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Preparation and reactivity of macrocyclic dienynes

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ABSTRACT

(1*E*,5*E*)-Cyclopentadeca-1,5-dien-3-yne (**1c**), which represents the first macrocyclic 1,5-dien-3-yne, can be obtained by thermal- or butyllithium-induced fragmentation of the corresponding 1,2,3-selenadiazole **8**. The (*E*,*E*)-dienyne functionality causes a geometrical strain E_g, which enhances the reactivity in addition (**1c**→**12**,**13**) and cycloaddition (**1c**→**10**) reactions and lowers the isomerization barrier to the unstrained (*E*,*Z*)-configuration **1d** ($E_g = 0$). A slow process **1c**→**1d** occurs even at ambient temperatures within several weeks.

Open-chain 1,5-dien-3-ynes are a well-known class of compounds with various applications in organic synthesis. Cyclization reactions to carbo- and heterocycles and cycloadditions, including Domino–Diels–Alder reactions, represent prominent examples for the reactivity of 1,5-dien-3-ynes.[1] Moreover, such dienynes are substructures of many carotenoids. On the contrary, very few cyclic 1,5-dien-3-ynes **1** have been studied.[2–5] In particular, the highly reactive cycloocta-1,5-dien-3-yne (**1a**)[6] and the 12-membered ring system **1b**,[7] which contains a further CC double bond, should be mentioned (Fig. 1).

Force field calculations and model studies revealed that the border line between 1,5-dien-3-ynes with and without angle strain (geometrical strain E_g) depends strongly on the configuration of the two double bonds.[7] $E_g = 0$ should be realized in 10-, 11-, or higher ring system for (*Z*,*Z*) configurations, in 13-, 14-, or higher ring system for (*E*,*Z*) configurations and in 17-membered and higher rings for (*E*,*E*) configurations. The larger the macrocyclic rings are, the more the ring strain can be distributed to bond angles, bond lengths, etc. This encouraged us to synthesize (1*E*,5*E*)-cyclopentadeca-1,5-dien-3-yne (**1c**).

We started the preparation with 3,14-dihydroxycyclopentadecan-1-one (**2**), a compound, which was used for the preparation of muscone and exaltone.[8] The dehydration of **2** with *p*-toluenesulfonic acid yielded (2*E*,14*E*)-cyclopentadeca-2,14-dien-1-one (**3**) as a primary product (Scheme 1). The isomeric dienones **5** and **6** are secondary products, which were generated by acid catalysis (**3**→**5**,**6**).[9] A comparably slower consecutive reaction yielded the bicyclic enone **4** by a Nazarov[10] cyclization (**3**→**4**). (2*E*,13*E*)-Cyclopentadeca-2,13-dien-1-one (**5**) was the major component (70–80% of the mixture **3**/**4**/**5**/**6**).[11] It could be purified by column chromatography (SiO_2, *n*-hexane/acetone gradient) and was obtained in a yield of 60–68% related to **2**. Dienone **5** was then transformed into its semicarbazone **7**, which exists as *syn*–*anti* mixture (2:1).[12] The reaction of **7** and SeO_2 afforded 1,2,3-selenadiazole **8**,[13] which represented the precursor for the desired dienyne **1c**. The fragmentation of **8** could be performed by thermolysis on Cu powder at 180 °C and 5–10 Pa (yield 54%) or by a very short treatment with *n*-butyllithium at −70 °C (yield 46%).[14] Thermolysis at higher pressure (~100 Pa) led to longer contact periods in the hot zone and to an isomerization of the strained ring system **1c** to the unstrained (*E*,*Z*)-dienyne **1d** ($E_g = 0$). The *E*→*Z* isomerization works even at room temperature with a half-life of about 20 d, which corresponds to a surprisingly low activation barrier for a stereoisomerization of an olefinic double bond. The second (*E*)-configured double bond is stable, since **1d** does not have a geometrical strain.

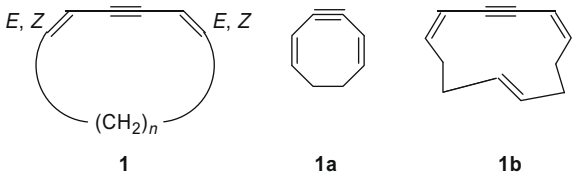

Figure 1. Cycloalka-1,5-dien-3-ynes.

When 1,2,3-selenadiazole **8** was refluxed in *p*-xylylene in the presence of tetraphenylcyclo pentadienone (**9**), 32% of the trapping product **10** was obtained (Scheme 2).[15] The isolated alkyne **1c** reacted even at room temperature to yield 65% **10**.

Treatment of **1c** with *n*-BuLi in *n*-hexane between −70 °C and room temperature gave a mixture of addition products. In principle, two types of 1,2-additions, a 1,4-addition and a 1,6-addition seem to be possible (Scheme 3). Apart from oligomerizations, we established a chemoselective 1,2-addition to the triple bond, which yielded an (*E*,*Z*,*E*)-triene, (**1c**→**12**) and a regioselective 1,4-addition to a vinylallene (**1c**→**13**). The oily mixture could be separated by

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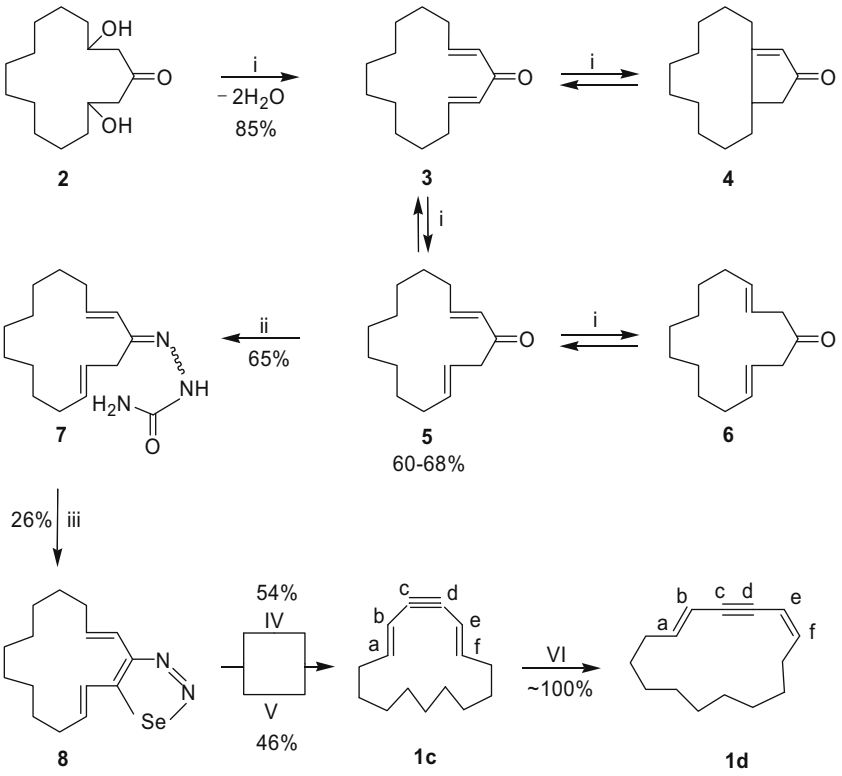
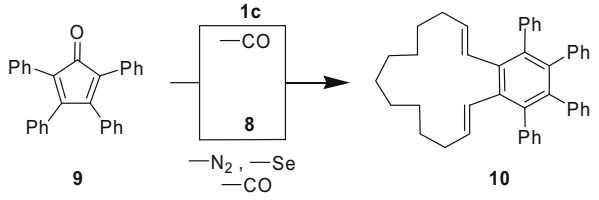
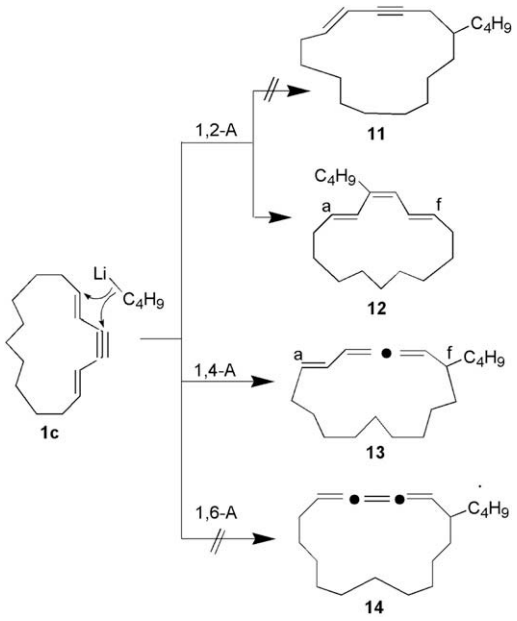


Scheme 1. Preparation of the cyclopentadeca-1,5-dien-3-ynes **1c** and **1d**. Reagents and conditions: (i) *p*-TsOH, toluene, 110 °C; (ii) H_2N–NH–$CONH_2$·HCl, NaOAc, EtOH, 78 °C; (iii) SeO_2, dioxane/H_2O (100:1), 25 °C; (iv) Cu, 180 °C, 5–10 Pa; (v) *n*-BuLi/*n*-hexane, 5 s at −70 °C; (vi) 25 °C, ca. 30 d or from **8** at 180 °C and 100 Pa.



Scheme 2. Cycloaddition reaction of isolated or in situ-formed **1c** and tetraphenylcyclopentadienone **9**.



Scheme 3. Addition reactions of (*E*,*E*)-dienyne **1c** and *n*-BuLi.

Table 1
^1H and ^{13}C NMR data of **1c**, **1d**, **12**, and **13** (δ values in $CDCl_3$, TMS as internal standard, δ (^{13}C) values within 1.0 ppm are interchangeable)

Compd	Olefinic and acetylenic positions						CH_2 (CH_3)
	a	b	c	d	e	f	
1c	6.12[a]	5.50[a]			5.50	6.12	2.16 (4H), 1.46 (4H), 1.34–1.18 (10H)
	146.7	110.3	93.0	93.0	110.3	146.7	33.1, 31.8, 29.7, 28.4, 27.0
1d	6.15[b]	5.58[b]			5.51[c]	6.12[c]	2.23 (2H), 2.16 (2H), 1.48–1.20 (14H)
	146.0	110.4	93.9	85.9	110.3	144.4	32.9, 29.5, 28.5, 28.2, 28.2, 27.7, 26.8, 26.7, 26.2
12	5.65	6.15		5.82	6.36	5.58	2.11 (6H), 1.40–1.18 (18H), 0.87 (3H,CH_3)
	131.3	128.9	138.9	128.3	125.3	132.3	35.8, 31.1, 30.9, 29.8, 27.9, 27.9, 27.4 27.2, 27.0, 26.6, 25.9, 22.5, 14.0 (CH_3)
13	5.60	5.80	5.71		4.93	2.09	2.08 (2H), 1.38–1.17 (22H), 0.87 (3H, CH_3)
	131.4	126.5	92.7	206.5	96.2	39.7	35.8, 34.8, 31.8, 29.8, 28.7, 28.1, 27.6, 27.3, 27.2, 26.6, 26.3, 22.7, 14.1 (CH_3)

[a] $^3J_{trans}$ = 15.4 Hz.
[b] $^3J_{trans}$ = 15.3 Hz.
[c] $^3J_{cis}$ = 10.1 Hz.

column chromatography (SiO_2, *n*-pentane) and gave first 15% pure **13** and then 12% pure **12**. Within the detection limit of 3%, we could exclude the presence of **11** and **14** in the product mixture.[16]

The unstrained dienyne **1d** has a much lower reactivity. It did not add *n*-BuLi at room temperature, in *n*-hexane at 60 °C a lot of oligomers and 15% of **13** were formed.

The hydrocarbons **1c, 1d, 12**, and **13** are colorless oils. Their ^1H and ^{13}C NMR data are listed in Table 1.[17] The reactivity of these highly unsaturated compounds makes them together with the known macrocyclic 1,3-dien-5-ynes[18,19] interesting candidates for the synthesis of further macrocyclic systems.

Acknowledgments

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References and notes

1. Altogether more than 2000 hits of (*E*,*E*)-, (*E*,*Z*)- and (*Z*,*Z*)-alka-1,5-dien-3-ynes are listed in reaction data banks.
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11. The portion of **5** in a basic medium is lower.
12. Yield 65%; mp 166 °C. ^1H NMR ($CDCl_3$): δ 8.39 (s, 1H, NH of *anti* configuration)/ 8.07 (s, 1H, NH of *syn* configuration, proved by NOE measurement), 6.24–5.91 (m, 2H, 2-H, 3-H), 5.15–5.50 (m, 2H, 13-H, 14-H), 3.06 (m, 2H, 15-H), 2.25–1.92 (m, 4H, 4-H, 12H), 1.18–1.28 (m, 14H, 5-H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H).
13. 7,8,9,10,11,12,13,14-Octahydro-(4*E*,15*E*)-6*H*-cyclo-pentadeca-1,2,3-selenediazole: oil, yield 26%. ^1H NMR ($CDCl_3$): δ 6.72 (dt, ^3J = 16.0 Hz, ^4J = 1.4 Hz, 1H, 4-H), 6.53 (dt, ^3J = 15.6 Hz, ^4J = 1.4 Hz, 1H, 16-H), 6.40 (dt, ^3J = 16.0 Hz, ^3J = 7.0 Hz, 1H, 5-H), 6.10 (dt, ^3J = 15.6 Hz, ^3J = 7.0 Hz, 1H, 15-H), 2.35 (m, 2H, 6-H), 2.24 (m, 2H, 14-H), 1.62–1.10 (m, 14H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H).
14. To the fragmentation processes see Ref. 4–7.
15. Mp 226 °C, ^1H NMR ($CDCl_3$): δ 6.98 (m, 10H, aromat. H), 6.77 (m, 10H, aromat. H), 6.18 (d, $^3J_{trans}$ = 16.2 Hz, 2H, 5-H, 17-H), 5.21 (dt, $^3J_{trans}$ = 16.2 Hz, ^3J = 6.8 Hz, 2H, 6-H, 16-H), 1.83 (m, 4H, 7-H, 15-H), 1.38–1.23 (m, 12H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H). EI MS (70 eV): *m*/*z* (%) = 559 (100) [$M+H^+$].
16. With the same limit of detection, we could exclude the generation of 1-butyl-cyclopentadeca-1,3,5-triene and 1-butyl-cyclopentadeca-1,2,4-triene. Both should be thermodynamically more stable isomers of **13**.
17. *E* and *Z* configurations of the olefinic double bonds in **1c**, **1d**, **12**, and **13** can be easily distinguished by the vicinal coupling constants: $^3J_{trans}$ = 15.4 ± 0.2 Hz, $^3J_{cis}$ = 10.1 ± 0.1 Hz. The central double bond in **12** has *Z* configuration, which was proved by a positive NOE between 4-H and α-CH_2 on C-3.
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