

Triquinanes from Linear Alkylidene Carbenes via Trimethylenemethane Diyls

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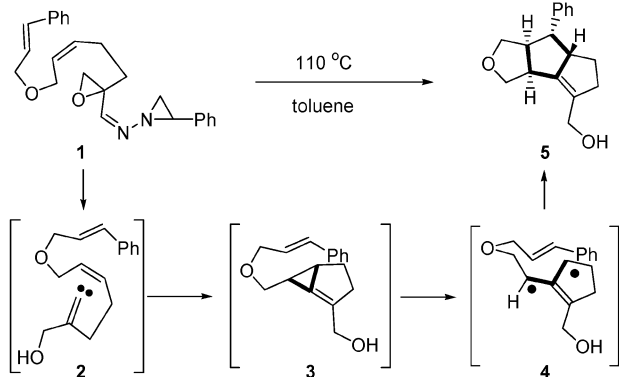
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Carbenes are useful intermediates in organic synthesis.¹ While alkylidene carbene² has been used for the C–H insertion reaction,³ it has been much less used for the cyclopropanation reaction⁴ presumably due to the instability of the products from the intramolecular cyclopropanation reaction.⁵ This was well exemplified in Koebrich's reports⁶ in which the intramolecular cyclopropanation reaction of the 2-methyl-1-hexa-1,5-dienylidene carbene system formed the reactive bicyclo[3.1.0]hex-1-ene system that underwent subsequent transformation to form various dimeric products. The mechanism and reactive intermediates of the formation of dimeric products were thoroughly studied by Berson,⁷ and one of the reactive intermediates was the trimethylenemethane (TMM).⁸ TMM diyls, its metallo-analogues, and its zwitterionic analogues are well known to undergo a [2+3] cycloaddition reaction with olefins to form cyclopentane rings.⁹ As the [2+3] cycloaddition reaction of TMM diyls has been applied to the total synthesis of various polycyclic natural products,¹⁰ we were intrigued by a possibility of utilizing alkylidene carbene as a source of TMM diyl that would undergo a [2+3] cycloaddition reaction or radical reactions because carbenes have rarely been used as sources for diradicals.^{5b}

Herein, we report a tandem cycloaddition reaction of alkylidene carbenes of linear substrates into tricyclic compounds through sequential formation of alkylidene carbenes and the TMM diradical intermediates as shown in Scheme 1. We selected epoxyaziridinylienes as the source of alkylidene carbenes^{11c} among several popular sources for alkylidene carbenes¹¹ because the reaction conditions for generation of alkylidene carbenes from epoxyaziridinylienes were deemed most suitable for the transformation of the initially formed methylenecyclopropane intermediates into the TMM diradicals before other reaction pathways could prevail.¹²

Scheme 1



When a solution of **1** in toluene was heated at 110 °C until all of the starting material disappeared, a single major product **5** was isolated. The observation of a single major product formation was quite gratifying because the reaction could yield not only isomeric

products from the [2+3] cycloaddition reaction of TMM diyls but also produce compounds through other reaction pathways such as the ene reaction or [2+2] cycloaddition reaction of **3**. The reaction was believed to proceed through the alkylidene carbene and the subsequently formed TMM diradical intermediates. Along the way, one existing C=C bond was cleaved, and four new C–C bonds were formed with four contiguous stereocenters. Although **4** could form regioisomeric products, only a single regioisomeric product was observed, and complete stereoselectivity for the cis-anti isomer was also observed. The complete stereoselectivity in the current cycloaddition reaction was presumed to be due to a severe 1,3-allylic interaction of the hydroxymethyl substituent of the TMM diradical intermediate with the tethered alkyl chain during the cycloaddition reaction.¹³

With the successful transformation of **1** into **5**, we examined the cyclization reaction with substrates having various substitution patterns on the terminal olefin (Table 1). The reaction preserved the stereochemistry of the olefins during the [2+3] cycloaddition reaction¹⁴ and was not affected much by the electronic environment of the olefins as most substrates produced tricyclic compounds in similar yields except entry 7.

Table 1.

entry	product	R ¹	R ²	R ³	yield (%)
1	5	Ph	H	H	68
2	22a	Ph	H	H	54
3	22b	CO ₂ Et	H	H	49
4	22c	H	H	H	52
5	22d	Me	H	H	50
6	22e	H	H	Me	52
7	22f	H	H	H	35

The efficiency of this tandem reaction was demonstrated by application of the current methodology to a total synthesis of hirsutene.¹⁵ The tricyclic precursor (**6**) for hirsutene could be assembled from the linear epoxyaziridinyliene (**7**), which, in turn, could be prepared through the Wittig reaction of a known aldehyde (**8**)¹⁶ and a phosphonium salt containing an allylic alcohol moiety (**9**) (Figure 1).

The synthesis started from a known compound (**10**) obtained from the reaction of the dianion of methallyl alcohol with THP-ether of bromoethanol¹⁷ after the protecting group exchange (Scheme 2). The primary hydroxyl group was converted to triphenylphosphonium bromide (**11**) through standard activation

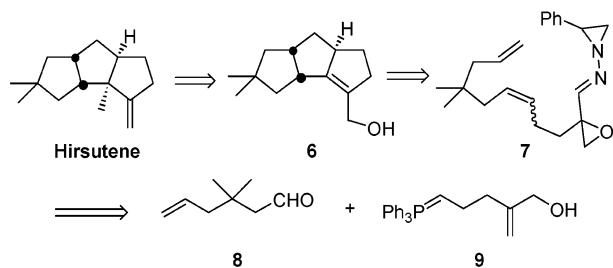
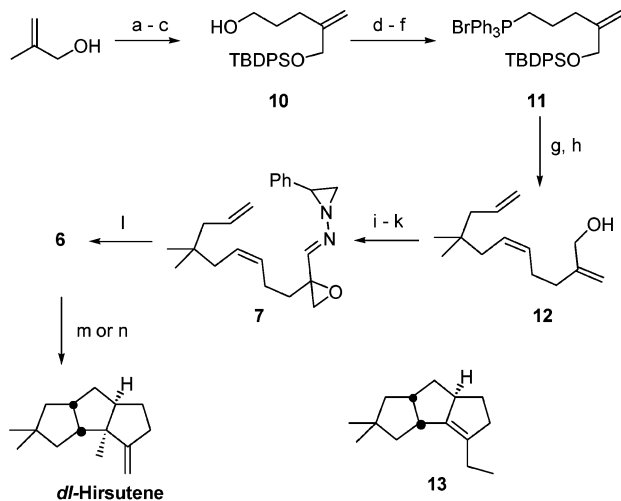


Figure 1. Synthetic analysis of DL-hirsutene.

followed by the substitution reaction sequence. Wittig reaction of the ylide of **11** with **8** and deprotection of TBDPS group afforded trienyl alcohol (**12**). This alcohol was transformed into epoxyzirindinylimine (**7**) through a three-step sequence of selective epoxidation of the allylic alcohol,¹⁸ oxidation of the epoxy alcohol by Dess–Martin periodinane,¹⁹ and condensation with *N*-amino-2-phenylaziridine.²⁰ The epoxyzirindinylimine (**7**) was heated in refluxing toluene to produce the triquinane alcohol (**6**), which was converted into hirsutene in a four-step sequence; the TMSCl assisted 1,4-addition²¹ of the methyl group to the corresponding unsaturated aldehyde followed by dehydration of the corresponding alcohol using Grieco's protocol.²² Hirsutene was also obtained directly from **6** through the NiCl₂(dppf)-catalyzed allylic alkylation reaction²³ of TMS–ether of **6**.^{23a,24}

Scheme 2^a



^a Reaction conditions: (a) 2.5 equiv of *n*-BuLi, TMEDA, Et₂O–THF, Br(CH₂)₂OTHP, 45%; (b) TBDPSCl, imidazole, CH₂Cl₂; (c) *p*-TsOH, MeOH, 89% for two steps; (d) MsCl, Et₃N, CH₂Cl₂; (e) LiBr, acetone, reflux, 90% for two steps; (f) PPh₃, NaHCO₃, CH₃CN, reflux, 79%; (g) *n*-BuLi, THF, **8**; (h) TBAF, THF, 75% for two steps; (i) VO(acac)₂, *t*-BuOOH, benzene, 84%; (j) Dess–Martin periodinane, CH₂Cl₂; (k) H₂NNCH₂CHPh, MeOH, 80% for two steps; (l) toluene, reflux, 57%; (m) TPAP–NMO/CH₂Cl₂, 81%; (ii) Me₂CuLi, TMSCl/Et₂O–THF, HCl, NaBH₄/MeOH 93%; (iii) *o*-NO₂PhSeCN–*n*-Bu₃P/THF, H₂O₂/THF, 81%; (n) (i) TMSCl, Et₃N, THF, 84%; (ii) MeMgBr, NiCl₂(dppf), benzene, reflux, 83% (hirsutene:**13** = 4:1).

In summary, a tandem reaction sequence starting from alkylidene carbenes of linear substrates to form triquinane compounds was developed and was successfully applied to a total synthesis of hirsutene.

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

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