Natural Product Synthesis

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Asymmetric, Stereodivergent Synthesis of (−)-Clusianone Utilizing a Biomimetic Cationic Cyclization**

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Abstract: *We report a stereodivergent, asymmetric total synthesis of (−)-clusianone in six steps from commercial materials. We implement a challenging cationic cyclization forging a bond between two sterically encumbered quaternary carbon atoms. Mechanistic studies point to the unique ability of formic acid to mediate the cyclization forming the clusianone framework.*

Polyprenylated polycyclic acylphloroglucinols (PPAPs)[1,2] are a structurally intriguing class of natural products containing a bicyclo[3.3.1]nonane-2,4,9-triketone core. (+)-Clusianone (**1**, Figure 1), a type B PPAP as indicated by the α-acyl

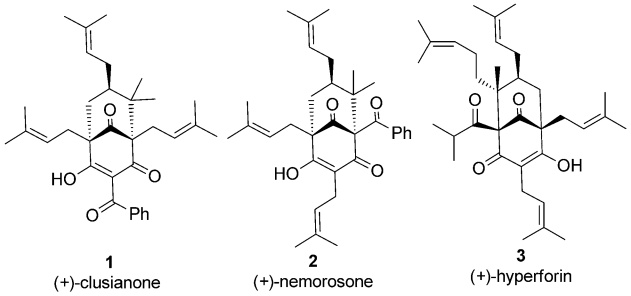

Figure 1. Representative PPAP natural products.

β-hydroxy enone,[1f] was first isolated and characterized in 1976 from the bark of *Clusia congestiflora*.[3a] Since the early 1990s, there have been a handful of isolation studies that address the molecule's structure.[3] However, it was not until 20 years after its initial isolation that reports began to emerge on clusianone's bioactivity.[3c,4] In 2005, the compound was shown to possess notable anti-HIV activity ($EC_{50} = 20$ nM) by inhibiting the gp120-sCD4 viral–receptor interaction.[3c] Clusianone's chemopreventative properties[4c,d] are thought in part to arise from its ability to inhibit histone acetyltransferase (HAT) enzymes. Nemorosone (**2**), an isomeric type A PPAP as indicated by the bridgehead-substituted acyl group α to a quaternary center,[1f] has notable anticancer properties in part due to its ability to activate HAT enzymes[4b,d,f] and serve as a protonophoric mitochondrial uncoupler.[4g] Hyperforin (**3**), a type A PPAP found in St. John's wort, is used to treat depression and possesses anti-inflammatory and antibiotic properties.[1,2d] Given the great diversity of bioactivities attributed to small structural changes among these PPAPs, it is not surprising that these compounds have become popular targets for synthetic chemists.[5,6] For example, elegant asymmetric syntheses of clusianone have been reported by both the Simpkins[6a] and Coltart[6b,c] laboratories.

Structurally, clusianone (**1**) and nemorosone (**2**) possess synthetically challenging, highly oxygenated bicyclo-[3.3.1]nonane cores adorned with prenyl side chains and three stereocenters that derive biosynthetically from the common cationic intermediate **6** (Figure 2).[7] For more than a decade, a number of research groups have been largely unsuccessful at achieving similar cationic cyclizations to access the fully functionalized cores of type A and B PPAPs. Such cyclizations have been reported only in the case of systems lacking the full functionality of the natural products.[5b,d,e,8,9] For example, Marazano and co-workers could not isolate C-cyclized products via cationic intermediates analogous to **6**.[8d] In a study by Couladouros and co-workers,[8e] it was shown that unconjugated tertiary carbocations could not be cyclized to the [3.3.1]-bicyclic core of **3**. The

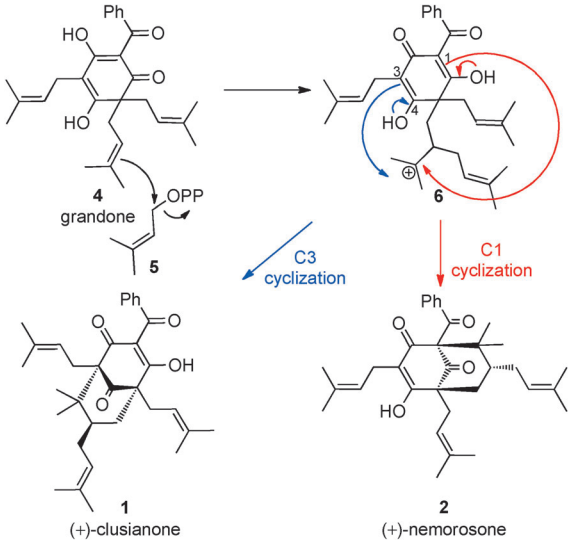

Figure 2. Proposed biosyntheses of (+)-clusianone (**1**) and (+)-nemorosone (**2**).

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difficulty of such a transformation likely stems from a high degree of strain in the transition state and from the steric demands of forming a hindered carbon bond between two sterically congested quaternary carbon atoms.

In line with our group's interest in gaining rapid access to PPAP natural products and derivatives,[2b,5d,8f,g,10] we hoped to develop a route to **1** and/or **2** possessing the brevity and flexibility necessary for structure–activity relationship (SAR) studies. Herein, we report a stereodivergent, asymmetric synthesis of (−)-**1** in only six steps from 5-methoxyresorcinol employing the first cationic cyclization to access the fully functionalized core of (−)-clusianone. Additionally, we present the selective synthesis of five novel architectures from the key cyclization substrate along with a new purification strategy for dearomatized phloroglucinols and type B PPAPs which should be of general utility for these types of compounds.

Inspired by the efficiency of their biosyntheses (Figure 2), we considered synthesizing **1** and/or **2** from **9**, a common intermediate employed in our group's total syntheses of both 7-*epi*-nemorosone[2b] and plukenetione A.[8f] For the case of (−)-**1**, we envisioned that (−)-**7** could be obtained through a cationic cyclization of dearomatized substrate **8** involving protonation of the 1,1-disubstituted olefin to generate a tertiary carbocation at C8 followed by intramolecular enol attack at C3 (Figure 3).

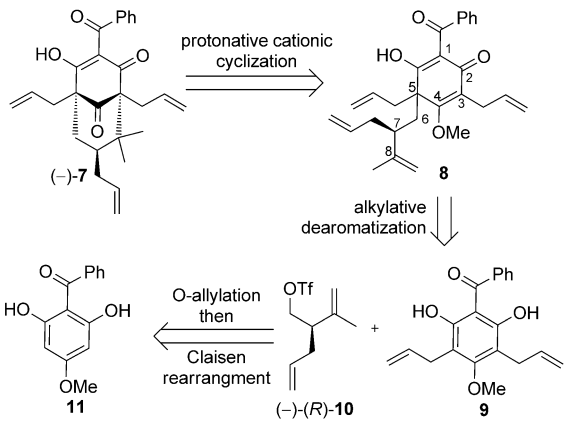
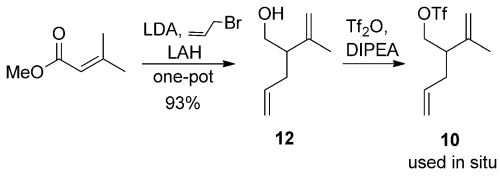


Figure 3. Retrosynthetic analysis of the PPAP core **7**.

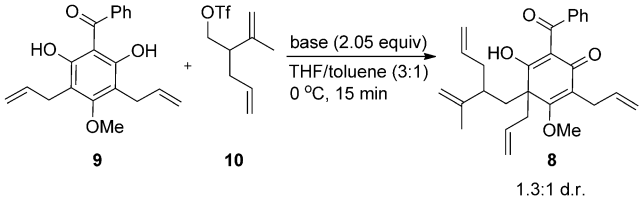
At the outset of our investigation, we had three principal concerns regarding the success of a protonative, cationic cyclization to access the bicyclo[3.3.1]nonane core: 1) control of O- versus C-selectivity in the cyclization, 2) whether the *O*-methyl protecting group at C4 could direct cyclization at C1 to the nemorosone core, and 3) if **8** would rearomatize under acidic conditions given reports that similar dearomatized intermediates underwent rearomatization under acidic conditions.[8a,d] We began our study by investigating an improved synthesis to acylphloroglucinol **9** which was previously prepared in 20% yield from **11** by direct aromatic substitution.[10] Pleasingly, we discovered that selective O-allylation of **11** proceeded in 71% yield which was followed by a thermolytic Claisen rearrangement to produce **9** (92%) on a multigram-scale.[11] Racemic alcohol **12** was prepared in a single pot in 93% yield by a modified procedure (Scheme 1).[12] Triflation of **12** with triflic anhydride afforded **10** which was used in situ.[11]



Scheme 1. Synthesis of racemic triflate **10**.

Alkylative dearomatization of **9** proved challenging in initial studies as little was known regarding factors that may control C- versus O-selectivity for the dearomatization of phloroglucinol substrates.[13] Due to the lack of literature precedent for alkylative dearomatizations involving unactivated alkyl electrophiles,[8e,10,14] it was necessary to carry out a systematic evaluation of reaction conditions. Table 1 shows

Table 1: Optimizing C- versus O-selectivity of the alkylative dearomatization.



Entry	Base	Yield[a] %C	%O
1	KHMDS	0	53
2[b]	NaHMDS	47	31
3	LiHMDS	73	6

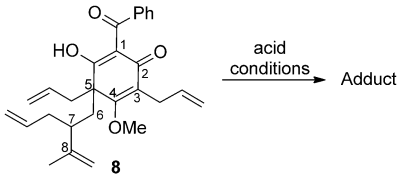
[a] Yield of the isolated product after silica gel chromatography.
[b] Reaction was carried out in THF/benzene (3:1). KHMDS = potassium bis(trimethylsilyl)amide. NaHMDS = sodium bis(trimethylsilyl)amide. LiHMDS = lithium bis(trimethylsilyl)amide.

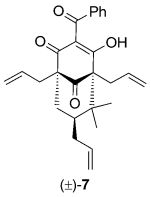
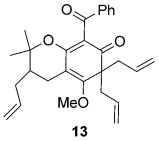
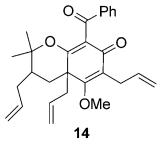
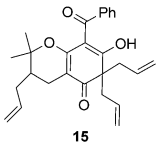
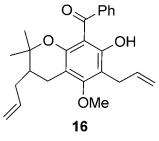
that the base counterion plays a critical role in preventing the undesired O-alkylation. The lithium counterion of the phenolate derived from **9** is likely tightly bound to the phenolate oxygen thereby preventing significant O-alkylation.[15,16] Not surprisingly, KHMDS produced only O-alkylation products as the relatively noncoordinating potassium counterion will expose a naked oxygen enolate. We speculate that lithium coordination to both the sulfonate and enolate oxygen (not shown) helps to facilitate C-alkylation.[17] A solvent screen showed that the reaction does not proceed to full conversion in THF and is very slow in toluene; optimal results were achieved with a combination of THF/toluene (3:1, 0.057 M).[11]

With ample quantities of dearomatized product **8** in hand, we evaluated conditions for cationic cyclization to **7** (Table 2). The success of our biomimetic cationic cyclization to achieve bond formation at C3 was revealed after investigating > 70 different reaction conditions consisting of various Brønsted acids, Lewis acids, solvents, concentrations, temperatures, and work-up variations.[11] Over 13 different products were isolated, five could be obtained selectively depending on the conditions,[8a,d,18] and only formic acid successfully formed a C-cyclized adduct. Highly polar solvents, such as TFA, HFIP, CH_3NO_2, and CH_3CN, favored the O-cyclized Cope rearrangement products **13** and **15**. However, the unique combination of LiBr and *p*-TsOH[19] in CH_2Cl_2 provided clean formation of **14** without Cope rearrangement. Using the latter combination in EtOAc, acetone, and 1,4-dioxane also afforded **14** but in significantly lower yields. Rearomatized product **16** was obtained in 97% yield under similar conditions in CH_2Cl_2 at slightly higher temperatures (Table 2, entry 7). We presume that LiBr increases the acidity of *p*-TsOH in CH_2Cl_2 by lithium coordination to the sulfonic acid such that cyclization is observed at temperatures below −40 °C.

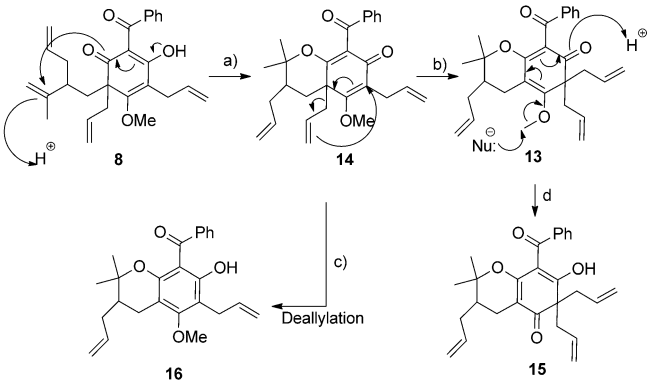
In rationalizing the various O-cyclization outcomes, we observed that pyranodienone **13** could be demethylated to afford product **15** (79%, Scheme 2). Rearomatization to

Table 2: Conditions favoring cationic cyclization products.



	Additive	Conditions	Adduct	Yield [%][a]
1[b]	formic acid	neat 10 °C to RT, 72 h	 (±)-**7**	30
2	*p*-TsOH (10 equiv) LiOTf (10 equiv)	HFIP (0.015 M) 50 °C, 12 h		89
3	TFA (0.14 M)	neat RT, 24 h	 **13**	97
4	*p*-TsOH (10 equiv) LiBr (10 equiv)	CH_3NO_2 (0.015 M) RT, 10 min		55
5	*p*-TsOH (10 equiv) LiBr (10 equiv)	CH_2Cl_2 (0.015 M) −40 °C, 30 h	 **14**	55[c]
6	*p*-TsOH (10 equiv) LiBr (10 equiv)	CH_3CN (0.015 M) 60 °C, 10 min	 **15**	35
7	*p*-TsOH (10 equiv) LiBr (10 equiv)	CH_2Cl_2 (0.015 M) −25 °C, 30 h	 **16**	97[d]

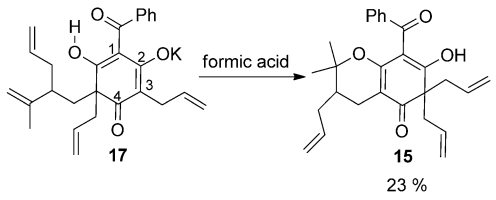
[a] Yield of the isolated product after silica gel chromatography. [b] Product **13** was also produced in 34% yield. [c] Product isolated as a mixture of *cis* and *trans* isomers. [d] Product obtained pure (^{1}H NMR) without need for further purification. HFIP: hexafluoroisopropanol.



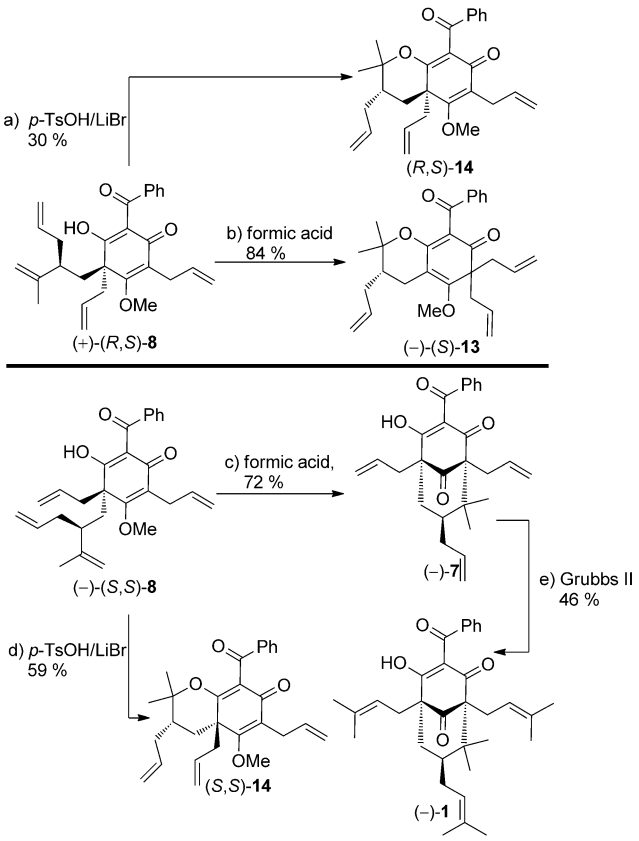
Scheme 2. Mechanistic rationale for O-cyclized products. a) LiBr, *p*-TsOH, CH_2Cl_2, −40 °C, 30 h, 55%; b) formic acid, 10 °C to RT, 12 h, quant.; c) LiBr, *p*-TsOH, CH_2Cl_2, −25 °C, 30 h, 97%; d) LiBr, *p*-TsOH, CH_2Cl_2, RT 5 min, 79%.

product **16** proceeds strictly from intermediate **14**, while **15** is obtained directly from demethylation of O-cyclized Cope product **13**. In all cases, demethylation and Cope rearrangement occurred after cyclization to **14**. Based on these observations, we propose a mechanism that accounts for the formation of the O-cyclized products **13**–**16** (Scheme 2). In contrast to the above results, neat formic acid uniquely led to stereodivergent cyclization of **8** which proceeded to afford both allyl clusianone **7** (30%, Table 2, entry 1) and Cope product **13** (34%). Moreover, we observed that C-cyclization proceeded less efficiently in the absence of an enol methyl ether at C4 providing decomposition and low yields of O-cyclization products including **15** in 23% yield (Scheme 3).

Alkylative dearomatization of **9** with chiral triflate (−)-(*R*)-**10**[12] (Figure 3) led to the production of (−)-(*S*,*S*)-**8** and (+)-(*R*,*S*)-**8** as a 1.3:1 mixture of diastereomers which were separated by preparative thin layer chromatography. When each was individually subjected to neat formic acid, diastereomer (−)-(*S*,*S*)-**8** converted in a stereodivergent manner to (−)-allyl clusianone (−)-**7** (72%) and Cope product (−)-(*S*)-**13** (13%, Scheme 4),[20] whereas diastereomer (+)-(*R*,*S*)-**8** exclusively afforded (−)-(*S*)-**13** (84%). (−)-Clusianone [(−)-**1**] was obtained following cross metathesis of (−)-**7**, and each diastereomer of **8** could be selectively converted into their



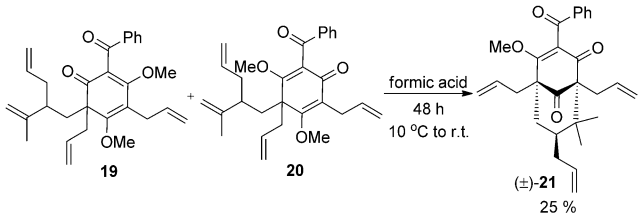
Scheme 3. The C4 methyl ether proved necessary for efficient C-cyclization.



Scheme 4. Stereodivergent syntheses of (−)-clusianone [(−)-**1**] and O-cyclized products.

corresponding O-cyclized adducts (*R*,*S*)-**14** and (*S*,*S*)-**14** in reasonable yields utilizing LiBr/*p*-TsOH at −40 °C.

As formic acid was the only condition out of > 70 others that led to C-cyclization products, it seemed likely that it may mediate the cyclization through a unique mechanism.[21] To simplify our analysis of this mechanism and the observed stereodivergence, we considered the possibility that one tautomer of methyl enol ether **8** might be responsible for the majority of C-cyclization to allyl clusianone **7**. We sought to test this hypothesis by first methylating **8** with $TMSCHN_2$[11] (TMS = trimethylsilane) which was followed by treatment of the resulting mixture of permethylated isomers **19** and **20** with formic acid (Scheme 5). Indeed, methyl ether (±)-**21**[22] was the only clusianone-type product isolated from the reaction in significant yield thereby indicating that cross-conjugated isomer **20** was largely



Scheme 5. Cross-conjugated isomer **20** is largely responsible for C-cyclization.

responsible for C-cyclization. Only O-cyclization products derived from product **19** were isolated from the reaction.

Contrary to other carboxylic acids (e.g. acetic acid), formic acid can add efficiently to 1,1-disubstituted olefins under ambient conditions[23] which we have demonstrated for the case of 2-methyl-1,5-hexadiene.[11] This could influence the cyclization of (−)-(*S*,*S*)-**8** through stabilization of the carbocation forming a tight ion pair in solution. It is also known that formic acid can add to electron-deficient and strained bridgehead ketones.[24] If we consider the possibility of formate addition to (−)-(*S*,*S*)-**8** at C2 of the cross-conjugated carbonyl (alternative 1, Figure 4 A), this would render C3 more electron-rich relative to its vinylogous ester counterpart.[11] Although alternative 1 may improve the probability for cyclization at C3, it is also possible that formate addition at C2 may not be necessary for cyclization (alternative 2, Figure 4 A). Cross-conjugated ketone **23a** is more electron-rich at C3 than its conjugated tautomer (not shown) and may be sufficient to cyclize to (−)-**7**.

Evidence for the proposed formate adduct intermediates in our cyclization was obtained from ultrahigh performance

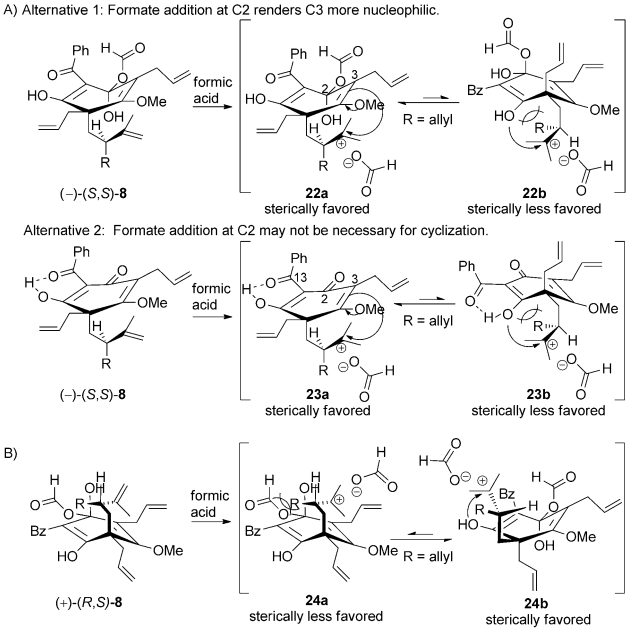


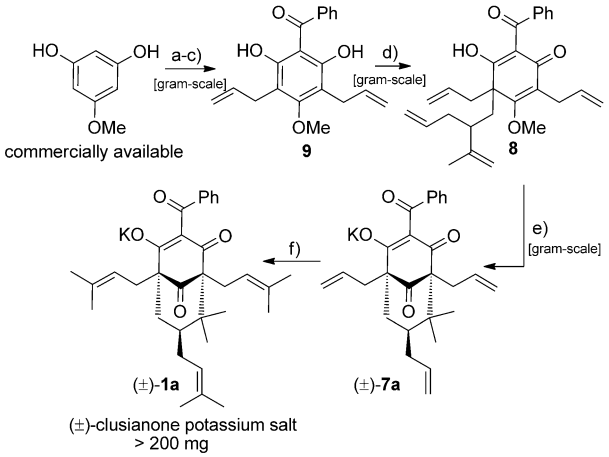
Figure 4. Stereochemical rationale for the observed stereodivergence. A) Stereochemical rationale for dominant C-cyclization of (−)-(*S*,*S*)-**8**. B) Stereochemical rationale for the observed O-cyclization of (+)-(*R*,*S*)-**8**.

liquid chromatography (UPLC) measurements in the reaction medium (98% formic acid) at various time intervals for both (−)-(*S*,*S*)-**8** and (±)-(*S*,*S*)-**20**.[11] The $[M+H^+]$ of the observed reaction components in the evaporative light scattering detector (ELSD) trace for (−)-(*S*,*S*)-**8** corresponded to monoformate and triformate adducts in the first 30 min of reaction; this indicates possible addition to C2 and/or C13 in addition to the 1,1-disubstituted double bond prior to cyclization. Substrate (±)-(*S*,*S*)-**20** was routinely monitored every few hours to observe the formation of monoformate and diformate adducts in the ELSD trace; the formate peaks gradually disappeared as the reaction proceeded to completion. For both substrates, the disappearance of all formate intermediates was observed after 24 h with only product remaining.[11]

The observed stereodivergent outcome (Scheme 4) may be governed by steric interactions as represented in Figure 4. Unfavorable steric interactions in cations **22b**/**23b**, derived from (−)-(*S*,*S*)-**8**, between the allyl group and the cyclohexadiene ring system likely cause the equilibrium to favor cations **22a**/**23a** (Figure 4A). Because the cations are proximal to the nucleophilic carbon at C3 in **22a**/**23a**, we observe dominant formation of the C-cyclized product. The preference for O-cyclization in the case of (+)-(*R*,*S*)-**8** may be rationalized by the close proximity of the cation to the enol depicted in the sterically favored conformation **24b** (Figure 4B). The configuration depicted in **24a** experiences destabilizing steric interactions between the allyl substituent and the cyclohexadiene core, thereby pushing the equilibrium to favor **24b**. Hence, **24b** should react to afford O-cyclization as the preferred stereodivergent outcome for diastereomer (+)-(*R*,*S*)-**8**.

To conclude our study, we wished to demonstrate that our synthesis of (±)-**1** could be achieved on a gram-scale which is not commonly reported for this class of compounds. The difficulty associated with synthesizing large quantities of PPAP natural products derives from their tendency to bind to silica and form salts.[8d,11] Our final synthesis of racemic clusianone (±)-**1a** utilized a general purification strategy for dearomatized phloroglucinols and type B PPAPs,[11] where the synthesis of acylphloroglucinol **9** and the subsequent alkylative dearomatization were achieved on a multigram-scale to provide **8** (30–37% over four steps, 1.3:1 d.r., Scheme 6). Without the need to separate diastereomers, the key cyclization in formic acid was conducted on scales of up to 2 g where products were separated by basic extraction to provide the potassium salt of allyl clusianone (±)-**7a** (26–32%) as a single isomer.[11] Olefin metathesis proceeded in 81% yield using the Grubbs second generation catalyst[2c] which was followed by basic workup to isolate more than 210 mg of racemic clusianone potassium salt (±)-**1a**. All salt products could be converted to their conventional protonated, tautomeric forms by simple extraction with 1M HCl.

In conclusion, we have developed a scalable, asymmetric, and stereodivergent synthesis of (−)-clusianone [(−)-**1**] in only six steps from commercial starting materials. Protonative cationic cyclization of **8** allowed selective access to five novel architectures. Mechanistic studies[11] underscore the ability of formic acid to mediate a unique biomimetic cyclization to access allyl clusianone **7**. Finally, we developed a general purification strategy for dearomatized phloroglucinols and type B PPAP derivatives, thereby rendering our entire synthesis column-free from phloroglucinol **9**.[11] Further studies regarding the synthesis and biological activity of PPAP natural products and derivatives are in progress and will be reported in due course.



Scheme 6. Large-scale synthesis of (±)-clusianone potassium salt (±)-**1a**. a) $AlCl_3$, BzCl, CH_2Cl_2, 0°C to RT, 3 h, 69%; b) K_2CO_3, $n$$Bu_4NI$, allyl bromide, acetone, 75°C, 16 h, 71%; c) 1,2-dichlorobenzene, 210°C, 12 h, 92%; d) LiHMDS, **10**, THF/Tol = 3:1, −20°C to RT, 2 h, 67–83%, 1.3:1 d.r.; e) formic acid, 10°C to RT, 48 h, 26–32%; f) Grubbs second generation catalyst (20 mol%), isobutylene, −78 to 60°C, 24 h, 81%.

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Keywords: cationic cyclization · dearomatization · formic acid · natural products · PPAPs

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Communications

Natural Product Synthesis

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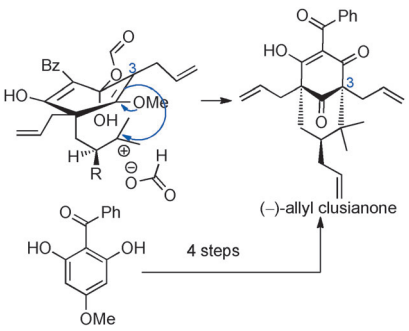
Asymmetric, Stereodivergent Synthesis of (−)-Clusianone Utilizing a Biomimetic Cationic Cyclization



Aim for selectivity: (−)-Clusianone was produced by a stereodivergent asymmetric total synthesis in six steps from commercial materials. The synthesis utilizes a challenging formic acid-mediated cationic cyclization forging a bond between two sterically encumbered quaternary carbon atoms.