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TOTAL SYNTHESIS OF THE ANGIOTENSIN-CONVERTING ENZYME INHIBITOR A58365A: ON THE USE OF PYROGLUTAMATE AS A CHIRAL EDUCT

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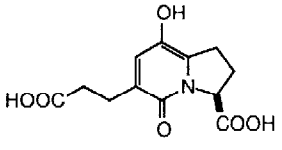
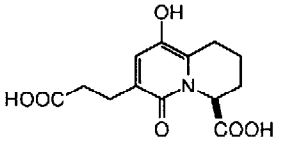
Abstract. Annulation of the known vinylogous urethane **4** with α-methyleneglutaric anhydride (**3**) is the key reaction in a seven step enantiospecific synthesis of the ACE inhibitor, A58365A (**1**).

The importance of angiotensin-converting enzyme (ACE) inhibitors in the treatment of hypertension has led to widespread interest in the design and discovery of new structural types with this capability.[1] Recently, workers at Eli Lilly & Co. have utilized a newly developed screening method to detect the presence of ACE inhibitors in the culture filtrate of *Streptomyces chromofuscus* NRRL 15098.[2,3] Isolation and characterization of the active constituents led to the assignment of a novel hydroxy-indolizidine structure for A58365A (**1**) and a homologous hydroxy-quinolizidine structure for A58365B (**2**).[4,5] Compounds **1** and **2** were found to be effective inhibitors of ACE at nanomolar concentrations. As part of a program aimed at evaluating the structural parameters necessary for their activity, the syntheses of **1** and **2** were undertaken. In this Letter we report the first total synthesis of **1**.



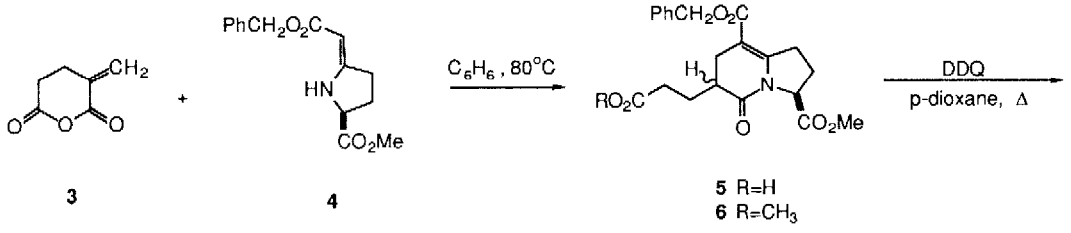
1 A58365A



2 A58365B

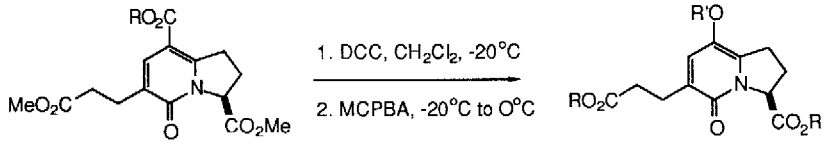
An important goal was that the final products emerge in enantiomerically homogeneous form in the natural L-configuration. We hoped that this objective might be accomplished for compound **1** by starting with L-pyroglutamate as the chiral educt. The four step conversion of commercially available L-pyroglutamic acid to vinylogous urethane **4** was carried out as previously described in the racemic series.[6] The annulation of **4** with α-methyleneglutaric anhydride (**3**)[7] proceeded in refluxing benzene to form hexahydroindolizidine **5** in 95% yield as a ca. 2:1 mixture of diastereomers.[8] Esterification (diazomethane) of **5** gave dimethylester **6** in 98% yield. A mixture of **6** and two equivalents of 2,3-dicyano-5,6-dichloroquinone (DDQ) in *p*-dioxane was allowed to reflux for 12h. A 41% yield of pyridone **7** was obtained. Stirring **7** in methanol over palladium/carbon in an atmosphere

of hydrogen provided monocarboxylic acid **8** in 96% yield. Carboxy-inversion[9] of **8** by successive treatment with dicyclohexylcarbodiimide (DCC) and meta-chloroperoxybenzoic acid (MCPBA) followed by silica gel chromatography (ethyl acetate/methanol) furnished A58365A-dimethyl ester (**9**), A58365A-dimethyl ester meta-chlorobenzoate (**10**) and trimethyl-A58365A (**11**) in 15, 21, and 5% yield respectively .[10] The formation of **11** is apparently due to the presence of acidic methanol on the column. Compounds **9** and **10** were converted to dibenzyl ester (**12**) (benzyl alcohol, toluene, Otera's catalyst,[11] reflux) to facilitate purification. Catalytic hydrogenation (palladium/carbon) of **12** in methanol afforded a 96% yield of pure A58365A (**1**) as a white foam which was identical (^{1}H NMR, IR, MS, optical rotation $[\alpha]_D^{25}$ -190.5° (H_2O,c 0.1)) with an authentic sample of natural A58365A (**1**).[12]



3 **4**

5 R=H
6 R=CH_3



7 R=CH_2Ph
8 R=H

9 R=Me, R'=H
10 R=Me, R'=*m*-ClC_6H_4
11 R=R'=Me
12 R=CH_2Ph, R'=H
1 R=R'=H

In summary, the synthesis of A58365A (**1**) in 11 steps starting from L-pyroglutamic acid has been achieved. This effort underscores the flexibility provided through the use of the vinylogous urethane (**4**) for condensation with the glutarate (**3**). The carboalkoxyl group mediates formation of the pyridone ring and serves as a latent hydroxyl group (by carboxy-inversion). Thus, a new route to 5-hydroxy-2-pyridones has been developed which should be amenable to a synthesis of A58365B (**2**).There are clearly some significant yield problems in this first generation synthesis. Nonetheless we are confident that the concise new route to enantiomerically homogeneous fused pyridones described here can be improved upon and will enjoy application. Efforts in this direction will be described in due course.

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Notes and References

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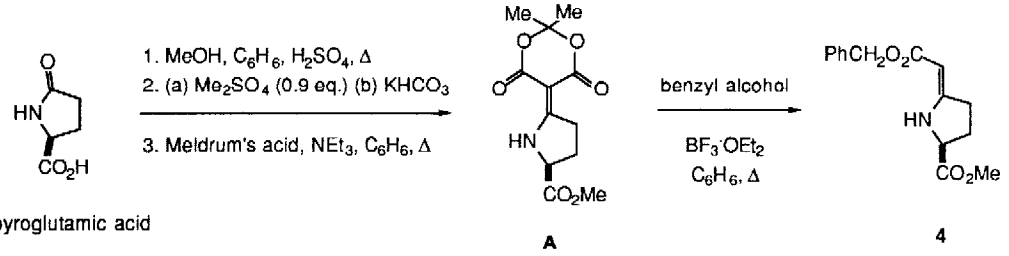
6. This compound was prepared as described for racemic **4** except starting with L-pyroglutamic acid instead of D,L-pyroglutamic acid: Nagasaka, J.; Tsukada, A.; Hamaguchi, F. *Heterocycles* **1986**, *24*, 2015.



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8. For some previous examples of the reaction of vinylogous urethanes with α,β-unsaturated carbonyl compounds leading to pyridone rings see: (a) Brunerie, P.; Celerier, J.-P.; Huche, M.; Lhommet, G. *Synthesis* **1985**, 735. (b) Nagasaka, T.; Inoue, H.; Hamaguchi, F. *Heterocycles* **1983**, *20*, 1099. (c) Nagasaka, J.; Inoue, H.; Ichimura, M.; Hamaguchi, F. *Synthesis* **1982**, 848. (d) Volkmann, R.; Danishefsky, S.; Eggler, J.; Solomon, D. M. *J. Am Chem. Soc.* **1971**, *90*, 7349. (e) Danishefsky, S.; Etheredge, S. J.; Volkmann, R.; Eggler, J.; Quick, J. *J. Am. Chem. Soc.* **1971**, *93*, 5575.
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10. Compounds **9** and **11** have been derived from A58365A (**1**) by workers at Eli Lilly & Co. (see ref. 5).

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12. A sample of natural A58365 (**1**) ($[\alpha]_D^{25}$ -191.0° (H_2O, c 0.2) was provided by Dr. Jon. S. Mynderse of Eli Lilly & Co.

13. All new compounds were characterized by spectroscopic methods, combustion analysis and/or high resolution mass spectroscospy, and melting point (where appropriate). **A**: white solid (mp 121-123°C); $[\alpha]_D^{25}$-22.8° (CH_2Cl_2, c 1.0). **4**: white solid (mp 53-54°C); $[\alpha]_D^{25}$ -114.8° (CH_2Cl_2, c 1.1), other data for **A** and **4** were in agreement with the literature values reported for the corresponding racemates. **5**: white foam; ca 2:1 mixture of diastereomers. **6**: colorless oil; ca 2:1 mixture of diastereomers. Anal. Calcd for $C_{22}H_{25}NO_7$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.67; H, 5.24; N, 9.92. **7**: colorless oil; $[\alpha]_D^{25}$ -103.1° (CH_2Cl_2, c 0.9), IR ν_{max} (CH_2Cl_2) 1745, 1710, 1655, 1610, 1560 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.85 (1H, s, C=CH), 7.34-7.43 (5H, m, ArH), 5.29 (2H, s, OCH_2) 5.13 (dd, J=9.8, 5.1 Hz, 1H, NCH), 3.79 (s, 3H, OCH_3), 3.69-3.38 (m, 2H, CH_2), 3.64 (s, 3H, OCH_3), 2.91-2.74 (m, 2H, CH_2), 2.64 (t, J=7.1 Hz, 2H, CH_2), 2.58-2.41 and 2.36-2.24 (m, 2H, $CHCH_2$). **8**: white foam, $[\alpha]_D^{25}$ -118.5° (CH_2Cl_2, c 2.5); IR ν_{max} (CH_2Cl_2) 3400-2400, 1740, 1685, 1645, 1560, 1435, 1360 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.86 (s, 1H, C=CH), 5.16 (dd, J=9.7, 3.4 Hz, 1H, NCH), 3.81 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.63-3.55 (m, 2H, CH_2), 2.95-2.85 (m, 2H, CH_2), 2.66 (t, J=7.2 Hz, 2H, CH_2), 2.53-2.33 (m, 2H, CH_2). **9**: white foam; $[\alpha]_D^{25}$-184.8° (CH_2Cl_2, c 1.5), IR ν_{max} (CH_2Cl_2) 3500-2500, 1740, 1670, 1550, 1440, 1410, 1365 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.20 (s,1H, C=CH), 5.13 (dd, J=9.5, 3.3 Hz, 1H, NCH), 3.76 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.12 (br t, J=8.2 Hz, 2H, CH_2), 2.91-2.74 (m, 2H, CH_2), 2.63 (t, J=6.7 Hz, 2H, CH_2), 2.62-2.44 and 2.39-2.26 (m, 2H, $CHCH_2$) **10**: colorless oil; $[\alpha]_D^{25}$-106.8° (CH_2Cl_2, c 1.0), IR ν_{max} (CH_2Cl_2) 1740, 1665, 1600, 1570, 1440, 1250, 1210 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 8.12 (apparent t, J=1.7 Hz, 1H, ArH), 8.03 (doublet of m, J=7.7 Hz, 1H, ArH), 7.63 (doublet of m, J=8.0 Hz, 1H, ArH). 7.47 (apparent t, J=7.9 Hz, 1H, ArH), 7.25 (s, 1H, C=CH), 5.14 (dd, J=9.4, 3.6 Hz, 1H, NCH), 3.81 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.22-3.00 (m, 2H, CH_2), 2.97-2.79 (m, 2H, CH_2), 2.68 (t, J=7.1 Hz, CH_2), 2.63-2.49 and 2.39-2.28 (m, 2H, $CHCH_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.4, 170.3, 163.3, 160.0, 139.4, 134.9, 134.6, 134.0, 130.4, 130.2, 130.0, 129.8, 128.3, 128.2, 62.1, 52.8, 51.5, 32.2, 28.1, 26.4, 26.1. **11**: colorless oil, $[\alpha]_D^{25}$ -165.0° (CH_2Cl_2, c 0.4), IR ν_{max} (CH_2Cl_2) 3080, 3000, 1740, 1675, 1600, 1450, 1270, 1220 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 7.28 (s, 1H, C=CH), 5.12 (dd, J=9.4, 3.5 Hz, 1H,NCH), 3.80 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.12 (dd, J=9.1, 6.3 Hz, 3H, OCH_3), 2.97-2.76 (m, 2H, CH_2), 2.67 (t, J=7.4 Hz) 2.60-2.45 and 2.37-2.25 (m, 2H, $CHCH_2$). **12**: white foam, $[\alpha]_D^{25}$-175° (CH_2Cl_2, c 0.4), IR (CH_2Cl_2 soln cell): 3500-2500, 1740, 1670, 1585, 1550, 1420, 1270, 1190 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.32 (m, 10H, ArH), 7.04 (s, 1H, C=CH), 5.48 (br s, 1H, OH), 5.19 (AB_q, J_{AB}=8.5 Hz, Δν=24.0 Hz,2H, OCH_2), 5.13 (dd, obscured by AB_q, 1H, NCH), 5.09 (s, 2H, OCH_2), 3.04 (br t, J=7.4 Hz, 2H, CH_2), 2.90-2.75 (m, 2H, CH_2), 2.70-2.64 (m, 1H, CH_2), 2.54-2.38 and 2.30-2.28 (m, 2H, $CHCH_2$).

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