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Angularly Fused Triquinanes from Linear Substrates through Trimethylenemethane Diyl [2 + 3] Cycloaddition Reaction

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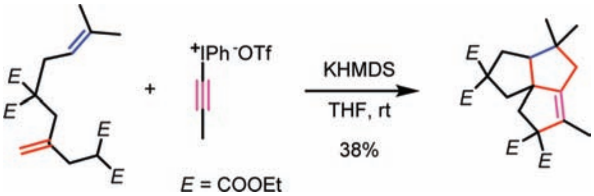
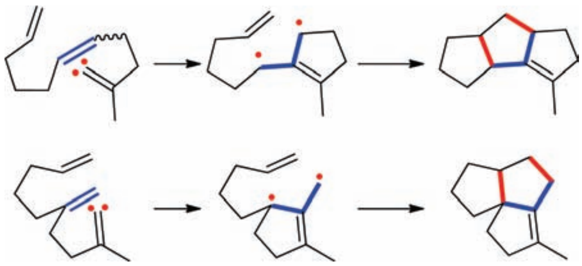
ABSTRACT



Angularly fused triquinanes were synthesized from linear dienes and phenyl(propynyl)iodonium salt through trimethylenemethane (TMM) diyl mediated [2 + 3] cycloaddition reaction. TMM diyl intermediates were obtained from alkylidene carbenes generated from reactions of alkynyliodonium salts with nucleophiles.

Cycloaddition reactions of trimethylenemethanes (TMMs)[1] provide a powerful tool for the synthesis of cyclopentanoids. The reactions proceed with good selectivity and have been applied to the total synthesis of structurally or biologically interesting compounds, especially the polyquinane natural products.[2] However, direct cycloaddition reactions of TMMs to form angularly fused triquinanes have not been reported yet, presumably because of the difficulty in the preparation of the appropriate precursors.[3,4] Recently, we reported new synthetic methodologies to generate TMM diyls from linear substrates through alkylidene carbenes,[5] and these new synthetic methodologies allow the easy preparation of linearly fused triquinanes. This alkylidene carbene route to TMM diyls can be extended to the construction of angularly fused triquinanes by simply altering the connectivity of the olefin that undergoes the intramolecular cyclopropanation reaction with the alkylidene carbene (Scheme 1). Formation of the angularly fused triquinanes should be less complicated than linearly fused triquinanes in the possible isomeric products as the reaction can produce only a single stereo- and regioisomeric triquinane product, whereas the linearly fused triquinane formation can produce stereo- as well as regioisomeric products.

Scheme 1. Synthetic Pathways to Triquinanes from Alkylidene Carbene



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[1] Yamago, S.; Nakamura, E. *Org. React.* **2002**, *61*, 1–217.
[2] Mehta, G. S. *Chem. Rev.* **1997**, *97*, 671–719.
[3] Little, R. D. *Chem. Rev.* **1996**, *96*, 93–114.
[4] Adam, W.; Finzel, R. *J. Am. Chem. Soc.* **1992**, *114*, 4563–4568.
[5] (a) Lee, H. Y.; Kim, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10156–10157. (b) Lee, H. Y.; Kim, W. Y.; Lee, S. *Tetrahedron Lett.* **2007**, *48*, 1407–1410. (c) Lee, H. Y.; Yoon, Y.; Lim, Y. H.; Lee, Y. *Tetrahedron Lett.* **2008**, *49*, 5693–5696.

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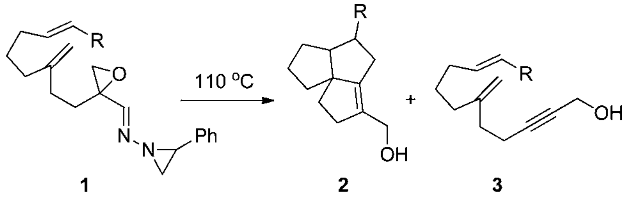
Herein, we report the first successful application of a TMM diyl [2 + 3] cycloaddition reaction to the synthesis of angularly fused triquinanes. Among the three strategies we have reported for the formation of alkylidene carbenes, the epoxyaziridinyl imine route was tested first as this route offers neutral reaction conditions and showed the highest efficiency among the three routes for the formation of linearly fused triquinanes (Scheme 2).[5a]

Scheme 2. Reactions of Epoxyaziridine Imines

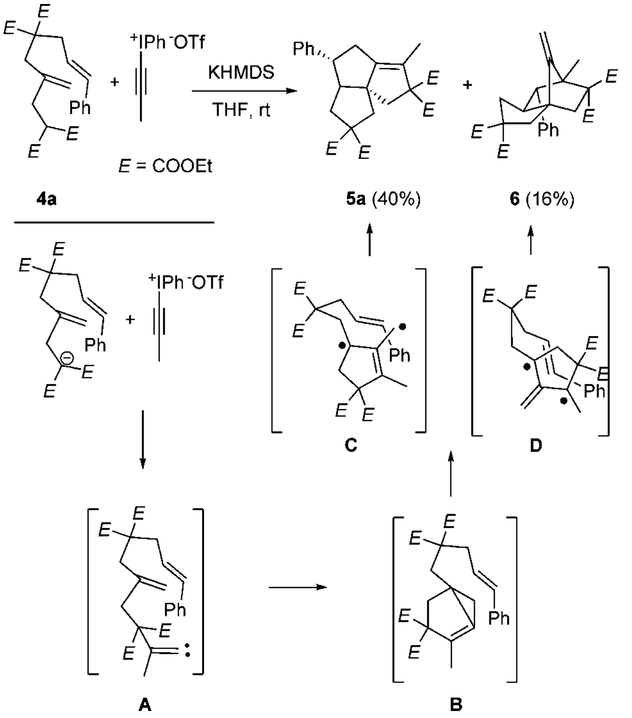


	1	2	3
a:	R=COOEt	18%	--
b:	R=CH_2OMe	8%	24%
c:	R=Me	--	36%
d:	R=H	--	26%

When the epoxyaziridinyl imine **1a** was heated at 110 °C, the desired angularly fused triquinane product **2a** was observed though the yield was low. When the ester group of **1a** was replaced by a methoxymethyl group, alkyne **3b** was obtained as the major product with desired product **2b** as the minor product. Formation of the rearranged alkyne product was unexpected since rearrangement of an alkyl group of the alkylidene carbene is much slower than hydrogen migration.[6] This result indicated that the intramolelcular cyclopropanation reaction onto the exocyclic olefin was not facile enough to compete with carbene rearrangement and retarded the formation of **2b**. Real disappointment came from the fact that the substrates with methyl or hydrogen on the olefin (**1c** and **1d**) produced the rearranged alkyne products without desired angularly fused triquinane products in detectable quantity. This result was not only synthetically inadequate but also quite surprising as the reactivity of the TMM diyl cycloaddition reaction has not been affected by the substitution pattern of the olefin counterpart except for the regioselectivity of the cycloaddition reaction.[7]

Since the inefficiency of the cascade reaction to form angularly fused triquinane product appeared to be mainly due to the competing carbene rearrangement to form an alkyne, lower reaction temperatures were thought to suppress the carbene rearrangement and to improve the yield of the desired products. As the alkynyl iodonium salt route to alkylidene carbene has been used to produce linearly fused triquinanes successfully at ambient temperature,[5c] they were explored next. When the anion of malonate **4a** was treated with propynyliodonium salt, the desired angularly fused triquinane product **5a** was obtained in 40% yield[8] along with the unanticipated regioisomeric product **6** as the minor product in 16% yield without forming rearranged alkyne product (Scheme 3).

Scheme 3. Reaction of Propynyliodonium Salt with Dienylated Malonate Anion and Detailed Mechanistic Pathway



The reaction starts with addition of the anion of **4a** to the propynyliodonium salt to form the alkylidene carbene **A**. Intramolecular cyclopropanation of **A** produces strained alkylidene cyclopropane **B** that breaks the cyclopropane ring to form TMM diyl. While [2 + 3] cycloaddition reaction of the TMM diyl with olefin could proceed via either **C** or **D**, the cyclopentane ring of **C** appears to be sterically less encumbered with the tether and the olefin than that of **D** and provides bias for **5a** as the major product. Though an unanticipated minor product was produced along with the desired product, the overall efficiency for the cascade reaction improved dramatically. With this successful result, we examined the cycloaddition reaction of substrates with various substitution patterns, and the results are summarized in Table 1.

All of the substrates in the table produced only the angularly fused triquinanes **5** with no sign of the formation of products analogous to **6**. It was only the phenyl substituent on the olefin that produced the regioisomeric products. This exception is presumed to be due to the steric interaction of the cyclopentene ring of **C** with the phenyl group of the olefin that reduces the preference of **C** over **D** in the cycloaddition reaction. The stepwise nature of the cycloaddition reaction might have contributed to the formation of **6** as the diradical intermediate formed from the first

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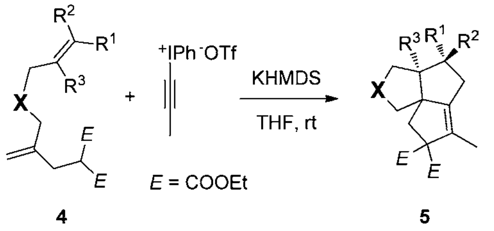
(6) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795–3849.

(7) Masjedizadeh, M. R.; Dannecker-Doering, I.; Little, R. D. *J. Org. Chem.* **1990**, *55*, 2742–2752.

(8) Starting material **4a** was not completely consumed, and the yield of **5a** was 45% based on the recovered starting material.

Table 1. Angularly Fused Triquinanes from Iodonium Salt and Malonate Anions



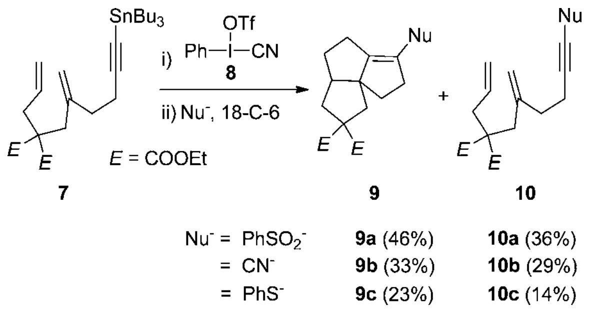
4	X	R^1	R^2	R^3	**5**	yield (%)
4b	$C(COOEt)_2$	H	H	H	**5b**	33
4c	$C(COOEt)_2$	Me	Me	H	**5c**	38
4d	$C(COOEt)_2$	H	H	Me	**5d**	34
4e	$C(OMe)_2$	H	H	Me	**5e**	28
4f	$C(S(CH_2)_3S)$	H	H	Me	**5f**	34
4g	O	H	H	Me	**5g**	0
4h	O	Ph	H	H	**5h**	0

bond formation between TMM diyl and the olefin is stabilized by the phenyl group and this radical intermediate survives long enough to react with either end of the allylic radical.[9] The moderate yield of the tandem cycloaddition reaction to angularly fused triquinane seems to reflect the ring strain during the cycloaddition reaction. Though the yields of angularly fused triquinanes appeared moderate, the synthetic strategy is useful for the synthesis of natural products as there were no other products in significant amount and relatively good per step efficiency of the multistep reaction sequence (70% per step).

Results in the Scheme 3 and Table 1 show that the tandem cycloaddition reaction for the formation of angularly fused triquinanes appeared to be quite general regardless of the substitution pattern of the olefin (**4c**, **4d**), whereas the cycloaddition reaction to form linearly fused triquinanes was sensitive to the substitution pattern as the *cis*-olefins and *exo*-olefins did not undergo cycloaddition reaction.[5a] On the contrary, substrates that contain relatively acidic protons (**4g**, **4h**) did not produce the desired products. This result might reflects the strain associated with cyclization,[10] since the substrates for the linear triquinane formation produced the desired linearly fused triquinanes, though the yields were low.[5b]

While the alkynyliodonium route to TMM diyls provides a convergent pathway to triquinanes, only the propynyliodonium salt can be used as the electrophile to form alkylidene carbenes because of the facile rearrangement of the acetylenic iodonium salt to an alkyne or C−H insertion reactions of the carbene intermediates that would be derived from other substituted alkynes.[11] To expand the substrate scope, we next examined the formation of TMM diyls obtainable from the substrates that possess an alkynyl iodonium salt in the same molecule (Scheme 4).

Scheme 4. From Linear Substrate to Angularly Fused Triquinane



	9	10
Nu^- = $PhSO_2^-$	**9a** (46%)	**10a** (36%)
= CN^-	**9b** (33%)	**10b** (29%)
= PhS^-	**9c** (23%)	**10c** (14%)

When the alkynyl iodonium salt prepared from the reaction of dieneyne **7** with **8** was treated with phenylsulfinate anion or thiophenoxide, the desired angularly fused triquinanes **9** were obtained along with substituted alkynes **10**. The formation of alkynes **10** occurred through the rearrangement of the corresponding alkylidene carbenes.[12] If the formation of **10** was from the corresponding alkylidene carbene, a carbon nucleophile would form an alkylidene carbene that will not rearrange easily. When cyanide anion that has not been reported as a nucleophile for alkynyl iodonium salts[13] was treated with the alkynyl iodonium salt in the hope that the rearrangement of the corresponding alkylidene carbene would not occur, result similar to that with the heteroatom nucleophiles was observed as the reaction produced the angularly fused triquinane product **9b** as well as the alkyne product **10b**.

In summary, we have demonstrated for the first time that the angularly fused triquinanes can be synthesized through TMM-mediated [2 + 3] cycloaddition reaction using tandem cycloaddition reaction of alkylidene carbene generated from alkynyl iodonium salts through TMM diyls. The new synthetic methodology can readily be applied to the total synthesis of various angularly fused triquinane natural products.[2]

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Note Added after ASAP Publication. Scheme 3 was incorrect in the version published ASAP May 10, 2010; the correct version reposted May 12, 2010.

Supporting Information Available: Synthetic schemes for the substrates, experimental details, and spectral data for cyclization products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Siemionko, R. K.; Berson, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 3870–3882.

(10) Examples of reactivity differences due to different substitution patterns of the olefin in the cyclopropanation reaction: (a) Mori, K. *Tetrahedron: Asymmetry* **2007**, *18*, 838. (b) Uchida, T.; Katsuki, T. *Synthesis* **2006**, 1715. Different cycloaddition mode of Pauson−Khand reaction to form angularly fused triquinanes: (c) Knudsen, M. J.; Schore, N. E. *J. Org. Chem.* **1984**, *49*, 5025. (d) Ishizaki, M.; Iwahara, K.; Niimi, Y.; Satoh, H.; Hoshino, O. *Tetrahedron* **2001**, *51*, 2729.

(11) (a) Tykwinski, R. R.; Stang, P. J.; Persky, N. E. *Tetrahedron Lett.* **1994**, *35*, 23–26. (b) Ochiai, M.; Kunishima, M.; Nagao, Y.; Fuji, K.; Shiro, M.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 8281–8283.

(12) (a) Ochiai, M.; Kunishima, M.; Tani, S.; Nagao, Y. *J. Am. Chem. Soc.* **1991**, *113*, 3135–3142. (b) Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927–10966.

(13) Ochiai, M.; Kunishima, M.; Fuji, K.; Nagao, Y. *J. Org. Chem.* **1988**, *53*, 6144–6145.