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De Novo Asymmetric Synthesis of two 5-Amino-5,6-Dideoxy-D-Allose Derivatives.

Albert Defoin*, Hervé Sarazin, Christiane Strehler and Jacques Streith

Ecole Nationale Supérieure de Chimie, Université de Haute Alsace
3, rue Alfred Werner, F-68093 Mulhouse, France

Summary. *- Diels-Alder cycloaddition of sorbic aldehyde derivative* ***9*** *and of sorbic acid* ***10*** *with the chiral chloro-nitroso dienophile* ***7*** *led with excellent regio- and diastereoselectivity to the chiral cycloadducts* ***11a*** *and* ***12****, respectively. Catalytic osmylation of their Bzl-derivatives* ***11b*** *and* ***13b****, followed by reductive cleavage of the N-O bonds, gave ultimately the chiral aminoallose derivatives* ***D-5*** *and* ***D-6*** *which are potential glycosidase inhibitors.*

Introduction. - The piperidine aminosugar family, of which nojirimycin **1** is a prominent member,[1] comprises some potent inhibitors of glycosidase enzymes. They act as mimics of the corresponding pyranoses by blocking the active site of the enzyme.[2] To quote but one example nojirimycin **1**, which is the 5-aza analogue of D-glucopyranose, mimics this latter one and strongly inhibits α- and β-glucosidase enzymes.

A large number of analogous sugar mimics have been discovered which act also as potent glycosidase inhibitors : i) piperidine sugars which are devoid of the anomeric hydroxyl moiety, like 1-deoxynojirimycine **2** (DNJ);[1-3] ii) pyranose- or piperidinose sugar derivatives whose anomeric CHOH group has been replaced by a carbonyl moiety, *i.e.* δ-lactones like D-gulonolactone,[4] and δ-lactames like D-gulanolactame **3**,[5] as well as some of their derivatives.[6,7] Furthermore it is worth noticing that 6-deoxy-sugars, like D-fucose or L-rhamnose, occur as natural products ; their 5-amino-5-deoxy derivatives exhibit glycosidase inhibitory properties.[8] Glycosidase inhibitors may be compared to magic bullets capable of turning off the catalytic activity of a single specific glycosidase.

We describe herein the asymmetric synthesis of D-5-amino-1,5,6-trideoxyallose **D-5**, and of the corresponding D-allolactame derivative **D-6**, by use of hetero Diels-Alder methodology with the chiral chloro-nitroso dienophile **7**. Nitroso compound **7** which had been prepared by Kresze, Vasella and their coworkers from D-mannose, was shown to lead to high asymmetric inductions when reacted with dienes.[9,10] We have described previously the synthesis of the racemic derivatives **4** and **5** of aminoallose via Diels-Alder cycloaddition of acylnitroso dienophiles with dimethylacetal **8** of hexadienal sorbaldehyde.[11,12] Belleau and An-Young had applied a similar methodology with sorbic acid **10** to prepare the corresponding racemic aminoallonic acid.[13] Furthermore the synthesis of enantiopure **L-5** has been reported recently by Hussain and Wyatt via Diels-Alder reaction of an acylnitroso dienophile with the cyclic aminoether derivative obtained from L-ephedrine and hexadienal.[14]

Asymmetric Synthesis of the Aminoallose Derivatives D-5 and D-6. - In a first attempt we tried to react chiral nitroso dienophile **7** with dimethylacetal of hexadienal **8** ; unfortunately **8** decomposed to give hexadienal. Next we turned our attention to a stable derivative of this latter aldehyde by making its O-methyl oxime **9** (mixture of (E,E) and (E,Z) isomers both appearing in their *syn* and *anti* form)[15]. When reacted with the chiral nitroso dienophile **7** according to Kresze's conditions,[9] it led to a mixture of two cycloadducts, the *cis* stereoisomer **11a** being the major product (*ca.* 80 %) which was not separated from the minor *trans* cycloadduct at this stage. Furthermore each cycloadduct appeared as a mixture of the *syn* and *anti* compounds (at the oxime level). Reaction of **11a** (mixture) with benzylchloroformate in the presence of aqueous N Na_2CO_3 gave the urethane derivative **11b** (only the major *cis* adduct is represented in the *Scheme*).

Catalytic osmylation of **11b** (mixture ; see above), in the presence of N-methylmorphine N-oxide (NMO) as a reoxidant, gave specifically the *cis*-glycol **14**. The *trans* isomer of **11b** did not react under these conditions and could easily be separated from **14** by column chromatography (AcOEt/cyclohexane 1:1). Compound **14**, which was obtained in 75 % overall yield from **9** is still a mixture of the *syn* and *anti* oximes. Catalytic hydrogenolysis (Pd/C) of the benzyloxy group, thence of the N-O bond of **14** and followed in this a one-pot reaction by reductive cyclisation led to the amino-allose derivative **D-5** as a homogenous and resinous compound (72 % overall yield) which was characterized as its tetraacetyl derivative, m.p. 120°C (iPr_2O), $[\alpha]^{16}_D = +7$ (c = 1.0, $CHCl_3$).[16] This derivative is the enantiomer of the known tetraacetyl derivative of **L-5**.[14] According to HPLC, ee > 98 % was measured.[17] These HPLC data clearly demonstrate a very pronounced diastereoselectivity during the Diels-Alder step.

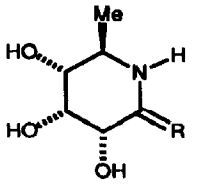
When submitted to the same experimental conditions, sorbic acid **10** reacted with complete diastereoselectivity with **7** to give *cis* cycloadduct **12** whose hydrochloride (75 %) precipitated with dry diethyl ether. The absolute stereochemistry (3R, 6S) of **12** was deduced from that of **13a** which had been ascertained by Kresze by cycloaddition of methyl sorbate with **7**. Compound **12,HCl** reacted with benzylchloroformate in methanol in the presence of Na_2CO_3, thence with anhydrous HCl in methanol, to give the urethane-ester derivative **13b** as a homogenous compound. Catalytic osmylation of **13b** led to *cis* diol **15** (65 %) whose hydrogenolysis gave directly **D-6** as a crystalline compound in 90 % yield. **D-6** : $[\alpha]^{23}_D = +53$ (c = 1.0, CH_3OH).

5-Amino-1,5,6-trideoxy-D-allose D-5. - A soln. of diol **14** (245 mg, 0.75 mmol) in water (25 ml) containing 5 % Pd/C (20 mg) was stirred under hydrogen atmosphere at 40°C. Some additional catalyst was added after 7 h and after 24 h. After 30 h the catalyst was separated by centrifugation and the solvent evaporated. The residue was taken up in water (10 ml), the resulting soln. stirred in the presence of Amberlyst-15 (H^+ form) for 90 min. The resin was filtered off, extracted with aqueous 1 N ammonia, and the aqueous ammoniacal soln. were evaporated to dryness leading thereby to **D-5** (79 mg, 72 %) as a colourless resin.[18]

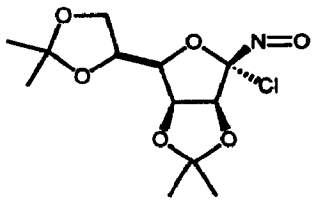
5-Amino-5,6-dideoxy-D-allopiperidinolactame D-6. - A soln. of diol **15** (156 mg, 0.48 mmol) in methanol (1.5 ml) containing 5 % Pd/C (10 mg) was stirred under hydrogen atmosphere at 40°C. Some additional catalyst (10 mg) was added after 9 h. After 24 h the catalyst was separated by centrifugation and the solvent evaporated. The residue was crystallised to yield **D-6** (69 mg, 90 %) as a colourless solid, m.p. = 212-213°C (EtOH).[18]

The conformation of D-5 and D-6 in water was deduced from the NMR-spectra.[18] The large $J_{4,5}$ (*ca.* 10 Hz) value in both compounds points to a chair conformation in which the Me-C(5) group appears to be predominantly equatorial, as indicated in the Scheme.

1 R = H,OH
2 R = H_2
3 R = O



D-4 R = H,OH
D-5 R = H_2
D-6 R = O



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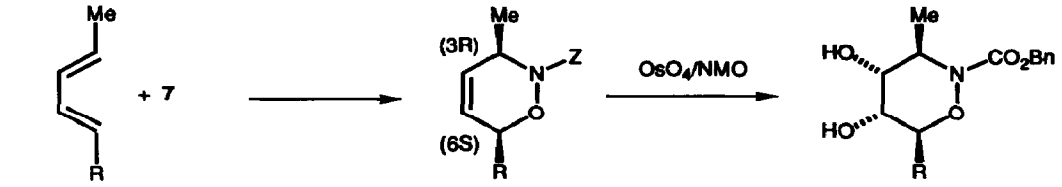
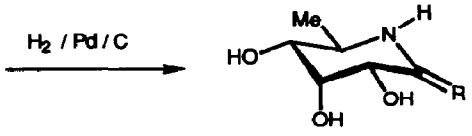


8 R = $CH(OMe)_2$
9 R = CH=NOMe
10 R = CO_2H

11a R = CH=NOMe ; Z = H
11b R = CH=NOMe ; Z = CO_2Bn
12 R = CO_2H ; Z = H
13a R = CO_2Me ; Z = H
13b R = CO_2Me ; Z = CO_2Bn

14 R = CH=NOMe
15 R = CO_2Me



D-5 R = H_2
D-6 R = O

References and notes

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15. Commercial hexadienal is a mixture of the (E,E) (80 %) and of the (E,Z) (20 %) isomers
16. For tetraacetyl derivative of **L-5** : mp = 119-120°C ; $[\alpha]^{20}_D$ = -4 (C=0.23, $CHCl_3$) ; see : 14.
    For racemic tetraacetyl derivative of (±) **5** : mp = 120-121°C ; see : 12.
17. HPLC : CHIRALPAK AD DAICEL column ; Solvent: n-hexane/iPrOH 90:10 ; 210 nm UV detector ; For the racemic product, measured D-L ratio: 489:511; retention time: 16.8 min (D) and 17.7 min (L).
18. **Compound D-5.** - ^{1}H-NMR (D_2O, TSP-D_4, 27°C ; ppm, J (Hz)) : 4.06 (t, H-C(3)), 3.71 (ddd, H-C(2)), 3.23 (dd, H-C(4)), 2.78 (dd, H-C(1)ax), 2.73 (dq, H-C(5)), 2.69 (dd, H-C(1) eq) , 1.12 (d, Me-C(5)), $J_{1eq,1ax}$ = 12.2 ; $J_{1ax,2}$ = 11.0 ; $J_{1eq,2}$ = 5.3 ; $J_{2,3}$ = 2.8 ; $J_{3,4}$ = 2.7 ; $J_{4,5}$ = 10.0 ; $J_{5,Me}$ = 6.4.

    Compound D-6. - ^{1}H-NMR (D_2O, TSP-D_4, 27°C ; δ (ppm), J (Hz) : 4.27 (dd, H-C(2)), 4.21 (dd, H-C(3)), 3.72 (dd, H-C(4)), 3.56 (ddq, H-C(5)), 1.28 (d, Me-C(5)) ; $J_{2,3}$ = 3.1 ; $J_{2,5}$ = 0.7 ; $J_{3,4}$ = 2.0 ; $J_{4,5}$ = 9.1 ; $J_{5,Me}$ = 6.3.

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