Tetrahedron Letters 51 (2010) 1870–1872

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# First total synthesis of (+)-Carainterol A

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ARTICLE INFO

*Article history:*
Received 6 December 2009
Revised 29 January 2010
Accepted 1 February 2010
Available online 4 February 2010

ABSTRACT

The first, stereospecific, and elegant synthesis of the natural product (+)-Carainterol A was developed by using the Robinson annulation reaction as a key step to build the eudesmane skeleton.



Eudesmane sesquiterpenoids are a large group of compounds that are abundant in structural diverse terpenes. These natural sesquiterpenoids have a number of biological activities,[1] such as anti-HIV,[2] anti-inflammation, anti-Pyricularia oryzae P-2b, antibacterial, antioxidant, α-amylase inhibitory, and anti-ulcer[3] activities. (+)-Carainterol A (**1**, Fig. 1) is first isolated from the *Torilis japonica* fruit in 2002[4] and it contains three contiguous stereogenic centers and one neighboring stereogenic center. In our previous study, its diverse range of biological activities has been reported.[5] It is demonstrated that (+)-Carainterol A can increase glucose consumption in $C_2C_{12}$ cells with an IC value of 10.7 μg/ml. To the best of our knowledge, there are no reports concerning the synthesis of (+)-Carainterol A or its enantiomer Verticillatol.[2]

Although the interesting bioactivities associated with this class of compounds[6] prompt studies on the synthesis of the eudesmane,[7–11] the number of known successful strategies to construct those stereocenters is limited. The elegant enantioselective total synthesis of Dihydrojunenol (**2**) (Fig. 1) has been reported by Chen and Baran[12] Nevertheless, the strategies they employ are not exploitable for access to the substituent at C1 on the decalin skeleton with the correct configuration. A novel approach for the construction of (±) Balanitol (**3**) is developed by Li and co-workers,[13] but it does not allow for the assembly at C5. As described above, a stereocontrolled construction of the eudesmane skeleton with substituents at the various positions remains challenging. In our present study, the first total synthesis of (+)-Carainterol A had been accomplished. Moreover, the strategy we developed could introduce different groups at C1, C4, C5, or C7 to systematically explore the biological activities of (+)-Carainterol A and its analogues.

Our strategy for the synthesis of (+)-Carainterol A is outlined in Scheme 1. This synthetic strategy relied on the use of tertiary amine oxide at C4 as a masked exocyclic double bond.

We envisaged that an asymmetric epoxygenation at the olefins C5–C6 could arise by means of the adjacent β-isopropyl group and by the interaction between the α-amino group and mCPBA. The face selectivity of the introduction of the isopropyl group could result from the α-bulky group at C4 of **5**. The compound **5** could be obtained from a Mannich reaction at C4 of **6**, which would be derived from an asymmetric Robinson annulation of the monomethylate of the dione **7**,[14] followed by reduction of the ketone at C1 and protection of the hydroxyl. We considered that the stereocenters at C1 and C5 could be derived from the established configuration at the C10. Therefore, the pivotal control element in this strategy would be the establishment of a C7 stereocenter and we sought to develop an efficient and selective means for assembling this moiety.

The synthetic procedure for compound **5** is described in Scheme 2. The intermediate **8**, which had been widely used in the synthesis of terpenoids and steroids, was synthesized from the starting material **7** by monomethylation, followed by an asymmetric process promoted by D-(+)-proline[14] (Scheme 2). The key Robinson

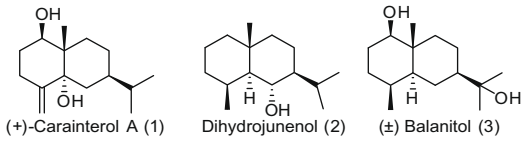
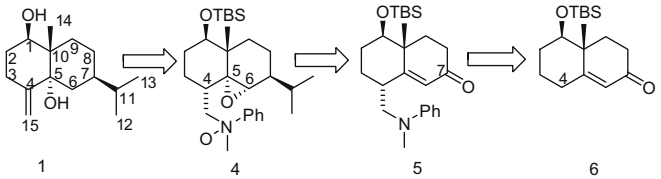



**Figure 1.** Representative eudesmane sesquiterpenoids.




**Scheme 1.** Retrosynthetic analysis of (+)-Carainterol A.

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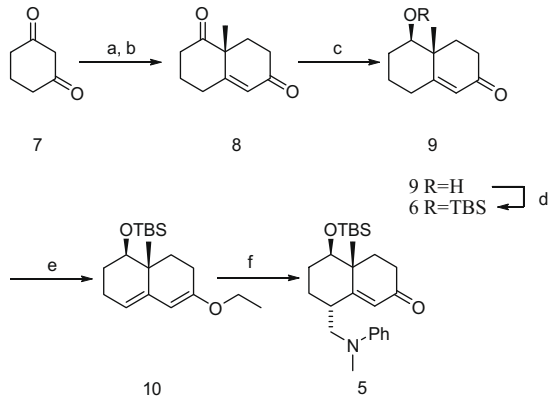
doi:10.1016/j.tetlet.2010.02.001




**Scheme 2.** Synthesis of **5**. Reagent and conditions: (a) NaOH, MeI, 10 h, 60%; (b) MVK, D-(+)-Proline, DMSO, 24 h, 65%; (c) $NaBH_4$, EtOH, 95%; (d) TBSCl, imidazole, DMF, 80%; (e) TsOH, $CH(OEt)_3$, THF, 95%; and (f) *N*-methylaniline, 40% $CH_2O$, EtOAc, 70%.

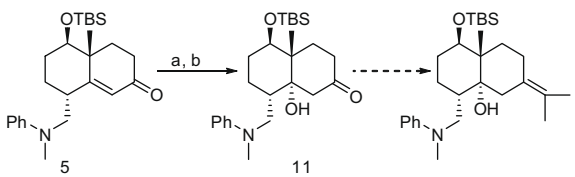
annulation allowed us to build a decalin skeleton with desired C10 quaternary stereocenter.

The angular methyl group at C10 of **8** offered a considerable steric hindrance from the β-face of the decalin. This inherent bias inflicted the facial selectivity, allowing for the reduction at the α-face of the ketone. Thus the reduction of **8** smoothly afforded **9** with the desired β configuration of hydroxyl.[15] We envisioned that the introduction of a bulky protective group at the β-hydroxyl could govern the attack of cationic carbon from the opposite face in the Mannich reaction. The protection of the hydroxyl at C1 of **9** was achieved by using a large excess of TBSCl and imidazole without elimination of the hydroxyl.[16]

At the next stage of the synthesis, conversion of enone **6** to dienol **10** paved the way for the introduction of a Mannich base at C4. After the substantial experimentations, it was subsequently found that the Mannich reaction could be best performed at 0 °C to provide **5** with 3:1 diastereoselectivity.[17,18]

The angular α-hydroxyl at C5 of **11** was derived from the olefins C5–C6 through epoxygenation, followed by reduction with organoselenium reagent phenylselenide anion ($PhSe^-$)[19] (Scheme 3). With the route to **11** having been secured, efforts were then directed toward the introduction of the C7 isopropyl group. At the onset of this synthetic endeavor, it was perceivable that the Wittig reaction should serve as an effective means for the construction of a C–C double bond at C7, followed by the catalytic hydrogenation. Unfortunately, it failed to undergo the Wittig reaction without the problematic elimination. Moreover, every attempt to protect the angular hydroxyl at C5 with various groups was troublesome.

For this transformation,[20,21] our studies were enlightened by those of de Groot and Wijnberg,[22] who employed $CeCl_3$ as a Lewis acid catalyst to introduce an isopropyl group, as well as the establishment of the C7 stereocenter with the desired configuration. We reasoned that the favored equatorial conformation might account for the facial selectivity. Therefore, the introduction of the isopropyl group to **5** at C7 was satisfactorily accomplished in 70% yield of **12** by using *i*-PrMgCl/$CeCl_3$ at −30 °C with moderate diastereoselectivity (4:1) by HPLC (Scheme 4).




**Scheme 3.** Synthesis of **11**. Reagent and conditions: (a) 50% $H_2O_2$, NaOH, EtOH and (b). $NaBH_4$, $(PhSe)_2$, EtOH.

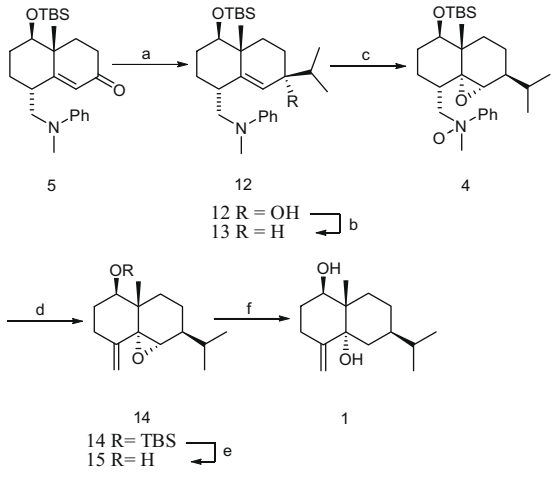
With **12** in hand, we started to explore the feasibility of the C–O bond cleavage at C7. Originally we assumed that **13** could be accessed with esterification of the hydroxyl at C7, followed by reduction with $LiAlH_4$. However, the esterification of the tertiary alcohol failed to afford the desired product presumably due to the steric hindrance of the adjacent isopropyl group at C7. The reported reduction[23–25] from tertiary alcohol to alkane with $ZnI_2$–$NaCNBH_3$ prompted us to investigate similar reaction with **12**. Nevertheless, several conditions provided intractable mixtures with no desired product. This result might be attributed to the formation of the B–N complex. Fortunately, **13** was achieved upon treatment of **12** with $AlCl_3$–$LiAlH_4$ at 0 °C with no isomerized by-product being formed.

We have now advanced to the stage for the completion of the total synthesis of (+)-Carainterol A. To this end, the directed epoxygenation of **13** was accomplished by using mCPBA to afford the epoxide **4** with diastereoselectivity (9:1 by GC) accompanied by the tertiary amine group being simultaneously converted to the N-oxide.[26] The N-oxide group of **4** was used as a handle on the introduction of the exocyclic double bond. Subsequent elimination of the N-oxide of **4** to form the exocyclic double bond was performed in a mild condition without opening of the epoxy ring.

The configuration of C7 at **14** was confirmed by means of NOESY experiments, which indicated a strong cross-peak connecting the C10 methyl group with the C7 isopropyl group. The signal for H-6 in the epoxide **14** was a singlet. Molecular models we established indicated that the dihedral angle of H-6 and H-7 was near to 90°. Therefore, the epoxy group was in the α-face.

Upon treatment with TBAF, **14** was easily transformed into its free alcohol. The opening of the epoxide with the cleavage of the C–O bond at the less hindered secondary carbon led to the target molecule **1**. All the spectral data of the synthetic (+)-Carainterol A were identical to those of the authentic isolated natural product.[4,5]

In summary, an efficient route to synthesize (+)-Carainterol A had been established in 12 steps with an overall yield of 4.5%. The approach reported herein also could be adapted for the enantioselective synthesis of Verticillatol, the enantiomer of (+)-Carainterol.[2] Due to the flexibility of our approach, the synthesis of additional eudesmanes from the intermediates reported in our synthetic route could be achieved.




**Scheme 4.** Synthesis of (+)-Carainterol A. Reagent and conditions: (a) *i*-PrMgCl, $CeCl_3$, THF, 70%; (b) $AlCl_3$, $LiAlH_4$, THF, 88%; (c) mCPBA, $CH_2Cl_2$, 75%; (d) 10% NaOH, $H_2O$, 78%; (e) TBAF, THF, 90%; and (f) $LiAlH_4$, THF, 70%.

## Acknowledgment

This research is supported by National Science Foundation of China (30672511).

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.001.

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