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Synthetic study on CP-263,114 (phomoidride B) by SET-mediated fragmentation

Takeshi Matsushita, Hiroshi Ashida, Tetsutaro Kimachi and Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan. E-mail: takemoto@pharm.kyoto-u.ac.jp; Fax: 81 75 753 4569; Tel: 81 75 753 4528

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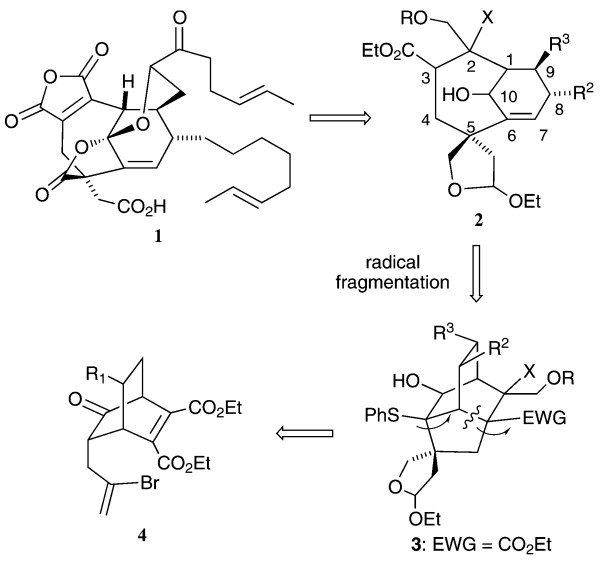
Assembly of the highly functionalized carbocyclic core of CP-263,114 has been accomplished by using radical-mediated fragmentation with lithium naphthalenide as a key step.

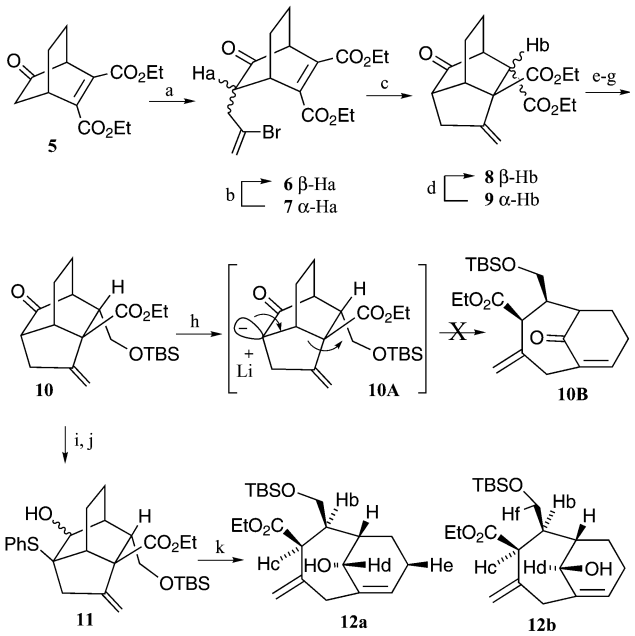
Since CP-263,114 **1** and CP-225,917 (phomoidride A and B) were isolated by the Pfizer research group in 1997,[1] numerous synthetic approaches to these compounds[2,3] have been investigated because of their attractive biological properties (inhibitory activities towards farnesyl transferase and squalene synthase) and complex structure. In this communication, we describe a new synthetic approach to a fully functionalized carbocyclic structure of **1**. Our retrosynthetic analysis focuses on the late-stage fragmentation of a completely functionalized [4.3.1.0^{3,7}] tricycle **3** into **2** by a single-electron transfer (SET) process. Recently, such a carbon-radical mediated fragmentation has been reported by several groups as well as the base-promoted Grob type-fragmentation.[4] By intramolecular radical cyclization, **3** would be obtained from the bromide **4**, which can easily be synthesised by Diels–Alder reaction (Scheme 1).

Our synthetic studies began with the readily available compound **5**,[5] alkylation of which gave rise to the alkenyl bromides **6** and **7** (Scheme 2). The radical cyclization of the major product **6** with *n*-Bu_3SnH gave the targeted tricyclic compound **8** in 92% yield as a diastereomixture (**8**:**9**, 1:1). Both undesired isomers **7** and **9** could be converted into the required isomers by treatment with DBU and KHMDS, respectively. The ketone **10**‡ was synthesized in good yield by the three-step sequence: 1) hydride reduction with $NaBH_4$, 2) regioselective protection of the resulting diol, 3) oxidation with TPAP/NMO. Having the targeted ketone, we next examined carbanion-mediated fragmentation for the construction of the desired bicyclo[4.3.1]decene skeleton (**10**→**10A**→**10B**).[6] Treatment of **10** with LDA did not afford the desired product, but resulted only in recovery of the starting material irrespective of the reaction temperature. Then, we investigated the reductive radical-mediated fragmentation of the sulfides **11**, which were easily derived from **10** by a two-step sequence. Although we met with no success in fragmentation of **11** using various tin hydrides, the desired products **12a**‡ and **12b**‡ were obtained in 73% yield (3:1 diastereomixture at C10) upon exposure of **11** to lithium naphthalenide in THF at −78 °C.[7] The stereochemistry of **12a** and **12b** was determined by the NOE experiments.†

Having established an efficient method for constructing the carbocyclic core of CP-263,114, we turned our attention to the quaternary carbon centre at C5 (Scheme 3). To this end, the enol triflate **13** was synthesised from **10** in moderate yield using standard three-step manipulation; 1) Lemiuex–Johnson oxidation, 2) alkylation with BOMCl, 3) sulfonylation with Tf_2NPh. The Pd-catalyzed reduction of **13** with Bu_3N and formic acid[8] was followed by the transformation of the protecting group, giving rise to the acetate **14**. After removal of the benzyl ether of **14** with BBr_3, iodoacetal formation furnished **15**, and subsequent treatment of **15** with *n*-Bu_3SnH in the presence of radical initiator V-70[9] at room temperature effected the stereoselective cyclisation, affording the 5-exo-trig products **16** as an inseparable diastereomixture (1:1). These diastereomers could be separated by silica gel column chromatography as the TBS ethers **17a**‡ and **17b**.‡



Scheme 1 Retrosynthetic analysis of CP-263,114.



Scheme 2 *Reagents and conditions*: (a) LDA, THF, HMPA, 2,3-dibromopropene, −78 °C, 76% (**6**:**7** = 3:1); (b) DBU (0.1 eq), CH_3CN, rt, 93% (**6**:**7** = 1.3:1); (c) *n*-Bu_3SnH, AIBN, toluene, 90 °C, 91% (**8**:**9** = 1:1); (d) $KN(TMS)_2$, THF, −78 °C, 72%; (e) $NaBH_4$, EtOH, rt, 85%; (f)TBSCl, imidazole, THF, 0 °C, 95%; (g) TPAP, NMO, CH_3CN, rt, 93%; (h) LDA, THF; (i) LDA, PhSSPh, THF, HMPA, −78 °C, 69%; (j) $NaBH_4$, EtOH, rt 97% (α-OH:β-OH = 3:1); (k) lithium naphthalenide, THF, −78 °C, 73% (**12a**:**12b** = 3:1).

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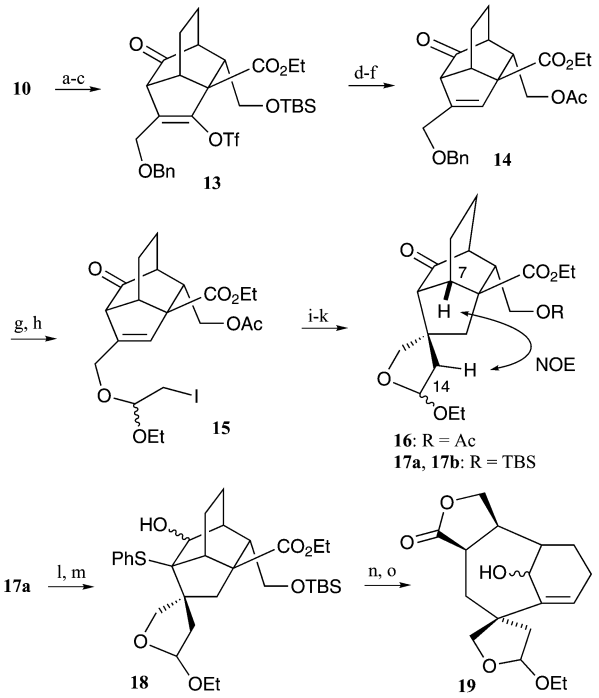

Scheme 3 *Reagents and conditions*: (a) cat. OsO_4, $NaIO_4$, acetone, H_2O, rt, 85%; (b) LDA, HMPA, $C_6H_5CH_2OCH_2Cl$, −35 °C, 48%; (c) KHMDS, Tf_2NPh, THF, −78 °C, 71%; (d) $Pd(acac)_2$, *n*-Bu_3P,*n*-Bu_3N, HCOOH, THF, 60 °C, 92%; (e) 3 N HCl, THF, rt; (f) Ac_2O, pyridine, DMAP, rt, 59%, (2 steps); (g) BBr_3, CH_2Cl_2, −78 °C, 89%; (h) NIS, ethyl vinyl ether, −10 °C, 80%; (i) *n*-Bu_3SnH, V-70, ether, rt, 94%; (j) K_2CO_3, EtOH, rt; (k) TBSCl, imidazole, DMAP, 79%, (2 steps, 1 : 1 diastereomixture); (l) LDA, PhSSPh, THF, HMPA, 59%; (m) BH_3·SMe_2, THF, rt, −79% (α-OH : β-OH = 1 : 1); (n) lithium naphthalenide, THF, −78 °C, 81%; (o) TBAF, THF, 90%.

Our final studies began with **17a**, which was converted to the sulfide **18** by the same procedure as described for **11**. To our delight, reaction of **18** with lithium naphthalenide at −78 °C proceeded smoothly (81% yield), and the subsequent treatment of the product with TBAF afforded the desired products **19**‡, which possess the requisite carbon substituents other than the C8- and C9- side chains, in high yield as a C10 diastereomixture (1 : 1).

We are currently applying this method to the fully functionalized carbocyclic core to complete the total synthesis of CP-263,114.

Notes and references

† The relative configurations of **12a** and **12b** were elucidated from the following NOE correlations; **12a**: Hb/Hc and Hd/He, **12b**: Hb/Hc and Hd/Hf.

‡ All targeted compounds exhibited satisfactory analytical and spectroscopic data.

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