Total synthesis of (*S*)-espicufolin and absolute structure determinaton of espicufolin

Hidemitsu Uno,*[a] Katsuji Sakamoto,[a] Erina Honda[a] and Noboru Ono[b]

[a] *Advanced Instrumentation Center for Chemical Analysis, Ehime University, Bunkyo-cho 2-5, Matsuyama 790-8577, Japan. E-mail: uno@dpc.ehime-u.ac.jp*

[b] *Department of Chemistry, Faculty of Science, Ehime University, Bunkyo-cho 2-5, Matsuyama 790-8577, Japan*

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(*S*)-Espicufolin was synthesized from 1,4-dimethoxybenzene in 16 steps *via* an intramolecular acyl-transfer reaction as the key step; the absolute stereochemistry at the 14-position of natural espicufolin was determined to be *R*.

In the disease ischemia, L-glutamic acid in the brain is believed to play an important role as an excitatory neurotransmitter, increasing the level of powerful oxidants such as superoxide anion and oxygen radicals in the neuronal cells, which then cause neuronal cell death.[1] Neuronal cell-protecting compounds for such events have attracted increasing attention from scientists in many fields. In 1996, Seto *et al.* found a novel neuronal cell-protecting substance in the culture broth of *Streptomyces* sp. cu39 in the course of their screening for suppressors of glutamate toxicity using neuronal hybridoma N18-RE-105 cells and named it espicufolin (**1**, Fig. 1).[2] However, the action mechanism of espicufolin **1** was suggested not to relate to antioxidative activity, from an experiment involving buthionine sulfoximine toxicity.[2,3] From a structural viewpoint, espicufolin **1** has an anthraquinone skeleton fused with a γ-pyrone ring and one unknown stereogenic centre at the 14-position. Espicufolin **1** is considered as a new member of the pyranoanthraquinone family;[4] these compounds are also reported to show antitumor and antibiotic activity. Thus, we aimed to synthesize espicufolin **1** *via* a route which can be applied to the syntheses of other family members in addition to espicufolin analogues.

Since the regioselective Diels–Alder reaction of chloronaphthoquinone with 1-methoxycyclohexa-1,3-diene has been established as one of the most reliable methods for construction of anthraquinones bearing hydroxy groups, we required pyranonaphthoquinone **2**. First, we focussed on the preparation of the intermediate **2** from the readily available naphthol **3** (Scheme 1), which was obtained from 1,4-dimethoxybenzene in 22% yield (5 steps).[5] As attempts to introduce an acetyl group at the 2-position of **3** *via* a Friedel–Crafts reaction and a Fris rearrangement failed, probably due to steric encumbrance, we thought to utilise the neighbouring hydroxymethyl group at the 3-position. After selective acetylation of the primary hydroxy group of **3** (90%), iodination[6] of **6** was carried out in CH_2Cl_2 (0.2 mol l^{-1}) to give **5** regioselectively in 31% yield, in addition to a mixture of dimers (38%). The dimer formation was simply suppressed by using an increased volume of solvent (0.05 mol l^{-1}) to give **5** in 77% yield. Protection with a MOM group followed by saponification of the acetyl group afforded **7** in 77% yield. The alcohol **7** was condensed with (*S*)-4-methylhex-2-ynoic acid,[7] which was in turn prepared from commercially available (*S*)-2-methylbutan-1-ol according to a literature procedure,[8] by treatment with bis(2-oxo-1,3-oxazolidin-3-yl)-phosphinic chloride (BOPCl) and Et_3N to afford **8** in 97% yield.[9] By treatment of **8** with Bu^nLi at −78 °C, a smooth iodine–lithium exchange reaction followed by spontaneous intramolecular acyl transfer occurred to give 2-acylnaphthalene **9**† in almost quantitative (95%) yield as an equilibrium mixture

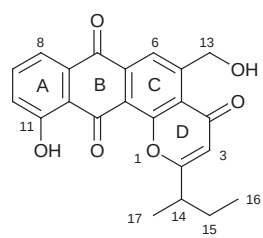
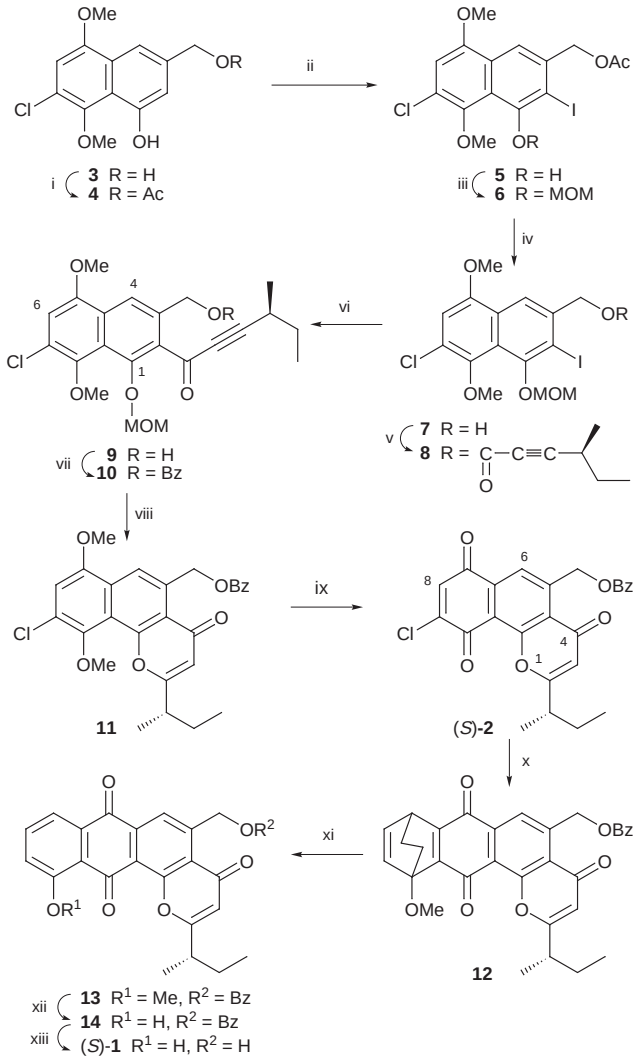


Fig. 1 Structure and numbering of espicufolin **1**.



Scheme 1 *Reagents and conditions*: i, Ac_2O, $HClO_4$, CH_2Cl_2, rt; ii, I_2, *N*-methylmorpholine, CH_2Cl_2, rt; iii, NaH, MOMCl, DMF, rt; iv, NaOH, aq. THF–MeOH, rt; v, *S*-4-methylhex-2-ynoic acid, BOPCl, Et_3N, CH_2Cl_2, rt; vi, BuLi, THF, −78 °C; vii, BzCl, Py, rt; viii, HCl, aq. THF–Pr^iOH, reflux; ix, CAN, aq. MeCN, 0 °C; x, 1-methoxycyclohexa-1,3-diene, CH_2Cl_2, rt; xi, 140 °C, neat; xii, BBr_3, −78 °C; xiii, NaOH, aq. THF–MeOH, 0 °C.

with its hemiacetal form. This mixture was treated with BzCl in pyridine to give benzoate **10** in 87% yield. Removal of the MOM group from **10** under acidic conditions brought about simultaneous intramolecular cyclization forming desired γ-pyrone **11** (64%) predominantly; formation of any furanone compound could not be detected. This cyclization was formally thought to be a successful example of the *6-endo-dig* process, which usually competed the *5-exo-dig* ring closure giving furanones in the cases under basic conditions.[10] However, it is not clear at this moment if the allenic carbocation generated by protonation to the ynone carbonyl oxygen is directly attacked by the intramolecular phenolic oxygen or by water followed by dehydrative ring closure.[11] The γ-pyrone **11** was converted to the intermediate **2**† in 75% yield.

The one-pot method[5] of anthraquinone formation from naphthoquinones and 1-methoxycyclohexa-1,3-diene was applied for construction of the A ring of **1**. However, an intractable mixture was obtained due to decomposition probably by HCl. Thus, the Diels–Alder adduct from **2** and 1-methoxycyclohexa-1,3-diene was treated with pyridine to afford the diastereomeric quinone **12** in 77% yield. Heating **12** at 140 °C afforded anthraquinone **13** in good yield (74%). Demethylation of **13** with BBr_3 (75%) followed by saponification (69%) gave (*S*)-espicufolin, spectral and physical data† of which were identical to those previously reported, except for $[\alpha]_D$.[2] The value for synthetic (*S*)-**1** was $[\alpha]_D^{23}$ −11 (*c* 0.021, $CHCl_3$), whereas the authentic espicufolin kindly provided by Professor Seto was $[\alpha]_D^{23}$ +9.4 (*c* 0.020, $CHCl_3$). Therefore, the unknown stereochemistry at the 14-position can be assigned as *R*; our synthetic sample is an enantiomer of natural espicufolin. Espicufolin must therefore be synthesized starting from (*R*)-2-methylbutanol, which can be readily prepared by a literature procedure.[12]

We have achieved the synthesis of the enantiomer of neuronal cell-protecting espicufolin in 1.3% overall yield from 1,4-dimethoxybenzene in 15 steps. The absolute stereochemistry of espicufolin **1** is determined to be *R*.

Notes and references

† *Selected data* for **9**: pale yellow crystals, mp 92–93 °C; 6 : 1 mixture of keto and hemiacetal forms in $CDCl_3$ at ambient temperature; keto form: δ_H 1.03 (3H, t, *J* 7.3, H6′), 1.24 (3H, d, *J* 7.3, 4′-Me), 1.56 (2H, m, H5′), 2.63 (1H, m, H4′), 3.04 (1H, br t, *J* 6.4, OH), 3.58 (3H, s, OCH_2OMe), 3.84 (3H, s, 5- or 8-OMe), 3.95 (3H, s, 5- or 8-OMe), 4.71 (2H, d, *J* 6.4, CH_2OH), 5.10 (3H, s, OCH_2OMe), 6.83 (1H, s, H6) and 8.04 (1H, s, H4); δ_C 11.5 (C6′), 19.4 (4′-Me), 28.1 (C5′), 29.0 (C4′), 56.0 (OCH_2OMe), 58.1 (5- or 8-OMe), 61.6 (5- or 8-OMe), 63.6 (CH_2OH), 83.3 (C2′), 101.3 (C3′), 102.2 (OCH_2OMe), 107.8, 119.0, 122.3, 125.9, 128.0, 133.9, 136.2, 144.7, 151.4, 152.0 and 181.8 (C1′); hemiacetal form (1 : 1 diastereomeric mixture): δ_H 1.02 (3H both, t, *J* 7.3, H5′), 1.18 (3H of one diastereomer, d, *J* 7.3, 3′-Me), 1.19 (3H of another diastereomer, d, *J* 7.3, 3′-Me), 1.53 (2H, m, H4′), 2.49 (1H, m, H3′), 3.71 (3H of one diastereomer, s, OCH_2OMe), 3.72 (3H of another diastereomer, s, OCH_2OMe), 3.85 (3H both, s, 5- or 8-OMe), 3.96 (3H both, s, 5- or 8-OMe), 5.0–5.4 (5H, m, CH_2OH and OCH_2OMe), 6.81 (1H both, br s, H6) and 7.89 (1H both, br s, H4); δ_C(typical signals) 14.0 (C6′), 15.2 (C6′), 20.2 (4′-Me), 20.2 (4′-Me), 27.5 (C5′), 27.5 (C5′), 29.5 (C4′), 29.6 (C4′), 57.9, 61.5, 65.8, 71.2 (C3), 71.2 (C3), 79.8 (C1′), 89.3, 98.5, 101.4, 101.4, 102.2, 106.6, 111.3, 123.0, 124.8, 129.2, 135.1, 137.8, 137.8, 144.9 and 147.0; ν_{max}(KBr)/cm^{-1} 3456, 2200, 1650, 1334 and 1068. For **2**: yellow needles, mp 196–198 °C; δ_H($CDCl_3$) 0.98 (3H, t, *J* 7.3, H3′), 1.43 (3H, d, *J* 6.7, 1′-Me), 1.80 (1H, m, H2′), 1.96 (1H, m, H2′), 2.74 (1H, m, H1′), 6.16 (2H, s, CH_2OBz), 6.31 (1H, s, H3), 7.26 (1H, s, H8), 7.53 (2H, m, *m*-Bz), 7.64 (1H, m, *p*-Bz), 8.19 (2H, m, *o*-Bz) and 8.25 (1H, s, H6); δ_C($CDCl_3$) 11.7 (C3′), 17.9 (1′-Me), 27.3 (C2′), 40.5 (C1′), 65.3 (CH_2OBz), 111.1 (C3), 118.9 (C6), 125.1 (C4a or C10a), 128.6 (*m*-Ph), 129.6 (*i*-Ph), 129.8 (*o*-Ph), 133.4 (*p*-Ph or C8), 134.0 (*p*-Ph or C8), 134.6 (C6a), 147.3 (C5 or C9), 147.9 (C5 or C9), 155.8 (C10b), 166.0 (Ph*C*O), 173.6 (C2), 174.9 (C4), 178.7 (C10), 181.5 (C7) and one carbon (C4a or C10a) could not be identified; ν_{max}(KBr)/cm^{-1} 1716, 1680, 1651, 1267, 883 and 711. For **1**: orange needles, mp 185–187 °C (184–186 °C for natural espicufolin[2]); δ_H(DMSO-d_6) 0.93 (3H, t, *J* 7.3, H16), 1.38 (3H, d, *J* 6.8, H17), 1.75 (1H, m, H15), 1.92 (1H, m, H15), 2.78 (1H, m, H14), 5.16 (2H, t, *J* 4.8, H13) 5.56 (1H, t, *J* 4.8, 13-OH), 6.34 (1H, s, H3), 7.38 (1H, d, *J* 8.3, H10), 7.68 (1H, d, *J* 7.3, H8), 7.77 (1H, dd, *J* 8.3, 7.3, H9), 8.51 (1H, s, H6) and 12.6 (1H, s, 11-OH); δ_C(DMSO-d_6) 11.2 (C16), 17.3 (C17), 26.6 (C15), 39.2 (C14), 62.1 (C13), 110.3 (C3), 116.6 (C11a), 118.5 (C8), 118.7 (C6), 119.6 (C12a), 123.9 (C4a), 124.4 (C10), 132.0 (C7a), 135.9 (C6a), 136.4 (C9), 153.1 (C5), 155.5 (C12b), 161.2 (C11), 172.4 (C2), 178.1 (C4), 181.4 (C7) and 186.8 (C12); ν_{max}(KBr)/cm^{-1} 3473, 1676, 1647, 1583, 1460, 1272 and 1220; *m/z* (EI) (20 eV) 378 (100%), 349 (18), 320 (9.1) and 267 (21) (Calc. for $C_{22}H_{18}O_6$: 378.1103. Found: 378.1104).

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