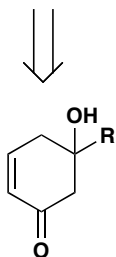
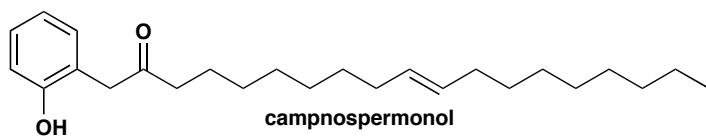
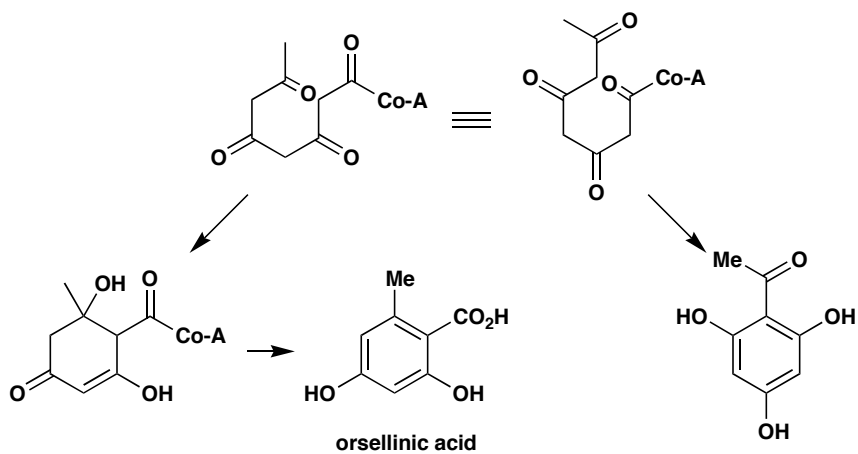


Biosynthesis of Polyketides

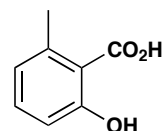
- 1907: J. N. Collie coined the term polyketenes to define fatty acids and terpenes as "polymers" of ketene subunits, which was later changed to polyketides
- 1951: acetyl Co-A already known to be involved in synthesis of steroids and fatty acids, Birch was interested in the product possibilities if the oxygen atoms were retained



- synthesis of these molecules could take place via aldol or claisen chemistry



- other Co-A esters are possible, explaining also flavanoid and anthocyanin synthesis
- loss of oxygen can be due to dehydration that gives rise to aromaticity
- aromaticity can be generated by enolization



- first polyketide with acetic acid as confirmed building block using tracer experiments

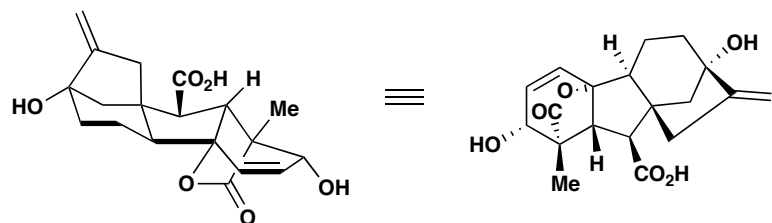
Birch, A. J.; Massy Westopp, R. A.; Moye, C. J. *Chem. Ind.*, 1955, 683

- C-methylation occurs as well and addition of other electrophiles

- Birch hypothesis for biosynthesis of polyketides was rejected from some of the best journals

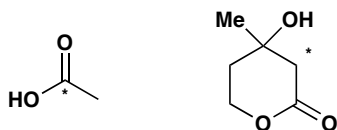
First hypothesis paper: Birch, A. J.; Donovan, F. W. *Aust. J. Chem.*, 1953, 6, 373

Birch, A. J. *Science*, 1967, 156, 202-206

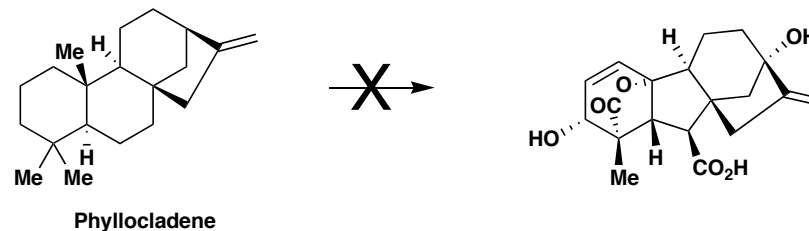
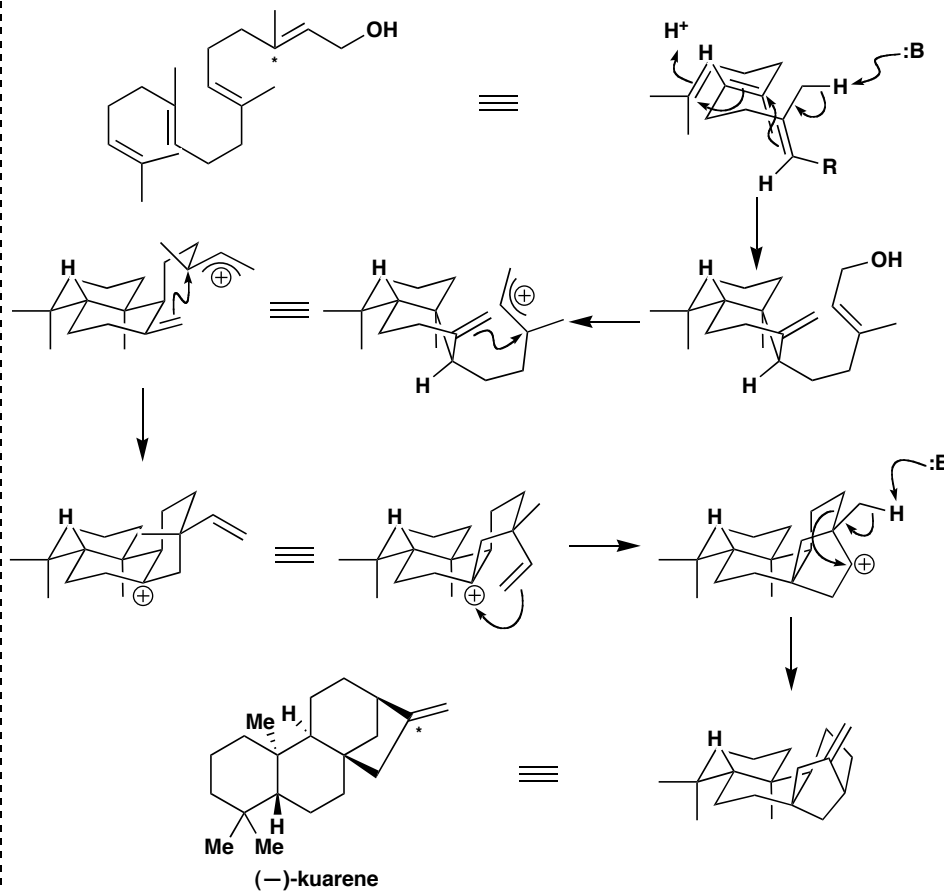
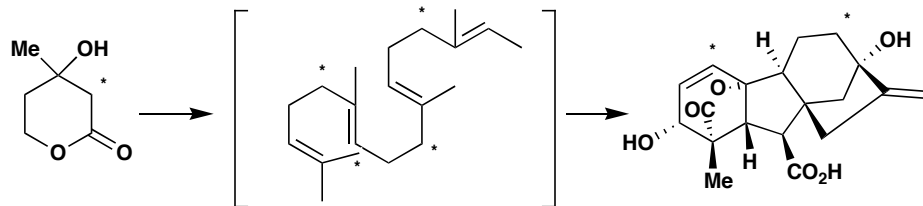
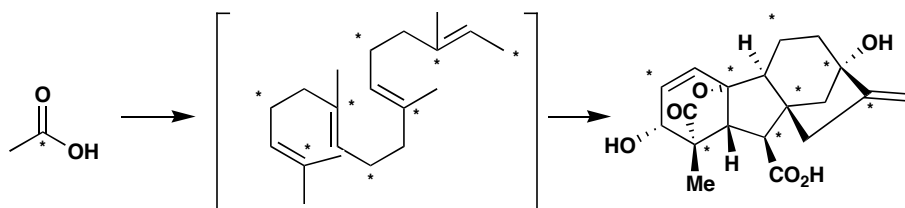
Biosynthesis**Gibberellic Acid and Rosenolactone**

- ^{14}C feeding experiments show production from acetic acid and mevalonic lactone which itself is made from acetic acid

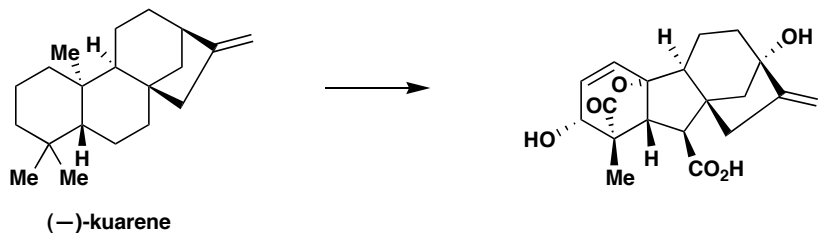
- labeled precursors



Gibberellic acid made from 4 molecules of mevalactone or 8 molecules of acetic acid



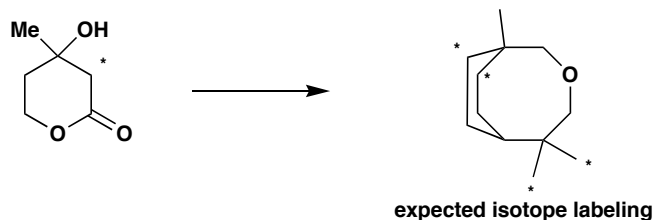
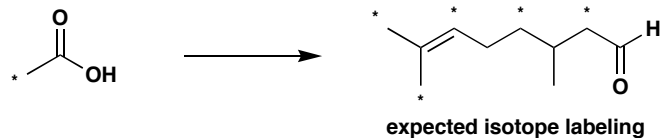
- lactone carbonyl does not contain ^{14}C label
 - \square -methyl group from phyllocladene contains ^{14}C label \square phyllocladene is not precursor to gibberellic acid



- addition of kuarene gave increase in gibberellic acid
 Birch, A. J.; Smith, R. H. *Tetrahedron*, 1959, 7, 241-251
 Birch, A. J.; Winter, J. *J. Chem. Soc.*, 1962, 5547

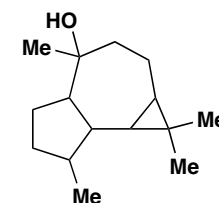
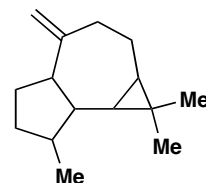
Citronellal and Cineol

- isotope labeled acetic acid and mevalactone fed into two varieties of *Eucalyptus*

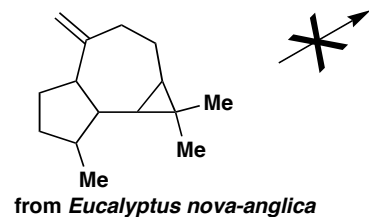
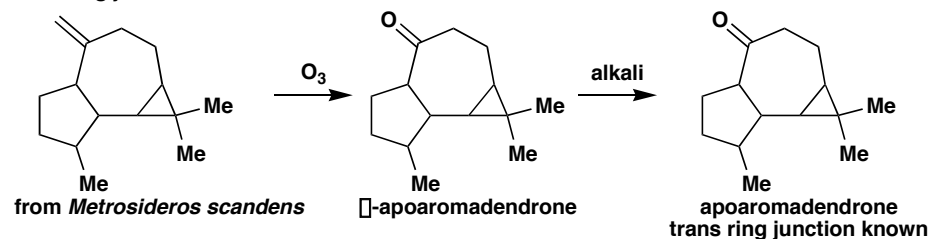


- degradation shows expected amounts of label incorporated into both products
 Birch, A. J.; Boulter, D.; Fryer, R. I.; Thomson, P. J.; Willis, J. L. *Tetrahedron Lett.*, 1959, 3, 1-2

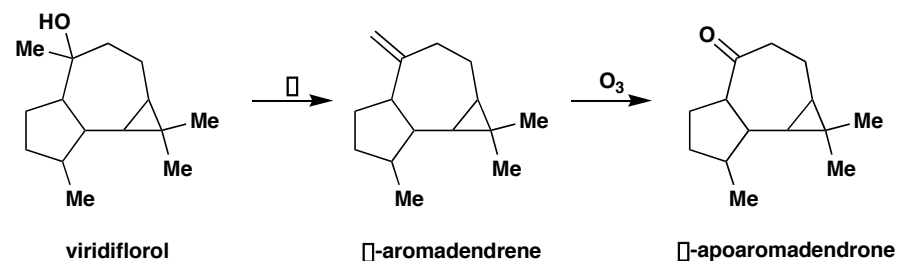
Aromadendrene and Viridiflorol

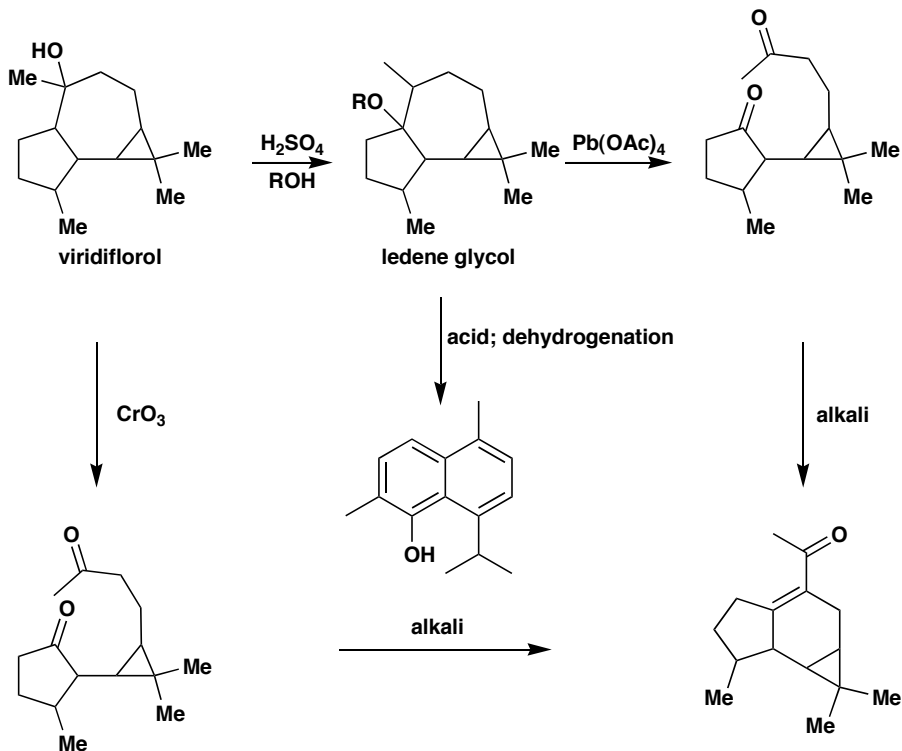


- trans cyclopentane ring junction assumed by analogy to aromadendrene from *Eucalyptus nova-anglica*, aromadendrene has trans ring junction, alloaromadendrene has a cis ring junction



* Aromadendrene from *E. nova-anglica* has cis ring junction and *M. scandens* produces trans





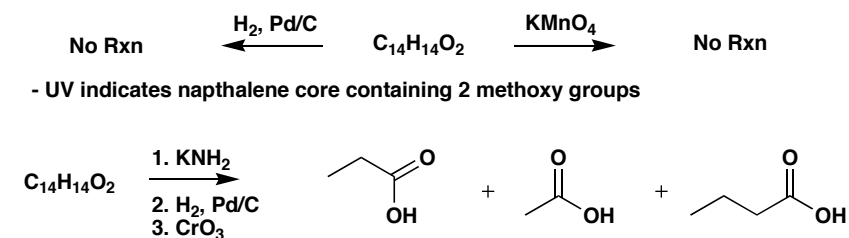
- concluded that ledol, palustrol, viridiflorol, and globulol are the four stereoisomers at the alcohol and ring junction positions

Birch, A. J.; Grimshaw, J.; Speake, R. N.; Gascoigne, R. M.; Hellyer, R. O. *Tetrahedron Lett.*, 1959, 3, 15-18

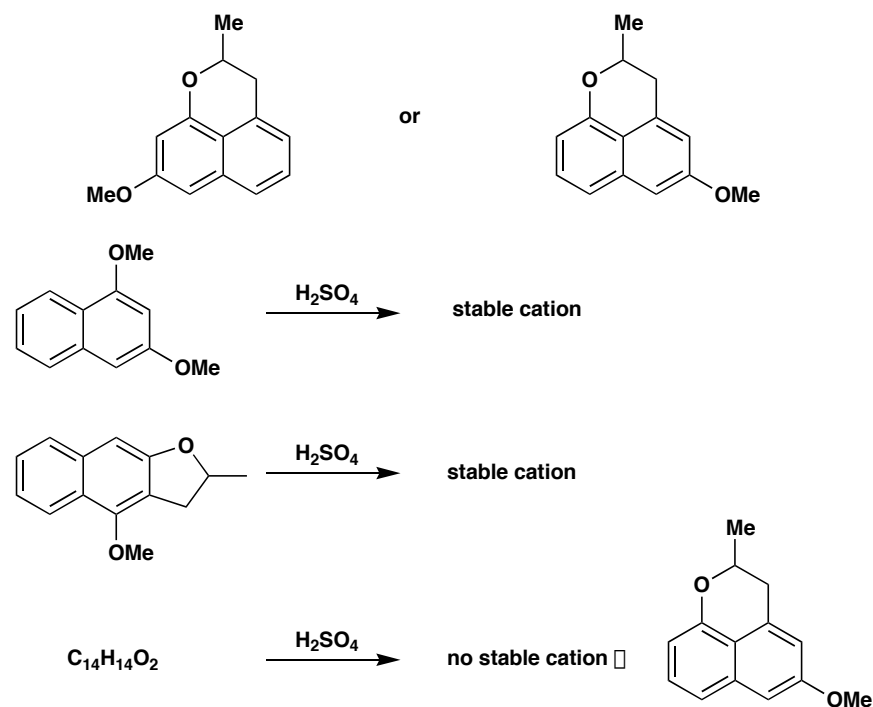
Xanthorrhoein

- from resin of *Xanthorrhoea Preisii* and *Xanthorrhoea reflexa*

- possible structures containing 1 C-methyl, 1 O-methyl, no carbonyl or hydroxyl groups
C₁₄H₁₄O₂



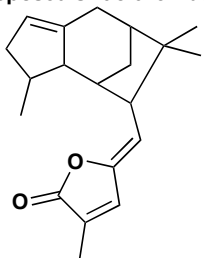
- UV indicates naphthalene core containing 2 methoxy groups



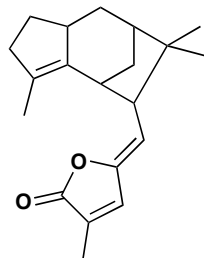
Birch, A. J.; Salahud-Din, M.; Smith, D. C. C. *Tetrahedron Lett.*, 1964, 25, 1623-1627

Eremolactone

- first proposed structure was incorrect

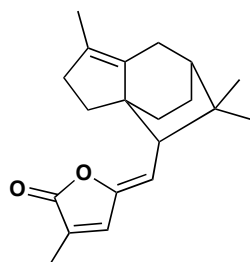


proposed eremolactone

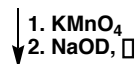
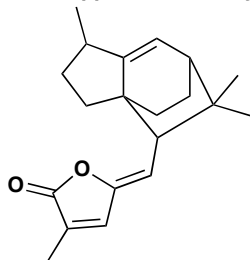


proposed isoeremolactone

- x-ray structure of isoeremolactone solved (Oh, Y.-L.; Maslen, E. N. *Tetrahedron Lett.*, 1966, 28, 3291)

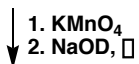
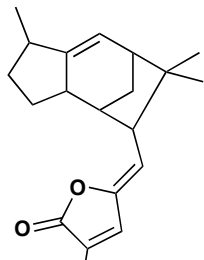


- classical approach taken by Birch to revise structure of eremolactone

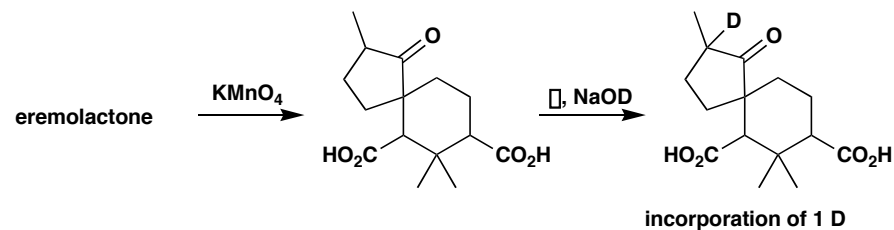


incorporation of 1 D expected

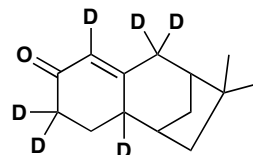
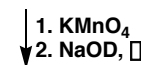
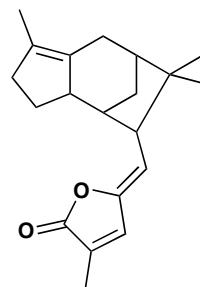
or



incorporation of 2 D expected

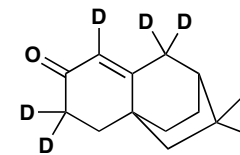
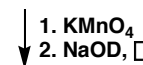
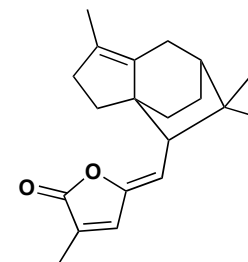


- same investigation with the proposed and x-ray structures of isoeremolactone



expected, not observed

or

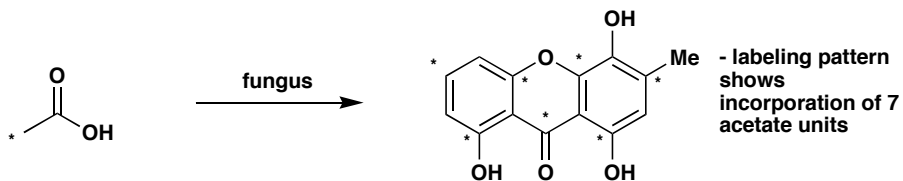
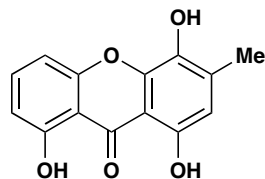


expected, observed

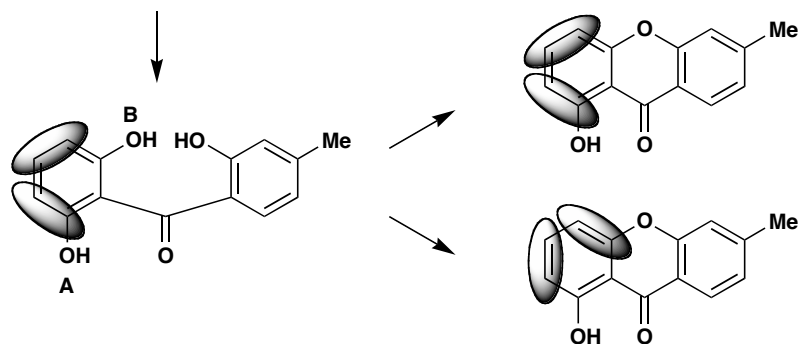
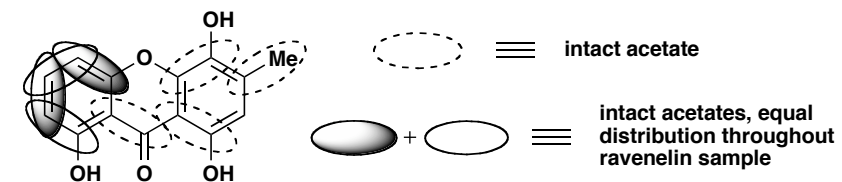
Birch, A. J.; Subba Rao, G. S. R. *Tetrahedron Lett.*, 1966, 39, 4749-4751

Ravenelin

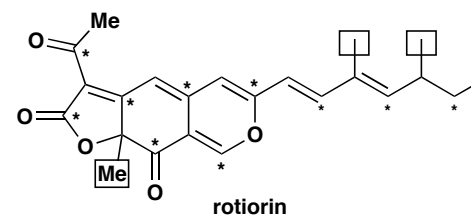
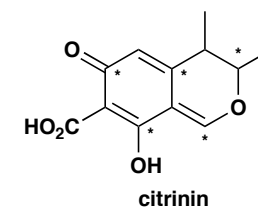
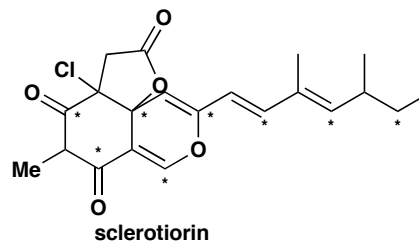
- biosynthetic studies using both 1-¹³C and 1, 2-¹³C acetate in fungi (*Helminthosporium*)



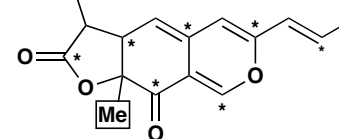
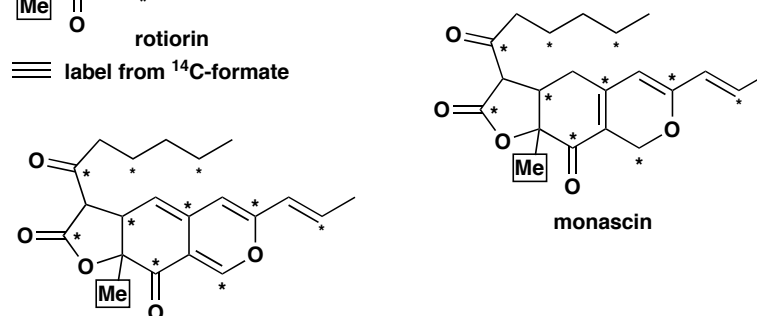
- ¹³C-¹³C coupling used to define intact acetate units.



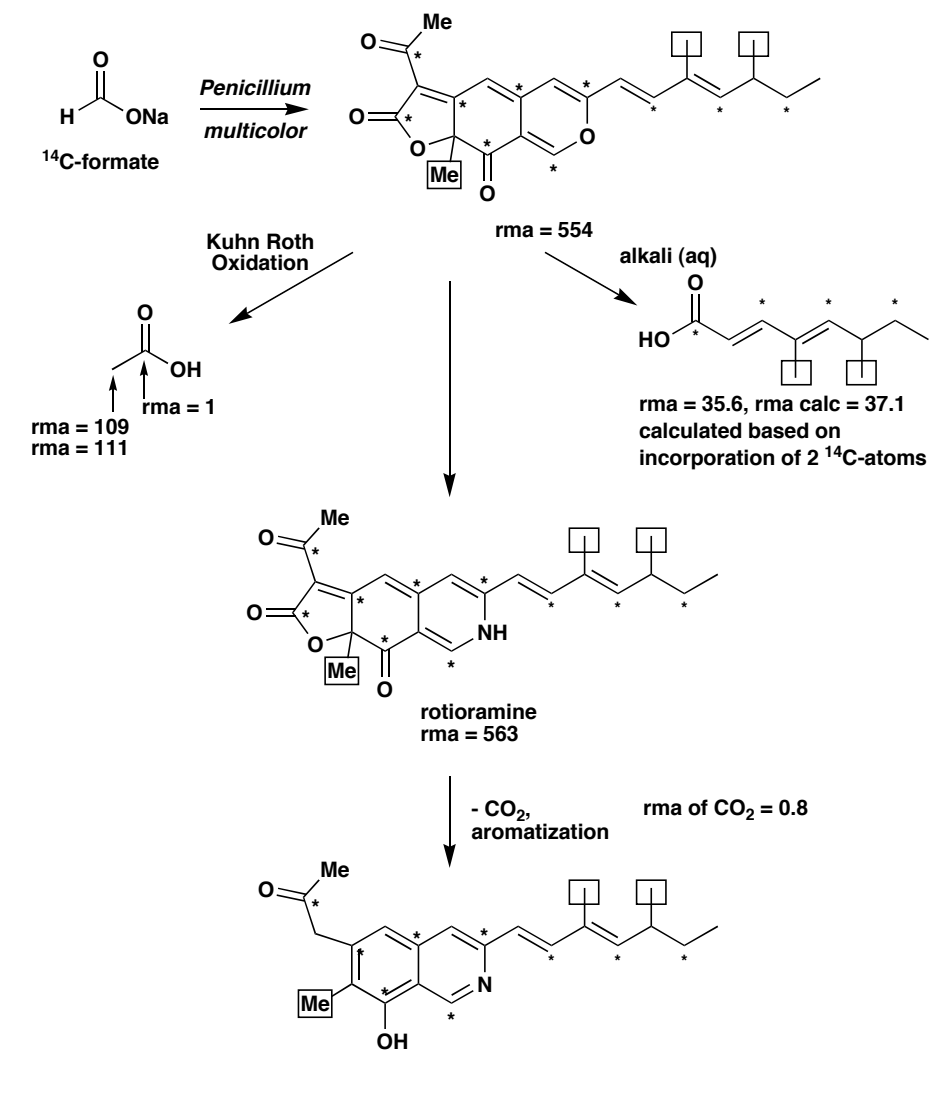
Sclerotiorin, Citrinin, Rotiorin, Monascin, Rubropuntatin



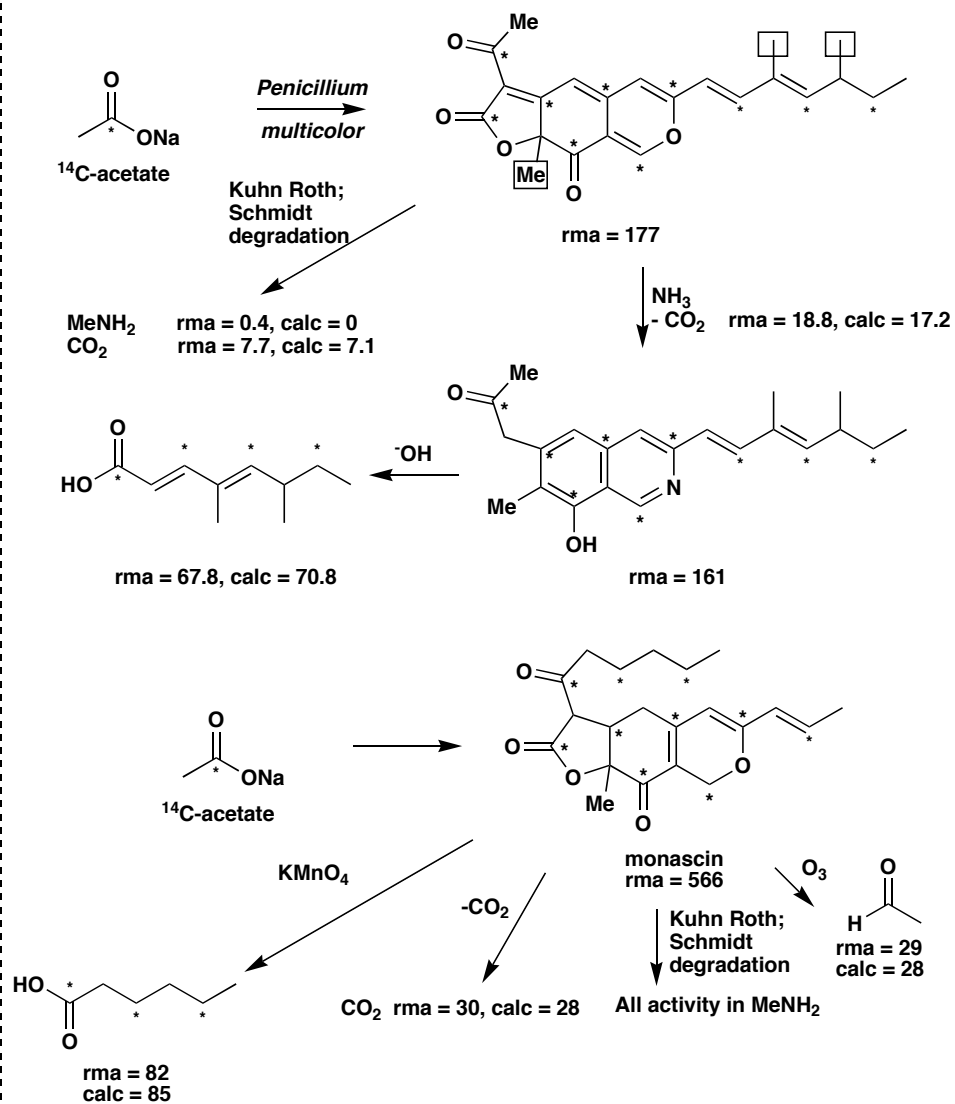
□ ≡ label from ¹⁴C-formate

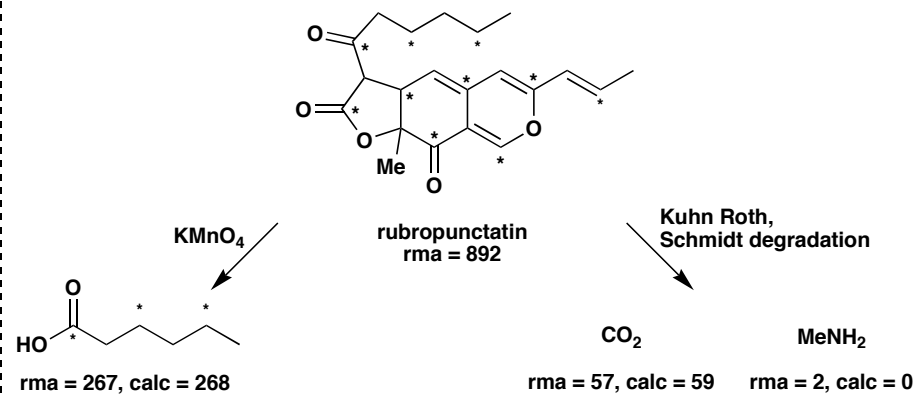
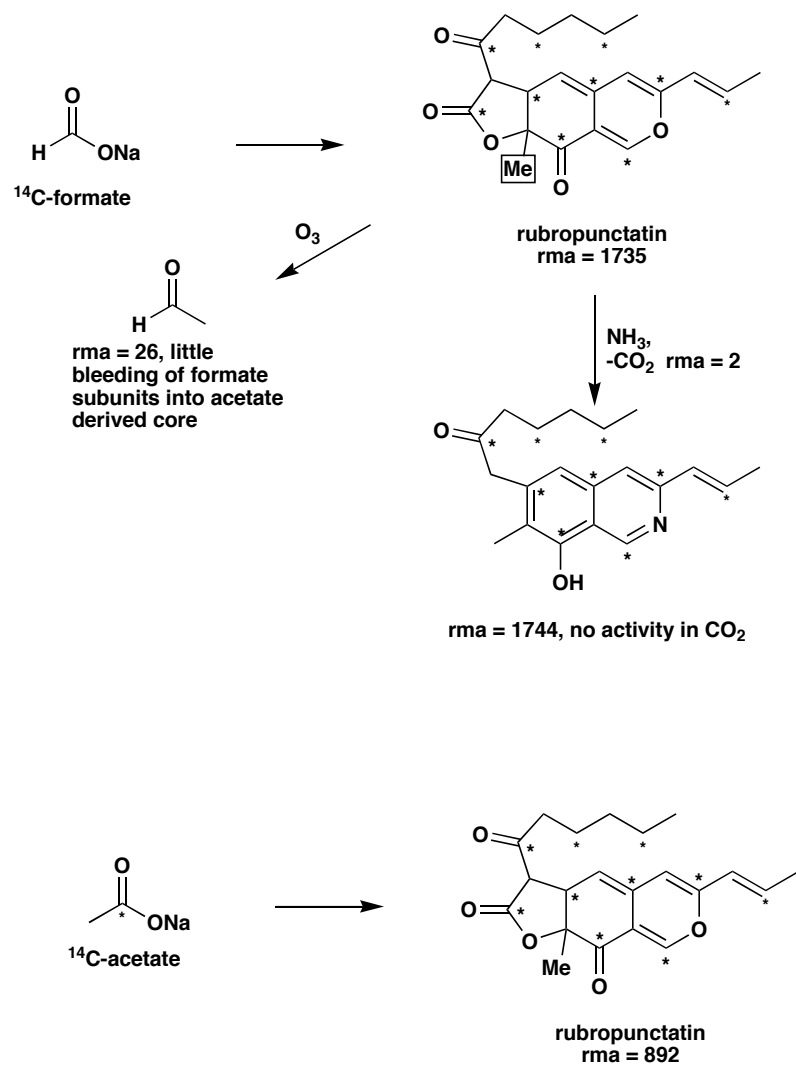


- tracer work on sclerotiorin and citrinin main skeleton demonstrated their polyketide origin and by analogy, labeling should be similar for the cores of rotiorin, monascin, rubropuntatin



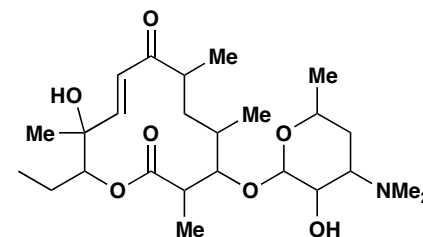
rma = relative molar abundance



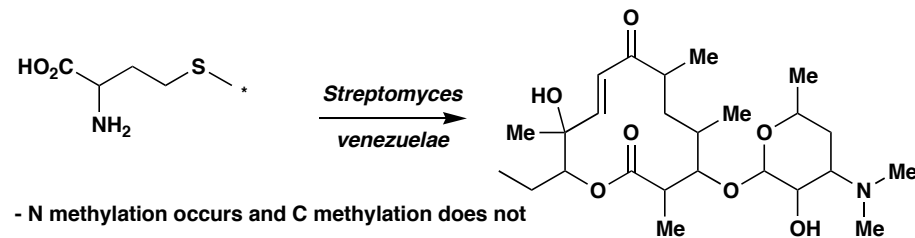


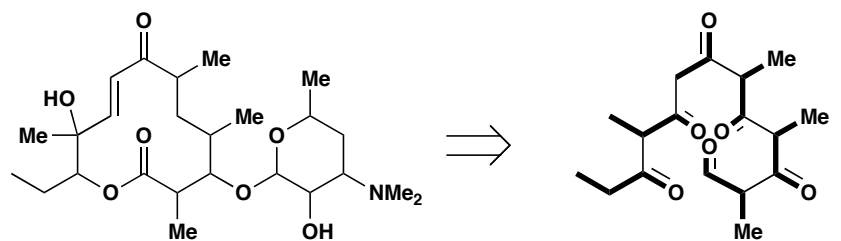
Birch, A. J.; Fitton, P.; Pride, E.; Ryan, A. J.; Smith, H.; Whalley, W. B. *J. Chem. Soc.*, 1958, 4576-4581
 Birch, A. J.; Cassera, A.; Fitton, P.; Holker, J. S. E.; Smith, H.; Thompson, G. A.; Whalley, W. B. *J. Chem. Soc.*, 1962, 3583-3586

Methymycin

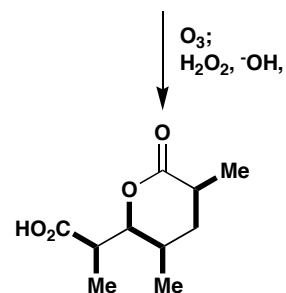


- acetyl Co-A as base unit for chains with addition of malonyl Co-A, methyl groups coming from methionine or choline
- C-methylation occurs at methylene of malonate
- proposed biosynthesis of macrolide antibiotics involves propionic acid subunits instead of acetate, Woodward, R. B. *Angew. Chem. Int. Ed.*, 1956, 68, 13





5 propionates, 1 acetate



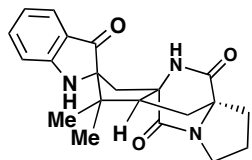
- feeding with labeled acetate showed no incorporation

- 3/5 rma of parent antibiotic from propionic acid feeding ($1-^{14}C$ -propionate)
 - feeding with $2-^{14}C$ -propionate gave same result

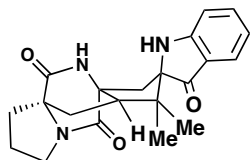
Birch, A. J.; Djerassi, C.; Dutcher, J. D.; Majer, J.; Perlman, D.; Pride, E.; Rickards, R. W.; Thomson, P. J. *J. Chem. Soc.*, 1964, 5274-5278

Brevianamides A-F

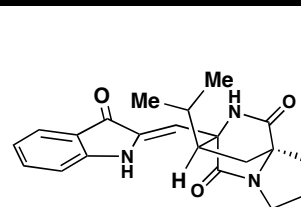
- isolated from *Penicillium brevi-compactum* in 0.1 to 10 mg / L of culture
 - structure elucidation as well as biosynthetic studies carried out



brevianamide A

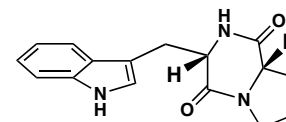


brevianamide B



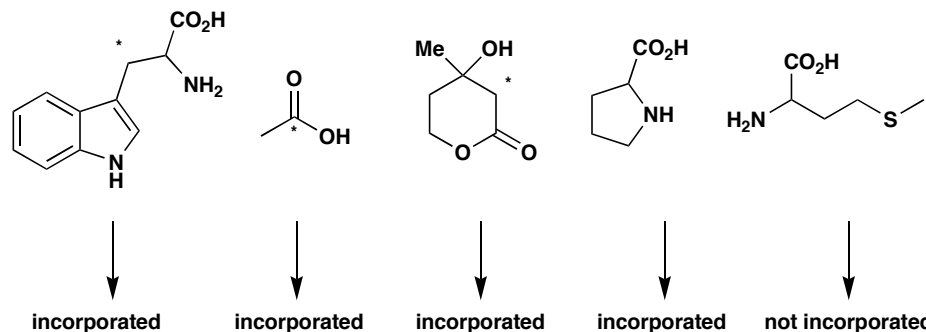
brevianamide C

brevianamide D
 (double bond isomer of brevianamide c)



brevianamide F

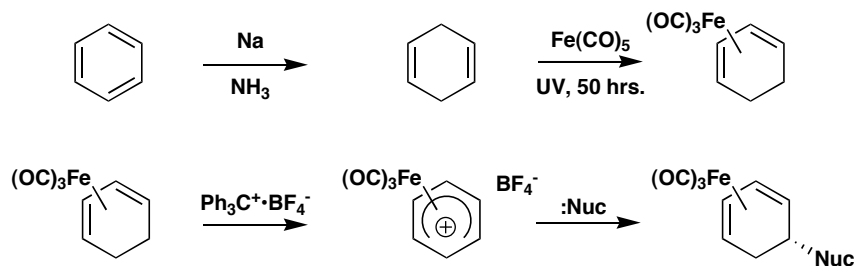
- biosynthetic work



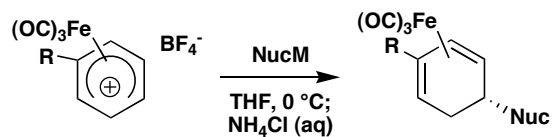
Birch, A. J.; Wright, J. J. *J. Chem. Soc.*, 1969, 644-645
 Birch, A. J.; Wright, J. J. *Tetrahedron*, 1970, 26, 2329-2344
 Birch, A. J.; Russell, R. A. *Tetrahedron*, 1972, 28, 2999-3008
 Baldas, J.; Birch, A. J.; Russell, R. A. *J. Chem. Soc., Perkin Trans. I*, 1973, 50-52

Organoiron Chemistry

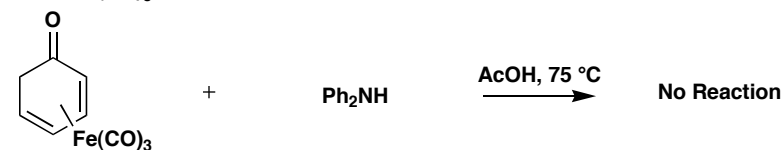
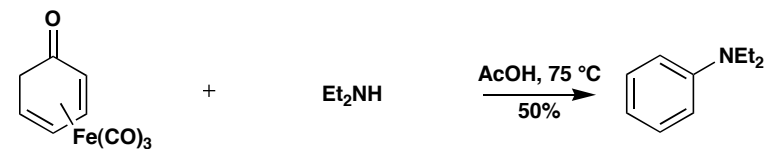
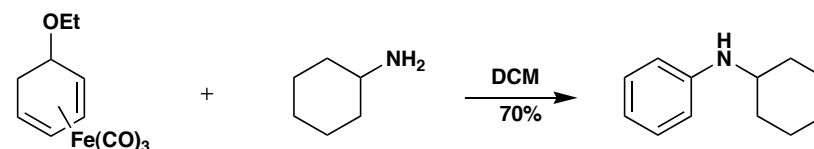
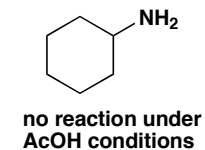
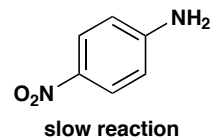
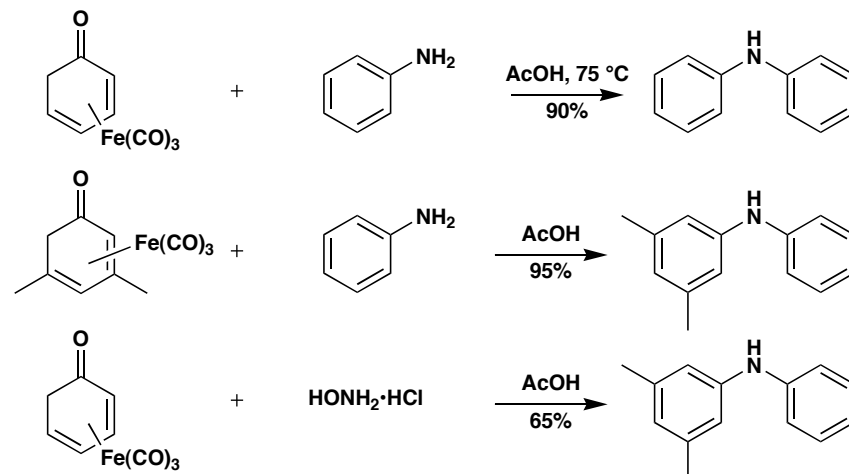
- $\text{Fe}(\text{CO})_3$ used to complex 1, 3 dienes that could be made the cation salt by hydride abstraction

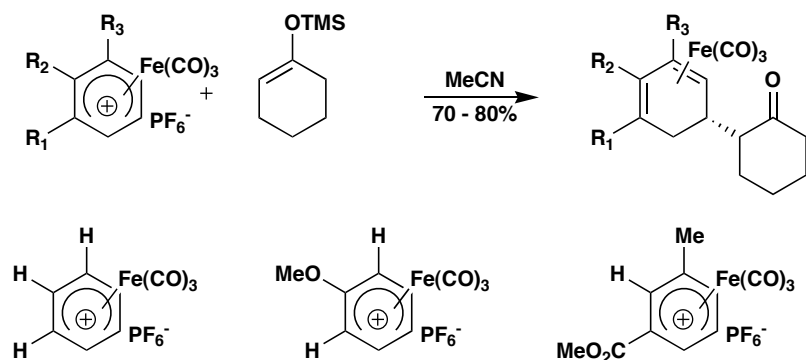


- Nuc = RNH_2 , OR , phosphites, sulfites, enamines, ketones
 - Grignard and alkyllithium addition gives reductive coupling or decomposition
 - organozinc and organocadmium reagents work well



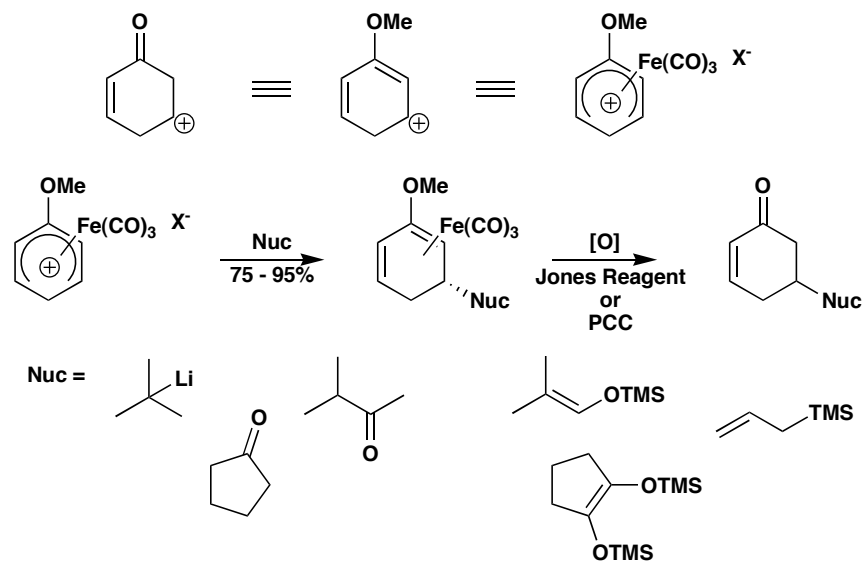
R	NucM	Yield %
H	$(\text{CH}_2\text{CH}=\text{CH})_2\text{Cd}$	82
H	$(\text{CH}_2\text{CH}=\text{CH})_2\text{Cd}$	40
H	Ph_2Cd	83
Me	$(\text{CH}_2\text{CH}=\text{CH})_2\text{Zn}$	50
OMe	$(\text{CH}_2\text{CH}=\text{CH})_2\text{Zn}$	35
H	Ph_2Cd	67





Kelly, L. F.; Narula, A. S.; Birch, A. J. *Tetrahedron Lett.*, 1979, 42, 4107-4110

Iron and Chemical Equivalents



Kelly, L. F.; Dahler, P.; Narula, A. S.; Birch, A. J. *Tetrahedron Lett.*, 1981, 22, 1433-1436