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Free Radical Fragmentation of Photoadduct Derivatives Leading to Allylic Systems. Regioselectivity of Reduction with Tin Hydrides and Samarium (II) Iodide

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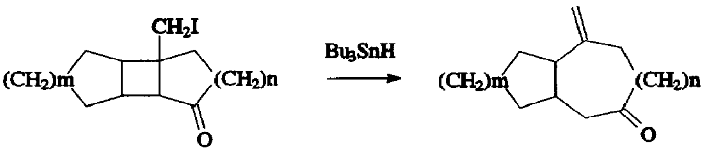
Abstract: Fragmentation of unsaturated photoadduct derivatives **5** and **8** with $(n\text{-Bu})_3SnH$, $(C_6H_5)_3SnH$ or SmI_2 generally gives mixtures of regioisomers. SmI_2 is the reagent of choice for these transformations because the yields are high (>90%) and with esters **8a/b** only one isomer, **11a/b**, is obtained.

Free radical *cyclization* reactions have been studied extensively[1] but investigations of free radical *fragmentation* reactions are much more limited.[2,3] We reported[3] the fragmentation of strained photoadduct derivatives **1** to yield bicyclic carbon skeletons (**2**) which are present in a variety of natural products (Scheme 1). We now report the results of a related study in which the initial fragmentation leads to an allylic radical. The isomeric mixture obtained upon reduction of this allylic radical will be shown to be dependent on the nature of the reducing agent employed.

Scheme 1

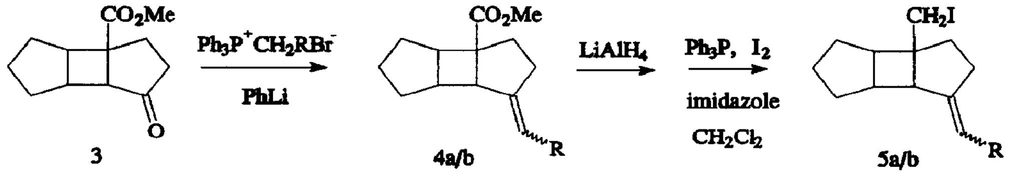


1 m, n = 1 or 2 **2**

The substrates for this investigation were prepared from the readily available photoadduct **3**.[4] From our earlier study[3] it was known that iodide **1** (m = n = 1), which was derived from **3**, fragmented in high yield (90%) to give the 5/7 ring system **2** (m = n = 1) present in terpenoids such as the guaianes and pseudoguaianes. The methylene substrate **5a** and ethylidene substrate **5b**[5] were prepared as outlined in Scheme 2.[6] The neopentyl alcohols, obtained by reduction of **4** with $LiAlH_4$, were converted to iodides **5** using our previously reported procedure.[7] The other substrates of interest, the α,β-unsaturated esters **8a** and **8b** were prepared from keto alcohol **6** using Wadsworth-Emmons methodology (Scheme 3). Preparation of **6** from photoadduct **3** has been reported.[4] ^1H NMR spectra indicated **8a** was a 50:50 mixture of E/Z isomers while **8b** was a 67:33 mixture.

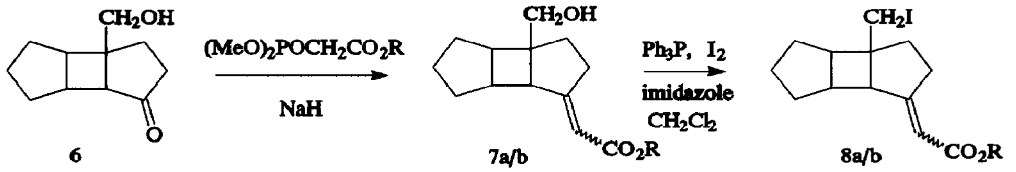
Each of the four substrates was fragmented using the following three reagents: $(n\text{-Bu})_3SnH$, $(C_6H_5)_3SnH$ and SmI_2. AIBN was employed as the initiator with the first two reagents in refluxing benzene

Scheme 2



"a" series, R = H ; "b" series, R = Me

Scheme 3



"a" series, R = Me ; "b" series, R = t-Butyl

while SmI$_2$ was freshly prepared in THF solution.[8] Scheme 4 shows the structures of the products formed in each fragmentation and the Table gives the percentage yield and product distribution from each substrate with the different reducing agents. In all reactions where two regioisomers (endo- and exocyclic) were formed the mixture was inseparable by flash chromatography and the ratios were determined by analysis of the ^{1}H NMR spectra of the mixtures.

Fragmentation of the methylene derivative **5a** with any of the three reducing agents gave in high yield a mixture of the endo isomer **9a** and the exo isomer **10a**. With the hydride reagents the exo isomer predominated while with the SmI$_2$ the endo product was favoured. A previous study involving tin hydride reduction of an allylic system indicated that reduction took place at the less hindered terminus to give the endo isomer as the major product.[9] Fragmentation of the ethylidene derivative **5b** with the three reagents gave in moderate to high yield a mixture of the endo isomer **9b** and the exo isomer **10b** with no strong preference for either product.

Fragmentation of the α,β-unsaturated esters **8a** and **8b** gave the bicyclic product in good yield but with significant differences in the regioisomer distribution. With the two tin hydride reagents both esters gave the exo isomer **12** as the major product (67-78% of mixture) while with SmI$_2$ the exclusive product formed was the endo isomer **11**. The t-butyl ester **8b** was used to impart additional steric hindrance at one end of the allylic system but the results are mixed. The comparison is complicated by the different E/Z ratios in the starting esters **8a** and **8b**.

The reagent of choice for effecting these fragmentations is clearly SmI$_2$ as all four reactions with it proceeded in greater than 90% yield. The reactions are clean, the work-up is simple (compared with the difficulty of removing the tin by-products) and the regioselectivity is excellent with substrates **8a** and **8b**.

Scheme 4

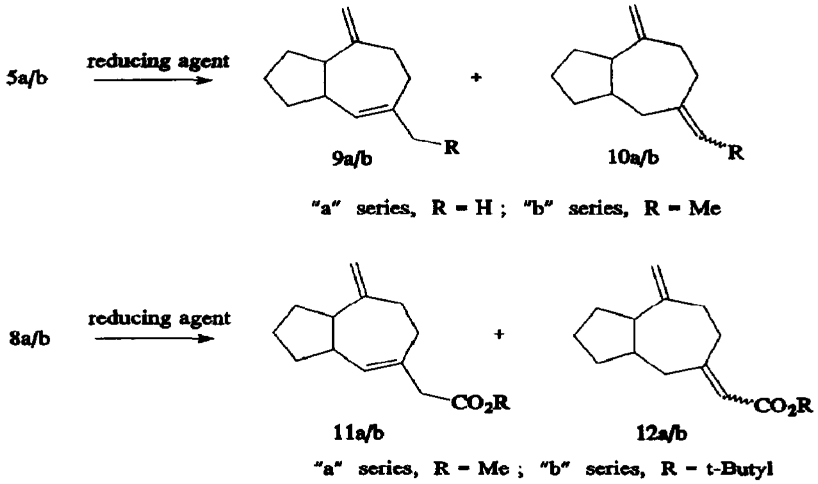
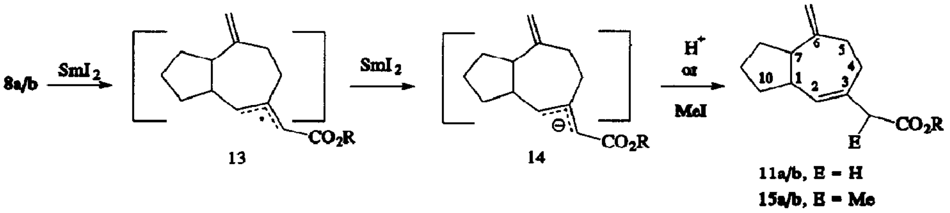


Table - Fragmentation Results with Various Reducing Agents

	(n-Bu)$_3$SnH[a]	Ph$_3$SnH[a]	SmI$_2$[b]
Fragmentation of 5a			
Ratio of **9a/10a**	36:64	44:56	68:32
Combined % Yield	94	86	96
Fragmentation of 5b			
Ratio of **9b/10b**	37:63	59:41	57:43
Combined % Yield	51	76	94
Fragmentation of 8a (E/Z 50:50)			
Ratio of **11a/12a**	33:67 (all E)	22:78[c]	99:1
Combined % Yield	53	78	93
Fragmentation of 8b (E/Z 67:33)			
Ratio of **11b/12b**	27:73[d]	32:68 (all E)	99:1
Combined % Yield	81	85	95

[a]1.5 equiv. of hydride used; [b]4 equiv. of SmI$_2$ used; [c]E/Z 56:44; [d]E/Z 70:30

In the reactions with the α,β-unsaturated esters **8a/b** we assume that the allylic radical **13**, which is formed after the fragmentation of the strained cyclobutylcarbinyl system, is reduced to the carbanion (enolate) **14**. Protonation of **14** at the α-carbon then gives the endo product **11**. Support for this suggestion is provided by the fact that quenching of **14** with excess methyl iodide gives the α-methylated product **15**. **15** has the carbon skeleton of a guaiane or pseudoguaiane except for a methyl group at C-10[10] or C-1 respectively. Also the double bond at the 2-position could be used for generation of the γ-lactone moiety present in the guaianolides. The application of this new fragmentation methodology for the synthesis of sesquiterpenoids is currently under investigation.



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5. Only one isomer was observed in the ^{1}H NMR spectrum of **5b** and of the fragmentation product **10b**.

6. We also wished to examine the isopropylidene derivative but were unable to prepare it in reasonable yield.

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10. Functionality such as a ketal at C-10 can readily be introduced in the initial photoaddition step.

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