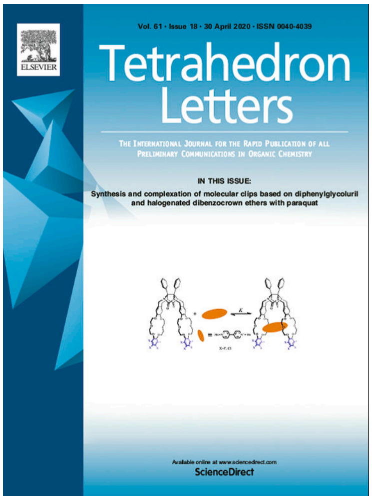

Efforts toward the total synthesis of (±)-toxicodenane A utilizing an oxidopyrylium-based [5+2] cycloaddition of a silicon-tethered BOC-pyranone

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Efforts toward the total synthesis of (±)-toxicodenane A utilizing an oxidopyrylium-based [5+2] cycloaddition of a silicon-tethered BOC-pyranone

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ABSTRACT

Synthetic efforts toward the tricyclic core of (±)-toxicodenane A are reported. This strategy takes advantage of the Feist-Benary furan annulation, Achmatowicz oxidative rearrangement, and oxidopyrylium-based [5+2] cycloaddition to access a key tetracyclic intermediate. This work provides a foundation that can be utilized toward the total synthesis of the natural product.

Introduction

(±)-Toxicodenane A is one of several tricyclic sesquiterpene natural products isolated from the lacquer tree, *Toxicodendron vernicifluum*, which has long been used in traditional Chinese medicine.[1] As part of a larger class of bicyclo [6.3.0] undecane sesquiterpenoids,[2] the toxicodenanes represent novel heterocyclic scaffolds.[3] Several members of the toxicodenane family possess a bridged polycyclic ether (Figure 1), which is a common structural feature in many biologically active natural products[4] and is often accessible via an oxidopyrylium-based [5+2] cycloaddition.[5]

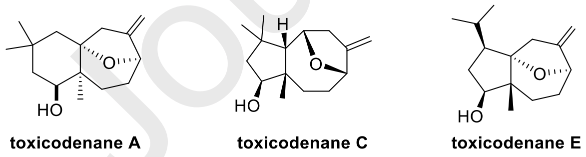
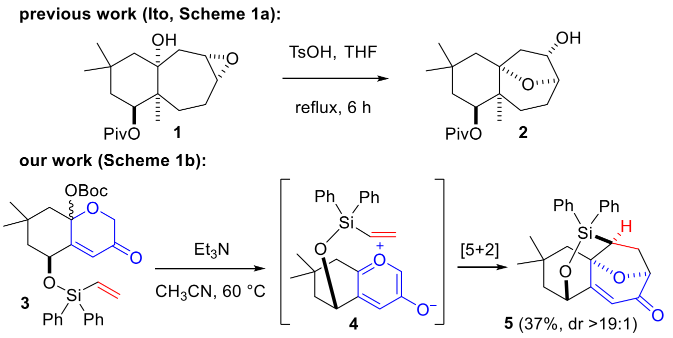


Figure 1. Toxicodenanes containing the bridged ether moiety

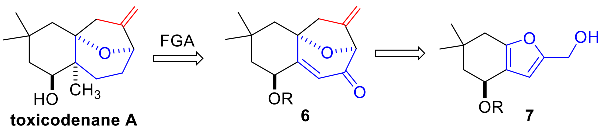
Ito reported an elegant initial total synthesis that included a diastereoselective reductive desymmetrization, ring-closing metathesis, and neighboring group-mediated diastereoselective etherification strategy (Scheme 1a).[6] Based on our previous work in the area of [5+2] cycloadditions,[7] efforts toward the tricyclic core **5** utilize a Feist-Benary annulation,[8] Achmatowicz oxidative rearrangement,[9] and oxidopyrylium-based [5+2] cycloaddition[5] of a silicon-tethered BOC-pyranone **3** (Scheme 1b).



Scheme 1. Synthesis of bridged polycyclic ether-silane **5**

Results and Discussion

Herein, we report our initial efforts toward a total synthesis of toxicodenane A utilizing an intramolecular oxidopyrylium-based [5+2] cycloaddition. Upon initial inspection of toxicodenane A, the [5+2] cycloaddition is not inherently obvious. Retrosynthetic Functional Group Addition (FGA), however, reveals an enone **6** that could arise from BOC-pyranone **3** (cf. Scheme 1b) derived from the furyl alcohol **7** (Scheme 2).



Scheme 2. Retrosynthetic analysis of toxicodenane A

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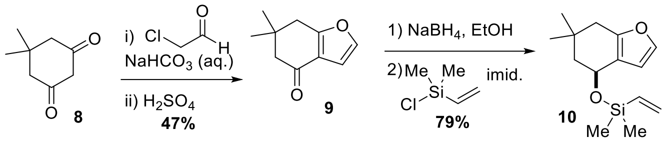
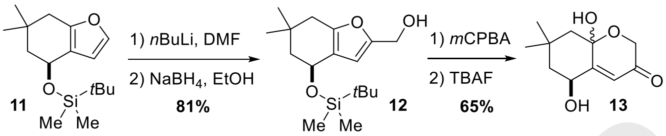
Feist-Benary[8] annulation of dimedone **8** which afforded furan **9** in moderate yield (Scheme 3). NaBH$_4$ reduction provided the alcohol (not shown) in excellent yield followed by efficient formation of the vinyl silane **10**. However, multiple attempts of formylation[10] (nBuLi, DMF; POCl$_3$, DMF; oxalyl chloride, DMF) were unsuccessful due to the sensitivity of vinyl silanes[11] and complications of Vilsmeier reactions with silyl groups in general.[12]



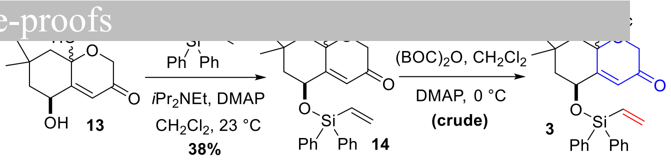
Scheme 3. Initial synthesis of furan **10** via Feist-Benary annulation

In fact, TBS-protected alcohol **11** did not undergo effective formylation under a variety of Vilsmeier conditions.[12] However, nBuLi and DMF provided clean aldehyde (not shown) in 90% yield and subsequent reduction gave furyl alcohol **12** in 79% yield (Scheme 4) over four steps from furan **9**.[13] mCPBA-mediated Achmatowicz oxidative rearrangement[9] was nearly quantitative and unoptimized TBAF-mediated deprotection provided hydroxypyrone **13** in suitable quantity.

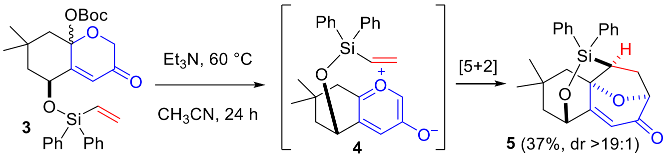


Scheme 4. Synthesis of lactol **13** via Achmatowicz rearrangement

Lactol-alcohol **13** was deemed to be a strategic intermediate to which a variety of functional groups could be selectively appended to the less hindered secondary alcohol (Scheme 5). Diphenyl vinyl silane **14** was formed in just 38% yield to give the lactol and the dimethyl variant (not shown) was less effective.[13] Both silylation reactions provided complex mixtures, but the diphenyl proved to be more dependable. Although not in large quantity and impure, some evidence of silylation of the lactol (i.e. bis-silylation) was observed by ^{1}H NMR and HRMS. Several attempts to acetylate the tertiary lactol with AcCl and Ac$_2$O were unsuccessful thus the *tert*-butoxycarbonyl (BOC) was envisioned as an alternative.[14] Therefore, treatment of lactol **14** with (BOC)$_2$O and catalytic DMAP afforded the desired BOC-pyranone **3** as a crude precursor for the [5+2] cycloaddition but with degradation on silica gel. Optimization of the amine base for [5+2] cycloaddition was then undertaken.[13] At room temperature, pyridine and iPr$_2$NEt gave trace conversion while DABCO and DBU resulted in complex mixtures. However, Et$_3$N and N-methylpyrrolidine afforded greater quantity of cycloadduct at room temperature and gave complete conversion at 60 °C. Et$_3$N proved to be superior and a two-step process was achieved on gram scale in which [5+2] cycloaddition was achieved in 37% yield (versus 24% with N-methylpyrrolidine). Thus, a solution of BOC-pyranone **3** and Et$_3$N in CH$_3$CN was heated to 60 °C for 24 hours to afford the complex tetracyclic silane **5** (Scheme 6) as a single diastereomer that was confirmed by X-ray crystallography (Figure 2).



Scheme 5. Synthesis of BOC-pyranone-vinyl silane **3**



Scheme 6. Oxidopyrylium-vinyl silane [5+2] cycloaddition

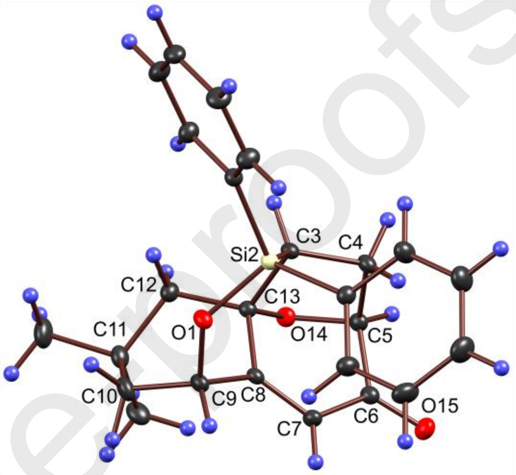
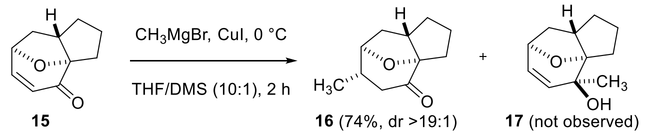
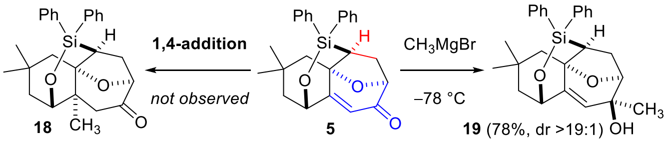


Figure 2. ORTEP of bridged polycyclic ether-silane **5**

Based on ample literature precedent for conjugate additions to enones, various reaction conditions were envisaged for the potential to promote the desired 1,4-addition.[15] In a “model” system, cycloadduct **15** afforded efficient and straightforward conjugate addition with CH$_3$MgBr and CuI in accordance with a previous report (Scheme 7).[13,16] However, when applied to the tetracyclic bridged ether-silane **5**, the presumed 1,4-addition product **18** was not detected by analysis of the ^{1}H NMR spectra of crude reaction mixtures (Scheme 8). In general, no reaction was observed at low temperatures and complex mixtures were observed at elevated temperatures. Several alkyl sources were attempted including CH$_3$MgBr, CH$_3$Li, Me$_2$Zn, and AlMe$_3$ with a wide variety of additives.[15] Repeatedly, the predominant by-product proved to be the 1,2-addition adduct **19** and this was confirmed by a reaction in which copper was excluded and the tertiary allylic alcohol **19** was very cleanly delivered in 78% yield. The enone **5** seems to be exceptionally sterically hindered thus preventing desired conjugate addition (i.e. **18**). In addition, preliminary attempts to manipulate the silyl group of adduct **5** to afford a less sterically hindered enone were unsuccessful.



Scheme 7. Successful “model” system for conjugate addition



Scheme 8. Formation of predominant 1,2-addition cycloadduct **19**

Conclusions

An intramolecular oxidopyrylium-alkene [5+2] cycloaddition of a silicon-tethered BOC-pyranone was successfully implemented toward formation of a tricyclic core of toxicodenane A. The precursor to the [5+2] cycloaddition was constructed via Feist-Benary furan annulation, Achmatowicz oxidative rearrangement, and BOC-protection of the lactol. Conjugate addition to the cycloadduct enone was unsuccessful, but cleanly delivered the 1,2-addition adduct. Future studies will include efforts toward alternative tethers, including allenes, en route to toxicodenane A.

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Crystallographic Data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number 2009209 CCDC. Copies of the data can be obtained, free of charge, on application to CCDC.

References

Highlights

2.

Supplementary Material

Supplementary material to this article can be found online at

Synthetic efforts toward the tricyclic core of (±)-toxicodenane A are reported

Feist-Benary, Achmatowicz, Boc-protection used to construct precursor

Oxidopyrylium-based [5+2] cycloaddition of Boc-pyranone-vinyl silane

1.

Graphical Abstract

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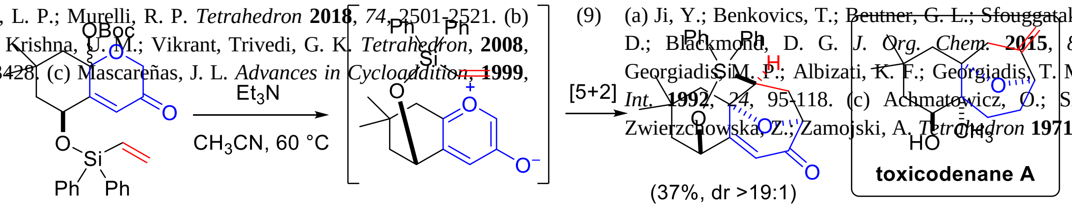

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