Stereoselective synthesis of methylene homologues of 4-deoxy anisomycin and related 3-hydroxypyrrolidines

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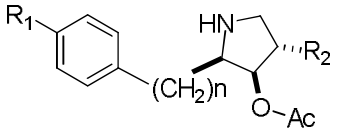
Abstract

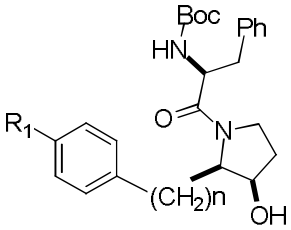
Here we would like to present an effective synthesis of 2-(2-aryletyl)-3-hydroxypyrrolidines and their derivatives based on key non-classical Wittig reaction of the enantiomerically pure α-amino-γ-substituted butyrolactones. Subsequent reductive treatment of bicyclic tetramic acid analogues has opened the door towards homologue of 4-deoxy anisomycins or their extrapolated L-phenylalanylamides – methylene homologues of known substances with potential anti-HIV activity.

Introduction

Anisomycin (**1**) is a natural biologically active compound produced by some *Streptomyces* bacteria. It has potential clinical applications in a number of areas. It is toxic to fungi, yeast, certain protozoa and plants. Toxicity is induced by inhibiting their protein synthesis.[1] These properties have been used in the clinical treatment of amoebic dysentery and vaginitis[2,3,4]. It is also proposed as a potential psychiatric drug, as it is known to affect protein synthesis on Amygdala, a brain part involved in memory.[5] Anisomycin has also been shown to exhibit antiviral and antitumor activities.[6,7]



Anisomycin(**1**) R_1=OMe; R_2=OH; n=1
Deoxyanisomycin(**2**) R_1=OMe; R_2=H; n=1
Target structures R_1=H,OMe,Me; R_2=H; n=2

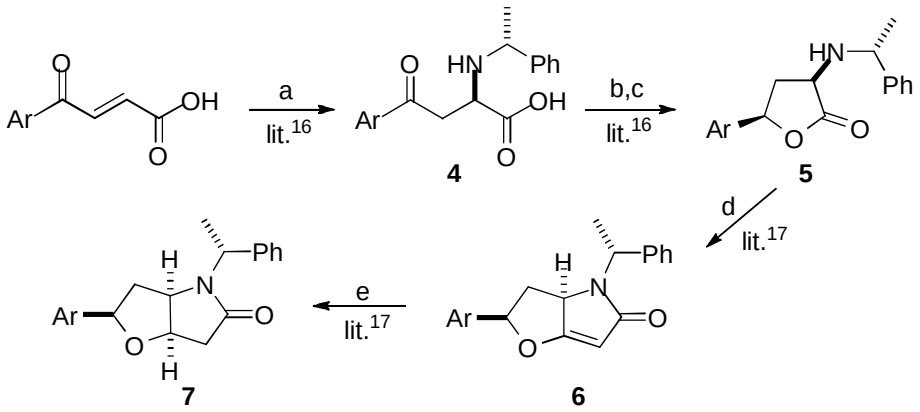


HIV protease inhibitor(**3**) R_1=H; n=1
Target structures R_1=H,OMe,Me; n=2

Anisomycin's activity against a range of tumor cell lines is largely unaffected by modest changes to the substituents at the C(4) position, as was confirmed for deoxyanysomycin (**2**).[8] Optically pure 2-substituted pyrrolidin-3-ols have been also widely used in the design of pseudopeptides as aspartyl,[9-11] serine,[12] cysteine[13,14] proteinase inhibitors, or non-peptidic neuraminidase inhibitors. Phenylalanyl amides (**3**) were studied as potential HIV-1 protease inhibitors.[15]

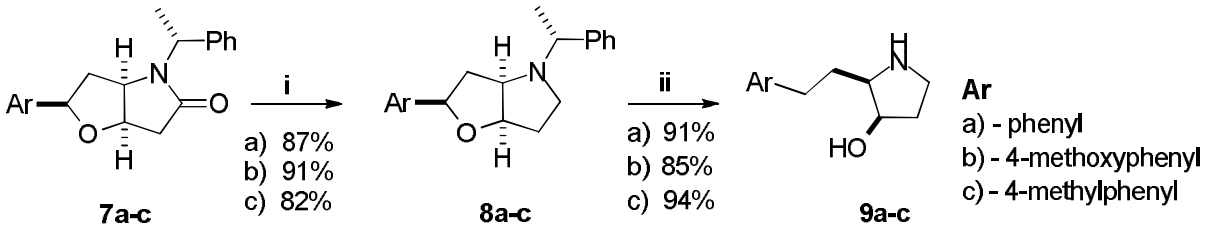
Results and discussion

Synthesis of (*R*,*R*)-2-substituted-3-hydroxypyrrolidines is based on our chemistry[16,17] *via* efficient synthetic transformations of enantiomerically pure (*R*,*R*)-2-aminobutano-4-lactones. *aza*-Michael addition of (*R*)-phenylethylamine to aroylacrylic acids combined with crystallization-induced asymmetric transformation (CIAT) produces diastereomerically pure 4-oxo-2-aminoacids **4**. $NaBH_4$ Non-selective carbonyl reduction of adducts and subsequent acid catalysed lactonisation under CIAT conditions renders enantiomerically pure 2-aminobutano-4-lactones **5**.[16] The key step of following synthetic steps is a tandem transamination - „non-classical" Wittig olefination of 2-aminobutano-4-lactones which produces bicyclic tetramic acids **6.**[17] Their diastereoselective hydrogenation offers the starting saturated heterocycles **7**.



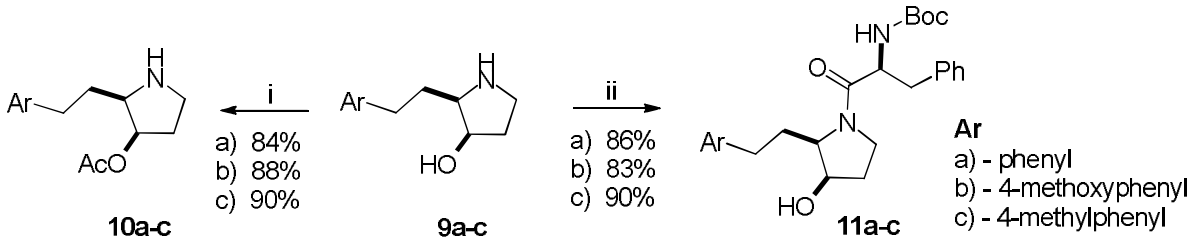
Scheme 1: a) (*R*)-1-phenylethylamine, MeOH, r.t. (CIAT); b) $NaBH_4$, MeOH, r.t.;
c) 8N HCl, 50 ^{o}C (CIAT); d) ethyl(triphenylphosphoranylidene)acetate, PhMe, 5mol.%HCl, reflux;
e) 1mol.%-Pd/C(5wt.%), H_2(balloon), EtOAc, r.t.

Classical reduction of bicyclic furopyrrolidones **7** by lithium aluminium hydride to corresponding bicyclic pyrrolidines **8** is followed by the final *N,O*-debenzylation of **8** under catalytic hydrogenation conditions and produces *cis*-2-substituted-3-hydroxypyrrolidines **9** in high yields and diastereo- and enantiomerical purity. Prepared (*R*,*R*)-2-(2-aryletyl)-3-hydroxypyrrolidines **9** have identical absolute configuration with natural anisomycin. This method enables also the preparation of opposite enantiomers by substituting the (*R*)-phenylethylamine for (*S*)-phenylethylamine as a chirality inductor.



Scheme 2: i) $LiAlH_4$ (4 equiv.), Et_2O, reflux, 3 hod., ii) 5 mol.%-Pd/C (10 wt.%), H_2 (balloon), 4 equiv. HCl, MeOH, 40 °C, 24 hod.

The target structures **10** and **11** were obtained as it is depicted on the scheme 3 *via* selective O-acetylation which forms methylene homologue of 4-deoxyanisomycins **10.** Acylation of **9** with hydroxysuccinimide ester of L-N-Boc-phenylalanine affords L-N-Boc-phenylalanylamides of 2-substituted-3-hydroxypyrrolidines **11** as methylene homologues of known substances with studied anti-HIV activity. [15]



Scheme 3: i) 5 equiv. 0,5 M HCl/AcOH, 5 equiv. Ac_2O, r.t. 24 hod., ii) 1.1 equiv. N-Boc-phenylalanine-NHS active ester, 1.5 equiv. diisopropylethylamine, CH_2Cl_2, r.t., 3 hod.

Conclusion

In summary, we report straightforward synthesis of 2-(2-aryletyl)-3-hydroxypyrrolidines from enantiomerically pure bicyclic tetramic acid derivatives and their transformation to homologues of related biologically active compounds.

Experimental section

Preparation of (2R,3aR,6aR)-2-arylhexahydro-2H-furo[3,2-b]pyrrole ***8a***

Bicyclic furopyrrolidone **7a** (5 mmol) was added to dispersion of lithiumaluminium hydride (20 mmol) in dry ether (20 ml) and reaction mixture was refluxed for 3 hours. Solution of sodium hydroxide (20 wt.% in water) was added to reaction mixture until clear ether layer is obtained. Organic phase was separated and inorganic residue was extracted three times with ether (15 ml). Evaporation of ether afforded crude product which was directly purified by flash column chromatography (silica gel, EtOAc/hexane/NH_3(aq)/$MgSO_4$ 1:5:0.05) Purified product **8a** was obtained as colorless oil in 87 % yield.

^{1}H NMR (300MHz, $CDCl_3$) 7.20-7.40 (m, 10H, H-Ar); 4.62-4.78 (m, 1H, H-6a, 1H, H-2); 4.05 (dd, 1H, J=7.4 Hz, J=14.9 Hz, H-3a); 3.48 (q, 1H, J=6.4 Hz, H-1´); 2.75 (dd, 1H, J=7.6 Hz, J=16.1 Hz, H-5A); 2.46-2.56 (m, 1H, H-5B); 1.9-2.08 (m, 2H, H-6, 1H, H-3A); 1.70-1.82 (m, 1H, H-3B); 1.44 (d, 3H, J=6.6 Hz, H-2´).
^{13}C NMR (75MHz, $CDCl_3$) 141.1, 128.4, 128.3, 127.6, 127.4, 127.2, 125.9 (C-Ar); 82.8 (C 6a); 81.8 (C-2); 66.5 (C-3a); 61.7 (C-1´); 49.6 (C-5); 37.3 (C-3); 29.7 (C-6); 22.2 (C-2´).

Preparation of (2*R*,3*R*)-2-arylethylpyrrolidin-3-ols ***9a-c***

Palladium on charcoal 10 wt.% (5 mol.%) was added to solution of Bicyclic furopyrrolidine **8** (3 mmol) in 0.5 M solution of hydrogen chloride in methanol (18 ml). Reaction mixture was stirred under hydrogen atmosphere (balloon) at 40 °C for 24 hours. Solvent evaporated under vacuum and the crude products were directly purified by flash column chromatography (silica gel, EtOAc/MeOH/NH_3(aq) 10:1:0.5 to 10:2:1) to afford products **9** as white solids [yield: Ar_1(91%), Ar_2(85%), Ar_3(94%)].
^{1}H NMR (600MHz, CD_3OD) **9a**: = 6.91-7.30 (m, 5H, H-Ar); 4.38-4.40 (m, 1H, H-3); 3.33-3.47 (m, 1H, H-2, 2H, H-5, 1H, NH); 2.68-2.82 (m, 2H, H-2´); 1.99-2.09 (m, 2H, H-4, 2H, H-1´).
^{13}C NMR (150 MHz, CD_3OD) **9a**: = 131.3, 129.7, 129.5, 129.3 (C-Ar); 72.7 (C-2); 70.8 (C-3); 65.8 (C-5); 33.5 (C-1´), 33.4 (C-2´); 33.2 (C-4).

Preparation of (2*R*,3*R*)-2-arylethylpyrrolidin-3-yl acetates ***10a-c***

Solution of corresponding hydroxypyrrolidine **9** (0.5mmol) in mixture of acetanhydride (2.5 mmol) and 0.5 M hydrogen chloride in acetic acid (5 ml) was stirred at room temperature for 24 hours. Acetic acid was removed under vacuum and residue was directly purified by flash column chromatography (silica gel, EtOAc/MeOH/NH_3(aq) 10:1:1 to 10:2:2) to afford purified product **10** as colorless oils [yield: Ar_1(91%), Ar_2(85%), Ar_3(94%)].
^{1}H NMR (300MHz, $CDCl_3$) **10a**: = 7.17-7.32 (m, 5H, H-Ar); 5.29 (ddd, 1H, J=2.7 Hz, J=5.3 Hz, J=7.7 Hz, H-3); 3.26 (dt, 1H, J=2.8 Hz, J=9.1 Hz, H-2); 2.89-3.00 (m, 1H, H-5A); 2.49-2.72 (m, 1H, H-5B); 2.22-2.35 (m, 2H, H-2´´); 2.11 (s, 3H, CH_3CO); 1.71-2.09 (m, 2H, H-1´, 2H, H-4, 1H, NH).
^{13}C NMR (75MHz, $CDCl_3$) **10a**: = 170.9 (CH 3 *CO);* 142.0, 128.4, 128.2, 125.9 (C-Ar); 74.6 (C-3); 67.3 (C-2); 47.9 (C-5); 32.6 (C-2´); 30.9 (C-1´); 29.0 (C-4); 21.3 (CH_3CO).

Preparation of tert-butyl (*S*)-1-((2*R*,3*R*)-3-hydroxy-2-phenethylpyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamate ***11a-c***

Solution of corresponding hydroxypyrrolidine **9** (0.5 mmol), diisopropylamine (0.75 mmol) and N-Boc-phenylalanine-NHS active ester (0.55 mmol) in dichloromethane was stirred at room temperature for 3 hours. Solvent evaporated under vacuum and residue was directly purified by flash column chromatography (silica gel, EtOAc/CH_2Cl_2/Hexane/NH_3(aq)/$MgSO_4$ 1:2:2:0.1 to 2:1:1:0.1) to afford product **11a-c** as colorless solids [yields: a) 91%, b) 85%, c) 94%.
^{1}H NMR (600MHz, $CDCl_3$) **11a**: = 7.13-7.24 (m, 10H, H-Ar); 5.31-5.35 (m, 1H, NH); 4.58 (dd, 1H, J=8.4 Hz, J=14.4 Hz, H-2´´); 4.19 (dd, 1H, J=4.7 Hz, J=9.7 Hz, H-3); 3.87-3.90 (m, 1H, H-2);

3.51-3.55 (m, 1H, H-5A); 2.96-3.02 (m, H-3´ minor); 2.84-2.93 (m, 2H, H-3´ major, 1H, H-5B); 2.57-2.65 (m, 2H, H-2´ major); 2.49-2.55 (m, H-2´ minor); 2.08-2.14 (m, 1H, H-1´A); 1.79-1.85 (m, 1H, H-4A); 1.66-1.73 (m, 1H, H-1´B, 1H, H-4B); 1.37 (s, $OC(CH_3)_3$ minor); 1.34 (s, 9H, $OC(CH_3)_3$ major).

^{13}C NMR (150MHz, $CDCl_3$) **11a**: = 170.9, 155.2 (C-1´´, NHCOO); 142.0, 136.3, 129.6, 129.4, 128.5, 128.4, 126.9, 125.9 (C-Ar); 79.7 ($OC(CH_3)_3$); 70.5 (C-3); 61.2 (C-2); 53.3 (C-2´´); 44.5 (C-5); 40.1 (C-3´´); 33.0 (C-4); 32.9 (C-2´); 29.9 (C-1´); 28.3 ($OC(CH_3)_3$).

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