Ti-Catalyzed Cross-Cyclomagnesiation of 1,2-Dienes in the Total $Z,Z,Z$-Stereoselective Synthesis of Natural Acetogenin—Chatenaytrienin-1

Vladimir A. D’yakonov, Regina A. Tuktarova, and Usein M. Dzhemilev

Laboratory of Catalytic Synthesis, Institute of Petrochemistry and Catalysis of RAS (IPC RAS), 141 Prospect Octyabrya, 450075 Ufa, Russian Federation

Supporting Information

ABSTRACT: The first total synthesis of natural acetogenin, chatenaytrienin-1, was performed in 10 steps and in 41% overall yield using cross-cyclomagnesiation of (6Z)-heptadeca-1,2,6-triene and trideca-11,12-dien-1-ol tetrahydrofuran acetal with EtMgBr in the presence of Mg metal and the Cp$_2$TiCl$_2$ catalyst (10 mol %) as the key step of the synthesis.

INTRODUCTION

Acetogenins, an abundant, structurally diverse group of natural compounds, are isolated from the Annonaceae plants, representing nonbranched fatty acids (C$_{32}$–C$_{34}$) with a γ-lactone moiety. In most cases, acetogenin molecules contain additional hydroxy, keto, epoxy, tetrahydrofuran, or tetrahydropyran groups as well as double and triple bonds. The enhanced interest in this class of compounds is due to a wide range of biological activities they exhibit such as antibacterial, immunosuppressive, antimalarial, anticancer, and antiprotozoal activities. Moreover, it has been shown that acetogenins, as well as compounds containing a 2,5-bis(hydroxymethyl)-tetrahydrofuran moiety, are capable of exerting a cytotoxic effect on multidrug-resistant tumors due to inhibition of the ATP synthesis and are among the most active of currently known mitochondrial complex I inhibitors. In addition, acetogenins can interact with DNA polymerases and topoisomerases, thus affecting the synthesis of deoxyribonucleic acids in the cell. The possibility of affecting the regulation of cell cycle by relatively low concentrations of these substances, together with pronounced antitumor action and a relatively beneficial effect on healthy cells, makes this class of compounds promising for the development of new highly effective antitumor agents. Since plants produce exceptionally low (nanogram) quantities of acetogenins, a chemical synthesis is the only option for obtaining these compounds for practical use. It is important to ensure high stereoselectivity of the resulting compounds since the activity of these bioregulators is crucially affected by the geometry of the double bonds and asymmetric centers present in molecules.

Currently, quite a number of examples of synthesizing of structurally diverse acetogenins and their analogues have been reported in the literature; in the vast majority of cases, these are representatives of the acetogenin family containing one to three furan moieties in the molecule, with the major synthetic strategy being successive assembly of the molecule from small blocks by known C–C bond formation protocols. Despite that an effective approach to cascade cyclization of the above-described unsaturated compounds has now been developed; at the same time, it has been shown that the crucial factor dictating the stereoselective formation of tetrahydrofurans and hydroxyl groups is a strict stereoreconfiguration of substituents at the double bonds.

The Ru-catalyzed oxidative cyclization of 1Z,5Z-dienes yields only anti,anti-stereoisomers of 2,5-bis(hydroxymethyl)-tetrahydrofurans, which exhibit the highest antitumor and antibacterial activities.

Development of the strategy for the total synthesis of acetogenins containing tetrahydrofuran moieties via the oxidative cyclization of the appropriate bis-methylene-separated di- and polyenes is mainly hampered, in our opinion, by the lack of an efficient synthetic approach to the latter. A survey of literature indicates that methods used, most often, to generate the 1Z,5Z-diene moiety are based on the Wittig reaction, olefin metathesis, and stereoselective catalytic hydrogenation of acetylenes. The task becomes more challenging if the synthesis implies the formation of compounds containing three or more Z-double bonds.

The previously developed Ti-catalyzed homo- and cross-cyclomagnesiation of 1,2-dienes, which leads to strictly stereoselective formation of metal–carbon and carbon–carbon bonds, could be successfully utilized as a convenient and...
versatile tool in the stereoselective synthesis of various 1Z,5Z,9Z-diene derivatives (Scheme 1).9 The results reported in the papers mentioned above9 can be used for the synthesis of a broad range of natural biologically active compounds, higher 5Z,9Z-dienoic acids, insect pheromones, lembehynes, unique macrocarbocycles, and also acetogenins.4,10

In particular, previously, we developed an original five-step synthesis of a natural acetogenin, muricadienin 1, a bioprecursor of cis-solamin 2 (Figure 1), giving the product in ∼60% yield. The synthesis involved cross-cyclomagnesiation of functionally substituted allenes with EtMgBr in the presence of Mg metal (halogen ion acceptor) and catalyzed by Ti complexes as the key step. In addition, we previously found that muricadienin exhibits inhibitory activity in vitro against key cell cycle enzymes human topoisomerases I and IIα and has high cytotoxicity against human embryonic kidney cells HEK293 (IC50 = 0.39 μM).4

RESULTS AND DISCUSSION
Initially, we carried out the retrosynthetic analysis of the chatenaytrienin-1 3, which implied the successive synthesis of (11Z,15Z,19Z)-triaconta-11,15,19-trienoic acid 6 by means of catalytic cross-cyclomagnesiation followed by the construction of α-substituted butenolide, with the Fries rearrangement being the final step of the synthesis of the target triene (Scheme 2).

The initial monomer needed for the preparation of Z,Z,Z-trienoic acid 6, (6Z)-heptadeca-1,2,6-triene 10, was synthesized in several steps using the alkylation of commercially available dodec-1-yne 8 with ethylene oxide (Scheme 3).13 The subsequent selective hydrogenation of alcohol 12 was carried out in the presence of Brown’s catalyst P2−Ni and afforded unsaturated alcohol 9 with Z-configuration of the double bond in ∼98% yield.14 Ethynylation of compound 13, obtained by bromination of alcohol 9 with LiBr,15 on treatment with lithium acetylide yielded (5Z)-hexadec-5-en-1-yne 14 in a quantitative yield.16 Allene 10 was obtained from allyne 14 by the Crabbe reaction that involves refluxing with paraformaldehyde, dicyclohexylamine, and copper iodide.17

According to the developed synthetic strategy, (11Z,15Z,19Z)-triaconta-11,15,19-trienoic acid 6 was prepared by the cross-cyclomagnesiation of (6Z)-heptadeca-1,2,6-triene 10 and trideca-11,12-dien-1-ol tetrahydropyran acetal 11 with EtMgBr in the presence of Mg metal and the Cp2TiCl2 catalyst.

Figure 1. Structures of muricadienin, chatenaytrienin-1 and 4, cis-solamin and membranacin.
(10 mol %) at room temperature (Scheme 4). The reaction proceeded via the intermediate magnesacyclopentane 15, which was hydrolyzed to give (11Z,15Z,19Z)-triaconta-11,15,19-trien-1-ol tetrahydropyran acetal 16 in 85% yield. The subsequent oxidation of tetrahydropyran acetal 16 with the Jones reagent gave the desired Z, Z, Z-trienoic acid 6.

All that remains for the synthesis of chatenaytrienin-l 3 was the formation of the terminal butenolide moiety, which was effected by a method that proved useful, 18 based on the Fries rearrangement catalyzed by DMAP (Scheme 5). Indeed, O-acylation of cyclic β-keto ether 7, which was obtained from (S)-ethyl lactate by a reported two-step procedure, 19 with acid 6 followed by the DMAP-initiated rearrangement afforded triene 17, which was then undergo reduction by NaBH3CN in acetic acid to produce α-alkylated butenolide 18 in a yield of more than 97%.

The hydroxyl group in the C3-position of butenolide was eliminated by successive synthesis of triflate 19 and its reduction with Bu3SnH catalyzed by Pd2(dba)3; this gave the target chatenaytrienin-l 3 in ~91% yield. 8k

**CONCLUSIONS**

Thus, we have achieved the first stereoselective 10 step synthesis of chatenaytrienin-l using Ti-catalyzed cross-cyclo-magnesiation of aliphatic and oxygenated 1,2-dienes with the Grignard reagent. This study demonstrates the enormous synthetic potential of the proposed method as a convenient tool for stereoselective preparation of 1Z,5Z-diene systems. Currently, our efforts are focused on the synthesis of a number of natural homologues of chatenaytrienin-l to obtain larger amounts of these products and conduct extensive studies of their antitumor, antibacterial, and antiparasitic activities.

**EXPERIMENTAL SECTION**

**General Information.** 1-Dodecyne, lithium acetylide, ethylene diamine complex, nickel (II) acetate tetrahydrate (Ni(OAc)2-4H2O), dicyclohexylamine, copper (I) iodide (CuI), bis(cyclopentadienyl)titanium (IV) dichloride (Cp2TiCl2), 4-dimethylaminopyridine (DMAP), N,N′-dicyclohexylcarbodiimide (DCC), sodium cyanoborohydride (NaBH3CN), trifluoromethanesulfonic anhydride (Tf2O), and tris(dibenzyldimine)dicarbonyl palladium(0) (Pd2(dba)3) were obtained from Sigma-Aldrich and Acros organics. All
reactions were carried out under an argon atmosphere. $^1$H and $^{13}$C NMR spectra were obtained using a Bruker Ascend 500 spectrometer in CDCl$_3$ operating at 500 MHz for $^1$H and 125 MHz for $^{13}$C and a Bruker AVANCE 400 spectrometer in CDCl$_3$ operating at 400 MHz for $^1$H and 100 MHz for $^{13}$C. IR spectra were recorded on a Bruker VERTEX 70V using KBr discs over the range of 400–4000 cm$^{-1}$. Mass spectra of MALDI TOF/TOF positive ions (matrix of sinapic acid) are recorded on a mass spectrometer Bruker AutoFlex III Smartbeam. Elemental analyses were measured on a 1106 Carlo Erba apparatus. Individuality and purity of the synthesized compounds were controlled using TLC on Sorbord plates; anisic aldehyde in acetic acid was used as a developer. Column chromatography was carried out on Acrus silica gel (0.060–0.200 mM).

Cross-Cyclomagnesiation of (6Z)-Heptadeca-1,2,6-triene (10) and 2-(Trideca-11,12-dien-1-yloxy)tetrahydro-2H-pyran (11) by EtMgBr in the Presence of Mg Metal and C$_6$H$_5$Cl$_2$ Catalyst (General Procedure).

Ethyl ether (50 mL) and CH$_2$Cl$_2$ (100 mL) were added dropwise. The reaction mixture was heated to 20 °C and stirred for 2 h. The reaction mixture was treated with a 5% solution of NH$_4$Cl in H$_2$O (30 mL) and extracted with CH$_2$Cl$_2$. Then, the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic phases were washed with a solution of 1 N HCl (10 mL) and brine, dried over MgSO$_4$, and concentrated in vacuo. To remove residual urea derivative, the mixture was dissolved in diethyl ether, filtered, and concentrated in vacuo to yield a brownish solid that was purified by column chromatography, hexane/EtOAc = 35:1, to afford compound 16.

Synthesis of (55)-4-Hydroxy-5-methyl-3-[(11Z,15Z,19Z)-triaconta-11,15,19-trien-1-yl]fluran-2(5H)-one (18). DIPEA (2.3 mL, 13.3 mmol) was added to a suspension of butenolide (1.5 g, 13.3 mmol), fatty acid (5.2 g, 11.7 mmol), 4-DMAP (0.4 g, 3.3 mmol), and DCC (2.7 g, 13.3 mmol) in DCM (50 mL) at 0 °C. The reaction mixture was stirred overnight with warming to room temperature. The yellow solution was filtered, and the solid was washed with diethyl ether. The filtrate was concentrated, and the residue was dissolved in ethyl acetate. The organic phase was washed with a solution of 1 N HCl and brine, dried over MgSO$_4$, and concentrated under reduced pressure. To remove residual urea derivative, the mixture was dissolved in diethyl ether, filtered, and concentrated in vacuo to yield a yellow oil that was purified by column chromatography over silica gel (hexane/EtOAc = 35:1) to afford compound 16.

Oxidation of 2-[[11Z,15Z,19Z]-Triaconta-11,15,19-trien-1-yloxy]tetrahydro-2H-pyran 16 with Jones Reagent. To a solution of 2-[[11Z,15Z,19Z]-triaconta-11,15,19-trien-1-yloxy]tetrahydro-2H-pyran 16 (8.0 g, 15.3 mmol) in acetone (100 mL) and CH$_2$Cl$_2$ (25 mL) at room temperature, Jones reagent (18.7 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 h, quenched with water (50 mL), and concentrated to remove the excess of acetone and CH$_2$Cl$_2$. Then, the aqueous layer was extracted with diethyl ether (3 × 100 mL). The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by column chromatography using hexane/EtOAc = 30:1 as the elution solvent to afford 11Z,15Z,19Z)-triaconta-11,15,19-trienoic acid 6.

(11Z,15Z,19Z)-Triaconta-11,15,19-trienoic Acid (6). Yield 5.3 g (78%), colorless oil. $^1$H NMR (500 MHz, CDCl$_3$, $\delta$): 5.45–5.35 (m, 6H), 2.36 (t, $J = 7.5$ Hz, 2H), 2.11 (m, 6H), 2.05 (m, 6H), 1.65 (m, 2H), 1.40–1.25 (m, 28H), 0.90 (t, $J = 6.4$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$, $\delta$): 180.1, 130.4, 130.3, 129.6 (signals of 2C), 119.1 (signals of 2C), 34.1, 31.9, 29.8–29.1 (signals of 12C), 27.5 (signals of 2C), 27.4 (signals of 2C), 27.3 (signals of 2C), 24.7, 22.7, 14.1; IR (film): 2926, 2851, 1712, 1466, 1374, 1309, 1283, 1260, 1230, 1102, 1183, 965, 935, 723, 722 cm$^{-1}$. Anal. Calcd for C$_{30}$H$_{54}$O$_2$: C, 80.49; H, 12.16. Found: C, 80.49; H, 12.14. MALDI TOF: m/z 469.508 ([M + Na]$^+$), 485.398, 469.508. 1H NMR (500 MHz, CDCl$_3$, $\delta$): 5.37 (m, 6H), 4.84 (q, $J = 6.5$ Hz, 2H), 2.11 (m, 6H), 2.05 (m, 6H), 1.65 (m, 2H), 1.52 (d, $J = 6.5$ Hz, 3H), 1.48 (m, 2H), 1.40–1.25 (m, 30H), 0.89 (t, $J = 6.5$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$, $\delta$): 177.7, 177.4, 130.4 (signals of 2C), 129.6 (signals of 2C), 129.1 (signals of 2C), 109.0, 75.3, 31.9, 29.7–29.4 (signals of 13C), 28.1, 27.5 (signals of 2C), 27.4 (signals of 2C), 27.3 (signals of 2C), 22.7, 21.1, 17.8, 14.1; IR (film): 3005, 2924, 2853, 1751, 1730, 1654, 1457, 1376, 1313, 1267, 1249, 1180, 1142, 1081, 7077, 772 cm$^{-1}$. Anal. Calcd for C$_{30}$H$_{54}$O$_2$: C, 79.49; H, 11.44; Found: C, 79.39; H, 11.41. MALDI TOF: m/z 515.518 ([M + Na]$^+$), 531.444, 567.481, 567.481, 567.481. Synthesis of (2S)-2-Methyl-5-oxo-4-[(11Z,15Z,19Z)-triaconta-11,15,19-trien-1-yl]fluran-2(5H)-one (18). DIPEA (2.3 mL, 13.3 mmol) was added to a suspension of butenolide (1.5 g, 13.3 mmol), fatty acid (5.2 g, 11.7 mmol), 4-DMAP (0.4 g, 3.3 mmol), and DCC (2.7 g, 13.3 mmol) in DCM (50 mL) at 0 °C. The reaction mixture was stirred overnight with warming to room temperature and then poured into a solution of 1 N HCl (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with H$_2$O and brine, dried over MgSO$_4$ and filtered, and concentrated in vacuo (3 × codistillation with toluene to remove acetic acid). The title compound 18 was obtained in analytically pure product.

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removed under reduced pressure. Silica gel column chromatography (hexane/EtOAc = 30:1) of the residue gave trflate 19.

(2S)-2-Methyl-5-oxo-4-[(11Z,15Z,19Z)-triaconta-11,15,19-trien-1-yl]-2,5-dihydrofurran-3-yl Trifluoromethanesulfonate (19). Yield 5.6 g (91%), pale yellow oil. [α]D21 + 17.0 (c 0.71, CHCl3). 1H NMR (500 MHz, CDCl3, δ): 5.46–5.37 (m, 6H), 5.13 (q, J = 6.8 Hz, 1H), 2.33 ( t, J = 7.2 Hz, 2H), 2.11 (m, 6H), 2.04 (m, 6H), 1.61 (m, 2H), 1.56 (d, J = 6.8 Hz, 3H), 1.40–1.23 (m, 30H), 0.90 (t, J = 6.4 Hz, 3H). 13C NMR (125 MHz, CDCl3, δ): 169.1, 163.4, 130.4 (signals of 2C), 129.6, 121.9, 118.4 (J = 319 Hz), 74.4, 31.9, 29.7–29.1 (signals of 13C), 27.5 (signals of 2C), 27.3 (signals of 2C), 26.7, 22.7 (signals of 2C), 17.7, 14.1. IR (film): 3005, 2924, 2853, 1759, 1654, 1547, 1376, 1313, 1267, 1249, 1180, 1142, 1081, 1078, 777, 722 cm−1. Anal. Calcd for C56H90F4O9S: C, 65.42; H, 9.00 Found: C, 65.36; H, 8.97. MALDI TOF: m/z 683.418 ([M + Na]+), calcd 683.404.

Synthesis of (5S)-5-Methyl-3-[(11Z,15Z,19Z)-triaconta-11,15,19-trien-1-ylfuran-2(5H)-one (Chatenaytrienin-l 3). Pd2(dba3) (13.7 mg, 0.015 mmol, 1.5 mol %) and PPh3 (39.3 mg, 0.15 mmol, 15.0 mol %) were dissolved in dry THF (10 mL). After stirring for 5 min at room temperature, trflate 19 (0.7 g, 1.0 mmol) and Bu3SnH (0.8 mL, 3.0 mmol) were added to the orange solution. The mixture was heated to 50 °C and stirred at this temperature for 5 h. After complete conversion of the starting material, the reaction was cooled to room temperature, diluted with H2O (30 mL). The combined organic phases were dried over MgSO4 and (M + Na+) +, calcd 535.449), 551.469 ([M + K] +, calcd 547.483). 1H NMR (500 MHz, CDCl3, δ): 5.46–5.37 (m, 6H), 5.13 (q, J = 6.8 Hz, 1H), 2.33 (t, J = 7.2 Hz, 2H), 2.11 (m, 6H), 2.04 (m, 6H), 1.61 (m, 2H), 1.56 (d, J = 6.8 Hz, 3H), 1.40–1.23 (m, 30H), 0.90 (t, J = 6.4 Hz, 3H). 13C NMR (125 MHz, CDCl3, δ): 169.1, 163.4, 130.4 (signals of 2C), 129.6, 121.9, 118.4 (J = 319 Hz), 74.4, 31.9, 29.7–29.1 (signals of 13C), 27.5 (signals of 2C), 27.3 (signals of 2C), 26.7, 22.7 (signals of 2C), 17.7, 14.1. IR (film): 3005, 2924, 2853, 1759, 1654, 1547, 1376, 1313, 1267, 1249, 1180, 1142, 1081, 1078, 777, 722 cm−1. Anal. Calcd for C56H90F4O9S: C, 65.42; H, 9.00 Found: C, 65.36; H, 8.97. MALDI TOF: m/z 683.418 ([M + Na]+), calcd 683.404.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b01951.

Methods of synthesis and characterization data of the products 3, 6, 9–14, 18, and 19 as well as copies of 1H and 13C NMR spectra of final products (PDF)
1113–1120. (b) Morré, D. J.; de Cabo, R.; Farley, C.; Oberlies, N. H.; McLaughlin, J. L. Mode of action of bullatcin, a potent antimutagen: Inhibition of NADH oxidase activity of HELA and HL-60, but not liver, plasma membranes. Life Sci. 1994, 56, 343–348.

(c) Landolt, J. L.; Ahammedashibi, K. L.; Hollingworth, R. M.; Barr, R.; Crane, F. L.; Buerck, N. L.; McCabe, G. P.; McLaughlin, J. L. Determination of structure-activity relationships of Annaceous acetylglucosides by inhibition of oxygen uptake in rat liver mitochondria. Chem.-Biol. Interact. 1995, 98, 1–13. (d) Jose, M. R.; Tormo, T.; Gallardo, R.; Aragón, D.; Cortes, E. E. Specific interactions of monotetrahydrofuranic annaceous acetylglucosides as inhibitors of mitochondrial complex I. Chem.-Biol. Interact. 1999, 122, 171–183.

(4) Dzhemilev, U. M.; D'yakonov, V. A.; Tukhtarova, R. A.; Dzhemileva, L. U.; Ishukhmatovet, S. R.; Yunusbaeva, M. M.; de Meijere, A. Short route to the total synthesis of natural Muricadienin and investigation of its cytotoxic properties. J. Nat. Prod. 2016, 79, 2039–2044.

(5) Matsumoto, T.; Kojima, N.; Akatsuka, Y.; Yamori, T.; Dan, S.; Iwasaki, H.; Yamashita, M. Convergent synthesis of stereoisomers of the THF ring moiety of acetylgenin thiophene analogue and their antiproliferative activities against human cancer cell lines. Tetrahedron 2017, 73, 2359–2366.

(6) (a) Astruc, D. The metathesis reactions: from a historical perspective to recent developments. New J. Chem. 2005, 29, 42–56. (b) Siau, W.-Y.; Zhang, Y.; Zhao, Y. Stereoselective synthesis of Z-alkenes. Top. Curr. Chem. 2012, 327, 33–58. (c) Byrne, P. A.; Gilheany, D. G. The modern interpretation of the Wittig reaction mechanism. Chem. Soc. Rev. 2013, 42, 6670–6696. (d) Michaelides, I. N.; Dixon, D. J. Catalytic stereoselective semihydration of alkynes to Z-alkenes. Angew. Chem., Int. Ed. 2013, 52, 806–808.

(7) Sinha, S. C.; Chen, Z.; Huang, Z.-Z.; Nakamura-Ogiso, E.; Pietrzaszkiewicz, H.; Edelstein, M.; Valeriote, F. Alteration of the bis-tetrahydrofuran core stereochemistries in asimicin can affect the cytotoxicity. J. Med. Chem. 2008, 51, 7045–7048.

(8) (a) Menas, P. L.; Pile, O.; Djerassi, C. Phospholipid studies of marine organisms. 7. Stereosepecific synthesis of (S,Z)-2, (S,E)-2, (S,E,Z)-2, and (S,E,E)-2,9-hexacosadienoic acid. J. Org. Chem. 1984, 49, 3260–3264. (b) Raederstorff, D.; Shu, A. Y. L.; Thompson, J. E.; Djerassi, C. Biosynthetic studies of marine lipids. 11. Synthesis, characterizations, and biological activities of tetradeca-4,8-dien-1-yl acetates as sex attractants of leaf-mining moth of the Genus Phyllonorycter (Lepidoptera: Gracillariidae). Chem. Biodiversity 2009, 6, 1388–1403. (c) Adrian, J.; Stark, C. B. W. Total Synthesis of Muricadinien, the putative key precursor in the Solanin biosynthesis. Org. Lett. 2014, 16, 5886–5889. (d) Schmidt, J.; Adrian, J.; Stark, C. B. Short and highly efficient synthesis of lipid peroxidation inhibitor pyrrolostatin and some analogues thereof. Org. Biomol. Chem. 2015, 13, 8173–8176. (m) Kunkalkar, R. A.; Laha, D.; Fernandes, R. A. De novo, protecting-group-free total synthesis of (+)-muricadienien, (+)-anespenoide and (+)-3-hexadecyl-5-methyl-furan-2-(S)-one. Org. Biomol. Chem. 2016, 14, 9072–9079.

(9) (a) D’yakonov, V. A.; Makarov, A. A.; Ibragimov, A. G.; Khalilov, L. M.; Dzhemilev, U. M. Novel Mg-organic reagents in organic synthesis. CP-TiCl2 catalyzed intermolecular cyclomagnesiation of cyclic and acyclic 1,2-dienes using Grignard reagents. Tetrahedron 2008, 64, 10188–10194. (b) D’yakonov, V. A.; Makarov, A. A.; Makarov, E. K.; Khalilov, L. M.; Dzhemilev, U. M. Synthesis and transformations of metalacystyres 41. Cyclomagnesiation of O-containing 1,2-dienes with Grignard reagents in the presence of CP-TiCl2. Russ. Chem. Bull. 2012, 61, 1943–1949. (c) D’yakonov, V. A.; Makarov, A. A.; Makarov, E. K.; Dzhemilev, U. M. Novel organocatalystic ene reactions in synthesis. Catalytic cyclomagnesiation of allenes in the synthesis of N-, O-, and Si-substituted 12,5-c-dienes. Tetrahedron 2013, 69, 8516–8526. (d) D’yakonov, V. A.; Makarov, A. A.; Dzhemileva, L. U.; Makarov, E. K.; Khusnutdinova, E. K.; Dzhemilev, U. M. The facile synthesis of the SZ9Z-dienoic acids and their topoisomerase I inhibitory activity. Chem. Commun. 2013, 49, 8401–8403.

(10) (a) D’yakonov, V. A.; Dzhemileva, L. U.; Makarov, A. A.; Mulyukova, A. R.; Bae, D. S.; Khusnutdinova, E. K.; Tolstikova, T. G.; Dzhemilev, U. M. nZ,(n + 4)Z-Dienoic fatty acids: a new method for the synthesis and inhibitory action on topoisomerase I and II. Med. Chem. Res. 2016, 25, 30–39. (b) D’yakonov, V. A.; Tukhtarova, R. A.; Ishukhmatovet, S. R.; Dzhemilev, U. M. The facile first total synthesis of a deuterated analog of natural muricadienin. Tetrahedron 2016, 72, 5783–5787. (c) 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, lembelhyne B—a selective inducer of early apoptosis in leukemia cancer cells. Org. Biomol. Chem. 2017, 15, 470–476. (d) 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. (e) D’yakonov, V. A.; Islamov, I. I.; Dzhemileva, L. U.; Khusnutdinovet, E. K.; Yunusbaeva, M. M.; Dzhemilev, U. M. Targeted synthesis of macrolides containing bis-methylene-separated Z-double bonds and their antitumor activity in vitro. Tetrahedron 2018, 74, 4606–4612.

(11) Gleye, C.; Raynaud, S.; Hoqueuemiller, R.; Laurens, A.; Fournier, C.; Serani, L.; Laprevote, O.; Roblot, F.; Leboeuf, M.; Fournet, A.; Rojas de Arias, A.; Figade, B.; Cavé, A. Muricadinien, muridieninen och chenatin, de vilka utgör de tidigaste av Annaceous acetylglucosides. Phytochemistry 1998, 47, 749–754.

(12) Adrian, J.; Stark, C. B. Modular and stereodivergent approach to unbranched 1,5,9,9-Polyenes: total synthesis of Chatterjaitrien-4. J. Org. Chem. 2016, 81, 8175–8186.

(13) Knight, J. A.; Diamond, J. H. Synthesis of some octenoic acids. J. Org. Chem. 1959, 24, 400–403.

(14) Liu, F.; Zhong, J.; Li, S.; Li, M.; Wu, L.; Wang, Q.; Mao, J.; Liu, S.; Zheng, B.; Wang, M.; Bian, Q. Total syntheses of (R)-Strongyloids C and D. J. Nat. Prod. 2016, 79, 244–247.

(15) André, V.; Robin, S.; Rousseau, G. Preparation of halo enol phosphonates by reaction of acetylenic phosphate monooesters with (bis-collidine)halo hexafluorophosphate. Tetrahedron Lett. 2008, 49, 5059–5062.

(16) Bernassau, J. M.; Bertranne, M.; Collongues, C.; Fettion, M. Center of mass displacement and relaxation times of linear alkynes. Tetrahedron 1985, 41, 3063–3069.
(17) Crabbe, P.; Fillion, H.; André, D.; Luche, J.-L. Efficient homologation of acetylenes to allenes. *J. Chem. Soc., Chem. Commun.* 1979, 859−860.

(18) Ghobril, C.; Kister, J.; Baati, R. A Synthetic route to α-substituted butenolides: enantioselective synthesis of (+)-Ancepsenolide. *Eur. J. Org. Chem.* 2011, 3416−3419.

(19) (a) Brandaenge, S.; Flodman, L.; Norberg, A. Studies on the intramolecular Claisen condensation; facile synthesis of tetronic acids. *J. Org. Chem.* 1984, 49, 927−928. (b) Spence, J. T. J.; George, J. H. Biomimetic total synthesis of ent-Penilactone A and Penilactone B. *Org. Lett.* 2013, 15, 3891−3893.