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A NEW AND STEREOSELECTIVE SYNTHESIS OF THE ANTIBIOTIC ANTICAPSIN.

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Summary : The title compound has been synthesized from 1,3-cyclohexadiene, by a route involving stereo- and regioselective palladium- catalyzed acetoxy chlorination. A key step is the homologation of a nitrile into an α-aminonitrile by the Moinet reaction[11].

Anticapsin, an exotic α-aminoacid 1 produced by Streptomyces griseoplanus[1] and Bacillus subtilis[2], is a powerful irreversible inhibitor of glucosamine synthetase of a wide variety of bacteria and of Candida albicans[3,4]. This molecule is also the C-terminal aminoacid of the dipeptide bacilysin[2], a secondary metabolite from Bacillus subtilis[5] and Bacillus pumilus[4] which possesses important antibacterial and antifungal activities.

We describe here a novel regio- and stereoselective total synthesis[6] of anticapsin.

The well-known intramolecular addition of the amino function to a conjugated cyclohexenone system[6b,7] prevented the use of 2 as intermediate in our strategy (Figure I). Consequently we decided to synthesize the allylic alcohol 7 which has the advantage of being epoxidizable with a high stereoselectivity[8].

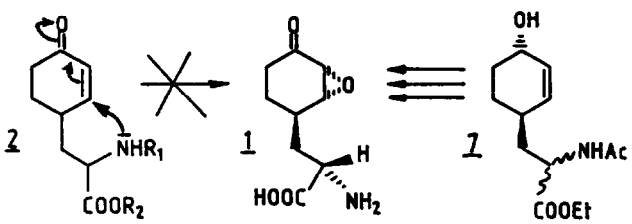

Figure I

Therefore 7 was prepared (Figure II) according to the method developped by Backvall et al.[9], affording 3[17c] in 88 % yield with a very good stereospecificity (>97 % cis). The chloro group of 3 was removed with inversion at carbon, by applying a classical S_N2 reaction[9] with ethylcyanoacetate, to form 4[17c] with a high diastereoselectivity (>98 %) , 95 % yield. 4 was then decarbethoxylated[10], by heating (160°C) with lithium chloride in wet dimethyl sulfoxide into 5[17c] ; 73 % yield. The synthesis of 6, a key intermediate in our strategy was

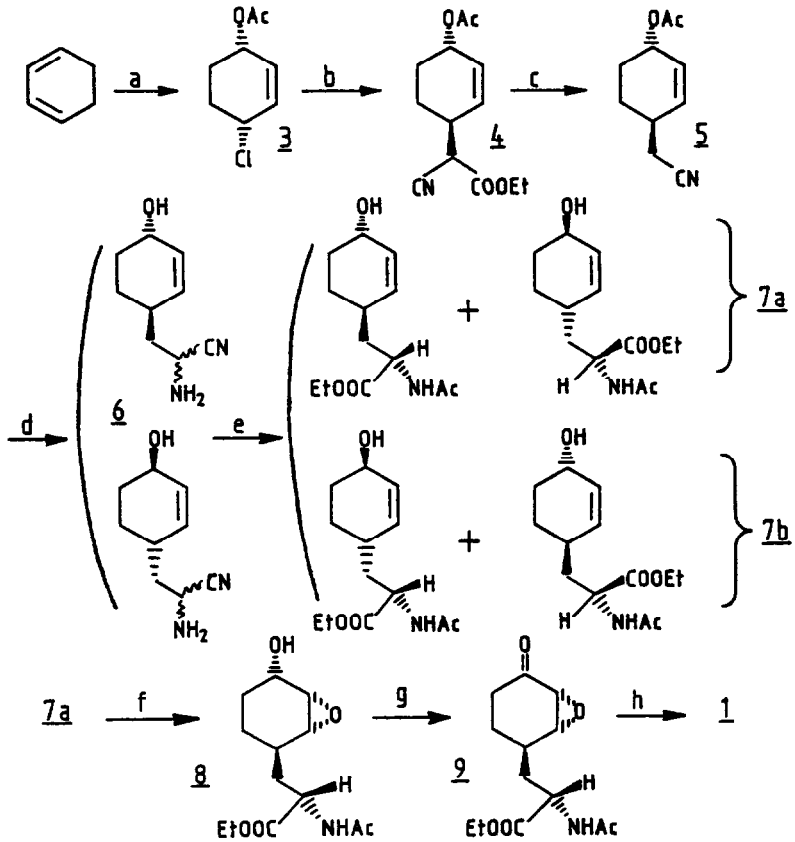

Figure II

For 3, 5, 8, 9 we used the racemic mixtures and related formulae are used for simplicity to denote both the two possible enantiomeric structures.

a : Pd $(OAc)_2$ 5 mol. % ; LiCl 2 mol. equiv. ; Li(OAc) $2H_2O$ 2 mol. equiv. ; p-benzoquinone 2 mol. equiv. , AcOH ; 88 % yield.

b : NaCHCN (COOEt) 1 mol. equiv. ; CH_3CN, reflux, 6 h ; 95 % yield.

c : H_2O 2 mol. equiv. ; LiCl 1 mol. equiv. ; DMSO, 160°C, 0.5 h ; 73 % yield.

d : 1) DIBAH* 3 mol. equiv. , toluene, -10°C, 4 h. 2) TMSCN* 2 mol. equiv. ; R.T., 4 h ; and then CH_3OH, H_2O for the hydrolysis ; 75 % yield.

e : 1) HCl gas, dry C_2H_5OH, R.T., 48 h. 2) Acetic anhydride 3 mol. equiv., dry C_2H_5OH, R.T., 24 h ; 55 % yield.

f : m-CPBA* 1.2 mol. equiv. ; CH_2Cl_2, R.T., 48 h ; 73 % yield.

g : dipyridine - chromium (VI) oxide complex 6 mol. equiv. ; CH_2Cl_2, R.T., 18 h ; 70 % yield

h : 1) 0.1 N aqueous NaOH 1 mol. equiv., 5°C, 15 min. 2) high ratio (1.5:1) porcine kidney acylase : substrate ; pH=7.0, 25°C, 18 h ; 30 % yield.

* DIBAH : diisobutylaluminum hydride. TMSCN : trimethyl silyl cyanide.
m-CPBA : m-chloroperoxybenzoic acid.

performed in two steps by the Moinet reaction[11] (see Figure II). Nitrile 5 was first reduced with diisobutylaluminum hydride into a transcient imine which after a nucleophilic attack by cyanide ion, led to 6[12,13,17c] in a good yield (75 %). Classical conversion of the cyano group into ester with HCl gas in dry ethyl alcohol and protection of the amine with acetic anhydride afforded 7 in 55 % yield. The diastereoisomers 7 were separated into 7a and 7b[17c] respectively by preparative HPLC (RP-18 phase, H_2O-CH_3OH (60·40) as eluant). The more polar isomer 7a (a couple of enantiomers) was submitted to a selective epoxidation[14] with m-chloroperoxybenzoïc acid in dichloromethane[8,13], 73 % yield 8[17c] was subsequently oxidized by dipyridine-chromium (VI) oxide complex into 9[15,17c], 70 % yield. This molecule showed identical ^1H NMR data and mass spectrum to N-acetyl anticapsin ethyl ester prepared[16] from authentic anticapsin.

Conversion of 9 into anticapsin 1 was performed by R.W. Rickards et al. method[6a] : alkaline hydrolysis of the ethyl ester (quantitative) followed by enzymic N-deacetylation with porcine kidney acylase[17a]. Anticapsin was isolated in a pure form (30 % yield) after ultrafiltration[17b] and preparative HPLC (RP-18 phase, H_2O-CH_3OH (99.1) as eluant). It has physicochemical and biological properties identical to those of an authentic sample[18].

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12. The utilisation of diisobutylaluminum hydride allows the removal of the acetate group at this stage and gives the allylic alcohol.

13. The purification was carried out by preparative HPLC (RP-18, H_2O-CH_3OH (60:40)).
14. As a matter of fact, the two couples of enantiomers 7a and 7b were converted into epoxy-ketone form (9) but only 9 from 7a showed identical 1H NMR data to the authentic N-acetylanticapsin ethyl ester.
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    c) ^1H NMR analysis performed on a 300 MHz and 90 MHz Bruker, IR on Perkin-Elmer 1420, mass spectrum on Nermag R10 10C, melting point on Mettler FP61. Preparative HPLC performed on Jobin-Yvon material with Lichroprep^R RP-18 Merck phase and H_2O-CH_3OH as eluant. All synthesized products were analysed by analytical HPLC Kratos material with Lichrosorb^R RP-18 Merck phase and H_2O-CH_3OH as eluant.
    3 and 4 are identical spectroscopic data to those obtained by J.E. Backvall et al.[9].
    5 light yellow oil ; ^1H NMR (90 MHz, $CDCl_3$) δ 5.80 (m, 2H, CH=CH), 5.25 (m, 1H, CHOAc), 2.05 (s, 3H, OAc), 2.70-1.20 (m, 7H) , IR (neat) ν_{max} 3010 (=C-H), 2920 (C-H), 2240 (C≡N), 1730 cm^{-1} (C=O). Mass spectrum, (CI), m/e 197 $(M+NH_4)^+$. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.04 , H, 7.26 ; N, 7.82. Found C, 67.27 , H, 7.20 , N, 7.72.
    6 m.p. 78-79°C ; ^1H NMR (90 MHz, D_2O) δ 5.80 (m, 2H, CH=CH), 4.55 (t, J=5 Hz, 1H, CHCN), 4.20 (m, 1H, CHOD), 2.50-1.25 (m, 7H) , IR (KBr) ν_{max} 3300 (O-H), 3000 (=C-H), 2910 (C-H), 2220 (CN), 1680 (C=C), 1620 cm^{-1} (NH_2). Mass spectrum, (CI), m/e 167 $(M+H)^+$, 184 $(M+NH_4)^+$. Anal. Calcd for $C_9H_{14}N_2O$ · C, 65.06 ; H, 8.43 , N, 16.87. Found : C, 64,72 ; H, 8.35 ; N, 16.80.
    7a and 7b colorless oil ; ^1H NMR (90 MHz, $CDCl_3$) δ 6.75 (br. d, J=8 Hz, 1H, NHAc), 5.70 (m, 2H, CH=CH), 4.65 (m, 1H, CHCOOEt), 4.20 (q, J=7 Hz, 2H, OCH_2CH_3), 4.15 (m, 1H, CHOH), 3.05 (br. s, 1H, OH), 2.00 (s, 3H, $COCH_3$), 2.30-1.10 (m, 7H), 1.25 (t, J=7 Hz, 3H, OCH_2CH_3). IR (CH_2Cl_2/NaCl) ν_{max} 3400 (O-H), 3000 (=C-H), 1715 (O=COEt), 1670 cm^{-1} (O=C-NH). Mass spectrum, m/e 255 M^+. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.18 ; H, 8.24 ; N, 5.49. Found : C, 61.60 ; H, 8.20 ; N, 5.45.
    8 amorphous white solid ; ^1H NMR (300 MHz, $CDCl_3$) δ 6.29 (d, J=8 Hz, 1H, NHAc), 4.64 (m, 1H, CHCOOEt), 4.15 (q, 2H, J=7 Hz, OCH_2CH_3), 4.02 (m, 1H, CHOH), 3.35 (t, J=4 Hz, 1H, H_3), 3.23 (m, 1H, H_2), 2.45 (d, J=9 Hz, 1H, OH), 2.00 (s, 3H, $NHCOCH_3$), 2.10-1.80 (m, 4H), 1.60-1.35 (m, 3H), 1.25 (t, J=7 Hz, OCH_2CH_3). IR (CH_2Cl_2/NaCl) ν_{max} 3400 (O-H), 2920 (C-H), 1720 (O=COEt), 1670 (O=C-NH). Mass spectrum, m/e 272 $(M^+ +1)$. Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.56 ; H, 7.75 ; N, 5.17. Found : C, 57.83 ; H, 7.76 ; N, 5.01.
    9 amorphous white solid ; ^1H NMR (300 MHz, $CDCl_3$) δ 6.18 (d, J=8 Hz, 1H, NHAc), 4.71 (m, 1H, CHCOOEt), 4.20 (q, J=7 Hz, 2H, OCH_2CH_3), 3.39 (d, J=4 Hz, H_3), 3.21 (d, J=4 Hz, H_2), 2.48 (m, 1H, H_4), 2.02 (s, 3H, $NHCOCH_3$), 2.20-1.50 (m, 6H), 1.27 (t, J=7 Hz, 3H, OCH_2CH_3). IR (CH_2Cl_2/NaCl) ν_{max} 2910 (C-H), 1720 (O=COEt), 1680 (C=O), 1670 (O=C-NH). Mass spectrum, m/e 270 $(M^+ +1)$. Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.99 , H, 7.06 ; N, 5.20. Found . C, 58.29 , H, 7.32 , N, 5.19.
18. $[\alpha]_D^{20}$=+25° (C, 0.5, H_2O) ; the encountered problems for this measure are identical with those of Ganem et al.[6b].

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