Concise Syntheses of *ent*-Aquilanol A and Aquilanol B via Retro-cycloisomerization of (-)-Caryophyllene Oxide. Access to Medium-sized Oxygenated Carbocyclic Scaffolds

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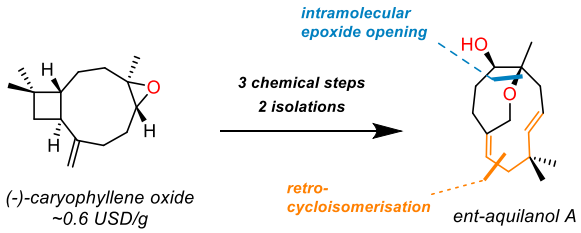
This work is dedicated to Prof. John K. Gallos on the occasion of his retirement



ABSTRACT: The first concise synthesis of naturally occurring aquilanols A and B, two unprecedented 7/10 bicyclic sesquiterpenoids, is presented. Key features of the synthesis are a retrocycloisomerization event on (-)-caryophyllene oxide to form the eleven-membered carbocyclic frame and an intramolecular epoxide opening to construct the bicyclic skeleton. The latter provides evidence to plausible biosynthesis of natural compounds, rendering our synthesis biomimetic. Our plan provides selectively access to other medium-sized carbocyclic oxygenated compounds, thus enhancing the structural diversity of final products.

Aquilanols A (**1**) and B (**2**) are naturally occurring sesquiterpenoids, isolated by Park *et al.*, in 2017 from the agarwood of *Aquilaria malaccensis* (Figure 1A).[1] Their intriguing structure comprises a 7/10 bicyclic skeleton, unprecedented within the humulene-type sesquiterpenoids family. The inherent strain of such medium-sized bicyclic frameworks is further intensified by the presence of a double bond on the junction of the two rings and a *trans*- disubstituted double bond incorporated into the 10-membered ring. Although, preliminary evaluation did not reveal any significant activity when tested against certain Gram-positive and Gram-negative bacteria, such strained molecular scaffolds hold high potential for biological activity, owned to strain-releasing-driven reactivity. This expectation is supported by the fact that agarwood is produced by the plant in response to microbials infections.[2]

Given the interest of our group in the synthesis of small-molecular weight antibacterial agents,[3] combined with the challenging structural features of aquilanols A and B, we embarked on the synthesis of the abovementioned compounds. Our interest became ever greater on the notice that no total synthesis has been reported so far and that price of agarwood, the natural source of aquilanols, is exceptional high and keeps rising due to emerging depletion of the Aquilaria tree population.[4]

On a first thought in designing of our synthetic plan, we wished to probe the viability of the biosynthetic hypothesis suggested by Park and co-workers.[1] According to their proposal, aquilanol A (**1**) was derived from an intramolecular epoxide opening event on a highly oxidized derivative of humulene (**3**) (Figure 1B, compound **4**). Consequently, our initial objective was oriented toward the assembly of the eleven-membered carbocyclic oxygenated intermediate **4**. A blueprint of our approach towards

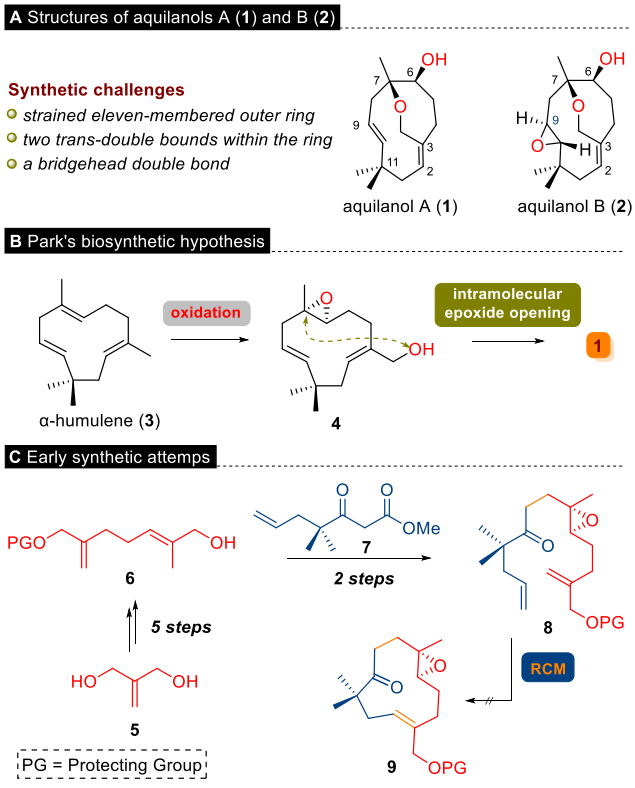


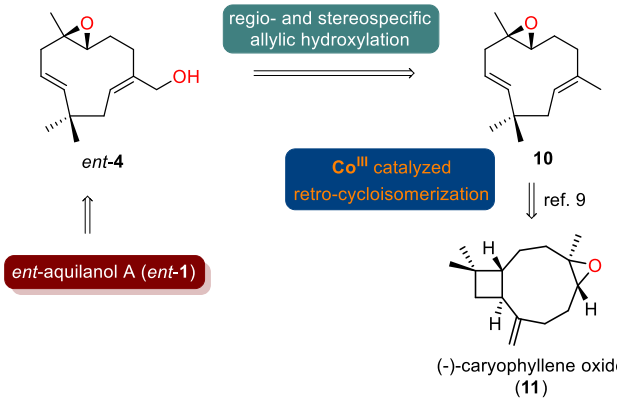
Figure 1. A) Structures of aquilanols A (**1**) and B (**2**); B) Biosynthetic hypothesis by Park; C) Early synthetic efforts by our group.

this goal encompassed the construction of polyunsaturated precursor **8**, upon which a ring closure metathesis would be applied to formulate the ring (Figure 1C). Albeit rare, such strategies

for the preparation of eleven-membered carbocycles are reported in the literature.[5] Unfortunately, this approach proved fruitless on our systems, despite several variations on the cyclisation substrate we attempted the reaction on.[6]

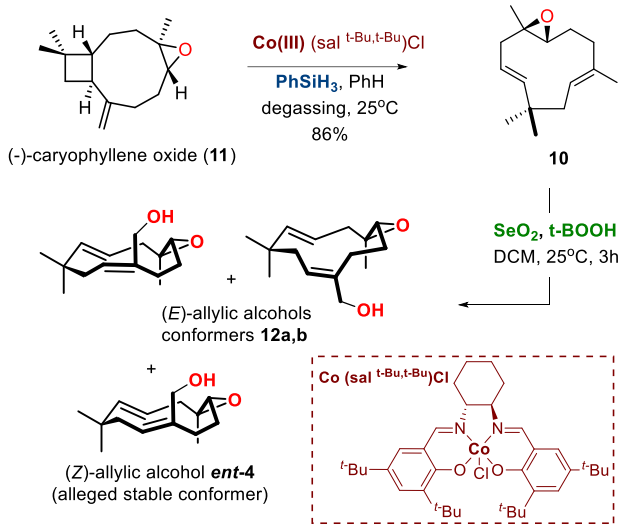
As often the case in terpene synthetic world, we turned our attention to terpene chiral pool to identify easily accessible natural compounds, that could serve as alternative starting materials to formulate the macrocyclic core.[7] Our interest was attracted by (-)-caryophyllene oxide (**11**), a naturally derived material, available in large quantities and low cost (*approx*. 0,6 USD/g) and in acceptable purity (>95%).[8] Shenvi have recently demonstrated the high added-value conversion of the latter to much more precious humulene oxide (**10**), stereoselectively, via a radical retro-cycloisomerization reaction catalyzed by Co(III)-salen species (Scheme 1).[9] This transformation perfectly suited to the needs of our plan. A retrosynthetic analysis capitalizing on the latter would encompass only an additional regio- and stereospecific allylic oxidation on the pendent methyl group of the trisubstituted double bond in **10** (Scheme 1). Unfortunately, (-)-caryophyllene oxide, the only enantiomer commercially available, leads to the enantiomer of the natural compound, *ent*-aquilanol A (*ent*-**1**). Even so, we decided to test our hypothesis as it constitutes a rapid and versatile access to the broader family of aquilanols.

Scheme 1. Retrosynthetic analysis of *ent*-aquilanol (*ent*-1) employing (-)-caryophyllene oxide as starting material.



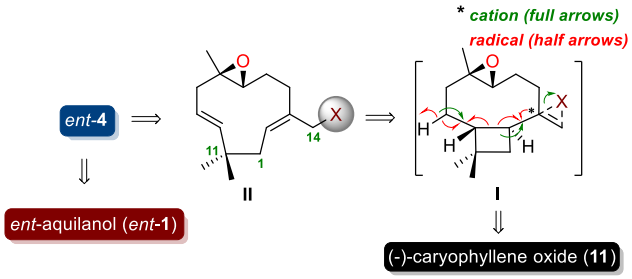
Truly, in our hands commercially available (-)-caryophyllene oxide (**11**), was converted in good yield and on multigram scale to humulene oxide (**10**), providing ease access to a valuable intermediate, that is very tricky to be reached otherwise (Scheme 2).[10] Next, we explored the allylic oxidation of **10**, using standard protocol employing SeO_2/*t*-BuOOH as the catalytic system.[11] Even though TLC monitoring of the reaction indicated an unexpectedly clean conversion, NMR analysis of the reaction mixture revealed the presence of an inseparable mixture of three isomeric allylic alcohols **12a,b** and *ent*-**4**. Indeed, Shirahama had previously reported that analogous oxidation on the same substrate leads to mixtures of geometrical isomers of allylic alcohols, one of them appearing in the form of two distinct and stable conformers.[12] Unfortunately, the produced mixture of alcohols was extremely difficult to separate, especially given the unstable nature of them under standard purification conditions. Even worse, the desired (*Z*)-allylic alcohol *ent*-**4**, was by far the minor component of the mixture, indicating that typical SeO_2 oxidation was not a productive solution to our problem. Any attempts to isomerize the mixture in favor of the anticipated (*Z*)-isomer (photochemical conditions, acidic treatment, I_2 catalysis) proved to be in vain. To the contrary the undesired (*E*)-alcohol was the one to be favored under any of the conditions explored.

Scheme 2. Attempted synthesis of allylic alcohol *ent*-4.



The above discouraging results prompted us to revise our synthetic plan. We envisioned that combining in one step functionalization of the specific position (pendent methyl group) and retro-cycloisomerization event may serve as a solution to our problem. The new concept is briefly described on Scheme 3. We thought that activation of the exocyclic double bond on (-)-caryophyllene oxide (**11**) with a suitable reagent could trigger a concomitant cationic (or radical) mediated retro-cycloisomerization and functionalization of C-14 (intermediate **II**). Subsequent functional group transformation would provide the desired monocyclic precursor *ent*-**4**.

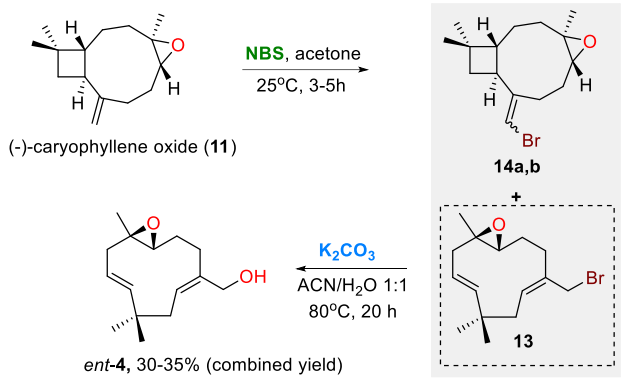
Scheme 3. Revised retrosynthetic analysis combining retro-cycloisomerization and functionalization of C-14.



Gratifyingly, our hypothesis proved correct. After much experimentation we found that treatment of (-)-caryophyllene oxide (**11**) with NBS in acetone afforded the expected humulene-type bromide **13**, with vinyl bromides **14a,b** accounting for the rest of the consumed starting material (Scheme 4). NBS proved unique electrophilic bromine source among a variety of similar activators tested. Different halogen electrophiles also turned out to be unproductive.[13] Unlikely, the polarity of all three bromides was very similar rendering purification problematic. To circumvent this adverse event, we proceeded with the hydrolysis of the reaction mixture with the expectation that vinylic bromides

14a,b would be inert to the reaction conditions. Indeed, the anticipated (*Z*)-allylic alcohol *ent*-**4** was the only alcohol detected in the reaction mixture, while bromides **14a,b** were recovered intact after fast purification using neutralized silica gel. The combined yield range of alcohol *ent*-**4** for the two-step sequence is 30-35%, consistently, regardless the scale of the reaction, typically applied on gram scale.

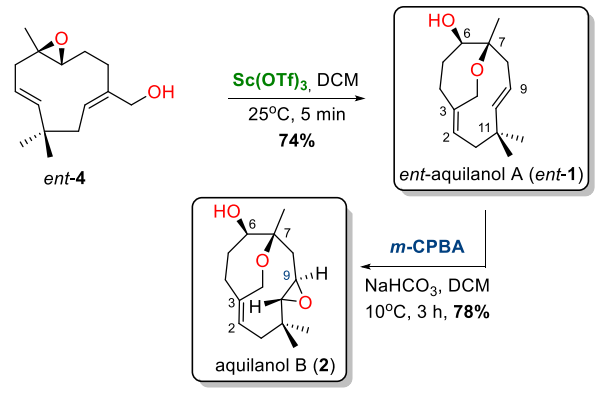
Scheme 4. Two-step synthesis of (*Z*)-alcohol ent-4 from (-)-caryophyllene oxide (11).



To further improve our synthesis, we envisioned direct installation of the hydroxyl group, while triggering the retro-cycloisomerization rearrangement. A recent work by Lei describes the visible light mediated anti-Markovnikov hydration of olefins,[14] that is claimed to proceed via a radical intermediate, thus deemed to be ideal for our purposes (Scheme 3; **I**: X = OH, * = radical). Regretfully, on our substrate, such a protocol proved ineffective, since it led to a rather complicated reaction mixture, the ^{1}H-NMR spectrum of which did not indicate any ring opening of the bicyclic core of caryophyllene oxide.

Having ensure a rapid access to the oxidized humulene-type substrate *ent*-**4**, we were in position to investigate the plausible biomimetic intramolecular epoxide opening. Apparently, acid catalysis was required to favor the anticipated regioselectivity, that forms a seven membered ring, in contrast to the six membered analogue that is expected to be preferred in a non-catalytic process. Thankfully, treatment of *ent*-**4** with various types of acids ($SnCl_4$, BF_3•Et_2O, TFA, $Sc(OTf)_3$), all brought about

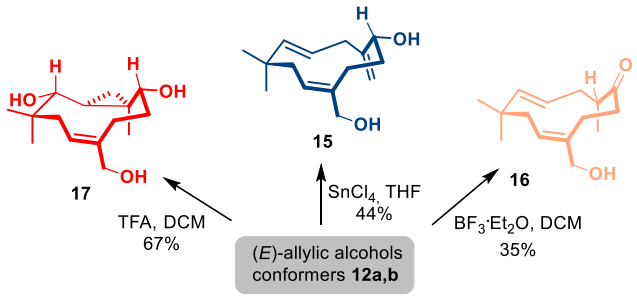
Scheme 5. Completion of the synthesis of *ent*-aquilanol A (*ent*-1) and aquilanol B (2). Prove of the biomimetic hypothesis.



the desired transformation (Scheme 5). Among them $Sc(OTf)_3$ gave the cleanest reaction profile, providing access to the enantiomer of natural aquilanol A (**1**) in 74% yield, presumable due to its ability of concomitant activation of epoxide and complexation of the allylic hydroxyl group, thus bringing in proximity the reacting components. Furthermore, m-CPBA oxidation of *ent*-**1**, led exclusively to natural aquilanol B (**2**) in 78% yield, with the disubstituted double bond $\Delta^{9,10}$ being the only reactive site. The spectroscopic and physical data were in excellent agreement with the reported ones by the isolation group.[1]

In addition, having ensure a rapid access to the respective (*E*)-allylic alcohol, in the form of two stable conformers **12a,b** (see Scheme 2), we were curious whether analogues of the natural product could be derived from. Against our expectations, treatment with various types of acids did not cause an analogous intramolecular epoxide opening, instead provided access to several structurally distinct products, often with admirable chemoselectivity, a fact that renders alcohols **12a,b** a valuable common intermediate to a versatile array of highly oxidized carbocyclic motifs (Scheme 6). In particular, treatment of **12a,b** with typical Lewis acids such as $SnCl_4$, or $TiCl_4$, afforded exomethylene allylic alcohol **15** as the major product (please see supporting information Scheme S1 for mechanistic interpretation). On the other hand, BF_3•OEt_2 resulted in the formation of a pinacol type rearrangement product, ketone **16**. When alcohols **12a,b** were subjected to the action of a Brønsted acid, regardless its strength, a known rearrangement took place, triggered by nucleophilic attack of the nearby disubstituted double bond, to provide cyclopropyl triol **17**.[15]

Scheme 6. Highly oxidized carbocyclic scaffolds from treatment of (*E*)-allylic alcohols 12a,b with various acids.



In summary, we have achieved the first synthesis of the enantiomer of naturally occurring aquilanol A (**1**) and its further oxidized congener aquilanol B (**2**), in three chemical steps starting from easily accessible (-)-caryophyllene oxide (**11**). Our strategy consists of an electrophilic activation of the exocyclic double bond on **11**, accompanied by a retro-cycloisomerization event to obtain the eleven-membered monocyclic intermediate bromide **13** and, after hydrolysis, alcohol *ent*-**4**. Intramolecular acid catalyzed epoxide opening on the (*Z*)-allylic alcohol precursor completes the synthesis (overall yield 24%), thus providing a logical basis to support the biosynthetic hypothesis by Park and co-workers. Further selective epoxidation of *ent*-**1** leads to aquilanol B (**2**) in good yield. Finally, various structurally distinct highly oxidized eleven-membered cyclic scaffolds were reached in a selective manner, all originated from common intermediate (*E*)-allylic alcohol **12a,b**, upon the action of specific acidic reagent.

ASSOCIATED CONTENT

Supporting Information

Full experimental details for the synthesis of all new compounds, its physical and spectroscopic data, as well as pictures of ^{1}H and ^{13}C NMR spectra.

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Notes

The authors declare no competing financial interest.

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KEYWORDS

Aquilanols • sesquiterpenes • natural products • retro-cycloisomerization • caryophyllene epoxide

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