Natural Product Synthesis | Hot Paper

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Total Syntheses of Secalonic Acids A and D**

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Abstract: *Total syntheses of the dimeric tetrahydroxanthone natural products secalonic acids A and D are described. Key steps involve kinetic resolution of the tetrahydroxanthone core structure using homobenzotetramisole catalysis and late-stage copper(I)-mediated homodimerization of complex aryl stannane monomers.*

Dimeric tetrahydroxanthones belong to a class of mycotoxins[1] which connect tetrahydroxanthone monomers by a 2,2′-biphenol linkage (Figure 1). Among these compounds, the

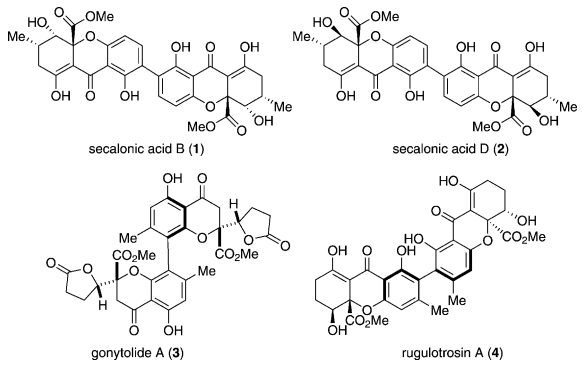

Figure 1. Representative dimeric tetrahydroxanthone natural products.

secalonic acids[2] were first isolated in 1960 and were found to exhibit interesting bioactivities. Secalonic acid B (**1**) has antitumor activity and its diastereomer secalonic acid D (**2**) shows potent cytotoxicity to HL60/K562 cells by down-regulation of c-Myc.[3a] The compound **2** has also been reported to inhibit DNA topoisomerase I.[3b] The enantiomer of **2**, secalonic acid A (not shown, *ent*-**2**) has antitumor properties and also reduces colchicine toxicity in rat cortical neurons.[4] Related natural products include gonytolide A[5] (**3**) and rugulotrosin A[6] (**4**), both of which possess axial chirality. Recently, our group[7] as well as those of Bräse,[8] Nicolaou,[9] and Tietze[10] have accomplished syntheses of monomeric tetrahydroxanthone natural products. Herein, we describe the first total syntheses of the dimeric natural products secalonic acids A and D by utilizing copper(I)-mediated dimerization of complex aryl stannane monomers to construct the requisite 2,2′-biphenol linkage.

On the basis of the proposed biosynthetic relationship[11] between tetrahydroxanthones and chromone lactones, and our previous synthetic studies,[7] we anticipated that secalonic acid D (**2**) could be obtained from the dimeric chromone lactone **5**[12] by double Dieckmann cyclization (Figure 2). We

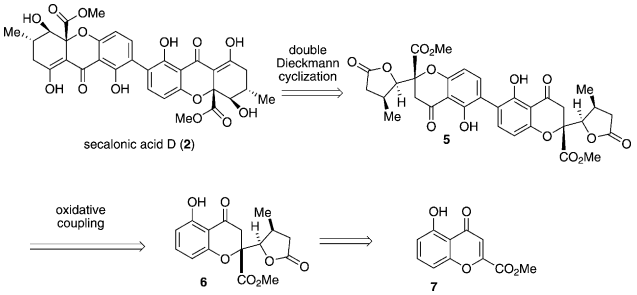

Figure 2. Initial retrosynthetic analysis for secalonic acid D.

initially envisioned that oxidative coupling of the chromone lactone **6** could be used to access the dimeric precursor **5**. By following our developed methodology,[7] compound **6** may be obtained by vinylogous addition of 2-(trimethylsiloxy)furan to a siloxybenzopyrylium species derived from the chromone ester **7**.

We first evaluated the possibility for oxidative coupling of a chromone lactone monomer as a result of the likely instability of the tetrahydroxanthone core structure. Accordingly, we prepared the model chromone lactone **8**[7] (Scheme 1) on a gram scale and investigated a number of oxidative coupling conditions[13] (e.g. $VOCl_3$, $[Mn(acac)_3]$, $FeCl_3$). However, we found that oxidative conditions afforded 2,2′-linked-chromone lactone dimers in very low yield, and in the case of $VOCl_3$, chlorinated products were formed. We then changed our focus to prefunctionalization of the monomers to achieve dimerization of the chromone lactone, an approach which we anticipated could provide selectivity for biaryl coupling. Both thallium-acetate-directed[14] or $Me_3NBnICl_2$-directed iodination[15,16] of **8** afforded a major *ortho*-iodinated product and subsequent base-mediated *O*-methylation provided the aryl iodide **9** (Scheme 1). Notably, traditional copper-mediated Ullmann coupling of **9** (10 equiv Cu, 160 °C) led to deiodination and decomposition products. Stannylation of **9** was mediated by palladium(0) catalysis in

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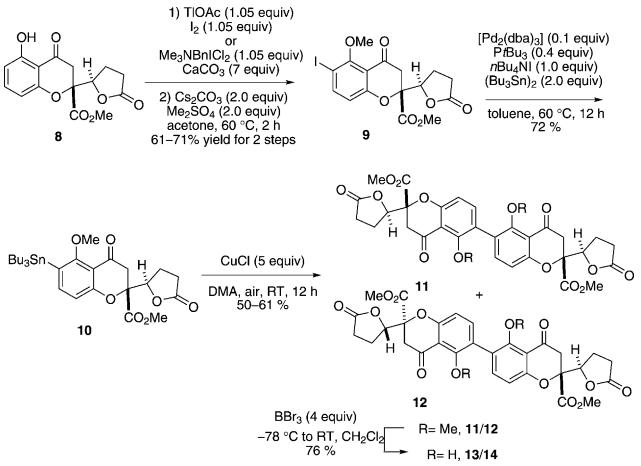
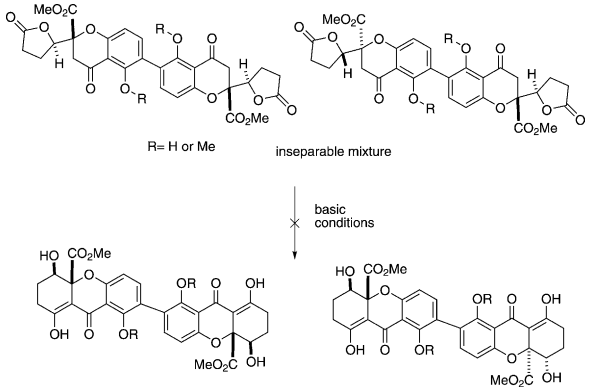
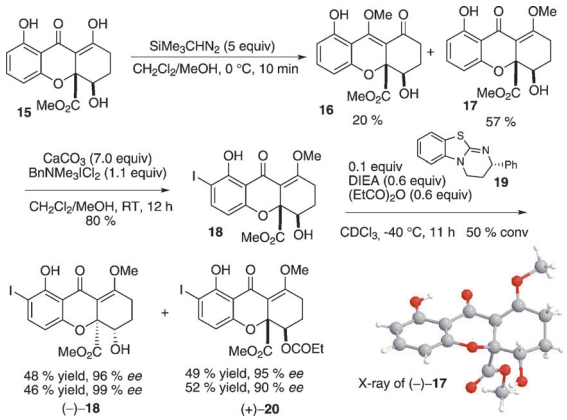


Scheme 1. Synthesis of a racemic, model 2,2′-linked chromanone dimer. dba = dibenzylideneacetone, DMA = *N*,*N*-dimethyl acetamide.



Scheme 2. Attempted double Dieckmann cyclization.

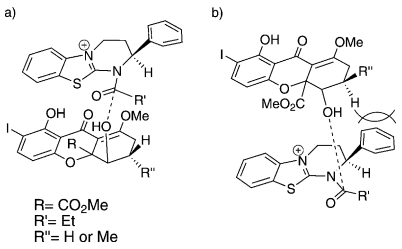


Scheme 3. Kinetic resolution on a model system. DIEA = diisopropylethylamine

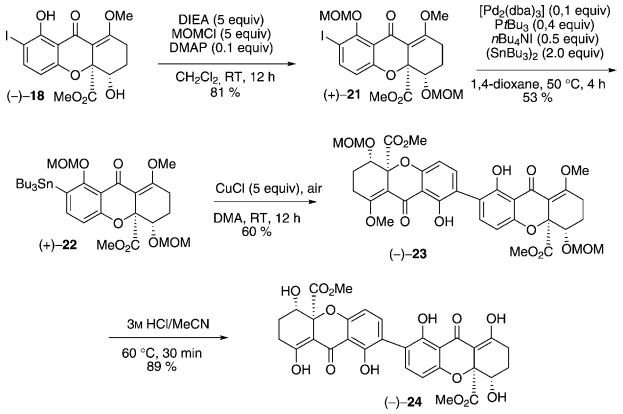
which case nBu$_4$NI[17] was found to be an essential additive to obtain full conversion to stannane **10**. With both **9** and **10** in hand, a number of palladium sources, ligands, and solvents were investigated for biaryl couplings. However, in these experiments the desired dimer was obtained in trace amounts. Intriguingly, we found that **10** was converted into an inseparable mixture of the C_2-dimer **11** and C_s-dimer **12** when the commercial reagent CuCl[18,19] was used as an additive for palladium(0)-mediated cross-coupling. Surprisingly, this pathway was totally suppressed using freshly prepared CuCl and degassed solvent. We found that using ambient air as the oxidant[20,21] was critical to enable reproducible dimerization chemistry, and that the polar aprotic solvent DMA enhanced the rate of transmetallation of tributyltin to copper(I). Treatment of the resulting dimers **11**/**12** with BBr_3 cleanly afforded the deprotected dimers **13**/**14**.

With the chromone lactone dimers in hand, we anticipated that double Dieckmann cyclization[7] could provide access to the dimeric tetrahydroxanthone. However, in contrast to monomeric substrates,[7] treatment of the dimers **11**/**12** or **13**/**14** under basic conditions (e.g. NaH/THF, NaH/Mg(OTf)$_2$, Et$_3$N/TMSOTf), did not lead to significant production of dimeric tetrahydroxanthone products or mono-rearranged products, but only led to decomposition of the starting material (Scheme 2). Accordingly, we investigated dimerization of the tetrahydroxanthone core structure. Protection of the enol moiety was necessary because of its high reactivity. The tetrahydroxanthone **15**[7] was successfully methylated with (trimethylsilyl)diazomethane to afford the desired enol ether **17** in 57% yield along with the isomer **16** (20%; Scheme 3). Strict control of reaction temperature and time was required to prevent double *O*-methylation. By employing the previous *ortho*-iodination conditions, iodide **18** was obtained in 80% yield. Utilizing the homobenzotetramisole (HBTM) catalyst **19** developed by Birman and co-workers,[22] kinetic resolution[23] proceeded smoothly to afford (−)-**18** in 48% yield (96% *ee*) and (+)-**20** in 49% yield (96% *ee*; s = 146). Furthermore, we were able to obtain (−)-**18** in 99% *ee* using a longer reaction time (13 h). The absolute stereochemistry of the kinetic resolution products was verified by single-crystal analysis of the deiodinated congener (−)-**17**.[16,24] We propose that the observed high selectivity for the kinetic resolution results from π stacking between the tetrahydroxanthone substrate and the HBTM catalyst,[22] thus leading to an assembly which minimizes steric repulsion (Scheme 4a). Steric repulsion between the phenyl group and the tetrahydroxanthone in (Scheme 4b) renders the latter assembly less favorable.

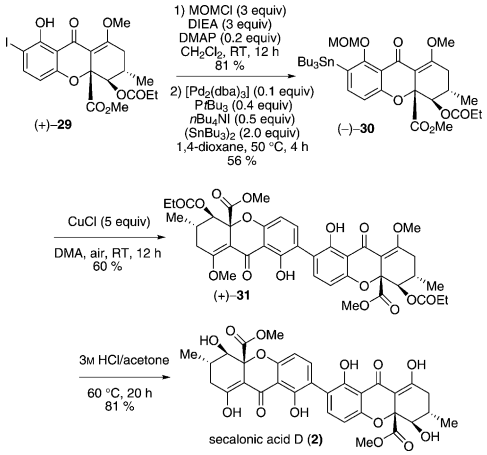
With the monomer (−)-**18** in hand, and after evaluating several protecting groups, we next prepared MOM-protected (+)-**21** (81% yield) which was then subjected to stannylation to afford the key intermediate (+)-**22** (Scheme 5). As before,



Scheme 4. Proposed assemblies for kinetic resolution.



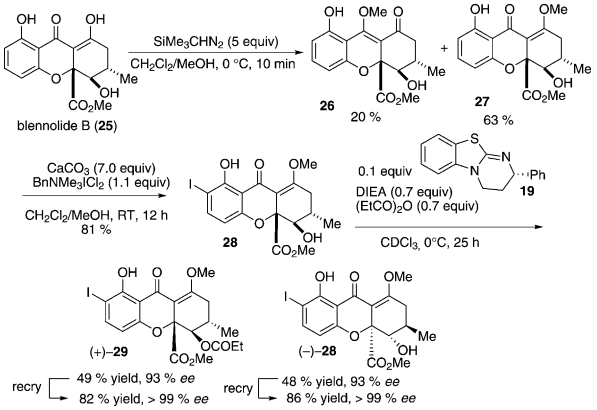
Scheme 5. Synthesis of a model 2,2′-linked tetrahydroxanthone dimer. DMAP = 4-(*N*,*N*-dimethylamino)pyridine, MOM = methoxymethyl.



Scheme 7. Synthesis of secalonic acid D.

the additive nBu$_4$NI was found to be crucial for palladium(0)-catalyzed stannylation. Furthermore, longer reaction times or increased amounts of additives led to enol ether deprotection. Gratifyingly, copper-mediated coupling of (+)-**22** proceeded smoothly to afford the 2,2′-linked dimer (−)-**23** in 60% yield. Finally, treatment of **23** with 3M HCl led to the fully deprotected tetrahydroxanthone dimer (−)-**24** in 89% yield.

Encouraged by our model studies, we initiated syntheses of secalonic acids A and D using the racemic blennolide B (**25**; Scheme 6).[7] Following previously optimized reaction



Scheme 6. Kinetic resolution of a blennolide derivative.

conditions, methyl enol ether protection and *ortho*-iodination afforded the blennolide derivative **28**. Because of the presence of an additional methyl group on the C ring, acylative kinetic resolution was much slower in comparison to the model substrate (25 h, 0°C). However, a longer reaction time and higher temperature provided both (−)-**28** and (+)-**29** in excellent yield and enantioselectivity. Fortunately, after recrystallization, both (+)-**29** and (−)-**28** could be obtained in greater than 99% *ee*.

With (+)-**29** in hand, we conducted MOM protection followed by stannane formation to obtain the enantioenriched tetrahydroxanthone (−)-**30** (Scheme 7). Copper-mediated oxidative coupling provided a single dimeric product

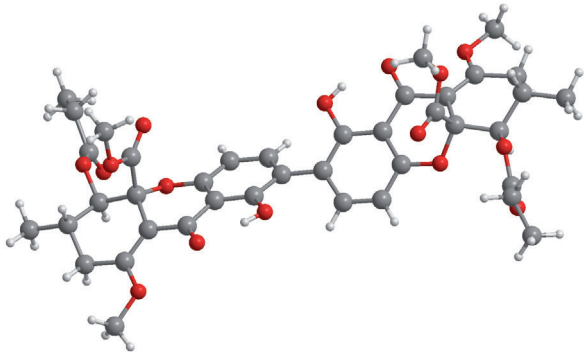
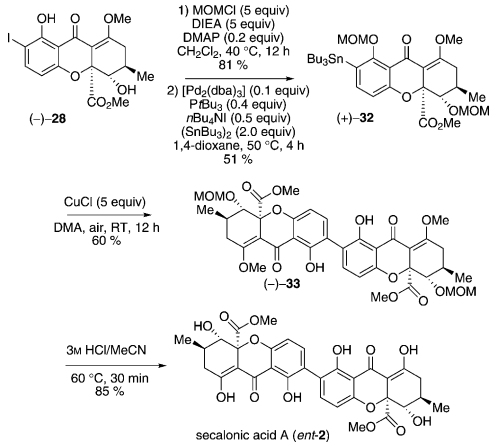


Figure 3. X-ray crystal structure of (+)-**31**.

((+)-**31**) whose absolute and relative stereochemistry were unambiguously verified by X-ray crystal structure analysis (Figure 3).[24] Global deprotection under acidic conditions provided secalonic acid D (**2**) in 81% yield. NMR spectra, UPLC retention times, and α_D values for **2** were found to be identical to those reported for the natural material.[16]

In a similar manner, the other compound accessed from kinetic resolution, (−)-**28**, was advanced to secalonic acid A (*ent*-**2**; Scheme 8). After MOM protection and stannane synthesis, (+)-**32** was obtained in 41% yield after two steps. Treatment of (+)-**32** with CuCl and air led to the production of the dimer (−)-**33** in 60% yield. Final deprotection using 3M HCl/acetonitrile afforded secalonic acid A (*ent*-**2**), the enantiomer of secalonic acid D, in 85% yield.

In summary, the bioactive tetrahydroxanthone dimers secalonic acids A and D have been synthesized for the first time. Birman's homobenzotetramisole (HBTM) catalysts were found to be highly effective for kinetic resolution of highly functionlized tetrahydroxanthone monomers. In addition, we found that copper(I) chloride under mild oxidative conditions could be used to access 2,2′-biphenols from complex aryl stannanes. These extremely mild dimerization conditions show excellent functional-group tolerance and should be useful for the synthesis of a range of dimeric 2,2′-linked chromone lactone and tetrahydroxanthone natural



Scheme 8. Synthesis of secalonic acid A.

products. Further studies on the detailed mechanism of copper-mediated coupling of aryl stannanes as well as asymmetric syntheses of additional tetrahydroxanthone natural product targets are currently under investigation and will be reported in due course.

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[24] CCDC 961591 [(–)-**17**}, 961692 [(+)-**31**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

