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Approaches to Epothilone Carboanalogs Starting from Δ^3-Carene

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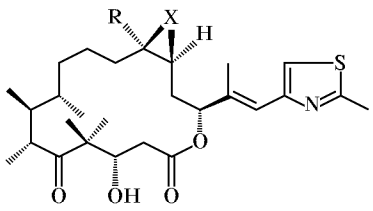
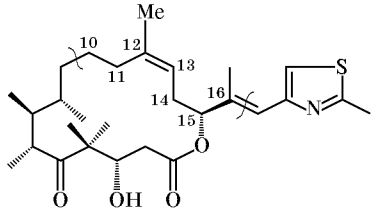
Abstract—Starting from (+)-Δ^3-carene, synthetic equivalents of the C^{10}–C^{16} fragment of epothilone carboanalogs were obtained.

Cytotoxic 16-membered macrolides produced by *Sorangium* mixobacteria, epothilones A (**I**), B (**II**), and D (**III**), are characterized by a taxol-like mechanism of biological action [1–3]. It is known that taxol induces polymerization of α,β-tubulin heterodimers and stabilizes tubulin microtubules, thus causing disturbance in the development of mitotic cycle and decay of cells [4–6]. According to the results of most tests, epothilones are more active than taxol and other tubulin-polymerizing agents, such as discodermolide, eleutherobins, sarcodictyins, and valdivone A) [6–10]. It is also very important that epothilones exhibit a high cytotoxic activity toward cancer cells which are resistant to taxol and other drugs. Moreover, from the viewpoint of chemistry, syntheses of epothilones require no strong efforts and expenses intrinsic to projects of the total synthesis of taxol [11]. Presumably, these factors have determined the present persistent interest and optimism of chemists, biologists, and clinicists in studying epothilones. However, despite high anticarcinogenic activity of epothilones A and B, there are some problems in their clinical application, which are associated with high toxicity *in vivo* and low therapic index. On the other hand, deoxyepothilone B (**III**) is free from the above disadvantages, and it is regarded as the most promising from the viewpoint of pharmaceutics [12].

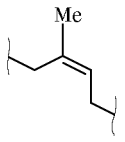
Taking into account extraordinary biological properties of epothilone **III**, we made an attempt to synthesize its carbo analog **IV**. We believed that a certain steric analogy between fragments **A** and **B** of molecules **III** and **IV** would give rise to some



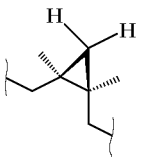
I, II, IV



III



A



B

I, **IV**, R = H; **II**, R = Me; **I**, **II**, X = O; **IV**, X = CMe_2.

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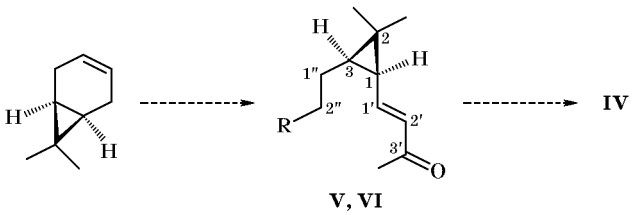
similarity in the properties of compound **IV** and epothilones **I**–**III**.

As starting compound for the synthesis of **IV** we selected (+)-Δ^3-carene. Oxidative splitting of the double bond in the latter opens a reasonable way to cyclopropane units (**V**) whose chiral centers have configurations necessary for building up target structure **IV** (Scheme 1).

Scheme 1.

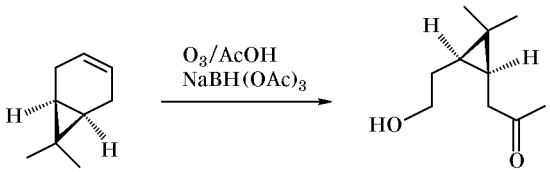


V, VI

V, R = OCH_2OMe; **VI**, R = Br.

In the present communication we describe the synthesis of compounds **V** and **VI** on the basis of known hydroxy ketone **VII** [13] (Scheme 2). Molecules **V** and **VI** possess various functional groups which make them suitable for use in the subsequent versions of building up elements constituting the bottom part of the macroring in **IV**.

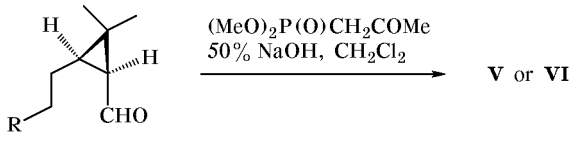
Scheme 2.



VII

Refunctionalization of the hydroxyethyl moiety in compound **VII** with a view to obtain synthons **V** and **VI** requires minimal efforts to be applied with the use of standard techniques. It seemed reasonable to effect the transformation of the methyl ketone fragment of **VII** into enone by the Wittig–Horner reaction of the corresponding cyclopropanecarbaldehydes **VIII** and **IX** (Scheme 3). In order to synthesize aldehyde **IX**, hydroxy ketone **VII** was initially converted into bromo ketone **X** by the action of CBr_4–PPh_3 in acetonitrile. Ketone **X** was oxidized to acetate **XI** with *m*-chloroperoxybenzoic acid in methylene chloride according to Baeyer–Villiger. Likewise, Baeyer–Villiger oxidation of **VII** gave acetate **XII** which was then converted into methoxymethyl ether **XIII**. By hydrolysis of acetates **XI** and **XIII** in methanol in the presence of potassium carbonate we obtained expected alcohols **XIV** and **XVI** together with methyl ether **XV** as by-product (yield 25%); the latter was formed by methanolysis of bromo derivative **XI**. In the final stage, alcohols **XIV** and **XVI** were oxidized in ~60% yield to aldehydes **VIII** and **IX** using pyridinium chlorochromate in CH_2Cl_2 (Scheme 4). Aldehydes **VIII** and **IX** were brought into the Horner–Emmons condensation with dimethyl 2-oxopropylphosphonate in the two-phase system CH_2Cl_2–50% aqueous NaOH in the presence of a catalytic amount of benzyltriethylammonium chloride. As a result, enones **V** and **VI** were isolated in 67% and 55% yield, respectively.

Scheme 3.



VIII, IX

VIII, R = OCH_2OMe; **IX**, R = Br.

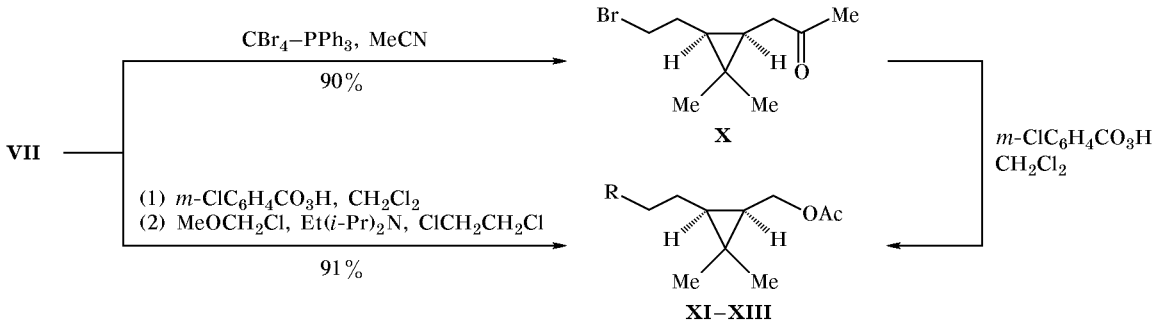
It should be noted that we failed to accomplish the synthesis of enone **V** from 4α-acetyl-2-carene (**XVII**) [14] (which seems to be more reasonable than the above-described approach) because of some difficulties encountered at the stage of transformation of **XXI** into **XXII** (Scheme 5).

EXPERIMENTAL

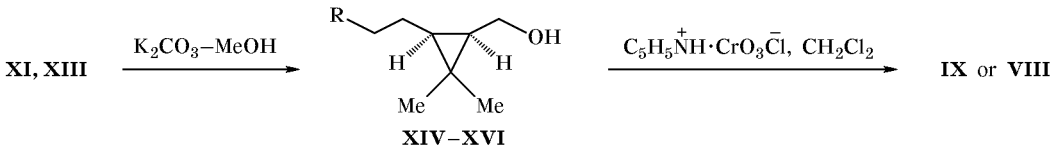
The IR spectra were recorded on UR-20 and Specord-80 spectrometers from samples prepared as thin films or suspensions in mineral oil. The ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-300 instrument at 300.13 and 75.47 MHz, respectively; tetramethylsilane was used as internal reference. The optical rotations were measured on a Perkin–Elmer-141 polarimeter.

(1*R*,3*S*)-(+)-2,2-Dimethyl-3-(2-methoxymethoxyethyl)-1-[(1*E*-3-oxobutenyl]cyclopropane (V). A mixture of 0.54 g (2.9 mmol) of aldehyde **VIII**, 0.65 g (4.35 mmol) of dimethyl 2-oxopropylphosphonate, 39 mg of benzyltriethylammonium chloride, 3 ml of 50% aqueous sodium hydroxide, and 15 ml of methylene chloride was stirred at room temperature until the initial aldehyde disappeared (~24 h; TLC). The mixture was diluted with 20 ml of methylene chloride, washed in succession with cold water and a saturated solution of sodium chloride, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel using ethyl

Scheme 4.

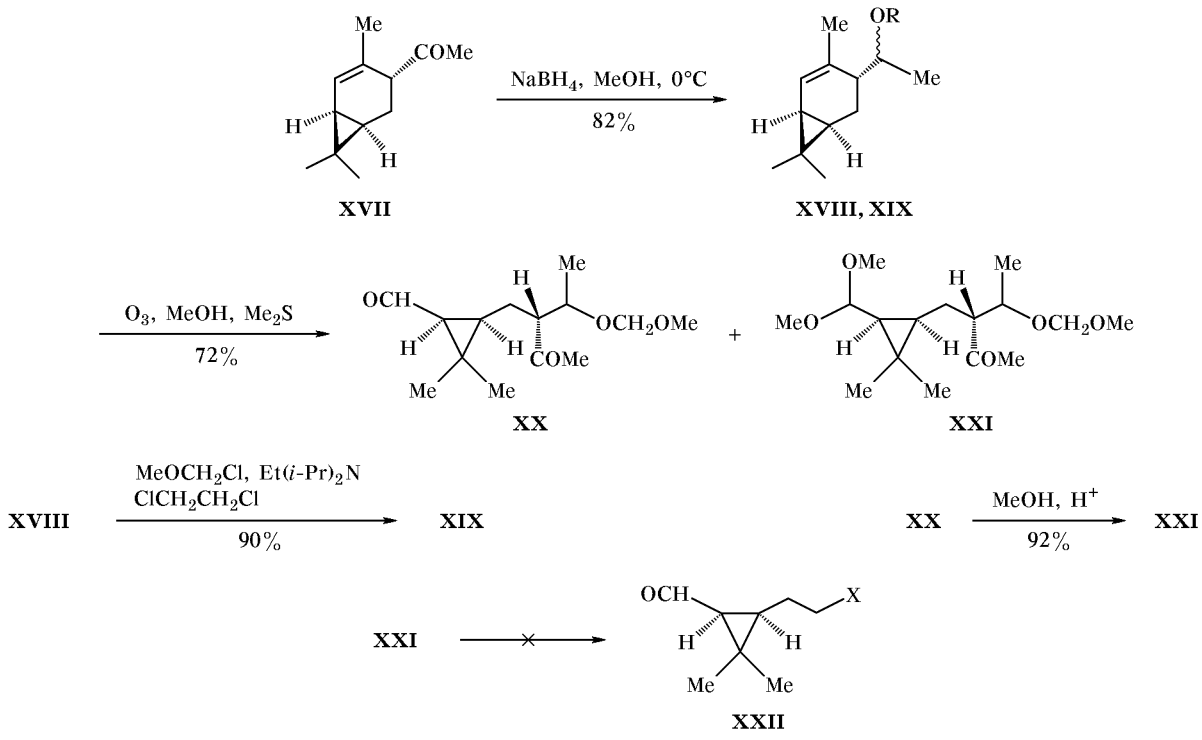


XI, R = Br; **XII**, R = OH; **XIII**, R = $MeOCH_2O$.



XIV, R = $BrCH_2$; **XV**, R = $MeOCH_2$; **XVI**, R = $MeOCH_2OCH_2$.

Scheme 5.



XVIII, R = H; **XIX**, R = OAc.

acetate–petroleum ether (1:5) as eluent. Yield 0.43 g (67%), yellow oily substance. $[\alpha]_D^{20}$ = +30.23° (*c* = 3.4, MeOH). IR spectrum, ν, cm^{-1}: 1680, 1640, 1620, 1370, 1270, 1170, 930. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.97 s and 1.11 s (6H, 2-CH_3), 1.14 m (1H, *J* = 8.7 Hz) and 1.40 d.d (1H, 3-H, 1-H, *J* = 8.7, 10.7 Hz), 1.71 m (2H, 1″-H, *J* = 6.8 Hz), 2.16 s (3H, CH_3CO), 3.30 s (3H, OCH_3), 3.49 t (2H, 2″-H, *J* =

6.8 Hz), 4.55 s (2H, OCH_2O), 6.2 d (1H, 2′-H, J = 15.5 Hz) and 6.57 d.d (1H, 1′-H, J = 15.5, 10.7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.68 and 28.74 (2-CH_3), 25.47 (C^2), 25.56 ($C^{1''}$), 27.08 and 30.90 (C^1, C^3), 30.94 ($C^{4'}$), 54.95 (OCH_3), 67.16 ($C^{2''}$), 96.22 (OCH_2O), 131.08 ($C^{1'}$), 147.22 ($C^{2'}$), 196.92 (C=O). Found, %: C 68.10; H 9.42. $C_{12}H_{20}O_3$. Calculated, %: C 67.92; H 9.43.

(1*R*,3*S*)-(–)-3-(2-Bromoethyl)-2,2-dimethyl-1-[(*E*)-3-oxobutenyl]cyclopropane (VI). A solution of 1.04 g (5.0 mmol) of alcohol **XIV** in 10 ml of dry CH_2Cl_2 was added in one portion to a suspension of 1.36 g (7.5 mmol) of pyridinium chlorochromate in 25 ml of dry CH_2Cl_2, stirred at 0°C. The mixture was stirred for 3 h at room temperature and filtered through a thin layer of silica gel, the precipitate was washed on a filter with methylene chloride (5 × 8 ml), and the filtrate was combined with the washings, dried over $MgSO_4$, and evaporated. The residue was subjected to column chromatography on silica gel using ethyl acetate–petroleum ether (1:5) as eluent to isolate 0.79 g (58%) of aldehyde **IX** as an oily substance which was brought into the next stage without additional purification.

To a solution of 0.79 g (3.75 mmol) of aldehyde **IX**, 0.83 g (5.62 mmol) of dimethyl 2-oxopropylphosphonate, and 50 mg of benzyltriethylammonium chloride in 20 ml of dry methylene chloride we added with stirring at room temperature 0.5 ml of a 50% solution of NaOH in a dropwise fashion, and the mixture was stirred until the initial aldehyde disappeared (~24 h, TLC). The mixture was diluted with 30 ml of CH_2Cl_2, washed in succession with cold water and a saturated solution of sodium chloride, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1:5) as eluent. Yield of **VI** 0.51 g (55%), yellow oily substance. $[\alpha]_D^{20}$ = –11.98° (c = 1.9, MeOH). IR spectrum, ν, cm^{-1}: 1688, 1664, 1608, 1376, 1264, 1160, 980. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.04 s and 1.06 s (6H, 2-CH_3), 1.1 m (1H, J = 8.9 Hz) and 1.41 d.d (1H, 3-H, 1-H, J = 8.9, 10.7 Hz), 1.94 m (2H, 1′′-H), 2.10 s (3H, CH_3CO), 3.27 m (2H, CH_2Br), 6.16 d (1H, 2′-H, J = 15.4 Hz) and 6.47 d.d (1H, 1′-H, J = 15.4, 10.7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.72 and 28.47 (2-CH_3), 25.42 (C^2), 27.24 ($C^{4'}$), 28.65 ($C^{1''}$), 30.77 and 32.60 (C^1, C^3), 32.46 (CH_2Br), 131.29 ($C^{1'}$), 146.08 ($C^{2'}$), 196.61 (C=O). Found, %: C 54.20; H 6.82; Br 32.96. $C_{11}H_{17}BrO$. Calculated, %: C 53.88; H 6.94; Br 32.65.

(1*R*,3*S*)-2,2-Dimethyl-3-(2-methoxymethoxyethyl)cyclopropane-1-carbaldehyde (VIII). A solution of 2.5 g (13.44 mmol) of alcohol **XVI** in 10 ml of dry CH_2Cl_2 was added in one portion to a suspension of 3.67 g (20.16 mmol) of pyridinium chlorochromate in 40 ml of dry CH_2Cl_2, stirred at 0°C. The mixture was stirred for 3 h at room temperature and filtered through a thin layer of silica gel, the precipitate was washed on a filter with methylene chloride (5 × 10 ml), and the filtrate was combined with the washings, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1:5) as eluent. Yield of aldehyde **VIII** 2.0 g (80%), oily substance. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.14 s and 1.26 s (6H, 2-CH_3), 1.42 m (1H) and 1.58 m (1H, 3-H and 1-H), 1.94 m (2H, 1′′-H), 3.28 s (3H, OCH_3), 3.48 m (2H, 2′′-H), 4.54 s (2H, OCH_2O), 9.47 m (1H, CHO). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.95 and 28.83 (2-CH_3), 29.37 (C^2), 24.42 ($C^{1''}$), 34.46 and 38.08 (C^1, C^3), 54.93 (OCH_3), 67.15 ($C^{2''}$), 96.14 (OCH_2O), 201.69 (CHO).

(1*R*,3*R*)-(–)-1-(2-Bromoethyl)-2,2-dimethyl-3-(2-oxopropyl)cyclopropane (X). Carbon tetrabromide, 3.8 g (11.46 mmol), was added in portions to a solution of 1.1 g (7.64 mmol) of alcohol **VII** and 3.0 g (11.46 mmol) of triphenylphosphine in 35 ml of anhydrous acetonitrile, stirred at room temperature. The mixture was stirred for 2 h at room temperature and evaporated, and the residue was subjected to column chromatography using ethyl acetate–petroleum ether (1:5) as eluent. Bromide **X** was isolated as a colorless oily substance. Yield 1.47 g (93%). $[\alpha]_D^{20}$ = –16.8° (c = 6.7, MeOH). IR spectrum, ν, cm^{-1}: 1730, 1715, 1370, 1180, 800. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.61 m (1H, 3-H, J = 7.0 Hz), 0.84 m (1H, 1-H, J = 7.2 Hz), 0.86 s and 1.04 s (6H, 2-CH_3), 1.72 q.d (2H, 1′′-H, J = 7.3, 2.3 Hz), 2.11 s (3H, CH_3CO), 2.31 d (2H, 1′-H, J = 7.2 Hz), 3.31 t (2H, CH_2Br, J = 7.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.89 and 29.52 (2-CH_3), 17.10 (C^2), 21.29 and 25.08 (C^1, C^3), 28.52 ($C^{1'}$), 29.52 ($\mathbf{C}H_3CO$), 32.86 (CH_2Br), 39.17 ($C^{1''}$), 208.34 (C=O).

(1*R*,3*S*)-(+)-1-Acetoxymethyl-3-(2-bromoethyl)-2,2-dimethylcyclopropane (XI). *m*-Chloroperoxybenzoic acid, 1.76 g (10.21 mmol), was added in portions to a solution of 2.0 g (8.51 mmol) of compound **X** in 10 ml of dry chloroform. The mixture was stirred for 48 h at room temperature, diluted with 20 ml of chloroform, and treated with excess saturated solution of $NaHCO_3$. The organic phase was separated, dried over $MgSO_4$, and evaporated to

obtain 1.95 g (91%) of compound **XI** as a colorless oily substance. $[\alpha]_D^{20}$ = +13.4° (*c* = 5.7, MeOH). IR spectrum, ν, cm^{-1}: 1750, 1730, 1380, 1040, 975, 670. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.72 q (1H, *J* = 7.0 Hz) and 0.90 q (1H, 1-H and 3-H, *J* = 8.4 Hz), 0.96 s and 1.04 s (6H, 2-CH_3), 1.83 q (1H, 1″-H, *J* = 7.2 Hz), 1.99 s (3H, CH_3CO), 3.33 m (2H, CH_2Br, *J* = 7.2 Hz), 3.95 d.d (1H, *J* = 8.45, 3.5 Hz) and 4.23 d.d (1H, 1′-H, *J* = 7.5, 4.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.83 and 28.63 (2-CH_3), 17.43 (C^2), 20.94 (**C**H_3CO), 24.33 and 26.23 (C^1, C^3), 28.25 ($C^{1''}$), 32.96 (CH_2Br), 62.25 (OCH_2), 171.03 (O**C**OCH_3).

(1*R*,3*S*)-(+)-1-Acetoxymethyl-3-(2-hydroxyethyl)-2,2-dimethylcyclopropane (XII) was synthesized in a similar way from 0.9 g (5.35 mmol) of ketone **VII** and 1.38 g (8.02 mmol) of *m*-chloroperoxybenzoic acid. Yield of **XII** 0.90 g (92%), oily substance. $[\alpha]_D^{20}$ = +7.63° (*c* = 3.3, MeOH). IR spectrum, ν, cm^{-1}: 3460, 1750, 1735, 1380. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.55 q (1H, *J* = 7.2 Hz) and 0.75 q (1H, 1-H and 3-H, *J* = 7.95 Hz), 0.86 s and 0.93 s (6H, 2-CH_3), 1.43 m (2H, 1″-H, *J* = 7.0 Hz), 1.89 s (3H, CH_3CO), 3.4 br.s (1H, OH), 3.47 d.d (2H, OCH_2, *J* = 6.3 Hz), 3.94 q (2H, OCH_2, *J* = 7.9 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.65 and 28.61 (2-CH_3), 17.83 (C^2), 20.77 (**C**H_3CO), 23.72 and 23.89 (C^1, C^3), 27.46 ($C^{1''}$), 62.43 (O$C^{2''}$N2), 62.51 ($C^{1'}$), 171.29 (C=O).

(1*R*,3*S*)-(+)-1-Acetoxymethyl-2,2-dimethyl-3-(2-methoxymethoxyethyl)cyclopropane (XIII). A solution of 0.98 ml (8.37 mmol) of methoxymethyl chloride and 1.56 ml (8.37 mmol) of ethyldiisopropylamine in 5 ml of dry dichloroethane was added with stirring at room temperature to a solution of 1.1 g (5.98 mmol) of compound **XII** in 20 ml of dry dichloroethane. The mixture was stirred for 24 h at 40°C, washed in succession with cold water and a saturated solution of sodium chloride, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1:9) as eluent. Yield of **XIII** 1.24 g (91%), yellow oily substance. $[\alpha]_D^{20}$ = +11.68° (*c* = 9.96, MeOH). IR spectrum, ν, cm^{-1}: 1760, 1380, 985, 930. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.68 q (1H, *J* = 7.5 Hz) and 0.86 q (1H, 1-H and 3-H, *J* = 7.9 Hz), 0.96 s and 1.03 s (6H, 2-CH_3), 1.57 m (2H, 1″-H), 1.99 s (3H, CH_3CO), 3.33 s (OCH_3), 3.49 m (2H, 1′-H), 4.04 m (2H, 2″-H, *J* = 8.45 Hz), 4.57 s (2H, OCH_2O). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.85 and 20.92 (2-CH_3), 18.19 (C^2), 24.08 and 24.11 (C^1, C^3), 24.88 ($C^{1''}$), 28.85 (**C**H_3CO), 54.95 (OCH_3), 62.58 ($C^{1'}$), 67.75 ($C^{2''}$), 96.30 (OCH_2O), 171.24 (C=O).

(1*R*,3*S*)-(+)-3-(2-Bromoethyl)-1-hydroxymethyl-2,2-dimethylcyclopropane (XIV) and (1*R*,3*S*)-(+)-1-hydroxymethyl-2,2-dimethyl-3-methoxyethylcyclopropane (XV). Freshly calcined powdered potassium carbonate, 1.07 g (7.77 mmol), was added under argon to a solution of 1.95 g (7.77 mmol) of compound **XI** in 20 ml of anhydrous methanol, and the mixture was stirred for 1 h at room temperature. The mixture was neutralized to pH ~7 with 5% hydrochloric acid, the organic phase was separated, washed in succession with water and a saturated solution of NaCl, dried over $MgSO_4$, and evaporated, and the residue was subjected to column chromatography on silica gel using ethyl acetate–petroleum ether (1:6) as eluent to isolate 1.04 g (64%) of alcohol **XIV** and 0.7 g (25%) of **XV**.

Compound **XIV**. $[\alpha]_D^{20}$ = +3.7o (*c* = 2.7, MeOH). IR spectrum, ν, cm^{-1}: 3360, 1480, 1460, 1380, 1040, 770. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.7 t.d (1H, *J* = 7.12, 1.8 Hz) and 0.9 d.t (1H, 2-H and 3-H, *J* = 7.65, 1.05 Hz), 1.03 s and 1.10 s (6H, 2-CH_3), 1.9 q (2H, 1″-H, *J* = 7.1 Hz), 1.96 br.s (1H, OH), 3.43 d.t (2H, CH_2Br, *J* = 7.06, 1.72 Hz), 3.64 d.d (2H, OCH_2, *J* = 7.87, 2.02 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.89 and 28.88 (2-CH_3), 18.14 (C^1), 26.22 and 28.48 (C^2, C^3), 28.28 ($C^{1''}$), 33.56 (CH_2Br), 59.79 (OCH_2).

Compound **XV**. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.52 m and 0.91 m (2H, 2-H and 3-H), 0.95 s and 1.04 s (6H, 2-CH_3), 1.47 m (1H) and 1.75 q.d (1H, 1″-H, *J* = 3.2 Hz), 3.37 s (3H, OCH_3), 3.44 m (2H, 1′-H), 3.55 q (2H, 2″-H, *J* = 4.1 Hz), 3.76 br.s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 15.1 and 24.48 (2-CH_3), 16.92 (C^1), 28.59 and 28.98 (C^2, C^3), 25.15 ($C^{1''}$), 58.49 (OCH_3), 58.83 ($C^{2''}$), 73.52 ($C^{1'}$).

(1*R*,3*S*)-(+)-1-Hydroxymethyl-2,2-dimethyl-3-(2-methoxymethoxyethyl)cyclopropane (XVI) was synthesized as described above for alcohol **XIV** from 3.5 g (15.35 mmol) of compound **XIII** in 30 ml of anhydrous methanol and 2.12 g (15.35 mmol) of freshly calcined K_2CO_3 powder. Yield 2.57 g (90%), colorless oily substance. $[\alpha]_D^{20}$ = +14.34° (*c* = 3.1, MeOH). IR spectrum, ν, cm^{-1}: 3460, 1165, 930. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.53 t.d (1H, *J* = 9.17, 4.0 Hz) and 0.88 m (1H, 1-H and 3-H, *J* = 9.6, 5.7 Hz), 0.94 s and 1.02 s (6H, 2-CH_3), 1.51 m (1H, *J* = 9.6, 10.6 Hz) and 1.72 d.d (1H, 1″-H, *J* = 9.2, 10.6 Hz,), 3.09 br.s (1H, OH), 3.3 s (3H, OCH_3), 3.44 d.d and 3.54 t.d (2H, 2″-H, *J* = 9.5, 4.2 Hz),

3.65 d.t (2H, 1′-H, J = 5.8 Hz), 4.6 s (2H, OCH_2O). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.06 and 25.00 (2-CH_3), 17.21 (C^2), 24.37 ($C^{1''}$), 28.52 and 29.04 (C^1, C^3), 55.31 (OCH_3), 58.85 ($C^{1'}$), 68.23 ($C^{2''}$), 96.26 (OCH_2O). Found, %: C 62.45; H 11.15. $C_9H_{18}O_3$. Calculated, %: C 62.06; H 11.39.

(1*R*,3*R*,6*R*)-3-[(1*RS*)-1-Hydroxyethyl]-4,7,7-trimethylbicyclo[4.1.0]hept-4-ene (XVIII). A solution of 1.50 g (8.38 mmol) of compound **XVII** in 5 ml of anhydrous methanol was added dropwise at 0°C under stirring to a suspension of 3.17 g (83.8 mmol) of $NaBH_4$ in 50 ml of anhydrous MeOH. The mixture was stirred for 4 h at that temperature (TLC), excess $NaBH_4$ was decomposed by addition of a small amount of a saturated solution of ammonium chloride, the solvent was evaporated, and the residue was extracted with chloroform (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and evaporated, and the residue was subjected to column chromatography on silica gel using ethyl acetate–petroleum ether (1 : 1) as eluent. Compound **XVIII** was isolated as a mixture of epimers at a ratio of ~5 : 4 (^1H NMR data). Yield 1.4 g (93%). IR spectrum, ν, cm^{-1}: 3395, 1465, 1380, 1065.

Major diastereoisomer. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.81 m and 1.22 m (2H, 1-H, 6-H), 0.84 s and 1.02 s (6H, 2-CH_3), 1.19 d (2H, 2′-H, J = 6.43 Hz), 1.42 m and 1.64 m (2H, 2-H), 1.69 s (3H, CH_3), 2.13 m (2H, 3-H, OH), 3.92 q (1H, 1′-H, J = 6.21 Hz), 5.51 m (1H, 5-H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.85 and 20.15 (2-CH_3), 18.45 ($C^{2'}H_3$), 20.52 (C^7), 21.22 and 23.33 (C^1, C^6), 23.54 (C^2), 27.58 (CH_3), 45.35 (C^3), 69.04 ($C^{1'}$), 122.36 (5-H), 137.52 (C^4).

Minor diastereoisomer. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.81 m and 1.22 m (2H, 1-H, 6-H), 0.83 s and 1.01 s (6H, 2-CH_3), 1.20 d (2H, 2′-H, J = 6.43 Hz), 1.42 m and 1.64 m (2H, 2-H), 1.72 s (3H, CH_3), 2.13 m (2H, 3-H, OH), 3.92 m (1H, 1′-H, J = 6.21 Hz), 5.51 m (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.85 and 20.15 (2-CH_3), 18.40 ($C^{2'}$), 20.68 (C^7), 21.38 and 23.62 (C^1, C^6), 24.14 (C^2), 27.58 (CH_3), 45.62 (C^3), 70.74 ($C^{1'}$), 121.64 (C^5), 137.78 (C^4).

(1*R*,4*R*,6*R*)-4-[(1*R*,*S*)-1-Methoxymethoxyethyl]-3,7,7-trimethylbicyclo[4.1.0]hept-2-ene (XIX) was obtained as a mixture of diastereoisomers (~5 : 4, ^1H NMR data) from 0.7 g (3.87 mmol) of alcohol **XVIII**, 0.4 g (5.03 mmol) of methoxymethyl chloride, and 0.65 g (5.03 mmol) of ethyldiisopropylamine in 15 ml of dichloroethane, following the procedure described above for the synthesis of compound **XIII**. Yield 0.78 g (90%). IR spectrum, ν, cm^{-1}: 2835, 1465, 1385, 1370, 1060, 930, 850, 820.

Major diastereoisomer. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.78 m and 1.22 m (2H, 1-H, 6-H), 0.84 s and 1.02 s (6H, 2-CH_3), 1.13 d (3H, 2′-H, J = 6.2 Hz), 1.42 m and 1.74 m (2H, 2-H), 1.69 s (3H, CH_3), 2.15 m (1H, 3-H), 3.39 s (3H, OCH_3), 3.81 q (1H, 1′-H, J = 6.57 Hz), 4.63 d (1H, J = 6.88) and 4.71 d (1H, OCH_2O, J = 7.74), 5.4 m (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.14 and 18.81 (2-CH_3), 18.49 ($C^{2'}$), 22.22 (C^2), 23.55 and 24.50 (C^1, C^6), 23.84 (C^7), 27.74 (CH_3), 44.72 (C^3), 55.44 (OCH_3), 75.72 ($C^{1'}$), 95.29 (OCH_2O), 122.24 (C^5), 138.05 (C^4).

Minor diastereoisomer. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.78 m and 1.22 m (2H, 1-H, 6-H), 0.82 s and 1.02 s (6H, 2-CH_3), 1.17 d (3H, 2′-H, J = 6.9 Hz), 1.42 m and 1.74 m (2H, CH_2), 1.69 s (3H, CH_3), 2.15 m (1H, 3-H), 3.32 s (3H, OCH_3), 3.81 q (1H, 1′-H, J = 6.57 Hz), 4.63 d (1H, J = 6.88) and 4.71 d (1H, OCH_2O, J = 7.74), 5.43 m (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 17.28 and 17.92 (2-CH_3), 18.44 ($C^{2'}$), 20.08 (C^2), 23.66 and 23.78 (C^1, C^6), 23.98 (C^7), 27.68 (CH_3), 43.19 (C^3), 55.09 (OCH_3), 75.34 ($C^{1'}$), 94.95 (OCH_2O), 121.41 (C^5), 137.75 (C^4).

(1*R*,3*S*)-3-(2-Acetyl-3-methoxymethoxy-1-butyl)-2,2-dimethylcyclopropane-1-carbaldehyde (XX) and (1*R*,3*S*)-3-(2-acetyl-3-methoxymethoxy-1-butyl)-1-dimethoxymethyl-2,2-dimethylcyclopropane (XXI). An ozone–oxygen mixture was passed through a solution of 1 g (3.83 mmol) of compound **XIX** in 40 ml of anhydrous methanol on stirring at –60°C until the solution turned blue. Excess ozone was removed by purging with argon, 5 ml of dimethyl sulfide was added, and the mixture was stirred for 30 min at –60oC and for 6 h at room temperature. It was then evaporated, the residue was dissolved in ethyl acetate, the solution was washed with a saturated solution of sodium chloride, and the organic phase was separated, dried over $MgSO_4$, and evaporated. The residue was subjected to column chromatography on silica gel using ethyl acetate–petroleum ether (1 : 2) as eluent to isolate 0.7 g (61%) of aldehyde **XX** (oily substance) and 0.3 g (21%) of dimethyl acetal **XXI**.

Compound **XX**. Major diastereoisomer. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.78 m and 1.21 m (2H, 1-H, 3-H), 1.04 d (3H, CH_3, J = 6.5 Hz), 1.20 s (6H, 2-CH_3), 2.14 s (3H, CH_3CO), 2.45 m (1H, 1′-H), 3.22 s (3H, OCH_3), 3.78 q (1H, OCH, J = 6.5 Hz), 4.56 m (2H, OCH_2O), 9.47 d (1H, CHO, J = 5.42 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.77 and 28.52

(2-CH_3), 17.48 (C^4), 22.06 (C^2), 30.39 ($C^{1'}$), 31.79 (**C**H_3CO), 35.84 and 38.12 (C^1, C^3), 51.09 (OCH_3), 58.28 ($C^{2'}$), 73.68 ($C^{3'}$), 94.79 (OCH_2O), 201.38 (CHO), 212.12 (C=O).

Minor diastereoisomer. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.78 m and 1.21 m (2H, 1-H, 3-H), 1.03 d (3H, CH_3, J = 6.3 Hz), 1.16 s (6H, 2-CH_3), 2.13 s (3H, CH_3CO), 2.45 m (1H, 1′-H), 3.22 s (3H, OCH_3), 3.78 q (1H, OCH, J = 6.5 Hz), 4.56 m (2H, OCH_2O), 9.48 d (1H, CHO, J = 5.41 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.65 and 28.52 (2-CH_3), 17.36 (C^4), 22.26 (C^2), 30.39 ($C^{1'}$), 32.02 (**C**H_3CO), 35.54 and 37.98 (C^1, C^3), 51.20 (OCH_3), 58.69 ($C^{2'}$), 73.94 ($C^{3'}$), 94.79 (OCH_2O), 201.26 (CHO), 210.99 (C=O).

Compound **XXI**. Major diastereoisomer. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.93 d (3H, CH_3, J = 13.3 Hz), 1.08 s (6H, 2-CH_3), 1.14 m and 1.40 m (2H, 1-H, 3-H), 1.71 m (2H, 2′-H), 2.16 s (3H, CH_3CO), 3.27 (6H, OCH_3), 3.29 s (3H, OCH_3), 4.06 m (1H, OCH), 4.48 m (2H, OCH_2O). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.19 and 28.73 (2-CH_3), 17.84 ($C^{4'}$), 18.16 (C^2), 23.54 (CH_2), 25.06 and 27.09 (C^1, C^3), 32.46 (**C**H_3CO), 52.19 (OCH_3), 55.32 (OCH_3), 57.62 ($C^{2'}$), 73.36 ($C^{3'}$), 94.68 (OCH_2O), 101.55 (OCHO), 211.19 (C=O).

Minor diastereoisomer. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.91 d (3H, CH_3, J = 17.7 Hz), 1.05 s (6H, 2-CH_3), 1.14 m and 1.40 m (2H, 1-H, 3-H), 1.71 m (2H, 2′-H), 2.16 s (3H, CH_3CO), 3.29 s (3H, OCH_3), 3.27 s (6H, OCH_3), 4.06 m (1H, OCH), 4.48 m (2H, OCH_2O). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.13 and 28.73 (2-CH_3), 18.24 (C^2), 18.37 ($C^{4'}$), 23.73 (CH_2), 24.75 and 27.03 (C^1, C^3), 32.69 (CH_3CO), 52.05 (OCH_3), 55.35 (OCH_3), 57.62 ($C^{2'}$), 73.59 ($C^{3'}$), 94.68 (OCH_2O), 101.47 (OCHO), 210.07 (C=O).

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