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An Approach to the Synthesis of Tricholomalide A: An Effective Means for Achieving Homo-Robinson Annulation

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Abstract

A procedure has been developed for the construction of 7,5-fused ring systems through ring expansion of silyl enol ethers. This method has been applied to the synthesis of an intermediate en route to the natural product, tricholomalide A.

The bicyclo[5.3.0]decane ring system (hydroazulene) appears to be a common structural motif in various natural products.[1] Despite ongoing efforts, the development of effective and useful methods for the construction of these substructures remains a challenge to the synthetic chemist.[2] We recently reported a route which leads to the 7,5-membered bicyclic ring motif of the guanacastepenes, via a so-called 'homo-Robinson annulation' (Figure 1).[3] In this process, we demonstrated that the 6-membered enone ring of hydrindane derivative **3** could be expanded into its corresponding **7**-membered dienone **5** through a four-step sequence involving: formation of silyl enol ether, cyclopropanation, oxidative ring opening, and dehydrohalogenation. This protocol appeared to allow for access to the important hydroazulene intermediate, **5**, in the early stage of the guanacastepene synthesis.[4] This intermediate cannot be reached via direct Robinson annulation.

Subsequently, we launched a program directed toward the total synthesis of the neurotrophic diterpene, tricholomalide A (**7**, Figure 2), isolated from the mushroom *Tricholoma* sp.[5] We envisioned that building block **5** could serve as a highly adaptable intermediate en route to tricholomalide A, due to its useful dienone functionality. However, in attempting to repeat the reaction procedure described in our earlier report, we were unable to obtain **5** in useful quantities. This surprising result led us to explore this reaction further. Mechanistically, there are two possible pathways of silyloxycyclopropane opening. Thus, cleavage of the *endo* bond proceeds to give the desired ring-expanded enone, which is subsequently advanced to the corresponding dienone **5** (path *a*, Figure 1). Alternatively, *exo* cleavage would afford an α-halomethyl ketone, which upon elimination, would generate the exo methylene compound **6** (path *b*, Figure 1).

Upon revisiting this protocol, we now found that, contrary to our previous claim, the major product of the ring expansion sequence starting with **4** is actually **6**. In addition, upon re-examination, other substrates described in the original report were also found to have preferentially undergone *exo*-fission, to produce *exo*-methylene type adducts as the major reaction products. The experimental details of these studies may be found in the accompanying Supporting Information. In this Communication, we disclose the reinvestigation of our Homo-

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Robinson annulation strategy and provide a procedure for the construction of the 7,5-fused ring structure of tricholomolide A (**7**) through a major modification of the original protocol.

In light of these findings, we sought to modify the originally reported procedure so as to promote formation of the desired isomeric product. In order to ensure that our ring opening process would occur through a radical intermediate, as proposed by Saegusa,[6,7] we used iron (III) nitrate as the oxidant, to effect cyclopropane ring opening, and diphenyldisulfide to trap the ensuing radical intermediate (Scheme 1).[8] The resulting mixture of sulfides **8a,b** was reduced by Raney nickel to provide a 6.9:1:1 inseparable mixture of **9, 6,** and **10.**[9] Thus, the oxidative ring cleavage had again predominantly occurred in an exo fashion to give the exo methylene compound as the major product.

Recognizing that the previously disclosed oxidative ring opening procedure would not serve as a viable route to our target system, tricholomalide A, we pursued a different ring opening approach that would not proceed through a radical intermediate. Indeed, we postulated that, by forming a *halo*cyclopropane intermediate, we could conceivably trigger the ring fission in the desired way through exposure to acid or silver cation.[10] Moreover, depending on the substrate, i.e. dihalo or methyl halocyclopropane, the ultimate product could be either an α-halo or an α-methyl enone. The latter could be a more synthetically useful intermediate toward tricholomalide A. The execution of this plan is illustrated in Scheme 2. Thus, enone **3**[11] was treated with LDA and TMSC1 to generate the silyl enol ether, which was then converted to the dibromocyclopropane **12** through addition of dibromocarbene. Happily, silver nitrate promoted the successful ring opening of **11** to afford the desired bromodienone **12** in 59% overall yield (3 steps). The structure of **12** was confirmed by NMR analysis of the reduced compound **5**, which was identical to the compound published in the literature (the yield of the reduction of **12** was not optimized). Following an analogous procedure, we synthesized the chloromethylcyclopropane **13**, which was also treated with silver nitrate to produce methyl dienone **14**. In this case, a slightly elevated temperature was required and a small amount of ethylidene enone, resulting from exo cleavage, was generated as a side product. It is noteworthy that we have successfully gained access to useful quantities of these bicyclic tricholomalide A building blocks (i.e. **12** and **14**) through modification of our original protocol.

With these functionalized hydroazulenes in hand, we attempted to address the installation of the C5 quaternary center in tricholomalide A, in which the C19 methyl group is anti to the angular methyl group at the ring juncture of the 7,5-bicyclic system (see **7**, Figure 1). We were able to elaborate bromodienone **12** to the α-ethynyl dienone **15** via Sonogashira coupling with ethynylsilane (Scheme 3). However, deconjugative alkylation of **15** preferentially afforded the undesired *O*-alkylated product **17** although the first deconjugation step had occurred at the desired γ-carbon.

Alternatively, we envisioned utilizing the resident α-methyl group of **14** to establish the quaternary center by installing the two carbon units via intramolecular cyclopropanation. Deconjugation of α-methyl dienone **14** followed by Luche reduction furnished a 3:1 mixture of two epimeric allylic alcohols, of which the minor alcohol **19** was easily converted into the major alcohol **18** in two steps (Scheme 4). Treatment of **18** with methyl malonyl chloride produced the malonate, which was converted to the diazomalonate **20** via the diazo transfer reaction developed by Davies.[12] Upon slow addition of **20** into copper (II) bis(salicylidene-*tert*-butylamine) at 110 °C,[13] intramolecular cyclopropanation proceeded smoothly to provide the cyclopropyl ester **21** as a single isomer in good yield. Next, we explored various nucleophiles, such as halide, phenylsulfide, and alcohol to accomplish the crucial nucleophilic ring opening of activated cyclopropane **21**.[14] We were ultimately able to obtain lactone **22**, along with the hydrolyzed acid congener, through treatment of **21** with lithium chloride and camphor sulfonic acid,[15] albeit in low yield. Meanwhile, we indirectly determined the

stereochemistry of the newly generated quaternary carbon (C5 of tricholomalide A) in **22** by analysis of the X-ray structure of lactone **24** (Figure 3), prepared from ally lie alcohol **19** through an analogous intramolecular cyclopropanation route.

In conclusion, we have reported the development of a new and reliable synthetic protocol for the construction of the hydroazulene motif of tricholomalide A. This method involves the cyclopropanation of a silyl enol ether with halocarbene, followed by silver promoted ring opening of the resulting cyclopropane, to produce a highly functionalized hydroazulene framework. In addition, we have developed an accessible route to an advanced intermediate (**22**) containing the important C5 quaternary center of tricholomalide A. Further application of this method toward the total synthesis of tricholomalide A is in progress and it will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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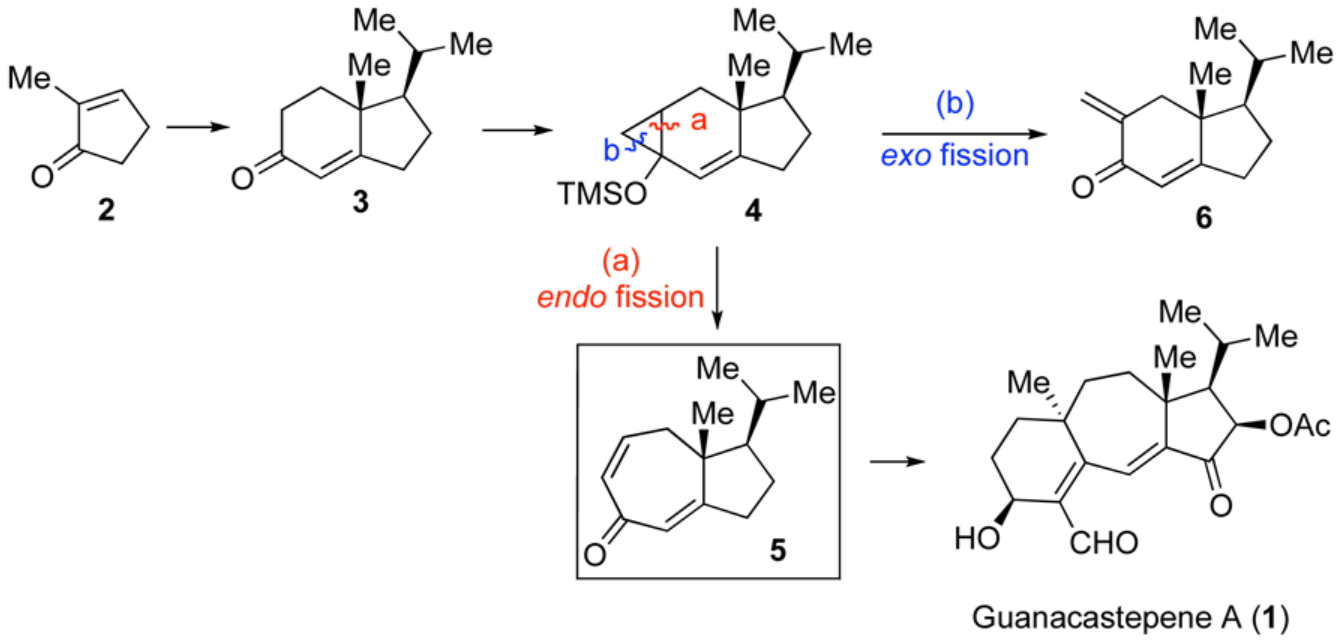


Figure 1.
Previously reported Homo-Robinson annulation route to **5**.

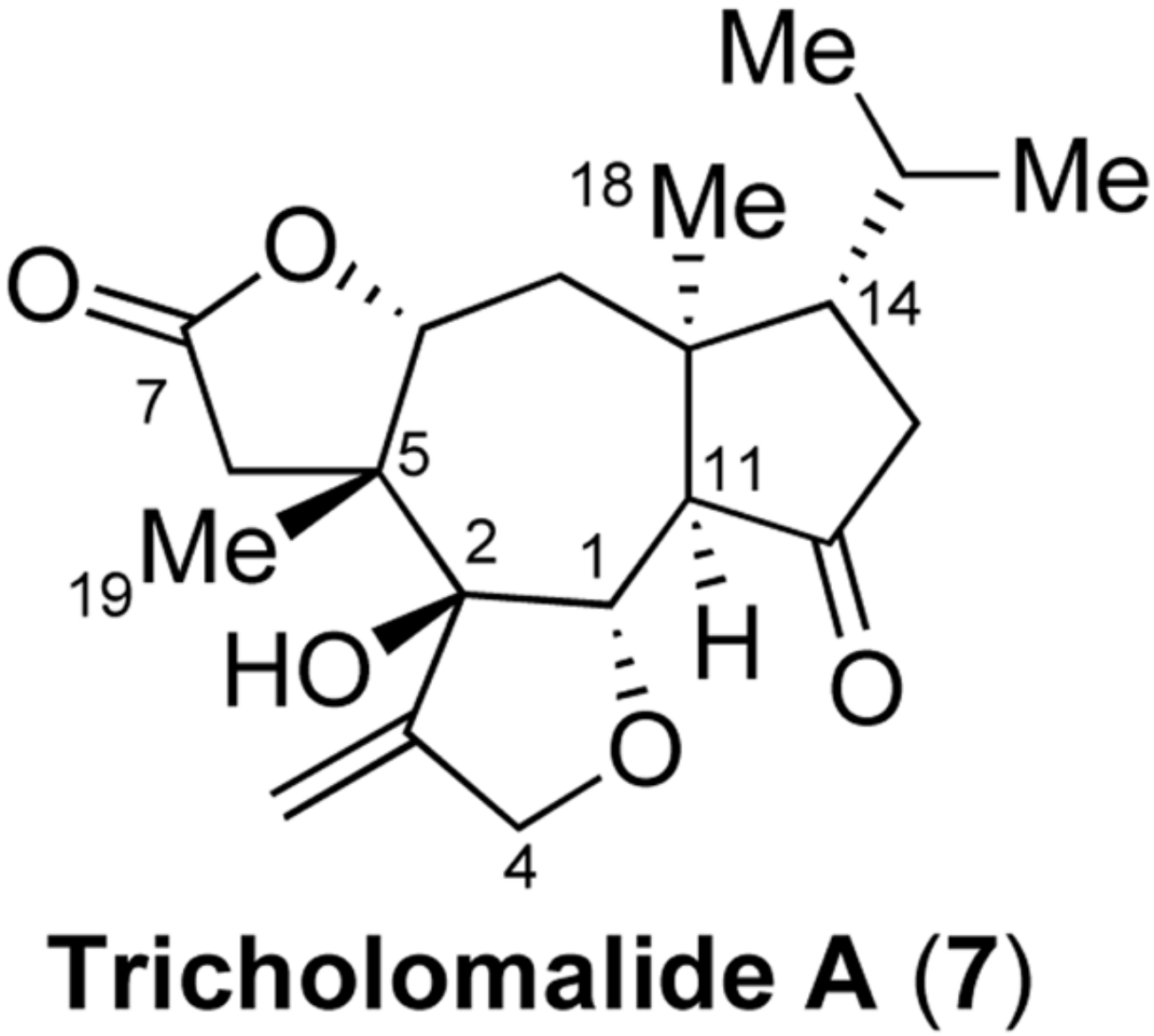


Figure 2.
Tricholomalide A (**7**).

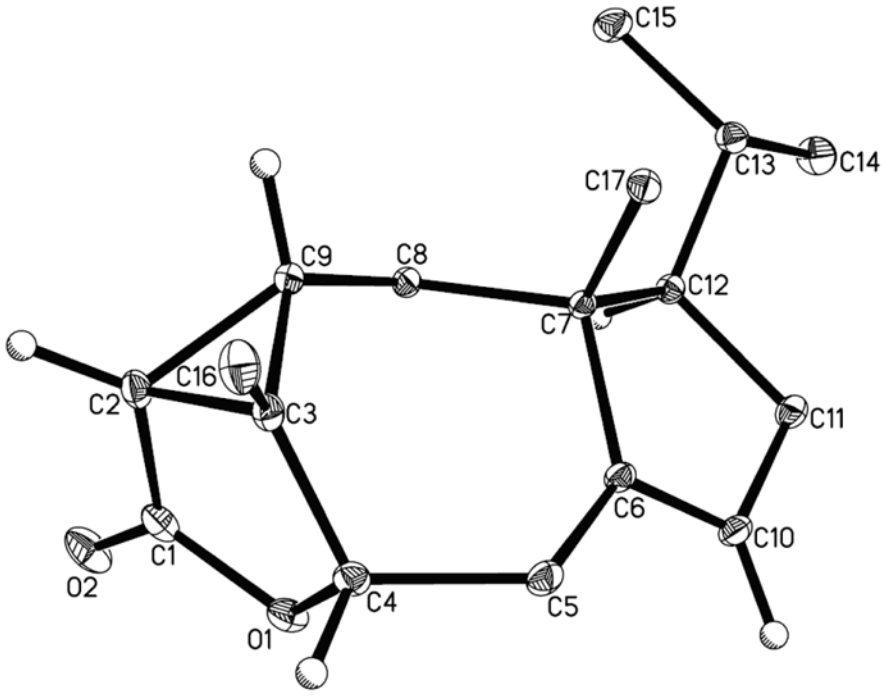
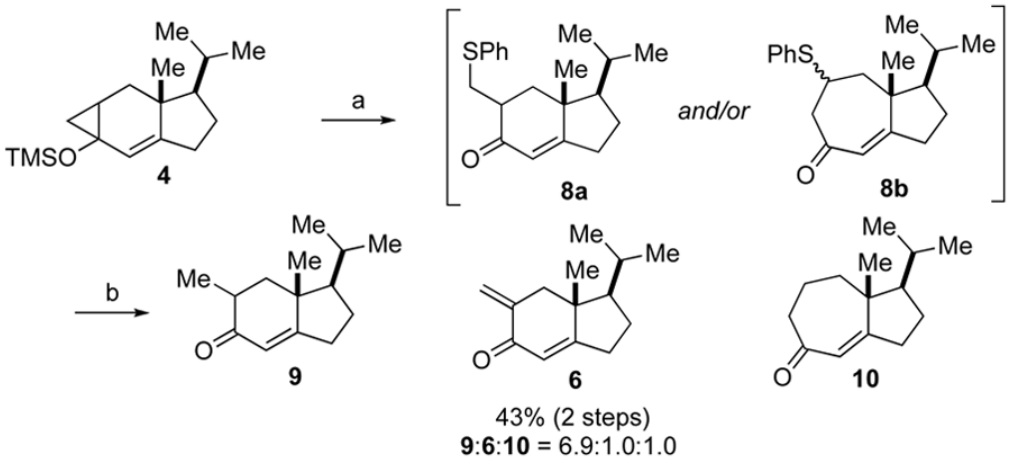
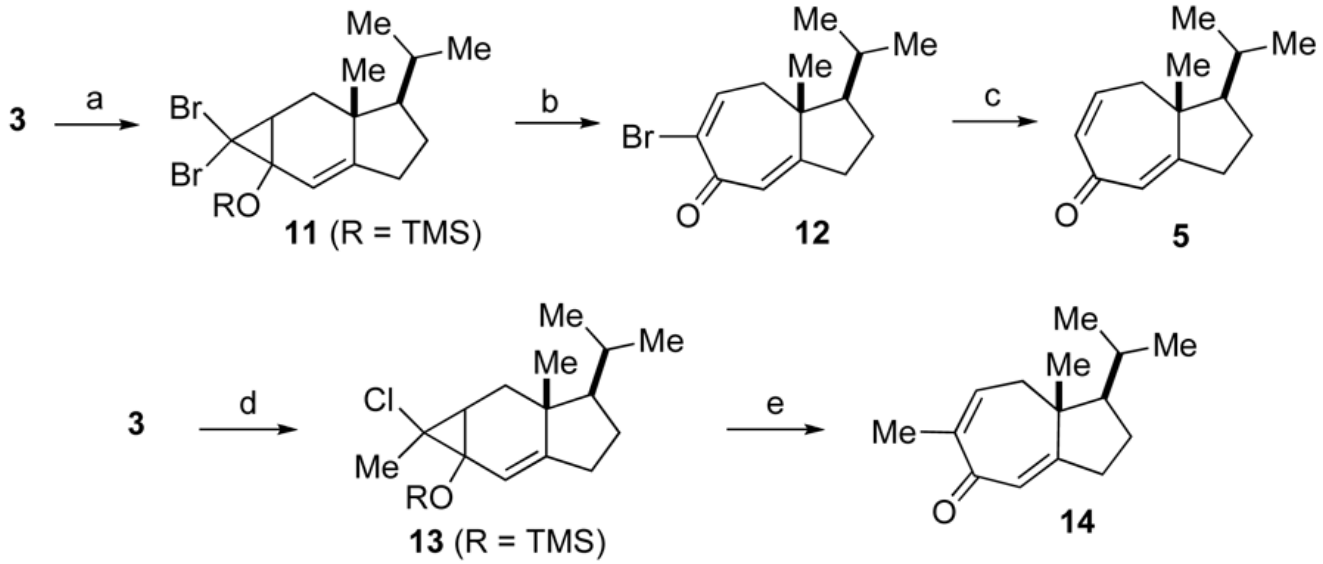


Figure 3.
X-ray structure of **24**.



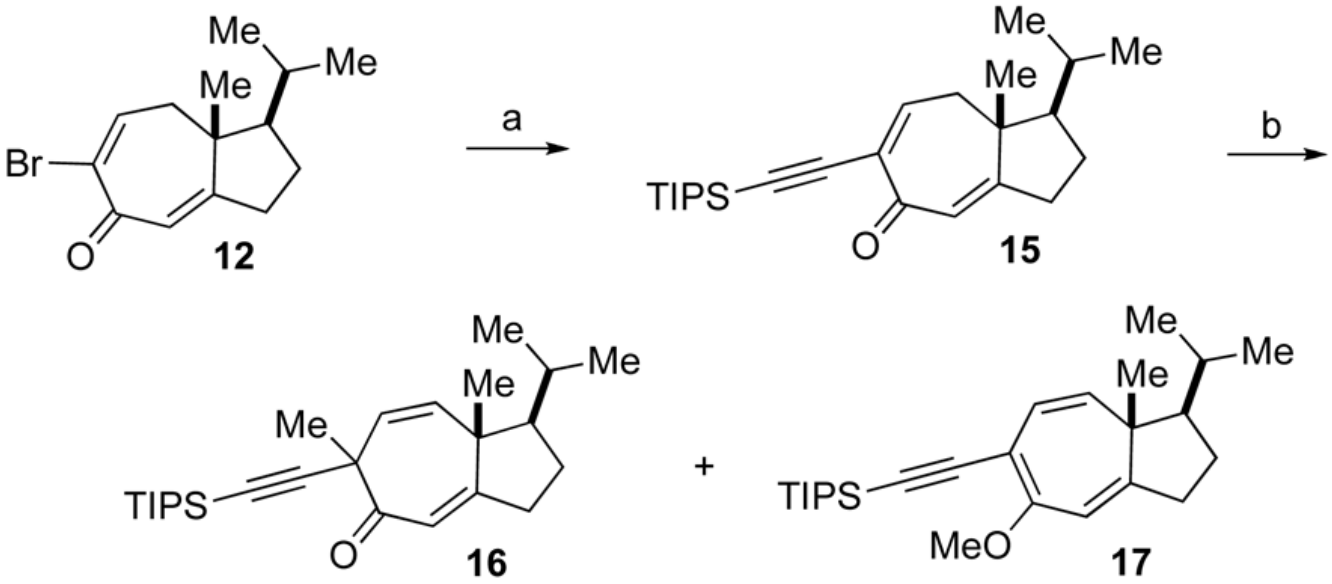
Scheme 1.

Ring expansion of **4** using $Fe(NO)_3$. Reagents and conditions: (a) $Fe(NO_3)_3$, PhSSPh, DMF, 0 °C to 23 °C. (b) Raney Ni, EtOH, 23 °C, 43% (**9:6:10** = 6.9:1.0:1.0,2 steps)



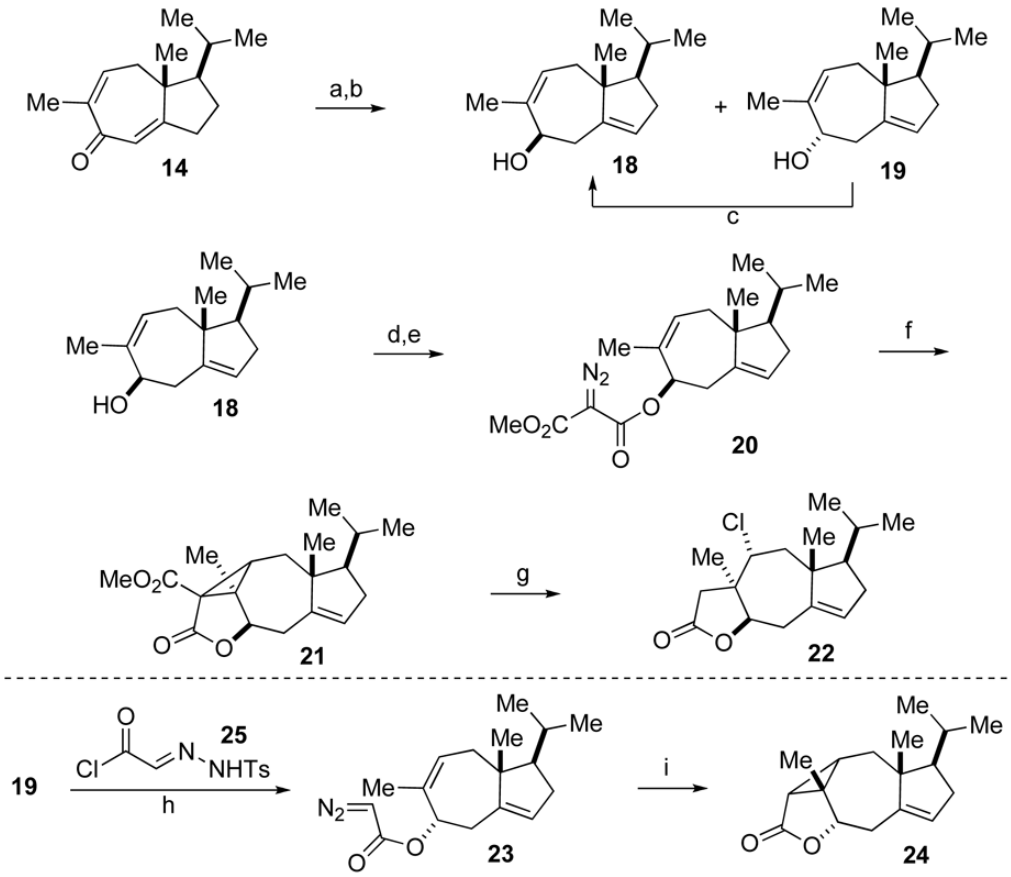
Scheme 2.

Synthesis of the ring expanded compounds **12** and **14**. Reagents and conditions: (a) i) LDA, TMSC1, THF, −78 °C. ii) $CHBr_3$, KO*t*Bu, pentane 0 °C to 23 °C. (b) $AgNO_3$, pyr, EtOH, 23 °C, 1.5 h, 59% (3 steps from **3**). (c) $BF_3{\cdot}OEt_2$, NaI, CH_3CN, 0 °C, 41%. (d) i) LDA, TMSC1, THF, −78 °C. ii) dichloroethane, *n*BuLi, THF, −35 °C to 0 °C. (e) $AgNO_3$, pyr, EtOH, 60 °C, 3.5 h, 45% (3 steps from **3**).



Scheme 3.

Synthetic approach toward tricholomalide A. Reagents and condtions: (a) TIPS-acetylene, $PdCl_2(PPh_3)_2$, CuI, iPr$_2$NH, THF, 0 °C to 23 °C, 90%. (b) KOtBu, MeI, THF, 0 °C to 23 °C, 78% **(16:17** = 1:3.2).



Scheme 4.

Synthesis of intermediate **22**. Reagents and conditions: (a) KHMDS, THF −78 °C; aq. NH_4Cl, 65% (BORSM). (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, 0 °C, 96% **(18:19** = 3.2:1). (c) i) *p*-NO_2BzOH, PPh_3, DIAD, toluene, 0 °C, 68%. ii) KOH, THF/MeOH/H_2O (2:2:1), 84%. (d) methyl malonyl chloride, Et_3N, CH_2C1_2, 0 °C to 23 °C, 84%. (e) *p*-AcNH-$PhSO_2N_3$, DBU, 0 °C, 99%. (f) copper(II) bis(salicylidene-*tert*-butylamine), toluene, 110 °C, 81%. (g) LiCl, CSA, DMF, 145 °C, 11%. (h) **25**, $PhNMe_2$, Et_3N, 0 °C to 23 °C, 50%. (i) copper(II) bis(salicylidene-*tert*-butylamine), toluene, 110 °C, 59%.