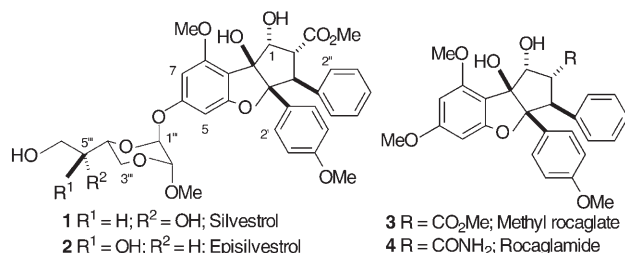


Total Synthesis of (–)-Episilvestrol and (–)-Silvestrol**

Mariana El Sous, Mui Ling Khoo, Georgina Holloway, David Owen, Peter J. Scammells, and Mark A. Rizzacasa*

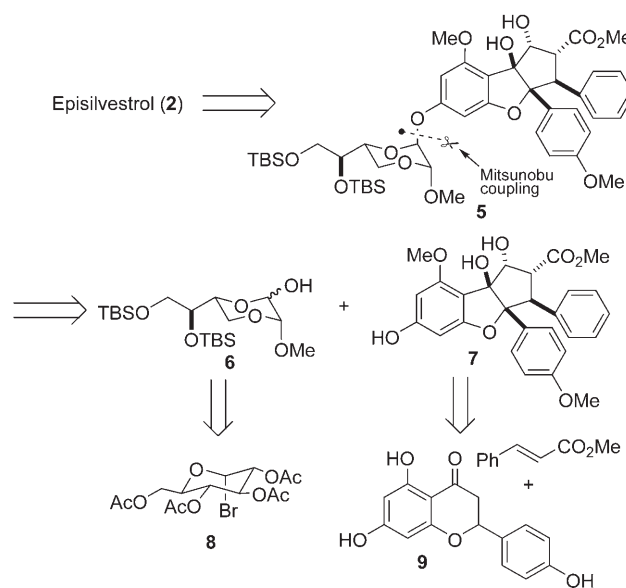
Extracts of the bark of the woody South-East Asian shrub *Aglaia leptantha*, Miq. (Meliaceae) show potent cytotoxic activity, which is attributed to two new molecules **1** and **2**.^[1]



Compounds **1** and **2** are diastereoisomers (epimers at 5'') that contain a common cyclopenta[*b*]benzofuran core,^[2] found in the related *Aglaia* metabolites aglaifolin^[3] (methyl rocaglate, **3**)^[4–6] and rocaglamide (**4**),^[6,7] as well as a novel, unprecedented 1,4-dioxanyloxy pseudosugar substituent. In addition, two metabolites, named silvestrol and episilvestrol were isolated from *Aglaia foveolata* Pannell by Kinghorn and co-workers and found to be identical to **1** and **2**, respectively.^[8] The structure of silvestrol (**1**) has been determined by NMR spectroscopy and X-ray analysis of a derivative which served to confirm the relative and absolute configuration of this compound.

Both silvestrol (**1**) and episilvestrol (**2**) show comparable potent cytotoxic activity against several human tumor cell lines including lung, prostate, and breast cancer with IC₅₀ values ranging from 1 to 7 nM.^[1,8] Recently, it has been demonstrated that the cytotoxicity induced by silvestrol (**1**) in human prostate cancer (LNCaP) cells is associated with a block in the cell cycle at the G2/M checkpoint.^[9] Specifically, compound **1** alters the expression of genes regulating apoptosis and cell cycle in a way that is not dependent on human tumor protein 53 (p53). Interestingly, compounds that possess only the parent cyclopenta[*b*]benzofuran, such as **3** and **4**, are significantly less active, suggesting that the presence of the 1,4-dioxanyloxy group is critical for activity.^[1] The in vivo activity of **1** has also been demonstrated. Administration of silvestrol (**1**) by intraperitoneal injection (3 mg kg^{–1}) to athymic mice with human prostate cell xenografts reduced tumor weights by about 60% after 29 days, while the body weight of the mouse was unaffected.^[1] Unfortunately, the paucity of both **1** and **2** from the natural source (0.01% isolated yield) precludes isolation as a sufficient supply of these important compounds. Therefore, an efficient chemical synthesis is an attractive alternative for accessing quantities of **1** or **2** as well as analogues for further biological evaluation. We now report the total synthesis of (–)-episilvestrol (**2**) and (–)-silvestrol (**1**) from common simple precursors which could address the supply problem.^[10]

Our retrosynthesis of episilvestrol (**2**; Scheme 1) is inspired, in part, by the proposed biosynthesis of the two



Scheme 1. Retrosynthetic analysis of episilvestrol (**2**). TBS = *tert*-butyl-dimethylsilyl.

[*] Dr. M. El Sous, M. L. Khoo, Prof. Dr. M. A. Rizzacasa
School of Chemistry
Bio21 Institute, The University of Melbourne
Melbourne, Victoria 3010 (Australia)
Fax: (+61) 3-9347-8396
E-mail: masr@unimelb.edu.au
Homepage: <http://www.chemistry.unimelb.edu.au/staff/masr/research/MARHomepage.html>

Dr. D. Owen^[†]
Cerylid Biosciences
Richmond, Victoria (Australia)

Dr. G. Holloway, Prof. Dr. P. J. Scammells
Department of Medicinal Chemistry
Victorian College of Pharmacy, Monash University
381 Royal Parade, Melbourne, Victoria 3052 (Australia)

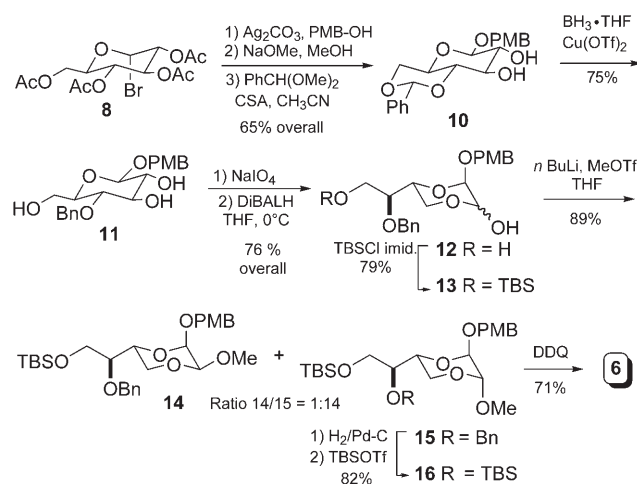
[†] Current address:
Starpharma Pty Ltd., Baker Building
75 Commercial Rd, Melbourne, Victoria 3004 (Australia)

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key fragments: the cyclopentabenzofuran core^[2,11] and the 1,4-dioxanyloxy fragment.^[12] Episilvestrol (**2**) could be produced by deprotection of precursor **5**, which in turn could be secured by a modified Mitsunobu-type^[13] coupling between the hemiacetal **6** and core phenol **7**. Compound **6** could arise from the known D-glucose derivative **8** by following a route based on a biosynthetic proposal suggested by us.^[12] The cyclopentabenzofuran core **7** could be secured from commercially available ($\pm$)-4',5,7-trihydroxyflavanone (naringenin, **9**) and methyl cinnamate by adapting the elegant oxidopyrylium [3+2] cycloaddition approach to these systems as reported by Porco and co-workers.^[5,6]

The synthesis of the dioxane fragment **6** (Scheme 2) is based on our approach to a model system.^[12] Glycosylation of commercially available bromide **8** with *p*-methoxybenzyl

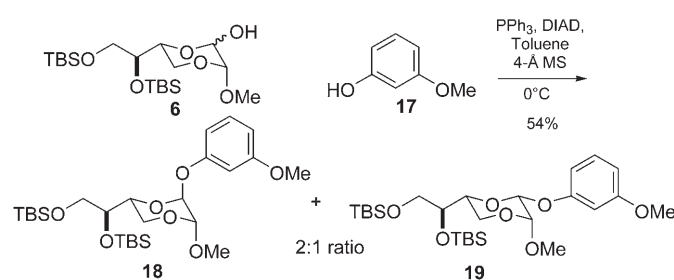


Scheme 2. Synthesis of 1,4-dioxane fragment **6**. PMB = *p*-methoxybenzyl, Bn = benzyl, CSA = 10-camphorsulfonic acid, DIBAL-H = diisobutylaluminum hydride, OTf = trifluoromethanesulfonate, DDQ = dichlorodicyanobenzoquinone.

alcohol mediated by silver carbonate followed by methanolysis of the acetate groups and benzylidene formation gave acetal **10**^[14] in a reasonable overall yield. Exposure of **10** to $\text{BH}_3\cdot\text{THF}$ in the presence of $\text{Cu}(\text{OTf})_2$ ^[15] effected highly selective C–O6 benzylidene cleavage to afford the O4-protected sugar **11**. Periodate cleavage^[16] followed by immediate selective reduction of the resultant aldehyde-lactol afforded lactol as an approximately 1:3 mixture of anomers.

Selective protection of the primary alcohol as the TBS ether and subsequent methylation of the lactol mixture using butyllithium and methyl triflate^[17] gave the desired axial product **15** in high yield, along with a small amount of equatorial ketal **14**. The observed selectivity can be explained by rapid alkylation of the intermediate axial alkoxide at faster rate than the corresponding equatorial alkoxide. A protecting-group exchange was then carried out to swap the benzyl ether for a TBS group to provide **16**. DDQ-induced removal of the PMB group gave the lactols **6** as a roughly 1:1 mixture.

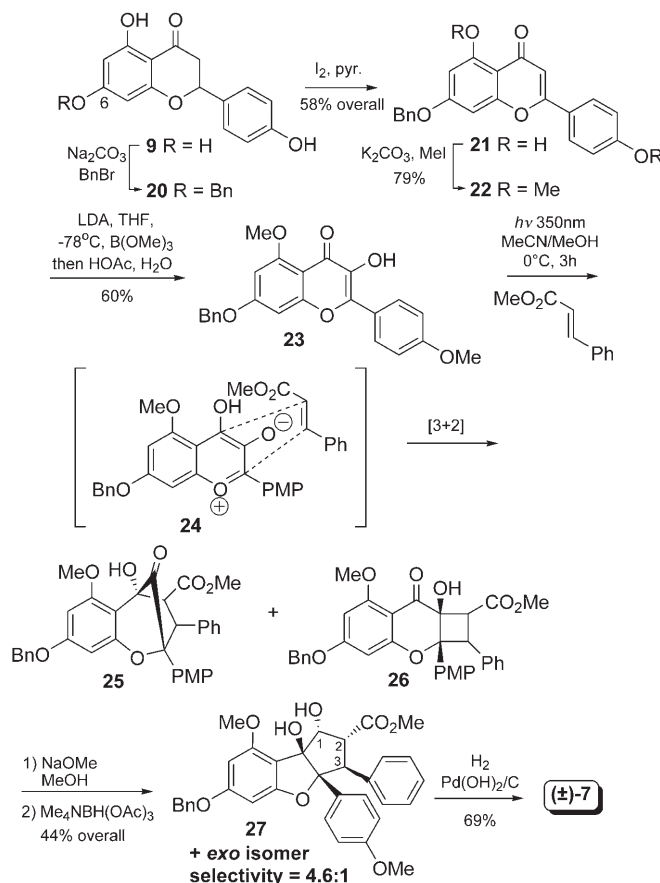
After some experimentation, we found that the Mitsunobu reaction as utilized by Roush and Lin for the synthesis of *O*-aryl glycosides^[18] could be applied to couple the model phenol **17** and lactols **6** (Scheme 3). The addition of 4-Å molecular



Scheme 3. Model Mitsunobu coupling. DIAD = diisopropylazodicarboxylate.

sieves was critical to the success of this reaction, and the adducts **18** and **19** were obtained in 54% yield favoring the desired axial isomer **18**. With the success of this coupling in a model system, we next prepared the aromatic core **7** required for the production of **2**.

The synthesis of the required cyclopentabenzofuran core **7** was achieved as detailed in Scheme 4. Selective O6 benzylation of ($\pm$)-naringenin (**9**) using Na_2CO_3 as base afforded ether **20**, which was oxidized to the flavone **21** upon exposure to iodine in pyridine. Methylation provided the ether **22**, which could be converted into the cycloaddition precursor **23** through C3 deprotonation with LDA^[19] and



Scheme 4. Synthesis of the cyclopentabenzofuran core ($\pm$)-**7**. Bn = benzyl, LDA = lithium diisopropylamide, pyr. = pyridine, PMP = *p*-methoxyphenyl.

quenching of the trimethylborate followed by oxidative workup. Irradiation^[20] of the 3-hydroxyflavone **23** (350 nm, 450-W medium-pressure Hg lamp) generated the dipole **24**, which underwent cycloaddition^[5] with methyl cinnamate to give a complex mixture of the adduct **25** along with the cyclobutane **26**, presumably as a result of an alternative [2+2] cycloaddition^[21] or α -ketol rearrangement. Treatment of this mixture with base, in analogy to that reported by Porco and co-workers,^[5] induced α -ketol rearrangement to a thermodynamically preferred β -ketoester, and subsequent selective *anti* reduction^[22] afforded the desired cyclopentabenzofuran **27** along with the corresponding *exo* isomer in a ratio of 4.6:1, respectively. The stereochemistry of the major *endo* isomer was assigned on the basis of its ¹H NMR spectrum, which displayed signals at δ = 5.03 ppm (1H, d, J = 6 Hz, H1), 4.31 ppm (1H, d, J = 14 Hz, H3), and 3.90 ppm (1H, dd, J = 14, 6 Hz, H2) suggesting a 1,2-*cis*, 2,3-*trans* arrangement. These H1–H3 signals matched those observed for episilvestrol (**2**).^[8] Hydrogenolysis of **27** gave the desired core **7** as a racemate. This short sequence provided useful quantities of ($\pm$)-**7** ready for coupling to the dioxane fragment.

The pivotal Mitsunobu coupling between **6** and ($\pm$)-**7** proceeded with selectivity for the desired axial diastereoisomers in reasonable yield based on recovered core **7** (Scheme 5). A higher selectivity for the axial isomers ($\approx$ 6:1 ax/eq ratio) was obtained when the coupling was run at 0°C and not warmed to room temperature, however, the con-

version was lower (14%, 49% based on recovered **7**). As expected, the combination of racemic core **7** with optically pure **6** afforded two major axial diastereoisomers **28** and **5** in equal amounts which were inseparable by conventional flash chromatography. Subsequent normal-phase HPLC (5 μ m silica, 250 mm $\times$ 10 mm, 2 mL min⁻¹ with 50% EtOAc/petroleum ether eluent) cleanly separated the isomers **5** (R_t = 10.10 min) and **28** (R_t = 10.48 min). It was difficult at this stage to determine which was the correct isomer required for the production of **2**, however, deprotection the slower eluting compound with TBAF afforded diastereoisomer **29** while deprotection of the isomer with the shorter retention time on HPLC, namely compound **5**, then afforded (–)-episilvestrol (**2**).

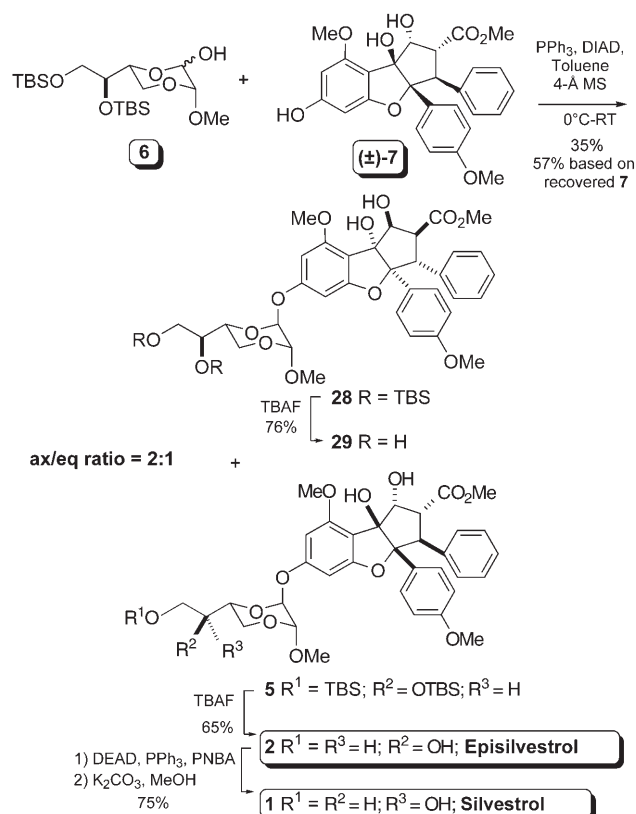
Synthetic episilvestrol (**2**) ($[\alpha]_D^{25}$ = –91.3, c = 0.03, CHCl₃) was identical to natural **2**^[1,8] (lit.^[8] $[\alpha]_D^{20}$ = –94.5, c = 0.43, CHCl₃) in all respects (¹H and ¹³C NMR, IR, and mass spectra), while isomer **26** ($[\alpha]_D^{24}$ = –23.9, c = 0.09, CHCl₃) displayed slightly different physical data. In addition, synthetic episilvestrol (**2**) displayed anticancer activity against human colon cancer cells LIM 1215 (IC₅₀ = 2.0 nM) comparable to that reported for the natural product, whilst compound **29** was less active by at least one order of magnitude (IC₅₀ = 56 nM). Thus, it appears that the stereochemistry of the core has some influence on the cytotoxicity. Finally, conversion of episilvestrol (**2**) into silvestrol (**1**) was easily achieved by a selective “double Mitsunobu” reaction, which resulted in inversion at 5'' (Scheme 5).^[10]

In conclusion, we have achieved a total synthesis of episilvestrol (**2**; 21 steps in total; longest linear sequence of 13 steps) from readily available precursors through a route inspired by the possible biogenesis of these compounds. In addition, episilvestrol (**2**) was converted into silvestrol (**1**). With the development of an asymmetric approach to the cyclopentabenzofuran core,^[6] the efficient synthesis of **2** and analogues which are not available from the natural products themselves is possible.

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Scheme 5. Completion of the total synthesis of episilvestrol (**2**) and silvestrol (**1**). TBAF = tetra-*n*-butylammonium fluoride, DEAD = diethylazodicarboxylate, PNBA = *p*-nitrobenzoic acid.

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