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An Efficient Entry Into Butenolides: Synthesis Of (±) Mintlactone#

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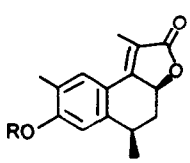
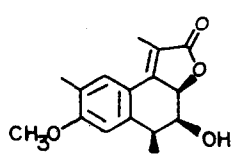
Abstract: *Osmylation of β,γ-unsaturated esters and acid catalysed cyclisation of the resultant diols generate butenolides in high yields.*

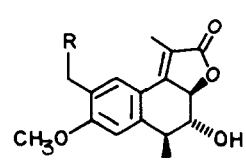
Butenolides constitute important moieties of a variety of natural products and have been the focus of current interest.[1] In continuation of our work and interest in the synthesis of heritol (**1a**),[2,3a] heritonin (**1b**),[2,3b] heritianin (**3b**), vallipin (**2**),[3b] vallapianin (**3a**),[3b] isolated recently from mangrove plant *Heritiera littoralis* by Miles and coworkers, we needed a general and efficient methodology to generate butenolides. These compounds are a new and novel class of sesquiterpenes and possess unusual oxygenation pattern not generally encountered in the cadinane family.



1a. R = H
1b. R = CH_3



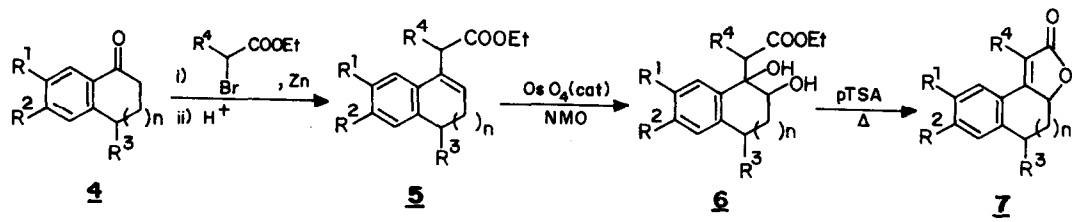
2 VALLIPIN



3a VALLAPIANIN R = OH
3b HERITIANIN R = H

This letter describes a convenient and efficient entry into butenolides. Ketones **4** were smoothly transformed to β,γ-unsaturated ester **5** *via* Reformatsky reaction[4] followed by acidic work up with concomitant dehydration. No trace of α,β-unsaturated esters could be detected. Catalytic osmylation[5] of the olefin **5** furnished the corresponding diols **6** in excellent yields. Treatment of diols **6** thus obtained, with PTSA (cat.) in refluxing benzene, smoothly afforded the corresponding butenolides **7** in good to excellent yields (Table). Occurrence of two steps in one pot *viz.* (i) lactonisation, (ii) concomitant dehydration are the noteworthy transformations in this step.

To demonstrate the effic acy and generality of our methodology, we decided to incorporate bulky substituent R^4 on the butenolide moiety. Accordingly, tetralone **4a**, was subjected to Reformatsky reaction with ethyl bromoacetate, ethyl bromo propionate, ethyl-2-bromobutyrate and ethyl-2-bromo-3-methyl butyrate to furnish the corresponding ß,¥-unsaturated esters **5a, 5b, 5c** and **5d** respectively.



Scheme-1

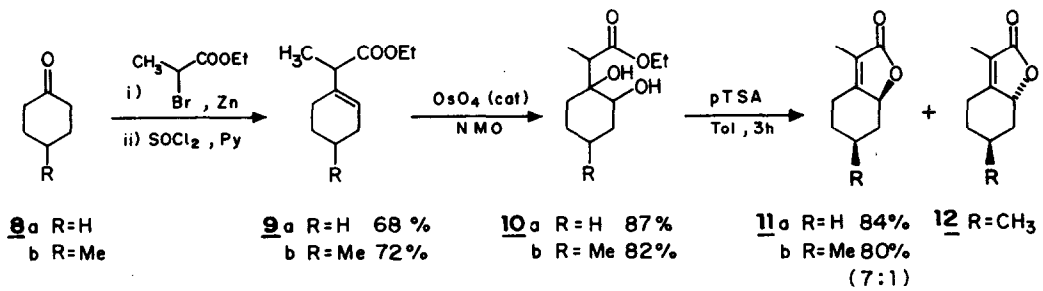
Table

Entry	n	R^1	R^2	R^3	R^4	5	6	7	Time, h
						% Yields			
1a	1	H	H	H	H	88	82	81	0.5
2b	1	H	H	H	Me	80	83	90	1.0
3c	1	H	H	H	Et	92	76	92	1.0
4d	1	H	H	H	i-Pr	82	84	90	0.5
5e	1	Me	H	Me	Me	76	79	73[a]	1.5
6f	1	Me	OMe	Me	H	79	89	76[a]	1.0
7g	1	Me	OMe	Me	Me	81	80	90[a]	1.0
8h	1	OMe	Me	H	Me	90	84	94	1.0
9i	2	H	H	H	H	68	81	93	1.0

a. A 3:2 mixture of cis:trans isomers was obtained.

Osmylation of **5a, 5b, 5c** and **5d** afforded the diols **6a, 6b, 6c** and **6d** respectively. It was heartening to note that all the diols underwent efficient cyclisation to furnish the corresponding butenolides **7a, 7b, 7c** and **7d** respectively in excellent yields. Suberone (**4i**) (entry 9), a seven membered ketone also underwent smooth transformation using the above protocol to furnish **7i** in high yields.

It is pertinent to mention that our methodology allows successful incorporation of bulky substituent on the butenolide moiety (entry 1-4) in contrast to the poor yields obtained in intramolecular Wittig reactions ascribed to *peri* interactions.[6]



Scheme- 2

Employing the above protocol, (±) mintlactone (**11b**),[7] (±) isomint- lactone (**12**), heritol (**1a**) and heritonin (**1b**) were synthesised to demonstrate the generality and efficacy of the methodology. Thus, 4-methyl cyclohexanone (**8b**) when subjected to Refortmasky reaction furnished the corresponding alcohol, which on dehydration using thionyl chloride and pyridine furnished **9b** in 72% overall yield. Catalytic dihydroxylation of **9b** afforded **10b** as a mixture of diastereomers. Since the stereochemistry at the methyl adjacent to ester was of no consequence to us as it would be destroyed during the formation of butenolide, no attempt was made to separate the diastereomers. The conversion of the diol **10b** to butenolide was accomplished by refluxing it with PTSA in toluene (3h) to afford (±) mintlactone (**11b**) and (±) iso-mintlactone **12** in 80% yield as a mixture of diastereomers as judged by NMR, GC analysis. Following the same sequence of reactions **11a** was also synthesised efficiently from cyclohexanone in high yields (Scheme-2).

We feel the abovementioned efficient methodology would find widespread usage to synthetic chemists for butenolides synthesis.

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NCL communication No: 5284

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8. All new compounds were characterised by spectroscopic data and exhibited satisfactory elemental analysis.

Typical Procedure; 6d-7d To a stirred solution of diol **6d** (0.2 g, 0.68 mmol) in dry benzene (20 mL), catalytic amount of PTSA was added and the reaction mixture was refluxed (0.5 h) with azeotropic removal of water (Dean-Stark). The reaction mixture was cooled, washed (aq. $NaHCO_3$), dried (Na_2SO_4) and concentrated under reduced pressure and the residue purified by chromatography (SiO_2) using 10% ethylacetate-pet. ether to furnish **7d** as a white solid (0.147 g, 94% yield), m.p. 142°C. Selected Spectral data; IR: 1760 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz); δ 1.32 (d, 3H, J = 7 Hz), 1.43 (d, 3H, J = 7 Hz), 1.75 (m, 1H); 3.2 (m, 2H), 3.27 (q, 1H, J = 7 Hz), 4.88 (dd, 1H, J = 4.9, 12.65 Hz), 7.34 - 7.64 (m, 4H); ^{13}C-NMR: δ 173.09 (s), 155.23 (s), 137.8 (s), 130.34 (d), 129,48 (d), 128.64 (s), 128.42 (s), 127.8 (d), 126.72 (d),; Mass: m/z 228 (M^+, 42), 200 (79), 91 (100%). Analysis calculated for $C_{15}H_{16}O_2$: C, 78.9; H, 7.01; Found C, 78.56, H, 7.32.

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