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Synthesis of (±)-pyranonaphthoquinone derivatives, a Cdc25A phosphatase inhibitor

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Abstract—The novel pyranonaphthoquinone **2**, carrying Cdc25A phosphatase inhibitory activity, has been successfully synthesized through tricyclic compound **16**, which was obtained from **15** by using the intramolecular Michael addition. The precursor **9** was derived from 5-bromoveratraldehyde.

The four pyranonaphthoquinones **1**–**4**, carrying Cdc25A inhibitory activity, were isolated from *Streptomyces* sp. by the Eli Lilly group in 1999.[1] Their structural features are that the benzoquinone moiety possessing amino substituents is located at an edge of the tricyclic molecule, instead of inside similar to those of nanaomycins,[2] eleutherin,[3] and frenolicins.[4] Accordingly, synthetic examples of such molecules have not been reported, to our knowledge.[5] In addition to activation of cell cycle progression by dephosphorylation of threonine and tyrosine, expression of Cdc25A is closely related to oncogenic transformations in the presence of RAS or RB deletion mutants. These biological activities would contribute to development of new cancer–chemotherapeutic agents. Against such background, we initiated a synthetic investigation of the pyranonaphthoquinones **1**–**4**. We describe herein synthesis of (±)-**2**, carrying relatively simple substitutions, as an early stage of access to a family of pyranonaphthoquinones (Fig. 1).

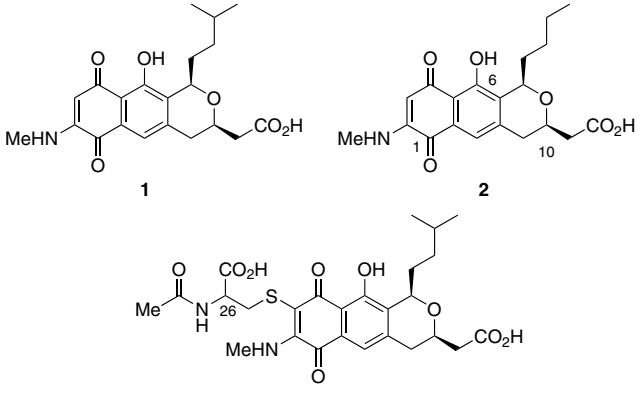

Figure 1. Structures of Cdc25A phosphatase inhibitors.

Our retrosynthetic analysis indicated that tricyclic compound **16** might be a readily accessible precursor of **2** (Scheme 1). The pyran ring moiety of **16** might be constructed by using the intramolecular Michael reaction of α,β-unsaturated aldehyde derivatives of **15**, which was produced by stepwise homologation of alkyl substituents from **9**. The naphthalene **9** might be obtained from 5-bromoveratraldehyde **5**.

Along this line, the synthesis commenced with conversion of **5** by a known procedure into benzaldehyde **6**,[6] which on Horner–Wadsworth–Emmons coupling with **7**,[7] followed by selective hydrolysis afforded **8** in 77% yield from **6** (Scheme 2). Treatment of **8** with KOAc–Ac_2O effected the desired cyclization to give naphthalene **9** in 92% yield. Compound **9** was submitted to basic conditions,[8] and then reduction with $LiAlH_4$ to give **10**. Regioselective bromination of **10** with Pyr·HBr_3 (80% yield from **9**),[9] followed by oxidation and methylation provided aldehyde **11** in 87% yield. Reaction of **11** with dimethylsulfonium methylide[10] gave epoxide **12** in excellent yield. After isomerization of **12** under $ZnBr_2$/

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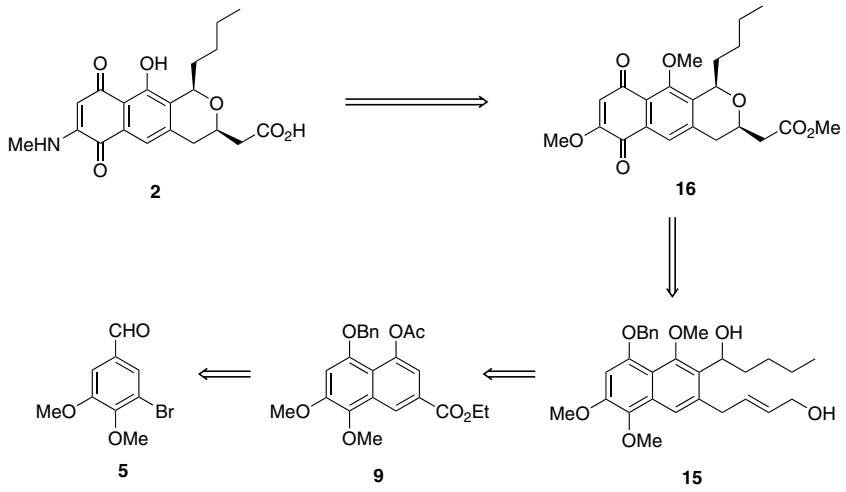
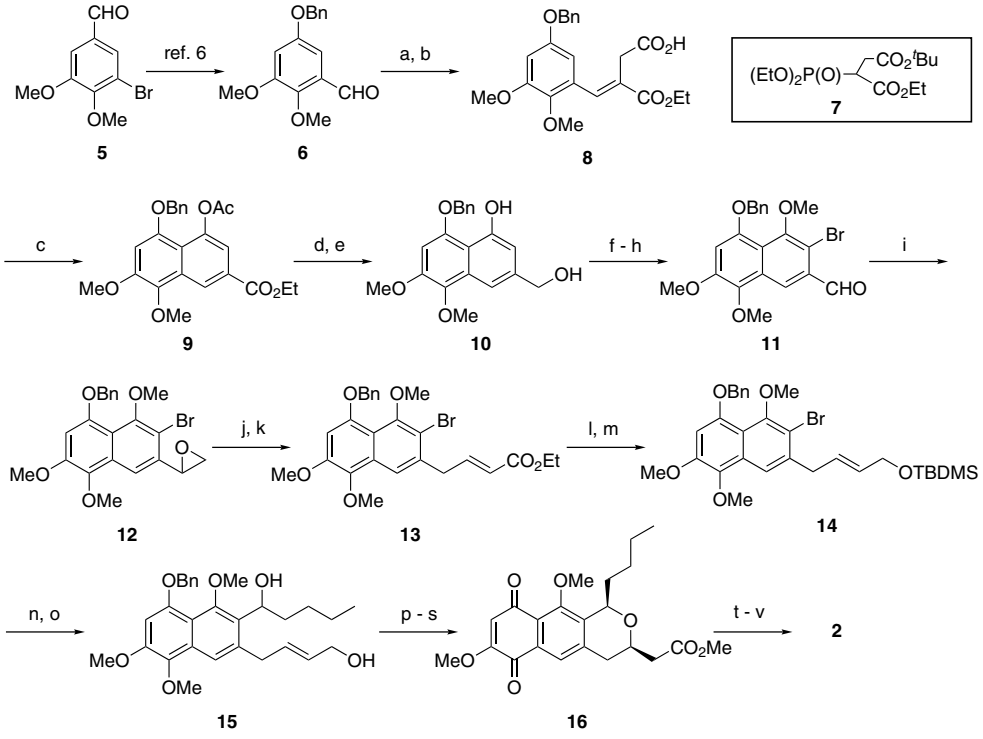
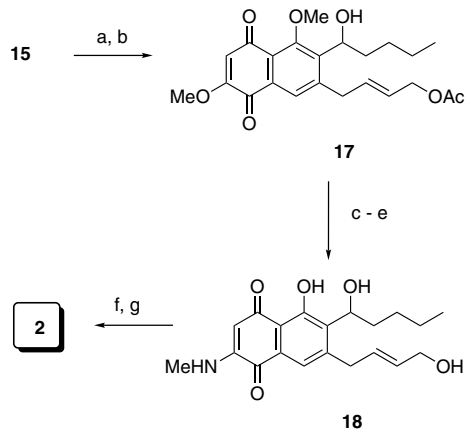


Scheme 1. Retrosynthetic analysis of **2**.



Scheme 2. Reagents and conditions: (a) **7**, NaH, THF, rt; (b) TFA, H_2O, rt, 77% in two steps; (c) Ac_2O, KOAc, reflux, 92%; (d) K_2CO_3, EtOH, rt; (e) $LiAlH_4$, THF, rt; (f) Pyr·HBr_3, THF, 0 °C, 80% in three steps; (g) SO_3·Pyr, TEA, DMSO, CH_2Cl_2, rt, 93%; (h) MeI, K_2CO_3, DMF, rt, 94%; (i) Me_3SI, NaH, DMSO, THF, 0 °C, 92%; (j) $ZnBr_2$, PhH, reflux; (k) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 °C, 85% in two steps; (l) DIBAL, THF, −78 °C, 93%; (m) TBDMSCl, imid., DMF, rt, 96%; (n) *n*-valeraldehyde, *n*-BuLi, THF, −78 °C; (o) TBAF, THF, 0 °C, 80% in two steps; (p) DDQ, *t*-BuOH, H_2O, CH_2Cl_2, rt; (q) MnO_2, CH_2Cl_2, 40 °C; (r) PDC, DMF, rt; (s) $TMSCHN_2$, MeOH, rt, 31% from **15**; (t) BBr_3, CH_2Cl_2, −78 to 0 °C, 41%; (u) $MeNH_2$, THF, rt, 87%; (v) KOH, H_2O, MeOH, 0 °C to rt, quant.

PhH conditions,[11] the resultant aldehyde was subjected to the Horner–Wadsworth–Emmons olefination to furnish the α,β-unsaturated ester **13** in 85% yield. Compound **13** was reacted with DIBAL, followed by protection of an allyl alcohol to afford silyl ether **14** in 89% yield. Bromine–lithium exchange reaction of **14**, followed by rapid quenching with *n*-valeraldehyde[12] and deprotection of the silyl group, provided benzyl alcohol **15** in 80% overall yield. Upon stepwise treatment of **15** with DDQ and then MnO_2, the resultant α,β-unsaturated aldehyde was unexpectedly converted into a cyclic aldehyde, which was immediately treated with PDC in DMF, followed $TMSCHN_2$ without purification, due to its instability, leading to **16** in 31% yield from **15**.[13] After treatment of **16** under acidic conditions to remove the methyl group at the C-6 position (41%),[14] exposure to $MeNH_2$[15] in THF underwent successful introduction of a *N*-methyl group (87%), followed by hydrolysis with KOH in MeOH quantitatively to give the pyranonaphthoquinone **2**, contaminated by the corresponding *trans*-



Scheme 3. Reagents and conditions: (a) Ac_2O, Pyr, CH_2Cl_2, rt, 85%; (b) DDQ, *t*-BuOH, H_2O–CH_2Cl_2, 0 °C, 78%; (c) BBr_3, CH_2Cl_2, −78 °C, 34%; (d) $MeNH_2$, THF, 0 °C, 99%; (e) K_2CO_3, MeOH, rt, 86%; (f) MnO_2, CH_2Cl_2, 40 °C, 86%; (g) PDC, DMF, rt, 22%.

isomer of substituents in the benzopyran moiety (*cis*:*trans* = 4/1).[16] To circumvent such undesired isomerization, compound **15** was acetylated, followed by oxidation to give *p*-quinone **17** in 66% yield (Scheme 3). Compound **17** was successively treated with BBr_3, and then a methylamino group was introduced in 33% yield from **17**. The following basic treatment provided **18** (86%), which on oxidation in two steps gave **2** in 19% yield,[17] spectroscopic data of which was superimposable to those of the reported data.[1]

In conclusion, we have accomplished a total synthesis of (±)-pyranonaphthoquinone **2** using intramolecular Michael addition for construction of the pyran ring system. This synthetic route would be used for synthesis of optically active derivatives and other pyranonaphthoquinones such as chloroquinocin.[18]

Acknowledgements

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12. Owing to the unstable character of an aromatic anion, *n*-valeraldehyde was rapidly added at low temperature.
13. An inseparable mixture of *cis*- and *trans*-isomers of alkyl substituents in the benzopyran moiety was formed in a ratio of ca. 1.6:1.
14. A ratio of the *cis*- and *trans*-isomers was changed to 1:1.5. Under BBr_3 conditions, two alkyl substituents of the dihydropyran moiety adopt thermodynamically more favorable *trans*-form than the corresponding *cis*-form. Examples of stability of the *trans*-form by thermodynamic control: (a) Ref. 5a; (b) Webb, A. D.; Harris, T. M. *Tetrahedron Lett.* **1977**, *18*, 2069–2072; (c) Li, T.-T.; Ellison, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 6263–6265; (d) Masquelin, T.; Hengartner, U.; Streith, J. *Synthesis* **1995**, 780–786.
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17. No contamination with the *trans*-isomer was monitored by ODS-W TLC (0.5% aq NH_4OAc–MeCN = 3/2).
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