Efficient Stereoselective Synthesis of 2-Aza-4′-demethylepipodophyllotoxin

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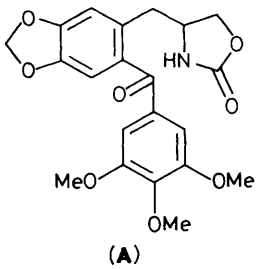
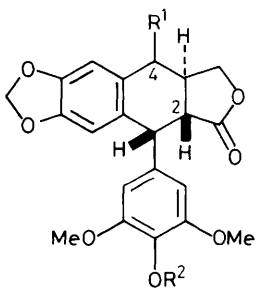
2-Aza-4′-demethylepipodophyllotoxin (**6**) has been efficiently synthesized in 40% yield from (**7**) in three steps by a highly regioselective and stereoselective cyclization of (**8**) with (**9**).

A long and fascinating history of podophyllotoxin, (**1**) in medicine has recently culminated in the semi-synthetic epi-analogues of clinically useful anticancer drugs (**2**) (etoposide and teniposide).[1,2] Since isomerization of cytotoxic (**1**) to inactive picropodophyllin is suggested to occur *via* epimerization at the C-2 centre under physiological conditions,[3] it is interesting to explore new podophyllotoxin analogues which cannot lose their configurational integrity at the C-2 centre. Recently we have reported a convenient synthesis of the 2-aza-4-deoxy-analogue (**3**), as a model study, by the reaction of (**7**) with (**9**).[4] We report here an efficient synthesis of 2-aza-4′-demethylepipodophyllotoxin (**6**).[5]

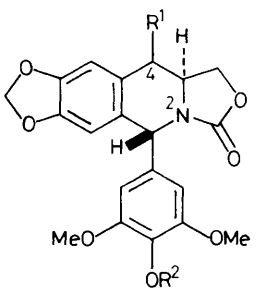
After exhaustive and fruitless attempts to introduce hydroxy group equivalents at the C-4 position of (**3**)†, we focused on the cyclization of (**8**) with (**9**). Treatment of (**7**)[4] with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[6] in acetic acid at 60 °C for 48 h provided (**8**) as a mixture of two diastereoisomers (10 : 7) in 70% yield (Scheme 1).‡ A mixture of (**8**) and (**9**) was treated with trifluoromethanesulphonic acid (2 equiv.) in CH_2Cl_2 at 0 °C to provide an intractable mixture. However, dilution with acetic acid was found to be effective in



(**A**)



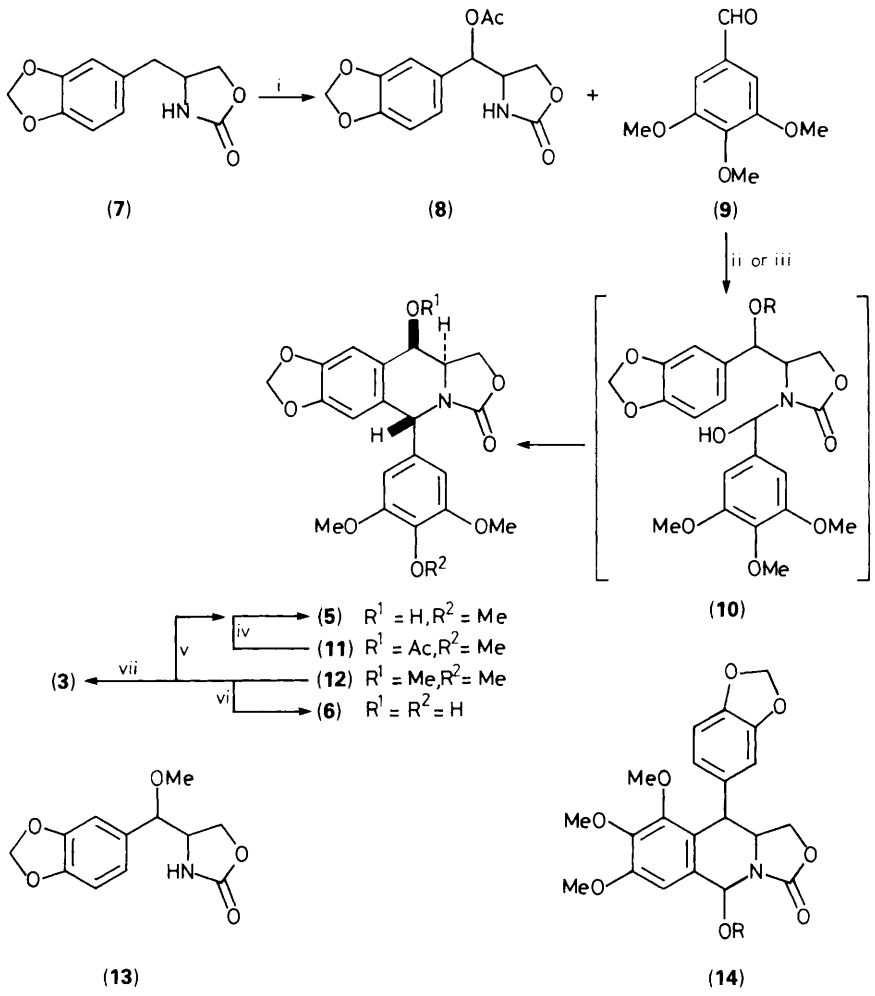
(**1**) R^1 = α-OH, R^2 = Me
(**2**) R^1 = β-*O*-sugar, R^2 = H



(**3**) R^1 = H, R^2 = Me
(**4**) R^1 = α-OH, R^2 = Me
(**5**) R^1 = β-OH, R^2 = Me
(**6**) R^1 = β-OH, R^2 = H

† For example, (**A**) (m.p. 159—161 °C) was obtained in 86% yield by treating (**3**) with DDQ.

‡ The compounds described are racemic and provided satisfactory analytical and spectroscopic data.



Scheme 1. *Reagents and conditions*: i, DDQ/AcOH, 60 °C, 48 h, 70%; ii, CF_3SO_3H/AcOH–CH_2Cl_2, 4 °C, 24 h, 34% for (**11**); iii, CF_3SO_3H/MeOH–CH_2Cl_2, 0 °C, 37 h, 94% for (**12**); iv, K_2CO_3/MeOH, room temp., 10 h, 95%; v, 10% aq. HCl/dioxane, 50 °C, 5 h, 82% for (**5**) and 12% for (**4**); vi, HBr/Cl$(CH_2)_2$Cl, 4 °C, 22 h, and then $BaCO_3$/aq. THF, room temp., 16 h, 60% for (**6**); vii, Et_3SiH/CF_3CO_2H, room temp., 1 h, 93%.

producing the desired (**11**). Thus reaction of (**8**) with (**9**) in a mixture of CH_2Cl_2 and acetic acid (10 : 1) in the presence of trifluoromethanesulphonic acid (2 equiv.) at 4 °C for 24 h afforded (**11**) (m.p. 236.5—237.5 °C) as a single isomer in 34% yield. Dilution with methanol (CH_2Cl_2–MeOH 10 : 1) afforded (**12**) (m.p. 225.5—226.5 °C) as a single isomer in 94% yield. The structure of (**12**) was determined by n.m.r. analysis and by chemical conversion to (**3**). Nuclear Overhauser enhancement was observed on irradiation of aromatic protons of the trimethoxyphenyl ring, which resulted in a 6% increase in integration at the H-3 methine proton; this indicates that (**12**) has a 1,3-*trans* relation. Further, the coupling constant between H-4 and H-3 is 1.8 Hz, indicating β-OMe at the C-4 position. Ionic reduction of (**12**) with Et_3SiH in CF_3CO_2H afforded (**3**) in 93% yield, also supporting the structural assignment of (**12**).

Since the intermediate (**13**) (3 : 2 mixture of two diastereoisomers) was isolated in 78% yield along with (**12**) (19%) when the reaction was conducted in the presence of sulphuric acid in CH_2Cl_2–MeOH (10 : 1), (**12**) is assumed to be produced *via* (**13**), by methanol attack on the corresponding benzylic cation species of (**8**). Cyclization is considered to proceed regioselectively *via* a benzylic cation species derived from the possible intermediate (**10**) to give (**11**) and (**12**) without formation of (**14**), which would arise from the alternative benzylic cation species. Stereoselective formation of the 1,3-*trans*-cyclization product is reasonable in light of the greater stability of the 1,3-*trans* isomer compared to the 1,3-*cis* isomer. Stereoselective formation of the C-4 centre would be the result of preferential attack of the oxy-functionality (MeOH and acetic acid) at the C-4 benzylic cation of (**11**) and (**12**), avoiding steric interference of the pseudo-axial trimethoxyphenyl ring.

The ester exchange reaction of the acetate (**11**) in the presence of K_2CO_3 in methanol provided the hydroxy compound (**5**) (m.p. 223—225 °C, decomp.) in 95% yield. The methoxy compound (**12**) was also converted to (**5**) and (**4**) (m.p. 225 °C) in 82 and 12% yields, respectively, by treatment with 10% aqueous HCl in dioxane.

The 4′-demethylepipodophyllotoxin analogue (**6**) (m.p. 246—248 °C) was synthesized in 60% yield by treating (**12**) with hydrogen bromide in 1,2-dichloroethane and then with $BaCO_3$ in aqueous tetrahydrofuran (THF). The C_2 symmetry of 3′,5′-dimethoxy-4′-hydroxyphenyl group of (**6**) was established by ^1H n.m.r. spectroscopy.§

§ *Spectroscopic data* for (**6**): ^1H n.m.r. (400 MHz, $CDCl_3$) δ 3.81 (s, 6H, OMe ×2), 5.53 (s, 1H, ArOH), and 6.43 (s, 2H, ArH).

Compounds (**4**), (**5**), (**6**), (**11**), and (**12**) exhibited promising growth inhibition against cells derived from human carcinoma of the nasopharynx (KB) [ED_{50} (**4**) <0.3, (**5**) <0.3, (**6**) 4.55, (**11**) 0.62, (**12**) 2.75 μg/ml].

Further studies including synthesis and anticancer activity evaluation of optically active compounds will be reported in a forthcoming article.[7] A part of the work was financially supported by a grant from the Hoansha Foundation and by Grant-in-Aid for Scientific Research (No. 01571143), the Ministry of Education, Science and Culture, Japan.

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