

Total Synthesis of Silychristin, an Antihepatotoxic Flavonolignan

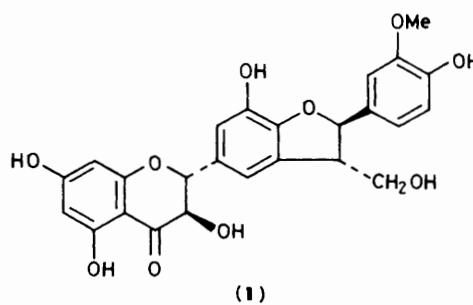
Hitoshi Tanaka, Masaru Hiroo, Kazuhiko Ichino, and Kazuo Ito*

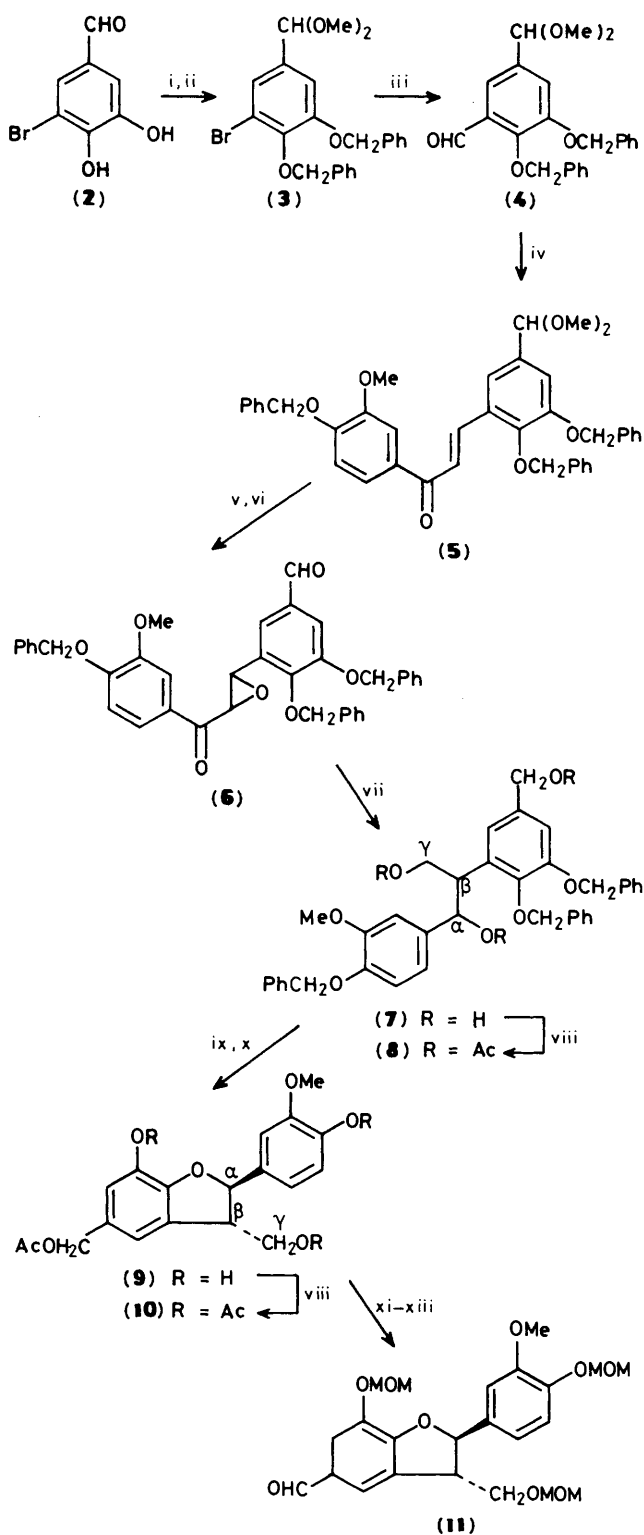
Faculty of Pharmacy, Meijo University, Tempaku-ku, Nagoya 468, Japan

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).

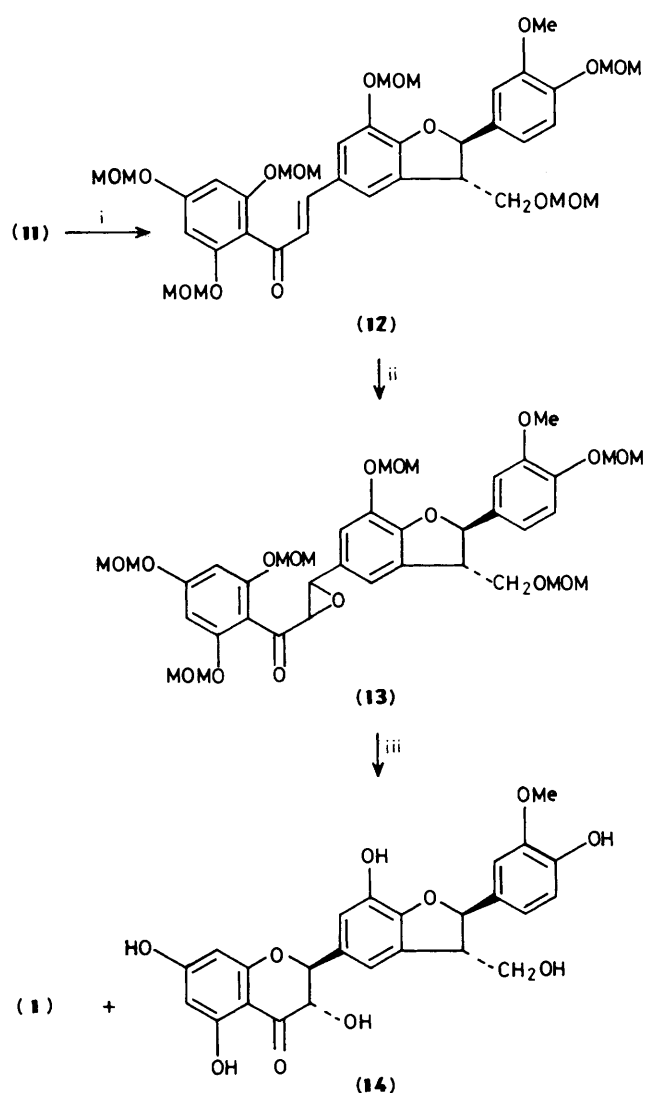
Silychristin (1), a component of the antihepatotoxic flavonolignans,¹ has been isolated² from seeds of *Silybum marianum* and the structure was established by Wagner *et al.*³ and Zanarotti.⁴ This compound possesses a novel skeleton which consists of a highly substituted dihydrobenzofuran ring and a 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





Scheme 1. Reagents and conditions (yields): i, PhCH_2Cl , K_2CO_3 , DMF (86%); ii, $\text{CH}(\text{OMe})_2$, 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, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, 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, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, AcOH (77%); xi, methoxymethyl chloride (MOMCl), Pr_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-trimethoxy-methoxyacetophenone, 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). Benzylolation 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 ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) 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 $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in acetic acid at 5 °C gave the more thermodynamically stable⁶ *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, ¹H 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, ¹H 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

We thank Professor A. Zanarotti, Politecnico di Milano, Dipartimento di Chimica for the supply of silychristin and Professor H. Wagner, München University, for spectral data (¹H n.m.r. and i.r.) for silychristin.

Received, 18th January 1988; Com. 8/001521

References

- 1 H. Hikino, Y. Kiso, H. Wagner, and M. Fiebig, *Planta Med.*, 1984, **50**, 248.
- 2 H. Wagner, O. Seligmann, L. Hörhammer, M. Seitz, and J. Sonnenbichler, *Tetrahedron Lett.*, 1971, 1895.
- 3 H. Wagner, O. Seligmann, M. Seitz, D. Abraham, and J. Sonnenbichler, *Z. Naturforsch., Ser. B*, 1976, **31**, 876.
- 4 A. Zanarotti, *Heterocycles*, 1982, **19**, 1585.
- 5 G. Brunow and K. Lundquist, *Acta. Chem. Scand., Ser. B*, 1984, **38**, 335.
- 6 R. Baker, N. G. Cooke, G. R. Humphrey, S. H. B. Wright, and J. Hirshfield, *J. Chem. Soc., Chem. Commun.*, 1987, 1102.