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Diastereoselective Total Synthesis of Salvileucalin C

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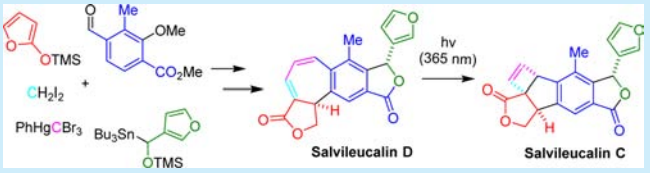
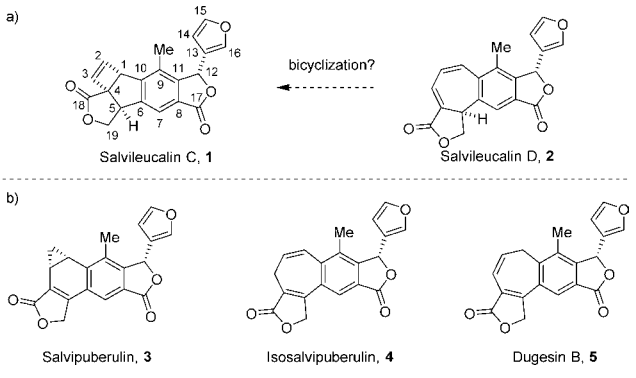
Supporting Information

ABSTRACT: A concise and efficient approach for the diastereoselective total synthesis of salvileucalin C, as well as their biosynthetically related diterpenoids salvileucalin D, salvipuberulin, isosalvipuberulin, and dugesin B, has been reported for the first time. The key features of the strategy are based on a Beckwith–Dowd ring expansion, a tandem diastereoselective Stille coupling/debromination/desilylation/lactonization reaction, and a photoinduced electrocyclic ring contraction.



Salvia is one of the largest genera in the Labiatae family of both economical and medicinal importance. Since ancient times, many species of this widely distributed genus have been used in folk medicine to treat a variety of illnesses.[1] Isolation studies targeting *Salvia* plants have yielded a wealth of structurally intriguing and biologically active natural products.[2] Recently, efforts toward identifying novel diterpenoids as potential medicinal leads resulted in the isolation of several new compounds from *Salvia leucantha* that possess unusual structures.[3,4] Salvileucalin C (**1**), a novel and highly rearranged neoclerodane diterpene, and a structurally closely related salvileucalin D (**2**) have recently been discovered (Scheme 1a).[5]

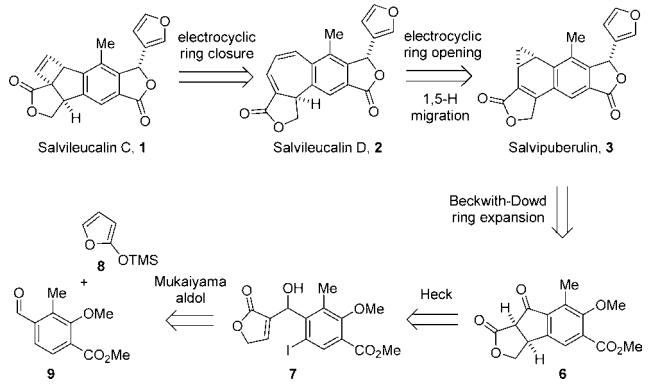
Scheme 1. (a) Structures and Biosynthetic Relationship of Salvileucalins C and D; (b) Structures of Salvipuberulin, Isosalvipuberulin, and Dugesin B



It was proposed that **2** is a biosynthetic precursor of **1**, whose bicyclo[3,2,0]hept-6-ene subunit was hypothesized to be formed through bicyclization of the cycloheptadiene structure. Challenges in achieving a diastereocontrolled synthesis are foreseeable since the two chiral centers at C(5) and C(12) locate far away from each other on the flat scaffold of the molecule. The unique structural feature of salvileucalin C (**1**) as well as their interesting biosynthetic relationship to other constituents from *Salvia* species[6–8] (Scheme 1b) prompted us to embark on its total synthesis. Herein, we report our recent efforts which culminated in a concise and diastereoselective approach to this diterpenoid, along with the total synthesis of salvileucalin D (**2**), salvipuberulin (**3**),[6] isosalvipuberulin (**4**)[7,8a] and dugesin B (**5**).[8]

Scheme 2 outlines our initial retrosynthetic analysis of salvileucalin C (**1**). We rationalized that **1** might be synthesized

Scheme 2. Initial Retrosynthetic Analysis of Salvileucalin C (1)



from salvileucalin D (**2**) through cyclobutene formation by a photoinduced 4π-electrocyclic ring closure,[9] while the latter could be derived from a 6π-electrocyclic ring-opening reaction of a benzonorcaradiene moiety of salvipuberulin (**3**) followed by [1,5]-sigmatropic hydrogen migration.[10] For the construction of **3**, we envisaged a radical initiated Beckwith–Dowd ring expansion[11] to forge the [5,6]-bicyclic framework of the molecule. The essential [5,5]-bicycle of **6** could be prepared through Heck cyclization[12] of butenolide **7**, which may in turn be obtained from the readily available building blocks **8**[13] and **9**.[14]

The realization of our synthetic strategy commenced with the construction of 4,5-dihydrosalvipuberulin (**19**, Scheme 3). $Zn(OTf)_2$ catalyzed Mukaiyama aldol reaction[15] of silyloxyfuran

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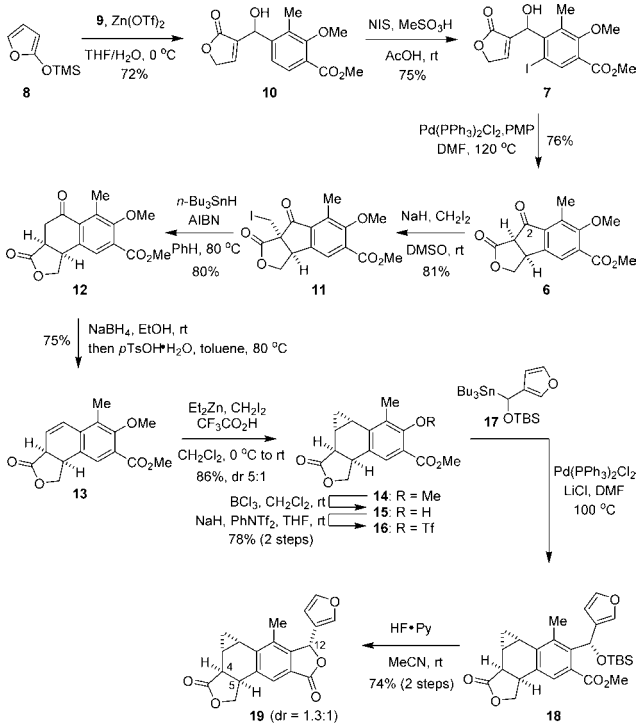
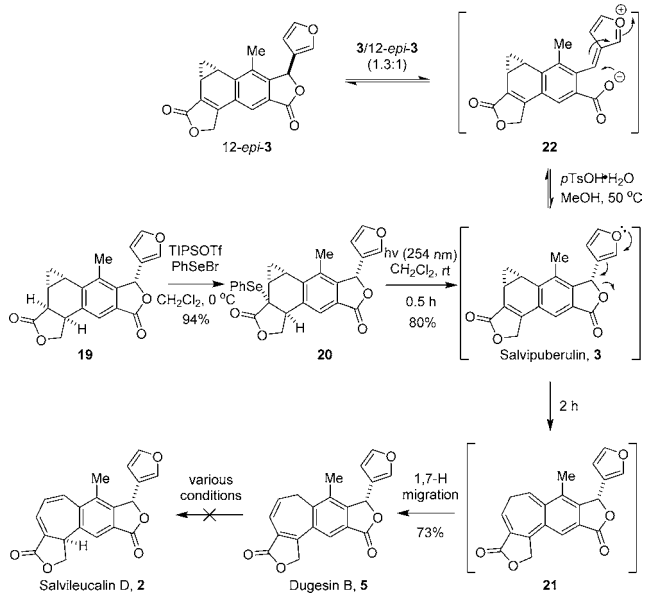
Scheme 3. Synthesis of 4,5-Dihydrosalvipuberulin (19)



Scheme 4. Synthesis of Salvipuberulin (3) and Initial Attempts in Its Conversion to Salvileucalin D (2)



8 and aldehyde **9** in aqueous media gave exclusively α-product **10** (72% yield), whose cyclization by the Nazarov reaction or direct cyclodehydration to produce the requisite [5,5]-biyclic skeleton was however unsuccessful. As an alternative, **10** was iodinated in the presence of NIS and $MeSO_3H$ to afford the precursor **7** in 75% yield. Although both radical and reductive Heck cyclization approaches gave satisfactory outcomes, we were interested in a more straightforward Heck reaction[16] to construct the C(2) ketone concomitantly. Pleasingly, under optimized conditions [$Pd(PPh_3)_2Cl_2$, 1,2,2,6,6-pentamethylpiperidine, DMF, 130 °C], the challenging intramolecular Heck cyclization of **7** proceeded smoothly to afford the desired indanone **6** in 76% yield. Subsequent iodomethylation of **6** provided iodide **11**, which was subjected to the Beckwith–Dowd ring-expansion reaction (n-Bu_3SnH, AIBN) to deliver **12** in 65% yield over the two steps.[17] A one-pot procedure involving ketone reduction and elimination of the resulting alcohol gave **13** (75% yield), which was then converted to **14** through CF_3CO_2H accelerated cyclopropanation[18] in 86% yield as a mixture of diastereomers (dr = 5:1).

With the rapid construction of cyclopropane **14**, the next task was to install the remaining γ-lactone bearing a furanyl moiety. Thus, triflate **16** was formed in two steps with 78% yield following standard procedures. Palladium-catalyzed Stille coupling[19] of **16** with stannane **17** followed by liberation of the TBS guarded secondary alcohol in **18** (HF·Py) resulted in spontaneous lactonization to furnish 4,5-dihydrosalvipuberulin (**19**) in 74% yield over the two steps as a separable mixture of diastereomers at C12 (dr = 1.3:1; structure of 12-*epi*-**19** was not shown).

The initial studies aiming at the total synthesis of salvileucalin D (**2**) are depicted in Scheme 4. Phenylselenation of the preformed TIPS enol ether[20] gave selenide **20** in 94% yield. Although oxidative elimination of organoselenium compounds has been well established, we were delighted to find that, upon exposure of **20** (degassed solution) to UV-light irradiation (λ = 254 nm), homolytic cleavage of the C–Se bond[21] followed by β-hydrogen radical abstraction occurred sequentially to afford salvipuberulin (**3**) in 80% yield. Prolonged irradiation of **3** led to electrocyclic ring opening of the benzonorcaradiene moiety together with [1,7]-sigmatropic hydrogen migration of the resulting cycloheptatriene **21**, furnishing dugesin B (**5**) in 73% yield from **20**. The spectroscopic (^1H and ^{13}C NMR) and mass spectrometric data of synthetic **3** and **5** were consistent with those reported for the natural salvipuberulin and dugesin B, respectively.[6,8] To our disappointment, all efforts on the isomerization of **5** to salvileucalin D (**2**) proved fruitless. Worthy of note, during attempts in the direct conversion of salvipuberulin (**3**) to salvileucalin D (**2**), we found that both pure forms of individual structures **3** and 12-*epi*-**3** could be slowly epimerized by treatment with catalytic pTsOH·H_2O (20 mol %) in MeOH at 50 °C, resulting in a 1.3:1 (**3**/12-*epi*-**3**) mixture.[22] A plausible lactone opening and closure process via intermediate **22** accounted for this transformation.

Having failed in accessing salvileucalin D (**2**) through a photoinduced electrocyclic reaction, a revised strategy that involved the base-promoted ring expansion of bromocyclopropane was pursued (Scheme 5).[23] In this instance, treatment of **13** with freshly prepared Seyferth reagent[24] ($PhHgCBr_3$) gave dibromocyclopropane **23** in 78% yield without any detectable diastereomer.[25] Subsequent demethylation of **23** followed by triflation of the resulting phenol delivered triflate **25** in 90% yield over the two steps, setting the stage for the γ-lactone installation.

Using conditions described for **16**, the Stille coupling of **25** with stannane **17** followed by HF·Py-promoted lactonization afforded products **27** and 12-*epi*-**27** in 68% and 14% yields, respectively (Table 1, entry 1). The improved diastereoselectivity (ca. 5:1) compared with that of **16** to **19** is noteworthy, and more detailed mechanistic studies are currently underway in our laboratory. To our surprise, albeit in low yield, the formation of monobromocyclopropane **28** was also observed,[26] which led us to optimize this one-pot Stille coupling/debromination reaction. Since the switch of the palladium catalyst did not affect the debromination (entry 2), we envisioned that the presence of

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Scheme 5. Total Synthesis of Salvileucalin C (1)

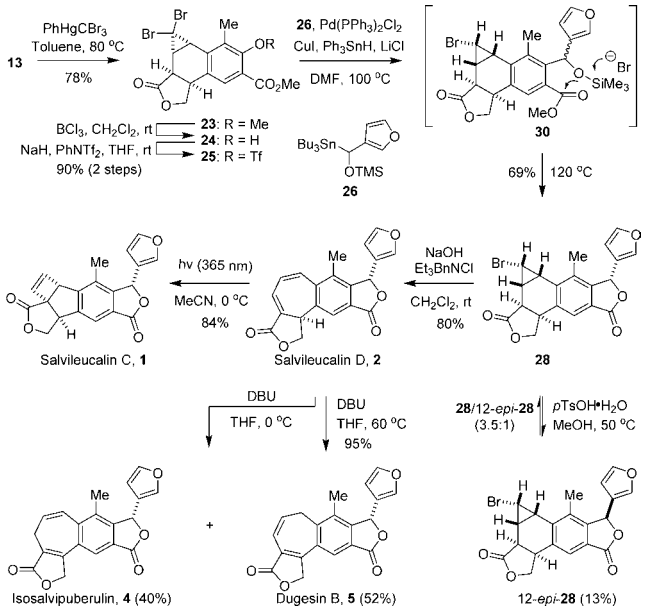
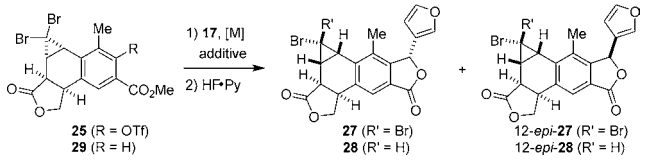


Table 1. Optimization of the One-Pot Stille Coupling/Debromination Reaction[a]



		yield (%)[b]				
entry	[M], additive	**27**	12-*epi*-**27**	**28**	12-*epi*-**28**	**29**
1	$Pd(PPh_3)_2Cl_2$	68	14	4	n.d.	n.d.
2	$Pd(PPh_3)_4$	55	10	3	n.d.	n.d.
3	$Pd(PPh_3)_2Cl_2$, *n*-Bu_3SnH	n.d.	n.d.	60	12	n.d.
4	$Pd(PPh_3)_2Cl_2$, Et_3SiH	27	8	3	n.d.	54
5	$Pd(PPh_3)_2Cl_2$, Ph_3SiH	n.d.	n.d.	65	13	n.d.
6	$Pd(PPh_3)_2Cl_2$, CuI, Ph_3SiH	n.d.	n.d.	73	15	n.d.

[a]Reaction conditions: 1) **25** (0.1 mmol), **17** (1.2 equiv), [Pd] (0.1 equiv), CuI (0.1 equiv), *n*-Bu_3SnH (1.2 equiv) or hydrosilane (1.2 equiv), and LiCl (3.0 equiv) in DMF (3 mL) at 100 °C; 2) HF·Py, MeCN, rt. n.d. = not detected. [b]Isolated yields of two steps.

a trace amount of *n*Bu_3SnH in stannane **17** would be the critical factor. Thus, stoichiometric *n*Bu_3SnH was employed as the hydride source and the yield of **28** was indeed dramatically improved to 60% (entry 3). In the presence of Et_3SiH, simple reductive detriflation product **29** was observed predominantly (entry 4). Further studies showed Ph_3SnH was a superior hydride donor (entry 5).[27] Moreover, catalytic CuI was found to be an effective additive to this reaction, with which **28** and 12-*epi*-**28** could be obtained in 73% and 15% yields, respectively (entry 6).

Based on the encouraging results, stannane **26** with a more labile trimethylsilyl group was employed in the Stille coupling reaction instead of **17** (Scheme 5). Much to our delight, **28** was formed directly in 69% yield, accompanied by 12-*epi*-**28** (13% yield). The γ-lactone formation was facilitated by deprotection of the TMS group, which was presumably the result of synergistic effects from both the *in situ* generated bromide during debromination and elevated temperature (**30**),[28] thus enabling a diastereoselective Stille coupling/debromination/desilylation/lactonization cascade in one step. 12-*epi*-**28** could be recycled by epimerization as described for 12-*epi*-**3**, giving a 3.5:1 mixture of diastereomers favoring **28**. Fortunately, treatment of bromocyclopropane **28** with aqueous sodium hydroxide solution in the presence of Et_3BnNCl afforded ring-expansion product salvileucalin D (**2**) in 80% yield. Other bases such as LDA, KHMDS, *t*-BuOK, K_2CO_3, DBU and pyridine, and silver salts (Ag_2O, Ag_2CO_3, $AgNO_3$, AgO_2CCF_3) either caused decomposition of **28** or gave a low yield of **2**. Under thermodynamic conditions, rapid conversion of salvileucalin D (**2**) to dugesin B (**5**) was observed (95% yield). While treating with DBU at 0 °C, **2** was transformed into isosalvipuberulin (**4**) and dugesin B (**5**) in 40% and 52% yields, respectively. Gratifyingly, upon UV-light irradiation (λ = 365 nm), electrocyclic ring closure took place smoothly and delivered salvileucalin C (**1**) in 84% yield.[29] Synthetic **1**, **2**, **4**, and **5** exhibited ^1H and ^{13}C NMR spectra identical in all respects to those reported for the natural products.[4,8a]

In summary, we have developed a concise and diastereoselective route to salvileucalin C, as well as their biosynthetically related diterpenoids salvileucalin D, salvipuberulin, isosalvipuberulin, and dugesin B. The key steps of the strategy entail a Beckwith−Dowd ring expansion, a tandem diastereoselective Stille coupling/debromination/desilylation/lactonization reaction, and a photoinduced electrocyclic ring contraction. The asymmetric synthesis enabling further biological evaluation of these molecules could be approached via the enantioselective Mukaiyama aldol reaction[15] of silyloxyfuran with aldehyde and the following intramolecular Heck cyclization strategy.[16b] Studies in this field are currently in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterizations, and copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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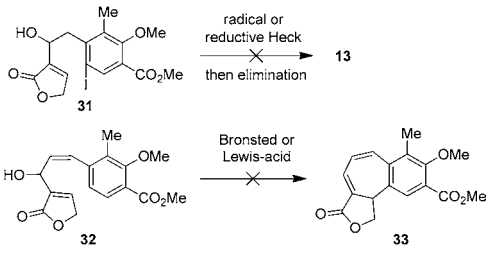
(17) It should be noted that precursors **31** and **32** have also been prepared in our earlier synthetic design, which unfortunately could not cyclize to provide **13** or **33** under various conditions.



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(22) Contrary to the work reported by Rodríguez-Hahn and co-workers who observed an exclusive conversion of salvipuberulin (**3**) to isosalvipuberulin (**4**) under thermodynamic conditions (see ref 6), **3** was sufficiently stable in our hands in the absence of acid.
(23) For the representative ring-opening reaction of dibromocyclopropane, see: (a) Christl, M.; Lang, R.; Herzog, C. *Tetrahedron* **1986**, *42*, 1585. (b) Kato, M.; Kasai, M.; Shiraki, K.; Furuichi, K.; Miwa, T. *Chem. Lett.* **1987**, *16*, 669. (c) Nishimura, T.; Unni, A. K.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2013**, *135*, 3243.
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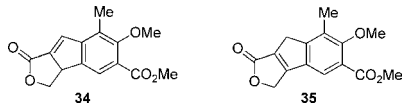
(25) Surprisingly, an oxidative aromatization of compound **13** leading to the formation of a naphthalene derivative was observed under basic cyclopropanation conditions.
(26) The structure of **28** was confirmed by detailed NOESY analysis.
(27) Compared to this Pd-involved debromination, radical mediated conversion of **27** to **28** was also investigated, which afforded a 75% yield under optimized conditions [Ph_3SnH (3.0 equiv), Et_3B (0.5 equiv), O_2, toluene, rt, 12 h]. For selected examples of radical debromination of dibromocyclopropane, see: (a) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143. (b) Kozhushkov, S. I.; Späth, T.; Kosa, M.; Apeloig, Y.; Yufit, D. S.; de Meijere, A. *Eur. J. Org. Chem.* **2003**, 4234. (c) DeGuire, S. M.; Ma, S.; Sulikowski, G. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 9940.
(28) The conclusion was based on the results of the following two controlled experiments: (a) Without LiCl, the reaction also proceeded although it afforded slightly decreased yields of **28** and 12-*epi*-**28** (58% and 12%, respectively); (b) in the absence of Ph_3SnH, desilylation of the Stille-coupling products was not observed even at elevated temperature.
(29) Direct construction of the bicyclo[3,2,0]hept-6-ene subunit of **1** by a [2 + 2] photocycloaddition of **34** and trimethylsilylacetylene was also considered. However, preparation of **34** met with failures due to its rapid isomerization to **35**.



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