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A Highly Efficient Chain-Extension Process in the Systematic Syntheses of Carotenoid Natural Products**

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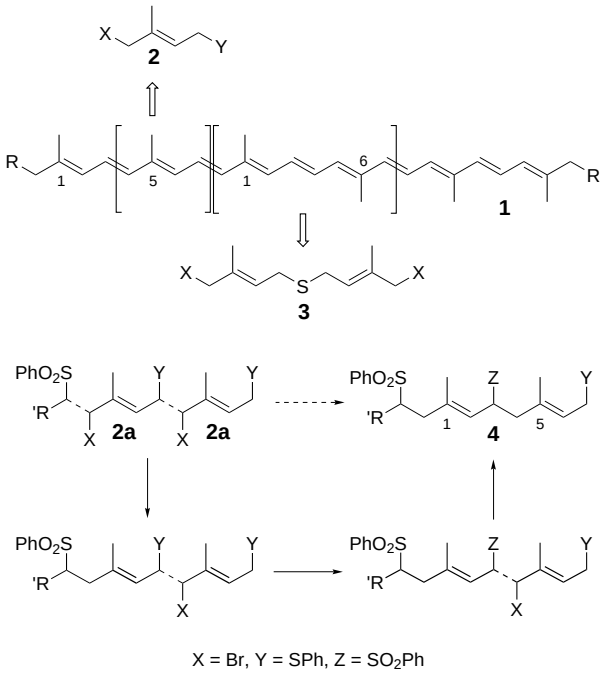
Dedicated to Professor Masato Koreeda on the occasion of his 60th birthday

Nature adopts isopentenyl pyrophosphate (IPP) or dimethylallyl pyrophosphate (DMAP) as building blocks for de novo syntheses of various isoprenoids, such as terpenoids, steroids, and carotenoids.[1] Enzymatic assembly of these basic C_5 units provides a diverse range of natural products. We are currently searching for such a mimic for IPP or DMAP in the chemical syntheses of isoprenoids, especially for carotenoids,[2] which show antioxidant activities for low-density lipoprotein and which are widely used as natural pigments. Certain carotenoids, such as lycopene,[3] also lower the propensity for humans to develop prostate cancers.

Carotenoids **1** have the general structure of two consecutive methyl groups attached to a conjugated polyene chain in either a 1,5 or 1,6 arrangement (Scheme 1). The symmetrical



Scheme 1. Generalized disconnection of the carotenoid structure **1** into the chain-extension unit **2** and the chain-termination unit **3**, as well as the proposed chain-extending process by repeated use of **2a**.

carotenoid structure can be divided into three parts for a systematic construction of such compounds: the chain-initiating unit, the chain-extending unit, and the chain-terminating unit. The Julia sulfone olefination protocol[4] is a perfect methodology to put the three components together, and allylic sulfone compounds were thus selected as the initiating unit. It was envisioned that bifunctionalized C_5 prenyl compound **2** might be an efficient chemical mimic for IPP or DMAP as a chain-extending unit, insofar as X is a good leaving group and Y can be easily transformed to a sulfonyl group. The carbanion-stabilizing ability of Y should be much less than that of the sulfonyl group of the chain-initiating unit to prevent the unfavorable base-promoted halide elimination process from occuring in compound **2**. It was thus appropriate to use 4-bromo-3-methyl-2-butenyl phenyl sulfide **2a** (X = Br, Y = SPh in **2**) to meet the above criteria. Repeated use of this chain-extending unit **2a** with each additional oxidation step to produce the corresponding sulfone would then produce the required 1,5-dimethyl-substituted carbon skeleton, such as structure **4**. This compound could accomplish the chain-extension process. We have already demonstrated that bis(haloallylic) sulfide **3** is a stable substitute for highly unstable 1,8-dihalo-2,7-dimethyl-2,4,6-octatriene in β-caro-

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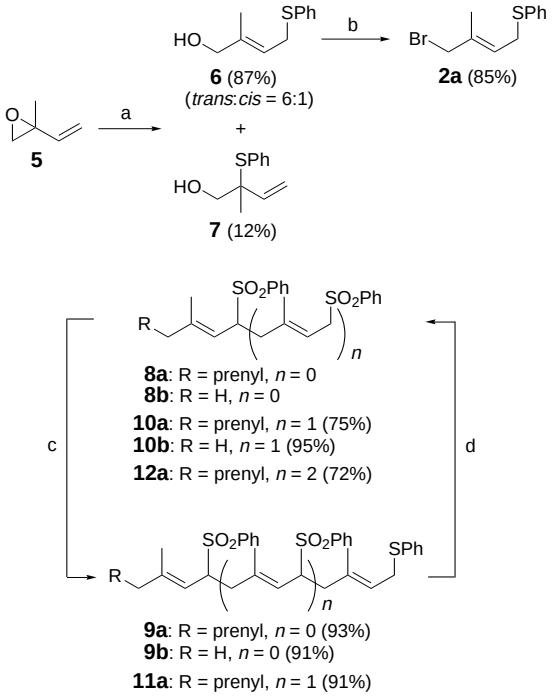
tene synthesis,[5] and it could serve as the chain-terminating unit in carotenoid syntheses.

Contrary to the easily obtainable chain-initiating allylic sulfones, not much chemistry has been known for 4-hydroxy-3-methyl-2-butenyl phenyl sulfide (**6**),[6] which is an apparent precursor to **2a** as a chain-extension unit. We herein report a highly efficient and practical method of synthesizing **6** by a Cu^I-catalyzed opening reaction of isoprene monoxide (**5**) with benzenethiol in DMF (Scheme 2). The use of the Cu^I salt and

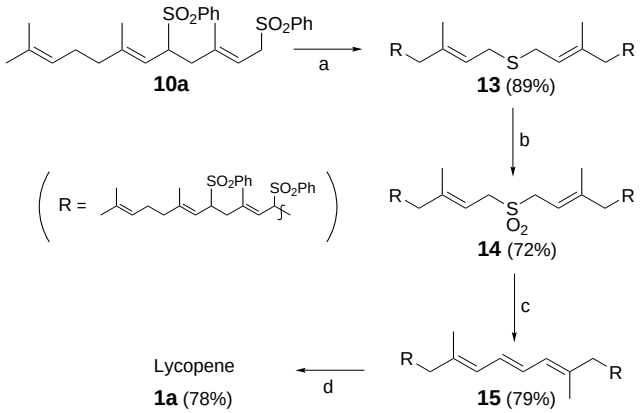


Scheme 2. The chain-extension process: preparation of the chain-extension unit **2a** and the chain-extended allylic sulfones **10** and **12**. Reaction conditions: a) PhSH and CuI (0.025 equiv) in DMF, b) PBr_3 in diethyl ether, c) *n*BuLi in THF at $-78\,^\circ C$ then **2a**, d) $LiNbMoO_6$ (0.05 equiv) and H_2O_2 (2.5 equiv) in MeOH.

DMF in this epoxide-opening reaction was crucial in that the allylic opening product **6** was obtained as the major product (87%) with a high *trans* selectivity (6:1 *trans:cis*). A small amount (12%) of the side product **7**, which arose from the opening at the more-substituted carbon end of epoxide **5**, was also obtained. Hydroxyallylic sulfide **6** was then easily converted into **2a** (85%) with PBr_3.

The chain-extension process by repeated use of **2a** has proven to be highly efficient and practical (Scheme 2). The carbanions of readily available allylic sulfones of geranyl **8a** and prenyl **8b** coupled with **2a** to produce the chain-extended thio–sulfone compounds **9a** (93%) and **9b** (91%), respectively, in excellent yields. Subsequent oxidation of the sulfur atom with the composite metal oxide catalyst $LiNbMoO_6$[7] and H_2O_2 produced the corresponding disulfones **10a** (75%) and **10b** (95%) without any formation of the undesirable, but expected, epoxidation products. The initiating allylic sulfones have been elongated by five carbon atoms by this reaction sequence. This procedure was then repeated for disulfone **10a** to provide trisulfone **12a** (72% from **11a**) via thio–disulfone **11a** (91%). This process can be repeated many times to reach the required number of carbon atoms in the allylic sulfone units.

The chain-extended allylic sulfones can couple with the chain-terminating bis(haloallylic) sulfide **3** to give rise to the required carbon skeletons for various carotenoid syntheses. As an example, the chain-elongated allylic disulfone **10a** from geranyl sulfone **8a** coupled with bis(bromoallylic) sulfide **3** to provide compound **13** which was required for the synthesis of lycopene (**1a**; Scheme 3). The dianion of disulfone **10a** was



Scheme 3. A representative example of carotenoid syntheses by coupling the chain-extended allylic sulfone **10a** and the chain-terminating bis(bromoallylic) sulfide **3**: synthesis of lycopene. Reaction conditions: a) *n*BuLi (2 equiv) in THF at $-78\,^\circ C$ then **3** (X = Br, 0.5 equiv), b) $LiNbMoO_6$ (0.05 equiv) and H_2O_2 (2.5 equiv) in MeOH, c) KOH in *t*BuOH and CCl_4, d) NaOEt in refluxing EtOH.

generated by the addition of *n*BuLi (2 equiv) at $-78\,^\circ C$ in THF and then treated with **3** (0.5 equiv) at that temperature to give **13** in 89% yield. It only required several functional-group transformations to obtain a fully conjugated carotenoid polyene chain **1** from the coupling product **13**. The central sulfur atom of **13** was oxidized to a sulfone (72% yield) by the composite metal oxide ($LiNbMoO_6$) and H_2O_2 oxidant system. A Ramberg–Bäcklund reaction[8] on the resulting diallylic sulfone unit of **14** provided the conjugated triene moiety at the center of **15** (79% yield). A base-promoted (EtONa/EtOH) elimination of the four sulfonyl groups[9] in **15** then produced the fully conjugated polyene chain, lycopene (**1a**), in 78% yield.[10]

In conclusion, we have developed a general synthetic method for the carotenoid polyene chain structure **1** which highlighted the use of 4-bromo-3-methyl-2-butenyl phenyl sulfide (**2a**) as a chain-extension unit in the Julia sulfone olefination reaction. We also demonstrated the usefulness of bis(haloallylic) sulfide **3** as a chain-termination unit and as a stable substitute for the highly unstable α,ω-dihalotriene. This polyene chain synthesis, which was exemplified for lycopene, is sufficiently general to be utilized for the synthesis of any carotenoid structure. Furthermore, this concept may well be applied to the syntheses of conducting organic compounds comprising a fully conjugated polyene chain.

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Dehydrogenation of $[\{(silox)_3Nb\}_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-}C_8H_8)]$ (silox = *t*Bu_3SiO) to $[\{(silox)_3Nb\}_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-}C_8H_6)]$ and Its Subsequent Alkene-to-Alkylidene Rearrangement**

Adam S. Veige, Peter T. Wolczanski,* and Emil B. Lobkovsky

The observed pyridine ring-opening of $[(silox)_3Nb(\eta\text{-}C,N\text{-}C_5H_5N)]$ (silox = *t*Bu_3SiO) to $[(silox)_3Nb{=}CHCH{=}CHCH{=}CHN{=}Nb(silox)_3]$, and related picoline chemistry[1, 2] suggested that carbon – carbon bond scission might occur by similar pathways. 1,3,5,7-Cyclooctatetraene (COT) was considered a prime candidate for ring opening because of its lack of resonance stabilization energy, but in binding to two $[(silox)_3Nb]$ units, COT functions as an aromatic dianion, which directs the chemistry toward C–H bond activation, dehydrogenation, and a subsequent alkene-to-alkylidene rearrangement.

Reduction of $[(silox)_3NbCl_2]$ (**1**)[3] with Na/Hg in THF with three equivalents of COT present resulted in the isolation of brown $[(silox)_3Nb(\eta\text{-}C_8H_8)]$ (**2**-COT, 40 %) [Eq. (1)].

$$[(silox)_3NbCl_2] + L\ (\text{excess}) \xrightarrow[Na/Hg,\ -2\,NaCl]{THF,\ 24\,h} [(silox)_3NbL] \qquad (1)$$
$$\mathbf{2}\text{-L}\ (L = COT,\ cC_6H_{10})$$

Abstraction of 4-picoline from $[(silox)_3Nb(\eta\text{-}C,N\text{-}4\text{-}MeC_5H_4N)]$ (**2**-4-pic) by $[(silox)_3Ta]$[2] in the presence of **2**-COT afforded $[(silox)_3Ta(\eta\text{-}4\text{-pic})]$ and burgundy, crystalline $[\{(silox)_3Nb\}_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-}C_8H_8)]$ ($\mathbf{2}_2$-COT, 33 %, Scheme 1). The synthesis of $\mathbf{2}_2$-COT must occur under mild conditions to avoid further reaction (vide infra). An X-ray crystal structure determination of $\mathbf{2}_2$-COT[4, 5] revealed the $[(silox)_3Nb]$ moieties (d(Nb–C) = 2.20(5) Å (av))[6, 7] in an *anti*-η^2,η^2-configuration about a planar COT ligand, although disorder problems hampered further analysis. The insolubility of $\mathbf{2}_2$-COT in unreactive hydrocarbon solvents prevented spectral characterization.

Upon thermolysis of two equivalents of $[(silox)_3Nb(\eta\text{-}C,N\text{-}4\text{-}MeC_5H_4N)]$ (**2**-4-pic) and COT, **2**-COT and presumably $\mathbf{2}_2$-COT were generated in situ, and dehydrogenation led to the gold-brown cyclooctatrieneyne[8] complex, $[\{(silox)_3Nb\}_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-}C_8H_6)]$ (**4**; Scheme 1). Although **4** was isolated in 50 % yield, ^{1}H NMR spectroscopy revealed the conversion to be > 95 % when the reaction was monitored in a sealed tube (C_6D_6). Olefin substitution reactions of **2**-4-pic, such as the synthesis of the 1-butene complex, $[(silox)_3Nb(\eta^2\text{-}C_4H_8)]$ (**2**-

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