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STEREOSELECTIVE SYNTHESIS OF A C-TERMINAL COMPONENT OF RENIN INHIBITORS VIA ITERATIVE HOMOLOGATION

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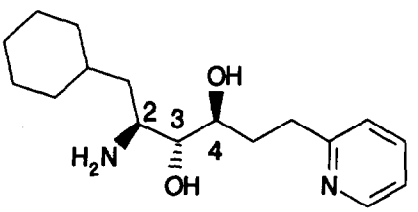
Abstract: A stereoselective synthesis of an aminodiol derivative (dipeptide mimic) has been developed via iterative homologation of protected cyclohexylalaninal (Dondoni reaction).

Considerable efforts have been made since the early 1980's to develop orally active renin inhibitors[1] as antihypertensive drugs. Although many potent inhibitors have been described, their limited oral resorption and short duration of action have prevented the development of therapeutically useful agents. One approach that has been applied towards solving these problems has been to design compounds with increased hydrophilicity by incorporation of polar groups[2] at the C-termini of these inhibitors. The search for such compounds led to aminodiols as C-terminal components[3].

During the course of our investigations on renin inhibitors[4] we have learned that incorporation of a pyridine into a C-terminal aminohydroxy derivative furnishes potent inhibitors.

Extension to aminodiol derivatives with C-terminal **1** provided compounds showing improved bioavailibility[5].



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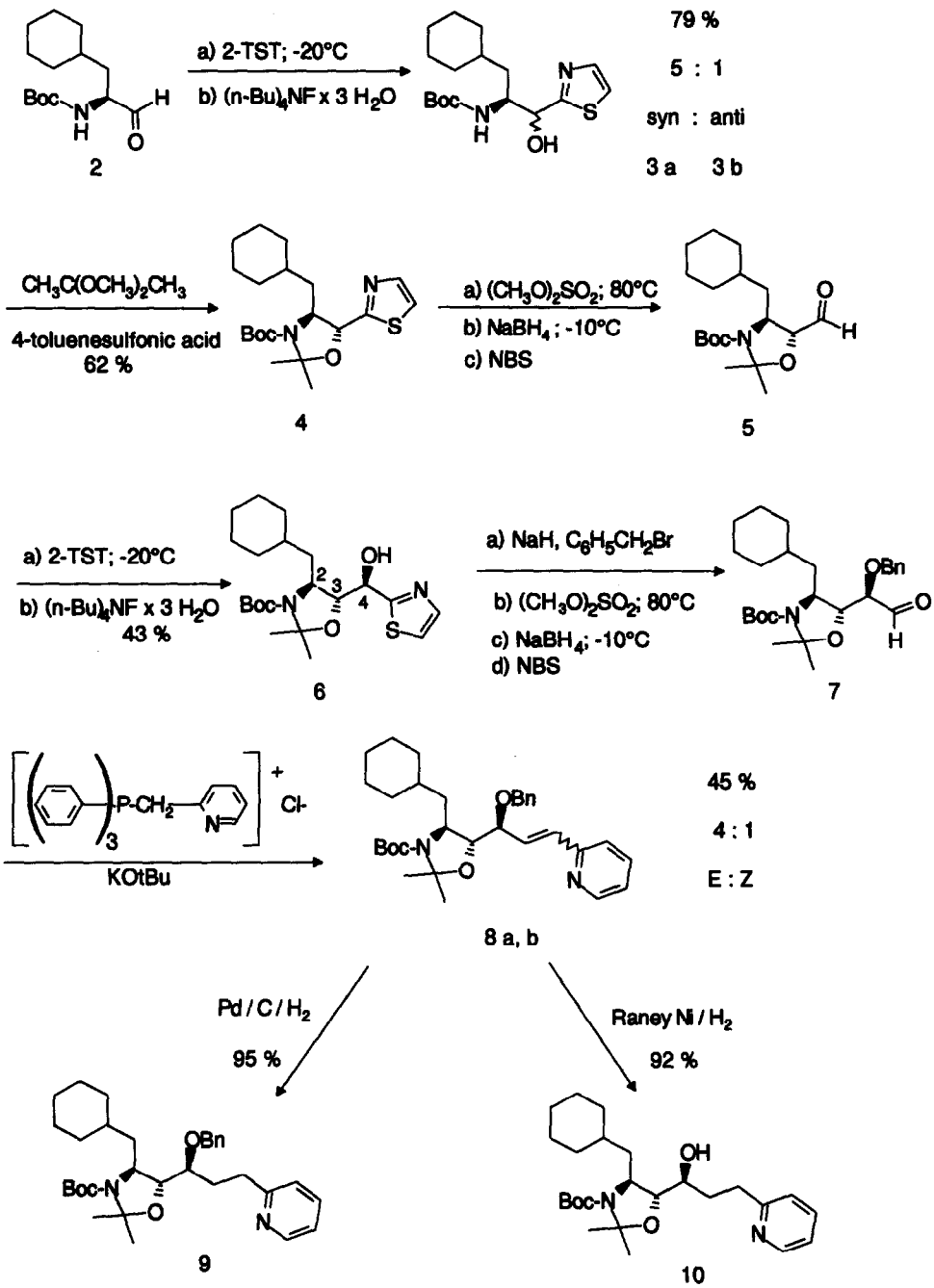
Herein, we report a stereoselective synthesis of protected **1** from cyclohexylalaninal **2**[6] via iterative homologation (Dondoni reaction)[7].

Hence, treatment of aldehyde **2** with 2-trimethylsilylthiazole (2-TST) according to the protocol, published by Dondoni and coworkers, furnished an inseparable 5:1 mixture[8] of syn and anti adduct (79 % yield).

Surprisingly, reaction with 2,2-dimethoxypropane containing a catalytic amount of 4-toluenesulfonic acid gave only acetonide **4**, which turned out to be the product of the syn adduct **3 a**, whereas the anti adduct **3 b** remained unchanged.



This allowed separation of **4** from **3 b** by flash column chromatography [62 % **4**, m.p. = 89-91°C; and 15 % **3 b** (oil), which contained a few percent of **3 a**].

In order to avoid heavy metal salts and low boiling alkylating reagents during the reaction sequence, the liberation of the formyl group from the thiazole moiety[7] was slightly modified.

Thus, successive treatment of **4** with dimethylsulfate[9], instead of methyliodide, followed by sodium borohydride and N-bromosuccinimide (NBS), instead of mercuric chloride, afforded aldehyde **5**. Repetition of the addition of 2-TST to the crude aldehyde **5** yielded the homologoues thiazole derivative **6** (43 % from **4**; m.p. = 176-178°C) with anti configuration of the vicinal groups regarding position 3 and 4 (>95 % diastereomeric exess).

O-benzylation with benzylbromide and sodiumhydride followed by unmasking the formylgroup generated aldehyde **7**. Wittig reaction of crude **7** with picolyltriphenylphosphonium chloride using potassium t-butoxide as base provided **8 a, b** as a readily separable (flash column chromatography) mixture of E/Z isomers (4:1; 45 % from **6**).

Hydrogenation of either the double bond with palladium on charcoal or concomitant debenzylation using Raney nickel gave **9** (95 % yield) or **10** (92 % yield). The stereochemistry of **9** and **10** was assumed to be 2S,3R,4S in accordance with Dondoni's methodology and biological activity[5].

In conclusion, we have developed a stereoselective synthesis of an aminodiol derivative as C-terminal component for renin inhibitors via iterative homologation of protected cyclohexylalaninal. A full paper covering in vitro and in vivo activity of corresponding renin inhibitors is in preparation.

Reference and Notes:

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5. A full paper covering in vitro and in vivo activity of corresponding renin inhibitors is in preparation.
6. Luly, J.R:, Hsiao, C.N., Ba-Maung, N., Plattner, J.J., *J. Org. Chem.* 1988, 53, 6109.
7. Dondoni, A., Fantin, G., Fogangnolo, M., Pedrini, P., *J. Org. Chem.* 1990, 55, 1439.
8. Determined by ^{1}H-NMR (270 MHz). - All new compounds were characterized by ^{1}H-NMR (270 MHz) and mass spectrometry. - Satisfactory microanalytical data were obtained, exept for **5** and **7**, which were used for the following reaction without purification.

9. Typical experimental procedure: 12.5 g (32.8 mmol) 4 were dissolved in 70 ml of acetonitrile. 3.9 ml (1.25 equivalents) of dimethyl sulfate were added and the mixture was refluxed for 7 hours. After standing overnight at RT, it was concentrated to dryness. The solid residue was dissolved in 150 ml of methanol. 4.3 g (13 mmol) of sodium borohydride were added at -10°C. After subsequently stirring at 0°C for 30 min, 40 ml of acetone were added. After concentrating, the residue was taken up in 500 ml of ethyl acetate and washed with 200 ml of sat. NaCl solution. After drying with Na_2SO_4, the solution was concentrated and the crude product was subjected to coarse purification by filtration through a little silica gel, 14 g being obtained. This product was redissolved in 250 ml of acetone/H_2O (95:5) and 16.5 g (92.7 mmol) NBS were added with cooling (< 25°C) in the course of 10 min. After the end of the addition, the mixture was strongly cooled and treated in small portions with 500 ml of sat. Na_2SO_3 solution (< 25°C, strongly exothermic!). After diluting with 500 ml of H_2O, the mixture was extracted 3 x with diethyl ether. The combined extracts were washed twice with H_2O and once with saturated NaCl solution, dried with Na_2SO_4 and concentrated. 5.9 g of aldehyde 5 were obtained, which were dissolved in 80 ml of CH_2Cl_2 and cooled to -40°C. 5.88 g (37.4 mmol) of trimethylsilylthiazole were injected and the mixture was slowly warmed to RT overnight. After concentrating, the residue was taken up in 80 ml of tetrahydrofuran and treated with 11.8 g (37.4 mmol) of tetrabutylammonium fluoride trihydrate. After 2 hours, the mixture was diluted with ethyl acetate, washed twice with H_2O and once with sat. NaCl solution, dried with Na_2SO_4 and concentrated. The crude product was recrystallized from acetonitrile to give **6** (5.8 g, 43 %).

10. Selected ^{1}H-NMR (270 MHz, $CDCl_3$) data:
    - **3 a:** d = 0.8-1.9 (m, 13H), d = 1.38 (s, 9H), 4.0 (m, 1H), 4.95 (brm, 2H), 5.0 (d, J = 3.8 Hz), 7.3 (d, J = 3.8 Hz, 1H), 7.72 (d, J = 3.8 Hz, 1H)
    - **3 b:** d = 0.75-1.9 (m, 13H), d = 1.45 (s, 9H), 4.15 (m, 1H), 4.65 (d, J = 7.5 Hz, 1 H), 5.0 (brs, 1H), 5.05 (brs, 1H), 7.32 (d, J = 3.8 Hz, 1H), 7.75 (d, J = 4.0 Hz, 1H)
    - **4:** d = 0.85-1.9 (m, 13H), 1.48 (s, 9H), 1.55 (s, 3H), 1.6 (s, 3H), 4.52 (ddd, J = 10.0 Hz, J = 3.5 Hz, J = 3.5 Hz, 1H), 5.12 (d, J = 3.5 Hz, 1H), 7.32 (d, J = 3.8 Hz, 1H), 7.75 (d, J = 3.8 Hz, 1H)
    - **6:** d = 0.8-1.9 (m, 13H), 1.5 (s, 9H), 1.57 (s, 3H), 1.68 (s, 3H), 3.98 (d, J = 8.0 Hz, 1H), 4.3 (brd, J = 10.0 Hz, 1H), 4.88 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 3.8 Hz, 1H), 7.77 (d, J = 3.8 Hz, 1H)
    - **8 a:** d = 0.8-1.9 (m, 13H), 1.48 (s, 9H), 1.52 (s, 3H), 1.6 (s, 3H), 3.9 (brs, 1H), 4.0 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 4.72 (d, J = 12.0 Hz, 1H), 6.65 (dd, J = 16.0 Hz, J = 7.5 Hz, 1H), 6.78 (d, J = 16.0 Hz, 1H), 7.15 (ddd, J = 6.0 Hz, J = 4.3 Hz, J = 1,3 Hz), 7.22-7.4 (m, 6H), 7.65 (ddd, J = 8.8 Hz, J = 8.8 Hz, J = 1.3 Hz), 8.58 (dd, J = 4.3 Hz, J = 1.3 Hz)
    - **8 b:** d = 0.8-1.9 (m, 19H), 1.48 (s, 9H), 3.95 (d, J = 8.0 Hz, 1H), 4.08 (brm, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 5.6 (brs, 1H), 5.8 (dd, J = 12.0 Hz, J = 10.0 Hz, 1H), 6.73 (d, J = 12.0 Hz, 1H), 7.1 (ddd, J = 8.0 Hz, J = 4.3 Hz, J = 1.3 Hz, 1H), 7.2-7.35 (m, 6H), 7.62 (ddd, J = 8.8 Hz, J = 8.8 Hz, J = 1.3 Hz, 1H), 8.52 (dd, J = 4.3 Hz, J = 1.3 Hz)
    - **9:** d = 0.8-1.9 (m, 19H), 1.48 (s, 9H), 2.1 (m, 1H), 2.28 (m, 1H), 2.98 (t, J = 8.3 Hz, 2H), 3.5 (m, 1H), 3.85 (d, J = 8.3 Hz, 1H), 3.95 (m, 1H), 4.5 (d, J = 12.0 Hz, 1H), 4.7 (d, J = 12.0 Hz, 1H), 7.1 (m, 2H), 7.3 (m, 5H), 7.58 (ddd, J = 8.1 Hz, J = 8.1 Hz, J = 1.3 Hz, 1H), 8.52 (d, J = 4.3 Hz, 1H)
    - **10:** d = 0.85-2.0 (m, 22H), 1.48 (s, 9H), 2.4 (brt, 1H), 3.0 (m, 1H), 3.13 (m, 1H), 3.6 (m, 2H), 4.15 (d, J = 10.0 Hz, 1H), 7.13 (ddd, J = 8.0 Hz, J = 4.3 Hz, J = 1.3 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.63 (ddd, J = 8.2 Hz, J = 8.2 Hz, J = 1.3 Hz), 8.48 (dd, J = 8.2 Hz, J = 1.3 Hz, 1H).

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