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Scalable Total Synthesis of *rac*-Jungermannenones B and C

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Abstract: *Reported is the first scalable synthesis of rac-jungermannenones B and C starting from the commercially available and inexpensive geraniol in 10 and 9 steps, respectively. The unique jungermannenone framework is rapidly assembled by an unprecedented regioselective 1,6-dienyne reductive cyclization reaction which proceeds through a vinyl radical cyclization/allylic radical isomerization mechanism. DFT calculations explain the high regioselectivity observed in the 1,6-dienyne reductive radical cyclization.*

The jungermannenones are new *ent*-kaurene-type diterpenoids isolated from the liverwort *Jungermannia* species (Figure 1).[1] Their structures were initially established based on extensive spectroscopic techniques and later confirmed unambiguously by X-ray crystallographic analysis. Preliminary biological tests disclosed that jungermannenones are promising candidates for cancer chemotherapy, thus displaying cytotoxicity against HL-60 cells (IC_{50} values of up to 0.49 μM). As apoptosis-inducing agents they are also useful tools for investigation into the mechanism of cell death.[1] From a synthetic point of view, jungermannenones present a formidable challenge because of their unique bicyclic-[3,2,1]octene framework possessing an endocyclic tetrasubstituted alkene moiety.[2] Indeed, despite the numerous successful syntheses of tetracyclic diterpenoids reported in recent years,[3,4] the jungermannenones have remained inaccessible so far. Herein we report our synthetic endeavors which ultimately lead to the scalable syntheses of *rac*-jungermannenones B (**1**) and C (**2**).

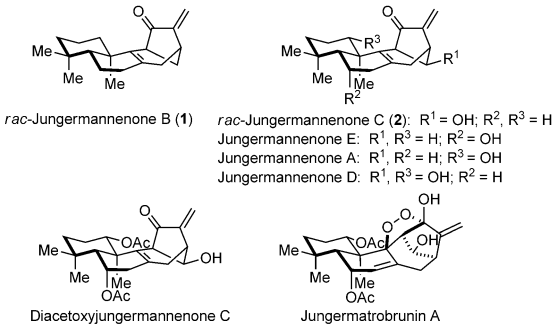
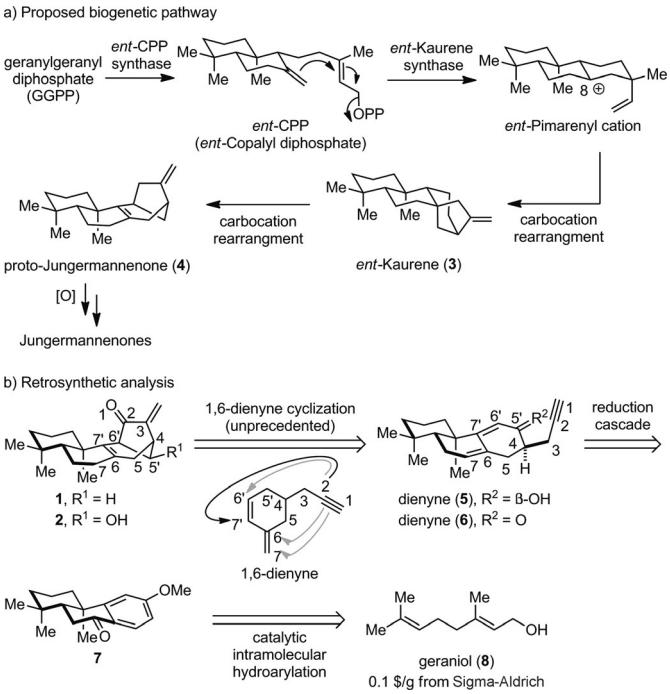


Figure 1. Representative structures of jungermannenones.

Nagashima and co-workers have hypothesized that the jungermannenones are rearranged *ent*-kaurene-type diterpenoids (Scheme 1a).[1b] Biogenetically, metabolites which possess the *ent*-kaurene skeleton are originally derived from geranylgeranyl diphosphate (GGPP). Bicyclic *ent*-copalyl diphosphate (*ent*-CPP) undergoes enzymatic cyclization followed by carbocation rearrangement to furnish *ent*-kaurene (**3**).[3,5] *ent*-Kaurene (**3**) subsequently undergoes a further carbocation rearrangement to generate proto-jungermannenone (**4**) as the key biosynthetic precursor. Subsequent site-selective oxidation of **4** during the oxidation phase provides the jungermannenones.

In our synthetic plan (Scheme 1b), we considered the feasibility of a 1,6-dienyne cyclization to assemble the desired scaffold. Whereas 1,*n*-enyne cyclizations have been studied extensively,[6–8] 1,6-dienyne cyclizations remain underex-



Scheme 1. Synthetic analysis of jungermannenones.

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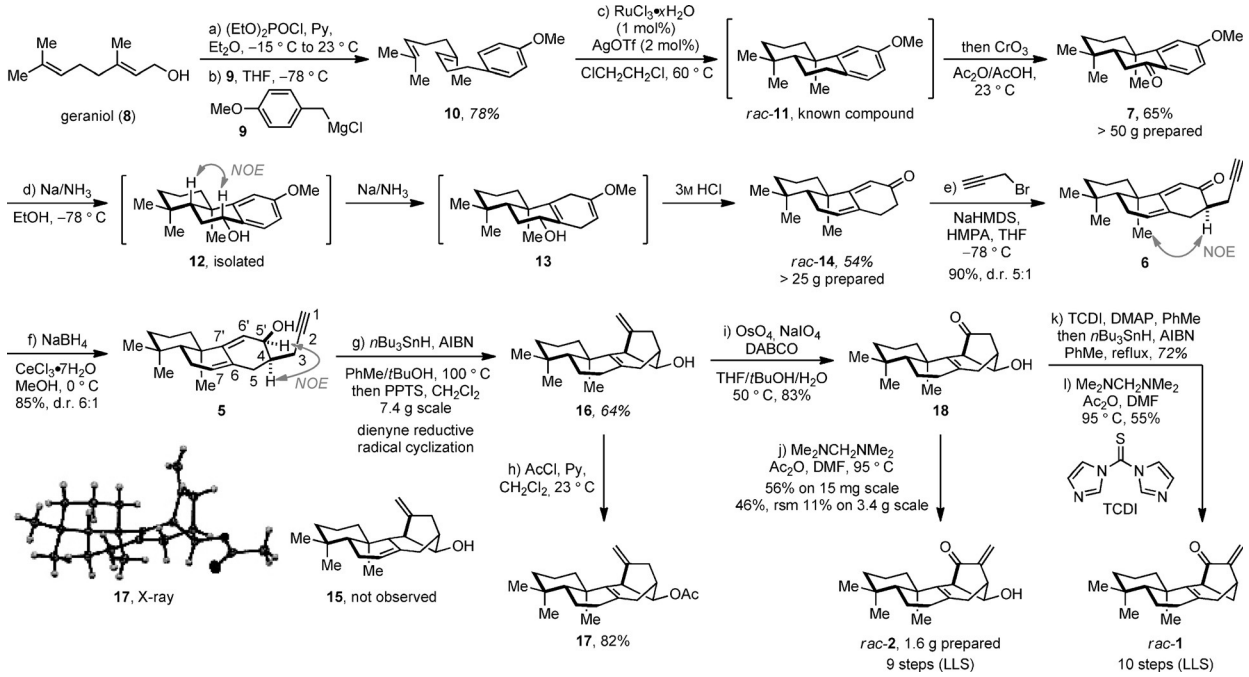


Scheme 2. Scalable synthesis of *rac*-Jungermannenones B (**1**) and C (2). AIBN = azobisisobutyronitrile, DABCO = 1,4-diazabicyclo[2.2.2]octane, DMAP = 4-*N*,*N*-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, HMPA = hexamethylphosphoramide, NaHMDS = sodium bis(trimethylsilyl)amide, PPTS = pyridinium *p*-toluenesulfonate, Py = pyridine, TCDI = *N*,*N*′-thiocarbonyldiimidazole, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

plored, presumably because of the severe regioselectivity concern in simple substrates. Nonetheless, we anticipated that, if successful, the jungermannenone framework could be installed in a straightforward manner from either the dienyne **5** or **6**. The dienyne **6** can be derived through a reductive cascade from the ketone **7**, which in turn may be generated from inexpensive geraniol (**8**) by a catalytic intramolecular hydroarylation reaction.[9]

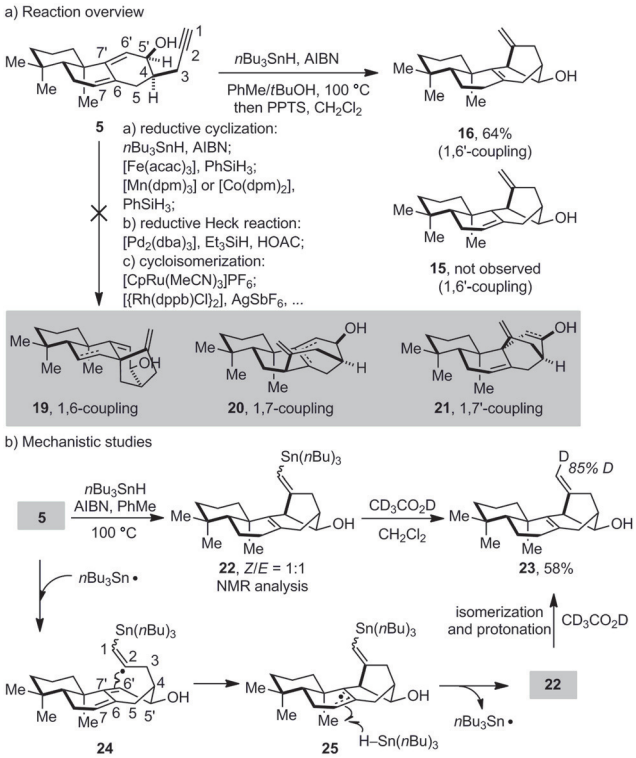
As shown in Scheme 2, our synthesis commenced with the preparation of 1-geranyl-4-methoxybenzene (**10**). The desired **10** was obtained in 78% yield over two steps on a 100 gram scale.[10] Subsequent intramolecular electrophilic hydroarylation of **10**, using Sames' protocol in the presence of 1 mol% $RuCl_3$, proceeded smoothly to furnish the known tricyclic intermediate *rac*-**11**.[9,11,12] Finally, the ketone **7** was obtained through a sequential hydroarylation/benzylic oxidation process within 65% yield.

Treatment of **7** with Birch reduction conditions (Na/NH_3, EtOH) at −78°C triggered a reductive cascade which generated the dienone *rac*-**14** in 54% yield upon isolation after acidic workup. The reduction cascade is believed to proceed through initial stereoselective reduction of the ketone to the alcohol **12**, with subsequent Birch reduction and final acid-mediated hydrolysis of **13** to yield *rac*-**14**.[13,14] The sequence was easily performed on a decagram scale for one run and more than 25 grams of *rac*-**14** has been prepared. Selective propargylation of *rac*-**14** provided **6** in 75% yield upon isolation (90% combined yield, d.r. 5:1).[15] Further Luche reduction of **6** yielded another dienyne substrate, **5**, in 73% yield upon isolation (85% combined yield, d.r. 6:1). In both cases, the stereochemistry of the major stereoisomers were elucidated based on two-dimensional (2D) NMR spectroscopic analyses.[16]

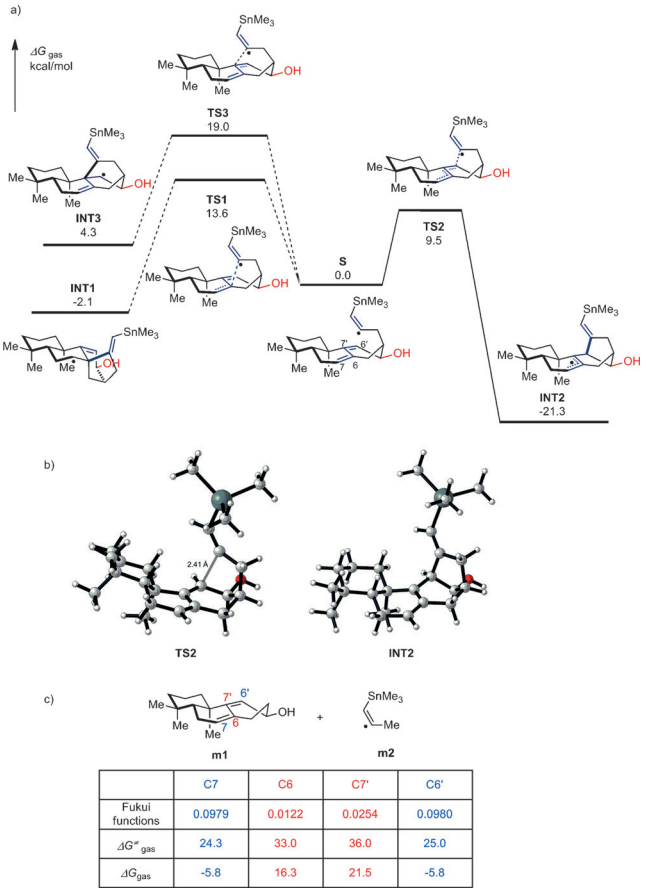
With the dienynes **5** and **6** in hand, we conducted 1,6-dienyne cyclizations with both substrates. Our initial attempts for the development of a catalytic 1,6-dienyne cyclization reaction led to failure using both **5** and **6**, despite extensive screening. Finally, upon treatment of **5** with tri-*n*-butyltin hydride (2 equiv) and AIBN (50 mol%), reductive radical cyclization occurred. Strikingly, we obtained the cyclization product **16** exclusively in 64% yield, rather than the product **15**, after in situ destannylation with PPTS. The structure of **16** was initially determined based on 2D NMR spectroscopy and later unambiguously confirmed by X-ray crystallographic analysis of its acetate derivative (**17**).[16,17] Thus, we managed to install simultaneously the bicyclic[3,2,1]octene skeleton and the endocyclic tetrasubstituted alkene moiety (the jungermannenone framework) by a 1,6-dienyne reductive radical cyclization using **5**.

Starting from **16** (Scheme 2), selective oxidative cleavage of the exocyclic double bond proceeded smoothly and provided the ketone **18** in 83% yield.[18] Final installation of exo-enone by α-methylenation using bis(dimethylamino)methane and acetic anhydride enabled the first scalable synthesis of *rac*-**2** in nine steps (1.6 g prepared).[4d] Barton–McCombie deoxygenation of **18** followed by α-methylenation delivered *rac*-**1**,[19] thus completing the first synthesis of *rac*-**1** in 10 steps. In both cases, the spectroscopic data fully matched that of the natural isolate.[1b,16]

The current 1,6-dienyne reductive radical cyclization is especially noteworthy for its scalability and regioselectivity (Scheme 3a). Using other reaction conditions (reductive



Scheme 3. 1,6-Dienyne reductive radical cyclization. Cp = cyclopentadiene, dba = dibenzylideneacetone, dpm = 2,2,6,7-tetramethyl-3,5-heptanedionato, dppb = 1,4-bis(diphenylphosphino)butane.



	C7	C6	C7'	C6'
Fukui functions	0.0979	0.0122	0.0254	0.0980
$\Delta G^{\ddagger}_{gas}$	24.3	33.0	36.0	25.0
ΔG_{gas}	-5.8	16.3	21.5	-5.8

Figure 2. a) Computed free-energy profile of dienyne reductive radical cyclization of **5** at the UB3LYP/SDD-6-311 + G(d,p)//UB3LYP/ SDD-6-31G(d) level of theory. b) Computed structures of **TS2** and **INT2**. c) Computed Fukui functions at C7, C6, C7′, and C6′ of the model substrate of **m1**, and the activation free energies and reaction free energies for the corresponding radical additions of **m2** to **m1** at these positions, calculated at the (U)B3LYP/SDD-6-31G(d) level of theory. Energies in kcal mol^{-1}.

coupling,[20] reductive Heck reaction,[7] cycloisomerization,[8] etc.), we were unable to isolate other potential cyclization products (**19**–**21**), despite the fact that similar polycyclic frameworks have already been reported.[21]

To gain more insight into this unprecedented 1,6-dienyne cyclization process, we conducted further mechanistic studies (Scheme 3b). Although in situ characterization of the unstable organostannane intermediate **22** obtained after cyclization disclosed a 1:1 mixture of *cis*- and *trans*-isomers, subsequent destannylation using deuterated acetic acid (CD_3CO_2D) provided **23** as the sole product (58% yield, 85% D).[16,22] Thus, we were able to draw the proposed mechanism as follows: the vinyl radical **24** is initially generated, similar to that found for enyne radical cyclization reactions.[6] Regioselective cyclization of **24** enables the formation of the allylic radical **25**,[23] which is quenched by nBu$_3$SnH at the most accessible site to achieve a double-bond isomerization and forge the endocyclic tetrasubstituted alkene moiety. Final destannylation provides **23** as the sole product, presumably through an isomerization/protonation process under acidic conditions.

We were curious to understand why high regioselectivity in the reductive radical cyclization of **5** was observed. We carried out DFT calculations[24] with the (U)B3LYP functional[25] to locate all possible radical addition transition states and their products (Figure 2a,b).[16,26] To simplify the calculations, tri-*n*-butyltin hydride was replaced with trimethyltin hydride in the model. The reaction begins with the addition of the trimethyltin radical to the alkynyl group in **5** to generate the vinyl radical intermediate **S**. The subsequent radical cyclization can occur at either C6, C7, C6′, or C7′. Radical attack at C7 is far away from the vinyl radical and such addition is impossible geometrically. Addition of the vinyl radical to C6′ via **TS2** only needs an activation free energy of 9.5 kcal mol^{-1} and this pathway is exergonic by 21.3 kcal mol^{-1} to furnish **INT2**. In contrast, radical additions to C6 (via **TS1**) and to C7′ (via **TS3**) are both disfavored relative to **TS2** (by 4.1 kcal mol^{-1} and 9.5 kcal mol^{-1}, respectively). The DFT calculations also indicated that radical additions to C6 and C7′ are disfavored thermodynamically compared to the addition to C6′. This difference can be understood by the fact that **INT2** is an allylic radical while **INT1** and **INT3** are both isolated radicals. The additions to C6 and C7′ should be reversible if they could happen. The radical addition to C6′ is kinetically favored and is also irreversible. Therefore, DFT calculations demonstrated that **INT2** with the skeleton of jungermannenones B and C can be generated exclusively from the intramolecular radical addition, which is favored both kinetically and thermodynamically. The calculation results are in consistent with the experimental results.

The above regioselective radical additions can be rationalized by considering both HOMO and LUMO orbitals of the diene fragment in **S** (the C7=C6-C7′=C6′ part). Therefore, Fukui functions[27] for radical attack were computed for the model substrate **m1**, and showed that C7 and C6′ are most reactive toward radical additions (Figure 2c).[16] DFT calculations of the intermolecular additions of the radical **m2** to the four positions supported this prediction: radical additions to C7 and C6′ have very close activation free energies, while attack to C6 and C7′ are both disfavored. Therefore, intrinsically both C7 and C6′ in **S** should be favored, but C7 is not accessible geometrically by the radical in **S** and this product was not generated.

In conclusion, we have accomplished the first scalable[28] and protecting-group-free[29] synthesis of *rac*-jungermannenones B (**1**) and C (**2**) starting from commercially available and inexpensive geraniol (**8**) in 10 and 9 steps, respectively. In the course of our synthetic studies, we have developed an unprecedented 1,6-dienyne reductive radical cyclization to simultaneously install the bicyclic[3,2,1]octene skeleton and an endocyclic tetrasubstituted alkene moiety (the jungermannenone framework). Preliminary mechanistic studies revealed a vinyl radical cyclization/allylic radical isomerization mechanism. Further DFT calculations identified radical additions to form the skeleton of the jungermannenones B and C, additions which are favored both kinetically and thermodynamically. Our current efforts will focus on the asymmetric synthesis of other jungermannenones with higher oxidation states, as well as follow-up chemical biology studies, which will be reported in due course.

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