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Facile approach to the bicyclo[5.3.0]decane ring system; efficient synthesis of (±)-7-*epi*-β-bulnesene

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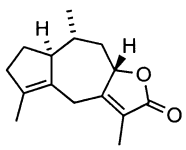
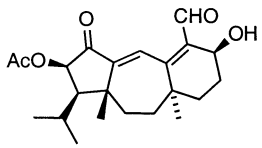
Abstract—An efficient strategy for the rapid construction of the guiane bicyclo[5.3.0]decane ring system from appropriately substituted 4-alkyn-1-ols has been developed. This methodology relies on a MeLi-catalyzed tandem 5-*exo*-dig cyclization/Claisen rearrangement sequence as the key ring forming step.

The bicyclo[5.3.0]decane ring system is prevalent in nature and has been identified as the key structural unit in a number of biologically active compounds.[1] Among them are the guianes and the tricyclic guanacastenes as well as the guaianolide sesquiterpenes, characterized by a γ-lactone ring fused to the 5–7 core. Although many of these interesting natural products have been isolated and synthesized over the past few decades,[2] several novel biologically active compounds incorporating the bicyclo[5.3.0] structure have been discovered only recently. Representative examples of these include the americanolides,[3] some of which exhibit activity against the human colon cancer cell line, and the unique diterpene guanacastepene which was found to possess novel and potent antibacterial properties.[4]

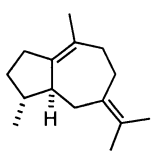


Americanolide D

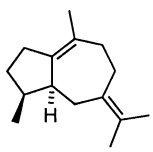


Guanacastepene

As part of our ongoing investigation probing the synthetic utility of the tandem anionic cyclization/Claisen rearrangement process[5] for the efficient synthesis of various cycloheptane-containing polycyclic natural products,[6–8] we have now applied this strategy to the rapid construction of (±)-7-*epi*-β-bulnesene. This compound has been previously synthesized in 13 steps by Negishi et al.[9,10] in 11 steps by Sammes et al.[11] and in 10 steps by Oppolzer et al.[12] Negishi employed Zr-promoted enyne bicyclization followed by transition metal or radical catalyzed cyclization of alkenyl iodides as the key steps for his synthesis,[9] and Sammes utilized intramolecular 1,3-dipolar cycloaddition of a 2-substituted 3-oxidopyrylium as the primary ring forming strategy in his approach. Oppolzer's synthesis relies on an intramolecular [2+2] cycloaddition of an appropriately substituted enol acetate to afford a tricyclo[5.3.0.0^{1,5}]decane intermediate, which subsequently undergoes base-induced fragmentation to produce the desired 5-7 ring system.[12]



7-*epi*-β-Bulnesene



β-Bulnesene

We envisioned that the bulnesene framework could be constructed from an appropriately substituted acetylenic alcohol using a straightforward one-pot process according to the retrosynthetic analysis shown in Scheme 1. This sequence involves a base-catalyzed 5-*exo*-dig cyclization of alkynol **3** to generate the 2-methylene tetrahydrofuran intermediate **2**, which then undergoes a spontaneous Claisen rearrangement under thermal conditions to provide the key bicyclic ketone **1**.[9,11,12] Installation of the exocyclic isopropylidene moiety on the B ring to complete the target 7-*epi*-β-bulnesene is achieved through standard Wittig chemistry.

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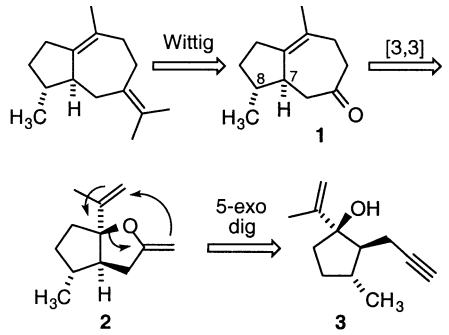
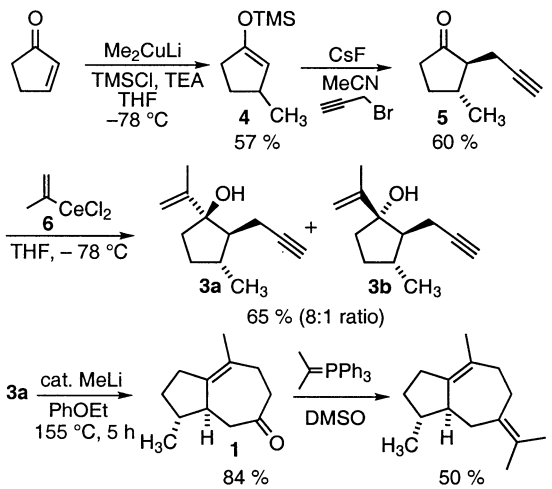


Scheme 1. Retrosynthetic analysis for (±)-7-*epi*-β-bulnesene.

The requisite alkynol **3** was synthesized in three steps from commercially available 2-cyclopenten-1-one as depicted in Scheme 2. Thus, conjugate addition using Me_2CuLi in the presence of chlorotrimethylsilane afforded the known[13] silyl enol ether **4** in 57% yield. On exposure to cesium fluoride and propargyl bromide in anhydrous acetonitrile at room temperature,[14] **4** was converted to *trans*-2-(2-propynyl)-3-methylcyclopentanone **5** in 60% isolated yield after column chromatography. The balance of the product mixture consisted mainly of 3-methylcyclopentanone, undoubtedly derived from premature protonation of the intermediate enolate anion. The maximum yield of the desired ketone product (60%) was obtained through the use of a syringe pump, allowing slow addition of **4** to the reaction mixture. The alkylation itself was approximately 94% diastereoselective in favor of the *trans* isomer as judged by GC analysis.

Reaction of ketone **5** with vinyl cerium **6**, generated in situ from the corresponding vinyllithium species, produced the 1*R**,2*S** alcohol **3a** and the undesired 1*S**,2*S** diastereomer **3b** (8:1 ratio) in a combined yield of 65%. At this point, the stage was set for the key intramolecular cyclization/Claisen rearrangement sequence which proceeded without incident on heating in the presence of catalytic MeLi (5–10 mol%) to provide the desired bicyclic ketone in 84% isolated yield.[15] The 5-step synthesis of (±)-7-*epi*-β-bulnesene[16] was completed by reacting ketone **1** with isopropylidenetriphenylphosphorane in DMSO according to the procedure of Oppolzer et al.[12]

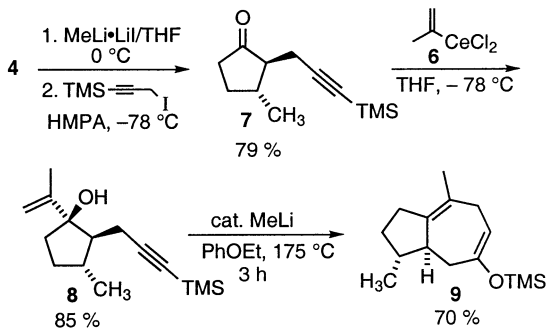


Scheme 2. Synthesis of (±)-7-*epi*-β-bulnesene.

It should be emphasized that, unlike other reported syntheses of the bulnesene ring system in which the crucial ring forming steps result in the formation of a mixture of stereoisomers,[9,11,12] the tandem sequence described here is completely stereoselective. Thus, the observed 7*S**,8*R** stereochemistry in **1** is a consequence of the *trans* relationship between the methyl and the propargyl substituents in **5**.

The silyl enol ether **4** was also readily alkylated[2b] with 3-iodo-1-trimethylsilyl-1-propyne to afford the corresponding trimethylsilyl substituted ketone **7** and subsequently converted to alcohol **8** in an excellent yield as shown in Scheme 3. We have previously reported[7] that, in cases where the triple bond bears a silicon-containing substituent (TMS or TBDMS) in the 4-alkyn-1-ol system, the cyclization/sigmatropic rearrangement sequence is accompanied by the Brook rearrangement,[17] resulting in regiospecific installation of a silyl enol ether functionality on the seven-membered ring. As expected, the trimethylsilyl substituted alcohol **8** exhibited analogous behavior on treatment of with catalytic MeLi (10 mol%) in refluxing phenetole, affording the silyl enol ether **9** as the ultimate reaction product. Although readily hydrolyzed with aqueous acid, **9** can be isolated by careful flash chromatography on florisil. The formation of this product is significant in that it provides future opportunities for regioselective functionalization and further elaboration of bicyclic 5-7 system as a potential route to more complex cycloheptanoid ring systems, such as the guainolide natural products.

In conclusion, we have achieved a rapid, 5-step synthesis of (±)-7-*epi*-β-bulnesene starting from commercially available 2-cyclopenten-1-one using a powerful one-pot 5-*exo*-dig cyclization/Claisen rearrangement process as the key ring forming operation. We are currently exploring the possibility of employing this strategy as a route to several tricyclic guainolide natural products through appropriate modification of starting materials and further elaboration of the 5–7 bicyclic core.



Scheme 3. Synthesis of bicyclic silyl enol ether **9**.

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15. Experimental procedure for the preparation of **1**: To a base-washed, flame-dried 10 mL round-bottomed flask, equipped with a reflux condenser were added 0.470 g (2.64 mmol) of **3a** and 1.5 mL of anhydrous phenetole. The solution was then heated under argon to 155°C (bath temperature), followed by dropwise addition of 1.30 mL of 0.203 M MeLi in phenetole (0.264 mmol, 10 mol%). The resulting solution was heated at 155°C for an additional 5 h. After cooling to room temperature, the mixture was chromatographed on silica gel, first eluting with 1% EtOAc/hexanes to remove phenetole then with 4% Et_2O/20% DCM/pentane to give 0.396 g of the desired product (84%) as a clear oil after solvent removal under vacuum. ^1H NMR (250 MHz, $CDCl_3$) δ 2.93–2.83 (m, 1H), 2.59 (d, $J=14.4$ Hz, 1H), 2.41–2.29 (m, 7H), 1.89–1.79 (m, 1H), 1.63 (s, 3H), 1.58–1.42 (m, 1H), 1.28–1.10 (m, 1H), 0.99 (d, $J=6.41$ Hz, 3H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$) δ 213.6, 140.3, 125.9, 47.4, 46.3, 42.6, 41.9, 33.7, 31.7, 31.2, 21.5, 18.1 ppm.
16. ^1H NMR (400 MHz, $CDCl_3$) δ 2.67 (d, $J=14.5$ Hz, 1H), 2.54–2.46 (m, 1H), 2.34–2.20 (m, 6H), 1.92–1.83 (m, 1H), 1.82–1.75 (m, 1H), 1.67 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H), 1.54–1.44 (m, 1H), 1.40–1.36 (m, 1H), 1.18–1.05 (m, 1H), 1.03 (d, $J=6.64$ Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 133.2, 126.4, 122.0, 49.3, 42.7, 37.1, 36.7, 33.9, 31.5, 29.4, 21.9, 20.2, 20.1, 18.6 ppm (lit.[12] 140.2, 133.2, 126.2, 121.7, 49.6, 42.8, 37.1, 36.8, 33.9, 31.5, 29.6, 21.9, 20.1, 18.7 ppm).
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