Synthesis of the Sesquiterpenes Trifarienols A and B via Anti-Selective α′-Intramolecular Carbomercuration

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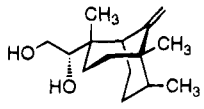
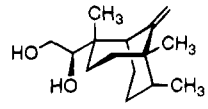
Trifarienols A and B (**1** and **2**, respectively), isolated recently from the Malaysian liverwort *Cheilolejeunea trifaria*,[1] represent a new carboskeletal class of sesquiterpenes. The substituted bicyclo[3.3.1]nonane skeleton of **1** and **2**, containing seven contiguous substituted and functionalized carbons, provides an array of synthetic challenges for efficient and stereoselective carbon–carbon bond formation. In exploring the scope and synthetic utility of carbannulation via intramolecular carbomercuration of alkynes by silyl enol ethers,[2,3] we have found that the trifarane system may be assembled rapidly using a one-pot Hg^{2+}/Pd^{2+}-mediated α′-carbannulation–carboxylation sequence. The details of this facile carbocycle construction method and its application to the synthesis of the novel sesquiterpene natural products **1** and **2** are reported here.

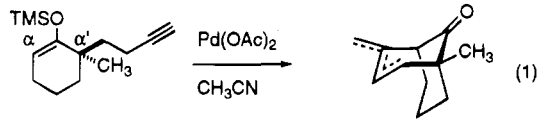


1

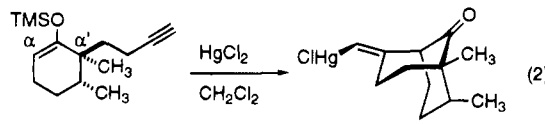


2

Among the few methods available for the direct assembly of bridged bicyclic systems is the Pd-catalyzed cycloalkenylation chemistry described by Kende[4] and Saegusa.[5] Kende showed that bicyclo[3.3.1]nonene derivatives could be constructed from an α′-(3-alkenyl)-tethered cyclohexanone enol ether (eq 1).[4] However,



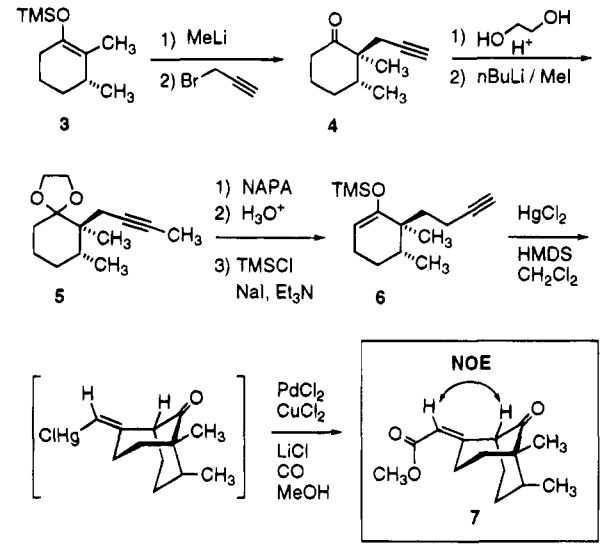
(1)



(2)

these Pd-catalyzed cycloalkenylations typically provide regioisomeric mixtures of alkene products in moderate yields.[4,5] In contrast, a similar annulation approach based upon the intramolecular carbomercuration[6] of an α′-alkynyl-tethered silyl enol ether seemed to offer several potential advantages for the synthesis of functionalized bridged bicyclic systems (eq 2). The mercuric salt-induced carbannulation reactions of simple alkynyl-

Scheme 1



branched silyl enol ethers have previously been shown to be mild and efficient and to provide regio- and stereochemically homogeneous exocyclic vinylmercurial cyclization products that may be elaborated into a variety of functionalized alkenes.[2,3,6–9] However, the stereoselectivity, mechanism, and synthetic utility of this annulation methodology has not been adequately explored. To probe the mechanism and synthetic utility of the α′-type intramolecular alkyne carbomercuration process, we have explored this methodology in the synthesis of the trifarienols (eq 2).

The construction of a cyclization precursor leading to **1** and **2** began with the conjugate addition of dimethyl cuprate to 2-methyl-2-cyclohexenone (Scheme 1). In situ trapping of the enolate with chlorotrimethylsilane gave enol ether **3**. Regeneration of the thermodynamic enolate by treatment with methyllithium and enolate alkylation with propargyl bromide then provided the α-propargyl cyclohexanone **4** in 60% combined yield from 2-methyl-2-cyclohexenone.[10] $A_{1,2}$ strain incurred en route to the anti 2,3-dimethyl diastereomer apparently favors the production of the syn 2,3-dimethyl product **4**. The propynyl side chain of **4** was homologated efficiently through a multi-step sequence. This involved carbonyl ketalization followed by alkyne deprotonation and methylation to give the 2-(2-butynyl) side chain of intermediate **5**. The internal alkyne was then isomerized quantitatively to the chain terminus using the monosodium salt of 1,3-diaminopropane.[11] Deketalization and trimethylsilyl enol ether formation[12] then gave the α′-

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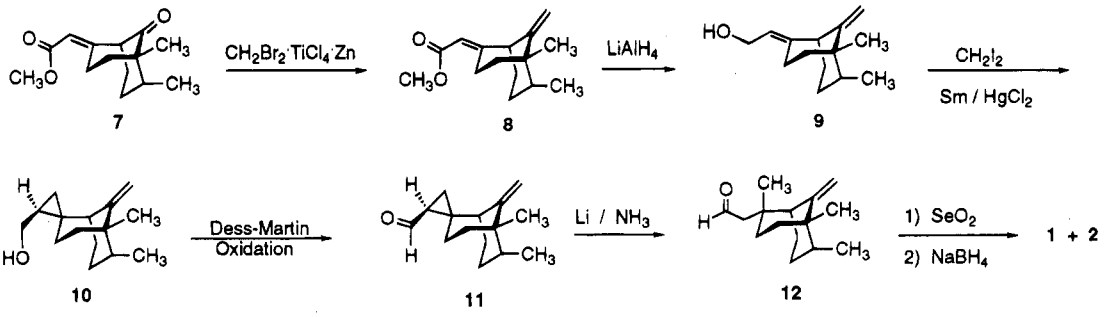
Scheme 2



(3-butynyl)cyclohexanone enol ether derivative **6** in nearly quantitative yield.

The pivotal α′-cyclization was effected by treatment of **6** with $HgCl_2$ (1.1 equiv) and HMDS (0.2 equiv) in CH_2Cl_2 at 25 °C. After 2 h, transmetalation and carbonylation were accomplished under Larock's conditions[13] without isolation of the intermediate vinyl mercurial. Replacement of the CH_2Cl_2 with methanol under Ar, addition of $PdCl_2$ (0.1 equiv), $CuCl_2$ (2 equiv), and LiCl (2 equiv), and stirring of the resulting mixture under 1 atm of CO for 14 h gave methyl ester **7** in 76% yield from **6** after workup and chromatography. The (*E*)-alkene configuration was unambiguously established by the observation of NOE enhancements between the α-keto and α-ester protons in **7**.[14] Because the steps involving vinylmercurial transmetalation and carboxylation are accepted to occur with retention of configuration,[13] the intermediate vinylmercurial is also assigned the (*E*)-configuration. Thus, the bicyclo[3.3.1]nonane framework was constructed by an efficient, anti-selective α′-intramolecular carbomercuration process. This may involve nucleophilic enolate addition to the metal-activated alkyne without the intermediacy of either the previously postulated[6] α-keto mercurial or *O*-Hg enolate.

Direct ketone methylenation of the sensitive vinylogous β-dicarbonyl substrate **7** was accomplished selectively using the Lombardo reagent[15] to give **8** in >80% yield (Scheme 2). Installation of the remaining quaternary center of **1** and **2** was achieved with essentially absolute stereo- and regiocontrol by a sequence involving hydroxyl-directed cyclopropanation and reductive fragmentation. $LiAlH_4$ reduction of **8** provided allylic alcohol **9** in 92% yield. Treatment of **9** with the reagent derived from CH_2I_2 and Sm[16] gave cyclopropane **10** in 89% yield; none of the α-face cyclopropanation diastereomer or regioisomeric cyclopropanation products were detected. Activation of the spiro-fused cyclopropyl group toward a regiospecific reductive cleavage[17] was accomplished by Dess–Martin oxidation[18] of **10** to provide aldehyde **11** in 79% yield. Treatment of **11** with Li in NH_3 then gave the β-methyl aldehyde **12** cleanly in 64% yield. A combination of ring strain and conjugation promotes this remarkably facile carbon–carbon bond scission.

The synthesis of the trifarienols was completed by the installation of the 1,2-diol moiety (Scheme 2). This was accomplished simply by SeO_2 oxidation of **12** in refluxing wet dioxane[20] followed by in situ $NaBH_4$ reduction of the α-oxo aldehyde to give a 3:1 mixture of **1** and **2** in 71% combined yield. Chromatographic separation provided the individual diastereomers (±)-**1** and (±)-**2**, the spectral and physical properties of which (mp, IR, ^1H and ^{13}C NMR, and HRMS) matched those reported for the natural products.[1] Thus, trifarienols A and B were prepared from 2-methyl-2-cyclohexenone in 16 steps and ca. 9% and 3% overall yield, respectively.

The anti selectivity of the central α′-type carbomercuration reaction is the same as that observed in the α-type intramolecular carbomercuration reactions that have been used to construct the functionalized spiro[4.5]-bicyclic spirojatamane[3] and *cis*-6-oxo-bicyclo[3.3.0]oct-3-en-2-one didemnenone[9] ring systems. Combined, these anti-selective alkyne carbomercuration reactions comprise an emerging synthetic methodology that is applicable to the facile and stereoselective construction of a variety of substituted ring systems containing tertiary and quaternary carbon centers and di- and trisubstituted alkenes. This methodology complements the Pd-catalyzed cycloalkenylation approach[4,5] for the construction of bridged polycyclic systems by providing high yields of isomerically homogeneous, functionalized exocyclic alkenes. The ability to elaborate the vinyl mercurials stereospecifically and easily into a range of substituted alkenes[13,20] contributes significantly to the utility of this methodology. Finally, the anti selectivity of enolate addition to tethered alkynes that has now been observed in several cases obviates any requirement for α-keto mercurial or *O*-Hg enolate intermediates.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1**–**12** and photocopies of ^1H and ^{13}C NMR spectra for synthetic **1** and **2** (11 pages).

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