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The Convergent Synthesis of CI-981, an Optically Active, Highly Potent, Tissue Selective Inhibitor of HMG-CoA Reductase

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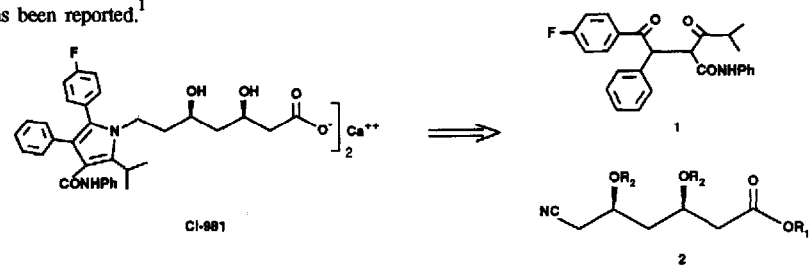
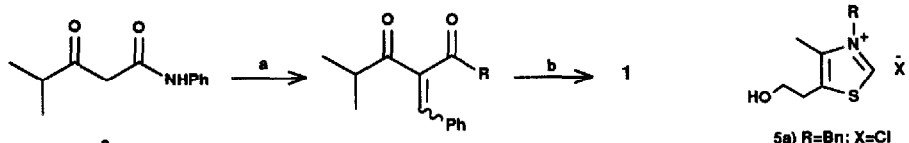
Abstract: *The synthesis of CI-981 is described starting from isobutyrylacetanilide (3) and the key chiral intermediate 2.*

CI-981, a potent and tissue selective inhibitor of HMG-CoA Reductase, is currently undergoing clinical trials and could prove to be an important addition to therapy for the treatment of hypocholesterolemia and the prevention of atherosclerosis.[1,2]

Economical, large scale syntheses of enantiomerically pure compounds as complex as CI-981 require, if possible, a convergent route.[3] A convergent synthesis of CI-981 required the preparation of two key intermediates; (1) and (2). However, a Paal-Knorr synthesis of such a complex pyrrole was by no means assured. The preparation of the 7-carbon side-chain acid derivative (2) has been reported.[1]



Diketone 1 was prepared in two steps from commercially available isobutyrylacetanilide (3). The addition of p-fluorobenzaldehyde to the Knoevenagle product **4a** was carried out using the Stetter reaction.[4] The choice of catalyst (5) proved to be the key to the success of this reaction.



3

4a) R=NHPh
4b) R=OMe

5a) R=Bn; X=Cl
5b) R=Et; X=Br
5c) R=Me; X=I

a. β-Alanine, AcOH, Hexane, Δ (85%); b. 5b, EtOH, Δ, then 4a, 4-F-C_6H_4CHO, NEt_3, Δ (80%)

Benzyl thiazolium catalyst (**5a**), which worked very well in the reaction of p-fluorobenzaldehyde with the methyl ester (**4b**)[2a], gave the benzoin condensation product of p-fluorobenzaldehyde as the major product when used in the reaction with **4a**.[5] However, use of either the ethyl (**5b**) or methyl thiazolium catalyst (**5c**) (20 mol. %) under **anhydrous**, concentrated conditions provided the diketone (1) in 80% yield.[6] To our knowledge this is the first example of the extension of the Stetter reaction to carboxamides.

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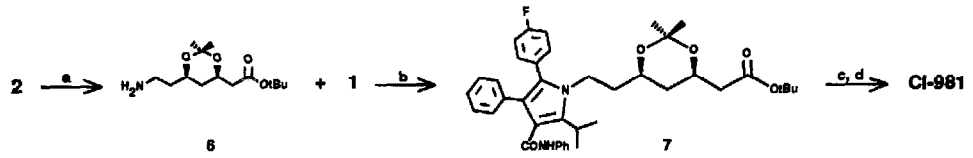
The preparation of the amine, (**6**)[7] from the intermediate nitrile (**2**) was accomplished in high yield using a Molybdenum doped Raney Nickel catalyst[8], under 50 psig hydrogen pressure, in ammonia-methanol at room temperature.

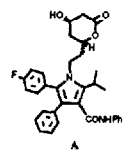


a. Ra-Ni, MeOH, 50 PSIG H_2 (95%); b. $(CH_3)_3CO_2H$, C_7H_8, C_7H_{16},C_4H_8O, Δ (75%); c.HCl, MeOH then NaOH; d. $Ca(OAc)_2$

After extensive optimization of the Paal-Knorr pyrrole formation,[9] conditions using a ternary solvent mixture of toluene-heptane-tetrahydrofuran (1:4:1) and pivalic acid catalysis, provided a 75% yield of **7**.[10] Conversion of **7** to CI-981 was carried out without isolation, by deprotection of the acetal using aqueous HCl/methanol, dilute base hydrolysis of the tert-butyl ester (anchimeric assistance) and treatment of the derived sodium salt with $Ca(OAc)_2$. The hemi-calcium salt, CI-981, was isolated as an amorphous solid in an overall yield of 60% from **2**, with an enantiomeric purity of ≥99.5%.[11,12]

References:

1. Brower, P. L.; Butler, D. E.; Deering, C. F.; Le, T. V.; Millar, A.; Nanninga, T. N.; Roth, B. D., *Previous paper.*
2. a) Roth, B. D.; Blankley, C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.; Sliskovic, D. R.; Stratton, C. D.; Wilson, M. W., *J. Med. Chem.*, **1991**, *34*, 357; b) Bocan, T. M. A.; Ferguson, E.; Shaw, M. K.; BakMueller, S.; Uhlendorf, P. D.; Roth, B. D.; Sliskovic, D. R.; Newton, R. S., *Abstracts of the Xth International Symposium on Drugs Affecting Lipid Metabolism;* Houston TX, Nov 8-11, 1989, p 55. c) Shaw, M. K.; Newton, R. S.; Sliskovic, D. R.; Roth, B. D.; Ferguson, E.; Krause, B. R., *Biochem. Biophys. Res. Comm.*, **1990**, *170*, 726.
3. For alternative approaches to the synthesis of CI-981 see reference 2a and *U.S. Patent* 5,003,080.
4. Stetter, H., *Angew. Chem. Int. Ed. Engl.*, **1976**, *15*, 639; Stetter, H. and Kuhlmann, H., *Org. React.*, **1991**, *40*, 407.
5. It is reported that benzoin formation is a fast reversible reaction that preceeds addition and that use of the appropriate benzoin in place of the aldehyde provides the same product. In our experience, when using p-fluorobenzaldehyde, the use of (**5a**) as the catalyst provided excellent conversion to the benzoin which, even under forcing conditions, could not be converted, in acceptable yield, to the required diketone (**1**). However use of the N-alkyl thiazolium catalysts (**5b** or **c**) provided excellent conversion to **1**, with very little benzoin formation observed (HPLC). Noteably, when using **5b** or **c**, benzoin formation is dramatically increased by dilution of the reaction mixture.
6. ^{1}H NMR spectrum of **1** (200 MHz, in $CDCl_3$) δ 1.03 (d, 3H), 1.22 d, 3H), 2.98 (quin., 1H), 4.91 (d, J=11 Hz, 1H), 5.51 (d, J=11 Hz, 1H), 6.98 - 7.43 (m, 12H), 8.17 (dd, 2H), 9.41 (br s, 1H); m.p. 208-209.5 C. Elemental analysis and FTIR were in accord with structure.
7. ^{1}H NMR spectrum of **6** (200 MHz, in $CDCl_3$) δ 1.0-1.2 (m, 1H), 1.22 (s, 3H), 1.31 (s, 12H), 1.35-1.45 (m, 3H), 2.15 (dd, J=6.2 and 15.1 Hz, 1H), 2.29 (dd, J=7.0 and 15.1 Hz, 1H), 2.66 (t, J=6.6 Hz, 2H), 3.82 (m, 1H), 4.12 (m, 1H); $[\alpha]_D$ +14.3° (c=1, $CHCl_3$). ^{13}C NMR, FTIR and Mass Spectral data were in accord with structure.
8. Available as A7000® from Activated Metals or 3100® from Grace Co.
9. Paal, C., *Ber.*, **1885**, *18*, 367; Knorr, L., *Ber.*, **1885**, *18*, 299.
10. ^{1}H NMR spectrum of **7** (200 MHz, in $CDCl_3$) δ 1.0-1.7 (m, 5H), 1.30 (s, 3H), 1.36 (s, 3H), 1.43 (s, 9H), 1.53 (d, J=7.1 Hz, 6H), 2.23 (dd, J=6.3 and 15.3 Hz, 1H), 2.39 (dd, J=6.3 and 15.3 Hz, 1H), 3.5-3.9 (m, 3H), 4.0-4.2 (m, 2H), 6.8-7.3 (m, 14H); [α] +4.71° (c=1, $CHCl_3$). ^{13}C NMR data was in accord with structure.
11. ^{1}H NMR spectrum of **CI-981** (200 MHz, in $CDCl_3$) δ 1.26 (m, 2H), 1.37 (m, 6H), 1.59 (m, 2H), 2.04 (m, 2H), 3.24-3.96 (m, 5H), 4.80 (brs, 1H), 5.75 (brs, 1H), 7.00-7.22 (m, 12H), 7.52 (d, 2H), 9.82 (s, 1H); $[\alpha]_D$ -7.4° (c=1, DMSO). Elemental analysis, ^{13}C NMR, FTIR and Mass Spectral data were in accord with structure.
12. The enantiomers of CI-981 have not been resolved by chiral HPLC. Conversion to lactone **A** allows determination of enantiomeric purity, by HPLC at 254 nm using a 25 cm Chiralcel OF column, with a mobile phase of hexane-IPA (82:18) at a flow rate of 1 ml/min.



A

^{1}H NMR spectrum of **A** (200 MHz, in $CDCl_3$) δ 1.37 (s, 3H), 1.40 (s, 3H), 1.5-1.8 (m, 4H), 2.25-2.66 (m, 2H), 3.24 (m, 1H), 3.9-4.1 (m, 3H), 4.49 (m, 1H), 5.18 (d, J=3.1 Hz, 1H), 6.9-7.4 (m, 12H), 7.52 (d, J=7.8 Hz, 2H), 9.82 (s, 1H); m.pt. 159.2-160.7°C; $[\alpha]_D$ +26.05° (c=1, $CHCl_3$). Elemental analysis, ^{13}C NMR, and FTIR data were in accord with structure.

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