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Rapid Assembly of the Salvileucalin B Norcaradiene Core

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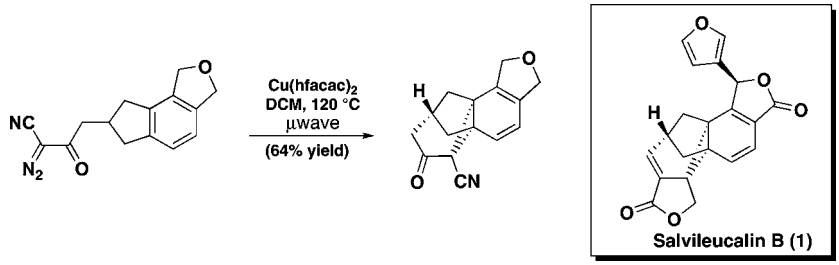
ABSTRACT



Preparation of the polycyclic core of the cytotoxic natural product salvileucalin B is described. The key feature of this synthetic strategy is a copper-catalyzed intramolecular arene cyclopropanation to provide the central norcaradiene. These studies lay the foundation for continued investigations toward an enantioselective total synthesis of 1.

Plants of the *Salvia* genus have a rich history in traditional medicine.[1] Indeed, the name *Salvia* derives from the Latin word *salvare*, which means, "to heal". Isolation studies targeting *Salvia* plants have yielded a wealth of structurally intriguing, biologically active natural products, including the potent hallucinogen salvinorin A.[2] Recently, studies aimed at identifying novel diterpenoids as potential medicinal leads resulted in the isolation of three new compounds from *Salvia leucantha* that possess unusual structures.[3] Of particular interest is the compound salvileucalin B (**1**), which exhibits promising cytotoxicity against A549 (human lung adenocarcinoma) and HT-29 (human colon adenocarcinoma) cells, and comprises an unusual norcaradiene core embedded within the polycyclic carbon skeleton. The structural assignment of compound **1** was confirmed by single-crystal X-ray diffraction.

The isolation of a norcaradiene-containing natural product is striking, as it is well-known that simple norcaradienes undergo facile electrocyclic ring-opening to provide the corresponding cycloheptatrienes.[4] Studies have shown that sterically[5] or electronically[6] biased, as well as geometrically constrained norcaradienes[7] (such as that found in **1**) can be stable at room temperature. The electrocyclic ring-opening of norcaradiene **1** would produce two bridgehead olefins within a strained [4.3.1]bicycle, and is therefore anticipated to be highly unfavorable.

In considering a synthesis of **1**, we were intrigued by the possibility of employing a late-stage intramolecular cyclopropanation reaction of a tricyclic arene such as **2** to directly form the norcaradiene core. Since the initial report by Buchner and Curtius in 1885 detailing the thermolysis of ethyl diazoacetate in benzene,[8] the cyclopropanation of

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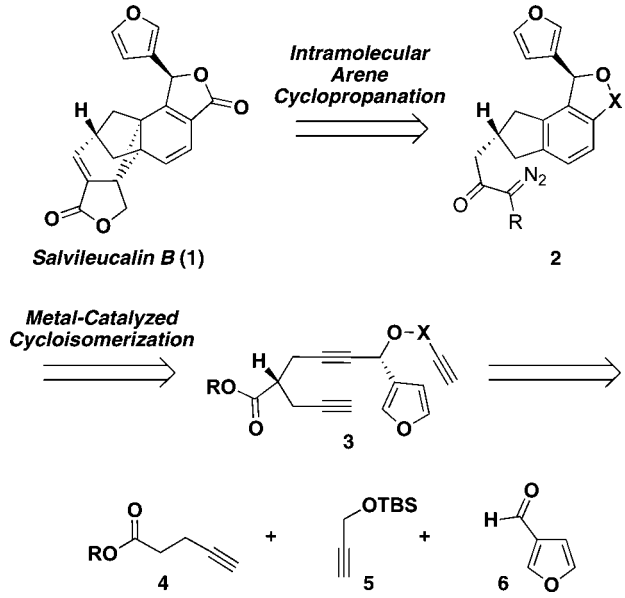
arenes has been the focus of numerous investigations. Thermal Buchner reactions generally provide the ring-opened cycloheptatriene products as mixtures of isomers.[4] With the advent of transition metal-catalyzed decomposition of stabilized diazo compounds,[9] several methodological studies have demonstrated that isomerically pure cycloheptatrienes can be isolated in synthetically useful yields from an appropriate diazo precursor and arene with use of Cu and Rh catalysts.[10−12] Despite the prevalence of cycloheptane containing natural products, the Buchner reaction is still under-utilized in total synthesis endeavors.[13]

Access to **1** via cyclopropanation of **2** requires the chemoselective intramolecular reaction of a metal-carbenoid (derived from the α-diazo carbonyl of **2**) with the arene π-system, in preference to highly favorable C−H insertion reactions at the adjacent, activated benzylic proton sites.[14] In addition, cyclopropanation to give **1** requires formation of a fully substituted cyclopropane. In this context, the cyclopropanation of **2** provides an interesting case study of the factors influencing benzylic C−H insertion versus arene cyclopropanation. In a synthetic sense, it is envisioned that arene **2** could easily arise from the cycloisomerization[15] of triyne **3**, which in turn could derive from the union of fragments **4**, **5**, and **6**. Reported herein are our initial forays into the execution of this synthetic plan (Scheme 1).

Scheme 1. Retrosynthetic Analysis of Salvileucalin B



Whereas an enantioselective synthesis of **1** would require an asymmetric alkylation reaction to prepare triyne **3**, for the purpose of rapidly accessing the α-diazo carbonyl compounds of interest, the compounds in this study were prepared as racemates. Thus, our model studies commenced with the alkylation of commercially available dimethyl propargyl malonate with TBS-protected propargyl bromide **8**,[16] followed by acid-mediated cleavage of the silyl ether to give diyne **9**[17] in 87% yield (Scheme 2). Alkylation of **9** with propargyl bromide provided the corresponding triyne, which, after exposure to $Pd(PPh_3)_4$ (2.5 mol %) in the presence of AcOH, smoothly delivered tricycle **10** in 78% yield (54% yield over the two-step sequence).[18,19] Krapcho dealkoxycarbonylation[20] of tricycle **10** was followed by saponification with potassium hydroxide to give carboxylic acid **11**. Subsequent conversion to the acid chloride and homologation with use of the Arndt−Eistert protocol[21] furnished carboxylic acid **12** in 75% yield. The α-diazo ketone **14** was prepared in good yield by treatment of the acid chloride derived from carboxylic acid **12** with an ethereal solution of diazomethane.

With α-diazo ketone **14** in hand, a number of metal catalysts were evaluated for their ability to promote the formation of norcaradiene **18**. Whereas Rh^{II} catalysts favored the formation of C−H insertion products (Table 1, entries 1−3),[22] $Cu(acac)_2$ provided more promising levels of cyclopropanation (entry 4). Further screening of several Cu^{II} catalysts revealed that the yields of norcaradiene **18** were highly catalyst dependent, with relatively electron-poor Cu^{II} salts providing the best results (entries 5−8). Although conducting the reactions in a microwave reactor proved useful in the context of catalyst screening, improved yields

Table 1. Catalysts Screened for Cyclopropanation of α-Diazo Ketone **14**

entry	catalyst	method[a]	% yield[b]
1	$Rh(OAc)_4$	A	14
2	$Rh(cap)_4$	A	1
3	$Rh(tfa)_4$	A	5
4	$Cu(acac)_2$	B	30
5	$Cu(tfacac)_2$	B	50 (73)[c]
6	$Cu(hfacac)_2$	B	40
7	$Cu(TMHD)_2$	B	28
8	$Cu(TBS)_2$	B	11

[a] Method A: [**14**] = 0.01 M, [cat.] = 0.001 M, CD_2Cl_2, 22 °C, 12 h. Method B: [**14**] = 0.01 M, [cat.] = 0.001 M, CD_2Cl_2, 100 °C (microwave), 1 min. [b] Determined by ^1H NMR analysis of crude reaction mixture, using an internal standard. [c] Isolated yield, slow addition of **14**, DCE, reflux.

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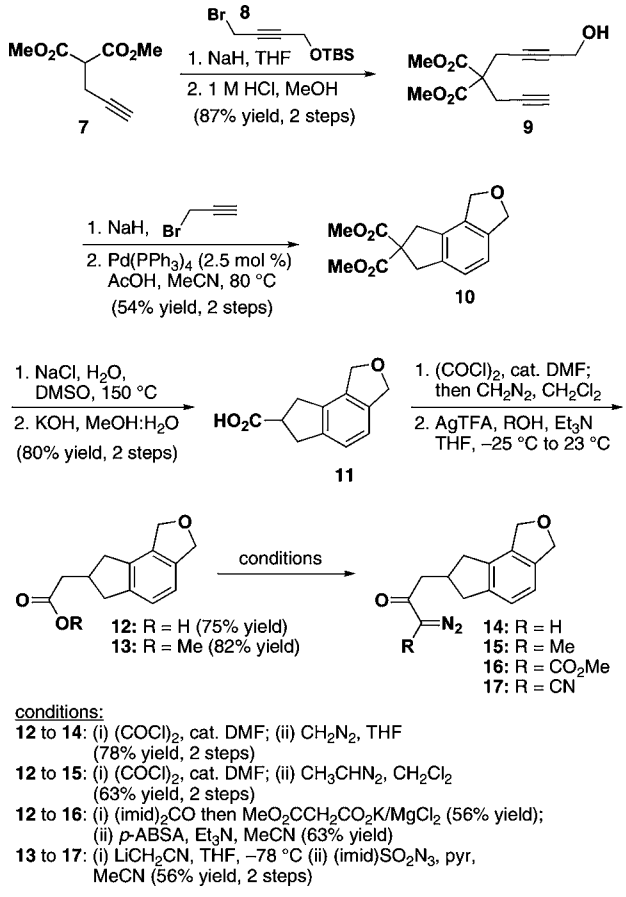
were obtained for substrate **14** by using a slow addition protocol. Thus, syringe pump addition of **14** to a solution of $Cu(tfacac)_2$ in dichloroethane at reflux cleanly provided norcaradiene **18** in 73% isolated yield. Notably, the ^1H NMR spectrum of **18** shows no evidence of the corresponding cycloheptatriene at room temperature.

There are several reports of Rh^{II} catalysts providing good yields of Buchner products; however, these systems generally lack benzylic protons, or geometrically disfavor C−H insertion.[23] In systems where C−H insertion is geometrically favorable, Cu^{II} catalysts provide improved selectivity for cyclopropanation.[24] Although we were pleased with our ability to prepare norcaradiene **18**, more functionalized norcaradienes were required to facilitate the implementation of an endgame strategy toward salvileucalin B (**1**). In particular, it was envisioned that use of α-diazo β-ketoester **16** or α-diazo β-ketonitrile **17** (Scheme 2) would provide

Scheme 2. Synthesis of Arene Cyclopropanation Substrates



norcaradienes with appropriate functionality for conversion to the required γ-lactone.

To this end, additional α-diazo carbonyl compounds were prepared from either carboxylic acid **12** or methyl ester **13**, each easily accessible from **11** by simply modifying the conditions of the Arndt−Eistert homologation.[21] Carboxylic acid **12** was converted to the corresponding acid chloride and treated with diazoethane (generated in situ from *N*-ethyl-*N*-nitrosourea) to provide α-diazo ketone **15** in 63% yield. α-Diazo β-ketoester **16** was prepared from acid **12** by a two-step procedure consisting of conversion to the ketoester,[25] followed by diazo transfer with *p*-ABSA. Alternatively, α-diazo β-ketonitrile **17** was prepared by treatment of methyl ester **13** with α-lithio-acetonitrile followed by diazo transfer with *N*-imidazole sulfonyl azide[26] in the presence of pyridine.

Whereas α-diazo carbonyls **15**[27] and **16** heavily favored dimerization and C−H insertion pathways when using a variety of catalysts and conditions,[28] more promising results were realized with α-diazo β-ketonitrile **17** (Table 2).

Table 2. Cyclopropanation of Functionalized Diazo Substrates

entry	R	catalyst[a]	product	% yield[b]
1	Me (**15**)	$Cu(acac)_2$	**19**	7[c,d]
2	CO_2Me (**16**)	$Cu(hfacac)_2$	**20**	<2
3	CN (**17**)	$Cu(TBS)_2$	**21**	14
4	CN (**17**)	$Cu(tfacac)_2$	**21**	6
5	CN (**17**)	$Cu(hfacac)_2$	**21**	66 (64)[d]

[a] [sub] = 0.01 M, [cat.] = 0.001 M, CD_2Cl_2, 120 °C (microwave), 1 min. [b] Determined by ^1H NMR analysis of crude mixture, using an internal standard. [c] Slow addition of **15**, DCE, reflux. [d] Isolated yield.

Although **17** was significantly less reactive than **14**, **15**, or **16**, exposure to 10 mol % $Cu(hfacac)_2$ in dichloroethane at 80 °C for 3 h provided approximately 10% yield[29] of the desired norcaradiene, in addition to significant quantities of unreacted starting material. After a survey of conditions, cyclopropane **21** was obtained in 64% yield by heating a solution of diazo substrate **17** and 10 mol % $Cu(hfacac)_2$ in dichloromethane to 120 °C for 1 min under microwave irradiation. It is envisioned that nitrile **21** should allow for elaboration to the southern lactone of salvileucalin B (**1**) in a short reaction sequence.

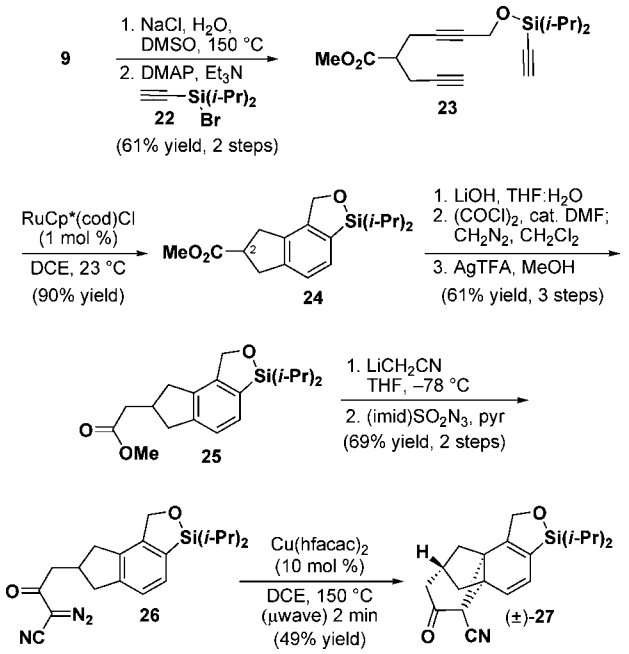
At this time, the source of the divergent reactivity of diazo substrates **14**, **15**, **16**, and **17** is unclear. A simple comparison of the cyclopropanation product yields from electronically similar diazo ketones **14** and **15** (R = H versus CH_3), or, diazo ester **16** and diazo nitrile **17** (R = CO_2Me versus CN), suggests that the steric profile of the metal carbenoid intermediate may be important.

Concomitant to our studies on substrates **14**−**17**, silyl analogue **26** was also prepared. It was envisioned that the silyl group could provide a useful handle for functionalization of the northern portion of **1**. Thus, α-diazo β-ketonitrile **26** was obtained by a short synthetic sequence from **9**, which began with Krapcho dealkoxycarbonylation[20] followed by silylation with alkynylsilyl bromide **22**[30] to give triyne **23** (61% yield, 2 steps). Exposure of **23** to 1 mol % of $RuCp^*(cod)Cl$ smoothly provided arene **24** in 90% yield.[19] Notably, the cycloisomerization of **23** clearly indicates that

the benefit of a "Thorpe−Ingold" effect from the gem-diester moiety is not required for cyclization.[31] This result lends support for proposed future work on an enantioselective route, which will require the cyclization of a chiral substrate bearing a tertiary center at C2 (salvileucalin numbering).

Homologation of arene **24** proceeded as before with use of the Arndt−Eistert protocol[21] to provide methyl ester **25**, which was converted in two steps to α-diazo *β*-ketonitrile **26**. Heating a solution of **26** in the presence of 10 mol % $Cu(hfacac)_2$ to 150 °C under microwave irradiation for 2 min provided cyclopropane **27** in 49% yield (Scheme 3). In this

Scheme 3. Cyclopropanation of Silyl Analogue **26**



case, the use of the microwave reactor significantly improved the efficiency of the reaction; heating under similar conditions in an oil bath to 80 °C for 6 h provided less than 5% yield of the desired cyclopropanation product.

The studies outlined here describe a synthetic approach that provides rapid access to the norcaradiene core of salvileucalin B. Whereas Rh^{II} catalysts favor C−H insertion products, selection of an appropriate Cu^{II} catalyst provides synthetically useful quantities of the required norcaradiene. These cyclopropanation reactions provide access to fully substituted cyclopropanes, and support for the viability of the synthetic strategy outlined in Scheme 1 for the synthesis of salvileucalin B (**1**). Application of this strategy to an enantioselective synthesis of **1** is the focus of ongoing work in our laboratory.

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Note Added after ASAP Publication. Scheme 3 contained errors in the version published ASAP on January 20, 2010; the corrected version was posted to the web on January 22, 2010.

Supporting Information Available: Experimental procedures and spectral data (^1H and ^{13}C NMR, IR, and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Exposure of α-diazo ketone **15** to Cu^{II} catalysts did not appear to result in significant formation of the corresponding Bamford−Stevens enone product.

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