Chinese Chemical Letters Vol. 16, No. 11, pp 1445-1447, 2005 1445
http://www.imm.ac.cn/journal/ccl.html

Studies on the Synthesis of Morphinan Alkaloid: Preparation of the Key Allylic Silyl Ether Precursor

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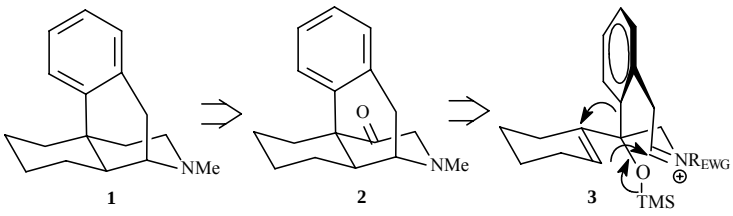
Abstract: A convergent strategy to the key allylic silyl ether precursor **4** in our synthetic efforts toward morphinan alkaloid is presented. The vital step is the selective 1,2-addition of the organocerium agent of **6** to ketene **5**.

Keywords: Morphinan alkaloid, Weinreb amide, cerium chloride, synthesis.

Morphinan alkaloid consisting of many diverse molecules has been attracting much attention of synthetic chemists because of their biologically significant activities and the intriguing structures[1]. As shown in the common nucleus **1** of these polycyclic frameworks, there is a unique quaternary carbon center with an aryl substituent representing a central synthetic challenge[2]. In connection with our constant investigations on the quaternary carbon chemistry[3], we proposed a general and conceptually new strategy based on the N-acyliminium induced semipinacol rearrangement[4] of the intermediate **3**, as shown briefly in **Scheme 1**. Herein, we wish to present the preparation of the key allylic silyl ether precursor **4** in our synthesis of this type of alkaloids.

Our retrosynthetic analysis is outlined in **Scheme 2**. We envisioned that this crucial precursor **4** could be obtained from the 1, 2-addition of organometallic reagent of

Scheme 1



1 **2** **3**

Nucleus of morphinan alkaloid

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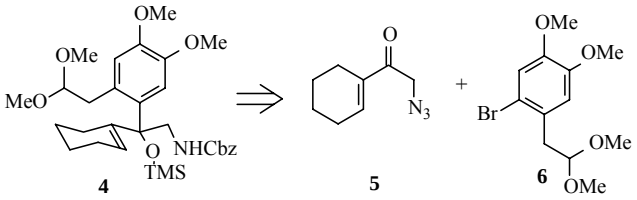
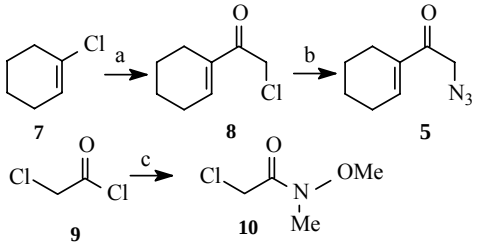
Scheme 2



Scheme 3



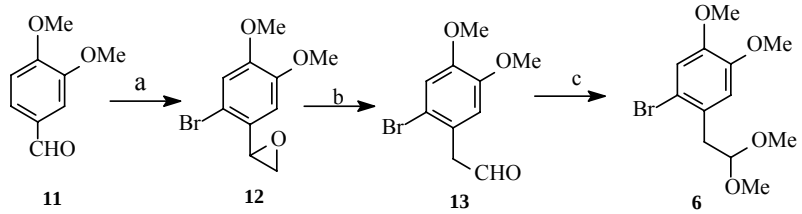
Conditions: a) Li, Et_2O, then **10**, 50%; b) NaN_3, DMF, 85%; c) N,N-dimethylaniline, HCl·NHMeOMe, CH_2Cl_2, 80%.

6 to ketene **5** and the subsequent functional transformations. In turn, these two compounds might be prepared easily from some simple and commercially available materials.

The starting point of the synthesis of **5** is cyclohexenyl chloride **7** (**Scheme 3**), which could be obtained from cyclohexanone in large scale according to the reported procedure[5]. The addition of vinyl lithium reagent of **7** to Weinreb amide **10** prepared from chloroacetyl chloride **9** and HCl·NHMeOMe gave rise to the ketene **8** in acceptable 50% yield[6]. And then, treatment of **8** with NaN_3 provided the desired compound **5** smoothly. The overall yield of this route is 34%.

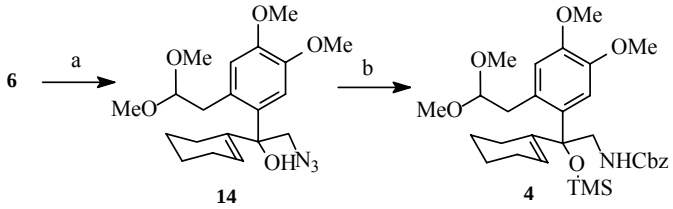
The synthesis of **6** was demonstrated in **Scheme 4**. Commencing with the commercially available 3, 4-dimethoxybenzaldehyde **11**, the epoxide **12** was furnished *via* the regioselective bromination[7] and Corey-Chaykovsky epoxidation[8]. And the subsequent BF_3·Et_2O-catalyzed rearrangement of the resulting epoxide afforded the aldehyde **13**. Finally, after acetalation of **13**, the acetal **6** was obtained in 60% overall yield *via* the above four steps.

Scheme 4



Conditions: a) i. Br_2, MeOH, then H_2O; ii. NaH, $(CH_3)_3S^+I^-$, DMSO, THF; b) BF_3·Et_2O, THF; c) $HC(OMe)_3$, MeOH, PTS. (60% overall yield in 4 steps)

Scheme 5



Conditions: a) *n*-BuLi, THF, then $CeCl_3$, **5**, 55%; b) i. TMSCl, Im, DMF; ii. Pd/C, H_2, MeOH; iii. CbzCl, Pyridinium, CH_2Cl_2. (80% overall yield in three steps)

With the desired segments of **6** and **5** in hand, the crucial 1, 2-additoion was investigated. Unfortunately, despite of the considerable efforts, ketene **5** is inert to the aryl lithium reagent of **6** from lithium-Br exchange with *n*-BuLi. We proposed that the ready enolation of **5** led to this failure and it is attributed to the organolithium reagent of **6** behaving more basic property than the corresponding nucleophilic property. So, the organocerium reagent of **6** generated from the exchange of its organolithium with anhydrous $CeCl_3$ was then utilized[9], which has the enhanced nucleophilic property and can activate the carbonyl group by the Lewis acidic characteristic of cerium. To our delight, the allylic alcohol **14** was formed successfully in 55% yield. *Via* the following three steps including: protection to silyl ether, reduction of azide group and amidation with CbzCl, **4** was afforded ultimately in 80% overall yield.

In summary, the preparation of the key precursor **4** in our synthesis of morphinan alkaloid was accomplished based on a convergent strategy. The further investigations on the designed N-acyliminium induced semipinacol rearrangement of **4** were ongoing in our group.

Acknowledgments

We are grateful for the financial support of the NNSFC (No., 30271488, 20021001, and 203900501).

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Received 28 February, 2005