

Attempted synthesis of casbene by intramolecular cyclopropanation

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This paper is dedicated to Al Padwa on the occasion of his 65th birthday in recognition of his outstanding contributions to organic chemistry

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Abstract

The antifungal diterpene casbene has been prepared in low yield by intramolecular cyclopropanation of the vinyl diazomethane reactant formed from geranylgeraniol. Careful analysis of the reaction mixture revealed relatively unselective addition catalyzed by dirhodium(II) and copper(I) catalysts.

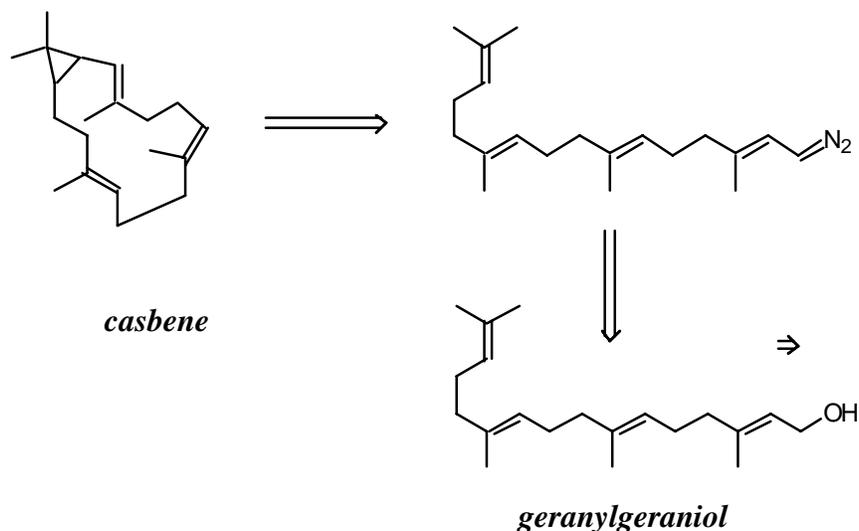
Keywords: Dirhodium(II) catalysis, vinyl diazomethane, copper(I) catalysis, diterpene, macrocyclization

Introduction

In 1982 T. Takahashi and coworkers at the University of Tokyo reported the synthesis of racemic casbene by intramolecular cyclopropanation of a vinyl diazomethane formed from all-trans geranylgeraniol (Scheme 1).¹ Casbene is an anti-fungal diterpene from cell-free extracts of castor bean² and is implicated in the biosynthesis of several diterpenes.³

Takahashi reported up to a 14% yield of casbene when the vinyl diazomethane intermediate was treated with two molar equivalents of copper(I) iodide in tetrahydrofuran, and no mention was made of other cyclopropanation products. There has been no subsequent report of this cyclization process.

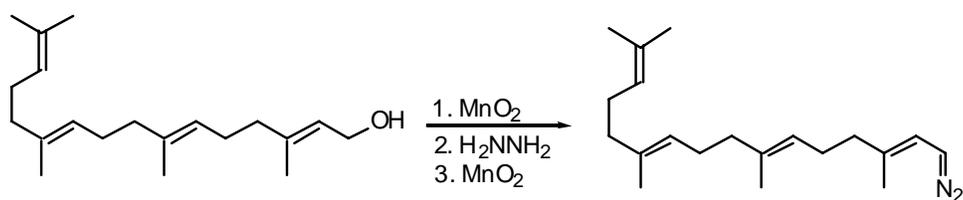
With our growing experience in macrocyclization chemistry employing transition-metal-catalyzed diazo decomposition⁴⁻⁶ we targeted the synthesis of casbene to ascertain the potential of a variety of catalysts— and especially those with chiral ligands—to effect this transformation. Rhodium(II) catalysts have shown advantages over those of copper(I) for catalytic cyclopropanation,⁷ but few examples have been reported of their uses beyond those with diazocarbonyl compounds.⁸



Scheme 1. Retrosynthetic analyses for casbene.

Results and Discussion

Our first task was to develop a reliable procedure for the oxidation of allylic alcohol, formation of hydrazone, and further oxidation to vinyl diazomethane (Scheme 2). The efficient conversion of vinyl-aldehydes into vinyl diazomethanes has been reported⁹ for model compounds, and this process was employed for the transformation in Scheme 2.

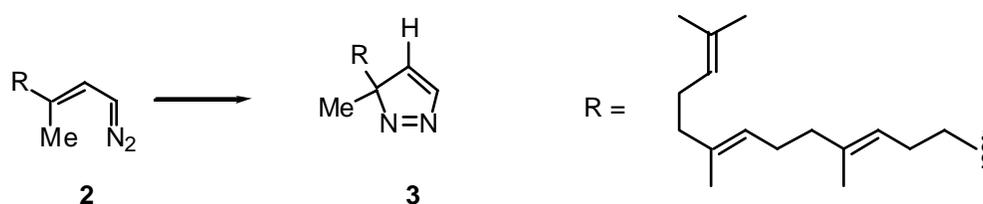


Scheme 2. Preparation of a substituted vinyl diazomethane from (geranylgeraniol) allyl alcohol.

The diazo compound formed in this way was red in solution, and used without further purification. Using MnO_2 as the oxidant did cause the conversion of up to 30% of the intermediate hydrazone to geranylgeraniol, but the presence of this aldehyde did not influence the selectivity for intramolecular cyclopropanation.

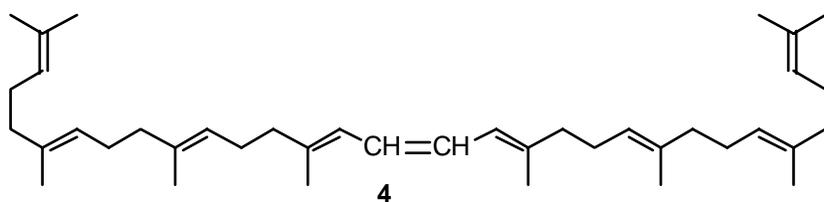
The importance of using the diazo compound **2** immediately, without further purification, was determined by its relative instability towards intramolecular dipolar cycloaddition (Scheme 3)—a process that is well known for vinyl diazoesters.¹⁰ This process was minimized by using the diazo compound for catalytic diazo decomposition without storage or separation of the

geranylgeranial from **3**. The resulting pyrazole (**3**) could then account for more than 50% of the isolated products.

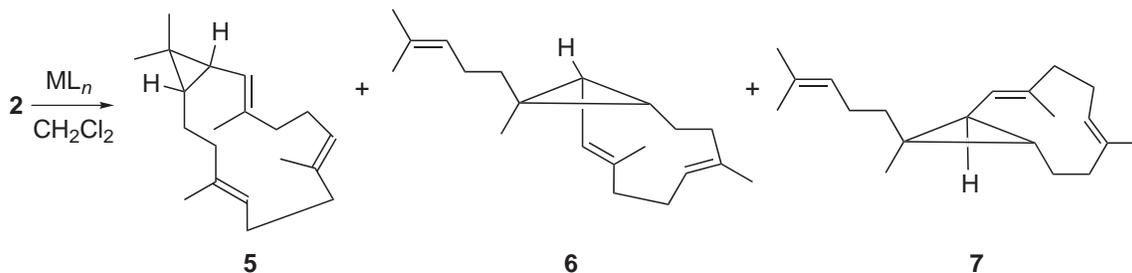


Scheme 3. Intramolecular dipolar cycloaddition.

Diazo decomposition was initially investigated with $\text{Rh}_2(\text{OAc})_4$ as the catalyst. In this case, as expected, the major products were the pyrazole **3**, geranylgeranial, and carbene dimer **4**. Only a 5% isolated yield of cyclization products was obtained, but three compounds were identified (Scheme 4), one of which was casbene (**5**).



The ^1H NMR spectrum of casbene (**5**)^{3,11} is characteristic in that this isomer is the only one with two methyl groups bound to an sp^3 -hybridized carbon and with adjacent cyclopropane ring hydrogens, one of which is at δ 0.5 and has the requisite coupling constants for a designated *cis*-geometry.



Scheme 4. Products formed by catalytic diazo decomposition of **2**, casbene.

This spectrum was sufficient to identify this product. Two other products, designated **6** and **7**, were formed, the latter as a minor component and, consequently, its structural designation is more speculative. Neither **6** nor **7** has been reported previously, but their spectra are consistent with these assignments.

Three chiral catalysts were used in attempts to prepare enantiomerically-enriched casbene. One of these was the copper(I) bis-oxazoline complex (**8**) previously demonstrated to be successful for enantioselective macrocyclizations,⁴⁻⁶ and the other two were based on dirhodium(II), as the chiral carboxamidate (**9**) or carboxylate (**10**).⁸ The isolated yields of **5-7** and their distribution are given in Table 1.

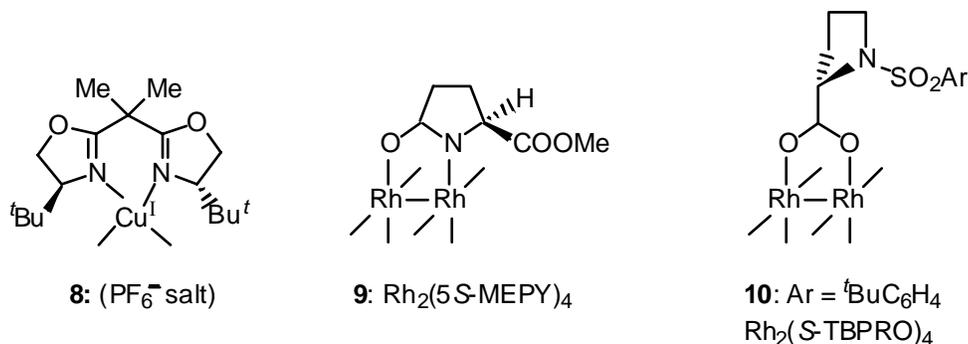
Table 1. Catalytic decomposition of **2** with copper and dirhodium catalysts ^a

Catalyst	Yield (%) ^b of	Ratio ^c of
	5 + 6 + 7	5 : 6 : 7
Rh ₂ (OAc) ₄	4.2	36 : 63 : 1
CuPF ₆ / bisoxazoline (8)	5.5	48 : 40 : 12
Rh ₂ (5 <i>S</i> -MEPY) ₄ (9)	4.5	7 : 92 : 1
Rh ₂ (<i>S</i> -TBPRO) ₄ (10)	7.8	69 : 28 : 3

^a Reactions were carried out in dichloromethane at 0° C with diazo compound: catalyst = 100:1.

^b Isolated yield after chromatography, based on starting geranylgeranial. ^c Determined by GC with a SPB-5 column.

Note that Rh₂(5*S*-MEPY)₄ favors formation of **6**, whereas Rh₂(*S*-TBPRO)₄ favors the formation of casbene.



Using Rh(*S*-TBPRO) as the catalyst, dimer **4** was isolated in 13% yield, and geranylgeranial was obtained in 30% yield (81% *trans*). The hydrocarbon fraction constituted a 7.8% yield, based on reactant geranylgeranial. Further purification of this sample to 85% **5** + 15% **6** by column chromatography on silica impregnated with silver nitrate gave an optical rotation of $[\alpha]_D^{22} = +25.8$ ($c=0.3$, CHCl₃) compared to the literature value for casbene of +201.³

The conclusion that we reach is that this methodology is not viable for the synthesis of casbene even though enantioselective macrocyclization does occur. Difficulties in the formation of vinyldiazo compounds, their stability once formed, and in the relatively unselective cyclopropanation, make this approach untenable for casbene or similar compounds.

Experimental Section

Synthesis of geranylgeranial. Geranylgeraniol (1.0 g, 3.4 mmol) was dissolved in 100 mL hexane in an ice-bath. To this solution active MnO₂ (2.8 g, 34 mmol, 10 equiv.) was added in one portion. The reaction mixture was stirred at 0° C for 2h, filtered through a layer of Celite to remove the MnO₂, and the filtrate evaporated under vacuum to give a yellow oil, which was purified by column chromatography (hexane:ethyl acetate = 12:1) to give geranylgeranial (0.66 g, 67%) as a colorless oil whose spectra confirmed this assignment. ¹H NMR (250 MHz, CDCl₃): 9.95 (1H, d, J = 8 Hz), 5.88 (d, J = 8.1 Hz, 1H), (t, J = 6.3 Hz, 3H), 2.25 (s, 3H), 2.18 (s, 3H), 1.9-2.15 (m, 12H), 1.70 (s, 3H), 1.58 (s, 6H).

Synthesis of the vinylic diazomethane 2. Geranylgeranial (1.0 g, 3.4 mmol) and triethylamine (2.4 mL 17 mmol, 5 equiv.) were mixed in 10 mL anhydrous ethanol at 0° C. To this solution was added anhydrous hydrazine, 0.52 mL (17 mmol, 5 equiv.), over 10 minutes, and the solution was stirred for 1 h. The solvent and excess reagents were removed under vacuum, keeping the solution at 0° C. A light yellow oil was obtained, which was dissolved in 10 mL of pre-chilled dichloromethane, and used immediately in the next step.

To a suspension of active MnO₂ (2.8 g, 34 mmol, 10 equiv.) and Na₂CO₃ (3.6 g, 34 mmol, 10 equiv.) in 25 mL dichloromethane at 0° C was added the preceding solution of geranylgeranyl hydrazone in dichloromethane, in one portion. The resulting mixture was stirred for 2 h at 0° C. After the excess MnO₂ was filtered off through a layer of Celite, a red solution was obtained and used immediately in the next step. IR (neat): 2056 cm⁻¹ (C=N₂).

Catalytic decomposition of 3. To a solution of the catalyst (0.034 mmol, 0.01 equiv.) in 5 mL dichloromethane at 0° C was added the solution of diazo compound **3** in dichloromethane over 0.5 h. The resulting mixture was stirred for 1 h at 0° C. The solvent was removed under vacuum and the residue purified by chromatography (hexane) to give the hydrocarbon fraction as colorless oil. Continued elution with hexane:ethyl acetate, 30:1 furnished the dimer as an oil. Eluting with hexane: ethyl acetate, 12:1, furnished geranylgeranial as colorless oil. The hydrocarbon fraction was analyzed by GC on an SPB-5 column (30m x 0.25 mm). RT for compound **1**, 19.01 min, RT for compound **2**, 18.47 min, RT for compound **3** (casbene), 18.81 min. (flow rate: 1mL/min, oven temp: 100° C for 2 min., then 10° C/min to 275° C).

Casbene. ¹H NMR (500 MHz, CDCl₃): 0.59 (dt, 1H, J = 8.7, 1.5 Hz), 0.91 (s, 3H), 1.05 (s, 3H), 1.22 (t, 1H, J = 8.7 Hz), 1.54 (s, 3H), 1.65 (s, 3H), 1.66–2.33 (m, 12H), 4.85-4.93 (m, 2H), 4.97 (t, 1H, J = 6.0 Hz). MS (EI, 70 EV) with *m/e* (rel. abund.): 272 (M, 20), 136 (50), 121 (100), 107 (65), 93 (80), 67(40).

Compound 6. ¹H NMR (500 MHz, CDCl₃): 0.83 (s, 3H), 0.88 (t, 1H, J = 7.0, Hz), 1.12–1.18 (m, 1H), 1.54 (s, 6H), 1.60 (s, 3H), 1.65–2.10 (m, 12H), 5.07–5.14 (m, 2H), 5.52–5.56 (m, 1H). MS

(EI, 70 EV) with m/e (rel. abund.): 272 (M, 6), 187 (25), 159 (20), 119 (92), 107 (40), 93 (60), 69 (100), 55 (25), 41 (50).

Compound 7. ^1H NMR (500 MHz, CDCl_3): 0.81–0.89 (m, 1H), 0.98 (d, 1H, $J = 7.0$ Hz), 1.25 (s, 3H), 1.53 (s, 3H), 1.59 (s, 6H), 1.66 (s, 3H), 1.93–2.20 (m, 12H), 5.05–5.13 (m, 2H), 5.67–5.73 (m, 1H). MS (EI, 70 EV) with m/e (rel. abund.): 272 (M, 12), 136 (50), 121 (100), 107 (70), 93 (90), 67 (55).

Dimer 4. ^1H NMR (250 MHz, CDCl_3): 1.61 (s, 18H), 1.70 (s, 6H), 1.78 (s, 6H), 1.9–2.18 (m, 24H), 5.08–5.16 (m, 6H), 5.86–5.94 (m, 2H), 5.31–5.40 (m, 2H).

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