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Synthesis of Enantiomerically Pure Pyrrolidinones as Endothelin Receptor Antagonists

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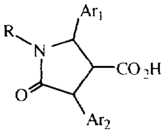
Abstract: Enantiomerically pure pyrrolidinones were synthesized as endothelin receptor antagonists. A [2+2] cycloaddition of an imine and an enantiomerically pure acid chloride gave two diastereomeric β-lactams which were separated and rearranged to give the enantiomerically pure pyrrolidinones which could be reduced to give the corresponding pyrrolidines. Copyright © 1996 Elsevier Science Ltd



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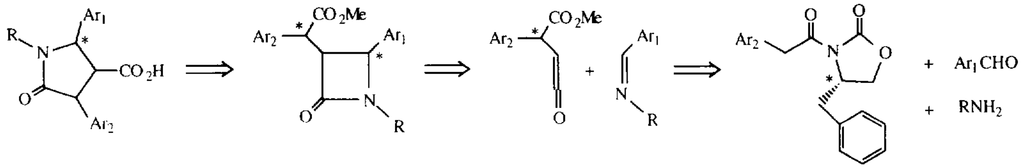
We desired a synthesis of the pyrrolidinones (**1**) of the type shown below which were designed to be endothelin receptor antagonists.[1] A retrosynthetic plan (Scheme I) was designed for the rapid construction of a variety of analogs. It was envisioned that the pyrrolidinones could be prepared by the rearrangement of a β-lactam which, in turn, could arise from a [2+2] cycloaddition of an imine and an acid chloride.[2] We planned on rearranging the diastereomeric β-lactams under different conditions to prepare the stereoisomers of the pyrrolidinones. Furthermore, if the β-lactam was enantiomerically pure, one could obtain enantiomerically pure pyrrolidinones. The acid chloride component required for the cycloaddition could be prepared enantioselectively using the acyloxazolidinone alkylation method. Thus, [2+2] cycloaddition of a variety of imines and acid chloride partners and subsequent rearrangment of the resulting β-lactams would provide pyrrolidinones with a wide range of substituents.

Scheme I



A representative synthesis is shown in Scheme II. (3,4-Methylenedioxy)phenylacetic acid was converted to the corresponding acid chloride and treated with the lithium salt of S-(-)-4-benzyl-2-oxazolidinone to give the acyloxazolidinone (**2**) shown. Alkylation of the lithium enolate of **2** with *t*-butyl bromoacetate gave the acyloxazolidinone **3**. Hydrolysis of the acyloxazolidinone moiety of **3** followed by esterification with diazomethane, hydrolysis of the *t*-butyl ester and treatment with oxalyl chloride gave the acid chloride **4**. The [2+2] cycloaddition was attempted initially by allowing **4** to react with **5**, the 3-oxa-hexylimine of 4-methoxybenzaldehyde, in CH_2Cl_2 and Et_3N at 0 °C which gave the dimer derived from the [2+2] cycloaddition of the ketene as the major product. It was apparent that the imine was less reactive at 0 °C to participate in the

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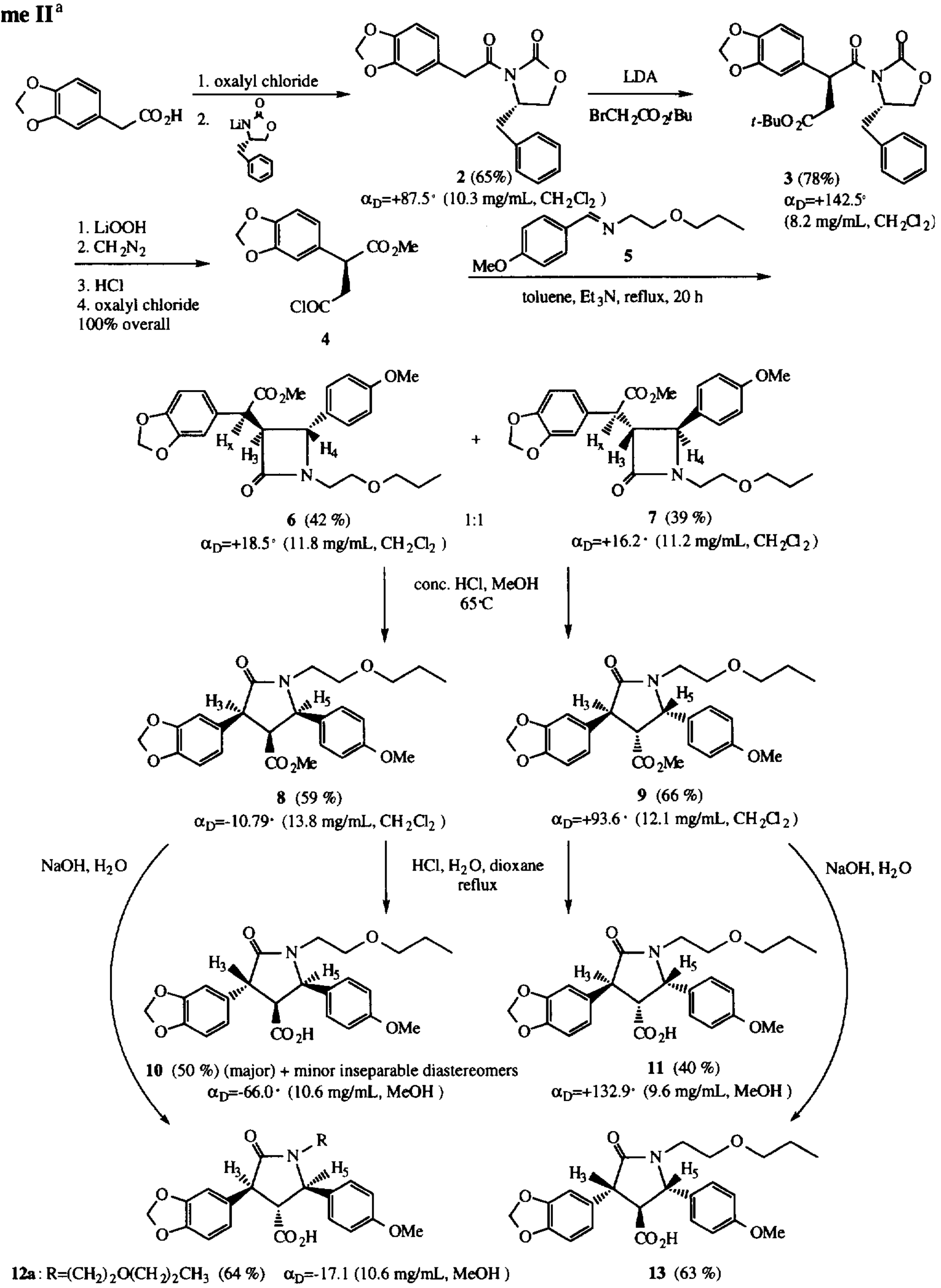
Scheme II[a]

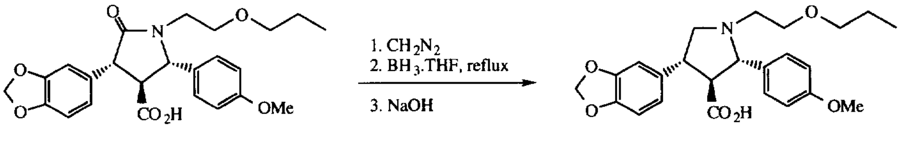


12a: R=$(CH_2)_2O(CH_2)_2CH_3$ (64 %) α_D=-17.1 (10.6 mg/mL, MeOH)
12b: R=$CH_2C_6H_5$; **12c**: R=3,4-$CH_2C_6H_3(OCH_3)_2$; **12d**: R=C_6H_5;
12e: R=$CH_2C_6H_{11}$; **12f**: R=$(CH_2)_2SiMe_3$; **12g**: $CH_2CH{=}CH_2$

[a] Yields are unoptimized and all compounds had IR, NMR and MS consistent with the assigned structure. The elemental analyses of **6-14** were found to be within ±0.4% of the calculated values. Spectral data for **6-13** are given in the footnotes.

cycloaddition. When the temperature was raised to 110 °C using toluene as the solvent and Et_3N as the base, the desired [2+2] adduct was obtained as a chromatographically separable mixture of the diastereomeric β-lactams **6** (42%) and **7** (39%). These adducts were identified as the trans-β-lactams **6** and **7** based on the ^{1}H-coupling constants.[3] In a paper published after the completion of this work, it has been reported that [2+2] cycloaddition of unactivated racemic acid chlorides proceeds smoothly in toluene and Bu_3N at reflux to give trans-adduct as the major product.[4] Interestingly, the asymmetric center in the acid chloride component did not favour the selective formation of either **6** or **7** in the cycloaddition. Attempted cycloaddition of the acid chloride derived from the acyloxazolidinone **3** under different conditions gave only traces of the desired cycloadduct.

Although the relative stereochemistry of the substituents on the β-lactam ring could be determined from the ^{1}H-coupling constants (observed J=2.2 Hz for **6** and **7**; reported J_{trans}=2-3 Hz and J_{cis}=5-6 Hz), the absolute stereochemistry of **6** and **7** had to be deduced from that of **8** and **9**, the products derived from the rearrangement of **6** and **7**. Treating **6** and **7** separately with concentrated HCl and MeOH at 65 °C rearranged the β-lactams to the corresponding γ-lactams, **8** and **9** respectively.[5] The relative stereochemistry of the substituents on the γ-lactams was determined from the ^{1}H-NMR difference NOE studies. In the case of **8**, NOE enhancements were observed between H_3 and H_4 and H_4 and H_5, indicating that they are cis- to each other. NOE enhancement was observed between H_4 and H_5 in the case of **9** indicating that they are cis- to each other. Irradiation at the frequency of H_3 enhanced only the protons of the aromatic ring at C_3 of **9** indicating that H_3 is trans- to H_4. The stereogenic center at the 3-position of **8** and **9** is unlikely to be epimerized under the acidic conditions of the rearrangement. Thus, the absolute configuration of this center together with the information on relative stereochemistry helped us assign the absolute configuration of the β- and γ-lactams. Hydrolysis of the methyl ester of **8** and **9** with aqueous HCl in dioxane at reflux gave the pyrrolidinones **10** (contaminated with minor inseparable diastereomers) and **11**.[6] NOE enhancement between H_4 and H_5, and not between and H_3 and H_4, of **10** was oberved. This information together with the unlikely possibility of epimerization of H_5 under the reaction conditions led us to propose the shown stereochemistry for **10**. The difference NOE pattern for **11** was similar to that of **9** and hence the shown stereochemistry. The all cis-diastereomer (**8**) has a high propensity to undergo epimerization even under the aqueous acidic conditions to give **10**, while **9** does not. Saponification of **8** and **9**, on the other hand, gave the most stable diastereomers **12** and **13**.[7] The difference NOE pattern of both **12** and **13** showed enhancement between H_4 and the aromatic protons and none between H_4 and either H_3 or H_5 indicating that H_4 is trans- to H_3 and H_5 in these compounds. Since the chiral center at the 5-position of **8** and **9** is unlikely to epimerize under the basic conditions while those at 3- and 4-position are likely to do so, the absolute stereochemistry of **12** and **13** were assigned as shown. Thus, one can prepare enantiomeric pyrrolidinones such as **12** and **13** starting from the same enantiomerically pure acid chloride. It should be noted that if one were to obtain the corresponding cis-substituted β-lactam using a different method, one could rearrange (no need to epimerize) them to the desired pyrrolidinones, **12** and **13**. Many analogs of **12** and **13** have been prepared using this strategy. Some of the analogs of **12** are shown in Scheme II. The analogs listed here have been prepared using imines with the propoxyethyl, benzyl, 3,4-dimethoxybenzyl, trimethylsilylethyl and allyl substituents. The last two groups listed were designed to be protecting groups for the nitrogen atom so that one can replace them with other substituents at the end of the synthesis. Compound **12e** was obtained by hydrogenation of **12b**. Treatment of the methyl ester of racemic **13** with borane in THF at reflux followed by ester hydrolysis gave the corresponding pyrrolidine **14** in 47% unoptimized yield.



(±)13 (±)14 (47 %)

In summary, we have prepared enantiomerically pure pyrrolidinones using a [2+2] cycloaddition of enantiomerically pure acid chlorides with a variety of imines and rearranging and saponifying the resulting β-lactams. These pyrrolidinones were found to be potent endothelin receptor antagonists, details of which will be described in a future publication.

Acknowledgement: We thank Mr. Philip Keyes and Karl Gunderson for performing the difference NOE studies and helping to assign the stereochemistry of the compounds.

References and Notes

1. Warner, T. D. *Cardiovasc. Drug Rev.* **1994**, 12, 105-122.
2. Georg, G. I., Ed.; *The Organic Chemistry of β-Lactams*, Verlag Chemie, New York, 1992, chapter 6, p. 295-368.
3. **6**: IR (CH_2Cl_2) 1746, 1614, 1520, 1495, 1243, 1044 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.0 (d, J=8.7 Hz, 2H), 6.82 (d, J=8.7 Hz, 2H), 6.78 (m, 3H), 5.92 (s, 2H), 4.30 (d, J=2.2 Hz, H_4), 3.94 (d, J=8.5 Hz, H_x), 3.77 (s, 3H), 3.67 (s, 3H), 2.7-3.6 (m, 7H), 1.50 (sextet, J=7.4 Hz, 2H), 0.86 (t, J=7.4 Hz). **7**: IR (CH_2Cl_2) 1751, 1616, 1514, 11495, 1244, 1043 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.17 (d, J=8.7 Hz, 2H), 6.87 (d, J=8.7 Hz, 2H), 6.74 (m, 3H), 5.91 (s, 2H), 4.49 (d, J=2.2 Hz, H_4), 3.96 (d, J=8.9 Hz, H_x), 3.79 (s, 3H), 3.65 (s, 3H), 3.6-2.9 (m, 7H), 1.52 (sextet, J=7.4 Hz, 2H), 0.87 (t, J=7.4 Hz, 3H).
4. Browne, M.; Burnett, D. A.; Caplen, M. A.; Chen, L.-Y.; Clader, J. W.; Domalski, M.; Dugar, S.; Pushpavanam, P.; Sher, R.; Vaccaro, W.; Viziano, M.; Zhao, H. *Tetrahedron Lett.* **1995**, 36, 2555-2558.
5. **8**: IR (CH_2Cl_2) 1735, 1698, 1618, 1520, 1507, 1242, 1178, 1041 cm^{-1}; ^{1}H-NMR (CD_3OD) δ 7.21 (d, J=8.7 Hz, 2H), 7.0-6.7 (m, 5H), 5.88 (s, 2H), 5.13 (d, J=6.6 Hz, H_5), 4.2 (d, J=7.9 Hz, H_3), 4.0 (m, 1H), 3.79 (s, 3H), 3.6-3.0 (m, 6H), 3.07 (s, 3H), 1.56 (sextet, J=7.4 Hz, 2H), 0.87 (t, J=7.4 Hz, 3H). **9**: IR (CH_2Cl_2) 1743, 1694, 1614, 1520, 1506, 1242, 1181, 1039 cm^{-1}; ^{1}H-NMR (CD_3OD) δ 7.08 (d, J=8.7 Hz, 2H), 6.91 (d, J=8.7 Hz, 2H), 6.73 (m, 3H), 5.90 (s, 2H), 5.2 (d, J=9.2 Hz, H_5), 4.26 (d, J=10.3 Hz, H_3), 3.86 (m, 1H), 3.77 (s, 3H), 3.67 (dd, J=10.3, 9.1 Hz, H_4), 3.55-3.3 (m, 4H), 3.29, (s, 3H), 2.85 (m, 1H), 1.59 (sextet, J=7.4 Hz, 2H), 0.93 (t, J=7.4 Hz, 3H).
6. **10**: IR (CH_2Cl_2) 1754, 1699, 1612, 1513, 1421, 1240, 1116, 1040 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.10 (d, J=8.7 Hz, 2H), 6.85 (d, J=8.7 Hz, 2H), 6.75 (m, 3H), 5.93 (s, 2H), 5.18 (d, J=9.0 Hz, H_5), 4.25 (d, J=10.9 Hz, H_3), 4.0 (m, 1H), 3.8 (s, 3H), 3.55-3.0 (m, 5H), 2.81 (m, 1H), 1.8 (br, 1H), 1.65 (sextet, J=7.4 Hz, 2H), 0.96 (t, J=7.4 Hz, 3H). **11**: IR (CH_2Cl_2) 1754, 1699, 1513, 1444, 1240, 1110, 1040 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.07 (d, J=8.7 Hz, 2H), 6.83 (d, J=8.7 Hz, 2H), 6.75 (m, 3H), 5.91 (s, 2H), 5.15 (d, J=9.1 Hz, H_5), 4.21 (d, J=10.8 Hz, H_3), 3.98 (m, 1H), 3.79 (s, 3H), 3.65-3.25 (m, 5H), 2.78 (m, 1H), 1.59 (sextet, J=7.4 Hz, 2H), 0.95 (t, J=7.4 Hz, 3H).
7 **12a**: IR (CH_2Cl_2) 1750, 1694, 1612, 1514, 1421, 1240, 1115, 1040 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.22 (d, J=8.7 Hz, 2H), 6.94 (d, J=8.7 Hz, 2H), 6.77 (m, 3H), 5.95 (s, 2H), 4.95 (d, J=8.3 Hz, H_5), 4.02 (d, J=10.3 Hz, H_3), 3.83 (s, 3H), 3.6-3.2 (m, 5H), 3.10 (dd, J=10.3, 8.3 Hz, H_4), 2.8 (m, 1H), 2.1 (br, 1H), 1.58 (sextet, J=7.4 Hz, 2H), 0.90 (t, J=7.4 Hz, 3H). **13**: IR (CH_2Cl_2)1750, 1694, 1612, 1514, 1421, 1239, 1115, 1040 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 7.24 (d, J=8.7 Hz, 2H), 6.93 (d, J=8.7 Hz, 2H), 6.78 (m, 3H), 5.95 (s, 2H), 4.95 (d, J=8.3 Hz, H_5), 4.02 (d, J=10.3 Hz, H_3), 3.82 (s, 3H), 3.55-3.25 (m, 5H), 3.1 (dd, J=10.3, 8.3 Hz, H_4), 2.78 (m, 3H), 1.75 (br, 1H), 1.57 (sextet, J=7.4 Hz, 2H), 0.91 (t, J=7.4 Hz, 3H).

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