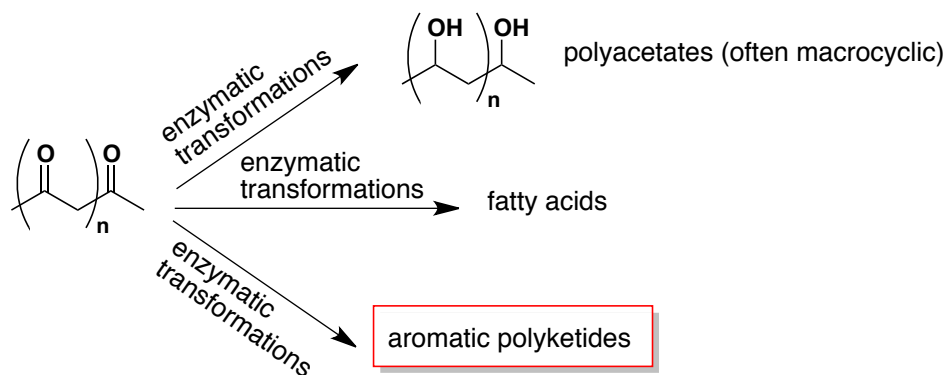


Poly(β -carbonyl)s, intermediates in polyketides biosynthesis

This group meeting will mainly focus on poly(β -carbonyl)s with unsubstituted methylenes at the α -position:

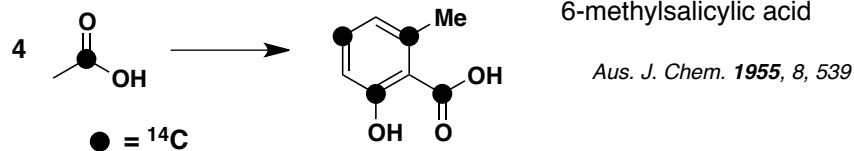


Polyketides rapid overview:

* name coined in 1907 by John Norman Collie (polyketenes hypothesis)

J. Chem. Soc. **1907**, *91*, 1806.

* correct biosynthetic pathway proposed by A. Birch in the 1950s ("head-to-tail" condensation of acetate units)

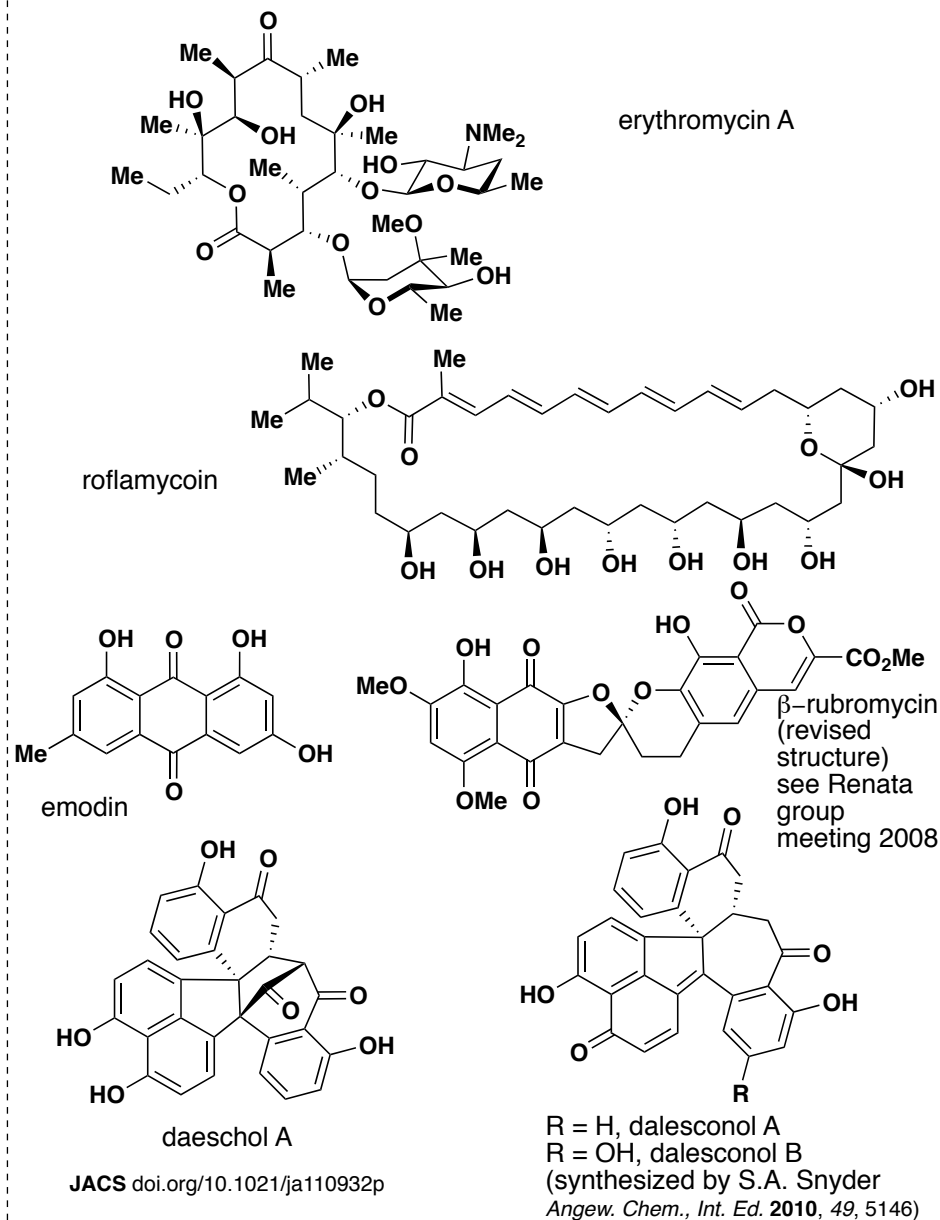


* first polyketide synthase (PKS) was isolated in the 1970s

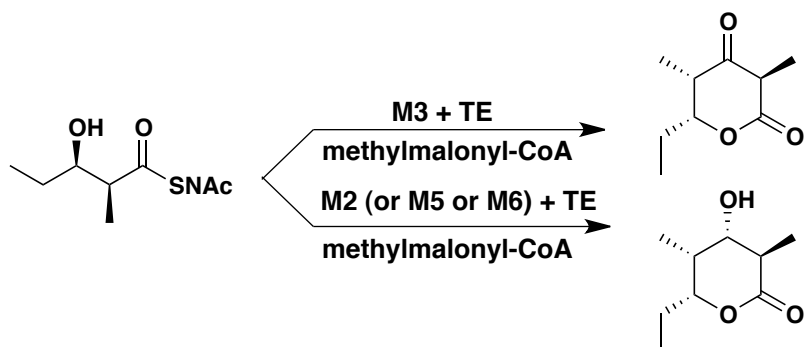
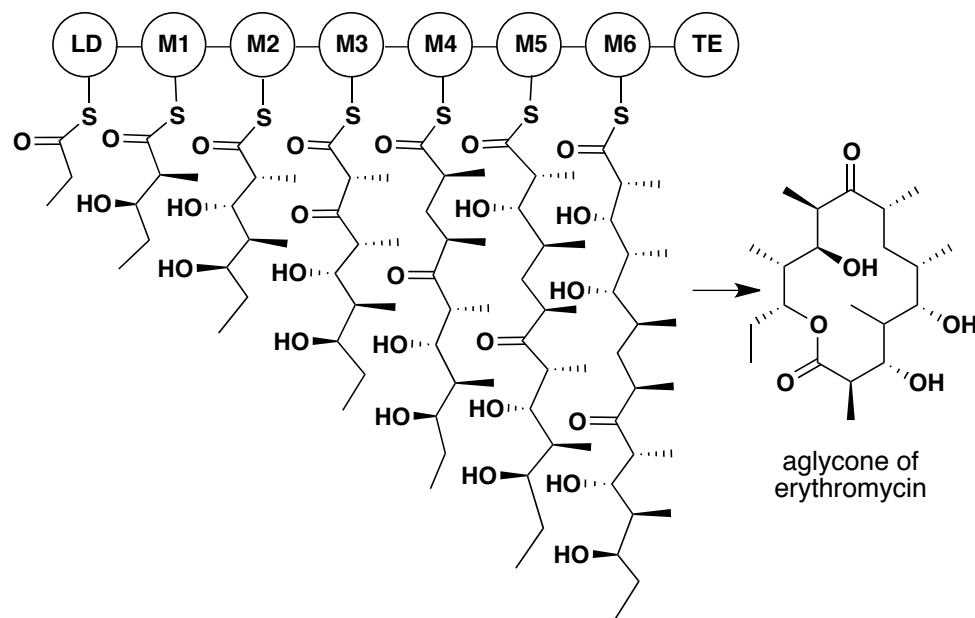
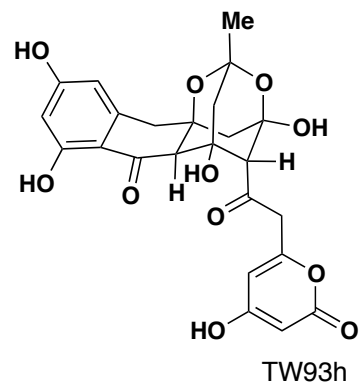
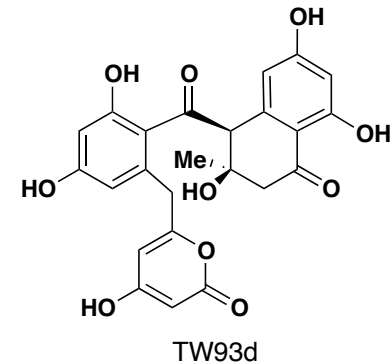
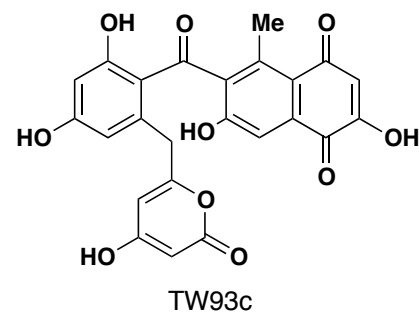
* secondary metabolites of microorganisms (*bacteria*, *fungi*, etc.)

* 20 marketed drugs out of some 7000 characterized polyketide structures, "hit rate" of 0.3 % *Science* **2009**, *325*, 161.

A few examples of polyketides:

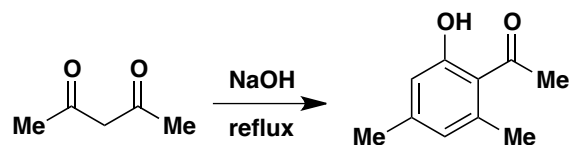


Polyketides bioengineering:

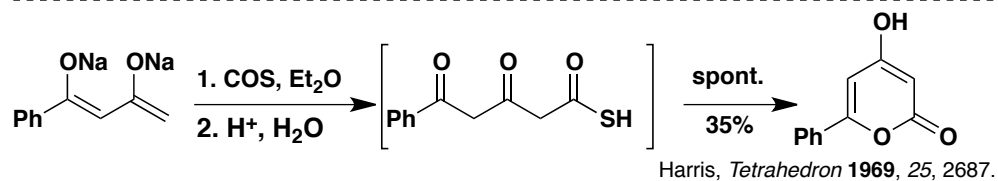
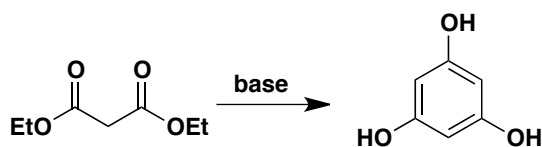
LD: loading domain
M: module
TE: thioesteraseEctopic expression of polyketide synthase, the minimal *whiE* (Moore *et al.*)Khosla, *Science* 1999, 284, 482*Proc. Natl. Acad. Sci. U.S.A.* 1999, 96, 3622

Chemistry of poly(β -carbonyls): the 'cyclase phase':

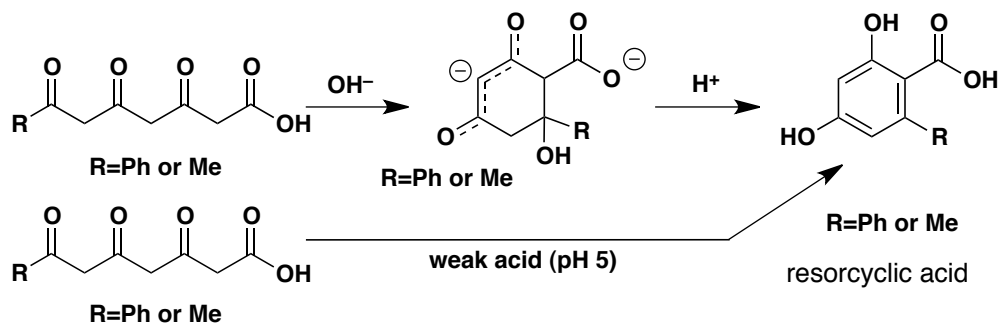
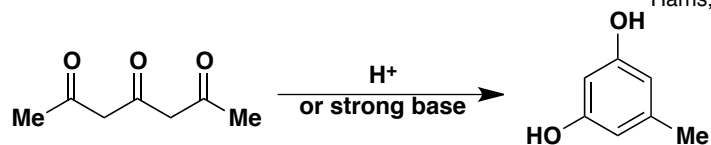
Poly(β -carbonyls) are highly reactive (methylenes have a pKa around 13–14) and cyclize easily due to concomitant aromatization: for a review, see Harris *et al.*, *Tetrahedron* **1977**, *33*, 2159.



Takeshita, *Tetrahedron Lett.* **1977**, *19*, 1657.

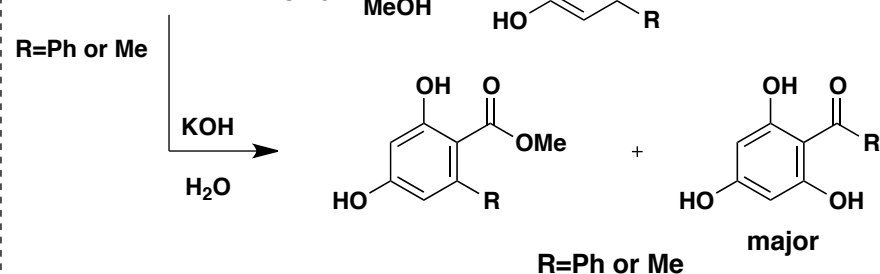
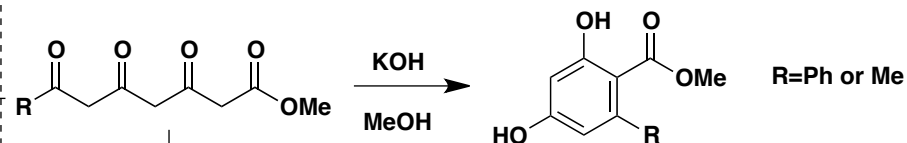
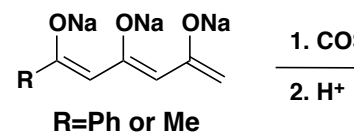
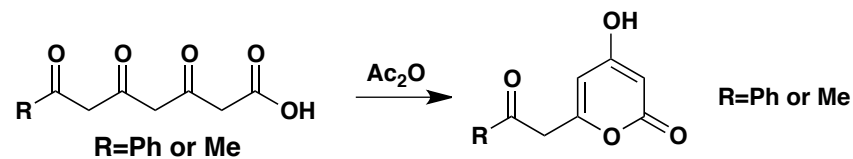
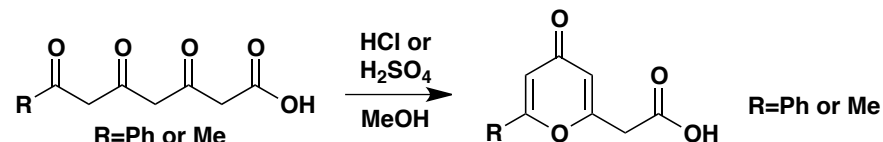
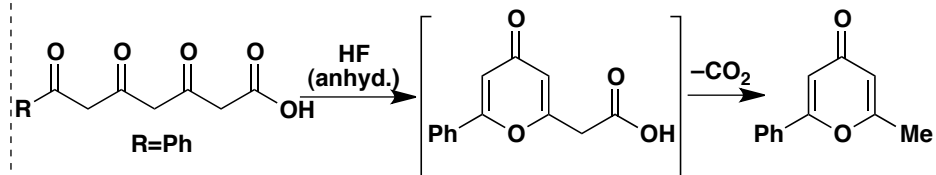


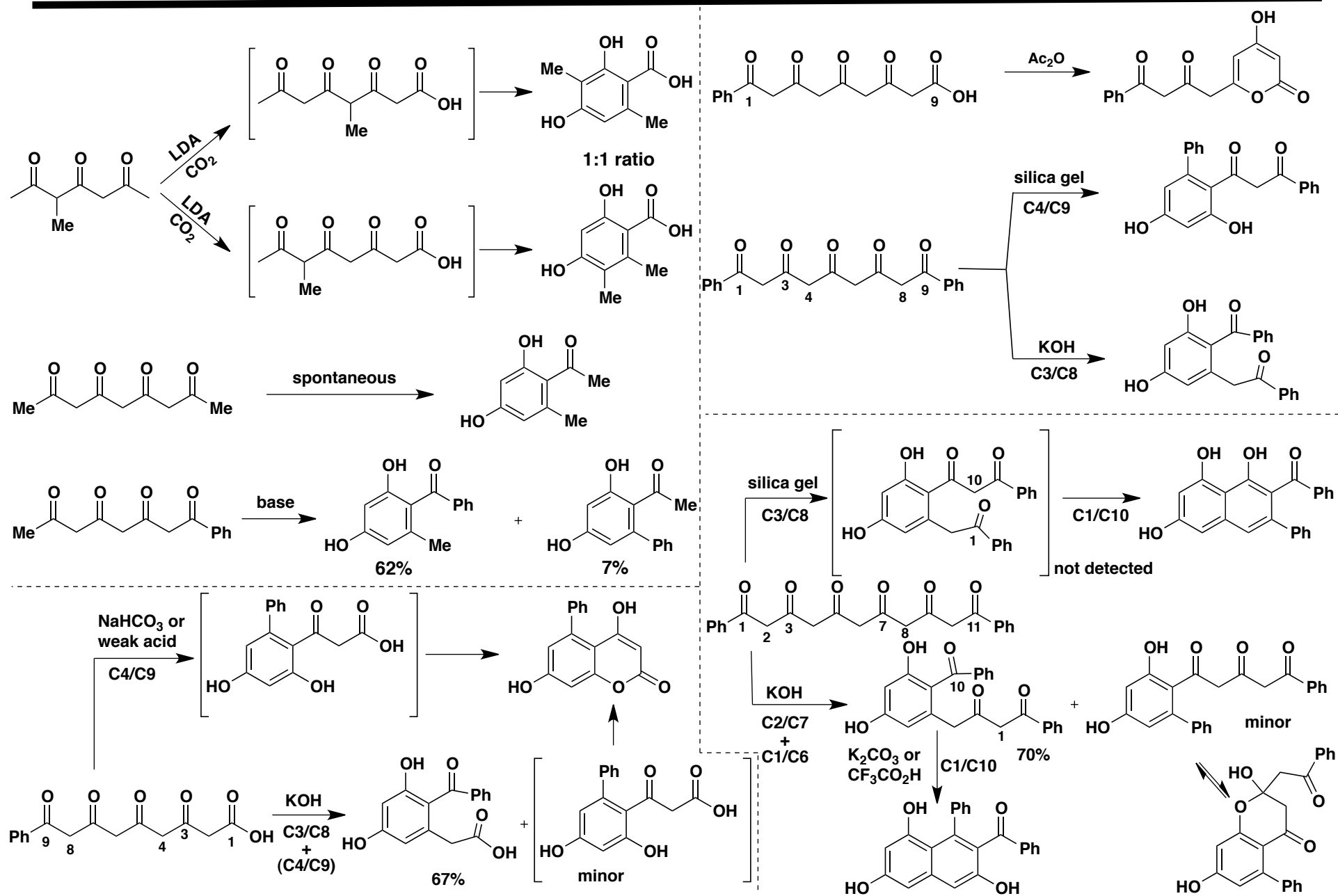
Harris, *Tetrahedron* **1969**, *25*, 2687.

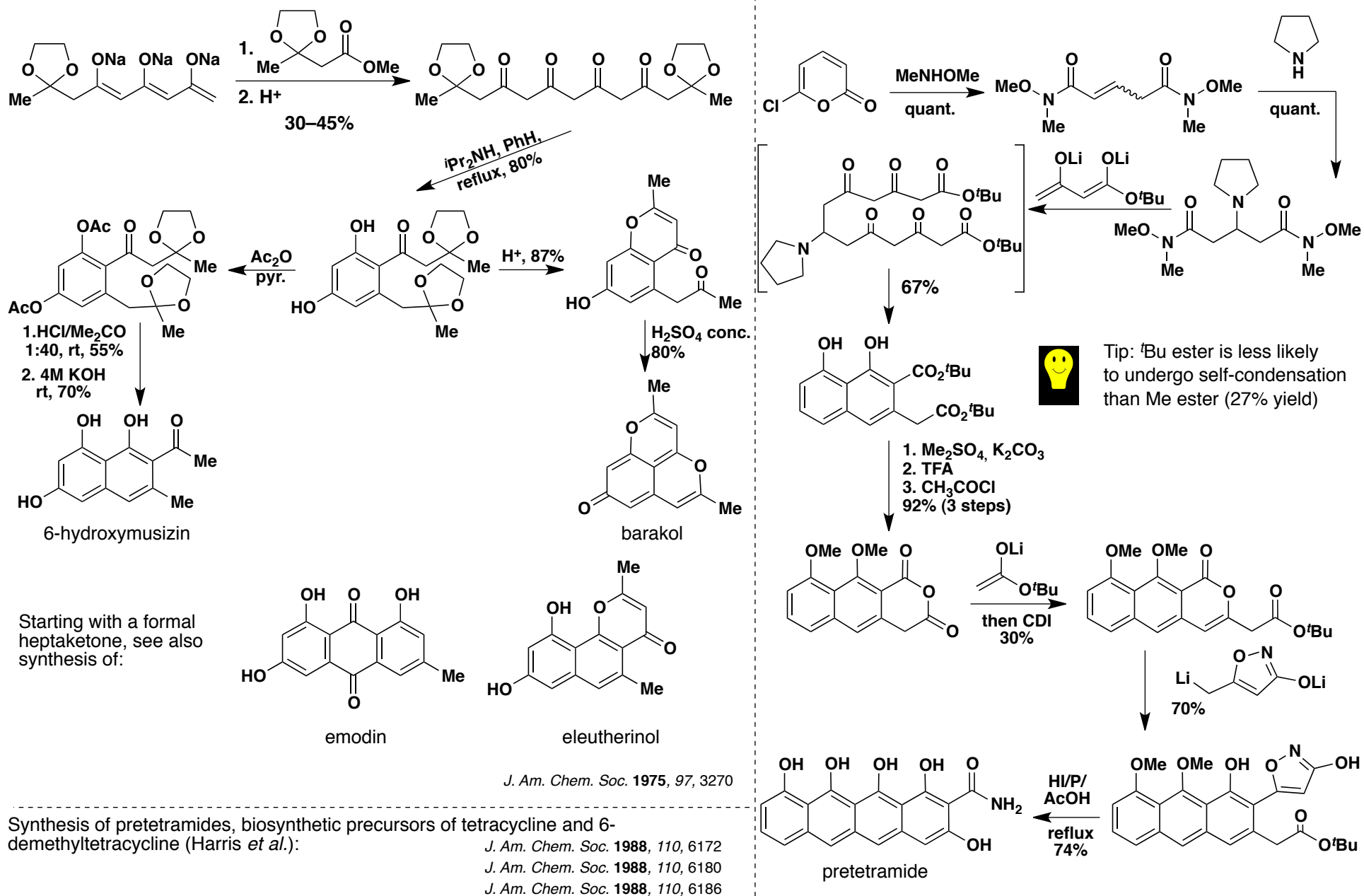


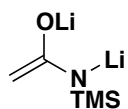
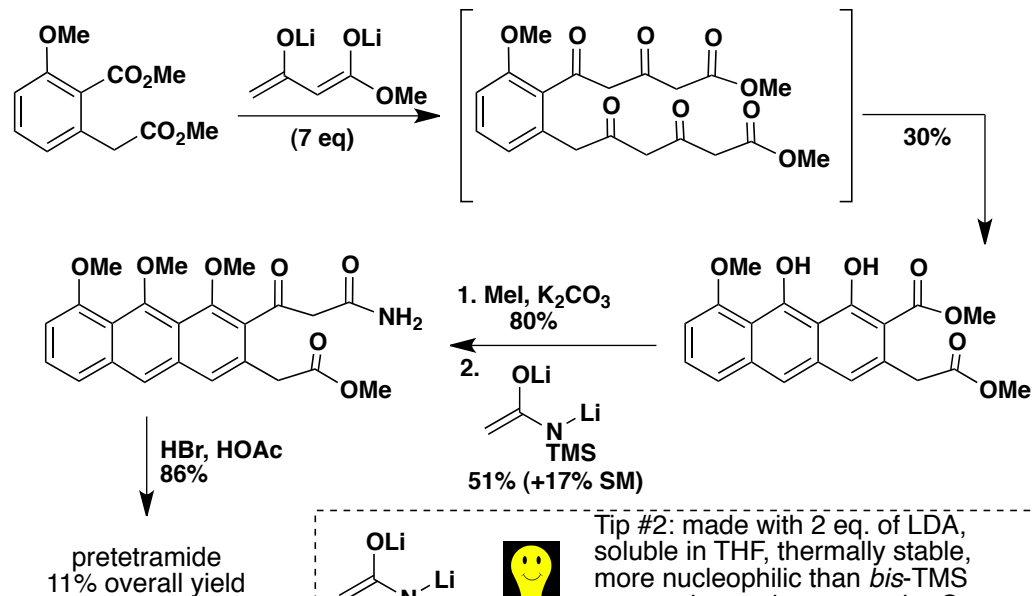
weak acid (pH 5)

resorcylic acid





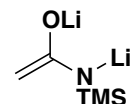




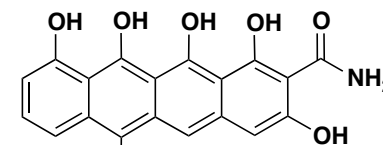
Tip #2: made with 2 eq. of LDA, soluble in THF, thermally stable, more nucleophilic than *bis*-TMS monoanion and reacts at the C-position instead of the N-position.
J. Org. Chem. **1984**, *49*, 2015.

1. KOH, MeOH
85%

2. NaH then



3. CH_2N_2 25% (2 steps)
4. HBr, HOAc, 50%



6-methylpretetramide

See also bio-inspired synthesis of alternariol and lichexanthone

J. Am. Chem. Soc. **1977**, *99*, 1631

and bio-inspired synthesis of eleutherin

Tetrahedron Lett. **1977**, *24*, 2069

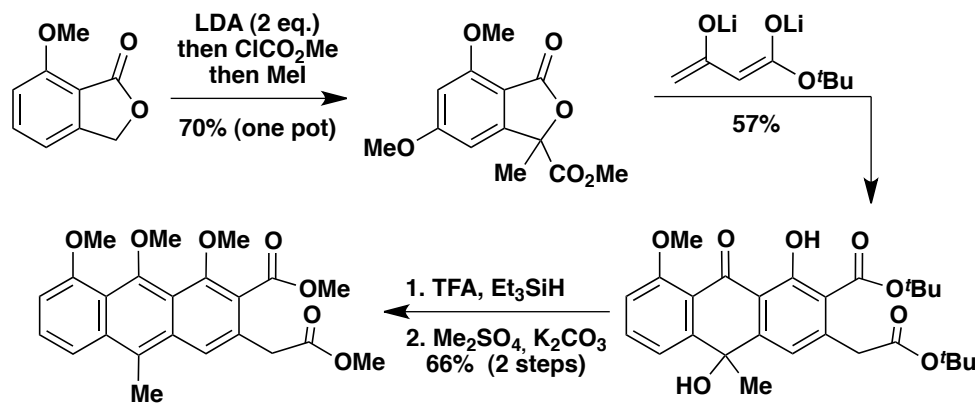
Summary of the 'cyclase phase':

* Regio- and chemoselective cyclizations conditions of poly(β -carbonyl)s in the literature are scarce and all of them involve simple reagents

* The main issue is the synthesis of long poly(β -carbonyl) chains due to their high instability in acidic, basic or oxidative conditions.

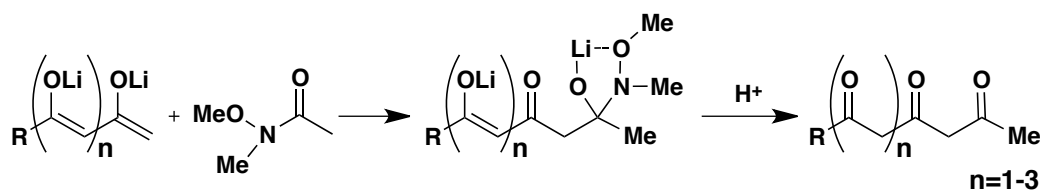
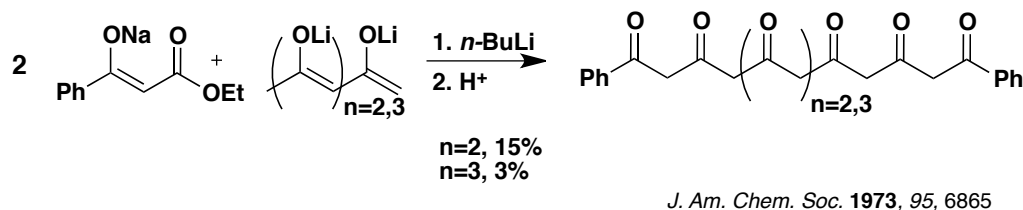
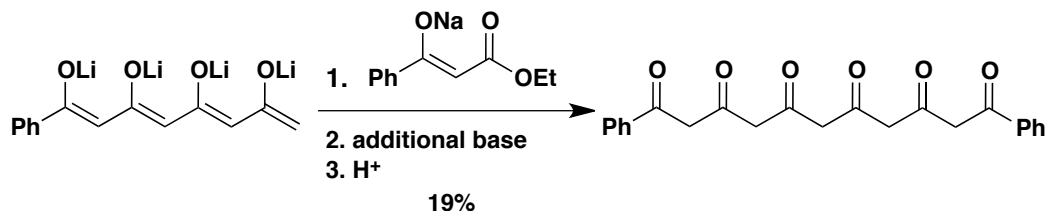
* Poly(β -carbonyl)s with terminal ketones are more eager to cyclize than esters or carboxylic acids, as well as those with terminal methyl groups than terminal phenyl groups.

* Some total synthesis of natural products use partially protected poly(β -carbonyl)s, but fully deprotected poly(β -carbonyl)s are never isolated.



Chemistry of poly(β -carbonyl)s: the 'elongation phase':

Direct condensation of poly(β -carbonyl)s (Harris and coworkers):



Tetrahedron Lett. 1983, 24, 1851

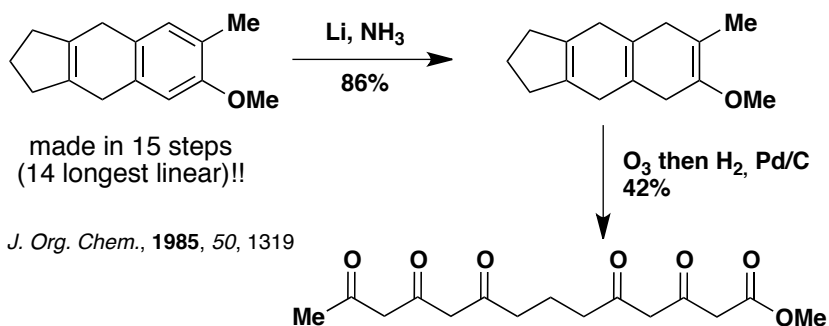
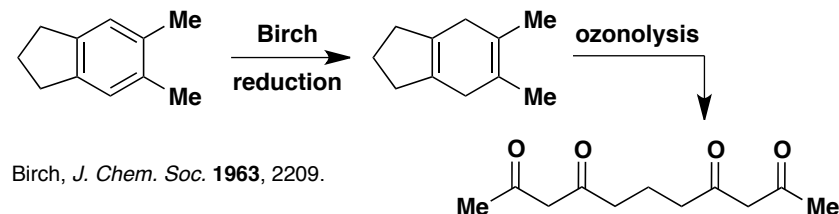
R=Ph n=0 0%
n=1 86% (56% isolated yield)
n=2, 80% (75%)
n=3, 88% (55%)
R=Me n=2 96% (60%)

* Yields drop with increasing chain length.

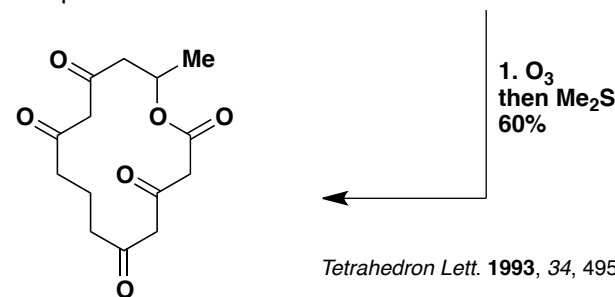
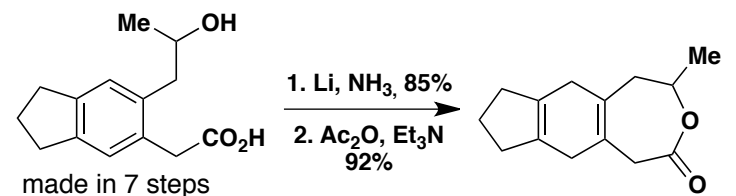
* Octaketone is the longest chain reported.

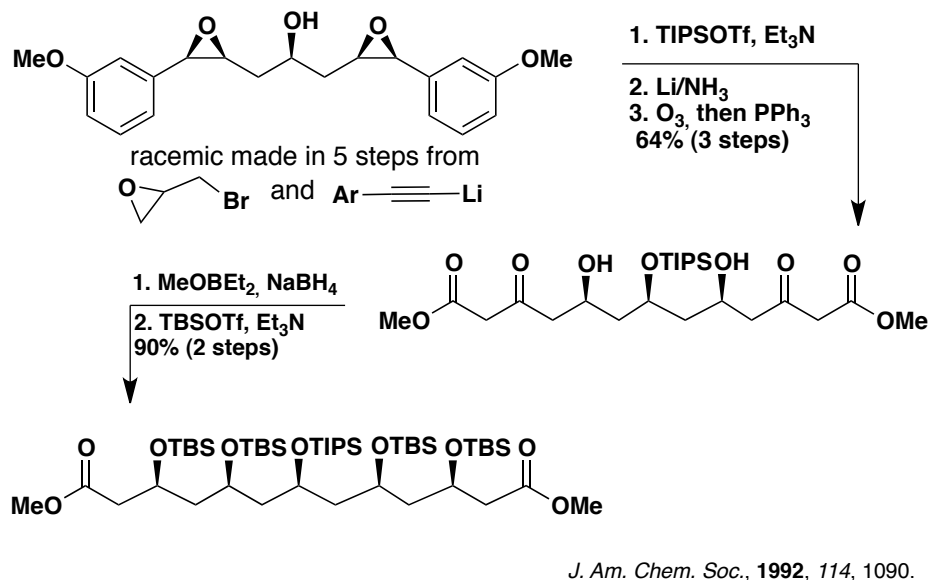
Aromatic compounds as synthons for 1,3-dicarbonyl derivatives:

For a review, see *Chem. Soc. Rev.*, 2009, 38, 3082

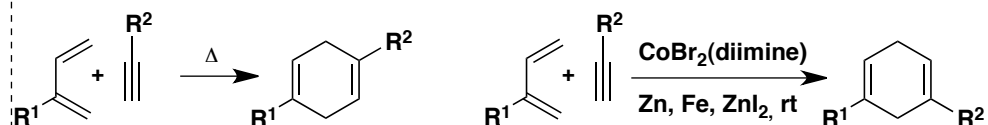


"Comparison of the UV spectrum of [this molecule] with the spectra of other polyketide structures (Table I) was especially informative."

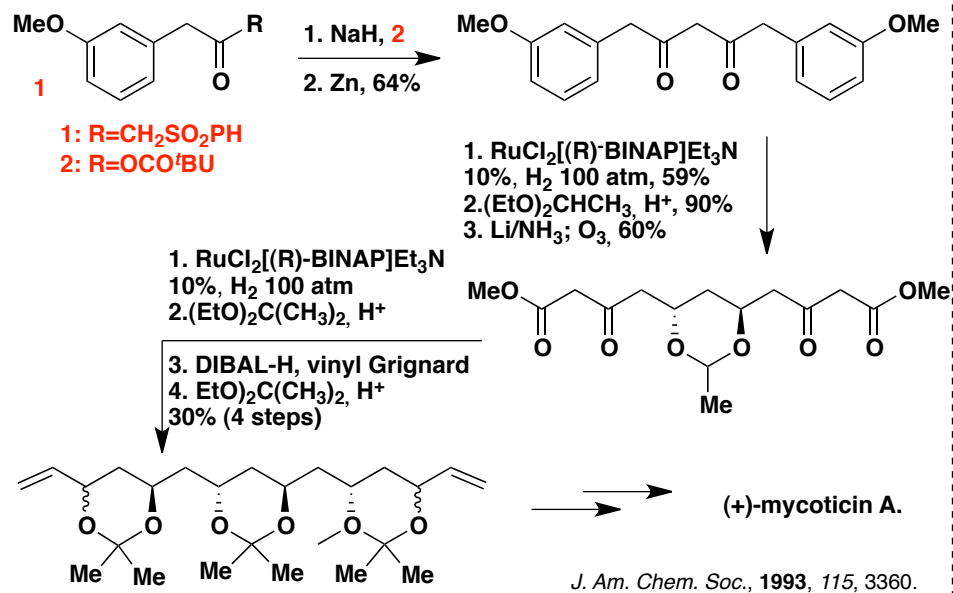
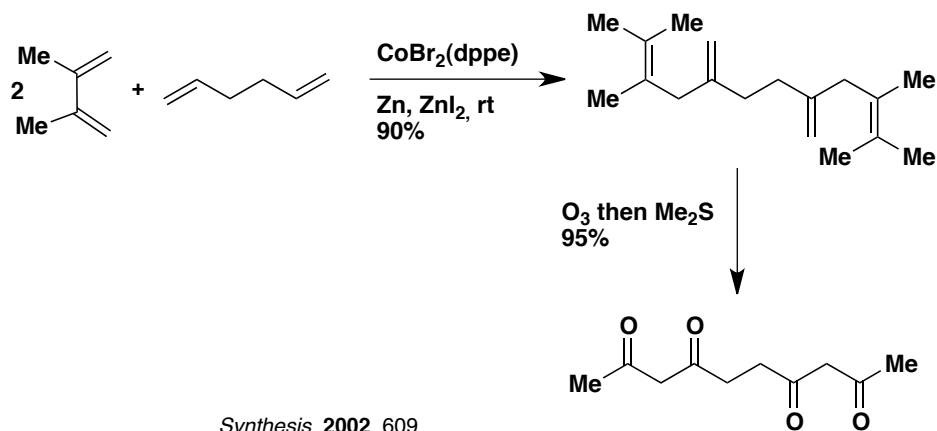




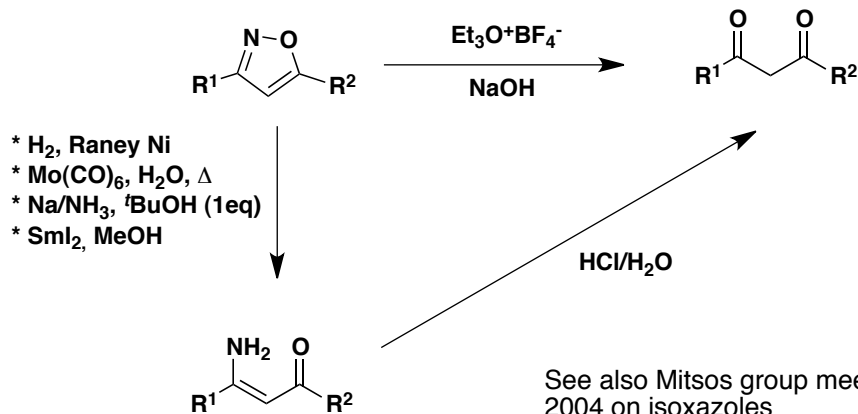
* A major drawback: only few substituents can tolerate Birch reduction and ozonolysis conditions. An alternative to avoid Birch reduction is to use [4+2] or 1,4-hydrovinylation to make the polyene.



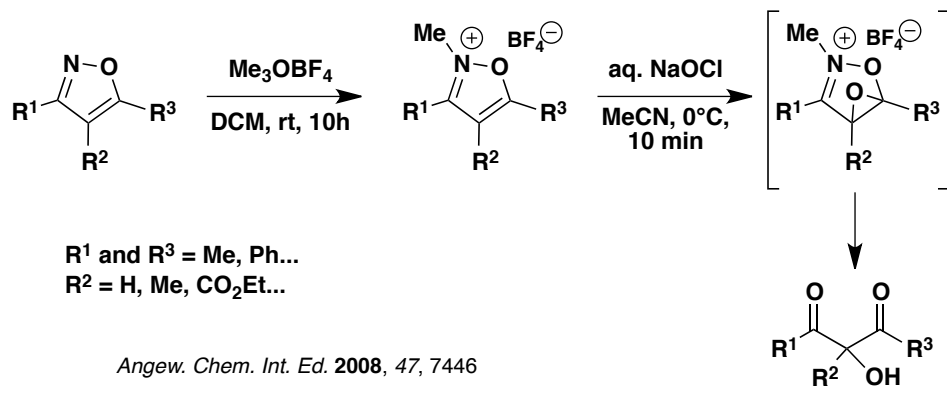
In that case, R can be an aromatic group, that allows to make polyketones with a terminal aromatic group with the Birch/ozonolysis sequence.



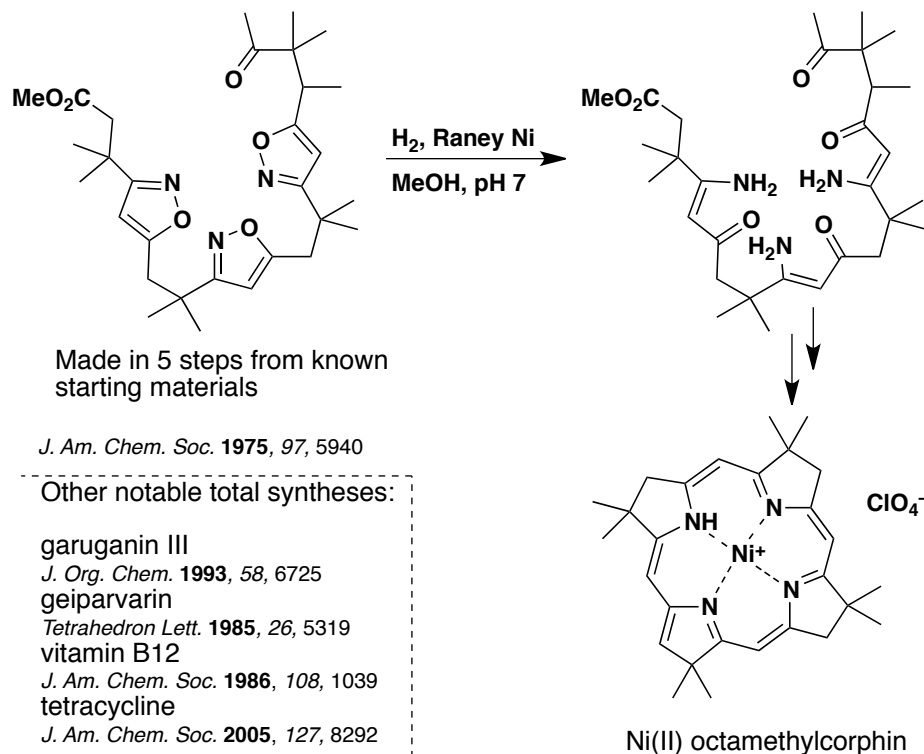
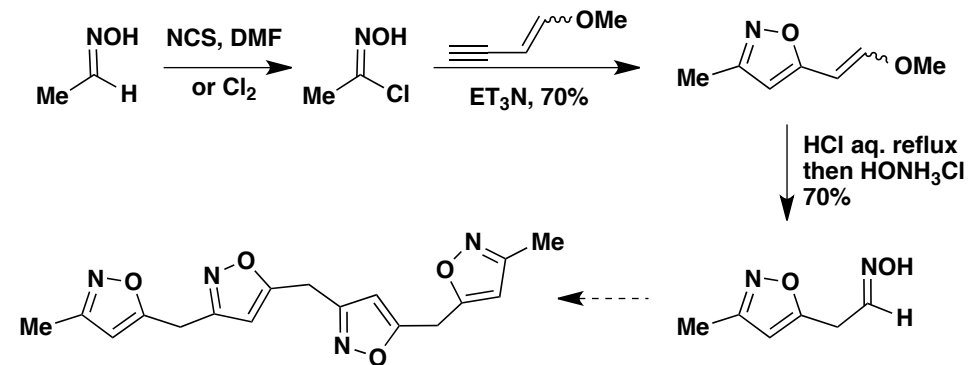
Isoxazole as synthons for 1,3-dicarbonyl derivatives:



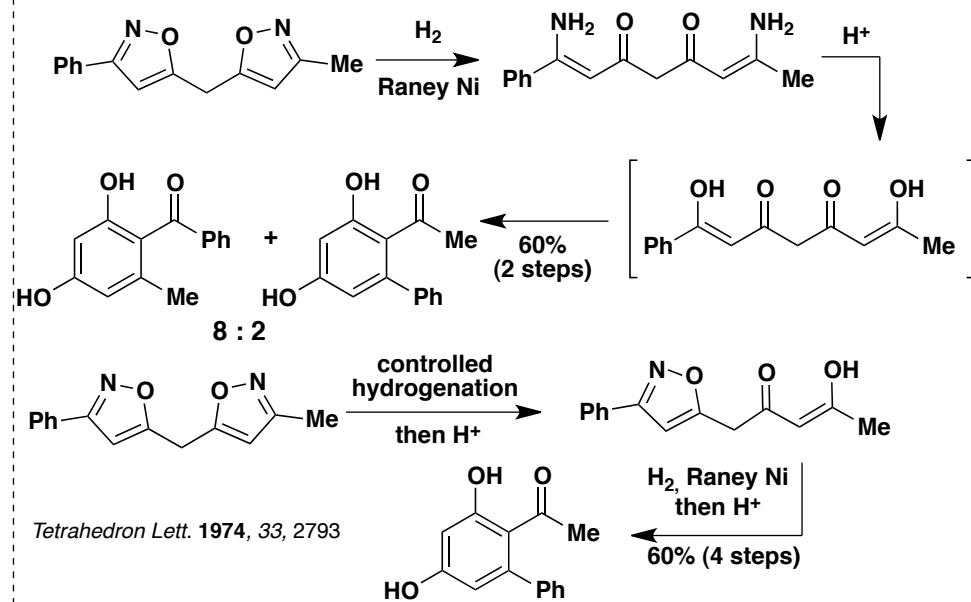
An oxidative ring opening has also been reported recently:



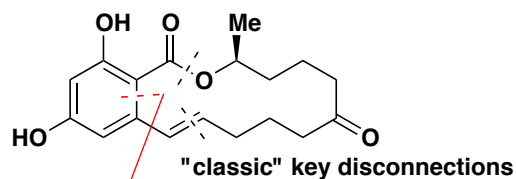
Isoxazole opening in total synthesis:

Polyisoxazoles as hidden poly(β -carbonyl)s:* Bis-, tris- and tetraisoxazoles have been synthesized by Aurrichio *et al.*

* Cleavage of bisisoxazoles have been reported by the same team:



To conclude, a biomimetic synthesis of (-)-zearalenone: *Tetrahedron* 2010, 6331



biomimetic key disconnection

