A TMM Cycloaddition Strategy to the Bicyclo[6.3.0]undecyl Ring System. A Total Synthesis of 11-Hydroxyjasionone

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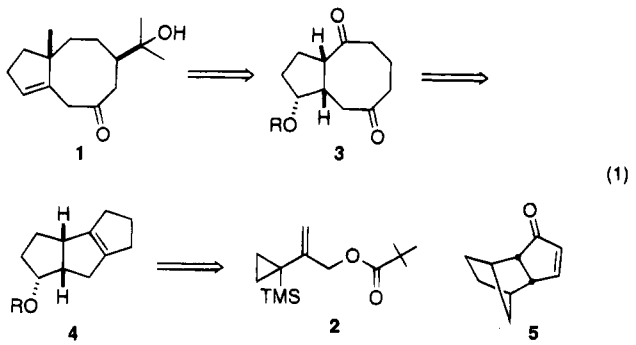
Summary: A palladium-catalyzed cycloaddition with 2-(1-(trimethylsilyl)-1-cyclopropyl)allyl pivalate sets the stage for easy entry into a 5,8-fused bicyclic core with suitable functionality for elaboration into natural products as illustrated by a total synthesis of 11-hydroxyjasionone.

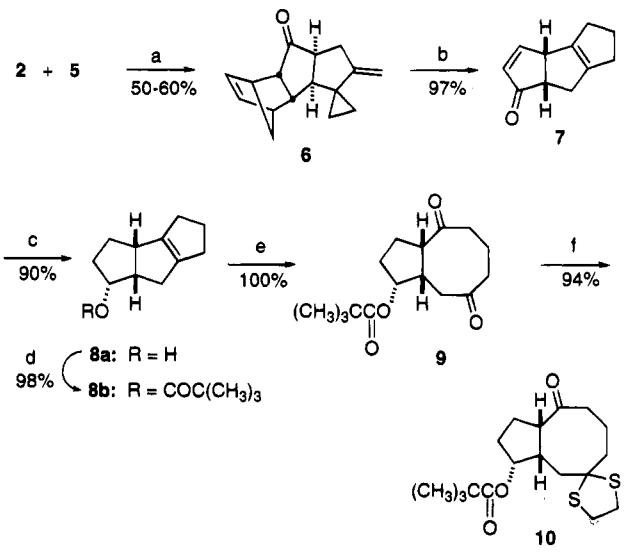
The 5,8 fused ring system, an increasingly important structural motif among natural products, has become a target for the development of synthetic strategies.[1] One such compound, 11-hydroxyjasionone (**1**),[2] is a constituent of the essential oil[3] derived from the aerial parts of *Jasionia* Montana which showed antibacterial activity against *Bacillus subtilis* and antifungal activity against *Trichophyton mentagrophytes*, *Cryptococcus neoformans*, and *Candida Albicans*.[4] We report a new strategy to this ring system derived from our development of 2-(1-(trimethylsilyl)-1-cyclopropyl)allyl pivalate (**2**)[5] as a novel conjunctive reagent which culminated in the synthesis of (±)-**1**.

Equation 1 illustrates the key aspects of the retrosynthetic analysis in which the bicyclo[6.3.0]undecyl compound **3** represents a flexible intermediate possessing a



juxtaposition of functionality that can access many members of this family of natural products. Its derivation from tricycle **4** is obvious. The latter becomes easily available from the well-known ketone **5**[6] capitalizing upon our conjunctive reagent **2** using a novel cycloaddition–cycloreversion–isomerization.

Scheme 1. Synthesis of Functionalized Core 5,8 Ring System[a]



[a] Key: (a) 5 mol % $Pd(OAc)_2$, 50 mol % $(i\text{-}C_3H_7O)_3P$, dioxane, 150 °C (b) FVT, 600 °C, 0.06 mmHg; (c) $NaBH_4$, C_2H_5OH, reflux; (d) $(CH_3)_3CCOCl$, 10% DMAP, $(C_2H_5)_3N$, CH_2Cl_2, rt; (e) O_3, $NaHCO_3$, CH_3OH, CH_2Cl_2, −78 °C; (f) $HSCH_2CH_2SH$, $Zn(OSO_2CF_3)_2$, CH_2Cl_2, rt.

The palladium-catalyzed trimethylenemethane (TMM) cycloaddition was performed by heating a 1 M equimolar mixture of the two reactants **2** and **5** with mol % palladium acetate and 50 mol % triisopropyl phosphite in 1,4-dioxane at 150 °C for 1 h.[7] Subjecting the reaction mixture directly to flash chromatography gave a 50–60% yield of the desired adduct **6**[8] (Scheme 1). Flash vacuum thermolysis (FVT) at 600 °C effected tandem retro-Diels–Alder reaction and vinylcyclopropane–cyclopentene rearrangement to triquinane **7**[8] in nearly quantitative yield. Chemoselective saturation of the conjugated double bond concomittantly with carbonyl reduction proceeds readily with sodium borohydride[9] to give **8a**[8] which set the stage for the final oxidative cleavage to diketone **9**.[8] Chemoselective protection of the less hindered carbonyl group succeeded with ethanedithiol in the presence of fresh zinc triflate[10] to **10**.[8]

The remarkable effects of the conformation of this 5,8 ring system became evident as we embarked upon introduction of the two appendages, the methyl and 2-propanol fragments (see Scheme 2). Introduction of the isopropyl fragment required formation of the enone **11** which failed by normal selenenylation or sulfenylation

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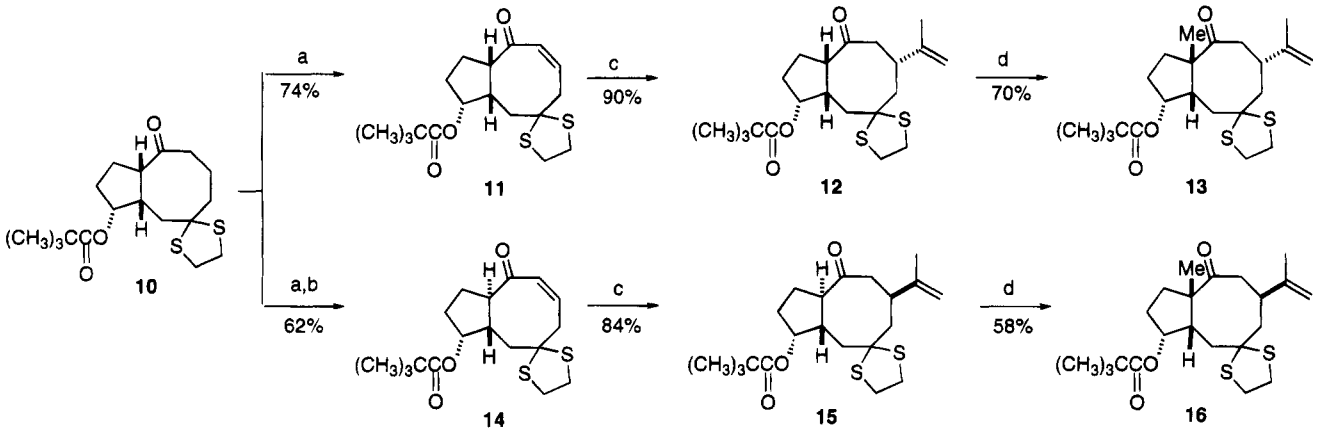
Scheme 2. Attachment of Alkyl Appendages to 5,8 Core[a]



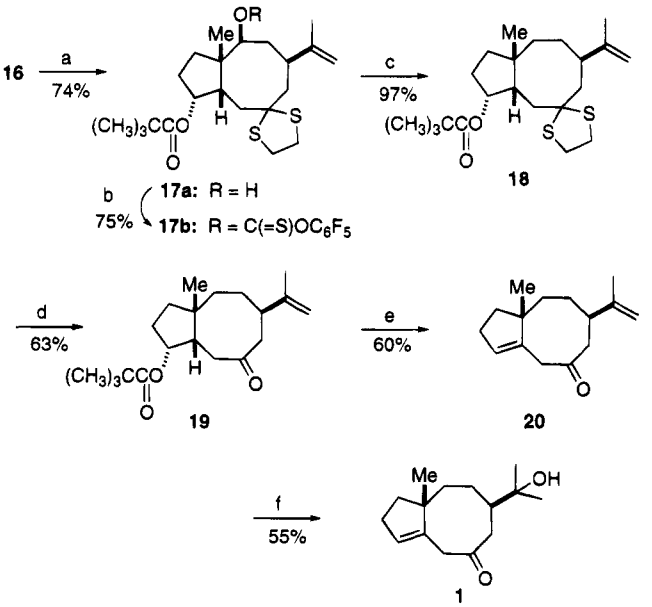
[a] Key: (a) KH, methyl 2-pyridinesulfinate, DME, rt then $CuSO_4$, $PhCH_3$, reflux; (b) DBU, $CHCl_3$, rt; (c) $[CH_3C(=CH_2)]_2CuCNLi_2$, ether, −78 °C; (d) KH, CH_3I, THF, 25 °C.

protocols. On the other hand, sulfinylation with methyl 2-pyridinesulfinate followed by copper-assisted elimination[11] resolved the impasse to form **11**. Conjugate addition of isopropenyl[12] and regioselective methylation of the thermodynamic enolate[13-15] generated a single diastereomeric product whose X-ray structural analysis[16] showed it to be **13** indicating that conjugate addition occurred exclusively from the more hindered face to give **12**. In complete contrast to this observation, the *trans* ring juncture isomer **14**, available by thermodynamic epimerization of **11** with DBU, gave an isomeric product **16** via the identical sequence indicating a stereocomplementary course of conjugate addition to give **15**. While the source of this contrasting behavior has not been established, molecular modeling suggests that ground-state conformational differences cannot account for it. An attractive explanation invokes coordination of the copper reagent with an ideally oriented axial-like sulfur of the thioketal which then delivers the cuprate to the α face of **11** to give **12** and the β face of **14** to give **15**.

The final assault requires adjustment of oxidation level (see Scheme 3). The radical deoxygenation procedure of Barton succeeded admirably to convert **17a** to **18** only when triethylborane and oxygen was used as the radical initiator.[17] Thioacetal (to **19**) and pivalate hydrolyses followed directly by regioselective dehydration gave **20** which was chemoselectively hydrated[18] to produce (±)-11-hydroxyjasionone (**1**) whose spectral characteristics correspond to those reported for the natural product.

The flexibility offered by this strategy should prove useful for the synthesis of other 5,8 fused ring systems. The enones **11** and **14** provide a possible extension of 5,8,5 fused ring systems.[1] The core triquinane **7** which begins the sequence also sets the stage for assaults on triquinane terpenoids.[19] Since resolution of the alcohol precursor of **5** has been reported,[6] this synthesis also provides an entry into either enantiomer of the product.

Scheme 3. Adjustment of Oxidation Level. Synthesis of (±)11-Hydroxyjasionone[a]



[a] Key: (a) $NaBH_4$, C_2H_5OH, reflux; (b) $C_6F_5OC(=S)Cl$, DMAP, $PhCH_3$, 80 °C; (c) $(C_4H_9)_3SnH$, $(C_2H_5)_3B$, O_2, neat, rt; (d) $AgNO_3$, C_2H_5OH, 65 °C; (e) KOH, C_2H_5OH, 70 °C and then $(CF_3SO_2)_2O$, C_5H_5N, rt; (f) $Hg(OAc)_2$, $THF-H_2O$, rt then $Na(AcO)_3BH$, rt.

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Supplementary Material Available: Procedures and characterization data and IR and ^1H, ^{13}C NMR spectra (31 pages). This material is contained in libraries, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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