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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 (HBTM) catalysis and late-stage copper (I)-mediated homodimerization of complex aryl stannane monomers.

Keywords

secalonic acids; dimeric tetrahydroxanthone; stannane coupling; kinetic resolution

Dimeric tetrahydroxanthones belong to a class of mycotoxins[1] which connect tetrahydroxanthone monomers *via* a 2,2′-biphenol linkage (Figure 1). Among these compounds, the 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] 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 laboratory[7] as well as the Bräse,[8] Nicolaou,[9] and Tietze[10] groups 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 utilizing copper (I)-mediated dimerization of complex aryl stannane monomers to construct the requisite 2,2′-biphenol linkage.

Based on the proposed biosynthetic relationship[11] between tetrahydroxanthones and chromone lactones and our previous synthetic studies,[7] we anticipated that secalonic acid

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D (**2**) could be obtained from the dimeric chromone lactone **5**[12] *via* double Dieckmann cyclization (Figure 2). We initially envisioned that oxidative coupling of chromone lactone **6** could be used to access dimeric precursor **5**. Following our developed methodology,[7] substrate **6** may be obtained by vinylogous addition of 2-(trimethylsiloxy)furan to a siloxybenzopyrylium species derived from chromone ester **7**.

We first evaluated the possibility for oxidative coupling of a chromone lactone monomer due to the likely instability of the tetrahydroxanthone core structure. Accordingly, we prepared 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. We then changed our focus to prefunctionalize the monomers to achieve dimerization of the chromone lactone 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 which was followed by base-mediated *O*-methylation to provide aryl iodide **9** (Scheme 1). Noteably, traditional copper-mediated Ullmann coupling of **9** (10 equiv Cu, 160 °C) led to deiodination and decomposition products. Stannylation of **9** was mediated by Pd(0) catalysis in which case nBu_4NI[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 Pd 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 stannane **10** was converted into an inseparable mixture of C_2 dimer **11** and C_s dimer **12** when the commercial reagent CuCl[18,19] was used as additive for Pd(0)-mediated cross coupling. Surprisingly, this pathway was totally suppressed using freshly prepared CuCl and degassed solvent.

We found that using ambient air as 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 dimers **13/14** under basic conditions (*e.g.* NaH/THF, NaH/$Mg(OTf)_2$, Et_3N/TMSOTf), did not lead to significant production of dimeric tetrahydroxanthone products or mono-rearranged products and only led to decomposition of starting material (Scheme 2). Accordingly, we investigated dimerization of the tetrahydroxanthone core structure. Protection of the enol moiety was necessary due to its high reactivity. Tetrahydroxanthone **15**[7] was successfully methylated with (trimethylsilyl)diazomethane to afford the desired enol ether **17** in 57 % yield along with isomer **16** (20 %) (Scheme 3). Strict control of reaction temperature and time was required to prevent double *O*-methylation. Employing the previous *ortho*-iodination conditions, iodide **18** was obtained in 80 % yield. Utilizing the homobenzotetramisole (HBTM) catalyst **19** developed by Birman and coworkers,[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 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] leading to an assembly which minimizes steric repulsion (Scheme 4, A). Steric repulsion between the phenyl group and the tetrahydroxanthone in B renders the latter assembly less favorable.

With monomer (−)-**18** in hand, and after evaluating several protecting groups, we prepared MOM-protected (+)-**21** in 81 % yield which was stannylated to afford the key intermediate (+)-**22** (Scheme 5). As before, the additive nBu$_4$NI was found to be crucial for Pd(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 racemic blennolide B (**25**)[7]. Following previously optimized conditions, methyl enol ether protection and *ortho*-iodination afforded blennolide derivative **28** (Scheme 6). Due to 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 >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 **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 80 % 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 49 % yield after two steps. Treatment of (+)-**32** with CuCl and air led to the production of dimer (−)-**33** in 65 % 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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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.

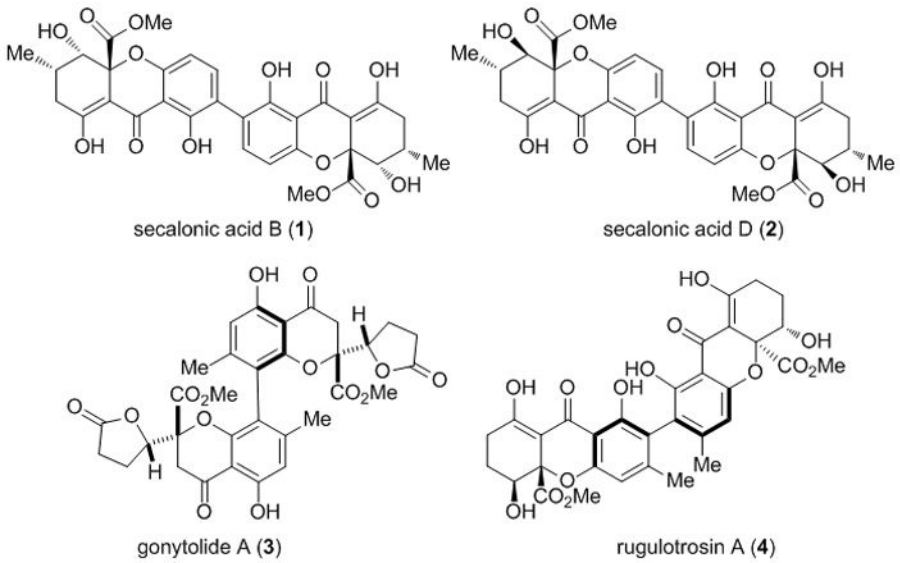


Figure 1.
Representative dimeric tetrahydroxanthone natural products

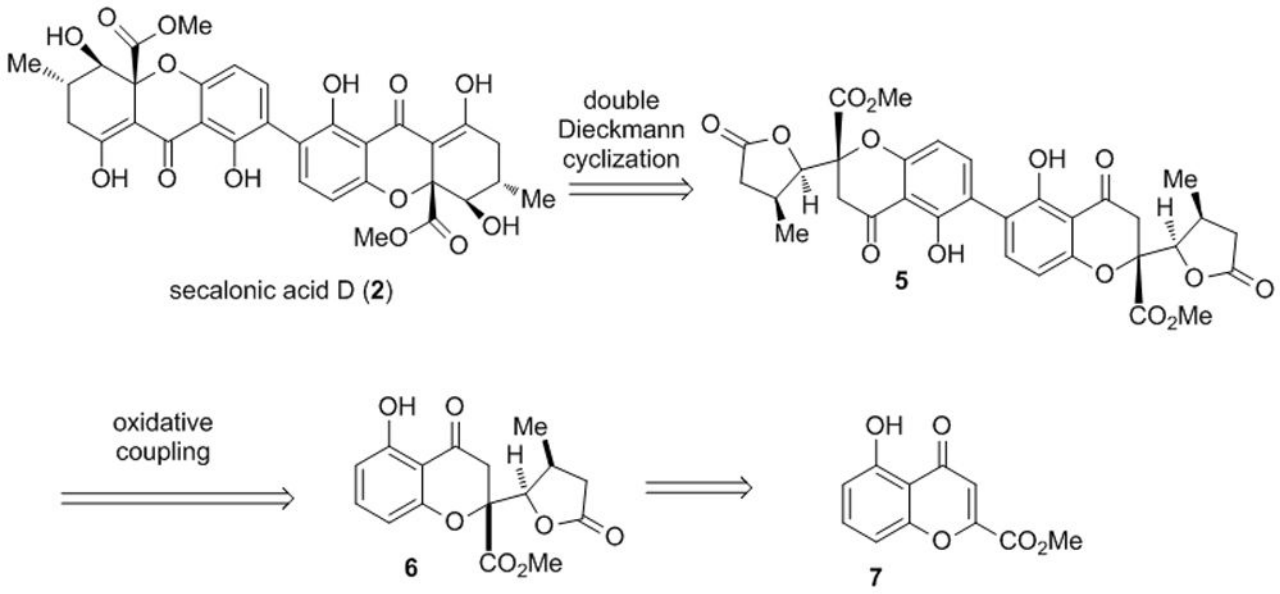


Figure 2.
Initial retrosynthetic analysis for secalonic acid D

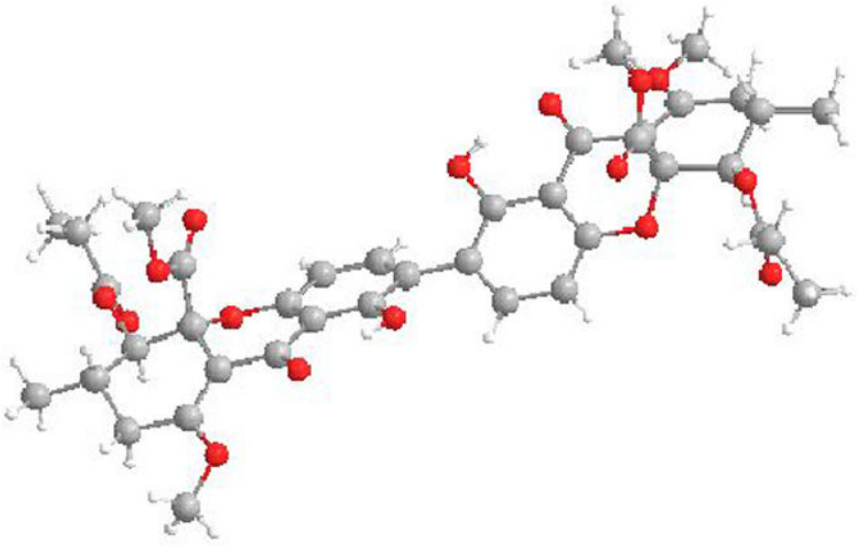
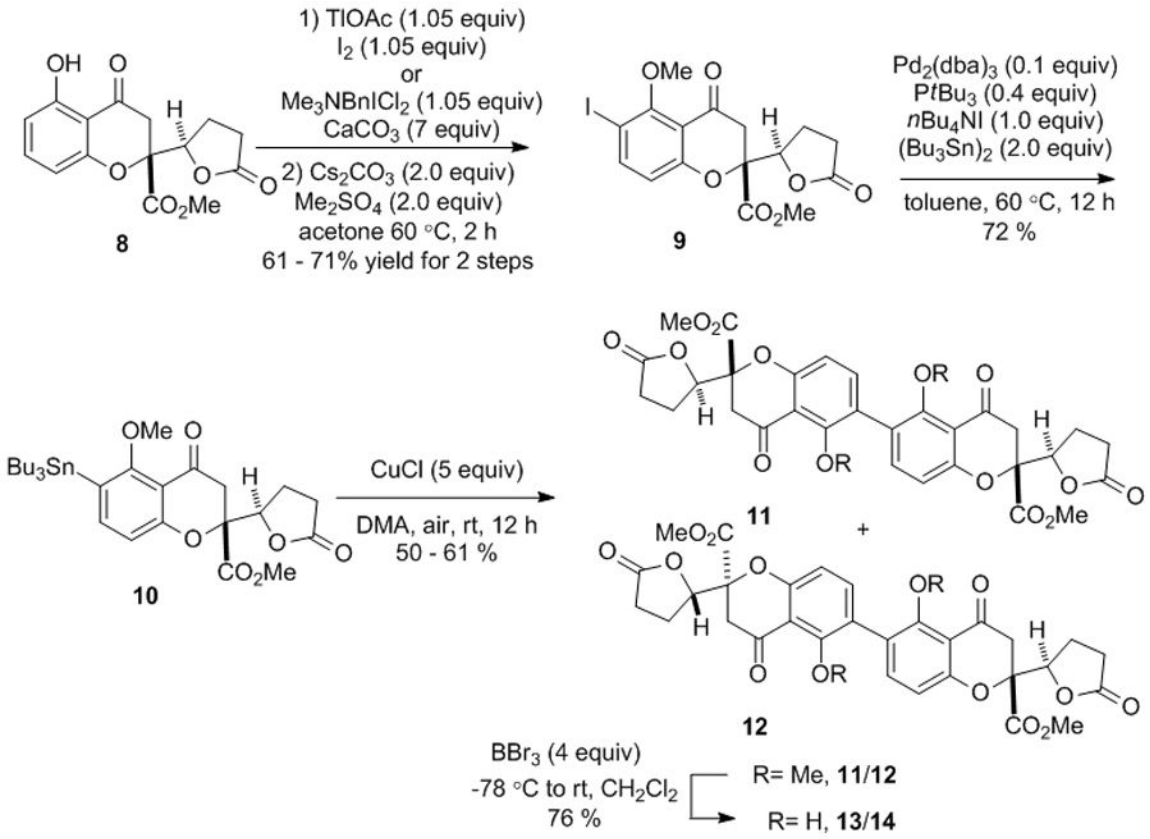
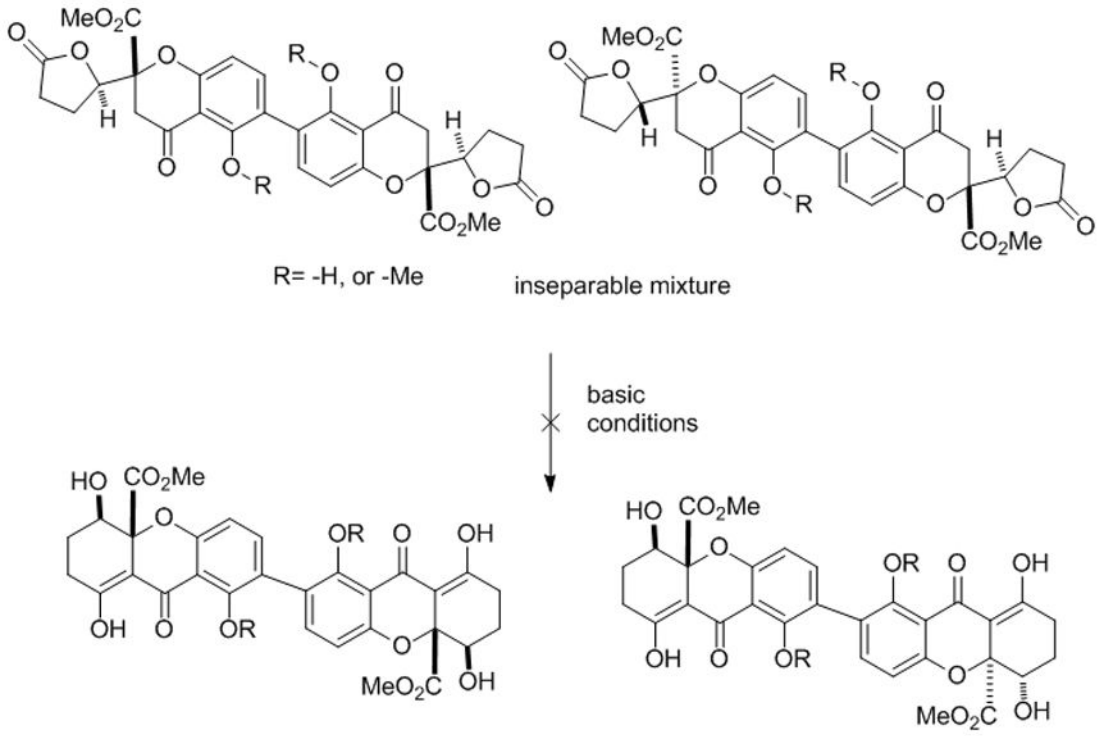


Figure 3.
X-ray crystal structure of (+)-**31**

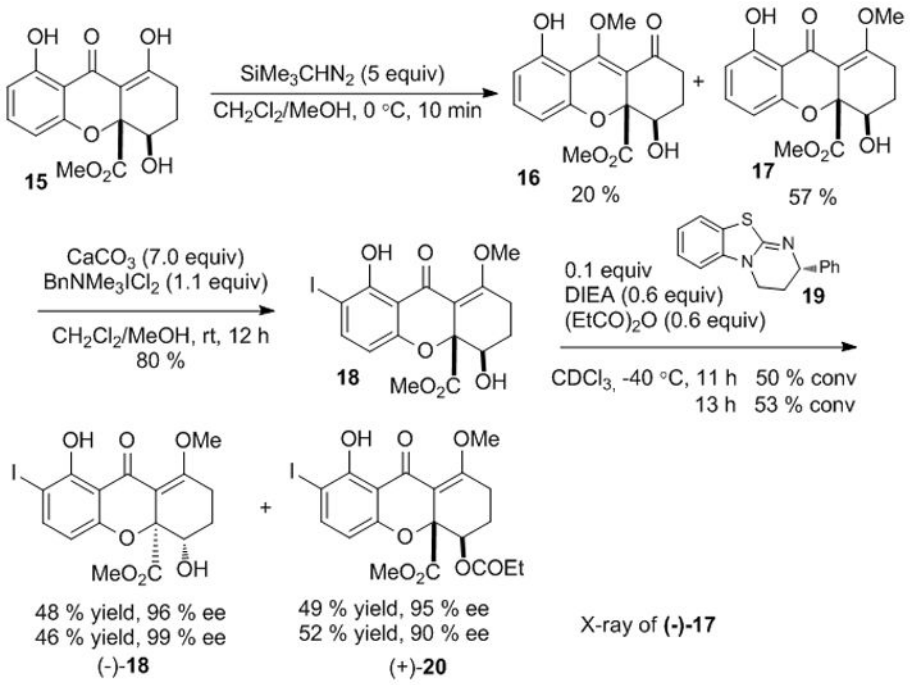


Scheme 1.

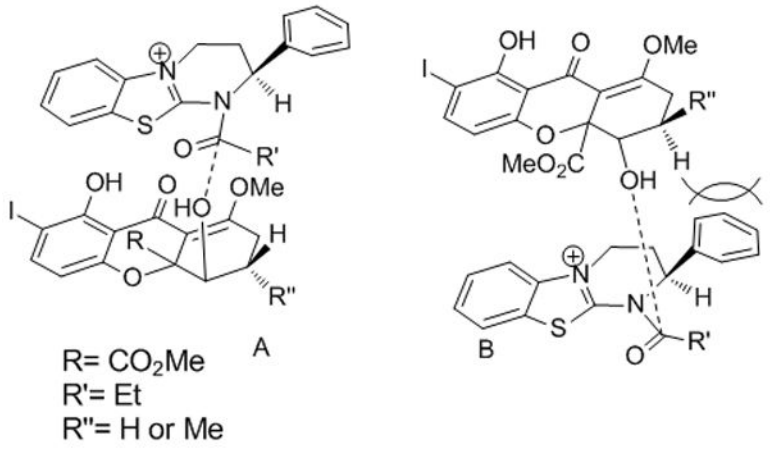
Synthesis of a racemic, model 2,2′-linked chromanone dimer



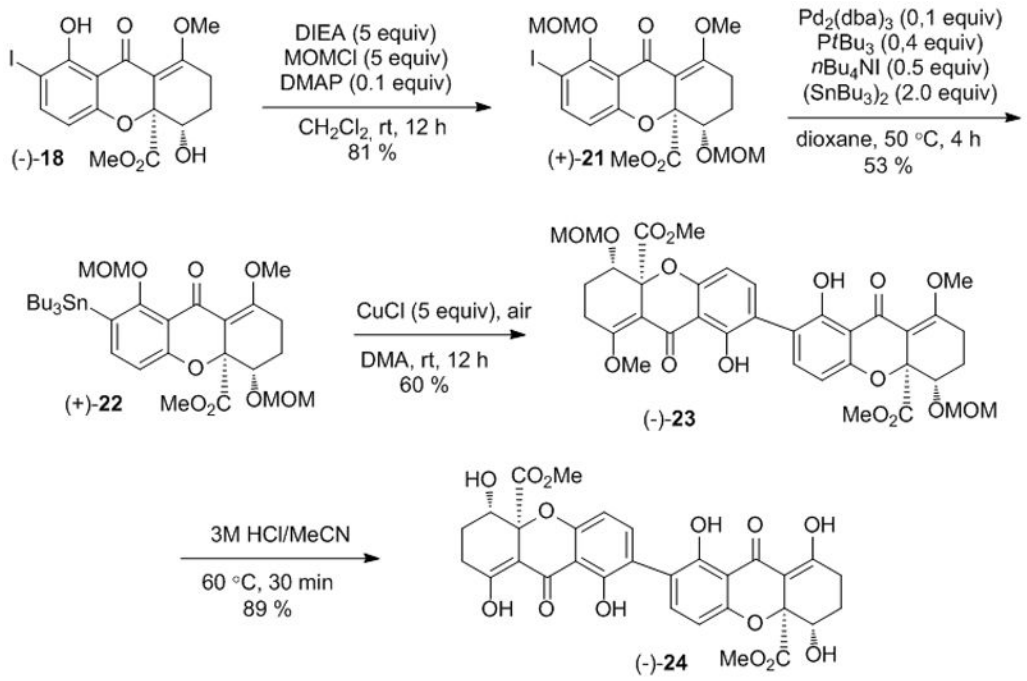
Scheme 2.
Attempted double Dieckmann cyclization



Scheme 3.
Kinetic resolution on a model system

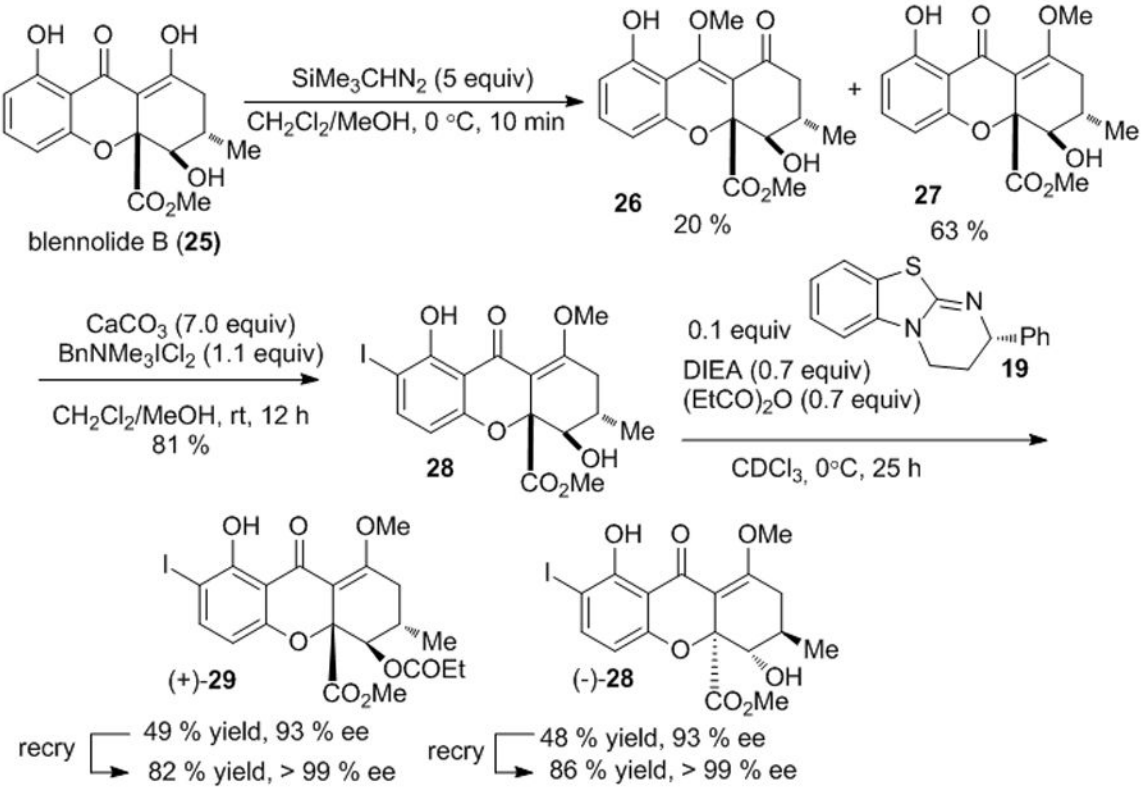


Scheme 4.
Proposed assemblies for kinetic resolution

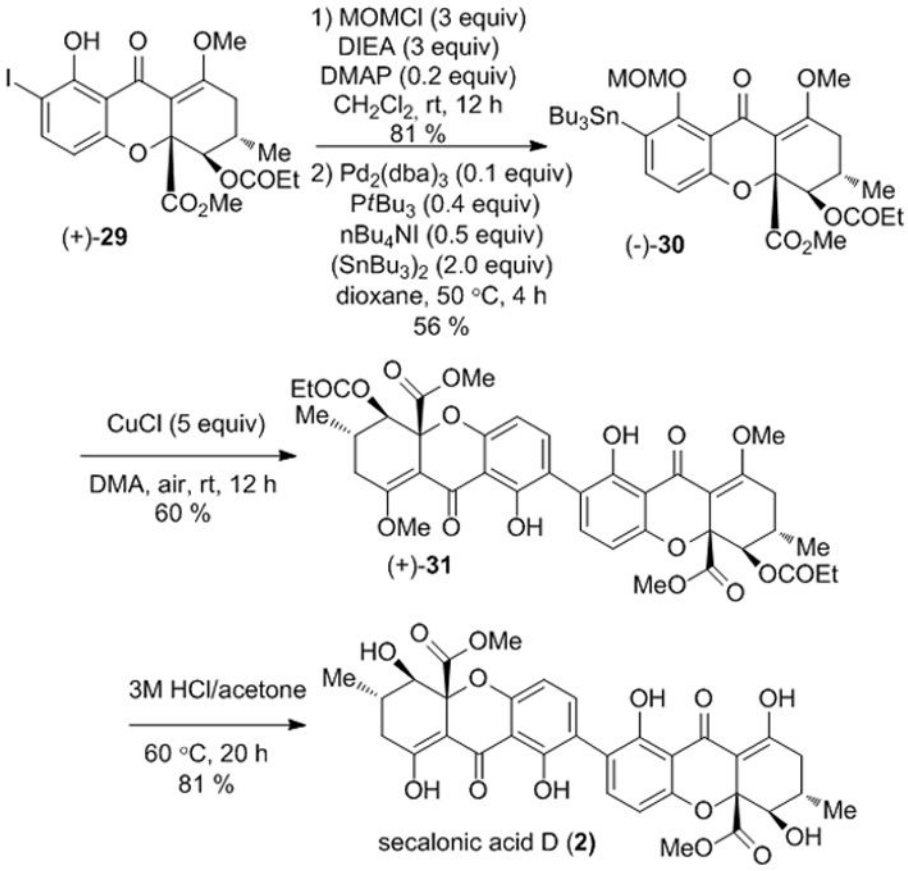


Scheme 5.

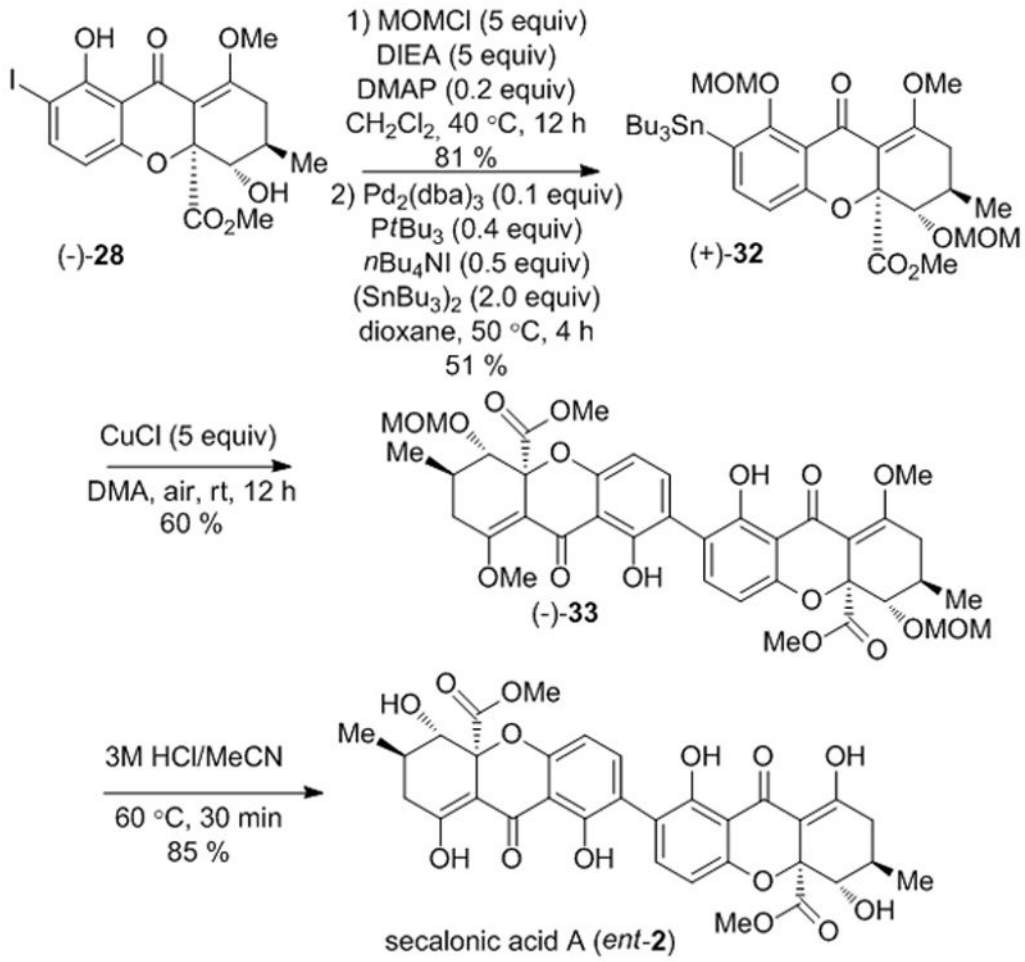
Synthesis of a model 2,2′-linked tetrahydroxanthone dimer



Scheme 6.
Kinetic resolution of a blennolide derivative



Scheme 7.
Synthesis of secalonic acid D



Scheme 8.
Synthesis of secalonic acid A