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Eleuthesides and Their Analogs: II.* Side Chain Construction in the A Ring. Specific Action of Red-Al

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Abstract—Side chains were constructed in the modified A ring of eleutheside analog. The structure of the transformation product of 6-oxiranylcyclohex-3-ene-1-carbonitrile by the action of Red-Al, (1*S*,2*R*,6*R*,7*S*)-7-[(1*S*,2*S*)-1,2-isopropylidenedioxy-2-methylbut-3-yn-1-yl]-2-methylbicyclo[4.1.0]hept-3-ene-1-carbaldehyde, was determined by X-ray analysis.

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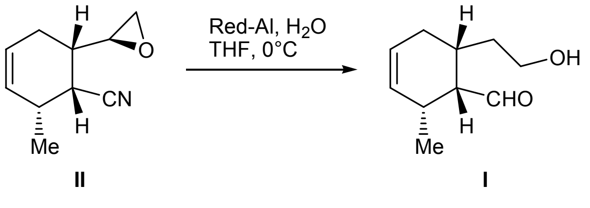
In continuation of our studies on the synthesis of eleutheside analog with modified A ring, side chains were built up in methylcyclohexene derivative **I** [1]. Following the known strategy of eleutheside synthesis [2], the aldehyde moiety in compound **I** was protected via dithioacetalization with propane-1,3-dithiol. The subsequent transformations were characterized by poor yields and low selectivity. These difficulties could be attributed to specific properties of the thioacetal fragment [3–5]. However, despite fairly convincing agreement between the calculated and experimental spectral parameters, some doubt appeared concerning the structure of key hydroxy aldehyde **I**. Its ^{1}H NMR spectrum seemed to be plausible, whereas the JMOD ^{13}C NMR spectrum of **I** displayed persistently low intensity of the C^1 signal at δ_C 38.56 ppm as compared to the other signals. Furthermore, it remained difficult to rationalize the nature of the transformation of oxiranyl-substituted cyclohexenecarbonitrile **II** into hydroxy aldehyde **I** by the action of Red-Al (Scheme 1).

These data prompted us to perform additional studies with a view to prove the structure of the product formed by opening of the oxirane ring in **II**. ^{13}C NMR experiments with the use of COM, DEPT 135°, and DEPT 90° techniques showed that the signal at δ_C 38.56 ppm belongs to a quaternary carbon atom, which is responsible for its low intensity in the JMOD spectrum. Two signals at δ_C 57.81 and 20.47 ppm were assigned to methylene carbon atoms, the signal at δ_C 19.27 ppm, to the CH_3 group, and the other signals, to CH carbon atoms. The quaternary carbon atom (δ_C 38.56 ppm) showed coupling with the aldehyde proton in the HMBC spectrum. The latter also contained cross peaks due to couplings of the aldehyde carbon atom (δ_C 201.80 ppm) with protons on C^7 (δ 1.81 ppm) and C^6 (δ 1.72 ppm). These findings led us to conclude that the C^1, C^6, and C^7 atoms constitute a cyclopropane ring.

Methylene protons in the CH_2OH group are diastereotopic, and they appear as doublets of doublets in the ^{1}H NMR spectrum. These protons displayed geminal coupling constant and different vicinal coupling constants with 7-H. The latter gave a double doublet of doublets at δ 1.81 ppm ($J_{7,8A}$ = 6.1, $J_{7,8B}$ = 8.1, $J_{7,6}$ = 9.7 Hz), and the 6-H proton resonated as a doublet of doublets at δ 1.72 ppm (J = 9.7, 7.3 Hz). The 2-H signal characteristically appeared at δ 3.25 ppm (q.d.d, J = 7.3, 2.7, 2.4 Hz). Thus the transformation of epoxy nitrile **II** into hydroxy aldehyde **III** may be represented by Scheme 2.

Side chains in bicyclic hydroxy aldehyde **III** were built up according to Scheme 3. The hydroxy group in

Scheme 1.



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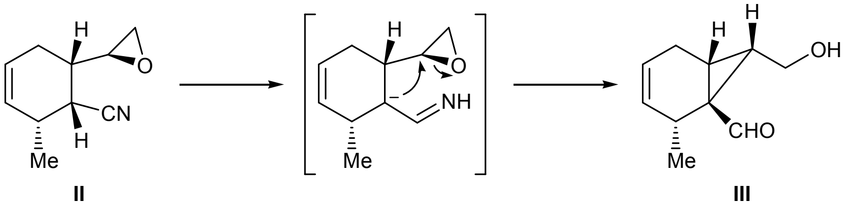
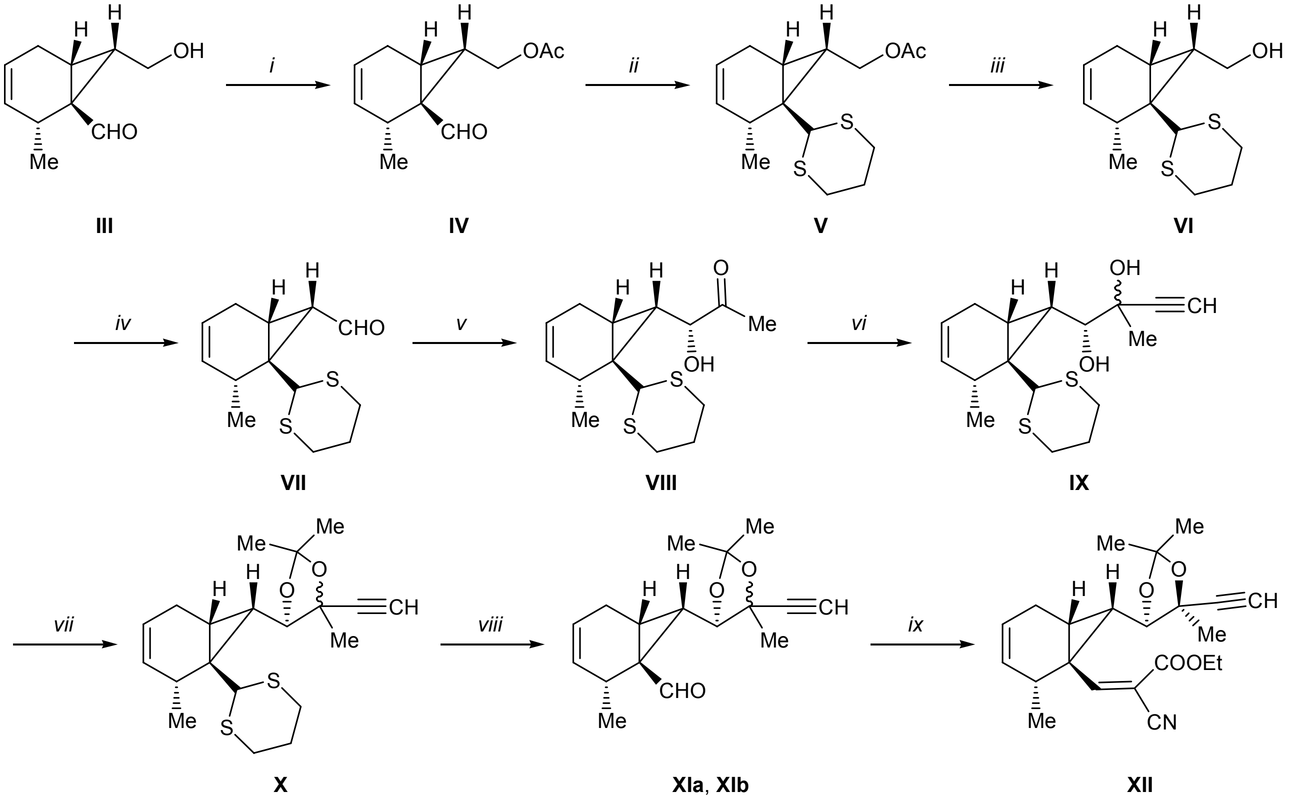
* For communication I, see [1].

Scheme 2.



Scheme 3.



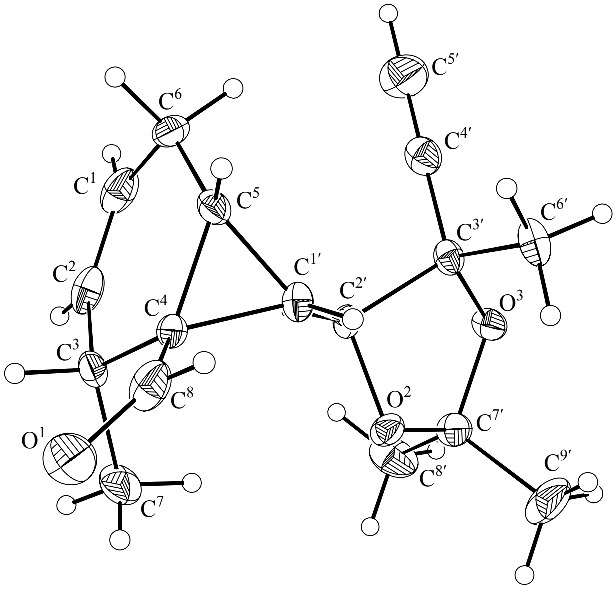
Reagents and conditions: *i*: Ac_2O, pyridine, 0°C; *ii*: $HS(CH_2)_3SH$, TsOH, CH_2Cl_2; *iii*: KOH, EtOH–H_2O; *iv*: PCC, CH_2Cl_2; *v*: CH_2=CHOEt, BuLi, THF, –78°C; *vi*: CH≡CMgCl, THF, 0°C; *vii*: $(MeO)_2C(Me)_2$, TsOH, CH_2Cl_2; *viii*: MeI, $CaCO_3$, MeCN–H_2O; *ix*: $NCCH_2CO_2Et$, β-alanine, EtOH.

III was acetylated, and the aldehyde group was protected via transformation into dithioacetal **V**. Hydrolysis of acetate **V** gave alcohol **VI** which was oxidized to aldehyde **VII** with pyridinium chlorochromate (PCC). The aldehyde proton signal of compound **VII** was observed in the ^1H NMR spectrum at δ 9.38 ppm (d, J = 7.1 Hz), and the carbonyl carbon atom resonated in the ^{13}C NMR spectrum at δ_C 199.44 ppm.

Unlike published data, the reaction of aldehyde **VII** with 1-ethoxyvinyllithium according to the procedure described in [2] was stereospecific, and the resulting hydroxy ketone **VIII** has *S* configuration of the new asymmetric center. Compound **VIII** characteristically displayed in the ^1H NMR spectrum a signal at δ 2.95 ppm ($^3J_{2,\mathrm{Me}}$ = 7.3, $^3J_{2,3}$ = 2.7, $^4J_{2,4}$ = 2.2 Hz). The 7-H proton resonated at δ 2.05 ppm as a doublet of doublets ($J_{6,7}$ = 9.5, $J_{7,8}$ = 10.8 Hz), indicating *S* configuration of C^7. The SCHS proton gave a singlet at δ 3.79 ppm. Presumably, stereospecificity of the addition is determined by stereocontrol by the bicycloheptane system which favors approach of organometallic reagent from the β-side.

High stereoselectivity was also expected at the next (acetylenation) stage due to both α-chelate control and effect of the bicycloheptane fragment. In fact, the 1,2-addition of ethynylmagnesium chloride to compound **VIII** gave a mixture of (3′*S*)- and (3′*R*)-isomers **IX** at a ratio of 4 : 1, the overall yield being 83%.

Vicinal diol **IX** was protected by transformation into acetonide **X**. Attempted deprotection of the aldehyde moiety in **X** by treatment with HgO–$BF_3 \cdot Et_2O$ in THF–H_2O resulted in the formation of a complex mixture of products, presumably due to side transformations involving the cyclopropane fragment. We succeeded in smoothly removing the thioacetal protecting group by the action of methyl iodide in aqueous acetonitrile. The target (7*S*,8*S*)-epimer **XIa** was isolated from the obtained diastereoisomer mixture **XIa**/**XIb** by crystallization. The structure of aldehyde **XIa** was proved by ^1H and ^{13}C NMR spectroscopy and X-ray analysis (see figure).



Structure of the molecule of (1*S*,2*R*,6*R*,7*S*)-7-[(1*S*,2*S*)-1,2-isopropylidenedioxy-2-methylbut-3-yn-1-yl]-2-methylbicyclo[4.1.0]hept-3-ene-1-carbaldehyde (**XIa**) according to the X-ray diffraction data.

Construction of side chains at the methylcyclohexene ring was completed by Knoevenagel condensation of aldehyde **XI** with ethyl cyanoacetate in the presence of β-alanine [2]. The ^1H NMR spectrum of ester **XII** thus obtained contained a singlet at δ 7.52 ppm due to proton at the exocyclic double bond, and the ester ethyl group gave rise to quartet and triplet signals at δ 4.32 and 14.16 ppm, respectively ($J = 7.1$ Hz). In the ^{13}C NMR spectrum of **XII** carbon atoms in the cyano and carbonyl groups resonated at δ_C 114.26 and 162.32 ppm, respectively.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on Bruker AM-300 (300 MHz for ^1H, 75.47 MHz for ^{13}C) and Bruker Avance III (500 MHz for ^1H) spectrometers using $CDCl_3$ as solvent. The melting points were measured on a Kofler S30A/G hot stage (DDR). Analytical TLC was performed using Sorbfil PTSKh-AF-A plates (*Sorbpolimer* close corporation, Krasnodar, Russia). The IR spectra were recorded on UR-20 and Specord M-80 instruments from films or mulls in mineral oil. The mass spectra were obtained on a Hewlett Packard HP 5973 mass-selective detector coupled with an HP 6890 gas chromatograph. The optical rotations were measured on a Perkin Elmer-341 polarimeter. Commercial Red-Al [a 70% solution of sodium dihydridobis(2-methoxyethoxy) aluminate in toluene; Lancaster] was used as reducing agent.

(1*S*,2*R*,6*R*,7*S*)-7-Hydroxymethyl-2-methylbicyclo[4.1.0]hept-3-ene-1-carbaldehyde (III). A mixture of 0.18 ml (0.9 mmol) of Red-Al and 0.001 ml (0.06 mmol) of water in THF was added under argon to a solution of 0.05 g (0.3 mmol) of compound **II** in 15 ml of THF, cooled to 0°C. When the reaction was complete, 3% hydrochloric acid was added until the mixture turned homogeneous. The mixture was extracted with ethyl acetate (3×10 ml), the extract was dried over $MgSO_4$ and evaporated, and the residue was purified by chromatography. Yield 0.042 g (82%). Colorless crystals, mp 85.7°C, $[\alpha]_D^{20} = -105.2°$ ($c = 1.0$, $CHCl_3$), R_f 0.3 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 3400, 2970, 1640, 1700, 1370, 1070, 920. ^1H NMR spectrum, δ, ppm: 1.07 d.d.d (3H, CH_3, $J = 2.4$, 2.7, 7.3 Hz), 1.72 d.d (1H, 6-H, $J = 7.3$, 9.7 Hz), 1.81 d.d.d (1H, 7-H, $J = 6.1$, 8.1, 9.7 Hz), 2.35 d.d (1H, 5-H_A, $J = 4.7$, 19.2 Hz), 2.50 d.d (1H, 5-H_B, $J = 7.3$, 19.2 Hz), 3.25 d.d.d (1H, 2-H, $J = 2.4$, 2.7, 7.3 Hz), 3.80 d.d (1H, 8-H_A, $J = 8.1$, 11.2 Hz), 3.92 d.d.d (1H, 8-H_B, $J = 6.1$, 8.1, 11.2 Hz), 5.50 d.d.d.d (1H, 4-H, $J = 2.4$, 4.7, 6.0, 10.3 Hz), 5.57 d.d.d (1H, 3-H, $J = 2.4$, 2.7, 3.0 Hz), 8.80 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 19.27 (CH_3), 19.81 (C^6), 20.47 (C^5), 25.13 (C^7), 27.69 (C^2), 38.56 (C^1), 57.81 (C^8), 122.96 (C^4), 129.96 (C^3), 201.80 (CHO). Found, %: C 72.26; H 8.49. $C_{10}H_{14}O_2$. Calculated, %: C 72.25; H 8.50.

(1*S*,2*R*,6*R*,7*S*)-1-Formyl-2-methylbicyclo[4.1.0]-hept-3-en-7-yl acetate (IV). A solution of 0.429 g (2.6 mmol) of hydroxy aldehyde **III** in 30 ml of pyridine was cooled to 0°C, 0.9 ml (5.2 mmol) of acetic anhydride was added dropwise under stirring, and the mixture was allowed to warm up to room temperature. The mixture was kept for 40 min, treated with ethyl acetate, washed with water, and dried over $MgSO_4$, and the solvent was distilled off. Yield 0.493 g (91%), oily substance, $[\alpha]_D^{20}$ = –103.78° (*c* = 3.75, $CHCl_3$), R_f 0.65 (petroleum ether–EtOAc, 1:1). IR spectrum, ν, cm^{-1}: 2719, 1739, 1707, 933. ^1H NMR spectrum, δ, ppm: 1.05 d (3H, CH_3, *J* = 7.3 Hz), 1.71 d.d (1H, 6-H, *J* = 7.0, 9.5 Hz), 1.83 d.d.d (1H, 7-H, *J* = 6.6, 8.3, 9.5 Hz), 2.03 s (3H, CH_3CO), 2.32 d.d (1H, 5-H_A, *J* = 1.71, 18.4 Hz), 2.51 d.d.d (1H, 5-H_B, *J* = 2.8, 5.9, 18.4 Hz), 3.22 d.d.d (1H, 2-H, *J* = 2.3, 2.8, 7.3 Hz), 4.20 d.d (1H, 8-H_A, *J* = 11.8, 8.3 Hz), 4.32 d.d (1H, 8-H_B, *J* = 6.6, 11.8 Hz), 5.50 d.d.d (1H, 3-H, *J* = 2.8, 2.8, 10.3 Hz), 5.57 d.d.d (1H, 4-H, *J* = 2.3, 5.9, 10.3 Hz), 8.78 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 18.97 (CH_3), 19.91 (C^6), 20.30 (C^5), 20.87 (**C**H_3CO), 25.01 (C^7), 25.99 (C^2), 38.38 (C^1), 59.75 (C^8), 122.97 (C^4), 129.95 (C^3), 170.84 (CH_3**C**O), 201.29 (CHO). Found, %: C 69.21; H 7.74. $C_{12}H_{16}O_3$. Calculated, %: C 69.20; H 7.74.

(1*S*,2*R*,6*R*,7*S*)-1-(1,3-Dithian-2-yl)-2-methylbicyclo[4.1.0]hept-3-en-7-yl acetate (V). Acetate **IV**, 0.08 g (0.38 mmol), was dissolved in 5 ml of methylene chloride, 0.11 ml (1.14 mmol) of propane-1,3-dithiol and 0.004 g (5%) of *p*-toluenesulfonic acid were added, and the mixture was stirred for 30 min (TLC). The mixture was treated with water, the organic phase was separated, the aqueous phase was extracted with methylene chloride (3×5 ml), the extracts were combined with the organic phase and dried over $MgSO_4$, the solvent was distilled off on a rotary evaporator, and the residue was purified by chromatography on silica gel. Yield 0.105 g (91%), oily substance, $[\alpha]_D^{20}$ = –11.4° (*c* = 0.4, $CHCl_3$), R_f 0.48 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 2960, 1732, 968, 910. ^1H NMR spectrum, δ, ppm: 1.13 d (3H, CH_3, *J* = 7.3 Hz), 1.42 d.d (1H, 7-H, *J* = 6.3, 8.9 Hz), 1.81 d.d (1H, 6-H, *J* = 5.9, 8.9 Hz), 2.02 s (3H, CH_3CO), 2.15 d.d.d.d (1H, 5-H_B, *J* = 2.3, 3.0, 5.9, 19.3 Hz), 2.44 d.d (1H, 5-H_A, *J* = 2.3, 19.3 Hz), 2.90 d.d (1H, 2-H, *J* = 2.3, 7.3 Hz), 2.72–2.90 m (6H, 4′-H, 5′-H, 6′-H), 3.60 s (1H, 2′-H), 3.90 d.d (1H, 8-H_B, *J* = 8.9, 11.5 Hz), 4.25 d.d (1H, 8-H_A, *J* = 6.3, *J* = 11.5 Hz), 5.53 d.d.d (1H, 4-H, *J* = 3.0, 5.9, 10.2 Hz), 5.37 d.d.d.d (1H, 3-H, *J* = 2.3, 2.3, 2.3, 10.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.02 (**C**H_3CO), 20.62 (C^5), 20.68 (C^6), 20.68 (C^7), 25.78 ($C^{5'}$), 26.44 (C^2), 27.92 (CH_3), 30.60 (C^1), 31.25 ($C^{4'}$), 31.91 ($C^{6'}$), 60.71 ($C^{2'}$), 61.07 (C^8), 123.45 (C^4), 130.60 (C^3), 170.90 (C=O). Found, %: C 60.36; H 7.43; S 21.49. $C_{15}H_{22}O_2S_2$. Calculated, %: C 60.37; H 7.42; S 21.50.

[(1*S*,2*R*,6*R*,7*S*)-1-(1,3-Dithian-2-yl)-2-methylbicyclo[4.1.0]hept-3-en-7-yl]methanol (VI). A solution of 0.507 g (1.7 mmol) of acetate **V** and 0.30 g of potassium hydroxide in a mixture of 1 ml of water and 2 ml of ethanol was stirred for 1 h (TLC). The mixture was neutralized with 10% hydrochloric acid to pH 7 and extracted with ethyl acetate (3×5 ml), the combined extracts were washed with a saturated solution of sodium chloride, dried over $MgSO_4$, and evaporated, and the residue was purified by chromatography. Yield 0.407 g (93%), oily substance, $[\alpha]_D^{20}$ = –46.68° (*c* = 5.85, $CHCl_3$), R_f = 0.18 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 3400, 910. ^1H NMR spectrum, δ, ppm: 1.11 d (3H, CH_3, *J* = 7.3 Hz), 1.35 d.d.d (1H, 7-H, *J* = 2.7, 6.1, 8.8 Hz), 1.80 d.d (1H, 6-H, *J* = 7.3, 8.8 Hz), 2.12 d (1H, 5-H_A, *J* = 17.0 Hz), 2.43 d.d.d.d (1H, 5-H_B, *J* = 2.4, 3.2, 7.3, 17.0 Hz), 2.80 d.d (1H, 2-H, *J* = 2.3, 7.3 Hz), 2.82 m (6H, 4′-H, 5′-H, 6′-H), 3.52 d.d (1H, 8-H_A, *J* = 2.7, 10.8 Hz), 3.55 s (1H, 2′-H), 3.79 d.d (1H, 8-H_B, *J* = 6.1, 10.8 Hz), 5.38 d.d.d (1H, 3-H, *J* = 2.3, 2.4, 10.3 Hz), 5.55 d.d.d (1H, 4-H, *J* = 3.2, 3.5, 10.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.24 (C^6), 20.47 (C^7), 20.55 (C^5), 25.71 ($C^{5'}$), 27.90 (CH_3), 30.22 (C^1), 30.51 (C^2), 31.11 ($C^{4'}$), 31.78 ($C^{6'}$), 58.28 (C^8), 61.07 ($C^{2'}$), 123.42 (C^4), 130.43 (C^3). Found, %: C 60.89; H 7.86; S 25.01. $C_{13}H_{22}OS_2$. Calculated, %: C 60.90; H 7.87; S 25.79.

(1*S*,2*R*,6*R*,7*S*)-1-(1,3-Dithian-2-yl)-2-methylbicyclo[4.1.0]hept-3-ene-7-carbaldehyde (VII). Pyridinium chlorochromate, 0.43 g (2.0 mmol), was added in small portions under vigorous stirring to a solution of 0.25 g (1.0 mmol) of alcohol **VI** in 10 ml of methylene chloride. The mixture was stirred for 1 h (TLC), 5 ml of diethyl ether was added, the precipitate was filtered off, the filtrate was evaporated, and the residue was purified by chromatography on silica gel. Yield 0.157 g (63%), oily substance, R_f 0.4 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 2233, 1695, 925. ^1H NMR spectrum, δ, ppm: 1.20 d (3H, CH_3, *J* = 7.15 Hz), 1.81 d.d (1H, 7-H, *J* = 7.0, 7.1 Hz), 2.07 d.d.d (1H, 6-H, *J* = 2.0, 6.2, 7.0 Hz), 2.39 d (1H, 5-H_B, *J* = 19.4 Hz), 2.80 m (6H, 4′-H, 5′-H, 6′-H), 2.64 d.d.d.d (1H, 5-H_A, *J* = 3.0, 3.0, 6.2, 19.4 Hz), 3.07 d.d.d (1H, 2-H, *J* = 1.6, *J* = 2.6, 3.07 Hz), 3.67 s (1H, 2′-H), 5.54 d.d.d.d (1H, 3-H, *J* = 2.0, 2.5, 2.6, 10.3 Hz), 5.64 d.d.d.d (1H, 4-H, *J* = 1.6, 3.0, 3.0, 10.3 Hz), 9.38 d (1H, CHO, *J* = 7.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.72 (C^6), 21.74 (C^5), 20.47 (C^7), 25.54 ($C^{5'}$), 27.72 (CH_3), 28.15 (C^2), 31.08 ($C^{4'}$), 31.62 ($C^{6'}$), 38.63 (C^1), 58.87 (C^8), 122.67 (C^4), 130.65 (C^3), 199.24 (CHO). Mass spectrum: *m*/*z* 355 $[M + H]^+$. Found, %: C 61.37; H 7.13; S 25.21. $C_{13}H_{18}OS_2$. Calculated, %: C 61.40; H 7.20; S 25.11. *M* 354.

(1*S*)-1-[(1*S*,2*R*,6*R*,7*S*)-1-(1,3-Dithian-2-yl)-2-methylbicyclo[4.1.0]hept-3-en-7-yl]-1-hydroxypropan-2-one (VIII). A solution of 0.53 ml (5.6 mmol) of ethyl vinyl ether in 30 ml of THF was cooled to –78°C, 3.9 ml (5.0 mmol) of a 1.27 M solution of butyllithium in hexane was added under argon, and the mixture was allowed to warm up to room temperature and stirred for 40 min. The mixture was cooled again to –78°C, and 0.708 g (2.8 mmol) of aldehyde **VII** was added dropwise. When the reaction was complete (TLC), the mixture was treated with 3% hydrochloric acid and extracted with diethyl ether (3 × 10 ml), the extract was dried over $MgSO_4$ and evaporated, and the residue was purified by chromatography. Yield 0.627 g (76%), oily substance, R_f 0.3 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 2895, 1550, 1373, 1008. ^{1}H NMR spectrum, δ, ppm: 1.41 d (3H, CH_3, J = 7.37 Hz), 1.81 d.d (1H, 6-H, J = 5.0, 6.3 Hz), 2.05 d.d (1H, 7-H, J = 9.5, 10.8 Hz), 2.23 s (3H, CH_3), 2.35 d.d (1H, 5-H_B, J = 5.0, 19.1 Hz), 2.60 d.d.d.d (1H, 5-H_A, J = 2.8, 6.3, 6.5, 19.1 Hz), 2.60–2.90 m (6H, 4′-H, 5′-H, 6′-H), 2.95 d.d.d (1H, 2-H, J = 2.7, 2.7, 7.37 Hz), 3.79 s (1H, 2′-H), 4.12 d (1H, 8-H, J = 10.8 Hz), 5.45 d.d.d (1H, 3-H, J = 2.7, 2.8, 11.1 Hz), 5.60 d.d.d (1H, 4-H, J = 2.7, 6.5, 11.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 19.18 (CH_3), 21.61 (C^5), 21.75 (C^6), 25.73 (**C**H_3CO), 25.58 (C^2), 25.75 ($C^{5'}$), 28.58 (C^7), 31.30 ($C^{4'}$), 32.01 ($C^{6'}$), 60.21 ($C^{2'}$), 72.91 (C^8), 122.97 (C^4), 132.25 (C^3), 209.59 (C=O). Found, %: C 60.36; H 7.43; S 21.49. $C_{15}H_{22}O_2S_2$. Calculated, %: C 60.40; H 7.33; S 21.49.

(1*S*,2*S*)-1-[(1*S*,2*R*,6*R*,7*S*)-1-(1,3-Dithian-2-yl)-2-methylbicyclo[4.1.0]hept-3-en-7-yl]-2-methylbut-3-yne-1,2-diol (IX). A solution of 0.992 g (3.3 mmol) of compound **VIII** in 10 ml of THF was added at 0°C to a solution of 16.5 mmol of ethynylmagnesium chloride in 60 ml of THF. When the reaction was complete (TLC), the mixture was treated with a saturated solution of ammonium chloride and extracted with ethyl acetate (3 × 15 ml), the extract was dried over $MgSO_4$, the solvent was distilled off, and the residue was purified by chromatography on silica gel. Yield 0.856 g (83%). R_f 0.38 (petroleum ether–EtOAc, 2:1). IR spectrum, ν, cm^{-1}: 3300, 2966, 1024, 665. ^{1}H NMR spectrum, δ, ppm: 1.42 d [1.43 d]** (3H, CH_3, J = 7.4 Hz), 1.52 s (6H, CH_3), 1.81 d.d.d (2H, 6-H, J = 5.1, 6.3, 9.5 Hz), 2.06 d.d (1H, 7-H, J = 9.5, 10.1 Hz), [2.10 d.d (1H, 7-H, J = 9.5, 9.6 Hz)], 2.39 d (2H, 5-H_B, J = 5.1 Hz), 2.48 s [2.51 s] (1H, 11-H), 2.52 d.d.d (2H, 5-H_A, J = 2.8, 6.3, 6.3 Hz), 2.75–2.87 m (12H, 4′-H, 5′-H, 6′-H), 2.96 d.d.d.d (2H, 2-H, J = 2.2, 2.7, 2.8, 7.4 Hz), 3.65 s [3.71 s] (1H, 2′-H), 3.69 d (1H, 8-H, J = 10.1 Hz), [3.71 d (1H, 8-H, J = 9.6 Hz)], 5.41 d.d (2H, 3-H, J = 2.7, 10.3 Hz), 5.56 d.d.d (2H, 4-H, J = 2.2, 6.3, 10.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.03 [19.94], 22.67 (C^5), 23.47 (C^6) [23.77], 25.39 [25.69] (C^2), 26.05 ($C^{5'}$), 28.97 [29.20] (CH_3), 30.90 [30.88] (C^7), 30.99 [31.02] (C^1), 31.61 ($C^{4'}$), 32.43 ($C^{6'}$), 61.50 [61.09] ($C^{2'}$), 71.19 [71.21] (C^9), 72.06 (C^{11}), 72.60, [73.27] (C^8), 86.59 [85.45] (C^{10}), 123.26 [123.05] (C^4), 132.22 [132.67] (C^3). Mass spectrum: *m/z* 326 $[M + H]^+$. Found, %: C 61.90; H 7.14; S 20.66. $C_{17}H_{22}O_2S_2$. Calculated, %: C 62.00; H 7.15; S 20.68. *M* 322.

2-{(1*S*,2*R*,6*R*,7*S*)-7-[(1*S*,2*S*)-1,2-Isopropylidenedioxy-2-methylbut-3-yn-1-yl]-2-methylbicyclo-[4.1.0]hept-3-en-1-yl}-1,3-dithiane (X). Diol **IX**, 0.48 g (1.5 mmol), was dissolved in 20 ml of methylene chloride, 0.7 ml (5.9 mmol) of 2,2-dimethoxypropane and 0.014 g (5%) of *p*-toluenesulfonic acid were added, and the mixture was stirred for 10 min. When the reaction was complete (TLC), the mixture was concentrated on a rotary evaporator, and the residue was purified by chromatography on silica gel. Yield 0.418 g (76%), oily substance, R_f = 0.46 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 3277, 2983, 1708, 1373, 1080. ^{1}H NMR spectrum, δ, ppm: 1.31 d (3H, CH_3, J = 7.3 Hz), [1.32 d (3H, CH_3, J = 7.4 Hz)], 1.38 s (3H, CH_3), 1.45 s [1.48 s] (3H, CH_3), 1.48 s [1.55 s] (3H, CH_3), 1.60 s (3H, CH_3), 1.81 d.d.d (2H, 6-H, J = 5.1, 6.3, 9.5 Hz), 2.05 d.d [2.10 d.d] (1H, 7-H, J = 9.5, 9.6 Hz), 2.28 m (2H, 5-H_B), 2.45 s [2.56 s] (1H, 11-H), 2.48–2.56 m (2H, 5-H_A), 2.76–2.92 m (12H, 4′-H, 5′-H, 6′-H), 2.95 d (2H, 2-H, J = 7.3 Hz), 3.82 s [3.88 s] (1H, 2′-H), [3.86 d (1H, 8-H, J = 10.1 Hz)], 4.39 d (1H, 8-H, J = 9.6 Hz), 5.47 m (2H, 3-H), 5.56 m (2H, 4-H). ^{13}C NMR spectrum, δ_C, ppm: 18.91 [19.09] (CH_3), 20.59 [20.80] (C^6), 22.18 [22.53] (C^5), 23.91 (CH_3), 24.91 [25.32] (CH_3), 25.99 ($C^{5'}$), 27.57 [26.69] (CH_3), 28.14 [28.04] (C^2), 28.53 [28.83] (C^7), 30.93 (C^1), 31.42 ($C^{4'}$), 32.04 ($C^{6'}$), 60.08 [59.95] ($C^{2'}$), 71.71 (C^9), 74.83 (C^{11}), 78.10 [79.42] (C^8), 86.16 [84.19] (C^{10}), 108.06 [108.33] (Me_2**C**), 124.11 [123.06] (C^4), 131.27 [132.62] (C^3). Found, %: C 65.10; H 7.48; S 18.30. $C_{17}H_{22}O_2S_2$. Calculated, %: C 65.00; H 7.47; S 18.32.

(1*S*,2*R*,6*R*,7*S*)-7-[(1*S*,2*S*)-1,2-Isopropylidenedioxy-2-methylbut-3-yn-1-yl]-2-methylbicyclo[4.1.0]-hept-3-ene-1-carbaldehyde (XIa). Compoubd **X**, 0.798 g (2.3 mmol), was dissolved in 10 ml of MeCN–H_2O (5:1), 1.6 ml of methyl iodide and 0.7 g of cal-

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** Hereinafter, signals of the minor isomer are given in brackets.

cium carbonate were added, and the mixture was stirred at room temperature until the reaction was complete (TLC). The precipitate was filtered off, the filtrate was evaporated on a rotary evaporator, and the residue was subjected to chromatography on silica gel. Yield 0.55 g (93%), colorless crystals, mp 16.0°C, $[\alpha]_D^{20}$ = –6° (c = 0.133, $CHCl_3$), R_f 0.43 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 2880, 1690, 1280. ^1H NMR spectrum, δ, ppm: 1.22 d (3H, CH_3, J = 7.3 Hz), 1.75 d.d (1H, 6-H, J = 6.8, 9.8 Hz), 1.39 s (3H, CH_3), 1.41 s (3H, CH_3), 1.52 s (3H, CH_3), 1.67 d.d (1H, 7-H, J = 9.8, 9.8 Hz), 1.75 d.d (1H, 6-H, J = 6.8, 9.8 Hz), 2.48 s (1H, 11-H), 2.52 d.d (1H, 5-H_B, J = 6.8, 18.6 Hz), 2.71 d.d.d (1H, 5-H_A, J = 2.3, 2.6, 18.6 Hz), 3.27 d.d.d (1H, 2-H, J = 3.2, 3.8, 7.3 Hz), 4.52 d (1H, 8-H, J = 9.8 Hz), 5.52 br.s (2H, 3-H, 4-H), 8.88 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 17.97 (CH_3), 20.44 (C^6), 21.42 (C^5), 23.91 (CH_3), 24.83 (CH_3), 26.58 (C^2), 27.76 (CH_3), 28.34 (C^7), 39.09 (C^1), 74.89 (C^9), 77.44 (C^8), 78.27 (C^{10}), 85.59 (C^{11}), 123.33 (C^4), 130.30 (C^3), 201.37 (CHO).

(1*S*,2*R*,6*R*,7*S*)-7-[(1*S*,2*R*)-1,2-Isopropylidenedioxy-2-methylbut-3-yn-1-yl]-2-methylbicyclo[4.1.0]-hept-3-en-1-carbaldehyde (XIb). Signals were identified in the NMR spectra of isomer mixture **XIa**/**XIb**. ^1H NMR spectrum, δ, ppm: 1.22 d (3H, CH_3, J = 7.3 Hz), 1.39 s (3H, CH_3), 1.41 s (3H, CH_3), 1.52 s (3H, CH_3), 1.75 d.d (1H, 6-H, J = 6.8, 9.8 Hz), 1.95 d.d (1H, 7-H, J = 9.8, 10.1 Hz), 2.52 s (1H, 4′-H), 2.52 d.d (1H, 5-H_B, J = 6.9, 18.6 Hz), 2.71 d.d.d (1H, 5-H_A, J = 2.3, 2.6, 18.6 Hz), 3.27 d.d.d (1H, 2-H, J = 3.2, 3.8, 7.3 Hz), 3.95 d (1H, 8-H, J = 10.1 Hz), 5.52 br.s (2H, 3-H, 4-H), 8.82 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 18.14 (CH_3), 20.17 (C^6), 21.68 (C^5), 23.94 (CH_3), 23.94 (CH_3), 25.06 (CH_3), 25.52 (C^7), 28.37 (C^2), 38.81 (C^1), 76.76 (C^9), 77.15 (C^8), 77.35 (C^{10}), 83.65 (C^{11}), 122.18 (C^4), 131.78 (C^3), 201.37 (CHO). Mass spectrum: m/z 294 $[M + H]^+$. Found (for isomer mixture **XIa**/**XIb**), %: C 74.42; H 8.08. $C_{17}H_{22}O_3$. Calculated, %: C 74.43; H 8.10. M 274.

Ethyl 2-cyano-3-{(1*S*,2*R*,6*R*,7*S*)-7-[(1*S*,2*S*)-1,2-isopropylidenedioxy-2-methylbut-3-yn-1-yl]-2-methylbicyclo[4.1.0]hept-3-en-1-yl}prop-2-enoate (XII). Aldehyde **XIa**, 0.086 g (0.33 mmol), was dissolved in 7 ml of ethanol, 1.14 ml (10.0 mmol) of ethyl cyanoacetate and 0.12 g (1.3 mmol) of β-alanine were added, and the mixture was stirred at room temperature until the initial compound disappeared (TLC). The mixture was diluted with 3 ml of water and extracted with petroleum ether (10×7 ml). The combined extracts were dried over $MgSO_4$ and concentrated, and the residue was purified by chromatography on silica gel. Yield 0.098 g (84%), R_f 0.4 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 3275, 2983, 2933, 1730, 1604, 1371, 1257, 1078, 368. ^1H NMR spectrum, δ, ppm: 1.34 d (3H, CH_3, J = 7.3 Hz), 1.39 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 1.42 s (3H, CH_3), 1.48 s (3H, CH_3), 1.49 s (3H, CH_3), 1.65 t (1H, 7-H, J = 10.0 Hz), 2.05 d.d (1H, 6-H, J = 6.3, 10.0 Hz), 2.51 s (1H, 11-H), 2.64 d.d.d (1H, 5-H_A, J = 2.6, 4.7, 6.3 Hz), 2.74 d.d (1H, 5-H_B, J = 2.4, 18.7 Hz), 3.22 d.d.d (1H, 2-H, J = 2.4, 2.8, 7.3 Hz), 4.32 q (2H, OCH_2, J = 7.1 Hz), 4.68 d (1H, 8-H, J = 10.0 Hz), 5.51 d.d.d (1H, 3-H, J = 2.6, 2.8, 10.4 Hz), 5.65 d.d.d.d (1H, 4-H, J = 2.4, 2.4, 4.7, 10.4 Hz), 7.52 s (1H, 1′-H). ^{13}C NMR spectrum, δ_C, ppm: 14.16 ($CH_2\mathbf{C}H_3$), 18.26 (CH_3), 22.31 (C^5), 23.99 (CH_3), 25.26 (C^6), 24.97 (CH_3), 27.88 (CH_3), 29.36 (C^2), 32.93 (C^7), 32.19 (C^1), 62.58 (OCH_2), 72.64 (C^9), 74.7 (C^8), 75.02 (C^{10}), 85.48 (C^{11}), 104.54 ($C^{2'}$), 114.26 (CN), 124.25 (C^4), 130.10 (C^3), 162.32 (C=O). Mass spectrum: m/z 356 $[M + H]^+$. Found, %: C 70.96; H 7.09; N 3.94. $C_{21}H_{25}NO_4$. Calculated, %: C 70.90; H 7.08; N 3.90. M 355.

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