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Construction of Bicyclo[2.2.2]octane Ring System *via* Homoallyl-Homoallyl Radical Rearrangement

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Abstract: We designed a sequential three-step, one-pot reaction (homoallyl-homoallyl radical rearrangement reaction) to generate highly functionalized bicyclo[2.2.2]octane ring system, and succeeded in developing a novel synthetic method to bicyclo[2.2.2]octane compounds from simple cyclohexene derivatives.

Until a decade ago radical reactions were commonly regarded as a domain for mechanistically oriented research, and the use of free radical species for organic synthesis has been limited mainly due to lack of regio- and stereoselectivity.[1] However, in recent years a large number of well-designed radical reactions which give high yields of desired products have been reported.[2] Sequential free radical reactions offer a particularly attractive route to polycyclic compounds.[3]

The cyclopropylcarbinyl radicals **2**, produced from the homoallyl radicals **1**, always rearrange rapidly into the thermodynamically more stable homoallyl isomers **3**.[4] Especially from the viewpoint of biogenetic cascade rearrangements,[5] the generation of one bond *via* a *3-exo-trig* cyclization and the sequential cleavage of another bond (**1** → **2** → **3**) is a crucial synthetic tool for skeletal transformation.

1 **2** **3**

Although the homoallyl-homoallyl radical rearrangement process is a powerful strategy for construction of polycyclic compounds, relatively little is known about successful application of the above reaction to biologically active natural product syntheses.[6] We have investigated the synthetic potential of the homoallyl-homoallyl radical rearrangement reaction and recently reported the total synthesis of (±)-methyl atis-16-en-19-oate as our first contribution to this area.[7]

Since the above skeletal transformation of a kaurene-type compound into an atisirene-type one *via* homoallyl-homoallyl radical rearrangement with a reasonable degree of efficiency and yield has been developed, the elaboration of suitably functionalized cyclohexene derivatives into bicyclo[2.2.2]octane skeleton emerged as an attractive option. Herein we show a powerful one-pot reaction sequence which uses the sequential process to generate bicyclo[2.2.2]octane ring system from monocyclic compounds.

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The general reaction design is depicted in Scheme I. Namely, the initially generated vinyl radical **6**[8] from acetylene **4** or vinyl halide **5** was expected to cyclize to produce bicyclic radical through a *5-exo-trig* fashion.[9] This homoallyl radical **7** was expected then to occur a *3-exo-trig* cyclization. The resulting cyclopropylcarbinyl radical **8** was set up for ring opening to give bicyclo[2.2.2]octane ring system **12**.

The requisite cyclohexene derivative **4** (R^1=Me, R^2, R^3=H) for exploring the feasibility of the designed reaction sequence was prepared as follows. Heating a toluene solution of 1,3-butadiene and methyl acrylate at 170 °C in a sealed tube for 10 h afforded the corresponding cycloadduct,[10] which was then treated with propargyl bromide in the presence of LDA at -78 °C to furnish **4** in 74% yield. The other substrates were also prepared in the same manner.

The sequential three-step, one-pot reaction of **4** was triggered under standard radical generation conditions ($^nBu_3SnH$, AIBN, toluene, reflux) and afforded the product, which was subjected to protodestannylation on silica gel (48 h).[11] The product was a mixture of the desired bicyclo[2.2.2]octane compound **14** (R^1=CO_2Me, R^2, R^3=H) and the bicyclo[3.2.1]octane derivative **13** (R^1=CO_2Me, R^2, R^3=H) as evidenced by the presence of two sets of characteristic *exo*-olefin peaks in ^{1}H-NMR, in a ratio of approximately 3:2 (entry 1). In order to confirm each of the structures, the mixture was converted to the corresponding ketones by ozonolysis.[12] Changing the side chain from propargyl to bromopropenyl had a slight improvement on the proportion, however, a small amount of the reduced product **15** (R^1=CO_2Me, R^2=R^3=H) was also produced (entry 2).

Next, substrates with methyl group in the R^2 position were investigated. In the event, the proportion of **14** increased considerably (entries 3 and 4). The transition state **17** has been proposed to account for the observed bicyclo[2.2.2]octane-selectivity. In this case, the ensuing 3-*exo-trig* cyclization proceeds smoothly, giving the rearranged product **14** as a major product, probably due to the nonbonding interaction between the R^2 substituent and $^nBu_3Sn\bullet$.

A reversal selectivity was observed for compounds **4** and **5** (entries 5 and 6) bearing methyl group in the R^3 position. The preferred formation of **13** can be rationalized by the stability of the resulting tertiary radical species and the nonbonding interaction between R^3 and Y substituents in the transition state **16**. Interestingly, the γ-lactone moiety in the compound **5** plays a crucial role in the control of the product (entry 7). This selectivity indicates that the steric congestion between the methylene and $^nBu_3Sn\bullet$ in the transition state **18**, makes it less favorable than the alternative transition state **19**. In addition, electronic repulsion between radical and ester group in the transition state **17** plays an important role in effecting further cyclization (entry 8).

With the evidence that a substituent in the R^2 position is essential to attain excellent bicyclo[2.2.2]octane-selectivity, we then turned our attention to the reaction of the compound **4** and **5** (entries 9 and 10) with a larger substituent in the R^2 position. The reaction of these substrates produced the corresponding bicyclo[2.2.2]octane derivatives almost exclusively, indicating that the selectivity is highly dependent on the bulkiness of the R^2 substituent.

To our knowledge, there is little precedent for such results in the field of homoallyl-homoallyl radical rearrangement reactions. Noteworthy is that the homoallyl-homoallyl radical rearrangement sequence produces a highly functionalized bicyclo[2.2.2]octane ring system, a substitution pattern found in many biologically important natural products, such as 9-isocyanopupukeanane (sesquiterpene),[13] atisirene (diterpene),[14] and aspidofractinine (alkaloid).[15]

In conclusion, a sequential three-step,[16] one-pot reaction has been designed which affords highly functionalized bicyclo[2.2.2]octane compounds in high selectivity. Applications to the synthesis of biologically active natural products are currently under active investigation in our laboratory.

Scheme I

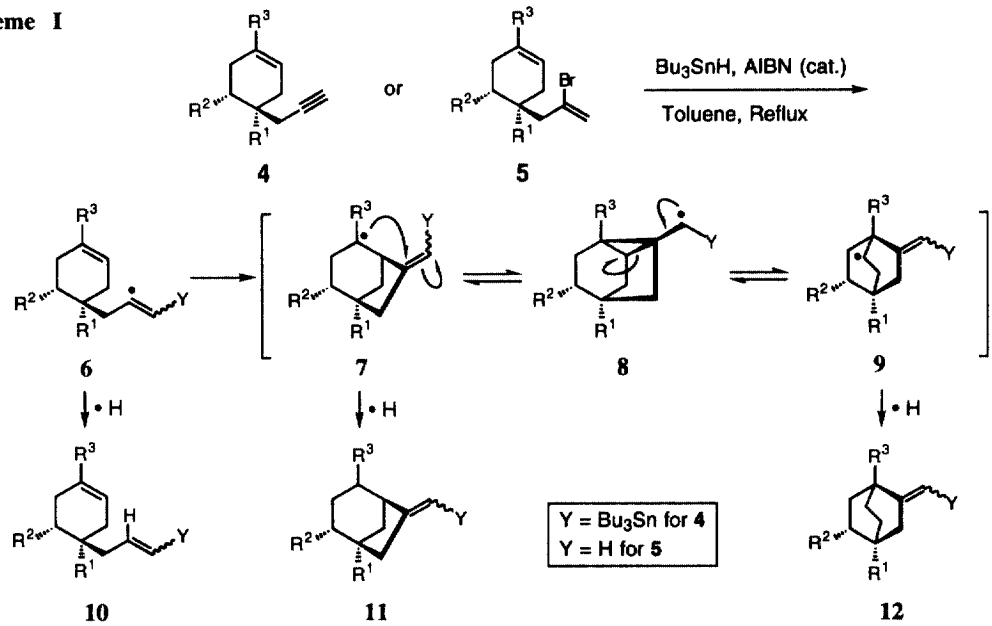
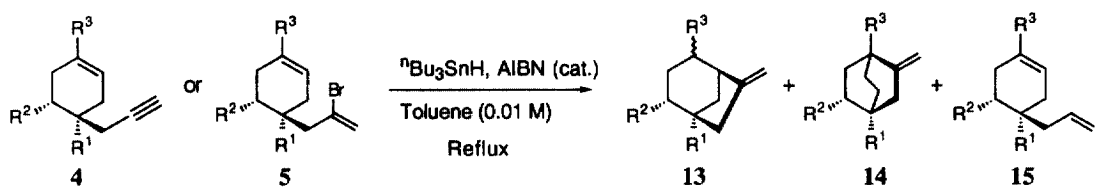
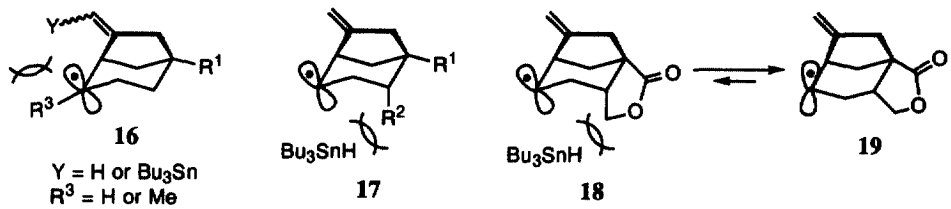


Table I **Homoallyl-Homoallyl Radical Rearrangement Reaction of Cyclohexene Derivatives (4 and 5)**



entry	substrate	R^1	R^2	R^3	ratio of products 13 : 14 : 15	13 : 14	yield (%)
1	**4**	CO_2Me	H	H	39 : 61 : 0	39 : 61	80
2	**5**	CO_2Me	H	H	25 : 61 : 14	29 : 71	68
3	**4**	CO_2Me	Me	H	32 : 68 : 0	32 : 68	69
4	**5**	CO_2Me	Me	H	1 : 82 : 6	13 : 87	61
5	**4**	CO_2Me	H	Me	94 : 6 : 0	94 : 6	75
6	**5**	CO_2Me	H	Me	83 : 17 : 0	83 : 17	71
7	**5**	$-CO_2CH_2-$		H	90 : 10 : 0	90 : 10	77
8	**5**	CO_2Me	CO_2Me	H	11 : 76 : 13	13 : 87	80
9	**4**	CH_2OBn	CH_2OBn	H	0 : 100 : 0	0 : 100	50
10	**5**	CH_2OH	$C(Me)_2OH$	H	0 : 46 : 54	0 : 100	100

Figure I



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12. One of the products was methyl 6-oxobicyclo[3.2.1]octan-1-carboxylate and its reported spectral data were identical with those of our synthetic compound. The structure of the other compound was easily established by spectral analyses. H. Stetter, H. Kuhlmann, *Liebigs Ann. Chem.* **1979**, 1122-1124.
    The structures of the new compounds in Table were fully consistent with their ^{1}H-NMR, IR, MS spectra and elemental analyses.
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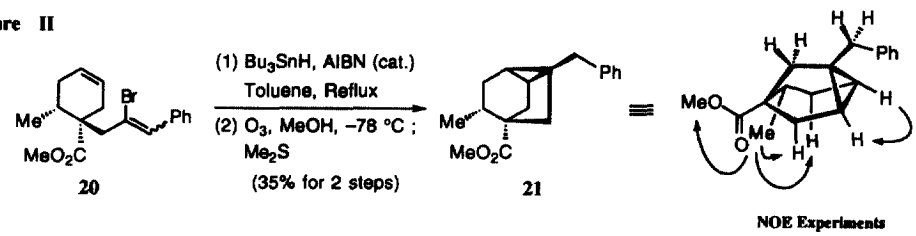
16. In order to trap the cyclopropylcarbinyl radical, the reaction intermediate of the aforementioned sequential process, the compound **20** was prepared and subjected to the same reaction conditions. Although trapping of the phenyl-substituted cyclopropylcarbinyl radical without nitroxyl radical scavenger[17] is quite difficult, the desired three-membered ring product **21** was fortunately isolated after ozonolysis.[18] The structural assignment to **21** was conclusively established by a combination of difference NOE and ^{1}H-COSY NMR experiments. Enhancements, shown in Figure II, were proofs of the proposed structure. This result indicates that the ratio of the products (**13** and **14**) depends on the stability of the intermediates (**7** and **9**) in the equilibration.

Figure II



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18. At this stage, the other products such as monocyclized unsaturated compound were oxidized to give the corresponding carbonyl compounds. Although 35% yield, the isolation of the monobenzyl-substituted cyclopropane product is a rare case.