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# The synthesis of chiral 5-methylene pyrrol-2(5*H*)-ones via photooxygenation of homochiral 2-methylpyrrole derivatives

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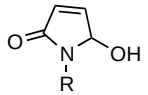
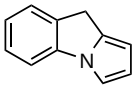
**Abstract**—Homochiral 2-methylpyrrole derivatives are synthesized in high yields starting from chiral amines, amino alcohols and amino acid esters. The photooxygenation of these pyrrole derivatives in the presence of a photosensitiser furnishes the corresponding α,β,γ,δ-unsaturated γ-lactams as the major products in good yields. 

## 1. Introduction

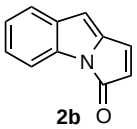
The photooxygenation of heterocycles has been extensively studied because heterocyclic systems such as pyrroles,[1] imidazoles[2] and other heterocycles[3] are involved in photobiosynthesis and other biological processes. Singlet oxygen is capable of oxidizing a wide range of substrates. However, very limited success has been achieved in terms of applying these reactions to practical organic synthesis.[4] One of the problems associated with these photooxidations is their low chemoselectivity. Thus, photooxidations of pyrroles often give a mixture of products derived from both 1,2- and 1,4-oxygen addition. Using pyrrole derivatives that had been extensively studied earlier, Wasserman et al. recently showed that when both electron-releasing and electron-withdrawing groups are present on the hetero ring, the oxidations may take place under more control.[5] The photooxidation of *N*-substituted pyrroles to form hydroxylactams of the type **1** has been applied by Franck and Auerbach.[6] In particular, a phenyl substituted system was of interest as it was envisaged that the product of oxidation would contain certain features related to the mitomycin antibiotics. Thus, photooxidation of heterocycle **2a** in aqueous THF containing 10% pyridine proceeded smoothly to afford the indole lactam **2b** in 70% yield.




**1**



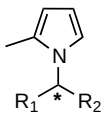

**2a**



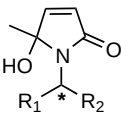

**2b**

Similar reactions performed without added pyridine gave low yields of the desired product. Presumably, the presence of base in the reaction medium serves to facilitate β-elimination of the initially formed endoperoxide. In their study of dye-sensitized pyrrole photooxygenation Lightner et al.[7] observed the formation of 5-hydroxy lactams in methanol solvent. Such products are obtained when the pyrrole α-position is free or substituted by alkyl, formyl, carbomethoxy or acyl groups.

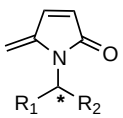
In our earlier works, we reported a new synthetic method for the efficient preparation of 2-substituted pyrrole derivative from haloenones and amines, amino alcohols and amino acids. The cyclization proceeds without racemization.[8] In the study presented herein, attention was focused on the singlet oxygen oxidation of 2-methyl substituted homochiral pyrroles **4**, in which the nitrogen atom is carrying chiral groups, in order to obtain 5-hydroxy γ-lactams **5**, which can be then converted into unsubstituted γ-lactam **6**.




**4**




**5**




**6**

Unsaturated γ-lactams with the structure of **5** and **6** are important synthons for the preparation of a variety of biologically active compounds.[9] These compounds can be used in routes to various alkaloids and are suitable

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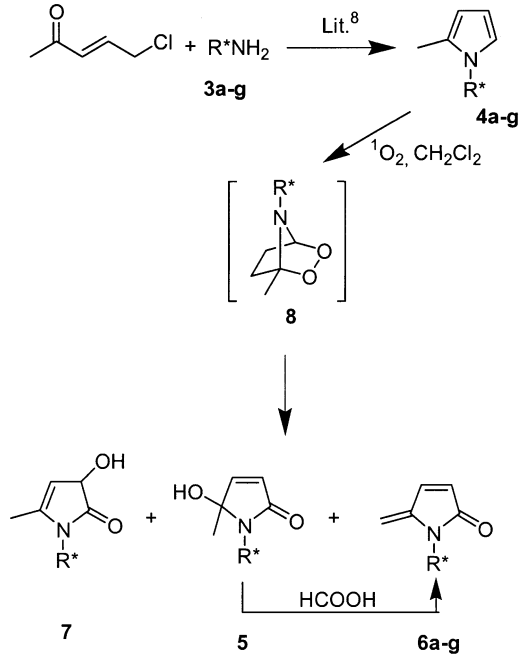
precursors for unusual amino acids. Due to the multifunctional nature of these compounds, they can take part in several stereoselective transformations, such as conjugate additions, cycloadditions, acyliminium chemistry and allylic substitutions.

## 2. Results and discussion

The reaction of amines, amino alcohols and esters of amino acids **3a**–**g** with 5-chloro-3-pentene-2-one gave the 2-methylpyrrole derivative **4a**–**f** in 75–90% yields, without racemization as previously reported[8] (Scheme 1). The oxidation of (*S*)-**4a** in dichloromethane took place at rt in the presence of TPP in a stream of oxygen under irradiation with a 150 W sodium lamp. The color of the reaction mixture changed from violet to green in 15 min. The reaction was monitored by TLC and GC–MS analyses. After all of the starting material was consumed (1 h), the solvent was removed and the products were separated by flash column chromatography. According to the $^{1}H$ and $^{13}C$ NMR spectra and the mass spectrum, the major product was identified as 5-methylene-1-(1-phenylethyl)-1,5-dihydro-2*H*-pyrrol-2-one (*S*)-**6a** in 76% yield along with 9% of the 5-hydroxy derivatives **5** and 3-hydroxy derivative **7** as a mixture. The separation of hydroxy lactams **5** and **7** by column chromatography was not possible. Monitoring the reaction by GC–MS showed the formation of (*S*)-**6a** in 80%, **5** in 10% and the isomeric hydroxy lactam **7** in 5% yields, with some minor impurities after a reaction time of 1 h (Scheme 1). Treatment of these crude reaction mixtures with formic acid at 0°C for 30–40 min increases the yield of (*S*)-**6a** to ca. 5–8%. During this process the hydroxy lactam **5** was converted to (*S*)-**6a**. Because of the possibility of overoxidation it is necessary to monitor the reaction by TLC or GC–MS in order to obtain the desired product in good yield. Additional product formation was observed over a prolonged reaction time due to the additional reaction of singlet oxygen with **5**, **6** and **7**.




**Scheme 1.**

We suggest that the base-catalyzed opening of the *endo*-peroxide could increase the yield of (*S*)-**6a** based on the observation of Quannes and Wilson with tertiary amines.[10] They demonstrated that tertiary amines quench singlet oxygen. Auerbach et al.[6] showed that the addition of pyridine in aqueous solvents does not act as a quencher, but does serve to improve the yield of the elimination product **2b**. For base-catalyzed opening of the *endo*-peroxide **8**, pyridine (10%) was added to the solvent ($CH_2Cl_2$) for a photooxidation experiment and it was found that the yield and selectivity decreased compared to the reaction completed without pyridine.

As shown in Table 1, different homochiral 2-methylpyrroles, synthesized from amino alcohols and amino acid derivatives, were used as starting materials and the corresponding unsaturated γ-lactams were isolated in comparable yields of 58–76%. According to the spectroscopic data, under similar reaction conditions the serine derivative (*S*)-**4g** furnished the bicyclic compound **6g** in 61% yield. This type of photooxidation reaction and the stereoselectivities it affords are still under investigation.

The products are derived from a reactive *endo*-peroxide intermediate **8**, which is formed by 1.4-addition of $^{1}O_2$ to **4**. Thus, **6** can be formed by either the internal rearrangement of **8** or the hydrolysis of **8** by water formed when 5-hydroxylactam **5** undergoes elimination of water to form **6**.

## 3. Conclusions

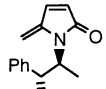
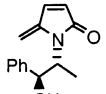
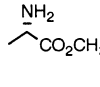
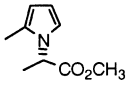
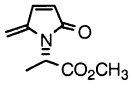
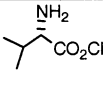
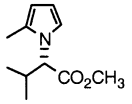
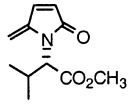
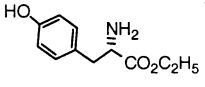
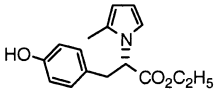
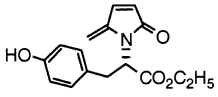
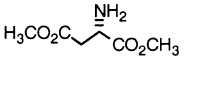
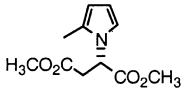
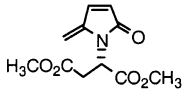
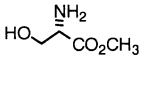
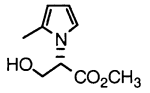
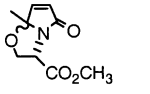
In summary, the simple available homochiral 2-methylpyrroles can be converted into unsaturated γ-lactams in good yields via singlet oxygen oxidation. These lactams are valuble intermediates for many different bioactive compounds.

## 4. Experimental

### 4.1. General methods

NMR spectra were recorded on a Bruker DPX 400. Column chromatography was conducted on silica gel 60 (mesh size 40–63 μm). GC–MS spectra were determined on a phenomenex Zebron ZB-5 capillary column (5% phenylmethylsiloxane, 30 m, 250 μm; $T_{GC}$ (injector) = 250°C, $T_{MS}$ (ion source) = 200°C, time program (oven): $T_{0\ min}$ = 60°C, $T_{3\ min}$ = 60°C, $T_{14\ min}$ = 280°C (heating rate 20°C $min^{-1}$), $T_{19\ min}$ = 280°C, $T_{20\ min}$ = 300°C (heating rate 20°C $min^{-1}$), $T_{25\ min}$ = 300°C, MS: EI, 70 eV). Optical rotations were measured with a Perkin–Elmer 241 polarimeter. 5-Methylpyrrole deriva-

**Table 1.** 5-Methylene-1,5-dihydropyrrole-2-one derivatives

| Amine compounds, **3** | 5-Methylpyrrole derivatives, **4** Yield (%) | | 5-Methylene-1,5-dihydropyrrole-2-one derivatives, **6** Yield (%) | | Reaction Time (min.) |
|---|---|---|---|---|---|
|  (*R*)-**3a** |  (*R*)-**4a** | 90 |  (*R*)-**6a** | 76 | 60 |
|  (*S*)-**3a** |  (*S*)-**4a** | 85 |  (*S*)-**6a** | 73 | 60 |
|  (1*R*,2*S*)-**3b** |  (1*R*,2*S*)-**4b** | 78 |  (1*S*,2*R*)-**6b** | 68 | 60 |
|  (1*S*,2*R*)-**3b** |  (1*S*,2*R*)-**4b** | 76 |  (1*R*,2*S*)-**6b** | 70 | 60 |
|  (*S*)-**3c** |  (*S*)-**4c** | 80 |  (*S*)-**6c** | 66 | 60 |
|  (*S*)-**3d** |  (*S*)-**4d** | 75 |  (S)-**6d** | 63 | 60 |
|  (*S*)-**3e** |  (*S*)-**4e** | 82 |  (*S*)-**6e** | 58 | 60 |
|  (*S*)-**3f** |  (*S*)-**4f** | 78 |  (*S*)-**6f** | 59 | 120 |
|  (*S*)-**3g** |  (*S*)-**4g** | 75 |  (*S*,*R*/*S*)-**6g** | 61 | 90 |

tives were synthesized according to the recently published methods and all spectroscopic data were in agreement with published values.[8]

### 4.2. General procedure for photooxygenation

A solution of pyrrole (750 mg) and TPP (30 mg) in dichloromethane (250 mL) was irradiated with a 150 W sodium lamp in a water-cooled vessel while $O_2$ was passed through the solution. The color of the mixture changed from violet to green in 15 min. The reaction was monitored by TLC and GC–MS. Then the solvent was evaporated and the crude product was purified by column chromatography (1:5 EtOAc:hexane) to give the product.

**4.2.1. (*S*)-5-Methylene-1-(1-phenylethyl)-1,5-dihydro-2*H*-pyrrol-2-one (*S*)-6a**. Yellow oil. $[\alpha]_D^{20}=+42.5$ (*c* 3.2, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.75 (d, $J=7.2$ Hz, 3H, $CH_3$), 4.60 (s, 1H, CH), 4.65 (s, 1H, CH), 5.70 (q, $J=7.1$ Hz, 1H, CH), 6.20 (d, $J=5.6$ Hz, 1H, CH), 6.85 (d, $J=5.7$ Hz, 1H, CH), 7.20–7.35 (m, 5H, Ar); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 17.71, 48.68, 99.32, 124.51, 126.84, 127.44, 127.60, 128.00, 128.80, 138.45, 140.94, 144.06, 170.72; MS (*m*/*z*) (rel. abund.): 199 [$M^+$] (93), 184 (21), (14), 105 (100), 77 (94). Anal. calcd for $C_{13}H_{13}NO$ (199.25): C, 78.36; H, 6.58; N, 7.03; found: C, 78.19; H, 6.51; N, 7.43%.

**4.2.2. (*R*)-5-Methylene-1-(1-phenylethyl)-1,5-dihydro-2*H*-pyrrol-2-one (*R*)-6a**. Yellow oil. $[\alpha]_D^{20}=-42.9$ (*c* 3.2, $CHCl_3$). All other data as for (*S*)-**6a**.

**4.2.3. 1-[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl]-5-methylene-1,5-dihydro-2*H*-pyrrol-2-one (1*R*,2*S*)-6b**. Yellow oil. $[\alpha]_D^{20}=+14.5$ (*c* 5.5, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.27 (d, $J=7.0$ Hz, 3H, $CH_3$), 3.92 (m, 1H, CH), 4.74 (s, 2H, $CH_2$), 4.86 (s, 1H, CH), 5.08 (s, 1H, OH), 6.08 (d, $J=4.6$ Hz, 1H, CH), 6,84 (d, $J=5.7$, 1H, CH), 7.13–7.41 (m, 5H, ArH); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 12.23, 56.64, 75.53, 97.98, 125.43, 126.50, 127.81, 128.25, 138.04, 142.53, 145.84, 172.14. Anal. calcd for $C_{14}H_{15}NO_2$ (229.27): C, 78.34; H, 6.59; N, 6.11; found: C, 78.48; H, 6.47; N, 6.01%.

**4.2.4. 1-[(1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]-5-methylene-1,5-dihydro-2*H*-pyrrol-2-one (1*S*,2*R*)-6b**. Yellow oil. $[\alpha]_D^{20}=-14.4$ (*c* 5.5, $CHCl_3$). All other data as for (1*R*,2*S*)-**6b**.

**4.2.5. (*S*)-Methyl 2-(2-methylene-5-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)propanoate (*S*)-6c**. Yellow oil. $[\alpha]_D^{20}=-66.5$ (*c* 0.2, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.48 (d, $J=7.3$ Hz, 3H, $CH_3$), 3.64 (s, 3H, $OCH_3$), 4.74 (s, 2H, $CH_2$), 4.90 (q, $J=7.3$ Hz, 1H, CH), 6.12 (d, $J=5.5$ Hz, 1H, CH), 6.91 (d, $J=5.7$ Hz, 1H, CH); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 15.65, 48.13, 52.71, 97.32, 124.77, 138.56, 144.27, 169.79, 171.27; MS (*m*/*z*) (rel. abund.): 181 [$M^+$] (10), 122 (100), 94 (20), 81 (18). Anal. calcd for $C_9H_{11}NO_3$ (181.19): C, 59.66; H, 6.12; N, 7.73; found: C, 59.51; H, 6.32; N, 7.51%.

**4.2.6. (*S*)-Methyl 3-methyl-2-(2-methylene-5-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanoate (*S*)-6d**. Yellow oil. $[\alpha]_D^{20}=-20.4$ (*c* 4.3, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.76 (d, $J=6.7$ Hz, 3H, $CH_3$), 1.11 (d, $J=6.2$ Hz, 3H, $CH_3$), 2.58 (m, 1H, CH), 3.70 (s, 3H, $OCH_3$), 4.59 (d, $J=10.7$ Hz, 1H, CHN), 4.84 (s, 1H, CH), 5.14 (s, 1H, CH), 6.22 (d, $J=5.5$ Hz, 1H, CH), 6.96 (d, $J=5.7$ Hz, 1H, CH); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 18.85, 21.02, 28.16, 58.86, 99.23, 124.19, 134.40, 138.61, 144.41, 170.12, 170.49. Anal. calcd for $C_{11}H_{15}NO_3$ (209.24): C, 63.14; H, 7.23; N, 6.69; found: C, 63.32; H, 7.41; N, 6.60%.

**4.2.7. (*S*)-Ethyl 3-(4-hydroxyphenyl)-2-(2-methylene-5-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)propanoate (*S*)-6e**. Yellow oil. $[\alpha]_D^{20}=-15.6$ (*c* 3.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.18 (t, $J=3.1$ Hz, 3H, $CH_2CH_3$), 3.10 (m, 1H, CH of $CH_2$), 3.29 (dd, 1H, CH of $CH_2$), 4.14 (m, 2H, $CH_2CH_3$), 4.77 (s, 1H, $=CH_2$), 4.82 (s, 1H, $=CH_2$), 5.01 (m, 1H, CHN), 6.02 (d, $J=5.4$ Hz, 1H, CH), 6.54 (d, $J=8.1$ Hz, 2H, ArH), 6.83 (d, $J=5.9$ Hz, 1H, CH), 6.85 (d, $J=8.2$ Hz, 2H, ArH); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 14.54, 34.67, 54.83, 61.96, 99.32, 115.77, 124.23, 127.80, 130.21, 138.62, 144.39, 155.79, 170.05, 171.00; MS (*m*/*z*) (rel. abund): 287 [$M^+$] (23), 214 (14), 192 (100), 164 (17), 147 (39), 120 (42), 107 (90), 96 (44). Anal. calcd for $C_{16}H_{17}NO_4$ (287.31): C, 66.89; H, 5.96; N, 4.88; found: C, 66.78; H, 5.81; N, 4.66%.

**4.2.8. (*S*)-Dimethyl 2-(2-methylene-5-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)succinate (*S*)-6f**. Yellow oil. $[\alpha]_D^{20}=-53.9$ (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 2.85 (dd, 1H, CH of $CH_2$), 3.25 (dd, 1H, CH of $CH_2$), 3.62 (s, 3H, $OCH_3$), 3.66 (s, 3H, $OCH_3$), 4.83 (s, 1H, $=CH_2$), 4.91 (s, 1H, $=CH_2$), 5.11 (m, 1H, CHN), 6.13 (d, $J=5.5$ Hz, 1H, CH), 6.95 (d, $J=5.7$ Hz, 1H, CH); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 34.73, 49.88, 52.26, 53.09, 97.27, 124. 88, 138.74, 144.68, 169.72, 169.98, 171.00. Anal. calcd for $C_{11}H_{13}NO_5$ (239.22): C, 55.23; H, 5.48; N, 5.86; found: C, 55.21; H, 5.32; N, 5.61%.

**4.2.9. (*S*,*S*/*R*)-Methyl 7a-methyl-5-oxo-2,3,5,7a-tetrahydropyrrolo[2,1-*b*][1,3]oxazole-3-carboxylate (*S*,*S*/*R*)-6g**. Yellow oil. $[\alpha]_D^{20}=-77.5$ (*c* 0.2, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.53 (s, 3H, $CH_3$), 3.74 (s, 3H, $OCH_3$), 4.35 (m, 2H, $CH_2$), 4.55 (m, 1H, CHN), 5.98 (d, $J=5.7$, 1H, CH), 7.02 (d, $J=5.7$ Hz, 1H, CH); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 21.79, 52.62, 56.44, 72.11, 101.39, 127.43, 151.22, 170.59, 176.64. Anal. calcd for $C_9H_{11}NO_4$ (197.19): C, 54.82; H, 5.62; N, 7.10; found: C, 54.66; H, 5.45; N, 6.88%.

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