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Total Synthesis of Propolisbenzofuran B†

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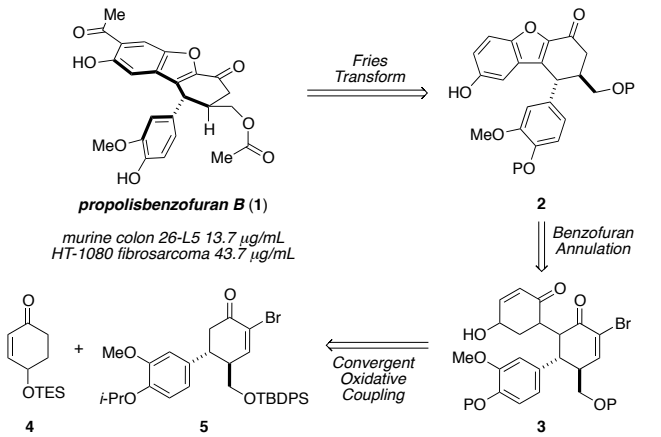
The first total synthesis of propolisbenzofuran B, a bioactive natural product isolated from honeybee propolis resin, is reported. The convergent synthesis makes use of a silicon-tether controlled oxidative ketone–ketone cross-coupling and a novel benzofuran-generating cascade reaction to deliver the core structure of the natural product from readily prepared precursors.

Introduction

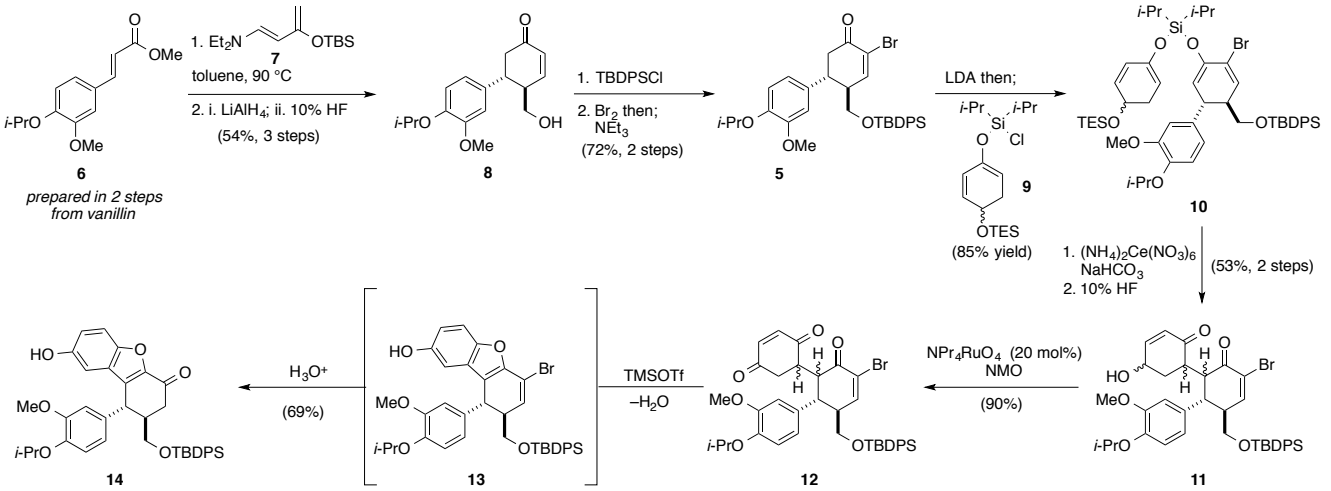
Ubi apis, ibi salus (latin: wherever there are bees, there is health), a phrase used by Pliny the Elder in his ancient text *Naturalis Historia*, highlights the long-known health benefits of honeybee products.[1] Propolis, a resinous mixture produced and utilized by honeybees within hive structures, has a particularly prominent role in this respect.[1-2] This resin is produced from the combination of plant material isolated by the bees from the bark and buds of various trees, which once collected is mixed with beeswax and secreted β-glucosidase to generate propolis in its useful form. The resulting material is used by the bees to maintain a sterile environment within the hive by preventing microbial growths, and is used to mummify carcasses and waste to prevent putrefaction.[3] Traditional folk medicines across the globe have used propolis to treat diseases for centuries, and more recently propolis has been found to possess a plethora of biological and pharmacological properties[4] including antibiotic,[5] anti-oxidant,[6] anti-fungal,[7] anti-cancer, and anti-inflammatory activities.[2] Others studies have shown propolis to be non-toxic towards humans and other mammals except in very high doses.[1] Because of these desirable activities and low toxicity, the chemical constituents of propolis have attracted the attention of chemists searching for small-molecules as drugs or lead compounds.[8]

Our interest in propolis related research was sparked by the report of propolisbenzofuran B (**1**), a novel benzofuran natural product isolated from Brazilian propolis by Banskoda and co-workers in 2000.[9] Preliminary biological data reported by the isolation chemists, showed **1** to have cytotoxic effects toward murine colon 26-L5 carcinoma and human HT-1080 fibrosarcoma cells (13.7 and 43.7 μg/mL, respectively). While these activities are of modest potency, the 1-aryl-2,3-dihydrodibenzo[*b,d*]furan-4(*1H*)-one core of **1** is unique amongst known natural products.[10] We therefore wished to devise a synthesis of propolisbenzofuran B that would enable a rapid assembly of this unusual ring-system in order to provide a platform for its future biological evaluation. In addition, we viewed **1** as an interesting structure to explore a new benzofuran annulation strategy centered upon oxidative enolate coupling.[11] Our plan for the synthesis of propolisbenzofuran B (**1**) is shown in retrosynthetic format within Scheme 1.



Scheme 1 Retrosynthetic analysis of propolisbenzofuran B (**1**).

We envisioned a late-stage Fries acylation would install the acetyl group, thereby simplifying our target to phenol-



Scheme 2 Synthesis of the core benzofuran **14** through a novel aromatizing benzofuran annulation.

substituted benzofuran **2**. Rather than build **2** using a benzofuran starting material, we wished to generate this key substructure using a novel aromatizing annulation from 1,4-diketone **3**.[12] Thus, subsequent disconnection of the σ-bond linking the two cyclohexenone moieties within **3** by application of an oxidative coupling transform, led us to a convergent plan beginning from γ-silyloxy enone **4** and the more complex **5**. The vinyl bromide within enone **5** was designed as a mask for the ketone functionality of benzofuran **2**.[13]

Results and Discussion

Our synthesis of the benzofuran core structure of propolisbenzofuran B (**1**) commenced from enoate **6**, which was readily prepared from vanillin in two steps (Scheme 2). Heating enoate **6** in toluene in the presence of the Rawal–Kozmin diene (**7**) led to smooth Diels–Alder reaction to produce an initial cycloadduct, which was converted to enone **8** by reduction with $LiAlH_4$ and treatment with 10% HF in acetonitrile without purification (54% over three steps).[14] Protection of the primary alcohol within **8** as its corresponding TBDPS ether, followed by selective α-bromination of the enone, generated subtarget **5** in a robust and scalable fashion. Enone **4** was prepared by triethylsilylation of the known and easily prepared γ-hydroxycyclohexenone (see Supporting Information for details).[15]

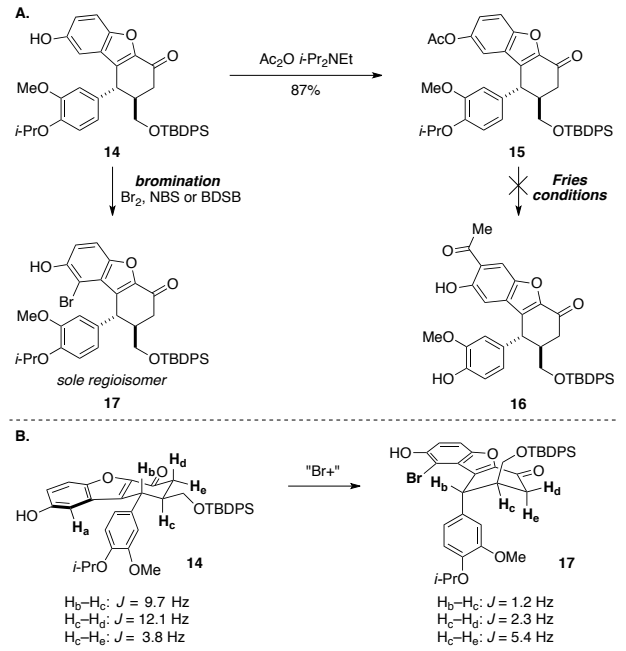
While there are some limited examples of selective cross-coupling of enolates where both substrates are used in an equal ratio, most notably by the Baran[16] and Flowers groups,[17] typical examples require the sacrificial use of one enolate in excess which greatly diminishes synthetic efficiency.[11] As part of a research program focused on the development and utilization of oxidative coupling processes,[18] we have been actively investigating the use of silicon-tethers as a means to control cross-coupling.[19] We therefore targeted the formation of silyl bis-enol ether **10** as the first step towards synthesizing the key 1,4-diketone **11**. In previous studies,[18a-c] we had employed a protocol for preparing unsymmetrical silyl bis-enol ethers initially reported by Rathke and coworkers.[20] This protocol requires the separate formation and isolation of an amino enol silane from one ketone, which can then be activated with an acid chloride and exposed to the enolate of a second ketone, thereby ensuring that neither of the two possible dimers is formed. Attempts to generate and isolate amino enol silanes from either **4** or **5** were met with decomposition, necessitating an alternative approach. We wondered if we might be able to conduct a sequential addition of the lithium enolates derived from enones **4** and **5** to a dichlorosilane. Typically, this approach suffers from issues associated with double addition of the first enolate to the dichlorosilane, which after addition of the second enolate to the reaction flask leads to complex mixtures of all three possible silyl bis-enol ethers. In line with this issue, an intractable mixture was observed when we attempted to first add the lithium enolate of **5** to dichlorodiisopropylsilane followed by the corresponding lithium enolate derived from enone **4**.[21] Fortunately, a reversal in the order of addition proved to be highly efficient. First, chloro enolsilane **9** was generated from enone **4** and dichlorodiisopropylsilane at –78 °C, and then to this solution was added the lithium enolate derived from enone **5** (precooled to –78 °). In this way, an 85% yield of the complex silyl bis-enol ether **10** could be obtained following column chromatography. It appears that adding the enolate of the more hindered ketone to the chloroenol silane of the less hindered ketone provides the most efficient means to effect this delicate transformation.

Exposure of silyl bis-enol ether **11** to ceric ammonium nitrate [$(NH_4)_2Ce(NO_3)_6$] under our previously detailed[18a-c] conditions for related oxidative coupling reactions provided the desired 1,4-diketone, which was treated with 10% HF solution to remove the OTES ether and allow for ease of purification. Accordingly, diketone **11** was

obtained in 53% yield from **10**. As indicated by its complicated ^{1}H and ^{13}C NMR spectra, compound **11** was generated as a mixture of stereoisomers as indicated in Scheme 2. This fact is inconsequential to the formation of the natural product, since only the relative configuration between the aryl and hydroxymethyl groups must be controlled and these were set during the initial Diels–Alder reaction.

Oxidation of the hydroxyl group within diketone **11** to dihydroquinone **12** was best conducted using catalytic NPr_4RuO_4 according to the Ley procedure.[22] Other mild oxidants, such as MnO_2, led to formation of the corresponding quinone by over oxidation. The keto form of dihydroquinone **12** proved quite stable; we never observed the corresponding bisphenolic tautomer. We next investigated conditions to induce our desired benzofurans annulation. After screening a variety of Lewis and Brønsted acids we eventually discovered that the addition of TMSOTf (1 equivalent) to dihydroquinone **12** allowed for rapid cyclocondensation and the isolation of benzofuran **14** in 69% yield. In some cases, we managed to isolate vinyl bromide **13**, indicating that this species is most likely the immediate precursor to the final product. Under the reaction conditions, however, the vinyl bromide is unstable and is hydrolyzed to the corresponding ketone, as we had planned from the outset. Presumably, the vinyl bromide is protonated by adventitious acid to form a "benzylic" carbocation, which is trapped by water to form an unstable bromohydrin that collapses to the ketone with loss of HBr.

Our plan for completing the synthesis relied upon conducting a selective *ortho*-acylation of hydroxybenzofuran core of **14**. To this end, we first investigated the possibility of engaging a Fries rearrangement to achieve this task,[23] and thus phenol **14** was acylated to generate acetate **15** in 87% yield (Scheme 3A). Exposure of **15** to a variety of Lewis acids typically employed for Fries rearrangements (i.e., $TiCl_4$, $AlCl_3$, $Sc(OTf)_3$, $ZrCl_4$) failed to provide any of the desired product (i.e., **16)**. Instead, we noted the formation of products arising form acetate, isopropyl and/or *tert*-butyldiphenylsilyloxy cleavage. Similarly, attempts to realize the corresponding photo-Fries rearrangement of **15** using a 240 nm lamp were unsuccessful. Likewise, Friedel–Crafts and other direct acylation methods were also unsuccessful. We therefore considered other possibilities, such as first conducting an *ortho*-bromination of **14** as a prelude to a palladium-catalyzed acylation. Frustratingly, under all conditions we investigated (i.e., Br_2, NBS and BDSB),[24] bromination occurred with high *ortho*-selectivity, but with incorrect regioselectivity to deliver bromide **17**. This regioselectivity was established by disappearance of the benzofuran proton (H_a), and by a characteristic change in the coupling patterns observed for the aliphatic protons. In the starting material, the *J*-values for H_b–H_c, H_c–H_d, and H_c–H_e (9.7, 12.1 and 3.8 Hz respectively) are indicative of a trans-diaxial arrangement

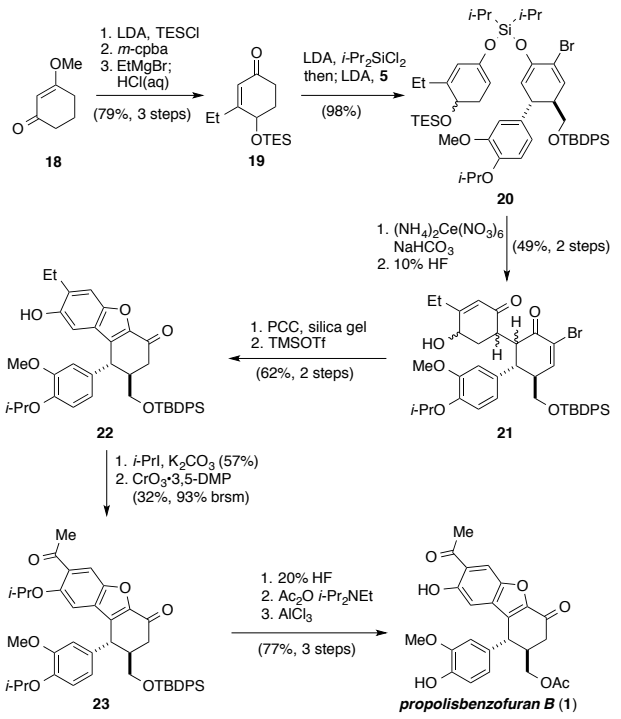


Scheme 3 A. Attempted late-stage functionalization of the benzofuran core. **B.** ^{1}H NMR spectroscopic analysis

of the protons, placing the aryl and hydroxymethyl substituents of **14** in an equatorial conformation as shown in Scheme 3B. Upon bromination of **14**, H_b only weakly couples to H_c, appearing as an apparent singlet in the ^{1}H NMR spectrum, while the *J*-value for H_c–H_d has been reduced to 2.3 Hz from 12.1 Hz. Together, these observations are consistent with the aryl substituent within **17** occupying an axial position in order to avoid severe steric interactions with the newly installed bromine atom. While we had anticipated bromination would proceed at the other *ortho* position on account of steric hindrance, it appears that dominant electronic factors dictate the opposite outcome.[25] A new route to install the acyl group was clearly required.

Failure of our strategy based upon late-stage installation of the acyl group led us to next explore prospective routes where a functional handle for acyl group formation would be incorporated at an earlier stage in the synthesis. To this end, we keyed upon the idea of incorporating an ethyl group at the appropriate position with the end goal of conducting a late-stage selective benzylic oxidation (Scheme 4). The ethyl group would be compatible with our established route and afford an opportunity to explore some of the recent methods for C–H bond activation in the context of a natural product synthesis.[26] The ethyl-substituted enone **19** was readily synthesized in three steps from commercially available enone **18** by way of a Rubottom oxidation[27] followed by a Stork–Danheiser transposition.[28] Coupling of enone **19** with previously prepared bromoenone **5** to form the silyl

bis-enol ether **20** proceeded in excellent yield under the same conditions developed for synthesizing **10**. Oxidative coupling of **20** proceeded similarly to that for the prior case of **10**, providing 1,4-diketone **21** in 49% yield.



Scheme 4 Completion of the synthesis.

Conversion of **21** to dihydroquinone **22** was best achieved with PCC on silica (95% yield). The Ley oxidation that worked in the previous route proved to be inefficient and returned significant starting material, despite increases in catalyst loading, indicating that the adjacent ethyl group likely hinders initial generation of the requisite ruthenate ester. Fortunately, the ethyl substituent did not affect our aromative benzofuran cascade reaction, which afforded the key ethyl substituted benzofuran **23** in 65% yield.

As a prelude to our planned benzylic oxidation we protected the free phenol as its isopropyl ether (57% yield). Conversion of the ethyl substituent into the corresponding acyl group proved to be less straightforward as we had hoped. Our attempts to conduct modern catalytic methods for C–H oxidation led, in most instances, to either substrate decomposition or provided no reaction.[29] Some success was found using the $Pd(OH)_2$/C and *t*-BuOOH system reported by Corey and Yu,[30] but significant substrate and/or product decomposition limited isolated yields to <30% with full consumption of starting material. After investigating alternative approaches we ultimately found that the use of stoichiometric CrO_3•3,5-dimethylpyrazole (20 equivalents) generated the desired ketone **23** very cleanly in 32% isolated yield.[31] Despite being a very clean reaction, which yielded only product and unchanged starting material, we were never able to increase the yield of this reaction further. Extended reaction times and increased temperatures did not help, and the use of more oxidant (either at the beginning of the reaction or through the addition of extra portions as the reaction proceeded) typically led to lower overall yields or returned starting material. Recovery of unchanged starting material was straightforward, however, which under our optimized conditions led to a 93% yield of **23** based on recovered starting material.

Completion of the synthesis from this point was straightforward. Removal of the silyl ether with 20% HF and acetylation of the resulting primary alcohol proceeded smoothly and set the stage for selective deprotection of the isopropyl ethers with $AlCl_3$.[32] These three steps proceeded in 77% yield overall and gave synthetic propolisbenzofuran B (**1**) that displayed identical spectral data to that reported for the natural product (IR, ^{1}H, ^{13}C, MS).[9,33]

Conclusions

In summary, we have completed the first total synthesis of propolisbenzofuran B (**1**) in 17 steps from vanillin. Key aspects of the synthesis include a convergent silicon-tethered oxidative ketone cross-coupling, a novel aromatizing benzofuran annulation reaction and the late-stage use of C–H oxidation in a natural product synthesis. Difficulties associated with the final C–H oxidation highlight the importance of continued efforts in this area, while the efficiency of our benzofuran cascade indicates that it may find applications for the preparation of other complex benzofuran containing molecules.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and spectral data (NMR, MS, IR) for all new compounds. See DOI: 10.1039/b000000x/

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