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Synthesis and Structure of a Stabilized 10-Membered Cyclic Enediyne

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Abstract: The synthesis and structure of an acetal protected 10-membered cyclic enediyne-1,2-diol *rac*-**10** is reported. The conformational constrain of the unsaturated macrocycle by the acetal protection group prevents the thermal cyclization reaction of the endiyne during synthesis and purification.

Strained cyclic enediynes or cumulene-eneynes are the origin of the cytotoxic properties of natural products, such as Calicheamicin γ_1^I, Dynemicin A, or Neocarzinostatin.[1] They undergo spontaneous thermal cyclization to yield reactive aryl or benzyl diradicals which abstract hydrogen atoms leading to DNA strand cleavage and ultimately to cell death.[2] To fulfill their biological function the reactivity of the unsaturated macrocycles must be regulated. In nature this is achieved either by trigger mechanisms which unlock conformationally constrained precursors[3] or proteins which tightly bind and stabilize the enediyne or cumulene-eneynes chromophore.[4] The same regulation of reactivity is desirable for enediyne model compounds and several strategies to achieve this have been reported. Among them the release of a conformational constrain that prohibits spontaneous cyclization,[5] isomerization of enediynes to the more reactive cumulene-eneynes,[6] generation of the enediyne system by retro-Diels−Alder,[7] S_N2' reaction,[8] or alkyne deprotection,[9] and induction of the cyclization by catalytic antibodies,[10] metal cations,[11] or light[12] are the most widely applied methods.[13] We report here the synthesis and structure of an acetal-protected[14] cyclic 10-membered enediyne *rac*-**10**,[15] which belongs to the class of model compounds which are temporarily stabilized by a removable conformational constrain.

The synthesis of the acetal-protected enediyne *rac*-**10** was accomplished in 6 steps starting from diastereomerically pure butadiene bis-epoxide **2** and THP protected propargylic alcohol **1**. Twofold addition of the lithium acetylide of **1** to **2** gave diol *rac*-**3** in 82% yield. In compound *rac*-**3** all functionalized carbon atoms of the target molecule *rac*-**10** are already in place. Removal of the THP protection and introduction of a cyclic acetal

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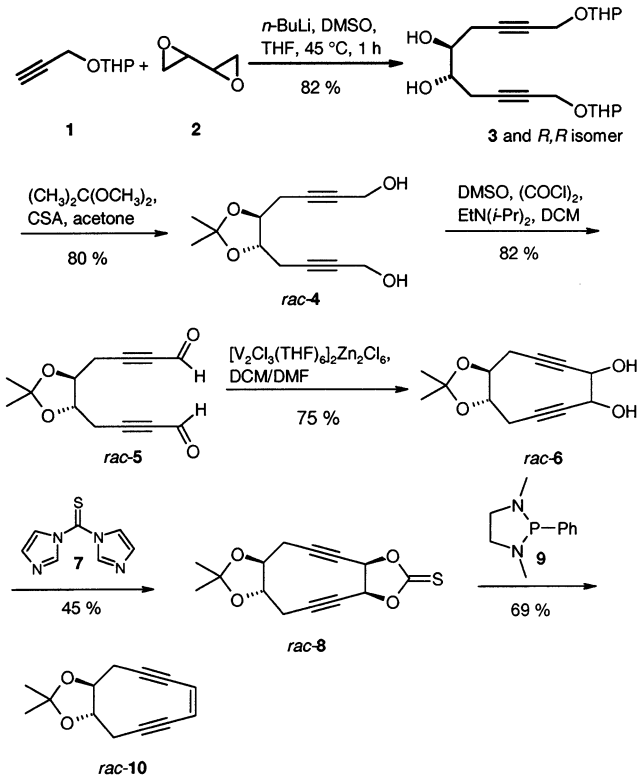
SCHEME 1. Synthesis of Enediyne *rac*-10



gave *rac*-**4**, which was oxidized to *rac*-**5** by Swern−Moffatt-type oxidation. The dialdehyde is a very sensitive compound that easily decomposes by polymerization in neat form. For the following steps a sequence of reactions previously used by Banfi et al.[5d] and Semmelhack et al.[16] was employed. Vanadium-mediated ring closure yielded a mixture of diastereomeric diols with the desired cis-diol isomers of *rac*-**6** as the major compounds.[17] By reaction with thiocarbonyl diimidazole they were converted into the thiocarbonate *rac*-**8**.[18] An X-ray analysis proofed its structure and the suggested relative stereochemistry of the thiocarbonate (see Supporting Information for details). The phosphine-mediated elimination of the thiocarbonate group finally gave the target enediyne *rac*-**10**.[18] All attempts to obtain **10** by LiHMDS/HMPA induced cyclization of **11** or **12** following the procedure introduced by Jones et al.[19] failed and resulted either in decomposition of the starting material, as with **11-Br**,[20] or a 2-fold 1,4-elimination yielding an acyclic diene-diyne from **12**.[21] Enediyne *rac*-**10** is a stable solid due to its locked conformation by the annelated acetal ring. The compound was analyzed by GC-MS (injector temperature 200 °C) without decomposition. A high thermal stability

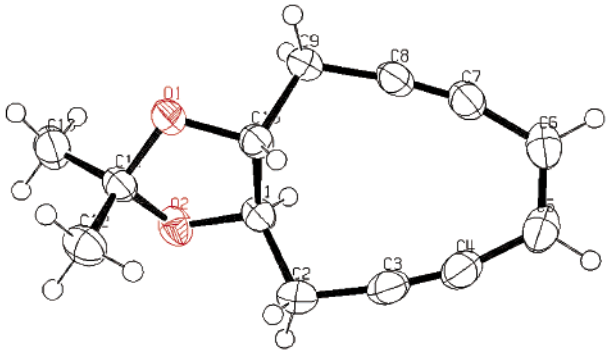
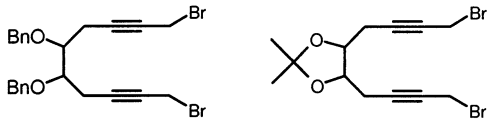


FIGURE 1. Structure of *rac*-**10** in the crystal.

SCHEME 2. Precursors Used for Attempted Cyclization with LiHMDS/HMPA



11-Br **12**

was expected from the earlier results of Nicolaou et al.[5a] on structurally related cyclic carbonate functionalized 10-membered enediynes. Removal of the acetal protecting group of *rac*-**10** is conveniently achieved by treatment with 1,2-ethane thiol, yielding a highly reactive 10-membered cyclic enediyne. The deprotected cyclic enediyne undergoes spontaneous cyclization with a half-life in the same order ($t_{1/2} \sim 2$ h at 50 °C) as the very similar systems which have already been studied experimentally[5a,22] and theoretically[23] in great detail.

The structure of compound *rac*-**10** was confirmed by X-ray analysis, which showed a distance of 333 pm between the acetylenic carbon atoms C3 and C8. This value is very similar to the 335 pm suggested for the same distance in nonactivated and therefore conformationally locked calicheamicin.[24] The propargylic carbon atoms of *rac*-**10** bear hydrogen substituents, which should allow its base-mediated propargyl-allene isomerization. Treatment of a DMSO solution of *rac*-**10** with Cs_2CO_3 indeed leads to the formation of the corresponding cyclic eneyne-allene system, which was identified by its characteristic signals in the proton NMR. The equilibrium of enediyne and eneyne-allene remains at a ratio of approximately 10:1. This prohibits the isolation of the pure eneyne-allene.[25] However, the observation indicates that cyclic eneyne-allenes can be stabilized in conformational constrained structures, too.

In summary we have reported the convenient synthesis of the new enediyne *rac*-**10**, which is a useful stable

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(25) Separation of the isomers on TLC or column chromatography was not successful. Separation by gas chromatography is possible, but the equilibrium of isomers is thermally shifted in the injector favoring the enediyne even more.

precursor to study thermal cyclization reactions and their consequences.

Experimental Section

General. All ^{1}H NMR spectra were recorded at 400 MHz and all ^{13}C NMR spectra at 100 MHz in $CDCl_3$ unless otherwise stated. The multiplicity of the ^{13}C signals was determined with the DEPT technique and quoted as follows: (+) for CH_3 or CH, (−) for CH_2, and (C_{quat}) for quaternary carbons. CC means column chromatography on silica gel. PE means petrol ether with a boiling range of 60−70 °C. EA means ethyl acetate.

(5*RS*,6*RS*)-1,10-Bis(tetrahydropyran-2-yloxy)deca-2,8-diyne-5,6-diol (*rac*-3): To a solution of 2-prop-2-ynyloxytetrahydropyran (14.7 g, 105 mmol, **2**) in 50 mL of THF was added at −78 °C *n*-BuLi (70 mL, 105 mmol, 1.5 mol/L in hexane). The reaction mixture was stirred for 30 min then allowed to warm to 0 °C and 2.0 mL (26.3 mmol) of **1** and DMSO (30 mL) were added. The reaction mixture was heated to 45 °C for 1 h and poured into saturated aqueous NH_4Cl (10 g in 140 mL of H_2O), the aqueous phase was extracted with ether (5 × 50 mL), the combined organic phases were washed with saturated aqueous NH_4Cl (3 × 40 mL) and dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by CC (PE/Et_2O, 2:3; R_f 0.23, Et_2O) to yield 7.95 g (82%) of *rac*-**3**, as a colorless oil. IR (neat): $\tilde{\nu}$ 3423 (OH), 2942, 2237 (C≡C) cm^{-1}. −UV (CH_3CN): λ_{max} (log ϵ) 192 (3.321), 224 (2.510, sh), 246 (2.080, sh) nm. ^{1}H NMR (200 MHz): δ 1.59 (m, 12 H), 2.46 (m, 4 H), 3.26 (s, 2 H), 3.45 (m, 2 H), 3.71 (m, 2 H), 3.80 (m, 2 H), 4.18 (m, 4 H), 4.72 (m, 2 H). ^{13}C NMR (50 MHz): δ 18.8 (−), 24.2 (−), 25.1 (−), 30.0 (−), 54.4 (−), 61.8 (−), 70.8 (+), 78.0 (C_{quat}), 82.5 (C_{quat}), 96.7 (+). MS (CI, pos, NH_3) (70 eV), *m*/*z* (%): 384 (4) [M + NH_4^+], 102 (100) [OTHP + 1]. Anal. Calcd for $C_{20}H_{30}O_6$ (366.45): C 65.55, H 8.25. Found: C 65.17, H 8.68. Molar mass 366 (MS).

(4*RS*,5*RS*)-4,5-Bis(4'-hydroxybut-2'-ynyl)-2,2-dimethyl-[1,3]dioxolane (*rac*-4): A mixture of **3** (2.00 g, 5.46 mmol), 2,2-dimethoxypropane (0.80 mL, 682 mg, 6.55 mmol), and campher sulfonic acid (12 mg, 0.05 mmol) in 30 mL of dry acetone was stirred for 8 h at room temperature. The reaction mixture was poured into 100 mL of brine and extracted with Et_2O (4 × 30 mL), the combined organic phases were dried over Na_2SO_4, and the solvent was removed in vacuo. CC (PE/Et_2O, 1:1; R_f 0.23, Et_2O) of the crude product gave 1.04 g (80%) of *rac*-**4**, as a slightly yellow oil. IR (neat): $\tilde{\nu}$ 3406, 2934, 2226, 1380 cm^{-1}. UV (CH_3CN): λ_{max} (log ϵ) 210 (2.356), 224 (2.019), 268 (1.894) nm. ^{1}H NMR: δ 1.40 (s, 6 H), 2.61 (m, 4 H), 3.94 (m, 2 H), 4.23 (t, 4 H, ^5J = 2.0 Hz). ^{13}C NMR: δ 23.2 (−), 27.2 (+), 51.0 (−), 78.2 (+), 81.0 (C_{quat}), 81.1 (C_{quat}), 109.3 (C_{quat}). MS (EI, 70 eV), *m*/*z* (%): 237 (1) [M^+ − H], 223 (100) [M^+ − CH_3]. Anal. Calcd for $C_{13}H_{18}O_4$ (238.28): C 65.53, H 7.61. Found: C 65.22, H 7.61.

(4*RS*,5*RS*)-4-[2,2-Dimethyl-5-(4-oxobut-2-inyl)-[1,3]dioxolan-4-yl]but-2-ynone (*rac*-5): To a solution of DMSO (2.98 mL, 42.0 mmol) in 300 mL of CH_2Cl_2 were added subsequently at −78 °C $(COCl)_2$ (2.36 mL), after 15 min a solution of diol *rac*-**4** (1.99 g, 8.4 mmol) in 20 mL of CH_2Cl_2, and finally after 15 min Et*N*(*i*-Pr)$_2$ (14.6 mL, 84.0 mmol). The reaction mixture was stirred for 4 h at −78 °C and 2 h at −40 °C and then poured into 250 mL of a 5% aqueous $(NH_4)H_2PO_4$ solution. The aqueous phase was extracted with ether (4 × 50 mL) and washed with aqueous $(NH_4)H_2PO_4$ solution, water, and brine, and the solvent was removed in vacuo. Benzene was added to the residue twice and distilled off to remove traces of water. The sensitive compound was obtained in 82% (1.61 g, R_f 0.72, Et_2O) and used for the next step without further purification. ^{1}H NMR (250 MHz): δ 1.40 (s, 6 H), 2.80 (m, 4 H), 4.00 (m, 2 H), 9.17 (s, 2 H). ^{13}C NMR (62.5 MHz): δ 23.3 (−), 27.1 (+), 83.1 (+), 92.6 (C_{quat}), 110.1 (C_{quat}), 176.6 (C_{quat}).

(6*RS*,7*RS*;1*RS*,2*SR*)-2′,2′-Dimethyl-6,7-[1,3]dioxolecyclodeca-3,9-diyne-1,2-diol (*rac*-6): To a solution of VCl_3·3THF (3.14 g, 8.4 mmol) in CH_2Cl_2 (120 mL) was added zinc powder (368 mg, 5.6 mmol) and the mixture was stirred for 0.5 h. The suspension was diluted with CH_2Cl_2 (120 mL) and DMF (14 mL), a solution of dialdehyde **5** (200 mg, 0.85 mmol) in CH_2Cl_2 (140 mL) was added over 2 h, and the reaction mixture was stirred for 0.5 h. The mixture was poured into 300 mL of water, and the organic phase was washed with aqueous sodium−potassium-tartrate (40%) and brine. The solvent was removed in vacuo and CC (PE:EA, 1:1; R_f 0.23) gave 148 mg (75%) of diastereomeric *rac*-**6** as a colorless solid, mp 100−106 °C. IR (KBr): $\tilde{\nu}$ 3324, 2988, 2935, 2220, 1140, 867 cm^{-1}. ^{1}H NMR: δ 1.38 (s, 6 H, CH_3), 2.41 (m, 2 H, CH_2), 2.58 (m, 2 H, OH), 2.74 (m, 1 H, CH_2), 2.81 (m, 1 H, CH_2), 4.14 (m, 2 H, CH), 4.44 (m, 2 H, CH). ^{13}C NMR: δ 25.8 (−, CH_2), 26.0 (−, CH_2), 27.0 (+, CH_3), 27.0 (+, CH_3), 65.9 (+, CH), 66.2 (+, CH), 80.8 (+, CH), 80.8 (+, CH), 83.2 (C_{quat}), 83.5 (C_{quat}), 84.2 (C_{quat}), 85.8 (C_{quat}), 109.7 (C_{quat}). MS (EI), *m*/*z* (%): 221 (14) [M^+ − CH_3], 43 (100) [*i*-Pr + 1].

(6*RS*,7*RS*;1*RS*,2*SR*)-2′,2′-Dimethyl-6,7-[1,3]dioxolecyclodeca-3,9-diyne-1,2,2″-thion (*rac*-8): A solution of the *rac*-**6** (120 mg, 0.51 mmol) and *N*,*N*′-thiocarbonyldiimidazole (271 mg, 1.52 mmol, **7**) in 25 mL of THF was heated to reflux for 4 h, the solvent was removed in vacuo, and the crude product was purified by CC (PE/EA, 3:1, R_f 0.32) to yield 63 mg (45%) of diastereomeric *rac*-**8** as a slightly yellow solid, mp 150−160 °C. IR (KBr): $\tilde{\nu}$ 2984, 2905, 2242, 1815, 1270, 1055 cm^{-1}. ^{1}H NMR (250 MHz, acetone-d_6): δ 1.35 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 2.62 (m, 2 H, CH_2), 2.88 (m, 2 H, CH_2), 4.10 (m, 1 H, CH), 4.25 (m, 1 H, CH), 5.93 (m, 2 H, CH). ^{13}C NMR (62 MHz, acetone-d_6): δ 25.8 (−), 25.9 (−), 27.0 (+), 27.1 (+), 76.5 (+), 77.3 (C_{quat}), 77.5 (C_{quat}), 81.2 (+), 81.2 (+), 92.2 (C_{quat}), 92.4 (C_{quat}), 110.2 (C_{quat}), 190.8 (C_{quat}). MS (EI), *m*/*z* (%): 278 (44) [M^+], 263 (40) [M^+ − CH_3], 43 (100) [*i*-Pr + 1].

(1*RS*,10RS)-2,2-Dimethyl-3,7-diin-5-encyclodeca[1,3]-dioxol (*rac*-10): A solution of thione *rac*-**8** (63 mg, 0.23 mmol) and 2-phenyl-1,3-dimethyl-1,3,2-diazaphospholidine (**9**, 312 mg, 1.60 mmol) in dioxane (15 mL) was stirred for 4 h at 40 °C. The solvent was removed in vacuo and the crude product was purified by CC (PE/EA, 21:4; R_f 0.63) to yield 32 mg (69%) of *rac*-**10** as a colorless solid, mp 56 °C. IR (KBr): $\tilde{\nu}$ 2995, 2936, 2359, 2190, 1373, 1256, 1056, 741 cm^{-1}. ^{1}H NMR (250 MHz, acetone-d_6): δ 1.36 (s, 6 H, CH_3), 2.67 (m, 2 H, CH_2), 2.88 (m, 2 H, CH_2), 4.22 (m, 2 H, CH), 5.95 (s, 2 H, CH). ^{13}C NMR (62 MHz, acetone-d_6): δ 27.3 (+, CH_3), 27.4 (−, CH_2), 82.1 (+, CH), 85.3 (C_{quat}), 98.9 (C_{quat}), 109.6 (C_{quat}), 124.2 (+, CH). MS (EI), *m*/*z* (%): 202 (24) [M^+], 187 (12) [M^+ − CH_3], 144 (8) [M^+ − O*i*Pr], 115 (100). HRMS calcd for $C_{13}H_{14}O_2$: 202.0993 ppm. Found: 202.0990 ± 1.88 ppm.

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Supporting Information Available: Structure of compound *rac*-**8** in the crystal; details of X-rays structure analyses of *rac*-**8** and *rac*-**10**; experimental procedures for the preparation of compound **11**; proton and carbon NMR spectra of compounds *rac*-**5**, *rac*-**6**, *rac*-**8**, *rac*-**10**, and **11**; and proton NMR spectra of *rac*-**10** in DMSO-d_6 after addition of Cs_2CO_3. This material is available free of charge via the Internet at http://pubs.acs.org.

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