Total synthesis of urdamycinone B *via* *C*-glycosidation of an unprotected sugar and Diels–Alder reaction of *C*-glycosyl juglone

Goh Matsuo, Yuko Miki, Masaya Nakata, Shuichi Matsumura and Kazunobu Toshima*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223, Japan

The total synthesis of *C*-glycosyl angucycline, urdamycinone B 1, was achieved *via* *C*-glycosidation of naphthol 6 and the unprotected D-olivose 7, and Diels–Alder reaction of the unprotected *C*-glycosyl juglone 9 and the diene 17 as the key steps.

The angucyclines with a unique benz[*a*]anthraquinone as a common structure are a rapidly growing new class of antibiotics and show a variety of biological activities including antitumour activity and enzyme inhibition.[1] Among them, urdamycinone B **1**, which is obtained from antibiotic urdamycin B by careful cleavage of the two *O*-glycoside moieties, also exhibits antitumour activity.[2] The elegant total syntheses of (−)-urdamycinone B, the enantiomer of the natural urdamycinone B, and urdamycinone B **1** have been reported by Yamaguchi[3] and Sulikowski,[4] respectively. Here we report the total synthesis of *C*-glycosyl angucycline, urdamycinone B **1**, by a novel strategy, Fig. 1.

Our synthetic approach began with the conversion of juglone **2** into the glycosyl acceptor **6**, Scheme 1.† Naphthol **6** was readily obtained using standard procedures in four steps and in 61% overall yield. The aryl *C*-glycosidation[5] of **6** and the unprotected D-olivose **7** was accomplished by a method recently developed in our laboratories.[6] Thus the reaction of **6** (2.0 equiv.) and **7** (1.0 equiv.) in the presence of $Me_3SiOSO_2CF_3$ (0.5 equiv.) in MeCN at 25 °C for 1 h gave the desired aryl β-*C*-glycoside **8** in 27% yield as the only isolated product. This novel approach led to the total synthesis of urdamycinone B **1** without using any protecting group in the sugar moiety. The β-*C*-naphthylglycoside **8** was then debenzylated by hydrogenolysis using 10% Pd–C in MeOH at 25 °C for 1 h to afford directly the unprotected *C*-glycosyl juglone **9** in 78% yield.

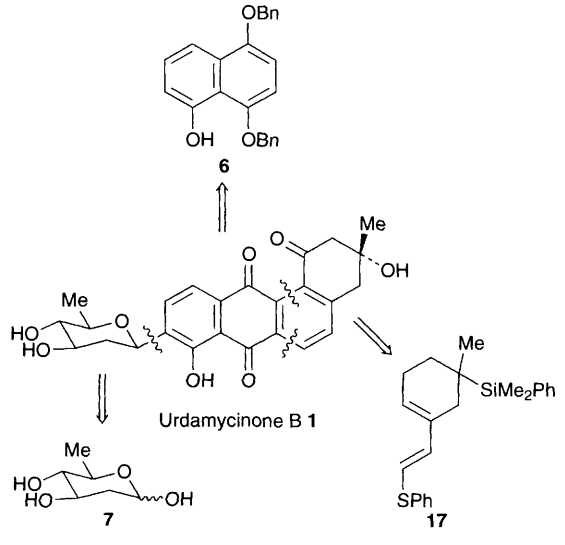
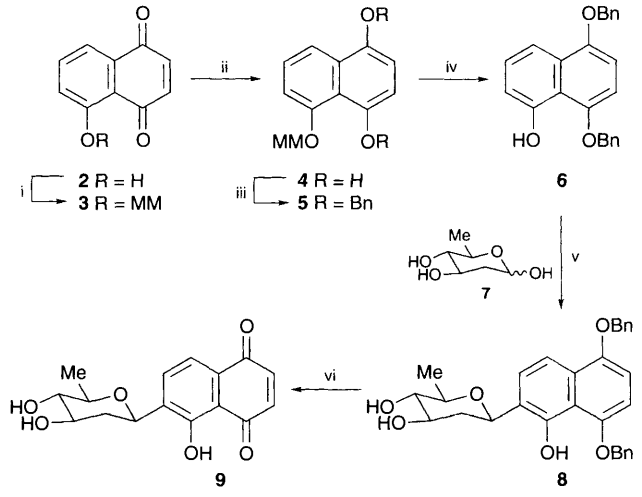
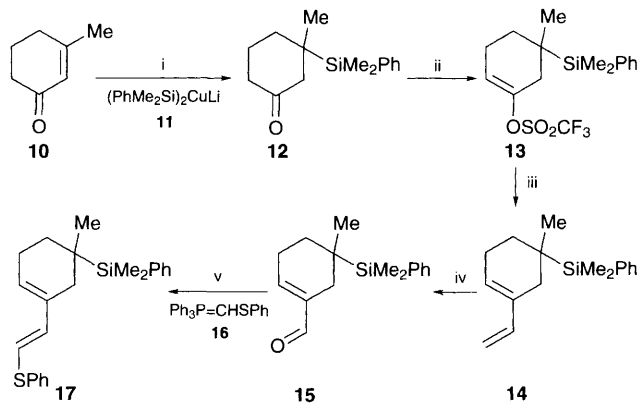


Fig. 1 Urdamycinone B **1** and its proposed retrosynthetic analysis

With the *C*-glycosyl juglone **9** as a dienophile for the Diels–Alder reaction in hand, our attention turned to the preparation of an appropriate diene (Scheme 2). For this purpose, cyclohexanone **12**,[7] which was obtained from 3-methylcyclohex-2-enone **10** and the silylcuprate **11**, was selected as the starting material. The cyclohexanone **12** had a phenyldimethylsilyl group as a masked hydroxy group.[8] Regioselective enolate formation of **12** with LDA and trapping of the intermediate enolate with $(CF_3SO_2)_2NPh$ afforded only the desired regioisomer of the vinyl triflate **13** in 94% yield. The high



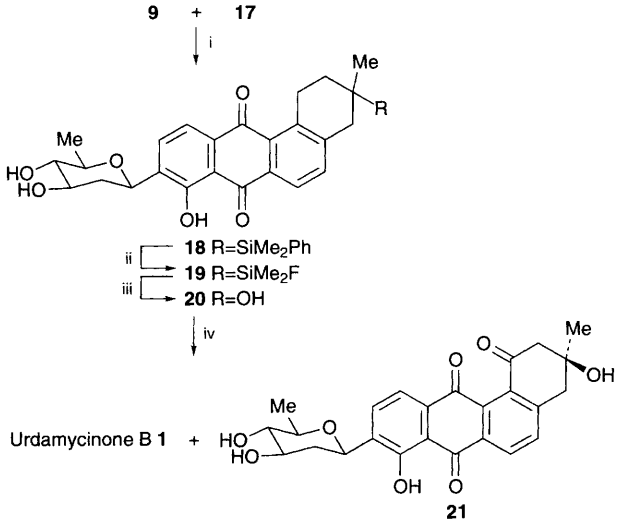
Scheme 1 *Reagents and conditions*: i, $MeOCH_2Cl$ (MMCl) (4.0 equiv.), NaH (3.0 equiv.), THF, 25 °C, 18 h, 85%; ii, H_2, 10% Pd–C, EtOAc, 25 °C, 1 h; iii, BnBr (3.0 equiv.), NaH (3.4 equiv.), DMF, 25 °C, 1 h, 86% from **3**; iv, CF_3CO_2H (1.2 equiv.), CH_2Cl_2, 25 °C, 1 h, 85%; v, $Me_3SiOSO_2CF_3$ (0.5 equiv.), MeCN, 25 °C, 1 h, 27%; vi, H_2, 10% Pd–C, MeOH, 25 °C, 1 h, 78%



Scheme 2 *Reagents and conditions*: i, ref. 7; ii, LDA (1.0 equiv.), $(CF_3SO_2)_2$ NPh (1.1. equiv.), THF, −78 to 25 °C, 1 h, 94%; iii, CH_2=$CHSnBu_3$ (1.1 equiv.), $(Ph_3P)_4Pd$ (0.02 equiv.), LiCl (7.0 equiv.), DMF, 70 °C, 1 h, 93%; iv, AD-mix-β, Bu^tOH–H_2O, 0 °C, 12 h then $NaIO_4$ (2.0 equiv.), THF–H_2O, 25 °C, 1.5 h, 81%; v, THF, 25 °C, 0.5 h, 77%

regioselectivity resulted from a combination of the steric shielding from the methyl and silyl groups and the β-effect of the silicon.[9] The cross-coupling reaction[10] of the vinyl triflate **13** and vinyltributyltin using a catalytic amount of $(Ph_3P)_4Pd$ and LiCl in DMF at 70 °C for 1 h yielded the diene **14** in 93% yield. The selective dihydroxylation of the *exo* double bond in **14** by the Sharpless AD reaction[11] with AD-mix-β followed by oxidative cleavage of the resulting diol using $NaIO_4$ gave the α,β-unsaturated aldehyde **15** in 81% overall yield. The subsequent Wittig reaction of **15** with phenylthiomethylene triphenylphosphorane **16** (2.0 equiv.)[12] in THF proceeded stereospecifically to give only the desired (*EE*)-diene **17** in 77% yield.

We next focused on the cycloaddition of **17** with **9** and total synthesis of **1** (Scheme 3). The regiospecific Diels–Alder cycloaddition between the unprotected *C*-glycosyl juglone **9** (1.0 equiv.) and the diene **17** (1.0 equiv.) using $B(OAc)_3$[13] followed by treatment of the resulting product by DBU afforded the cycloadduct **18** in 58% overall yield. Conversion of the silyl group into the tertiary hydroxy group was achieved by the Fleming's method[8,14] in two steps to give **20** *via* the fluoride **19** in 42% overall yield. Finally, the oxygenation of **20** was successfully carried out by mild photooxygenation,[15] in which



Scheme 3 *Reagents and conditions*: i, $B(OAc)_3$ (3.0 equiv.), CH_2Cl_2, 25 °C, 2 h, then DBU (2.2 equiv.), CH_2Cl_2, 25 °C, 0.5 h, 58%; ii, $HBF_4{\cdot}Et_2O$ (20 equiv.), CH_2Cl_2, 25 °C, 2 h, 78%; iii, KF (3.0 equiv.), $KHCO_3$ (3.0 equiv.), 31% H_2O_2 (9.0 equiv.), THF–MeOH, 25 °C, 14 h, 53%; iv, O_2, sunlight, MeOH, 25 °C, 24 h, 71%

a MeOH solution of **20** was exposed to daylight, to furnish urdamycinone B **1** (36%) and the C-3 epimer **21** (35%) after separation by reversed-phase preparative TLC.[3] The structure of the faster moving isomer was confirmed by comparison with natural urdamycinone B (^1H and ^{13}C NMR, IR and $[\alpha]_D$).‡

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Footnotes

† The direct aryl *C*-glycosidations of juglone **2** and olivose **7** under several conditions were unsuccessful.

‡ Although urdamycinone B **1** and the C-3 epimer **21** showed very similar ^1H and ^{13}C NMR and IR spectra, the $[\alpha]_D$ differed significantly. Also see ref. 3.

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