Total Syntheses of Secalonic Acids A and D

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J. A. Porco, Jr. *et al.*
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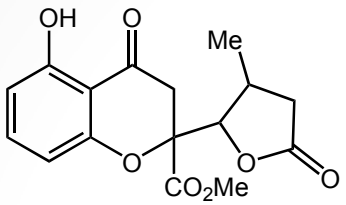
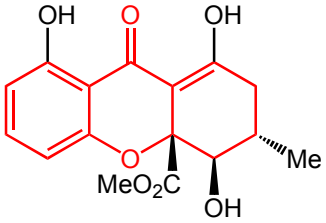
Representative mono- and dimeric tetrahydroxanthone natural products

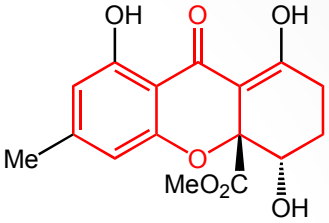
Monomeric tetrahydroxanthone natural products



Paecilin B

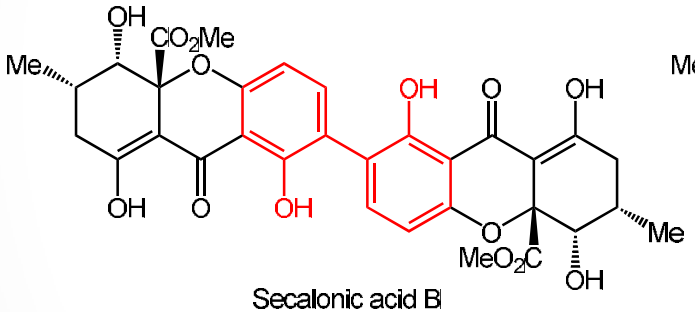


Blennolide B

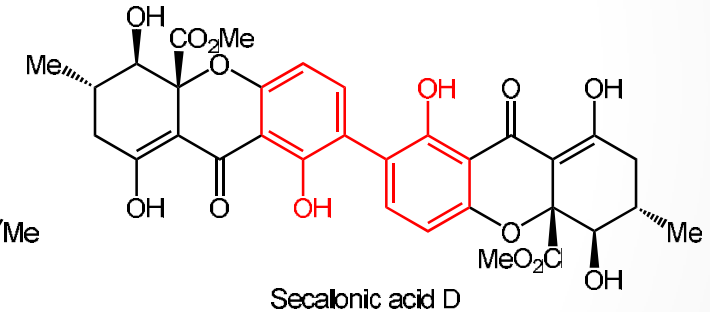


Blennolide C

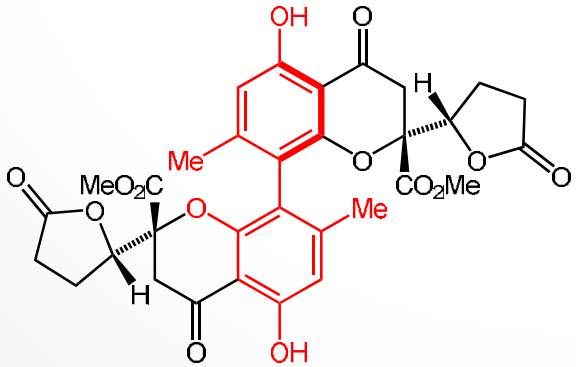
Dimeric tetrahydroxanthone natural products



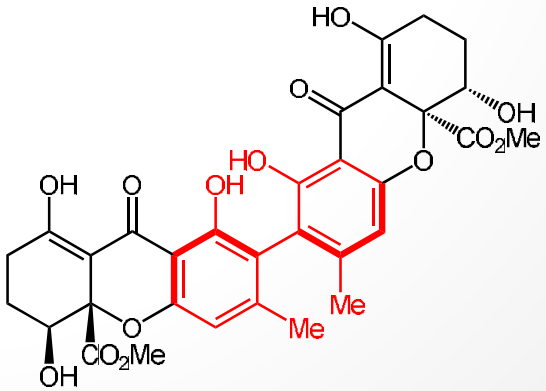
Secalonic acid B



Secalonic acid D



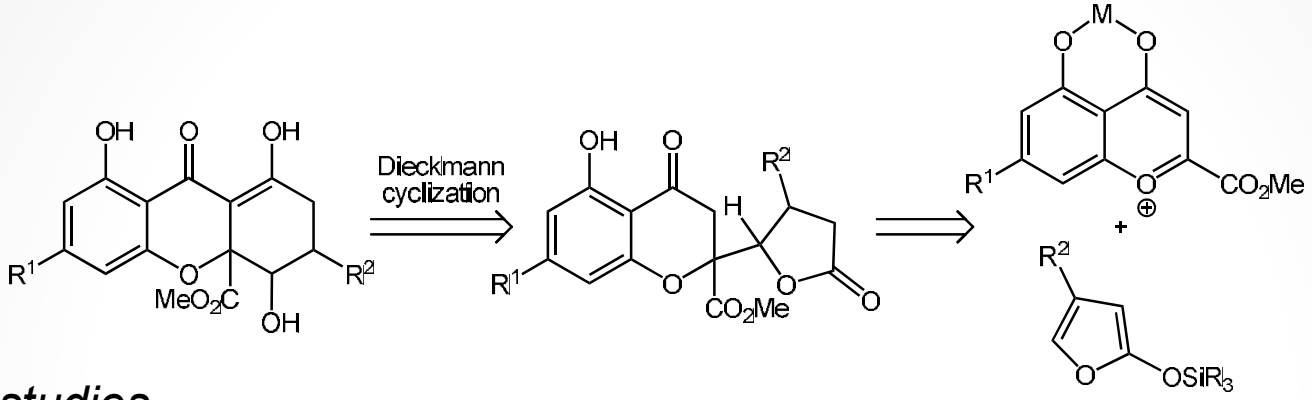
Gonytolide A



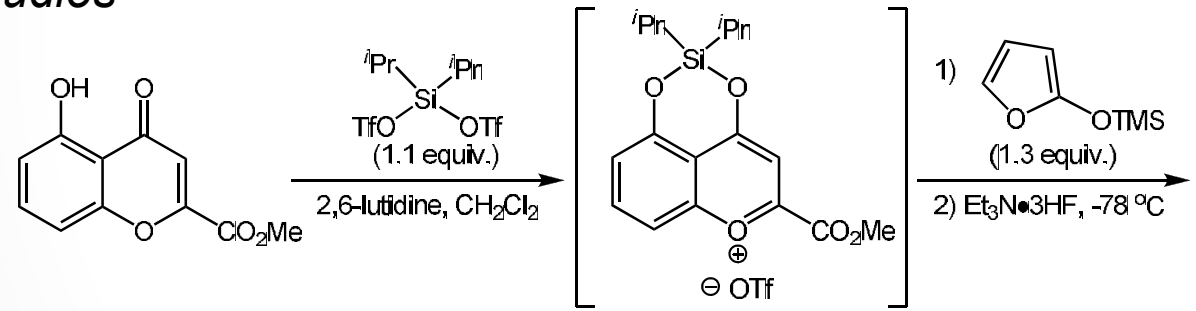
Rugulotrosin A

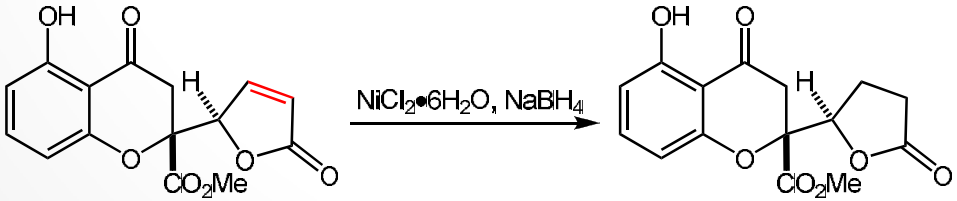
Synthesis of monomeric tetrahydroxanthones

Retrosynthetic analysis



Model studies





dr = 15:1

1

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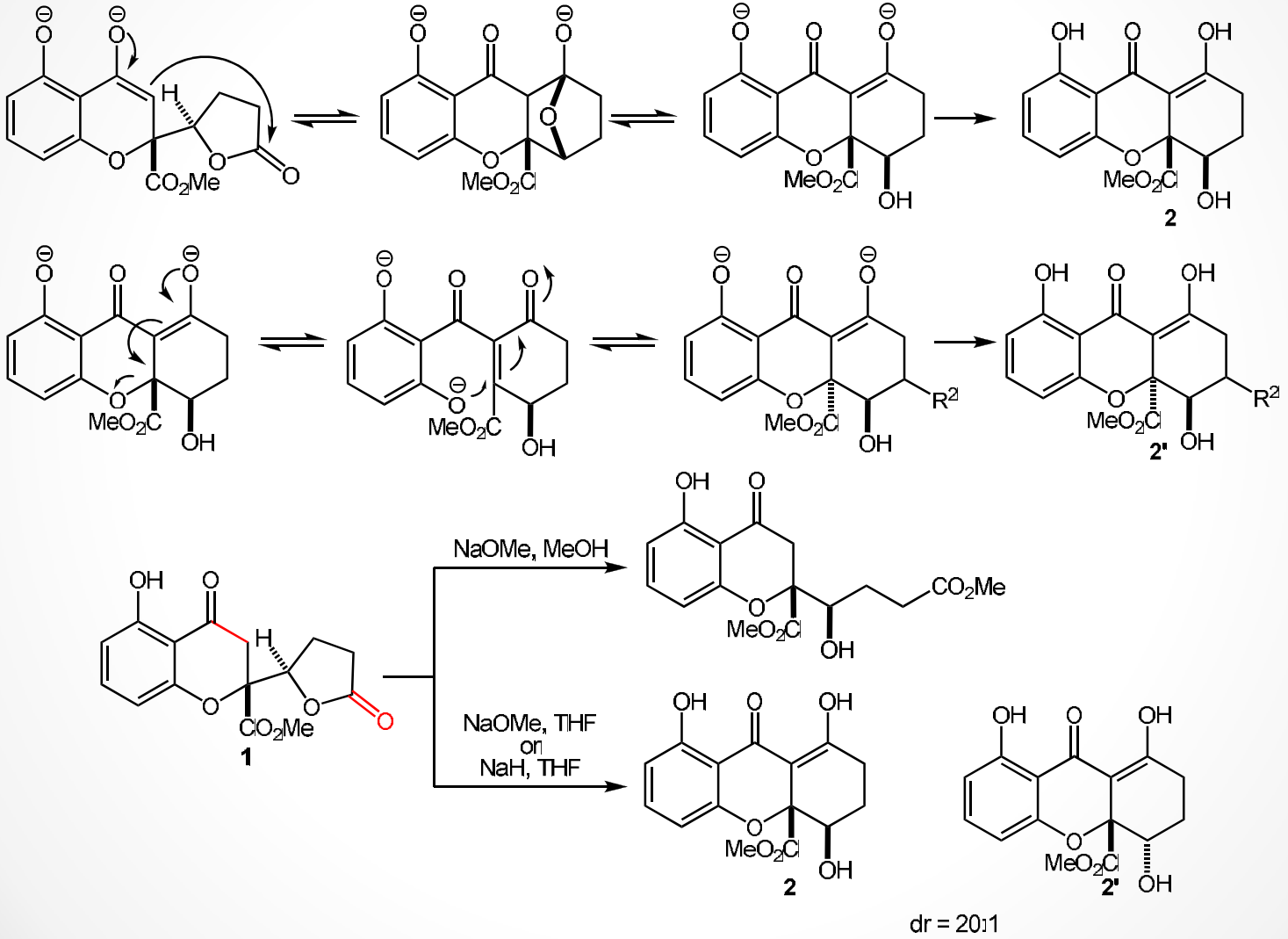
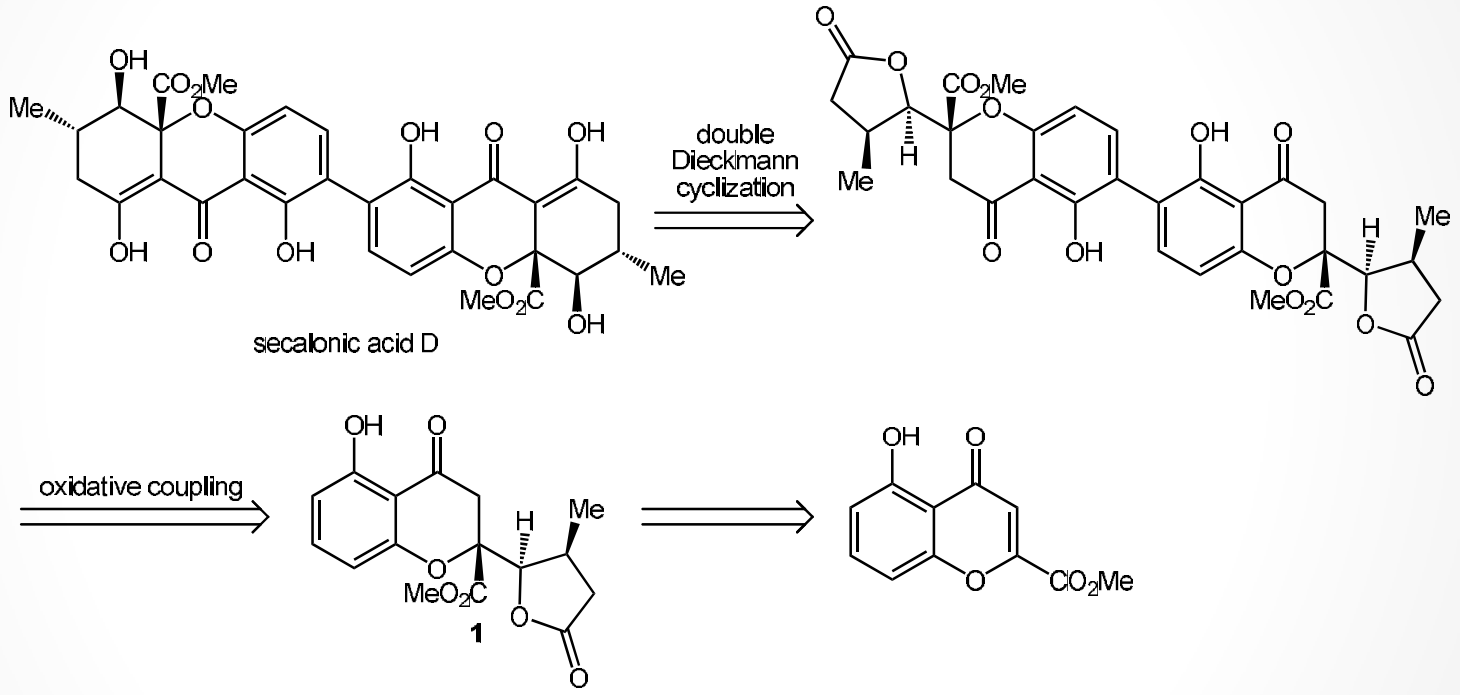
Synthesis of monomeric tetrahydroxanthones

Dieckmann cyclization



Synthesis of dimeric tetrahydroxanthones



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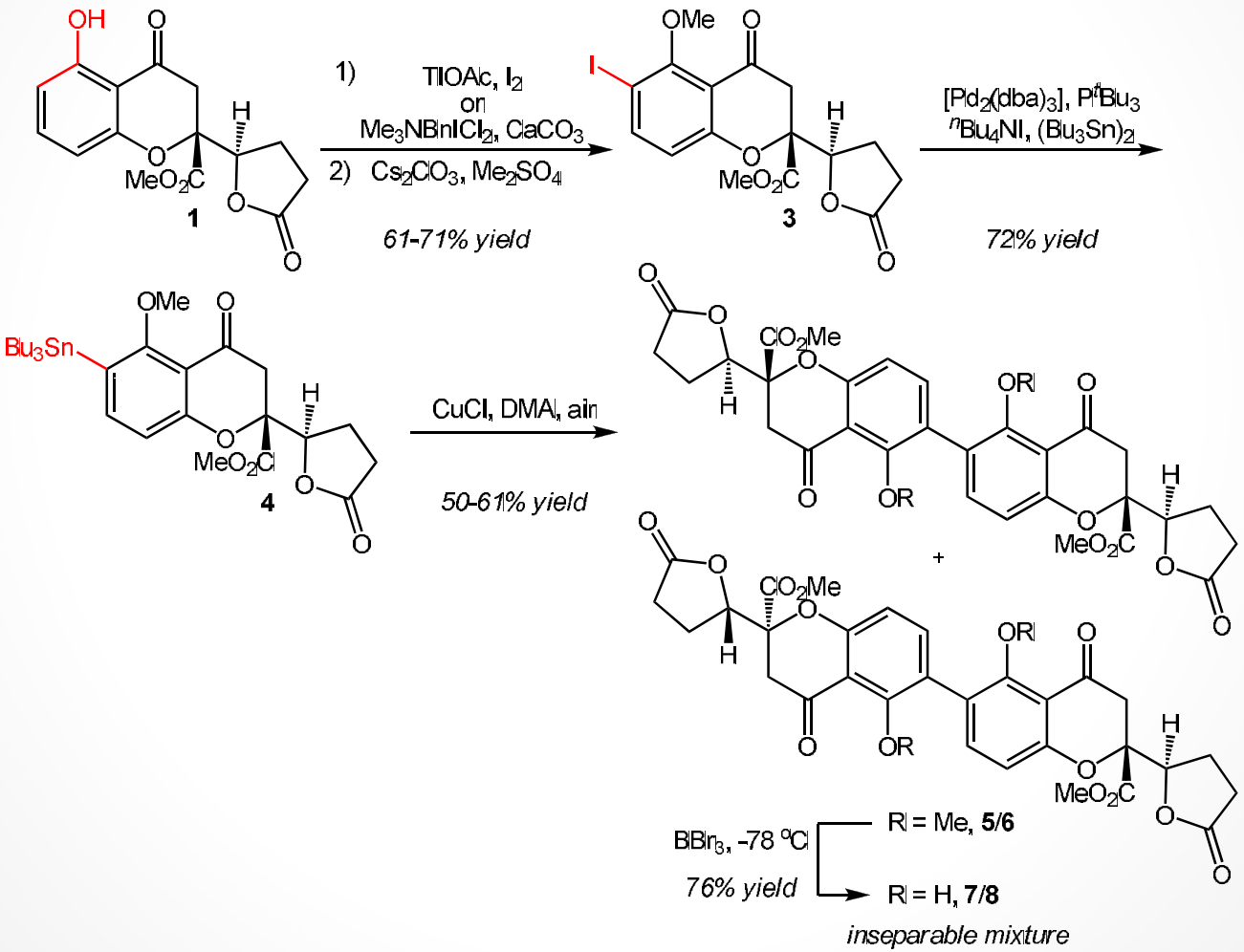
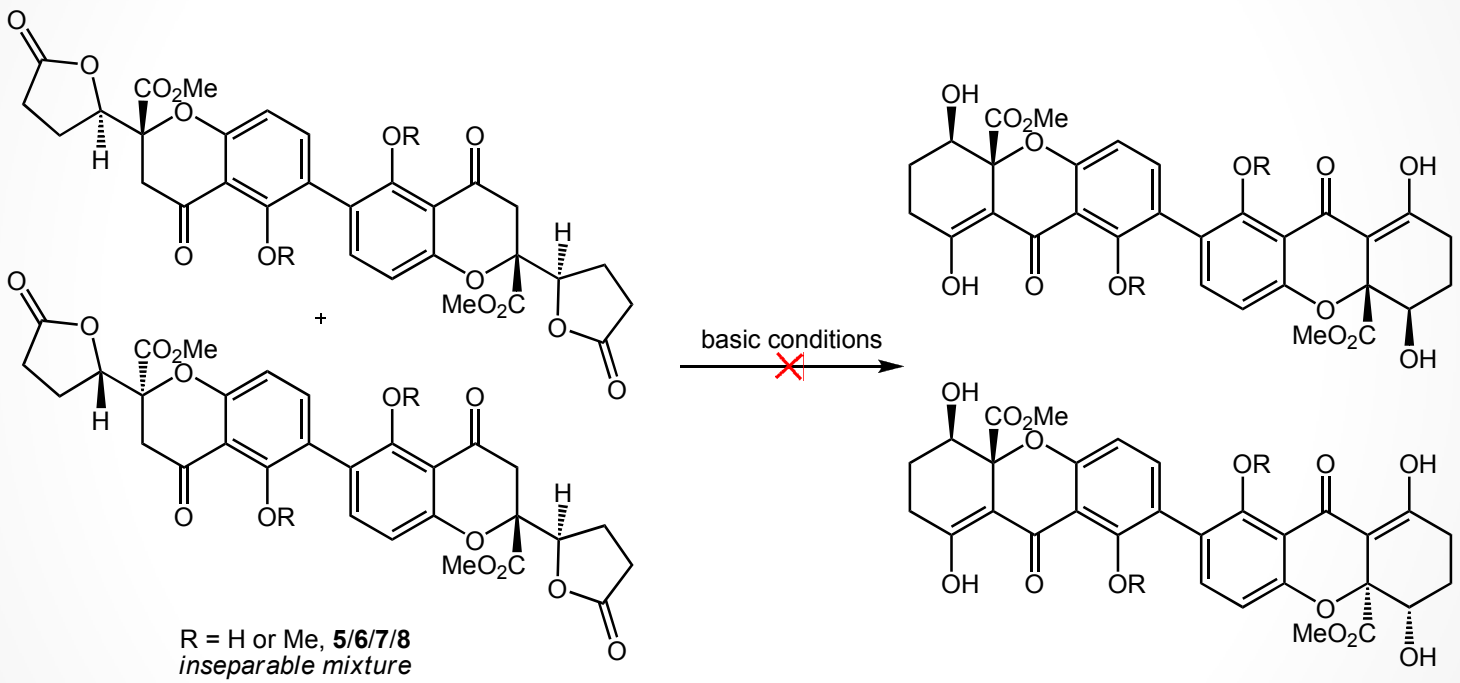
Synthesis of dimeric tetrahydroxanthones

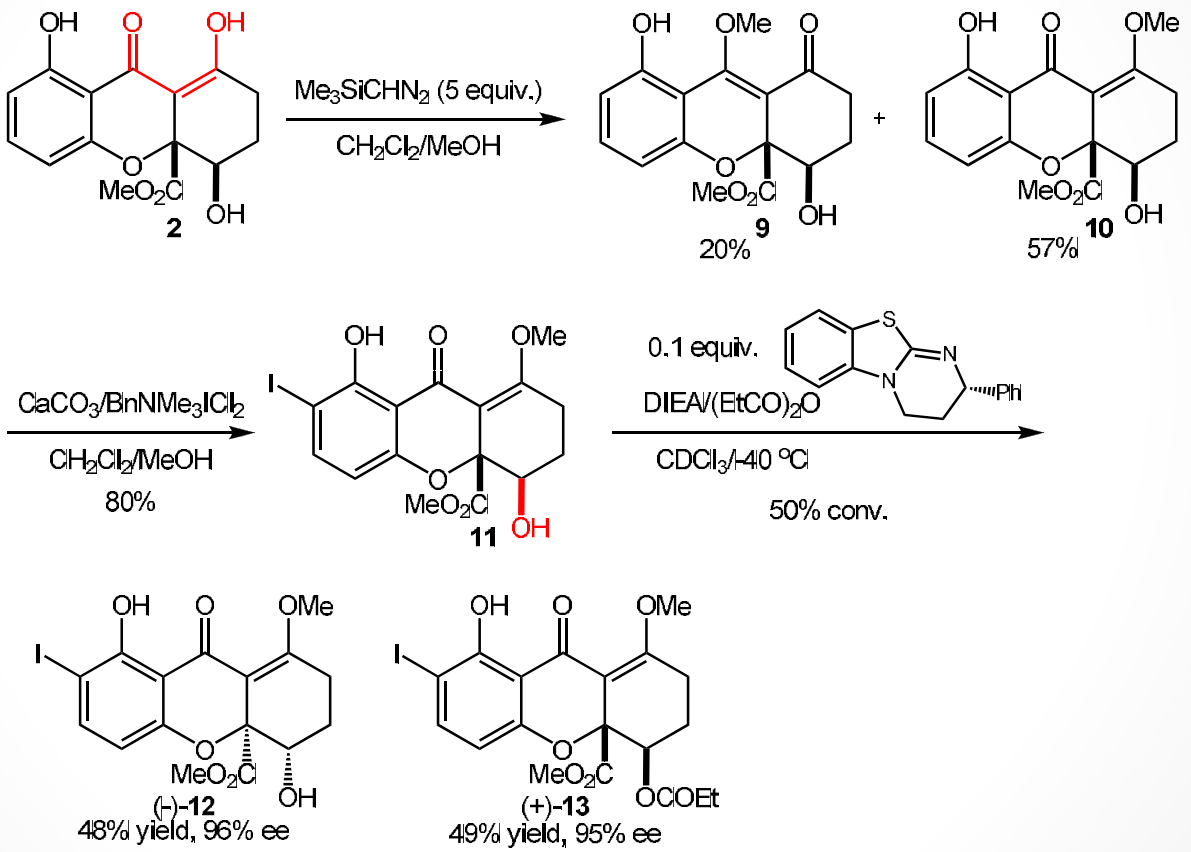


Synthesis of dimeric tetrahydroxanthones

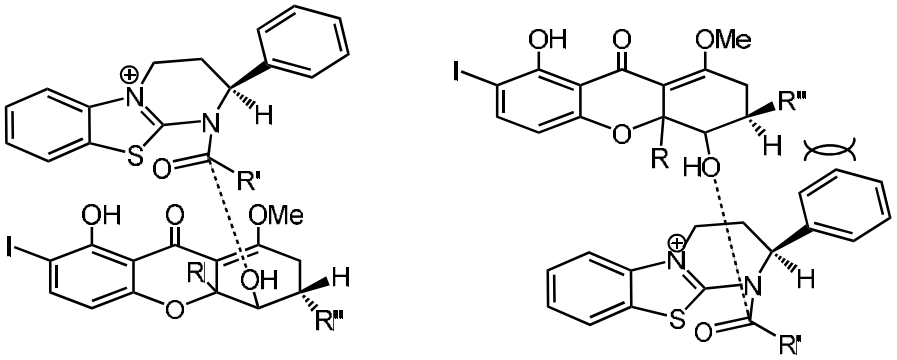


R = H or Me, **5**/**6**/**7**/**8**
inseparable mixture

Synthesis of dimeric tetrahydroxanthones

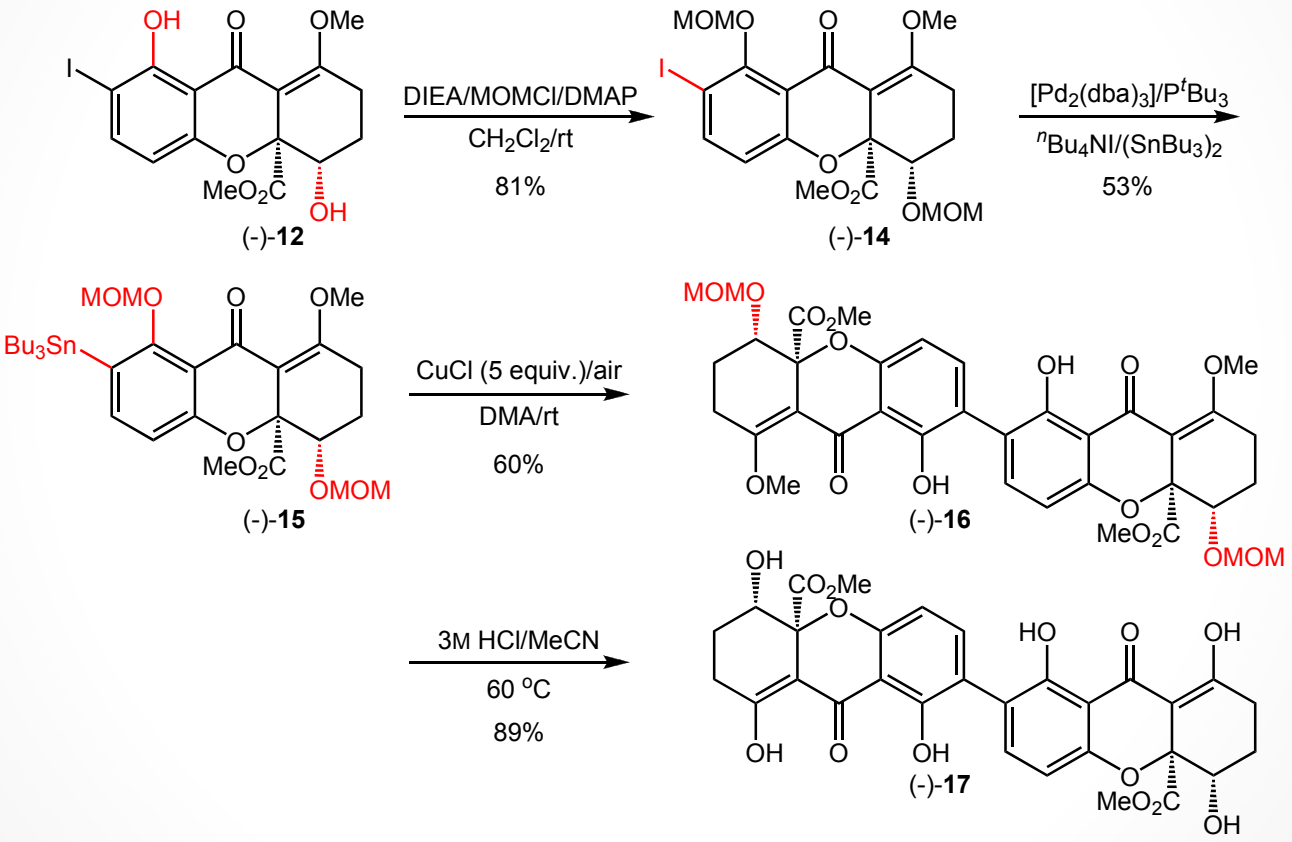


Proposed assemblies for kinetic resolution

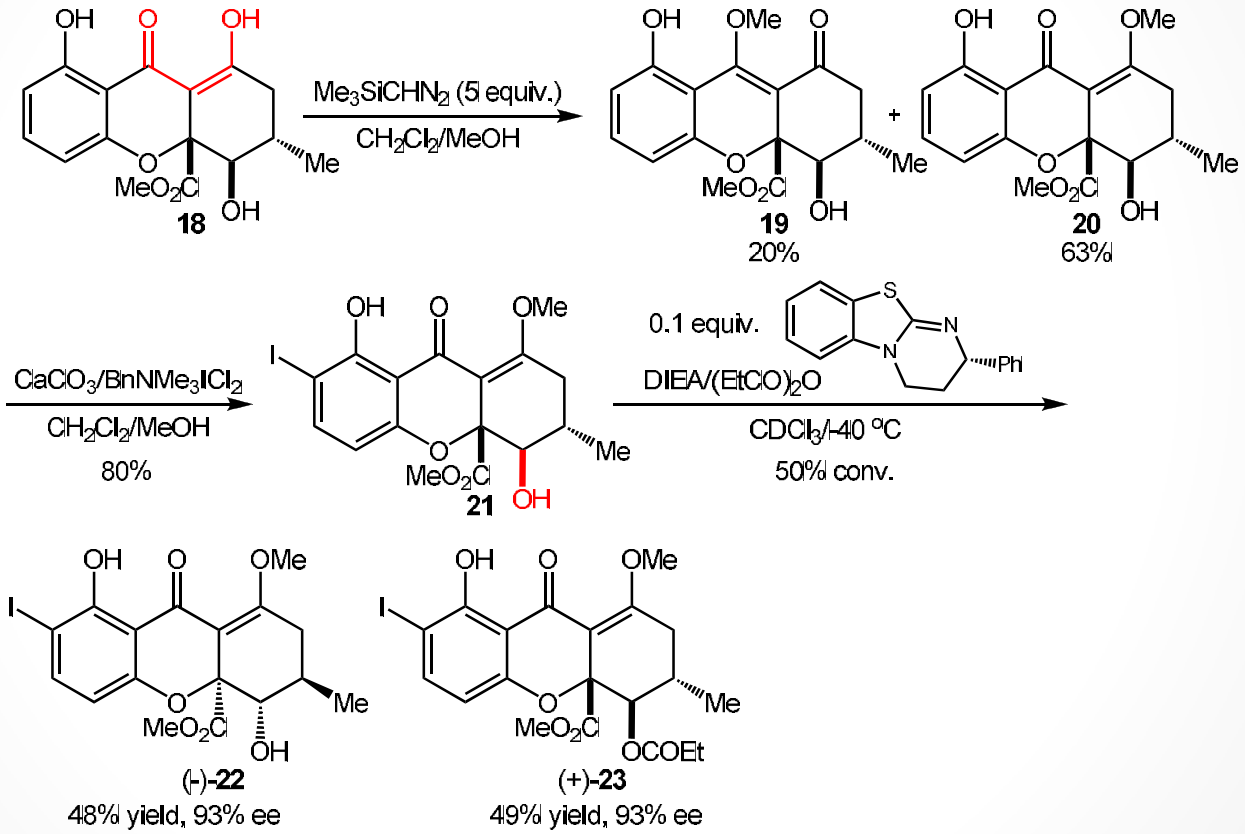


R = CO_2Me, R' = Et, R'' = H or Me

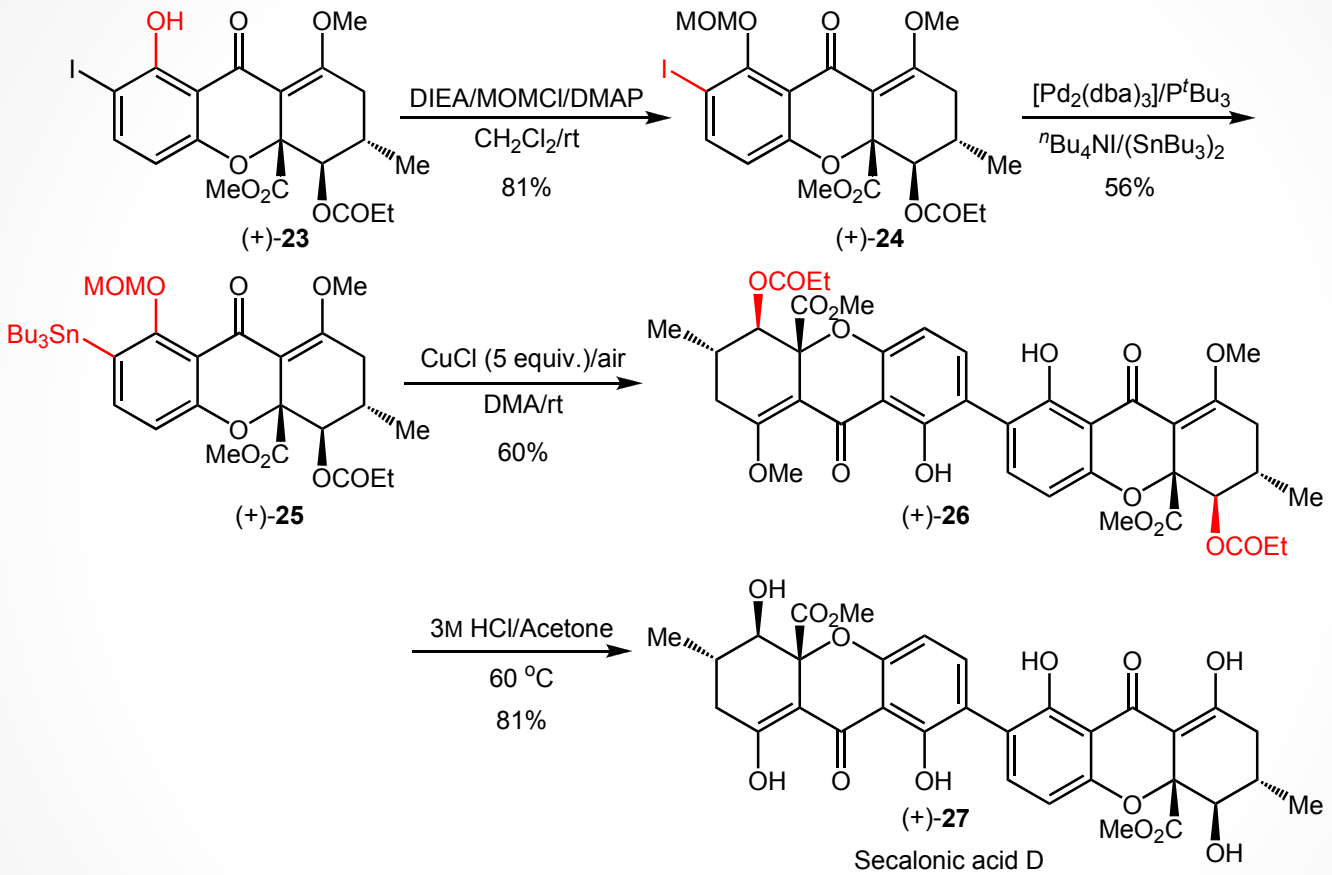
Synthesis of secalonic acid D



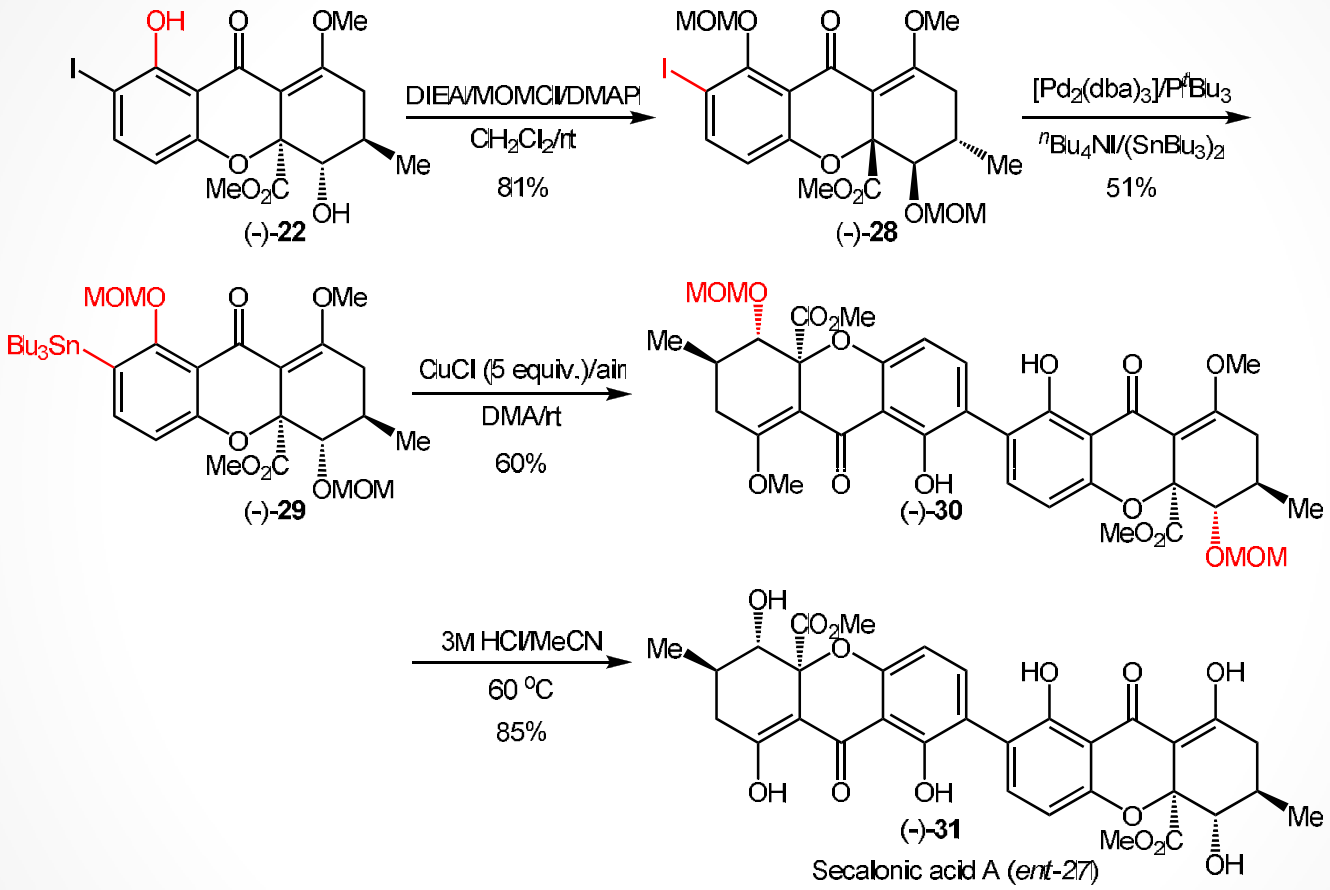
Synthesis of secalonic acid D



Synthesis of secalonic acid D



Synthesis of secalonic acid A



Dimeric tetrahydroxanthones belong to a class of mycotoxins which connect tetrahydroxanthone monomers by a 2,2'-biphenol linkage. Among these compounds, the secalonic acids were first isolated in 1960 and were found to exhibit interesting bioactivities. Secalonic acid B has antitumor activity and its diastereomer secalonic acid D shows potent cytotoxicity to HL60/K562 cells by down-regulation of c-Myc. The compound secalonic acid D has also been reported to inhibit DNA topoisomerase I. The enantiomer of secalonic acid D, secalonic acid A (*ent-27*) has antitumor properties and also reduces colchicine toxicity in rat cortical neurons. Related natural products include gonytolide A and rugulotrosin A, both of which possess axial chirality. Recently, our group as well as those of Bräse, Nicolaou, and Tietze 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.

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.