Tetrahedron Letters,Vol.28,No.14,pp 1493-1496,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

SIMPLE ROUTE TO SUBSTITUTED TETRALONES

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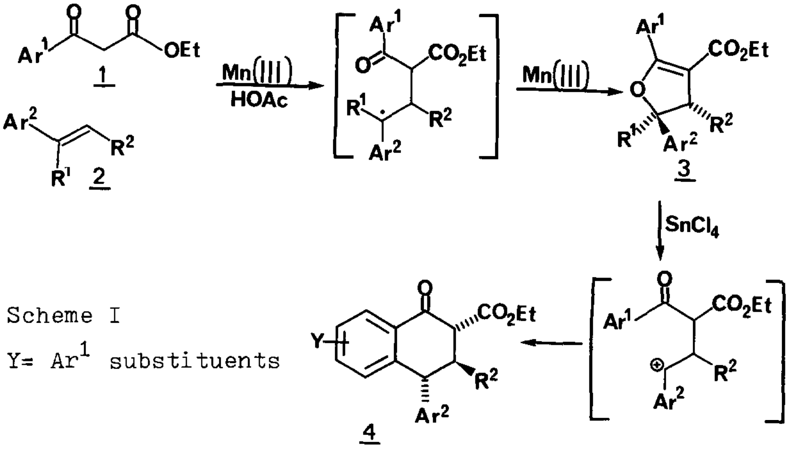
Abstract: A two step route to highly substituted tetralones via Mn(III) oxidation and cyclization has been demonstrated.

The 4-arylnaphthalene family of naturally occurring lignans contains many biologically active members such as Justicidins A-F and podophyllotoxin.[1] The common structural features of the ring system and a high level of oxygen containing functionality led us to adapt Mn(III) chemistry as a general route to this skeleton.

Manganese(III) acetate oxidation of β-dicarbonyl compounds in the presence of alkenes has been explored and found to give carbonyl lactones from β-carbonyl acids,[2] dihydrofurans from diketones,[3] and other products.[4] When an aroylacetate, 1, was treated with manganese(III) acetate in the presence of a styrene derivative, 2, very clean conversion to dihydrofuran 3 was observed, Scheme I. Employing very reactive aroylacetates is particularly useful in conjunction with the electron rich styrene derivatives because it avoids the known but slower oxidation of the styrene double bond.[5] The dihydrofurans were easily opened by stannic chloride and cyclized onto the electron rich aromatic ring to form tetralones 4.



Scheme I
Y= Ar^1 substituents

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Table I

Entry	Ar^{1a}	Ar^{2a}	R^{1b}	R^{2b}	Conditions^c	Dihydrofuran % yield	Eq. $SnCl_4$	Time (hr)	Tetralone % yield
1	A	A	1	1	A	27			
2	A	A	2	1	A	56			
3	A	A	1	3	A	40	15	72	0
4	A	A	1	4	A	61			
5	B	C	1	2	A	52	15	5	84
6	B	B	1	5	A	57			
7	B	B	1	4	A	48	15	5	36
8	B	D	1	4	B	58	15	5	84
9	B	D	1	5	A	57			
10	D	D	1	5	A	71	5	22	86
11	D	D	1	5	B	71			
12	D	D	1	4	B	55	15	6	64
13	D	E	1	5	A	56	5	70	81
14	D	E	1	5	B	54			
15	E	D	1	4	B	65			

a Ar: A = phenyl; B = 3,4-dimethoxyphenyl; C = 4-methoxyphenyl; D = 3,4-methylenedioxyphenyl; E = 3,4,5-trimethoxyphenyl.

b R: 1 = H; 2 = CH_3; 3 = CO_2Me; 4 = CH_2OAc; 5 = CO_2Et.

c Conditions: See footnote 8.

Heiba and Dessau had previously reported that acetophenone could be oxidized by Mn(III) to $PhCOCH_2\bullet$. This radical added to simple alkenes and cyclized directly to a tetralone in one step.[6] We were unable to effect such a one step process with the substrates described herein. The lack of direct cyclization may be ascribed to the benzylic radicals which are produced in Scheme I, and the ease with which they are oxidized to a cation. The cation was then kinetically trapped by the carbonyl rather than the aromatic ring. Closure to the tetralone required the use of thermodynamically controlled conditions.

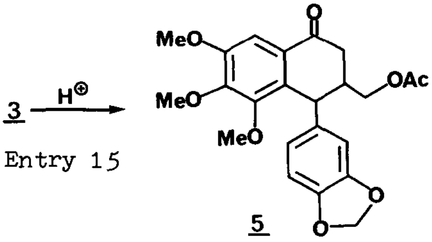
The results are summarized in Table I. After the model systems, entries 1-4, were completed with commercially available materials, the aroylacetates[7] and styrene derivatives used in the tetralone syntheses were those required for eventual conversion to lignan natural products.

Radical addition to methyl cinnamate (entry 3) can result in two possible intermediates, a radical alpha to the carbonyl or a benzyl radical. A dihydrofuran corresponding to the benzyl radical intermediate was the only product isolated. Since an aromatic substituent at the 5-position of the dihydrofuran was necessary for successful conversion to the 4-arylnaphthalene skeleton this regiospecificity was required. All other dihydrofurans were formed stereo- and regiospecifically as well.

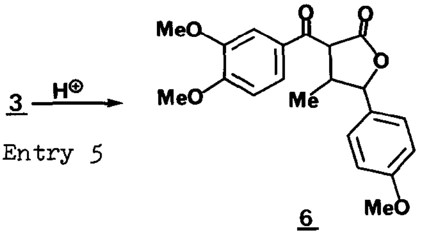
Previous attempts to perform the well established lactone annulation reaction with acetic acid and an alkene, anethole, as a substrate resulted only in single electron transfer oxidation of the double bond to form the vicinal diacetate, ArCH(OAc)CH(OAc)CH_3.[5] The formation of a dihydrofuran from an aroylacetate and anethole (entry 5), indicated that the ease of enolization of the β-ketoester allowed this process to compete favorably with diacetate formation. Because of the large number of electron donating groups in the lignan targets, this result was crucial.

No more than trace amounts of vicinal diacetates were observed with the most electron rich styrene derivatives. Small amounts (5-10%) of starting materials were recovered in the Mn(III) reaction. The use of more oxidant simply destroyed the dihydrofuran. Two set of conditions for the Mn(III) oxidation were developed;[8] however, both appear to give similar results; see entries 10, 11 and 13, 14. The oxidation conditions were optimized for entries 10 and 11, and these standard conditions were used for the remaining entries. This may explain the higher yields for these two entries.

The conversion of some of these dihydrofurans to substituted 4-aryltetralones by stannic chloride proceeded in good yield at room temperature.[9] Attempts to effect this conversion, using stronger Lewis acids, were unsuccessful. Our inability to convert the dihydrofuran from entry 3 to tetralone revealed the importance of the electron donating groups on the nucleophilic aromatic moiety. Treatment of the dihydrofuran 3 under protic acid conditions led to different reactions depending on the structure of Ar^1 in 3, Eqs. 1 and 2. When Ar^1 was a



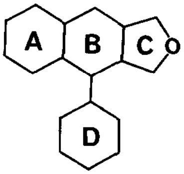
Equation 1

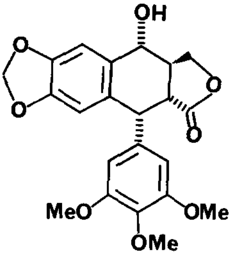


Equation 2

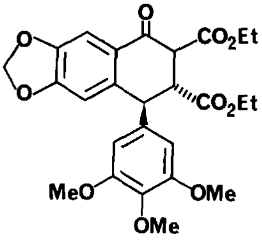
trimethoxyphenyl, Friedel-Crafts cyclization still occurred. However, the initial product was rapidly decarboethoxylated to 5. When Ar^1 was the less electron rich dimethoxyphenyl group, attack by the ester prevailed to give the keto lactone 6.

In two steps, substituted 4-aryltetralones, containing the A, B, and D rings of the target lignans were obtained in high yield. We are currently investigating the conversion of the appropriate functionalities to the remaining C lactone ring of the lignans.





Podophyllotoxin



4 Entry 13

Acknowledgement. Entry 15 was provided by Andreas B. Ernst. Funding for this research was provided by the National Science Foundation and the National Institutes of Health.

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8. One equiv. of aroylacetate (0.2M) and 1 equiv. of styrene derivative (0.2M) were added to a solution of acetic acid and 2.2 equiv. of manganese(III) acetate and stirred until the dark brown solution turned yellow. Condition A = Manganese(III) acetate hydrate, 75-85° C, 10-30 minutes. Condition B = Anhydrous manganese(III) acetate, ambient temperature, 1-4 days. Manganese(III) acetate preparations: Brauer, G. "Handbook of Preparative Inorganic Chemistry;" Vol. 2, 2nd ed.; Academic Press: New York, 1965; p. 1469-70.
9. Tin(IV) chloride was added to the dihydrofuran (0.04M) in chloroform or dichloromethane and stirred at ambient temperature.

(Received in USA 2 December 1986)