Tetrahedron: Asymmetry Vol. 1. No. 6, pp. 403415.1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

SYNTHESIS OF CAIRAL AMINOCYCLITOLS VIA EPOXYEPIMINATION

H. Braun, W. Burger, G. Kreszet, F. P. Schmidtchen*

Organisch Chemisches Institut, TU Miinchen
8046 Garching, FRG

J. L. Vaerman, H. G. Viehe

Lab. de Chimie Organique, Université Catholique de Louvain
Louvain la Neuve, Belgique

(Received23 April 1990)

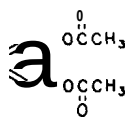
Abstract: Asymmetric Hetero-Diels-Alder reactions of cyclohexadienes 1 and (±)2 with the a-chloronitroso derivative of D-mannose 6 give the chiral dihydrooxazines 3-5. After N-functionalisation with the chloro-olefin 10 the N-vinyl-dihydrooxazines 11-13 thermally rearrange to epoxyepimines 14-16. The formation of konduramine byproducts 18 and 19 indicates a biradical mechanism. Opening of oxirane and aziridine rings of 14 and acidic enamine hydrolysis lead to chiral aminocyclitols.

Aminocyclitols form the aglycon part of numerous aminoglycoside antibiotics e.g. streptomycin, gentamycin and fortimycin. Although several routes to aminocyclitols were described in the past [1-4], the access to chiral aminocyclitols remains limited to only a few examples [5,6]. In this paper we report a general enantiospecific total synthesis of aminocyclitols starting from chiral a-chloronitroso compounds and using the Hetero-Diels-Alder and epoxyepimination reactions. This approach is advantageous as it starts from easily obtainable materials and does not require tedious separations of diastereomers or enantiomers.

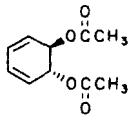
From previous work on the Hetero-Diels-Alder reaction we had at our disposal the chiral dihydrooxazines (+)3, (-)4, and (+)5. These are available in high chemical and optical yield by cycloaddition of the 1,3-cyclohexadienes 1, (-)2a and (+)2b with the a-chloronitroso derivative of D-mannose 6 [7,8,9]. The corresponding enantiomeric dihydrooxazines can be obtained using the a-chloronitroso derivative of D-ribose 7 instead of 6 [7,9].

For the conversion of dihydrooxazines to aminocyclitols the cleavage of the N-O bond and the subsequent functionalization of the carbon-carbon double bond is required. A reaction that allows to achieve both goals in one step is the rearrangement of dihydrooxazines 8 to epoxyepimines 9 [10,11]. The rearrangement is stereospecific with regard to the aziridine-

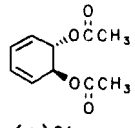
† deceased on September 18th, 1987



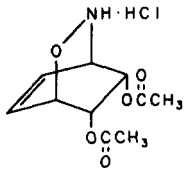
1



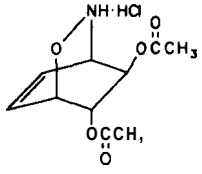
(−)2a



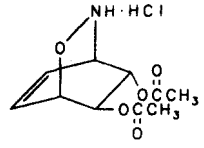
(+)2b



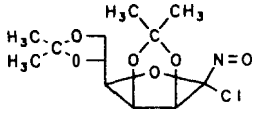
3



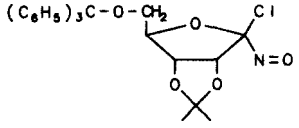
4



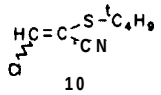
5



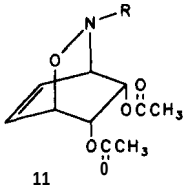
6



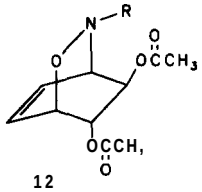
3 4



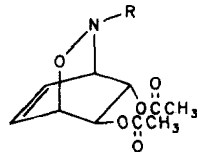
10



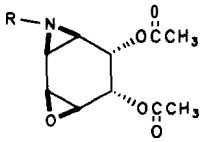
11



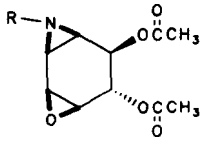
12



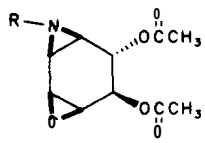
13



14



15



16

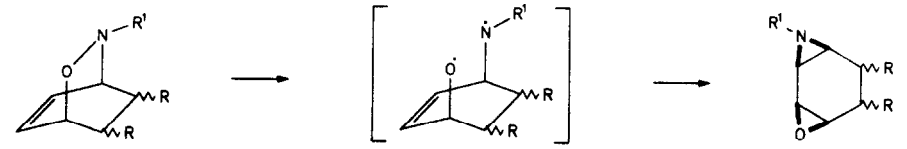
and oxirane rings being cis to each other.

However, this reaction is strongly dependent on the nature of the N-substituent [10]. The chlorovinyl derivative 8a that is formed by nitroso-olefin addition to cyclohexadienes has been described earlier [11], whereas captodative vinyl substituents (e.g. in 8b or 8c) have been reported recently.

In order to prepare derivative 8b the stereoisomeric bicyclic dihydrooxazines 3, 4 and 5 were allowed to react with the captodative chloro-olefin 10. In all three cases the N-functionalized dihydrooxazines 11-13 were obtained in good to excellent yields as mixtures of E,Z isomers. The isomers can easily be distinguished by the $^{1}H/^{13}C$ coupling constants of the olefinic proton to the nitrile group [12], the E-isomer exhibiting always the larger values.
Upon heating in toluene at 110°C the N-substituted dihydrooxazines 11-13 isomerised within 24 hours to the corresponding epoxyepimines 14-16 in about 80% yield. In no case diastereomeric products could be detected.

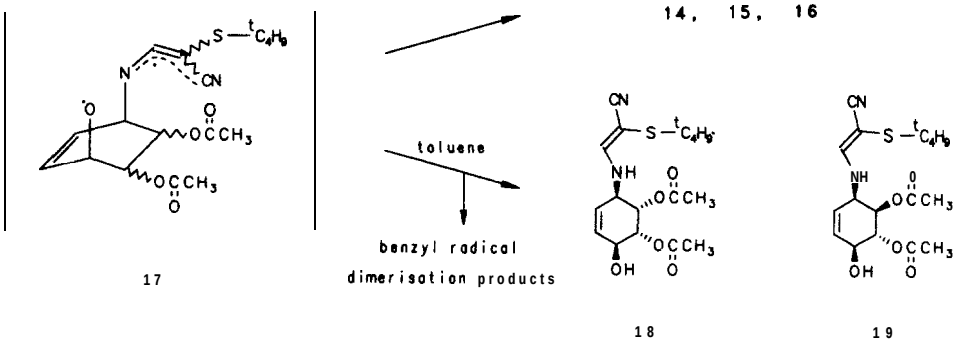
From the reaction of the dihydrooxazines 11 and 12 the konduramine derivatives 18 and 19 were isolated in minor yields together with a mixture of dimerisation products of the benzyl radical. The occurance of these byproducts supports the proposed biradical mechanism. The biradicals (e.g. 17) can react either intramolecularly to epoxyepimines 14-16 or abstract hydrogen from the toluene solvent to give the konduramines 18, 19.

The conversion of the epoxyepimines to aminocyclitols was carried out starting from 14 as an example. Chemo- and regioselective aziridine ring opening was achieved by treating 14 with 2.5% aqueous perchloric acid at room temperature. After acetylation the reaction yielded the oxirane (-)20 as the sole product. The configurational pattern of (-)20 follows from the magnitude of the ^{1}H coupling constants $J_{3,4}$ = 1.6 Hz and $J_{4,5}$ = 9.6 Hz, which prove the cis-relationship of the H-3 and H-4 protons and the trans configuration of the H-4 and H-5 protons [13]. Thus, in this case again the usually observed trans opening of aziridines is found [14].
Under forcing conditions (20% aqueous $HClO_4$) the opening of the oxirane as well as the aziridine rings of 14 took place simultaneously with enamine hydrolysis, giving the inosamine hexa-acetate 21, after acetylation in 80% yield. The allo-configuration of (-)21 was confirmed by the respective ^{1}H coupling constants.



8	R^1
a	$-CCl=CCl_2$
b	$-CH=C(CN)-S-{}^tC_4H_9$
c	$-CH=C(COOC_2H_5)-SCH_3$

9



14, 15, 16

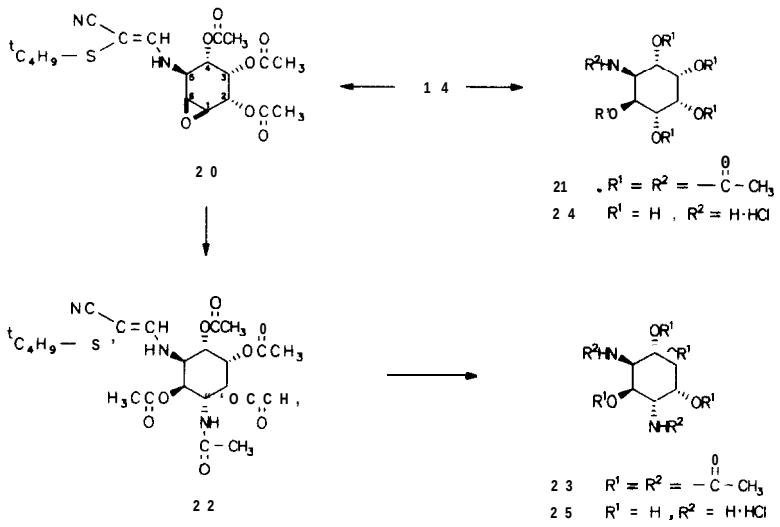
toluene

benzyl radical dimerisation products

17

18

19



20

21 $R^1 = R^2 = -\overset{O}{\overset{\|}{C}}-CH_3$

24 $R^1 = H$, $R^2 = H\cdot HCl$

22

23 $R^1 = R^2 = -\overset{O}{\overset{\|}{C}}-CH_3$

25 $R^1 = H$, $R^2 = H\cdot HCl$

For introduction of a second nitrogen function into the aminocyclitol system the oxirane (-)20 was treated with aqueous ammonia. Subsequent acetylation afforded the expected product (-)22 in 74% yield with the same allo-diastereomeric pattern on the cyclohexane ring as in (-)21. Acidic hydrolysis and acetylation of the enamine (-)22 gave the inosdiamine hexaacetate (-)23.

The desired target compounds (-)24 and (-)25 were readily obtained as hydrochlorides by refluxing the hexaacetates (-)21 and (-)23 in HCl/methanol/water.

In conclusion we have found that the epoxyepimination of Hetero-Diels-Alder adducts is a valuable access route to chiral aminocyclitols.

Experimental part:

(1S,4R,7S,8S)-7,8-diacetoxy-3-(E,Z-2'-cyano-2'-tert.butylmercapto-ethenyl)-3-aza-2-oxabicyclo[2.2.2]oct-5-ene 11

Dihydrooxazine 3 (5.0 g, 19.0 mmol) was suspended in 40 ml CH_2Cl_2 and 3.85 g (38 mmol) triethylamine was added resulting in a clear solution. Then 3.34 g (19.0 mmol) 10 in 10 ml CH_2Cl_2 was added dropwise. The mixture was stirred at room temp. under nitrogen until t.l.c. indicated a complete reaction (n-hexane/ ethylacetate 3:2, ca. 24 h). The mixture was extracted several times with water, the organic phase was dried over $MgSO_4$, filtered and evaporated. After chromatography (silica, n-hexane/ ethylacetate 3:2) an oily product was obtained consisting of the E,Z isomers 11.
The E-isomer was obtained in pure form by crystallization from ether/ n-hexane.
(+)11 (E-isomer): Yield: 5.71 g (82%), colourless crystals, m.p. 143°C (decomp.)
$[\alpha]_D^{23}$ = +158 (c = **0.5**, $CHCl_3$). **IR**(KBR): 3050, 2980, 2200, 1745, 1600, 1380, 1250. **^{1}H-NMR** (360 MHz, $CDCl_3$): 6 = 6.79 (d, H-l'); 6.69-6.54 (m, 2H, H-5, H-6); 5.38 (dd, H-7); 5.33 (dd, H-8); 5.03 (m, H-l); 4.53 (m, H-4); 2.05, 2.04 (s, 6H, 2 x OAc); 1.32 (s, 9H, H-4'); $^3J_{1,6} = J_{4,5}$ = 5.7 Hz; $^3J_{1,7} = {}^3J_{4,8}$ = 3.5 Hz: $^3J_{5,6}$ = 8 Hz; $^3J_{7,8}$ = 7.8 Hz: $^4J_{1,5}$ = 1.7 Hz; $^4J_{4,6}$ = 1.8 Hz; $J_{4,1}$ < 1 Hz. **^{13}C-NMR** (90 **MHz**, $CDCl_3$): 6 = 169.3 (2 x C=O two signals): 154.1 (C-l'); 130.6, 130.2 (C-5, C-6); 119.8 (CN); 75.2, 70.9, 66.8, 66.3 (C-l, C-7, C-8, C-2'): 56.4 (C-4); 47.2 (C-3'); 30.2 (C-4'); 20.3, 20.2 (2 x CH_3 ester); $^3J_{H1',CN}$ = 11.0 Hz. **MS**(EI) m/z(%I): 366 ($M^{+\cdot}$,12); 31C (28); 94 (46); 43 (100).

$C_{17}H_{22}N_2O_5S$ (366.4)
calc. C 55.72 H 6.05 N 7.64
found. C 55.39 H 6.03 N 7.66

11 (Z-isomer): **^{1}H-NMR** (360 MHz, $CDCl_3$): δ = 7.04 (d, H-l'); 6.67-6.50 (m, 2H, H-5, H-6); 5.61 (m, H-4); 5.21-5.14 (m, 2H, H-7, H-8); 4.76 (m, H-l); 2.02, 2.01 (s, 6H, 2 x OAc); 1,28 (s, 9H, H-4'). **^{13}C-NMR** (90 MHz, $CDCl_3$): 6 = 169.1, 169.0 (2 x C=O); 153.7 (C-1');131.2, 130.1 (C-5, C-6); 121.5 (CN); 73.3, 69.6, 66.3, 65.3 (C-l, C-7, C-8, C-2'); 54.2 (C-4); 49.7 (C-3'); 29.7 (C-4'); 20.0, 19.8 (2 x CH_3 ester); $^3J_{H\text{-}1',CN}$ = 5.9 Hz.

(1S, 4R, 7S, 8R)-7,8-diacetoxy-3-(E,Z-2'-cyano-2'-tert.butyl-mercaptoethenyl)-3-aza-2-oxabicyclo [2.2.2] oct-5-ene 12

Compound 4 [7] (6.4 g, 24.3 mmol) was suspended in 50 ml CH_2Cl_2. Then 5.06 g (50 mmol) triethylamine was added and a clear solution was obtained. Subsequent to the addition of (4.26g, 24.3 mmol) 10 in 10 ml CH_2Cl_2 the mixture was refluxed under nitrogen until t.l.c. indicated a complete reaction (n-hexane/ ethyl acetate 3:2, ca. 3d). Work up and chromatography were carried out as described with 11. The compound 12 was obtained as a mixture of E,Z isomers. The E-isomer could be crystallized from ether/ n-hexane.
(-)12 (E-isomer): Yield: 5.17 g (58%) colourless crystals, m.p. 107°C (dec.)
$[\alpha]_D^{25}$ = -19 (c = 0.5, $CHCl_3$)
IR (KBr): 3080, 3060, 2990, 2975, 2200, 1750, 1595, 1570, 1230, 1115, 980, 915, 740, 710. **^{1}H-NMR** (360 MHz, $CDCl_3$): 6 = 6.75 (d, H-l'); 6.64-6.59 (m, 2H, H-5, H-6); 5.11 (dd, H-7); 5.02 (m, H-l); 4.66 (dd, H-8); 4.53 (m, H-4); 2.17, 2.06 (s, 6H, 2 x OAc); 1.32 (s, 9H, H-4'); $^3J_{1,7}$ = 4.2 Hz; $^3J_{4,5}$ = 5.3 Hz; $^3J_{4,8}$ = 2.9 Hz; $^3J_{7,8}$ = 1.7 Hz; $^4J_{1,5}$ < 1 Hz; $^4J_{4,6}$ = 1.1 Hz. **^{13}C-NMR** (90 MHz, $CDCl_3$): 6 = 170.3, 169.3 (2xC=O); 153.9 (C-1'); 130.3, 129.7 (C-5, c-6); 120.1 (CN); 73.5, 72.9, 71.3, 70.3 (C-l, C-7, C-8, C-2'); 59.1 (C-4); 47.1 (C-3'); 30.2 (C-4'); 20.8, 20.6 (2 x CH_3 ester); $^3J_{H\text{-}1',CN}$ = 11.4 Hz. MS (EI) m/z(%): 366 ($M^{+\cdot}$, 5.9); 310 (26); 94 (38); 57 (38); 43 (100).
$C_{17}H_{22}N_2O_5S$ (366.4)
calc. C 55.72 H 6.05 N 7.64
found. C 55.88 H 6.08 N 7.46

12 (Z-isomer): ^{1}H-NMR (360 MHz, $CDCl_3$): 6 = 7.05 (d, H-l'); 6.52-6.38 (m, 2H, H-5, H-6); 5.54 (m, H-4); 4.90 (dd, H-7); 4.74 (m, H-l); 4.51 (dd, H-8); 2.15, 2.04 (s, 6H, 2 x OAc); 1.28 (s, 9H, H-4'). ^{13}C-NMR (90 MHz, $CDCl_3$): 6 = 169.4, 168.8 (2 x C=O); 153.5 (C-1'); 130.5, 129.7 (C-5, C-6); 121.8 (CN); 72.1, 70.8, 70.1, 69.7 (C-l, C-7, C-8, C-2'); 57.0 (C-4); 48.8 (C-3'); 30.1 (C-4'); 20.2, 20.1 (2 x CH_3 ester); $^3J_{H-1',CN}$ = 5.6 Hz.

(1S,4R,7R,8S)-7,8-diacetoxy-3-(E,Z-2'-cyano-2'-tert.butyl-mercaptoethenyl)-3-aza-2-oxabicyclo[2.2.2]oct-5-ene 13

800 mg (3 mmol) of a 1:1 mixture of 4 and 5 [9] were suspended in 10 ml CH_2Cl_2 and 300 mg (3 mmol) triethylamine was added, whereby a clear solution was obtained. Then 260 mg (1.5 mmol) 10 in 2 ml CH_2Cl_2 was added dropwise and the mixture was stirred under nitrogen until t.l.c. indicated a complete reaction (n-hexane/ ethylacetate 3:2, 24 h). Work up and chromatography were carried out as described with 11.
13 was obtained as a mixture of E,Z isomers. Yield: 430 mg (79%) colourless oil. 'H-NMR (360 MHz, $CDCl_3$): 6 = 7.16, 6.81 (d, H-l'); 6.71-6.50 (m, 2H, H-5, H-6); 5.88, 4.48 (m, H-4); 5.01, 4.62 (m, 3H, H-l, H-7. H-8); 2.19, 2.17, 2.08, 2.07 (s, 6H, OAc); 1.43, 1.42 (s, 9H, H-4'). ^{13}C-NMR (90 MHz, $CDCl_3$): δ= 169.9 (two signals), 169.2, 169,1 (C=O); 153.6 (C-l'); 130.5, 129.7, 129.6, 129.3 (C-5, C-6); 121.7, 119.8 (CN); 74.1, 74.0, 73.9, '73.8, 69.8, 69.0 (C-l, C-7, C-8, C-2'); 56.0, 54.0 (C-4); 49.9, 49.7 (C-3'); 30.4, 29.8 (C-4'): 20.6, 20.5, 20.4, 20.3 (CH_3 ester).

General procedure for the rearrangement of 11-13 to epoxyepimines:
A 0.1 m solution of 11, 12 or 13 was stirred at 110°C in dry toluene under nitrogen for 24 h. In each case t.l.c. (n-hexane/ethylacetate 3:2) showed three large spots (R_f = 0.90, 0.20, 0.08). The toluene was evaporated and the products were separated by column chromatography. The ^{1}H-NMR-spectra of the first fraction (R_f = 0.9) were identical in all cases: ^{1}H-NMR (360 MHz, $CDCl_3$): 7.0-7.6 (m), 1.0-1.7 (m). The GC/MS analysis of this first fraction showed four products with m/z = 182.
Reaction of 11 (4.80 g, 13.1 mmol): Second fraction (R_f = 0.20)
(1S,2S,4S,5R,6S,7R)-5,6-diacetoxy-8-(E,Z-2'-cyano-2'-tert.butylmercaptoethenyl)-8-aza-3-oxatricyclo[5.1.0.0^{2,4}]octane 14
Yield: 3.85 g (80%), colourless oil. IR (film): 2990, 2205, 1755, 1530, 1440, 1380, 1240, 1055.

MS (EI) m/z(%): 366 ($M^{+\cdot}$, 5.8); 310 (6); 43 (100).

$C_{17}H_{22}N_2O_5S$

calc. C 55.72 H 6.05 N 7.64

found. c 55.77 H 6.18 N 7.32

14 (E-isomer)

^{1}H-NMR (360 MHz, $CDCl_3$): δ= 7.20 (s, H-l'); 5.41 (t, H-5); 5.05 (t, H-6); 3.68 (dd, H-21: 3.31 (t, H-4); 3.10 (dd, H-l); 2.60 (dd, H-7); 2.10, 2.08 (s, 6H, 2 x OAc); 1.32 (s, 9H, H-4'); $^3J_{1,2}$ = 2.9 Hz; $^3J_{2,4}$ = 3.6 Hz; $^3J_{4,5}$ = $^3J_{5,6}$ = $^3J_{6,7}$ = 3.2 Hz; $^3J_{1,7}$ = 6.2 Hz. **^{13}C-NMR** (90 MHz, $CDCl_3$): 6 = 169.7 (C=O); 162.5 (C-1); 117.4 (CN); 87.7 (C-2'); 67.7, 67.4 (C-5, C-6); 52.0, 47.7, 47.2 (C-2, C-4, C-3'); 38.7, 37.7 (C-1, C-7); 30.3 (C-4'); 20.6 (CH_3 ester); $^3J_{H\text{-}1',CN}$ = 11.2 Hz.

14 (Z-isomer)

^{1}H-NMR (360 MHz, $CDCl_3$): 6 = 7.39 (s, C-l'); 5.27 (t, H-5); 5.24 (t, H-6); 3.65 (dd, H-2); 3.26 (t, H-4); 3.03 (dd, H-l); 2.60 (dd, H-7); 2.09, 2.02 (s, 6H, 2 x OAc); 1.42 (s, 9H, H-4'). **^{13}C-NMR** (90 MHz, $CDCl_3$): 6 = 169.7 (C=O); 159.7 (C-1'); 119.8 (CN); 90.3 (C-2'); 67.9, 67.4 (C-5, C-6); 51.6, 51.0, 47.6 (C-2, C-4, C-3'); 40.7, 37.9 (C-l, C-7); 31.0 (C-4'); 20.8 (CH_3 ester); $^3J_{H\text{-}1',CN}$ = 5.8 Hz.

The third fraction was crystallised from CH_2Cl_2/n-hexane:

(1R,2S,3R,4S)-1-(Z-2'-cyano-2'-tert.butylmercaptoethenyl)amino)-2,3-diacetoxy-4-hydroxycyclohex-5-ene 18

Yield: 230 mg (5%), colourless crystals, m.p. 181°C. $[\alpha]_D^{25}$ = -198° (c = 0.5, $CHCl_3$). IR (KBr): 3360, 2980, 2195, 1745, 1625, 1380, 1250, 1055. **^{1}H-NMR** (360 MHz, $CDCl_3$): 6 = 7.37 (d, H-l'); 5.97 (m, H-5); 5.89 (dd, NH); 5.72 (ddd, H-6); 5.17 (dd, H-3); 5.14 (dd, H-2); 4.31 (m, H-4); 4.10 (m, H-l); 2.81 (d, OH); 2.11, 2.07 (s, 6H, 2 x OAc); 1.35 (s, 9H, H-4'); $^3J_{1,2}$ = 7.2 Hz; $^3J_{2,3}$ = 2.4 Hz; $^3J_{3,4}$ = $^3J_{4,5}$ = 4.0 Hz: $^3J_{5,6}$ = 10.0 Hz; $^3J_{1,6}$ = 2.5 Hz; $^3J_{4,OH}$ = 5.5 Hz; $^3J_{1,NH}$ = 9.0 Hz; $^4J_{1,5}$ = 0.5 Hz; $^4J_{4,6}$ = 1.9 Hz. **^{13}C-NMR** (90 MHz, $CDCl_3$): 6 = 170.4, 170.2 (2 x C=O); 155.3 (C-1'); 130.1, 127.8 (C-5, C-6); 122.4 (CN); 72.0, 72.9, 68.8 (C-2, C-3, C-2'); 66.6 (C-4); 55.2 (C-l); 49.4 (C-3'); 30.6 (C-4'); 20.9, 20.8 (CH_3 ester); $^3J_{H\text{-}1',CN}$ = 4.8 Hz. MS (EI) m/z(%): 368 ($M^{+\cdot}$, 14); 312 (36); 192 (52); 43 (100).

$C_{17}H_{24}N_2O_5S$ (368.5).

calc. C 55.41 H 6.57 N 7.60

found. C 55.08 H 6.64 N 7.42

Reaction of 12 (4.00 g, 10.9 mmol); second fraction (R_f = 0.2):
(1S,2S,4S,5R,6R,7R)-5,6-diacetoxy-8-(E,Z-2'-cyano-2'-tert.butylmercapto-ethenyl)-8-aza-3-oxatricyclo[5.1.0.0^{2,4}]octane 15.
The E-isomer was obtained in pure form by crystallization from ether/n-hexane:
15 (E-isomer); Yield: 3.09 g (77%), colourless crystals, m.p. 131°C
$[\alpha]_D^{25}$ = -10 (c = 0.5, $CHCl_3$).
IR (KBr): 3060, 2980, 2205, 1745, 1575, 1420, 1385, 1375, 1245, 1230.
'H-NMR (360 MHz, $CDCl_3$): 6 = 7.10 (s, H-l'); 5.18 (dd, H-6); 5.05 (dd, H-5); 3.54 (t, H-2); 3.10 (dd, H-7); 3.06 (dd, H-4); 2.98 (dd, H-l); 2.14, 2.12 (s, 6H, 2 x OAc); 1,35 (s, 9H, H-4'); $^3J_{1,2}$ = 3.5 Hz; $^3J_{2,4}$ = 3.9 Hz; $^3J_{4,5}$ = 1.5 Hz; $^3J_{5,6}$ = 9.2 Hz; $^3J_{6,7}$ = 2.5 Hz; $^3J_{1,7}$ = 6.2 Hz. **^{13}C-NMR** (90 MHz, $CDCl_3$): δ = 171.0, 169.6 (2 x C=O); 162.0 (C-1'); 116.9 (CN); 88.6 (C-2'); 69.4, 69.3 (C-5, C-6); 53.2, 48.0, 47.3 (C-2, C-4, C-3'); 41.7, 37.5 (C-l, C-7); 30.6 (C-4'); 20.9, 20.7 (CH_3 ester); $^3J_{H-1',CN}$ = 11.7 Hz.
MS (EI) m/z(%): 366 ($M^{+\cdot}$, 10); 310 (8); 57 (32); 43 (100).
$C_{17}H_{22}N_2O_5S$ (366.4).
calc. C 55.72 H 6.05 N 7.64
found. C 55.42 H 6.18 N 7.65.

15 (Z-isomer): 'H-NMR (360 MHz, $CDCl_3$): δ = 7.30 (s, H-l'); 5.15 (dd, H-6); 5.02 (dd, H-5); 3.53 (t, H-2); 3.09-3.04 (m, 2H, H-4, H-7); 2.90 (dd, H-l); 2.10, 2.09 (s, 6H, 2 x OAc); 1.46 (s, 9H, H-4'). **^{13}C-NMR** (90 MHz, $CDCl_3$): δ = 170.3, 169.3 (2 x C=O); 160.1 (C-1'); 119.7 (CN); 91.0 (C-2'); 70.7, 70.5 (C-5, C-6); 53.0, 49.6, 47.9 (C-2, C-4, C-3'); 40.7, 39.6 (C-l, C-7); 30.8 (C-4'); 20.8, 20.6 (CH_3 ester); $^3J_{H-1',CN}$ = 4.9 Hz.
The third fraction (R_f = 0.08) was crystallized from CH_2Cl_2/n-hexane.
(1R,2R,3R,4S)-1-(Z-2'-cyano-2'-tert.butylmercaptoethenyl)amino)-2,3-diacetoxy-4-hydroxycyclohex-5-ene 19; Yield: 140 mg (3.5%), colourless crystals. m.p. 134°C. $[\alpha]_D^{25}$ = -265° (c = 0.5, $CHCl_3$).
IR (KBr): 3420, 3340, 2980, 2200, 1740, 1620, 1230, 1040, 770
^{1}H-NMR (360 MHz, $CDCl_3$): 6 = 7.19 (d, H-l'); 5.98 (ddd, H-5); 5.78 (m, 2H, H-6, NH); 5.02 (m, 2H, H-2, H-3); 4.30 (m, H-4); 4.25 (m, H-l); 2.81 (d OH): 2.14, 2.12 (s, 6H, 2 x OAc); 1.39 (s, 9H, H-4'): $^3J_{1,2}$ = 4,1 Hz; $^3J_{3,4}$ = 5.2 Hz: $^3J_{4,5}$ = 2.6 Hz: $^3J_{5,6}$ = 10.2 Hz; $^3J_{1,6}$ = 5.0 Hz; $^3J_{4,OH}$ = 5.7 Hz; $^3J_{1',NH}$ = 13.3 Hz; $^4J_{1,5}$ = 1.9; $^4J_{4,6}$ = 1.0 Hz. **^{13}C-NMR** (90 MHz, $CDCl_3$): δ = 171.1, 169.9 (2 x C=O); 155.2 (C-l'); 133.4, 123.6 (C-5, C-6); 122.3 (CN); 72.6, 70.5, 69.8, 69.0 (C-2, C-3, C-4, C-2'); 54.0 (C-1); 49.7 (C-3'); 30.7 (C-4'); 20.8, 20.7 (CH_3 ester); $^3J_{H-1',CN}$ = 4.6 Hz. MS (EI) m/z(%): 368 ($M^{+\cdot}$, 7.8); 312 (24); 192 (34); 57 (32); 43 (100).

$C_{17}H_{24}N_2O_5S$ (368.5)
calc. C 55.41 H 6.57 N 7.60
found. C 55.29 H 6.57 N 7.63

Reaction of 13 (350 mg, 1mmol); Second fraction (R_f = 0.2):
(1S,2S,4S,5S,6S,7R)-5,6-diacetoxy-8-(E,Z-2'-cyano-2'-tert.butylmercapto-ethenyl)-8-aza-3-oxatricyclo[5.1.0.0^{2,4}]octane 16;
Yield: 260 mg (74%), colourless oil; IR (film): 2995, 2200, 1745, 1575, 1435, 1375, 1235, 1050, 900. MS (EI) m/z(%): 366 ($M^{+\cdot}$, 4.8); 310 (10); 43 (100).
$C_{17}H_{22}N_2O_5S$ (368.5)
calc. C 55.72 H 6.05 N 7.64
found. C 55.54 H 6.10 N 7.36

16 (E-isomer)
^{1}H-NMR (360 MHz, $CDCl_3$):δ= 7.25 (s, H-l'); 5.39 (d, H-5); 4.88 (dd, H-6); 3.77 (dd, H-21; 3.36 (d, H-4); 3.06 (dd, H-l); 2.43 (dd, H-7); 2.10. 2.09 (s, 2 x OAc, not distinguishable from the Z-isomer); 1.34 (s, H-4', 9H); $^3J_{1,2}$ = 2.8 Hz; $^3J_{2,4}$ = 4.0 Hz; $^3J_{4,5}$ < 1 Hz; $^3J_{5,6}$ = 9.8 Hz; $^3J_{6,7}$ = 2.5 Hz; $^3J_{1,7}$ = 6.2 Hz. **^{13}C-NMR** (90 MHz, $CDCl_3$):δ= 170.5, 170.0 (2 x C=O); 160.0 (C-l'); 120.0 (CN); 87.6 (C-2'); 70.8, 69.7 (C-5, C-6); 54.9, 49.2, 48.9 (C-2, C-4, C-3'); 40.8, 39.6 (C-l, C-7); 31.0 (C-4'); 20.8 (CH_3 ester); $^3J_{H-1',CN}$ = 11.2 Hz.
16 (Z-isomer)
'H-NMR (360 MHz, $CDCl_3$): 6 = 7.47 (s, H-l'); 5.39 (d, H-5); 4.90 (dd, H-6); 3.72 (dd, H-2); 3.36 (d, H-4); 2.99 (dd, H-l); 2.37 (dd, H-7); 2.10, 2.09 (s, 2 x OAc, not distinguishable from the E-isomer); 1.43 (s, 9H, H-4'). **^{13}C-NMR** (90 MHz, $CDCl_3$): δ= 170.5, 170.1 (2 x C=O); 162.5 (C-1'); 120.0 (CN); 87.6 (C-2'); 70.6, 69.4 (C-5, C-6); 55.0, 50.5, 47.3 (C-2, C-4, C-3'); 40.2, 38.4 (C-l, C-7); 30.3 (C-4'); 20.8 (CH_3 ester); $^3J_{H-1',CN}$ = 5.0 Hz.

(1S,2R,3S,4S,5R,6S)-2,3,4-triacetoxy-5-(Z-2'-cyano-2'-tert.butylmercapto-ethenyl)amino-7-oxabicyclo[4.1.0]heptane 20
1.0 g (2.7 mmol) 14 was dissolved in 10 ml CH_3CN, 3 ml of 2.5% $HClO_4$ was added and the mixture was stirred at room temperature until t.l.c. indicated a complete reaction (n-hexane/ethylacetate 1:1, ca. 30 h). The mixture was neutralized with sodium carbonate. The solvents were evaporated and the residue was acetylated with 10 ml Ac_2O/pyridine 1:1 (30 min). After evaporation i. vac. the residue was extracted with CH_2Cl_2/H_2O. The organic phase was dried over $MgSO_4$, filtered and evaporated. Crude 20 was purified by column chromatography (silica, n-hexane/ethylacetate 1:1) and crystallized from ether/n-hexane.

Yield: 0.91 g (78%), colourless crystals, m.p. 85°C; $[\alpha]_D^{25}$ = -165 (c = 0.5, $CHCl_3$).
IR (KBr): 3335, 2990, 2195, 1760, 1630, 1380, 1250, 1230, 1045.
^{1}H-NMR (360 MHz, $CDCl_3$):δ= 7.37 (d, H-l'); 5.89 (dd, NH]; 5.42 (ddd, H-3); 5.16 (d, H-2); 4.82 (dd, H-4); 3.99 (ddd, H-5); 3.49 (t, H-6); 3.27 (dd, H-l); 2.17, 2.09, 2.04 (s, 9H, 3 x OAc); 1.35 (s 9H, H-4'); $^3J_{1,2}$ < 1 Hz; $^3J_{2,3}$ = 3.8 Hz: $^3J_{3,4}$ = 1.6 Hz: $^3J_{4,5}$ = 9.6 Hz: $^3J_{5,6}$ = 2.1 Hz; $^3J_{1,6}$ = 3.6 Hz: $^4J_{1,3}$ = 1.9 Hz. **^{13}C-NMR** (90 MHz, $CDCl_3$): 6 = 169.6, 169.5, 169.0 (3 x C=O); 155.2 (C-l'); 122.0 (CN); 70.0, 68.8, 68.5, 66.4 (C-2, C-3, C-4, C-2'); 55.7, 55.3, 55.1 (C-l, C-6, C-3'); 49.4 (C-5); 30.6 (C-4'); 20.7, 20.6, 20.4 (3 x CH_3 ester); $^3J_{H\text{-}1',CN}$ = 4.7 Hz. MS (EI) m/z(%): 426 ($M^{+\cdot}$, 6); 370 (37); 328 (59); 43 (100).

1L-5-amino-5-deoxy-allo-inositole-hexaacetate 21

0.65 g (1.8 mmol) 14 was dissolved in 10 ml CH_3CN. Then 3 ml of 20% $HClO_4$ was added and the mixture was stirred at room temp. for 7d. Work up and acetylation as described with 20 followed by crystallization from CH_2Cl_2/n-hexane yielded 560 mg (73%) 21 as colourless crystals m-p. 143°C; $[\alpha]_D^{25}$ = -5° (c ≈ 0.5, $CHCl_3$).
IR (KBr): 3410, 3300, 2980, 1755, 1665, 1550, 1380, 1230. **^{1}H-NMR** (360 MHz, $CDCl_3$): 6 = 5.58 (m, 2H, H-3, NH); 5.33 (t, H-l); 5.24 (dd, H-4); 5.22 (t, H-6); 5.16 (t, H-2); 4.90 (ddd, H-5); 2.19, 2.17, 2.16, 2.06, 2.00, 1.95 (s, 18H, 6 x CH_3); $^3J_{1,2} = {}^3J_{2,3}$ = 3.4 Hz: $^3J_{3,4}$ = 3.2 Hz; $^3J_{4,5}$ = 11.2 Hz; $^3J_{5,6}$ = 3.0 Hz; $^3J_{1,6}$ = 3.5 Hz. **^{13}C-NMR** (90 MHz, $CDCl_3$):δ= 171.1, 170.1, 169.9, 169.5, 169.2, 169.0 (6 x C=O); 70.2, 68.6, 67.6, 67.2, 66.1 (c-l, C-2, C-3, C-4, C-6); 46.0 (C-5); 23.2, 20.8, 20.8, 20.7, 20.5 (6 x CH_3). MS (EI) m/z(%): 432 ($M^{+\cdot}$+1, 0.7); 209 (38); 183 (81); 43 (100).
$C_{18}H_{25}NO_{11}$ (431.4)
calc. C 50.12 H 5.84 N 3.25
found. C 50.03 H 5.64 N 3.24

(1S,2R,3R,4R,5S,6R)-1,2,3,5-tetraacetoxy-4-acetylamino-6-(Z-2'-cyano-2'-tert.butylmercaptoethenyl)aminocyclohexane 22

340 mg (0.8 mmol) 20 was dissolved in 10 ml CH_3OH/H_2O 1:1. The solution was saturated with ammonia and stirred for 5d at room temperature. The mixture was evaporated and the residue was acetylated (5 ml Ac_2O/pyridine 1:1, 30 min). The excess of Ac_2O/pyridine was removed in vacuo. Crude 22 was purified by column chromatography (silica, ethylacetate) and crystallized from CH_2Cl_2 /n-hexane.

Yield: 310 mg (74%), colourless crystals, m.p. 248°C; $[\alpha]_D^{25}$ = -51 (c = 0.5, $CHCl_3$).
IR (film): 3320, 2970, 2195, 1750, 1670, 1620, 1370, 1220, 1045. **^{1}H-NMR** (360 MHz, $CDCl_3$): δ= 7.35 (d, H-l'); 6.35 (d, NH(C-4)); 5.80 (dd, NH(C-6)); 5.71 (br, H-2); 5.36 (t, H-5); 5.30 (dd, H-3); 5.22 (dd, H-1); 4.64 (ddd, H-4); 3.94 (ddd, H-6); 2.30, 2.26, 2.12, 2.09 (s, 15H, 5 x CH_3 ester, amide); 1.37 (s, 9H, H-4'); $^3J_{1,2}$ = 3.1 Hz; $^3J_{2,3}$ = 3.2 Hz; $^3J_{3,4}$ = 3.9 Hz; $^3J_{4,5}$ = $^3J_{5,6}$ = 3.4 Hz; $^3J_{1,6}$ = 10.8 Hz. **^{13}C-NMR** (90 MHz, $CDCl_3$): 6 = 169.6, 169,1, 168.7 (C=O); 155.6 (C-l'); 122.4 (CN); 71.5, 70.5, 69.4, 68.2, 64.5 (C-l, C-2, C-3, C-5, C-2'); 53.6 (C-3'); 49.4, 49.1 (C-4, C-6); 30.6 (C-4'); 23.3, 20.8, 20.5 (CH_3 ester, amide).
MS (EI) m/z(%): 527 ($M^{+\cdot}$, 0.9); 471 (3.2); 43 (100).
$C_{23}H_{33}N_3O_9S$ (527.6)
calc. C 52.36 H 6.30 N 7.96
found. C 52.02 H 6.24 N 7.85

1L-1,5-diamino-1,5-dideoxy-allo-inositole-hexaacetate 23

To 200 mg (0.4 mmol) 22 dissolved in 5 ml CH_3CN 3 ml of 20% $HClO_4$ were added and the solution was stirred for 6d at room temp.. Work up and acetylation were carried out as described with 20. Crystallization from CH_2Cl_2/ether/n-hexane yielded 130 mg (80%) 23 as colourless crystals, m.p. 188°C; $[\alpha]_D^{25}$ = -20 (c = 0.5, $CHCl_3$).
IR (film): 3280, 2980, 1745, 1660, 1540, 1370, 1230, 1050.
^{1}H-NMR (360 MHz, CD_3CN, 327 K): δ= 6.55, 6.45 (d, 2H, 2 x NH); 5.56 (br); 5.17 (t); 5.10 (m, 2H); (H-2, H-3, H-4, H-6); 4,36 (H-1(5)); 4.53 (H-5 (1)); $^3J_{1,6(4,5)}$ = 10.0 Hz; $^3J_{4,5(1,6)}$ = $^3J_{2,3(5,6)}$ = 4.9 Hz.
^{13}C-NMR (90 MHz, CD_3CN, 317 K): δ= 171.0, 170.9, 170.8, 170.6, 170.5 (C=O); 70.4, 69.5, 69.5, 67.3 (C-2, C-3, C-4, C-6); 49.4, 46.8 (C-l, C-5); 23.1, 22.9, 21.1, 21.0, 20.9, 20.8 (6 x CH_3). MS (EI) m/z(%): 431 ($M^{+\cdot}$+1, 0.5); 208 (68); 43 (100).
$C_{18}H_{26}N_2O_{10}$ (430.4)
calc. C 50.23 H 6.09 N 6.51
found. c 50.04 H 6.21 N 5.96

General procedure for the deacylation of 21 and 23
A stream of gaseous HCl was passed through 20 ml CH_3OH/H_2O 9:1. This solution was added to 21 or 23 and the mixture was refluxed for 48-72 h. The solvent was evaporated, the residue was dissolved in CH_3OH and the product was precipitated by the addition of ether.
Reaction of 21 (120 mg, 2.8 mmol) yielded **1L-5-amino-5-desoxy-allo-**

^{1}H-NMR (360 MHz, D_2O): 6 = 3.99 (t, H-6): 3.94 (br, H-2); 3.82 (t, H-l); 3.73 (m, 2H, H-3, H-4); 3.43 (dd, H-5); $^3J_{1,2} = {}^3J_{2,3} = {}^3J_{5,6}$ = 3.2 Hz; $^3J_{3,4}$ = 3.0 Hz; $^3J_{4,5}$ = 10.1 Hz; $^3J_{1,6}$ = 3.5 Hz. ^{13}C-NMR (90 MHz, D_2O): 6 = 74.6, 74.2, 69.7, 67.9, 66.7 (C-l, C-2, C-3, C-4, C-6); 51.0 (C-5).

Reaction of 23 (90 mg, 2.1 mmol) yielded **1L-1,5-diamino-1,5-dideoxy-allo-inositole-dihydrochloride** 25 (40 mg, 77%) as colourless solid, m.p. 239°C (dec.). $[\alpha]_D^{25}$ = -72° (c = 0.5, H_2O).
^{1}H-NMR (360 MHz, D_2O): 6 = 4.29 (t); 4.05 (m, 2H); 3.86 (dd); (H-2, H-3, H-4, H-6); 3.52 (m, 2H, H-l, H-5). ^{13}C-NMR (90 MHz, D_2O):δ =73.1, 66.7, 65.4, 63.4 (C-2, C-3, C-4, C-6); 55.1, 49.8 (C-l, C-5).

Acknowledgement: This work was supported by DFG (Sonderforschungsbereich 145) and Fonds der Chem. Industrie. A generous gift of starting materials by ICI is gratefully acknowledged.

References:

(1) T. Suami, S. Ogawa, N. Tanno, M. Saguro, K. L. Rinehart,jr., J. Am. Chem. Soc. 98, 7110 (1976)
(2) D. Semeira, M. Philippe, J. M. Delaumeny, A. M. Sepulchre, S. D. Gero, Synthesis 710 (1983)
(3) S. Knapp, M. J. Sebastian, H. Ramanathan, J. Org. Chem. 48, 4786 (1983)
(4) C. H. Kuo, N. L. Wendler, Tetrahedron Let. 25, 2291 (1985)
(5) H. Paulsen, W. Rdben, F. R. Heiker, Chem. Ber. 114, 3242 (1981)
(6) J. Schubert, K. Schwesinger, L. Knothe, H. Prinzbach, Ann. Chem. 1986, 2009
(7) H. Felber, Dissertation Thesis TU-Miinchen 1988
(8) 0. Werbitzky, W. Piepersberg, unpublished results
(9) A. Ritter, Dissertation Thesis 1989, manuscript in preparation
(10) a) B. Ascherl, G. Kresze, J. L. Vaerman, B. Vandenbulke, Cogette, Bull. Soc. Chim. Belge 96, 51 (1986);
b) J. L. Vaerman, H. E. Viehe, Tetrahedron 45, 3183 (1989)
(11) H. G. Viehe, R. Merenyi, E. Francotte, M. Van Meersche, G. Germain, J. P. Declerq, J. Bodart-Gilmont, J. Am. Chem. Soc. 99, 2340 (1977)
(12) P. E. Hansen, Prog. in NMR-Spectroscopy 14, 175 (1981)
(13) K. Torri, K. Tomeno, T. Nakagawa, J. Org. Chem. 29, 1136 (1964)
(14) A. Fürst, P. A. Plattner: Abstracts of Papers, 12th International Congress of Pure and Applied Chemistry (New York) p. 405 (1951)