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A Modular Synthesis of Salvileucalin B Structural Domains

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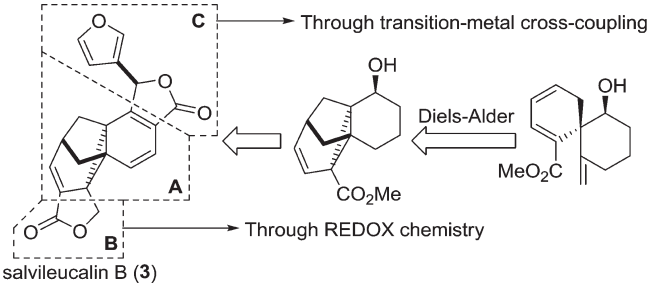
ABSTRACT



A modular strategy leading to the salvileucalin B core structure has been accomplished. The developed synthetic strategy featured a bioinspired intramolecular Diels–Alder reaction to construct domain "A", REDOX chemistry to functionalize domain "B", and a palladium-mediated cross-coupling to install domain "C". This flexible approach should facilitate further chemical and biological investigations of this fascinating class of compounds.

Architecturally complex natural products continue to serve as a testing ground for state-of-the-art synthetic organic chemistry and as a powerful vehicle for the invention of novel synthetic technologies and strategies. In conjunction with the biological potential possessed by these novel molecular entities, their value in advancing chemistry and biology cannot be understated.[1] Among the recent isolates, salvileucalins A and B (**1** and **3**, respectively, Scheme 1) were obtained from the aerial parts of *Salvia leucantha* Cav. and characterized by their neoclerodane skeleton after extensive NMR spectroscopic and X-ray crystallographic analysis.[2] The minor of the two isolates, salvileucalin B (**3**), possesses a highly unusual norcaradiene core which has been hypothesized to originate biosynthetically from salvileucalin A (**1**) via an enzymatic oxidation and followed by a subsequent intramolecular Diels–Alder reaction (**1** → **2** → **3**, Scheme 1).[2] Furthermore, salvileucalin B (**3**) was found to exhibit cytotoxic activities against A549 (human lung adenocarcinoma) and HT-29 (human colon adenocarcinoma) cells.[2] The unprecedented molecular architecture of salvileucalin B (**3**) and its biological potential has sparked interest from the scientific community,[3] with the first total synthesis of (+)-salvileucalin B elegantly accomplished by the Reisman group in early 2011.[3b] Here, we report the realization of our objective to develop a modular strategy to access potentially both the natural and designed salvileucalins.

In order to fulfill our ultimate objective of systematically investigating the chemistry and biology of salvileucalin B (**3**), and potentially accessing the naturally occurring substance itself [i.e., (**3**)], we opted for a strategy that retrosynthetically divided the global structure of salvileucalin B (**3**) into three domains (Scheme 1, **A**, **B**, and **C**). As outlined in Scheme 1, we envisaged a transition-metal-mediated

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(1) Nicolaou, K. C.; Montagnon, T. *Molecules That Changed the World*; Wiley-VCH: Weinheim, 2008, p 366.

(2) Aoyagi, Y.; Yamazaki, A.; Nakatsugawa, C.; Fukaya, H.; Takeya, K.; Kawauchi, S.; Izumi, H. *Org. Lett.* **2008**, *10*, 4429–4432.

(3) (a) Levin, S.; Nani, R. R.; Reisman, S. E. *Org. Lett.* **2010**, *12*, 780–783. For total synthesis of (+)-salvileucalin B, see:(b) Levin, S.; Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 774–776.

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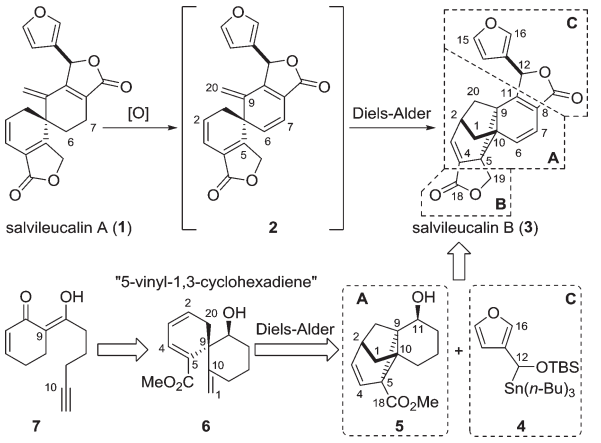
Scheme 1. [a]



[a] Molecular structure of salvileucalin A (**1**), proposed biosynthetic intermediate **2**, and salvileucalin B (**3**) indicating the three key structural domains **A**, **B**, and **C**. Retrosynthetic analysis of salvileucalin B (**3**) leading to stannane **4** and synthetic intermediates **5**, **6**, and **7**. TBS = *tert*-butyldimethylsilyl.

cross-coupling reaction to install subdomain **C** [for example, a Stille coupling reaction[4] engaging stannane **4** to install the furanyl moiety of salvileucalin B (**3**)]. Upon executing this opening retrosynthetic maneuver, our attention immediately turned to the most challenging aspect of the foreseeable synthetic campaign, namely the construction of subdomain **A** containing the norcaradiene core of salvileucalin B (**3**). Inspired by the biosynthetic proposal, we were intrigued with the possibility of a carefully designed triene system (e.g., **6**) to undergo an intramolecular Diels–Alder reaction,[5] thereby furnishing the tetracyclic core structure represented by advanced intermediate **5**. Indeed, several examples of an intramolecular Diels–Alder reaction of 5-vinyl-1,3-cyclohexadiene have been documented.[6] Furthermore, a recent quantum mechanical calculation study has unveiled the influence of functional groups present in both the substrate and the possible enzyme active site that could accelerate the intramolecular Diels–Alder reaction leading to the formation of the norcaradiene core of salvileucalin B (**3**).[7] Finally, the spirocyclic motif within hydroxy methyl ester **6** could be conceived from a Conia–ene reaction[8] engaging alkynyl β-diketone **7** (represented in its enol form).

(4) (a) Negishi, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 6738–6764. (b) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6722–6737.

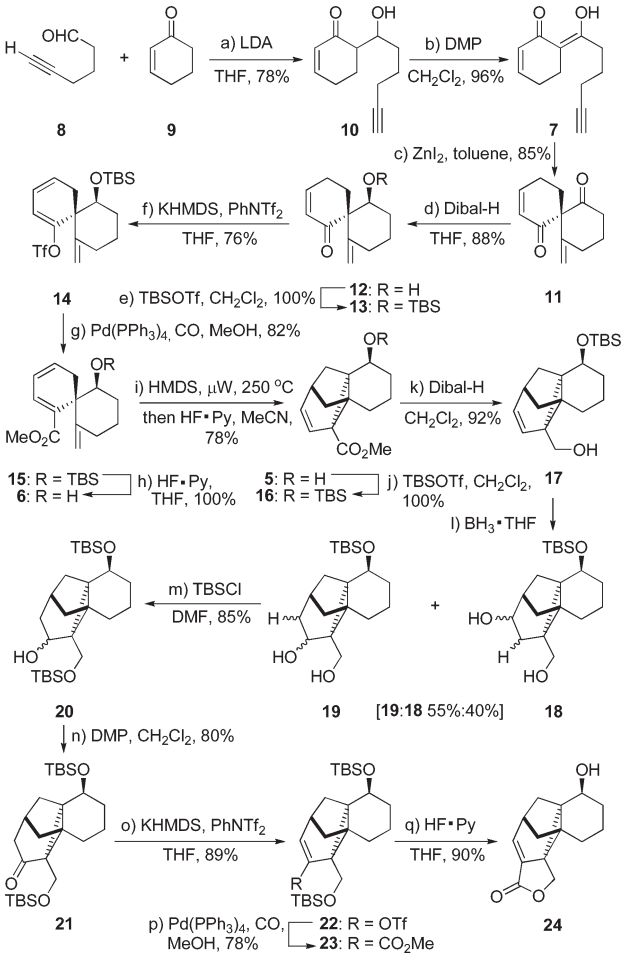
(5) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698.

(6) For examples of Diels–Alder reaction involving 5-vinyl-1,3-cyclohexadiene, see: (a) Heimbach, P.; Ploner, K. J.; Thömel, F. *Angew. Chem., Int. Ed.* **1971**, *10*, 276–277. (b) Imagawa, T.; Nakagawa, T.; Kawanisi, M.; Sisido, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1506–1510. (c) ten Have, R.; van Leusen, A. M. *Tetrahedron* **1998**, *54*, 1913–1920. (d) Moses, J. E.; Baldwin, J. E.; Adlington, R. M.; Cowley, A. R.; Marquez, R. *Tetrahedron Lett.* **2003**, *44*, 6625–6627. (e) Ng, S. M.; Beaudry, C. M.; Trauner, D. *Org. Lett.* **2003**, *5*, 1701–1704. (f) Abad, A.; Agullo, C.; Cunat, A. C.; de Alfonso, I.; Navarro, I.; Vera, N. *Molecules* **2004**, *9*, 287–299. (g) Dubarle-Offner, J.; Marrot, J.; Rager, M.-N.; Bideau, F. L.; Jaouen, G. *Synlett* **2007**, 800–802.

(7) Tantillo, D. J. *Org. Lett.* **2010**, *12*, 1164–1167.

(8) Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, *1*, 1–19.

Scheme 2. Synthesis of Pentacyclic Hydroxy Lactone **24**[a]



[a] LDA = lithium diisopropyl amide, DMP = Dess–Martin periodinane, Dibal-H = diisobutylaluminium hydride, KHMDS = potassium hexamethyldisilazide, Tf = trifluoromethanesulfonyl, OTf = trifluoromethanesulfonate, py = pyridine, HMDS = hexamethyldisilazane.

The realization of our synthetic strategy began with the preparation of the proposed intramolecular Diels–Alder precursor **6**, and thereby accessing the key synthetic intermediate **5** harboring subdomain **A**, as shown in Scheme 2. Thus, a lithium aldol reaction (LDA) between cyclohexenone (**9**) and alkynyl aldehyde **8** afforded β-hydroxy ketone **10**, which was further oxidized to diketone **7** (represented in its enol form) under DMP conditions in 75% overall yield. A Conia–ene reaction[8] engaging alkynyl diketone **7** was examined under a variety of reaction conditions, and ultimately ZnI_2 was revealed as the most effective promoter for this transformation, giving spirocyclic diketone **11** in 85% yield. Chemo- and stereoselective reduction of keto enone **11** under the Dibal-H conditions led to hydroxy enone **12** as a single diastereoisomer, which was subsequently protected as its TBS ether (TBSOTf, **13**, 85% yield over the two steps). In preparation for the proposed intramolecular Diels–Alder reaction, enone **13** was converted to methyl ester **15** through the intermediacy of triflate **14** (KHMDS, $PhNTf_2$, 76% yield) and its reaction under the standard carboxymethylation

conditions [$Pd(PPh_3)_4$, CO, MeOH, 82% yield]. While TBS ether **15** failed to undergo the much anticipated intramolecular Diels–Alder reaction, gratifyingly, its desilylated version (**6**, HF•py, 100% yield) underwent the desired transformation to deliver tetracycle **5** in 79% yield. After extensive experimentation, this reaction was best carried out through iterative microwave heating[9] with HMDS as an additive in 1,2-dichlorobenzene. The structural validity of the Diels–Alder product **5** was confirmed through an X-ray crystallographic analysis of its enone derivative (**5a**),[10] as shown in Figure 1.[11]

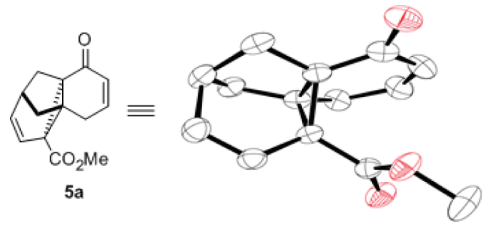
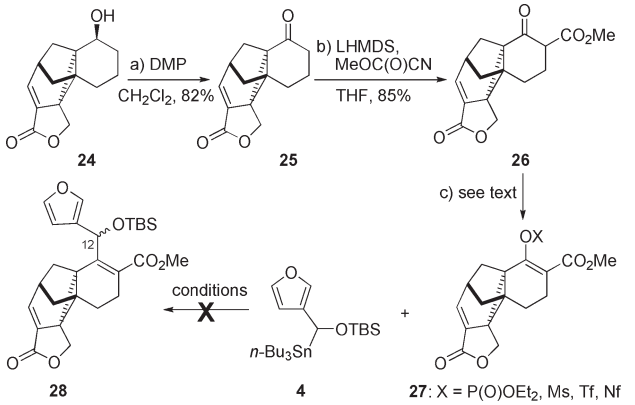


Figure 1. X-ray derived ORTEP representation of **5a**.[11]

With a synthetic route successfully charted for accessing domain **A** and a sufficient quantity of the crucial building block **5** secured, we began to investigate the chemistry associated with the structural domain **B** [see Scheme 1]. As such, we first assembled the α-methylene γ-lactone moiety required for salvileucalin B (**3**). Thus, a two-step procedure involving silyl protection of the secondary alcohol **5** (TBSOTf) and reduction of the so-obtained methyl ester **16** (Dibal-H) furnished homoallylic alcohol **17** in 92% overall yield. A hydroxyl-directed hydroboration of **17** was envisaged for the functionalization at C_4. In this instance, while the reaction proceeded with excellent conversion (95% yield), only a modest level of regioselectivity in favor of the desired regioisomer **19** (**19**:**18** ca. 1.4:1, chromatographic separable) was observed. Next, a four-step transformation smoothly delivered the one-carbon homologated α,β-unsaturated methyl ester **23** from diol **19**, through the intermediacy of bis-TBS ether **20** (TBSCl–Et_3N, 85% yield), ketone **21** (DMP, 80% yield), enol triflate **22** (KHMDS, $PhNTf_2$, 89% yield), and reaction of the latter compound under the carboxymethylation conditions [$Pd(PPh_3)_4$, CO, MeOH, 78% yield]. Finally, casting of the γ-lactone moiety was effected through global desilylation of the bis-TBS ether **23** (HF•py), to afford hydroxy lactone **24** in 90% yield. With the construction of the α-methylene γ-lactone moiety for salvileucalin B (**3**) successfully secured, we should mention that intermediates **5** and **16**–**24** are all valuable building blocks in our ensuing salvileucalin studies.[12]

Now, we turned our attention to the final missing piece of the puzzle, namely the assembly of structural domain **C** (see Scheme 1). In accordance with our original proposal (Scheme 1), we first attempted to introduce the furanyl moiety onto the growing pentacyclic γ-lactone **24** through a Stille[4] coupling reaction engaging enol derivative **27** and stannane **4**.[13] However, after extensive experimentation, neither the preparation of enol derivative **27** nor its Stille coupling with stannane **4** could be accomplished (Scheme 3).

Scheme 3. Initial Attempts in the Installation of the Furanyl Moiety through Stille Coupling Engaging Enol Derivative **27** and Stannane **4** [a]



[a] Ms = methansulfonyl, Nf = nonafluorobutanesulfonyl.

The unsuccessful union between enol derivatives **27** and stannane **4**[13] generally resulted in the production of an unidentified byproduct where the alkenyl γ-lactone moiety was either absent or significantly compromised. Thus, a revised strategy that involved the introduction of the furanyl moiety in the absence of the C_4/C_5 γ-lactone was pursued in earnest (Scheme 4). In this instance, the readily accessible Diels–Alder product **5** was conveniently transformed to β-keto ester **30** through oxidation (DMP, 82% yield) and α-acylation (LHMDS, Mander's reagent[14]). Conversion of the so-obtained β-keto ester **30** to enol triflate **31** (Comin's reagent, NaH, 81% yield from **29**) proceeded smoothly, where the latter compound (**31**) underwent palladium-catalyzed Stille[4] coupling with stannane **4**[13] to afford furanyl derivative **32** in a pleasing 80% yield as a mixture of diastereoisomers (ca. 2:1) epimeric at C_{12}. Finally, liberation of the TBS guarded secondary alcohol in **32** (HF•py) resulted in spontaneous lactonization to furnish the hexacyclic, γ-lactone containing methyl ester **33**.

(9) For experimental details, see Supporting Information.

(10) For preparation of enone **5a** from Diels–Alder product **5**, see Supporting Information.

(11) CCDC-793468 contains the supplementary crystallographic data for **5a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) The synthesis and biological evaluation of natural and designed salvileucalin compounds will be reported in the full account of this work.

(13) For preparation of furanyl stannane **4**, see Supporting Information.

(14) Crabtree, S. R.; Chu, W. L. A.; Mander, L. N. *Synlett* **1990**, 169–170.

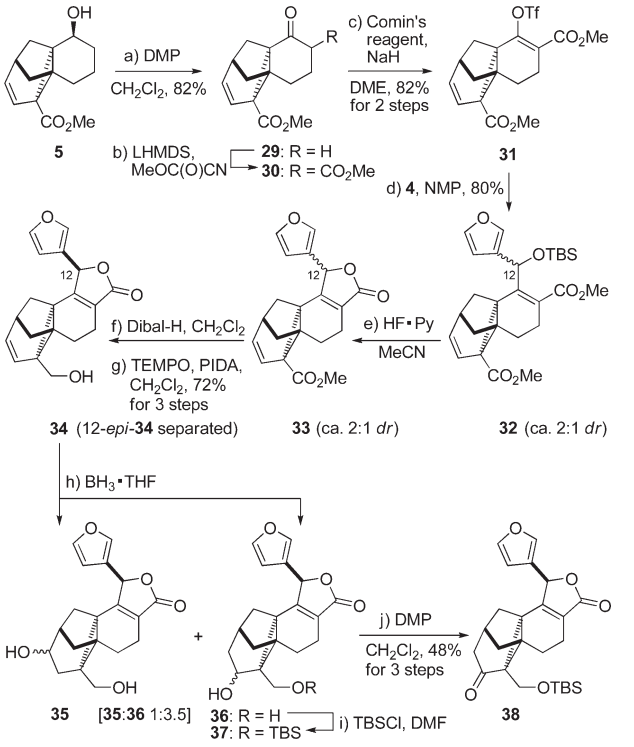
The successful preparation of triflate **31** and its facile participation under the palladium-mediated cross-coupling reactions (e.g., Stille coupling)[4] should enable a variety of furan substitutes to be introduced.

In order to examine the synthetic feasibility of the furanyl bearing γ-lactone **33** in accessing domain **B** analogues of salvileucalin B (**3**), particularly in view of the potential liability of the furanyl and γ-lactone functionalities, further synthetic transformations were carried out as shown in Scheme 4. In this context, γ-lactone containing methyl ester **33** was subjected to a two-step reduction (Dibal-H)/selective-oxidation (TEMPO, PIDA) sequence to afford primary alcohols **34** and 12-*epi*-**34** (ca. 2:1, chromatographically separated) in 72% combined yield (from **32**). In an analogous fashion to the preparation of ketone **21** (Scheme 2), chemoselective hydroboration of homoallylic alcohol **34** followed by oxidative workup afforded a chromatographically separable mixture of diols **35** and **36** (**35**:**36** ca. 1:3.5 dr), where selective silylation of the latter compound (**36**) was achieved through the action of TBSCl and imidazole. Final oxidation of the hydroxy TBS ether **37** afforded ketone **38**, an intermediate that should be amenable for both the preparation of domain **B** analogues or salvileucalin B (**3**) through the late-stage chemistry reported by Reisman[3b] and in accordance to Scheme 2.

In summary, a modular synthetic strategy with flexibility in addressing the salvileucalin B structural domains **A**, **B**, and **C**, as outlined in Scheme 1, has been demonstrated. The developed synthetic sequence featured a ZnI_2-mediated Conia–ene spirocyclization, a bioinspired intramolecular Diels–Alder reaction, and a palladium-mediated cross-coupling reaction. Furthermore, key intermediate **12** has been prepared in its optically active form through an analogous ZnI_2-mediated Conia–ene spirocyclization reaction.[15] The synthetic technology and strategy disclosed herein illustrated an entry to the entire carbocyclic framework salvileucalin B, which is therefore path-determining for the preparation of both designed and natural substances for further chemical and biological investigations.[12]

(15) An asymmetric synthesis of spirocyclic hydroxy enone **12** has been accomplished. For details, see Supporting Information.

Scheme 4. Synthesis of Ketone **38** [a]



[a] DME = ethylene glycol dimethyl ether; NMP = *N*-methyl-2-pyrrolidone; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy; PIDA = phenyliodine diacetate.

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Supporting Information Available. Experimental procedures, compound characterization (PDF), and cif file for compound **5a**. This material is available free of charge via Internet at http://pubs.acs.org.