nucleotide **3**. This new chemoenzymatic strategy should find use in the synthesis of other iminocyclitol nucleotides. We believe that compounds **1**–**3** should be useful as general inhibitors of fucosyltransferases.

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Cyanoethynylethenes: A Class of Powerful Electron Acceptors for Molecular Scaffolding[**]

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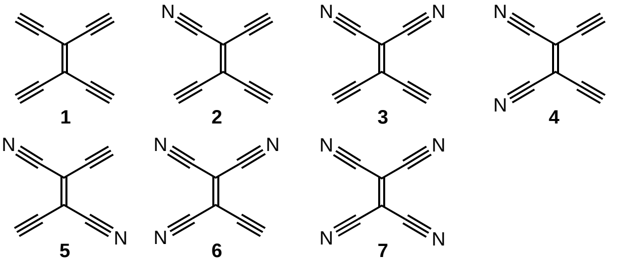
Tetraethynylethene (**1**, TEE, Scheme 1) was introduced in 1991 as a useful building block for the synthesis of one- and two-dimensional π-conjugated scaffolds, such as poly(triacetylene) oligomers, expanded radialenes, and dehydroannulenes.[1] Incorporation of donor and acceptor substituents resulted in interesting electronic[1e,2] and nonlinear optical properties.[1e,3] Furthermore, the strain-free planarity allows reversible, photochemical *cis*–*trans* isomerization of *cis*- and *trans*-arylated TEEs without competition from undesirable thermal isomerization.[4]



Scheme 1. Progression from tetraethynylethene (TEE, **1**) to tetracyanoethene (TCNE, **7**).

Cyanoethynylethenes (**2**–**6**, CEEs) are an interesting class of hybrid derivatives combining the scaffolding power of TEE with the electronic properties of tetracyanoethene (**7**, TCNE), which is one of the strongest organic electron acceptors known, and has been widely used in the formation of charge-transfer complexes.[5] So far, only derivatives of **3**, with $SiMe_3$ (**8b**, Scheme 2) or phenyl substituents,[6] and arylated derivatives of **6**[7] have been reported. Hopf and Kreutzer demonstrated that there was an enhanced reactivity of the triple bonds in derivatives of **3** and **6** towards Diels–Alder reactions[6] and in the [2+2] cycloaddition to tetrathiafulvalene, with subsequent ring opening.[8] A similar reaction was also observed by Hirsch and co-workers at the terminal acetylene moiety of α,ω-dicyanopolyynes.[9]

We have now extended the family of CEEs and report herein the synthesis of **9**–**11a** (Scheme 2), silylated derivatives

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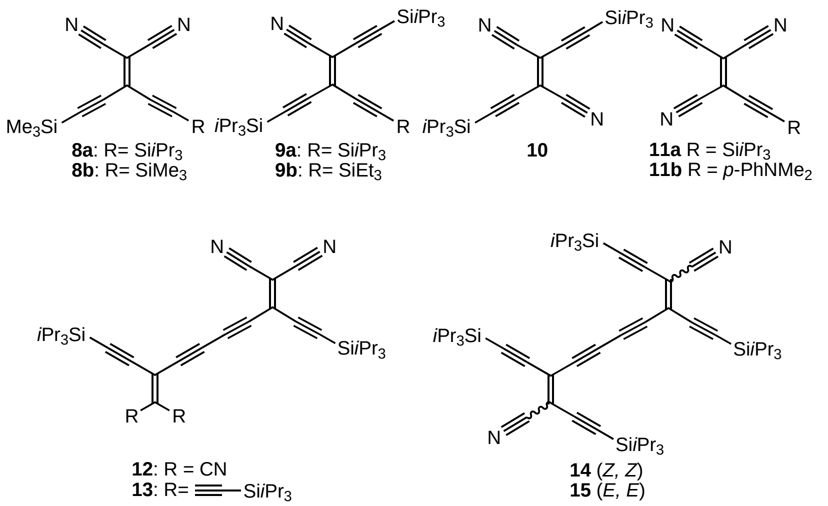
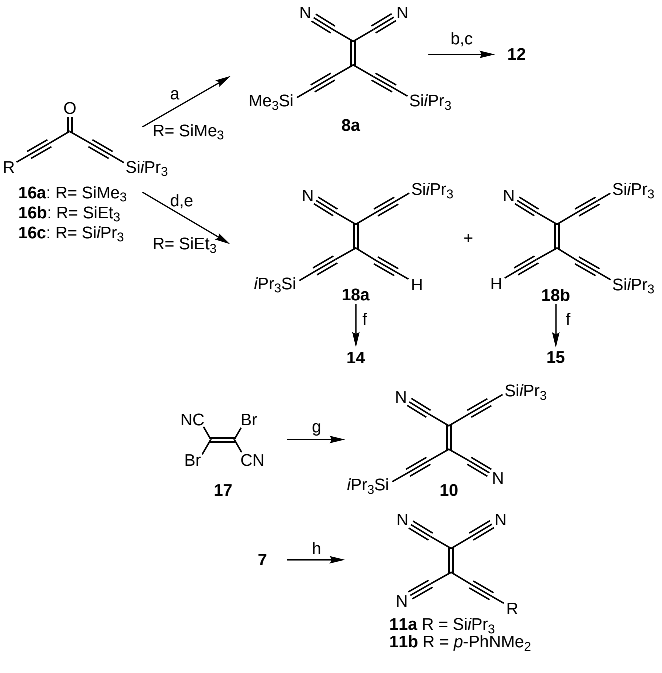


Scheme 2. New cyanoethynylethenes (CEEs) and extended cyanoethynylethenes for molecular scaffolding.

of the missing parent members **2**, **5**, and **6**. In addition, the first extended CEEs **12**–**15** are reported and the electron-accepting properties of both classes of chromophores are investigated by cyclic voltammetry (CV). Furthermore, a donor-acceptor-substituted CEE (**11b**) with promising advanced materials properties will be described.

In the series of CEEs (Scheme 3), the geminal dinitrile **8a** was obtained from ketone **16a** by a Knoevenagel reaction according to the procedure used by Hopf and Kreutzer to prepare **8b**.[6][10] Monocyanotriethynylethene **9a** (Scheme 2) was also obtained in 97% yield by a Knoevenagel reaction of ketone **16c** (R = SiiPr$_3$) with $i\mathrm{Pr_3SiC{\equiv}C{-}CH_2{-}CN}$ and $i\mathrm{Pr_2EtN}$. Remarkably, while this conversion required stirring for 8 h at 50 °C, the corresponding reaction of the sterically less-encumbered **16b** (R = $\mathrm{SiEt_3}$) to give **9b** (47%) was completed within 1 min at 20 °C.[11]



Scheme 3. Reagents and conditions: a) $\mathrm{CH_2(CN)_2}$, $\mathrm{Al_2O_3}$ (act. II–III), $\mathrm{CH_2Cl_2}$, 40 °C, 85%; b) THF/MeOH 1:5, 20 °C; c) $\mathrm{Cu(OAc)_2}$, $\mathrm{CH_2Cl_2}$, 20 °C, 22% (two steps); d) $i\mathrm{Pr_3SiC{\equiv}CCH_2CN}$, $i\mathrm{Pr_2EtN}$, EtOH, 20 °C, 47% (**9b**), 27% (**18a**), 15% (**18b**); e) $\mathrm{K_2CO_3}$, THF/MeOH 1:1, 20 °C, 46% (**18a**), 29% (**18b**); f) CuCl, TMEDA, $\mathrm{CH_2Cl_2}$, 20 °C, 91% (**14**), 85% (**15**); g) $\mathrm{[PdCl_2(PPh_3)_2]}$, $i\mathrm{Pr_3SiC{\equiv}CH}$, $i\mathrm{Pr_2NH}$, CuI, 20 °C, 30%; h) $i\mathrm{Pr_3SiC{\equiv}CLi}$, CuBr, THF, 50 °C, 33% (**11a**) or $\mathrm{HC{\equiv}CPhNMe_2}$, CuOAc, THF, 50 °C, 29% (**11b**). TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

Sonogashira cross-coupling[12] of dibromide **17** with $i\mathrm{Pr_3SiC{\equiv}CH}$ gave *trans*-dicyanodiethynylethene **10** in 30% yield. Replacing $i\mathrm{Pr_2NH}$ with $i\mathrm{Pr_2EtN}$ as the base in this reaction resulted in a lower yield (19%) whereas the use of $\mathrm{Et_3N}$ only gave undefined side products. Tricyanoethynylethenes **11a** and **b** were prepared according to the method of Dulog et al.[7b] by nucleophilic substitution of TCNE with the corresponding copper(I) acetylide.

In the series of extended CEEs, tetranitrile **12** was obtained starting from **8a** (Scheme 3). An attempt to remove the $\mathrm{Me_3Si}$ group of **8a** under standard conditions ($\mathrm{K_2CO_3}$, MeOH/THF) only led to decomposition. Gratifyingly, mono-deprotection could be accomplished by simply stirring **8a** in the solvent mixture in the absence of $\mathrm{K_2CO_3}$. Copper(II)-mediated oxidative acetylenic couplings are usually carried out in the presence of nitrogen-containing ligands.[13] Use of these ligands, however, caused a severe problem in the coupling of mono-deprotected **8a**. Even 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) caused instantaneous decomposition of the starting material. The delicate, highly electrophilic cyanoethynylated chromophores readily undergo nucleophilic additions with amines and probably also participate in electron-transfer processes. Finally, it appeared that the activating (p*K*-lowering) effect of the two cyano groups was large enough to enable oxidative coupling in the absence of any ligand, thus affording **12**.

For the preparation of **14** and **15**, **9b** was mono-deprotected to give *Z*-configured **18a** and the less stable *E* isomer **18b**. Oxidative Hay coupling of **18a** and **18b** subsequently led to the extended CEEs **14** (*Z*,*Z*-configured) and **15** (*E*,*E*-configured), respectively. Unambiguous proof for the configurational assignments of **14** and **15** (and of **18a** and **b**) was obtained from the X-ray crystal structure of **14** (Figure 1),[14] which clearly showed the *Z* configuration of both CEE moieties. The structure reveals planarity in the carbon–nitrogen core, with the largest out-of-plane deviation being approximately 0.05 Å.

All CEE derivatives are air-stable, but their sensitivity towards nucleophiles increases with their acceptor potential. Thus, the strong acceptors **11a** and **12** decompose rapidly in the presence of any nucleophile. CEE derivatives **8**–**11a** are nearly colorless oils, whereas the extended systems **12**–**15** are bright-yellow solids or oils.

The electron-accepting properties of the CEE derivatives were investigated by cyclic voltammetry in $\mathrm{CH_2Cl_2}$ (+0.1 M $\mathrm{Bu_4NPF_6}$) as previously described (Table 1).[2b] All species gave a reversible one-electron reduction as well as a second

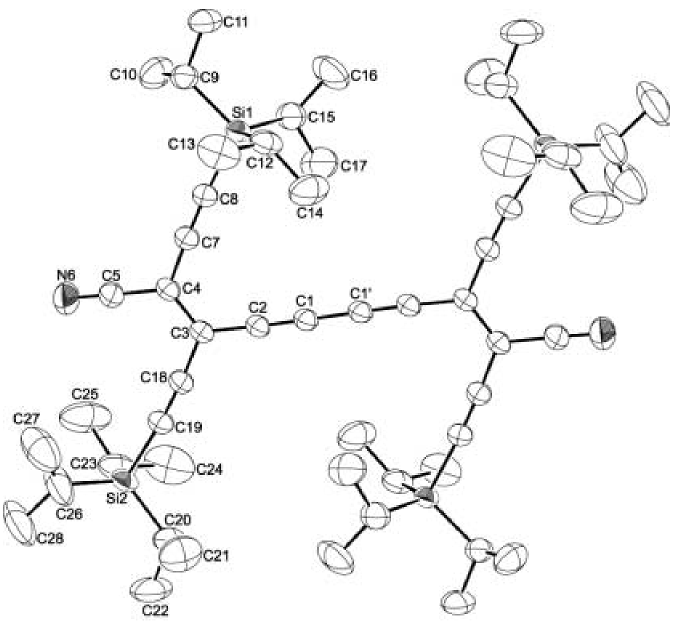
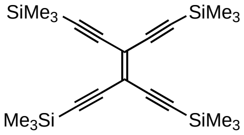


Figure 1. ORTEP representation of **14** with vibrational ellipsoids shown at the 30% probability level. H atoms are omitted for clarity. Selected bond lengths [Å] and bond angles [°]: C5-N6 1.142(4), C4-C5 1.430(5), C3-C4 1.364(4), C2-C3 1.413(4), C1-C2 1.200(4), C1-C1′ 1.369(7); N6-C5-C4 178.9(4), C3-C4-C5 119.2(3), C4-C3-C2 119.7(3), C1-C2-C3 177.6(3), C2-C1-C1′ 179.5(4).

Table 1. Cyclic voltammetry data in CH_2Cl_2 (+0.1 M Bu_4NPF_6).[a]



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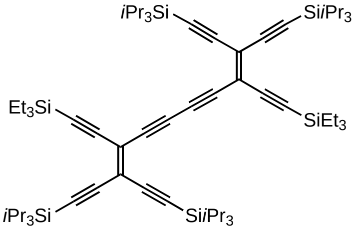

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	E° [V][b]	E_p [V][c]		E° [V][b]	E_p [V][c]
19[d]	−1.96		**20**[d]	−1.52	
9a	−1.58			−1.89	
		−2.34			−2.90
10	−1.25		**14**	−1.07	
		−2.05		−1.37	
8a	−1.15		**15**	−1.06	
		−1.95		−1.36	
11a	−0.72		**13**	−0.90	
		−1.69		−1.44	
7	−0.32		**12**	−0.57	
		−1.35		−0.84	
11b	+0.79				−2.24
		−0.86			

[a] Potentials versus the ferrocene/ferrocenium couple. Working electrode: glassy carbon electrode; counter electrode: Pt; reference electrode: Ag/AgCl. [b] $E^\circ = (E_{pc} + E_{pa})/2$, where E_{pc} and E_{pa} are the cathodic and anodic peak potentials. [c] E_p = Irreversible peak potential at v = 0.1 V s^{-1}. [d] Solvent: THF.[2a]

reduction, which was irreversible for **8**–**11a** and reversible for **12**–**15**.

All CEE derivatives are much stronger electron acceptors than the corresponding TEE derivatives such as **19** and **20**. On the basis of the first reduction potentials of the monomeric CEEs **8**–**11a**, the increase in electron-acceptor strength upon substituting one $RC\equiv C$- group by a $N\equiv C$- group is, on average, 380 mV, whereas replacing one NC–C–CN group with $RC\equiv C–C–C\equiv CR$ increases the average electron-acceptor strength by 830 mV.[15] A linear correlation (R = 0.994) was obtained between the calculated electron affinities (B3LYP, 3-21G)[16] and the first reduction potentials for CEEs **8**–**11a**, TCNE (**7**), and TEE (**19**). The extended CEE **12** is an exceptionally good electron acceptor, which approaches the strength of TCNE (**7**). A clear increase in acceptor strength with extension of π-electron conjugation was observed (**8a** versus **13**), however the effects of adding a cyanide group and extension of conjugation could not yet be quantified.

The deep-blue solid CEE **11b**, which has an *N*,*N*-dimethylanilino substituent, is a donor-acceptor derivative with potentially interesting nonlinear optical properties. The UV/Vis spectrum exhibits an intense intramolecular charge-transfer band at 591 nm (λ_{max}, $\varepsilon = 43800\,M^{-1}cm^{-1}$, Figure 2), a bathochromic shift of 60 nm (0.24 eV) relative to the corresponding band in 4-(tricyanovinyl)-*N*,*N*-dimethylaniline (λ_{max} = 530 nm, ε = ca. $40000\,M^{-1}cm^{-1}$).[17] Most importantly, **11b** can be sublimed without decomposition (100 °C, 0.1 mbar), which indicates the potential for ultra-thin film preparation by vapor deposition techniques, which has not been possible with donor-acceptor-substituted TEEs. Investigations of **11b** for optoelectronic applications are under way. In addition, the powerful new CEE acceptors have now been introduced through acetylenic scaffolding into larger molecular systems for modulation of the properties.

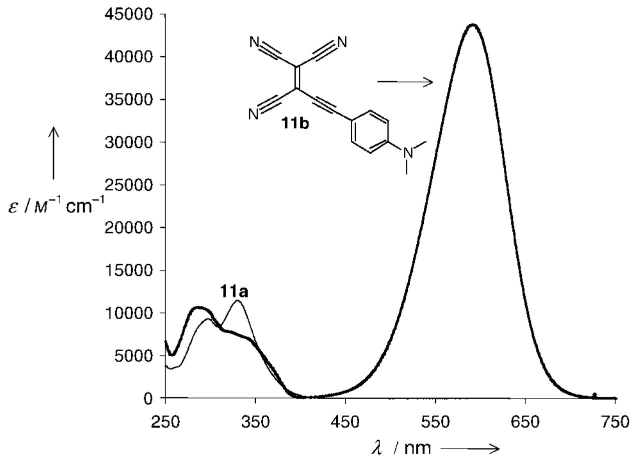

Figure 2. UV/Vis spectrum ($CHCl_3$) of **11b** with λ_{max} = 591 nm ($\varepsilon = 43800\,M^{-1}cm^{-1}$) and **11a** ($\lambda_{max}$ = 330 nm, $\varepsilon = 11500\,M^{-1}cm^{-1}$).

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[10] All new compounds were fully characterized by ^{1}H and ^{13}C NMR spectroscopy, FT-IR spectroscopy, EI or MALDI mass spectrometry, and elemental analysis or high-resolution mass spectrometry.

[11] Partial deprotection of **9b** in this reaction was unavoidable and, in addition to **9b** (47%) which was separated and characterized in its pure form, the ethynyl derivatives **18a** (27%) and **18b** (15%) were also obtained.

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[14] X-ray crystal data for **14** at 295 K ($C_{54}H_{84}N_2Si_4$, $M_r = 436.8$): monoclinic, space group $P2_1/n$ (no. 14), $\rho_{calcd} = 0.996\ \mathrm{g\,cm^{-3}}$, $Z = 2$, $a = 13.320(4)$, $b = 7.766(2)$, $c = 28.722(5)$ Å, $\beta = 101.30(2)°$, $V = 2913.5(13)$ Å^3. Nonius CAD4 diffractometer, $\mathrm{Cu_{K\alpha}}$ radiation, $\lambda = 1.5418$ Å. A single crystal with linear dimensions of ca. $0.20 \times 0.07 \times 0.04$ mm was grown in a capillary from hexane at 273 K. A semi-empirical absorption correction, based on psi scans was applied to the data ($T(\mathrm{max}) = 0.99$, $T(\mathrm{min}) = 0.89$). The structure was solved by direct methods (SIR92) and refined by full-matrix least-squares analysis (SHELXL97), using an isotropic extinction correction, and $w = 1/[\sigma^2(F_o^2) + (0.078P)^2 + 1.792P]$, where $P = (F_o^2 + 2F_c^2)/3$. All heavy atoms were refined anisotropically and H atoms isotropically. H-atom positions are based on stereochemical considerations. Final $R(F) = 0.049$, $wR(F^2) = 0.137$ for 305 parameters and 2536 reflections with $I > 2\sigma(I)$ and $3.14 < \theta < 54.97°$ (corresponding R values based on all 3630 reflections are 0.079 and 0.166, respectively). CCDC-182715 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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A Structural and Functional Model of Galactose Oxidase: Control of the One-Electron Oxidized Active Form through Two Differentiated Phenolic Arms in a Tripodal Ligand

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Galactose oxidase (GOase) is a type II copper protein (68 kDa) that catalyzes the oxidation of primary alcohols to aldehydes with the concomitant reduction of molecular oxygen.[1] Its crystal structure[2] reveals a unique mononuclear copper site with two nitrogen (from histidine imidazole groups) and two oxygen (from one axial and one equatorial tyrosine group) donor atoms, plus an exogenous water or acetate molecule in a distorted square-pyramidal coordination. The enzyme exists in three well-defined oxidation levels: the EPR-silent active form (cupric ion antiferromagnetically coupled to the equatorial tyrosyl radical), an intermediate form, and the reduced copper(I) form [Eq. (1)].

$$\mathrm{Cu^{II}-Tyr^{+\cdot}} \overset{e^-}{\rightleftharpoons} \mathrm{Cu^{II}-Tyr} \overset{e^-}{\rightleftharpoons} \mathrm{Cu^{I}-Tyr} \qquad (1)$$

The axial tyrosine group is involved in protonation–deprotonation processes during the catalytic cycle (Scheme 1b).

Among the structural models of the active site of GOase described,[3] only a few contain two phenolic arms and involve the $[N_2O_2]$ copper coordination sphere of the enzyme.[4] Some of the functional models of GOase involve salen-type ligands and exhibit interesting catalytic activity only with activated alcohols as substrates.[5] The best results have been obtained by Wieghardt et al. with a very nice set of complexes in which the redox chemistry during the catalytic cycle is ligand-based.[6–7] Another interesting model developed by Wieghardt and co-workers involves true GOase chemistry but is not, strictly speaking, a structural model.[8]

We have previously described a model, unfortunately not functional, involving an axial phenoxyl radical associated with a $\mathrm{Cu^{II}}$ center possessing a $[N_2O_2]$ coordination sphere. It was built from a tripodal ligand (Scheme 1a).[9] With a model close to ours, the phenoxyl radical species was obtained spontaneously by disproportionation.[10]

We present here a structural and functional model of galactose oxidase. Our strategy was based on the differentiation of the two phenolic arms in the tripodal ligand

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