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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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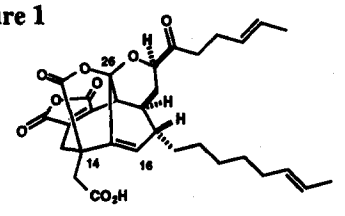
Abstract

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.

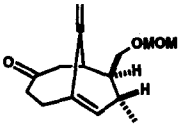
Keywords: Bicyclic aliphatic compounds; Fragmentation reactions; Olefination; Photochemistry

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



CP-263,114 (1)



2

Bicyclic ring system of 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).

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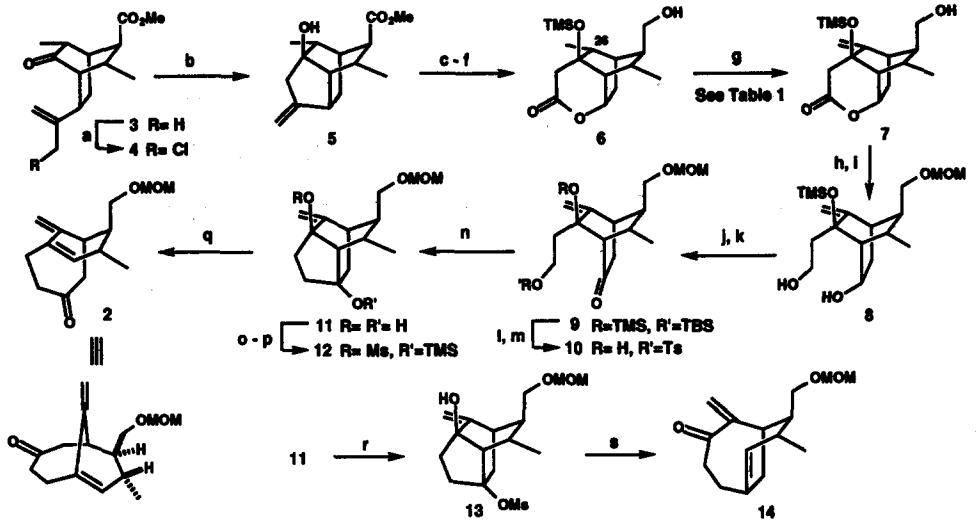
PII: S0040-4039(99)00941-7

Scheme 1



Reagents and conditions: (a) $Ca(OCl)_2$, aq. CH_2Cl_2, rt, 81%; (b) SmI_2, HMPA, THF, 0°C, 72%; (c) TMSOTf, Et_3N, CH_2Cl_2, -78°C–rt, 81%; (d) LAH, THF, 0°C, 98%; (e) O_3, CH_2Cl_2, -78°C, then Ph_3P, -78°C–rt, 94%; (f) mCPBA, Na_2HPO_4, CH_2Cl_2, rt, 99%; (g) hv (150W tungsten lamp), I_2, IBDA, benzene, 0°C, 68%; (h) MOMCl, *i*PrNEt, CH_2Cl_2, 0°C–rt, 85%; (i) LAH, dioxane, reflux, 97%; (j) TBSCl, Et_3N, CH_2Cl_2, 0°C–rt, 66%; (k) TPAP, NMO, MeCN, rt, 98%; (l) TBAF, THF, rt, 100%; (m) TsCl, Et_3N, DMAP, CH_2Cl_2, 0°C–rt, 97%; (n) SmI_2, HMPA, THF, -78°C–-20°C, 84%; (o) TMSCl, Et_3N, DMAP, CH_2Cl_2, -78°C, 61%; (p) MsCl, Et_3N, DMAP, CH_2Cl_2, -78°C–rt, 94%; (q) TBAF, THF, 0°C, then NaH, 15-Crown-5, 0°C–rt, 92% (2 steps); (r) MsCl, Et_3N, DMAP, CH_2Cl_2, -78°C–0°C; (s) NaH, THF, 15-Crown-5, 0°C–rt, 45% (2 steps).

Allylic chlorination [16] of **3** followed by reductive cyclization mediated by 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].

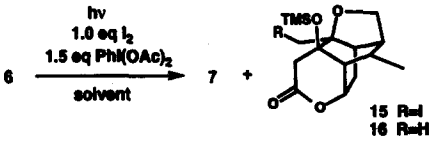


Table 1 Intramolecular alkoxy radical functionalization of 6[a]

entry	solvents	time (min)	yield (%) 7	15	16
1	Benzene-*c*-hexane (1 : 3)	40	21	36	36
2	Benzene	30	68	12	8
3	CH_2CH_2	15	9	48	12

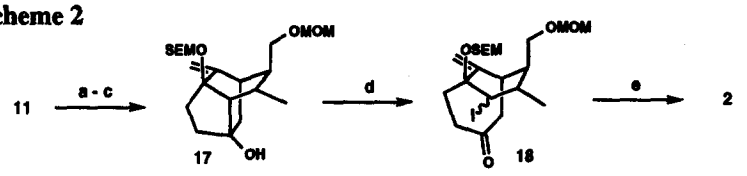
[a] The reaction was carried out at 0-5°C with irradiation by visible light (150W tungsten lamp).

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 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 β-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, Et_3N, DMAP, CH_2Cl_2, -78°C, 61%; (b) SEMCl, Et_3N, DMAP, CH_2Cl_2, 0°C~rt~reflux; (c) TBAF, THF, 0°C, over 2 steps, 90%; (d) hv, I_2, IBDA, CH_2Cl_2, 0°C; (e) Zn, AcOH, MeOH, rt, 2 (32% from 17), 17 (40%).

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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[26] Data of **14**: $[\alpha]^{25}_{D}$ -56.9° (c 0.049, $CHCl_3$); IR (neat) 1688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (d, *J*=6.6 Hz, 1H), 5.37 (d, *J*=2.0 Hz, 1H), 5.12 (m, 1H), 4.62 (d, *J*=6.2 Hz, 1H), 4.59 (d, *J*=6.2 Hz, 1H), 3.37 (s, 3H), 3.38-3.30 (m, 3H), 3.01-2.90 (m, 1H), 2.50-2.41 (m, 4H), 2.26 (d, *J*=13.4 Hz, 1H), 1.98-1.89 (m, 1H), 1.76-1.69 (m, 1H), 1.11 (d, *J*=7.2 Hz, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 207.2, 153.7, 137.2, 130.2, 120.6, 96.7, 69.5, 55.5, 49.8, 43.3, 39.6, 32.6, 32.5, 31.3, 21.9; HRMS m/z calcd for $C_{15}H_{22}O_3$ (M^+): 250.1570, found: 250.1572.

[27] Data of **2**: $[\alpha]^{25}_{D}$ -126.8° (c 0.139, $CHCl_3$); IR (neat) 1701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{15}H_{22}O_3$ (M^+): 250.1570, found: 250.1569.

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