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Efficient synthesis of 8,11-dimethylene-bicyclo[5.3.1]undecan-2-one

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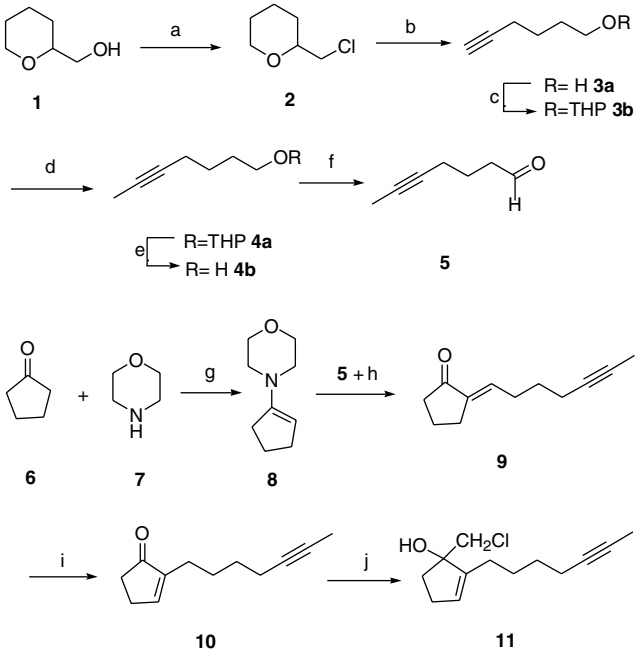
Abstract—We report here, an effective methodology for the preparation of 8,11-dimethylene-bicyclo[5.3.1]undecan-2-one. The key steps in these reactions were chloromethylation, cationic-alkyne cyclization and anionic fragmentation sequence.

The bicyclo[5.3.1]undecane ring system is a substructure of naturally occurring taxanes. Among them, the most prominent representative compound is taxol,[1] a clinically useful anti-cancer drug. Due to its therapeutic potential and its limited availability, enormous efforts have been directed towards the chemical synthesis of taxol in the past decade.[2] The construction of the AB-ring core of taxol, which involves the bicyclo[5.3.1]undecane moiety, is among the most challenging facets of the taxane synthesis and not yet practical. As a solution to the problem, some efficient methods for the construction of bicyclic undecanes have been developed recently.[3] We wish to report here, an efficient route for the construction of the AB-ring core with evident advantages of good yields and scaleable to larger quantities.

We start our effect from 2-hydroxymethyl-tetrahydro-pyran **1** (Scheme 1). An adaptation of the procedure used by Jones[4] to prepare tetrahydrofurfuryl chloride was used to prepare 2-chloromethyl-tetrahydro-pyran **2**. Whiting's double elimination was used to prepare 5-hexyn-1-ol **3a**. Dihydropyran protection and C-methylation of the 5-hexyn-1-ol **3a** gave the tetrahydropyranyl ether of 5-heptyl-1-ol **4a**, which was cleanly deprotected and then oxidized with PCC to give aldehyde **5** for the alkylation of the five-membered ring. The α,β-unsaturated ketone **9** was synthesized by aldol condensation of aldehyde **5** with enamine **8** made by the reaction of cyclopentanone **6** with morpholine **7**. Acid-catalyzed isomerization of the *exo*-methylenecyclopentanone **9** formed the cyclopentenone **10**, because the *endo*-double bond is thermodynamically more stable than the *exo*-double bond in the α,β-unsaturated five-membered



Scheme 1. Reagents and conditions: (a) $SOCl_2$, pyridine, 45 °C, 8 h, 65%; (b) (1) $NaNH_2$ (3 equiv)/NH_3(l); $Fe(NO_3)_3{\cdot}9H_2O$ (cat); (2) NH_4Cl, 85%; (c) DHP, H_3O^+; (d) $NaNH_2$ (3 equiv)/NH_3(l), $Fe(NO_3)_3{\cdot}9H_2O$ (cat); (2) CH_3I; (3) NH_4Cl, 69%; (e) *p*-toluenesulfonic acid, 98%; (f) PCC, CH_2Cl_2, 70%; (g) reflux in toulene, 77%; (h) (1) reflux in toluene; (2) 6 N HCl, 81%; (i) *n*-butanol, HCl (concd), reflux, 95 °C, 2 h, 75%; (j) *n*-BuLi, $ClCH_2I$, THF, ether, −100 °C, 95%.

Keywords: 8,11-Dimethylene-bicyclo[5.3.1]undecan-2-one; Chloromethylation; Cationic-alkyne cyclization; Anionic fragmentation.
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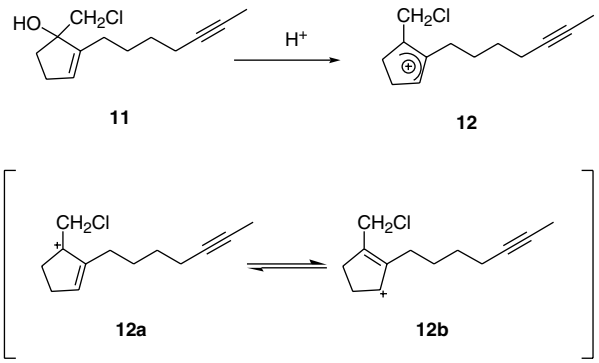
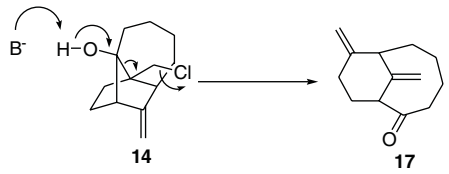


Scheme 2.

rings. The key step in Scheme 1 was the addition of chloromethyl lithium to the cyclopentenone **10** to form chlorohydrin **11**, which was crucial for the fragmentation reaction. We first adopted Sadhu and Matteson's method[5] to perform the chloromethylation reaction but it did not give the satisfied result. Upon further investigation, we found when the reaction temperature descended to −100 °C and the amount of base (*n*-BuLi) was no more than 1.5 equiv, the yield of the desired chlorohydrin **11**[6] was increased to 95%. The yield of the product was dramatically decreased when excessive base, longer reaction time and higher temperature (above −78 °C) were used.

With this cyclopentenol precursor **11** in hand, test for the feasibility of the proposed cationic-alkyne cyclization–anionic fragmentation strategy to form the bicyclo[5.3.1]undecane skeleton was undertaken. Cyclopentenol **11** can easily form an allyl-cation **12**, an equilibrium of **12a** and **b**, under an acidic condition (Scheme 2). We did not observe any cationic-alkyne cyclization products of **12b**, because the cation **12b** is less stable than the cation **12a**.

In our investigations of the cationic-alkyne cyclization of cationic **12a**, we found not only the *exo*-product **14** but also the *endo*-cyclization product, the 5,8-bicyclic compound **16** was formed. Massive optimization research shows that the sequential cyclization is a rapid reaction, and the tricyclic cation **13** is rapidly reacted with available nucleophiles. With proper acid, short reaction time and fast workup, we obtained **14**[7] as the sole product (Scheme 3).



Scheme 4.

The pre-settled chloromethyl group and the high energy of its strained structure can be relieved with ring opening, making compound **14** a good candidate for fragmentation to form the bicyclo[5.3.1]undecane ring. Good proton trapper and proper solvent system were found to be the best for conversion of the starting material to the desired product (Scheme 4).[8]

In summary, we have developed a methodology using a chloromethylation reaction, cationic-alkyne cyclization and anionic fragmentation sequence as key steps to synthesize the bicyclo[5.3.1]undecane ring system. With intensive experimentations, conditions for the last three reactions have been well established. Thus, a useful synthetic methodology with high expected yields and scaleable to larger quantities, is now available for further exploitation.

Acknowledgement

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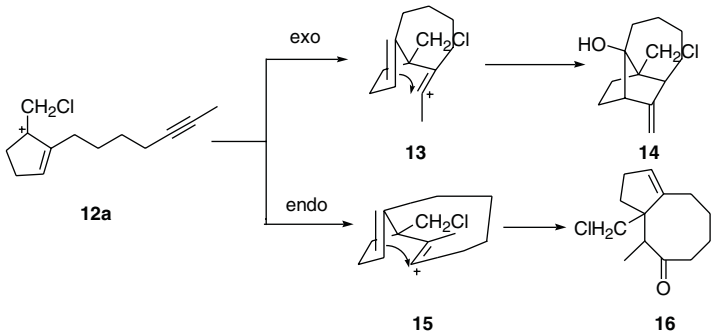

Scheme 3.

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6. Typical preparation of chlorohydrin **11** is described as follows: a solution of fleshly distilled 2-(5-heptynyl) cyclopent-2-enone **10** (0.352 g, 2 mmol) and iodochloromethane (0.512 g, 3 mmol) in 5 mL ethyl ether and 5 mL dry THF was cooled to −100 °C under argon. 1.5 mL *n*-BuLi (2.0 M in hexane, 3 mmol) was added dropwise over a period of 10 min. The mixture was allowed to set for another 10 min at −100 °C before quenched with 1 mL water. The mixture was treated with saturated ammonium chloride and extracted with ether. Dryness followed by purification via flash chromatography with *n*-hexane–EtOAc (4:1, v/v) as the eluent gave 0.43 g (95%) chlorohydrin **11**.
7. Typical preparation of 8-chloromethyl-2-hydroxy-11-methylene-tricyclo[5.3.1.0]undecane **14** is described as follows: to a solution of 100 mg chlorohydrin **11** in 2 mL ether, 30 mL trifluoroacetic acid was added at 0 °C with stirring. The mixture was neutralized with excess cold potassium carbonate solution within a minute and extracted with ether. Dryness followed by purification via flash chromatography with *n*-hexane–EtOAc (4:1, v/v) as the eluent gave 98 mg (98%) 8-chloromethyl-2-hydroxy-11-methylene-tricyclo[5.3.1.0]undecane **14**. Oil; ^{1}H NMR ($CDCl_3$) δ 4.92 (1H, d, $J = 2.4$ Hz), 4.72 (1H, d, $J = 2.4$ Hz), 3.92 (1H, d, $J = 11.2$ Hz), 3.74 (1H, d, $J = 11.2$ Hz), 2.59–2.55 (1H, m), 2.47–2.44 (1H, m), 1.24–2.20 (13H, m); ^{13}C NMR ($CDCl_3$) δ 157.8, 103.7, 85.5, 55.5, 54.0, 47.7, 46.6, 38.9, 34.9, 29.1, 28.1, 26.0, 22.9; MS *m*/*z* 226 (M^+, 100), 228 (M^++2, 33); IR ν_{max} 1623, 1470, 1411, 1095 (cm^{-1}). Elemental analysis calcd for $C_{13}H_{19}ClO$: C, 68.86; H, 8.45; Cl, 15.64. Found: C, 69.03; H, 8.51; Cl, 15.56.
8. Typical preparation of 8,11-dimethylene-bicyclo[5.3.1]-undecan-2-one **17** is described as follows: to a solution of 50 mg tricyclo[5.3.1.0]undecane **14** in 1.5 mL DMF, NaH (0.3 g) was added with stirring. After about 45 s, the mixture was neutralized with excess saturated ammonium chloride and extracted with hexane. Dryness followed by purification via flash chromatography with *n*-hexane–CH_2Cl_2 (4:1, v/v) as the eluent gave 41 mg (98%) 8,11-dimethylene-bicyclo[5.3.1]undecan-2-one **17**. Oil; ^{1}H NMR ($CDCl_3$) δ 5.12 (1H, d, $J = 1.4$ Hz), 5.04 (1H, d, $J = 1.4$ Hz), 4.64 (1H, d, $J = 2.0$ Hz), 4.56 (1H, d, $J = 2.0$ Hz), 3.05–3.02 (1H, m), 2.94–2.90 (2H, m), 2.44–2.54 (2H, m), 1.98–2.10 (2H, m), 1.21–1.86 (7H, m); ^{13}C NMR ($CDCl_3$) δ 195.9, 151.5, 147.6, 115.5, 107.4, 56.0, 54.5, 39.1, 32.1, 30.9, 29.7, 26.1, 24.2; MS *m*/*z* 190 (M^+, 100); IR ν_{max} 1711, 1627, 1466 (cm^{-1}). Elemental analysis calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.17; H, 9.58.