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Tetrahedron: *Asymmetry* 15 (2004) 259–265
Tetrahedron: *Asymmetry*

Synthesis and photooxygenation of homochiral 2-methylpyrrole derivatives of chiral amino alcohols: simple, selective access to chiral bicyclic lactams

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Received 26 September 2003; revised 5 November 2003; accepted 13 November 2003

Abstract—Homochiral 2-methylpyrrole derivatives are synthesized in high yields starting from chiral amino alcohols and 5-chloro-3-pentene-2-one. The photooxygenation of these compounds in the presence of a photosynthesizer furnishes the pyrrolooxazolone structures in high diastereoselectivities. In all of the examples, *trans*-isomers are formed as the major products.
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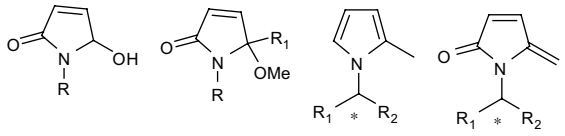
1. Introduction

Singlet oxygen is capable of oxidizing a wide range of substrates. However, only very limited success has been achieved in terms of applying these reactions to practical organic synthesis.[1] One of the problems associated with these photooxidations is low chemoselectivity. The photooxygenation of heterocycles is important because heterocyclic systems such as pyrroles,[2] imidazoles,[3] and other heterocycles[4] are involved in photobiosynthesis and other biological processes. Photooxidations of pyrroles often produce a mixture of products derived from both (1,2)- and (1,4)-oxygen addition. Wasserman et al. recently showed that when both electron-releasing and electron-withdrawing groups are substituted on the hetero ring, oxidations can take place with more control.[5] The photooxidation of N-substituted pyrroles, to form hydroxylactams of type **1**, has been applied by Franck and Auerbach.[6]



1 **2** **3** **4**

Dye sensitized pyrrole photooxygenation followed by solvolysis of the formed *endo*-peroxide in methanol yielded lactam **2**. Such products are formed when the pyrrole α-position is free or substituted by an alkyl, formyl, carbomethoxy, or acyl group.[7]

Previously, we reported a new synthetic method for the efficient preparation of 2-substituted pyrrole derivatives **3** from haloenones and amines, and amino alcohols and amino acids. This cyclization works without any racemization.[8] Recently, we also showed that the homochiral 2-methylpyrroles can be converted into unsaturated γ-lactams **4** in good yields using singlet oxygen.[9]

Herein, attention is focused on the singlet oxygen oxidation of 2-methyl substituted homochiral pyrroles **6** that are derived from various amino alcohols **5**, in which the nitrogen atom is carrying chiral groups, in order to obtain chiral bicyclic lactams **8** (Scheme 1).

A number of reports have demonstrated the synthetic utility of chiral bicyclic lactams. These systems have provided access to a number of enantiomerically pure materials bearing quaternary carbon centers including cyclobutanes, cyclopentenones, cyclohexanes, and cyclohexenones. They are also used as starting materials by the formal total synthesis of some natural products.[10,11] Some methods have already been published reporting the synthesis of these bicyclic lactams starting from different compounds,[11,12] but the most relevant synthetic route to these bicyclic lactams involves heating

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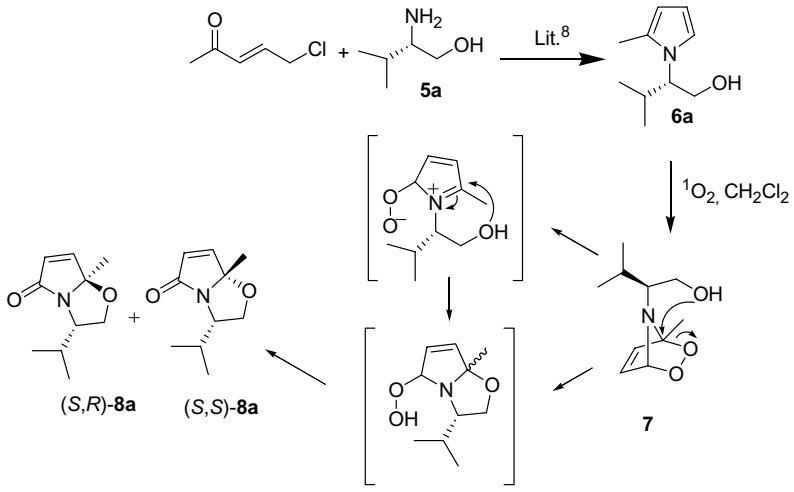
doi:10.1016/j.tetasy.2003.11.011



Scheme 1.

the appropriate anhydride with a chiral 2-amino alcohol. The subsequent reduction of these imides followed by the treatment of the resulting alcohols with TFA provides the bicyclic lactams.[13] Only a few *cis*-bicyclic lactams have been described and some of these compounds are commercially available. As far as we know, no work has been previously published for the synthesis of *trans*-isomers of these compounds.

2. Results and discussion

The reaction of amino alcohols and the esters of amino acids **5a**–**g** with 5-chloro-3-pentene-2-one provided the 2-methylpyrrole derivatives **6a**–**g** in 75–95% yields without any racemization as previously reported[8] (Scheme 1). The oxygenation of (*S*)-**6a** was performed using several methods of singlet oxygen generation.[2,14] In most cases, a low yield of bicyclic lactam was obtained. The best yield of bicyclic lactam was gained by using the following conditions: The oxidation of (*S*)-**6a** 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 turned from violet to green in 10–20 min. The reaction was monitored by TLC and GC–MS. After all of the starting material was consumed (1 h), the solvent was removed and the product separated by flash column chromatography. According to the ^{1}H and ^{13}C NMR spectra, along with the MS, the major product was identified as 3-isopropyl-7a-methyl-2,3-dihydropyrrolo[2,1*b*][1,3]oxazol-5(7a*H*)-one as a diastereomeric mixture with a 49% yield along with tarry residues from a mixture of oxidation and polymeric products. The structural assignment was carried out by using NMR techniques (NOESY, HMBC) and also by the comparison of their data with a known, commercially available compound. The major isomer was identified as (*S*,*S*)-**8a** and the minor (*S*,*R*)-**8a** (the spectroscopic data of this isomer is identical with a commercially available compound). As shown in Scheme 1, the formation of the *trans*-product is favored.

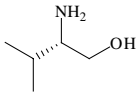
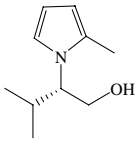
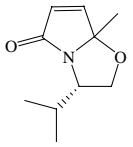
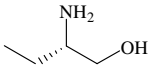
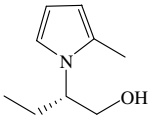
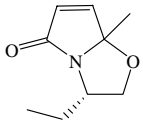
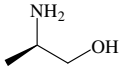
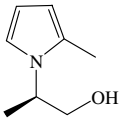
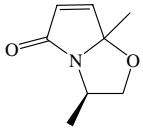
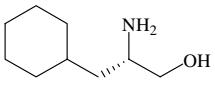
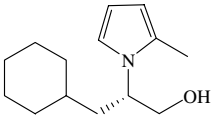
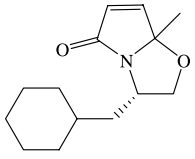
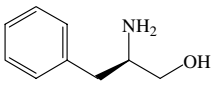
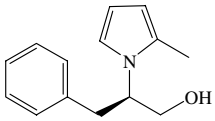
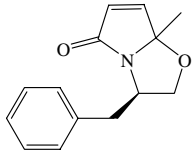
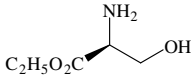
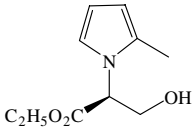
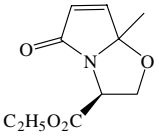
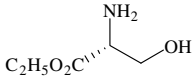
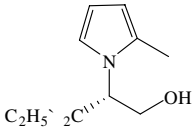
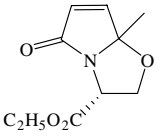
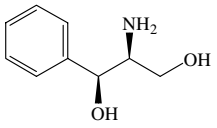
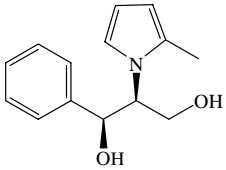
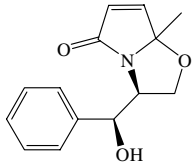
Carrying out the reaction with (*R*)-**6a** provided the enantiomers (*R*,*R*)-**8a** and (*R*,*S*)-**8a**. The reaction of *rac*-**6a** gave *trans*-*rac*-**8a** as the major product (Scheme 1). Identification of the isomeric products was easily performed by using NMR techniques, GC–MS, and HPLC.

As shown in Table 1, different homochiral 2-methylpyrroles, synthesized from amino alcohols and the amino acid ester, were used as starting materials and the corresponding bicyclic lactams isolated in comparable yields (47–56%). According to the spectroscopic data, the bicyclic lactams were obtained as a diastereomeric mixture with a similar selectivity as described for (*S*,*RS*)-**8a** (Table 1). Starting from (*R*)-**6e** the corresponding bicyclic lactam **8e** was obtained in a 55% yield with which it was possible to separate the diastereomers by flash column chromatography to give both isomers (*R*,*S*)-**8e** and (*R*,*R*)-**8e** in their enantiomerically pure form. In the case of **6f**, both enantiomers of the amino alcohol are commercially available and the bicyclic lactams (*S*,*RS*)-**8f** and (*R*,*RS*)-**8f** can be synthesized starting from both the enantiomers of **6f**. The flash column chromatographic separation of the isomers supplied all of the possible enantiomers of **8f** diastereomerically pure. The enantiomers were analyzed by HPLC using a chiral column (Scheme 2).

The photooxygenation of **6g** only gave the bicyclic lactam with a primary hydroxy group. No cyclization was observed with the secondary hydroxy group. In accordance with this result, the oxidation reaction of pyrrole **9**, which was derived from norephedrine, mainly supplied the γ-lactam elimination product **10**. Only a trace amount of cyclization product, which was detected by GC–MS, was obtained under the above mentioned reaction conditions (Scheme 3). Sterical hindrance is likely the reason for this result.

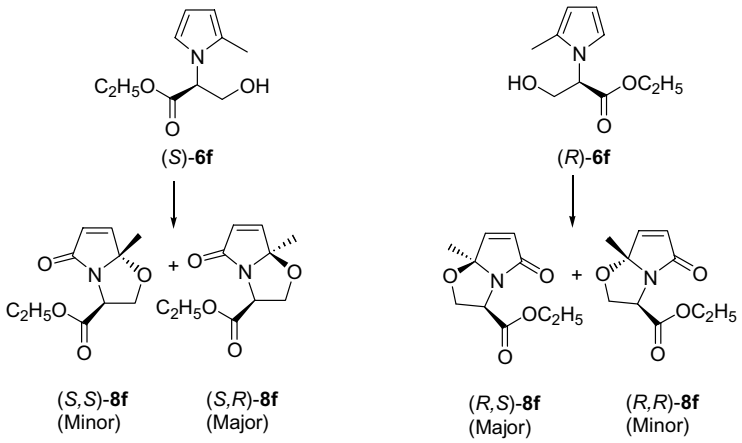
The products were derived from a reactive *endo*-peroxide intermediate **7** (Scheme 1), which was formed by the 1,4-addition of $^{1}O_2$ to **6**. Thus, **7** was able to undergo alcoholysis to form a hydroperoxides. The latter was then decomposed to yield **8**.

Table 1. Pyrrolooxazole derivatives

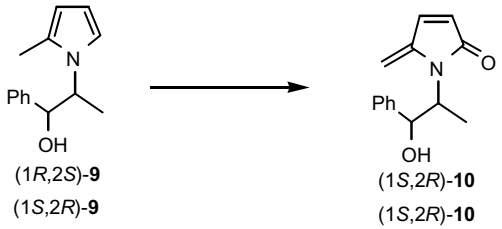
Amine compounds **5**	Pyrrole compounds **6**	Yield (%)	Pyrrolooxazole compounds **8**	Yield (%)	React. time (min)	Isomer ratio[a]
 (*S*)-**5a**	 (*S*)-**6a**	92	 (*S*,*RS*)-**8a**	49	60	*S*,*R*/*S*,*S* 1:5
(*R*)-**5a**	(*R*)-**6a**	93	(*R*,*RS*)-**8a**	54	50	*R*,*S*/*R*,*R* 1:5
rac-**5a**	*rac*-**6a**	92	*rac*-**8a**	47	60	*cis*/*trans* 1:6
 (*S*)-**5b**	 (*S*)-**6b**	90	 (*S*,*RS*)-**8b**	56	50	*S*,*R*/*S*,*S* 1:5
 (*R*)-**5c**	 (*R*)-**6c**	95	 (*R*,*SR*)-**8c**	51	60	*R*,*S*/*R*,*R* 1:5
 (*S*)-**5d**	 (*S*)-**6d**	78	 (*S*,*RS*)-**8d**	50	45	*S*,*R*/*S*,*S* 1:4
 (*R*)-**5e**	 (*R*)-**6e**	84	 (*R*,*SR*)-**8e**	55	60	*R*,*S*/*R*,*R* 1:6 (separated)
 (*S*)-**5f**	 (*S*)-**6f**	75	 (*S*,*RS*)-**8f**	53	90	*S*,*S*/*S*,*R* 1:5 (separated)[b]
 (*R*)-**5f**	 (*R*)-**6f**	79	 (*R*,*RS*)-**8f**	48	90	*R*,*R*/*R*,*S* 1:5 (separated)[b]
 (*S*,*S*)-**5g**	 (*S*,*S*)-**6g**	81	 (*S*,*S*,*RS*)-**8g**	54	90	(*S*,*S*,*S*/*S*,*S*,*R*) 1:3

[a] Determined by ^{1}H NMR spectroscopy.

[b] The enantiomers were analyzed by HPLC using chiral column (Chiralcel OD), UV detection at 254 nm, eluent: hexane/2-propanol 9:1, flow rate 0.80 mL min^{-1}, 20 °C.



Scheme 2.



Scheme 3.

The mechanism of formation of the bicyclic lactam from the *endo*-peroxide is either the direct nucleophilic involvement of –OH in an *endo*-peroxide decomposition mode or an open Zwitter ion is attached by –OH as shown in Scheme 1. The stereocontrolled formation of an intermediate can result from the stereoselective 1,4-addition of $^1O_2$ to the pyrrole ring to form the *endo*-peroxide followed by stereoselective intramolecular alcoholysis to form the bicyclic lactam. It should be noted that the mechanistic details of the present reaction are still under investigation.

3. Conclusion

In summary, the simple homochiral 2-methylpyrroles, derived from chiral amino alcohols, can be converted selectively into bicyclic lactams with good diastereomeric ratio and chemical yields using singlet oxygen. The diastereomers can then be separated by using column chromatography. These bicyclic lactams with a quaternary stereocenter are valuable 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. Melting points were measured on a Gallenkamp melting point apparatus in an open capillary. 2-Methylpyrrole derivatives were synthesized according to the recently published procedure.[8] The synthesis of **6a** and **9** (described previously) and all spectroscopic data were in agreement with published values.[8a,9] Enantiomeric excesses were determined by HPLC analysis using a Thermo Quest (TSP) LC–MS equipped with an appropriate optically active column, as described in the footnotes of the corresponding tables.

4.2. General procedure for photooxygenation

A solution of pyrrole (1 mmol) and TPP (20 mg) in dichloromethane (200 mL) was irradiated with a 150 W sodium lamp in a water-cooled vessel with O_2 passed through the solution. The color of the mixture changed from violet to green in 10–20 min. The reaction was monitored by TLC and GC–MS. The solvent was then evaporated and the crude product purified by way of column chromatography (1:3 EtOAc/hexane) to produce the product.

4.2.1. (*S*)-2-(2-Methyl-1*H*-pyrrol-1-yl)butan-1-ol (*S*)-6b. Light yellow oil (414 mg). $[\alpha]_D^{20} = -20.7$ (*c* 4.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.70 (t, $J = 7.3$ Hz, 3H, CH_3), 1.52 (m, 1H, CH_A), 1.63 (m, 1H, CH_B), 2.11 (s, 3H, CH_3), 2.33 (br s, 1H, OH), 3.47 (m, 2H, CH_2), 3.76 (m, 1H, CH), 5.71 (s, 1H, =CH), 5.92 (s, 1H, =CH), 6.39 (s, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.0, 12.8, 25.5, 59.7, 66.3, 106.5, 108.0, 115.7, 129.7. Anal. Calcd for $C_9H_{15}NO$ (153.12): C, 70.55; H, 9.87; N, 9.14.

4.2.2. (*R*)-2-(2-Methyl-1*H*-pyrrol-1-yl)propan-1-ol (*R*)-6c. Light yellow solid (396 mg). Mp 70–73 °C; $[\alpha]_D^{20} = -9.6$ (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (d, $J = 6.9$ Hz, 3H, CH_3), 1.42 (s, 1H, OH), 2.17 (s, 3H, CH_3), 3.60 (d, $J = 6.3$ Hz, 2H, CH_2), 4.14 (m, 1H, CH), 5.73 (s, 1H, =CH), 5.97 (s, 1H, =CH), 6.51 (s, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.6, 18.0, 53.1, 67.5, 107.1, 108.3, 115.5, 129.0. Anal. Calcd for $C_8H_{13}NO$ (139.10): C, 69.03; H, 9.41; N, 10.06.

4.2.3. (*S*)-3-Cyclohexyl-2-(2-methyl-1*H*-pyrrol-1-yl)propan-1-ol (*S*)-6d. Light yellow oil (518 mg). $[\alpha]_D^{20} = -25.9$ (*c* 3.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.73 (m, 2H, CH_2), 0.96 (m, 4H, CH_2), 1.21 (br s, 1H, OH), 1.42 (m, 6H, CH_2), 1.59 (m, 1H, CH), 2.07 (s, 3H, CH_3), 3.51 (m, 2H, CH_2), 3.99 (m, 1H, CH), 5.64 (br s, 1H, =CH), 5.90 (m, 1H, =CH), 6.39 (m, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8, 26.3, 26.5, 26.8, 33.3, 34.2, 34.3, 39.8, 55.4, 67.1, 106.8, 108.3, 115.7, 129.5. Anal. Calcd for $C_{14}H_{23}NO$ (221.18): C, 75.97; H, 10.47; N, 6.33.

4.2.4. (*R*)-3-Phenyl-2-(2-methyl-1*H*-pyrrol-1-yl)propan-1-ol (*R*)-6e. Light yellow oil (542 mg). $[\alpha]_D^{20} = +73.2$ (*c* 4.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.77 (s, 3H, CH_3), 2.08 (br s, 1H, OH), 2.75 (m, 1H, CH_A), 2.84 (m, 1H, CH_B), 3.60 (m, 2H, CH_2), 4.01 (m, 1H, CH), 5.60 (m, 1H, =CH), 5.96 (m, 1H, =CH), 6.54 (m, 1H, =CH), 6.79 (m, 2H, ArH), 7.06 (m, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 39.5, 59.8, 65.5, 106.7, 108.5, 115.6, 127.0, 128.8, 129.3, 130.0, 138.1. Anal. Calcd for $C_{14}H_{17}NO$ (215.13): C, 78.10; H, 7.96; N, 6.51.

4.2.5. (*S*)-Ethyl-3-hydroxy-2-(2-methyl-1*H*-pyrrol-1-yl)-propanoate (*S*)-6f. Yellow oil (443 mg). $[\alpha]_D^{20} = -37.8$ (*c* 5.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, $J = 7.0$ Hz, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.39 (br s, 1H, OH), 3.83 (m, 1H, CH_A), 4.03 (m, 1H, CH_B), 4.12 (m, 2H, CH_2), 4.63 (t, $J = 6.6$ Hz, 1H, CH), 5.77 (br s, 1H, =CH), 5.97 (m, 1H, =CH), 6.55 (br s, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.9, 18.5, 53.1, 66.5, 73.4, 107.2, 108.6, 115.5, 129.4, 170.7. Anal. Calcd for $C_{10}H_{15}NO_3$ (197.11): C, 60.90; H, 7.67; N, 7.10.

4.2.6. (*R*)-Ethyl-3-hydroxy-2-(2-methyl-1*H*-pyrrol-1-yl)-propanoate (*R*)-6f. Light yellow oil. $[\alpha]_D^{20} = +37.9$ (*c* 5.2, $CHCl_3$).

4.2.7. (*S*,*S*)-2-(2-Methyl-1*H*-pyrrol-1-yl)-1-phenylpropan-1,3-diol (*S*)-6g. Colorless solid (561 mg). Mp 160–161 °C; $[\alpha]_D^{20} = +34.7$ (*c* 0.7, MeOH); ^1H NMR (400 MHz, DMSO-d_6): δ 1.63 (s, 3H, CH_3), 3.58 (m, 1H, CH_A), 3.84 (m, 1H, CH_B), 3.97 (m, 1H, CH), 4.59 (br s, 1H, OH), 4.96 (d, $J = 3.5$ Hz, 1H, CH), 5.21 (br s, 1H, OH), 5.49 (s, 1H, =CH), 5.80 (m, 1H, =CH), 6.81 (br s, 1H, =CH), 7.02 (m, 2H, ArH), 7.14 (m, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 62.6, 63.1, 72.6, 105.5, 106.4, 119.4, 127.0, 127.5, 128.2, 129.1, 143.8. Anal. Calcd for $C_{14}H_{17}NO_2$ (231.13): C, 72.70; H, 7.41; N, 6.06.

4.2.8. (*S*,*RS*)-3-Isopropyl-7a-methyl-2,3-dihydropyrrolo-[2,1*b*][1,3]oxazol-5(7a*H*)-one (*S*,*RS*)-8a. Yellow oil (89 mg). $[\alpha]_D^{20} = -6$ (*c* 2.0, $CHCl_3$); IR ($CHCl_3$): ν 2989, 1717, 1642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ for (*S*,*S*)-**8a** 0.76 (d, $J = 6.7$ Hz, 3H, CH_3), 1.16 (d, $J = 6.4$ Hz, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.65 (m, 1H, CH), 3.32 (m, 1H, CH_A), 3.57 (m, 1H, CH_B), 4.03 (m, 1H, CH), 5.87 (d, $J = 5.7$ Hz, 1H, =CH), 6.91 (d, $J = 5.7$ Hz, 1H, =CH); for (*S*,*R*)-**8a** 0.86 (d, $J = 6.6$ Hz, 3H, CH_3), 1.01 (d, $J = 6.6$ Hz, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.65 (m, 1H, CH), 3.57 (m, 1H, CH_A), 3.98 (m, 1H, CH_B), 4.17 (m, 1H, CH), 5.91 (d, $J = 5.7$ Hz, 1H, =CH), 6.93 (d, $J = 5.7$ Hz, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ for (*S*,*S*)-**8a** 19.2, 22.7, 23.3, 25.7, 65.0, 73.3, 101.1, 129.4, 150.1, 174.2; for (*S*,*R*)-**8a** 19.6, 20.8, 33.2, 62.7, 74.0, 100.6, 128.2, 150.8, 177.7; MS (*m*/*z*) (rel abund): 181 [M^+] (20), 165(96), 150(100), 137(100), 122(64), 109(98), 93(98), 80(86). Anal. Calcd for $C_{10}H_{15}NO_2$ (181.11): C, 66.27; H, 8.34; N, 7.73.

4.2.9. (*S*,*RS*)-3-Ethyl-7a-methyl-2,3-dihydropyrrolo-[2,1*b*]-[1,3]oxazol-5(7a*H*)-one (*S*,*RS*)-8b. Yellow oil (94 mg). $[\alpha]_D^{20} = +27.5$ (*c* 2.0, $CHCl_3$); IR ($CHCl_3$): ν 2989, 1719, 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ for (*S*,*S*)-**8b** 0.97 (t, $J = 7.3$ Hz, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.63 (m, 1H, CH_A), 2.30 (m, 1H, CH_B), 3.54 (m, 2H, CH_2), 4.15 (m, 1H, CH), 5.87 (d, $J = 5.6$ Hz, 1H, =CH), 6.92 (d, $J = 5.6$ Hz, 1H, =CH); for (*S*,*R*)-**8b** 0.97 (t, $J = 7.3$ Hz, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.63 (m, 2H, CH_2), 3.54 (m, 1H, CH_A), 3.73 (m, 1H, CH_B), 3.86 (m, 1H, CH), 5.91 (d, $J = 5.6$ Hz, 1H, =CH), 6.93 (d, $J = 5.6$ Hz, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ for (*S*,*S*)-**8b** 12.1, 21.1, 23.3, 59.6, 75.5, 101.3, 129.4, 150.2, 174.2; for (*S*,*R*)-**8b** 11.5, 23.1, 28.1, 58.1, 74.8, 100.7, 128.1, 151.2, 177.9; MS (*m*/*z*) (rel abund): 167 [M^+] (4), 151(37), 136(100), 122(9), 109(43), 93(25), 80(66). Anal. Calcd for $C_9H_{13}NO_2$ (167.21): C, 64.65; H, 7.84; N, 8.38.

4.2.10. (*R*,*SR*)-3-7a-Dimethyl-2,3-dihydropyrrolo[2,1*b*]-[1,3]oxazol-5(7a*H*)-one (*R*,*SR*)-8c. Yellow oil (78 mg). $[\alpha]_D^{20} = -42.1$ (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): ν 2987, 1719, 1642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ for (*R*,*R*)-**8c** 1.42 (s, 3H, CH_3), 1.48 (d, $J = 6.7$ Hz, 3H, CH_3), 3.50 (m, 1H, CH_A), 3.75 (m, 1H, CH_B), 4.16 (m, 1H, CH), 5.89 (d, $J = 5.7$ Hz, 1H, =CH), 6.94 (d, $J = 5.7$ Hz, 1H, =CH); for (*R*,*S*)-**8c** 1.31 (d, $J = 6.7$ Hz, 3H, CH_3), 1.51 (s, 3H, CH_3), 3.80 (m, 1H, CH_A), 3.98 (m, 1H, CH_B), 4.16 (m, 1H, CH), 5.90 (d, $J = 5.7$ Hz, 1H, =CH), 6.92 (d, $J = 5.7$ Hz, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ for (*R*,*R*)-**8c** 13.9, 23.3, 53.1, 76.9, 101.3, 129.6, 150.4, 174.3; for (*R*,*S*)-**8c** 20.7, 27.4, 52.0, 76.1, 100.8, 128.1, 151.2, 177.9; MS (*m*/*z*) (rel abund): 153 [M^+] (1), 137(100), 122(74), 107(30), 93(61), 79(38). Anal. Calcd for $C_8H_{11}NO_2$ (153.18): C, 62.73; H, 7.24; N, 9.14.

4.2.11. (*S*,*RS*)-3-(Cyclohexylmethyl)-7a-methyl-2,3-dihydropyrrolo[2,1*b*][1,3]oxazol-5(7a*H*)-one (*S*,*RS*)-8d. Colorless oil (118 mg). $[\alpha]_D^{20} = +21.8$ (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): *v* 2989, 2979, 1719, 1642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ for (*S*,*S*)-**8d** 1.14 (m, 6H, CH_2), 1.42 (s, 3H, CH_3), 1.61 (m, 7H, CH_2+CH), 3.40 (m, 1H, CH_A), 3.72 (m, 1H, CH_B), 4.12 (m, 1H, CH), 5.87 (d, $J = 5.7$ Hz, 1H, =CH), 6.91 (d, $J = 5.7$ Hz, 1H, =CH); for (*S*,*R*)-**8d** 1.14 (m, 6H, CH_2), 1.49 (s, 3H, CH_3), 1.61 (m, 7H, CH_2+CH), 3.40 (m, 1H, CH_A), 3.80 (m, 1H, CH_B), 3.95 (m, 1H, CH), 5.90 (d, $J = 5.7$ Hz, 1H, =CH), 6.91 (d, $J = 5.7$ Hz, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ for (*S*,*S*)-**8d** 23.7, 26.6, 26.9, 33.3, 34.1, 34.6, 36.2, 43.1, 56.2, 75.8, 101.1, 129.4, 150.4, 173.8; for (*S*,*R*)-**8d** 23.7, 26.6, 33.2, 33.4, 35.2, 43.0, 54.5, 75.0, 101.1, 128.4, 151.1, 177.2; MS (*m*/*z*) (rel abund): 235 [M^+] (6), 220(16), 204(100), 191(6), 138(24), 122(58), 109(28), 93(56), 80(34). Anal. Calcd for $C_{14}H_{21}NO_2$ (235.32): C, 71.46; H, 8.99; N, 5.95.

4.2.12. (*R*,*R*)-3-Benzyl-7a-methyl-2,3-dihydropyrrolo-[2,1*b*][1,3]oxazol-5(7a*H*)-one (*R*,*R*)-8e. Colorless oil (101 mg). $[\alpha]_D^{20} = -50.8$ (*c* 0.3, $CHCl_3$); IR ($CHCl_3$): *v* 3013, 2978, 1707, 1637 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 3H, CH_3), 2.69 (m, 1H, CH_A), 3.64 (m, 1H, CH_B), 3.85 (m, 1H, CH), 3.93 (m, 2H, CH_2), 5.93 (d, $J = 5.7$ Hz, 1H, =CH), 6.95 (d, $J = 5.7$ Hz, 1H, =CH), 7.13 (m, 3H, ArH), 7.19 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 32.4, 56.8, 73.5, 99.7, 125.0, 127.1, 127.2, 127.5, 136.8, 148.7, 172.6; MS (*m*/*z*) (rel abund): 229 [M^+] (30), 198(12), 137(100), 109(66), 90(90), 77(42). Anal. Calcd for $C_{14}H_{15}NO_2$ (229.11): C, 73.34; H, 6.59; N, 6.11.

4.2.13. (*R*,*S*)-3-Benzyl-7a-methyl-2,3-dihydropyrrolo-[2,1*b*][1,3]oxazol-5(7a*H*)-one (*R*,*S*)-8e. Colorless oil (16 mg). $[\alpha]_D^{20} = +11.0$ (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): *v* 3013, 2978, 1707, 1637 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 3H, CH_3), 2.82 (m, 1H, CH_A), 3.07 (m, 1H, CH_B), 3.95 (m, 2H, CH_2), 4.15 (m, 1H, CH), 5.92 (d, $J = 5.7$ Hz, 1H, =CH), 6.93 (d, $J = 5.7$ Hz, 1H, =CH), 7.18 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.3, 40.6, 57.3, 73.3, 100.8, 126.6, 128.0, 128.9, 129.7, 137.3, 151.3, 178.0.

4.2.14. (*S*,*R*)-Ethyl-7a-methyl-5-oxo-2,3,5,7a-tetrahydropyrrolo[2,1*b*][1,3]oxazole-3-carboxylate (*S*,*R*)-8f. Light yellow oil (80 mg). HPLC (Chiralcel OD): $t_R = 26.5$ min; $[\alpha]_D^{20} = +44.6$ (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): *v* 2983, 1719, 1637 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, $J = 7.1$ Hz, 3H, CH_3), 1.57 (s, 3H, CH_3), 4.18 (m, 2H, CH_2), 4.29 (m, 2H, CH_2), 4.50 (m, 1H, CH), 5.96 (d, $J = 5.7$ Hz, 1H, =CH), 7.00 (d, $J = 5.7$ Hz, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 22.2, 57.0, 62.0, 72.5, 101.7, 127.7, 151.5, 170.4, 176.9; Anal. Calcd for $C_{10}H_{13}NO_4$ (211.21): C, 56.86; H, 6.20; N, 6.63.

4.2.15. (*S*,*S*)-Ethyl-7a-methyl-5-oxo-2,3,5,7a-tetrahydropyrrolo[2,1*b*][1,3]oxazole-3-carboxylate (*S*,*S*)-8f. Light yellow oil (14 mg). HPLC (Chiralcel OD): $t_R = 26.9$ min; $[\alpha]_D^{20} = +102.0$ (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): *v* 2983, 1719, 1637 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, $J = 7.1$ Hz, 3H, CH_3), 1.47 (s, 3H, CH_3), 4.15 (m, 3H, CH_2+CH_A), 4.26 (m, 1H, CH_B), 4.40 (m, 1H, CH), 5.97 (d, $J = 5.8$ Hz, 1H, =CH), 7.00 (d, $J = 5.8$ Hz, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 22.3, 57.3, 62.0, 73.3, 101.9, 129.2, 150.4, 168.6, 174.5.

4.2.16. (*R*,*S*)-Ethyl-7a-methyl-5-oxo-2,3,5,7a-tetrahydropyrrolo[2,1*b*][1,3]oxazole-3-carboxylate (*R*,*S*)-8f. Light yellow oil (82 mg). HPLC (Chiralcel OD): $t_R = 27.1$ min; $[\alpha]_D^{20} = -40.8$ (*c* 0.4, $CHCl_3$).

4.2.17. (*R*,*R*)-Ethyl-7a-methyl-5-oxo-2,3,5,7a-tetrahydropyrrolo[2,1*b*][1,3]oxazole-3-carboxylate (*R*,*R*)-8f. Light yellow oil (12 mg). HPLC (Chiralcel OD): $t_R = 28.2$ min; $[\alpha]_D^{20} = -108.9$ (*c* 0.5, $CHCl_3$).

4.2.18. (*S*,*S*,*RS*)-3-[Hydroxy(phenyl)methyl]-7a-methyl-2,3-dihydropyrrolo[2,1*b*][1,3]oxazol-5(7a*H*)-one (*S*,*S*,*RS*)-8g. Colorless oil (132 mg). $[\alpha]_D^{20} = +74.1$ (*c* 1.2, $CHCl_3$); IR ($CHCl_3$): *v* 3013, 2978, 1707, 1637 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ for (*S*,*S*,*S*)-**8g** 1.45 (s, 3H, CH_3), 3.60 (d, $J = 7.9$ Hz, 1H, CH_A), 3.80 (m, 1H, CH_B), 4.00 (m, 1H, CH), 4.91 (dd, $J = 3.3$, 6.3 Hz, 1H, CH), 6.01 (d, $J = 5.7$ Hz, 1H, =CH), 6.98 (d, $J = 5.7$ Hz, 1H, =CH), 7.26 (m, 5H, ArH); for (*S*,*S*,*R*)-**8g** 1.64 (s, 3H, CH_3), 3.60 (d, $J = 7.9$ Hz, 1H, CH_A), 3.69 (m, 1H, CH_B), 4.00 (m, 1H, CH), 4.76 (d, $J = 9.3$ Hz, 1H, CH), 6.03 (d, $J = 5.7$ Hz, 1H, =CH), 7.10 (d, $J = 5.7$ Hz, 1H, =CH), 7.26 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ for (*S*,*S*,*S*)-**8g** 24.5, 64.7, 72.7, 84.8, 102.3, 127.0, 128.8, 129.1, 129.0, 139.8, 151.1, 174.8; for (*S*,*S*,*R*)-**8g** 22.9, 57.6, 67.1, 73.5, 100.4, 126.7, 128.7, 128.8, 129.1, 137.8, 152.4, 175.8; MS (*m*/*z*) (rel abund): 244 [M−1] (1), 226(3), 149(5), 138(100), 122(17), 108(51), 96(94), 76(86). Anal. Calcd for $C_{14}H_{15}NO_3$ (245.27): C, 68.56; H, 6.16; N, 5.71.

4.2.19. 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*)-10.[9] Yellow oil. $[\alpha]_D^{20} = +14.5$ (*c* 5.5, $CHCl_3$); IR ($CHCl_3$): *v* 2986, 1715, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 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, $J = 5.7$ Hz, 1H, =CH), 7.27 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.2, 56.6, 75.5, 97.9, 125.4, 126.5, 127.8, 128.2, 138.0, 142.5, 145.8, 172.1. Anal. Calcd for $C_{14}H_{15}NO_2$ (229.27): C, 73.34; H, 6.59; N, 6.11. Found: C, 73.48; H, 6.47; N, 6.01.

4.2.20. 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*)-10.[9] Yellow oil. $[\alpha]_D^{20} = -14.4$ (*c* 5.5, $CHCl_3$).

Acknowledgements

Financial support was funded by the Middle East Technical University (BAP-2003), the Scientific and Technical Research Council of Turkey (TUBITAK), the Turkish Academy of Sciences (TUBA), the Turkish State Planning Organization (DPT), and the Yildiz Technical University is gratefully acknowledged.

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