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Original catalytic synthesis of macrodiolides containing a 1*Z*,5*Z*-diene moiety

Vladimir A. D'yakonov,* Ilgiz I. Islamov, Elvina M. Khusainova and Usein M. Dzhemilev

Institute of Petrochemistry and Catalysis, Russian Academy of Sciences, 450075 Ufa, Russian Federation. Fax: +7 347 284 2750; e-mail: DyakonovVA@gmail.com

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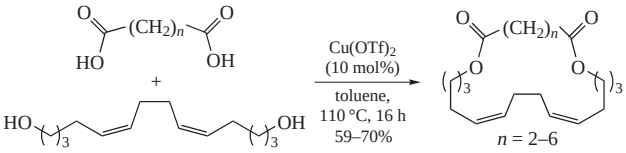
Macrodiolides containing a 1*Z*,5*Z*-diene moiety were obtained with high selectivity (>98%) and in good yields (59–70%) by the $Cu(OTf)_2$-catalyzed intermolecular esterification of aliphatic α,ω-dicarboxylic acids with tetradeca-5*Z*,9*Z*-diene-1,14-diol. This diol was accessed by homocyclomagnesiation of hepta-5,6-dien-1-ol tetrahydropyranyl ether using EtMgBr/Mg reagent system and Cp_2TiCl_2 catalyst.



The steadily increasing interest in polyfunctional macrocarbocycles is due to a wide range of their useful properties. They are used as high-grade fragrances, pheromones, extractants, ionophores, and highly efficient drugs.[1,2] Of particular value are macrocyclic mono- and dilactones containing heteroatoms and multiple carbon–carbon bonds, which exhibit high antitumor, antiviral, antibacterial and fungicidal activities.[3,4] For example, Balticolide, the 12-membered macrolide, found in marine fungi exhibits high activity (IC_{50} 0.45 μM) against herpes simplex virus (anti-HSV),[5] all-*Z*-polyene macrolides (aplyolides A–E) are effective ichthyotoxins,[6,7] polyfunctional macrocarbocycles (aplyronines A–H and pladienolide B) exert cytotoxic effects against tumor cell lines with IC_{50} 0.075–9.8 nM.[8] Macrocyclic eushearilide isolated from fungi of the Penicillum family, which contains a 1,5-diene fragment, has a wide spectrum of fungicidal action against fungal infections in people with weakened immune system, in HIV-infected and oncological patients.[9,10]

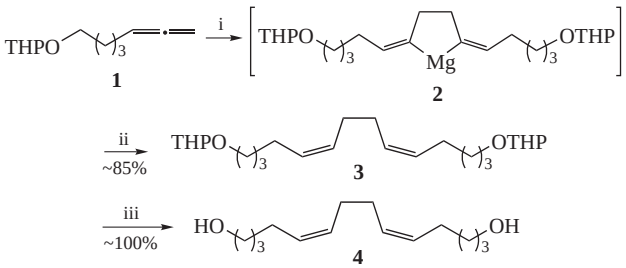
In continuation of our previous studies on the stereoselective synthesis of biologically active compounds containing 1*Z*,5*Z*-diene moiety,[11–21] we aimed to design original approaches to all-*Z*-unsaturated macrodiolides.

The synthesis strategy of desired macrodiolides includes the synthesis of *Z*,*Z*-α,ω-(*n*),(*n*+4)-dienediols based on Ti-catalyzed intermolecular homocyclomagnesiation reactions of O-containing 1,2-dienes with Grignard reagents. The subsequent intermolecular esterification of such alkadienediols with aliphatic α,ω-dicarboxylic acids was expected to afford the desired macrocycles. Previously,[19] we have shown that among the series of 1*Z*,5*Z*-dienoic acids derivatives of higher acids containing two *cis*-C=C bonds in 5- and 9-positions have the greatest antitumor potential.

Scheme 1 depicts the access to the key tetradeca-5*Z*,9*Z*-diene-1,14-diol **4** *via* intermolecular homocyclomagnesiation of hepta-5,6-dien-1-ol THP ether **1**† with EtMgBr in the presence of metallic magnesium and Cp_2TiCl_2 catalyst affording intermediate magnezacyclopentane **2**. Its subsequent acidic hydrolysis led to diol diether **3** in good yield (~85%) and with stereoselectivity more than 98%. The final deprotection with TsOH afforded the desired dienediol **4** in quantitative yield.

The final stage of the assembly of the target macrodiolides involved the intermolecular esterification of diol **4** with aliphatic α,ω-dicarboxylic acids. After thorough analysis of the literature data in this field[22] we have chosen the Collins method based on application of transition metal triflates as catalysts.[23]

In our hands, boiling equimolar amounts of dienediol **4** and saturated dicarboxylic acids (C_4–C_8) **5a**–**e** in toluene in the presence of 10 mol% $Cu(OTf)_2$ for 8–16 h led to the corresponding macrodiolides **6a**–**e** in 59–70% yield (Scheme 2).‡ Note that



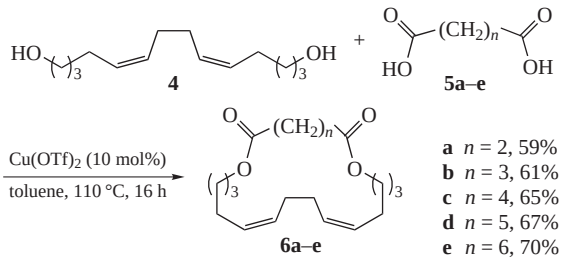
Scheme 1 *Reagents and conditions*: i, EtMgBr, Mg, Cp_2TiCl_2 (10 mol%), Et_2O, ~20 °C; ii, H_3O^+; iii, TsOH, $CHCl_3$, MeOH.

† 2-(Hepta-5,6-dien-1-yloxy)tetrahydro-2*H*-pyran **1** was prepared from commercially available hex-5-yn-1-ol by a reported procedure.[26]

‡ *General procedure for the synthesis of macrodiolides* **6a**–**e**. Dicarboxylic acid (0.2 mmol, 1.0 equiv.) and (5*Z*,9*Z*)-tetradeca-5,9-diene-1,14-diol **4** (45 mg, 0.2 mmol, 1.0 equiv.) were dissolved in toluene (40 ml). Then $Cu(OTf)_2$ (85 mg, 0.02 mmol, 0.1 equiv.) was added, and the mixture was heated to 110 °C and stirred at this temperature for 16–18 h. After cooling to room temperature, silica gel (~1 ml) was added and the slurry was concentrated under reduced pressure and purified by column chromatography (elution with light petroleum–EtOAc, 20 : 1) to afford the desired products.

1,6-Dioxacycloicosa-11Z,15Z-diene-2,5-dione **6a**: yield 59%, colourless oil. IR (ν/cm^{-1}): 1734 (C=O), 1246, 1180 (C–O). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.44–1.47 (m, 4H, CH_2, H-7, H-16), 1.61–1.67 (m, 4H, CH_2, H-6, H-17), 2.03–2.12 (m, 8H, =CH–CH_2, H-8, H-11, H-12, H-15), 2.63–2.65 (m, 4H, CH_2, H-2, H-3), 4.10–4.13 (m, 4H, OCH_2, H-5, H-18), 5.35–5.47 (m, 4H, =CH, H-9, H-10, H-13, H-14). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.0 (COO, C^1, C^4), 129.7 (CH, C^9, C^{14}), 129.7 (CH, C^{10}, C^{13}), 64.5 (CH_2O, C^5, C^{18}), 29.8 (CH_2, C^2, C^3), 28.0 (CH_2, C^6, C^{17}), 27.6 (CH_2, C^8, C^{15}), 26.5 (CH_2, C^{11}, C^{12}), 25.8 (CH_2, C^7, C^{16}). MS (MALDI-TOF), *m*/*z*: 308 $[M]^+$. Found (%): C, 70.14; H, 9.19. Calc. for $C_{18}H_{28}O_4$ (%): C, 70.10; H, 9.15.

For characteristics of compounds **6b**–**e**, see Online Supplementary Materials.



Scheme 2

lower diacids such as oxalic and malonic ones did not give the corresponding macrodiolides. At the same time, starting with succinic acid **5a** with an elongation of the hydrocarbon chain the yield of macrodiolides **6a**–**e** increased.

The structure of the resulting macrocycles has been established by one-dimensional (^{1}H, ^{13}C) and two-dimensional heteronuclear correlation NMR experiments (HSQC, HMBC), as well as mass spectrometry. In the ^{13}C NMR spectra, the doubling intensity of the carbon signals was observed for all macrocycles thus indicating evidence for their symmetry. The *Z*-arrangement of substituents around the double bonds can be deduced from the diagnostic chemical shifts (δ_C ~27 ppm) of the internal allylic carbon atoms, which confirms their *cis* spatial tension with the external allylic carbon atoms.[24]

In conclusion, we have performed the original stereoselective synthesis of macrodiolides with a 1*Z*,5*Z*-diene moiety in good yields (59–70%) and with high stereoselectivity (>98%). The method is based on successive application of the intermolecular homocyclomagnesiation reaction of O-containing 1,2-dienes[25] and intermolecular esterification of aliphatic α,ω-dicarboxylic acids with tetradeca-5*Z*,9*Z*-diene-1,14-diol catalyzed by copper triflate $Cu(OTf)_2$. We believe that the developed method has a great synthetic potential for the preparation of polyfunctional macrodiolides by varying the structure and the length of the hydrocarbon chain of initial O-containing 1,2-dienes and α,ω-dicarboxylic acids, as well as by addition of diverse functional groups to the multiple C–C bonds in the resulting macrocycles. These studies are actively continued and, in the near future, we are planning to significantly widen the assortment of the synthesized macrodiolides, as well as their production in a larger scale and testing for antitumor, antibacterial, antiviral and fungicidal activity.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.09.017.

References

1 E. M. Driggers, S. P. Hale, J. Lee and N. K. Terrett, *Nat. Rev. Drug Discov.*, 2008, **7**, 608.
2 A. K. Yudin, *Chem. Sci.*, 2015, **6**, 30.
3 *Macrocyclic Lactones in Antiparasitic Therapy*, eds. J. Vercruysse and R. S. Rew, CABI, 2002.
4 *Natural Lactones and Lactams: Synthesis, Occurrence and Biological Activity*, ed. T. Janecki, Wiley-VCH, 2013.
5 M. A. M. Shushni, R. Singh, R. Mentel and U. Lindequist, *Mar. Drugs*, 2011, **9**, 844.
6 A. Spinella, T. Caruso, M. Martino and C. Sessa, *Synlett*, 2001, **12**, 1971.
7 G. Bruno, T. Caruso, A. Peluso and A. Spinella, *Phytochem. Rev.*, 2004, **3**, 417.
8 M. Ojika, H. Kigoshi, K. Suenaga, Y. Imamura, K. Yoshikawa, T. Ishigaki, A. Sakakura, T. Mutou and K. Yamada, *Tetrahedron*, 2012, **68**, 982.
9 T. Hosoe, K. Fukushima, K. Takizawa, T. Itabashi, N. Kawahara, V. Vidotto and K. Kawai, *J. Antibiot.*, 2006, **59**, 597.
10 T. Tonoi, R. Kawahara, Y. Yoshinaga, T. Inohana, K. Fujimori and I. Shiina, *Tetrahedron Lett.*, 2015, **56**, 1356.
11 N. M. Carballeira, *Prog. Lipid Res.*, 2008, **47**, 50.
12 N. M. Carballeira, J. E. Betancourt, E. A. Orellano and F. A. González, *J. Nat. Prod.*, 2002, **65**, 1715.
13 N. M. Carballeira, N. Montano, L. A. Amador, A. D. Rodríguez, M. Y. Golovko, S. A. Golovko, R. M. Reguera, R. Álvarez-Velilla and R. Balaña-Fouce, *Lipids*, 2016, **51**, 245.
14 T. Nemoto, G. Yoshino, M. Ojika and Y. Sakagami, *Tetrahedron*, 1997, **53**, 16699.
15 S.-J. Chen, C.-P. Hsu, C.-W. Li, J.-H. Lu and L.-T. Chuang, *Food Chem.*, 2011, **126**, 1708.
16 K. Xie, E. A. Miles and P. C. Calder, *J. Funct. Foods*, 2016, **23**, 464.
17 V. A. D'yakonov, A. A. Makarov, A. R. Salimova, E. N. Andreev and U. M. Dzhemilev, *Mendeleev Commun.*, 2017, **27**, 234.
18 V. A. D'yakonov, A. A. Makarov, L. U. Dzhemileva, E. N. Andreev and U. M. Dzhemilev, *Mendeleev Commun.*, 2017, **27**, 122.
19 V. A. D'yakonov, L. U. Dzhemileva, A. A. Makarov, A. R. Mulyukova, D. S. Baev, E. K. Khusnutdinova, T. G. Tolstikova and U. M. Dzhemilev, *Med. Chem. Res.*, 2016, **25**, 30.
20 V. A. D'yakonov, L. U. Dzhemileva, R. A. Tuktarova, A. A. Makarov, I. I. Islamov, A. R. Mulyukova and U. M. Dzhemilev, *Steroids*, 2015, **102**, 110.
21 G. A. Abakumov, A. V. Piskunov, V. K. Cherkasov, I. L. Fedushkin, V. P. Ananikov, D. B. Eremin, E. G. Gordeev, I. P. Beletskaya, A. D. Averin, M. N. Bochkarev, A. A. Trifonov, U. M. Dzhemilev, V. A. D'yakonov, M. P. Egorov, A. N. Vereshchagin, M. A. Syroeshkin, V. V. Jouikov, A. M. Muzafarov, A. A. Anisimov, A. V. Arzumanyan, Yu. N. Kononevich, M. N. Temnikov, O. G. Sinyashin, Yu. H. Budnikova, A. R. Burilov, A. A. Karasik, V. F. Mironov, P. A. Storozhenko, G. I. Shcherbakova, B. A. Trofimov, S. V. Amosova, N. K. Gusarova, V. A. Potapov, V. B. Shur, V. V. Burlakov, V. S. Bogdanov and M. V. Andreev, *Russ. Chem. Rev.*, 2018, **87**, 393.
22 A. Parenty, X. Moreau and J.-M. Campagne, *Chem. Rev.*, 2006, **106**, 911.
23 M. de Léséleuc and S. K. Collins, *Chem. Commun.*, 2015, **51**, 10471.
24 G. Levy and G. Nelson, *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, Wiley, New York, 1972.
25 V. A. D'yakonov, A. A. Makarov, E. Kh. Makarova and U. M. Dzhemilev, *Tetrahedron*, 2013, **69**, 8516.
26 V. A. D'yakonov, A. A. Makarov, E. Kh. Makarova, L. M. Khalilov and U. M. Dzhemilev, *Russ. Chem. Bull., Int. Ed.*, 2012, **61**, 1943 (*Izv. Akad. Nauk, Ser. Khim.*, 2012, 1928).

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