

Stereoselective Synthesis of Butenolide and Butyrolactone Derivatives

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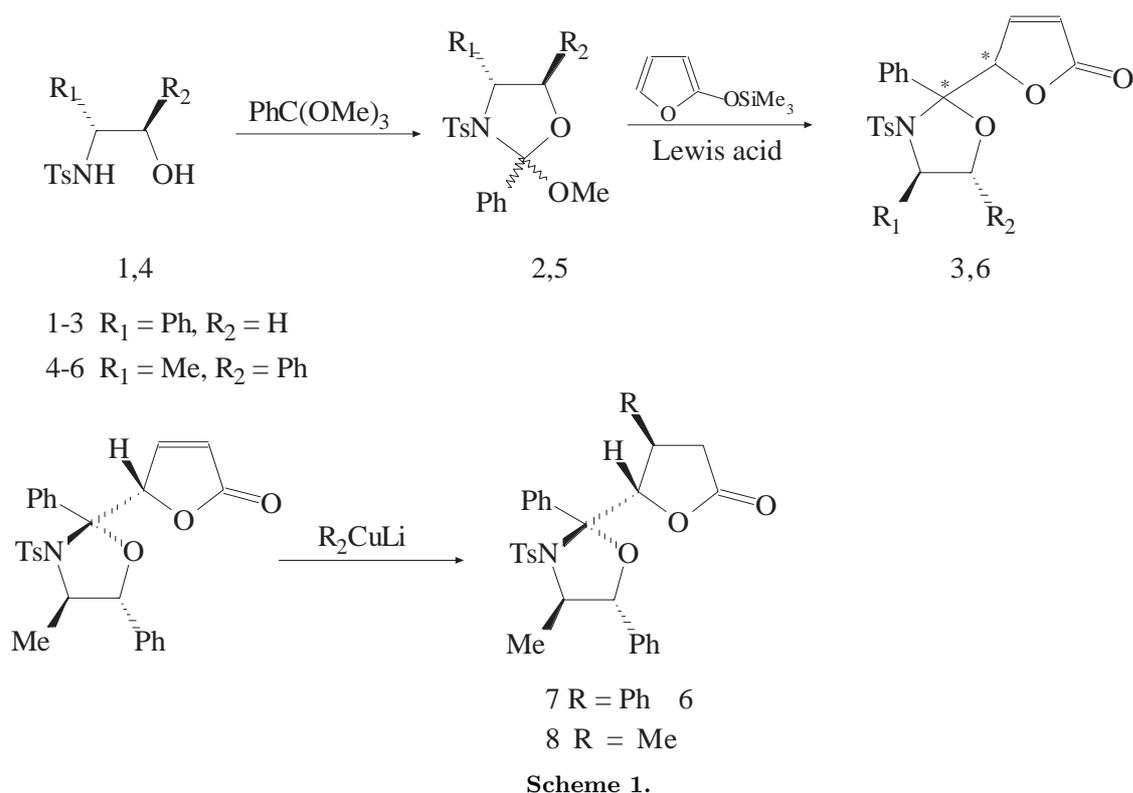
Optically active butenolide and γ -butyrolactone derivatives were prepared by removing (R)-phenyl glycinol and (1R, 2R)-norpseudoephedrine used as chiral auxiliaries from butenolides and γ -butyrolactones in two steps. The structures of these products were determined using ^1H NMR, ^{13}C NMR, Mass spect., IR and microanalysis

1. Introduction

Chiral butenolides and butyrolactones represent either the key entity or a substructure of a more complex assembly in numerous biologically important natural and synthetic products. In recent years 2(5H)-butenolides and γ -butyrolactones have emerged as precious chiral synthons for the synthesis of terpenoidal lactone pheromones; (+)- and (-)-eldanolide^{1,2}, antileukaemic lignans; (+)-trans-burseran³, (-)-isostegane³, (+)- and (-)-steganacin^{4,5}, (-)-verrucarinolactone⁶, prostacycline analogues⁷⁻⁹, chrysanthemic acid¹⁰, polyoxin J¹¹, (-)-ranunculin¹², lasalocid A¹³ and other biologically active natural products and considerable effort has been expended on preparing butenolide and γ -butyrolactone chirons from chiral and nonchiral sources.

In synthetic approaches to chiral butenolides and their derivatives when starting with nonchiral materials, asymmetry can be introduced via the resolution of intermediates somewhere in the sequence^{1,2}, asymmetric transformations resulting from the treatment of an optically inactive precursor with chiral reagents¹⁴⁻¹⁶ or the use of bulky, detachable chiral auxiliaries for steering the processes toward the production of the least sterically encumbered asymmetric systems^{17,18}.

Pelter et al.¹⁹ reported that optically active oxazolidines (**2,5**), prepared by reacting N-tosyl-(R)-phenylglycinol (**1**) and N-tosyl-(1R,2R)-norpseudoephedrine (**4**) with an excess of trimethyl orthobenzoate, were reacted with 2-trimethylsiloxyfuran in the presence of Lewis acids and afforded the chiral butenolides (**3,6**). Compound **6** was stereoselectively converted into the butyrolactone derivatives (**7,8**) by an asymmetric conjugate addition reaction, but the chiral auxiliaries remained after generating new chiral centers (Scheme 1).



In the present work, chiral butenolides and butyrolactone derivatives were obtained by removing the chiral auxiliaries in two steps²⁰ (Scheme 2). Reaction of butenolides (**3a**, **3b**, **6**) or butyrolactones (**7,8**) with 1,2-ethanedithiol in the presence $\text{BF}_3 \cdot \text{Et}_2\text{O}$ afforded the thioether derivatives **9**, **11**, **14**, **17**. Treatment of crude products with $\text{CaCO}_3\text{-MeI}$ mixture proceeded in 54-68 % yields to give the related sulphur-free butenolides (**10,12**) and butyrolactones (**15,18**). The products were isolated by flash chromatography and the structures were assigned on the basis of their ^1H , ^{13}C NMR, mass spect., IR and microanalysis.

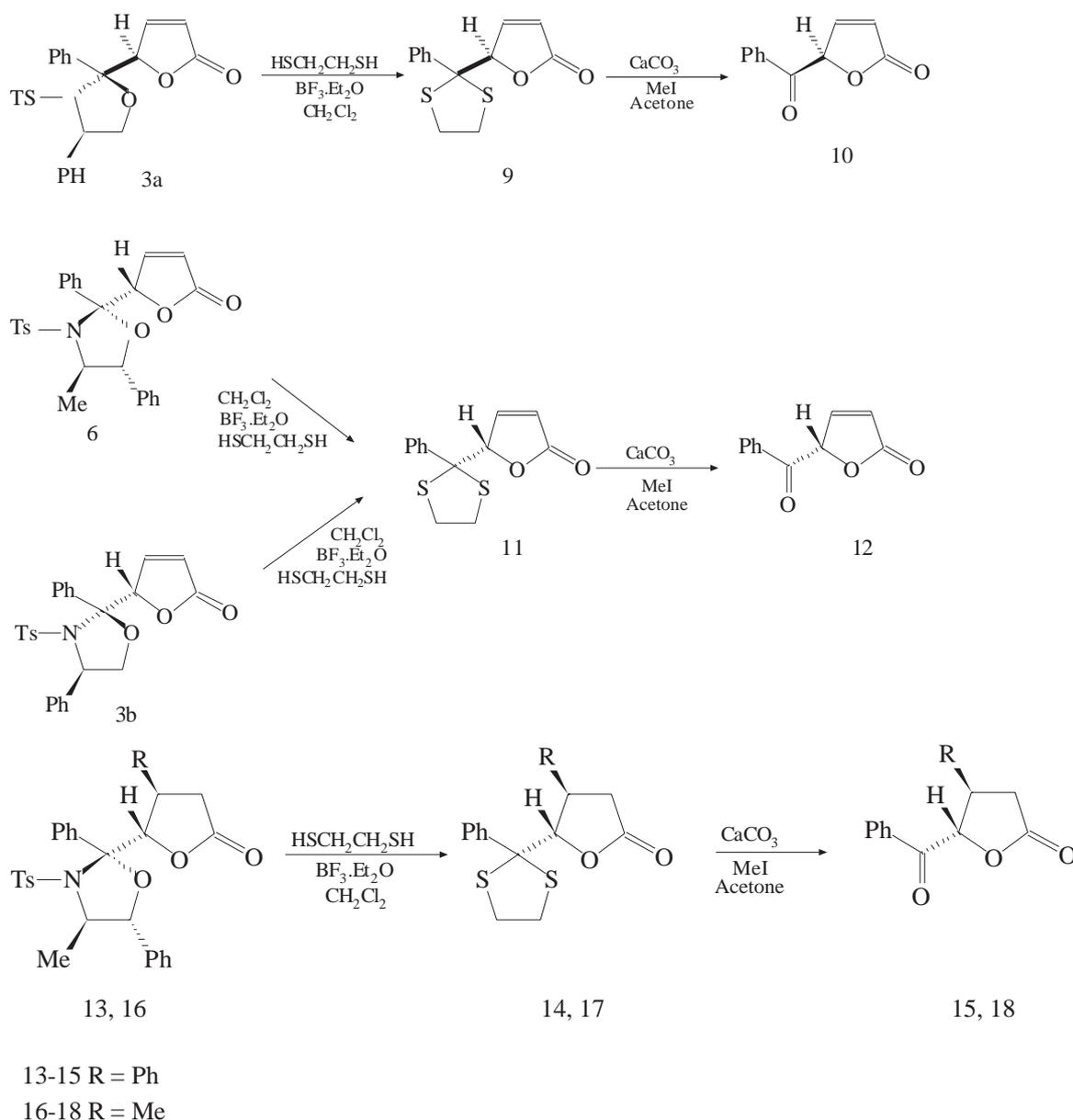
2. Experimental

Infrared spectra were recorded on a Pye Unicam SP1025 spectrometer. ^1H nmr and ^{13}C nmr spectra were recorded on a Bruker AC 200L spectrometer. All spectra used tetramethylsilane as the internal standard, and were run in deuterated chloroform. The mass spectra were recorded on a VG ZabSpec high resolution spectrometer. Elemental analysis were obtained using a Carlo Erba 1106 automatic elemental analysis instrument. Optical rotation values were obtained from an A. Krüss polarimeter. Flash chromatography was performed with silica gel (Merck 9385, Kieselgel 60, 230-400 mesh). Thin layer chromatography was carried out on Merck 5735 Kieselgel 60 F_{254} fluorescent plates.

Starting materials **3a**, **3b**, **6**, **7** and **8** were synthesized by the method described previously¹⁹. The other necessary chemicals were obtained from Aldrich and Merck.

Preparation of Butenolides (10,12) and γ -butyrolactones (15,18). General Procedure. To a solution of butenolide **3a,b,6** or γ -butyrolactone **7,8** (1 mmol) in dry CH_2Cl_2 (8ml) were added 1,2-ethanedithiol (10 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.4 mmol) and the reaction mixture was allowed to stand for 15 h at room temperature. The mixture was quenched with a 5% aqueous NaHCO_3 solution and extracted

with CH_2Cl_2 . The organic layers were dried over Na_2SO_4 and filtered, and the solvent was evaporated. The crude reaction mixture, dissolved in acetone/water 4:1 (2 ml) and treated with CaCO_3 (3 mmol), and MeI (10 mmol) was stirred for 12 h at 60°C . The resulting mixture was filtered on a celite pad. The filtrate was washed with a 5M ammonium acetate solution and then with brine, and dried, and the solvent evaporated under reduced pressure. The crude product was separated and purified by flash chromatography.



Scheme 2.

10: oil, yield 54.3%, ^1H NMR: 4.95 (1H, dd, 2.0, 5.60), 7.90 (1H, m), 6.02 (1H, t, 2.10), 7.30-7.75 (5H, m, Ar); ^{13}C NMR: 173.14 (C-2), 82.51 (C-3), 149.11 (C-4), 121.34 (C-5), 189.73 (C-6), 126.35-142.60 (Ar); $[\alpha]_D^{21}$: + 20.12 (C: 0.650 CHCl_3) IR: (NaCl film): 1790, 1760, 1620; M/Z: (M+ NH_4) $^+$ 206, (M+H) $^+$ 189, (PhCO) $^+$ 105, (butenolide) $^+$ 83, (Ph) $^+$ 77; (Found: C, 70.39; H, 4.48 $\text{C}_{11}\text{H}_8\text{O}_3$ requires: C, 70.21; H, 4.25).

12: oil, yield. 68.7%, ^1H NMR: 5.18 (1H dd, 1.95, 5.65), 8.10 (1H m), 6.20 (1H t, 1.82), 7.40-7.70 (5H, m, Ar); ^{13}C NMR: 173.65 (C-2), 83.15(C-3), 140.42 (C-4), 121.58 (C-5), 189.97 (C-6), 127.10-143.38 (Ar); $[\alpha]_D^{21}$: -27.32 (C: 0.450 CHCl_3); IR: (NaCl film): 1785, 1750, 1610; M/Z: $(\text{M}+\text{NH}_4)^+$ 206, $(\text{M}+\text{H})^+$ 189, $(\text{PhCO})^+$ 105, (butenolide) $^+$ 83, (Ph) $^+$ 77; (Found: C, 70.46; H, 4.52 $\text{C}^{11}\text{H}_8\text{O}_3$ requires: C, 70.21; H, 4.25).

15: oil, yield: 66.12%, ^1H NMR: 2.65 (1H dd, 2.60, 18.30), 3.20 (1H dd, 11.02, 18.30), 3.30-3.60 (1H m), 6.85 (1H d, 2.00), 6.95-7.38 (10H, m, Ar); ^{13}C NMR: 179.12 (C-2), 38.78 (C-3), 41.24 (C-4), 95.19 (C-5), 192.06 (C-6), 126.60-142.77 (Ar); $[\alpha]_D^{21}$: -23.92 (C: 0.604 CHCl_3); IR: (NaCl film): 1780, 1750; M/Z: $(\text{M}+\text{NH}_4)^+$ 284, $(\text{M}+\text{H})^+$ 267, (lactone) $^+$ 161, $(\text{PhCO})^+$ 105, (Ph) $^+$ 77; (Found: C, 76.84; H, 5.41 $\text{C}_{17}\text{H}_{14}\text{O}_3$ requires: C, 76.69; H, 5.26).

18: oil, yield: 63.5%, ^1H NMR: 2.15 (1H dd, 1.50, 17.65), 2.95 (1H dd, 8.60, 17.60), 2.45-2.70 (1H m), 6.50 (1H d, 1.30), 1.25 (3H, d, 6.45), 7.20-7.40 (5H, m); ^{13}C NMR: 178.42 (C-2), 30.14 (C-3), 33.37 (C-4), 92.46 (C-5), 192.13 (C-6), 19.55 (Me), 127.13-136.91 (Ar); $[\alpha]_D^{21}$: -69.23 (C: 0.740 CHCl_3); IR: (NaCl film): 1785, 1755; M/Z: $(\text{M}+\text{NH}_4)^+$ 222, $(\text{M}+\text{H})^+$ 205, $(\text{PhCO})^+$ 105, (lactone) $^+$ 99, (Ph) $^+$ 77; (Found: C, 70.83; H, 6.04 $\text{C}_{12}\text{H}_{12}\text{O}_3$ requires: C, 70.58; H, 5.88).

3. Results and Discussion

The chiral butenolide and γ -butyrolactone derivatives were synthesized for the first time. The structures of synthesized compounds were identified by spectral and elemental analysis. The butenolides and γ -butyrolactones prepared in this paper represent alternative, readily starting materials for the asymmetric synthesis of natural products.

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