Letters to the Editor

(+)-δ-Cadinol as a promising starting compound in the synthesis of eleuthesides

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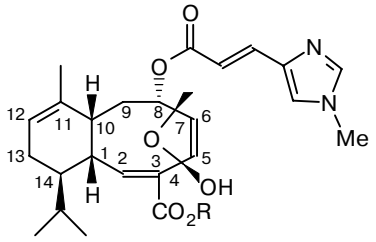
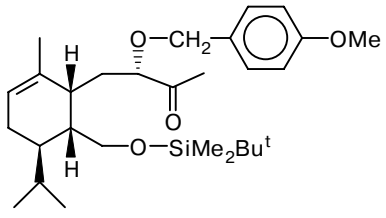
In the mid-90s of the 20th century, compounds with related structures and the mechanism of cytotoxic effect similar to that of taxol were found in soft corals. These compounds have later been grouped in a family of eleuthesides.[1—4]. Two independent syntheses of eleutherobine and sarcodictyines **1** developed afterwards were based on the use of monoterpenes (+)-carvone[2,3] and (−)-α-phellandrene[4] and differed strategically in the order of glycosylation and the method of construction of the oxygen bridge of the ten-membered ring. Monocyclic compound **2** served as a precursor in the synthesis.



1

Sarcodictyine A (R = Me); sarcodictyine B (R = Et

We studied the possibility of using another starting substrate in the synthesis of eleuthesides, *viz.*, accessible bicyclic sesquiterpenoid (+)-δ-cadinol (**3**) isolated from the oleo-resin of Siberian pine *Pinus sibirica* R. Mayr.[5—9] The absolute configuration of this compound was established from ^{13}C and ^{1}H NMR spectroscopic data (see Refs. 5 and 6) and confirmed by X-ray diffraction methods.[7] The key problem of the formation of the tricyclic core of eleuthesides by the route proposed by us is the development of the allylic oxidation of (+)-δ-cadinol, which would allow an alternative approach to the synthesis of compound **2** obtained previously from (+)-carvone, which contains precursors of carbon chains at the C(1) and C(10) atoms and oxygen functions at C(7) and C(8).



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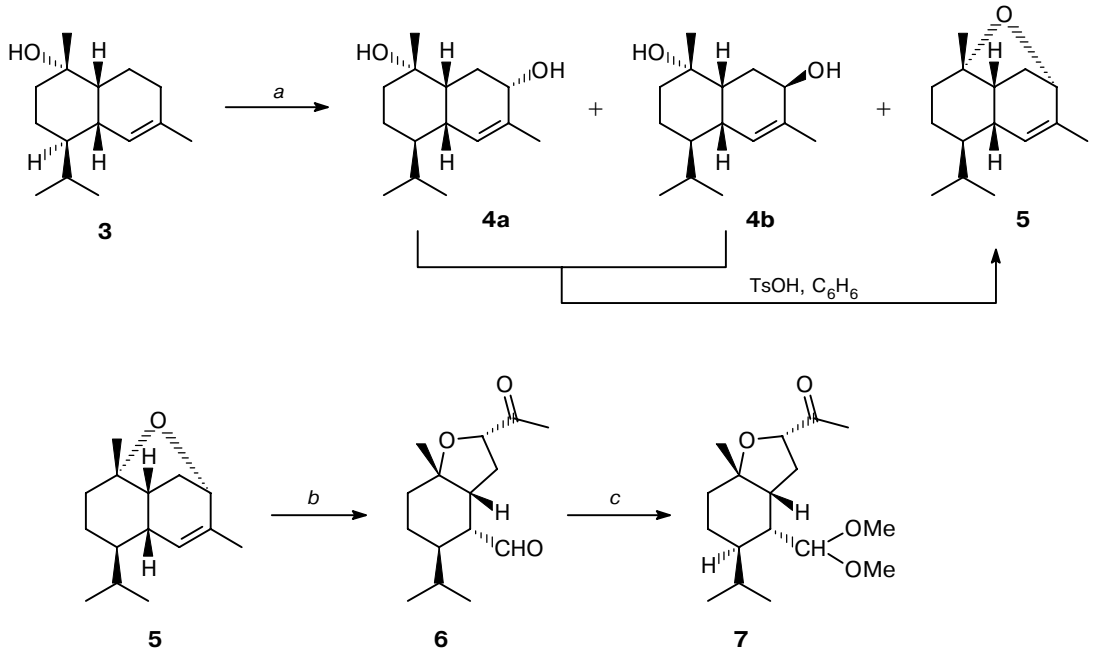
Scheme 1



Reagents and conditions: *a*. 1) SeO_2—Ac_2O, 70 °C, 2) MeONa; *b*. 1) O_3, MeOH, −78 °C, 2) Me_2S; *c*. MeOH, TsOH.

The oxidation of (+)-cadinol with SeO_2—Ac_2O followed by hydrolysis of the acyloxylation products gave a mixture of diols and epoxide (**4a,b** + **5**) from which α-epimer **4a** was isolated in 32% yield. The criterion for the assignment of epimeric alcohols **4a,b** is the upfield shift of the signals for β-epimer **4b** in the ^{13}C NMR spectrum due to the *syn*-interaction of the C(3) atom and its substituent with the environment in the $^1H_2$ conformation of the cyclohexene fragment and the low spin-spin coupling constant $J_{2,3}$ = 4.4 Hz in the ^1H NMR spectrum of this epimer. The latter confirmed the equatorial orientation of H(3), unlike its axial arrangement in α-epimer **4a**. Note that the chemical shift of H(7) in β-epimer δ 1.82 indicates the shift of equilibrium toward a conformer with the axial orientation of the isopropyl group compared with the α-epimer (δ 1.37). The subsequent steps in the transformation of diol **4a** into structure **2** are evident.

Minor 1,4-epoxide **5** seems to be a very attractive alternative to the structure of diol **4a**: it is "self-protected" in the rigid tricyclic system, which, in addition to decreasing the number of "blocking" steps, allows one to expect the efficient solution of stereochemical problems of synthesis after cyclohexene ring opening. These arguments favored the study of synthetic transformations of this compound.

With this purpose, we optimized the procedure of the preparation of 1,4-epoxide **5**: the treatment of the (**4a,b** + **5**) mixture with TsOH in benzene resulted in the target epoxide **5** in 73% yield over three stages. The ozonolysis of **5** followed by the reduction of the ozonide and selective acetalization of aldehyde **6** affords intermediate **7** in 77% yield. The latter contains in the latent form the oxygen function at C(8) of the eleutheside core and differentiated carbonyl groups, which is important for the progress of the synthesis (Scheme 1).

Compounds **4a**, **5**, and **7** were identified by NMR spectroscopy on a Bruker AM 300 instrument with a working frequency of 300.13 for ^1H and 75.47 MHz for ^{13}C. Signals for the protons and the corresponding C atoms were assigned from the CH-correlation spectra; only reliably established spin-spin coupling constants are presented. Mass spectra were obtained on an MX-1320 instrument (EI, 70 eV), and optical rotation was determined on a Perkin—Elmer 141 polarimeter. (+)-δ-Cadinol used in the synthesis had m.p. 137.8 °C and $[\alpha]_D^{20}$ +100.3 (*c* 1.0, $CHCl_3$).

(1*R*,3*S*,6*S*,7*R*,10*S*)-7-Isopropyl-4,10-dimethylbicyclo[4.4.0]-dec-4-ene-3,10-diol (4a). M.p. 102—103 °C. Found (%): C, 75.78; H, 11.19. $C_{15}H_{26}O_2$. Calculated (%): C, 75.58; H, 10.99. $[\alpha]_D^{26}$ +49.1 (*c* 1.0, $CHCl_3$). IR, ν/cm^{-1}: 3420—3240 (OH); 2990 (CH, CH_2, CH_3); 1480 (CH_3); 1380 (CH—Me_2); 1130, 1030 (OH); 990 (C=C). ^1H NMR ($CDCl_3$), δ: 0.81 (d, 3 H, CH_3, J = 7.0 Hz); 0.88 (d, 3 H, CH_3, J = 7.0 Hz); 1.20 (m, 1 H, H(9)); 1.25 (s, 3 H, CH_3); 1.37 (m, 1 H, H(7)); 1.50 (m, 3 H, CH_2(8), H(9)); 1.67 (m, 1 H, H_{eq}(2), J_{gem} = 9.5 Hz, $J_{2,3}$ = 5.0 Hz, $J_{2,1}$ was not determined*); 1.73 (m, 1 H, H(1)); 1.75 (d, 3 H, CH_3, $J_{Me,5}$ = 1.5); 1.88 (dqq, 1 H, H(13), $J_{13,7}$ = 4.5, $J_{13,Me}$ = 7.0 Hz); 2.05 (m, 1 H, H(6), $J_{6,5}$ = 5.0 Hz); 2.24 (dd, 1 H, H_{ax}(2), $J_{2,1}$ = 0, J_{gem} = 9.5 Hz, $J_{2,3}$ = 7.5 Hz); 2.56 (br.s, 1 H, OH); 4.03 (dd,

* We failed to determine $J_{2,1}$ by the double resonance method due to the superposition of signals from other protons.

1 H, H(3), $J_{3,2eq}$ = 5.0 Hz, $J_{3,2ax}$ = 7.5 Hz); 5.54 (qd, 1 H, H(5), $J_{5,Me}$ = 1.5 Hz, $J_{5,6}$ = 5.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 16.2 (CH_3); 19.6 (CH_3); 21.1 (C(8)); 21.7 (CH_3); 26.5 (C(13)); 27.7 (CH_3); 29.8 (C(2)); 35.1 (C(9)); 37.2 (C(6)); 43.3 (C(7)); 44.4 (C(1)); 70.7 (C(3)); 72.1 (C(10)); 128.4 (C(5)), 137.3 (C(4)).

(1*R*,3*R*,6*S*,7*R*,10*S*)-7-Isopropyl-4,10-dimethylbicyclo[4.4.0]-dec-4-ene-3,10-diol (4b). M.p. 69—71 °C. Found (%): C, 75.67; H, 11.08. $C_{15}H_{26}O_2$. Calculated (%): C, 75.58; H, 10.99. $[\alpha]_D^{22}$ +93.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$), δ: 0.78 (d, 3 H, CH_3, J = 7.0 Hz); 0.82 (d, 3 H, CH_3, J = 7.0 Hz); 1.05 (m, 1 H, H(9)); 1.22 (s, 3 H, CH_3); 1.27 (m, 1 H, H(8)); 1.42 (m, 1 H, H(9)); 1.47 (m, 1 H, H(8)); 1.68 (dd, 1 H, H(2), $J_{2,1}$ = 0, $J_{2,3}$ = 4.4 Hz, J_{gem} = 10.1); 1.72 (d, 1 H, CH_3, $J_{Me,5}$ = 1.5 Hz); 1.78 (m, 1 H, H(2), $J_{2,3}$ = 1.7 Hz, J_{gem} = 10.1 Hz, $J_{2,1}$ was not determined); 1.82 (m, 1 H, H(7)); 1.87 (dqq, 1 H, H(13), $J_{13,7}$ = 3.2 Hz, $J_{13,Me}$ = 7.0 Hz); 1.95 (m, 1 H, H(1)); 2.0 (m, 1 H, H(6)); 3.94 (dd, 1 H, H(3), $J_{3,2}$ = 1.7 Hz, $J_{3,2}$ = 4.4 Hz), 5.65 (qd, 1 H, H(5), $J_{5,Me}$ = 1.5 Hz, $J_{5,6}$ = 5.6 Hz). ^{13}C NMR ($CDCl_3$), δ: 15.4 (CH_3); 21.0 (CH_3); 21.3 (C(8)); 21.5 (CH_3); 26.8 (C(13)); 28.0 (C(2)); 28.1 (CH_3); 34.6 (C(9)); 36.9 (C(6)); 39.6 (C(7)); 42.6 (C(1)); 68.4 (C(3)); 71.8 (C(10)); 129.0 (C(5)), 134.7 (C(4)).

(1*S*,4*R*,5*S*,8*S*,10*R*)-4-Isopropyl-1,7-dimethyl-11-oxatricyclo[6.2.1.0^{5,10}]undec-6-ene (5). Oil. Found (%): C, 81.64; H, 10.69. $C_{15}H_{24}O$. Calculated (%): C, 81.81; H, 10.91. $[\alpha]_D^{26}$ −58.0 (*c* 1.0, $CHCl_3$). IR, ν/cm^{-1}: 2970—2850 (CH, CH_2, CH_3); 1480 (CH_3); 1380 (CH—(CH_3)$_2$); 1040, 1280 (C—O—C); 990 (C=C). ^{1}H NMR ($CDCl_3$), δ: 0.83 (d, 3 H, CH_3, J = 6.5 Hz); 0.86 (d, 3 H, CH_3, J = 6.5 Hz); 1.02 (m, 1 H, H(4)); 1.08 (s, 3 H, C(1)—C$\underline{H}_3$); 1.28 (m, 1 H, H(3)); 1.40 (m, 1 H, H(2)); 1.53 (m, 1 H, H(3′); 1.62 (m, 2 H, H(9), H(12)); 1.65 (d, 3 H, C(7)—C$\underline{H}_3$, $J_{Me,6}$ = 1.7 Hz); 1.72 (m, 1 H, H(2′)); 1.90 (ddd, 1 H, H(10), $J_{10,9'}$ = 5.0 Hz, $J_{10,5}$ = 5.4 Hz, $J_{10,9}$ = 8.0 Hz); 2.25 (ddd, 1 H, H(9′), $J_{9',10}$ = 5.0 Hz, $J_{9',8}$ = 5.4 Hz, J_{gem} = 10.8 Hz); 2.50 (m, 1 H, H(5)); 3.94 (d, 1 H, H(8), J = 5.4 Hz); 4.88 (m, 1 H, H(6)). ^{13}C NMR ($CDCl_3$), δ: 19.3 (C(3)); 20.8 (2 CH_3); 20.9 (CH_3); 25.4 (C(13)); 30.2 (CH_3); 30.5 (C(2)); 35.4 (C(9)); 38.5 (C(10)); 38.9 (C(5)); 44.9 (C(4)); 76.6 (C(8)); 81.6 (C(1)); 127.3 (C(6)); 140.2 (C(7)). MS (EI), m/z (I_{rel} (%)): 220 $[M]^+$ (25).

(1*R*,2*R*,3*R*,6*S*,8*S*)-8-Acetyl-2-dimethoxymethyl-3-isopropyl-6-methyl-7-oxabicyclo[4.3.0^{1,6}]nonane (7). Oil. Found (%): C, 68.74; H, 9.81. $C_{17}H_{30}O_4$. Calculated (%): C, 68.45; H, 10.07. $[\alpha]_D^{26}$ +19.4 (*c* 1.0, $CHCl_3$). IR (KBr), ν/cm^{-1}: 2830 (—O—CH_3); 1780 (C=O); 1380 (CH—(CH_3)$_2$); 1280 (C—O—C). ^{1}H NMR ($CDCl_3$), δ: 0.72 (d, 3 H, CH_3, J = 7.0 Hz); 0.83 (d, 3 H, CH_3, J = 7.0 Hz); 1.08—1.20 (m, 3 H, CH); 1.25 (s, 3 H, CH_3); 1.38 (m, 1 H, CH); 1.43—1.58 (m, 3 H, CH); 1.78 (m, 2 H, CH_2); 2.12 (s, 3 H, CH_3); 2.20 (m, 1 H, CH); 3.33 (s, 6 H, OCH_3); 4.23 (d, 1 H, C$\underline{H}$(OCH_3)$_2$, $J_{1',2}$ = 3.5 Hz); 4.35 (m, 1 H, H(8)). ^{13}C NMR ($CDCl_3$), δ: 15.1 (CH_3); 21.5 (CH_3); 21.8 (C(4)); 24.5 (CH_3); 26.2 (CH_3); 26.2 ($\underline{C}$H(CH_3)$_2$); 32.1 (C(9)); 34.5 (C(5)); 37.5 (C(1)); 39.9 (C(2)); 44.3 (C(3)); 56.1 (OCH_3); 56.5 (OCH_3); 82.6 (C(8)); 83.5 (C(6)); 107.1 ($\underline{C}$H(OCH_3)$_2$); 210.9 (C=O). MS (EI), m/z (I_{rel} (%)): 298 $[M]^+$ (37).

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