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

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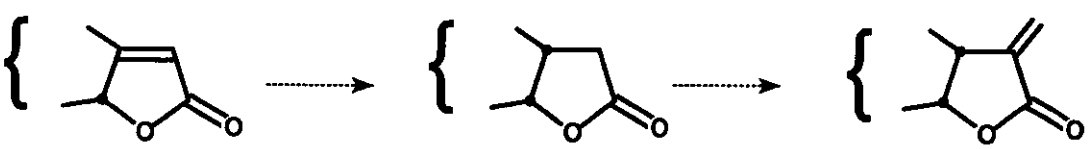
Abstract — The cycloaddition of nitrones (**4**) to propene, followed by sequential treatment with methyl trifluoromethanesulfonate, H_2-Pd/C, and *m*-chloroperbenzoic acid, is shown to provide a general method for the preparation of a variety of volatile streptomyces lactones.

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



1 **2** **3**

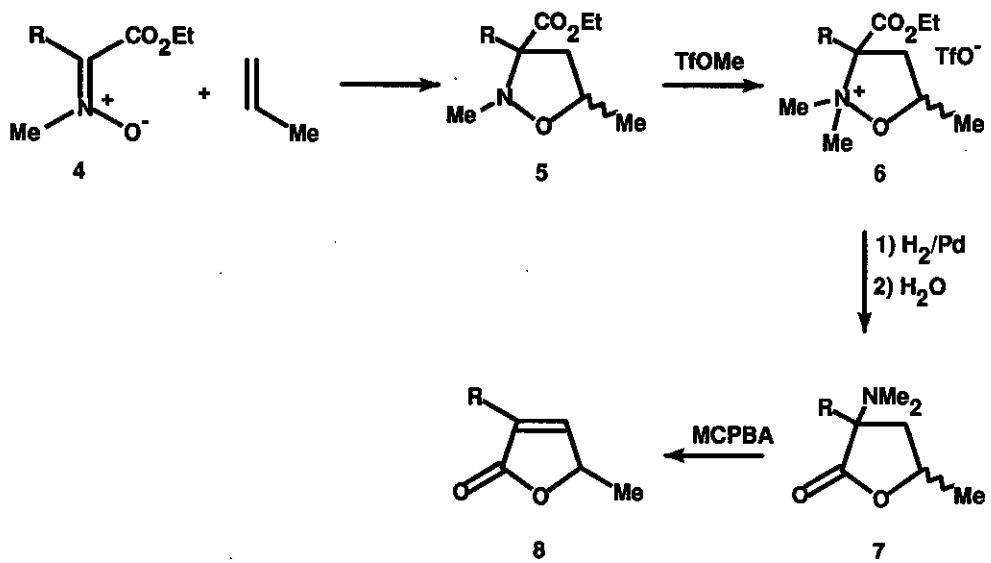
However, methodology for the preparation of α,γ-disubstituted butenolides is limited and the synthesis of streptomyces lactones has remained somewhat elusive. A multi-step synthetic pathway towards α,γ-disubstituted butenolides has been developed using as a key step sequential addition/alkylation to anions generated from 2,2-dimethyl-5-methylene-1,3-dioxane.[7]

Recently, intramolecular [3 + 2] cycloadditions of nitrile oxydes have been exploired.[8] 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 streptomyces 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.[9] The different unimolecular rearrangement processes are controlled by the pattern of substitution on the heterocyclic precursors and by the experimental conditions adopted.

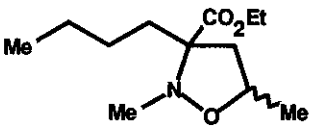
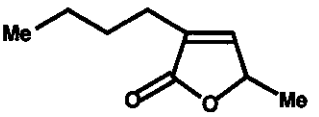
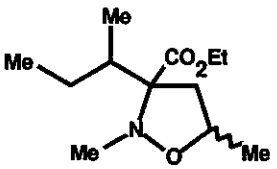
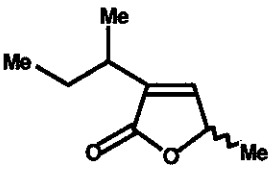
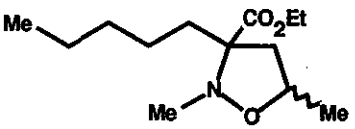
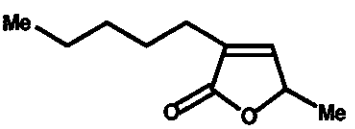
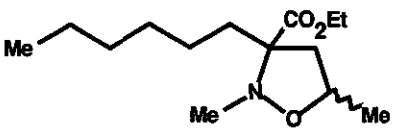
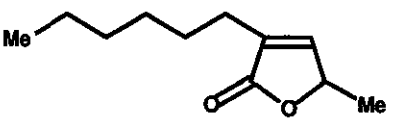
The formation of 1,3-amino alcohols by reductive scission has been well established.[10] On this basis a synthetic pathway to α,γ-disubstituted butenolides (**8**) has been conceptualized as reported in Scheme 1.

Scheme 1



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

Table 1. Synthesis of α,γ-disubstituted butenolides (**8**) from isoxazolidines (**5**).

Entry	Isoxazolidine	Products	Yield %[a]
1	 **5a**	 **8a**[b]	82
2	 **5b**	 **8b**	90
3	 **5c**	 **8c**	86
4	 **5d**	 **8d**[b]	88

a) Yields of compounds isolated from column chromatography.

b) See ref. 11.

Further reaction with methyl trifluoromethanesulfonate (TfOMe) in dry CCl_4 at 0 °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 °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_2Cl_2 at 0 °C for 4 h; lactones (**8**) have been obtained in good yields (Table 1).[12]

Noteworthy, Cope elimination occurs regioselectively to afford esclusively butenolides (**8**); regioisomeric γ-methylenelactones were not detected in the crude reaction mixture.

In conclusion, α,γ-disubstituted butenolides (**8**) have been prepared in only four steps, starting from suitable α-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) ν: 2960, 2920, 1750, 1650, 1450, 1220, 1190, 1100 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$) δ 0.89 (3H, t, J=6.4 Hz, CH_3), 1.15 (3H, d, J=6.9 Hz, CH_3), 1.41 (3H, d, J=6.8 Hz, CH_3), 1.38-1.75 (2H, m, CH_2), 2.44-2.61 (1H, m, CH), 4.99 (1H, q, J=6.8 Hz, H_5), 6.96 (1H, br s, H_4). ^{13}C Nmr (50.3 MHz, $CDCl_3$) δ 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 (M^+), 139, 125, 111, 93, 81, 67, 55 (base). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.20; H, 9.13.

8c: Ir (neat) ν: 2940, 2910, 2840, 1750, 1640, 1450, 1310, 1190, 1060, 1010, 790 cm^{-1}. ^1H Nmr (200 MHz, $CDCl_3$) δ 0.91 (3H, t, J=6.5 Hz, CH_3), 1.21-2.05 (6H, m), 1.40 (3H, d, J=6.8 Hz, CH_3), 2.27 (2H, dt, J=7.5 and 1.5 Hz, CH_2), 4.99 (1H, dq, J=6.8 and 1.5 Hz, H_5), 6.99 (1H, dt, J=1.5 and 1.5 Hz, H_4). ^{13}C Nmr (50.3 MHz, $CDCl_3$) δ 13.98, 19.22, 22.37, 25.13, 27.07, 31.35, 77.45, 134.29, 148.92, 173.97. Ms: *m/z* 168 (M^+), 153, 139, 112 (base), 95, 93, 67, 55. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.63; H, 9.55.

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