Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 293–295
Tetrahedron Letters

Biomimetic synthesis of the novel 1,4-dioxanyloxy fragment of silvestrol and episilvestrol

Mariana El Sous and Mark A. Rizzacasa*

School of Chemistry, The University of Melbourne, Victoria 3010, Australia

Received 28 October 2004; accepted 9 November 2004
Available online 26 November 2004

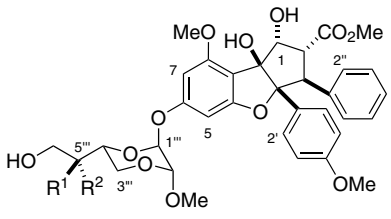
Abstract—The biomimetic synthesis of the 1,4-dioxanyloxy fragment of silvestrol (**1**) and episilvestrol (**2**) from D-glucose is described.

Aglaia is a large genus of the family Meliaceae, which consists of over 100 species of mostly woody trees and shrubs found throughout the rainforests of Indo-Malaysia. Extracts of the bark of *Aglaia leptantha*, Miq. (Meliaceae) showed potent cytotoxic activity, which was attributed to two new molecules **1** and **2** (Fig. 1).[1] Compounds **1** and **2** contain a common cyclopenta[*b*]benzofuran core found in the related *Aglaia* metabolites aglafolin (methyl rocaglate) (**3**)[2,3] and rocaglamide (**4**)[4,5] as well as a novel, unprecedented 1,4-dioxanyloxy 'pseudosugar' substituent. Initially, the dioxanyloxy moiety was placed at C8 of the cyclopenta[*b*]benzofuran core[1] but was later corrected to be located at C6 by extensive spectroscopic analysis of the derived 5‴,6‴-diacetate.[6]

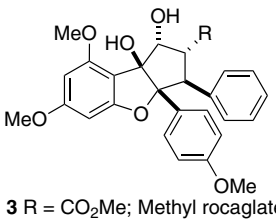
Recently, two metabolites, named silvestrol and episilvestrol were isolated from *Aglaia foveolata* Pannell, by Kinghorn and co-workers and found to be identical to **1** and **2**, respectively.[7] The structure of silvestrol (**1**) was determined by X-ray analysis of the derived 5‴,6‴-di-*p*-bromobenzoate, which served to confirm the relative and absolute configuration of this compound.[7]

Both silvestrol (**1**) and episilvestrol (**2**) showed comparable potent cytotoxic activity against several human tumour cell lines including lung (for **1** $LC_{50} = 11\,nM$,[6] $ED_{50} = 1.2\,nM$[7]), prostate (for **1** $LC_{50} = 12\,nM$,[6] $ED_{50} = 1.5\,nM$[7]) and breast cancer[7] ($ED_{50} = 1.5\,nM$). Interestingly compounds, which possess only the parent core cyclopenta[*b*]benzofuran are significantly less active than **1**, in particular against THP-1 (human promonocytic leukaemia) cells, suggesting the presence of the unusual dioxanyloxy group is critical for activity.[6]

Several syntheses of rocaglamide **4**[8] have been reported, while Porco and co-workers have described an elegant



1 R^1 = H; R^2 = OH; Silvestrol
2 R^1 = OH; R^2 = H; Episilvestrol

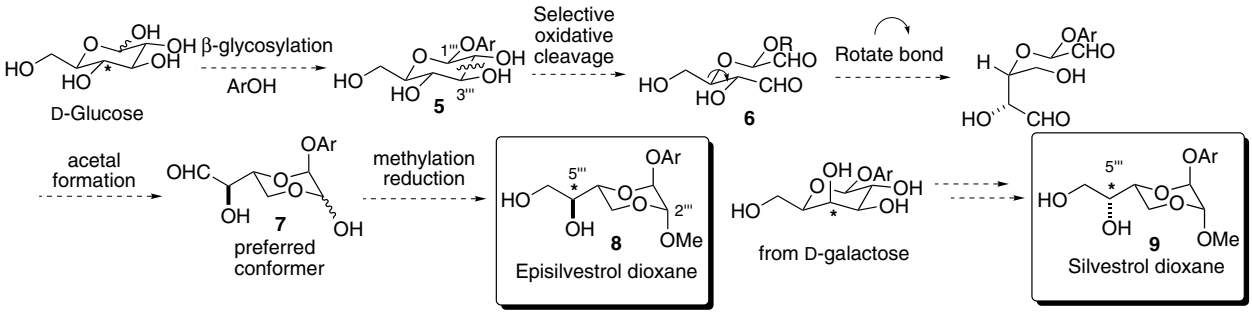


3 R = CO_2Me; Methyl rocaglate or Aglafolin
4 R = $CONH_2$; Rocaglamide

Figure 1. Related *Aglaia* natural products.

* Corresponding author. Tel.: +61 3 8344 6488; fax: +61 3 9347 5180; e-mail: masr@unimelb.edu.au

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2004.11.057

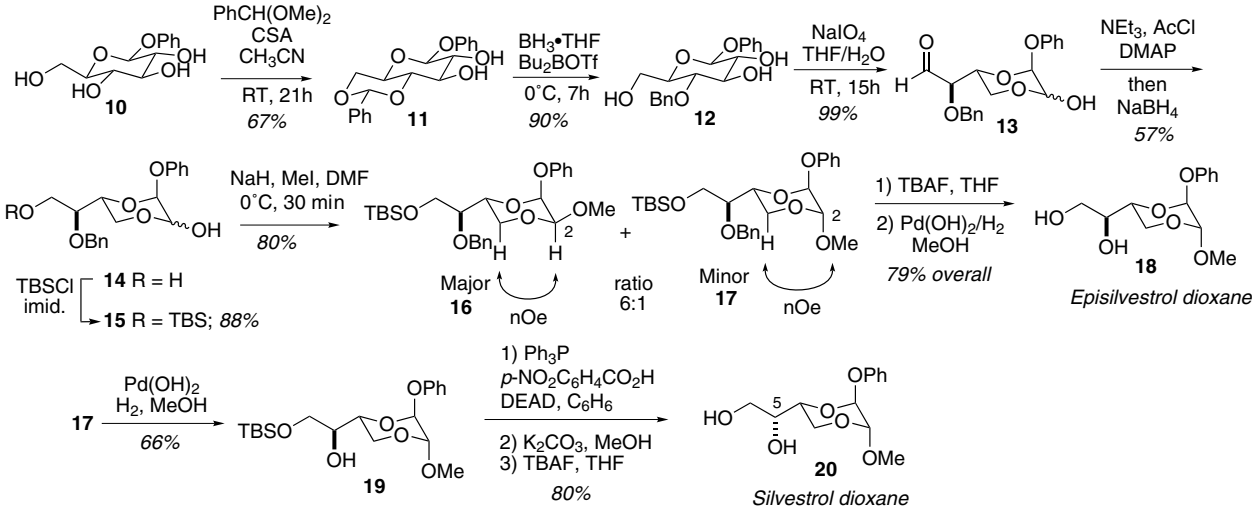


Scheme 1. Proposed biosynthesis of the dioxylanoxy fragment of silvestrol (**1**) and episilvestrol (**2**).

biomimetic synthesis of racemic **3**.[9] We were intrigued by the novel 1,4-dioxanyloxy moiety present in **1** and **2** and now describe a biomimetic approach to this fragment from D-glucose.

A proposed biosynthetic origin of the dioxanyloxy 'pseudosugar' fragment of both **1** and **2** is depicted in Scheme 1. It is not unreasonable to suggest that the 6 carbons of the 1,4-dioxane arise from a rearrangement of a hexopyranoside precursor. Thus, the initially formed β-D-glycoside **5**, generated from glycosylation of the aromatic core with D-glucose, could undergo selective 2,3-oxidative cleavage to provide dialdehyde **6**, which after bond rotation and intramolecular acetal formation gives dioxane **7** as the preferred conformer. Subsequent reduction and acetal methylation then yields the 1,4-dioxanyloxy fragment **8** of episilvestrol (**2**). Thus the stereochemistry at C1‴ originates from the initial β-glucosidation while the stereochemistry at C4‴ is derived from the D-sugar configuration. The stereochemistry at the marked C5‴ asymmetric centre is therefore related to the corresponding C4 hexose configuration. The origin of the C5‴ epimeric dioxanyloxy fragment **9** present in silvestrol (**1**) can be therefore be simply traced back to D-galactose (Scheme 1).

Based on this hypothesis, we embarked on a biomimetic synthesis of the dioxanyloxy system as detailed in Scheme 2. Inspired by the work of Heidleberg and Thiem,[10] we elected to investigate the oxidative cleavage of a C4 protected β-glycoside to avoid anticipated competitive diol cleavage. The route began with commercially available β-D-phenyl glucopyranoside **10** (Scheme 2). Benzylidene formation provided **11**, which upon selective acetal cleavage[11] at C6 yielded the C4 benzyl ether **12**.[12] Treatment with $NaIO_4$[10] smoothly provided the 1,4-dioxane **13** as a ~3:1 anomeric mixture at C2. Reduction of the aldehyde in the presence of the hemiacetal proved challenging but was achieved by temporary lactol acetylation followed by treatment with $NaBH_4$, which resulted in the formation of alcohol **14**. On a large scale, DiBALH proved more effective giving compound **14** in reasonable yield directly from **13**. Selective silylation gave the ether **15** ready for introduction of the C2 methoxy group. Acid mediated acetal formation proved fruitless while several glycosylation[13] methods gave low yields. The most effective method was methylation of the lactol alkoxides with MeI, which provided the methyl acetals **16** and **17** in excellent yield. Unfortunately, the major isomer **16** possessed the incorrect C2 configuration as verified by NOE experiments. The use of MeOTf[14] as the electrophile only gave a slight improvement on the selectivity (ratio **16**:**17** = 5:1) in comparable yield. Deprotection of the minor isomer **17** provided the episilvestrol model 1,4-dioxane **18** in good yield. The NMR data for the model compound **18**



Scheme 2. Synthesis of the model dioxanyloxy fragments of episilvestrol (**2**) and silvestrol (**1**).

Table 1. Comparisons of ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) data for model dioxanes **18** and **20** with dioxanyloxy fragment signals for natural products **2** and **1**

Proton	Diol (**18**)		Episilvestrol (**2**)		Diol (**20**)		Silvestrol (**1**)	
	^{1}H δ, mult, J (Hz)	^{13}C δ	^{1}H δ, mult, J (Hz)	^{13}C δ	^{1}H δ, mult, J (Hz)	^{13}C δ	^{1}H δ, mult, J (Hz)	^{13}C δ
1‴	5.27, s	93.5	5.26, s	93.4	5.34, s	93.5	5.28, s	94.0
2‴	4.60, s	95.4	4.60, s	95.2	4.62, s	95.3	4.59, s	95.2
OCH_3	3.47, s	55.0	3.5, s	55.0	3.49, s	55.0	3.49, s	55.1
3‴H_{ax}	3.97, t, 11.1	59.7	4.02, t, 11.2	59.6	4.13, t, 11.1	59.0	4.13, t, 11.2	59.0
3‴H_{eq}	3.75, dd, 11.1, 2.7		3.78, dd, 11.7, 2.4		3.56, m		3.56, dd, 11.7, 2	
4‴	4.11, m	67.4	4.12, ddd, 11, 7, 2.8	67.6	4.24, dt, 10.8, 2.7	68.4	4.23, br t, 11.3	68.3
5‴	3.56, m	71.6	3.61, dd, 10.4, 4.4	71.4	3.55, m	70.5	3.61, m	70.6
6‴H_a	3.59, br s	62.8	3.66–3.72, m	62.5	3.56, br s	63.5	3.61, br s	63.3
6‴H_b	3.59, br s		3.66–3.72, m		3.56, br s		3.61, br s	

compared very well with the same signals due to the dioxanyloxy fragment in the natural product **2** (Table 1).

The synthesis of the silvestrol dioxanyloxy fragment from D-galactose would require an alternative protecting group strategy so we investigated a route from the common intermediate **17** as shown in Scheme 2. Hydrogenolysis of the benzyl group afforded the alcohol **19**, which was subjected to a modified Mitsunobu inversion.[15] Methanolysis of the resultant *p*-nitrobenzoate and TBS group removal gave the model silvestrol dioxane **20**. Again, the data for compound **20** compared well to the natural product signals for **1** (Table 1).

In conclusion, we have developed an enantiospecific route to the 1,4-dioxanyloxy fragments of silvestrol (**1**) and episilvestrol (**2**) from D-glucose based on a proposed biosynthetic pathway. The total synthesis of **1** and **2** is currently under investigation.

Acknowledgements

We are indebted to Cerylid Pty Ltd (Melbourne, Australia) for generous funding for this project as well as authentic samples of **1** and **2**.

References and notes

1. Meurer-Grimes, B. M.; Yu, J.; Vario, G. L. PTC Int. Appl. WO 2002002566, A1 20020110, 2002, 60pp.
2. (a) Ko, F. N.; Wu, T. S.; Liou, M. J.; Huang, T. F.; Teng, C. M. *Eur. J. Pharmcol.* **1992**, *218*, 129; (b) Wu, T.-S.; Liou, M.-J.; Kuoh, C.-S.; Teng, C.-M.; Nagao, T.; Lee, K.-H. *J. Nat. Prod.* **1997**, *60*, 606.
3. Ishibashi, F.; Satasook, C.; Isman, M. B. *Phytochemistry* **1993**, *32*, 307.
4. King, M. L.; Chiang, C. C.; Ling, H. C.; Fugita, E.; Ochiai, M.; McPhail, A. T. *J. Chem. Soc., Chem. Commun.* **1982**, 1150.
5. Proksch, P.; Edrada, R.; Ebel, R.; Bohnenstengel, F. I.; Nugroho, B. W. *Curr. Org. Chem.* **2001**, *5*, 923.
6. Meurer-Grimes, B. M.; Yu, J.; Vario, G. L. U.S. Patent US6710075 B2, 2004, 28pp.
7. Hwang, B. Y.; Su, B.-N.; Chai, H.; Mi, Q.; Kardono, L. B. S.; Afriastini, J. J.; Riswan, S.; Santarsiero, B. D.; Mesecar, A. D.; Wild, R.; Fairchild, C. R.; Vite, G. D.; Rose, W. C.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M.; Swanson, S. M.; Kinghorn, A. D. *J. Org. Chem.* **2004**, *69*, 3350. Correction: *J. Org. Chem.* **2004**, *69*, 6156.
8. (a) Kraus, G. A.; Sy, J. O. *J. Org. Chem.* **1989**, *54*, 77; (b) Trost, B. M.; Greenspan, P. D.; Yang, B. V.; Saulnier, M. G. *J. Am. Chem. Soc.* **1990**, *112*, 9022; (c) Davey, A. E.; Schaeffer, M. J.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2657.
9. Gerard, B.; Jones, G., II; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 13620.
10. Heidleberg, T.; Thiem, J. *J. Prakt. Chem./Chem. Ztg.* **1998**, *340*, 223.
11. Jiang, L.; Chan, T.-H. *Tetrahedron Lett.* **1998**, *39*, 355.
12. All new compounds provided data in accord with their assigned structures.
13. Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.
14. Schmidt, R. R.; Reichrath, M.; Moering, U. *Tetrahedron Lett.* **1980**, *21*, 3561; Schmidt, R. R.; Reichrath, M.; Moering, U. *J. Carbohydr. Chem.* **1984**, *3*, 67.
15. Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.