

# An approach to the synthesis of CP-263,114: complementary routes to the bicyclic ring system via two kinds of fragmentation reaction

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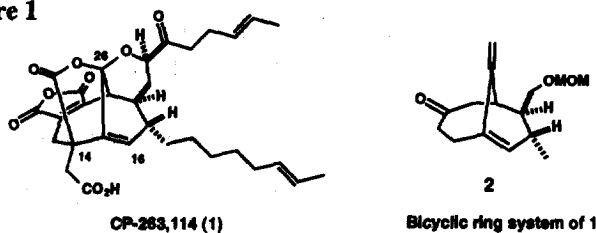
## Abstract

Two complementary methods for the construction of the ring system of CP-263,114 (1), one relying on the Grob fragmentation reaction and the other on a sequential photolytic alkoxy radical fragmentation-reduction, are described. © 1999 Elsevier Science Ltd. All rights reserved.

**Keywords:** Bicyclic aliphatic compounds; Fragmentation reactions; Olefination; Photochemistry

CP-263,114 (1), a novel inhibitor of ras farnesyl transferase and squalene synthase which are medicinal targets of great interest, was recently isolated by the Pfizer research group (Figure 1) [1,2]. Both its biological significance and highly oxygenated molecular architecture, which consists of the bridgehead double bond and the quaternary stereocenter embedded in bicyclo[4.3.1]dec-1(9)-ene system, have attracted much interest in synthetic studies on complex natural products [3-13]. We wish to disclose herein a new route to the synthesis of the bicyclic ring system of 1. Our approach features a reductive cyclization of the

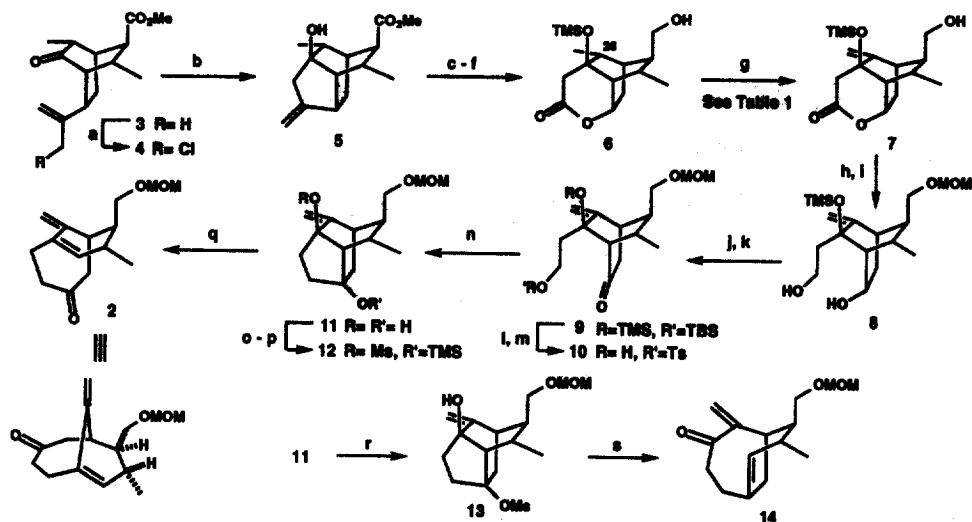
Figure 1



chiral bicyclic compound 4, a novel olefination via intramolecular photolytic alkoxy radical functionalization of 6, and fragmentation reaction of the tricyclic intermediates prepared through tosylate-carbonyl coupling reaction. The fragmentation reaction involves two types: either the Grob reaction of 12 or the sequential photolytic alkoxy radical fragmentation-reduction of 17 furnished the bicyclic framework of 1.

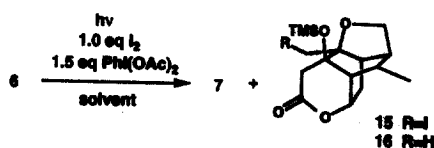
The synthesis started with the known chiral bicyclo[2.2.2]octane derivative 3 [14,15] prepared by sequential Michael reaction of (*S*)-carvone with methyl crotonate (Scheme 1).

## Scheme 1



Reagents and conditions: (a)  $\text{Ca}(\text{OCl})_2$ , as,  $\text{CH}_2\text{Cl}_2$ , rt, 81%; (b)  $\text{SmI}_2$ , HMPA, THF,  $0^\circ\text{C}$ , 72%; (c) TMSOTf,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ -rt, 81%; (d) LAH, THF,  $0^\circ\text{C}$ , 99%; (e)  $\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , then  $\text{Ph}_2\text{P}$ ,  $-78^\circ\text{C}$ -rt, 94%; (f) MCPBA,  $\text{Na}_2\text{HPO}_4$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 96%; (g) hv (180W tungsten lamp),  $\text{I}_2$ , BDA, benzene,  $0^\circ\text{C}$ , 69%; (h)  $\text{Mg}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ -rt, 97%; (i) TBSCl,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ -rt, 99%; (j) TPAP, NMO, DMSO, rt, 98%; (k) TBAP, THF, rt, 100%; (l)  $\text{YbCl}_4$ ,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ -rt, 97%; (m)  $\text{SmI}_2$ , HMPA, THF,  $-78^\circ\text{C}$ - $20^\circ\text{C}$ , 84%; (n) TBSCl,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 61%; (o)  $\text{MeCl}$ ,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ -rt, 98%; (p) TBAP, THF,  $0^\circ\text{C}$ , then NaH, 18-Crown-5,  $0^\circ\text{C}$ -rt, 92% (2 steps); (r)  $\text{MeCl}$ ,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ - $0^\circ\text{C}$ ; (s) NaH, THF, 18-Crown-5,  $0^\circ\text{C}$ -rt, 48% (2 steps).

Allylic chlorination [16] of 3 followed by reductive cyclization mediated by  $\text{SmI}_2$  in the presence of HMPA [17-19] afforded the tricyclic compound 5 having tertiary hydroxy functionality which would be necessary for the fragmentation reaction. After protection of the hydroxy group as a trimethylsilyl (TMS) ether, ozonization followed by Baeyer-Villiger oxidation with MCPBA gave lactone 6. It was envisioned that the oxygen functionality of CP-263,114 (1) at C26 could be elaborated via intramolecular alkoxy radical functionalization of 6. The photo-initiated functionalization of 6 under the Suarez conditions [20-22], however, afforded unexpected olefin 7, iodoether 15 which could be converted to 7 by treatment with Zn, and ether 16 in moderate to good yields (Table 1) [23].

Table 1 Intramolecular alkoxy radical functionalization of 6<sup>a</sup>

entry	solvents	time (min)	yield (%)		
			7	15	16
1	Benzene- <i>o</i> -hexane (1:3)	40	21	36	36
2	Benzene	30	68	12	8
3	$\text{CH}_2\text{Cl}_2$	15	9	48	12

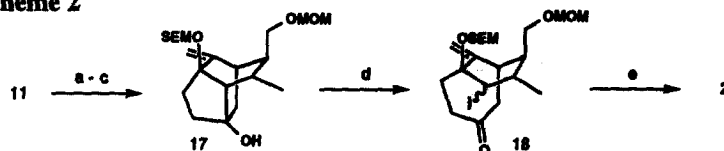
<sup>a</sup> The reaction was carried out at  $0$ - $5^\circ\text{C}$  with irradiation by visible light (180W tungsten lamp).

The conversion of olefin 7 into the key intermediate diol 11 was accomplished as follows. Thus, 7 was converted to MOM ether which was then reduced with LAH in refluxing 1,4-dioxane to provide diol 8. Selective protection of the primary hydroxy group with TBSCl, followed by oxidation of the secondary alcohol with TPAP, afforded 9. The ketone

was then treated with TBAF to give a diol, tosylation of which furnished **10**. A reductive cyclization of **10**, leading to diol **11**, was achieved in good yield by the use of  $\text{SmI}_2$  in the presence of HMPA [18]. With this key intermediate **11** in hand, we first examined the Grob fragmentation reaction [24,25] for the construction of the bicyclic ring system bearing the bridgehead olefin. The fragmentation reaction required an activation of the allylic hydroxy group of diol **11**. Although the task seemed to be easily achieved by regioselective mesylation of the less hindered hydroxy group, the reaction unexpectedly provided a regio-isomer **13** whose structure was unambiguously confirmed by the conversion into enone **14** via fragmentation reaction [26]. This problem was solved by the following sequence. Thus, **11** was selectively converted to a mono-TMS ether which, upon mesylation, afforded **12**. The Grob fragmentation of mesylate **12** was achieved by removal of the TMS group with TBAF, followed by treatment of the resultant alcohol with NaH in the presence of 15-Crown-5 to furnish the bicyclic compound **2** consisting of bicyclo[4.3.1]dec-1(9)-ene quantitatively [27].

While this strategy rendered the bicyclic ring system available, it was envisaged that an alternative route to the ring system of **1** under nonbasic conditions would allow greater flexibility in the synthetic design of this target molecule. Thus, a photolytic ring cleavage [28-32] of alcohol **17** followed by removal of the  $\beta$ -haloether functionality [33], providing the diene **2**, was next evaluated (Scheme 2). Alcohol **17**, derived from **11** in 54% overall

Scheme 2



Reagents and conditions: (a) TMSCl,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 61%; (b) SEMCl,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ –rt–reflux; (c) TBAF, THF,  $0^\circ\text{C}$ , over 2 steps, 90%; (d) hv,  $I_2$ , IBDA,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ; (e) Zn, AcOH, MeOH, rt, **2** (32% from **17**), **17** (46%).

yield, was irradiated with visible light in the presence of iodobenzenediacetate (IBDA) and iodine [30] to give iodo ketone **18** as a diastereomixture (ca. 1 : 4) containing an unidentified byproduct. This inseparable mixture was then treated with zinc-acetic acid in MeOH to provide **2** along with **17**, which could be recycled, in moderate yield. Although the yield of this route remains to be improved, it should be noted that this method leading to bicyclo[4.3.1]dec-1(9)-ene **2** is highly feasible because of its applicability to base-sensitive substrates.

In summary, we have developed a new route to the bicyclic ring system of **1**. The strategy features either the Grob fragmentation reaction or the sequential photolytic alkoxy radical fragmentation-reduction to furnish the bicyclic ring system **2** consisting of bicyclo[4.3.1]dec-1(9)-ene. In the course of this synthetic study, we also found a useful olefination via intramolecular photolytic alkoxy radical functionalization under the Suarez conditions. The strategy disclosed herein has now been applied to asymmetric total synthesis of CP-263,114 (**1**) and the results will be reported in due course.

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- [27] Data of 2:  $[\alpha]_D^{25}$  -126.8° (c 0.139, CHCl<sub>3</sub>); IR (neat) 1701 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.34 (d, *J*=3.7 Hz, 1H), 5.03 (s, 1H), 4.93 (d, *J*=1.5 Hz, 1H), 4.64 (d, *J*=6.4 Hz, 1H), 4.61 (d, *J*=6.7 Hz, 1H), 3.55 (dd, *J*=9.7, 4.0 Hz, 1H), 3.42 (dd, *J*=9.7, 8.2 Hz, 1H), 3.38 (s, 3H), 2.85 (ddd, *J*=7.6, 2.7, 2.4 Hz, 1H), 2.81-2.76 (m, 1H), 2.62 (ddd, *J*=11.3, 7.9, 0.6 Hz, 1H), 2.55-2.51 (m, 1H), 2.37-2.31 (m, 2H), 2.24 (ddd, *J*=12.5, 2.7, 0.9 Hz, 1H), 1.80-1.73 (m, 1H), 1.41-1.36 (m, 1H), 1.08 (d, *J*=7.0 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 211.9, 148.0, 139.5, 132.7, 108.4, 96.6, 69.5, 55.3, 53.7, 50.4, 44.7, 42.6, 31.4, 29.5, 18.9; HRMS *m/z* calcd for C<sub>15</sub>H<sub>22</sub>O<sub>3</sub> (M<sup>+</sup>): 250.1570, found: 250.1569.
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