Straightforward syntheses of biradical-producing bicyclic dienediynes—dienediyne ketones cycloaromatize *via* the Saito–Myers and not *via* the neocarzinostatin pathway

Fabiola Ferri,[a,b] Reinhard Brückner*,[a] and Rainer Herges†,[c]

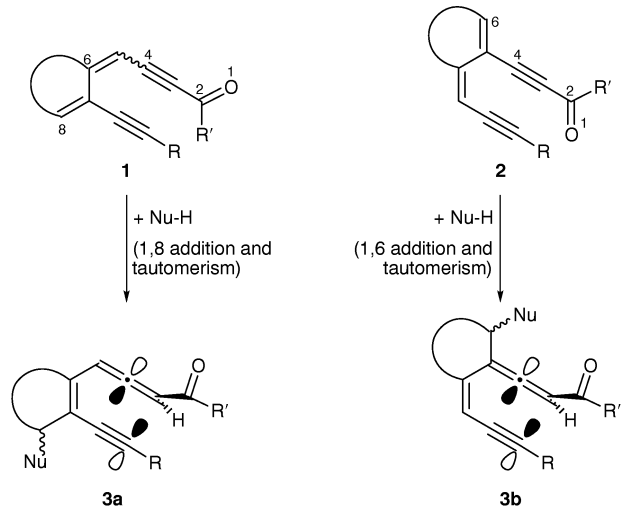
[a] *Institut für Organische Chemie der Georg-August-Universität, Tammannstr. 2, D-37077 Göttingen, Germany*
[b] *New Address: Laboratoire des Réactions Organiques Sélectives, Institut de Chimie Moléculaire de l'Université Paris Sud, 15, rue Georges Clémenceau, Bât. 420, F-91405 Orsay, France*
[c] *Institut für Organische Chemie der Technischen Universität, Hagenring 30, D-38106 Braunschweig, Germany*

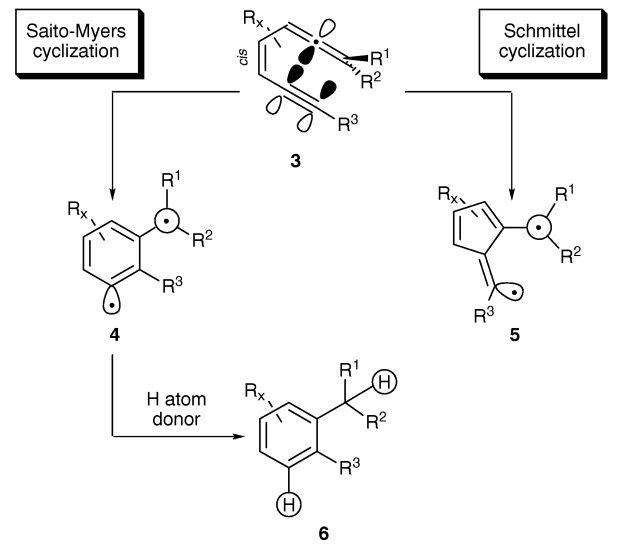
The dienediyne models **23** and **28** of the pharmacophore of the antitumor natural product neocarzinostatin were prepared. Each synthesis requires only six steps from α-formylcyclohexanone. Our approach uses two key steps. The first consists of one-pot biscoupling reactions between propargyl alcohol, 2,2-dimethyl-3-butyn-1-ol and the bis(enoltrifluoromethanesulfonate) **17**. The second key step corresponds to ring-closing pinacol coupling reactions of the dialdehydes **20** and **25**. The dienediyne models **23** and **28** cycloaromatized efficiently when treated with methyl thioglycolate and 1,4-cyclohexadiene at 25 °C *via* a Saito–Myers cyclization[4] (to give the octahydroanthracenones **29**, *iso*-**29** and octahydrophenanthrenones **34**, **35**, respectively); in addition, we isolated compounds tentatively assigned as the octahydrobenzazulenones **30** and *iso*-**30**, which would stem from a competing Schmittel cyclization. According to density functional theory (B3LYP/6-31G*) and *ab initio* calculations [CASMP2(2.2)/6-31G//CAS(2.2)/6-31G], the core structures of the octahydroanthracenones and octahydrophenanthrenones obtained here and elsewhere form *via* the Saito–Myers cyclization of enyneallenyl ketones **53** to toluene-α,*meta* biradicals **55** and not *via* neocarzinostatin-like cycloaromatizations of the tautomeric enyne[3]cumulenols **54** to styrene α,*meta*-biradicals **56**. This is so because, on the one hand, the two cyclization modes are predicted to have similar activation barriers (Saito–Myers: 16.0 kcal mol^{-1}; neocarzinostatin type: 18.3 kcal mol^{-1}) but, on the other hand, the enyneallenyl ketone **53** is a much more stable (21.1 kcal mol^{-1}) cycloaromatization substrate than the enynecumulenol **54**. In addition, the Saito–Myers cyclization product **55** is calculated to be considerably more stable (35.3 kcal mol^{-1}) than the neocarzinostatin-type cycloaromatization product **56**.

The addition of neocarzinostatin, the calichemicins, the esperamicins, dynemicin A, kedarcidin, C-1027 and maduropeptin to the arsenal of anticancer agents has inspired many chemists to participate in a world-wide search for chemotherapeutics that function by similar mechanisms as these natural products.[1] Most of the latter compounds (the calichemicins, the esperamicins, dynemicin A, kedarcidin, C-1027) contain or form (maduropeptin) a highly strained 1,5-hexadiyn-3-ene substructure, which isomerizes at body temperature or below to a benzene-1,4-biradical by a Bergman cyclization.[2] Neocarzinostatin is a highly strained dienediyne that can react to 7-octyne-1,2,3,5-tetraenes,[3] which in turn cycloaromatize to styrene biradicals ('neocarzinostatin cyclization'). In 1989, Saito and Myers and their respective coworkers recognized that 6-heptyne-1,2,4-trienes (from now on 'enyneallenes', **3**) can also cycloaromatize ('Saito–Myers cyclization', Scheme 1).[4] They thereby form short-lived toluene-α,*meta* biradicals **4**, which abstract hydrogen atoms from easily oxidizable compounds (1,4-cyclohexadiene, thiols or DNA) to give toluenes **6**. Saito–Myers cyclizations have since then been encountered in many enyneallenes **3**,[5] including enynallenyl ketones **3a**,**b**.[6–16] Recently, Schmittel *et al.*[17] and Gillmann *et al.*[18] found that some enyneallenes **3** undergo a different biradical-producing cyclization reaction, furnishing fulvene-1,3-diyls **5** ('Schmittel cyclization'). This increasingly observed[19] reaction mode is not a *cycloaromatization* and in this regard is distinct from Bergman, neocarzinostatin and Saito–Myers cyclizations. Whether a given enyneallene **3** cyclizes *via* the Saito–Myers (to give **4**) or the Schmittel (to give **5**) modes depends on whether the in-plane π orbitals of substrate **3** cause better 1,6 or 1,5 overlaps.

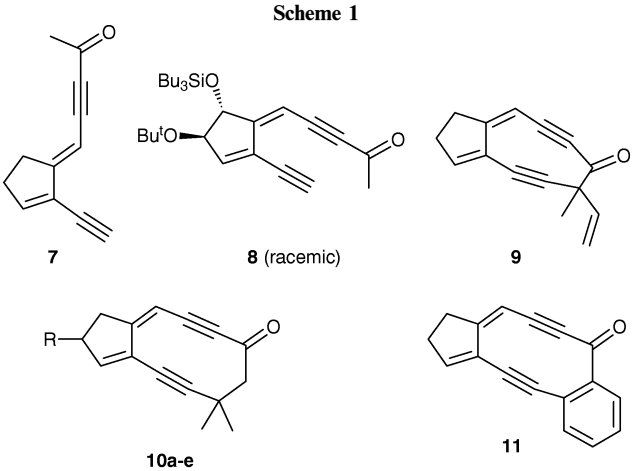
The common access (exception: ref. 16) to enynallenyl ketones **3a**,**b** is the 1,6-addition of a nucleophile to dienediyne ketones **1** or the 1,8-addition of a nucleophile to dienediyne ketones **2** (Scheme 1). Previously synthesized type-**1** dienediyne ketones were compounds **7**–**11**,[6–13] and type-**2** dienediyne ketones were compounds **12**–**14**[14,15] (Scheme 2). The *diene* moieties of these dienediyne ketones are integrated into 5- (**7**–**12**) or 6-membered (**13**, **14**) carbocycles. This ensures that derived enyneallenyl ketone **3** possess a *cis* C=C bond, which is a prerequisite for Saito–Myers cyclizations, **3** → **4**. The *diyne* moieties of the dienediyne ketones **9**–**14** are part of 9- to 11-membered rings. This ensures that the in-plane π orbitals of derived enyneallenyl ketones **3** interact in a *trans-annular* fashion and thus particularly efficiently. Accordingly, the *bicyclic* dienediyne ketones in Scheme 2 cycloaromatize at lower temperatures and with higher yields (**9**: −30 °C/54%;[8] **10a**: 20 °C/31%[9a] or 25 °C/55%;[9b] **10b**: 25 °C/56%;[10] **10c**: 25 °C/54%;[10] **10d**: 25 °C/64%;[11] **10e**: room temp./28%;[12] **11**:

* Fax: +49-551-392944; E-mail: rbrueck@gwdg.de
† Fax: +49-531-3915388; E-mail: R. Herges@tu-bs.de

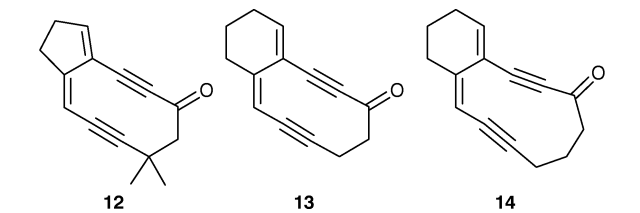




Scheme 1



a: R = H; **b:** R = α-OH; **c:** R = α-O_2C-Ar;
d: R = α-CH_2-CH_2-O_2CR; **e:** R = CH_2-CH_2-S-Ac



Scheme 2 Type-**1** dienediyne ketones (upper rows) and type-**2** dienediyne ketones (bottom row) from the literature

0 °C/20%;[13] **12**: 25 °C/38%;[14] **13**: 35–37 °C/24%;[15] **14**: 35–37 °C/ > 35%[15]) than the *monocylic* dienediyne ketone **7** (70 °C/15%[6]).

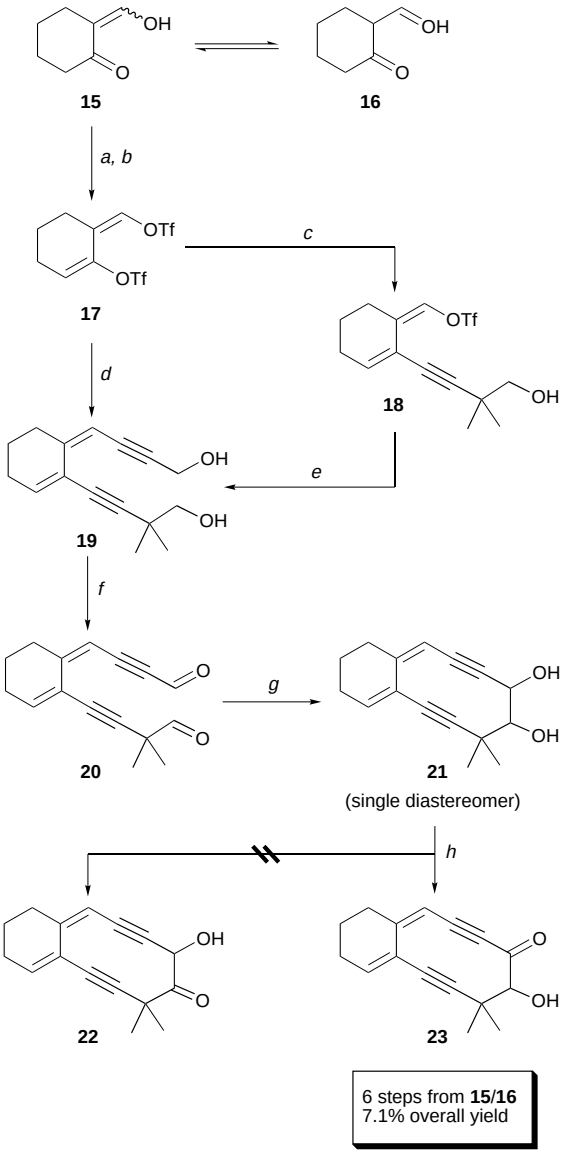
A dream of many researchers is that one day Saito–Myers cyclizations **3** → **4** will occur in synthetic anti-cancer agents endowed with tumor cell specificity by a yet unknown method. In this respect it would be desirable that biradical-forming bicyclic enyneallenyl ketones **3a**,**b** be made available by paths that are as efficient and short as possible. In contrast to this, present-day synthesis path lengths for their dienediyne ketone precursors vary between 8 (**10a**[9]) and 15 steps (**10e**[12]); the synthesis of the more elaborate and enantiopure neocarzinostatin model **10d**[11] required even 22 steps. We felt that there is not only a need but also leeway for improvement. We report below the presently shortest syntheses of dienediyne models of neocarzinostatin forming biradicals below body temperature. One leads to a type-**1** and the other to a type-**2** dienediyne ketone.

Results

The novel dienediyne ketone syntheses (Schemes 3, 4) use our bis(trifluoromethanesulfonate) ('bistriflate') → dienediyne strategy. This strategy was originally developed for accessing neocarzinostatin models containing a cyclopentene ring.[20] It was subsequently extended to the cyclohexene ring.[15,21,22] The starting material of these syntheses is the equilibrium mixture between the tautomers **15** and **16** of 2-formylcyclohexanone. Upon treatment with *tert*-butyllithium in THF the enol fraction forms a *Z*-configurated enolate. It is scavenged with triflic anhydride as a *Z*-monotriflate.[15] The lithium enolate formed from the latter compound and hexamethyldisilazide is sulfonylated with triflic anhydride once more. It thereby gives the stereopure bistriflate **17**.[15]

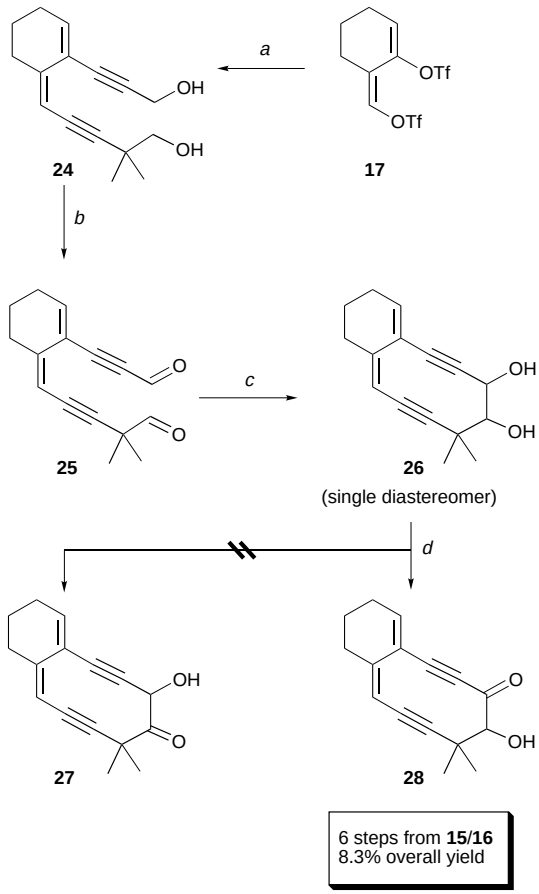
As already described[21] and several times exploited,[15,22] bistriflate **17** couples under Pd catalysis with *in situ* formed copper acetylides *via* dienyne monotriflates to dienediynes. This occurs such that a fast first coupling reaction occurs at the C_{quat}—O bond. A much slower second coupling follows at the C_{tert}—O bond. Thus, successive additions of first 1.0 equiv of a first alkyne and a couple of hours later of ⩾1.0 equiv of a second alkyne to bistriflate **17** lead to the formation of a dienediyne with predictable attachment sites of the alkynyl arms. Reversing the order in which the two alkynes are added is therefore tantamount to synthesizing a different dienediyne. Accordingly, coupling the bistriflate **17** in a one-pot reaction first with 2,2-dimethyl-3-butyn-1-ol and thereafter with propargyl alcohol gave the dienediynediol **19** (Scheme 3). The opposite order of couplings in the complementary one-pot reaction of Scheme 4 led to the dienediynediol **24**. Unfortunately, the positional selectivities of the first couplings were not perfect. Thus, the desired bicyclic product **19** was contaminated with up to 10% of isomer **24** and the biscoupling product **24** with up to 10% of isomer **19**. We coped with this imperfection best by purifying each biscoupling product *several* times by means of thorough flash chromatography on silica gel.[23] This is because compound **19** accumulates in the early and compound **24** in the late fractions. Alternatively, we isolated the *monocoupling* product **18** of bistriflate **17** and 2,2-dimethyl-3-butyn-1-ol en route to the biscoupling product **19**. However, separating **18** from 5–7% of the isomeric monocoupling product was difficult, too, and **18** polymerized more easily than directly formed **19**.

The next step in the syntheses of Schemes 3 and 4 were oxidations of the dienediynediols **19** and **24** with the Dess–Martin reagent[24] to the dienediyne dialdehydes **20** [58% admixed with 10% of the *E* isomer; $\delta_{Z\text{-}C(=O)H} = 9.28$ (d, $^5J = 1.2$ Hz) and 9.52 (s)] and **25** [83%; $\delta_{C(=O)H} = 9.31$ and 9.49 (2 s)], respectively. Subsequently, these dialdehydes were pinacol-coupled under our previously described condi-



Scheme 3 (*a*) Ref. 15: Bu^{t}Li (1.1 equiv.), THF, −78 °C, 10 min; Tf_2O (1.1 equiv.), 78 °C, 15 min; 57%. (*b*) Ref. 15: LiHMDS (1.1 equiv.), THF, −78 °C, 1 h; Tf_2O (1.1 equiv.), −78 °C, 20 min; 74%. (*c*) 2,2-Dimethyl-3-butyn-1-ol (1.2 equiv.), $Pd(PPh_3)_4$ (5 mol %), CuI (10 mol %), piperidine (2.0 equiv.), THF, room temp., 3 h; 75%. (*d*) 2,2-Dimethyl-3-butyn-1-ol (1.1 equiv.), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %), Et_2O : Pr^i_2NH (3 : 1), 0 °C, 3 h; addition of propargyl alcohol (1.0 equiv.), 0 °C, overnight; room temp., 10 h; 80% (slightly contaminated). (*e*) Propargyl alcohol (1.1 equiv.), $Pd(PPH_3)_4$ (5 mol %), CuI (10 mol %), piperidine (2.0 equiv.), room temp., overnight; 83%. (*f*) Dess–Martin periodinane (2.2 equiv.), CH_2Cl_2, room temp., 30 min; 68% of a 85 : 15 mixture with the presumed *E* isomer. (*g*) 'Low-valent Ti' from $TiCl_3$ (18 equiv.) and Zn/Cu couple (55 equiv.), DME, −45 °C,, 5.5 h; 56%. (*h*) Bu^{t}OMgBr from EtMgBr solution in THF (3.0 equiv.) and Bu^{t}OH (3.0 equiv.), azodicarbonyldipiperidide (1.2 equiv.), THF, 0 °C, 30 min; 55%

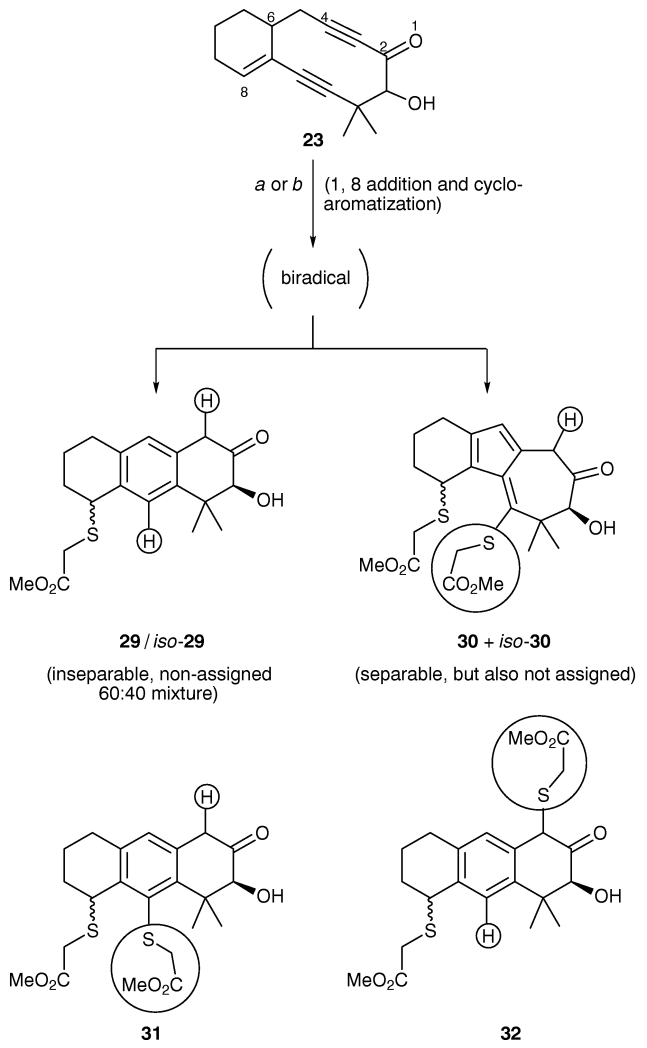
tions,[22d–f] *i.e.* with 'low-valent titanium'[25] generated from $TiCl_3$ and the Zn/Cu couple[26] in DME. Working at −45 °C avoided the potentially competing[22d–f] McMurry olefination.[27] The reduction products on which we concentrated, because they were readily isolable without contaminants were the bicyclic dienediynediols **21** [56%; $\delta_{CH(OH)} = 3.64$ (d, J_{vic} = 8.6 Hz) and 4.41 (d, $J_{vic} = 8.3$ Hz)] and **26** [80%; $\delta_{CH(OH)} = 3.64$ (d, $J_{vic} = 8.7$ Hz) and 4.40 (d, $J_{vic} = 8.6$ Hz)]. They were pure diastereomers according to the appearance of *single* δ_H and δ_C sets in the 300 MHz ^{1}H and 75 MHz ^{13}C NMR spectra. Their configurations are suspected to be *cis* but are unestablished.



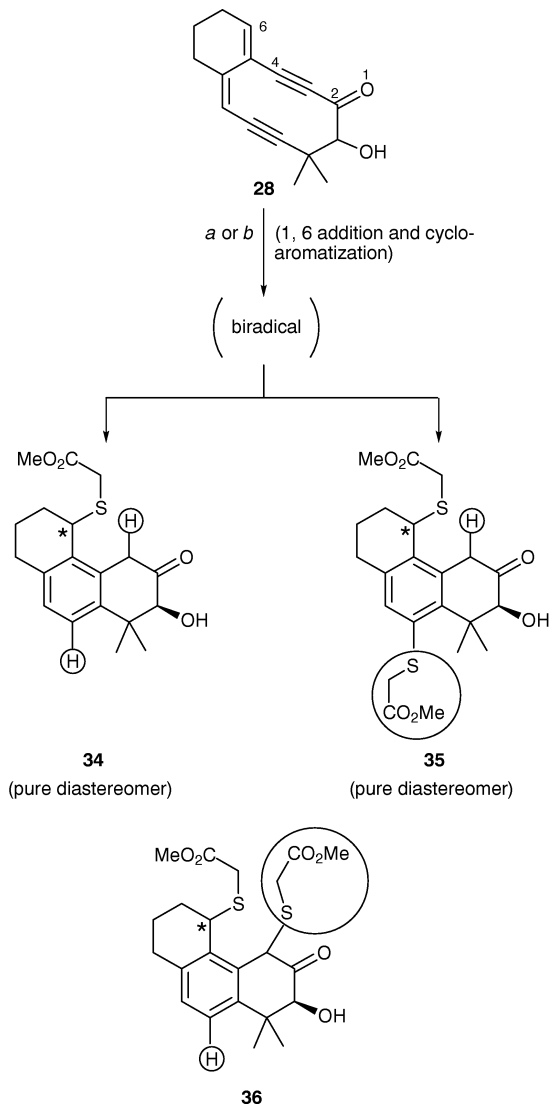
Scheme 4 (*a*) Propargyl alcohol (1.1 equiv.), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %), Et_2O–Pr^i_2NH (3 : 1), room temp., 3 h; addition of 2,2-dimethyl-3-butyn-1-ol (1.0 equiv.), room temp., overnight; 39% pure **24** or 62% **24** containing typically 8 rel % of 'regioisomer' **19**. (*b*) Same as (*f*) in Scheme 3; 83% of isomerically pure material. (*c*) Same as (*g*) in Scheme 3; 80%. (*d*) Same as (*h*) in Scheme 3; 76%

We had envisaged to finish the dienediyne ketone syntheses of Schemes 3 and 4 by an oxidation of the dienediynediols **21** and **26**. However, Cr^{VI} reagents (PCC, PDC, Collins' reagent) or the Dess–Martin periodinane effected glycol cleavages in dienediynediols **21** or **26**. Thus, their precursors, *i.e.* the dienediyne dialdehydes **20** and **25**, respectively, were obtained again. Swern's oxidation conditions destroyed dienediynediols **21** and **26**. Finally, we tried Narasaka *et al.*'s version[28] of the Oppenauer oxidation. It is basically a hydride abstraction by azodicarboxylic acid dipiperidide from the magnesium salt of the alcohol in question. Applied to our diols **21** and **26**, this method brought about a chemoselective *monooxidation* in both instances. The propargylic OH group reacted while the electronically unactivated and sterically hindered OH group remained untouched. Thus, the ketones **23** (55%) and **28** (76%) were obtained.

The dienediyne ketones **23** and **28** are acyloins. They can be distinguished from their isomers **22** and **27**, respectively, through their 300 MHz ^{1}H NMR spectra. The shifts of the protons at the C=C bonds *protruding from* or *lying within* the 6-membered ring of acyloin **23** [$\delta_{C=CH_{exocyclic}} = 5.47$ (m_c); $\delta_{C=CH_{endocyclic}} = 6.45$ (td, $J_{vic} = 4.7$ Hz, $^5J = 1.5$ Hz)] resemble more those of the analogous protons in dialdehyde **20** [$\delta_{C=CH_{exocyclic}} = 5.56$ (br s); $\delta_{C=CH_{endocyclic}} = 6.51$ (td, $J_{vic} = 4.4$ Hz, $^5J = 1.2$ Hz)] than those of the diol **21** [$\delta_{C=CH_{exocyclic}} = 5.25$ (br s); $\delta_{C=CH_{endocyclic}} = 6.20$ (br t, $J_{vic} = 4.5$ Hz)]. This signifies that in acyloin **23** both C=CH groups are remotely conjugated with the C=O bond, like they are in **20**. This supports the assignment of structure **23** at the expense of the alternative **22**.



Scheme 5 (*a*) Methyl thioglycolate (2.1 equiv.), NEt_3 (1.0 equiv.), C_6H_6, room temp., 10 h; 60 : 40 **29**/*iso*-**29** (27%), **30** (27%) and *iso*-**30** (7%). (*b*) Same as (*a*) but without 1,4-cyclohexadiene; 60 : 40 **29**/*iso*-**29** (16%), **30** (23%) and *iso*-**30** (16%). Entities taken up by the biradical intermediates to give the observed products or the indicated unobserved alternative structures are encircled



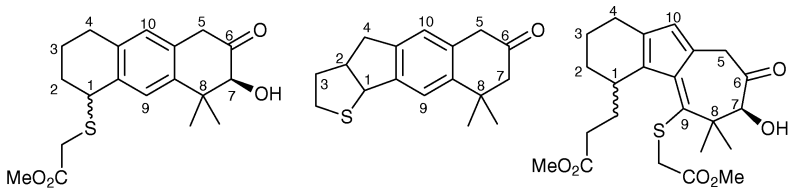
Scheme 6 (*a*) Methyl thioglycolate (2.1 equiv.), NEt_3(1.0 equiv.), 1,4-cyclohexadiene (23 equiv.), CH_2Cl_2, room temp., 2 h; **34** (38%) and **35** (16%). (*b*) Methyl thioglycate (20 equiv.), NEt_3 (1.0 equiv.), CH_2Cl_2, room temp., 10 h; **34** (18%) and **35** (30%). Entities taken up by the biradical intermediate to give the observed products or the indicated unobserved alternative structure are encircled

To the acyloin of Scheme 4 we assign structure **28**. This seems justified even if the proton at the C=C bond *protruding from* the 6-membered ring [$\delta_{C=CH_{exocyclic}} = 5.35$ (td, $^4J_{9,11} \approx {}^5J_{9,14} \approx 1.2$ Hz)] is characterized by the shift average of the analogous protons in dialdehyde **25** [$\delta_{C=CH_{exocyclic}} = 5.52$ (d, $^5J = 0.7$ Hz)] and in diol **26** [$\delta_{C=CH_{exocyclic}} = 5.20$ (br s)] and thus leaves open the question whether this C=C bond is conjugated with or isolated from the C=O group. Clarity comes from the proton at the C=C bond *embedded in* the 6-membered ring of acyloin **28** [$\delta_{C=CH_{endocyclic}} = 6.59$ (td, $J_{vic} = 4.5$ Hz, $^5J = 1.5$ Hz)]. The chemical shift resembles that of the corresponding proton in dialdehyde **25** [$\delta_{C=CH_{endocyclic}} = 6.70$ (td, $J_{vic} = 4.5$ Hz, $^5J = 1.4$ Hz)] and not in diol **26** [$\delta_{C=CH_{endocyclic}} = 6.22$ (t, $J_{vic} = 4.4$ Hz)]. This resemblance and discrepancy mean that the acyloin of Scheme 4 contains the same substructure HC=C—C≡C—C(=O) as the dialdehyde **25** and is devoid of the substructure HC=C—C≡C—CH(OH) of the diol **26**. Since formula **28** contains this substructure and formula **27** does not, the former is correct.

The newly prepared dienediyne ketones **23** and **28** cyclized/cyloaromatized when we treated them *at room temperature* with methyl thioglycolate and triethylamine for 2–10 h (Schemes 5, 6). Whether 1,4-cyclohexadiene was present or not at the same time affected the yields and product compositions only marginally. Each of the mentioned dienediyne ketones afforded *two* types of products. Their combined yields reached 61% starting from **23** and 54% starting from **28**; these numbers match the highest values reported in the literature systems[6,8–15] (64% for **10d**,[11] 56% for **10b**[10]). One product type corresponds to the uptake of *one equivalent* of methyl thioglycolate and *one equivalent* of hydrogen; the other is characterized by the uptake of *two equivalents* of methyl thioglycolate. Specifically, the dienediyne ketone **23** and methyl thioglycolate provided up to 27% type-**1** product (**29**/*iso*-**29**) as an unseparable 60 : 40 mixture of unassigned diastereomers or up to 39% type-2 products (**30**/*iso*-**30**) as separable major and minor diastereomers, respectively. Similarly, the dienediyne ketone **28** and methyl thioglycolate gave to up to 38% type-1 product (**34**) or up to 30% type-2 product (**35**), both of which were single diastereomers. Product **35** is distinguishable from the isomeric structure **36** by the presence of one instead of two sp^2-bound protons.

The structures of the cyclized/cycloaromatized products **29**, *iso*-**29**, **30**, *iso*-**30**, **34** and **35** were deduced from their NMR spectra unequivocally (**29**, *iso*-**29**, **34**, **35**; Tables 1 and 2) or represent, in the absence of crystal structure analyses, tentative assignments (**30**, *iso*-**30**; Table 1). The formation of *pairs of diastereomers* was inferred from the occurrence of *two* very

Table 1 Selected 300 MHz ^{1}H and 75.5 MHz ^{13}C NMR data ($CDCl_3$) of the cycloaromatized/cyclized products obtained from ketone **23** (500 MHz ^{1}H- and 125.7 MHz ^{13}C NMR for compounds **30** and *iso*-**30**) and, for comparison, of the known compound **33**.[9b] Coupling constants in Hz

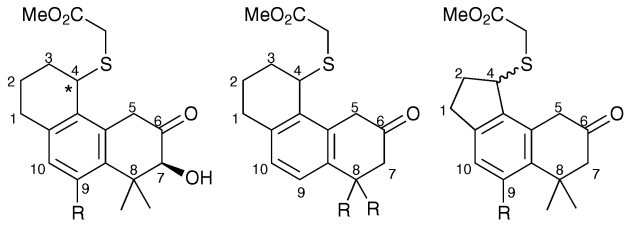


29/*iso*-**29** **33** **30**/*iso*-**30**

Nucleus	**29**/*iso*-**29**	**33**	**30**	*iso*-**30**
1-H	4.30[a] (t)/4.31[a] (t)	4.84 (br d)	4.41 (br s)	4.20 (m_c)
5-H_2	3.74 (J_{gem} unknown)	3.63 (br d)	2.89 and 3.22 (J_{gem} = 17.8)	2.69 and 3.64 (J_{gem} = 16.8)
7-H_2	4.20 (J = 3.7)/4.17 (J = 3.4)	2.48 and 2.51 (J_{gem} = 15.0)	4.18 (J = 2.5)	4.13 (J = 2.5)[b]
9-H (s)	7.43[c]/7.42[c]	7.27	—	—
10-H	6.86[c]	6.92	6.99	6.98
S-CH_2 (J_{gem})	3.23 and 3.36 (J = 15.1)/3.21 and 3.35 (J = 14.9)	2.75 and 3.09 (J = 16.3)	3.19 and 3.36 (J = 14.5)/3.66 and 3.70 (J = 15.2)	3.19 and 3.36 (J = 14.7)/3.65 and 3.71 (J = 15.2)
C-1	52.37/52.39	[d]	41.31	41.08
C-6	209.74	[d]	198.98	199.06
C-7	80.22/80.32	[d]	80.21	80.66
CO_2CH_3	171.16/171.11	[d]	169.96 and 170.72	169.94 and 170.64

[a] Assignment exchangeable. [b] Assignment exchangeable. [c] Assignment exchangeable. [d] No ^{13}C NMR spectrum of this compound has been published.

Table 2 Selected ^{1}H and ^{13}C NMR data ($CDCl_3$) of the cycloaromatized products (500 MHz/125.7 MHz) obtained from ketone **28** and, for comparison, of the known compounds **37** (300 MHz/75.5 MHz),[15] **38** (500 MHz/125.7 MHz; C_6D_6),[29] **39** (400 MHz)[14] and **40** (400 MHz).[14] Coupling constants in Hz



34: R = H
35: R = S-CH_2-CO_2Me

37: R = H
38: R = Me

39: R = H
40: R = S-CH_2-CO_2Me

Nucleus	**34**	**37**	**38**	**39**	**35**	**40**
4-H	4.12 (br s)	4.18 (br s)	4.02	4.40 (br d)	4.12 (br s)	4.41 (br d)
5-H_2	3.67 and 4.29 (J_{gem} = 22.1)	3.50 and 4.00 (J_{gem} = 20.4)	3.44 and 4.43 (J_{gem} = 21.7)	3.52 and 4.07 (J_{gem} = 22.0)	3.65 and 4.28 (J_{gem} = 22.1)	3.48 and 4.04 (J_{gem} = 22.0)
7-$H_{(2)}$	4.23	2.56 or 3.03	2.22	2.50 and 2.58 (J_{gem} = 14.5)	4.21	2.49 and 2.57 (J_{gem} = 14.8)
9-H	7.30[a] (d, $J_{9,10}$ = 8.1)	7.05[b] (d, $J_{9,10}$ = 7.9)	7.03[c] (d, $J_{9,10}$ = 8.0)	7.31[d] (d, $J_{9,10}$ = 8.0)	—	—
10-H	7.07[a] (d, $J_{10,9}$ = 8.1)	6.95[b] (d, $J_{10,9}$ = 7.9)	6.81[c] (d, $J_{10,9}$ = 8.3)	7.15[d] (d, $J_{10,9}$ = 7.9)	7.36 (s)	7.36 (s)
S-CH_2 (J_{gem})	3.20 and 3.35 (J = 14.4)	3.19 and 3.36 (J = 14.4)	2.73 and 2.93 (J = 14.1)	3.25 and 3.32 (J = 14.8)	3.19 and 3.34 (J = 14.4), 3.67 (2×)	3.24, 3.32, 3.63 and 3.66 (J = 14.6 and 14.8)
C-4	42.39	41.80	42.34	[e]	42.51	[f]
C-6	209.65	210.75 or 210.76	207.60	[e]	209.33	[f]
C-7	79.73	38.41 or 40.54	53.61	[e]	79.49	[f]
CO_2CH_3	170.73	170.80	170.14	[e]	170.03 and 170.67	[f]

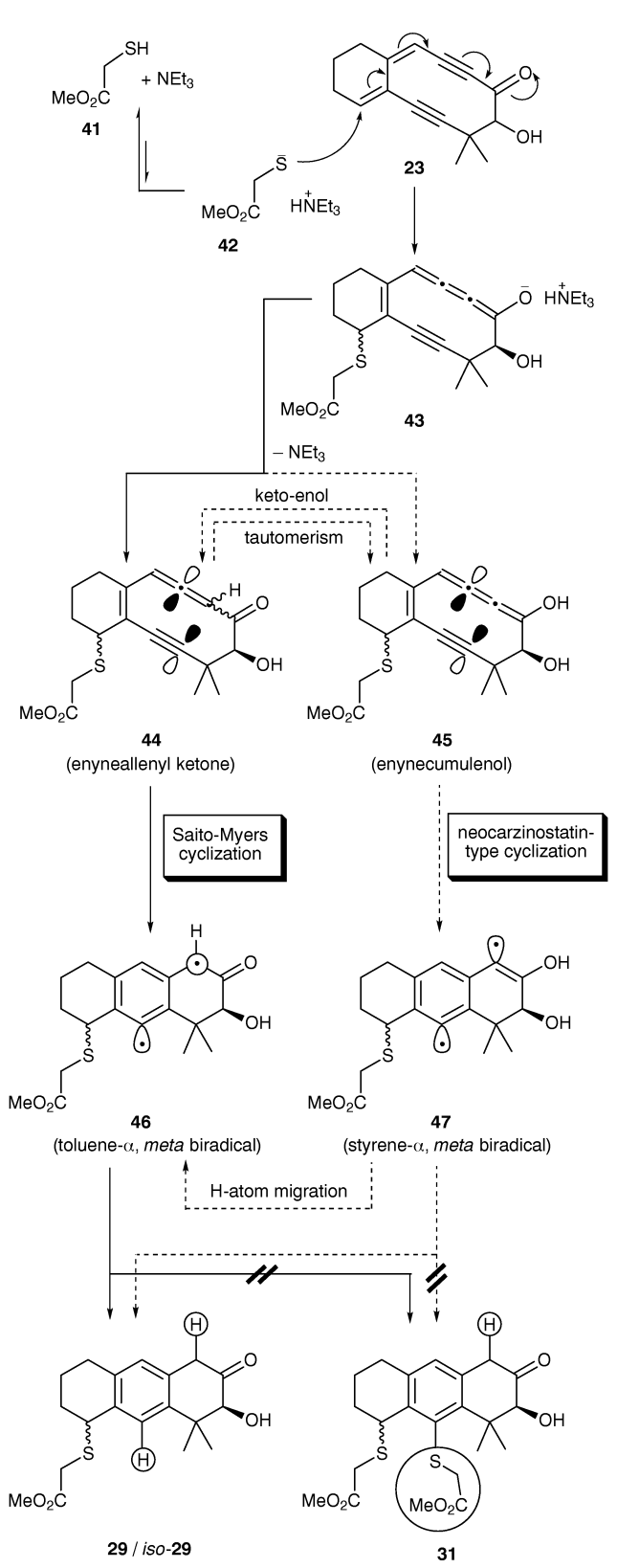
[a] Assignment interchangeable. [b] Assignment interchangeable. [c] Assignment interchangeable. [d] Assignment interchangeable. [e] No ^{13}C NMR spectrum of this compound has been published. [f] No ^{13}C NMR spectrum of this compound has been published.

similar ^{1}H and ^{13}C NMR data sets for the compound pairs **29**/*iso*-**29** and **30**/*iso*-**30**. Conversely, the most likely interpretation for observing *single* ^{1}H and ^{13}C NMR data sets in the compounds **34** and **35** is that each of them is *diastereomerically pure*.

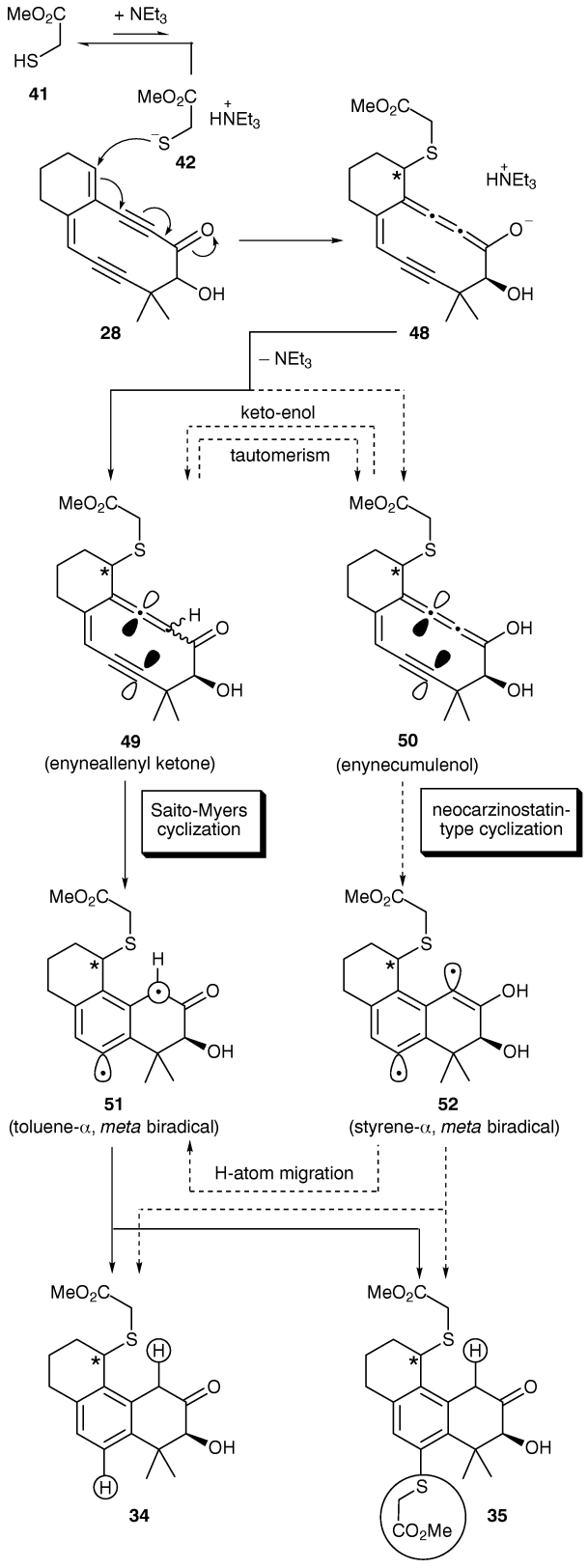
Let us first consider pertinent NMR data of the safely assignable cyclization/cycloaromatization products. Compounds **29** and *iso*-**29** are octahydrophenanthrenones (Table 1). They exhibit singlets for their *para*-positioned aromatic protons. The resonances of 5-H_2 in **29** and *iso*-**29** resemble the 5-H_2 shifts in the related compound **33**.[9b] Moreover, the aliphatic proton signals of **29** and *iso*-**29** in general resemble those of the newly prepared octahydroanthracenones **34** and **35** (Table 2). The latter two compounds, in turn, resemble the aliphatic ^{1}H NMR resonances of their deoxygenated analogues **37**[15] and **38**[29] or their deoxygenated/demethylated analogues **39**[14] and **40**[14] (Table 2). These analogies in the ^{1}H NMR data are paralleled by a reliable similarity of the ^{13}C

NMR shifts of all carbon centers that are analogously substituted. Naturally, this statement can be probed only as far as these ^{13}C NMR shifts are available; they are unknown for the reference compounds **33**,[9b] **39**,[14] and **40**.[14]

Let us now turn to the structures of compounds **30** and *iso*-**30** obtained from the dienediyne ketone **23** through the net uptake of two equivalents of methyl thioglycolate. Contemplating the ^{1}H and ^{13}C NMR spectra of each of these species (Table 1) separately one can take them for the diastereomeric octahydroanthracenones **31** depicted in Scheme 5. Clearly, these compounds were not the isomers **32** because they contain one sp^2-bound proton and not two. However, upon



Scheme 7



Scheme 8

closer scrutiny one doubts that the structures **31** are correct. There are two singularities in juxtaposing the NMR data in question and the NMR data of the reference compounds **29**, *iso*-**29**, **33**–**35** or **37**–**40** (Tables 1, 2). (*a*) The geminal coupling constant between the diastereotopic protons 5-H_2 of **30** and *iso*-**30** measures 17.8 and 16.8 Hz, respectively; this is different from the reference values of $20.4 \leqslant J_{gem} \leqslant 22.1$ Hz for *benzylic* 5-H_2 groups. (*b*) The keto group of **30** and *iso*-**30** resonates 10 ppm upfield from the standard value of 210 ± 1 ppm encountered elsewhere. As a consequence we tend to discard the octahydrophenanthrenone structure **31** and tentatively suggest in place of them the octahydrobenzoazulenone structures shown. These species would arise from a Schmittel cyclization of the enyneallenyl ketone **44** (formula: Scheme 7) followed by a regioselective addition of methyl thioglycolate to the resulting fulvene biradical. We are unaware of related octahydrobenzoazulenones and the chemical shift of *their* C=O groups. Therefore, we are not able to substantiate the validity of the proposed structural assignments.

Discussion

The structurally unambiguous cycloaromatization products **29** and *iso*-**29** are proposed to arise from the Saito–Myers biradical **46** (Scheme 7). They are formed through a two-step 1,6-addition of methyl thioglycolate to the C=C−C=C−C≡C motif of the dienediyne ketone **23**, the addition product being the enyneallenyl ketone **44**. Biradical **46** is a toluene biradical, *i.e.* a species that contains, at a qualitative level of consideration, one localized and one delocalized radical center. It gives the valence-saturated species **29** and its diastereomer *iso*-**29** through the uptake of two hydrogen atoms. They stem from methyl thioglycolate and/or from 1,4-cyclohexadiene.

The cycloaromatizations starting from the dienediyne ketones **7** *and* **9**–**14** *of Scheme 2 could* a priori *also* proceed by a neocarzinostatin-type cycloaromatization mechanism, *i.e. by an enyne*[*3*]*cumulene → styrene biradical conversion.*[3a] If this alternative mechanism applied, a two-step 1,8-addition of methyl thioglycolate to the C=C−C=C−C≡C−C=O moiety of ketone **23** would be the starting point of *our* reaction and lead to the enyne[3]cumulenol **45** (Scheme 7). Its neocarzinostatin-type cycloaromatization would give the styrene biradical **47**. The latter could either isomerize to the Saito–Myers biradical **46** and continue to react as already described. Or, it could itself pick-up two hydrogen atoms from methyl thioglycolate and/or from 1,4-cyclohexadiene. Diastereomeric enols would form whose ketone tautomers are identical with the observed cycloaromatization products **29** and *iso*-**29**.

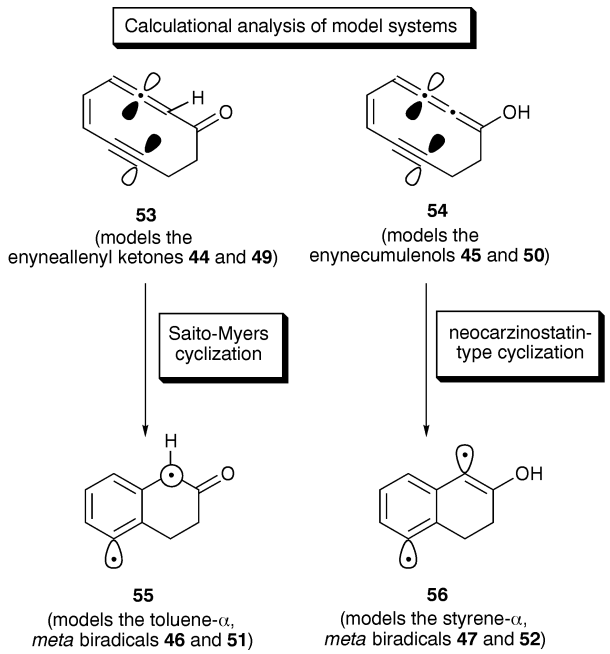
The styrene biradical **47** is a species with two nonconjugated radical centers. Therefore, a styrene biradical like **47** should be less stable and probably also less rapidly formed than an isomeric toluene biradical like **46**. One would expect an exception to this generalization only if a ring-size effect destabilizes the styrene biradical less than the toluene biradical. However, such an exception can be excluded for the case at hand by density functional theory, as described in the subsequent part of this paper. These calculations do not only suggest that compounds **29** and *iso*-**29** form *only via* the Saito–Myers pathway but also that the Saito–Myers mechanism prevails for the cycloaromatization of dienediyne ketones **10**–**13** in which the C=O bond lies in a 10-membered ring.

Having thus established that the biradical precursor of the cycloaromatization of Scheme 7 is **46**, one can now interpret the chemoselectivity of its quenching reaction. As Scheme 5 shows, we obtained the hydrogen addition products **29** and *iso*-**29** and none of the thiol addition products **31** or **32**. This selectivity can be rationalized as follows. (*a*) The phenyl radical moiety of biradical **46** is sterically hindered through two *ortho* substituents, one of which is additionally once and the other twice branched. Accordingly, this radical center cannot combine as fast with a MeO_2C-CH_2-S· radical, even if the latter is formed close by, as it abstracts an H atom from methyl thioglycolate or 1,4-cyclohexadiene. (*b*) The benzyl radical moiety of biradical **46** is considerably more stable than the phenyl radical moiety. Hence, it, too, scavenges MeO_2C-CH_2-S· radicals only slowly. It is long-lived enough to be saturated by an H-atom transfer from methyl thioglycolate or from 1,4-cyclohexadiene (to give **29**/*iso*-**29**, *q. e. d.*).

The other genuine *cycloaromatization* products **34** and **35** of the present study arose from the dienediyne ketone **28**. For compounds **34** and **35**, too, there is the dichotomy of a Saito–Myers or a neocarzinostatin-type formation mechanism (Scheme 8). For the reasons given in the discussion of Scheme 7, in Scheme 8 the Saito–Myers mechanism (two-step 1,6-addition of methyl thioglycolate → enyneallenyl ketone **49** → toluene biradical **51** → **34**/**35**) should again be preferred over the neocarzinostatin pathway (two-step 1,8-addition of methyl thioglycolate → enynecumulenol **50** → styrene biradical **52** → **34**/**35** or enol form of **34**/**35**). In light of this insight, comparing the chemoselectivities of the quenching reactions of the most likely biradical intermediates **51** (Scheme 8) and **46** (Scheme 7) is instructive. In both instances the *benzyl* radical moiety reacts only with methyl thioglycolate or 1,4-cyclohexadiene and not with MeO_2C-CH_2-S· (which would have furnished the non-observed quenching product **36**); a plausible reason was given in the context of Scheme 7. The phenyl radical moiety is less sterically hindered in biradical **51** than in biradical **46**; consequently, other than **46**, **51** has a choice of combining with a MeO_2C-CH_2-S· radical (to give **35**) or abstracting an H atom from methyl thioglycolate or 1,4-cyclohexadiene (to give **34**).

Calculations

In the preceding discussion it was pointed out that there are two conceivable reaction paths, namely the Saito–Myers and the neocarzinostatin-type cyclizations, by which methyl thioglycolate addition products of the dienediyne ketone **23** (*i.e.*, the enyneallenyl ketone **44** or the tautomeric enynecumulenol **45**; Scheme 7) or of the dienediyne ketone **28** (*i.e.*, the enyneallenyl ketone **49** or the tautomeric enynecumulenol **50**; Scheme 8) could lead to the aromatics **29**/*iso*-**29** (from **23**) or **34** and **35** (from **28**). The same ambiguity concerns the cyclo-



Scheme 9

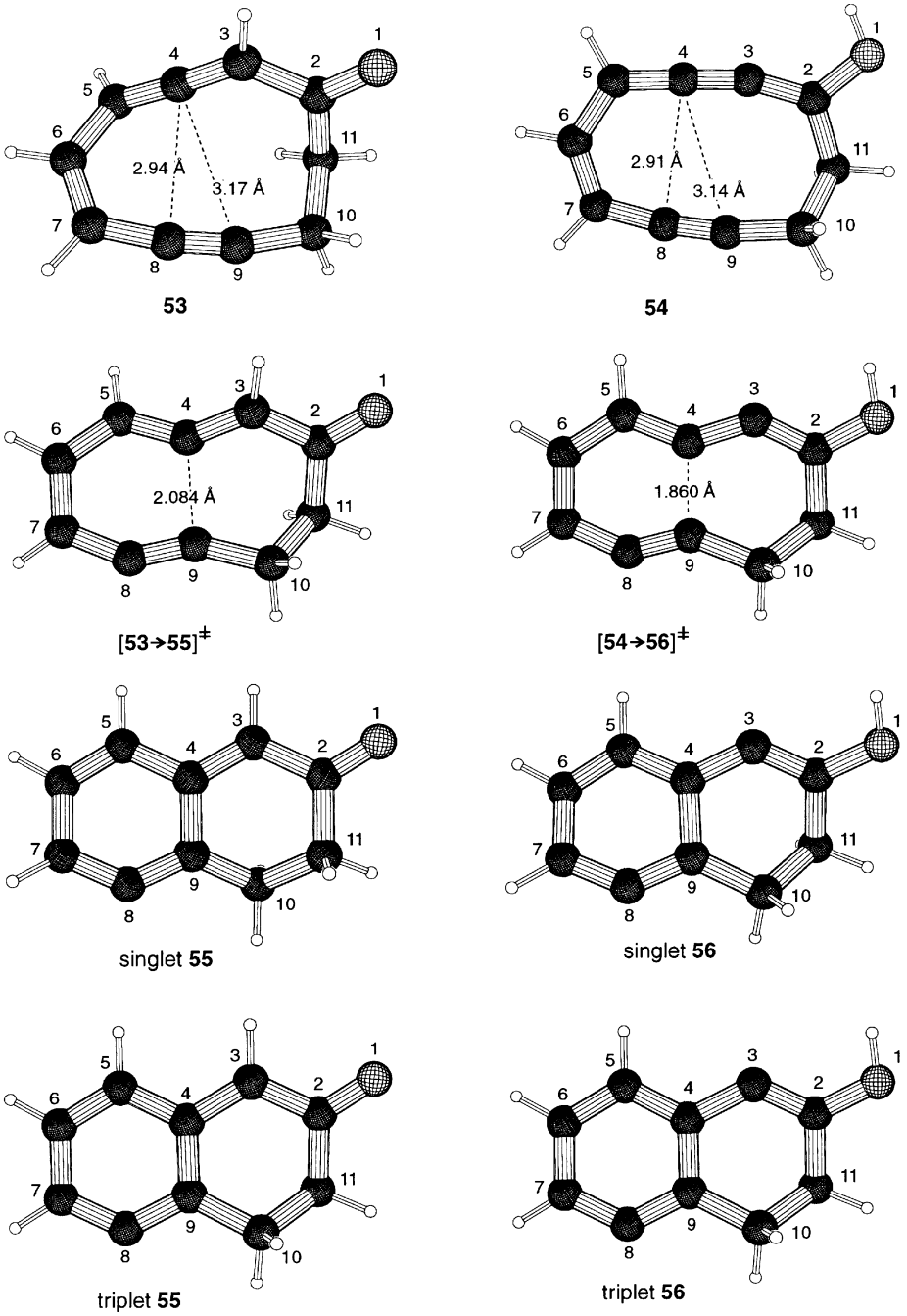


Fig. 1 Geometries of reactants **53**, **54** and transition states $[\mathbf{53} \rightarrow \mathbf{55}]^{\neq}$, $[\mathbf{54} \rightarrow \mathbf{56}]^{\neq}$ calculated at the B3LYP/6-31G* level. Geometries of the products: singlet **55** and singlet **56** [CAS(2,2)/6-31G] and triplet **55** and triplet **56** (UB3LYP/6-31G*)

aromatization mechanism of all previously cycloaromatized dienediyne ketones (**7**, **9**, **10a–e**, **11–14**). A mechanistic clarification seems therefore important. We provide it here by a density functional theory treatment of the most abundant subclass of these reactions where a *ten*-membered ring core structure participates. Specifically, we investigated the energy hypersurfaces of the Saito–Myers reaction **53** → **55** and the neocarzinostatin-type cycloaromatization **54** → **56** (Scheme 9). Both reactions describe a transition from a closed-shell to an open-shell hypersurface. Therefore, different methods had to be employed for computationally treating the starting materials, transition structures and products (methodological and computational details: captions of Fig. 1 and 2). Selected bond lengths and bond angles of reactants, transitions states and products are given in Table 3 (geometries: Fig. 1). Fig. 2 depicts the energies of the stationary points on the hypersurface of both reactions.

According to our density functional theory calculations (B3LYP/6-31G*[30,31]) the allenyl ketone **53** is 21.1 kcal mol^{-1} more stable than the tautomeric cumulenol **54**. The cycloaromatization product, toluene singlet biradical **55**, is thermodynamically favored over the tautomeric styrene singlet biradical **56** by as much as 35.3 kcal mol^{-1}, according to *ab initio* calculations [CASMP2(2,2)/6-31G//CAS(2,2)/6.31–G].[32]

Biradicals **55** and **56** differ fundamentally in their electronic structure. In biradical **56** the two 'radical centers' interact strongly with one another mainly by through-bond conjugation. The orbital degeneracy that would be expected for a 'pure' biradical is thereby cancelled in the following way. One of the two in-plane p-('radical') orbital combinations—which would be weakly (!) *bonding* through space—is raised in energy, the other—which would be weakly (!) *antibonding* through space—is somewhat lowered. The biradical character of a species can be expressed by the occupancy of both active MOs in a two-orbital two-electron multireference description. According to our CAS(2,2) calculations there are 0.77 and 1.23

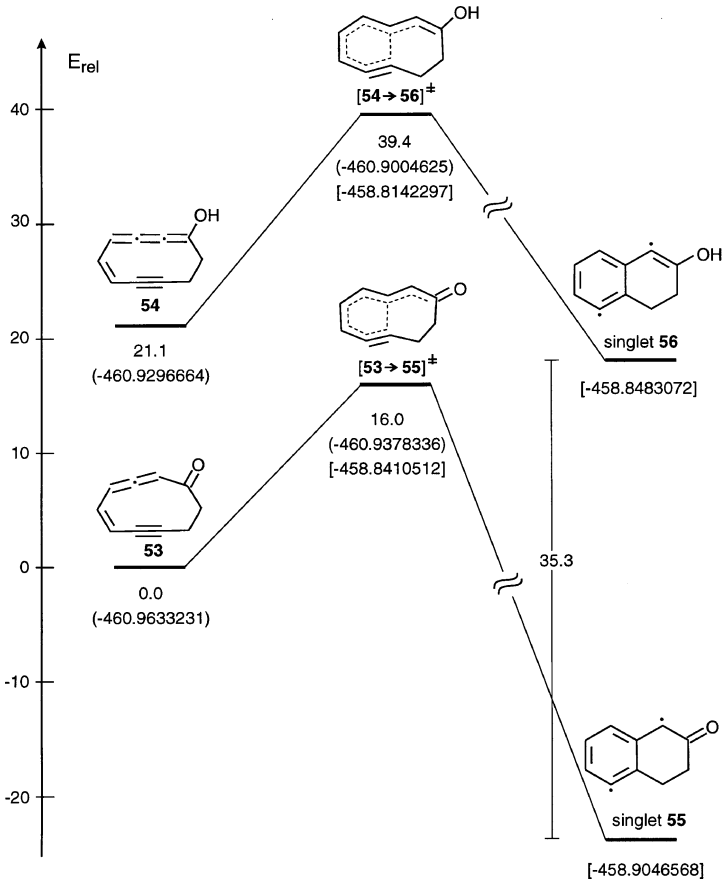


Fig. 2 Calculated relative energies of the stationary points of the Saito–Myers reaction **53** → **55** and the neocarzinostatin-type cyclization **54** → **56**. Absolute energies (a.u.) by B3LYP/6-31G*/B3LYP/6-31G* in parentheses ( ), by CASMP2(2,2)/6-31G/CAS(2,2)/6-31G in brackets [ ]. Relative energies in kcal mol^{-1} without parentheses; energies of cumulenol **54** and of transition states are relative to allenyl ketone **53** at the B3LYP level; energy differences between biradical products **55** and **56** calculated at the CAS level

electrons in the through-bond bonding and antibonding in-plane p-orbital combination, respectively (both of them are mainly located at the 'radical centers'). This is about the same degree of biradical character as *o*-didehydrobenzene, in which the occupancies of the respective MOs are 0.80 and 1.20.

In biradical **55** the unpaired electrons do not interact with one another on (approximate) symmetry grounds. They occupy orbitals that are almost orthogonal. One is mainly located at the dehydro position of the benzene ring, *i.e.* in-plane. The second is delocalized over the π system and exhibits the largest coefficient in the α position with respect to the carbonyl group. The orbital occupancy of both active orbitals is 1.06 and 0.94, which indicates an almost pure biradical state.

The activation barrier of the Saito–Myers cyclization **53** → **55** (16.0 kcal mol^{-1}) is slightly lower than that of the neocarzinostatin-type cyclization **54** → **56** (18.3 kcal mol^{-1}) (B3LYP/6-31G*). More importantly, the transition state [**53** → **55**]$^{\neq}$ of the Saito–Myers cyclization lies 23.4 kcal mol^{-1} below the transition state [**54** → **56**]$^{\neq}$ of the

Table 3 Selected bond distances [Å] and bond angles [°] of **53**, **54**, singlet **55**, triplet **55**, singlet **56**, triplet **56** and the transition states [**53** → **55**]$^{\neq}$ and [**54** → **56**]$^{\neq}$. The numbering of atoms is shown in Fig. 1 and does not follow IUPAC nomenclature

	53[a]	**54**[a]	singl. **55**[b]	tripl. **55**[a]	singl. **56**[b]	tripl. **56**[a]	[**53** → **55**]$^{\neq}$[a]	[**54** → **56**]$^{\neq}$[a]
1-2	1.222	1.368	1.227	1.234	1.371	1.363	1.225	1.364
2-3	1.493	1.333	1.453	1.450	1.381	1.332	1.469	1.333
3-4	1.315	1.263	1.449	1.422	1.449	1.441	1.346	1.338
4-5	1.317	1.338	1.399	1.420	1.390	1.404	1.362	1.375
5-6	1.469	1.452	1.386	1.387	1.391	1.396	1.424	1.418
6-7	1.356	1.363	1.393	1.410	1.388	1.404	1.379	1.378
7-8	1.417	1.415	1.375	1.381	1.379	1.381	1.394	1.397
8-9	1.214	1.215	1.374	1.370	1.367	1.374	1.252	1.272
9-10	1.459	1.464	1.511	1.513	1.516	1.519	1.467	1.497
4-9	3.173	3.139	1.409	1.438	1.417	1.428	2.084	1.860
4-8	2.936	2.905	—	—	—	—	—	—
2-3-4	127.7	163.6	121.6	122.9	126.4	126.9	125.9	135.1
3-4-5	174.8	178.0	121.3	121.5	124.1	124.4	142.4	139.6
7-8-9	169.9	171.8	125.7	126.9	126.2	126.6	145.2	141.0
8-9-10	166.6	169.5	123.4	124.6	124.5	125.0	153.3	143.4

[a] B3LYP/6-31G*. [b] CAS(2,2)/6-31G.

neocarzinostatin-type cyclization (B3LYP/6-31G*). Since under the reaction conditions, *i.e.* in the presence of NEt_3, the tautomerism **54** → **53** should be faster than the two cycloaromatizations in question, the considerably greater stability of the Saito–Myers *vs.* the neocarzinostatin-type transition state means that the far preferred cycloaromatization in this system is the Saito–Myers reaction.

Scrutinizing the structures (Table 3, Fig. 1) of the reactants, transition states and products of these cycloaromatizations one notes large deviations from linearity at the sp-hybridized carbon atoms of the reactants **53** and **54**. They indicate high ring strain. The transannular distance of the carbon atoms between which the C—C single bond forms in the course of the cycloaromatization is similar in **53** (3.173 Å) and **54** (3.139 Å). It is, of course, shortened considerably in the corresponding transition states $[\mathbf{53} \rightarrow \mathbf{55}]^{\neq}$ and $[\mathbf{54} \rightarrow \mathbf{56}]^{\neq}$, respectively, but interestingly not to the same extent. In $[\mathbf{53} \rightarrow \mathbf{55}]^{\neq}$ it measures 2.084 Å as opposed to 1.860 Å in $[\mathbf{54} \rightarrow \mathbf{56}]^{\neq}$. This bond length difference is in agreement with the Hammond postulate. The exothermic Saito–Myers cyclization occurs over a more reactant-like transition state with a still long C···C distance and the almost thermoneutral neocarzinostatin-type cyclization occurs over a less reactant-like transition state with an already shorter C···C distance.

Experimental

Methodological and computational details

All calculations were performed using the implementation of the B3LYP functional,[30,31] the CASSCF and CASMP2 procedure and the standard 6-31G and 6-31G* basis set available in the Gaussian94 package.[32] The CASSCF active space for the treatment of the singlet diradicals **55** and **56** comprised two electrons distributed in two orbitals. Because both species are not perfectly planar, only approximate symmetry considerations could be used for the selection of the active orbitals. For **55** a CAS(UNO)[33] calculation was performed and the highest occupied σ-type MO with a very large coefficient at C-8 (for numbering see Fig. 1) and the singly occupied π-type orbital were selected for the CASSCF treatment. For **56** the two σ-type orbitals with coefficients mainly located at the 'diradical centers' C-3 and C-8 were included in the two-electron two-orbital treatment. During optimization of **55** the orbital ordering had to be readjusted several times. The multiconfiguration approach was used in order to take into account the large nondynamical correlation effects, especially in **55**. However, it is known that dynamical correlation has to be included in multiconfigurational treatments to obtain results that are quantitatively or even qualitatively reliable.[34] We performed CASMP2[35,36] single-point calculations at the CAS(2,2)/6-31G geometry, including second-order Møller–Plesset perturbation theory,[37] to provide dynamic correlation (between electrons considered in the active space and the remaining electrons) for the CAS wavefunction. Both transition states $[\mathbf{53} \rightarrow \mathbf{55}]^{\neq}$ and $[\mathbf{54} \rightarrow \mathbf{56}]^{\neq}$ were also calculated at the above level [CASMP2(2,2)/6-31G//CAS(2,2)/6-31G]. The low occupancy of the higher orbital (diagonal entries in the symbolic CAS density matrix: 1.91, 0.09 for $[\mathbf{53} \rightarrow \mathbf{55}]^{\neq}$ and 1.92, 0.08 for $[\mathbf{54} \rightarrow \mathbf{56}]^{\neq}$) accounts for the low diradical character of the transition states. The density functional theory calculations at the B3LYP/6-31G* level, therefore, should provide an estimated value for the activation enthalpies for ring closure. A large diradical character is developed only at a later stage of the reaction coordinate. The occupancies of the two active orbitals are 1.06, 0.94 for **55**, which corresponds to an almost pure diradical, and 1.23, 0.77 for **56**. Benchmark calculations using the above levels on the parent system of the Bergman cyclization are in very good agreement with experimental data:[38] $\Delta H^{\ddagger}$ (cyclization) = 31.0 kcal mol^{-1} (B3LYP/6-31G*), 28.2 kcal mol^{-1} (expt.), $\Delta H^{\ddagger}$ (ring opening) = 19.7 kcal mol^{-1} [CASMP2(6-31G)/CAS(2,2)/6-31G], 21.6 kcal mol^{-1} (expt.). For optimizing the structures of **53**, **54**, singlet **55**, triplet **55**, singlet **56**, triplet **56**, and the transition states $[\mathbf{53} \rightarrow \mathbf{55}]^{\neq}$ and $[\mathbf{54} \rightarrow \mathbf{56}]^{\neq}$ we used the B3LYP hybrid functional[30,31] and the 6-31G* basis set. All stationary points were characterized by harmonic frequency analysis.

Synthetic details

All reactions were performed in oven-dried (100 °C) glassware under N_2. THF was freshly distilled from K and CH_2Cl_2 from CaH_2. Products were purified by flash chromatography[23] on Merck silica gel 60 (eluents given in brackets). Yields refer to analytically pure samples. Isomer ratios were derived from suitable ^1H NMR integrals. ^1H [$CHCl_3$ (7.26 ppm) as internal standard in $CDCl_3$ or C_6HD_5 (7.16 ppm) as internal standard in C_6D_6] and ^{13}C [$CDCl_3$ (77.00 ppm) as internal standard in $CDCl_3$ or C_6D_6 (128.00 ppm) as internal standard in C_6D_6] NMR spectra were acquired on Varian VXR 200, Bruker AMX 300, and Varian VXR 500S spectrometers; integrals are in accord with assignments; coupling constants in Hz; APT ^{13}C NMR spectra: "+" for CH or CH_3, "−" for CH_2 or $C_{quat.}$. The assignments of ^1H and ^{13}C NMR resonances refer to the IUPAC nomenclature with primed numbers belonging to the side-chain(s) in the order of their IUPAC appearance in the name. Combustion analyses: M. Beller, Institute of Organic Chemistry, University of Göttingen. MS: Dr. G. Remberg, Institute of Organic Chemistry, University of Göttingen. IR spectra: Perkin-Elmer 1600 Series FTIR as $CDCl_3$ solution in a NaCl cuvette.

***Z*-[2-(3,3-Dimethyl-4-hydroxy-1-butynyl)-2-cyclohexenylidene]methyl trifluoromethanesulfonate (18).** At room temperature, we first added a solution of 2,2-dimethyl-3-butyn-1-ol (634 mg, 6.44 mmol, 1.2 equiv.) in THF (6 mL) and then CuI (102.0 mg, 0.536 mmol, 10 mol %) to the bistriflate **17** (2.094 g, 5.36 mmol), $Pd(PPh_3)_4$ (309.6 mg, 0.268 mmol, 5 mol %) and piperidine (1.10 μL, 914 mg, 10.7 mmol, 2.0 equiv.) in THF (34 mL). The mixture was stirred for 3 h and then hydrolyzed with brine (20 mL). After extraction with ether, the organic layer was dried over $MgSO_4$. The solvent was removed *in vacuo* at 0 °C. Flash chromatography of the residue (pentane–ether, 2 : 1) afforded **18** (1.295 g, 75%). IR ($CDCl_3$): ν = 3585, 3435, 3100, 2975, 2870, 2250, 1730, 1655, 1415, 1210, 1135, 1115, 1055, 1015, 915 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.22 [s, 3″-$(CH_3)_2$], 1.68–1.78 (m, 5′-H_2), 2.10–2.23 (m, 6′-H_2), 2.27 (dt, $J_{4',3'} = J_{4',5'} = 4'$-$H_2$), 3.43 (s, 4″-$H_2$), 3.70 (br s, OH), 6.34 (td with strong roof effect towards lower field, $J_{3',4'} = 4.4$, $^5J_{3',1} = 1.6$, 3′-H), 6.38 (s, 1-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = "−" 21.82 (C-5′), "+" 25.14 [3-$(CH_3)_2$], "−" 26.50 and "−" 27.54 (C-4′, C-6′), "−" 34.76 (C-3″), "−" 71.46 (C-4″), "−" 79.70 and "−" 94.05 (C-1″, C-2″), "−" 115.87 and "−" 124.20 (C-1′, C-2′), "−" 118.64 (q, $^1J_{C,F} = 321.4$, CF_3), "+" 129.10 (C-1), "+" 143.22 (C-3′). $C_{14}H_{17}O_4F_3S$ [M^+]: calcd. 338.0799; the exact molecular mass (±2 ppm; $R = 10000$) was confirmed by EI HRMS (70 eV).

***Z*-4-[2-(3,3-Dimethyl-4-hydroxy-1-butynyl)-2-cyclohexenylidene]-2-butyn-1-ol (19).** *Procedure A*: To a solution of the monocoupling product **18** (1.295 g, 4.02 mmol), $Pd(PPh_3)_4$ (232.2 mg, 0.201 mmol, 5 mol %) and CuI (76.6 mg, 0.402 mmol, 10 mol %) in THF (15 mL) was first added a solution of propargyl alcohol (451.1 mg, 8.04 mmol, 1.1 equiv.) in ether (5 mL) and then piperidine (0.80 mL, 69 mg, 8.0 mmol, 2.0 equiv.). The mixture was stirred overnight at room temperature and then hydrolyzed with brine (30 mL). After

extraction with ether, the organic layer was dried over $MgSO_4$. The solvent was removed *in vacuo* at 0 °C. Flash chromatography of the residue (pentane–ether, 1 : 1) afforded **19** (834.4 mg, 83%). *Procedure B*: A solution of the bistriflate **17** (1.179 g, 3.02 mmol), $PdCl_2(PPh_3)_2$ (106.0 mg, 0.151 mmol., 5 mol %) and CuI (57.5 mg, 0.302 mmol, 10 mol %) in ether (15 mL) was cooled to 0 °C. A solution of 2,2-dimethyl-3-butyn-1-ol (327.1 mg, 3.32 mmol, 1.1 equiv.) in ether (15 mL) and Pr^i_2NH (10 mL) were added in this order. The mixture was stirred for 3 h at this temperature. Propargyl alcohol (169.4 mg, 3.02 mmol, 1.0 equiv.) dissolved in ether–Pr^i_2NH (3 : 1; 8 mL) was added. The resulting mixture was stirred overnight at 0 °C and for 10 h at room temperature and then hydrolyzed with brine (30 mL). After extraction with ether, the organic layer was dried over $MgSO_4$. The solvent was removed *in vacuo* at 0 °C. Flash chromatography of the residue (pentane–ether, 1 : 1) afforded **19** (590.0 mg, 80%) admixed with some of the 'regioisomer' **24**. **19** could be liberated from **24** by keeping the early fractions and re-chromatographying several times the late fractions of the preceding separation. IR ($CDCl_3$): ν = 3505, 3155, 2970, 2935, 2870, 2255, 1795, 1650, 1470, 1380, 1165, 1095, 1050, 1015, 900 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.25 [s, 3″-$(CH_3)_2$], 1.68–1.77 (m, 5′-H_2), 2.22–2.32 (m, 4′-H_2, 6′-H_2), *ca.* 2.70 (br s which is only detectable in the integral, OH), 3.43 (s, 4″-H_2), 4.40 (d, $^5J_{1,4}$ = 2.7, 1-H_2), 5.45 (almost not resolved d, $^5J_{4,1}$ = 1.1, 4-H), 6.32 (td, $J_{3',4'}$ = 4.4, $^5J_{3',4}$ = 1.4, 3′-H). ^{13}C NMR [75.5 MHz, $CDCl_3$]: δ = "−" 22.42 (C-5′), "+" 25.51 [3″-$(CH_3)_2$], "−" 26.87 and "−" 33.43 (C-4′, C-6′), "−" 35.23 (because of relatively low intensity: C-3″), "−" 51.70 (C-1), "−" 71.87 (C-4″), "−" 81.30, "−" 82.90, "−" 94.27 and "−" 94.91 (C-2, C-3, C-1″, C-2″), "+" 104.75 (C-4), "−" 120.17 (C-2′), "+" 143.00 (C-3′), "−" 143.78 (C-1′). $C_{16}H_{20}O_2$ [M^+]: calcd. 244.1463; the exact molecular mass (±2 ppm; R = 10000) was confirmed by EI HRMS (70 eV).

***Z*-4-[2-(4-Oxo-3,3-dimethyl-1-butynyl)-2-cyclohexenylidene]-2-butyn-1-al (20):** (contaminated with varying amounts of the presumed *E* isomer after chromatography). To a stirred solution of the Dess–Martin periodinane (1.593 g, 3.75 mmol, 2.2 equiv.) in CH_2Cl_2 (15 mL) a solution of diol **19** (417.2 mg, 1.71 mmol) in CH_2Cl_2 (10 mL) was added at room temperature. After 30 min the reaction mixture was diluted with ether (30 mL) and poured into a saturated aqueous solution of $NaHCO_3$ containing a sevenfold excess of $Na_2S_2O_3$. The mixture was stirred for *ca.* 10 min until the solid was dissolved. Then the layers were separated. The organic layer was washed with water and dried over $MgSO_4$. The solvent was removed *in vacuo* at 0 °C. Isolation by flash chromatography (pentane–ether) gave an unseparable mixture of compounds presumed to constitute a 85 : 15 mixture of the title compound and its *E* isomer (279.1 mg, 68%). The NMR spectra of the described and other mixtures obtained similarly allowed us to identify the resonances of **20**. IR ($CDCl_3$): ν = 2985, 2935, 2865, 2255, 2165, 1730, 1650, 1600, 1460, 1390, 1270, 1180, 1075 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.36 [s, 3″-$(CH_3)_2$], 1.73–1.82 (m, 5′-H_2), 2.32 (tdm$_c$, $J_{4',3'} \approx J_{4',5'} \approx$ 5.5, 4′-H_2), 2.36–2.42 (m, 6′-H_2), 5.56 (br s, 4-H), 6.51 (td, $J_{3',4'}$ = 4.4, $^5J_{3',4}$ = 1.2), 9.28 (d, $^5J_{1,4}$ = 1.2, 1-H), 9.52 (s, 4″-H). ^{13}C NMR [75.5 MHz, $CDCl_3$; contains small peaks of contaminant(s)]: δ = "−" 21.90 (C-5′), "+' 22.41 (2″-CH_3), "−" 26.79 and "−" 33.41 (C-4′, C-6′), "−" 43.14 (C-2″), "−" 82.33, "−" 91.20, "−" 93.83 and "−" 95.02 (C-2, C-3, C-3″, C-4″), "+" 102.41 (C-4), "−" 120.17 (C-2′), "+" 146.45 (C-3′), "−" 151.21 (C-1′), "+" 176.80 (C-1), "+" 198.26 (C-1″). $C_{16}H_{16}O_2$ [M^+]: calcd. 240.1150; the exact molecular mass (±2 ppm; R = 10000) was confirmed by EI HRMS (70 eV).

4,4-Dimethylbicyclo[8.4.0]tetradeca-1(14),9-diene-2,7-diyne-5,6-diol (21): (single diastereomer of unknown configuration). $Cl_3Ti(DME)_2$ was prepared by refluxing $TiCl_3$ (6.6 g, 42.8 mmol, 17.9 equiv.) in freshly distilled DME (200 mL) for 1.5 days. The Zn/Cu couple (8.5 g, 131.04 mmol, 54.6 equiv.) was added. The resulting mixture was refluxed for 5 h. A solution of the crude dialdehyde **20** (because of its presumed $Z \rightarrow E$ isomerization upon isolation, it was used crude in the following experiment, assuming that it was formed in 70% yield by the Dess–Martin oxidation of diol **19**; 574 mg, 2.39 mmol) in DME (80 mL) was added at −45 °C by means of a syringe pump over a period of 5 h. After 30 min, the reaction mixture was diluted with ether and then hydrolyzed by adding a saturated aqueous solution of $NaHCO_3$ (50 mL). After filtration over celite, the aqueous layer was extracted with ether, the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* at 0 °C. Flash chromatography (pentane–ether, 2 : 3) of the residue gave **21** (324.4 mg, 56%). IR ($CDCl_3$): ν = 3560, 3415, 2975, 2935, 2870, 2250, 1730, 1465, 1385, 1260, 1180, 1060 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$; contains ether): δ = 1.24 and 1.34 [2s, 4-$(CH_3)_2$], 1.64–1.74 (m, 12-H_2), 2.21 (td, $J_{13,12} = J_{13,14}$ = 5.5, 13-H_2), 2.33 (tm$_c$, $J_{11,12} \approx$ 6.1, 11-H_2), 2.48 (br s, OH), 2.98 (br s, OH), 3.64 (d, $J_{5,6}$ = 8.6, 5-H), 4.41 (d, $J_{6,5}$ = 8.3, 6-H), 5.25 (br s, 9-H), 6.20 (br t, $J_{14,13}$ = 4.5, 14-H). ^{13}C NMR (75.5 MHz, $CDCl_3$; contains ether): δ = "+" 21.62 and "+" 27.36 [4-$(CH_3)_2$], "−" 22.06 (C-12), "−" 26.28 and "−" 33.33 (C-11, C-13), "−" 34.27 (because of relatively low intensity: C-4), "+" 64.77 (C-6), "+" 79.13 (C-5), "−" 80.78, "−" 87.27, "−" 94.27 and "−" 97.50 (C-2, C-3, C-7, C-8), "+" 104.18 (C-9), "−" 120.99 (C-1), "+" 139.79 (C-14), "−" 145.03 (C-10). $C_{16}H_{18}O_2$ [M^+]: calcd. 242.1306; the exact molecular mass (±2 ppm; R = 10000) was confirmed by EI HRMS (70 eV).

5-Hydroxy-4,4-dimethylbicyclo[8.4.0]tetradeca-1(14),7-diene-2,7-diyn-6-one (23). To a stirred solution of Bu^tOMgBr [prepared by adding EtMgBr (2.0 M in THF, 4.35 mL, 8.70 mmol, 3.0 equiv.) to an ice-bath cooled solution of Bu^tOH (0.83 mL, 8.7 mmol, 3.0 equiv.) in THF (15)] was added at −10 °C a solution of the diol **21** (702.1 mg, 2.90 mmol) in THF (12 mL). After 5 min, a solution of azodicarbonyldipiperidide (877.2 mg, 3.47 mmol, 1.2 equiv.) in THF (10 mL) was added. The reaction mixture was stirred at 0 °C for 30 min. After dilution with ether (20 mL), it was hydrolyzed by addition of brine (20 mL). After extraction with ether, the organic layer was dried over $MgSO_4$. The solvent was removed *in vacuo* at 0 °C. Flash chromatography of the residue (ether–pentane, 8 : 2) afforded **23** (380.6 mg, 55%). IR ($CDCl_3$): ν = 3695 (very small), 3155, 2985, 2900, 2255, 2170, 1815, 1795, 1650, 1560, 1470, 1380, 1295, 1165, 1095 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.09 and 1.37 [2s, 4-$(CH_3)_2$], 1.67–1.84 (m, 12-H_2), 2.29 (td, $J_{13,12} = J_{13,14}$ = 5.53, 13-H_2), 2.44 (td, $J_{11,12}$ = 6.4, $^4J_{11,9}$ = 1.5, 11-H), 3.84 (d, $J_{OH,5}$ = 4.9, OH), 4.32 (d, $J_{5,OH}$ = 5.3, 5-H), 5.47 (m$_c$, 9-H), 6.45 (td, $J_{14,13}$ = 4.7, $^5J_{14,9}$ = 1.5, 14-H). ^{13}C NMR (75.5 MHz, $CDCl_3$; contains ether): δ = "+" 21.16 and "+" 26.47 [4-$(CH_3)_2$], "−" 21.70 (C-12), "−" 26.37 and "−" 33.63 (C-11, C-13), "−" 35.89 (because of relatively low intensity: C-4), "−" 81.20, "−" 94.16, "−" 97.99 and "−" 104.46 (C-2, C-3, C-7, C-8), "+" 82.98 (C-5), "+" 102.48 (C-9), "−" 121.00 (C-1), "+" 143.27 (C-14), "−" 153.39 (C-10), "−" 187.36 (C-6). $C_{16}H_{16}O_2$ [M^+]: calcd. 240.1150; the exact molecular mass (±2 ppm; R = 10000) was confirmed by EI HRMS (70 eV).

***Z*-5-[2-(3-Hydroxy-1-propynyl)-2-cyclohexenylidene]-2,2-dimethyl-3-pentyn-1-ol (24).** To a solution of the bistriflate **17** (1.844 g, 4.72 mmol), $Cl_2Pd(PPh_3)_2$ (166.4 mg, 2.41 mmol, 5 mol %) and CuI (90.1 mg, 0.472 mmol, 10 mol %) in ether (40 mL) was added at room temperature a solution of propargyl alcohol (291.3 mg, 5.19 mmol, 1.1 equiv.) in ether (11 mL) and then Pr^i_2NH (17 mL). The mixture was stirred for 3 h at this temperature. Then 2,2-dimethyl-3-butyn-1-ol (462.7 mg, 4.72

mmol, 1.0 equiv.) dissolved in Et_2O–Pr^i_2NH (3 : 1, 12 mL) was added. The resulting mixture was stirred at room temperature overnight and then hydrolyzed with brine (30 mL). After extraction with ether, the organic layer was dried over $MgSO_4$. The solvent was removed *in vacuo* at 0 °C. The desired compound **24** was purified by flash chromatography (pentane–ether, 1 : 1). It could be liberated from some accompanying 'regioisomer' **19** by keeping the late fractions and rechromatographying several times the early fractions of the preceding separation; thus, we obtained absolutely isomerically pure **24** (446.2 mg, 39%). In a similar experiment, a single chromatography afforded **24** (629.9 mg, 62%) contaminated with 6% of the 'regioisomer' **19**. IR ($CDCl_3$): ν = 3500, 2970, 2930, 2870, 2255, 1450, 1425, 1395, 1365, 1285, 1200, 1045, 1020 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.21 [s, 2-$(CH_3)_2$], 1.70–1.76 (m, 5′-H_2), 2.20–2.30 (m, 4′-H_2, 6′-H_2), 3.18 (s, OH), 3.40 (s, 1-H_2), 4.37 (s, 1″-H_2), 5.40 (br s, 5-H), 6.34 (poorly resolved td, $J_{3',4'}$ = 4.3, $^5J_{3',5}$ = 1.1, 3′-H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = "−" 22.27 (C-5′), "+" 25.38 [2-$(CH_3)_2$], "−" 26.85 and "−" 33.13 (C-4′, C-6′), "−" 35.18 (because of relatively low intensity: C-2), "−" 51.21 (C-3″), "−" 71.57 (C-1), "−" 79.87, "−" 83.82, "−" 88.38 and "−" 100.95 (C-3, C-4, C-2″, C-3″), "+" 105.29 (C-5), "−" 120.06 (C-2′), "−" 142.09 (C-1′), "+" 143.60 (C-3′). $C_{16}H_{20}O_2$ [M^+]: calcd. 244.1463; the exact molecular mass ($\pm$2 ppm; R = 10000) was confirmed by EI HRMS (70 eV).

***Z*-5-[2-(3-Oxo-1-propynyl)-2-cyclohexenylidene]-2,2-dimethyl-3-pentyn-1-al (25).** To a stirred solution of the Dess–Martin periodinane (1.29 g, 3.04 mmol, 2.2 equiv.) in CH_2Cl_2 (20 mL) was added a solution of diol **24** (337.6 mg, 1.38 mmol) in CH_2Cl_2 (10 mL) at room temperature. After 30 min the reaction mixture was diluted with ether (20 mL) and poured into a saturated aqueous solution of $NaHCO_3$ containing a sevenfold excess of $Na_2S_2O_3$. The mixture was stirred for *ca.* 10 min until the solid was dissolved. Then the layers were separated. The organic layer was washed with water and dried over $MgSO_4$. The solvent was removed *in vacuo* at 0 °C. Flash chromatography (pentane–ether, 85 : 15) of the residue afforded **25** (274.5 mg, 83%). IR ($CDCl_3$): ν = 2980, 2935, 2865, 2810, 2255, 2190, 1730, 1655, 1570, 1455, 1420, 1390, 1250, 1195, 1135, 1070, 980, 895 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.34 [s, 2-$CH_3)_2$], 1.74–1.84 (m, 5′-H_2), 2.31–2.40 (m, 4′-H_2, 6′-H_2), 5.52 (hardly resolved d, $^5J_{5,3'}$ = 0.7, 5-H), 6.70 (td, $J_{3',4'}$ = 4.5, $^5J_{3',5}$ = 1.4, 3′-H), 9.31 (s, 3″-H), 9.49 (s, 1-H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = "−" 21.76 (C-5′), "+" 22.44 [2-$(CH_3)_2$], "−" 27.34 and "−" 32.52 (C-4′, C-6′), "−" 43.48 (because of relatively low intensity: C-2), "−" 81.78, "−" 89.82, "−" 94.63 and "−" 97.08 (C-1″, C-2″, C-3, C-4), "+" 106.29 (C-5), "−" 118.87 (C-2′), "−" 141.18 (C-1′), "+" 150.10 (C-3′), "+" 176.81 (C-3″), "+" 197.99 (C-1). $C_{16}H_{16}O_2$ [M^+]: calcd. 240.1150; the exact molecular mass ($\pm$2 ppm; R = 10000) was confirmed by EI HRMS (70 eV).

6,6-Dimethylbicyclo[8.4.0]tetradeca-1(14),9-diene-2,7-diyne-4,5-diol (26): (single diastereomer of unknown configuration). $Cl_3Ti(DME)_2$ was prepared by refluxing $TiCl_3$ (6.33 g, 41.0 mmol, 17.9 equiv.) in freshly distilled DME (160 mL) for 1.5 days. The Zn/Cu couple (8.118 g, 125.03 mmol, 54.6 equiv.) was added. The resulting mixture was refluxed for 5 h. At −45 °C a solution of the dialdehyde **25** (550.8 mg, 2.29 mmol) in DME (60 mL) was added by means of a syringe pump over 5 h. After 30 min, the reaction mixture was diluted with ether and hydrolyzed by adding a saturated aqueous solution of $NaHCO_3$ (30 mL). After filtration over celite, the aqueous layer was extracted with ether, the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* at 0 °C. Flash chromatography (pentane–ether, 45 : 55) of the residue gave **26** (443.9 mg, 80%). IR ($CDCl_3$): ν = 3565, 2935, 2875, 1730, 1575, 1540, 1420, 1235, 1190, 1115, 1090 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$; contains ether): δ = 1.20 and 1.29 [2s, 6-$(CH_3)_2$], 1.67 (tt, $J_{12,11} = J_{12,13}$ = 6.1, 12-H_2), 2.20 (td, $J_{13,12} = J_{13,14}$ = 5.4, 13-H_2), 2.29 (br t, $J_{11,12}$ = 6.2, 11-H_2), 3.24 (br s, 2 × OH), 3.64 (d, $J_{4,5}$ = 8.7, 4-H), 4.40 (d, $J_{5,4}$ = 8.6, 5-H), 5.20 (br s, 9-H), 6.22 (t, $J_{14,13}$ = 4.4, 14-H). ^{13}C NMR (125.7 MHz, $CDCl_3$; contains ether): δ = "+" 21.29 and "+" 26.97 [6-$(CH_3)_2$], "−" 21.94 (C-12), "−" 26.24 and "−" 33.05 (C-11, C-13), "−" 34.49 (because of relatively low intensity: C-6), "+" 64.20 (C-4), "+" 79.16 (C-5), "−" 81.26, "−" 86.64, "−" 89.75 and "−" 102.66 (C-2, C-3, C-7, C-8), "+" 105.82 (C-9), "−" 120.52 (C-1), "+" 139.98 (C-14), "−" 142.33 (C-10). $C_{16}H_{18}O_2$ [M^+]: calcd. 242.1306; the exact molecular mass ($\pm$2 ppm; R = 10000) was confirmed by EI HRMS (70 eV).

5-Hydroxy-6,6-dimethylbicyclo[8.4.0]tetradeca-1(14),9-diene-2,7-diyn-4-one (28). To a stirred solution of Bu^tOMgBr [prepared by adding EtMgBr (2.0 M in THF, 4.0 mL, 8.0 mmol, 3.0 equiv.) to an ice-bath cooled solution of Bu^tOH (0.77 mL, 8.0 mmol, 3.0 equiv.) in THF (15)] was added at −10 °C a solution of the diol **26** (650.4 mg, 2.68 mmol) in THF (15 mL). After 5 min, a solution of azodicarbonyldipiperidide (811.9 mg, 3.35 mmol, 1.2 equiv.) in THF (15 mL) was added. The reaction mixture was stirred at 0 °C for 30 min. After dilution with ether (30 mL) it was hydrolyzed by addition of brine (20 mL). After extraction with ether, the organic layer was dried over $MgSO_4$. The solvent was removed *in vacuo* at 0 °C. Flash chromatography of the residue (pentane–ether, 8 : 2) afforded **28** (489.3 mg, 76%). IR ($CDCl_3$): ν = 3470, 3155, 2975, 2935, 2870, 2340, 2255, 2195, 1655, 1600, 1385, 1565, 1465, 1270, 1250 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$; contains ether and a little pentane): δ = 1.07 and 1.34 [2s, 6-$(CH_3)_2$], 1.66–1.82 (m, 12-H_2), 2.32 (td, $J_{13,12} = J_{13,14}$ = 5.7, 13-H_2), superimposed partly by 2.38 (td, $J_{11,12}$ = 5.8, $^4J_{11,9}$ = 1.3, 11-H_2), 3.81 (d, $J_{OH,5}$ = 5.3, OH), 4.31 (d, $J_{5,OH}$ = 5.3, 5-H), 5.35 (only partly resolved td, $^4J_{9,11} = {}^5J_{9,14} \approx$ 1.2, 9-H), 6.59 (td, $J_{14,13}$ = 4.5, $^5J_{14,9}$ = 1.5, 14-H). ^{13}C NMR (125.7 MHz, $CDCl_3$; contains ether): δ = "+" 21.05 and "+" 25.97 [6-$(CH_3)_2$], "−" 21.36 (C-12), "−" 26.89, "−" 32.56 and "−" 36.30 (C-6, C-11, C-13), "−" 81.61, "−" 89.77, "−" 102.50 and "−" 102.58 (C-2, C-3, C-7, C-8), "+" 83.57 (C-5), "+" 106.72 (C-9), "−" 119.52 (C-1), "−" 141.65 (C-10), "+" 147.48 (C-14), "−" 187.85 (C-4). $C_{16}H_{16}O_2$ [M^+]: calcd. 240.1150; the exact molecular mass ($\pm$2 ppm; R = 10000) was confirmed by EI HRMS (70 eV)

Cycloaromatization/cyclization of dienediyne 23. *Experiment A.* At room temperature, NEt_3 (22 mL, 16 mg, 0.16 mmol, 1.0 equiv.), 1,4-cyclohexadiene (0.34 mL, 290 mg, 3.6 mmol, 23 equiv.) and methyl thioglycolate (30 μL, 35 mg, 0.33 mmol, 2.1 equiv.) were added under argon to a stirred solution of the hydroxyketone **23** (37.3 mg, 0.155 mmol) in C_6H_6 (1.5 mL). After 10 h, addition of brine (2 mL), extraction with ether, and drying over $MgSO_4$, the solvent was removed *in vacuo*. Flash chromatography (pentane–ether, 75 : 25) of the residue afforded in the early fractions **29**/*iso*-**29** as a 60 : 40 mixture of unassigned diastereomers (14.8 mg, 27%), in the middle fractions pure **30** (14.8 mg, 21%), and in the late fractions a 46 : 54 mixture (as determined from the 1-H integrals at $\delta_{\mathbf{in\,30}}$ = 4.41 and $\delta_{\mathbf{in}\ iso\text{-}\mathbf{30}}$ = 4.21; 9.2 mg, 13%) of **30** and *iso*-**30**. The overall yield of **30** was therefore 19.0 mg (27%) and that of *iso*-**30** was 4.9 mg (7%).

Experiment B. At room temperature, NEt_3 (20 μL, 15 mg, 0.14 mmol, 1.0 equiv.) and methyl thioglycolate (27 μL, 31 mg, 0.30 mmol, 2.1 equiv.) were added under argon to a stirred solution of the hydroxyketone **23** (33.9 mg, 0.141 mmol) in C_6H_6 (1.5 μL). After 10 h, brine (2 μL) was added. The same work-up procedure as in *Experiment A* delivered a 60 : 40 mixture of unassigned diastereomers **29** and *iso*-**29** (8.0 mg, 16%), pure **30** (12.6 mg, 20%) and a 16 : 84 mixture (12.5 mg,

19%) of **30** and *iso*-**30**. Thus, we obtained a total of 14.7 mg (23%) of **30** and 10.4 mg (16%) of *iso*-**30**.

From the combined **30**/*iso*-**30** mixtures of several cycloaromatizations like the ones described above we obtained—by enrichment in the late fractions of renewed attempts of purification by flash chromatography—a sufficiently pure sample of *iso*-**30** for characterization.

Methyl-2-[(1,2,3,4,5,6,7,8-octahydro-7-hydroxy-8,8-dimethyl-6-oxoanthracen-1-yl)thio]acetate: (60 : 40 mixture of unassigned diastereomers **29** and ***iso*-29** as determined by integration of the 1′-H_2 resonances). IR ($CDCl_3$): ν = 3500, 2935, 2870, 2255, 1720, 1605, 1500, 1435, 1385, 1365, 1275, 1190, 1160, 1130, 1085, 895 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$; slightly contaminated; for the numbering *cf.* Table 1): δ = 0.95 and 1.58 {2s, 8-$(CH_3)_2$ [**29**], 0.96 and 1.57 {2s, 8-$(CH_3)_2$[*iso*-**29**]}, 1.24–1.33 and 1.74–1.86 (2m, 3-H_2), 1.98–2.22 (m, 2-H_2, OH), 2.64–2.86 (m, 4-H_2), AB signal {δ_A = 3.21, δ_B = 3.35, J_{AB} = 14.9, 1′-H_2 [*iso*-**29**]}, AB signal {δ_A = 3.23, δ_B = 3.36, J_{AB} = 15.1, 1′-H_2 [**29**]}, 3.74 (s, 5-H_2), 3.78 (s, CO_2Me), 4.17 {d, $J_{7,OH}$ = 3.4, 7-H [*iso*-**29**]}, superimposed partly by 4.20 {d, $J_{7,OH}$ = 3.7, 7-H [**29**]}, 4.30 {poorly resolved t, $J_{1,2}$ = 3.8, 1-H [**29***]}, superimposed partly by 4.31 {poorly resolved t, $J_{1,2}$ = 4.1, 1-H [*iso*-**29***]}, 6.86 (s, 10-H)**, 7.42 {s, 9-H** [*iso*-**29**]}, 7.43 {s, 9-H** [**29**]}; *,** assignments interchangeable. ^{13}C NMR (75.5 MHz, $CDCl_3$; contains small peaks of contaminant(s) at δ = "−" 33.16 and "+" 52.45; for the numbering *cf.* Table 1): δ = "−" 18.62 (C-3), "+" 23.43 and "+" 24.19 {8-$(CH_3)_2$ [*iso*-**29**]}, "+" 23.62 and "+" 24.27 {8-$(CH_3)_2$ [**29**]}, "−" 28.29 and "−" 33.08* {C-2, C-4 [*iso*-**29**]}, "−" 28.34 and "−" 33.06* {C-2, C-4 [**29**]}, "−" 41.06, "−" 41.09 and "−" 42.19 (3 signals for 4 differents carbons, C-1′, C-5), "−" 42.11 (because of relatively low intensity: C-8), "+" 44.02 (CO_2CH_3), "+" 52.37 {C-1 [**29**]}, "+" 52.39 {C-1 [*iso*-**29**]}, "+" 80.22 {C-7 [**29**]}, "+" 80.32 {C-7 [*iso*-**29**]}, "+" 127.41 and "+" 129.45 {C-9, C-10 [*iso*-**29**]}, "+" 127.43 and "+" 129.41 {C-9, C-10 [**29**]}, "−" 129.24 (double intensity), "−" 134.85, "−" 134.90, "−" 136.48, "−" 136.49, "−" 141.03 and "−" 141.10 (7 signals for 8 differents carbons: C-4*a*, C-8*a*, C-9*a*, C-10*a*), "−" 171.11 {CO_2CH_3 [*iso*-**29**]}, "−" 171.16 {CO_2CH_3 [**29**]}, "−" 209.74 (C-6); * interchangeable. $C_{19}H_{24}O_4S$ [M^+]: calcd. 348.1395; the exact molecular mass (±2 ppm; *R* = 10000) was confirmed by EI HRMS (70 eV). $C_{19}H_{24}O_4S$ (348.46); calcd.: C 65.49, H 6.94; found: C 65.74, H 7.18.

***S*′,*S*″-{2,3,4,6,7,9-Hexahydro-7-hydroxy-6,6-dimethyl-8-oxo-^{1}H-benzo[*a*]azulene-4,5-diyl}bis[methyl-(2-sulfanylacetate)] (30):** (single diastereomer of unknown configuration). IR ($CDCl_3$): ν = 3470, 2955, 2870, 2255, 1730, 1665, 1575, 1435, 1390, 1270, 1200, 1130, 1085, 1020 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$; slightly contaminated but not with a diastereomer; for the numbering—which exceptionally does not refer to the IUPAC name—*cf.* Table 1): δ = 0.79 and 1.33 [2s, 8-$CH_3)_2$], 1.80–1.87 and *ca.* 2.24 − 2.32 (m, 3-H_2),① ② 1.88–1.96 and 2.18 − *ca.* 2.24 (m, 2-H_2),① ② AB signal [δ_A = 2.79, δ_B = 2.89, J_{AB} = 17.9, in addition split by $J_{A,3\text{-}H(1)}$* = 12.3, $J_{A,3\text{-}H(2)}$* = 6.4, $J_{B,3\text{-}H(1)}$** = 5.7 (whereas $J_{B,3\text{-}H(2)}$** ≈ 0), 4-H_2],① ② superimposes A part of AB signal (δ_A = 2.89, δ_B = 3.22, J_{AB} = 17.8, 5-H_2),③ AB signal (δ_A = 3.19, δ_B = 3.36, J_{AB} = 14.5, 1′-H_2),③ AB signal (δ_A = 3.66, δ_B = 3.70, J_{AB} = 15.2, 1″-H_2),[J] 3.75 and 3.80 (2s, CO_2Me), 3.94 (d, $J_{OH,7}$ = 2.6, OH),④ 4.18 (d, $J_{7,OH}$ = 2.5, 7-H),④ 4.41 (br s, 1-H),① 6.99 (s, 10-H); *, ** assignments interchangeable; ① starting from $\delta_{1\text{-}H}$ (br s at 4.41 ppm) crosspeaks in a 500 MHz H,H-correlation spectrum allowed us to identify the chemical shifts of 2-H_2 (2 m at 1.88–1.96 and 2.18–*ca.* 2.24) and, continuing from there, to recognize 3-H_2 (2 m at 1.80–1.87 and *ca.* 2.24–2.32) and ultimately 4-H_2 (AB signal, δ_A = 2.79, δ_B = 2.89); ②③*gem*-relationship between these protons underlined by the occurrence of crosspeaks in the 500 MHz one-bond C,H-correlation spectrum with pairwise the same ^{13}C resonance; ③5-H_2 distinguished from 1′-H_2/1″-H_2 by means of a 500 MHz long-range C,H-correlation spectrum through the lack of a crosspeak with either of the CO_2CH_3 resonances in the first case and the occurrence of such crosspeaks in the second (δ_C = 170.72) and third (δ_C = 169.96) cases; ④distinguished because of the absence of a crosspeak in the 500 MHz one-bond C,H-correlation spectrum for δ_H = 3.94 and the occurrence of such a crosspeak for δ_H = 4.18 (with δ_C = 80.21). ^{13}C NMR (APT spectrum, 125.7 MHz, $CDCl_3$; for the numbering—which exceptionally does not refer to the IUPAC name—*cf.* Table 1): δ = "−" 16.97 (C-3),① "+" 18.42 and "+" 28.18 [8-$(CH_3)_2$], "−" 27.20 (C-2),① "−" 30.30 (C-4),① "−" 33.10 and "−" 34.42 (C-1′, C-1″), "−" 38.21 (C-8),② "−" 39.33 (C-5),② "+" 41.31 (C-1),① "+" 52.43 and "+" 52.69 (2 × CO_2CH_3), "+" 80.21 (C-7), "+" 124.00 (C-10), "−" 125.29, "−" 130.11, "−" 140.40, "−" 143.69 and "−" 144.28 (C-9, C-4*a*, C-8*a*, C-9*a*, C-10*a*), "−" 169.96 and "−" 170.72 (2 × $COOCH_3$), "−" 198.98 (C-6); ① assigned because of the occurrence of crosspeaks in the 500 MHz one-bond C,H-correlation spectrum with the unambiguously assignable protons 1-H, 2-H_2, 3-H_2 and 4-H_2; ②distinguished through the absence of a crosspeak in the 500 MHz one-bond C,H-correlation spectrum with a proton in the case of δ_C = 38.21 and the occurrence of such a crosspeak in the case of δ_C = 39.33 (with δ_H = 2.89 and 3.22). $C_{22}H_{28}O_6S_2$ [M^+]: calcd. 452.1327; the exact molecular mass (±2 ppm; *R* = 10000) was confirmed by EI HRMS (70 eV). $C_{22}H_{28}O_6S_2$ (452.58); calcd.: C 58.38, H 6.24; found: C 58.51, H 6.42.

***S*′,*S*″-{2,3,4,6,7,9-Hexahydro-7-hydroxy-6,6-dimethyl-8-oxo-^{1}H-benzo[*a*]azulene-4,5-diyl}bis[methyl-(2-sulfanylacetate)] (*iso*-30):** (single diastereomer of unknown configuration). IR ($CDCl_3$): ν = 3500, 2955, 2870, 2255, 1730, 1665, 1600, 1575, 1545, 1435, 1390, 1280, 1200, 1135, 1080, 1020 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$; slightly contaminated; for the numbering—which exceptionally does not refer to the IUPAC name—*cf.* Table 1): δ = 0.81 and 1.33 [2s, 8-$CH_3)_2$], 1.80–1.89 (!) and 2.16–2.22 (m, 2-H_2),① 1.80–1.89 (!) and 2.27–2.38 (m, 3-H_2),① AB signal (δ_A = 2.69, δ_B = 3.64, J_{AB} = 16.8, 5-H_2),② AB signal [δ_A = 2.79, δ_B = 2.91, J_{AB} = 18.2, in addition split by $J_{A,3\text{-}H(1)}$* = 12.0, $J_{A,3\text{-}H(2)}$* = 6.6, $J_{B,3\text{-}H(1)}$** = 6.4 (whereas $J_{B,3\text{-}H(2)}$** ≈ 0), 4-H_2],② AB signal (δ_A = 3.19, δ_B = 3.36, J_{AB} = 14.7, 1′-H_2),① AB signal (δ_A = 3.65, δ_B = 3.71, J_{AB} = 15.2, 1″-H_2),② low-field branch of B part almost overlapped by 3.74 and 3.80 (2s, 2 × CO_2Me), 3.95 (d, $J_{OH,7}$ = 2.6, OH),③ 4.13 (d, $J_{7,OH}$ = 2.5, 7-H),③ 4.20 (m_c, 1-H), 6.98 (s, 10–H); *, ** assignments interchangeable; ① starting from $\delta_{1\text{-}H}$ (m_c at 4.20 ppm) crosspeaks in a 500 MHz H,H-correlation spectrum allowed us to identify the chemical shifts of 2-H_2 (2 m at 1.80–1.89 and 2.16–2.22) and, continuing from there, to recognize 3-H_2 (2 m at 1.80–1.89 and 2.27–2.38) and ultimately 4-H_2 (AB signal, δ_A = 2.79, δ_B = 2.91); ②5-H_2 distinguished from 1′-H_2 and from 1″-H_2 by means of a 500 MHz long-range C,H-correlation spectrum through the lack of a crosspeak with either of the CO_2CH_3 resonances in the first case and the occurrence of such crosspeaks in the second (δ_C = 169.94) and third (δ_C = 170.64) cases; ③assignment by analogy to compound **30**. ^{13}C NMR [APT spectrum, 125.7 MHz, $CDCl_3$; contains peaks of contaminant(s); for the numbering—which exceptionally does not refer to the IUPAC name—*cf.* Table 1]: δ = "−" 16.96 (C-3)*, "+" 17.61 and "+" 28.10 [8-$(CH_3)_2$], "−" 26.24 (C-2)*, "−" 29.88 (C-4)*, "−" 33.05 and "−" 34.25 (C-1′, C-1″)*, "−" 38.49 and "−" 38.94 (C-5, C-8)*, "+" 41.08 (C-1), "+" 52.42 and "+" 52.68 (2 × CO_2CH_3), "+" 80.66 (C-7), "+" 123.78 (C-10), "−" 125.40, "−" 130.03, "−" 140.44, "−" 144.15 and "−" 144.43 (C-9, C-4*a*, C-8*a*, C-9*a*, C-10*a*), (C-9), "−" 169.94 and "−" 170.64 (2 × $COOCH_3$), "−" 199.06 (C-6); * assignments by analogy to

30 but tentative. $C_{22}H_{28}O_6S_2$ [M^+]: calcd. 452.1327; the exact molecular mass (± 2 ppm; $R = 10000$) was confirmed by EI HRMS (70eV). No combustion analysis was performed due to lack of material.

Cycloaromatization of dienediyne 28. *Experiment A*. Two hours of a room temperature reaction under argon atmosphere between NEt_3 (22 μL, 16 mg, 0.16 mmol, 1.0 equiv.), 1,4-cyclohexadiene (0.34 mL, 290 mg, 3.6 mmol, 23 equiv.), methyl thioglycolate (31 μL, 36 mg, 0.34 mmol, 2.1 equiv.) and hydroxyketone **28** (38.2 mg, 0.159 mmol) in CH_2Cl_2 (2 mL) delivered—after work-up (as detailed for the cycloaromatization of hydroxyketone **23**; flash chromatography with pentane–ether 7 : 3; *vide supra*)—**34** (21.2 mg, 38%) in the early fractions and **35** in the late fractions (11.6 mg, 16%).

Experiment B. Similarly to *Experiment A*, NEt_3 (15 μL, 11 mg, 0.11 mmol, 1.0 equiv.), methyl thioglycolate (0.20 mL, 230 mg, 2.2 mmol, 20 equiv.) and hydroxyketone **28** (26.6 mg, 0.111 mmol) in CH_2Cl_2 (1.3 mL) delivered after 10 h **34** (6.9 mg, 18%) and **35** (15.2 mg, 30%).

Methyl-[*S*-(1,2,3,4,5,6,7,8-octahydro-7-hydroxy-8,8-dimethyl-6-oxophenanthren-4-yl)-(2-sulfanylacetate)] (34): (single diastereomer of unknown configuration). IR ($CDCl_3$): ν = 3485, 2935, 2870, 2260, 1720, 1600, 1480, 1440, 1410, 1385, 1365, 1275, 1190, 1125, 1080, 1010, 910 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$; for the numbering *cf.* Table 2): $\delta = 0.94$ and 1.56 [2s, 8-$(CH_3)_2$], 1.81–1.87 and 2.23–2.33 (2 m, 2-H_2),① 1.87–1.95 and 2.16–2.21 (2 m, 3-H_2),① AB signal ($\delta_A = 2.77$, $\delta_B = 2.87$, $J_{AB} = 17.2$, in addition split by $J_{A,2\text{-}H(1)} = 11.8$*, $J_{A,2\text{-}H(2)} = 6.0$*, $J_{B,2\text{-}H(1)} = 6.0$**, whereas $J_{B,2\text{-}H(2)} \approx 0$**, 1-$H_2$),① AB signal ($\delta_A = 3.20$, $\delta_B = 3.35$, $J_{AB} = 14.4$, 1′-H_2),② AB signal ($\delta_A = 3.67$, $\delta_B = 4.29$, $J_{AB} = 22.1$, 5-H_2),② 3.84 (d, $J_{OH,7} = 4.0$, OH),③ 3.86 (s, CO_2CH_3), 4.12 (br s, 4-H),① 4.23 (br d, $J_{7,OH} = 3.9$, 7-H),③ 7.07 (d, $J_{10,9} = 8.1$, 10-H)***, 7.30 (d, $J_{9,10} = 8.1$, 9-H)***; *, **, *** assignments interchangeable; ① starting from $\delta_{4\text{-}H}$ (br s at 4.12) crosspeaks in a 500 MHz H,H-correlation spectrum allowed us to identify the chemical shifts of 3-H_2 (2 m at 1.87–1.95 and 2.16–2.21) and, continuing from there, to recognize 2-H_2 (2 m at 1.81–1.87 and 2.23–2.33) and ultimately 1-H_2 (AB signal, $\delta_A = 2.77$, $\delta_B = 2.87$); ②5-H_2 distinguished from 1′-H_2 by means of a 500 MHz long-range C,H-correlation spectrum through the occurrence of a crosspeak with the ketone resonance (δ_C = 209.65) and not with the CO_2CH_3 resonance in the first case and with the CO_2CH_3 resonance ($\delta_C = 170.73$) and not with the ketone resonance in the second case; ③OH and 7-H distinguished through the occurrence of a crosspeak in the 500 MHz one-bond C,H-correlation spectrum between δ_C = 79.73 (C-7) and $\delta_H = 4.23$ (7-H) and the absence of a crosspeak between δ_C = 79.73 (C-7) and $\delta_H = 3.84$ (OH). ^{13}C NMR (125.7 MHz gated decoupled; 75.5 MHz APT; $CDCl_3$; for the numbering *cf.* Table 2): δ = "−" 17.37 (C-2),① "+" 23.72 and "+" 24.63 [8-$(CH_3)_2$], "−" 27.38 (C-3),① "−" 29.00 (C-1),① "−" 33.24 (C-1′),① "−" 38.13 (C-5),① "+" 42.39 (C-4),① "−" 42.62 (C-8),② "+" 52.55 (CO_2CH_3), "+" 79.73 (C-7), "+" 124.74 and "+" 128.81 (C-9, C-10), "−" 129.97, "−" 132.90, "−" 136.54 and "−" 141.55 (C-4*a*, C-4*b*, C-8*a*, C-10*a*), "−" 170.73 (CO_2CH_3), "−" 209.65 (C-6); ① assigned because of the occurence of crosspeaks in the 500 MHz one-bond C,H-correlation spectrum with the unambiguously assignable protons 1-H_2, 3-H_2, 4-H, 5-H_2, 1′-H_2 and 1″-H_2, no crosspeak for 2-H_2 is detected; ②identified through the absence of a crosspeak in the 500 MHz one-bond C,H-correlation spectrum with any δ_H. $C_{19}H_{24}O_4S$ [M^+]: calcd. 348.1395; the exact molecular mass (± 2 ppm; $R = 10000$) was confirmed by EI HRMS (70 eV). $C_{19}H_{24}O_4S$ (348.46); calcd.: C 65.49, H 6.94; found: C 65.34, H 7.20.

***S′,S″*-(1,2,3,4,5,6,7,8-Octahydro-7-hydroxy-8,8-dimethyl-6-oxophenanthrene-4,9-diyl) bis[methyl-(2-sulfanylacetate)] (35):** (single diastereomer of unknown configuration). IR ($CDCl_3$): ν = 3500, 2955, 2870, 2255, 1725, 1600, 1460, 1440, 1390, 1280, 1195, 1130, 1090 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$; for the numbering *cf.* Table 2): $\delta = 0.94$ and 1.57 [2 s, 8-$(CH_3)_2$], 1.82–1.90 and 2.13–2.19 (2 m, 3-H_2),① 1.90–1.95 and 2.25–2.35 (2 m, 2-H_2),① AB signal ($\delta_A = 2.56$, $\delta_B = 3.00$, J_{AB} = 17.5, in addition split by $J_{A,2\text{-}H(1)} = 11.9$*, $J_{A,2\text{-}H(2)} = 6.1$*, $J_{B,2\text{-}H(1)} = 6.0$**, whereas $J_{B,2\text{-}H(2)} \approx 0$**, 1-$H_2$),① AB signal ($\delta_A = 3.19$, $\delta_B = 3.34$, $J_{AB} = 14.4$, 1′-H_2),② AB signal (δ_A = 3.65, $\delta_B = 4.28$, $J_{AB} = 22.1$, 5-H_2),② low-field branch of A part superimposed entirely by the two central lines of extreme AB signal ($\delta_A \approx \delta_B \approx 3.67$, J_{AB} not determinable because the two outer lines are too small, 1″-H_2),② 3.75 and 3.86 (2 s, 2 × CO_2CH_3), 3.83 (d, $J_{OH,7} = 4.0$, OH),③ 4.12 (br s, 4-H),① 4.21 (br d, $J_{7,OH} = 3.2$, 7-H),③ 7.36 (s, 10-H); *,** assignments interchangeable,① starting from $\delta_{4\text{-}H}$ (br s at 4.12) crosspeaks in a 500 MHz H,H-correlation spectrum allowed us to identify the chemical shifts of 3-H_2 (2 m at 1.82–1.90 and 2.13–2.19) and, continuing from there, to recognize 2-H_2 (2 m at 1.90–1.95 and 2.25–2.35) and ultimately 1-H_2 (AB signal, $\delta_A = 2.56$, $\delta_B = 3.00$); ②5-H_2 distinguished from 1′-H_2/1″-H_2 by means of a 500 MHz long-range C,H-correlation spectrum through the lack of a crosspeak with either of the CO_2CH_3 resonances [and the presence of a crosspeak with $\delta_C = 209.33$ (C-6)] in the first case and the occurence of such crosspeaks in the second ($\delta_C = 170.67$) and third ($\delta_C = 170.03$) cases; ③OH and 7-H distinguished through the occurrence of a crosspeak in the 300 MHz one-bond C,H-correlation spectrum between $\delta_C = 79.49$ (C-7) and $\delta_H = 4.21$ (7-H) and the absence of such a crosspeak with $\delta_H = 3.83$ (OH). ^{13}C NMR (125.7 MHz, $CDCl_3$; for the numbering *cf.* Table 2): δ = "−" 17.01 (C-2),① "+" 23.66 and "+" 24.45 [8-$(CH_3)_2$], "−" 26.42 (C-3),① "−" 26.70 (C-1),① "−" 33.05 (C-1′),① "−" 34.86 (C-1″),① "−" 37.95 (C-5),① "+" 42.51 (C-4),① "−" 42.87 (C-8),② "+" 52.49 and "+" 52.66 (2 × CO_2CH_3), "+" 79.49 (C-7), "+" 124.06 (C-10), "−" 128.16, "−" 133.86, "−" 134.51, "−" 135.39 and "−" 142.09 (C-9, C-4*a*, C-8*a*, C-4*b*, C-10*a*), "−" 170.03 and "−" 170.67 (2 × CO_2CH_3), "−" 209.33 (C-6); ① assigned because of the occurence of crosspeaks in the 300 MHz one-bond C,H-correlation spectrum with the unambiguously assignable protons 1-H_2, 2-H_2, 3-H_2, 4-H, 5-H_2, 1′-H_2, 1″-H_2; ②identified through the absence of a crosspeak in the 300 MHz one-bond C,H-correlation spectrum. $C_{22}H_{28}O_6S_2$ [M^+]: calcd. 452.1327; the exact molecular mass (± 2 ppm; $R = 10000$) was confirmed by EI HRMS (70 eV). $C_{22}H_{28}O_6S_2$ (452.58); calcd.: C 58.38, H 6.24; found: C 58.65, H 6.52.

Acknowledgements

We thank the European Union for making this work possible through a stipend of the Human Capital and Mobility Program for F.F. We are very grateful to DEGUSSA AG (Hanau) and BASF AG (Ludwigshafen) for supporting us with free-of-charge chemicals.

References

1 K. C. Nicolaou and W. M. Dai, *Angew. Chem.*, 1991, **103**, 1453; *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1387; M. Hirama, in *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*, ed. G. Lukacs, Springer, Berlin, 1993, vol. 2, pp. 293–329; J. A. Murphy and J. Griffiths, *Nat. Prod. Rep.*, 1993, 550; M. E. Maier, *Kontakte* (*Darmstadt*), 1994, 3; M. Hirama, *J. Synth. Org. Chem. Jpn.*, 1994, **52**, 980; M. E. Maier, *Synlett*, 1995, 13; K. C. Nicolaou and A. L. Smith, in *Modern Acetylene Chemistry*, ed. P. J. Stang and F. Diederich, VCH, Weinheim, 1995, pp. 203–283; H. Lhermitte and D. Grierson, *Contemp. Org. Synth.*,

1996, **3**, 41; 1996, **3**, 93; K. K. Wang, *Chem. Rev.*, 1996, **96**, 207; A. L. Smith and K. C. Nicolaou, *J. Med. Chem.*, 1996, **39**, 2103; J. W. Grissom, G. U. Gunawardena, D. Klingberg and D. Huang, *Tetrahedron*, 1996, **52**, 6453.
2 Thermal Bergman cyclization: R. R. Jones and R. G. Bergman, *J. Am. Chem. Soc.*, 1972, **94**, 660. Photochemical Bergman cyclization: N. J. Turro and A. Evenzahav, *Tetrahedron Lett.*, 1994, **35**, 8098.
3 (*a*) Induction by thiolate: A. G. Myers, *Tetrahedron Lett.*, 1987, **28**, 4493; A. G. Myers and P. J. Proteau, *J. Am. Chem. Soc.*, 1989, **111**, 1146; A. G. Myers, S. B. Cohen and B.-M. Kwon, *J. Am. Chem. Soc.*, 1994, **116**, 1670; H. Sugiyama, T. Fujiwara and I. Saito, *Tetrahedron Lett.*, 1994, **35**, 8825. (*b*) Aerobic induction: T. Tanaka, K. Fujiwara and M. Hirama, *Tetrahedron Lett.*, 1990, **31**, 5947. (*c*) Induction by base: O. D. Hensens, G. L. Helms, D. L. Zink, D.-H. Chin, L. S. Kappen and I. H. Goldberg, *J. Am. Chem. Soc.*, 1993, **115**, 11030. (*d*) Induction by light: T. Gomibuchi and M. Hirama, *J. Antibiot.*, 1995, **48**, 738. (*e*) *Cf.* also the deactivation of protein-bound neocarzinostatin chromophore by thiols: H. Sugiyama, K. Yamashita, T. Fujiwara and I. Saito, *Tetrahedron*, 1994, **50**, 1311; A. G. Myers, S. P. Arvedson and R. W. Lee, *J. Am. Chem. Soc.*, 1996, **118**, 4725.
4 R. Nagata, H. Yamanaka, E. Okazaki and I. Saito, *Tetrahedron Lett.*, 1989, **30**, 4995; A. G. Myers, E. Y. Kuo and N. S. Finney, *J. Am. Chem. Soc.*, 1989, **111**, 8057.
5 A. G. Myers and P. S. Dragovich, *J. Am. Chem. Soc.*, 1989, **111**, 9130; R. Nagata, H. Yamanaka, E. Murahashi and I. Saito, *Tetrahedron Lett.*, 1990, **31**, 2907; K. C. Nicolaou, P. Maligres, J. Shin, E. de Leon and D. Rideout, *J. Am. Chem. Soc.*, 1990, **112**, 7825; K. Toshima, K. Ohta, T. Ohake and K. Tatsuta, *J. Chem. Soc., Chem. Commun.*, 1991, 694; Y. W. Andemichael, Y. G. Gu and K. K. Wang, *J. Org. Chem.*, 1992, **57**, 794; Y. Sakai, Y. Banco, K. Shishido and M. Shibuya, *Tetrahedron Lett.*, 1992, **33**, 957; A. G. Myers, P. S. Dragovich and E. Y. Kuo, *J. Am. Chem. Soc.*, 1992, **114**, 9369; K. Toshima, K. Ohta, A. Ohtsuka, S. Matsumura and M. Nakata, *J. Chem. Soc., Chem. Commun.*, 1993, 1406; M.-J. Wu, C.-F. Lin, J.-S. Wu and H.-T. Chen, *Tetrahedron Lett.*, 1994, **35**, 1879; Y. Matsumoto, T. Hasegawa, Y. Kuwatani and I. Ueda, *Tetrahedron Lett.*, 1995, **36**, 5757; Y. Naoe, J. Kikuishi, K. Ishigaki, H. Iitsuka, H. Nemoto and M. Shibuya, *Tetrahedron Lett.*, 1995, **36**, 9165; M. Shibuya, M. Wakayama, Y. Naoe, T. Kawakami, K. Ishigaki, H. Nemoto, H. Shimizu and Y. Nagao, *Tetrahedron Lett.*, 1996, **37**, 865; N. Krause and M. Hohmann, *Synlett*, 1996, 89, *corrigendum* 590; K. K. Wang, Z. Wang, A. Tarli and P. Garrett, *J. Am. Chem. Soc.*, 1996, **118**, 10783.
6 P. A. Wender and M. J. Tebbe, *Tetrahedron Lett.*, 1991, **32**, 4863; *Tetrahedron*, 1994, **50**, 1419.
7 S. Caddick, S. Khan, N. J. Smith, D. M. Barr and V. M. Delisser, *Tetrahedron Lett.*, 1997, **38**, 5035; *cf.* also S. Caddick and S. Khan, *J. Chem. Soc., Chem. Commun.*, 1995, 1971.
8 T. Doi and T. Takahashi, *J. Org. Chem.*, 1991, **56**, 3465 (step 1 of the synthesis of compound **9** followed a procedure by A. B. Smith III, S. J. Branca, M. A. Guciaro, P. M. Wovkulich and A. Korn, *Org. Synth. Coll. Vol. VII*, 1990, 271, steps 2 and 3 from P. A. Wender, M. A. Harmata, D. Jeffrey, C. Mukai and J. Suffert, *Tetrahedron Lett.*, 1988, **29**, 909).
9 (*a*) M. Hirama, K. Fujiwara, K. Shigematu and Y. Fukazawa, *J. Am. Chem. Soc.*, 1989, **111**, 4120 (step 1 of the synthesis of compound **10a** identical with step 1 of the synthesis of compound **9**); (*b*) The original cycloaromatization conditions were improved by M. Hirama, M. Tokuda and K. Fujiwara, *Synlett*, 1991, 651.
10 M. Hirama, T. Gomibuchi, K. Fujiwara, Y. Sugiura and M. Uesugi, *J. Am. Chem. Soc.*, 1991, **113**, 9851 (steps 1 and 2 of the synthesis of compounds **10b**,**c** followed D. R. Deardorff, D. C. Myles and K. D. MacFerrin, *Tetrahedron Lett.*, 1985, **26**, 5615, step 3 the procedure of D. R. Deardorff, A. J. Matthews, D. S. McMeekin and C. L. Craney, *Tetrahedron Lett.*, 1986, **27**, 1255).
11 M. Tokuda, K. Fujiwara, T. Gomibuchi, M. Hirama, M. Uesugi and Y. Sugiura, *Tetrahedron Lett.*, 1993, **34**, 669 (steps 1 and 2 of the synthesis of compound **10d** followed a procedure by C. Le Drian and A. E. Greene, *J. Am. Chem. Soc.*, 1982, **104**, 5473).
12 M. Hirama, M. Tokuda and K. Fujiwara, *Synlett* 1991, 651 (steps 1 and 2 of the synthesis of compound **10e** followed a procedure by C. Le Drian and A. E. Greene, *J. Am. Chem. Soc.*, 1982, **104**, 5473).
13 Y. Matsumoto, Y. Kuwatani and I. Ueda, *Tetrahedron Lett.*, 1995, **36**, 3197 (step 1 of the synthesis of compound **11** followed a procedure of A. B. Smith III, S. J. Branca, M. A. Guciaro, P. M. Wovkulich and A. Korn, *Org. Synth. Coll. Vol. VII*, 1990, 271).
14 K. Fujiwara, A. Kurisaki and M. Hirama, *Tetrahedron Lett.*, 1990, **31**, 4329.
15 M. Eckhardt and R. Brückner, *Liebigs Ann.*, 1996, 473 (steps 1–2: ref. 22*b*; step 3: ref. 21).
16 Another enyneallenyl ketone—which cycloaromatized by the Saito–Myers mode at 45 or 60 °C in 22 and 52% yield, respectively—was synthesized from acetyltrimethylsilane and *o*-iodobenzaldehyde: R. F. Cunico, *Tetrahedron Lett.*, 1994, **35**, 2291 (steps 1 and 2); R. F. Cunico and S. K. Nair, *Tetrahedron Lett.*, 1997, **38**, 25 (steps 3–7).
17 M. Schmittel, M. Strittmatter and S. Kiau, *Tetrahedron Lett.*, 1995, **36**, 4975.
18 T. Gillmann, T. Hülsen, W. Massa and S. Wocadlo, *Synlett*, 1995, 1257.
19 M. Schmittel, M. Strittmattter, K. Vollmann and S. Kiau, *Tetrahedron Lett.*, 1996, **37**, 999; M. Schmittel, S. Kiau, T. Siebert and M. Strittmattter, *Tetrahedron Lett.*, 1996, **37**, 7691; M. Schmittel, M. Strittmattter and S. Kiau, *Angew. Chem.*, 1996, **108**, 1952; *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1843; M. Schmittel, M. Keller, S. Kiau and M. Strittmatter, *Chem. Eur. J.*, 1997, **3**, 807; M. Schmittel, M. Maywald and M. Strittmatter, *Synlett*, 1997, 165; M. Schmittel and S. Kiau, *Liebigs Ann./Recl.*, 1997, 733. Possibly related ring-closure reactions of enyne[3]cumulenes: J. G. Garcia, B. Ramos, L. M. Pratt and A. Rodríguez, *Tetrahedron Lett.*, 1995, **36**, 7391.
20 R. Brückner, S. W. Scheuplein and J. Suffert, *Tetrahedron Lett.*, 1991, **32**, 1449; S. W. Scheuplein, K. Harms, R. Brückner and J. Suffert, *Chem. Ber.*, 1992, **125**, 271.
21 M. Moniatte, M. Eckhardt, K. Brickmann, R. Brückner and J. Suffert, *Tetrahedron Lett.*, 1994, **35**, 1965.
22 (*a*) M. Eckhardt, R. Brückner and J. Suffert, *Tetrahedron Lett.*, 1995, **36**, 5167; (*b*) K. Brickmann, F. Hambloch, J. Suffert and R. Brückner, *Liebigs Ann.*, 1996, 457; (*c*) M. Eckhardt and R. Brückner, *Liebigs Ann.*, 1996, 473; (*d*) M. Eckhardt and R. Brückner, *Angew. Chem.*, 1996, **108**, 1185; *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1093; (*e*) M. Eckhardt and R. Brückner, *Liebigs Ann./Recl.*, 1997, 947; (*f*) F. Ferri and R. Brückner, *Liebigs Ann./Recl.*, 1997, 961.
23 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
24 D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155; beneficial effect of added H_2O: S. D. Meyer and S. L. Schreiber, *J. Org. Chem.*, 1994, **59**, 7549.
25 Mechanistic studies: B. Bogdanovic and A. Bolte, *J. Organomet. Chem.*, 1995, **502**, 109; paragraph 4 of ref. 27*d*; C. Villiers and M. Ephritikhine, *Angew. Chem.*, 1997, **109**, 2477; *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2380.
26 Procedure: J. E. McMurry and J. G. Rico, *Tetrahedron Lett.*, 1989, **30**, 1169.
27 Reviews: (*a*) J. E. McMurry, *Chem. Rev.*, 1989, **89**, 1513; (*b*) G. M. Robertson, in *Comprehensive Organic Synthesis*, ed. G. Pattenden, Pergamon Press, Oxford, 1991, vol. 3, pp. 563–611; (*c*) T. Lectka, in *Active Metals*, ed. A. Fürstner, VCH, Weinheim, 1996, pp. 85–131; (*d*) A. Fürstner and B. Bogdanovic, *Angew. Chem.*, 1996, **108**, 2582; *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2442.
28 Method: K. Narasaka, A. Morikawa, K. Saigo and T. Mukaiyama, *Bull. Chem. Soc., Jpn.*, 1977, **50**, 2773.
29 E. Rank and R. Brückner, *Eur. J. Org. Chem.*, in the press.
30 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.
31 C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785.
32 M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez and J. A. Pople, *Gaussian 94*, *Revision E.2*, Gaussian, Pittsburgh, PA, 1995.
33 J. M. Bofill and P. Pulay, *J. Chem. Phys.*, 1989, **90**, 3637.
34 For a review see: W. T. Borden and E. R. Davidson, *Acc. Chem. Res.*, 1996, **29**, 67.
35 P. M. Kozlowski and E. R. Davidson, *J. Chem. Phys.*, 1994, **100**, 3672.
36 The method is similar to CASPT2N: K. Anderson, P.-A. Malmqvist and B. O. Roos, *J. Chem. Phys.*, 1992, **96**, 1218.
37 C. Møller and M. S. Plesset, *Phys. Rev.*, 1934, **46**, 618.
38 W. R. Roth, H. Hopf and C. Horn, *Chem. Ber.*, 1994, **127**, 1765.

Received in Montpellier, France, 15*th December* 1997;
Paper 7/09205I