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Stereoselective synthesis and antitumor activity of macrodiolides containing 1*Z*,5*Z*-diene and 1,3-diyne moieties

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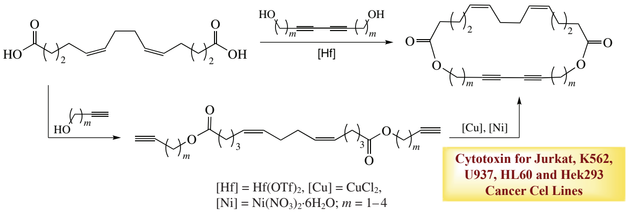
New macrodiolides incorporating 1*Z*,5*Z*-diene and 1,3-diyne moieties were obtained in 55–79% yields and with >98% stereoselectivity by $Hf(OTf)_4$-catalyzed intermolecular cyclocondensation of (5*Z*,9*Z*)-tetradeca-5,9-diene-1,14-dioic acid with α,ω-diols. Alternative route included intramolecular oxidative coupling of α,ω-diynes, esterification products of (5*Z*,9*Z*)-tetradeca-5,9-diene-1,14-dioic acid with alkynols. The macrodiolides synthesized exhibit *in vitro* cytotoxic activity toward Jurkat, K562, U937, HL-60, HeLa and Hek293 cell lines.



Macrocyclic lactones are abundant in nature and find use in organic and medicinal chemistry, biochemistry and materials science due to their great structural diversity and the vast spectrum of biological activity they manifest.[1,2] Taking into account their high demand, numerous total syntheses were accomplished based mostly on macrolactonization of ω-hydroxy acids, alkene and alkyne metathesis, the Wittig reaction, and intramolecular Pd-catalyzed cross-coupling.[3,4]

Despite the progress in the synthesis of macrocyclic lactones, there is still a high need for the development of new efficient routes for their preparation. We believe that 1,3-diyne moiety is highly attractive for introducing new functional groups such as thiophene, furan, pyrrole, isoxazole and pyrazole into a molecule. For example, using the reaction of 1,3-diyne macrocycles with nucleophiles, macrolactones containing heterocyclic pharmacones can be obtained in one stage, which can drastically affect not only the structural features of the molecule, but also its biological activity.[5,6] Natural bioactive 1,3-diyne macrolactones are known. For example, macrocyclic lactones Ivorenolide A and Ivorenolide B with a 1,3-diyne fragment were isolated from trees of genus *Khaya Ivorenesis A.*[7–12] These lactones showed high immunosuppressive activity and surprisingly high inhibition of ConA-induced T-cell proliferation.

In view of the aforesaid and in continuation of our previous studies on the preparation of polyfunctional macrocycles based on the catalytic cyclometallation of alkynes and 1,2-dienes,[13–16] herein we report the synthesis of new macrodiolides containing, along with a 1*Z*,5*Z*-diene group, a 1,3-diyne moiety.

(*Z*,*Z*)-α,ω-Alka-*n*,(*n*+4)-dienedicarboxylic acids obtained by the previously developed Ti-catalyzed homocyclomagnesation of O-containing 1,2-dienes using Grignard reagents[17] were selected as the key monomers. The target macrodiolides were prepared in two ways. The first one was based on the intermolecular cyclocondensation of alkadienedicarboxylic acids with α,ω-diols containing an internal 1,3-diyne moiety. The second route involved the catalytic esterification of these alkadienedicarboxylic acids with various alkynols followed by intramolecular oxidative coupling of the terminal acetylene groups.

To implement the intended strategy, (5*Z*,9*Z*)-tetradeca-5,9-diene-1,14-dioic acid **1** was first synthesized using the protocol that we developed previously (Scheme 1).[17] At the final stage of assembling the target macrodiolides, *viz*., the intermolecular esterification of diacid **1** with diynic α,ω-diols, the well-proven intermolecular macrolactonization in the presence of catalytic amounts of transition metal triflates[18] was employed. As a result, we were the first to obtain macrodiolides **2a–d** containing 1*Z*,5*Z*-diene and 1,3-diyne moieties in 55–64% yields.[†]

To realize the second approach to the synthesis of macrodiolides, symmetric α,ω-diynes **3a–d** were first obtained by catalytic esterification of (5*Z*,9*Z*)-tetradeca-5,9-diene-1,14-dioic acid **1** with commercially available terminal alkynols using DCC/DMAP (see Scheme 1). At the final stage, the use of

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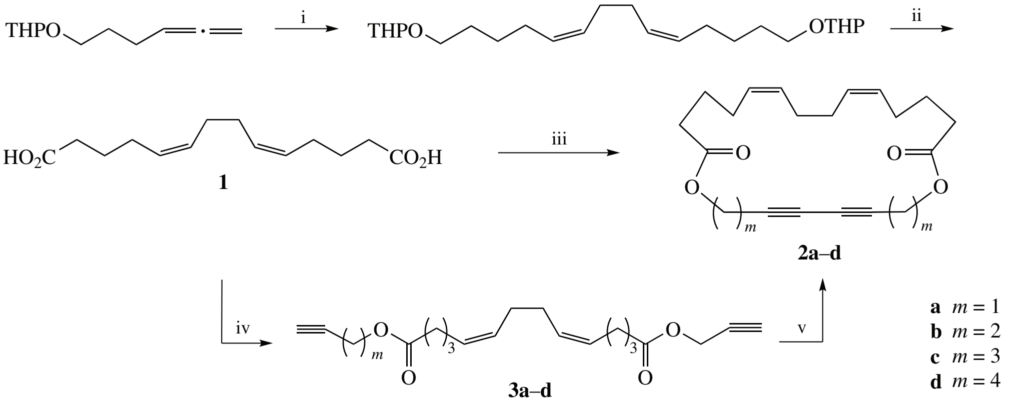
[†] *General procedure for the synthesis of macrodiolides. Method 1.* (5*Z*,9*Z*)-Tetradeca-5,9-dienedioic acid **1** (51 mg, 0.2 mmol) and diynediol (0.2 mmol) were dissolved in toluene (40 ml). Then $Hf(OTf)_4$ (15 mg, 0.02 mmol, 0.1 equiv.) was added, the mixture was heated to 110 °C and stirred at 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. Column chromatography (elution with light petroleum/EtOAc, 15 : 1) afforded the desired product as a colorless oil.

Method 2. A vial equipped with a stirring bar was charged with $CuCl_2$ (5.0 mg, 0.44 mmol, 25 mol%) and $Ni(NO_3)_2 \cdot 6H_2O$ (8.5 mg, 0.44 mmol, 25 mol%). Polyethylene glycol 400 (3.05 ml), triethylamine (0.046 ml, 0.33 mmol, 3 equiv.) and pyridine (0.046 ml, 0.55 mmol, 5 equiv.) were added, and the mixture was stirred at room temperature for 15 min or until the metals were solubilized. Diyne diester **3a–d** (0.11 mmol) was added to the homogenous mixture as a methanol solution (1.5 ml) in one portion. Oxygen was bubbled through the solution for 5 min, and the vial was closed with a screw cap. The vial was warmed to 60 °C upon TLC monitoring the consumption of the starting material (oxygen was bubbled through the solution every 12 h). When the starting material was completely consumed, the reaction mixture was cooled to room temperature and the crude mixture was loaded directly onto a silica column. Elution with light petroleum/EtOAc (15 : 1) afforded the desired product as a colorless oil.



Scheme 1 *Reagents and conditions*: i, EtMgBr, Mg, Cp_2TiCl_2 (10 mol%), Et_2O, room temperature, 8 h, then H_3O^+; ii, Jones reagent, acetone, CH_2Cl_2, 1 h; iii, $HO(CH_2)_mC{\equiv}CC{\equiv}C(CH_2)_mOH$, $Hf(OTf)_4$ (10 mol%), PhMe, 110 °C, 16 h; iv, $HC{\equiv}C(CH_2)_mOH$, DCC, DMAP, CH_2Cl_2, room temperature, 6 h; v, $CuCl_2$, $Ni(NO_3)_2{\cdot}6H_2O$, Py, Et_3N, O_2, MeOH, PEG 400, 60 °C, 48 h.

Table 1 Cytotoxic activity of synthesized macrodiolides **2a–d** *in vitro* on cell cultures (Jurkat, K562, U937, HL-60, Hek293 and HeLa).

Compound	Jurkat (IC_{50}, μM)	K562 (IC_{50}, μM)	U937 (IC_{50}, μM)	HL-60 (IC_{50}, μM)	Hek293 (IC_{50}, μM)	HeLa (IC_{50}, μM)
2a	0.151 ± 0.022	0.314 ± 0.059	0.128 ± 0.025	0.106 ± 0.021	0.769 ± 0.069	0.749 ± 0.083
2b	0.282 ± 0.041	0.341 ± 0.091	0.218 ± 0.044	0.197 ± 0.043	0.749 ± 0.081	0.711 ± 0.079
2c	0.267 ± 0.091	0.324 ± 0.072	0.234 ± 0.049	0.208 ± 0.044	0.821 ± 0.085	0.769 ± 0.094
2d	0.061 ± 0.016	0.144 ± 0.022	0.054 ± 0.013	0.046 ± 0.015	0.644 ± 0.067	0.594 ± 0.071
CPT	0.374 ± 0.059	0.469 ± 0.089	0.299 ± 0.035	0.303 ± 0.042	0.912 ± 0.095	0.946 ± 0.089

modified Glaser-Hay's intramolecular oxidative coupling developed by Collins *et al.*,[19] provided the target macrodiolides **2a–d** in 58–79% yields.

The structure of the resulting macrocycles **2** was determined using mass spectrometry and ^1H, ^{13}C NMR spectroscopy. The *Z*-configuration of the substituents at the double bonds in the resulting 1,5-diene can be inferred from the diagnostic high field signals of the internal allylic carbon atoms at ~27 ppm in their ^{13}C NMR spectra (*cf.* ref. 20).

We were the first to determine the *in vitro* antitumor activity of the macrodiolides **2a–d** synthesized toward cell lines Jurkat, K562, HL-60, U937, Hek293 and HeLa, including the determination of IC_{50} by flow cytometry using the Guava Via Countreagent kit (Millipore).

The studies revealed that macrocarbocycles **2a–d** exhibited a cytotoxic effect toward selected cell lines that was found to be comparable or somewhat superior to the effect shown by the previously synthesized macrocarbocycles lacking 1,3-diene moiety,[13] as well as the cytotoxicity of camptothecin (CPT). Macrodiolide **2d** exhibited the greatest cytotoxicity toward Jurkat, U937 and HL-60 cell lines (Table 1).

In conclusion, we have developed two original routes for synthesizing macrodiolides containing 1Z,5*Z*-diene and 1,3-diyne moieties in 55–79% yields and with stereoselectivity >98%. The macrodiolides synthesized were found to exhibit *in vitro* cytotoxic activity toward Jurkat, K562, U937, HL-60, HeLa and Hek293 cell lines.

We believe that the synthetic schemes that we developed can have a great potential for obtaining polyfunctional macrodiolides by varying the structure and length of the initial O-containing 1,2-dienes and α,ω-diols, as well as a potential possibility to incorporate additional functional groups at multiple carbon–carbon bonds in the resulting macrocarbocycles. We are continuing studies in this field and are planning to expand significantly the range of macrodiolides that can be synthesized in the near future, as well as test them for antitumor, antibacterial, antiviral and fungicidal activities.

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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.2019.11.002.

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(13Z,17Z)-1,8-Dioxacyclodocosa-13,17-diene-3,5-diyne-9,22-dione **2a**. Yield 55% (method 1) or 58% (method 2), colourless oil. MS (MALDI-TOF), *m/z*: 328 $[M]^+$. Found (%): C, 73.09; H, 7.29. Calc. for $C_{20}H_{24}O_4$ (%): C, 73.15; H, 7.37. IR (ν/cm^{-1}): 1737 (C=O), 1240, 1165 (C–O). ^1H NMR (500 MHz, $CDCl_3$) δ: 5.59–5.26 (m, 4H, =CH, H^{11}, H^{12}, H^{15}, H^{16}), 4.76 (s, 4H, O–CH_2, H^1, H^6), 2.42–2.32 (m, 4H, CH_2, H^8, H^{19}), 2.21–1.96 (m, 8H, H^{10}, H^{13}, H^{14}, H^{17}), 1.75 (m, 4H, CH_2, H^9, H^{18}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.6 (COO, C^7, C^{20}), 130.8 (CH, C^{11}, C^{16}), 128.6 (CH, C^{12}, C^{15}), 76.8 (C, C^2, C^5), 73.7 (C, C^3, C^4), 51.6 (CH_2O, C^1, C^6), 32.8 (CH_2, C^8, C^{19}), 27.1 (CH_2, C^{10}, C^{17}), 26.0 (CH_2, C^{13}, C^{14}), 24.5 (CH_2, C^9, C^{18}).

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