Chinese Chemical Letters Vol. 16, No. 3, pp 293-295, 2005 433
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# An Efficient Cationic Cyclization Approach for the Construction of Labdane Diterpenoid Decalin Ring Skeleton

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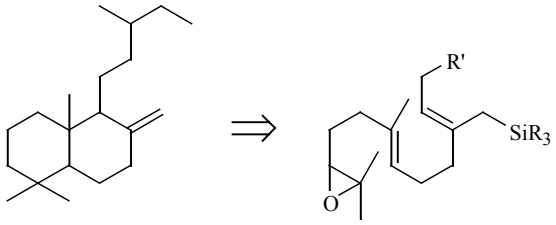
**Abstract:** An effective approach for the construction of the decalin ring skeleton of labdane diterpenoids was developed based on a key biomimetic cationic polyene cyclization of an epoxy allylsilane precursor. The synthetic approach demonstrated here would be useful in the enantioselective and diastereoselective total synthesis of natural labdane diterpenoids in general.

**Keywords:** Allylsilane, labdane skeleton, cationic cyclization, biomimetic synthesis.

A large number of labdane diterpenoids have been found in many medicinal plants, and they often exhibit a wide range of biological activities[1]. Although some studies[2] on the total synthesis of this class of natural diterpenoids have been reported over the past decades, the development of an efficient, stereocontrolled (both enantioselective and diastereoselective) general synthetic approach is still desirable. We disclose herein a synthetic approach for the stereocontrolled construction of the decalin skeleton **1** of labdanes possessing multiple hydroxyl functional groups based on a well-established biomimetic cationic ployene cyclization strategy (**Figure 1**)[3]. The epoxy allylsilane **2** was devised as the cyclization precursor by taking advantage of the allylsilane as effective terminating unit[4] of this sequential electrophilic polyene cyclization initiated by a Lewis acid-mediated epoxy ring-opening. This preliminary report demonstrated a novel general synthesis of the epoxy allylsilane **2** and the its cyclization.

**Figure 1**




Labdane **1** **2**

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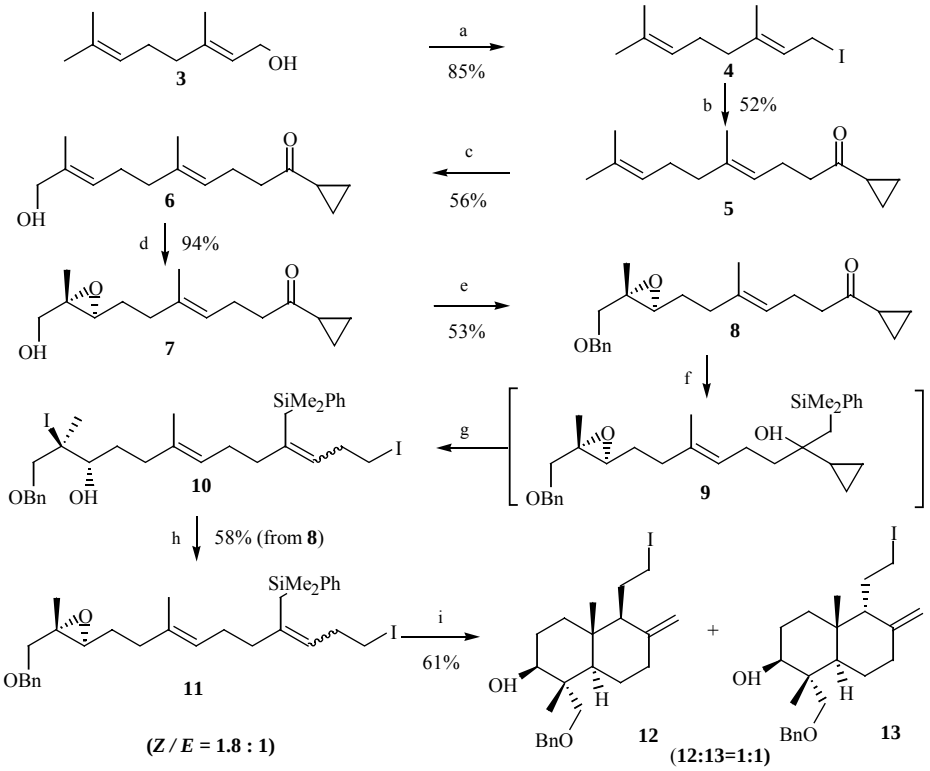
As outlined in **Scheme 1**, geranyl iodide **4** was alkylated (LDA, -78 ºC, THF) with cyclopropyl methyl ketone to give cyclopropyl ketone **5** in 52% yield, which was then hydroxylated ($SeO_2$, TBHP, $CH_2Cl_2$, r.t.) at the terminal olefin to afford the allylic alcohol **6** (56%). Standard Sharpless epoxidation of **6** with L-(+)-DET as chiral ligand followed by *O*-benzylation finished epoxy benzyl ether **8** (50% from **6**). (Dimethylphenylsilyl)methylcerium chloride was prepared from (dimethylphenylsilyl)-methylmagnesium chloride and freshly dried cerium (III) chloride , upon the addition of the epoxy ketone **8** to the above reagent at 0 ºC in THF and warmed to room temperature, the desired keto carbonyl adduct **9** was produced after neutral extractive workup, which without further purification on silica gel, was taken in anhydrous diethyl ether and treated with a freshly prepared solution of $MgI_2$ etherate (*ca*. 0.25 mol/L, 1:1 diethyl ether- benzene)[5] at 0ºC for 10 min to give the bis-iodo allylsilane **10**[6] after flash silica gel chromatography[7]. Brief treatment of the allylsilane **10** with $K_2CO_3$ in methanol at 0 ºC

**Scheme 1**

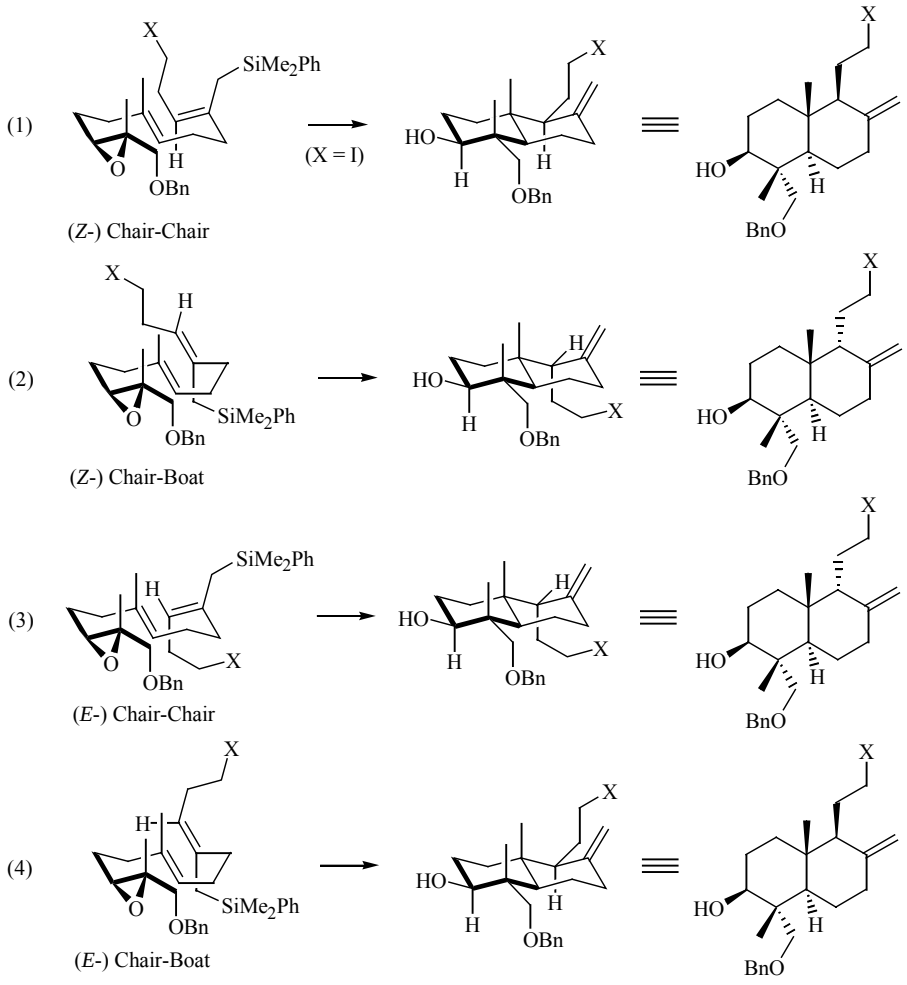



Reagents and conditions: a) $Ph_3P$, imidazole, $I_2$, $Et_2O$-$CH_3CN$, 0°C, 30 min, 85%; b) LDA, cyclopropyl methyl ketone, -78 °C, 30 min, then **4**, THF, -78 °C ~ rt., 52%; c) $SeO_2$, TBHP, $CH_2Cl_2$, rt., 2 h, 56%; d) $Ti(O^iPr)_4$, L-(+)-DET, TBHP, $CH_2Cl_2$, -20°C, 5h, 94%, 96%ee; e) NaH, BnBr, $Bu_4NI$, THF, rt., 1.5 h, 53%; f) $ClMgCH_2SiMe_2Ph$, $CeCl_3$, THF, 0 °C, 1 h; g) $MgI_2$•$(OEt_2)_n$, $Et_2O$, 0 °C, 15 min; h) $K_2CO_3$, MeOH, 0 °C, 30 min, 58% from **8**; i) $BF_3$•$OEt_2$, $CH_2Cl_2$, -78 °C, 15 min, 61%.

gave the epoxy allylsilane **11** as an inseparable mixture of geometric isomers (*Z/E* =1.8 : 1)[8] in 58% overall yield from epoxy ketone **8**. Exposure of the epoxy allylsilane **11** (mixture of isomers) to $BF_3$ etherate in $CH_2Cl_2$ at –78 ºC for 15 min and quenched with saturated aqueous sodium bicarbonate at -78 ºC finished the bicyclic product **12** and **13** (61%) as a mixture of two diastereomers (*ca.* 1:1), which were separable by normal phase HPLC (hexane-isopropanol 40:1). The structure of cyclized product **12** and **13** was fully characterized by spectroscopic analysis[9].

It is worthy to note that the diastereomeric ratio of the cyclization product **12** and **13** is scrambled in regards to the geometric ratio of epoxy allylsilane precursor **11**, which implies one of the solution conformations (chair-chair *vs.* chair-boat) for the cyclization slightly predominated over the other one (see **Equation 1-4**). Further work will be needed to address this interesting mechanistic aspect through the preparation (or separation) of geometrically pure isomers of precursor **11**.

**Equation 1-4**



In summary, the above-described synthetic strategy is suitable for the efficient assembly of the decalin skeleton of labdane diterpenoids in a stereocontrolled manner. A novel and effective synthesis of the designated epoxy allylsilane precursor **2** is critical for the success of this approach. Studies towards the total synthesis of typical labdane diterpenoids based on this method is underway in our Laboratory.

## Acknowledgments

We are grateful financial support from the National Outstanding Youth Fund (No. 29925204).

## Reference and Notes

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6. Similar epoxide ring-opening by the action of metal halide Lewis acids has been recorded, see: ref. 2a.
7. Detailed studies on this novel trisubstituted allylsilane synthesis was submitted as a separate publication elsewhere. For a general collection of synthetic methods of allylsilanes, see: E. W. Colvin, "*Silicon Reagents in Organic Synthesis*", Academic Press: New York, **1988**, 24-37.
8. The *Z*- and *E*-isomers were assigned by NOE experiments, and ratio was determined by $^1$H-NMR integration.
9. Spectral data: compound **12**: $[\alpha]_D^{20}$-52 (c 0.4, $CHCl_3$); IR: (KBr) ν 3372, 1081, 1062 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 300MHz, δ ppm): 7.34(m, 5H, ArH), 4.77, 4.68(s, 2H, $=CH_2$), 4.52 (dd, 2H, *J*=24, 12Hz, $OCH_2Ph$), 3.60(m, 1H, OCH), 3.48 (d, 1H, *J*=8.4Hz, OCH), 3.23 (d, 1H, *J*=8.4 Hz, OCH), 3.17(m, 1H, ICH), 2.86(dd, 1H, *J*=18, 8.2Hz, ICH), 2.18-1.12 (m, 12H, CH, $CH_2$), 0.96, 0.89(s, 6H, $CH_3$); $^{13}$C NMR ($CDCl_3$, 300MHz, δ ppm): 146.32, 137.90, 128.50, 127.78, 127.49, 111.28, 79.95, 73.56, 57.97, 42.02, 40.61, 37.48, 36.43, 33.91, 30.69, 30.42, 29.67, 26.37, 23.33, 22.46, 12.13, 6.01; HRMS(ESI) calcd. for $(M+H)^+$, 469.1598, found for $(M+H)^+$: 469.1601. Compound **13**: $[\alpha]_D^{20}$ 19 (c 0.2 $CHCl_3$); IR: (KBr) ν 3372, 1081, 1062 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 300MHz δ ppm): 7.33(m, 5H, ArH), 4.84, 4.47(s, 2H, $=CH_2$), 4.52 (dd, 2H, *J*=23.4, 12Hz, $OCH_2Ph$), 3.68(m, 1H, OCH), 3.49 (d, 1H, *J*=6.9Hz, OCH), 3.32(m, 1H, ICH), 3.23 (d, 1H, *J*=8.4Hz, OCH), 3.04(dd, 1H, *J*=16.2, 8.1Hz, ICH), 2.38-1.12 (m, 12H, CH, $CH_2$), 0.96, 0.71(s, 6H, $CH_3$); $^{13}$C NMR ($CDCl_3$, 300MHz, δ ppm): 146.72, 137.92, 131.93, 128.50, 127.80, 127.58, 106.69, 79.75, 73.61, 57.16, 49.28, 42.15, 40.61, 39.22, 37.65, 36.40, 29.68, 28.86, 26.63, 24.05, 15.09, 6.56; HRMS(ESI) calcd. for $(M+H)^+$, 469.1598, found for $(M+H)^+$: 469.1601.

Received 16 January, 2004