Highly Stereoselective Aminohydroxylations of *exo*-2-Cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl Acetate

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Dedicated to Professor Horst Prinzbach on the occasion of his 60th birthday

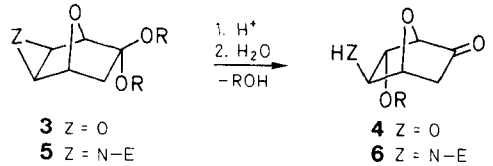
Protected forms of *exo*-5-amino-*exo*-6-hydroxy-7-oxabicyclo [2.2.1]heptan-2-one and of *exo*-5-amino-*endo*-6-hydroxy-7-oxabicyclo[2.2.1]heptan-2-one can be obtained readily and with high stereoselectivity from *exo*-2-cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl acetate (±)-(**7**). The processes involve acid promoted rearrangements of *N*-carbonyl aziridines **10** [(1*RS*,2*SR*,4*RS*,5*RS*, 6*SR*)-6-cyano-8-oxa-3-azatricyclo[3.2.1.$0^{2,4}$]oct-6-yl acetate derivatives] derived from (±)-**7**.

The optically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives (+)-**1** [and its diastereomer derived from (1*R*)-camphanic acid], (+)-**2** [and its enantiomer (−)-**2**] are useful chirons ("naked sugars")[1,2] for the total synthesis of rare carbohydrates, *C*-nucleosides, cyclitols and other compounds of biological interest.[3]

(+)-**1** R = (1S)-camphanoyl
(±)-**7** R = Ac

(+)-**2**

Their stereospecific substitution at centers C(5) and C(6) can be achieved through electrophilic additions of their endocyclic double bond,[1] or by acid-promoted rearrangements of the epoxy-acetals **3** giving the corresponding partially protected *trans* diols **4**. Similarly, acid-promoted rearrangement of the 3-aza-8-oxatricyclo[3.2.1.$0^{2,4}$]-octan-6-one acetals **5** into **6** was found to be a convenient route to the stereospecific *trans*-aminohydroxylation at C(5) and C(6) of the "naked sugars" (Scheme **1**).[4] We report here efficient methods for the stereoselective *exo-cis*- and *-trans*-aminohydroxylation of the olefinic moiety in (±)-*exo*-2-cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl acetate (±)-(**7**).[5,6]



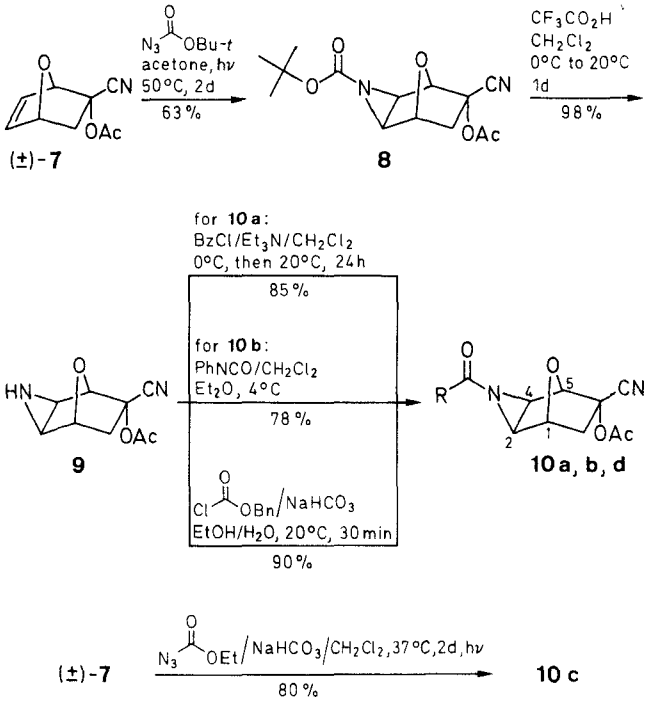
3 Z = O
5 Z = N–E

4 Z = O
6 Z = N–E

R = Me, Bn
E = CO_2Et, CO_2Bu-*t*, PhCO

Scheme 1

Heating a 1.2:1 mixture of *tert*-butyl azidoformate and (±)-**7** followed by irradiation led to the protected aziridine derivative **8** (63%). Acidic hydrolysis gave **9** (98%) which was benzoylated into **10a** (85%) on treatment with benzoyl chloride and triethylamine. The corresponding urea derivative **10b** (78%) was obtained by reacting **9** with phenyl isocyanate. The corresponding ethyl carbamate **10c** (80–90%) was prepared by irradiation of the triazoline mixture resulting from the cycloaddition of ethyl azidoformate to (±)-**7**. The benzyl carbamate **10d** (90%) was obtained by treatment of **9** with 1.2 equivalent of benzyl chloroformate and sodium hydrogen carbonate.



10	**a**	**b**	**c**	**d**
R	Ph	PhNH	EtO	BnO

Scheme 2

Heating a solution of **10a** in anhydrous 1,1,1,3,3,3-hexafluoro-2-propanol (HFP) containing 0.35 equivalent of trifluoromethanesulfonic acid to 80°C for 2 hours gave, after aqueous work-up with sodium hydrogen carbonate and extraction with dichloromethane, the dihydroxazole derivative **11a** nearly quantitatively (81% after recrystallization).[7] Under similar conditions (20°C, 1 d) the aziridine derivatives **10b** and **10c** were transformed into **11b** (74%) and **11c** (87%), respectively, while the benzyl carbamate **10d** afforded exclusively the cyclic carbamate **12** (52%).

Saponification of the cyanoacetate **11a** gave ketone **13a** (71%). Similarly, treatment of **11b** and **11c** afforded **13b** (78%) and **13c** (85%), respectively. Under similar conditions, **12** gave **14**, together with product of decomposition due to retro-aldolization of the β-hydroxy ketone. Compounds **11a–c**, **12** and **13a–c** are various forms of

Table 1. Aziridines **8**, **9**, **10a–d** Prepared

Starting Material	Product	Yield (%)	mp (°C)	Molecular Formula	^{1}H-NMR (250 MHz, $CDCl_3$/TMS) δ, J (Hz)	^{13}C-NMR (90.55 MHz, $CDCl_3$/TMS) δ, $^1J_{C,H}$ (Hz)
(±)-**7**	**8**	63	164–165	$C_{14}H_{18}N_2O_5$ (294.3)	5.08 (s, H-C5), 4.76 (d, J = 5.5, H-1), 2.82 (dd, J = 14.0, 5.5, H_{exo}-7), 2.81, 2.78 (2d, J = 3.5, H-C2, H-4), 2.18 (s, $COCH_3$), 2.00 (d, J = 14.0, H_{endo}-7), 1.45 [s, $C(CH_3)_3$]	168.9, 158.8 (2s, CO), 117.7 (s, CN), 81.6 (s), 79.1 (d, J = 175, C5), 75.5 (s, C6), 74.9 (d, J = 170, C1), 42.1 (t, J = 140, C7), 35.6 (d, J = 190, C4), 32.5 (d, J = 195, C2), 27.9 (q, J = 135), 20.3 (q, J = 125)
8	**9**	98	oil	$C_9H_{10}N_2O_3$ (194.2)	4.89 (s), 4.50 (d, J = 5), 2.76 (dd, J = 13.5, 5.0, H_{exo}-7), 2.35 (s, H-4), 2.36 (s, H-2), 2.29 (s, $COCH_3$), 1.96 (d, J = 13.5, H_{endo}-7)	169.0 (s), 117.9 (s, CN), 79.0 (d, J = 170), 75.4 (s), 74.8 (d, J = 165), 42.4 (t, J = 140), 26.7 (d, J = 195), 25.9 (d, J = 195), 20.1 (q, J = 130)
9	**10a**	85	146–147	$C_{16}H_{14}N_2O_4$ (298.3)	7.92, 7.47 (2m, 5H), 4.90 (s, H-5), 4.64 (d, J = 5.0, H-1), 3.19, 3.13 (2d, J = 4.0, H-2, H-4), 2.79 (dd, J = 14.0, 5.0), 2.21 (s, $COCH_3$), 2.00 (d, J = 14.0)	175.8, 168.9, 132.9 (3s), 132.7, 128.6, 128.0 (3d, J = 160), 117.4 (s), 78.8 (d, J = 175), 75.4 (s), 74.6 (d, J = 170), 41.8 (t, J = 140), 36.8, 34.2 (2d, J = 190), 20.3 (q, J = 130)
9	**10b**	78	183–185.5	$C_{16}H_{15}N_3O_4$ (313.3)	8.83 (s, NH), 7.55–7.52, 7.27–7.21, 7.0–6.94 (3m, 5H), 5.14 (s, H-5), 4.87 (d, J = 5.0, H-1), 3.04, 2.99 (2d, J = 3.5, H-4, H-2), 2.73 (dd, J = 14.0, 5.0), 2.20 (s, $COCH_3$), 2.19 (J = 14.0)[a]	170.3 (s), 159.2 (s), 140.6 (s), 129.4, 123.3, 119.6 (3d, J = 160), 119.0 (s), 80.4 (d, J = 175), 76.4 (s), 76.4 (d, J = 170), 42.9 (t, J = 135), 37.0, 33.8 (2d, J = 195), 20.3 (q, J = 130)[a]
(±)-**7**	**10c**	90	86–87	$C_{12}H_{14}N_2O_5$ (266.3)	5.13 (s, H-5), 4.78, (d, J = 5.5, H-1), 4.17 (q, J = 7.0), 2.89, 2.86 (2d, J = 3.5, H-2, H-4), 2.85 (dd, J = 14.0, 5.5, H_{exo}-7), 2.19 (s, $COCH_3$), 2.01 (d, J = 14.0, H_{endo}-7), 1.28 (t, J = 7.0)	168.9, 160.3, 117.5 (3s), 79.1 (d, 175), 74.9 (d, J = 170), 62.5 (t, J = 145), 42.1 (t, J = 140), 35.7 (d, J = 190), 32.6 (d, J = 195), 20.3 (q, J = 130), 14.3 (q, J = 125)
9	**10d**	90	85–89	$C_{17}H_{16}N_2O_5$ (328.3)	7.39–7.30 (m, 5H), 5.13, 5.07 (2d, J = 12.0), 5.07 (s), 4.72 (d, J = 5.5), 2.90, 2.85 (2d, J = 3.5), 2.78 (dd, J = 13.5, 5.5), 2.15 (s, $COCH_3$), 1.96 (d, J = 13.5)	168.8, 160.2, 135.5 (3s), 128.5, 128.4, 128.3 (3d, J = 165), 117.4 (s), 79.0 (d, J = 175), 75.3 (s), 74.9 (d, J = 170), 68.2 (t, J = 150), 41.9 (t, J = 140), 35.8, 32.7 (2d, J = 195), 20.2 (q, J = 130)

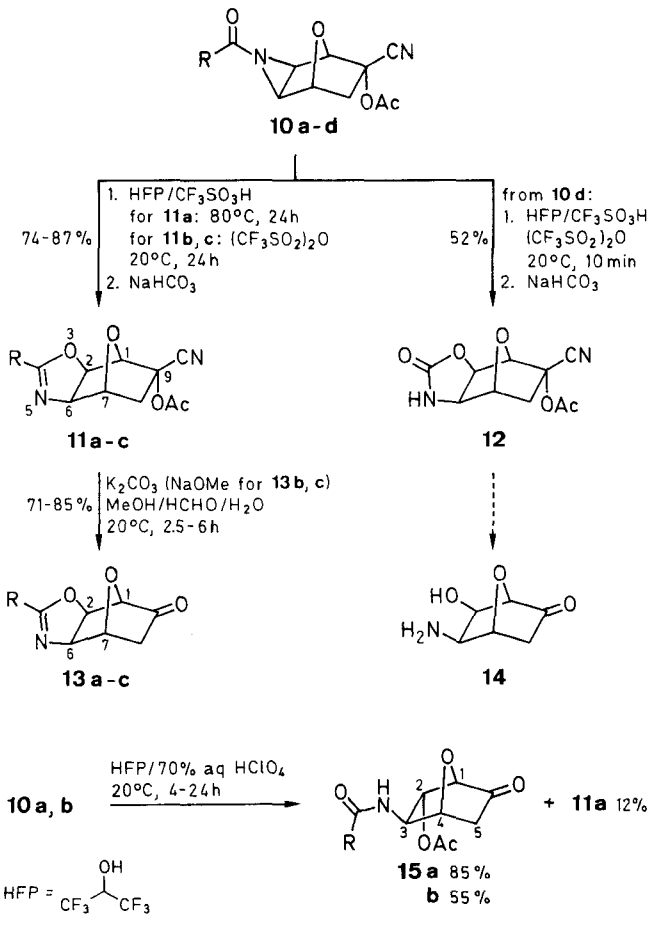
[a] In acetone-d_6.

[b] In CD_3OD.

protected *exo*-5-amino-*exo*-6-hydroxy-7-oxabicyclo [2.2.1]heptan-2-one (**14**), thus the transformations (±)-**7** → **10** → **11** realize a highly facial and regioselective *cis*-aminohydroxylation of the double bond in the "naked sugars".

Interestingly, when aqueous acidic conditions were used to induce the rearrangement of the aziridines **10**, products **15** of *trans*-aminohydroxylation were formed concurrently with **11** (Scheme **3**). In the case of the benzamide **10a**, a 7:1 mixture of **15a** and **11a** was formed on treatment with a catalytical amount of 70% aqueous perchloric acid in HFP. Column chromatography on silica gel afforded pure **15a** (85%) and **11a** (12%). Under similar conditions the urea derivative **10b** was transformed quantitatively (250 MHz, ^{1}H-NMR spectrum of the crude reaction mixture) into **15b** (55%). Less selective processes were observed for the aqueous acidic treatment of derivatives **10c** and **10d** which were accompanied by decomposition.

The structures of all new compounds **10–15** were given by their elemental analyses and their spectroscopic data. Vicinal H–H coupling constants[8](while the *endo* protons of 7-oxabicyclo[2.2.1]heptane derivatives do not couple with the vicinal bridgehead protons, the *exo* protons show a coupling constant of ca. 5 Hz with the vicinal bridgehead protons) in their ^{1}H-NMR spectra allowed one to establish the relative configuration of centers C(2) and C(6) in **11** and **13** and of centers C(2) and C(3) in **15**. NOE measurements in the ^{1}H-NMR spectra confirmed our signal attributions.



Scheme 3

Table 2. 3,10-Dioxa-5-azatricyclo[5.2.1.$0^{2,6}$]dec-4-enes **11a–c**, **13a–c**, **18**, 4-Oxo-3,10-dioxa-5-azatricyclo[5.2.1.$0^{2,6}$]decane **12** Prepared

Starting Material	Product	Yield (%)	mp (°C)	Molecular Formula	^{1}H-NMR (250 MHz, $CDCl_3$/TMS) δ, J (Hz)	^{13}C-NMR (90.55 MHz, $CDCl_3$/TMS) δ, $^1J_{C,H}$ (Hz)
10a	**11a**	99	190–192	$C_{16}H_{14}N_2O_4$ (298.3)	7.92–7.39 (m, 5H), 5.21 (s, H-1), 5.0, 4.55 (2d, J = 7.0, H-2, H-6), 4.73 (d, J = 6.0, H-7), 2.84 (dd, J = 14.0, 6.0, H_{exo}-8), 2.24 (s, $COCH_3$), 2.01 (d, J = 14.0, H_{endo}-8)	168.7, 166.1 (2s), 131.9, 128.5, 128.4 (3d, J = 160), 126.5, 117.5 (2s), 84.4, 80.8, 79.6, 75.0 (4d, J = 165), 72.9 (s), 41.5 (t, J = 140), 20.4 (q, J = 130)
10b	**11b**	74	133–135	$C_{16}H_{15}N_3O_4$ (313.3)	7.54–7.39 (m, 4H), 4.19–7.12 (m, 1H), 5.20 (s), 5.19 (s), 5.19 (d, J = 6.5), 4.70 (d, J = 6.0), 4.53 (d, J = 6.5), 2.83 (dd, J = 14.0, 6.0), 2.35 (s, $COCH_3$), 2.21 (d, J = 14.0)[b]	170.8, 160.8, 141.0 (3s), 129.8, 123.7, 120.4 (3d, J = 160), 119.3 (s), 85.5 (d, J = 170), 83.1, 79.9 (2d, J = 165), 74.2 (s), 73.3 (d, J = 160), 41.8 (t, J = 140), 20.3 (q, J = 130)[b]
10c	**11c**	87	166–167.5	$C_{12}H_{14}N_2O_5$ (266.3)	5.05 (s, H-1), 4.91, 4.23 (2d, J = 6.5), 4.54 (d, J = 6.0), 4.33–4.12 (m, 2H), 2.75 (dd, J = 14.0, 6.0), 2.17 (s), 1.87 (d, J = 14.0), 1.33 (t, J = 7.0, CH_3)	168.6, 164.4, 117.5 (3s), 83.8 (d, J = 175), 81.0 (d, J = 170), 79.9 (d, J = 160), 72.7 (s), 71.6 (d, 155), 67.4 (t, J = 145), 41.0 (t, J = 140), 20.3 (q, J = 130), 14.1 (q, J = 125)
11a	**13a**	95	183–185	$C_{13}H_{11}NO_3$ (229.2)	7.94 (m, 2H), 7.54–7.40 (m, 3H), 4.99 (dd, J = 6.0, 1.0, H-7), 4.95, 4.67 (2d, J = 7.0), 4.57 (brs, J = 1.0, H-1), 2.66 (ddd, J = 17.5, 6.0, 1.5), 2.22 (d, J = 17.5)	208.4, 166.1 (2s), 131.9, 128.6, 128.4 (3d, J = 160), 126.7 (s), 84.8 (d, J = 175), 81.0 (d, J = 165), 80.0 (d, J = 165), 75.5 (d, J = 155), 42.2 (t, J = 135)
11b	**13b**	78	180–182	$C_{13}H_{12}N_2O_3$ (244.25)	7.42–7.28 (m, 4H), 7.03 (m, 1H), 4.88 (m, J = 6.0, 1.0), 4.78, 4.53 (2d, J = 6.5), 4.47 (m, J = 1.0, 0.9), 2.58 (ddd, J = 18.0, 6.0, 0.9), 2.12 (d, J = 18.0)	208.7, 157.9, 138.4 (3s), 129.1, 123.0, 118.5, (3d, J = 160), 84.3, 81.7, 79.0, 74.3 (4d, J = 170), 41.6 (t, J = 135)
11c	**13c**	85	117–118.5	$C_9H_{11}NO_4$ (197.2)	4.83, 4.38 (2d, J = 6.5), 4.82 (dd, J = 6.0, 1.0), 4.47 (brs), 4.291, 4.290 (2q, J = 7.0), 2.56 (ddd, J = 18.0, 6.0, 1.0), 2.10 (d, J = 18.0), 1.37 (t, J = 7.0)	208.1, 164.1 (2s), 84.1, 81.1 (2d, J = 170), 80.2 (d, J = 165), 72.0 (d, J = 150), 67.4 (t, J = 150), 41.8 (t, J = 135), 14.1 (q, 130)
13a	**18**	92	oil	$C_{15}H_{17}NO_4$ (275.3)	7.94–7.90 (m, 2H), 7.51–7.36 (m, 3H), 5.13, 4.48 (2d, J = 7.0), 4.54 (m, J = 1.0), 4.59 (d, J = 6.0), 3.30, 3.26 (2s, $2CH_3O$), 2.08 (dd, J = 13.0, 6.0), 1.69 (d, J = 13.0)	
10d	**12**	52	184–190	$C_{10}H_{10}N_2O_5$ (238.2)	6.98 (brs, NH), 5.16, 4.23 (2d, J = 6.5), 5.03 (s), 4.62 (d, J = 6.0), 2.69 (dd, J = 14.5, 6.0), 2.20 (s, $COCH_3$), 2.12 (d, J = 14.5)[a]	172.3, 152.4, 118.8 (3s), 85.0 (d, J = 170), 82.0 (d, J = 165), 77.1 (d, J = 165), 73.4 (s), 59.3 (d, J = 155), 40.8 (t, J = 140), 20.4 (q, J = 130)[a]

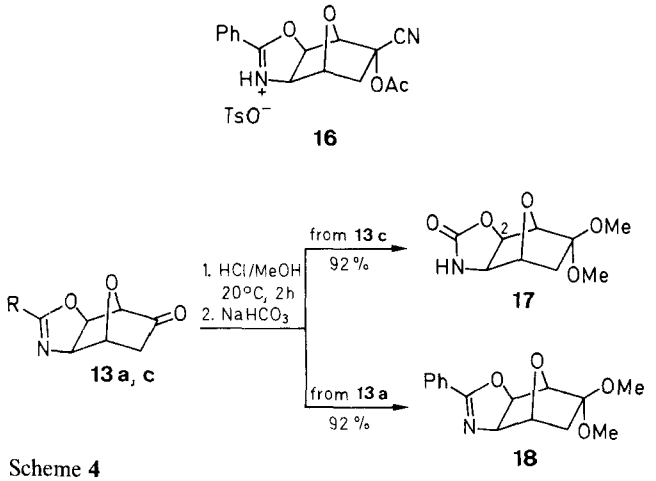
[a] In acetone-d_6. [b] In CD_3OD.

Table 3. *N*-Substituted *exo*-3-Amino-6-oxo-7-oxabicyclo[2.2.1]hept-*endo*-2-yl Acetates **15a, b** Prepared

Starting Material	Product	Yield (%)	mp (°C)	Molecular Formula	^{1}H-NMR (250 MHz, $CDCl_3$/TMS) δ, J (Hz)	^{13}C-NMR (90.55 MHz, $CDCl_3$/TMS) δ, $^1J_{C,H}$ (Hz)
10a	**15a**	85	142–145	$C_{15}H_{15}NO_5$ (289.3)	7.82–7.79 (m, 2H), 7.57–7.42 (m, 3H), 6.77 (brd, J = 7.5, NH), 5.02 (ddd, J = 5.5, 2.0, 1.5, H-2), 4.83 (m, J = 6.0, 1.5, 1.0, H-4), 4.58 (m, J = 5.5, 1.0, 0.9, H-1), 4.47 (dd, J = 7.5, 2.0, H-3), 2.61 (ddd, J = 18.0, 6.0, 0.9), 2.35 (d, J = 18.0), 2.07 (s, $COCH_3$)	205.7, 169.9, 167.3 (3s), 133.2 (s), 131.9, 128.5, 126.9 (3d, J = 160), 81.7, 79.4 (2d, J = 170), 77.2 (d, J = 160), 58.3 (d, J = 150), 40.3 (t, J = 135), 20.2 (q, J = 130)
10b	**15b**	55	156–158	$C_{15}H_{16}N_2O_5$ (304.3)	7.37–7.09 (m, 5H), 6.88 (brs, NH), 5.61 (brd, J = 7.5, NH), 4.82 (m, J = 5.5, 1.5), 4.77 (m, J = 6.0, 1.5, 1.0), 4.51 (m, J = 5.5, 2.0, 1.0), 4.19 (dd, J = 7.5, 2.0), 2.57 (ddd, J = 18.0, 6.5, 2.0), 2.28 (d, J = 18.0), 2.05 (s, $COCH_3$)	205.9, 170.3, 155.2, 137.8 (4s), 129.5, 124.5, 121.3 (3d, J = 160), 82.1 (d, J = 160), 79.5 (d, J = 160), 77.4 (d, J = 160), 59.0 (d, J = 150), 40.4 (t, J = 135), 20.5 (q, J = 130)

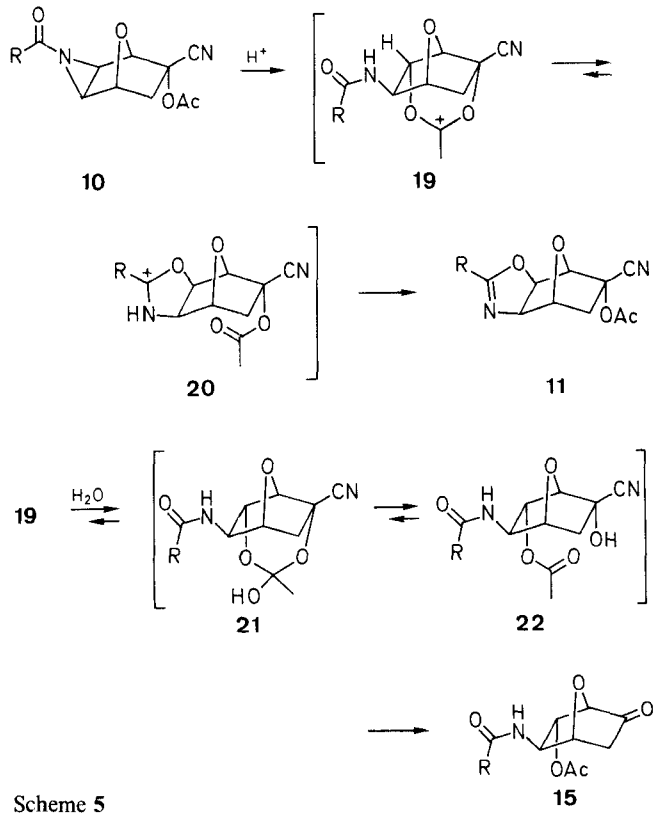
As expected, the chemical shifts of H-6 (substituted by the N function) were smaller than those of H-2 (substituted by O function) in the 5-aza-3,10-dioxatricyclo [5.2.1.$0^{2,6}$]decane derivatives **11a–c**, **12** and **13a–c**. When one equivalent of *p*-toluenesulfonic acid was added to a $CDCl_3$ solution of **11a**, the corresponding imminium salt **16** was formed for which H-2 and H-6 resonates at δ_H = 6.01 and 5.48. Thus, the protic acid induced chemical shift for H-6 was larger ($\Delta\delta_H$ = 1.46 ppm) than for H-2 ($\Delta\delta_H$ = 0.48). Since NOE measurements in the ^{1}H-NMR

spectra of **13c** were not conclusive about the structure of this compound, we reacted it with methanol and gaseous hydrogen chloride. This led to the acetal **17** for which the structure could be established unambiguously by NOE measurements in its ^{1}H-NMR spectrum (NOE's were measured in particular between the signals of H-6 and NH, and between H-2 and the *endo* MeO group). Treatment of **13a** with methanol/hydrogen chloride gave **18** whose structure could also be established unambiguously by NOE measurements in its ^{1}H-NMR spectrum.



Scheme 4

The rearrangements **10** → **11** can be interpreted in terms of the participation of the *endo* acetoxy group in **10** to the aziridine ring opening, leading to the relatively stable dialkoxycarbenium ion intermediates **19**.[9] In the absence of water (nucleophile), intramolecular S_N2 attack of the carboxyl group of the benzamide, urea or carbamate moiety leads to the even more stable aminoalkoxycarbenium ion intermediates **20** that furnish the corresponding dihydroxazoles **11** on neutralization (Scheme **5**). In the presence of water, the tricyclic intermediates **19** generate probably the corresponding hemiorthoesters **21** which open under acidic conditions and yield the corresponding cyanohydrines **22** that are decomposed into the corresponding ketones **15**.



Scheme 5

The results establish efficient and highly stereoselective methods for the transformation of "naked sugars" into *exo*-5-amino-*exo*-6-hydroxy- and *exo*-5-amino-*endo*-6-hydroxy-7-oxabicyclo[2.2.1]heptan-2-one derivatives. These compounds are expected to become useful synthetic intermediates for the preparation of rare aminodeoxyhexoses, -cyclitols and *C*-nucleosides.[1,2]

Melting points were taken with a Tottoli apparatus (not corrected). IR spectra were measured with Beckmann IR 4230 instrument, ^{1}H-NMR-spectra with Bruker 250 FT, ^{13}C-NMR spectra with Bruker WH-360 FT and Mass spectra (MS) with Nermag R10-10C instrument. Elemental analyses were performed by the laboratory of Ilse Beetz Kronach, Germany. All solvents and reagents were obtained from Fluka or Aldrich. Silica gel used for the purifications: Merck 9385

***tert*-Butyl (1*RS*,2*SR*,4*RS*,5*RS*,6*SR*)-*endo*-6-Acetoxy-*exo*-6-cyano-8-oxa-3-azatricyclo[3.2.1.0^{2,4}]octane-3-carboxylate (8):**

A mixture of (±)-**7**[10] (2 g, 11 mmol) and N_3CO_2Bu-*t* (2.1 g, 15 mmol) in acetone (4 mL) is heated to 50 °C for 2 d in the dark. After solvent evaporation the residue is dissolved in acetone (150 mL) and irradiated with a Philips HPK 125 Hg-lamp in a quartz vessel (0 °C, 5 h). The solvent is evaporated and the residue purified by column chromatography or silica gel (Et_2O/CH_2Cl_2, 1:1); yield: 2.1 g (63 %), colorless crystals, mp 164–165 °C.

$C_{14}H_{18}N_2O_5$	calc.	C 57.12	H 6.18	N 9.52
(294.3)	found	56.85	6.00	9.46

MS (CI, NH_3): *m/z* (%) = 312 ($M^{+\cdot}$ + 18,94), 237 (100).

IR (KBr): *v* = 2980, 2940, 1760, 1715, 1370, 1335, 1300, 1250, 1190, 1155, 1090 cm^{-1}.

(1*RS*,2*SR*,4*RS*,5*RS*,6*SR*)-3-Benzoyl-*exo*-6-cyano-8-oxa-3-azatricyclo[3.2.1.0^{2,4}]oct-*endo*-6-yl Acetate (10a):

CF_3CO_2H (6 mL, freshly distilled over P_2O_5) is added dropwise to a stirred solution of **8** (2.1 g, 7.3 mmol) in anhydr. CH_2Cl_2 (20 mL) cooled to 0 °C, under N_2 atmosphere. After stirring 15 h at 20 °C, the mixture is poured into sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (4 × 50 mL). After filtration (cotton) and solvent evaporation aziridine **9** is obtained. It is then dissolved in anhydr. CH_2Cl_2 (14 mL) and the solution cooled to 0 °C, Et_3N (2.2 g, 21.8 mmol) and BzCl (2.05 g, 14.6 mmol) are added slowly and the mixture stirred at 20 °C for 24 h. The mixture is poured into 1 N HCl (50 mL) and extracted with CH_2Cl_2 (4 × 50 mL). The organic extracts are combined and washed with sat. aq $NaHCO_3$ (50 mL). The solvent is evaporated and the residue purified by filtration through a short column of silica gel (EtOAc/light petroleum ether, 2:1); yield: 1.84 g (85 %) of a colorless oil which crystallizes from CH_2Cl_2/Et_2O: 1.81 g (83 %), colorless crystals, mp 146–147 °C.

$C_{16}H_{14}N_2O_4$	calc.	C 64.42	H 4.73	N 9.39
(298.3)	found	64.31	4.79	9.41

MS (CI, NH_3): *m/z* = 300 (19), 299 (100, $M^{+\cdot}$ + 1), 298 (1, $M^{+\cdot}$).

IR (KBr): *v* = 1740, 1665, 1595, 1575, 1485, 1445, 1375, 1325, 1290, 1240, 1215, 1390, 1065, 1045, 1020, 970, 905, 875, 715, 620 cm^{-1}.

(1*RS*,2*SR*,4*RS*,5*RS*,6*SR*)-*exo*-6-Cyano-3-(phenylcarbamoyl)-8-oxa-3-azatricyclo[3.2.1.0^{2,4}]oct-*endo*-6-yl Acetate (10b):
Phenyl isocyanate (0.36 g, 3.03 mmol) is added slowly to a stirred solution of crude **9** (see above, 0.534 g, 2.75 mmol) in anhydr. CH_2Cl_2 (11 mL). Et_2O (15 mL) is added and the solution allowed to stand at 4 °C; yield: 676 mg (78%), colorless crystals, mp 183–185.5 °C.

MS (CI, NH_3): *m/z* = 315 (22), 314 (100, $M^{+\bullet}$ + 1), 313 (11), 195 (41).

IR (KBr): *v* = 3350, 3060, 2240, 1755, 1690, 1600, 1535, 1495, 1445, 1370, 1320, 1235, 1190, 1075, 1030, 1015, 905, 835, 800 cm^{-1}.

(1*RS*,2*SR*,4*RS*,5*RS*,6*SR*)-*exo*-6-Cyano-3-ethoxycarbonyl-8-oxa-3-azatricyclo[3.2.1.0^{2,4}]oct-*endo*-6-yl Acetate (10c):
A mixture of (±)-**7** (1.00 g, 5.58 mmol), CH_2Cl_2 (1 mL), N_3CO_2Et (0.77 g, 6.7 mmol) and $NaHCO_3$ (0.25 g) is stirred at 37 °C for 2 d in the dark. The mixture is poured into ice-cold sat. aq $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (4 × 25 mL). The extracts are combined, filtered (cotton) and the solvent is evaporated. The residue is recrystallized from CH_2Cl_2/Et_2O (20 °C) yielding 1.39 g (85%) of a mixture of the corresponding triazolines which is dissolved in acetone (150 mL) and irradiated by a high-pressure Hg-lamp (Philips HPK 125) in a quartz vessel at 0 °C (ca. 2 h). Solvent evaporation affords 1.19 g (80%, based on (±-**7**) of a colorless oil.

(1*RS*,2*SR*,4*RS*,5*RS*,6*SR*)-3-Benzyloxycarbonyl-*exo*-6-cyano-8-oxa-3-azatricyclo[3.2.1.0^{2,4}]oct-*endo*-6-yl Acetate (10d):
A mixture of $ClCO_2Bn$ (1.16 mL, 8.2 mmol), crude **9** (1.3 g, 6.8 mmol) and $NaHCO_3$ (1.3 g) in EtOH/H_2O (1:1) (12 mL) is stirred at 20 °C for 30 min. The mixture is poured into ice-water (50 mL) and extracted with CH_2Cl_2 (4 × 30 mL). After solvent evaporation, the residue is filtered through a short column of silica gel (Et_2O); yield: 2.01 g (90%), colorless oil.

$C_{17}H_{16}N_2O_5$	calc.	C 62.19	H 4.91	N 8.53
(328.3)	found	62.14	4.99	8.52

MS (CI, NH_3): *m/z* = 347 (11), 346 (61), 345 (34), 330 (14), 329 (81), 328 (49, $M^{+\bullet}$), 195 (24), 108 (41), 91 (100).

IR (CH_2Cl_2): *v* = 3025, 2980, 2250, 1760, 1730, 1390, 1370, 1320, 1220, 1185, 1080, 1025, 890, 805 cm^{-1}.

(1*RS*,2*RS*,6*RS*,7*RS*,9*SR*)-*exo*-9-Cyano-4-phenyl-3,10-dioxa-5-azatricyclo[5.2.1.0^{2,6}]dec-4-en-*endo*-9-yl Acetate (11a):
A mixture of **10a** (0.4 g, 1.34 mmol), HFP (4 mL) and CF_3SO_3H (0.2 mL, 2.28 mmol) is sealed in a pyrex tube under vacuum. The tube is heated to 80 °C in the dark for 24 h. The tube is cooled to 20 °C, opened, and the mixture poured into a mixture of CH_2Cl_2 (15 mL) and sat. aq $NaHCO_3$. The mixture is extracted with CH_2Cl_2 (4 × 15 mL). The extracts are combined, filtered through cotton and the solvent is evaporated. The residue (396 mg, 99%) is recrystallized from MeOH/Et_2O at 20 °C; yield: 322 mg (81%), colorless crystals mp 190–192 °C.

$C_{16}H_{14}N_2O_4$	calc.	C 64.42	H 4.73	N 9.39
(298.3)	found	64.47	4.72	9.39

MS (CI, NH_3): *m/z* = 301 (3), 300 (19), 299 (100), 298 (3, $M^{+\bullet}$).

IR (KBr): *v* = 3320, 3070, 3010, 2970, 2930, 2240, 1740, 1710, 1645, 1580, 1525, 1490, 1445, 1375, 1355, 1325, 1305, 1285, 1250 cm^{-1}.

(1*RS*,2*RS*,6*RS*,7*RS*,9*SR*)-*exo*-9-cyano-4-phenylamino-3,10-dioxa-5-azatricyclo[5.2.1.0^{2,6}]dec-4-en-*endo*-9-yl Acetate (11b):
A mixture of **10b** (0.8 g, 2.56 mmol), HFP (16 mL) and 4 mL of 0.5 M CF_3SO_3H and 0.5 M $(CF_3SO_2)_2O$ in HFP is stirred at 20 °C for 24 h. The mixture is poured into ice-cold sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (4 × 30 mL). The extracts are combined, filtred through cotton and the solvent is evaporated. The residue (0.9 g) is filtered through a short column of silica gel (8 g, EtOAc/Et_2O, 1:1); yield: 736 mg (74%), colorless oil which can be crystallized from CH_2Cl_2/Et_2O (4 °C), colorless crystals, mp 133–135 °C.

$C_{16}H_{15}N_3O_4$	calc.	C 61.34	H 4.83	N 13.41
(313.3)	found	61.37	4.85	13.48

MS (CI, NH_3): *m/z* = 315 (20), 314 (100 $M^{+\bullet}$ + 1), 313 (19, $M^{+\bullet}$).

IR (KBr): *v* = 3400, 3060, 2240, 1760, 1650, 1600, 1550, 1500, 1445, 1365, 1325, 1225, 1180, 1040, 890 cm^{-1}.

(1*RS*,2*RS*,6*RS*,7*RS*,9*SR*)-*exo*-9-Cyano-4-ethoxy-3,10-dioxa-5-azatricyclo[5.2.1.0^{2,6}]dec-4-en-*endo*-9-yl Acetate (11c):
A mixture of **10c** (1.00 g, 3.76 mmol), HFP (2 mL) and 0.5 M CF_3SO_3H and 0.5 M $(CF_3SO_2)_2O$ in HFP (2 mL) is allowed to stand at 20 °C for 24 h. The mixture is poured into sat. aq $NaHCO_3$ (200 mL) and extracted with CH_2Cl_2 (4 × 25 mL). The organic extracts are combined, dried (cotton), and the solvent evaporated. The residue (1.8 g, oil) is purified by flash chromatography on silica gel (10 g, EtOAc/Et_2O, 1:1); yield: 0.87 g (87%), colorless crystals, mp 166–167 °C.

$C_{12}H_{14}N_2O_5$	calc.	C 54.13	H 5.30	N 10.52
(266.3)	found	54.18	5.29	10.48

MS (CI, NH_3): *m/z* = 268 (14), 267 (100, $M^{+\bullet}$ + 1), 266 (2, $M^{+\bullet}$).

IR (KBr): 3005, 2980, 2245, 1755, 1735, 1455, 1425, 1365, 1300, 1255, 1225, 1185, 1135, 1075, 1055, 1020, 930, 870 cm^{-1}.

(1*RS*,2*RS*,6*RS*,7*RS*,9*SR*)-*exo*-9-Cyano-4-oxo-3,10-dioxa-5-azatricyclo[5.2.1.0^{2,6}]dec-*endo*-9-yl Acetate (12):
A solution of 0.5 M of CF_3SO_3H and 0.5 M of $(CF_3SO_3)_2O$ in HFP (1.7 mL) is added dropwise to a stirred solution of **10d** (341 mg, 1.04 mmol) in HFP (15 mL). After stirring at 20 °C for 10 min (formation of a yellowish precipitate), the mixture is poured into ice-cold sat. aq $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (4 × 30 mL). The extracts are combined, dried (cotton), and the solvent evaporated. The residue (245 mg, 99%) is recrystallized from acetone/Et_2O/petroleum ether (4 °C); yield: 129 mg (52%), colorless crystals, mp 184–190 °C.

$C_{10}H_{10}N_2O_5$	calc.	C 50.42	H 4.23	N 11.76
(238.2)	found	50.53	4.35	11.67

MS (CI, NH_3): *m/z* = 257 (12), 256 (100), 239 (10), 238 (0.3, $M^{+\bullet}$).

IR (KBr): *v* = 3300, 3150, 3010, 2980, 2250, 1750, 1435, 1390, 1370, 1305, 1230, 1185, 1120, 1075, 1055, 1020, 1010, 970 cm^{-1}.

(1*RS*,2*RS*,6*RS*,7*RS*)-4-Phenyl-3,10-dioxa-5-azatricyclo-[5.2.1.0^{2,6}]dec-4-en-9-one (13a):
A mixture of **11a** (120 mg, 0.403 mmol), MeOH (6 mL), K_2CO_3 (60 mg) and 37% HCHO in H_2O (0.12 mL) is stirred at 20 °C for 2.5 h. The mixture is poured into sat. aq NaCl (20 mL) cooled to 0 °C. Extraction with CH_2Cl_2 (4 × 20 mL) and the usual work-up yields 87 mg (95%) of an oil that crystallizes from CH_2Cl_2/Et_2O (4 °C): 65 mg (71%), colorless crystals, mp 183–185 °C.

$C_{13}H_{11}NO_3$	calc.	C 68.11	H 4.84	N 6.11
(229.2)	found	68.07	4.73	6.18

MS (CI, NH_3): *m/z* = 231 (15), 230 (100, $M^{+\bullet}$ + 1), 229 (14, $M^{+\bullet}$).

IR (KBr): *v* = 3060, 2990, 2940, 1765, 1650, 1580, 1495, 1450, 1350, 1295, 1225, 1060, 1025, 995, 920 cm^{-1}.

(1*RS*,2*RS*,6*RS*,7*RS*)-4-(Phenylamino)-3,10-dioxa-5-azatricyclo-[5.2.1.0^{2,6}]dec-4-en-9-one (13b):
A mixture of **11b** (160 mg, 0.511 mmol), MeOH (6 mL), 30% NaOMe in MeOH (40 µL) and 37% aq HCHO (0.4 mL) is stirred at 20 °C for 6 h. The mixture is poured into ice-cold brine (20 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The extracts are combined, filtered through cotton and the solvent is evaporated. The residue (115 mg, 92%) is purified by flash column chromatography on silica gel (1.6 g, EtOAc/Et_2O, 1:1); yield: 98 mg (78%), colorless crystals [recrystallization from CH_2Cl_2/Et_2O at 4 °C: 60 mg (48%)], mp 180–182 °C.

$C_{13}H_{12}N_2O_3$	calc.	C 63.93	H 4.95	N 11.47
(244.1)	found	63.87	4.88	11.47

MS (CI, NH_3): *m/z* = 246 (11), 245 (58, $M^{+\bullet}$ + 1), 244 (100, $M^{+\bullet}$).

IR (KBr): *v* = 3350, 3060, 3000, 2940, 1770, 1685, 1590, 1500, 1450, 1420, 1325, 1230, 1120, 1025, 920, 745 cm^{-1}.

(1*RS*,2*RS*,6*RS*,7*RS*)-4-Ethoxy-3,10-dioxa-5-azatricyclo-[5.2.1.0^{2,6}]dec-4-en-9-one (13c):
Same procedure as for **13b**, starting with **11c** (20 mg, 0.075 mmol). Yield: 126 mg (85%), colorless crystals, mp 117–118.5 °C.

$C_9H_{11}NO_4$ calc. C 54.82 H 5.62 N 7.10
(197.2) found 54.80 5.57 7.09

MS (CI, NH_3): m/z = 200 (2), 199 (10), 198 (100, $M^{+\bullet}$ + 1), 197 (2).

IR (KBr): ν = 2995, 2940, 1765, 1665, 1405, 1375, 1305, 1015, 910, 855, 790 cm^{-1}.

(1*RS*,2*RS*,3*RS*,4*RS*)-*exo*-3-Benzamido-6-oxo-7-oxabicyclo[2.2.1]hept-*endo*-2-yl Acetate (15a):

A mixture of **10a** (0.2 g, 0.67 mmol), HFP (5 mL) and 70% aq $HClO_4$ (20 µL) is stirred at 20°C for 1 d. The mixture is poured onto an ice-cold sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (4 × 25 mL). The extracts are combined, filtered (cotton) and the solvent is evaporated. The residue is purified by flash chromatography on silica gel (5 g, EtOAc/petroleum ether, 2:1). The first fraction (R_f 0.66) gives 164 mg (85%) of **15a**, the second, 24 mg (12%) of **11a**. Recrystallization of **15a** from CH_2Cl_2/Et_2O 84°C) affords 157 mg, colorless crystals, mp 142–145°C.

$C_{15}H_{15}NO_5$ calc. C 62.28 H 5.23 N 4.84
(289.3) found 62.18 5.14 4.88

MS (CI, NH_3): m/z 291 (7), 290 (42), 289 (15, $M^{+\bullet}$).

IR (KBr): ν = 3260, 3020, 2940, 1775, 1750, 1640, 1600, 1540, 1365, 1315, 1210, 1055, 1010, 905, 830, 785, 745, 700 cm^{-1}.

(1*RS*,2*SR*,3*RS*,4*RS*)-6-Oxo-*exo*-3-(3-phenylureido)-7-oxabicyclo-[2.2.1]hept-*endo*-2-yl Acetate (15b):

A mixture of **10b** (0.5 g, 1.6 mmol), HFP (25 mL) and 70% aq $HClO_4$ (50 µL) is allowed to stand at 20°C for 4 h. The mixture is poured into sat. aq $NaHCO_3$ (500 mL) and extracted with CH_2Cl_2 (4 × 200 mL). The organic extracts are combined, dried ($MgSO_4$) and the solvent is evaporated. The residue is recrystallized from acetone/Et_2O (4°C); yield: 268 mg (55%), colorless crystals, mp 156–158°C.

MS (CI, NH_3): m/z = 306 (17), 305 (100, $M^{+\bullet}$ + 1), 304 (5 $M^{+\bullet}$).

IR (KBr) ν = 3320, 1770, 1740, 1640, 1590, 1550, 1500, 1440, 1365, 1310, 1230, 1150, 1055, 1010, 900, 735 cm^{-1}.

(1*RS*,2*RS*,6*RS*,7*RS*)-9,9-Dimethoxy-3,10-dioxa-5-azatricyclo-[5.2.1.$0^{2,6}$]decan-4-one (17):

Gaseous HCl is bubbled through a solution of **13c** (50 mg, 0.25 mmol) in anhydr. MeOH (5 mL) for 1 min. After stirring at 20°C for 2 h, solid $NaHCO_3$ is added until neutralization. CH_2Cl_2 (10 mL) is added and the precipitate filtered off. The solvent is evaporated and the residue taken with CH_2Cl_2 (4 mL). After filtration, the solvent is evaporated and the residue recrystallized from Et_2O; yield: 50 mg (92%), colorless crystals, mp 118–120°C.

$C_9H_{13}NO_5$ calc. C 50.23 H 6.09 N 6.51
(215.2) found 50.34 6.03 6.50

MS (CI, NH_3): m/z = 234 (11), 233 (96), 217 (10), 216 (100, $M^{+\bullet}$ + 1).

IR (CH_2Cl_2): ν = 3460, 3260, 2960, 2840, 1760, 1405, 1380, 1340, 1325, 1295, 1220, 1190, 1165, 1135, 1105, 1055, 970, 950, 930, 910 cm^{-1}.

^{1}H-NMR (250 MHz, $CDCl_3$/TMS): δ = 6.79 (br s, NH), 5.06, 3.99 (2 d, J = 7.0), 4.46 (br s), 4.41 (d, J = 6.0), 3.24, 3.23 (2 s, 2 CH_3), 1.99 (dd, J = 13.0, 6.0), 1.54 (d, J = 13.0).

(1*RS*,2*RS*,6*RS*,7*RS*)-9,9-Dimethoxy-4-phenyl-3,10-dioxa-5-aza-tricyclo[5.2.1.$0^{2,6}$]dec-4-ene (18):

Same procedure as for **17**, starting with (20 mg, 0.09 mmol) **13a**; yield: 22 mg (92%), colorless crystals.

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