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Tetrahedron Letters 48 (2007) 1407–1410
Tetrahedron Letters

Triquinanes from linear ketones via trimethylenemethane diyls

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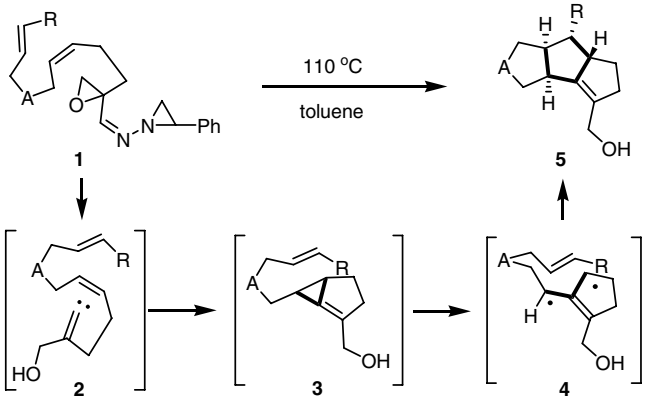
Received 22 November 2006; revised 14 December 2006; accepted 18 December 2006
Available online 20 December 2006

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.

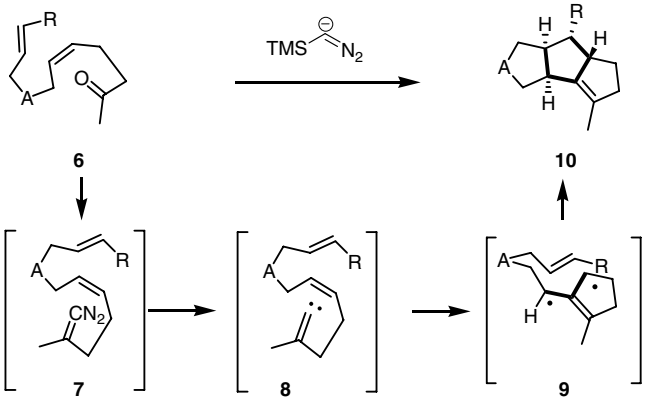
Recently, we have reported a tandem cycloaddition reaction of alkylidene carbenes of linear substrates into triquinane compounds through the sequential formation of alkylidene carbenes followed by trimethylenemethane (TMM) diradical intermediates.[1] As shown in Scheme 1, alkylidene carbenes were generated 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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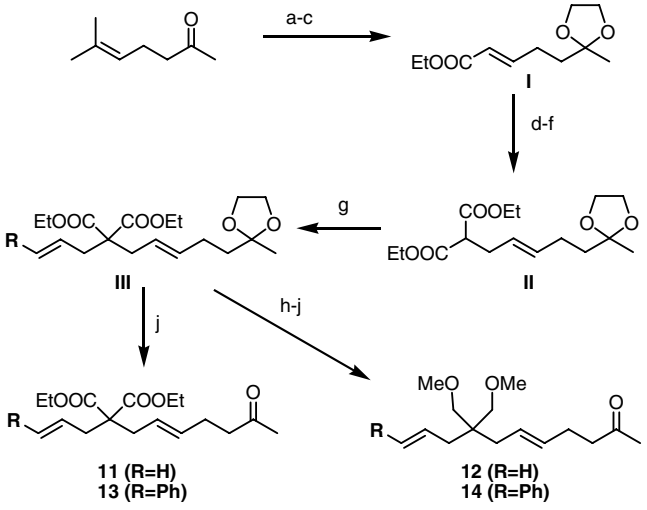
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.12.099

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.

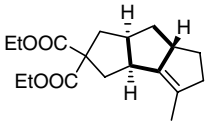
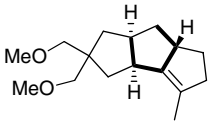
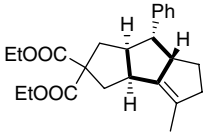
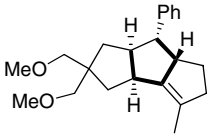


Scheme 3. Reagents and conditions: (a) ethylene glycol, TsOH/PhH, 94%; (b) O_3/CH_2Cl_2, −78 °C; PPh_3; (c) $Ph_3P{=}CHCOOEt$/PhH, reflux, 61% for two steps; (d) DIBAL–H/CH_2Cl_2, rt, 74%; (e) Ph_3P–NBS/CH_2Cl_2, −30 °C, 74%; (f) diethyl malonate, NaH/THF, rt, 80%; (g) NaH/THF; $RCH{=}CHCH_2Br$, rt, 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.

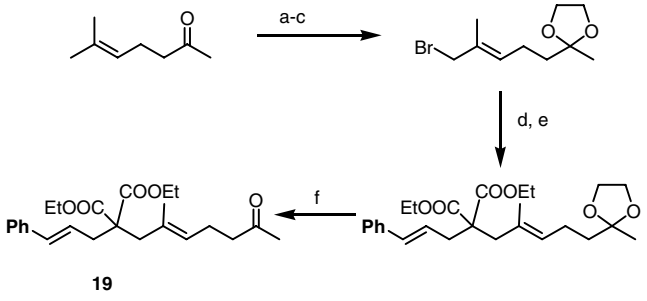
Substrate	Major product	Yield (%)	
		Method A	Method B
11	 **15**	21	25
12	 **16**	38	21
13	 **17**	34	27
14	 **18**	53	31

reaction. The precursor for the cycloaddition reaction was readily prepared from 6-methyl-5-hepten-2-one (Scheme 4). After the selective hydroxylation of the allylic methyl group, the allylic alcohol was converted into the bromide. From this allylic bromide, substrate **19** was prepared in the same way as the compounds in Scheme 3.

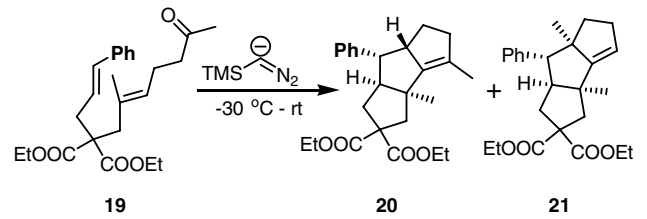
When **19** was reacted with $TMSCLiN_2$ using method A, two major products **20** and **21** were obtained in a 54% yield with the ratio of 3:1 (Scheme 5).

The structures of **20** and **21** were also confirmed through NMR spectroscopy. Product **20** has the usual *cis-anti-cis* triquinane structure and **21** has the *cis-syn-cis* triquinane structure. The relative stereochemistry was assigned unambiguously by coupling constants of tertiary hydrogens of **21** and through the NOE experiment on the ozonolysis product **22** (Scheme 6).

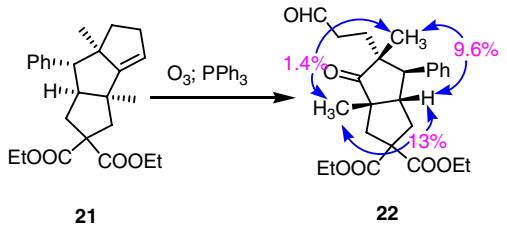
This result allowed us to rationalize the selectivity of [2+3] diyl cycloaddition reaction among isomeric products through comparison of four conformations of transition states (Scheme 7). Although the formation of **21**



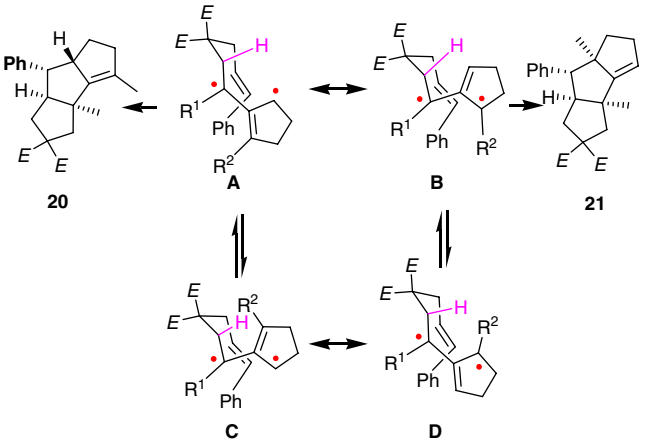
Scheme 4. Reagents and conditions: (a) ethylene glycol, TsOH/PhH, 94%; (b) SeO_2, *t*-BuOOH/CH_2Cl_2, 0 °C; 53%; (c) Ph_3P–NBS/CH_2Cl_2, −30 °C, 83%; (d) diethyl malonate, NaH/THF, rt; 88%; (e) NaH/THF; PhCH=CHCH$_2$Br, rt, 95% and (f) 10% HCl (aq)/THF, rt, 93%.



Scheme 5.



Scheme 6. NOE experiment.



Scheme 7.

has been somewhat anticipated, the relative stereochemistry of **21** was not obvious as the transition state for the formation of **21** could be either the transition state **B** or **D** in Scheme 7. For the compounds with $R^1 = H$, interaction between axially oriented hydrogen of the tether and cyclopentene ring showed a clear preference of cycloaddition reaction product from **A.** That explained why the product from transition state **C** or **D** was not observed. For the compounds with $R^1 = R^2 = Me$, it looked apparent that the steric interaction between two methyl groups in transition state **A** was bigger than the one in transition state **B** or **D** and it was thought that transition state **B** or **D** might have a similar energy to that of transition state **A**. Even with the added steric interaction, however, the product from transition state **A** was the major product and only the *cis-syn-cis* product **21** was produced as the minor product with no other possible isomers detected. Since **21** was the product from transition state **B** rather than the transition state **D**, it became clear that the general preference for the transition states to form *cis-anti-cis* isomers could have been overcome by the bigger steric interaction between axial hydrogens in the tether and the methyl group of the cyclopentene ring in transition state **D** than the steric interaction between two methyl groups in the transition state **B**.

In summary, we have demonstrated that the alkylidene carbenes generated from readily available ketones and $TMSCLiN_2$ were suitable for the TMM diyl [2+3] cycloaddition reaction and offered a supplementary synthetic strategy to the previously reported epoxyaziridinyl imine route for the construction of triquinanes. The current result explains the selectivity of the cycloaddition reaction of unsymmetrical TMMs and provides the valuable information for the future synthetic design and expected outcome for compounds with various substitution patterns.

Acknowledgments

We greatly acknowledge financial support from KOSEF through the center of molecular design and synthesis,

and from MarineBio21, Ministry of Maritime Affairs and Fisheries, Korea.

References and notes

1. Lee, H.-Y.; Kim, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10156.
2. (a) Platz, M. S.; Berson, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 6743; (b) Duncan, C. D.; Corwin, J. A.; Davis, J. H.; Berson, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 2350.
3. (a) Kirmse, W. *Angew. Chem., Int. Ed.* **1997**, *36*, 1164; (b) Wolinsky, J.; Clark, G. W.; Thorstenson, P. C. *J. Org. Chem.* **1976**, *41*, 745; (c) Seyferth, O.; Marmor, R. M.; Hilbert, P. H. *J. Org. Chem.* **1971**, *36*, 1379; (d) Shioiri, T.; Aoyama, J. *J. Synth. Org. Chem. Jpn.* **1996**, *54*, 918; (e) Kim, S.; Cho, C. M. *Tetrahedron Lett.* **1994**, *35*, 8405; (f) Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274.
4. Trost, B. M. *Science* **1991**, *254*, 1471.
5. Little, R. D.; Ott, M. M. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Health Science: Amsterdam, 2000; Vol. 22, p 195.
6. Sasaki, A.; Aoyama, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 3687.
7. *Method A*: To a THF solution (0.02 M) of $TMSCHN_2$ (2 equiv to the substrate) was added *n*-BuLi (2 equiv) at −78 °C under argon atmosphere. The mixture was stirred for 10 min at −78 °C and then was warmed to −30 °C before a solution of the substrate in THF was added over 20 min period. The reaction mixture was stirred for 10 min at −30 °C and then was allowed to warm to room temperature for 1 h. Brine was added to the reaction mixture and products were extracted with diethyl ether. The ether solution was dried over $MgSO_4$ and was concentrated. The crude product was purified by flash chromatography. *Method B*: To a solution of $TMSCHN_2$ (2 equiv) and the substrate in THF (0.01 M) was added $KN(TMS)_2$ (2 equiv, 0.5 M/toluene) over 20 min at −30 °C under argon atmosphere. Then the rest of the reaction followed the procedure in method A.
8. $TMSCKN_2$ instead of $TMSCLiN_2$ gave the better result for the tandem reaction sequence.
9. *Spectral data of* **16**–**21**. Compound **15**: ^{1}H NMR (200 Hz, $CDCl_3$); δ 0.92–1.08 (m, 1H), 1.04–1.15 (m, 6H), 1.16–1.29 (m, 1H), 1.52 (s, 3H), 1.40–1.52 (m, 1H), 1.54–1.73 (m, 2H), 1.87–1.97 (m, 1H), 2.11–2.24 (m, 1H), 2.26–2.38 (m, 1H), 2.41–2.54 (m, 2H), 2.70–2.83 (m, 2H), 3.01 (br, 1H), 3.90–4.06 (m, 4H). Compound **16**: ^{1}H NMR (200 Hz, $CDCl_3$); δ 0.88–1.07 (m, 3H), 1.15–1.32 (m, 1H), 1.41–1.56 (m, 1H), 1.52 (s, 3H), 1.64–1.81 (m, 2H), 1.86–1.99 (m, 1H), 2.11–2.23 (m, 1H), 2.42–2.50 (m, 1H), 2.67–2.80 (m, 2H), 2.92–3.06 (m, 1H), 3.00 (s, 2H), 3.05 (s, 2H), 3.12 (s, 3H), 3.15 (s, 3H). Compound **17**: ^{1}H NMR (200 Hz, $CDCl_3$); δ 0.76–0.96 (m, 2H), 1.12–1.39 (m, 6H), 1.62 (s, 3H), 1.60–1.72 (m, 1H), 1.84–2.09 (m, 2H), 2.34–2.52 (m, 1H), 2.53–2.79 (m, 2H), 2.80–3.03 (m, 2H), 3.05–3.19 (m, 1H), 3.57 (br, 1H), 4.10–4.22 (m, 4H), 6.85–7.24 (m, 5H). Compound **18**: ^{1}H NMR (300 Hz, $CDCl_3$); δ 0.75–0.83 (m, 1H), 1.07–1.25 (m, 3H), 1.47–1.57 (m, 1H), 1.52 (s, 3H), 1.82–1.94 (m, 3H), 2.36–2.43 (m, 1H), 2.65–2.68 (d, $J = 7.91$ Hz, 1H), 2.84–2.93 (m, 2H), 2.95–3.17 (m, 10H), 3.44 (br, 1H), 6.68–7.04 (m, 5H); ^{13}C NMR (75 Hz, C_6D_6); δ 14.60, 24.47, 38.90, 39.04, 39.96, 42.46, 50.91, 51.97, 53.34, 55.89, 59.22, 59.27, 74.36, 77.51, 125.75, 127.12, 128.10, 128.69, 144.95, 147.50. Compound **20**: ^{1}H NMR (500 Hz, Benzene-d_6); δ 0.85 (t, $J = 7.10$ Hz, 3H), 0.94 (t, $J = 7.05$ Hz, 3H), 1.13 (s, 3H), 1.49 (m, 1H), 1.58 (s, 3H), 1.84 (m, 1H), 2.18 (dd, $J = 5.7$, 10.1 Hz, 1H), 2.42 (m, 1H), 2.43 (d, $J = 16.5$), 2.45 (dd, $J = 16.9$, 9.5 Hz, 1H), 2.58 (dd, $J = 5.7$, 10.1, 1H), 2.72 (m, 1H), 2.85 (dd, $J = 5.7$, 12.0, 1H), 2.88 (d, $J = 16.5$ Hz, 1H), 3.13 (m, 1H), 3.91 (m, 2H), 4.02 (q, $J = 7.10$ Hz, 2H), 7.06–7.29 (m, 5H); ^{13}C NMR (125 Hz, Benzene-d_6); δ 14.60, 14.73, 15.78, 23.15, 30.61, 32.33, 33.63, 41.91, 42.50, 48.96, 49.41, 61.94, 62.05, 63.86, 64.60, 67.73, 127.10, 127.93, 129.49, 129.76, 129.88, 143.53, 148.86, 172.92, 173.55. Compound **21**: ^{1}H NMR (300 Hz, $CDCl_3$); δ 0.80 (s, 3H), 1.15–1.23 (m, 6H), 1.25 (s, 3H), 1.58–1.67 (m, 1H), 1.90–1.99 (m, 2H), 2.27–2.32 (m, 1H), 2.33–2.43 (m, 1H), 2.48–2.64 (m, 1H), 2.66–2.76 (m, 3H), 3.02–3.11 (m, 1H), 4.07–4.20 (m, 4H), 5.23–5.26 (m, 1H), 7.15–7.29 (m, 5H); ^{13}C NMR (75 Hz, $CDCl_3$); δ 13.97, 14.01, 19.15, 28.93, 35.05, 38.20, 41.42, 47.76, 47.96, 58.52, 61.39, 61.48, 61.78, 61.81, 63.36, 116.62, 126.01, 127.29, 128.06, 128.22, 140.14, 165.66, 172.24, 172.65.
10. Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 2744.