Enantiocontrol by Intrinsic Antiparallel Double Repulsion on Diacetone-D-Glucose Template. Enantioselective Synthesis of Alanine and Chirally Deuterated Glycine

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Abstract: A divergent and highly enantioselective synthetic methodology not only for both enantiomers of α amino acids but for both chirally deuterated glycines from a single starting material was developed by making use of stereocontrol with antiparallel double repulsion on the diacetone-D-glucos-3-ulose template.

Carbohydrates have long been and still are important sources of chirality in organic synthesis, especially for the synthesis of physiologically significant natural products.¹ During our earlier studies on the enantioselective synthesis of 3-alkylmalic acids,² we became aware of possible stereochemical control elements to be exploited in which the intrinsic molecular architecture of a carbohydrate may play an important role as a template for chirality transcription irrespective of individual chiral carbons. This paper deals with an application of a stereochemically bi-directional template, diacetone-D-glucos-3-ulose (1), to the divergent and highly enantioselective synthesis of both enantiomers of optically active α -amino acids and chirally deuterated glycine from a common starting material.

The molecular architecture of 1,2:5,6-di-O-isopropylidene- α -D-*ribo*-hexos-3-ulose 1 can be regarded as possessing a sort of C_2 symmetric nature about the C-3 carbonyl axis, because it includes both an α -oriented bulky 1,2-O-isopropylidene protecting group and a β -oriented large substituent at C-4 in the five-membered furanose ring. Thus, as might be anticipated, α - and β -substituents introduced onto the C-3 position must sterically interact with these two bulky substituents so that the β -substituent at C-3 tends to depart from the bulky C-4 substituent and the α -substituent at C-3 tends to depart from the 1,2-O-isopropylidene group. In other words, the inherent antiparallel double repulsion, as illustrated below, may well predetermine a unique orientation of the two substituents on the C-3 position of 1, thereby making the newly created stereochemistry by a reaction between the



substituents at C-3 predictable. With this anticipation, we first attempted to develop a novel method to control the stereochemistry for the synthesis of chiral α -amino acids and targeted D- and L-alanine in this case, since alanine is by any means the smallest chiral α -amino acid so that the capability of the present approach for the stereochemical control may be appropriately demonstrated. Crucial manipulations involve transformation of propyne, the C₃ starting material, linked to the chiral template 1 into D- or L-alanine *via* stereospecific reduction to an (*E*)- or (*Z*)-allylic alcohol, followed by the Overman protocol³ involving a [3,3]-sigmatropic rearrangement of the derived imidates to stereoselectively introduce a nitrogen atom, as illustrated in the Scheme. This protocol was successfully applied previously to the synthesis of racemic α -amino acids by Takano *et al.*⁴

A versatile synthon in the present approach is crystalline 3-C-ethynyl-1,2:5,6-di-O-isopropylidene- α -D-allofuranose 2, which was prepared in good yield and with high stereoselectivity from 1 as described previously.⁵ The starting material for alanine, 3-C-(propyn-1-yl)-1,2:5,6-di-O-isopropylidene- α -D-allofuranose 3⁶ was prepared from 2 via: 1) trimethylsilylation of the OH group, 2) methylation of the acetylene, and 3) desilylation, in 70 % overall yield, mp: 103 °C; v 2240 cm⁻¹. Stereospecific reduction of 3 to the (E)-olefin 4,⁶ mp 111 °C, δ 5.44 (1H dd, J=1.5 and 15.6 Hz) and 5.95 ppm (1H dd, J=6.6 and 15.6), was carried out (85 % yield) with LiAlH₄ in THF at room temp, which in turn was transformed to a crystalline imidate 5.6 mp; 115-116 °C, v 3340 and 1665 cm⁻¹, δ 1.79 (3H, br.d, J= 5.8 Hz), 5.50 (1H br.d, J=16.6 Hz), 5.63 (1H dq, J=16.6 and 6.0 Hz) and 8.39 ppm (1H br.s, NH), by a method adopted from the Overman's protocol in 76 % yield.³ The crucial [3,3]sigmatropic rearrangement of 5 was carried out in xylene under reflux for 36 hr to afford in 90 % yield a trichloroacetamide 6 (syrup), δv 3425 and 1710 cm⁻¹; δ 1.42 (3H d, J=6.8 Hz), 4.85 (1H sextet, J=6.8 Hz), 5.88 (1H dt, J=5.9 and 1.5 Hz) and 7.39 ppm (1H br.d, J=7 Hz). The stereoselectivity of the reaction turned out to be as high as 94 : 6 as determined by ¹H-NMR analysis after removal of the solvent from the reaction mixture. Minor signals were assumed to be derived from a product formed by a reaction on the opposite face of the double bond, but were not rigorously assigned. The stereochemistry of 6 was assigned by ¹H-NMR differential NOE experiments, in which irradiation of the olefinic proton signal at 5.88 ppm clearly affected mutual signal enhancement of the H-4 signal at 4.63 ppm (1H dq, J=6.0 and 1.5 Hz) of the furanose ring but not of the H-2 signal at 5.17 ppm (1H br.d, J = 4.4 Hz), thereby suggesting the Z-geometry for the resulting double bond. This suggested that the nitrogen attacked to the re-face of the double bond of 5. Based on these results as well as the mechanistic rationale of the signatropic rearrangement, the absolute configuration of the crucial methine group attached to the amide group was assigned as R. This was ultimately confirmed by the following transformations of 6 into D-alanine. Thus, ruthenium oxidation of 6 under the Sharpless's conditions⁷ afforded in 36 % yield trichloroacetyl alanine 7, $[\alpha]_{\rm D}$ -20.1° (CHCl₃, c=0.52). Acid hydrolysis of 7 finally provided D-alanine 8,8 $[\alpha]_{\rm D}$ -12.7° (5M HCl, c=0.51, lit.9 for L-isomer: +14.6°), in 69 % yield.

As to the enantioisomeric L-alanine, the (Z)-allyl alcohol 9,⁶ mp 97 °C, v 1670 cm⁻¹, δ 5.32 (1H dd, J=1.7 and 11.7 Hz) and 5.83 ppm (1H dq, J=7.3 and 11.7 Hz), obtained by hydrogenation of 3 over Pd/CaCO₃ in 78 % yield, was similarly converted in 68 % yield to the corresponding imidate 10,⁶ v 3340 and 1665 cm⁻¹, δ 1.84 (3H dd, J=1.5 and 7.5 Hz), 5.15 (1H dd, J=12 and 1.5 Hz), 5.85 (1H dq, J=12 and 7.5 Hz) and 8.44 ppm (1H br.s, NH), which was then subjected similarly as above to the rearrangement. Solvent was removed from the reaction mixture by evaporation and the residue was directly analyzed by ¹H-NMR, which suggested almost quantitative transformation to 11 (syrup),⁶ v 3430 and 1710 cm⁻¹, δ 1.44 (3H δ , J=6.8 Hz), 4.77 (1H ddq, J=9.8, 6.8 and 6.8 Hz), 5.70 (1H dt, J=9.8 and 1.9 Hz) and 6.77 ppm (1H br. d, J=6.9 Hz). Essentially no trace of signals due to isomeric products was observed. In other words, the reaction proceeded almost stereospecifically. The Z-geometry for the double bond in 11 was confirmed again by ¹H-NMR NOE experiments, in which irradiation of

Scheme.



Reagents: a. CH=CMgBr; b. 1) TMSCl/Pyr; 2) nBuLi; 3) CH₃I; 4) K_2CO_3 ; c. LiAlH₄ or H₂/Pd/CaCO₃; d. KH/CCl₃CN; e. Δ /xylene; f. RuCl₃/NaIO₄; g. H⁺

the vinylic proton signal at 5.70 ppm enhanced the H-4 signal at 4.77 ppm and *vice versa*. Consequently, the *si*-face attack of the nitrogen atom on the double bond of **10** proved to be taken place during the rearrangement and the *S*-configuration was strongly implied for the amide-carrying methine group. The rearranged product **11** was converted to L-alanine **12**,⁸ [α]_D 15.7° (H₂O, *c* =0.44), through the same treatment as described above.

The fact that, irrespective of the olefin geometry in 6 or 10, the same face of the double bond was involved in the crucial [3,3]-sigmatropic rearrangement to afford the products 7 and 11 with (Z)-geometry, respectively, clearly rationalized our prediction of the stereochemical outcome based on the antiparallel double repulsion incorporated in the intrinsic architecture of diacetone-D-glucose. Only one enantiomer of the chiral starting material is required for the preparation of both enantiomers of alanine. Furthermore, since the alkylation of 2 is operationally quite simple and varieties of alkyl substituent can be introduced, the potential usefulness of the present method for the chiral synthesis of a wide variety of α -amino acids may well be anticipated.

Attempts were then directed to evaluate the effectiveness of the present approach by using the simplest allylic alcohol system, *i.e.* (Z)- and (E)-monodeuterated allyl alcohols **13** and **14**, which must be potential precursors of the chirally deuterated glycines. The chirally deuterated glycines are important in bioorganic research. The methods so far developed for chiral glycine preparation are rather specific in terms of starting material and chemistry involved.^{10,11} Little is known as to the synthetically divergent methodology in which a common starting material can be converted into both chiral α -amino acids and chiral glycine.¹¹

Reduction of 2 with LiAl²H₄ gave regio- and stereoselectively a deuterated allyl alcohol 13 in good yield as already described.⁵ A deuterium was introduced into the γ -position relative to the OH group and less than 5 % of the product was β-deuterated as judged by high field ¹H-NMR spectroscopy.¹² The allylic alcohol 13 was then transformed to an oily imidate 15,⁶ v 3320 and 1665 cm⁻¹; δ 5.40 (1H d, *J*=11.7 Hz), 5.92 (1H d, *J*=11.5 Hz) and 8.42 ppm (1H br.s, NH), in 89 % yield. The crucial [3,3]-sigmatropic rearrangement of 15 was carried out in xylene under reflux for 36 hr to afford in 97 % yield a trichloroacetamide 16, v 3420 and 1690 cm⁻¹; δ 4.29 (1H br.t, *J*=7.5 Hz), 6.03 (1H dt, *J*=7.3 and 1.7 Hz) and 7.23 ppm (1H br.s NH). The stereochemistry was assigned as described above by ¹H-NMR differential NOE experiment, which again demonstrated clearly mutual signal enhancement between H-4 at 4.65 ppm (1H dq, J=6.4 and 1.5 Hz) and the olefinic proton at 6.03 ppm and no NOE between H-2 at 5.24 ppm (1H dt, J=4.5 and 1.5 Hz) and the olefinic proton. Thus, the Z-geometry was suggested for the resulting double bond. The content of the (*E*)-isomer was estimated to be 9 % (Z : E = 10 : 1). Further transformations involving RuCl₃ oxidation and acid hydrolysis were carried out to afford in 32 % yield

(2S)- $[2-^{2}H_{1}]$ glycine 17,⁸ mp 234 °C (dec.); δ (D₂O) 3.80 ppm; $[\alpha]_{230}$ -49.0° (H₂O, c =2.1) (lit.¹³ -54.8°). The absolute configuration of 17 implied that the imidate attack took place to the *si*-face of the deuterated double bond of 16 and this stereochemical feature was completely identical with that of the methylated cases. Complementary results were obtained as anticipated by starting the same reaction sequence using the regioisomerically deuterated olefin 14⁵ as a starting material. (2*R*)-[2-²H₁]Glycine 18,⁸ mp 230 °C (dec.); $[\alpha]_{230}$ 42.6° (H₂O, c =0.85), was produced, when a less deuterated (approximately 95 % enriched) material was used.

Although the yields of some steps have not been optimized, the methodology described above is of significance in that the acetylenic compound 2 is divergently utilized not only for both D- and L-alanine but for chirally deuterated (*R*)- and (*S*)-glycine as well, thereby demonstrating an alternative way to utilize the chirality of carbohydrate derivatives. Furthermore, it appears that intramolecular control of chiral alignment of reaction sites by the antiparallel or circularly directed double repulsion is to be further exploited for stereochemically defined synthesis.

Acknowledgement. This work was supported in part by a Grant-in-Aid for Scientific Research from The Ministry of Education, Science and Culture, and by a Grant from The Fujisawa Foundation.

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(Received in Japan 1 June 1991)