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A 4+3 Cycloaddition Approach to the Synthesis of (±)-Sterpurene

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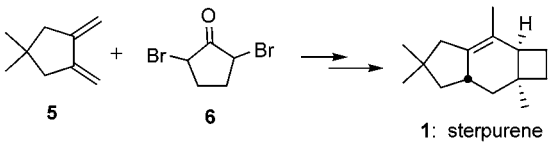
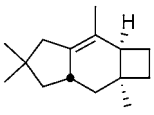
ABSTRACT



A synthesis of the sesquiterpene sterpurene is presented. Key steps include a 4+3 cycloaddition reaction and a quasi-Favorskii rearrangement.

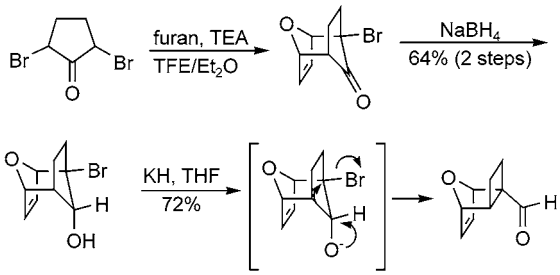
In the 1980s, Ayer reported the isolation of a new class of sesquiterpenes, the sterpuranes.[1] These compounds were isolated as metabolites of the fungus *Chondrostereum perpureum.* This fungus is widespread in North American



forests and fruit orchards and is known to cause the "silver leaf" disease. Known for its silvering effect of leaves, it can lead to the death of the host tree. More recently, similar metabolites were found from *Gloephyllum sp. 97022*, a fungus that causes brown rot of the colonized wood.[1g] These metabolites all have the same cyclic skeleton as represented by sterpurene (**1**). Since its reported isolation in 1981,[1a] there have been a variety of syntheses of sterpurene, which include studies on the biomimetic route,[1d−e,2] and some novel syntheses based on unique methodologies.[3]

Recently, we introduced a reaction sequence involving the 4+3 cycloaddition of a cyclic, halogenated oxyallylic cation followed by a quasi-Favorskii rearrangement of the resultant cycloadduct.[4] In the case of dibromocyclopentanone, the overall sequence results in the formation of a cyclobutane-containing structure, as illustrated in Scheme 1. We applied

Scheme 1



this cycloaddition/quasi-Favorskii rearrangement methodology to the formal total synthesis of spatol.[5]

In an effort to expand the scope of this process, we decided to explore a synthesis of sterpurene, using our methodology to construct six- and four-membered rings of the target. A retrosynthesis of sterpurene based on this approach is shown in Scheme 2.

The diene (**5**) needed for the cycloaddition process was prepared as shown in Scheme 3. We began with diazotiza-

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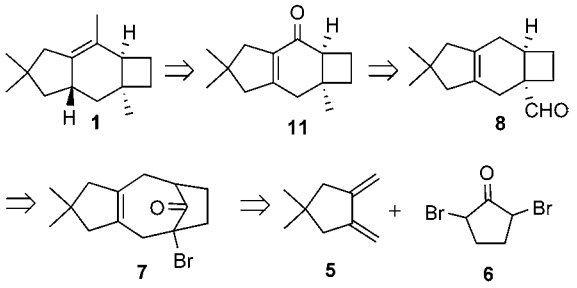
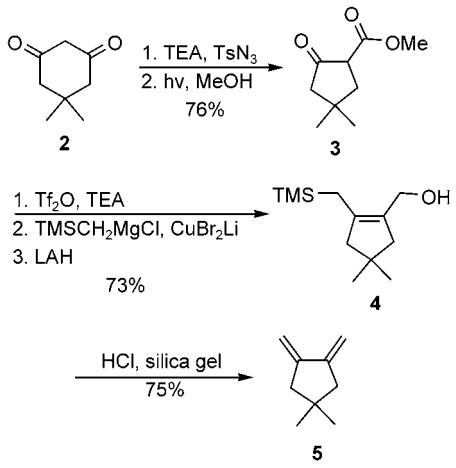
Scheme 2



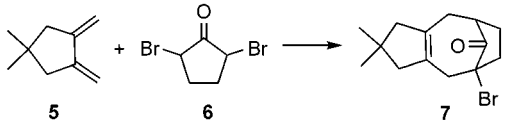
tion[6] of commercially available dimedone (**2**). This was then photolyzed in methanol to give the β-ketoester **3** in a 76% yield via a Wolff rearrangement.[7] Treatment with triethylamine and triflic anhydride yielded the vinyl triflate, which was then coupled with trimethylsilylmethyl cuprate[8] and reduced to afford the alcohol **4** in 73% overall yield. The alcohol **4** was then treated with acidic silica gel to provide the diene **5** in 75% yield via a vinylogous Peterson olefination.[9]

Scheme 3



In an effort to optimize the 4+3 cycloaddition step of **5** and 2,5-dibromocyclopentanone (**6**),[10] we investigated several alternative conditions (Table 1). These reactions were conducted with between 1.1 and 1.3 equiv of **6** with respect to the diene **5**. We found trifluoroethanol is required as the solvent for the cycloaddition to proceed with an acceptable yield. Interestingly, when benzene was added as a cosolvent, the yield increased by around 20%. It is important to note that the use of essentially only 1 equiv of diene in this reaction is unusual and may have important implications for other 4+3 cycloaddition reactions using this methodology. In general, 4+3 cycloaddition reactions using this methodology are only effective when a large excess of diene is used. Whether the reaction conditions used here represent a general solution to that problem remains to be discovered.

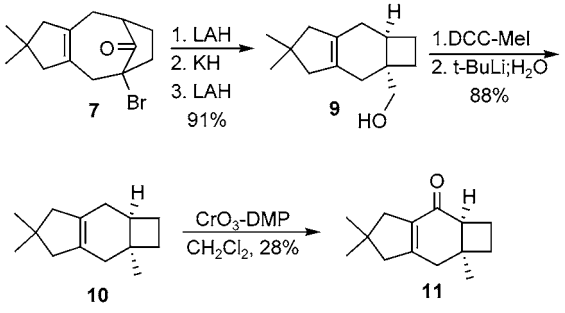
Table 1. 4+3 Cycloaddition Reaction between **5** and **6** under Various Conditions



entry	t (°C)	solvent	time (min)	yield (%)[a]
1	−78 to rt	MeCN	60	trace
2	−78 to rt	Et_2O	40	0
3	−78 to rt	toluene	60	10
4	0	TFE/Et_2O	90	41
5	23	TFE	60	43
6	−30	TFE/$PhCH_3$	20	47
7	−30	TFE/$PhCH_3$	40	47
8	−30	TFE/$PhCH_3$	60	40
9	−30	TFE/PhH	40	64
10	−7	TFE/PhH	50	74[b]

[a] Yields for entries 1−9 are based on **4**. [b] Yield based on cycloaddition step alone.

Scheme 4



The ketone **7** was carefully reduced with $LiAlH_4$ at 0 °C, making sure not to reduce the bridgehead bromide. The crucial quasi-Favorskii rearrangement step turned out to be somewhat capricious. Initial attempts gave not only the

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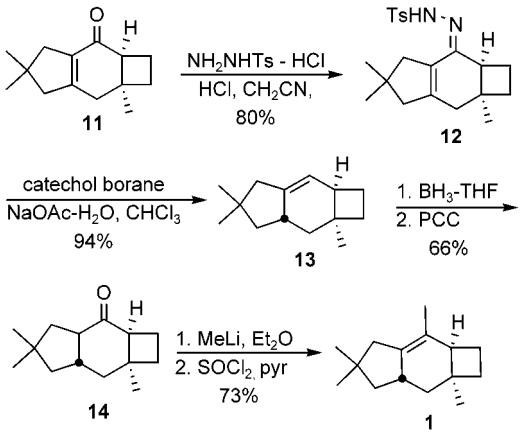
desired aldehyde but also the corresponding acid, alcohol and ester, presumably as a result of Tischenko and Cannizzaro reactions. Although these side reactions could be suppressed at lower concentrations, it proved to be inconsequential in the context of our synthetic goals. Reduction of the mixture gave the alcohol **9** in a 91% yield for three steps. Successful removal of the hydroxyl group was performed via conversion to the iodide[11] followed by lithium−halogen exchange and an aqueous quench. The hydrocarbon **10** was isolated in 88% yield.

To introduce a functionality at the desired carbon, we envisioned a regioselective allylic oxidation, directed to the six-membered ring[12] at the less sterically hindered carbon.[13] Although we did see selectivity, competitive over-oxidation kept the yield low. A wide range of oxidizing agents, including NBS−H_2O, SeO_2, $Co(OAc)_2$, $SiO_2/ZrO_2/Cr(VI)$, $KMnO_4/SiO_2$, and CrO_2Cl_2, were tried and all gave very poor yields. The best reagents found were the CrO_3−dimethylpyrazole complex,[14] or Collins reagent, which gave similar results, affording **11** in a 28% yield.

With enone **11** in hand, the tosyl hydrazone **12** was formed in a straightforward fashion. Reduction of the hydrazone **12** with catecholborane[15] gave the olefin **13** with all the chiral centers of sterpurene in place (Scheme 5). Hydroboration with borane followed by PCC oxidation[16] afforded ketone **14** in a 66% yield for two steps. The reaction of ketone **14** with methyllithium followed by dehydration afforded sterpurene (**1**) in 73% yield. The proton and carbon NMR data for ketone **14**, and (±)-sterpurene **1**, matched those reported by Helquist.[3i]

Scheme 5



In conclusion, we have accomplished a new synthesis of the sesquiterpene, sterpurene (**1**), using a 4+3 cycloaddition reaction of a halogenated, oxyallylic cation and a rigid diene, followed by a quasi-Favorskii rearrangement. The entire process proceeds in a 6.0% overall yield over 13 steps from the cycloaddition step of diene **5.** Future studies include other applications of the 4+3 cycloaddition/quasi-Favorskii sequence along with other total syntheses, which are in progress.

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Supporting Information Available: Experimental procedures, copies of spectral data for the intermediates, and X-ray crystal data for **7** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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