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Synthesis of the Tetracyclic Core of the Kempanes by a Ring-Closing Metathesis Strategy

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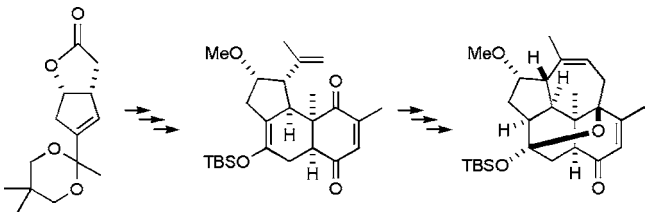
ABSTRACT



The synthesis of the tetracyclic ring system of the kempane diterpenes was achieved through the highly regio- and stereoselective Diels–Alder reaction of an isopropenyl-diene with 2,6-dimethyl-*p*-benzoquinone, addition of an allyl group, and ring-closing metathesis of the isopropenyl and allyl groups.

Kempanes (**1**−**4**) (Figure 1) are a small group of tetracyclic diterpenes from the soldiers of termite species that rely exclusively on chemical forms of defense.[1] Although there have been a few attempts at the synthesis of various kempanes, only one route culminated in the preparation of a kempane (**1**).[2] An approach to **2** led to the conjugated isomer of **2**, but attempts to deconjugate the double bond to produce the natural product failed.[3] The synthesis of kempanes **1**−**4** from the highly functionalized pentacyclic compound **5** (Figure 2) was foiled by the refusal of the lactone function of **5** to open in a synthetically useful manner.[4−6]

The synthesis of compound **6**, which has the requisite functionality and stereochemistry for elaboration into kempanes, was reported recently.[7] Biomimetic cyclizations have been exploited to produce the kempane ring system,[8] and subsequent elaboration led to the tetracyclic alcohol **7**.[9] Tetracycle **8** has been synthesized efficiently via an intramolecular Diels−Alder reaction of a fulvene.[10] The transformation of α-santonin into the ring system of a closely related termite diterpene, rippertane **9**, has been disclosed,[11] but no further synthetic work has been reported on rippertane.

The problem previously encountered in kempane syntheses with establishing the double bond in the seven-membered ring[3] and with the generation of the required functionality in the same area of the molecule[6] demanded a change in

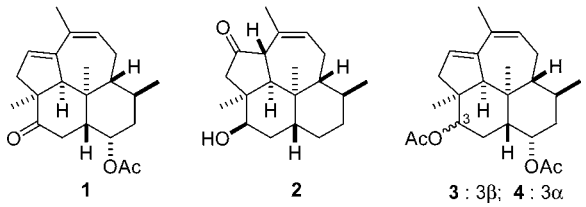


Figure 1. Kempane diterpenes.

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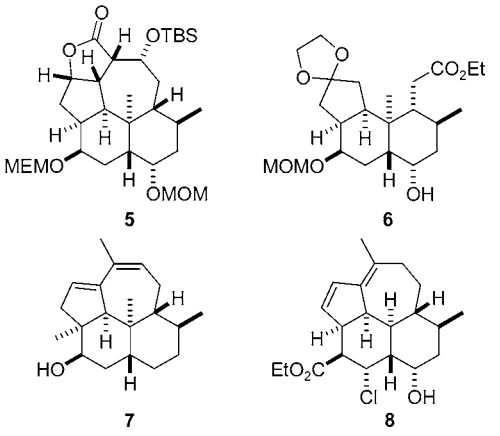

Figure 2. Synthetic compounds **5**−**8**.

strategy. It was decided to focus on the creation of the seven-membered ring in conjunction with the formation of the troublesome double bond. An approach was formulated in which the seven-membered ring would arise by ring-closing metathesis (RCM).[12] The viability of this approach has been tested in the preparation of the ring system of the kempanes, and salient results are presented here.

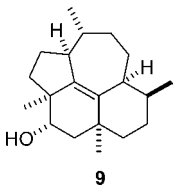

Figure 3. Rippertane.

The Diels−Alder reaction had been used with considerable success to assemble tricyclic substructures similar to **20**.[4,5] To employ the same key reaction, a diene was required, bearing two oxygen functions matching the positions of oxygens in **1**−**4** and an isopropenyl group that would serve later in the RCM. The decision was to have the isopropenyl group and a methoxy group in the diene on the same side of the cyclopentenyl ring so that these groups would act in concert in providing the crucial control of the facial selectivity in the Diels−Alder reaction.

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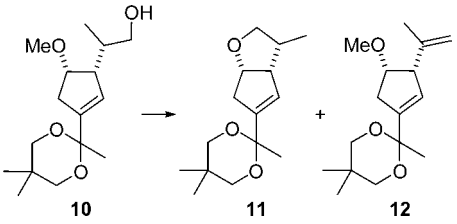
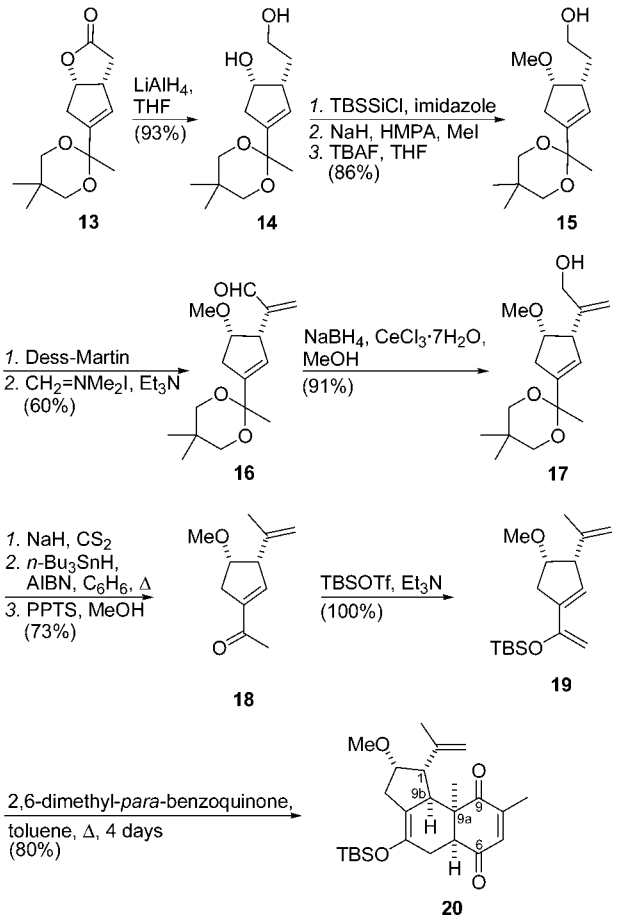
Scheme 1



Inital attempts to prepare the required diene by dehydration of alcohol **10** led to the surprisingly facile formation of tetrahydrofuran **11** under a variety of conditions and very little of the desired alkene **12** (Scheme 1).

The ultimately successful preparation of the diene **19** (Scheme 2) began with the acetal-lactone **13**.[5] Reduction of

Scheme 2



the lactone gave the diol **14**. The secondary alcohol was converted into the methyl ether **15**, via protection and deprotection of the primary alcohol. The primary alcohol was oxidized to the aldehyde with Dess−Martin periodinane, and treatment of the aldehyde with Eschenmoser's salt gave the enal **16** efficiently. The reduction of the aldehyde to the alcohol **17**, followed by the Barton−McCombie process, left the methyl group. The dioxane protecting group was removed

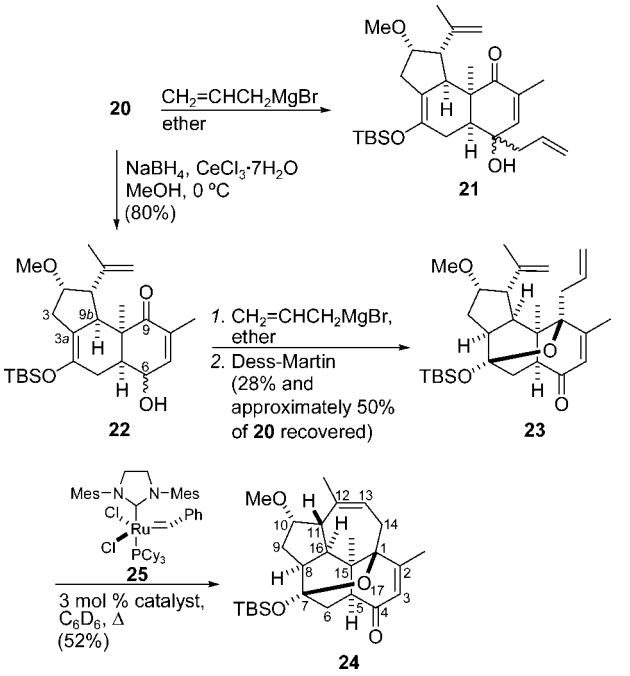
easily, without affecting the isopropenyl group, giving the methyl ketone **18**. Diene **19** was prepared quantitatively from **18** with a silyl triflate. The Diels−Alder reaction of **19** with 2,6-dimethyl-*p*-benzoquinone was slow (4 days in refluxing toluene), but adduct **20** was the only isolated product. This Diels−Alder reaction had taken place with the desired regioselectivity, and the reaction had occurred via an *endo* addition state, onto the face of the diene opposite to the isopropenyl and methoxy groups. (The relative stereochemistry of **20** was determined by the measurement of NOEs.)

The Diels−Alder reaction had established the key relative stereochemistry at C1, C9*a*, and C9*b*. The next task was to attach an allyl group at C9. It had been found that additions of acetylide to cyclohexenediones similar to **20** would take place almost exclusively to the apparently more hindered carbonyl (C9), *syn* to the methyl group at C9*a*. The reason for this remarkable selectivity was thought to be steric, and a consequence of an axial attack by acetylide.[13] Although with an unsymmetrical, conformationally mobile cyclohex-2-ene-1,4-dione there are four possible types of axial attack on one carbonyl, with molecules similar to **20** there would be only one type of axial attack that would be unhindered by a *syn* axial substituent (two carbons away). The result of reduction of **20** with $NaBH_4$ was not in accord with prediction. The major product was one isomer of **22**, although there were significant amounts of the epimeric products of reduction at C9. It is likely that the proximity of the isopropenyl group in **20** reduced reactivity at C9.

Thus, not unexpectedly, allylmagnesium bromide reacted with **20** to give **21**, an epimeric mixture of products of addition at C6 (Scheme 3). Treatment of **20** with $NaBH_4$ under Luche conditions[14] enhanced the regioselectivity of the mono-reduction, and the product was **22**, but as a mixture of the alcohols resulting from reduction at C6. Allylindium reagents have shown their tolerance of hydroxyl functions in the substrate,[15] but prolonged treatment of **22** with allylindium in DMF left the substrate unchanged. Treatment of **22** with an excess of allylmagnesium bromide gave a mixture of diols in a disappointing yield, but also a significant amount of unreacted **22** was returned. Chromatography at this point was complicated by the presence of diastereomeric products, so the mixture was treated with Dess−Martin periodinane. The product mixture now contained only two compounds. Chromatography provided diketone **20**, which was produced from the unreacted **22** and could be recycled, and product **23** with one ketone function and an allyl group was obtained.

The NMR spectra of this product led to some initial consternation. The ^{1}H NMR spectrum included one "extra" C−H signal, which the COSY spectrum revealed was coupled with the signals for the hydrogens at C3 and C9*b*. The ^{13}C NMR spectrum contained signals for only two olefinic carbons, but it included a signal for an "extra" sp^3-carbon and a signal at δ 99.4 that pointed to an acetal. After addition of the allyl

Scheme 3



group, the new tertiary alcohol at C9 had closed onto the double bond of the silyl enol ether to form **23**. Transannular hemiacetal formation involving a tertiary alcohol at C9 had been seen previously in kempane chemistry.[4,6,7] The formation of the acetal was fortuitous proof of the relative stereochemistry at C9, as the tertiary alcohol of opposite configuration cannot form an oxygen bridge to C4.

Despite the congested environment of its two noncyclic olefins, compound **23** in refluxing benzene cyclized in 1 h to **24** by RCM in the presence of Grubbs' catalyst **25**.[16] The relative stereochemistry of **24** was verified by an NOE study. The most important proximities detected were the C5-hydrogen with the C8-hydrogen, the C16-hydrogen, and the methyl on C15; and the C15-methyl with the hydrogens on C13, C16, and the C12-methyl.

Compound **24** represents the tetracyclic core of the kempane diterpenes. It has a double bond in the seven-membered ring at the required position along with oxygen functions at the correct locations on the remaining rings. Effort can now be directed toward modification of this route to produce kempanes **1**−**4**.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada, the Killam Trust, and Merck-Frosst Canada for funding.

Supporting Information Available: Synthetic procedures, spectral data, and NMR spectra for **14**−**20** and **22**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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