Total Synthesis of Silychristin, an Antihepatotoxic Flavonolignan

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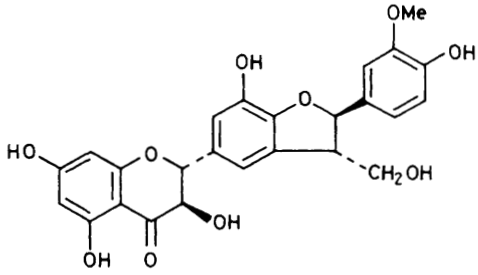
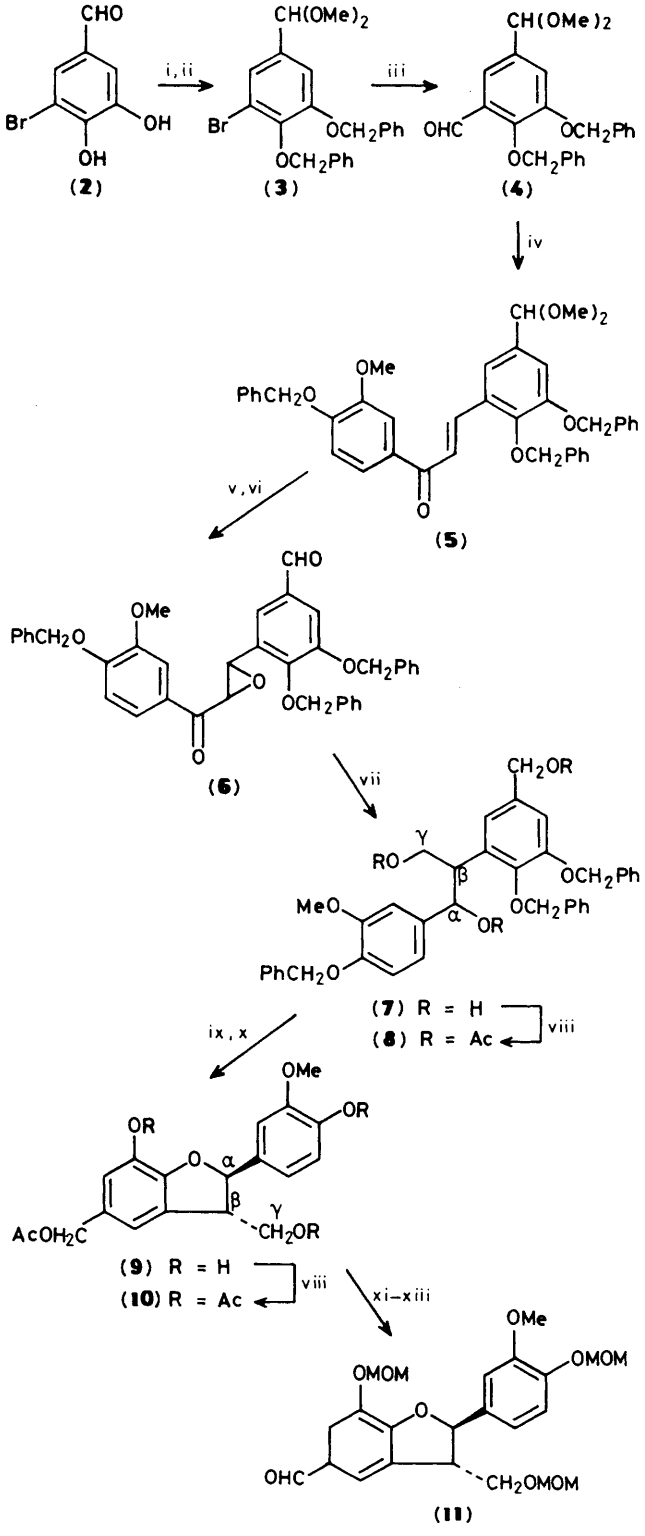
The first total synthesis of silychristin is reported; the key intermediate [the dihydrobenzofuran (**9**)] was easily prepared in three steps from the readily available chalcone epoxide (**6**).

Silychristin (**1**), a component of the antihepatotoxic flavonolignans,[1] has been isolated[2] from seeds of *Silybum marianum* and the structure was established by Wagner *et al.*[3] and Zanarotti.[4] This compound possesses a novel skeleton which consists of a highly substituted dihydrobenzofuran ring and a flavanonol moiety.

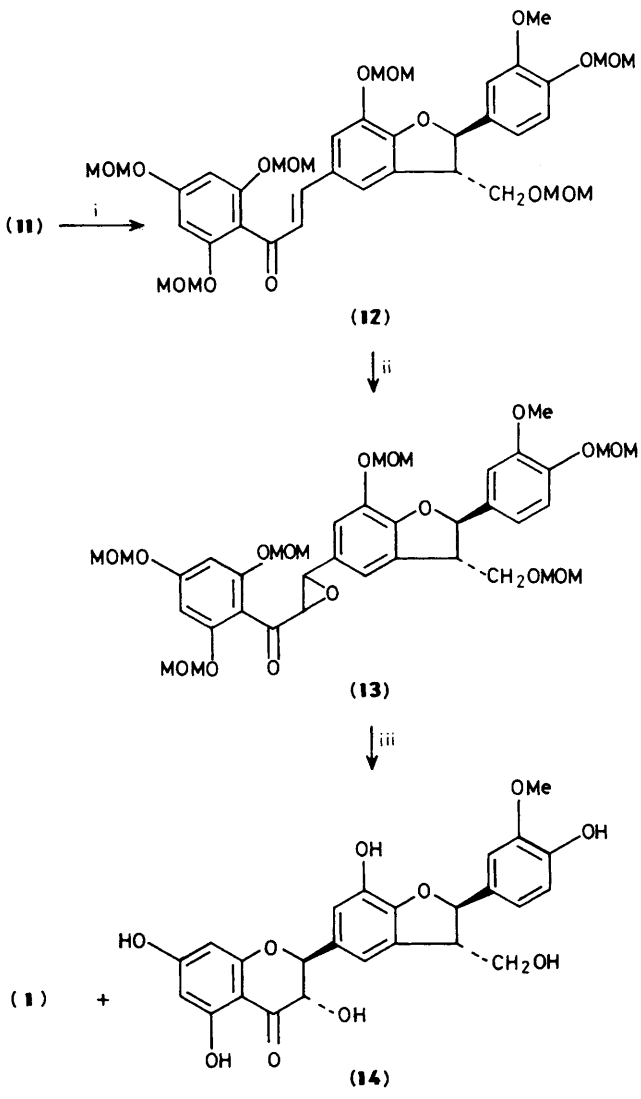
We now report an efficient total synthesis of silychristin *via* a condensation reaction of the aldehyde (**11**) with 2,4,6-trimethoxymethoxyacetophenone, and also describe a facile transformation of the *trans*-dihydrobenzofuran (**9**) from a readily available chalcone epoxide (**6**) according to the procedure developed by Brunow and Lundquist.[5]



(**1**)



Scheme 1. *Reagents and conditions (yields)*: i, $PhCH_2Cl$, K_2CO_3, DMF (86%); ii, $CH(OMe)_3$, NH_4Cl, MeOH (91%); iii, Bu^nLi, dry Et_2O, then DMF, −78 °C to room temp. (94%); iv, 4-benzyloxy-3-methoxyacetophenone, KOH, absolute EtOH (93%); v, conc. HCl, MeOH, dioxane (87%); vi, 30% H_2O_2, 5% NaOH, MeOH, dioxane (92%); vii, $BF_3{\cdot}Et_2O$, dry benzene, 0 °C, then $NaBH_4$, THF (39%); viii, Ac_2O, pyridine [(**8**) 97, (**10**) 92%]; ix, H_2, 10% Pd–C, MeOH (66%); x, $BF_3{\cdot}Et_2O$, AcOH (77%); xi, methoxymethyl chloride (MOMCl), Pr^i_2NEt, dry CH_2Cl_2 (66%); xii, 1M NaOH, MeOH (91%); xiii, active MnO_2, CH_2Cl_2 (95%).



Scheme 2. *Reagents and conditions (yields)*: i, 2,4,6-trimethoxymethoxyacetophenone, NaOH, absolute EtOH (94%); ii, 30% H_2O_2, 5% NaOH, MeOH (96%); iii, conc. HCl, MeOH, 70 °C.

The aldehyde segment (**11**) was prepared as follows (Scheme 1). The chalcone (**5**) was obtained in four steps from 5-bromo-3,4-dihydroxybenzaldehyde (**2**). Benzylation of (**2**), followed by acetalization, gave (**3**),† which was converted into (**4**) by treatment with n-butyl-lithium and dimethylformamide (DMF). Compound (**4**) was condensed with 4-benzyloxy-3-methoxyacetophenone under alkaline conditions affording the chalcone (**5**) in good yield. As the acetal group in (**5**) was sensitive to alkaline hydrogen peroxide, this was removed by treatment with HCl prior to epoxidation which afforded the chalcone epoxide (**6**). Treatment of (**6**) with boron trifluoride–diethylether ($BF_3{\cdot}Et_2O$) in benzene at 0 °C and subsequent reduction with $NaBH_4$ provided a mixture which, after separation by column chromatography, afforded exclusively

† All new compounds were characterized on the basis of their spectroscopic data and high resolution mass spectra and/or elemental analyses.

the *erythro*-diarylpropanediol (**7**).‡ Debenzylation of (**7**) with hydrogen over a palladium catalyst followed by reaction with $BF_3 \cdot Et_2O$ in acetic acid at 5 °C gave the more thermodynamically stable[6] *trans*-dihydrobenzofuran (**9**) as a single product.‡ Protection of the hydroxyl groups in (**9**) (by methoxymethylation) followed by elimination of the acetyl group, afforded a benzyl alcohol derivative which was oxidized with manganese dioxide to yield the aldehyde (**11**). Base-catalysed condensation of (**11**) with 2,4,6-trimethoxymethoxyacetophenone provided the chalcone (**12**) in good yield, which on treatment with alkaline hydrogen peroxide gave the unstable epoxide (**13**) (Scheme 2).

‡ *Data* for (**8**), the acetate of (**7**): colourless oil, ^{1}H n.m.r. ($CDCl_3$, 270 MHz): δ 1.89, 1.92, 2.11 (9H, 3 × s, 3 × OAc), 3.70 (3H, s, OMe), 3.89 (1H, dd, *J* 7.1 and 11.1 Hz, γ-H), 4.04 (1H, m, β-H), 4.22 (1H, dd, *J* 6.1 and 11.1 Hz, γ-H), 4.60 (1H, d, *J* 11.1 Hz, OCH_2Ph), 4.96 (1H, d, *J* 11.1 Hz, OCH_2Ph), 5.05 (2H, d, *J* 2.0 Hz, CH_2OAc), 5.10, 5.11 (4H, 2 × s, 2 × OCH_2Ph), 6.06 (1H, d, *J* 7.8 Hz, α-H), 6.66 (1H, d, *J* 1.7 Hz), 6.72 (1H, dd, *J* 1.7 and 8.4 Hz), 6.78 (1H, d, *J* 8.4 Hz), 6.94 (1H, *J* 1.7 Hz), 7.02 (1H, *J* 1.7 Hz), 7.23—7.46 (15H, m).

For (**10**), the acetate of (**9**): colourless oil, ^{1}H n.m.r. ($CDCl_3$, 270 MHz): δ 2.08, 2.09 (6H, 2 × s, 2 × OAc), 2.31 (6H, s, 2 × OAc), 3.74 (1H, m, β-H), 3.83 (3H, s, OMe), 4.30 (1H, dd, *J* 7.7 and 11.1 Hz, γ-H), 4.45 (1H, dd, *J* 5.7 and 11.1 Hz, γ-H), 5.03 (2H, s, CH_2OAc), 5.59 (1H, d, *J* 5.7 Hz, α-H), 6.89 (1H, dd, *J* 2.0 and 8.4 Hz), 7.01 (1H, d, *J* 1.7 Hz), 7.02 (1H, d, *J* 8.4 Hz), 7.03 (1H, d, *J* 2.0 Hz), 7.09 (1H, d, *J* 1.7 Hz).

Finally, on heating with HCl at 70 °C, (**13**) underwent removal of the methoxymethyl groups and simultaneous cyclization to yield silychristin (**1**) and its diastereoisomer (**14**) which, after separation by chromatography on silica gel followed by h.p.l.c. (octadecylsilane), furnished the pure silychristin (**1**) in 19% yield. The synthetic silychristin (**1**) was identified by comparison of its spectroscopic data and chromatographic behaviour (t.l.c. and h.p.l.c.) with those of an authentic sample.[4]

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