Diastereoselective Synthesis of Diamino 1,2-Diols from Homochiral \( \alpha \)-Aminoacylsilanes

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Received 01 January 2001

Abstract: We have developed a new synthetic access to stereodefined diamino 1,2-diols starting from homochiral \( \alpha \)-aminoacylsilanes. A [3+2] cycloaddition with benzo nitrile oxide of the vinylated adducts and a reductive ring opening constitute key steps of the reaction sequence.

Key words: \( \alpha \)-aminoacylsilanes, vinylation, dipolar cycloaddition, aminopolyols

Stereodefined hydroxy amino alcohols are well recognised as key components for a variety of protease inhibitors and other new generation pharmaceutics and as ligands for asymmetric catalysis.\(^1\) We recently reported\(^2\) the stereoselective synthesis of functionalized amino alcohol units and of statine analogs via three- and two-carbon elongations respectively, from \( \alpha \)-aminoacylsilanes. The use of these synthetic equivalents of aldehydes, allows to overcome\(^2\) the serious problems due to the easy racemization and avoids the special precautions necessary for the synthesis, handling and storing frequently encountered with \( \alpha \)-amino aldehydes.\(^3\) In this paper we present a new approach to the two-carbon homologation of acylsilanes based on the delivery of a vinyl unit to a carbonyl group. The reaction under study is aimed at the synthesis of stereodefined aminopolyols possessing the core-unit present in dihydroxypropylamine derivatives capable of highly efficient renin\(^4\) and HIV-1 protease\(^5\) inhibitions (Fig.1).

Our approach started with the homochiral aminoacylsilanes 1 and 2 derived from phenylalanine and isoleucine.\(^2\) Since the addition of vinylmagnesium and lithium organometallics to acylsilanes studied by Kuwajima\(^6\) gives rise to extensive amounts of silyl enol ethers along with the expected allylic alcohols, in a previous paper\(^7\) we devised a convenient new entry to silylated allylic alcohols from acylsilanes by using the magnesium to cerium transmetallation technique.

Treatment of 1 and 2 with the vinylmagnesium bromide/\( \text{CeCl}_3\) complex, led (Scheme 1) to the formation of adducts 3 and 4 in good isolated yields and high diastereoselectivities (99% d.e.).\(^8\)

Scheme 1

For introducing new hydroxy and amino functionalities in the vinyl moiety we envisioned the [3+2] cycloaddition with nitriloxides. Cycloadditions of this type are usually regarded as mildly electrophilic in character. Therefore (\( \alpha \)-hydroxyallyl)ilanes in which the preferred location of allylic substituents maximizes\(^9\) electron donation should, as shown by Curran,\(^10\) as efficient dipolarophiles. When 3 and 4 were reacted with the in situ prepared benzo nitrile oxide, isoxazolines 5 and 6 were obtained in 70% and 55% yields. In contrast with the modest diastereomeric excess (20%) observed in the case of 5, only one diastereoisomer (99% d.e.) could be detected and isolated in the case of 6. The diastereomeric couple 5a,b could be

Scheme 2

Figure 1

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The subsequent desilylation of the α-hydroxysilane cycloadducts carried out on a model compound, was disappointing. Under the action of bases the β-elimination of silanol led to ring opening with generation of an enolic form which upon rearrangement resulted in the formation of the desilylated hydroxylamino derivative 7 (Scheme 3).

To prevent the occurrence of the above mentioned Peterson elimination reaction from the β-hydroxysilane moiety in the presence of strong bases, isoxazolines 5a, the major diastereoisomer, and 6 were subjected to an oxidative desilylation. This reaction, although already reported in the literature, has been however scarcely investigated. Since the oxidation with pyridinium dichromate (PDC) has found an useful and high yielding short route to diamino 1,2-diols starting from homochiral α-aminoacilsilanes. The importance of the target compounds highlights the significance of this new synthetic protocol in which in a single reductive-unfolding step, three new functional groups are generated.

The reductive ring opening of the oxazolidine ring aimed at the formation of the new hydroxy and amino functionalities was then performed. To avoid reaction conditions able to promote an acidic proton abstraction, we exploited the use of NaBH₄ in methanol in the presence of NiCl₂·6H₂O. Exposure of 8 and 9 to this reagent at ~30 °C according to the literature led to heterocyclic ring opening and reduction of the carbonyl function and afforded after 65 h, the expected aminopolys. These were directly converted to the corresponding bis-Boc derivatives: in both cases one diastereoisomer was found to largely prevail which was isolated by column chromatography and characterized. By this procedure N-Boc protected aminopolys 10 and 11 are produced in 35% and 30% overall yields in three steps from oxazolidines 5a and 6 respectively. Connectivity of diamino 1,2-diols 10 and 11 was achieved by homonuclear and heteronuclear correlation. The stereochemical assignment of the three unknown stereogenic centers of 11 was attempted on the basis of 2D-NOCY constraints and molecular modelling. The 15 observed constraints restricted the choice to two possible solutions: in both cases the three unknown centres are expected to display the same chirality and either configuration SSSS or SSRR, could be considered for 11 (Figure 2). To solve this ambiguity a single crystal X-ray diffraction was performed. The configuration was found to be SSSS (Figure 2, left). Work is in progress to establish also the stereochemistry of compound 10.

In conclusion we have established the viability of a new short route to diamino 1,2-diols starting from homochiral α-aminoacilsilanes. The importance of the target compounds highlights the significance of this new synthetic protocol in which in a single reductive-unfolding step, three new functional groups are generated.

Acknowledgement
This work has been supported by University of Bologna (Funds for Selected Research Topics, A.A. 1999-2001) and by the National Project “Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni 1999-2001”.

References and Notes

(8) 3: Yellowish oil: [α]D₂₀ = -49.3 (c = 2.0, CHCl₃); 'H NMR (200 MHz, CDCl₃) δ = 0.38 (s, 3H, Si-CH₃); 1H NMR (200 MHz, CDCl₃) δ = 3.38 (s, 3H, Si-CH₃), 1.24 (s, 9H, C(CH₃)₃), 1.46 (s, 1H, OH), 2.54 (dd, 1H, J = 13.6, 10.4 Hz, CH₂-Ph), 2.90 (dd, 1H, J = 13.6, 3.6 Hz, CH₂-Ph).
(9) For discussions of such electronic effects of allylic substituents see: (a) Eyer, M.; Seebach, D.

(11) Representative procedure: preparation of (5a-b):
Triethylamine (0.27 mL, 1.90 mmol) and 3 (600 mg, 1.52 mmol) were dissolved in Et2O (15 mL). To this solution benzhydroxynonyl chloride (300 mg, 1.90 mmol) in Et2O (10 mL) was slowly added (3.5 h) through a funnel. After the addition was completed the reaction was stirred for 48 h. The solvent was evaporated and the crude was purified by column chromatography on silica gel (petroleum ether : Et2O /3:1) affording a 560 mg (70%) of two diastereoisomers in the ratio 60:40. Major diastereoisomer (5a): Rf = 0.042 cm (petroleum ether : Et2O : CHCl3 = 60:40), [α]20D = +23.65 (c = 4.0, CHCl3); 1H NMR (300 MHz, CDCl3) δ: 0.55 (s, 9H, SiMe2), 0.71-0.92 (m, 8H, C(CH3)3), 1.57-1.80 (m, 1H, C(CH3)3), 2.95 (dd, 1H, CH2-O), 3.46 (dd, 1H, CH2=Ph), 3.64-3.90 (m, 1H, CH-O), 7.05-7.54 (m, 15H, Ar-H); 13C NMR (75.46 MHz, CDCl3) δ: -2.83, -2.63, 28.09, 36.83, 58.76, 73.72, 79.46, 85.47, 126.32, 126.64, 128.03, 128.33, 128.53, 128.83, 128.38, 129.54, 129.98, 134.77, 137.46, 138.21, 156.35, 156.72. HRMS (EI): m/z found: 517.2529 C30H27N2O4Si requires 517.2523. Minor diastereoisomer (5b): Rf = 0.11 cm (petroleum ether : Et2O : CHCl3 = 60:40), [α]20D = -107.63 (c = 4.0, CHCl3); 1H NMR (300 MHz, CDCl3) δ: 0.52 (s, 3H, Si-CH3), 0.79 (s, 3H, Si-CH3), 1.24 (s, 9H, C(CH3)3), 2.56 (dd, 1H, CH2-O), 3.22 (dd, 1H, CH-O), 4.10-4.25 (m, 1H, CH-Ph), 3.30 (bs, 1H, OH), 3.38 (dd, 1H, CH-CH2-O), 4.26 (d, 1H, J = 9.0, NH), 4.38-4.44 (m, 1H, CH-N), 5.40 (t, 1H, J = 10.1 Hz, CH-O), 7.05-7.54 (m, 15H, Ar-H); 13C NMR (75.46 MHz, CDCl3) δ: -3.55, -3.30, 28.09, 36.83, 58.76, 73.72, 79.46, 85.47, 126.32, 126.64, 128.03, 128.33, 128.53, 128.83, 128.38, 129.54, 129.98, 134.77, 137.46, 138.21, 156.35, 156.72. HRMS (EI): m/z found: 517.2529 C30H27N2O4Si requires 517.2523.

Figure 2: The two alternative structures of 11 obtained on the basis of 2D-NOESY constraints. (oxygenes are represented as black, nitrogens as grid)

(16) Representative procedure: preparation of 10: To a solution of 8 (297 mg, 0.75 mmol) in methanol (19.3 mL) stirred under Ar, EtOAc (297 mg, 98%) as 11.35 (s, 9H, C(CH3)3), 1.70 (bs, 1H, OH), 2.10 (bs, 1H, OH), 1.40-1.50 (m, 2H, CH2Ph), 2.40-2.50 (m, 2H, PhCH2), 3.10 (d, 1H, J = 9.9 Hz, CH2Ph), 3.60-3.65 (m, 1H, PhCH2CH2), 3.70-3.75 (m, 1H, PhCH2CH2), 4.55-4.60 (m, 1H, PhCH(CH2)CH2OH), 4.90-5.00 (m, 1H, PhCNH), 5.10 (d, 1H, J = 10.1 Hz, PhCHNPh), 7.00-7.40 (m, ArH, 10H); 13C NMR (50.3 MHz, CDCl3) δ: 28.33, 28.46, 36.68, 39.08, 52.14, 53.04, 67.11, 75.26, 77.72, 79.64, 127.74-127.93, 137.68, 142.06, 156.05, 156.76. HRMS (EI): m/z found: 500.2894 C23H26N2O4 requires 500.2886. 11: White solid: 30% overall yield for three reaction steps. M.p. 184-186 °C; [α]D257 = -11.46 (c = 3.0, CHCl3); 1H NMR (200 MHz, CDCl3) δ: 0.15-0.20 (m, 1H, CH2Ph), 0.60-0.80 (2S, 6H, CH2CH2CH2CH2), 1.00-1.10 (m, 1H, CH2), 1.30-1.55 (m, 19H, 2MeC, CH2Ph), 1.85-1.95 (m, 1H, CH2), 1.95-2.05 (m, 1H, NHCHCH2OH), 2.35-2.40 (m, 1H, CH2CH2Ph), 2.80-2.85 (m, 1H, CH(OH)CHNPh), 3.40-3.45 (m, 1H, CH(NH)CHNPh), 3.60-3.65 (m, 1H, CH2CH2), 4.00-4.10 (d, 1H, J = 9.8 Hz, CH2CH2), 4.60-4.70 (s, 1H, CH2OH), 5.20-5.25 (m, 1H, PhCH2), 6.10 (d, 1H, J = 10.0 Hz, PhCHNPh), 7.10-7.40 (m, 5H, ArH); 13C NMR (200 MHz, CDCl3) δ: 12.05, 16.65, 22.93, 38.74, 28.10, 28.29, 38.74, 52.37, 57.39, 67.06, 73.30, 73.94, 80.07, 126.09, 128.20, 142.43, 142.25, 155.77, 157.68. HRMS (EI): m/z found: 466.3052 C22H20N2O3 requires 466.3043.

(17) NMR spectra were recorded at 400 MHz in CDCl3. Homonuclear correlations were obtained by the gCOSY sequence. Heteronuclear correlations were obtained by edited- HOMMIX sequence. 2D-NOESY spectra were recorded using mixing times of 1.5 s and 2.0 s. Conformational search was performed with PC-Spartan Pro v1.05, using the MMFF Force Field, and then the conformational minima were refined using PC-Model V7.5 and the MMX Force Field.

(18) Crystal Data of 11: C23H26N2O4 (466.61), Orthorhombic, Space group P212121, a = 4, α = 10.8904(6), b = 11.2652(6), c = 22.9595(12) Å, V = 2771.9(3) Å3, Dc = 1.118 g cm-3, F(000) = 1016, μMo = 0.079 cm-1, T = 298 K. Data were collected using a graphite monochromated Mo-Kα X-radiation (λ = 0.7107 Å) in the range 3.25° < θ < 30.00°. Of 31346 reflections measured, 8104 were found to be independent (Rint = 0.0847), 3670 of which were considered as observed (Fobs > 4σ(Fobs)) and used in the refinement of 302 parameters leading to a final R1 = 0.0546 and a R2 of 0.1141. The structure was solved by direct method and refined by full-matrix least squares on F2, using SHELXTL 97 program packages. In refinements were used weights according to the scheme w = [σ2(Fo)+0.0895P2]+0.000000P4, where P = (Fo2 + 2Fo2)1/2. The hydrogen atoms were located by geometrical calculations and refined using a "riding" method; wR1 was equal to 0.1447. The other atoms were anisotropically refined except the two t-butyl groups that were disordered and so split into two position and isotropically refined. The goodness of fit parameters S was 0.846. The largest difference between peak and hole was 0.572 and -0.272 e Å-3. Crystallographic data (excluding structure factors and including selected torsion angles) have been deposited with the Cambridge Crystallographic Data Center. CCDC-160358.

Article Identifier: 1437-2096;E:2001;0,SL0995,0998,txt,en;Y03801ST.pdf

Synlett 2001, SI, 995–998 ISSN 0936-5214 © Thieme Stuttgart · New York