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Enantioselective Total Synthesis of (+)-Salvileucalin B

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Supporting Information

ABSTRACT: An enantioselective total synthesis of the diterpenoid natural product (+)-salvileucalin B is reported. Key findings include a copper-catalyzed arene cyclopropanation reaction to provide the unusual norcaradiene core and a reversible retro-Claisen rearrangement of a highly functionalized norcaradiene intermediate.

Salvileucalin B (**1**; Figure 1) was isolated in 2008 by Takeya and co-workers during studies aimed at identifying new medicinal leads from the plant *Salvia leucantha*.[1,2] The structure of **1** is striking in that it contains a stable norcaradiene core embedded within a caged polycyclic skeleton. Construction of this unusual motif requires the formation of a fully substituted cyclopropane,[3] which remains a challenging transformation despite extensive research in the area of metal-catalyzed cyclopropanation.[4] In this communication, we report the first enantioselective total synthesis of (+)-salvileucalin B, which was realized by the successful implementation of an intramolecular arene cyclopropanation reaction to prepare a highly functionalized norcaradiene.[5,6]

Our retrosynthetic analysis was guided by preliminary studies in our laboratory, which determined that α-diazo-β-ketonitriles similar to **3** (Figure 1) are uniquely effective in copper-catalyzed arene cyclopropanation reactions to provide norcaradienes bearing fully substituted cyclopropanes.[7] In addition, we found that the *iso*-dihydrofuran moiety of compounds similar to **2** is prone to oxidation upon prolonged exposure to air. On the basis of these observations, it was hypothesized that the required lactone of **1** may be accessible by chemoselective allylic C−H oxidation at C(17) of *iso*-dihydrofuran **2**, which in turn could be prepared by a sequence involving arene cyclopropanation of α-diazo-β-ketonitrile **3**. α-Diazo-β-ketonitrile **3** was expected to arise from triyne **4** by a series of steps including a transition-metal-catalyzed cycloisomerization reaction. Triyne **4** was further deconstructed into the three simple building blocks **5**, **6**, and **7**.

In the forward sense, enantioselective 1,2-addition of the zinc acetylide derived from **6** to 3-furaldehyde (**7**) was promoted by chiral mandelamide ligand **8** to provide alcohol **9** in 85% yield and 93% ee (Scheme 1).[8] Alcohol **9** was converted to the corresponding propargyl bromide (**10**) in a three-step sequence involving O-propargylation, deprotection of the silyl ether, and Finkelstein-type bromination.[9]

Alkylation of pseudoephedrine amide **11** with propargyl bromide **10** using the conditions developed by Myers and co-workers[10] provided triyne **12** in excellent yield and >10:1 dr (Scheme 1). Simultaneous cleavage of the alkynyl silane and saponification of the amide could be achieved using 5 equiv of *n*-Bu_4NOH in aqueous *t*-BuOH at 90 °C; however, under these conditions, the carboxylic acid was isolated with erosion of the dr (4:1).[11] Efforts to identify conditions under which the amide could be hydrolyzed without competitive epimerization proved unsuccessful.

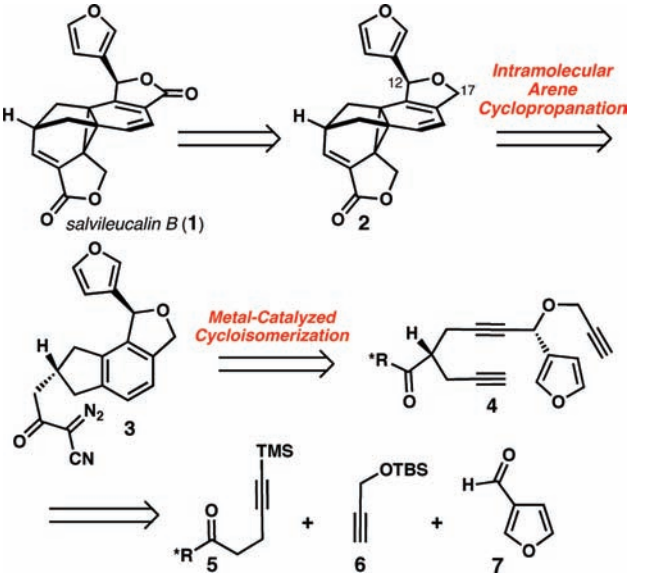

Figure 1. Retrosynthetic analysis for (+)-salvileucalin B (**1**).

On the other hand, desilylation of alkyne **12** using TBAF followed by exposure of the triyne to a dichloromethane solution of RuCp*(cod)Cl catalyst smoothly effected the cycloisomerization (Scheme 2). At this stage, cleavage of the amide was realized without epimerization to furnish carboxylic acid **13** in 74% yield (over three steps) as a 10:1 mixture of diastereomers. With this sequence, gram quantities of tricycle **13** were easily prepared. Conversion of **13** to the α-diazoketone was followed by Arndt−Eistert homologation[12] in the presence of methanol to provide ester **14**. Treatment of ester **14** with the sodium salt of acetonitrile delivered the β-ketonitrile, which underwent diazo transfer with 1*H*-imidazole-1-sulfonyl azide[13] to give key cyclopropanation substrate **3**. We were pleased to find that exposure of α-diazo-β-ketonitrile **3** to 10 mol % $Cu(hfacac)_2$ under our previously optimized conditions provided norcaradiene **15** in 65% yield. The structure of **15** was confirmed by single-crystal X-ray diffraction.[11]

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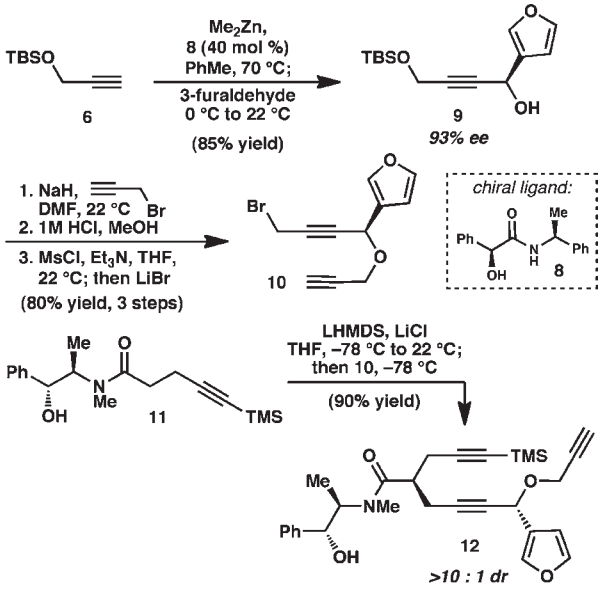
In order to advance norcaradiene **15** to **1**, our synthetic plan required a three-step sequence involving conversion to the enol triflate, chemoselective reduction of the nitrile to a hydroxymethyl group, and Pd-catalyzed intramolecular carbonylative cyclization. To this end, ketone **15** was treated with NaHMDS at −78 °C and trapped with *N*-phenylbis(trifluoromethanesulfonimide) to provide the corresponding enol triflate in 90% yield. The enol triflate was treated with excess DIBAL at −40 °C and quenched with dilute aqueous acetic acid; however, analysis of the crude reaction mixture by ^{1}H NMR spectroscopy revealed that the major product was not the desired aldehyde **16**. After further analysis, the major product was tentatively assigned as vinyl ether **17**, the product of a retro-Claisen rearrangement.[14]

Scheme 1. Enantioselective Synthesis of Triyne 12

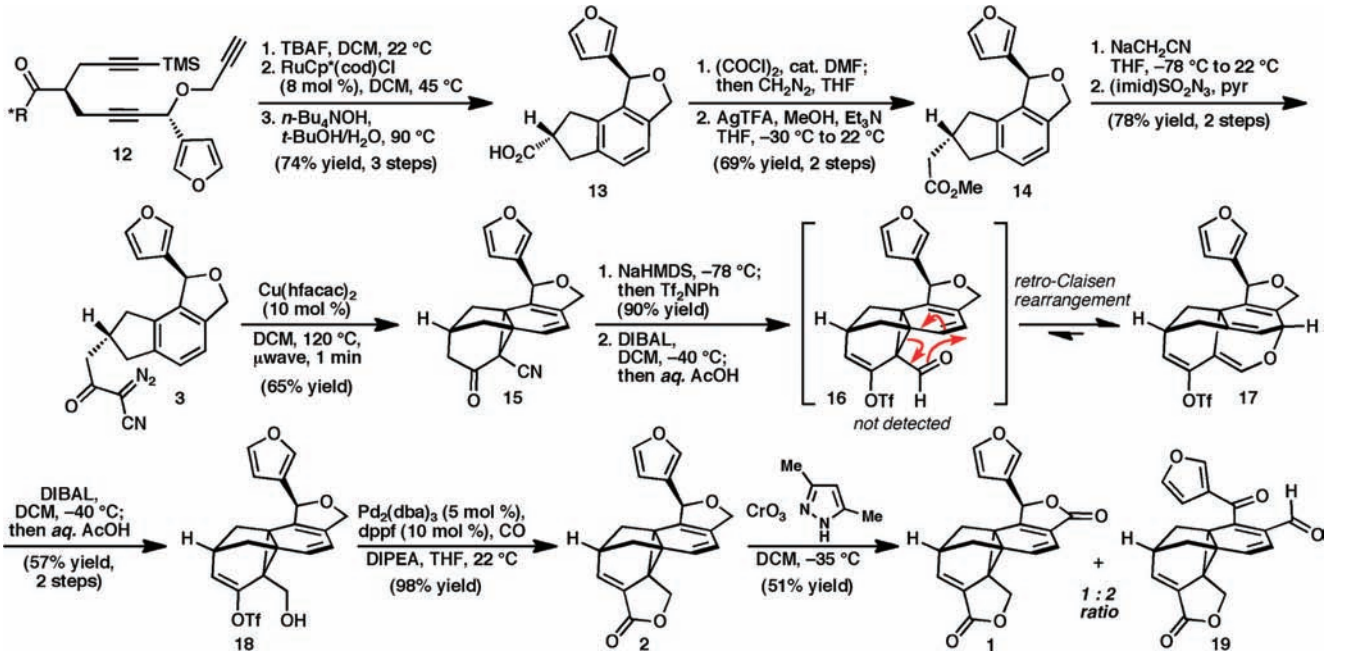


Elegant studies by Boeckman and co-workers[15] previously demonstrated that similar ring-opening Claisen rearrangements are reversible. Although the equilibrium heavily favors vinyl ether **17** (aldehyde **16** is not detected by ^{1}H NMR spectroscopy), it was hypothesized that kinetic trapping of the presumed aldehyde **16** may be possible using an appropriate reducing agent. We were pleased to find that exposure of vinyl ether **17** to DIBAL at −40 °C resulted in rapid reduction to deliver primary alcohol **18**, which was isolated in 57% yield over two steps. Less Lewis acidic reductants such as $LiBH_4$ reacted with lower rates and resulted in lower yields of **18** due to competitive cleavage of the enol triflate. This observation is consistent with Boeckman and co-workers' finding that Lewis acids accelerate the retro-Claisen rearrangement.[15] Vinyl ether **17** is sensitive to both light and oxygen; the moderate yield is attributed to some decomposition of **17** during workup. Attempts to promote the sequential reductions in a one-pot process by hydrolysis of the intermediate imine with a slight excess of protic acid followed by addition of a second DIBAL aliquot proved unfruitful. Subjection of triflate **18** to standard Pd-catalyzed carbonylation conditions provided lactone **2** in excellent yield.

With access to the entire carbon skeleton of **1**, what remained was oxidation of the *iso*-dihydrofuran of **2** to the required lactone. After considerable experimentation, it was found that exposure of **2** to chromium trioxide−3,5-dimethylpyrazole complex at −35 °C provided a 1:2 mixture of **1** and the isomeric ketoaldehyde **19**.[16,17] The characterization data obtained for synthetic **1** were fully consistent with Takeya and co-workers' reported data for the natural compound.[1] Although the yield of **1** was moderate, the implementation of this late-stage C−H oxidation circumvented the need for extraneous protecting-group and redox manipulations and thus represents a strategic advantage.[18]

In conclusion, the first total synthesis of (+)-salvileucalin B has been accomplished in 18 steps (longest linear sequence) from commercially available materials. These studies resulted in the development of a copper-catalyzed arene cyclopropanation

Scheme 2. Synthesis of (+)-Salvileucalin B (1)



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reaction to access a norcaradiene bearing a fully substituted cyclopropane ring. The systematic study and application of metal-catalyzed arene cyclopropanation reactions is the subject of ongoing research in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details, characterization data, NMR spectral charts, and X-ray crystal data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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