where this is an important consideration. An especially important advantage of the new alkene synthesis is that numerous sulfones and nitriles are commercially available at minimal cost by comparison with phosphonium salts. Although our method requires prior isolation of the tosylhydrazone, this step is generally trivial and often provides a convenient means for purification of commercially available aldehydes. Finally, we note that synthetic intermediates of current interest such as vinyl sulfides (entry 5), vinyl ethers (entry 6), and allylic silanes (entry 13) can be prepared from appropriate precursors.

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References and Notes

(1) For addition of alkyllithium reagents to aldehyde tosylhydrazones, see E. Vedejs and W. T. Stolle, *Tetrahedron Lett.*, 135 (1977).
(2) A similar intermediate is apparently formed in the reaction of CH_3Li + $PhCH_2CH_2CH(OCH_2OCH_3)CH{=}NNHTs \rightarrow PhCH_2CH_2CH{=}CHCH_3$ (~20%): E. Vedejs and J. Dolphin, unpublished results.
(3) Low molecular weight sulfone anions occasionally precipitate under the standard conditions. Nitrile anion condensations are homogeneous throughout.
(4) Addition of >1 equiv of LDA to the tosylhydrazone will cause some fragmentation to a nitrile (see ref 1): $RCH{=}NNHTs \rightarrow RCN$. If the resulting nitrile has acidic α protons, the derived anion will form and will attack starting tosylhydrazone to afford alkene products of "self-condensation". This side reaction is seen in trace amounts with most reactions in Tables I and II.
(5) R. H. Shapiro, *Org. React.*, **23**, 405 (1976).
(6) Shapiro elimination is not normally observed when aldehyde tosylhydrazones are treated with LDA or alkyllithium reagents.[1]

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Efficient Guaiazulene and Chamazulene Syntheses Involving [6 + 4] Cycloadditions

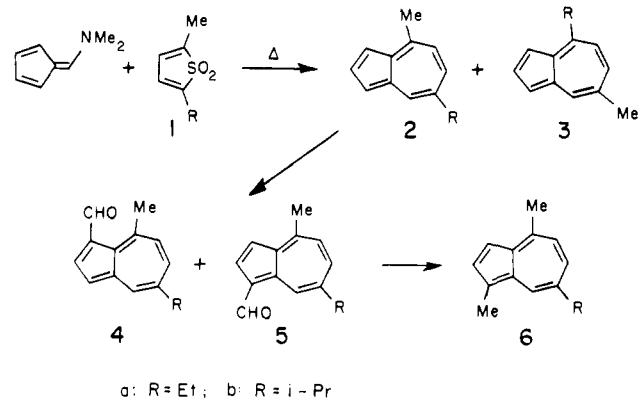
Sir:

Guaiazulene[1] and chamazulene[2] are obtained from natural sources by the degradation of hydroazulene sesquiterpenes.[3] The best azulene syntheses[4] are not generally applicable to the ready preparation of these compounds, so that only extremely lengthy and low yield total syntheses of both of these azulenes have been reported.[5] We report the application of two new azulene syntheses involving [6 + 4] cycloadditions[6,7] to the synthesis of these substances.

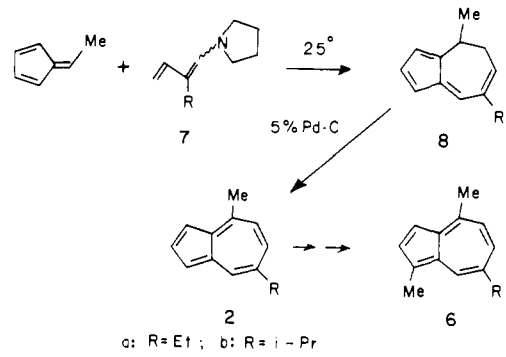
Model studies showed that the 1,4,7-trisubstitution pattern present in guaiazulene and chamazulene could not be produced directly owing to the incorrect regioselectivity of the cycloadditions in the five-membered ring.[8] However, either [6 + 4] cycloaddition sequence selectively gives the 4,7-disubstituted azulenes, and the 1-methyl substituent could be introduced selectively utilizing the propensity of azulenes to undergo electrophilic substitution at the 1 (or 3) position and the greater hindrance to attack of the 3 position in the 4,7-disubstituted azulene.

Although high regioselectivity was not anticipated for the aminofulvene, thiophene dioxide route (Scheme I), in practice this sequence proved quite efficaceous. The appropriate thiophene dioxides (**1a** and **1b**) were prepared from 2-acetyl-5-methylthiophene[9] as follows. Wolff–Kishner reduction (hydrazine hydrate, KOH, diethylene glycol, 210 °C, 3 h) gave 2-ethyl-5-methylthiophene, bp 150–152 °C (72%), which was oxidized (*m*-chloroperbenzoic acid, $NaHCO_3$, CH_2Cl_2, 10 °C, 2 days) in 69% yield to **1a** (viscous oil). The use of solid sodium bicarbonate to neutralize the chlorobenzoic acid formed represents a considerable improvement over the one-phase oxidation of Melles and Backer, which gives low yields and tarry byproducts.[10]

Scheme I



Scheme II



Addition of methyl Grignard to 2-acetyl-5-methylthiophene, followed by dehydration of the crude product with $KHSO_4$ at 200 °C, gave 2-methyl-5-(2-propenyl)thiophene (42%). Hydrogenation of the propenyl group over 5% $Pd/BaSO_4$ proceeded quantitatively to give 2-isopropyl-5-methylthiophene, which was oxidized as before to give the thiophene dioxide (**1b**, 71%).

Reaction of **1a** (1.3 g) with 6-dimethylaminofulvene (1.2 g) in refluxing benzene, and workup as described previously,[6] gave a mixture of 7-ethyl-4-methylazulene (**2a**) and 4-ethyl-7-methylazulene (**3a**) in a total yield of 11%. By carrying out this and related cycloadditions in refluxing pyridine, the yield can be improved to a more tolerable 20%.[11] NMR spectra (for example, the ratio of the 4-methyl resonance in **2a** at δ 2.79 to the 7-methyl resonance in **3a** at δ 2.49)[12] indicated that the desired isomer (**2a**) and the undesired one (**3a**) were formed in a ratio of 4:1. Steric effects must control the regioselectivity of these cycloadditions: the most nucleophilic site (C-2) of the aminofulvene becomes attached to the less hindered site of the thiophene dioxide, even though the final adduct may be more crowded.[6]

The methyl group at C-1 was introduced by Vilsmeier formylation ($POCl_3$, DMF, 0 °C), which gave a mixture of the 1,5,8-trisubstituted azulene (**4a**) and the 1,4,7 isomer (**5a**), which were easily separated by column chromatography (alumina, benzene) in isolated yields of 13 and 68%, respectively. The anisotropy of the aldehyde makes identification by NMR of the isomers simple: in **4a**, Me_8 resonates at δ 3.13 and H_4 at 8.32, while, in **5a**, Me_4 resonates at δ 2.78 and H_4 at 9.53. Wolff–Kishner reduction of **5a** gave chamazulene (**6a**, 50%) as a purple oil.[13]

The synthesis of guaiazulene proceeded similarly. The cycloaddition of **1b** (1.3 g) with 6-dimethylaminofulvene (1 g) gave **2b** and **3b** in a ratio of 4:1 (NMR), from which 60 mg of **2b** could be isolated by column chromatography. Vilsmeier

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formylation gave **4b** and **5b** in 15 and 61% isolated yields, respectively, and Wolff-Kishner reduction of **5b** produced guaiazulene (**6b**, 51%) as a dark purple oil.

Dienamine-fulvene cycloadditions (Scheme II) provided even more facile routes to 4-methyl-7-alkylazulenes, since the cycloadditions are completely regiospecific. The required pyrrolidine dienamines were prepared by reaction of the lithium salts of the *N*-cyclohexylimines of butyraldehyde or isovaleraldehyde (LDA, ether, 0 °C) with acetaldehyde at −70 °C,[14] followed by hydrolysis with oxalic acid and steam distillation, to give 2-ethylcrotonaldehyde (bp 130–131 °C)[15] and 2-isopropylcrotonaldehyde (bp 142–144 °C) in 48 and 52% yield, respectively. Refluxing these aldehydes with pyrrolidine and K_2CO_3 in toluene gave the corresponding pyrrolidine dienamines (**7a**, bp 65–70 °C (2 mm) and **7b**, bp 72–75 °C (4 mm)) as mixtures of geometric isomers.

The cycloadditions of the pyrrolidine dienamines **7a** and **7b** to methylfulvene, prepared by the method of Hafner and Sturm,[16] were carried out at room temperature in ether. Workup as described previously[7] gave the dihydroazulenes **8a** and **8b** in 52 and 50% yield, respectively. These dihydroazulenes were converted into the corresponding azulenes (**2a** and **2b**) in 17 and 35% yield, respectively, by refluxing with 5% Pd/C at 170 °C in triglyme. The azulenes prepared in this way are identical with the major isomers obtained from the thiophene dioxide cycloadditions, and could be converted as described above into chamazulene and guaiazulene.

Adaptations of these routes to the synthesis of hydroazulene sesquiterpenes are under investigation.

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(11) The workup procedure consists only of evaporation and column chromatography to remove polar byproducts. Pyridine solvent more than doubles yields reported earlier[6] with other alkylthiophene dioxides.
(12) Meuche, D.; Molloy, B. B.; Reid, D. H.; Heilbronner, E. *Helv. Chem Acta.* **1963,** *46*, 2483.
(13) NMR resonances due to the ring protons of chamazulene in several solvents are essentially identical with those reported for guaiazulene.[12] Chamazulene, **6a**, in $CDCl_3$: δ 2.62 (Me_1), 7.56 (H_2), 7.15 (H_3), 2.75 (Me_4), 6.83 (H_5), 7.25 (H_6), 2.75 (CH_2), 1.29 (Me_7), 8.08 (H_8) (J_{23} = 4.0, J_{56} = 10.5, J_{68} = 1.5 Hz).
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(17) On leave from the Indian Association for the Cultivation of Science, Jadavpur, India, 1976-1978.

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An ^{18}O Isotope Shift upon ^{13}C NMR Spectra and Its Application to the Study of Oxygen Exchange Kinetics

Sir:

Numerous examples of the effects of isotopic substitution upon the NMR resonance positions of various nuclei are known. The ^2H-isotope effects on ^1H NMR spectra and ^2H- and ^{13}C-isotope effects on ^{19}F NMR spectra have been known for some time.[1,2] The ^{13}C- and ^{15}N-isotope effects on ^{59}Co NMR spectra and the ^{34}S-isotope effect on ^{13}C NMR spectra have been characterized;[3-5] the β-deuterium (*O*-deuterium) isotope effect on ^{13}C NMR spectra has been successfully employed in carbohydrate research.[6] Most recently ^{18}O-isotope effects have been reported for ^{55}Mn and ^{95}Mo NMR spectra[7] and for ^{31}P NMR spectra.[8] The latter observation has already proved useful[9-11] for studying the exchange of phosphate oxygen from phosphate ion, and it is clear that a comparable technique would be of significant utility in carbon chemistry. Jameson[12] has predicted an ^{18}O-isotope effect on ^{13}C NMR spectra, in particular an upfield shift in ^{18}O-labeled $^{13}CO_2$ which is dependent on the number of ^{18}O atoms in the molecule. We have now observed such an isotope shift in ^{13}C NMR spectra and it provides a very useful method for studying oxygen exchange kinetics.

We find an upfield shift in the natural abundance ^{13}C NMR spectrum of the hydroxyl carbon of *tert*-butyl alcohol when ^{18}O rather than ^{16}O is bonded to the carbon. [^{18}O]-*tert*-butyl alcohol was synthesized by passing dry HCl into 99 atom % excess [^{18}O]water (Norsk Hydro, Oslo), adding *tert*-butyl alcohol to the acidic [^{18}O]water, and allowing the exchange reaction to proceed at 55 °C for 60 h. The [^{18}O]-*tert*-butyl alcohol was then isolated by addition of salt, separated, dried, and distilled. Mass spectral analysis showed it to contain 83.7% ^{18}O. All natural abundance ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer equipped with a 10-mm variable-temperature probe. A 5-mm internal diameter capillary of D_2O was used to provide an instrumental lock signal. A total of 50 scans, 200-Hz sweep width, 20.5-s acquisition

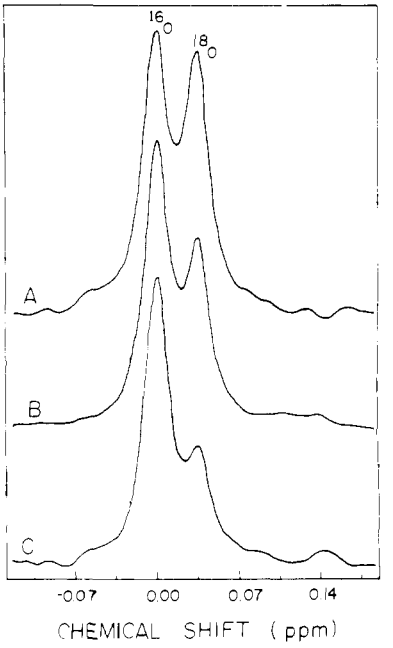

Figure 1. Natural abundance ^{13}C spectra of C-1 of *tert*-butyl alcohol made from known concentrations of [^{18}O]- and [^{16}O]-*tert*-butyl alcohol in water-deuterium oxide. An upfield shift occurs owing to ^{18}O isotopic substitution at the hydroxyl carbon. The unlabeled hydroxyl carbon is arbitrarily assigned the value 0.0 ppm. The spectra were recorded on a Varian CFT 20 spectrometer. Curve A, 48% [^{18}O]-*tert*-butyl alcohol; curve B, 40% [^{18}O]-*tert*-butyl alcohol; curve C, 31% [^{18}O]-*tert*-butyl alcohol.

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