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Enyne-2-pyrone [4 + 4]-Photocycloaddition: Sesquiterpene Synthesis and a Low-Temperature Cope Rearrangement

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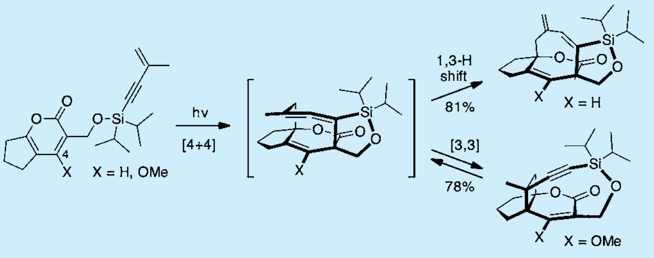
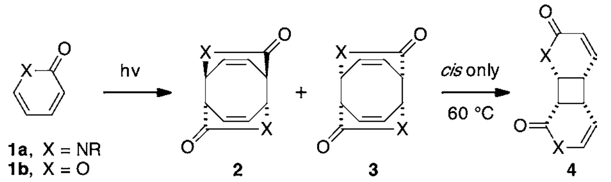
Ⓢ *Supporting Information*

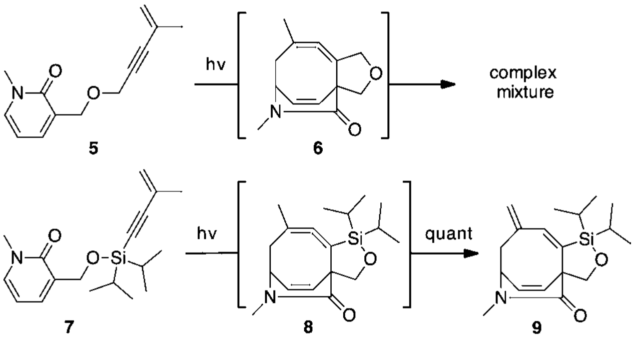
ABSTRACT: Intramolecular [4 + 4] photoreaction of 2-pyrones with a 1,3-enyne yields an unstable 1,2,5-cyclooctatriene product. Without a C4 pyrone substituent, 1,3-hydrogen migration converts the allene to a 1,3-diene, with a skeleton related to dactylol. With methoxy substitution, Cope rearrangement yields a nine-membered ring fused to a cyclobutane. Both structures were confirmed by X-ray crystallography. The Cope rearrangement is apparently reversible, reforming the allene which undergoes a proton shift to the more stable 1,3-diene product.



Scheme 1. Pyridones and Pyrones Undergo [4 + 4] Head-to-Tail Dimerization



Scheme 2. Intramolecular Reaction of 2-Pyridones with Enynes[11,12]



The aromatic 2-pyridones (**1a**) and 2-pyrones (**1b**) are well-known for their ability to undergo regioselective, head-to-tail, [4 + 4] photodimerization, Scheme 1.[1−3] Photodimers **2a**/**3a** and **2b**/**3b** were described more than 50 years ago,[4,5] and both reactions have been extensively explored.[3,6] These [4 + 4]-photocycloadditions can be extended to reactions between **1** and other aromatics such as furan, naphthalene, and substituted benzenes.[7−9] The strain of the photoadducts **2** and **3** promotes a variety of rearrangement reactions, including low-temperature Cope rearrangement when the bridging lactones/lactams are cis (**3**).[5,10]

Recently we have turned our attention to the intramolecular photoreaction of 2-pyridones with enynes, reactions that lead to allene products with greater strain than **2** and **3** (Scheme 2).[11,12] When the resulting 1,2,5-cyclooctatriene product was relatively unhindered (**6**), intermolecular [2 + 2] dimerization of the 1,2,5-cyclooctatriene led to complex mixtures.[11] Steric shielding of the reactive allene, however, resulted in more stable photoproducts.[12] In the case of substrate **7**, the combination of diisopropylsilyl and methyl substitutions on initially formed **8** gave rise to a 1,3-hydrogen shift and transformation of the allene to the more stable 1,3-diene **9**.[12] Intrigued by this very efficient cycloaddition, we have explored the use of this enyne with other substrates and found it also reacts quantitatively with anthracene and naphthalene derivatives.[13] Our initial exploration of this chemistry with 2-pyrone substrates is described here.

An intramolecular reaction between a 2-pyrone and the enyne was anticipated to yield a lactone-bridged structure similar to the pyridone examples (Scheme 2) and thereby provide a straightforward route to a number of natural products. As outlined in Scheme 3, dactylol might be accessed via **10**, a product that would be formed by [4 + 4] photocycloaddition of **12** followed by a 1,3-hydrogen shift of intermediate **11**.[14] To study this possibility we elected to begin with pyrone **13**, without the C9 methyl substitution in **12** (dactylol numbering).

Readily available pyrone **14**[15] required only installation of a 3-hydroxymethyl group, and we elected to explore the photochemistry with and without the 4-oxygen substituent (Scheme 4). After *O*-methylation of **14** with methyl tosylate, we found that direct Rieche formylation proceeded in good yield

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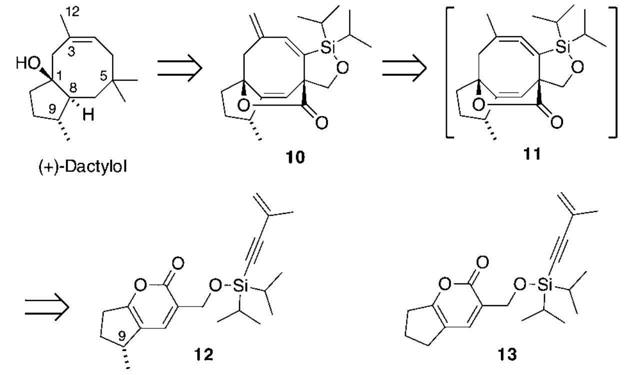
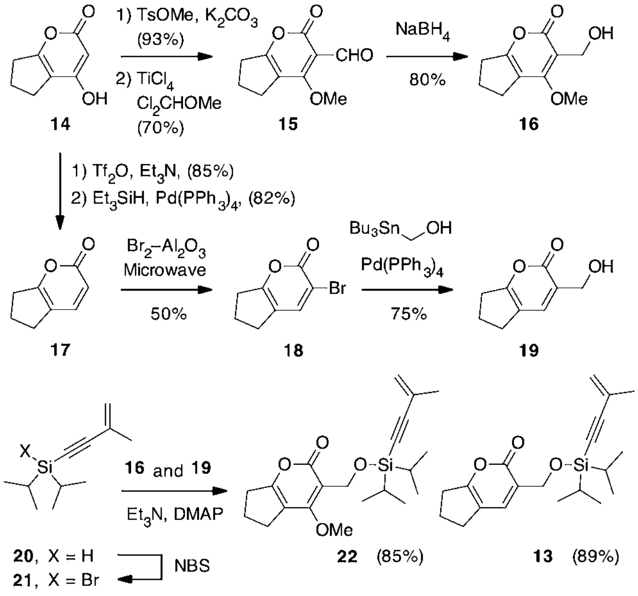
Scheme 3. (+)-Dactylol Synthesis Using 2-Pyrone−enyne Photocycloaddition



Scheme 4. Preparation of Cyclopentane-Substituted 3-Hydroxymethyl-2-pyrone Substrates 13 and 22

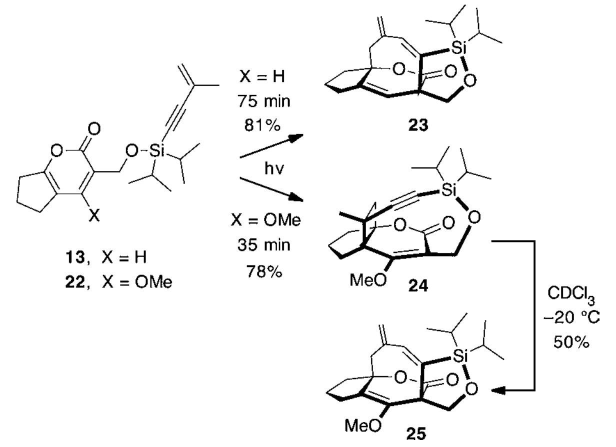


to give **15**.[16] Reduction of aldehyde **15** with sodium borohydride then gave the desired alcohol **16**. Removal of the 4-hydroxyl group of **14** to give **17** was readily accomplished by palladium-catalyzed reduction of the corresponding triflate. Bromide **18** was best prepared using Khanna's solvent-free method with bromine adsorbed on alumina and microwave activation.[17] Coupling of **18** with tributyl hydroxymethylstannane produced **19** in 75% yield.

The 3-hydroxymethyl-2-pyrones **16** and **19** were coupled with diisopropylsilyl enyne **20** using the protocol developed earlier (Scheme 4).[12] Treatment of **20** with NBS converted the silane to silyl bromide **21**. Addition of the alcohol, base, and DMAP gave the silyl ethers **13** and **22** in good yield.

With the pyrone−enyne substrates in hand, irradiation was conducted in benzene solution, using a medium-pressure mercury lamp and Pyrex filtration (Scheme 5). For pyrone **13**, irradiation for just over 1 h gave complete conversion of starting material. The desired 1,3-diene **23** was isolated as a single product in 81% yield, consistent with previously studied substrates.[12,13] In contrast, 4-methoxy pyrone **22** underwent a more rapid photoreaction, yielding only the apparent [2 + 2] adduct **24** in 78% yield. The structures of both products were confirmed by X-ray crystallography, Figure 1. Surprisingly, when the cyclobutane product **24** was allowed to stand at −20 °C in $CDCl_3$ it slowly converted to the desired triene **25**, which was isolated in 50% yield.

Scheme 5. Divergent Photochemical Results for 13 and 22



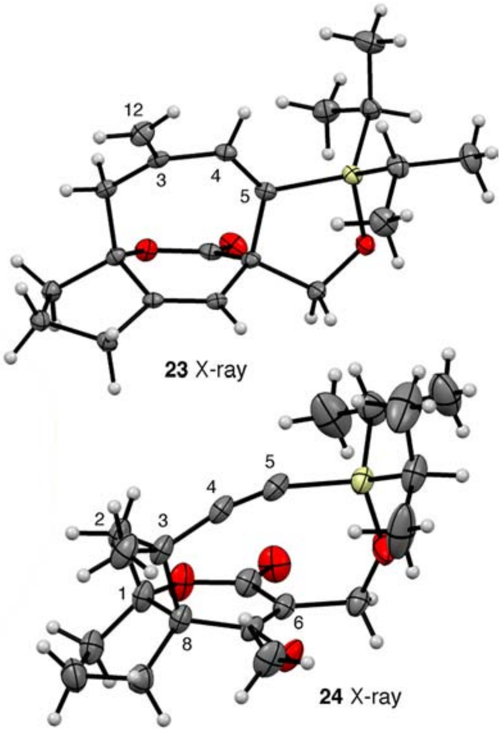


Figure 1. Crystal structures of **23** and **24** (dactylol numbering).

Several aspects of the crystal structures of **23** and **24** are notable (Table 1). For triene **23** the torsional angle about the central bond of the 1,3-diene is out of planarity by 35°. In the

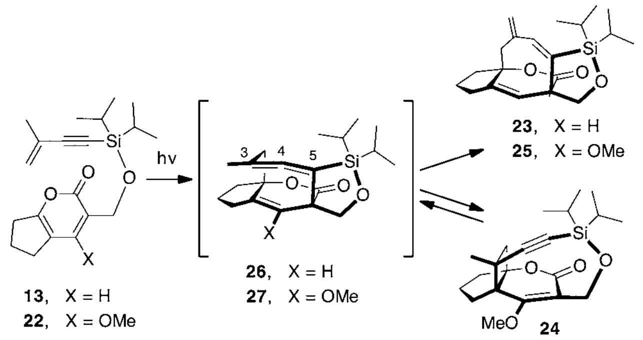
Table 1. Key Measurements from Crystal Structures of 23 and 24

structure	angle/distance	measurement
23	C12−C3−C4−C5	144.5°
24	C1−C2	1.537 Å
24	C3−C8	1.616 Å
24	C3−C4−C5	165.4°
24	C4−C5−Si	159.6°
24	C5−C6	3.108 Å

structure of **24**, the allylic−propargylic cyclobutane bond (C3−C8) was found to be long (1.616 Å) relative to the other three cyclobutane bonds (1.572, 1.537, and 1.570 Å). The alkyne is far from linear, with the C−C−C and C−C−Si bond angles differing from 180° by 25° and 30°, respectively.

The dichotomy observed for the photochemistry of **13** and **22**, as well as the conversion of **24** to triene **25**, may be explained by the transformations outlined in Scheme 6. It seems unlikely that a direct [2 + 2] cycloaddition between the remote pyrone alkene and the enyne alkene of **22** would lead to the clearly strained nine-membered ring found in structure **24**. It is possible that the photoreactions of both **13** and **22** lead initially to the [4 + 4] adducts **26** and **27**. In the case of **26**, this intermediate undergoes a 1,3-proton shift to yield the observed triene **23**, consistent with the analogous pyridone case in which **7** yields **9**, Scheme 2. In earlier studies, this proton shift was found to be a polar process.[12] Methoxy substituted **27**, instead of the proton shift, undergoes a Cope rearrangement to produce alkyne **24**. This Cope rearrangement is similar to, but much faster than, the Cope rearrangements observed for cis pyridone dimers **3** (Scheme 1).[10,18] It is tempting to speculate on the role of the enol of **27**, complementing the activation of the allene by the silicon and promoting formation of the cyclobutane bond of **24**. In most cases, electron-donating substituents lower activation barriers and accelerate [3,3] rearrangements.[19,20]

Scheme 6. A Mechanism for the Photochemical and Thermal Transformations of 13, 22, and 24



If the [3,3] rearrangement of allene **27** to alkyne **24** were reversible, one would expect that the intermediate **27** would eventually undergo an irreversible proton shift to yield the more stable triene **25**. The long cyclobutane bond found in the crystal structure of **24**, the rather close positioning of the carbons at the reactive ends of the enyne **24** (C5−C6, Table 1), and the distortion of the alkyne[21] are consistent with this postulated reversible Cope rearrangement. Substitution on these products is apparently delicately balanced, biased toward the unusual cyclobutane **24**.

Consistent with the proposed pathway between alkyne **24** and triene **25**, the transformation of **24** to **25** at 5 °C had an approximate half-life of 20 days (NMR). Heating the chloroform solution of **24** to ca. 60 °C led to complete conversion of **24** to **25** in less than 12 h.

Reversibility has been a cornerstone of the Cope rearrangement since its inception.[22] Reversible Cope rearrangements well below room temperature are exemplified by bullvalene and its congeners, which are based on the 1,2-divinylcyclopropane structure.[23,24] Rearrangement of **24** to **27** is much more facile than *cis*-1,2-divinyl cyclobutane, which requires 120 °C for Cope rearrangement.[25] Cope rearrangement of the 1,2,5-heptatriene unit found in **27** to give a 1,5-enyne (e.g., **24**) had been considered in our earlier enyne-pyridone photochemistry studies but was believed to be an unlikely pathway.[11] Huntsman demonstrated that the parent 1-hexen-5-yne underwent Cope rearrangement to give 1,2,5-hexatriene at 340 °C.[26] Computational studies suggest that these pathways do not require radical intermediates.[27,28]

To address the potential for an equilibrium between **24** and **27**, we calculated the heat of formation of the alkyne **24**, as found in the crystal structure, and compared it to that of the postulated allene intermediate **27**. Using B3LYP 6-31G*, alkyne **24** was found to be less stable than allene **27** by 2.4 kcal/mol.[29] While not addressing the transition state barrier for this transformation, the relatively similar energies of **24** and **27** are consistent with a reaction surface populating both species and providing an accessible intermediate **27** on a path to triene **25**. The triene **25** was also evaluated and found to be more than 17 kcal/mol lower in energy than alkyne **24** (see Supporting Information).

The bond lengths and angles calculated for structures **24** and **25**, Table 2, are very similar to those of the crystal structure (Table 1). The bend of the allene in **27** is also similar to the structures calculated for other eight-membered ring allenes.[30]

Table 2. Calculated Structure Measurements for 24, 25, and 27

structure	angle/distance	measurement	Δcalcd X-ray
24	C1−C2	1.546 Å	0.009 Å
24	C3−C8	1.636 Å	0.020 Å
24	C5−C6	3.129 Å	0.021 Å
24	C3−C4−C5	166.2°	0.8°
24	C4−C5−Si	160.1°	0.5°
25	C12−C3−C4−C5	142.2°	2.3°
27	C3−C4−C5	154.9°	−

Photocycloaddition of an enyne tethered through silicon to a 3-hydroxymethyl-2-pyrone gives a high yield of an eight-membered ring product **23**, derived from a [4 + 4] cycloaddition followed by a 1,3-proton shift of the allene intermediate, but this is only true in the case of the 4-unsubstituted pyrone. When the pyrone is 4-methoxy-substituted, only an apparent [2 + 2] adduct **24** is produced, also in very good yield. This structure has a nine-membered silyl ether ring with at least three points of strain, a cyclobutane bond, a bent alkyne, and a trans double bond. In solution this adduct slowly transforms to the originally anticipated 1,3-diene cyclooctanoid product **25**, a surprising reaction that is most easily explained as a consequence of a facile, reversible Cope rearrangement that regenerates an initial 1,2,5-cyclooctatriene intermediate and then undergoes a 1,3-proton shift to the more stable, 1,3-diene structure **25**.

Calculated energies of the three methoxy-substituted adducts, cyclobutane **24**, 1,3-diene **25**, and the postulated allene intermediate **27**, indicate that the allene **27** and the alkyne **24** are close in energy. A low energy barrier to interconversion of these two structures would provide a presence of the allene **27** and a pathway for transformation of **24** into **25** by a 1,3-proton shift of **27**. The 1,3-diene containing product **25** is calculated to be far more stable than either **24** or **27**, and therefore it is the thermodynamic well of the equilibria. Further studies of the rearrangements described here and the application of these chemistries to the synthesis of dactylol are currently under study.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02207.

Crystallographic data for **23** (CIF)
Crystallographic data for **24** (CIF)
Experimental details, spectra for new compounds, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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