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Triquinanes from linear ketones via trimethylenemethane diyls

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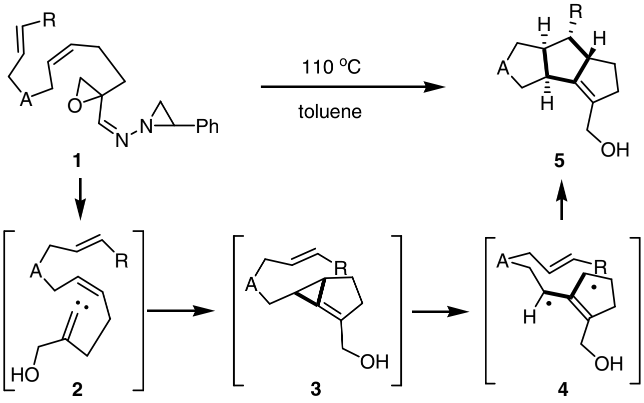
Abstract—Linear compounds containing a ketone and diene functional groups reacted with the anion of TMS–diazomethane to produce alkylidene carbenes that underwent intramolecular cyclopropanation followed by the formation of trimethylenemethane diyls which underwent [2+3] cycloaddition reaction to produce linearly fused triquinanes.

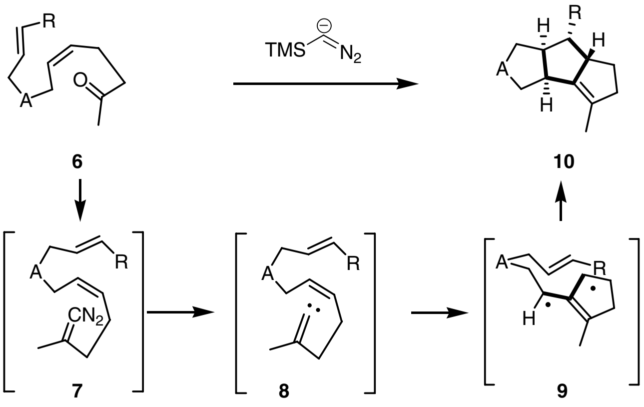
Recently, we have reported a tandem cycloaddition reaction of alkylidene carbenes of linear substrates into triquinane compounds through the sequential formation of alkylidene carbenes followed by trimethylenemethane (TMM) diradical intermediates.[1] As shown in Scheme 1, alkylidene carbenes were generated from epoxyaziridinyl imines that underwent intramolecular cyclopropanation reaction to form highly strained intermediate **3**. Then methylenecyclopropane ring opened to trimethylenemethane (TMM) diyl **4** that underwent [2+3] cycloaddition reaction to form linearly fused triquinanes regio- and stereo-selectively.



Scheme 1.

Epoxyaziridinyl imine was chosen for the precursor of alkylidene carbenes among several candidates because the reaction condition was neutral and a relatively high reaction temperature would guarantee the formation of TMM diyls from cyclopropane rings.[2] Since other methods of generating alkylidene carbenes[3] have their own advantages, we decided to examine another way to generate alkylidene carbene for the synthesis of triquinanes.

Since alkylidene carbenes can be generated from the reaction of ketones with the anion of TMS–diazomethane,[3d] compounds with properly located olefins and a ketone **6** can undergo tandem cycloaddition reaction when reacted with the anion of TMS–diazomethane (Scheme 2).



Scheme 2.

Keywords: Alkylidene carbene; Trimethylenemethane; Diyl; Triquinane.

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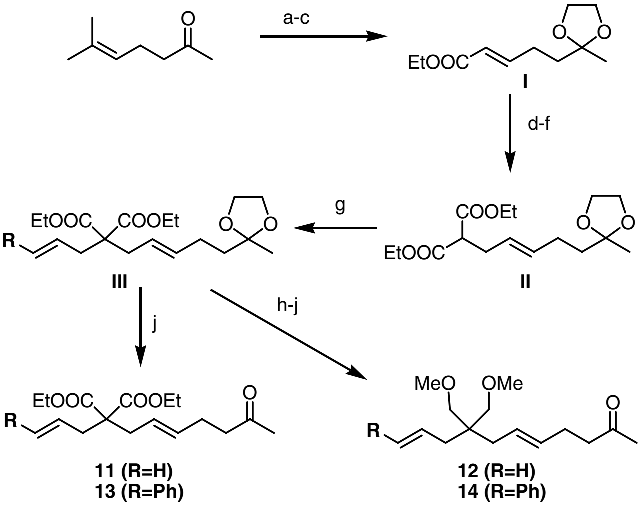
When compared to the aziridinylimine route,[1] the current route has advantages of being very high in atom economy[4] and having readily available substrates through straightforward synthesis. However, the current route might show possible complications due to the basic nature of the reaction condition and instability of the anion at a higher temperature than 0 °C.

Substrates for the tandem reaction were prepared from commercially available 6-methyl-5-hepten-2-one (Scheme 3). After protection of the ketone as the corresponding acetal, isopropenyl group was replaced with the allylic bromide in a four step sequence. Ozonolysis followed by Wittig olefination with $Ph_3PCHCOOEt$ produced unsaturated ester (I). DIBAL–H reduction of the ester to the alcohol followed by bromination reaction produced corresponding allylic bromide. This allylic bromide was reacted with malonate anion followed by subsequent allylation to afford ketodienes (**11, 13**) after the hydrolysis of acetals. Phenyl group was introduced to the terminal olefin to examine the stereoselectivity and reactivity of the TMM diyl [2+3] cycloaddition reaction.[5] Compounds with reduced esters (**12**, **14**) were also prepared to minimize possible side reactions due to the nucleophilic nature of the reaction conditions for alkylidene carbene generation.

These substrates were subjected to a modified Shioiri's reaction conditions[6] to generate alkylidene carbene from ketones and $TMSCLiN_2$.[7] To ensure the transformation of methylenecyclopropane ring of the intermediate to the TMM intermediate and to minimize the decomposition of $TMSCLiN_2$, the reaction was carried out at −30 °C in two different ways. While $TMSCLiN_2$ was generated before the addition of the ketone substrates in method A, $TMSCKN_2$ was generated in the presence of the substrates in method B. In method A, the generation of $TMSCLiN_2$ before the addition of the ketone minimizes the reaction of the ketone with BuLi but might decompose before the desired reaction proceeds in completion. In method B, it was hoped that $TMSCKN_2$[8] would react with ketones before decomposition even at a reaction temperature higher than −30 °C. Contrary to what we hoped for method B was not any better than method A. It was presumed that the lower concentration of the anion in method B than in method A and different counter cations in two methods made method B less effective than we had expected. The result was summarized in Table 1.

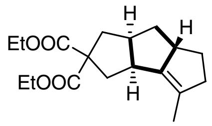
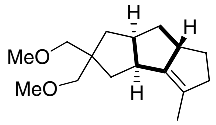
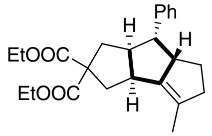
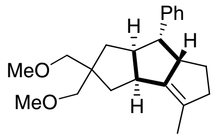


Scheme 3. Reagents and conditions: (a) ethylene glycol, TsOH/PhH, 94%; (b) O_3/CH_2Cl_2, −78 °C; PPh_3; (c) $Ph_3P{=}CHCOOEt/PhH$, reflux, 61% for two steps; (d) DIBAL–H/CH_2Cl_2, rt, 74%; (e) Ph_3P–NBS/CH_2Cl_2, −30 °C, 74%; (f) diethyl malonate, NaH/THF, rt, 80%; (g) NaH/THF; $RCH{=}CHCH_2Br$, rt, 84% (R = Ph), 91% (R = H); (h) LAH/ Et_2O, 0 °C, 72% (R = Ph), 77% (R = H); (i) NaH, MeI/THF, rt, 84% (R = Ph), 87% (R = H) and (j) 10% HCl (aq)/THF, rt, 82% (**11**), 71% (**14**), 84% (**12**, **13**).

The reactions produced single major products[9] whose structures were determined unambiguously by NMR through comparison to the previous reports.[1,10] As expected, substrates without the electrophilic substituents (**12**, **14**) yielded a better result than carbonyl containing ones (**11**, **13**) and phenyl groups attached to the terminal olefins (**13**, **14**) provided better result than the unsubstituted ones (**11**, **12**). The effect of the substituents on the [2+3] cycloaddition reaction was bigger than the effect observed in the previous report[1] probably due to a lower reaction temperature for a better selectivity. The basic nature of the reaction and the instability of the anion of $TMSCHN_2$ probably was the reason for the low yield of the products.

The current synthetic strategy allowed us to examine the effect of the methyl substituted TMM diyl to the tandem cycloaddition reaction as the methyl group provided a more steric interaction during the [2+3] cycloaddition

Table 1.

Substrate	Major product	Yield (%)	
		Method A	Method B
11	 **15**	21	25
12	 **16**	38	21
13	 **17**	34	27
14	 **18**	53	31