

## A NEW SYNTHESIS OF STREPTOMYCES LACTONES BY 1,3-DIPOLAR CYCLOADDITION

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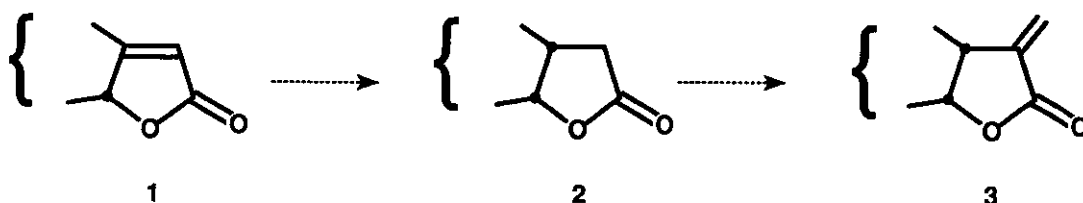
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**Abstract** — The cycloaddition of nitrones (4) to propene, followed by sequential treatment with methyl trifluoromethanesulfonate, H<sub>2</sub>-Pd/C, and *m*-chloroperbenzoic acid, is shown to provide a general method for the preparation of a variety of volatile streptomyces lactones.

The 2(5*H*)-furanones are widespread in nature and examples are found in the sesquiterpenes<sup>1</sup> and lichen-pulvinic acid derivatives;<sup>2</sup> accordingly, butenolides have attracted a considerable amount of synthetic activity.<sup>3</sup> In addition, it is now well established that butenolides of type (1) can be selectively reduced to the corresponding  $\gamma$ -lactones (2),<sup>4</sup> which in turn are useful precursors for elaboration to methylenelactones (3),<sup>5</sup> from which annelation reactions provide a facile and efficient entry to a wide variety of other natural products.<sup>6</sup>



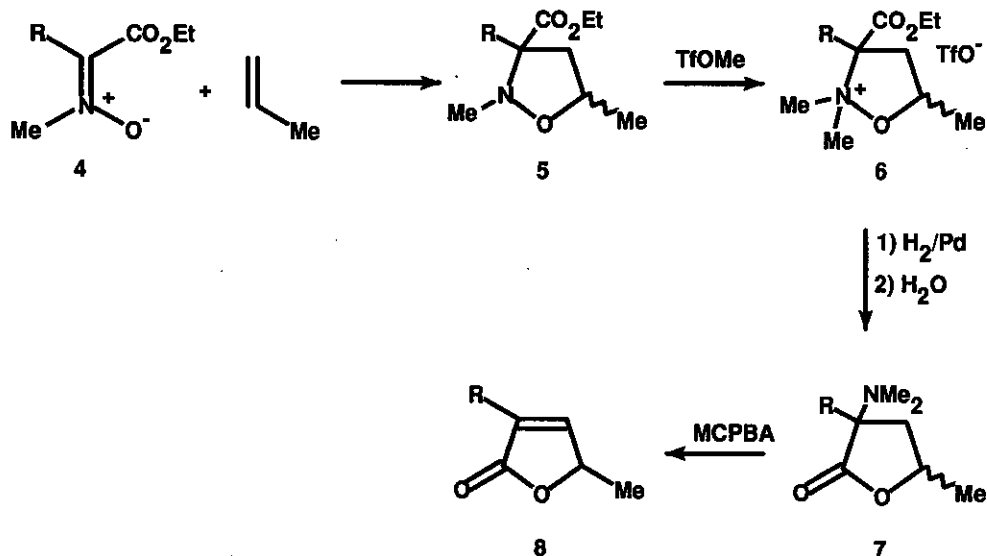
However, methodology for the preparation of  $\alpha,\gamma$ -disubstituted butenolides is limited and the synthesis of streptomycetes lactones has remained somewhat elusive. A multi-step synthetic pathway towards  $\alpha,\gamma$ -disubstituted butenolides has been developed using as a key step sequential addition/alkylation to anions generated from 2,2-dimethyl-5-methylene-1,3-dioxane.<sup>7</sup>

Recently, intramolecular [3 + 2] cycloadditions of nitrile oxydes have been explored.<sup>8</sup> We describe here a new solution to this synthetic problem, based on the 1,3-dipolar cycloaddition approach, as illustrated by the synthesis of a series of volatile streptomycetes lactones.

Our strategy takes advantage of the fact that isoxazolidine derivatives, easily accessible by 1,3-dipolar cycloaddition of nitrones to alkenes, undergo chemical ring-opening reactions leading to variously functionalized open-chain derivatives.<sup>9</sup> The different unimolecular rearrangement processes are controlled by the pattern of substitution on the heterocyclic precursors and by the experimental conditions adopted.

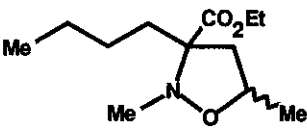
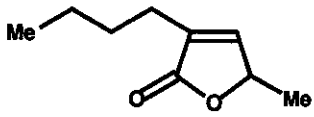
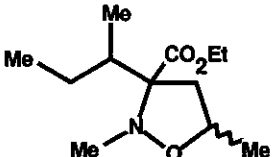
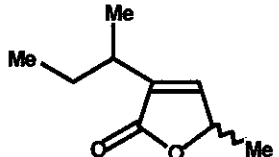
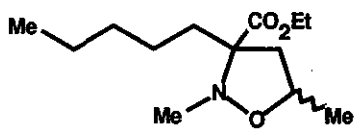
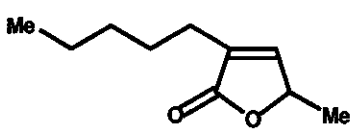
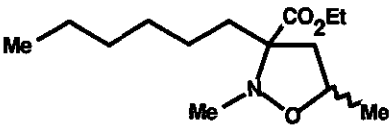
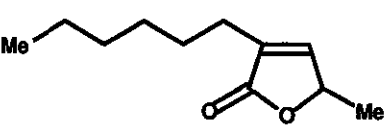
The formation of 1,3-amino alcohols by reductive scission has been well established.<sup>10</sup> On this basis a synthetic pathway to  $\alpha,\gamma$ -disubstituted butenolides (**8**) has been conceptualized as reported in Scheme 1.

Scheme 1



Thus, cycloaddition of nitrones (**4**), prepared from suitable keto esters and *N*-methylhydroxylamine, to propene in decalin at  $150^\circ\text{C}$  for 60 h afforded a mixture of epimeric isoxazolidines (**5**) (55-68% yield), which have not been separated.

**Table 1.** Synthesis of  $\alpha,\gamma$ -disubstituted butenolides (**8**) from isoxazolidines (**5**).

Entry	Isoxazolidine	Products	Yield % <sup>a</sup>
1	 5a	 8a <sup>b</sup>	82
2	 5b	 8b	90
3	 5c	 8c	86
4	 5d	 8d <sup>b</sup>	88

a) Yields of compounds isolated from column chromatography.

b) See ref. 11.

Further reaction with methyl trifluoromethanesulfonate (TfOMe) in dry  $\text{CCl}_4$  at  $0^\circ\text{C}$  for 3 h gave rise, in a nearly quantitative yield, to epimeric isoxazolidinium salts (**6**), as white sticky oils. Hydrogenolysis with 10% palladium on activated carbon in dry MeOH at  $50^\circ\text{C}$  for 36 h led to lactones (**7**) in high yields (90-95%).

The last step of the synthetic scheme has been smoothly accomplished by Cope elimination of the corresponding transient *N*-oxide obtained by treatment of **7** with *m*-chloroperbenzoic acid (MCPBA) in dry CH<sub>2</sub>Cl<sub>2</sub> at 0 °C for 4 h; lactones (**8**) have been obtained in good yields (Table 1).<sup>12</sup>

Noteworthy, Cope elimination occurs regioselectively to afford exclusively butenolides (**8**); regioisomeric  $\gamma$ -methylene lactones were not detected in the crude reaction mixture.

In conclusion,  $\alpha,\gamma$ -disubstituted butenolides (**8**) have been prepared in only four steps, starting from suitable  $\alpha$ -keto acids, with overall high yields and virtually complete regiochemical control. The usefulness of our synthetic approach is furthermore evidenced by the close structural resemblances between system (**8**) and a variety of naturally occurring compounds.

Extension of this process to the synthesis of sesquiterpene lactones is in progress.

#### ACKNOWLEDGMENTS

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12. All compounds were fully characterized by elemental analyses and spectral data. Spectral data of new butenolides are reported below.
- 8b** (epimeric mixture): Ir (neat)  $\nu$ : 2960, 2920, 1750, 1650, 1450, 1220, 1190, 1100  $\text{cm}^{-1}$ .  $^1\text{H Nmr}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.89 (3H, t,  $J=6.4$  Hz,  $\text{CH}_3$ ), 1.15 (3H, d,  $J=6.9$  Hz,  $\text{CH}_3$ ), 1.41 (3H, d,  $J=6.8$  Hz,  $\text{CH}_3$ ), 1.38-1.75 (2H, m,  $\text{CH}_2$ ), 2.44-2.61 (1H, m, CH), 4.99 (1H, q,  $J=6.8$  Hz,  $\text{H}_5$ ), 6.96 (1H, br s,  $\text{H}_4$ ).  $^{13}\text{C Nmr}$  (50.3 MHz,  $\text{CDCl}_3$ )  $\delta$  11.29, 11.43, 18.31, 19.34, 27.79, 31.76, 31.90, 77.24, 138.96, 148.01, 173.40. Ms:  $m/z$  154 ( $\text{M}^+$ ), 139, 125, 111, 93, 81, 67, 55 (base). Anal. Calcd for  $\text{C}_9\text{H}_{14}\text{O}_2$ : C, 70.10; H, 9.15. Found: C, 70.20; H, 9.13.
- 8c**: Ir (neat)  $\nu$ : 2940, 2910, 2840, 1750, 1640, 1450, 1310, 1190, 1060, 1010, 790  $\text{cm}^{-1}$ .  $^1\text{H Nmr}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.91 (3H, t,  $J=6.5$  Hz,  $\text{CH}_3$ ), 1.21-2.05 (6H, m), 1.40 (3H, d,  $J=6.8$  Hz,  $\text{CH}_3$ ), 2.27 (2H, dt,  $J=7.5$  and 1.5 Hz,  $\text{CH}_2$ ), 4.99 (1H, dq,  $J=6.8$  and 1.5 Hz,  $\text{H}_5$ ), 6.99 (1H, dt,  $J=1.5$  and 1.5 Hz,  $\text{H}_4$ ).  $^{13}\text{C Nmr}$  (50.3 MHz,  $\text{CDCl}_3$ )  $\delta$  13.98, 19.22, 22.37, 25.13, 27.07, 31.35, 77.45, 134.29, 148.92, 173.97. Ms:  $m/z$  168 ( $\text{M}^+$ ), 153, 139, 112 (base), 95, 93, 67, 55. Anal. Calcd for  $\text{C}_{10}\text{H}_{16}\text{O}_2$ : C, 71.39; H, 9.59. Found: C, 71.63; H, 9.55.

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