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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7797–7799

Synthesis of the tetracyclic ring system of cumbiasin via tandem radical cyclizations

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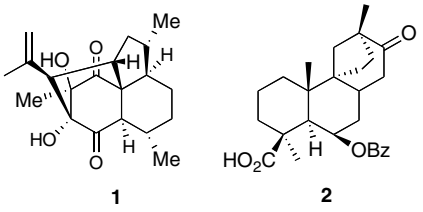
Received 1 June 2006; revised 21 August 2006; accepted 22 August 2006
Available online 15 September 2006

Abstract—The tetracyclic ring system of cumbiasin was synthesized by a Diels–Alder reaction followed by tandem ring forming reactions from an alpha-keto radical.

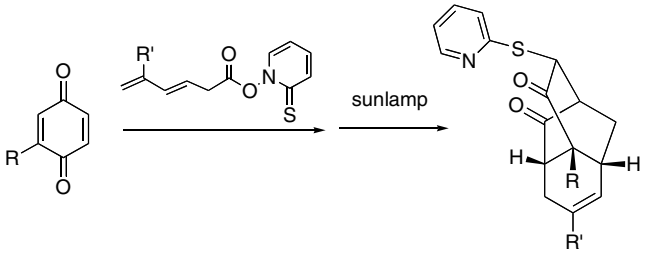
The structural diversity of polycyclic fused natural products has spawned a number of useful synthetic methods.[1–3] Among these methods, tandem reaction sequences have shown great potential to rapidly generate advanced synthetic intermediates.[4] Recently, natural products such as cumbiasin (**1**)[5] and scopadulcic acid (**2**)[6] have been discovered to have potentially useful biological activity. We describe herein an approach featuring sequential radical cyclizations that construct the tetracyclic ring system of **1** in a few steps.



1 **2**

We recently described a novel tandem Diels–Alder/radical cyclization protocol for the construction of bridged ring systems.[7] In this case, the radical precursor, a thiopyridyl ester, was located on the diene. We now describe a related strategy in which a Diels–Alder reaction is followed by two sequential radical cyclizations.

The initially conceived plan is illustrated below. A Diels–Alder reaction of quinone **3** with triene **4** is expected to produce **5**. The radical precursor X in **5** then gives rise to a radical that should cyclize to generate **6**.



Initially, we attempted to convert benzoquinone carboxylic acid into quinone **3** wherein X was a thiopyridyl ester. Unfortunately, all attempts to generate the thiopyridyl ester quinone led to decomposition products.

We next reacted commercially available 2,5-dibromobenzoquinone with enol ether **4** (R = OTMS). The reaction led to a deeply colored solution at subambient temperature from which no adduct could be isolated. Suspecting that electron transfer was intervening, we reacted 2,5-dibromobenzoquinone with the less electron-rich triene **4** (R = Me) and obtained adduct **7** in quantitative yield at 100 °C in toluene. Remarkably, no dehydrohalogenation occurred under these conditions.

Among the many radical cyclizations that have been reported, alpha-keto radical cyclizations comprise a relatively small subset.[8–11] All of the alpha-keto radical cyclizations wherein the carbonyl group is not part of the connecting chain proceed in a 5-exo manner, generating a single five-membered ring. Sha has utilized radical cyclizations onto trimethylsilylacetylenes to synthesize triquinanes and pinguisenol.[10,11] Radical

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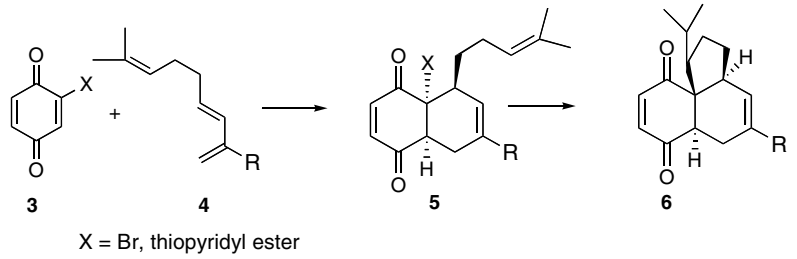
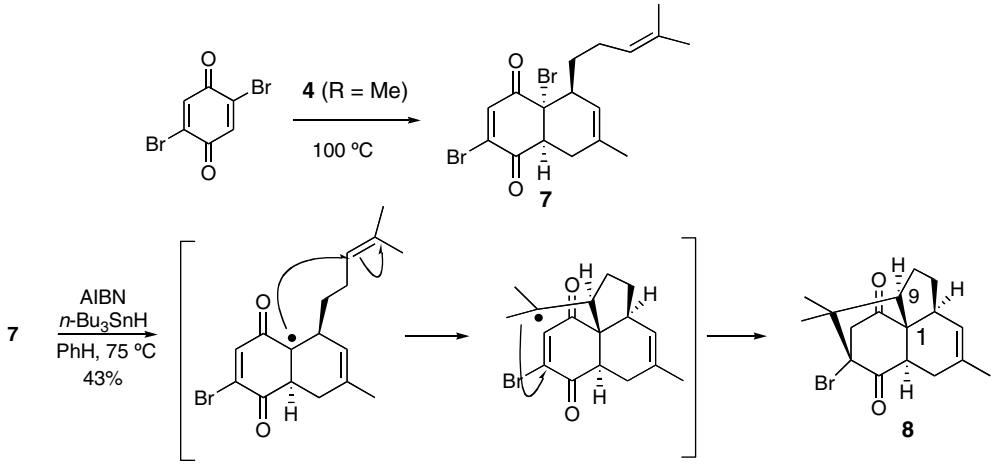
doi:10.1016/j.tetlet.2006.08.081



generation using tri-*n*-butyltin hydride and AIBN in boiling benzene afforded tetracyclic diketone **8** in 43% yield after silica gel chromatography. As expected, the vinyl bromide was much less reactive than the tertiary bromide in the radical generation step. Although proton NMR and ^{13}C NMR spectroscopy established the connectivity, the relative stereochemistry was ultimately determined by X-ray crystallography.

Reaction of **9** with 2,5-dibromobenzoquinone afforded adduct **10**. Because this adduct could not be purified by chromatography without significant dehydrobromination to a quinone, it was subjected to radical cyclization without purification. Adduct **11** was isolated by chromatography in 36% yield from **9**. Its structure was confirmed by X-ray crystallography.[13] Unfortunately, the undesired stereochemistry at C-9 was obtained.

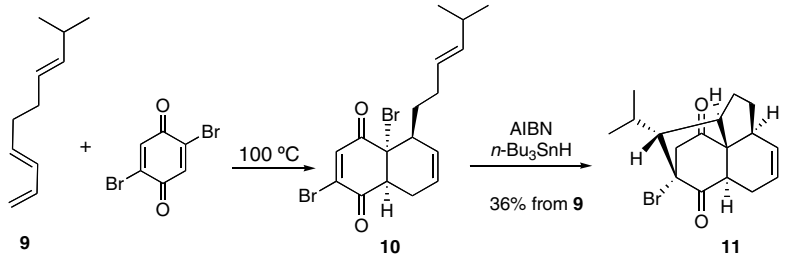


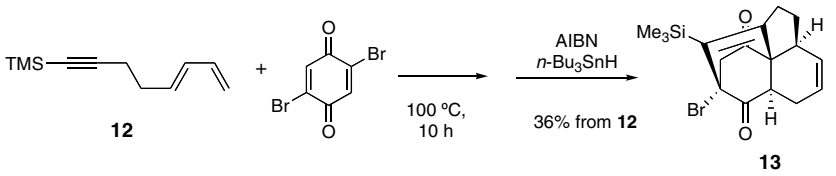
The cis-fused stereochemistry of the newly formed five-membered ring in **8** was anticipated. However, the stereochemistry at C-9 (cumbiasin numbering) was unexpected. Interestingly, the radical formed after the 5-exo-trig cyclization with the *desired* stereochemistry at C-9 appeared to be less sterically hindered than the radical which led to the formation of **8**. The observed stereochemistry in **8** is likely the result of kinetic control.

We then generated triene **9** by a Wittig reaction with readily available[12] 4,6-heptadienal. This triene had an alkene radical acceptor that would cyclize to produce an analog closer in structure to the cumbiasin skeleton.

In order to circumvent the stereochemical problems, we employed an alkyne in the radical cyclization. This would allow us to introduce the desired C-9–C-10 stereochemistry later in the synthesis by hydride addition to an enone. To this end, diene **12** was synthesized from 6-bromo-1,3-hexadiene[14] by reaction with the anion of trimethylsilylacetylene. A Diels–Alder reaction of diene **12** with 2,5-dibromobenzoquinone furnished an adduct that was taken directly to the radical cyclization step because it decomposed upon chromatography. Vinyl silane **13** was isolated in 36% yield from **12**.

The Diels–Alder/sequential radical cyclization sequence described herein, rapidly generates three rings with four





new stereogenic centers. The use of an acetylenic silane preempts stereochemical problems described above and provides a vinyl silane from which an unsaturated ketone can later be generated.

Acknowledgment

We thank the Iowa State University Institute for Physical Research and Technology for financial support.

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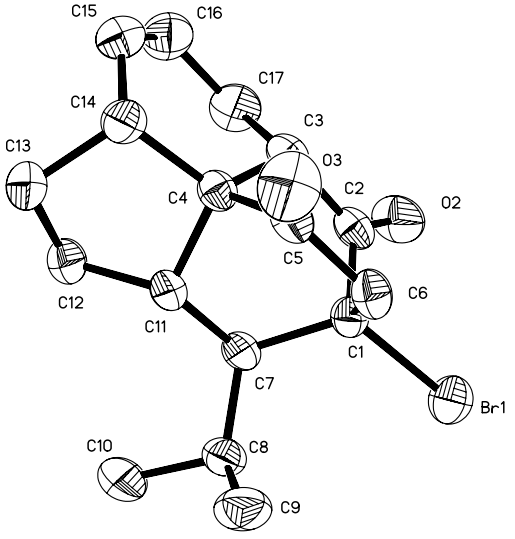

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