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Cobalt Mediated Intramolecular [2+2+2]-Cycloaddition of Enediynes Towards Linear Annelated Polycycles[1]

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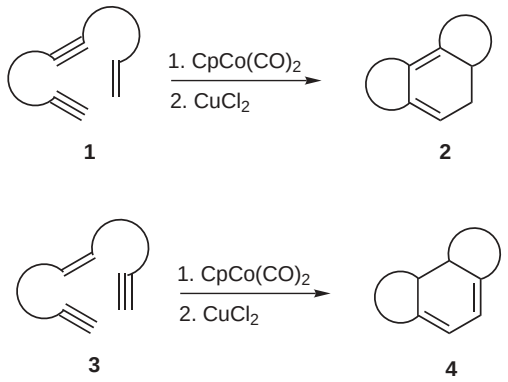
Abstract: The cobalt mediated [2+2+2]-cycloaddition of enediynes **13** and **18** affords linear annelated polycycles such as the hexahydro naphthalene **14** and the decahydro anthracene **19**. This latter compound can be transformed into the enantiomerically pure anthracene derivative **21** in only two reaction steps. 1,9,10-Trihydroxy octahydro anthracene (**21**) represents the ABC-framework of many anthracycline antibiotics such as the antitumor active daunomycine.

Key words: [2+2+2]-cycloaddition, enediynes, annelated polycycles

Generally, the cobalt mediated intramolecular [2+2+2]-cycloaddition[2] of enediynes such as **1** and **3** affords angular annelated polycycles such as **2**[3] and **4** (Scheme 1).[4] For the synthesis of linear annelated polycycles the intermolecular co-cyclization of diynes with olefines was used until now.[5] This intermolecular approach appears to be problematic due to a lack of chemo- and regioselectivity of the [2+2+2]-cycloaddition.



Scheme 1

In our hands the reaction of diyne **5** with 1.5 equivalents of olefin **8** in the presence of $CpCo(CO)_2$ under irradiation afforded exclusively the cyclobutadiene cobalt complex **7** in 76% yield (Scheme 2).[6] None of the regioisomeric tricycles **9a** or **9b** could be detected. In the first reaction step the cobaltacyclopentadiene **6** is formed. Obviously, the rate of irreversible rearrangement of this complex into the unreactive cyclobutadiene cobalt complex is much faster than a Diels–Alder type cycloaddition. This undesired side reaction might be suppressed by using olefin **8** as a solvent or by adding the diyne slowly to a solution containing an excess of olefin **8** in a suitable solvent. For an application of this reaction in natural product synthesis by using valuable olefins such as **8**, both reaction pathways did not seem to be suitable due to economical reasons and from the point of view of regioselectivity and the overall yield.

Therefore, the following approach was chosen: prior to cyclization the diyne and the olefin should be linked via a temporary silicon oxygen tether.[7] In this case the [2+2+2]-cycloaddition can be performed in an intramolecular manner which proceeds much faster and with a complete regioselective control. After the [2+2+2]-cycloaddition this tether can be cleaved hydrolytically or oxidatively.

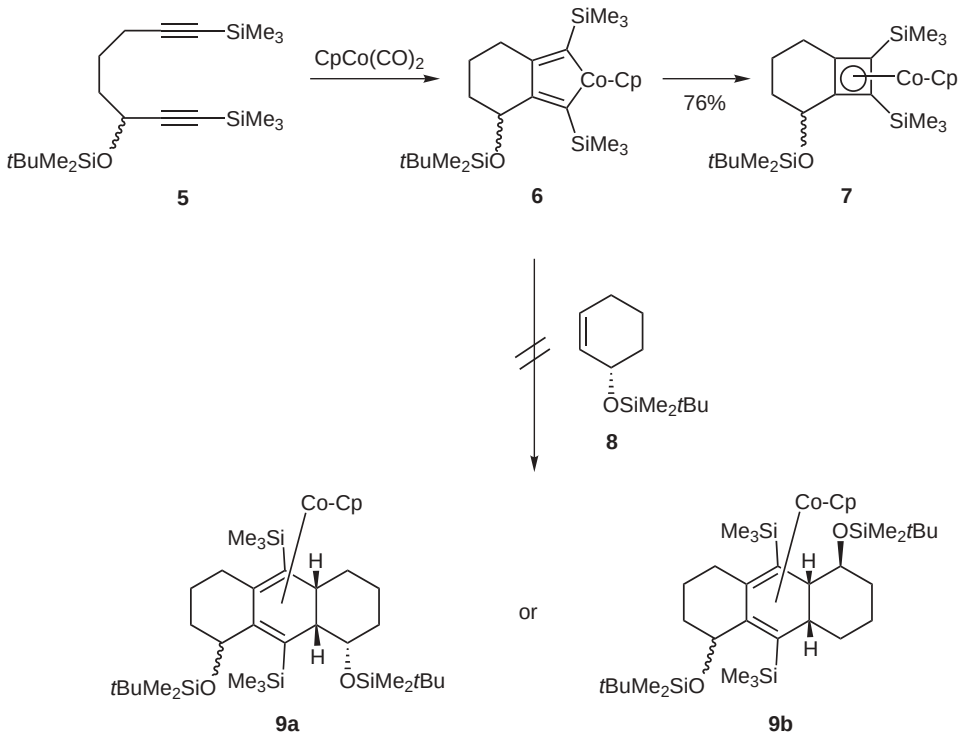
Consequently, 1-trimethylsilyl-octa-1,7-diyne (**10**) was deprotonated by *n*-BuLi and allowed to react with $Me_2Si(NEt_2)Cl$ to form the disilylated octadiyne derivative **11**. This was treated in situ with allylic alcohols **12** or **17**[8] to form enediynes **13** and **18** (Scheme 3) under liberation of diethyl amine, which was removed from the reaction mixture under a nitrogen stream. After distillation the enediynes **13** and **18** were isolated in 80–96% yield in analytically pure form. Subsequent $CpCo(CO)_2$ mediated [2+2+2]-cycloaddition followed by oxidative demetallation using $FeCl_3$ afforded dienes *rac*-**14a–d** and **19** in yields up to 81% (Scheme 3, Table 1). The [2+2+2]-cycloaddition was completed within 2.5 h. The cyclization could be scaled up to 3.00 g without any loss of regio-, chemo- and stereoselectivity or decrease in yield. The configuration of dienes *rac*-**14b** and **19** could be determined by NOESY NMR-spectroscopy. Moreover, an X-ray structure of *rac*-**14b** could be obtained,[9] which is in agreement with the NOESY spectroscopic determination of the structure of *rac*-**14b**.

Table 1 Synthesis and [2+2+2]-Cycloaddition of the Enediynes **13**

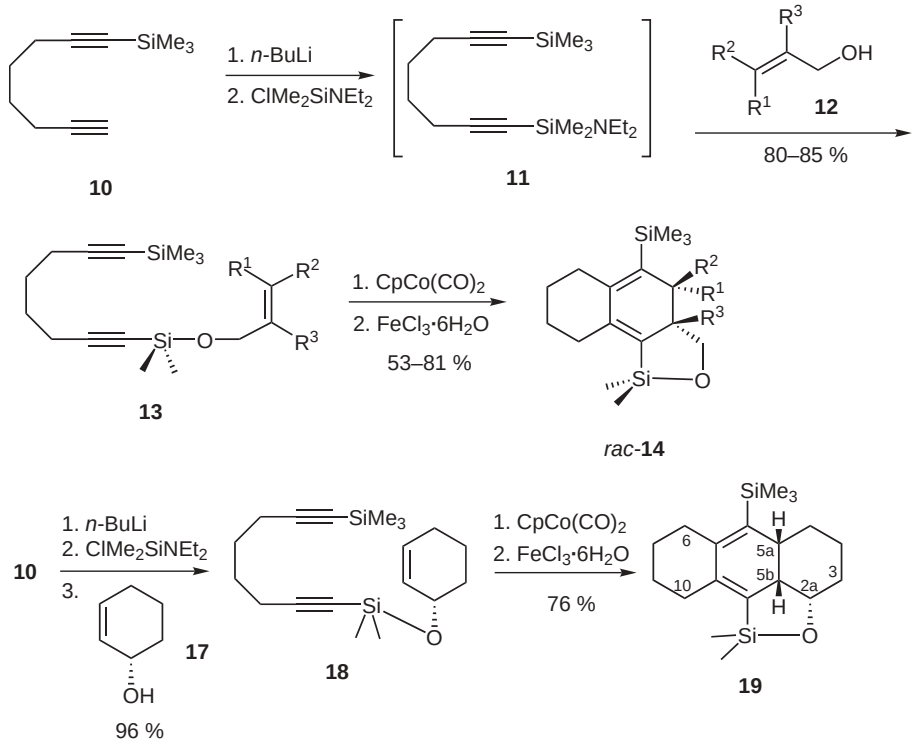
12	R^1	R^2	R^3	Yield of **13** (%)	Yield of *rac*-**14** (%)
a	H	H	H	80	63
b	CH_3	H	H	81	53
c	H	CH_3	H	82	<5
d	H	H	CH_3	85	81

The cyclization of enediyne **13c** is unusual. Starting from this *trans*-enediyne the formation of less than 5% of the corresponding *trans*-octahydronaphthofurane *rac*-**14c** was observed. Instead 7% of *cis*-octahydronaphthofurane *rac*-**14b**, 35% of the corresponding cobaltacyclobutadiene complex **15** and some starting material were isolated in reproducible experiments (Scheme 4).

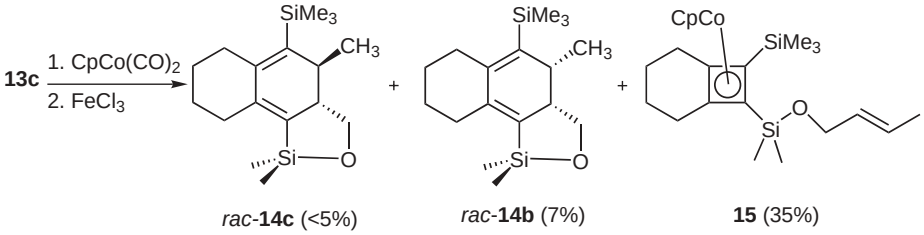
This result is in agreement with the following proposed reaction mechanism: In the first step, the π-complex between Cp–Co and the triple bonds of the octadiyne unit



Scheme 2



Scheme 3

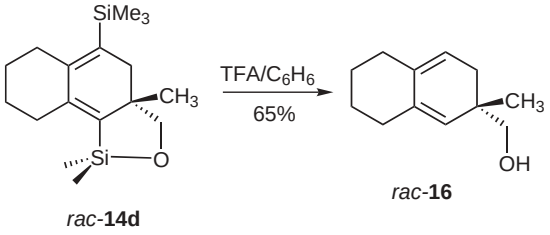


Scheme 4

of **13**, which proceeds via 'Cp–Co' or more likely via 'Cp–Co(CO)', which is liberated by photochemical removal of the CO-ligands, is formed which undergoes an oxidative addition towards a cobalt(III)cyclopentadiene of type **6** (Scheme 2). This compound reacts in an intramolecular Diels –Alder type cycloaddition to cobaltbicycloheptene which isomerizes to a thermodynamically more stable cobalt(I)cyclohexadiene complex of type **9** (Scheme 2).

In the transition state **A** (Figure 1) for the [4+2]-cycloaddition of cobalt(III)cyclopentadiene, a sterically disfavored interaction between the methyl group at the *trans*-double bond and the sterically demanding trimethyl silyl group can take place which will inhibit the [4+2]-cycloaddition to *rac*-**14c**. Instead the *trans*-double bond isomerizes photochemically to the *cis*-double bond or a rearrangement into the unreactive cyclobutadiene cobalt complex takes place. In the transition state **B** (Figure 1) a fast [4+2]-cycloaddition takes place like in the case of **13b** and after isomerization and oxidative demetallation the *cis*-octahydronaphtofurane *rac*-**14b** was isolated.

In order to prove the synthetic utility of this reaction the cleavage of the Si–O tether by protodesilylation and oxidative desilylation was investigated next. Octahydronaphthofurane *rac*-**14d** was treated with trifluoroacetic acid (2.2 equiv) in benzene and after aqueous work up the hexahydronaphthalene **16** was isolated in 65% yield (Scheme 5).



Scheme 5

Prior to oxidative cleavage of the Si–O tether, diene **19** was dehydrogenated by using DDQ to afford aromatic octahydroanthracene **20** in 81% yield (Scheme 6).[10] Oxidative desilylation of **20** was carried out by using lead(IV) trifluoroacetate in TFA–CCl_4 to afford 72% of 1,9,10-trihydroxyoctahydroanthracene (**21**).[11]

The method for the synthesis of linear annelated polycycles[12] presented herein will allow a simple and efficient approach towards many carbo- and heterocyclic natural products. For example 1,9,10-trihydroxyoctahydroanthracene (**21**) represents the ABC-framework of many anthracycline antibiotics. A pharmacologically important member of this class of antibiotics is the antitumor active daunomycine.[13] Consequently, a total synthesis of daunomycine is under current investigation.

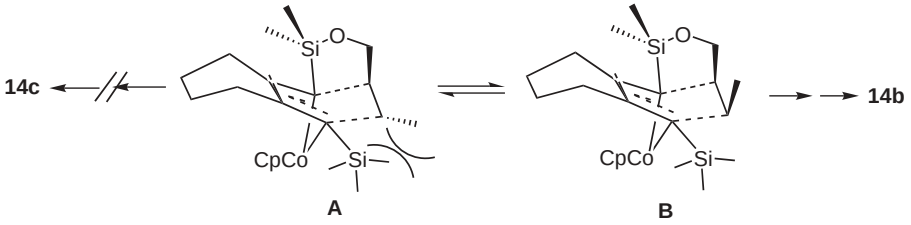
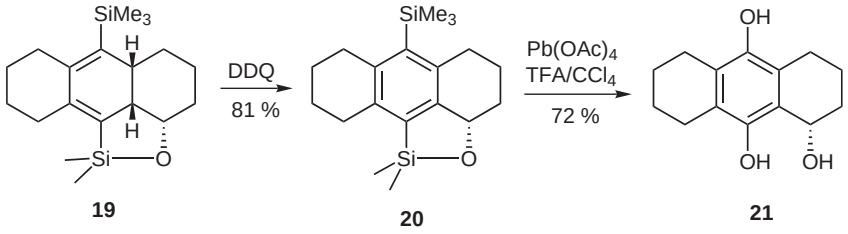


Figure 1 Proposed transition states **A** and **B** for the [4+2]-cycloaddition of the cobaltacyclopentadiene derived from enediyne **13c**.



Scheme 6

Acknowledgement

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(12) **Typical Experimental Procedure:**
To a solution of 1-trimethylsilyl-octa-1,7-diyne (**10**) (1.10 g, 6.2 mmol) in THF (30 mL) was added a solution of *n*-BuLi in hexane (1.6 M, 4.05 mL, 6.5 mmol) at –78 °C within 20 min. The reaction mixture was allowed to warm to –30 °C and stirring was continued for 45 min. A solution of $Me_2Si(NEt_2)Cl$ (DDSCl) (1.12 g, 6.8 mmol) in THF (5 mL) was added at –78 °C and the reaction mixture was allowed to warm to r.t. within 12 h. A solution of the allylic alcohol **12** or **17** (7.4 mmol) in THF (3 mL) was added at –78 °C, the reaction mixture was allowed to warm to r.t. and the reaction was monitored by TLC analysis. When none of the temporarily formed enyne diethyl amino dimethyl silane was detectable by TLC analysis (after ca 12 h) the solvent was removed in vacuo (35 °C, 12 torr). The residue was dissolved in Et_2O (10 mL) and the inorganic components were removed by filtration over silica gel (deactivated by silylation with HMDS) or celite. The solvent was removed in vacuo (20 °C, 12 torr) and the residue was purified by bulb-to-bulb distillation to afford enediynes **13** or **18**.
A solution of enediyne **13** or **18** (1.1 mmol) in *iso*-octane (30 mL) was cooled to –70 °C and the apparatus was evacuated for 15 min (0.5 torr). The flask was allowed to warm to r.t. and Ar was allowed to fill up the apparatus. The solution was cooled again to –70 °C and the procedure was repeated twice as described above. $CpCo(CO)_2$ (0.41 g, 2.3 mmol) was added and the reaction mixture was refluxed under irradiation with visible light until no starting material could be detected by TLC analysis (afte ca 2 h). The reaction mixture was cooled down to r.t. and volatile components were removed in vacuo (30 °C/0.1 torr). The red brown residue was dissolved in degassed pentane (30 mL) and filtered through celite under an Ar atmosphere. Ferrous chloride hexahydrate (1.54 g, 5.7 mmol) was dissolved in MeCN (12 mL) and the solution cooled to –30 °C. At this temperature the filtrate was added under stirring and stirring was continued for 30 min. The reaction mixture was cooled to –70 °C and the pentane layer was removed from the frozen MeCN layer. The MeCN layer was allowed to warm to –30 °C, pentane (20 mL) was added and the procedure was repeated three times as described above. The pentane layers were combined, the solvent was removed in vacuo (30 °C, 12 Torr) and the residue purified by chromatography on silica gel with Et_2O–petroleum ether–Et_3N (1:20:0.01) to afford dienes **14** or **19**.
Analytical data of selected compounds:
Compound 13a: R_f = 0.44 (Et_2O–petroleum ether, 1:20); bp 110–120 °C (0.05 torr). IR(film): 2160 (C≡CSi), 1635 (C=C), 1240 (SiC) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.12 [s, 9 H, $Si(CH_3)_3$], 0.22 [s, 6 H, $Si(CH_3)_2O$], 1.54–1.68 (m, 4 H, CH_2), 2.16–2.22 (m, 4 H, $CH_2C{\equiv}C$), 4.21 (dt, ^3J = 5.0 Hz, ^4J = 1.3 Hz, 2 H, CH_2O), 5.09 (ddt, J_{cis} = 10.0 Hz, $^2J = {}^4J$ = 1.3 Hz, 1 H, CH=CH_2, H-*cis*), 5.25 (ddt, J_{trans} = 17.0 Hz, $^2J = {}^4J$ = 1.3 Hz, 1 H, CH=CH_2, H-*trans*), 5.93 (ddt, J_{trans} = 17.0 Hz, J_{cis} = 10.0 Hz, ^3J = 5.0 Hz, 1 H, CH=CH_2). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 0.11 [$Si(CH_3)_3$], 0.21 [$Si(CH_3)_2O$], 19.21, 19.32 (CH_2), 27.40, 27.56 ($CH_2C{\equiv}C$), 64.28 (CH_2O), 82.46, 84.72 (C≡CSi), 106.82, 107.55

(C≡CSi), 114.85 (CH=CH_2), 136.80 (CH=CH_2). MS (70 eV): *m*/*z* (%) = 277 (2) [$M^+ - CH_3$], 133 (90) [$C_8H_9Si^+$], 73(100) [$C_3H_9Si^+$]. Anal. Calcd for $C_{16}H_{28}OSi_2$ (292.6): C, 65.68; H, 9.64. Found: C, 65.76; H, 9.51.

Compound *rac*-14a: R_f = 0.19 (Et_2O–petroleum ether, 1:20); mp 74 °C. IR(film): 1620 (C=C), 1240 (SiC) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.14 [s, 9 H, $Si(CH_3)_3$], 0.26, 0.28 [2 × s, 6 H, $Si(CH_3)_2O$], 1.34–1.63 (m, 3 H, CH_2CH_2), 2.05–2.24 (m, 2 H, CH_2C=C), 2.26–2.52 (m, 3 H, CH_2C=C), 2.58–2.76 (m, 1 H, CHC=C), 3.40 (dd, $^2J = {}^3J$ = 9.5 Hz, 1 H, $SiMe_2OCH_2$), 4.27 (dd, ^2J = 9.5 Hz, ^3J = 7.6 Hz, 1 H, $SiMe_2OCH_2$). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = –0.56, 0.16 [$Si(CH_3)_2O$], 0.33 [$Si(CH_3)_3$], 24.43, 24.60 29.73, 31.31, 33.11 (CH_2), 40.06 (CHC=C), 72.40, (CH_2O), 131.02, 135.37, 143.25, 145.49 (C=C). MS (70 eV): *m*/*z* (%) = 292 (6) [M^+], 73 (70) [$C_3H_9Si^+$], 57 (100) [$C_3H_5O^+$]. Anal. Calcd for $C_{16}H_{28}OSi_2$ (292.6): C, 65.68; H, 9.64. Found: C, 65.85; H 9.55.

Compound 18: R_f = 0.47 (Et_2O–petroleum ether, 1:20). bp 130–140 °C (0.005 torr). $[\alpha]^{20}_D$ = –30.6 (*c* 1.0, $CHCl_3$). IR(film): 3005 (CH, alkene), 2160 (C≡CSi), 1640 (C=C), 1240 (SiC) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.12 [s, 9 H, $Si(CH_3)_3$], 0.22 [s, 6 H, $Si(CH_3)_2O$], 1.46–2.03 (m, 10 H, CH_2), 2.18–2.30 (m, 4 H, CH_2C≡C), 4.31–4.41 (m, 1 H, CHO), 5.62–5.82 (m, 2 H, CH=CH). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 0.10 [$Si(CH_3)_3$], 0.83, 0.89 [$Si(CH_3)_2O$], 19.21, 19.31, 24.92, 27.42, 27.55, 31.95 (CH_2), 67.08 (OCH), 83.17, 84.68 (C≡CSi), 106.84, 107.08 (C≡CSi), 129.53, 130.44 (CH=CH). MS (70 eV): *m*/*z* (%) = 332 (1.1), [M^+], 133(42) [$C_8H_9Si^+$], 73(100) [$C_3H_9Si^+$]. Anal. Calcd for $C_{19}H_{32}OSi_2$ (332.6): C, 68.61; H, 9.70. Found: C, 68.58; H, 9.75.

Compound 19: R_f = 0.22 (Et_2O–petroleum ether, 1:20). $[\alpha]^{20}_D$ = –40.2 (*c* 0.8, $CHCl_3$). IR(film): 1620 (C=C), 1240 (SiC) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.14 [s, 9 H, $Si(CH_3)_3$], 0.21, 0.35 [s, 6 H, $Si(CH_3)_2O$], 0.89 (m, 1 H, C-5), 0.99 (m, 1 H, C-4), 1.14 (m, 1 H, C-3), 1.16–1.24 (m, 1 H, C-5), 1.38–1.57 (m, 3 H, 1 H of C-8 and C-9, 1 H of C-4), 1.65–1.84 (m, 2 H, C-8 and C-9), 1.90–2.02 (m, 1 H, C-3), 2.13–2.38 (m, 4 H, 1 H of C-7, 2 H of C-10 and 1 H of C-5a), 2.57 (m, 1 H, C-7), 2.72 (m, 1 H, C-5b), 4.19 (m, 1 H, C-2a). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 0.00, 2.40 [$Si(CH_3)_2O$], 0.29 [$Si(CH_3)_3$], 22.16 (C-4), 23.78, 23.96 (C-8 and C-9), 26.72 (C-5), 31.05 (C-7), 32.46 (C-10), 33.57 (C-3), 36.86 (C-5a), 44.53 (C-5b), 77.63 (C-2a), 132.43, 134.72, 142.60, 143.52 (C=C). MS (70 eV): *m*/*z* (%) = 332 (61) [M^+], 258(53) [$C_{17}H_{26}Si^+$], 184(90) [$C_{14}H_{18}Si^+$], 73 (100) [$C_3H_9Si^+$]. Anal. Calcd for $C_{19}H_{32}OSi_2$ (332.6): C, 68.61; H, 9.70. Found: C, 68.54; H, 9.63.

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