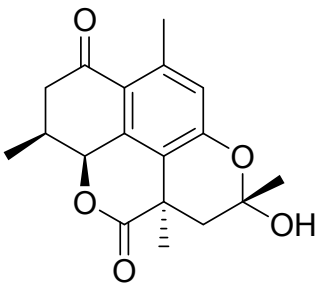
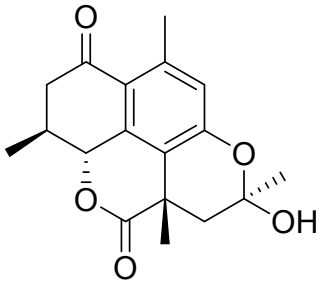
Asymmetric Total Synthesis of Commiphoranes A and B



Commiphorane A



Commiphorane B

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ABSTRACT

Commiphoranes A and B isolated from *Resina commiphora* were recently found to inhibit organ fibrosis. They have the potential to be developed as novel therapies against this disease. The total synthetic plans for these compounds are presented in this proposal. The key steps include closing ring A by an improved Friedel-Crafts acylation protocol, as well as performing an intramolecular Heck reaction to construct the C-11 stereocenters.

INTRODUCTION

Four novel natural products, commiphoranes A-D (**1-4**), were recently isolated by Dong et al. from a natural aromatic oleogum resin known as myrrh (Figure 1), which originates from plant species of the genus *Commiphora*.[1-2] The medicinal values of this plant were explored centuries ago in many parts of the world.[1, 3] A major advantage of myrrh is that it is safe for humans, and the US Food and Drug Administration (US FDA) approved this substance for medicinal uses.[2] The versatility of myrrh, administered either orally or topically, is remarkable.[4] It is exemplified by its various applications in treating several maladies including parasite infections, pain, and inflammation.[1-2]

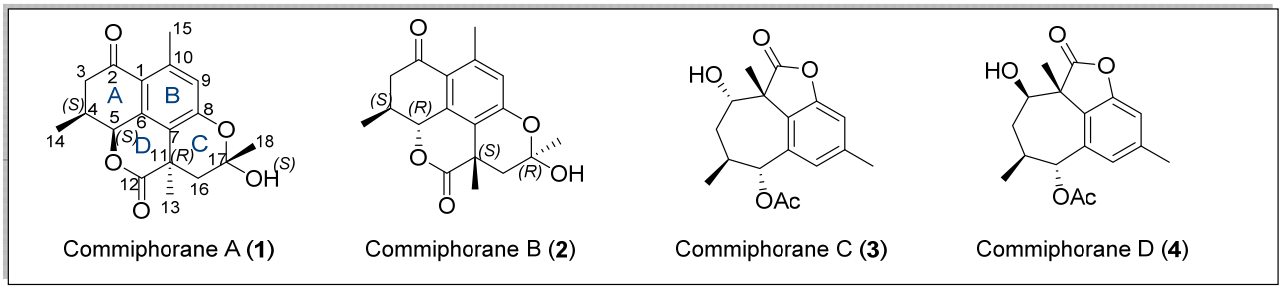


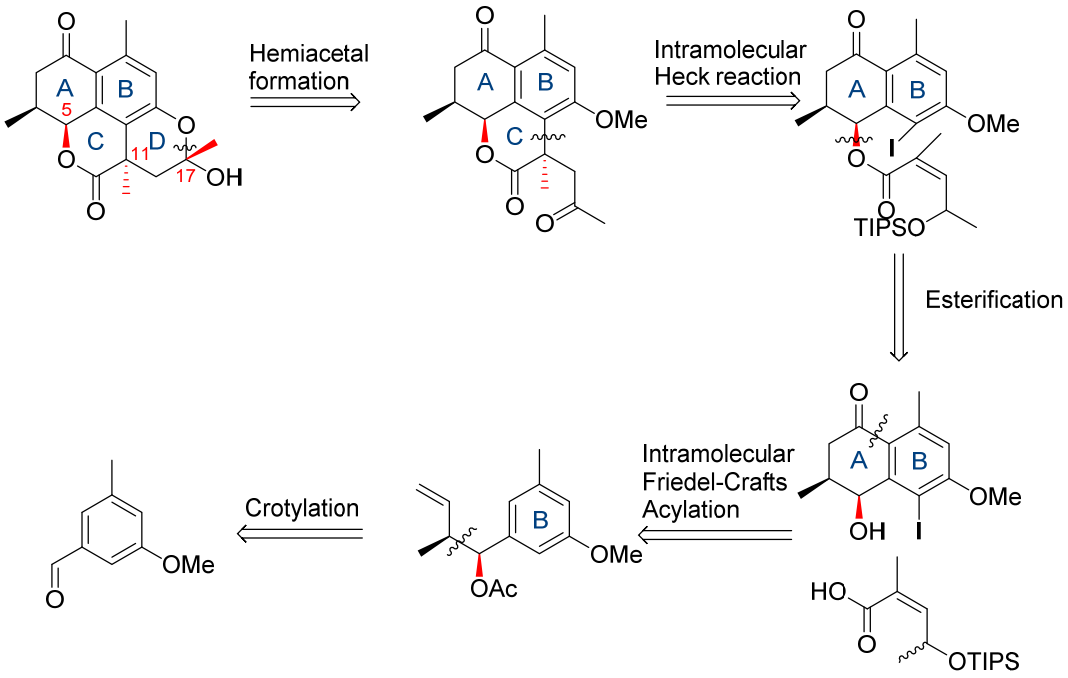
Figure 1. Chemical structures of commiphoranes A-D (**1-4**).

Commiphoranes A-D belong to a class of aromatic terpenoids, in which they are biosynthesized by precursors including farnesyl pyrophosphate (FPP) and isopentenyl pyrophosphate (IPP).[1] Notably, these compounds possess a novel structural backbone. Commiphoranes A and B (**1** and **2)** contain a 6/6/6/6 ring system, whereas commiphoranes C and D (**3** and **4**) feature a 5/6/7 rings scaffold.[1] Total synthesis strategies for these compounds are yet to be reported due to their novelties. Compounds **1-3** were found to ameliorate fibrosis.[1] Patients having this disease suffer undesired aggregation of the tissues of their organs, leading to a loss of function.[5] Initiated by acute inflammation, damaged tissues produce fibrous connective tissues such as collagen and fibronectin to repair the damage. The protein known as transforming

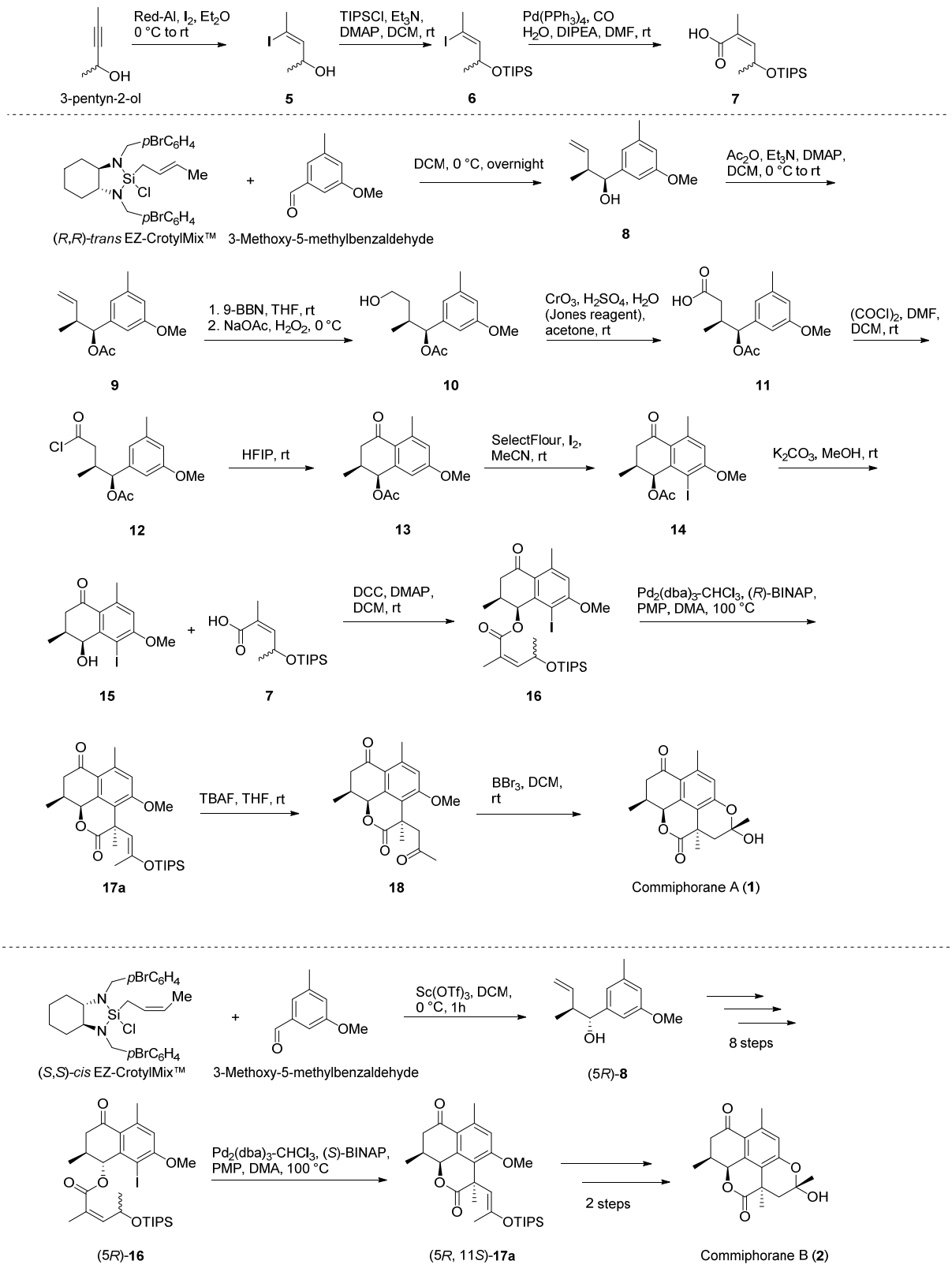
growth factor-β1 (TGF-β1) is responsible for stimulating fibroblast cells to synthesize these connective tissues.[5] However, dysregulated chronic inflammation results in excessive accumulation of these tissues and damage to the organs. Due to the severity of fibrotic diseases, its mechanisms are extensively studied to discover potential therapeutic approaches. Examples of FDA-approved antifibrotic treatments include small molecule drugs bortezomib and anakinra, which treat fibrosis of different types.[5] Compounds **1-3** inhibit the action of TGF-β1 producing fibers in cells, resulting in significantly reduced quantities of collagen and fibronectin generated after treatment.[1] In this study, the total syntheses of **1** and **2** will be discussed. This proposed strategy also allows other stereoisomers of **1** and **2** to be obtained by only slight modifications. Hence, synthesizing these compounds affords a potential for developing new therapies against fibrosis.

METHODOLOGY

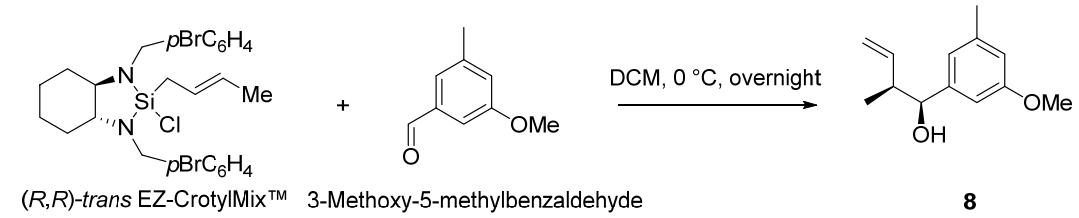
Compounds **1** and **2** are analyzed retrosynthetically (Scheme 1). By analyzing the four rings of **1**, the synthesis strategy will begin with the aromatic ring B, followed by rings A, D and C, mimicking the order for their biosynthesis.[1] Retrosynthetically, the final product **1** will be synthesized from cyclization of the hemiketal ring C by an intramolecular hemiacetal formation reaction. Subsequently, an intramolecular Heck reaction will enantioselectively establish the quaternary center at C-11 by cyclizing ring D to afford a lactone. The precursor for the Heck cyclization will be furnished by standard esterification coupling of rings A and B with the α,β-unsaturated carboxylic acid fragment. Then the cyclohexanone ring A will be closed by regioselective intramolecular Friedel-Crafts acylation of its precursor compound, which can be obtained enantioselectively by crotylation of the commerically available compound 3-methoxy-5-methylbenzaldehyde. This plan can also be applied to **2**, the diastereomer of **1**, by inverting all stereocenters corresponding to C-5, C-11, and C-17. Thus, the complete synthetic scheme is illustrated in Scheme 2.



Scheme 1. Retrosynthetic analysis of commiphorane A (**1**). May be applied for commiphorane B (**2**) by inverting the stereocenters of C-5, C-11, and C-17.

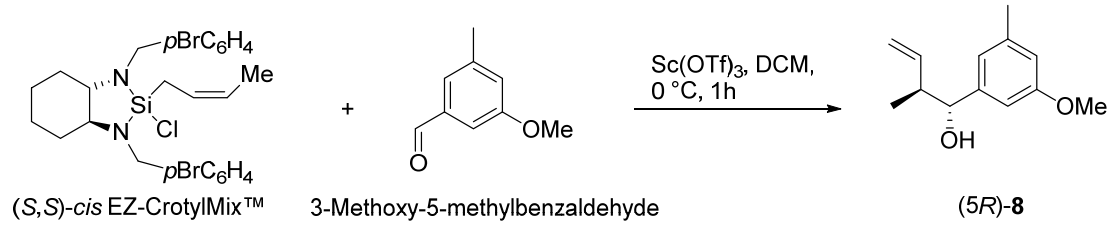


Scheme 2. Complete synthetic scheme for commiphoranes A and B (**1** and **2**).



Scheme 3.

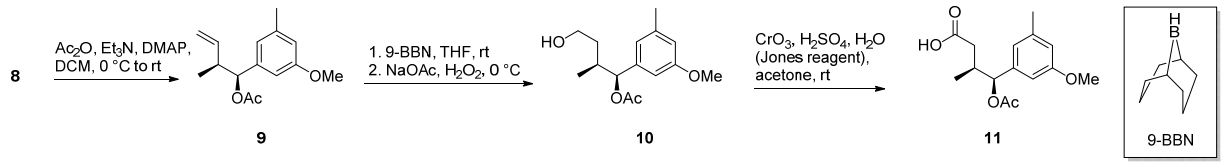
The synthesis of commiphorane A (**1**) will begin with enantioselective crotylation by the protocol reported by Leighton et al. (Scheme 3).[6-7] This experimental technique is not only trivial, but it also creates two stereocenters in any desired combination of configurations in one step based on the stereochemistry of the reagent used. The reagent, (*R*,*R*)-*trans* EZ-CrotylMix™ is stable in a crystalline form, which is commercially available (CAS No. 804559-39-5, Strem Catalog No. 14-1883). The (*R,R*) isomer of the reagent produces the (*S*) stereocenter at the alcohol position and vice versa, while the *cis* and *trans* alkene isomers of the reagent yield *syn* and *anti* substituents respectively. A similar reaction was reported with the reagent (*R*,*R*)-*trans* EZ-CrotylMix™ reacting with benzaldehyde with 54% yield and 93% ee. Thus, it is expected to work for the commercially available substituted benzaldehyde substrate of 3-methoxy-5-methylbenzaldehyde to afford high enantioselectivity to afford the desired compound **8** as the (4*S*, 5*S*) isomer. Due to the fairly high price for the reagent ($207/1g), the classical crotylation protocols reported by Brown et al., Roush et al. and others could be implemented instead.[6, 8]



Scheme 4.

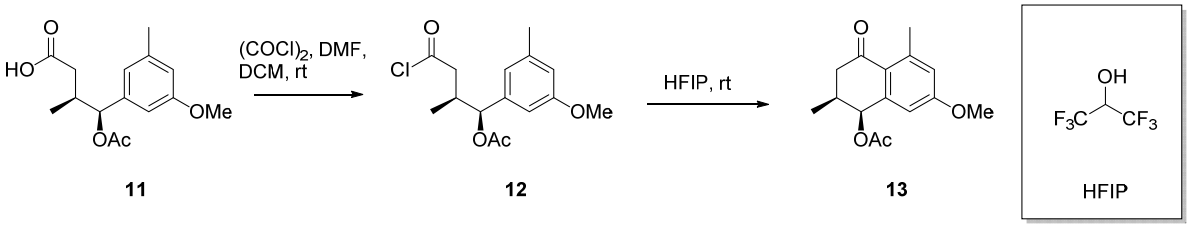
Likewise, the synthesis of commiphorane B (**2**), the diastereomer of **1**, will begin with the same crotylation protocol by Leighton et al., but with the reagent (*S*,*S*)-*cis* EZ-CrotylMix™ (Sigma Aldrich Catalog No. 737666),[6-7, 9] the diastereomer of the reagent in the previous case (Scheme 4). Catalytic $Sc(OTf)_3$ is included in this reagent by Sigma Aldrich, because it significantly increases the yield of crotylation reactions to >90% as previously reported. The

catalyst acts as a lewis acid by protonating the aminochlorosilane of the reagent.[9] Addition of $Sc(OTf)_3$ might also increase the efficiency for synthesizing **8** in the previous case. Thus, the desired (4*S*, 5*R*) diastereomer of **8**, (5*R*)-**8**, with the alcohol stereochemistry opposite to the previous case, can be obtained by reacting the same substrate with the diastereomer of the reagent. For the sake of clarity, the subsequent reactions will be illustrated for the synthesis of **1** and can be applied to its diastereomer **2**, and the stereocenters corresponding to C-5 of the final product **2** for all intermediate compounds are inverted unless otherwise stated.



Scheme 5.

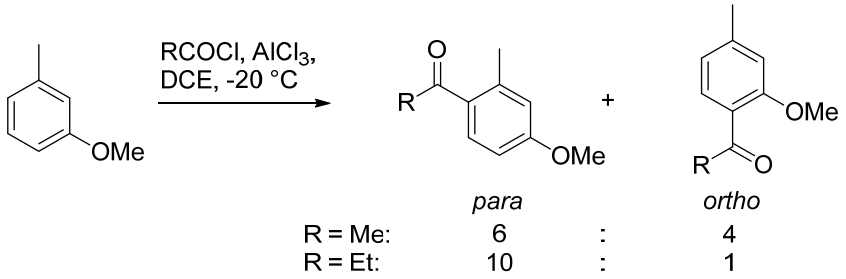
Intermediate **11** will be synthesized by standard 3-step sequence of alcohol acetylation, hydroboration-oxidation reaction followed by Jones oxidation (Scheme 5).[10] Hydroboration with bulky 9-borabicyclo[3.3.1]nonane (9-BBN) reagent affords high regioselectivity in which the terminal olefin carbon reacts with the borane almost exclusively (Anti-Markovnikov rule). Subsequent workup will generate the alcohol by treatment with hydrogen peroxide with sodium acetate.[11] Thus, compound **10** is afforded, and the newly generated alcohol will be subjected to oxidation with the classical Jones reagent, while leaving the acetate group intact to afford **11**.[12]



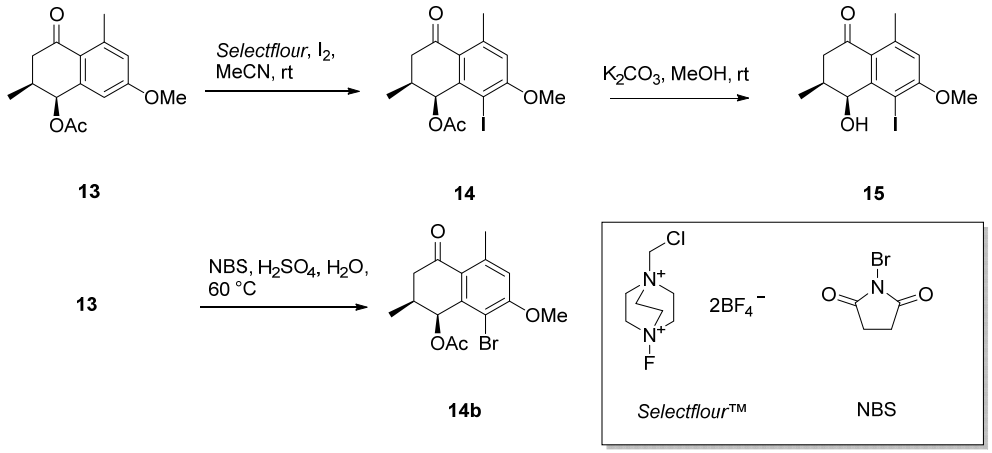
Scheme 6.

The formation of the cyclohexanone ring can proceed by a recently reported variation of the intramolecular Friedel-Crafts acylation (Scheme 6).[13] Conversion of the carboxylic acid **11** to acyl chloride will be carried out by standard reaction condition with oxalyl chloride to afford acyl chloride **12** while tolerating the acetyl protected alcohol.[14] Compound **12** is subsequently cyclized by Friedel-Crafts acylation. Dissolution of compound **12** in hexafluoroisopropanol

(HFIP) spontaneously initiates cyclization to afford compound **13**. HFIP is a very strong hydrogen bond donor which allows it to act as a solvent as well as a Lewis acid equivalent.[13] This reaction was observed to proceed even with steric hindrance by substituents at the *ortho* positions with respect to the reacting carbon. Regarding the regioselectivity of the cyclization, it is possible that the connection will be made in either *ortho* or *para* to the methoxy group of the aryl ring. Although the authors did not report anything about regioselectivity, they illustrated examples in which the connection is made as far from the methoxy group as possible, presumably because the *para* position is more electron rich. As a result, the connection is expected to be made *para* to the methoxy group predominantly. In addition, it is reported that the classical intermolecular Friedel-Crafts acylation affords remarkable regioselectivity for similar substrates of 3-methylanisole and an acyl chloride.[15] Notably, the regioselectivities for ethyl acyl chloride substrate are far superior to the methyl equivalent (*para*: *ortho* = 10:1), so it can be inferred that remarkable regioselectivity to the *para* position can be achieved with a reasonably large acyl chloride substrate (Scheme 7). The poor selectivity for MeCOCl may be explained by $MeCO^+$ cation being too reactive during the transition state. The minor product should be able to be separated due to a significant difference in polarities between the two products.



Scheme 7. Regioselectivities for Friedel-Crafts acylation of 3-methylanisole.[15]

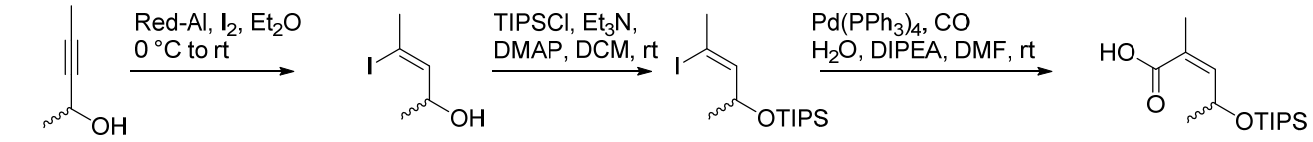


13 **14** **15**

13 **14b**

Scheme 8.

The regioselective iodination of **13** will be performed by a new technique reported by Stavber et al., such that the aromatic ring will be regioselectively iodinated at the *para* position of the aryl methyl under the directing effect of the ketone, with a solution of *Selectfluor* and molecular iodine in MeCN (Scheme 8). The iodine will be at the *ortho* position to the aryl methyl for the minor regioisomer product, which should be separable by flash chromatography and recrystallization as reported.[16] Regarding the mechanism of this reaction, molecular iodine will be oxidized and activated by *Selectfluor* to generate an electrophilic reactive species, then an electrophilic aromatic substitution will take place.[16] The potentially sensitive acetyl group should be tolerated by *Selectfluor* as reported.[17] Alternatively, **13** could be brominated instead using a reported condition also by Stavber et al. of using *N*-bromosuccinimide (NBS) with sulfuric acid and water at 60 °C regioselectively to afford the aryl bromide **14b** which is *ortho* to the aryl methoxy group.[18] After that, compound **14** will be subjected to mild hydrolysis by potassium carbonate at room temperature, which tolerates the labile aryl iodide to remove the acetate group and afford alcohol **15**.[19]

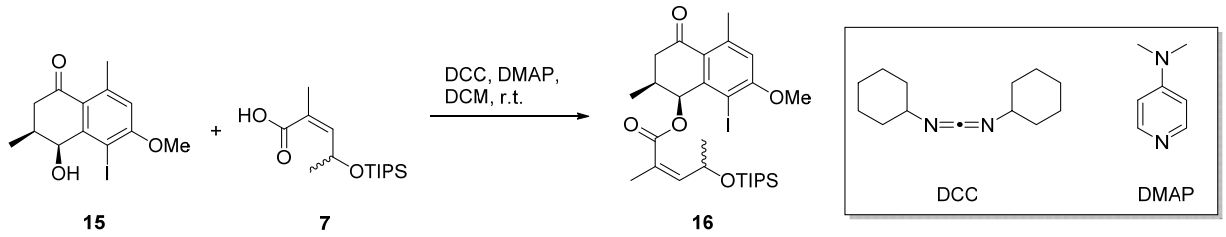


3-pentyn-2-ol **5** **6** **7**

Scheme 9.

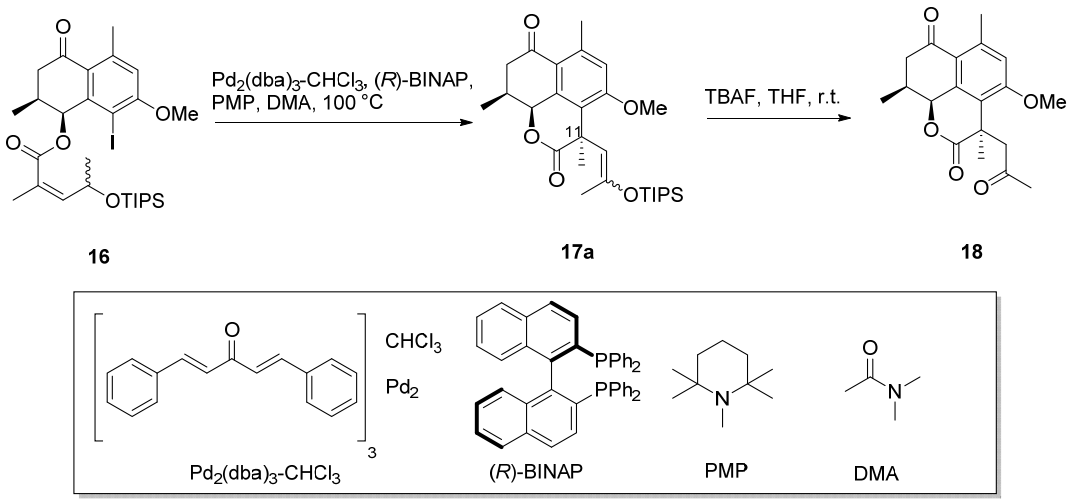
Compound **7** will be synthesized by three steps beginning with commerically available 3-pentyn-2-ol (Scheme 9). The alkyne is first selectively reduced to the *trans* alkene aluminium

complex by Red-Al reagent, followed by trapping with molecular iodide to yield known compound **5**.[20] The free hydroxyl is subjected to standard protection protocol by triisopropylsilyl chloride (TIPSCl) with Et_3N and DMAP to afford **6**.[20] Finally, palladium catalyzed carbonylation of **6** affords compound **7**.[21-22] Overman et al. performed the same carbonylation reaction with a similar substrate to **6**, but without the methyl group on the silyl ether carbon. They also esterified the carboxylic acid with the addition of methanol.[21] Thus, addition of that methyl carbon should be unlikely to deleteriously affect this reaction as previously reported by Heck et al.[23]



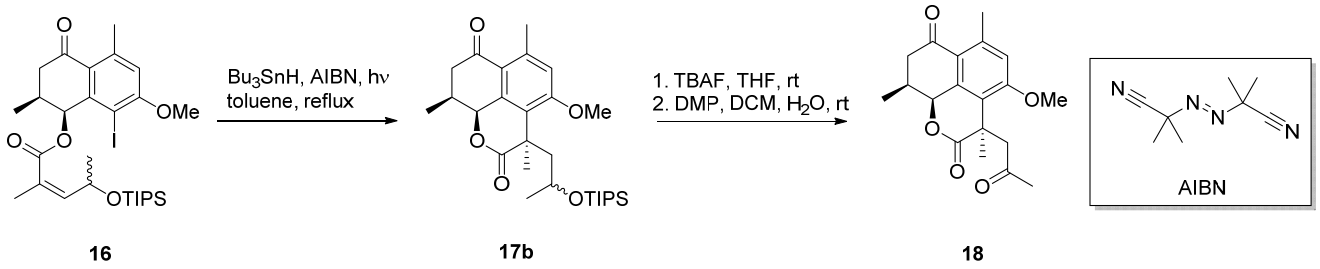
Scheme 10.

Compound **16** will be synthesized by a mild *N*,*N*'-dicyclohexylcarbodiimide (DCC)-mediated esterification coupling reaction, by using alcohol substrate **15** and the carboxylic acid substrate **7** (Scheme 10). This reaction is reported to be tolerant to a potentially labile aryl iodide group. More importantly, it retains the stereo-configuration of the secondary alcohol.[24] Other esterification techniques such as HBTU or hydroxybenzotriazole (HOBt) mediated esterification reactions may also be explored.



Scheme 11.

The last key step for the total synthesis of **1** is to construct the quaternary center on C-11. Enantioselective intramolecular Heck reaction is chosen for this purpose because the stereochemistry can be controlled by less than a molar equivalent of chiral ligands, and it is highly tolerant to various functional groups including esters (Scheme 11).[25-26] The Heck reaction conditions reported by Overman et al. in their synthesis of the natural products (–)-physostigmine and (–)-physovenine will be followed, in which they synthesized a γ-lactam while generating an enol silyl ether (84% yield, 95% ee)[22]. Compound **16** will be subjected to palladium-catalyzed intramolecular Heck reaction with the chiral ligand (*R*)-BINAP (2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthalene) in dimethylacetamide (DMA). 1,2,2,6,6-pentamethylpiperidine (PMP) will be added to act as a base and scavenger of the byproduct HI. Regarding the regioselectivity for the cyclization, one of the two carbons of the olefin can react with the aryl iodide to cyclize either in a 6-*exo* or a 7-*endo* fashion. However, a 6-membered ring is much more thermodynamically favored than a 7-membered ring, and Overman et al. states that 5-*exo* or 6-*exo* is the most favorable for Heck cyclization. A 6-membered ring is expected to form as a result.[25] Then the *β*-hydride elimination step of the Heck reaction evokes alkene migration to generate enol silyl ether to afford product **17a**. It is also reported that a *Z* olefin substrate affords much greater stereoselectivity than an *E* olefin to yield the 11*R* isomer. In addition, the leaving group can also be an aryl triflate or bromide.[25] Standard tetrabutylammonium fluoride (TBAF) deprotection of the enol silyl ether of **17a** will afford an enol, which will tautomerize to afford a ketone in compound **18**.[27]



16 **17b** **18**

Scheme 12.

Alternatively, classical radical cyclization may be attempted with tributyltin hydride and AIBN as the radical initiator at the presence of an ester group (Scheme 12).[28] Stork et al. reported that a 6-*exo* cyclization could be implemented easily by shining UV light on the reaction mixture, without any 7-*endo* cyclization.[29] A decent diastereoselectivity is expected due to the geometry of the possible diastereomeric products as well as the transition state, which is expected to look as shown in Figure 2. The carbonyl and the olefin force C-11 and C-12 to be planar. In order to produce the other diastereomer, the planar carbons would have to bend to accommodate the transition state. More importantly, the crystal structure of **1** illustrates that the newly formed ring has a folded conformation with the planar carbons C-6, C-7, C-11 and the oxygen.[1] The unfavorable diastereomer would have a high ring strain on the ester, because the planar carbonyl carbon would have to bend itself. Thus, radical cyclization will afford compound **17b**, and it will be subjected to TBAF deprotection and standard Dess-Martin periodinane (DMP) oxidation to furnish product **18**.

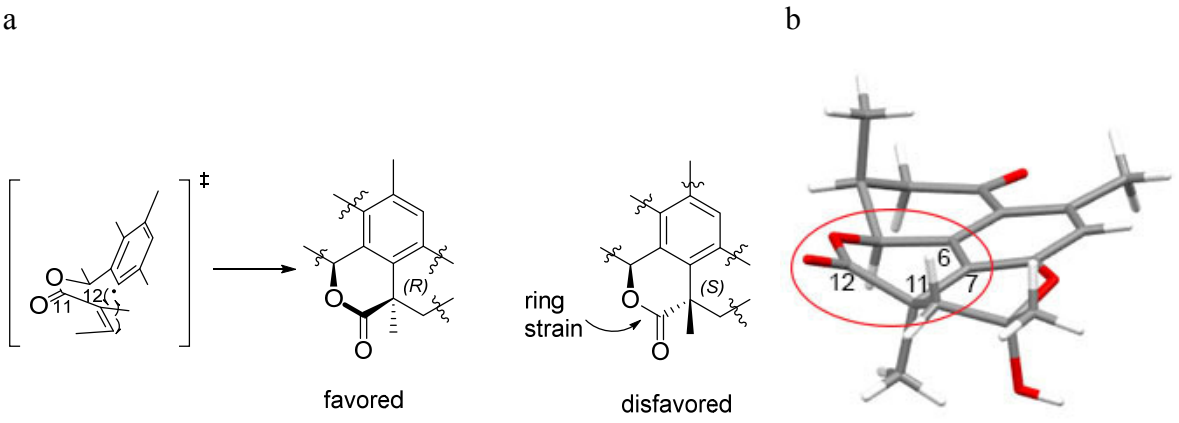
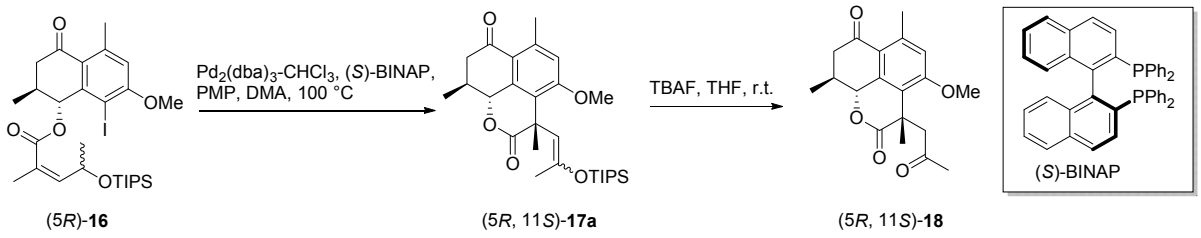
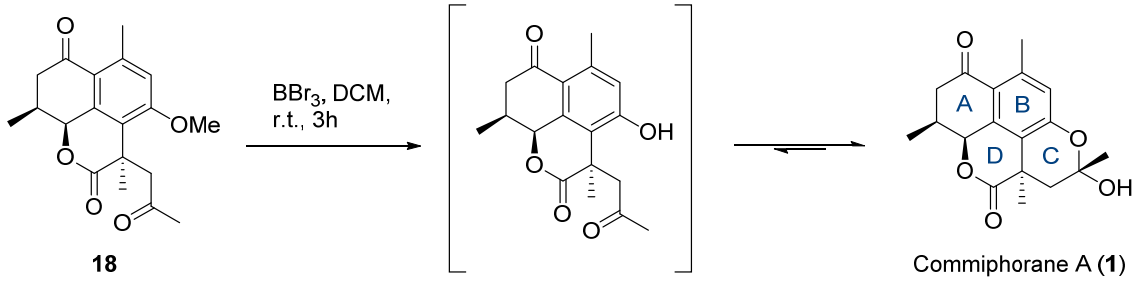


Figure 2. (a) Proposed diastereoselectivity for radical-induced cyclization for **17b**; (b) Crystal structure of **1** highlighting the folded δ-lactone ring.[1]



Scheme 13.

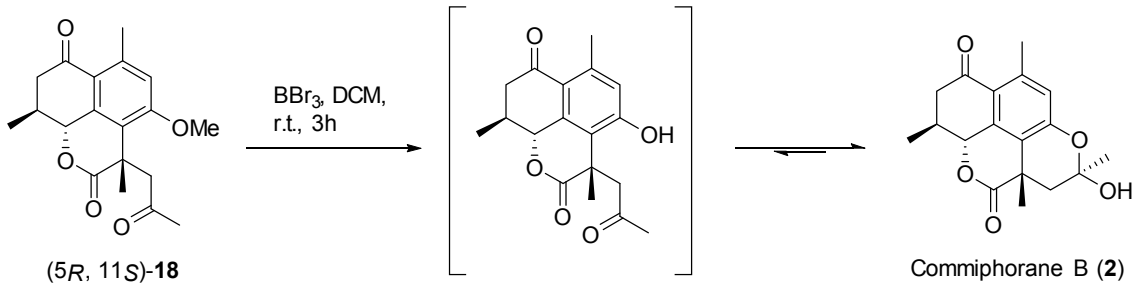
Likewise, the diastereomer of compound **18** can be obtained by implementing the same Heck cyclization but with the opposite enantiomer of the BINAP ligand followed by TBAF deprotection, which is expected to give (5*R*, 11*S*)**-18** (Scheme 13). Classical radical cyclization may also be considered for analogous reasons.



Scheme 14.

The formation of commiphorane A (**1**) will begin with standard deprotection of methyl ether on compound **18** with BBr_3, in the presence of ester and ketones (Scheme 14).[30] Spontaneous cyclization of ring C resulting in a formation of a 6-membered hemiketal is

expected.[31] The stereoselectivity of the hemiketal is determined by the anomeric effect of 6-membered cyclic hemiacetals or hemiketals.[32] The crystal structure of **1** shows that ring C approximates a half-chair conformation due to the planar aryl group, with the axial hydroxyl group is opposite to the oxygen.[1] Additionally, a donor-acceptor interaction will be formed by the orbital of the ether oxygen aligning with the anti-bonding orbital of the alcohol (Figure 3). Thus, the formation of the 17*S* isomer is favored over the 17*R* isomer.



Scheme 15.

Likewise, final product commiphorane B (**2**) will be obtained by deprotection of the aryl methoxy group, followed by spontaneous diastereoselective cyclization to form the chiral hemiketal. The anomeric effect will then favor the 17*R* isomer instead because of the inverted geometry of the rings (Figure 3c).[32]

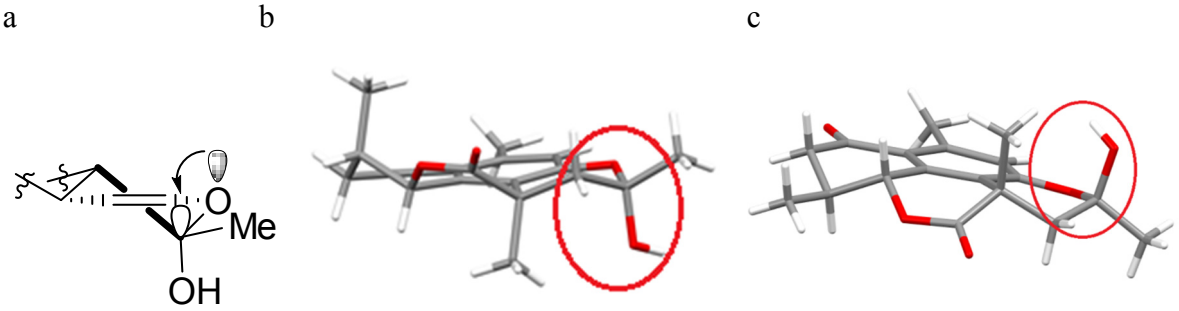


Figure 3. (a) Illustration of the anomeric effect, which is formed by a donor-acceptor interaction; (b, c) Crystal structures of **1** and **2** showing the hydroxyl group and the ether oxygen linkage are aligned opposite of each other.[1]

CONCLUSION

In summary, the total syntheses of commiphoranes A and B (**1** and **2**) will be performed with stereoselective reactions to afford stereochemically pure products. This reported strategy also allows synthesis of other diastereomers of commiphoranes A and B. Their biological activities against organ fibrosis will be investigated afterwards, and possible drug candidates may be developed in the future.

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