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An Original Method for the Synthesis of Partially Deuterated Natural Lembehyne B and the Study of Its Biological Activity †

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Abstract: An efficient method for the synthesis of a partially deuterated analogue of the natural neuritogenic alkynol, lembehyne B, has been developed for the first time, based on the use of a new reaction of Ti-catalyzed cross-cyclomagnesiation of O-containing 1,2-dienes and terminal aliphatic 1,2-dienes using EtMgBr in high yield. The introduction of two deuterium atoms is carried out at the stage of treatment of the formed in situ magnesacyclopentane with D_2O.

Keywords: 1,2-dienes; cross-cyclomagnesiation; d_2-lembehyne B

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1. Introduction

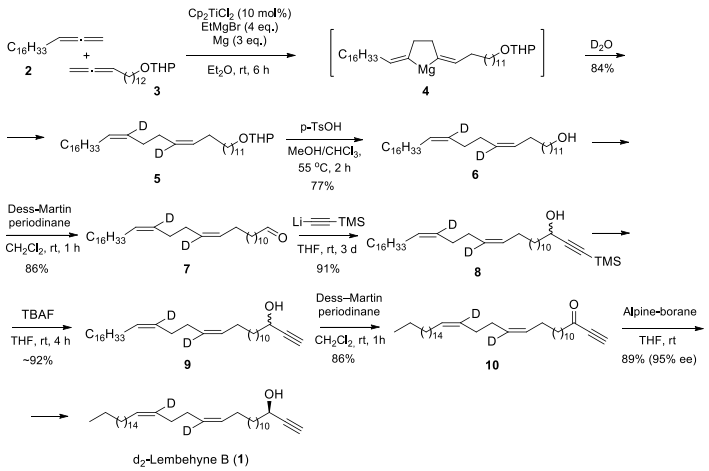
Acetylene alcohol lembehyne B, isolated in trace amounts from the Indonesian sea sponge *Haliclona* sp. [1], exhibits neuritogenic activity on Neuro-2A neuroblastoma cells [2], and is also an inducer of early apoptosis of Jurkat, HL-60 and K562 cell cultures [3].

Numerous studies carried out in recent years have shown that partially deuterated analogues of drugs have better pharmacokinetic characteristics, lead to changes in the mechanisms of biotransformation and a decrease in toxicity [4].

Earlier, at the Laboratory of Catalytic Synthesis of the Institute of Petrochemistry and Catalysis of the Ufa Federal Research Center of the Russian Academy of Sciences, a complete synthesis of natural lembehyne B was carried out for the first time [3], using the Ti-catalyzed cross-cyclomagnesiation of terminal allenes at the key stage of the reaction (the Dzhemilev reaction) [5–16]. Having obtained positive results of the study of the cytotoxicity of this alkynol, we obtained its deuterated analogue and studied its cytotoxicity in vitro.

2. Results and Discussion

At the first stage, the reaction of cross-cyclomagnesiation of 1,2-nonadecadiene **2** and tetrahydropyran ether 13,14-pentadecadienol **3** was carried out using EtMgBr in the presence of metallic Mg and a catalyst Cp_2TiCl_2 (10 mol%), through the stage of formation of magnesacyclopentane **4**, the deuterolysis of which gives tetrahydropyran ether 14,17-Dideutero-(13*Z*,17*Z*)-tetraconte-13,17-dienol **5** in 84% yield. Successive reactions of removal of tetrahydropyranyl protection and oxidation of unsaturated deuterated alcohol **6** using Dess-Martin periodinan led to 14,17-Dideutero-(13*Z*,17*Z*)-tetrakont-13,17-dienal **7** in ~86% yield. As a result of the reaction of the previously synthesized lithium (trimethylsilyl)acetylenide with aldehyde **7** and removal of the trimethylsilyl protection with TBAF, racemic d_2-lembehyne B is formed in ~92% yield. Oxidation of hydroxyl group **9** with Dess-Martin periodinane gives ketone **10**, and subsequent stereoselective reduction leads to the target d_2-lembehyne B 1 (Scheme 1).



Scheme 1. Complete synthesis d_2-lembehyne B.

For the synthesized compound, the in vitro antitumor activity was assessed on Jurkat, K562, HL-60, U937 cell lines and fibroblasts, including the determination of IC50 using flow cytometry and multiplex analysis.

3. Conclusions

Thus, we have obtained for the first time a partially deuterated analogue of lembehyne B, using the reaction of Ti-catalyzed cross-cyclomagnesiation of 1,2-dienes (Dzhemilev reaction) at the key stage of synthesis, and also studied its antitumor activity using modern methods of flow cytometry and multiplex analysis.

4. Experimental Part

Commercially available reagents (Sigma-Aldrich and Acros) were used. Reactions with organomagnesium compounds were carried out under dried argon atmosphere. 1,2-dienes was prepared according to the known procedure. Reaction products were analyzed on a Carlo Erba chromatograph (a Hewlett Packard Ultra-1 glass capillary column, 25 m × 0.2 mm, flame ionization detector, operating temperature 50–170 °C, carrier gas helium). TLC was performed on Silufol UV-254 plates. Elemental composition of compounds was determined using a Carlo Erba-1106 instrument. Mass spectra were obtained using a Bruker MALDI-TOF/TOF Autoflex III instrument. 1H and 13C NMR spectra were recorded on a Bruker Avance 400 spectrometer (100.62 MHz for 13C and 400.13 MHz for 1H). Chemical shifts of 1H and 13C nuclei (δ) are given relative to the residual signals of the deuterated solvent (δ 7.28 for protons and 77.2 for carbon nuclei).

Cross-cyclomagnesiation of nonadeca-1,2-diene (**2**) *and 2-(pentadeca-13,14-dien-1-yloxy)tetrahydro -2H-pyran* (**3**) *with EtMgBr in the presence of Mg metal and* Cp_2TiCl_2 *catalyst*. Diethyl ether (30 mL), nonadeca-1,2-diene (**2**) (1.27 g, 4.8 mmol), 2-(pentadeca-13,14-dien-1-yloxy) tetrahydro-2H-pyran (3) (1.23 g, 4.0 mmol), EtMgBr (16.0 mmol) (as 1.5 M solution in Et_2O), Mg powder (0.29 g, 12.0 mmol) and Cp_2TiCl_2 (0.1 g, 0.4 mmol) were placed in a glass reactor with stirring under argon (~0 °C). The reaction mixture was warmed-up to room temperature (20–22 °C) and stirred for 6 h. The reaction mixture was treated with D_2O (20 mL) and extracted with diethyl ether (2 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Silica gel column chromatography (hexane/EtOAc (35/1)) of the residue gave compound 5 (1.98 g, 88 %) as a pale yellow oily liquid.

14,17-Dideutero-2-[(13Z,17Z)-tetratriaconta-13,17-dien-1-yloxy]tetrahydro-2H-pyran (**5**). Yeld 84%. R_f = 0.40. IR (film) υ_{max} 724, 815, 1075, 1110, 1254, 1303, 1360, 1384, 1468, 2853, 2924 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J* = 6 Hz, C<u>H</u>$_3$), 1.25–1.70 (48H, m, C<u>H</u>$_2$), 1.78–1.85 (6H, m, C<u>H</u>$_2$), 1.95–2.05 (8H, m, C<u>H</u>$_2$), 3.32–3.87 (4H, m, C<u>H</u>$_2$-O), 4.54–4.56 (1H,

m, C<u>H</u>-O), 5.32–5.39 (2H, m, C<u>H</u>=). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 14.07, 19.56, 22.68, 25.54, 26.27, 27.20, 27.28, 29.21, 29.25, 29.32, 29.38, 29.51, 29.56, 29.62, 29.72, 29.76, 30.73, 31.94, 61.99, 67.53, 98.61, 130.06. MS (MALDI-TOF), *m*/*z*: 577 $[M]^+$. $C_{39}H_{72}D_2O_2$. Found (%): C, 81.26; H, 12.90. Calc. for $C_{39}H_{72}D_2O_2$ (%):C, 81.18; H, 13.27.

THP-deprotection of ether (**5**) *was carried out with p-TsOH in* CH_2Cl_2*/MeOH using known method [17]. 14,17-Dideutero-(13Z,17Z)-tetratriaconta-13,17-dien-1-ol* (**6**). Yeld 77%. R_f = 0.43 (hexane/EtOAc—5:1). IR (film) υ_{max} 674, 729, 1034, 1078, 1124, 1159, 1180, 1204, 1354, 1382, 1441, 1662, 2853, 2924 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.91 (3H, t, *J* = 6 Hz, C<u>H</u>$_3$), 1.26–1.37 (44H, m, C<u>H</u>$_2$), 1.55–1.61 (2H, m, C<u>H</u>$_2$), 1.98–2.10 (8H, m, C<u>H</u>$_2$), 3.64–3.68 (2H, m, C<u>H</u>$_2$-O), 5.40–5.42 (4H, m, C<u>H</u>=). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 14.12, 22.70, 25.76, 27.24, 27.32, 29.28, 29.34, 29.41, 29.47, 29.55, 29.58, 29.62, 29.65, 29.71, 29.75, 31.94, 32.83, 63.09, 130.24. MS (MALDI-TOF), *m*/*z*: 492 $[M]^+$. $C_{34}H_{64}D_2O$. Found (%): C, 82.11; H, 13.44. Calc. for $C_{34}H_{64}D_2O$ (%): C, 82.85; H, 13.90.

The oxidation of the alcohol (**6**) *with Dess-Martin periodinane was carried out according known procedure [18]. 14,17-Dideutero-(13Z,17Z)-tetratriaconta-13,17-dien-1-al* (**7**). Yeld 86%. IR (film) υ_{max} 721, 910, 1091, 1466, 1729, 2852, 2922, 3009 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (3H, t, CH_3, *J* = 6 Hz), 1.27–1.35 (44H, m, CH_2), 1.60–1.67 (3H, m), 2.00–2.08 (8H, m, =CH-C<u>H</u>$_2$), 2.40–2.44 (2H, m, O=CH-C<u>H</u>$_2$), 5.36–5.43 (4H, m, =C<u>H</u>), 9.76–9.77 (1H, t, O=C<u>H</u>, *J* = 6 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 14.10, 22.09, 22.70, 27.23, 27.30, 29.29, 29.37, 29.44, 29.52, 29.56, 29.59, 29.62, 29.68, 29.72, 29.76, 31.94, 43.91, 130.16, 130.19, 202.24. MS (MALDI-TOF), *m*/*z*: 490 $[M]^+$. $C_{34}H_{62}D_2O$. Found (%): C, 83.44; H, 13.23. Calc. for $C_{34}H_{62}D_2O$ (%): C, 83.19; H, 13.55.

Procedure for preparation of alkyne (**8**). To a solution of trimethylsilyl acetylene 0.58 g (6 mmol) in THF (10 mL) was added dropwise a solution of 4 ml n-BuLi (1.5 M in hexane) at −40 °C. The solution was stirred for 1 h at −40 to 0 °C. Then the solution was added dropwise to THF solution of 1.5 g (3.08 mmol) dienal (**7**) at −10 °C. The reaction mixture was warmed-up to room temperature (20–22 °C) and stirred for 3 days. The reaction mixture was treated with a 5% solution of NH_4Cl in H_2O (20 mL) and extracted with diethyl ether (2 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Silica gel column chromatography of the residue gave compound **8** (1.64 g, 91 %) as a pale yellow oily liquid.

16,19-Dideutero-(15Z,19Z)-1-(trimethylsilyl)hexatriaconta-15,19-dien-1-yn-3-ol (**8**). Yeld 91%. IR (film) υ_{max} 550, 627, 655, 720, 781, 808, 890, 909, 965, 1022, 1306, 1377, 1464, 1654, 2116, 2835, 2924, 3008, 3313 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.18 (9H, т, CH_3), 0.90 (3H, t, CH_3, *J* = 6 Hz), 1.28–1.75 (49H, m, CH_2), 1.91–2.14 (8H, m, =CH-C<u>H</u>$_2$), 4.35 (1H, t, HO-C<u>H</u>, *J* = 5 Hz), 5.36–5.43 (2H, m, =C<u>H</u>). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: -0.11, 14.13, 22.72, 25.14, 27.24, 27.32, 29.28–29.78, 31.97, 37.69, 62.76, 89.01, 107.19, 130.16. MS (MALDI-TOF), *m*/*z*: 590 $[M]^+$. $C_{39}H_{74}OSiD_2$. Found (%): C, 79.68; H, 12.85. Calc. for $C_{39}H_{74}OSiD_2$ (%): C, 79.51; H, 13.00.

Procedure for preparation of 16,19-Dideutero-(15Z,19Z)-dimethylhexatriaconta-15,19-dien-1 -yn-3-ol (**9**). To a solution of alkyne (**8**) 1.17 g (2 mmol) in THF (10 mL) was added TBAF (1M in THF, 1.2 equv.) at 0 °C, then the solution was stirred for 6 h at room temperature. Then the solution was added dropwise to THF solution of 1.5 g (3.08 mmol) dienal (**7**) at −10 °C. The reaction mixture was treated with saturated aq. NaCl and extracted with diethyl ether (2 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Silica gel column chromatography of the residue gave compound **1** (1.07 g, 99 %) as a colorless powder.

16,19-Dideutero-(15Z,19Z)-dimethylhexatriaconta-15,19-dien-1-yn-3-ol (**9**). Yeld 92%. $[\alpha]^{25}_D$ +0.43 (*c* 0.3, $CHCl_3$). IR (film) υ_{max} 551, 627, 655, 721, 781, 809, 890, 909, 965, 1022, 1307, 1377, 1464, 1654, 2116, 2835, 2924, 3008, 3311 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, t, CH_3, *J* = 6.7 Hz), 1.30–1.50 (44H, m, CH_2), 1.66–1.79 (2H, m, C<u>H</u>$_2$), 1.88–2.16 (8H, m,

=CH-C$\underline{H}_2$), 2.48 (1H, d, CH), 4.39 (1H, td, *J* = 7.0, 2.0 Hz), 5.40 (2H, t, =C$\underline{H}$, *J* = 6.7 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 14.14, 22.71, 25.03, 27.25, 27.32, 29.22, 29.26, 29.35, 29.39, 29.54, 29.59, 29.65, 29.68, 29.77, 31.95, 37.68, 62.37, 72.82, 85.03, 130.24. MS (MALDI-TOF), *m*/*z*: 516 $[M]^+$. $C_{36}D_2H_{64}O$. Found (%): C, 84.30; H, 12.57. Calc. for $C_{36}D_2H_{64}O$ (%): C, 84.11; H, 12.78.

The oxidation of the alcohol (**9**) *with Dess-Martin periodinane was carried out according [18]. (15Z,19Z)-16,19-Dideutero-(15Z,19Z)-hexaconta-15,19-dien-1-yl-3-one* (**10**). Yield 86%. IR (film) υ_{max} 553, 627, 655, 720, 786, 807, 890, 909, 965, 1022, 1306, 1377, 1461, 1654, 2116, 2835, 2924, 3008, 3312 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, t, CH_3, *J* = 6 Hz), 1.23–1.48 (44H, m, CH_2), 1.64–1.72 (2H, m, C$\underline{H}_2$), 2.04–2.10 (8H, m, =CH-C$\underline{H}_2$), 2.58–2.62 (2H, m, O=CH-C$\underline{H}_2$), 3.22 (1H, s, C$\underline{H}$), 5.39–5.42 (4H, m, =C$\underline{H}$). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 187.5 (C), 130.4 (CH), 130.3 (CH), 129.1 (2C, CH), 81.5 (C), 78.2 (CH), 45.5 (CH_2), 31.9 (CH_2), 29.3–29.7 (signals of 19C, CH_2), 28.9 (CH_2), 27.4 (2C, CH_2), 27.3 (2C, CH_2), 22.7 (CH_2), 23.8 (CH_2), 14.1 (CH_3). MS (MALDI-TOF), *m*/*z*: 514 $[M]^+$. $C_{36}D_2H_{62}O$.Found (%): C, 84.14; H, 12.80. Calc. for $C_{36}D_2H_{62}O$ (%): C, 84.19; H, 12.82.

The stereoselective reduction of ketone 10 with B-3-pinanyl-9-borabicyclo[3.3.1]nonane (Alpine-borane reagent) was carried out according procedure [15]. d$_2$*-Lembehyne B* (**1**). Yield 89% (95% ee). $[\alpha]^{25}_D$ +0.43 (*c* 0.3, $CHCl_3$). IR (film) υ_{max} 550, 627, 655, 721, 781, 809, 890, 909, 965, 1022, 1307, 1377, 1464, 1654, 2116, 2835, 2924, 3008, 3310 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, t, CH_3, *J* = 7 Hz), 1.23–1.54 (44H, m, CH_2), 1.71–1.75 (2H, m, C$\underline{H}_2$), 2.04–2.10 (8H, m, =CH-C$\underline{H}_2$), 4.39 (1H, td, *J* = 7.0, 2.0 Hz), 5.39–5.41 (4H, m, =C$\underline{H}$). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 130.4 (2C, CH), 129.2 (2C, CH), 85.0 (C), 72.8 (CH), 62.4 (CH), 37.7 (CH_2), 31.9 (CH_2), 29.3–29.7 (signals of 19C, CH_2), 29.2 (CH_2), 27.4 (2C, CH_2), 27.3 (2C, CH_2), 25.0 (CH_2), 22.7 (CH_2), 14.1 (CH_3).

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References

1. Aoki, S.; Matsui, K.; Wei, H.; Murakami, N.; Kobayashi, M. Structure–Activity Relationship of Neuritogenic Spongean Acetylene Alcohols, Lembehynes. *Tetrahedron* **2002**, *58*, 5417–5422. https://doi.org/10.1016/S0040-4020(02)00519-7.
2. Dembitsky, V.M.; Levitsky, D.O.; Gloriozova, T.A.; Poroikov, V.V. Acetylenic Aquatic Anticancer Agents and Related Compounds. *Nat. Prod. Commun.* **2006**, *1*, 405–429. https://doi.org/10.1177/1934578X0600100914.
3. Dzhemileva, L.U.; D'yakonov, V.A.; Makarov, A.A.; Andreev, E.N.; Yunusbaeva, M.M.; Dzhemilev, U.M. The first total synthesis of the marine acetylenic alcohol, lembehyne B—A selective inducer of early apoptosis in leukemia cancer cells. *Org. Biomol. Chem.* **2017**, *15*, 470–476. https://doi.org/10.1039/c6ob02346k.
4. Syroeshkin, A.V.; Elizarova, T.E.; Pleteneva, T.V.; Uspenskaya, E.V.; Levitskaya, O.V.; Zlatskiy, I.A.; Maksimova, T.V. The Influence of Deuterium on the Properties of Pharmaceutical Substances. *Drag Dev. Regist.* **2020**, *9*, 24–32.
5. D'yakonov, V.A.; Makarov, A.A.; Ibragimov, A.G.; Khalilov, L.M.; Dzhemilev, U.M. Novel Mg-organic reagents in organic sinthesis.Cp_2TiCl_2 catalized intermolecular cyclomagnesiation of cyclic and acyclic 1,2-dienes using Grignard reagents. *Tetrahedron* **2008**, *64*, 10188–10194.

6. Dyakonov, V.A.; Makarov, A.A.; Makarova, E.K.; Khalilov, L.M.; Dzhemilev, U.M. Cyclomagnesiation of N-Containing 1,2-Dienes Using Grignard Reagents Catalyzed by Cp_2TiCl_2. *Russ. J. Org. Chem.* **2012**, *48*, 357–361.
7. Dyakonov, V.A.; Makarov, A.A.; Makarova, E.K.; Khalilov, L.M.; Dzhemilev, U.M. Synthesis and transformation of metalcycles. Communication 41. Cyclomagnesiation of O-containing 1,2-dienes with Grignard reagents in the presence of Cp_2TiCl_2. *Russ. Chem. Bull. Int. Ed.* **2012**, *10*, 1928–1934.
8. D'yakonov, V.A.; Makarov, A.A.; Makarova, E.K.; Dzhemilev, U.M. Novel organomagnesium reagents in synthesis. Catalytic cyclomagnesiation of allenes in the synthesis of N-, O-, and Si-substituted 1Z,5Z-dienes. *Tetrahedron* **2013**, *69*, 8516-8526.
9. Dyakonov, V.A.; Makarov, A.A.; Makarova, E.K.; Dzhemilev, U.M. Catalytic cross cyclomagnesiation of 1,2-dienes in the synthesis of Z,Z-dienoic alcohols and 5Z,9Z-dienoic acids. *Mol. Complex. Mod. Chem.* **2014**, *92*.
10. D'yakonov, V.A.; Makarov, A.A.; Mulukova, A.R.; Dzhemilev, U.M. Catalytic cross cyclomagnesiation of 1,2-dienes in the synthesis of Z,Z-dienoic alcohols and 5Z,9Z-dienoic acids. *Russ. Chem. Bull. Int. Ed.* **2015**, *9*, 2135–2140.
11. D'yakonov, V.A.; Islamov, I.I.; Makarov, A.A.; Dzhemilev, U.M. Ti-Catalyzed cross-cyclomagnesiation of 1,2-dienes in the stereoselective synthesis of insect pheromones. *Tetrahedron Lett.* **2017**, *58*, 1755–1757. https://doi.org/10.1016/j.tetlet.2017.03.061.
12. D'yakonov, V.A.; Makarov, A.A.; Dzhemileva, L.U.; Andreev, E.N.; Dzhemilev, U.M. The first total synthesis of Lembehyne B, *Mendeleev Commun.* **2017**, *27*, 122–124. https://doi.org/10.1016/j.mencom.2017.03.004.
13. D'yakonov V, A.; Makarov, A.A.; Dzhemileva, L.U.; Andreev, E.N.; Dzhemilev, U.M. Total Synthesis of Neuritogenic Alkynes: Lembehyne B and Key Intermediate of Lembehyne A. *Chem. Sel.* **2017**, *2*, 1211–s1213. https://doi.org/10.1002/slct.201601988.
14. Dzhemileva, L.U.; Makarov, A.A.; Andreev, E.N.; Yunusbaeva, M.M.; Makarova, E.K.; D'yakonov, V.A.; Dzhemilev, U.M. New 1,3-Diynoic Derivatives of Natural Lembehyne B: Stereoselective Synthesis, Anticancer and Neuritogenic Activity. *ACS Omega* **2020**, *5*, 1974–1981 https://doi.org/10.1021/acsomega.9b03826.
15. D'yakonov, V.A.; Makarov, A.A.; Dzhemileva, L.U.; Andreev, E.N.; Makarova, E.K.; Dzhemilev, U.M. Total Synthesis of Natural Lembehyne C and Investigation of Its Cytotoxic Properties, *J. Nat. Prod*. **2020**, *83*, 2399–2409. https://doi.org/10.1021/acs.jnatprod.0c00261.
16. D'yakonov, V.A.; Tuktarova, R.A.; Dzhemilev, U.M. Ti-Catalyzed Cross-Cyclomagnesiation of 1,2-Dienes in the Total Z,Z,Z-Stereoselective Synthesis of Natural Acetogenin—Chatenaytrienin-1. *ACS Omega* **2019**, *4*, 14085–14091, https://doi.org/10.1021/acsomega.9b01951.
17. Kuisle, O.; Quiñoá, E.; Riguera, R. A general methodology for automated solid-phase synthesis of depsides and depsipeptides. Preparation of a valinomycin analogue. *J. Org. Chem*. **1999**, *64*, 8063–8075.
18. Meyer, S.D.; Schreiber, S.L. Acceleration of the Dess-Martin Oxidation by Water. *J. Org. Chem.* **1994**, *59*, 7549–7552.
19. Midland, M.M.; Tramontano, A.; Kazubski, A.; Graham, R.S.; Tsai, D.J.S.; Cardin, D.B. Asymmetric reductions of propargyl ketones. An effective approach to the synthesis of optically active compounds. *Tetrahedron* **1984**, *40*, 1371–1380.