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A novel extension of the Stork–Jung vinylsilane Robinson annelation procedure for the introduction of the cyclohexene of guanacastepene

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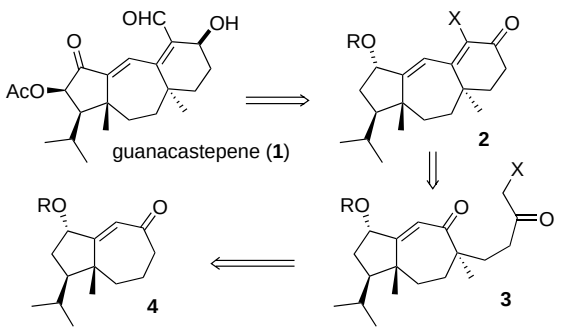
Abstract—A new annelation procedure has been developed in a model system to introduce the cyclohexene ring of guanacastepene. Cyclohexenone **16** is prepared by sequential methylation and alkylation with allylic iodide **15**. One-pot epoxidation, protodesilylation and hydrolysis of the THP forms dione **19**, which cyclizes with NaOMe to **24** in 57% overall yield. Reduction, Mitsunobu inversion, and selective oxidation of the primary alcohol forms model **29**. Phenyldimethylsilyl allylic iodide **36** is easier to make and more stable than trimethylsilyl allylic iodide **6** used by Stork.

The novel, diterpene antibiotic guanacastepene (**1**), which was isolated by Clardy from an unidentified fungus growing on the tree *Daphnopsis americana*, shows excellent activity toward methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*.[1] Further biological studies indicated that **1** has moderate activity against Gram-positive bacteria, poor activity against Gram-negative bacteria, and hemolytic activity against human red blood cells.[2] We recently reported a 12-step synthesis of **4** (Scheme 1), the functionalized hydroazulenone ring system of guanacastepene.[3] Danishefsky and Magnus have also reported routes to functionalized hydroazulene ring systems[4a,5] and Danishefsky has described alkylation studies of the hydroazulene core.[4b]



Scheme 1. Retrosynthetic analysis for guanacastepene (**1**).

Elaboration of **4** to guanacastepene could be carried out by introduction of a methyl group and an oxygenated side chain to give **3**. An aldol reaction would give **2**, in which X is an aldehyde precursor. Functional group modification in the five- and six-membered rings would complete a synthesis of guanacastepene. At first glance, the Robinson annelation seems well suited to the preparation of **2** from **4**. However, there are several concerns about this approach. First, a Michael addition to form **3** may not give the correct stereoisomer. Second, Robinson annelations on cycloalkenones, although known, are uncommon.[6] Third, the Nazarov reagent, $CH_2{=}CHCOCH_2CO_2R$, which would introduce $X{=}CO_2R$ that can be converted to an aldehyde, can only be used with 1,3-dicarbonyl compounds.

We decided to examine the Stork–Jung Robinson annelation procedure,[7] alkylation with 1-iodo-3-trimethylsilyl-2-butene (**6**) to introduce a 3-oxobutyl group, since either the methyl or trimethylsilylbutenyl group can be introduced first, increasing the likelihood that the stereochemistry of the new introduced center in **3** can be controlled (Scheme 2). 4,4-Dimethyl-2-cyclohexenone (**5**) was chosen as a readily available model for hydroazulenone **4**. Preparation of the lithium enolate of **5** with LDA and DMPU in THF at −78°C, addition of **6**, and slow warming to 25°C affords 78% of **7**. A second alkylation with LDA, DMPU and MeI provides 84% of bis-alkylated cyclohexenone **9**. Alkylation in the opposite order proceeds equally well giving 81% of **8**[8] in the first step and 82% of **9** in the second. Reaction of **9** with *m*-CPBA at 0°C forms the silyl

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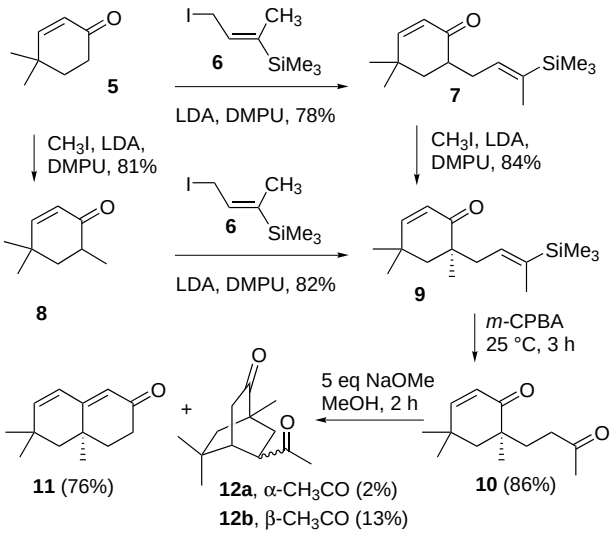
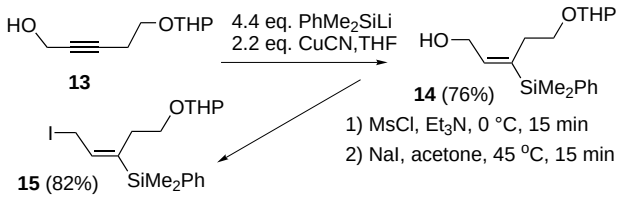


Scheme 2. Preparation of tetrahydronaphthalene **11**.

epoxide, which is cleaved by *m*-chlorobenzoic acid on stirring for 3 h at 25°C as described by Stork to give 86% of diketone **10**.

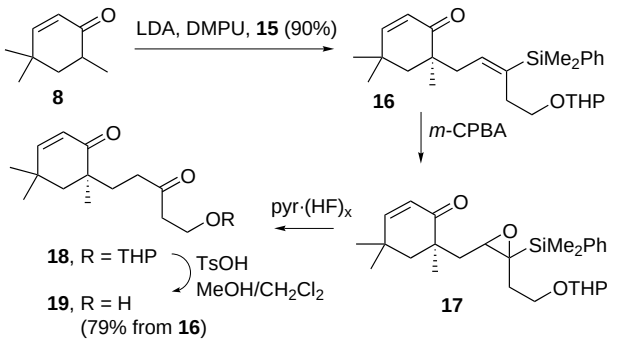
The aldol reaction of **10** to give dienone **11** was problematic since varying amounts of Michael adducts **12** are obtained. The best selectivity for **11** is achieved by using excess strong base (5 equiv. of 1 M NaOMe in MeOH), which gives 76% of the desired dienone **11** and 15% of a 7:1 mixture of **12b** and **12a**. More **12** (30–40%) is obtained with 1 equiv. of NaOMe and little **11** is formed with KOH in dioxane or DME or with pyrrolidine. The Michael adducts are formed as a 7:1 equilibrium mixture and are not converted to **11** with excess NaOMe in MeOH at reflux for 24 h, suggesting that the Michael reaction is not readily reversible. The aldol reaction is faster than the Michael reaction, but is probably reversible. Dehydration of the aldol product is irreversible and probably proceeds faster in excess base, providing a plausible explanation for the observation that excess base improves the yield of **11**. The formation of Michael adduct byproducts may be the reason for the limited use of Robinson annelations to prepare dienones from cycloalkenones.

We now turned our attention to adapting the Stork–Jung vinylsilane Robinson annelation to the introduction of a functionalized chain containing an aldehyde precursor. The functionalized 3-silylallylic iodide cannot be prepared analogously to **6** from trimethylsilylpropargyl alcohol. Fortunately, we found that addition of phenyldimethylsilylcuprate[9] to propargylic alcohol **13**[10] gives 76% of the desired phenyldimethylsilyl allylic alcohol **14** and only 1–2% of the regioisomer (Scheme 3). CuCN-catalyzed addition of $PhMe_2SiLi{\cdot}Et_2Zn$ as described by Oshima[11] gives 94% of a difficultly separable 84:16 mixture of **14** and the regioisomer. Formation of the mesylate of **14** with MsCl and Et_3N and displacement with NaI in acetone at 45°C provides 82% of the desired functionalized dimethylphenylsilyl allylic iodide **15**.



Scheme 3. Preparation of silyl allylic iodide **15**.

Alkylation of 4,4,6-trimethyl-2-cyclohexenone (**8**) with **15** provides 90% of **16** (Scheme 4). Alkylation of **5** with **15** proceeds in 75% yield and methylation of that product affords 87% of **16**, indicating that the alkylations can be carried out in either order, improving the likelihood of obtaining the desired stereoisomer from **4**. Epoxidation of **16** with *m*-CPBA in CH_2Cl_2 for 1 h at 0°C affords silyl epoxide **17**, which is not cleaved by *m*-chlorobenzoic acid at room temperature, indicating that dimethylphenylsilyl epoxide **17** is more stable to acid than the trimethylsilylepoxide formed from **9**. Addition of pyr·$(HF)_x$ to the reaction mixture and stirring at 25°C for 10 min efficiently cleaves silyl epoxide **17** to the ketone and partially hydrolyzes the THP providing a mixture of **18** and **19**. Addition of TsOH and MeOH and stirring at 25°C for 30 min completes the hydrolysis of the THP affording **19** in 79% yield from **16** in a one-pot reaction.

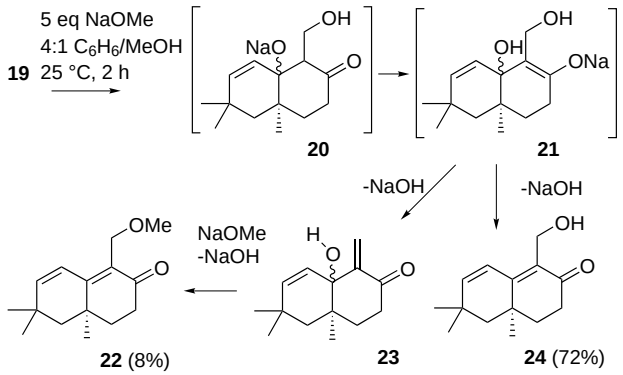


Scheme 4. Preparation of hydroxy dione **19**.

Treatment of **19** with 5 equiv. of NaOMe in MeOH for 4 h affords 64% of the desired hydroxymethyl tetrahydronaphthalenone **24**, 26% of the analogous methoxymethyl tetrahydronaphthalenone **22**, and 10% of Michael products analogous to **12** (Scheme 5). Aldol reaction gives alkoxide **20**, which can form enolate **21**. Elimination of the hydroxyl group at the ring fusion will give the desired product **24**. Elimination of the side chain hydroxyl group will give methylenecyclohexanone **23**, which can undergo addition of methoxide and then elimination of the ring fusion hydroxyl group to give **22**.[12] We thought that using a non-nucleophilic cosolvent might improve the selectivity for **24**.

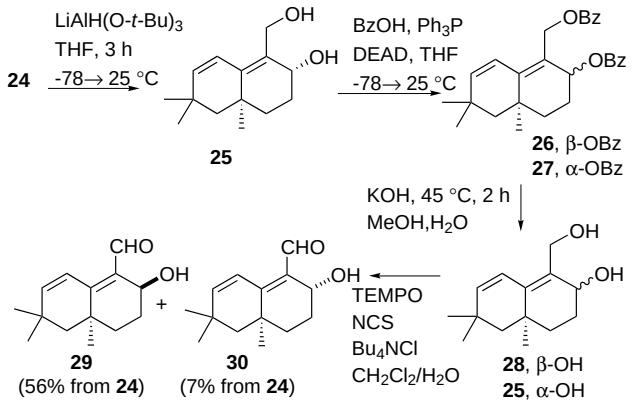
The best results are obtained by treating **19** with 5 equiv. of 0.2 M NaOMe in 4:1 benzene/MeOH, which gives 72% of the desired product **24**, 8% of methoxy adduct **22**, and 14% of Michael products. Treatment of THP ether **18** with 5 equiv. of NaOMe in MeOH

affords only **22** and Michael products, indicating that OTHP is a better leaving group than OH.



Scheme 5. Aldol reaction and dehydration to give **24**.

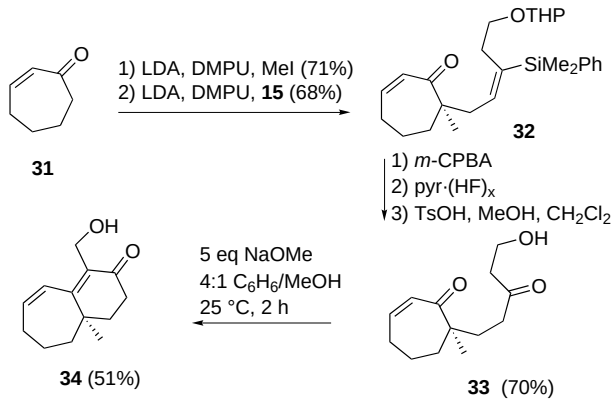
To complete the model study, we needed to reduce the ketone of **24** to the axial alcohol and oxidize the primary alcohol to the aldehyde to introduce the functionality present on the cyclohexene of guanacastepene (**1**). Reduction of **24** with L-Selectride affords mainly the equatorial cyclohexenol **25**, while reduction with K- or KS-Selectride[13] gives a complex mixture (Scheme 6). We therefore reduced **24** with $LiAlH(O\text{-}t\text{-}Bu)_3$ to give a 98:2 mixture of **25** and **28** and used a Mitsunobu reaction to invert the stereochemistry.[14]



Scheme 6. Preparation of hydroxyaldehyde **29**.

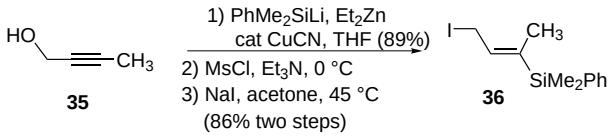
Treatment of **25** with 4 equiv. of PPh_3, DEAD and BzOH affords an 88:12 mixture of the desired dibenzoate **26** and stereoisomer **27**, which is probably formed by an S_N1 reaction. The Mitsunobu reaction with *p*-nitrobenzoic acid was less successful.[15] Hydrolysis of the mixture with KOH in 9:1 MeOH/H_2O gives a difficultly separable, acid-sensitive 88:12 mixture of **28** and **25** in 72% yield from **24**. Selective oxidation of the primary alcohol by Einhorn's procedure[16] with 2 equiv. of TEMPO, 4 equiv. of NCS, and 1 equiv. of Bu_4NCl in CH_2Cl_2/H_2O requires 16 h, but gives the desired hydroxyaldehyde **29** in 56% overall yield from **24** along with 7% of hydroxyaldehyde **30** formed from the **25** in the mixture.[17] The spectral data for **29** show the expected similarity to those of guanacastepene.

This annelation sequence works equally well on 2-cycloheptenone (**31**). Alkylation with MeI (71%) and then with **15** (68%) provides **32** (Scheme 7). Epoxidation, protodesilylation with pyr·$(HF)_x$ and hydrolysis with TsOH affords 70% of **33**, which cyclizes with 5 equiv. NaOMe in 4:1 benzene/MeOH to give 51% of hydroxy dienone **34**.



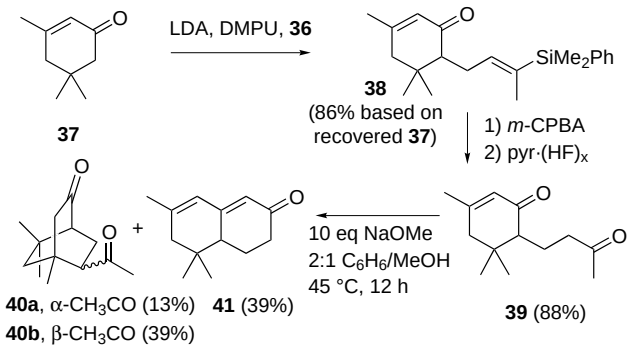
Scheme 7. Synthesis of **34**.

Regiospecific addition of the dimethylphenylsilyl anion to propargylic alcohols not only provides easy access to functionalized 3-silylallylic iodides, but is advantageous for the parent system. Oshima's procedure, CuCN-catalyzed addition of $Me_2PhSiLi\cdot Et_2Zn$ to 2-butyn-1-ol (**35**), provides 89% of the alcohol and 4% of the readily separable regioisomer (Scheme 8). In this case, use of the cuprate by Pancrazi's procedure gives 74% of the alcohol that is harder to purify. Mesylation and displacement with NaI proceeds in 86% yield, completing a three-step synthesis of the non-volatile, acid-stable 1-iodo-3-dimethylphenylsilyl-2-butene (**36**). In contrast, five steps are required for the preparation of volatile, acid-sensitive 1-iodo-3-trimethylsilyl-2-butene (**6**) from 2-propyn-1-ol. Preparation of **10** from **8** using **36** proceeds in 86% yield as compared to only 70% using **6**.



Scheme 8. Synthesis of **36**.

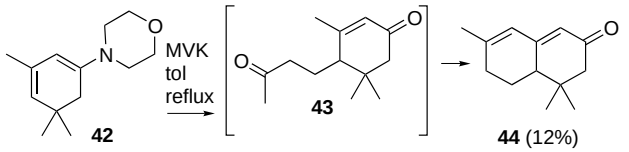
We decided to explore the utility of **36** with isophorone (**37**) since reaction of the morpholine dienamine of isophorone (**42**) with MVK has been reported to give only 12% of tetrahydronaphthalenone **41**.[18] Alkylation of **37** with **36** yields 86% of **38**, which is epoxidized and protodesilylated to give 88% of **39** (Scheme 9). Treatment of **39** with 10 equiv. of NaOMe in 2:1 benzene/MeOH affords 52% of a 3:1 mixture of Michael adducts **40b** and **40a**, and 39% of the desired dienone **41**. Although the data for **40b** are identical to those reported, the spectral data for **41** are similar to, but clearly different from those previously reported.[18] NOE studies confirmed the structure of **39**, suggesting that



Scheme 9.

we had prepared **41** and that the structure of the adduct of **42** and MVK had been misassigned.

The literature data[18] for the dienone prepared from dienamine **42** are identical to those reported for dienone **44**, which has been prepared by oxidation of β-ionone to give **43** and cyclization[19] (Scheme 10). Reaction of **42** with MVK could also give **43**, which will cyclize to **44**, not **41**.



Scheme 10.

In conclusion, we have extended the Stork–Jung Robinson annelation procedure by using **15** with cyclohexenone **5** and 2-cycloheptenone (**31**) to prepare hydroxymethyl dienones **24** and **34**. We have also developed a protocol to convert hydroxy ketone **24** to the desired hydroxy aldehyde **29**. This sequence should be suitable for annelation of the guanacastepene cyclohexene ring onto hydroazulene **4** to give **2** and further elaboration to complete the synthesis of guanacastepene (**1**). The regiospecific preparation of 3-silylallylic halides **15** and **36** from propargylic alcohols should significantly extend the scope of the Stork–Jung Robinson annelation procedure.

Acknowledgements

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