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First enantioselective synthesis of methyl (+)-7-methoxyanodendroate, an antitubercular dihydrobenzofuran

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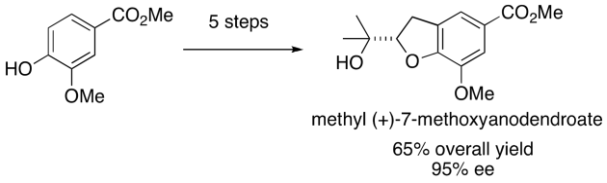

methyl (+)-7-methoxyanodendroate

65% overall yield
95% ee

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First enantioselective synthesis of methyl (+)-7-methoxyanodendroate, an antitubercular dihydrobenzofuran.

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ABSTRACT

An enantioselective synthesis of methyl (+)-7-methoxyanodendroate was achieved utilising a Claisen rearrangement, a Grubbs cross-metathesis, and a Shi epoxidation–cyclisation sequence, confirming the absolute configuration assigned to the natural product.

Methyl (+)-7-methoxyanodendroate (**1**, Figure 1) was first isolated, in 2008, from *Zanthoxylum wutaiense* Chen, an evergreen shrub endemic to the Pingtung County in Taiwan, during an antituberculotic bioactivity-guided screen of approximately 400 species of Taiwanese plants.[1] Compound **1** was shown to possess antitubercular activity against *Mycobacterium tuberculosis* H37Rv with a minimum inhibitory concentration of 35 μg/mL. Its structure[2] was elucidated using mass spectrometry, and 1D and 2D NMR spectroscopic techniques. The absolute configuration at C2 was assigned as the (*S*)-enantiomer, after comparison of the specific rotation of the natural product {$[\alpha]^{24}_{D}$ +31.7 (*c* 0.04, $CHCl_3$)},[1] with that of (–)-(*R*)-anodendroic acid {$[\alpha]^{15}_{D}$ –35.2 (*c* 0.682, EtOH)}.[3]

Insert Figure 1

The chiral 2-substituted 2,3-dihydrobenzofuran structure is present in a number of biologically important compounds and new enantioselective routes to these systems have recently been described.[4-7] Herein, our interest[5,8] in dihydrobenzofuran synthesis continues, and we report the first enantioselective synthesis of **1**, confirming the absolute configuration as methyl (+)-(*S*)-7-methoxyanodendroate.

Our retrosynthetic analysis (Scheme 1) proposed that the dihydrobenzofuran core of **1** could be derived from phenolic epoxide **2**, *via* base-promoted 5-*exo*-*tet* cyclisation. This epoxide would, in turn, be accessed from allylphenol **3** *via* olefin cross-metathesis to efficiently install the prenyl *gem*-dimethyl functionality,[5] and enantioselective epoxidation of the tri-substituted olefin utilising the Shi protocol. Allylphenol **3** would be obtained from commercially available methyl vanillate (**4**) after allylation and Claisen rearrangement of the resultant allyl ether.

Insert Scheme 1

The synthesis of our proposed Shi epoxidation substrate **6** began with allylation of methyl vanillate (**4**),[9] followed by Claisen rearrangement of allyl ether **5** to afford allylphenol **3** in 99% yield, requiring no purification (Scheme 2). Cross-metathesis of the terminal olefin with amylene (2-methylbut-2-ene) in the presence of Grubbs' 2nd generation catalyst furnished the desired prenyl derivative **6**.[10] The crude reaction mixture was adsorbed onto amino-bonded silica gel,[11] and subjected to flash chromatography (on regular silica gel). This proved to be the most effective method for removing ruthenium contaminants.

Insert Scheme 2

With tri-substituted olefin **6** in hand, we turned our attention to the proposed epoxidation–cyclisation sequence (Table 1). One-pot achiral epoxidation–cyclisation of **6** with freshly distilled dimethyldioxirane (DMDO) at 0 °C,[12] followed by direct addition of base (entry 1)[12,13] proceeded in excellent yield. Interestingly, DMDO generated *in situ*[14] caused degradation of our substrate and no epoxide or cyclised product was detected. Having successfully synthesised methyl (±)-7-methoxyanodendroate, an enantioselective strategy was investigated. Shi's epoxidation protocol, employing a chiral fructose-derived catalyst **7**, seemed particularly suitable, due to its proven ability to epoxidise enantioselectively tri-substituted alkenes.[15] Furthermore, Shi's

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mechanism-based correlation between catalyst configuration and resulting epoxide stereochemistry suggested that we could obtain the desired epoxide using the catalyst derived from naturally occurring D-fructose.[16]

Insert Table 1

Attempts to generate chiral epoxide **2** from **6** using a standard Shi epoxidation[16] involving hydrogen peroxide as the oxidant (entry 2)[17] resulted in substrate degradation. Whilst these results were not ideal, they were not altogether unexpected. Previous work within our group,[5] and a lack of precedent in the literature, suggests that Shi epoxidations on substrates bearing a free phenol, such as **6**, generally suffer from poor yields and stereoselectivities. Accordingly, we sought to protect our phenol as a silyl ether. Woggon *et al.* found that they achieved higher enantioselectivity in their Shi epoxidation of a similar prenylphenol using bulkier silyl ethers,[18] so we sought to test this methodology on our system. Protection of phenol **6** as silyl ethers **8a–c** proceeded smoothly in excellent yields. Gratifyingly, Shi epoxidation of the TBDPS ether **8a** using the Shi conditions again (entries 3[16] and 4,[17] respectively) gave the cyclised product **1** *via* epoxide **9a** in good yields and promising enantiomeric enrichment. Use of the H_2O_2-mediated Shi epoxidation conditions[17] (entry 4) provided a better yield. However, attempts to optimise the conditions by altering the temperature and ketone loading (entries 5–7) provided no significant improvement in yield or *ee*. Likewise, other silyl protecting groups (entries 8 and 9) failed to alter significantly the *ee* achieved, suggesting that catalyst **7** is not ideally suited to epoxidation of our substrate. Finally, application of the modified catalyst **10**, described by Shi[19] and Vidal-Ferran[20] using the conditions[20,6] described in entry 10 gave the product **1** in excellent enantiomeric excess (95% *ee*), as determined by chiral HPLC (AD-H column, 20-80% isopropanol in hexane, 1 mL.min^{-1}, R_t(major) 13.2 min, R_t(minor) 7.2 min), and 69% yield. The spectroscopic data (^{1}H and ^{13}C NMR, HRMS) and specific rotation for the synthetic material {$[\alpha]^{25}_D$ +60.4 (*c* 0.54, $CHCl_3$)} confirmed the assigned (*S*)-configuration of the natural product.

In summary, we have developed the first enantioselective total synthesis of the naturally occurring dihydrobenzofuran, methyl (+)-7-methoxyanodendroate (**1**) in 5 steps from commercially available methyl vanillate (**4**), with an overall yield of 65%, and an *ee* of 95%. This synthesis confirms the structure and absolute configuration of the natural product as methyl (+)-(*S*)-7-methoxyanodendroate. Furthermore, it is efficient and scalable, and paves the way for future structure-activity relationship studies.

Acknowledgements

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References and notes

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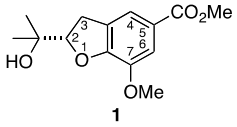
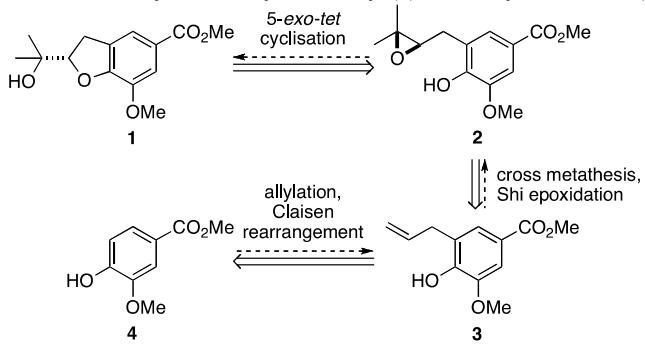
Supplementary Material

Supplementary data (experimental procedures and characterization data for all new compounds; ^{1}H and ^{13}C NMR spectra for all new compounds; chiral HPLC traces for Table 1) associated with this article can be found, in the online version, at doi:

Figure 1. Methyl (+)-7-methoxyanodendroate (**1**).



Scheme 1. Retrosynthetic analysis of methyl (+)-7-methoxyanodendroate (**1**).



Scheme 2 Synthesis of prenylphenol **6**.

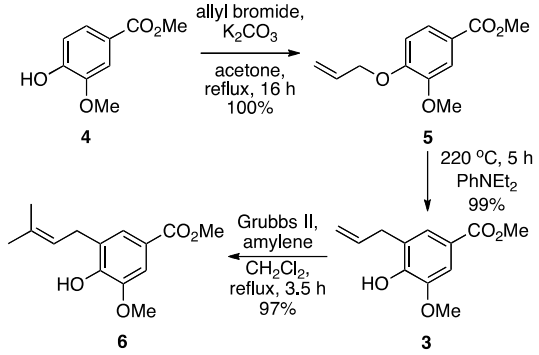
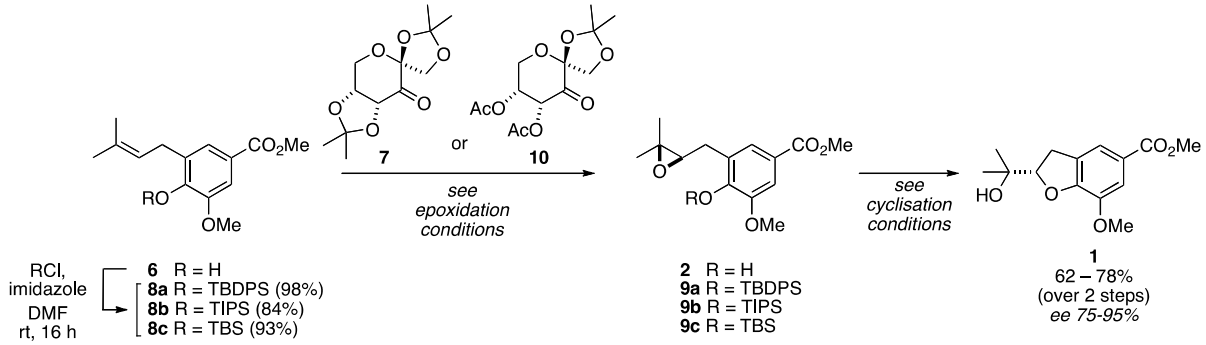


Table 1. Synthesis of methyl (+)-7-methoxyanodendroate via enantioselective epoxidation, then cyclisation.



Entry	Substrate	Epoxidation Reagents	Epoxidation Conditions	Cyclisation Conditions	Yield of **1**[a]	ee[b]
1	**6**	Freshly distilled DMDO (1.2 eq.), acetone	0 °C, 30 min then rt, 16 h	Et_3N, rt, 60 min	78%	(rac)
2	**6**	Method B[d] (0.4 eq. of **7**)	4 °C, 14 h	sat. $NaHCO_3$, rt, 60 min	–	–
3	**8a**	Method A[c] (0.25 eq. of **7**)	0 °C, 1.5 h	Method C[e] (using 2 M NaOH, 30 min)	62%	79%
4	**8a**	Method B[d] (0.4 eq. of **7**)	4 °C, 14 h	Method C[e] (using sat. $NaHCO_3$, 70 min)	84%	77%
5	**8a**	Method B[d] (0.4 eq. of **7**)	–15 °C, 7h	Method C[e] (using 1 M NaOH, 15 min)	63%[g]	78%
6	**8a**	Method B[d] (0.4 eq. of **7**)	rt, 1.5 h	Method C[e] (using 1 M NaOH, 15 min)	84%	75%
7	**8a**	Method B[d] (1.0 eq. of **7**)	0-6 °C, 2 h	Method C[e] (using 2 M NaOH, 30 min)	87%	77%
8	**8b**	Method B[d] (0.4 eq. of **7**)	4 °C, 14 h	Method C[e] (using sat. $NaHCO_3$, 70 min)	81%	76%
9	**8c**	Method B[d] (0.4 eq. of **7**)	4 °C, 14 h	Method C[e] (using sat. $NaHCO_3$, 70 min)	79%	76%
10	**8a**	Method D[f] (0.15 eq. of **10**)	0 °C, 22 h	TBAF, THF, 0 °C – rt, 75 min	69%	95%

[a] Isolated yield.

[b] *ee* values were determined by HPLC analysis using an AD-H column.

[c] Method A: Ketone **7**, $^nBu_4NHSO_4$ (0.1 eq.), Oxone (1.5 eq.), K_2CO_3 (1 M, 6 eq.), buffer [$Na_2B_4O_7$ (0.05 M), Na_2EDTA (4 x 10^{-4} M)]: dimethoxymethane (DMM) : CH_3CN (2:2:1),

[d] Method B: Ketone **7** and H_2O_2 (5.5 eq.) in buffer [2 M K_2CO_3 in 4 x 10^{-4} M Na_2EDTA] : CH_3CN : EtOH : CH_2Cl_2 (3:1:1:2),

[e] Method C: TBAF, THF, 0 °C, 15 min *then* aqueous base, rt,

[f] Method D: Ketone **10**, $^nBu_4NHSO_4$ (0.04 eq.), Oxone (1.5 eq.), K_2CO_3 (0.38 M, 2.4 eq.), pH 6 buffer [KOH (0.1 M):KH_2PO_4 (0.1 M):H_2O (5.6:50:44.4)], DMM:CH_3CN (2:1),

[g] Reaction did not proceed to completion, unreacted starting material (18%) was also recovered.