Pergamon

Tetrahedron Letters 40 (1999) 2829–2832

TETRAHEDRON
LETTERS

Highly Stereoselective Synthesis of 3-Amino-3,6-Dideoxy-Aldohexoses by Tin Triflate mediated Aldol Condensation Reaction of Tricarbonyl Iron α-Aminodienone Complexes. Total Synthesis of Multiprotected Mycosamine.

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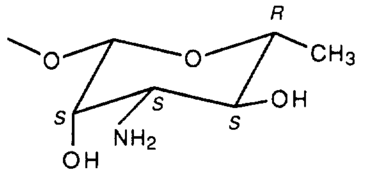
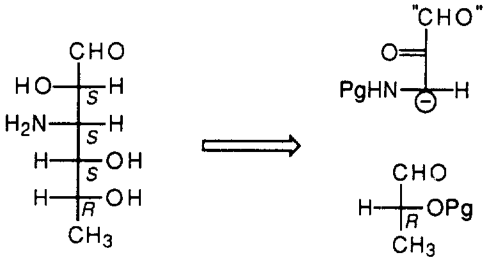
Received 22 December 1998; accepted 3 February 1999

Abstract : *The divalent tin enol ether of the racemic N-BOC α-aminodienone tricarbonyliron complex 4 reacts with both enantiomers of protected lactaldehydes to predominantly yield one optically active ketol diastereoisomer (45 %). From the enantiomerically pure complex **(S)-(+)-4** and **(R)-(+)** tert butyldimethylsilyloxylactaldehyde this ketol is obtained almost alone (isolated 86 %). From there, the multi-protected 3-amino-3,6-dideoxy-D-aldohexose mycosamine is obtained in a few high yielding steps (decomplexation, stereospecific reduction to a 1,3-diol, transformation into a diacetate and ozonolysis ; absolute configurations S,S,S,R). By reduction of the ketol before decomplexation, the stereochemistry of the reaction is completely reversed (control by the* $Fe(CO)_3$ *and not by the hydroxyl group), giving also access to the R,S,S,R series. (Structures determined by X-ray diffraction).*

Mycosamine is a 3-amino-3,6-dideoxy-D-aldohexose which represents the nitrogen-containing moiety of the polyene antifungal antibiotics nystatin, pimaricin, rimocidin and amphotericin B.[1] To our knowledge, the synthesis of derivatives of mycosamine has been reported only once, starting from glucose, by Nicolaou et al. in their total synthesis of amphotericin B.[2]



Mycosamine
(α-D-pyranose form)



Herein, we wish to report a quite different and shorter approach to mycosamine involving a highly diastereoselective crossed aldol condensation reaction between the divalent tin enolate of an α-aminodienone tricarbonyliron complex and (*R*)-(+) benzyloxy- or *t*-butyldimethylsilyloxylactaldehyde.

For this purpose, we had first to synthesize the protected α-aminoketone complex **4**. This was accomplished starting from the known bromodienone complex **2**[3] (obtained by bromination of the silyl enol ether) by SN2 displacement of the bromine with sodium azide, leading to the azide **3**. High yields (95 %) were

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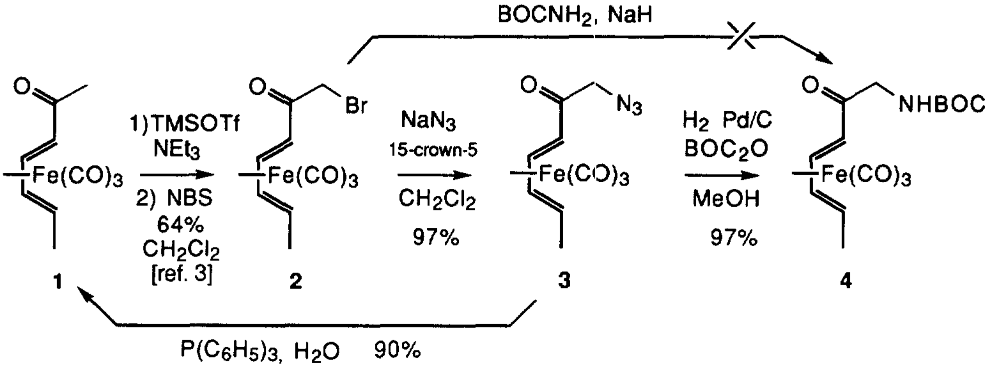
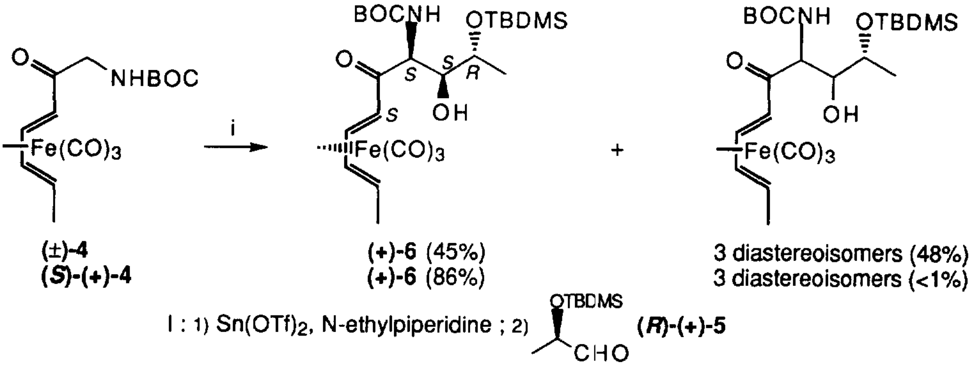
PII: S0040-4039(99)00271-3

achieved only when this reaction was carried out in the presence of 15-crown-5 ether,[2] more usual conditions giving the starting material back.[4] Attempted reduction of the azide with triphenylphosphine[5] was unsuccessful here, leading mainly to the unsubstituted dienone complex **1**.[6]

Following Saito's procedure,[7] the azide **3** was therefore reduced catalytically in the presence of BOC_2O, yielding nearly quantitatively the BOC-protected aminodienone complex **4**.

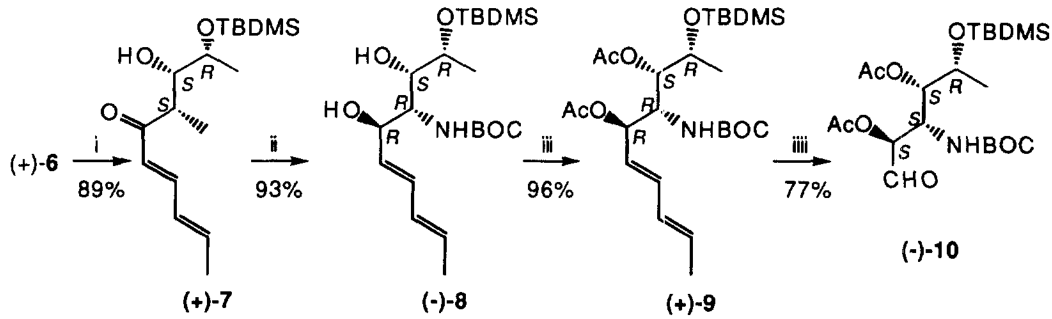


With the protected α-aminodienone complex in hand, we investigated crossed aldol condensation reactions with optically active α-hydroxyaldehydes. Although we had previously obtained good results for crossed aldol condensation reactions of silyl enol ethers of tricarbonyliron complexed dienones with aldehydes in the presence of $TiCl_4$,[8] these reactions were unsuccessful in this case, mainly due to the partial degradation of the amino enol ether. We therefore turned our attention towards divalent tin enolates which are known to display high reactivity and selectivity in aldol reactions in the presence of amines.[9] Indeed, in the presence of N-ethylpiperidine, the addition of the protected (*R*)-(+)-lactaldehyde **5** to the tin enolate of the racemic aminoketone (±)-**4** gave nearly quantitatively a mixture of four diastereoisomeric ketols from which the major product (+)-**6** ($[\alpha]_D$ = +44.7 ; c = 1 ; $CHCl_3$) could easily be isolated[10] by simple SiO_2 column chromatography (45 %). Although the aldolisation step provided this major ketol in only 45 % yield, this was a very significant result, *since this aldol reaction also constitutes a resolution.* When the same aldol condensation was carried out with the optically active complex (S)-(+)-**4**[11] which has the same absolute configuration at the iron attachment as the complex (+)-**6**, the product (+)-**6** ($[\alpha]_D$ = +45.6 ; c = 1.1 ; $CHCl_3$) was obtained in 86 % yield , and the three other diastereoisomers were isolated in less than 1 % yield.



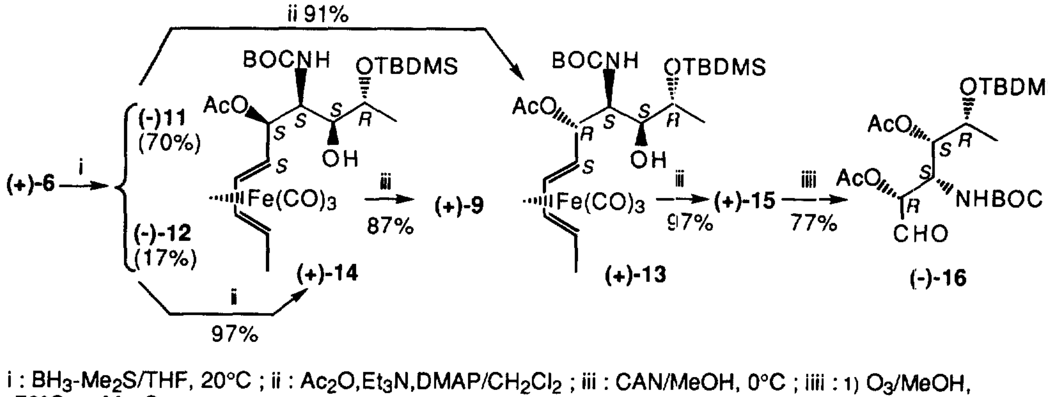
The described aldolisation reaction therefore constitutes an excellent way to introduce three of the four stereogenic centers present in mycosamine.

Since the reduction of an iron complexed dienone proceeds from the side opposite to the metal, the "enone" being in an s-*cis* conformation,[12] reduction of (+)-**6** leads to the "wrong" absolute configuration for the newly formed alcoholic center (*ψ-endo* alcohol) and not to that present in the natural product. To overcome this, we first carrried out the decomplexation (CAN, (+)-**7** as single diastereomer, 89 %) to take advantage of the highly diastereoselective reduction of β-hydroxyketones into *anti* 1,3-diols provided by tetramethylammonium triacetoxyborohydride.[13] Indeed, with this reagent, the β-hydroxyketone (+)-**7**, afforded exclusively the *anti* 1,3-diol (-)-**8** (93 %), with the required absolute configuration *R,S,R,R*.



i : CAN/MeOH, 0°C ; ii : $Me_4NHB(OAc)_3/CH_3CN$-AcOH ; iii : Ac_2O, Et_3N, $DMAP/CH_2Cl_2$;
iiii : 1) O_3/MeOH, -78°C, 2) Me_2S

For cleavage of the diene moiety into a formyl group, protection of the hydroxyl group is not absolutely necessary but gives better yields, especially for the acetoxy protecting group.[8] Thus, transformation of (-)-**8** into the diacetate (+)-**9** (96 % yield) followed by ozonolysis gave finally the protected mycosamine (-)-**10** (77 % ; configuration *S,S,S,R* ; $[\alpha]_D = -2.7$; c = 0.8 ; $CHCl_3$)



i : BH_3-Me_2S/THF, 20°C ; ii : Ac_2O,Et_3N,$DMAP/CH_2Cl_2$; iii : CAN/MeOH, 0°C ; iiii : 1) O_3/MeOH, -78°C, 2) Me_2S

The reduction of the complexed dienone (+)-**6** was also investigated. The *ψ-endo* alcohol (-)-**11** was obtained in 70 % yield, but in this particular case, the *ψ-exo* alcohol (-)-**12** was also formed (17 %). After easy separation by simple SiO_2 chromatography, both isomers were acetylated to give the complexed diacetates (+)-**13** (91 %) and (+)-**14** (97 %), which were decomplexed to afford the diene diacetates (+)-**15** and (+)-**9** (identical to the diene diacetate previously obtained). The ozonolysis of the major diacetate (+)-**15** then gave the protected 3-amino-3,6-dideoxy glucose (-)-**16** (77 % ; configuration *R,S,S,R* ; $[\alpha]_D$ = -18.4 ; c = 0.9 ; $CHCl_3$).

The complexed diacetates (+)-**13** and (+)-**14** could be obtained as single crystals, and their structures were determined by X-ray diffraction,[14] thus allowing the unambiguous complete structure determination for all compounds. Obviously from the (*S*)-(-) TBDMS protected lactaldehyde,[15] the protected 3-amino-3,6-dideoxy-aldohexoses (+)-*R,R,R,S* ($[\alpha]_D$ = +2.6 ; c = 1 : $CHCl_3$) and (+)-*S,R,R,S* ($[\alpha]_D$ = +20.9 ; c = 0.9 ; $CHCl_3$) (enantiomers of (-)-**10** and (-)-**16**) were also obtained. Since all products were obtained as pure diastereoisomers, their optical purity must be constant all along the synthesis. Therefore we can expect very high ees for the final compounds.[11]

Acknowledgment : we are grateful to BASF for gifts of Fe(CO)₅ and to Chiral Technologies-Europe (Dr. Cristina Suteu) for the ee determination by hplc.

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10. The other diastereoisomers could also be separated, but only by HPLC (reversed phase Zorbax ODX column, $MeOH/H_2O$ 3:1).
11. The optically active complex (*S*)-(+)-**4** [$[\alpha]_D$ = +218 (c=1; $CHCl_3$) ; ee = 98 % / hplc : Chiralcel OJ, isohexane / iPrOH] was obtained from the enantiomerically pure dienone complex (*S*)-(+)-**1** ($[\alpha]_D$ = +395; c=1; $CHCl_3$),[17] *via* the bromodienone complex (*S*)-(+)-**2** ($[\alpha]_D$ = +242; c =1.2; $CHCl_3$).
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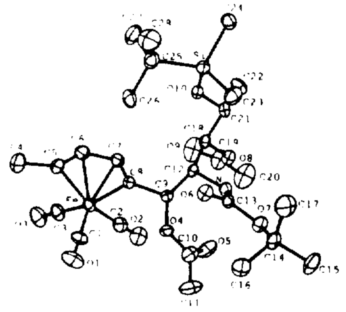
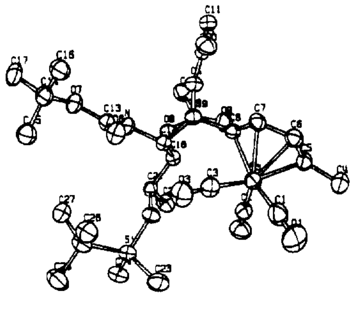


The details of the X-ray structures determinations will be given in the full paper.
Ortep views of (+)-**13** and (+)-**14** (Service Communs de Rayons X de la Fédération de Recherche Chimie de l'ULP).



(+)-**13** mp = 103°C
(+)-**14** mp = 121°C

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