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A facile tandem radical cyclization route to propellanes and its application to a total synthesis of modhephene

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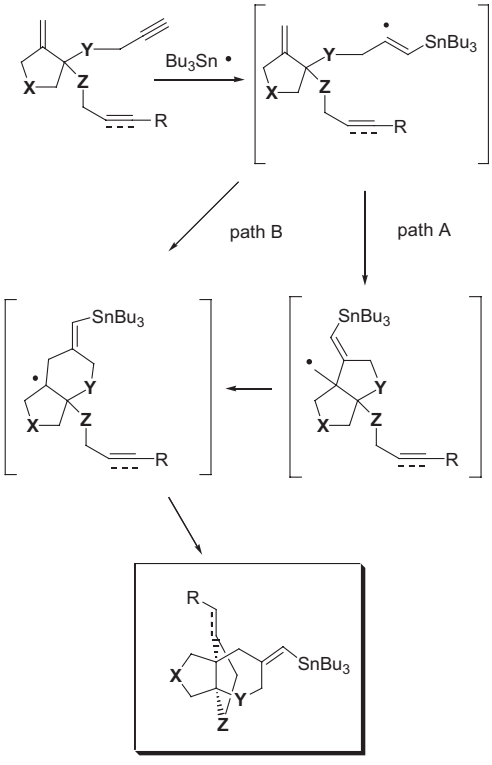
Abstract—A facile and versatile tandem radical cyclization route to propellanes from dieneyne compounds was developed and was applied to the total synthesis of modhephene.

Since the introduction of trialkyltin hydride mediated free radical reaction, radical cyclization has become one of the most powerful tools in organic synthesis[1] as the tandem cyclization could easily form complex polycyclic structures.[1d] Development of the vinyl radical cyclization reaction of 1-hexene-5-yne system with trialkyltin hydride offered even more attractive synthetic methodology for its simplicity and capability of further functionalization of the product.[2] Another unique feature of this radical cyclization reaction is the concentration-dependent formation of the *endo*-cyclization products through cyclopropyl methyl radical intermediates. As the result, exclusive formation of 6-*endo*-cyclization product was reported with 2-methyl-1-hexene-5-yne.[3] We envisioned that this exceptional *endo*-cyclization intermediate could further be utilized in the tandem radical cyclization reaction to form propellane structure of various ring sizes (Scheme 1).

The precursors for the radical reaction were prepared from cyclic β-keto esters through a straight forward synthetic route.[4] The radical cyclization was performed under the standard tin mediated radical cyclization reaction condition.[5] The destannylation and desilylation were accomplished by sequential treatment of the reaction mixture with SiO_2 and HCl. The result of tandem cyclization reaction was summarized in Table 1. As expected, *endo* cyclization proceeded smoothly to form the six-membered ring intermediates followed by the propellane formation (entries 1–3). *endo* Cyclization for the formation of the seven-membered rings also proceeded exclusively without the formation of *exo*-cyclization derived products (entries 3 and 6). When the



Scheme 1.

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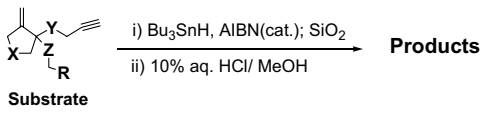
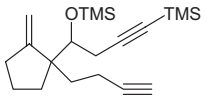
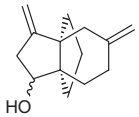
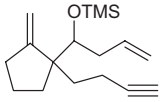
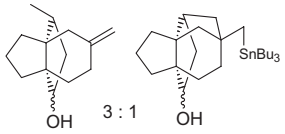
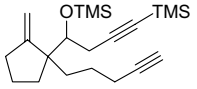
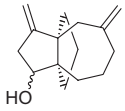
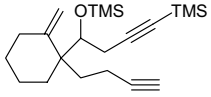
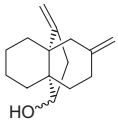
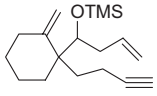
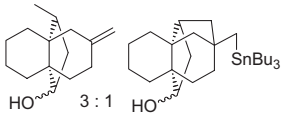
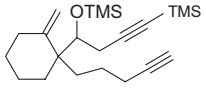
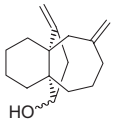
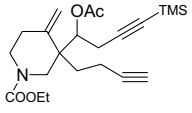
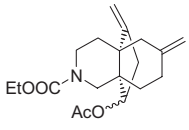
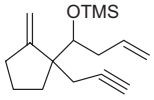
Table 1. Summary of the tandem radical cyclization reaction

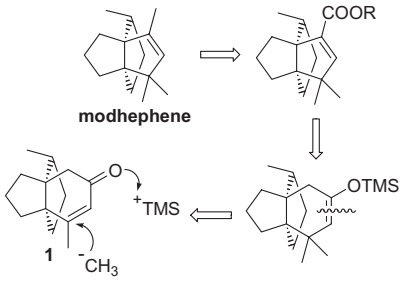


Entry	Substrate	Products	Yield (%)
1			76
2			82
3			51
4			62
5			65
6			42
7			90
8		No reaction	—

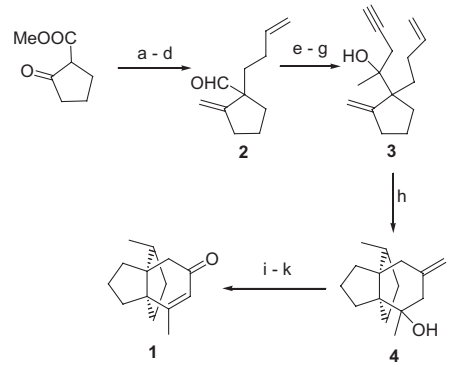
dienynes were subjected to the tandem cyclization reaction, unexpected tetracyclic compounds were obtained along with the desired propellane products (entries 2 and 5). These minor products were obtained from minor isomer of the second radical cyclization intermediates that has the methyl radical in close proximity of the vinyl group.

The current synthetic strategy also allowed the synthesis of a hetero-atom containing propellane without any difficulties (entry 7). When the butynyl chain was shortened to the propargyl group for the possible *endo* cyclization to form the [3.3.3]propellane structure, no cyclization reaction product was observed (entry 8). This result hinted that the overall *endo* cyclization during the first cyclization reaction, rearrangement of the initially formed *exo*-cyclization intermediate (path A in Scheme 1) could be the predominant pathway over the direct *endo* closure as the inability of the five-membered ring formation in the entry 8 could be due to the fact that the radical cyclization for the formation of cyclobutane ring through *exo* cyclization is not a favorable process.[6]

With the successful development of versatile methodology for propellane synthesis, we turned our attention to application of this methodology for the total synthesis of natural products. Modhephene and its derivatives[7] had been the only known natural products with propellane skeleton until new taxol derivatives were reported recently.[8] We chose modhephene as our initial target for the total synthesis.[9]



Scheme 2.



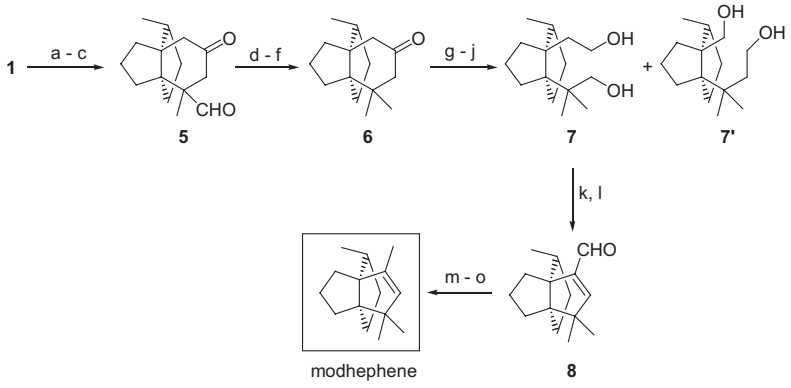
Scheme 3. Reagents and conditions: (a) 4-bromo-1-butene, K_2CO_3/DMF, 70%; (b) Ph_3PCH_3Br, *t*-BuOK/toluene, 92%; (c) LAH/Et_2O, 96%; (d) DMSO–$(COCl)_2$; Et_3N, 97%; (e) MeMgBr/Et_2O, 95%; (f) CrO_3-Pry./CH_2Cl_2, 96%; (g) TMS—≡—MgBr/Et_2O; TBAF/THF 92%; (h) Bu_3SnH, AIBN; SiO_2 70%; (i) OsO_4 (5 mol %), NMO/*t*-BuOH–H_2O–acetone; (j) $NaIO_4$/dioxane–H_2O, 78% for two steps; (k) MsCl, Et_3N/CH_2Cl_2, 87%.

Since the direct formation of [3.3.3]propellane structure of modhephene was not feasible through the current tandem radical cyclization reaction, the synthetic plan for modhephene started from the formation of [4.3.3]propellane structure, **1** that can be readily prepared from tandem radical cyclization reaction. For the synthesis of modhephene from **1**, 1,4-addition of methyl group to the conjugated enone with the trapping of the enolate intermediate as the silyl enolether followed by the ring contraction sequence through ozonolysis of the enol ether and subsequent intramolecular aldol condensation would furnish the modhephene structure (Scheme 2).

The synthesis of modhephene started from the synthesis of **1** from methyl cyclopentanone-2-carboxylate (Scheme 3). The keto-ester was butenylated and the keto-ester was converted into the olefinic aldehyde **2**. Propargyl group and a methyl group were introduced through treatment of the aldehyde of **2** with MeMgBr followed by oxidation of the alcohol product with CrO_3–pyridine to produce the ketone. TMS–propynyl magnesium bromide was added to the ketone and desilylation with TBAF afforded the radical cyclization reaction precursor **3** as a mixture of two diastereomers with equal amounts. As the relative stereochemistry of the tertiary alcohol in **3** was not deemed affecting the stereoselectivity of the tandem cyclization, **3** was used without separating the diastereomers. The crucial free radical cyclization reaction of **3** was performed under the general reaction conditions for tin hydride mediated vinylradical cyclization.

The desired propellane **4** was obtained in 70% yield after destannylation by SiO_2 with 10:1 ratio of methyl epimers.[10] Though we expected that the undesired minor isomer would undergo further cyclization to form a tetracyclic product in the same way as the example of entry 2 in Table 1, the third cyclization product of the minor isomer was not observed. Contrary to our expectation, the conformational difference during the cyclization reaction due to the difference in the substitution patterns affected the stereoselectivity and tandem reaction sequence. Dihydroxylation of **4** with catalytic OsO_4 and NMO followed by oxidative cleavage of resultant diol with $NaIO_4$ produced β-hydroxy-ketone and the resulting β-hydroxy-ketone was dehydrated into **1** using methanesulfonyl chloride and triethylamine.

With the propellane, **1** in hand, the total synthesis of modhephene was accomplished through modified



Scheme 4. Reagents and conditions: (a) Et_2AlCN/pentane, 85%; (b) ethyleneglycol, TsOH/benzene, 96%; (c) DIBAL/toluene; 1 N HCl, 86%; (d) LiAl(*t*-BuO)$_3$H/THF, 83%; (e) NaH, CS_2, MeI/THF 66%; (f) Bu_3SnH, AIBN/benzene, 84%; (g) TMSOTf, Et_3N/CH_2Cl_2; (h) O_3; PPh_3; HIO_4, 56% for two steps; (i) $TMSCHN_2$; (j) LAH/Et_2O, 63% for two steps; (k) DMSO–$(COCl)_2$; Et_3N; (l) AcOH-piperidine/benzene, 80% for two steps; (m) $NaBH_4$–$CeCl_3 7H_2O$/MeOH, 95%; (n) NaH, CS_2, MeI/THF, 71%; (o) Bu_3SnH, AIBN/benzene; TsOH/CH_2Cl_2, 65%.

sequence of reactions from the original plan in Scheme 2 (Scheme 4).[11] As the direct addition of the methyl anion to **1** was not fruitful, sterically less demanding cyanide was added to **1** using Et_2AlCN[12] and the nitrile was reduced to the desired methyl group. Protection of the ketone as the acetal with ethylene glycol followed by reduction of the resulting compound with DIBAL and deprotection of the acetal with HCl produced aldehydo-ketone **5**. Chemoselective reduction of the aldehyde of **5** with lithium tris-*tert*-butoxyaluminohydride[13] followed by deoxygenation of the alcohol[14] through the corresponding xantate formation and the subsequent reduction with tributyl tin hydride provided **6**. Since the ozonolysis of the corresponding silyl enolether of **6** produced the desired aldehydoacid along with the partially oxidized α-hydroxyketones, the reaction mixture was further oxidized with HIO_4 to complete the cleavage reaction and subsequent esterification followed by LAH reduction produced **7** and **7′** with the 2.5:1 ratio. The silyl enolether formation from **6** generated a mixture of regio-isomeric enol ethers with slight preference toward the desired one with 2.5:1 ratio that was transformed into **7** and **7′**. Diol **7** was oxidized to the corresponding dialdehyde using Swern's oxidation and intramolecular aldol condensation of the dialdehyde product using piperidino-acetate furnished the modhephene skeleton **8**. Finally, the aldehyde of **8** was reduced to the corresponding methyl group using the same protocol as the reduction of the aldehyde of **5** to yield modhephene with *epi*-modhephene as the minor product. Treatment of this mixture with acid produced isomerically pure modhephene.[15]

In summary, we developed a facile route to propellanes and demonstrated the versatility of the methodology through the total synthesis of modhephene.

Acknowledgements

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4. The cyclic β-keto ester was alkylated with a proper alkyl halide using K_2CO_3 in DMF and the ketone was transformed into the corresponding olefin using Ph_3PCH_2 through Wittig reaction. The remaining ester was converted into the aldehyde and reacted with propargylic or allylic Grignard reagents to provide the substrates for the radical reaction.
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10. The epimeric ratio of the cyclization products was determined by NMR after **4** was converted to **1**, since **4** was obtained as a mixture of four isomers not only at the methyl group but also at the alcohol containing carbon center, which made it difficult to determine the isomeric ratio of the reaction at that stage.
11. All the new compounds showed satisfactory spectroscopic data for the assigned structures. Spectral data of selected compounds; **1**, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (s, 1H), 2.43 (d, J = 16.1, 1H), 2.23 (d, J = 16.1, 1H), 2.00–1.93 (m, 1H), 1.91 (s, 3H), 1.75–1.60 (m, 8H), 1.39–1.28 (m, 1H), 1.25–1.19 (m, 1H), 0.91 (d, J = 6.5, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 166.5, 123.3, 57.5, 55.0, 45.1, 41.7, 39.2, 39.0, 34.3, 31.1, 23.9, 21.2, 13.6. IR (neat, cm^{-1}) 2952, 1670, 1622, 1455, 1378, 1273. HRMS: calculated for $C_{14}H_{20}O$: 204.1514, found: 204.1521. **6**, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (d, J = 17.9, 1H), 2.26 (d, J = 17.4, 1H), 2.23 (d, J = 17.9, 1H), 2.12–2.02 (m, 1H), 1.97 (d, J = 17.4, 1H), 1.58–1.50 (m, 4H), 1.37–1.30 (m, 6H), 1.00 (s, 3H), 0.91 (s, 3H), 0.83 (d, J = 6.4, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.1, 56.8, 54.6, 49.6, 47.4, 45.1, 37.8, 36.7, 36.5, 35.7, 30.2, 26.7, 25.9, 25.2, 13.0. **8**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H), 6.33 (s, 1H), 2.02–1.95 (m, 1H), 1.80–1.68 (m, 2H), 1.65–1.53 (m, 4H), 1.40–1.24 (m, 4H), 1.12 (d, J = 6.0, 3H), 1.11 (s, 6H). Synthetic modhephene, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (d, J = 1.3, 1H), 2.02–1.99 (m, 1H), 1.74–1.66 (m, 3H), 1.58 (d, J = 1.5, 3H), 1.45–0.98 (m, 7H), 0.97 (d, J = 6.4, 3H), 0.96 (s, 3H), 0.95 (s, 3H).
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