A Facile Synthesis of *dl*-Modhephene

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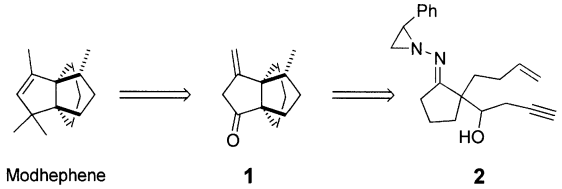
Recently, we have reported a total synthesis of modhephene[1] through tandem radical cyclization reaction using N-aziridinylimine intermediate.[2] Though the synthesis provided an expeditious route to propellanes, introduction of *gem*-dimethyl groups required tediously long steps to complete the total synthesis of modhephene. This drawback of the synthesis could have been circumvented by the introduction of those methyl groups before the crucial radical cyclization reaction. However, when the second quarternary center was introduced the ketone became unreactive to the imine forming reaction conditions.[3] Thus we have modified the synthetic route that would allow facile introduction of the *gem*-dimethyl groups while allowing the formation of the imine (Scheme 1).

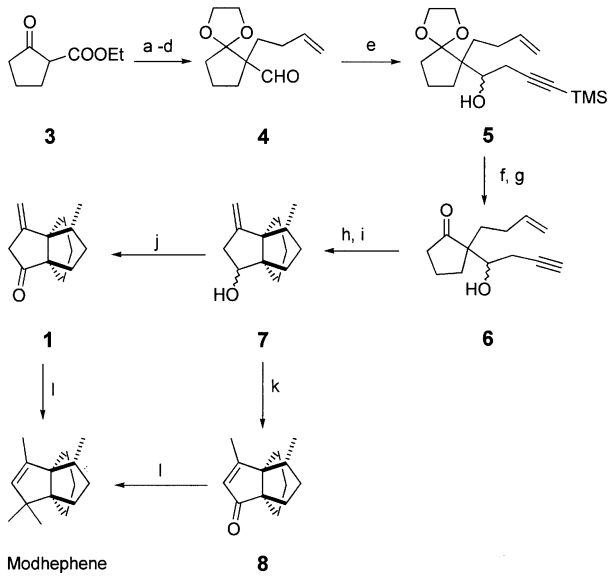
The key intermediate **1** would allow one step introduction of the *gem*-dimethyl groups as shown in the Curran's synthesis of modhephene[4]. The ketone **1** would be readily available through tandem radical cyclization reaction of the N-aziridinylimine **2** that could be prepared from the corresponding ketone since it would be conformationally more flexible than the one with two quarternary centers.

Our synthesis started with alkylation of **3** in presence of K_2CO_3. The ketone of the alkylated keto-ester was protected and the ester was converted to the aldehyde **4**. Addition of 3-Trimethylsilylpropargyl magnesium bromide to the aldehyde produced a mixture of diastereomeric alcohols (2.2 : 1) **5**. After desilylation of the acetylenic silyl group, deprotection of the ketal produced the ketone **6**. The ketone **6** was condensed with N-amino-2-phenylaziridine to afford **2**. This condensation was so sluggish that even after 14 days, the reaction did not proceed to completion. The imine **2** was separated from the starting ketone and the ketone was recycled to the imine forming reaction. Then the imine **2** was subjected to the standard radical cyclization reaction condition[5] to provide the propellane **7** that has the same diastereomeric ratio as **5**.

A possible cyclization product with the opposite methyl stereochemistry was not detected at all by NMR. The cyclization reaction seemed to have proceeded with complete stereocontrol. Oxidation of **7** produced single isomeric ketone



Scheme 1



Scheme 2. (a) 4-bromobutene, K_2CO_3, DMF (86%); (b) ethylene glycol, TsOH, PhH (88%); (c) LAH, Et_2O (90%); (d) DMSO, $(COCl)_2$, CH_2Cl_2; Et_3N (97%); (e) TMS-propargyl magnesium bromide, THF (95%); (f) KOH, MeOH (91%); (g) TsOH, acetone (93%); (h) N-amino-2-phenylaziridine, AcOH (cat.), 2 weeks (87%) BORSM); (i) Bu_3SnH, AlBN, PhH, SiO_2 (85%); (j) DMSO, $(COCl)_2$, CH_2Cl_2; Et_3N, -50 °C (92%); (k) DMSO, $(COCl)_2$, CH_2Cl_2; Et_3N, -50 °C → ρ.τ. (92%); (l) MeMgBr, $TiCl_4$.

1.[6] The ketone **1** showed very unusual spectroscopic characteristics. The chemical shift of the protons at the allylic position was recorded at δ=4.28 ppm which was far more down field shifted compared to the chemical shifts of normal methylene units in the other known compounds.[7] Slight change of the ring system to a [4.3.3.0]propellane compound showed the chemical shift of the same methylene protons moved back to δ=3.09 ppm.[8] This implied that the double bond could isomerize readily to the conjugate enone **8**. When the oxidation reaction of **7** was left for 30 minutes at room temperature in presence of triethylamine, only **8** was isolated without any trace of **1**. Comparison of the spectroscopic data of **8** with the reported ones[4] confirmed the structures of **1** and **8**. Though the exo olefin has high propensity of isomerization it was hoped that addition of a nucleophile to the ketone **1** could be faster than the isomerization. Otherwise, isomerization of the olefin before the methylation reaction would produce a mixture of regioisomeric products. When the ketone **1** was subjected to the *gem*-dimethylation condition, **1** produced modhephene with its regioisomeric product as well as **8**. Several attempts to minimize the

isomerization were not successful. Therefore the total synthesis of modhephene was accomplished through Curran's intermediate **8** that was directly prepared from **7** through standard Swern's oxidation[9] condition since the oxidation condition allowed the double bond isomerize during the base treatment step.

Currently, we are trying to find a way to prevent isomerization of the exo olefin of **1** to obtain a better regioselectivity of the methylation reaction.

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References

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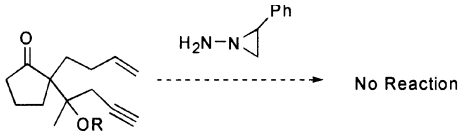
2. Lee, H. Y.; Kim, D. I.; Kim S. *J. Chem. Soc., Chem. Commun*. **1996**, 1539.
3. When another quarternary center was introduced to the cyclopentane ring, formation of the imine did not proceed at all.



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6. Spectral data of **1**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.04 (2H, t, *J*=1.47 Hz), 4.28 (2H, d, *J*=1.45 Hz), 2.04-1.24 (11H, m), 1.04 (3H, d, *J*=6.37 Hz); ^{13}C NMR (50MHz, $CDCl_3$) δ 212.3, 177.6, 129.8, 69.3, 68.0, 40.5, 40.1, 36.4, 36.1, 28.4, 25.3, 15.3; IR 1702, 1616, 1455, 1238, 755 cm^{-1}.
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