spectrum (δ, ppm, J/Hz): 0.80 [3H, d, J = 6.8, C<u>H</u>$_3$(CH$_3$)CH], 0.87 [3H, d, J = 6.8, CH$_3$(C<u>H</u>$_3$)CH], 1.18 (3H, s, CH$_3$C-1), 1.25 (1H, m, H-4), 1.35-1.45 (3H, m, CH$_2$-2 and H-8), 1.50-1.62 (3H, m, Me$_2$C<u>H</u>, CH$_2$-3), 1.75 (1H, ddd, $J_{1'\text{-}2}$ = 2.6, $J_{1'\text{-}8}$ = 9.6, J_{gem} = 11.0, H^a-1′), 2.05 (1H, ddd, $J_{1'\text{-}8}$ = 3.8, $J_{1'\text{-}2'}$ = 9.9, J_{gem} = 11.0, H^b-1′), 2.12 (3H, s, CH$_3$C-3′), 2.40 (1H, d, $J_{5\text{-}8}$ = 3.4, H-5), 3.30 (3H, s, OCH$_3$), 3.92 (1H, dd, $J_{2'\text{-}1'}{}^a$ = 2.6, $J_{2'\text{-}1'}{}^b$ = 9.9, H-2′), 4.30 (1H, d, J_{gem} = 10.8, C<u>H</u>$_2$Ph), 4.53 (1H, d, J_{gem} = 10.8, C<u>H</u>$_2$Ph), 4.70 (1H, s, $J_{5\text{-}6}$ = 0, H-6), 7.30 (5H, m, Ph). ^{13}C NMR spectrum (δ, ppm): 20.65 (CH$_3$), 22.03 (CH$_3$), 22.18 (CH$_3$), 22.29 (C-3), 25.45 (CH$_3$), 27.61 (<u>C</u>Me$_2$), 30.60 (C-2), 36.65 (C-1′), 40.28 (C-4), 43.35 (C-5), 48.03 (C-8), 54.71 (OCH$_3$), 72.02 (OCH$_2$Ph), 83.29 (C-2′), 86.22 (C-1), 109.22 (C-6), 127.84, 127.95, 128.02, 128.20, 128.37, 137.57 (Ph), 204.32 (C-3′).

1S,4R,5R,6R,8S-8-Acetyl-4-isopropyl-1-methyl-5-dimethoxymethyl-9-oxabicyclo[4.3.0^{1,6}]nonane (13). Compound **7** (0.22 g, 1 mmole) gave **13** (0.22 g, 72%) by the method described above. Oil, R_f 0.34 (petroleum ether—EtOAc, 3:1), $C_{17}H_{30}O_4$, $[\alpha]_D^{26}$ +19.4° (*c* 1.0, $CHCl_3$).

PMR spectrum (δ, ppm, J/Hz): 0.72 [3H, d, J = 7.0, C<u>H</u>$_3$(CH$_3$)CH], 0.83 [3H, d, J = 7.0, CH$_3$(C<u>H</u>$_3$)CH], 1.08-1.20 (3H, m, CH), 1.25 (3H, s, CH$_3$C-1), 1.38 (1H, m, CH), 1.43-1.58 (3H, m, CH), 1.78 (2H, m, CH$_2$), 2.12 (3H, s, CH$_3$), 2.20 (1H, m, CH), 3.33 (6H, s, OCH$_3$), 4.23 [1H, d, $J_{1'\text{-}5}$ = 3.5, C<u>H</u>(OMe)$_2$], 4.35 (1H, m, H-8). ^{13}C NMR spectrum (δ, ppm): 15.14 (CH$_3$), 21.55 (CH$_3$), 21.81 (C-3), 24.55 (CH$_3$), 26.18 (CH$_3$), 26.23 [<u>C</u>(Me)$_2$], 32.06 (C-7), 34.55 (C-2), 37.47 (C-6), 39.95 (C-5), 44.34 (C-4), 56.08 (OCH$_3$), 56.47 (OCH$_3$), 82.61 (C-8), 83.48 (C-1), 107.09 [<u>C</u>(OMe)$_2$], 210.94 (C=O′). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 298 $[M]^+$ (37).

1S,1′R,4R,5R,6R,8S-8-(2′-Hydroxybut-3′-yn-2′-yl)-4-isopropyl-1-methyl-5-dimethoxymethyl-9-oxabicyclo[4.3.0]nonane (14). A solution of HC≡CMgBr (1.92 mmole) in THF (25 mL) at 0°C was treated with **13** (0.29 g, 0.96 mmole) in THF (5 mL). After the reaction was finished (TLC monitoring) the reaction mixture was treated with saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc (3×10 mL). The extracts were combined, dried over $MgSO_4$, and concentrated. The solid was chromatographed to give **14** (0.15 g, 58%). Oil, R_f 0.15 (heptane—EtOAc, 3:1), $[\alpha]_D^{20}$ +66.1° (*c* 1.0, $CHCl_3$).

PMR spectrum (δ, ppm, J/Hz): 0.78 [3H, d, J = 6.7, C<u>H</u>$_3$(CH$_3$)CH], 0.92 [3H, d, J = 6.7, CH$_3$(C<u>H</u>$_3$)CH], 0.95 (1H, m, H^{ax}-3), 1.28 (3H, s, CH$_3$C-1), 1.40 (3H, s, CH$_3$C-2′), 1.50-1.62 (4H, m, H-5, CH$_2$-2, H^{eq}-3), 1.80-1.93 (4H, m, Me$_2$C<u>H</u>, CH$_2$-7, H-6), 2.22 (1H, tt, $J_{4\text{-}3}{}^{eq}$ = 6.4, $J_{4\text{-}Me2CH}$ = 6.4, $J_{4\text{-}3}{}^{ax}$ = 12.0, $J_{4\text{-}5}$ = 12.0, H-4), 4.03 (1H, dd, $J_{8\text{-}7}{}^a$ = 5.3, $J_{8\text{-}7}{}^b$ = 10.5, H-8), 4.30 [1H, d, $J_{(MeO)2CH\text{-}5}$ = 3.4, C<u>H</u>(OMe)$_2$]. ^{13}C NMR spectrum (δ, ppm): 15.75 (CH$_3$), 21.67 (CH$_3$), 21.84 (C-3), 25.0 (CH$_3$), 26.46 (<u>C</u>Me$_2$), 29.35 (C-7), 35.89 (C-2), 37.90 (C-3), 39.98 (C-5), 44.46 (C-6), 56.05 (OCH$_3$), 56.25 (OCH$_3$0, 67.69 (≡CH), 71.03 (C-1), 82.32 (<u>C</u>OH), 84.55 (C-8), 87.63 (≡C), 107.53 [<u>C</u>(OMe)$_2$].

1S,2′R,4R,5R,6R,8S-8-(2′-Hydroxybut-3′-yn-2′-yl)-4-isopropyl-1-methyl-9-oxa-5-formylbicyclo[4.3.0]nonane (15). A solution of **14** (0.08 g, 0.25 mmole) in $CHCl_3$ (5 mL) containing *i*-PrOH (2%) and SiO_2 (0.3 g) was treated with conc. HCl (1.1 mL), stirred until the reaction was finished (TLC monitoring), neutralized with saturated $NaHCO_3$ solution, filtered, evaporated at reduced pressure, and extracted with $CHCl_3$ (3×5 mL). The extracts were combined, dried over $MgSO_4$, and concentrated. The solid was chromatographed to give **15** (0.06 g, 65%). Oil, R_f 0.14 (heptane—EtOAc, 3:1), $[\alpha]_D^{20}$ +17.7° (*c* 1.0, $CHCl_3$).

PMR spectrum (δ, ppm, J/Hz): 0.78 [3H, d, J = 6.7, C<u>H</u>$_3$(CH$_3$)CH], 0.92 [3H, d, J = 6.7, CH$_3$(C<u>H</u>$_3$)CH], 1.10 (1H, m, CH), 1.30 (1H, m, CH), 1.34 (3H, s, CH$_3$C-1), 1.42 (3H, s, CH$_3$C-2′), 1.55-1.90 (5H, m, CH$_2$, CH), 2.05 (1H, m, CH), 2.22 (1H, m, CH), 2.45 (1H, s, H-4′), 2.50 (1H, m, CH), 2.75 (1H, br.s, OH), 4.04 (1H, dd, J = 5.1, J = 5.3, H-8), 9.62 (1H, d, J = 3.8, C<u>H</u>O). ^{13}C NMR spectrum (δ, ppm): 15.93 (CH$_3$), 21.36 (CH$_3$), 21.50 (C-3), 25.25 (CH$_3$), 25.53 (CH$_3$), 27.58 (C-7), 29.02 (<u>C</u>Me$_2$), 35.49 (C-2), 36.93 (C-4), 45.13 (C-6), 51.63 (C-5), 67.77 (≡CH), 71.72 (C-1), 82.32 (<u>C</u>OH), 84.63 (C-8), 86.93 (C≡), 204.53 (CHO).

1S,(2′R),4R,5S,6R,8S-8-(2′-Hydroxybut-3′-yn-2′-yl)-4-isopropyl-1-methyl-9-oxa-5-(2″-cyano-2″-ethoxycarbonylethenyl)bicyclo[4.3.0]nonane (16). A solution of **15** (0.04 g, 0.14 mmole) in EtOH (5 mL) was treated with

cyanoacetic ester (0.45 mL, 4.32 mmole) and β-alanine (0.05 g, 0.57 mmole), stirred at room temperature until the starting material disappeared (TLC monitoring), diluted with H_2O (5 mL), and extracted with EtOAc (3×10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. The solid was chromatographed to give **16** (0.05 g, 71%). Oil, R_f 0.15 (heptane—EtOAc, 3:1), $[\alpha]_D^{20}$ +50.6° (*c* 1.0, $CHCl_3$).

PMR spectrum (δ, ppm, J/Hz): 0.78 [3H, d, J = 6.8, $C\underline{H}_3(CH_3)CH$], 0.92 [3H, d, J = 6.8, $CH_3(C\underline{H}_3)CH$], 1.10 (1H, m, H^{ax}-3), 1.30 (1H, m, H^{eq}-3), 1.39 (3H, t, J = 7.2, $C\underline{H}_3CH_2O$), 1.44 (6H, s, CH_3C-1 and CH_3C-2′), 1.55-1.76 (4H, m, CH_2-2, Me_2CH, H-4), 2.10 (3H, m, CH_2-7, H-6), 2.50 (1H, s, H-4′), 2.60 (1H, br.s, OH), 3.0 (1H, ddd, J_{5-6} = 4.5, $J_{5-1''}$ = 11.0, J_{5-4} = 11.0, H-5), 4.02 (1H, d, J_{8-7}^{a} = 5.8, J_{8-7}^{b} = 10.3, H-8), 4.33 (2H, q, J = 7.2, OCH_2), 7.51 (1H, d, $J_{1''-5}$ = 11.0, H-1″). ^{13}C NMR spectrum (δ, ppm): 14.18 (CH_3), 15.66 (CH_3), 21.40 (CH_3), 21.70 (C-3), 25.33 (CH_3), 25.62 (Me_2C), 27.50 (CH_3), 29.74 (C-7), 35.76 (C-2), 41.40 (C-4), 42.87 (C-5), 48.77 (C-6), 62.76 (OCH_2), 67.76 (C-4′), 71.82 (C-1), 82.04 (C-2′), 84.45 (C-8), 86.8 (C-3′), 109.78 (C-2″), 113.50 (CN), 161.1 (C=O), 165.9 (C-1″).

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