Chemistry of Natural Compounds, Vol. 37, No. 5, 2001

B R I E F C O M M U N I C A T I O N S

APPROACHES TO FORMATION OF THE ELEUTHESIDE NUCLEUS BASED ON (+)-δ-CADINOL

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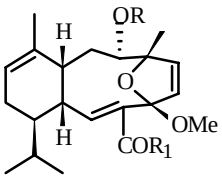
UDC 547.596.2

Schemes for synthesizing eleuthesides **1** [1], new cytotoxic marine metabolites, are based on the use of the monoterpenes (+)-carvone [2, 3] or (-)-α-phellandrene [4, 5]. We think that the sesquiterpenoid (+)-δ-cadinol (**2**) structure can act as an alternate platform for constructing the eleutheside nucleus through an intermediate like **3** [2, 3].



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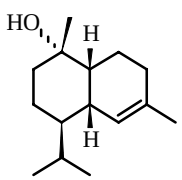

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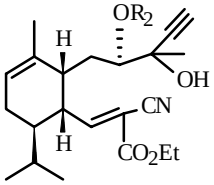

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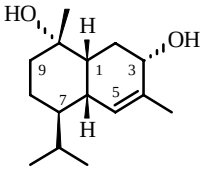
Thus, we studied methods for allylic oxidation of **2** followed by ozonolytic cleavage of the double bond with differentiation of the resulting carbonyls and steps for constructing the side chains before final closure into the tricyclic nucleus.

Diol **4** was prepared in 32% yield along with the β-isomer (42%) and 1,4-epoxide **5** (13%) by reacting (+)-δ-cadinol and SeO_2 in Ac_2O at 70°C followed by hydrolysis of the acetates. Ozonolysis of the monobenzylated derivative of **4** (1. O_3, MeOH, -78°C; 2. Me_2S, *p*-TsOH) gave ketoacetal **6**, a key intermediate for continuing the synthesis.



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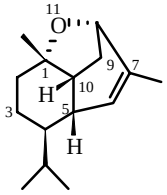

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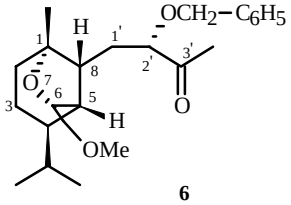

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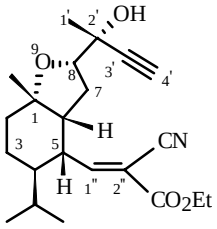

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Self-protection of the tricyclic ether **5** is an important advantage over other compounds for studying approaches to the formation of the tricyclic 4,7-oxaeunicellane nucleus. Thus, the method for preparing this compound was optimized. Boiling a benzene solution containing a catalytic amount of *p*-TsOH and the product mixture obtained after oxidation of (+)-δ-cadinol by SeO_2 in Ac_2O at 70°C gave the 1,4-epoxide **5** in 73% yield. The next steps of ozonolysis (1. O_3, MeOH, -78°C; 2. Me_2S, *p*-TsOH catalyst), acetylenation (HC≡CMgBr, Et_2O, 0°C), and Knoevenagel condensation ($NCCH_2CO_2Et$, EtOH, β-alanine) [2, 3] formed the intermediate **7**, a bicyclic analog of **3**.

^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300 instrument at working frequencies 300.13 (^1H) and 75.47 MHz (^{13}C). Signals for protons and C atoms were assigned based on C—H correlation spectra (CH-corr.). Mass spectra

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 0009-3130/01/3705-0490$25.00

were taken in an MX-1320 instrument (EI, 70 eV). Optical rotations were measured on a Perkin—Elmer 141 polarimeter. We used (+)-δ-cadinol with mp 137.8°C and optical rotation $[\alpha]_D^{20}$ +100.3° (*c* 1.0, $CHCl_3$).

1R,3S,6S,7R,10S-7-Isopropyl-4,10-dimethylbicyclo[4.4.0]dec-4-en-3,10-diol (4). mp 102-103°C (Et_2O), $[\alpha]_D^{26}$ +49.1° (*c* 1.0, $CHCl_3$).

PMR spectrum ($CDCl_3$, 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_2-8 and H_{eq}-9), 1.67 (1H, dd, J_{gem} = 9.5, J_{2eq-3} = 5.0, $J_{2eq-1}$was not determined, H_{eq}-2), 1.73 (1H, m, H-1), 1.75 (3H, s, CH_3C-4), 1.88 (1H, dqq, J_{Me_2CH-7} = 4.5, J_{Me_2CH-Me} = 7.0, Me_2CH), 2.05 (1H, m, J_{6-5} = 5.0, H-6), 2.24 (1H, dd, J_{gem} = 9.5, J_{2ax-3} = 7.5, H_{ax}-2), 2.50 (1H, br.s, OH), 2.56 (1H, br.s, OH), 4.03 (1H, dd, J_{3-2eq} = 5.0, J_{3-2ax} = 7.5, H-3), 5.54 (1H, qd, J_{5-Me} = 1.5, J_{5-6} = 5.0, H-5).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 16.22 (CH_3), 19.62 (CH_3), 21.15 (C-8), 21.70 (CH_3), 26.47 (Me_2C), 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).

Found (%): C 75.78, H 11.19, $C_{15}H_{26}O_2$.

Calc. (%): C 75.58, H 10.99.

1S,4R,5S,8S,10R-4-Isopropyl-1,7-dimethyl-11-oxatricyclo[6.2.1.0^{5,10}]undec-6-ene (5). $[\alpha]_D^{26}$ -58.0° (*c* 1.0, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.83 [3H, d, J = 6.5, C<u>H</u>$_3$(CH$_3$)CH], 0.86 [3H, d, J = 6.5, CH$_3$(C<u>H</u>$_3$)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_2CH), 1.65 (3H, d, J_{Me-6} = 1.7, CH_3C-7), 1.72 (1H, m, H_{eq}-2), 1.90 (1H, ddd, J_{10-9eq} = 5.0, J_{10-5} = 5.4, and J_{10-9ax} = 8.0, H-10), 2.25 (1H, ddd, J_{9eq-10} = 5.0, J_{9eq-8} = 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 ($CDCl_3$, δ, ppm): 19.33 (C-3), 20.83 (2CH_3), 20.92 (CH_3), 25.42 (Me_2C), 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).

Found (%): C 81.64, H 10.69, $C_{15}H_{24}O$.

Calc. (%): C 81.76, H 10.96.

1R,4R,5R,6R,8R-8-(2′-Benzyloxy-3′-oxobutyl)-4-isopropyl-1-methyl-6-methoxy-7-oxabicyclo[3.2.1^{1,5}]octane (6). $[\alpha]_D^{20}$ -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_3C-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_2CH, CH_2-3), 1.75 (1H, ddd, $J_{1'ax-2}$ = 2.6, $J_{1'ax-8}$ = 9.6, J_{gem} = 11.0, H_{ax}-1′), 2.05 (1H, ddd, $J_{1'eq-8}$ = 3.8, $J_{1'eq-2'}$ = 9.9, J_{gem} = 11.0, H_{eq}-1′), 2.12 (3H, s, CH_3C-3′), 2.40 (1H, d, J_{5-8} = 3.4, H-5), 3.30 (3H, s, OCH_3), 3.92 (1H, dd, $J_{2'-1'ax}$ = 2.6, $J_{2'-1'eq}$ = 9.9, H-2′), 4.30 (1H, d, J_{gem} = 10.8, CH_2Ph), 4.53 (1H, d, J_{gem} = 10.8, CH_2Ph), 4.70 (1H, s, 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 (CMe_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_2Ph), 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′).

Found (%): C 73.53, H 9.24, $C_{23}H_{34}O_4$.

Calc. (%): C 73.76, H 9.15.

1S,(2R),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 (7). $[\alpha]_D^{20}$ +50.6° (*c* 1.0, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.78 [3H, d, J = 6.8, C<u>H</u>$_3$(CH$_3$)CH], 0.92 [3H, d, J = 6.8, CH$_3$(C<u>H</u>$_3$)CH], 1.10 (1H, m, H_{ax}-3), 1.30 (1H, m, H_{eq}-3), 1.39 (3H, t, J = 7.2, C<u>H</u>$_3$CH$_2$O), 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_{8-7ax} = 5.8, J_{8-7b} = 10.3, H-8), 4.33 (2H, q, J_{Me_2CH-Me} = 6.1, OCH_2), 7.51 (1H, d, $J_{1''-5}$ = 11.0, H-1″).

^{13}C NMR spectrum ($CDCl_3$, 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″).

Found (%): C 70.33, H 8.58, N 3.29, $C_{22}H_{31}NO_4$.

Calc. (%): C 70.75, H 8.37, N 3.75.

ACKNOWLEDGMENT

The work was funded by the Russian Basic Research Foundation (grant No. 01-03-32050).

REFERENCES

1. T. Lindel, *Angew. Chem. Int. Ed. Engl.*, **37**, 774 (1998).
2. K. C. Nikolaou, J.-Y. Xu, S. Kim, T. Ohshima, S. Hosokawa, and J. Pfefferkorn, *J. Am. Chem. Soc.*, **119**, 11353 (1997).
3. K. C. Nikolaou, F. Van Delft, T. Ohshima, D. Vourloumis, J. Xu, S. Hosokawa, J. Pfefferkorn, S. Kim, and T. Li, *Angew. Chem.*, **109**, 2630 (1997).
4. X.-T. Chen, C. E. Gutteridge, S. K. Bhattacharya, B. Zhou, T. R. R. Pettus, T. Hascall, and S. J. Danishefsky, *Angew. Chem.*, **110**, 195 (1998).
5. X.-T. Chen, B. Zhou, S. K. Bhattacharya, C. E. Gutteridge, T. R. R. Pettus, and S. J. Danishefsky, *Angew. Chem. Int. Ed. Engl.*, **37**, 789 (1998).