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Synthesis of Diyne Substituted 2-Hydroxy Acids, Esters, and Amides

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A series of diyne substituted 2-hydroxy acids and derivatives have been prepared and characterized. Alkylation of butane-2,3-diacetal protected glycolic acid with haloalkyl substituted diyne compounds gave the corresponding diacetal protected diyne substituted 2-hydroxy acids. Diacetal deprotection through acid mediated hydrolysis, transesterification, or aminolysis afforded the 2-hydroxy-diyne acid, ester, or amide derivatives, respectively. A novel class of polydiacetylenes was produced through topochemical polymerization of a 2-hydroxy diyne acid and compared with the polymerization of non-hydroxylated diyne acids.

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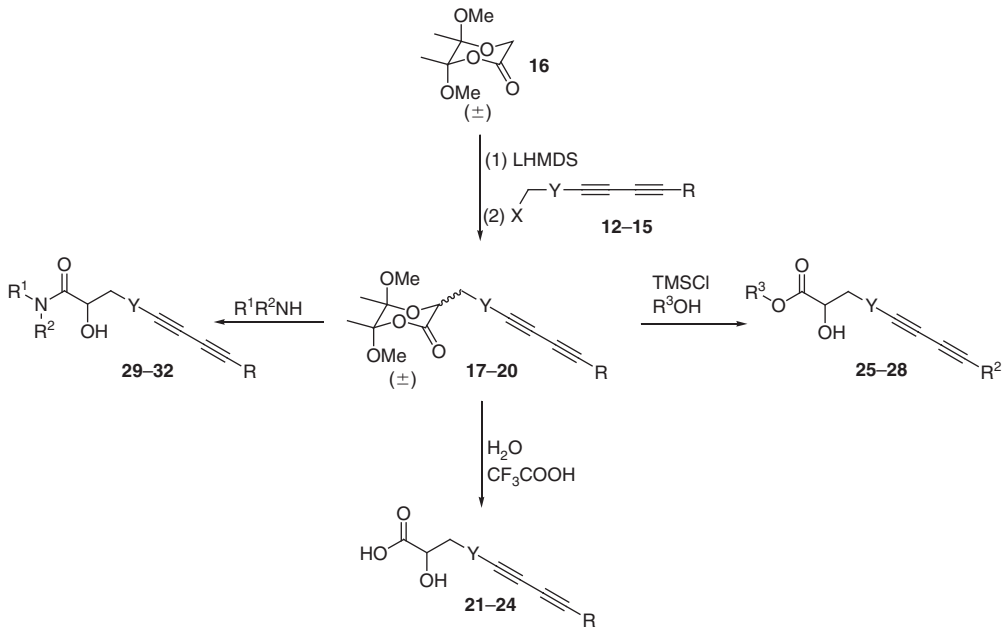
Alpha or 2-hydroxy fatty acids comprise a unique class of compounds found to occur in a variety of organisms. In vertebrates, they occur primarily in brain tissues, skin, and nerve tissues[1,2] but they are also found in many other organisms such as marine sponges,[3,4,5] crustaceans,[6] sea urchins,[7,8] earthworms,[9] starfish,[10] sea cucumbers,[11] plant leaves,[12,13] and bacteria including spirillum,[14] thiobacillus,[15] *Escherichia coli*,[16] and many others.[16–18] The 2-hydroxy-carboxylic acid motif is present in many pharmacologically important compounds.[19]

As a part of our ongoing studies into diyne-containing molecules we recognized a hitherto unreported class of 2-hydroxy-diyne acids and derivatives.[20] Conjugated diacetylenic compounds and their topochemical polymerization[21] in the solid state to form polydiacetylenes (PDAs) have been the subject of intense study since it was first reported by Wegner in 1969.[22] PDAs have now been incorporated into a wide variety of chemical systems, including silica nanocomposites,[23] silver-coated vesicles,[24] liposomes,[25,26]



Scheme 1. Synthesis 2-hydroxy diyne acid, esters, and amides.

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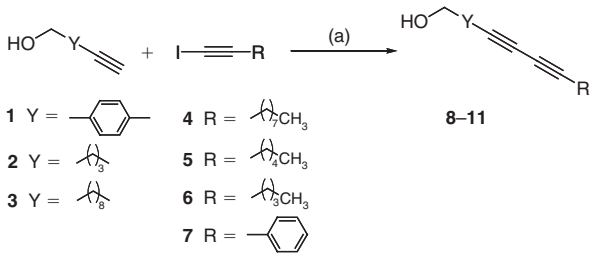

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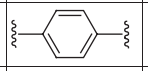
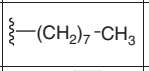
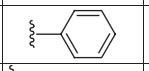
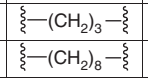
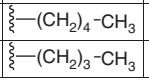
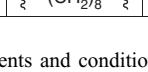
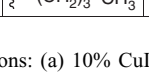
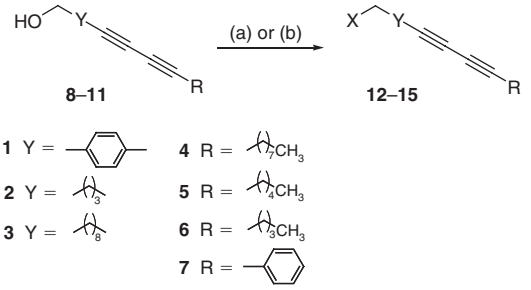
8			43
9			63
10			60
11			87

Scheme 2. Reagents and conditions: (a) 10% CuI, pyrrolidine, 30 min, 20°C.



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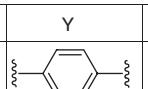
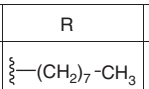
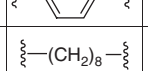
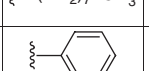
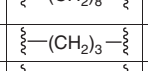
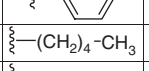
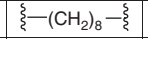
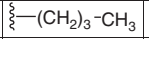
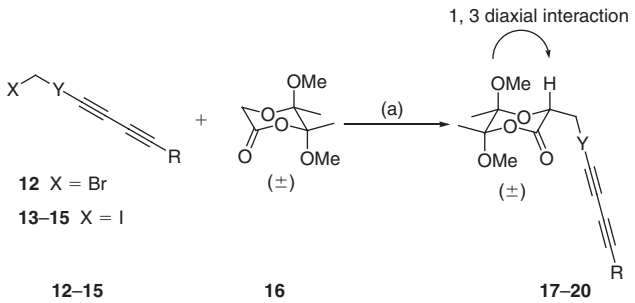
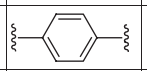
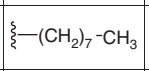
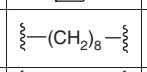
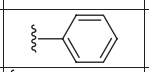
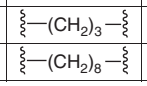
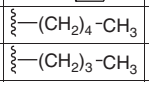
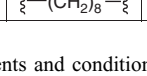
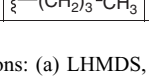
12			Br	85
13			I	61
14			I	93
15			I	92

Scheme 3. Reagents and conditions: products **13**–**15** (a) PPh_3, imidazole, I_2, CH_2Cl_2, 1 h, −10°C, product **12** (b) Ph_3PBr_2, pyridine, CH_3CN, 1 h, 0°C.



Product	Y	R	Yield [%]
17			88
18			39
19			39
20			42

Scheme 4. Reagents and conditions: (a) LHMDS, RX (**12**–**15**), AcOH, 3 h, −78°C to 20°C.

thin films,[27] gels,[28] and nanowires[29] among many others. The PDA applications currently under development cover fields such as chemosensors,[30] biosensors,[31,32] picosecond photoswitches,[33] micropatterning,[34] and strain sensors.[35]

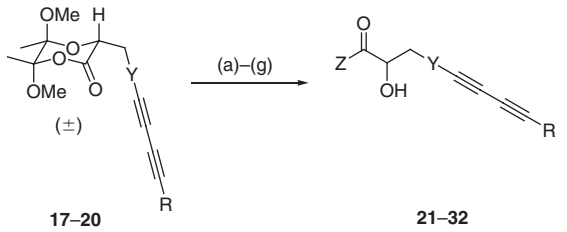
The polymerization of the conjugated diyne units requires the ordered packing of the diyne monomers to present the acetylenic moieties in an appropriate spatial arrangement in order to promote an efficient reaction. Such monomers typically have end groups (such as carboxylic acids) that facilitate the alignment of the monomers so that the required packing is achieved.[36,37] The hydrogen bonding ability of the α-OH acid motif present in 2-hydroxy-diyne acids has not previously been investigated for this application and is expected to enhance the self assembly of these diyne compounds, and lead to polymers with improved properties. The increased activity in the patent literature with respect to PDAs demonstrates the demand for novel and versatile PDAs and other innovative approaches to the pre-organization necessary for topochemical polymerization of the monomers have been produced.[38]

Diyne substituted 2-hydroxy acids and derivatives have previously not been described in the open literature. One of the most commonly adopted strategies for the 2-hydroxylation of unsaturated acids is the direct oxidation of enolate anions.[39] Our initial attempts to directly hydroxylate diyne acids via direct oxidation of the enolate anion were unsuccessful, as the sensitive diyne functionality is not stable under the highly basic conditions generally required for the deprotonation step. To avoid degradation of the diyne moiety and to allow easy access to ester and amide derivatives we adapted an approach described by Ley et al.[40] for the synthesis of 2-hydroxy acids. In the following we describe the efficient synthesis of novel 2-hydroxy diyne acid, ester, and amide derivatives (Scheme 1), as well as results of the initial polymerization experiments with one of the 2-hydroxy acid diyne products.

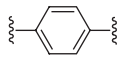
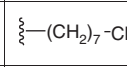
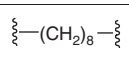
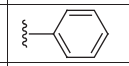
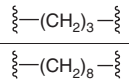
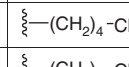
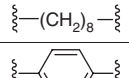
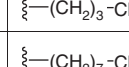
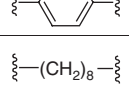
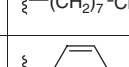
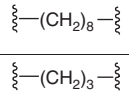
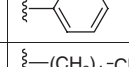
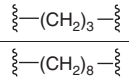
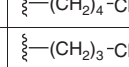
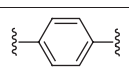
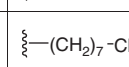
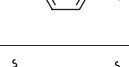
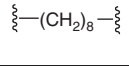
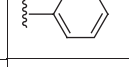
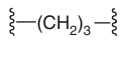
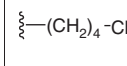
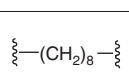
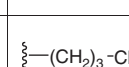
A modified Cadiot–Chodkiewicz reaction[41] of commercially available terminal alkynols **1**–**3** with 1-iodoalkynes **4**–**7**[42,43] afforded diyne alcohols **8**–**11**, isolated in 43–87% yields (Scheme 2).

Effective alkylation of the butane-2,3-diacetal of glycolic acid has previously been achieved with iodoalkanes (such as 1-iodo-butane) or benzyl bromide. The alcohols **8**–**11** were therefore converted into halides **12**–**15** with 61–93% yields (Scheme 3), following the procedures of Sandri et al.[44] and Liu et al.[45,46]

Protected glycolic acid **16** was deprotonated with lithium bis(trimethylsilyl)amide (LHMDS) (1.05 eq.) in THF at −78°C[47] and the corresponding anion of **16** alkylated with halo-diyne compounds **12**–**15** to give the protected hydroxy acid diynes **17**–**20**, isolated in 39–88% yields (Scheme 4). ^{1}H-NMR and ^{13}C-NMR spectroscopy performed on the products of these reactions indicated that in all cases only one diastereoisomer was formed. The stereochemistry of the phenylene linked product **17** was examined in detail using a NOESY experiment. The results showed that a 1,3-diaxial interaction occurred between the 5-methoxy group and the proton in position 3, demonstrating that the substituent bearing the diyne is equatorial.[40]



17–20 **21–32**

Product	Y	R	Z	Yield [%] (Conditions)	Overall yield*
21				93 (a)	30
22				93 (a)	14
23				91 (a)	20
24				91 (a)	31
25				95 (b)	31
26				86 (c)	14
27				96 (d)	21
28				95 (b)	32
29				47 (e)	15
30				83 (f)	28
31				78 (g)	17
32				73 (g)	11

Scheme 5. (a) (**21**–**24**) CF_3COOH/H_2O, 20°C; (b) (**25**, **28**) HCl, MeOH, 20°C; (c) (**26**) HCl, *i*-PrOH, reflux; (d) (**27**) HCl, EtOH, 50°C; (e) (**29**) benzylamine, 20°C, then TFA/H_2O; (f) (**30**) morpholine, 20°C, then TFA/H_2O; (g) (**31**, **32**) 2-methyl-propaneamine, 20°C, then TFA/H_2O. *Based on **1**, **2**, or **3**.

Diastereoselective alkylation of the protected glycol **16**, by long and highly unsaturated alkyl halides like **12**–**15** has not been previously reported, however, the results observed here are consistent with those obtained with shorter chain halides.[40]

The subsequent diacetal deprotection was accomplished as shown in Scheme 5. Acid catalyzed hydrolysis yielded 2-hydroxy-diyne acids **21**–**24** in 91–93% yields and high purity, after aqueous workup. Removal of the protecting group through transesterification was carried out with methanol (room temperature), ethanol (50°C), or isopropanol (80°C) giving the esters **25**–**28** in 86–96% yields. None of the products obtained through hydrolysis or transesterification required further purification. Aminolysis reactions were carried out in neat benzylamine, 2-methyl-propanamine, or morpholine. The desired amides **29**–**32** were obtained in 47–83% yields.

As indicated above, 2-hydroxy substituted diyne acids **21**–**24** are expected to self assemble into a unique two-dimensional packing array comprising a series of stacked one-dimensional sheets. In order to determine if the 2-hydroxy substituent on these long chain diyne compounds enhances the topochemical polymerization reaction, an experiment with the 2-hydroxy-diyne acid **23** was performed where several single crystals of **23** were prepared, as outlined in the Accessory Publication, and exposed to UV radiation at 254 nm. After a few seconds the crystals turned a deep blue colour, indicating that the polymerization of the diacetylene groups had occurred. By comparison, similar polymerization experiments with non-hydroxylated diyne acids produced less intense colour changes and required longer irradiation times. The hydrogen bonding function of the α-OH substituent thus does appear to enhance the self assembly and subsequent polymerization of these compounds. However, X-ray crystallographic investigations aimed at investigating the unique multi-dimensional packing arrangements of **21**–**24** have been unsuccessful due to the facile thermal polymerization of these compounds at room temperature.

Summary

We have described a convenient, high yielding, and stereoselective methodology for the preparation of 2-hydroxy-diacetylenic

compounds **21**–**32** through the hydrolysis, transesterification, or aminolysis of diacetal protected 2-hydroxy-diyne acids **17**–**20**. These diacetals can be readily synthesized through the alkylation of a butane-2,3-diacetal protected glycolic acid **16** with conjugated diyne halides **12**–**15**. Preliminary investigations with **23** have shown that the presence of the 2-hydroxy substituent significantly enhances its topochemical polymerization. This effect is being further investigated and results of these studies will be reported in due course.

Accessory Publication

Full experimental details and characterization data for all new compounds are available on the Journal's website.

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[46] The conversions into the halides were carried out under very mild conditions, which had no impact on the sensitive diyne functionality.
[47] After 15 min the reaction mixture was warmed to −50°C to −40°C, prior to addition of the halo-diyne compounds. The excess of base did not lead to dialkylation of **16** and had no impact on the sensitive diyne functionality of our electrophiles. The slightly increased temperature was necessary to avoid the precipitation of the halides in the reaction mixture at −78°C.