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Asymmetric Synthesis of the Core Structure of (−)-CP-263,114

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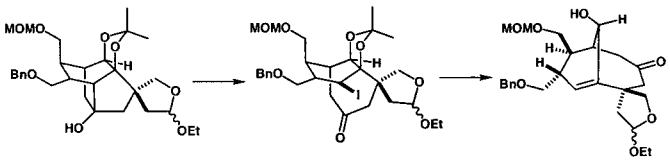
ABSTRACT



The enantioselective construction of a fully functionalized core structure of (−)-CP-263,114 (1), containing most of the required functionality for total synthesis, was conducted through sequential radical fragmentation−reductive olefination.

CP-263,114 (**1**) has been found a most challenging target compound for natural product synthesis in recent years (Figure 1).[1]

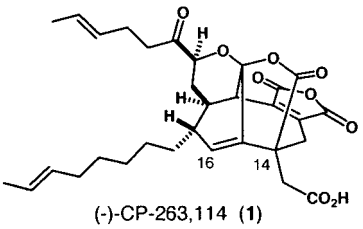


Figure 1.

The highly functionalized molecular architecture and biological significance of the CP molecule have stimulated considerable effort toward establishing routes for the total synthesis of this natural product.[2,3] We have developed two complementary methods for synthesizing a bicyclic ring model of **1**, one involving Grob fragmentation and the other,

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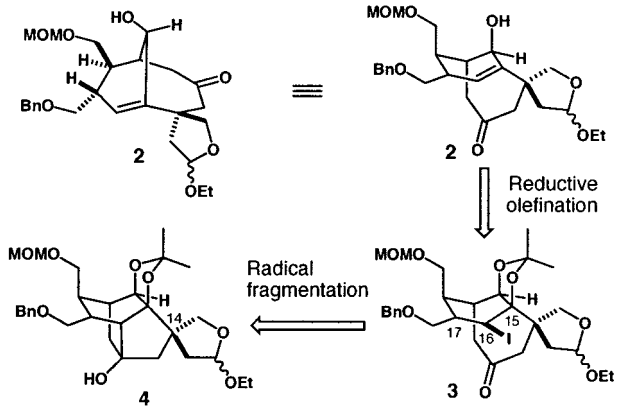
sequential radical fragmentation−reductive olefination.[4,5] The latter, using radical ring cleavage followed by reductive olefination to obtain the keto olefin, has been found an effective alternative to ionic fragmentation reaction usually requiring harsh conditions. The method has the following features: (1) applicability to base- or acid-sensitive substrates and (2) no requirement for conversion of alcohol intermediates to activated ones with leaving groups such as methanesulfonates and halides.

In the present study, the enantioselective construction of the fully functionalized core structure of natural (−)-**1** was accomplished by this method and is thus shown an effective means for the synthesis of CP-263,114 (**1**) (Scheme 1).

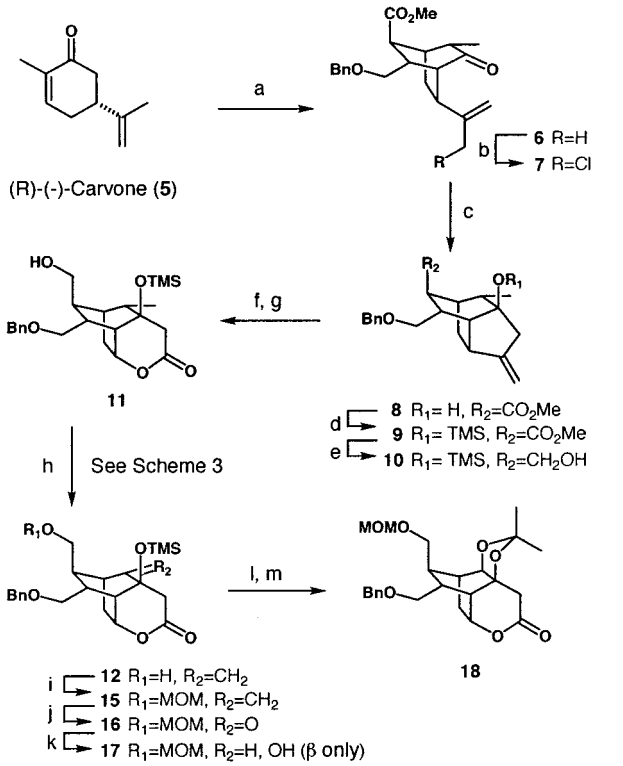
Scheme 1. Key Reaction for Constructing Core Structure of **1**



As the first step in the synthesis, bicyclic compound **6** was prepared by sequential Michael addition reaction of (*R*)-(−)-carvone (**5**) with α,*β*-unsaturated ester (Scheme 2). The allylic chlorination of **6** with $Ca(OCl)_2$ afforded **7**, which was cyclized with SmI_2 in the presence of HMPA to give tricyclic alcohol **8**. The silylation of **8** with TMSOTf and Et_3N gave **9**, which was then reduced with LAH to provide alcohol **10**. Following oxidative manipulation involving ozonolysis and Baeyer−Villiger oxidation with mCPBA, lactone **11** was obtained in 90% yield.

Photolytic olefination reaction of alcohol **11**, previously developed in our laboratory, led to the desired olefin **12**, iodo ether **13**, and cyclic ether **14** in moderate yields (Scheme 3).[6] The reduction of iodo ether **13** with Zn in the presence of acetic acid provided olefin **12**, thereby producing olefin **12** in 49% combined yield from **11**. Subsequent protection

Scheme 2[a]

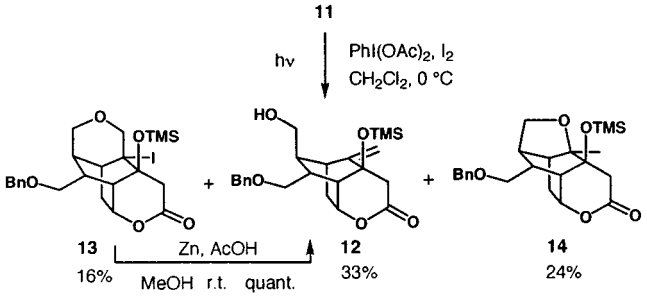


[a] Reagents: (a) LDA, (*E*)-methyl 4-benzyloxycrotonate, THF, −78 °C to rt, 65%; (b) $Ca(OCl)_2$, aq CH_2Cl_2, rt, 74%; (c) SmI_2, HMPA, THF, −78 °C; (d) TMSOTf, Et_3N, CH_2Cl_2, −78 °C, 66%, two steps; (e) LAH, THF, rt; (f) O_3, CH_2Cl_2, then Ph_3P, −78 °C to rt, 93%, two steps; (g) mCPBA, Na_2HPO_4, CH_2Cl_2, rt, 90%; (h) *hν* (150 W tungsten lamp), I_2, $PhI(OAc)_2$, CH_2Cl_2, 0 °C; (i) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 85%; (j) O_3, CH_2Cl_2, then Ph_3P, −78 °C to rt, 89%; (k) $Zn(BH_4)_2$, Et_2O, 0 °C; (l) TBAF, THF, 0 °C, 78%, twp steps; (m) 2,2-DMP, PPTS, acetone, rt, 93%.

of the hydroxy group of **12** with methoxymethyl chloride and ozonolysis of **15** afforded ketone **16** in good overall yield.

The reduction of ketone **16** with $Zn(BH_4)_2$ proceeded stereoselectively from its concave site to give a single diastereomer of alcohol **17**. Desilylation with TBAF provided the diol, whose subsequent protection with 2,2-dimethoxypropane and PPTS furnished acetonide **18** in 93% yield.

Scheme 3. Photolytic Olefination of **11**



(4) (a) Yoshimitsu, T.; Yanagiya, M.; Nagaoka, H. *Tetrahedron Lett.* **1999**, *40*, 5215. (b) For other fragmentation strategy for the construction of the core of CP-263,114, see: Crimmins, M. T.; Hauser, E. B. *Org. Lett.* **2000**, *2*, 281.

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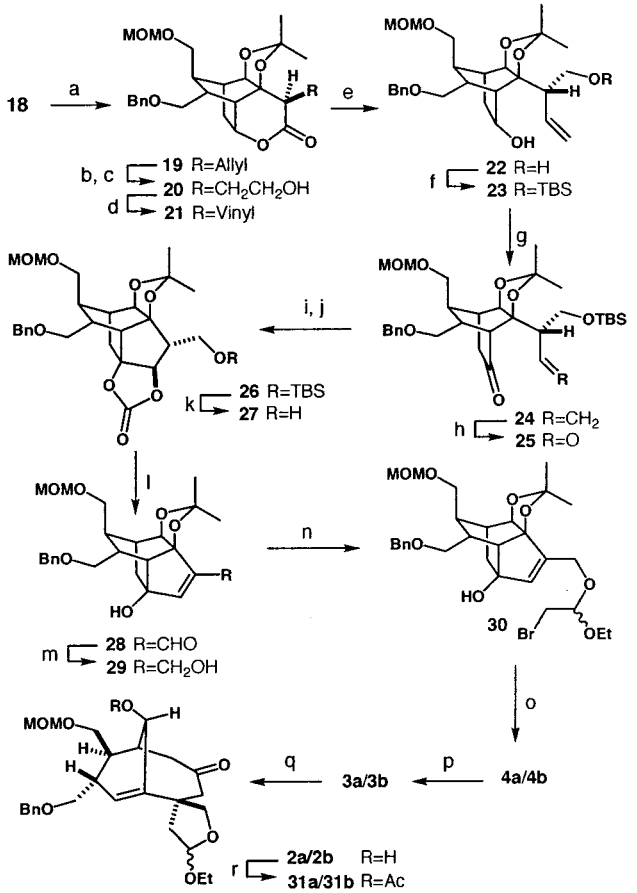
The allylation of **18** followed by one-carbon degradation through ozonolysis and reduction with $NaBH_4$ afforded alcohol **20** (Scheme 4). The olefination of **20** was conducted

Scheme 4[a]



[a] Reagents: (a) LHMDS, AllylBr, HMPA, THF, −78 °C, 86%; (b) O_3, CH_2Cl_2, then Ph_3P, −78 °C to rt; (c) $NaBH_4$, MeOH, rt; (d) *o*-$O_2NC_6H_4SeCN$, Bu_3P, THF, −78 to −40 °C to rt, then H_2O_2, rt; (e) LAH, 1,4-dioxane, reflux, 71%, five steps; (f) TBSCl, Et_3N, CH_2Cl_2, rt, 90%; (g) TPAP, NMO, MeCN, rt, 94%; (h) O_3, CH_2Cl_2, then Ph_3P, −78 °C to rt; (i) SmI_2, HMPA, THF, −40 °C, 91%, two steps; (j) CDI, DMAP, THF, rt; (k) TBAF, THF, rt, 95%, two steps; (l) Dess−Martin periodinane, CH_2Cl_2, rt, 98%; (m) $NaBH_4$, $CeCl_3$, MeOH, rt, 89%; (n) ethyl vinyl ether, NBS, Et_2O, 0 °C, 61% (ds = 1.5/1); (o) Bu_3SnH, AIBN, benzene, reflux, **4a** (42%) and **4b** (35%); (p) *hν*, I_2, $PhI(OAc)_2$, CH_2Cl_2, 0 °C, **3a** (80% from **4a**), **3b** (80% from **4b**); (q) *n*-BuLi, THF, −78 °C; (r) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, quant.

by the Grieco method[7] to provide vinyl lactone **21**, which was reduced with LAH to furnish diol **22** in 71% overall yield from **18**. Diol **22** was selectively protected as monosilyl ether **23**, whose secondary hydroxy group was oxidized in the presence of catalytic TPAP and 4-methylmorpholine *N*-oxide to provide ketone **24** in 94% yield. Ozonolysis followed by stereoselective intramolecular pinacol coupling of keto aldehyde **25** afforded the diol, whose treatment with 1,1′-carbonyldiimidazole gave cyclic carbonate **26**. The TBAF-mediated desilylation of **26** and Dess−Martin oxidation of **27** resulted in β-elimination to provide α,β-unsaturated aldehyde **28**. Aldehyde **28** was reduced with $NaBH_4$ in the presence of $CeCl_3$ to afford allylic alcohol **29** in 89% yield. The efficient construction of the quaternary stereogenic center at C14 of the CP molecule was achieved by Stork radical cyclization.[8] Alcohol **29** was treated with ethyl vinyl ether and NBS to give an inseparable diastereomixture of bromo ether **30**, which by radical cyclization with Bu_3SnH and AIBN gave **4a** and **4b** as separable diastereomers, respectively.

Using these pivotal intermediates, sequential radical fragmentation−reductive olefination for synthesis of the core motif of **1** was carried out. The original method[4a] using zinc−acetic acid for reductive olefination, however, provided only moderate yield of bridgehead olefin **2** as a result of competitive cyclization (Table 1). This situation required a more appropriate reagent, and *n*-BuLi was found effective for the reduction.[9]

Table 1. Reductive Olefination of β-Iodo Ether **3a** and **3b**

entry	substrate[a]	conditions	yields (%)
1	**3a**	Zn, AcOH/MeOH, rt	**2a** (14%)
			4a (49%)
2	**3a**	3.6 equiv *n*-BuLi/THF, −78 °C	**2a** (63%)
			3a (21%)
3	**3b**	1.2 equiv *n*-BuLi/THF, −78 °C	**2b** (49%)
			3b (28%)

[a] **3a** (R_f = 0.5), **3b** (R_f = 0.4); AcOEt/Hex 2:3.

Compounds **4a** and **4b** were thus separately irradiated with visible light under Suárez conditions[10,11] to give keto iodides **3a** and **3b** as single diastereomers, respectively.

The reductive removal of β-halo ether functionalities through metal−halogen exchange was achieved by treating **3a** and **3b** with *n*-BuLi in THF at −78 °C to provide the core motifs of the CP molecule, **2a** and **2b**, in good yields.[12] The structures of these motifs were unambiguously determined by NOE measurement of acetates **31a** and **31b** derived from **2a** and **2b** (Figure 2).[13]

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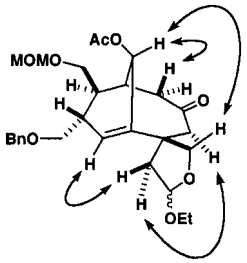
(11) For a recent application of alkoxyradical fragmentation in natural product synthesis, see: (a) Nowakowski, M.; Hoffmann, H. M. R. *Tetrahedron* **1997**, *53*, 4331. (b) Shultz, A. G.; Zhang, X. *Chem. Commun.* **2000**, 399. For pertinent reviews, see: (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (d) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (e) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.

(12) The stereochemistry of iodine atom at C16 of **3a**/**3b** was assigned to be *cis* to the adjacent oxygen at C15 on the basis of the coupling constants (J_{H16-17} = 12.2 Hz for **3a**, J_{H16-17} = 12.5 Hz for **3b**) and the NOE experiments. This result indicates that the olefination may proceed through *syn*-elimination mechanism.

Our reported enantioselective construction of the fully functionalized core motif of (−)-CP-263,114 demonstrates the successful utilization of sequential radical fragmentation−reductive olefination. The present method provides routes to both enantiomers of the CP-molecule simply by switching the chirality of readily available starting material and thus should constitute an effective means for the asymmetric total synthesis of natural and unnatural CP-263,114.



31a/31b

Figure 2. Key NOESY interactions in **31a/31b**.

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(13) **2a**: R_f = 0.39 (AcOEt/Hex 3:1); $[\alpha]^{28}_D$ +49.0 (*c* 0.102, $CHCl_3$); IR (neat) 3429, 2926, 1699, 1454, 1151, 1111, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 5.69 (dd, *J* = 2.44, 2.20 Hz, 1H), 5.19 (dd, *J* = 5.37, 1.95 Hz, 1H), 4.66 (s, 2H), 4.55 (d, *J* = 12.5 Hz, 1H), 4.52 (d, *J* = 12.2 Hz, 1H), 4.37 (bds, 1H), 4.11 (d, *J* = 8.30 Hz, 1H), 3.98 (d, *J* = 8.30 Hz, 1H), 3.73 (dq, *J* = 9.52, 7.08 Hz, 1H), 3.71 (dd, *J* = 9.03, 3.66 Hz, 1H), 3.59−3.53 (m, 3H), 3.45 (dd, *J* = 9.03, 6.10 Hz, 1H), 3.44 (dq, *J* = 9.52, 7.08 Hz, 1H), 3.35 (s, 3H), 2.86 (d, *J* = 11.7 Hz, 1H), 2.82−2.76 (m, 1H), 2.73 (dd, *J* = 11.7, 1.22 Hz, 1H), 2.68 (dd, *J* = 11.5, 8.05 Hz, 1H), 2.60−2.58 (m, 1H), 2.40 (dd, *J* = 13.2, 5.62 Hz, 1H), 2.12−2.08 (m, 1H), 1.95 (dd, *J* = 13.4, 1.95 Hz, 1H), 1.59−1.54 (m, 1H), 1.19 (t, *J* = 7.08 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0, 145.6, 138.3, 128.4, 128.2, 127.7, 127.5, 104.4, 96.6, 76.1, 73.2, 72.8, 69.9, 69.4, 63.4, 55.8, 55.1, 51.7, 47.7, 43.0, 42.0, 41.4, 35.2, 15.4; HRMS *m*/*z* calcd for $C_{26}H_{36}O_7$ (M^+) 460.2462, found 460.2467. **2b**: R_f = 0.36 (AcOEt/hex 3:1); $[\alpha]^{28}_D$ −81.2 (*c* 0.079, $CHCl_3$); IR (neat) 3441, 2926, 1699, 1454, 1151, 1113, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 5.71 (dd, *J* = 2.93, 1.71 Hz, 1H), 5.26 (dd, *J* = 5.37, 4.64 Hz, 1H), 4.66 (s, 2H), 4.53 (s, 2H), 4.38 (bds, 1H), 3.98 (d, *J* = 8.30 Hz, 1H), 3.93 (dd, *J* = 8.30, 1.00 Hz, 1H), 3.78 (dq, *J* = 9.52, 7.08 Hz, 1H), 3.72 (dd, *J* = 9.28, 3.90 Hz, 1H), 3.60-3.42 (m, 5H), 3.35 (s, 3H), 2.82−2.74 (m, 1H), 2.77 (d, *J* = 11.5 Hz, 1H), 2.71 (dd, *J* = 11.7, 8.06 Hz, 1H), 2.62−2.56 (m, 1H), 2.34 (dd, *J* = 11.5, 1.23 Hz, 1H), 2.27 (ddd, *J* = 13.4, 5.62, 1.00 Hz, 1H), 2.14−2.07 (m, 2H), 1.58−1.54 (m, 1H), 1.20 (t, *J* = 7.08 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9, 144.1, 138.3, 130.2, 128.4, 127.6, 127.5, 104.2, 96.6, 74.9, 73.2, 72.8, 69.6, 69.4, 63.8, 55.9, 55.4, 51.7, 49.5, 43.4, 42.0, 41.9, 35.2, 15.4; HRMS *m*/*z* calcd for $C_{26}H_{36}O_7$ (M^+) 460.2462, found 460.2465. **3a**: R_f = 0.50 (AcOEt/Hex 2:3); $[\alpha]^{28}_D$ −11.4 (*c* 0.333, $CHCl_3$); IR (neat) 2928, 1697, 1107, 1061 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.28 (m, 5H), 5.12 (d, *J* = 5.86 Hz 1H), 5.00 (d, *J* = 12.2 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.55 (s, 2H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.03 (dd, *J* = 8.06, 1.22 Hz, 1H), 3.97 (dd, *J* = 10.0, 2.44 Hz, 1H), 3.93 (d, *J* = 8.05 Hz, 1H), 3.75 (dq, *J* = 9.52, 7.08 Hz, 1H), 3.68 (dd, *J* = 10.0, 1.95 Hz, 1H), 3.61 (d, *J* = 2.44 Hz, 1H), 3.55−3.53 (m, 2H), 3.39 (dq, *J* = 9.52, 7.08 Hz, 1H), 3.30 (s, 3H), 3.23 (dd, *J* = 13.4, 0.73 Hz, 1H), 2.94 (dd, *J* = 13.4, 6.10 Hz, 1H), 2.78−2.72 (m, 2H), 2.60−2.55 (m, 1H), 2.49 (dd, *J* = 14.9, 3.42 Hz, 1H), 2.38−2.31 (m, 1H), 2.10−2.03 (m, 1H), 1.81 (d, *J* = 13.4 Hz, 1H), 1.64 (s, 3H), 1.36 (s, 3H), 1.18 (t, *J* = 7.08 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 138.2, 128.4, 127.8, 127.7, 108.7, 104.5, 96.7, 82.3, 80.4, 73.6, 71.8, 71.3, 70.8, 63.2, 55.5, 50.8, 50.3, 48.1, 43.4, 42.7, 41.2, 41.1, 29.9, 27.6, 26.3, 15.4; HRMS *m*/*z* calcd. for $C_{29}H_{41}O_8I$ (M^+): 644.1847, found: 644.1858.; **3b**: R*f* = 0.40 (AcOEt/Hex 2:3); $[\alpha]^{28}_D$ −85.7 (*c* 0.369, $CHCl_3$); IR (neat) 2899, 1693, 1150, 1105, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H), 5.15 (dd, *J* = 5.61, 5.37 Hz, 1H), 4.89 (d, *J* = 12.5 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.55 (s, 2H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.08 (dd, *J* = 8.05, 1.46 Hz, 1H), 3.96 (dd, *J* = 10.0, 2.44 Hz, 1H), 3.77 (dq, *J* = 9.76, 7.08 Hz, 1H), 3.73 (d, *J* = 2.44 Hz, 1H), 3.69−3.64 (m, 2H), 3.54 (d, *J* = 5.61 Hz, 2H), 3.48 (dq, *J* = 9.76 7.08 Hz, 1H), 3.30 (s, 3H), 2.77 (dd, *J* = 14.7, 8.55 Hz, 1H), 2.68 (dd, *J* = 13.7, 5.37 Hz, 1H), 2.64−2.56 (m, 3H), 2.51 (dd, *J* = 14.7, 3.66 Hz, 1H), 2.33−2.27 (m, 1H), 2.10−1.98 (m, 2H), 1.62 (s, 3H), 1.34 (s, 3H), 1.22 (t, *J* = 7.08 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 138.3, 128.4, 127.8, 127.7, 108.7, 104.3, 96.7, 81.4, 79.9, 73.5, 72.1, 71.0, 68.9, 64.0, 55.5, 52.2, 49.7, 48.1, 43.1, 42.9, 41.1, 40.9, 30.3, 27.5, 26.0, 15.4; HRMS *m*/*z* calcd for $C_{29}H_{41}O_8I$ (M^+) 644.1847, found 644.1845.