COMMUNICATIONS TO THE EDITOR

Total Synthesis of a Tetracyclic Anti-tumor, UCE6

Sir:

A tetracyclic compound, UCE6 (**1**) was isolated from fermentation broth of actinomycetes strain UOE6 to show strong anti-tumor activities.[1] The structure **1** was determined mainly by NMR studies to have a tetracyclic skeleton, although the absolute configuration remained undetermined.[2]

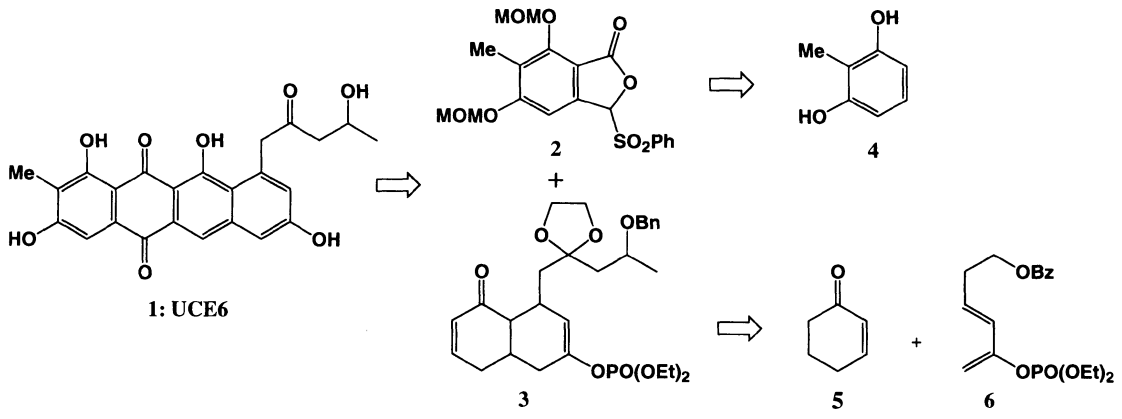
Herein, we describe the first total synthesis of (±)-UCE6 (**1**).

From the retrosynthetic perspective (Fig. 1), the tetracyclic skeleton is expected to be accessible by the tandem Michael-Dieckmann type reaction[3] of the benzofuranone **2** with the cyclic α,β-unsaturated ketone **3**. The former **2** is derived from 2-methylresorcinol (**4**).[4] The other **3** may be prepared by [4+2] cycloaddition reaction of 2-cyclohexen-1-one (**5**) with the diene **6**.

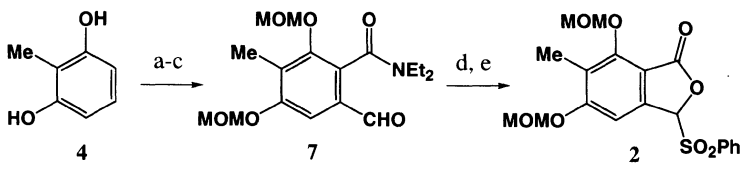
Methoxymethylation of **4** followed by amidation and formylation gave the aldehyde **7** (Scheme 1). Reaction of **7** with $PhSO_2Na$ gave a mixture of deprotected products, which again methoxymethylated to the desired segment **2** in a moderate yield.

The diene **6** was prepared from 1,2,4-trihydroxybutane (**8**) in 4 steps: 1) $NaIO_4$ oxidative cleavage; 2) Wittig reaction; 3) *O*-benzoylation; 4) enol phosphate formation (Scheme 2). Cycloaddition of **6** with 2-cyclohexen-1-one (**5**) proceeded smoothly by aid of $BF_3 \cdot Et_2O$ to give a diastereomeric mixture of the adduct **9**. The ^{1}H-NMR studies showed the adduct to be a 3 : 1 mixture due to the C-

Fig. 1.

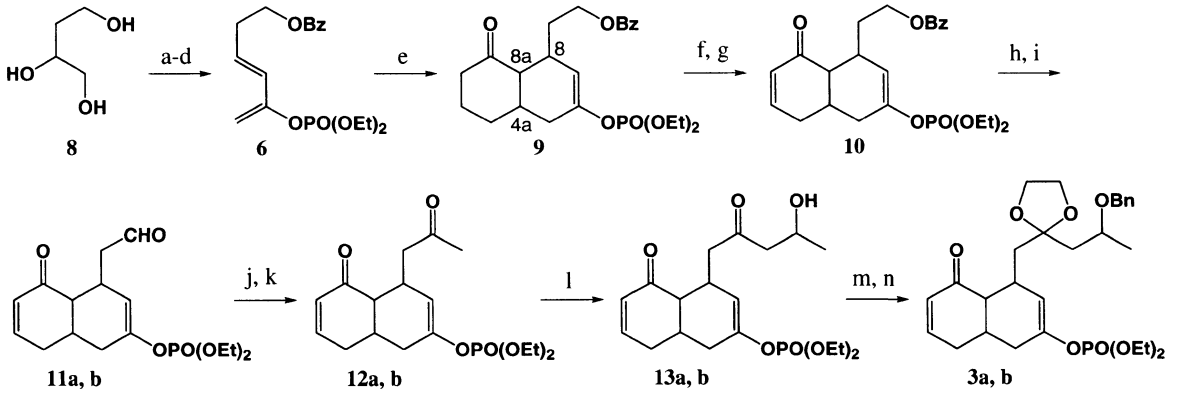


Scheme 1.



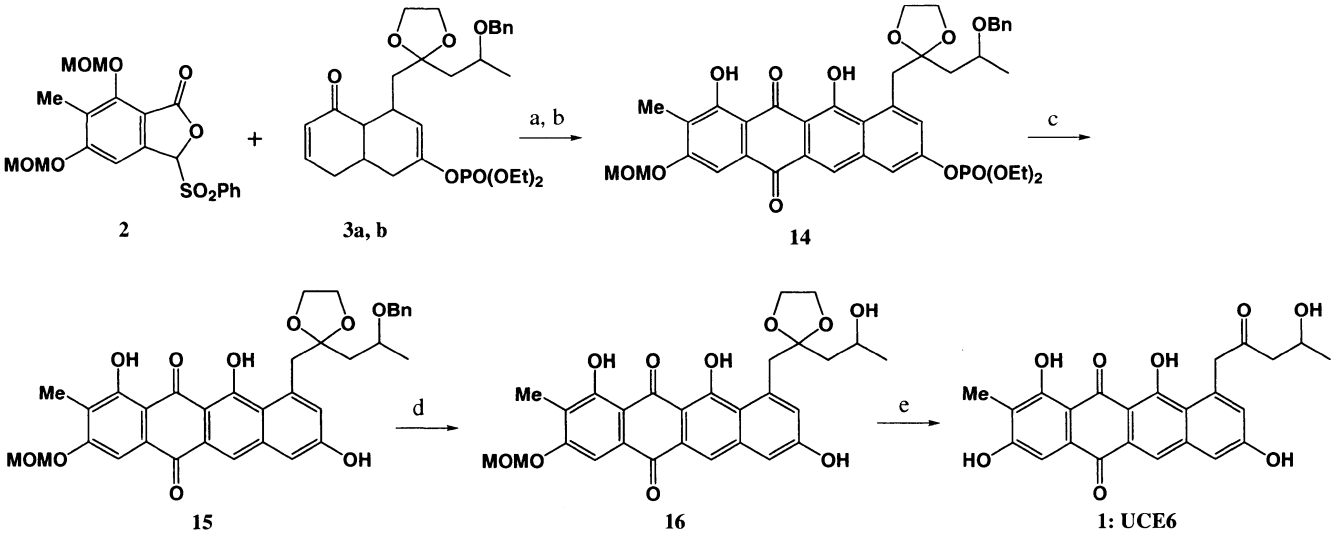
Conditions; (a) MOMCl, NaH/DMF, 0°C to rt, 0.5 hour; 87%
(b) $ClCONEt_2$, *s*-BuLi/THF, –78°C to rt, 0.5 hour; 78% (c) DMF, *s*-BuLi, TMEDA/THF, –78°C to rt, 0.5 hour; 82% (d) $PhSO_2Na$/AcOH, 80°C, 16 hours; 66% (e) MOMCl, *i*-Pr_2NEt/DMF, –40°C to rt, 0.5 hour; 74%.

Scheme 2.



Conditions; (a) $NaIO_4/H_2O$, 0°C, 5 minutes (b) Ph_3P=CHCOMe, NaOAc/$CHCl_3$-H_2O, rt, 12 hours (c) BzCl, Et_3N/CH_2Cl_2, rt, 12 hours; 58% in 3 steps (d) $ClPO(OEt)_2$, $LiN(TMS)_2$/THF, −78°C to rt, 10 minutes; 79% (e) 2-cyclohexen-1-one (**5**), BF_3•Et_2O/PhMe, rt, 12 hours; 64% (f) PhSeCl, $LiN(TMS)_2$/THF, rt, 5 minutes (g) 30% H_2O_2, aq. $NaHCO_3/CH_2Cl_2$, rt, 36 hours; 68% in 2 steps (h) $NaBH_4$, $CeCl_3$•$7H_2O$, NaOEt/EtOH, 0°C to 40°C, 12 hours; 81% (i) $(COCl)_2$, DMSO, Et_3N/ CH_2Cl_2, −78°C to rt, 1 hour; 86% (j) MeMgBr/THF, −10°C, 1 hour; 81% (k) *o*-iodoxybenzoic acid/PhMe-DMSO, rt, 3 hours; 84% (l) MeCHO, Ipc_2BCl, Et_3N/ CH_2Cl_2, −78°C to rt, 4 hours; 85% (m) $BnOC(=NH)CCl_3$, TMSOTf/CH_2Cl_2-cyclohexane, rt, 2 hours; 75% (n) 1,2-bis(trimethylsilyloxy)ethane, TMSOTf/CH_2Cl_2, −78°C to 0°C, 1 hour; 75%.

Scheme 3.



Conditions; (a) $LiN(TMS)_2$/THF, −78°C to 60°C, 2 hours (b) Pd-C, BnOMe/PhMe, 110°C, 15 hours; 64% in 2 steps (c) *t*-BuOK, H_2O/*t*-BuOH, 60°C, 15 minutes; 85% (d) H_2, $Pd(OH)_2$-C/1,4-dioxane, rt, 2 hours; 90% (e) $LiBF_4$/THF-MeCN-H_2O, 70°C, 72 hours; 76%.

Table 1-1. Physico-chemical properties of compounds.

Compds.	Mp (°C)	^{1}H-NMR (400, 500 or 600 MHz; δ ppm; *J* Hz) IR(KBr; cm^{-1}) FAB-MS (*m/z*)
1	>300 (decomp.) red solid (THF)	^{1}H-NMR(CD_3CO_2D): δ 1.28(3H, d, *J*=6.0), 2.19(3H, s), 2.89(1H, dd, *J*=17.0& 4.0), 2.99(1H, dd, *J*=17.0&8.0), 4.09-4.14(1H, m), 4.42(1H, d, *J*=17.0), 4.47 (1H, d, *J*=17.0), 7.05(1H, d, *J*=2.0), 7.32(1H, d, *J*=2.0), 7.36(1H, s), 8.11(1H, s) IR(KBr): 1697, 1655, 1604, 1442, 1377, 1329, 1278, 1218 FAB-MS: 437$(M+H)^+$
2	119 prisms (hexane-acetone)	^{1}H-NMR($CDCl_3$): δ 2.12(3H, s), 3.51(3H, s), 3.52(3H, s), 5.03(1H, d, *J*=7.0), 5.27(1H, d, *J*=7.0), 5.31(1H, d, *J*=7.0), 5.45(1H, d, *J*=7.0), 6.01(1H, s), 7.34(1H, s), 7.51(2H, dd, *J*=8.0&8.0), 7.66(1H, dddd, *J*=8.0, 8.0, 1.0&1.0), 7.83(2H, dd, *J*=8.0&1.0) FAB-MS: 409$(M+H)^+$
3a[1)]	oil	^{1}H-NMR($CDCl_3$): δ 1.17, 1.18(1:1, 3H in total, each d, *J*=6.0), 1.31-1.38(6H, m), 1.86-1.94(1H, m), 2.01-2.08(1H, m), 2.14-2.36(7H, m), 2.46-2.54(1H, m), 2.85 (1H, br s), 3.80-4.01(5H, m), 4.09-4.20(4H, m), 4.50-4.58(2H, m), 5.83(1H, br s), 5.98, 5.99(1:1, 1H in total, each d, *J*=10.0), 6.83-6.89(1H, m), 7.28-7.38(5H, m) FAB-MS: 535$(M+H)^+$
6	oil	^{1}H-NMR($CDCl_3$): δ 1.33(6H, dt, *J*=7.0&1.0), 2.61(2H, ddt, *J*=7.0, 7.0&1.0), 4.16(2H, ddq, *J*=10.0, 8.0&7.0), 4.18(2H, ddq, *J*=10.0, 8.0&7.0), 4.39(2H, t, *J*=7.0), 4.78(1H, dd, *J*=2.0&2.0), 5.02(1H, dd, *J*=2.0&2.0), 6.03(1H, ddt, *J*= 15.0, 2.0&1.0), 6.11(1H, dt, *J*=15.0&7.0), 7.44(2H, dd, *J*=8.0&7.5), 7.56(1H, dddd, *J*=7.5, 7.5, 1.0&1.0), 8.03(2H, dd, *J*=8.0&1.0) FAB-MS: 355$(M+H)^+$
7	oil	^{1}H-NMR($CDCl_3$): δ 1.03(3H, t, *J*=7.0), 1.30(3H, t, *J*=7.0), 2.29(3H, s), 3.10(1H, dq, *J*=7.0&7.0), 3.14(1H, dq, *J*=7.0&7.0), 3.50(3H, s), 3.57(3H, s), 3.61(2H, q, *J*=7.0), 5.02(1H, d, *J*=6.0), 5.08(1H, d, *J*=6.0), 5.26(1H, d, *J*=7.0), 5.28(1H, d, *J*=7.0), 7.43(1H, s), 9.91(1H, s) FAB-MS: 340$(M+H)^+$
9	oil	^{1}H-NMR($CDCl_3$): δ 1.06-1.12(6H, m), 1.20-2.28(13H, m), 3.96-4.09(4H, m), 4.16-4.26, 4.36-4.43(3:1, 2H in total, each m), 5.69, 5.73(1:3, 1H in total, each br s), 7.05-7.14(3H, m), 8.16, 8.26(3:1, 2H in total, each d, *J*=7.0) FAB-MS: 451$(M+H)^+$
11	oil	**11a**: ^{1}H-NMR($CDCl_3$): δ 1.36(6H, br t, *J*=7.0), 2.15-2.42(5H, m), 2.49-2.58 (2H, m), 3.05-3.10(1H, m), 3.18(1H, br s), 4.12-4.19(4H, m), 5.36(1H, br s), 6.01(1H, ddd, *J*=10.0, 2.0&0), 6.92(1H, ddd, *J*=10.0, 6.0&2.0), 9.81(1H, s) **11b**: ^{1}H-NMR($CDCl_3$): δ 1.34(6H, dt, *J*=7.0&1.0), 2.16-2.57(6H, m), 2.63-2.72(2H, m), 3.35(1H, br s), 4.08-4.20(4H, m), 5.45(1H, br s), 5.98(1H, ddd, *J*=10.0, 2.0&2.0), 6.89(1H, ddd, *J*=10.0, 4.0&4.0), 9.74(1H, s) FAB-MS: 343$(M+H)^+$
12a[1)]	oil	^{1}H-NMR($CDCl_3$): δ 1.34(3H, dt, *J*=7.0&1.0), 1.35(3H, dt, *J*=7.0&1.0), 2.13-2.33(4H, m), 2.15(3H, s), 2.36(1H, dddd, *J*=11.0, 11.0, 1.0&1.0), 2.42(1H, dd, *J*=17.0&9.0), 2.52(1H, ddd, *J*=19.0, 6.0&4.0), 3.08(1H, br s), 3.16(1H, dd, *J*= 17.0&3.0), 4.10-4.18(4H, m), 5.35(1H, br s), 5.99(1H, ddd, *J*=10.0, 2.0&0), 6.90(1H, ddd, *J*=10.0, 6.0&2.0) FAB-MS: 357$(M+H)^+$

Table 1-2. Continued.

Compds.	Mp (°C)	^{1}H-NMR (300, 400 or 600 MHz; δ ppm; *J* Hz) IR(KBr; cm^{-1}) FAB-MS (*m/z*)
13a[1)]	oil	^{1}H-NMR($CDCl_3$): δ 1.18, 1.19(1:1, 3H in total, each d, *J*=6.0), 1.31-1.37(6H, m), 2.21-2.36(3H, m), 2.52(1H, dd, *J*=17.0&9.0), 2.60, 2.61(1:1, 1H in total, each dd, *J*=17.0&3.0), 2.68-2.78(2H, m), 2.84, 2.90(1:1, 1H in total, each dd, *J*=18.0&7.0), 2.95(1H, ddd, *J*=17.0, 4.0&4.0), 3.05(1H, br s), 3.33, 3.37(1:1, 1H in total, each dd, *J*=18.0&7.0), 4.08-4.27(5H, m), 5.31(1H, br s), 5.86-5.89(1H, m), 6.71-6.76(1H, m) FAB-MS: 401$(M+H)^+$
14	orange wax	^{1}H-NMR($CDCl_3$): δ 1.30(3H, d, *J*=6.0), 1.40(6H, dt, *J*=7.0&1.0), 1.86(1H, dd, *J*=14.0&5.0), 2.21-2.25(1H, m), 2.26(3H, s), 3.34-3.38(1H, m), 3.40-3.44(1H, m), 3.53(3H, s), 3.70-3.74(2H, m), 3.84-3.90(1H, m), 3.98(1H, d, *J*=14.0), 4.05 (1H, d, *J*=14.0), 4.25-4.32(4H, m), 4.51(1H, d, *J*=12.0), 4.59(1H, d, *J*=12.0), 5.40(2H, s), 7.28-7.32(3H, m), 7.34-7.37(2H, m), 7.45(1H, d, *J*=2.0), 7.61(1H, s), 7.69(1H, d, *J*=2.0), 8.17(1H, s), 12.62(1H, s), 14.96(1H, s) FAB-MS: 751$(M+H)^+$
15	219-221 (decomp.) orange solid (acetone)	^{1}H-NMR[$(CD_3)_2CO$]: δ 1.25(3H, d, *J*=6.0), 1.83(1H, dd, *J*=14.0&6.0), 2.20 (1H, dd, *J*=14.0&6.0), 2.22(3H, s), 3.48-3.60(2H, m), 3.52(3H, s), 3.77-3.82 (2H, m), 3.85(1H, tq, *J*=6.0&6.0), 3.96(1H, d, *J*=14.0), 4.01(1H, d, *J*=14.0), 4.47(1H, d, *J*=12.0), 4.55(1H, d, *J*=12.0), 5.49(2H, s), 7.18(1H, dd, *J*=7.0&7.0), 7.26(2H, dd, *J*=7.0&7.0), 7.29(1H, d, *J*=2.0), 7.32(2H, d, *J*=7.0), 7.36(1H, d, *J*=2.0), 7.60(1H, s), 8.03(1H, s), 9.58(1H, br s), 12.68(1H, s), 15.01(1H, br s) FAB-MS: 615$(M+H)^+$
16	160 red solid (MeOH)	^{1}H-NMR[$(CD_3)_2CO$]: δ 1.09(3H, d, *J*=6.0), 1.85-1.88(2H, m), 2.22(3H, s), 3.56-3.64(2H, m), 3.57(3H, s), 3.84-3.92(3H, m), 4.01-4.08(1H, m), 4.08-4.14(1H, m), 5.49(2H, s), 7.25(1H, br s), 7.36(1H, br s), 7.59(1H, s), 8.01(1H, s), 12.70(1H, br s), 15.03(1H, br s) FAB-MS: 525$(M+H)^+$

1) The ^{1}H-NMR spectra of **3b**, **12b** and **13b** are very similar to those of **3a**, **12a** and **13a**, respectively.

8 position, because the stereochemistry between C-4a and C-8a was presumed to be *cis* according to experimental facts.[5)] The mixture was led to the enone **10** by phenylselenylation and H_2O_2 oxidation. Hydride reduction of **10** with de-*O*-benzoylation was followed by oxidation to afford a 3 : 1 mixture of the aldehyde **11**, which was isolated by silica-gel column chromatography (toluene - acetone 3 : 1) to give **11a** [the major product: Rf 0.45 on TLC (toluene - acetone 1 : 1)] and **11b** (the minor: Rf 0.40). Direct de-*O*-benzoylation of **10** gave no desired product. The *C*-methyl group was introduced onto the aldehydes **11a** and **11b** by Grignard reaction and the resulting alcohols were oxidized[6)] to the corresponding methyl ketones **12a** and **12b**, respectively. While all the asymmetric centers at C-4a, C-8 and C-8a disappeared by aromatization on the later stage (**3**→**14**), all isomers were isolated and used for the next step to obtain the optically active products. Each compound **12a** and **12b** was treated with acetaldehyde in the presence of optically active diisopinocampheylchloroborane (Ipc_2BCl)[7)] to give the alcohol **13a** and **13b**, respectively, each of which was a 1 : 1 diastereomeric mixture due to the newly produced asymmetric center. Although many kinds of enantioselective aldol reaction conditions were tested,[8)] the optically active UCE6 (**1**), which could be finally derived from the product **13a** or **13b**, was not obtained. However, only the use of Ipc_2BCl gave a fairly good yield of diastereomers **13a** and **13b**, which were converted into **3a** and **3b**, respectively, by *O*-benzylation and ethylene acetal formation.

With **2** and **3** in hand, we turned to the tandem Michael-

Dieckmann type reaction[3] (Scheme 3). The coupling was effectively carried out by treatment with $LiN(TMS)_2$ to yield the tetracyclic product, which was aromatized to the racemic alcohol **14** as a single product under mild oxidation conditions by reduction of benzyl methyl ether in the presence of Pd-C. One of the two *O*-MOM groups was recognized to be readily removed by the effect of the quinone carbonyl group. De-*O*-phosphonation of **14** to give **15** was followed by removal of *O*-benzyl group to produce quantitatively **16**. Finally, all protective groups of **16** were removed to give the desired product, UCE6 (**1**), which was identical in all respects with the natural product.[9]

Acknowledgment

We are grateful to Advanced Research Institute for Science and Engineering, Waseda University, and High-Tech Research Center Project the Ministry of Education, Science, Sports and Culture for the generous support of our program. The present work was financially supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture.

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(Received August 5, 2002)

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