Aminoglycoside Antibiotics – Modified, Enantiopure Sannamine- and Sporamine-Type Glycosyl Acceptors

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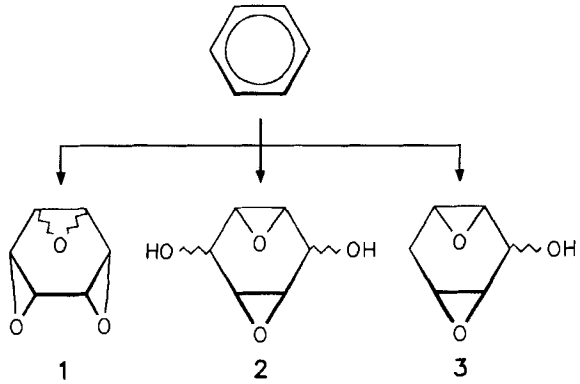
Received March 3, 1994

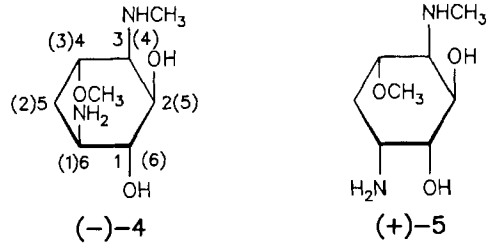
Key Words: Sannamines / Sporamines / Glycosyl acceptors, 4-epimers, fluorinated, enantiopure

Along an established scheme, 1,2:3,4-dianhydrodeoxy-*epi*-inositol (**3**) – readily available from benzene – has been applied to expeditious syntheses of suitably protected, fluorinated, and epimerized aminoglycoside building blocks related to sannamine (*rac*-**14a**, *rac*-**16a**, *rac*-**18a**, *rac*-**31a**) and sporamine (*rac*-**21a**, *rac*-**23a**, *rac*-**26a**, *rac*-**34a**). By separation of diastereomers formed with (+)-(1-phenylethyl)amine (**14c/14'c**; **16c/16'c**) or with (–)-camphanic acid (**14e/14'e**) and by enzymatic hydrolysis (*rac*-**14b**) access is gained to enantiopure glycosyl acceptors.

The transformation of benzene into highly functionalized cyclohexanes is a matter of topical interest[1]. To us, the development of highly expeditious routes to the triepoxycyclohexanes **1** [trianhydro-*cis*(*allo*)-inositols, *cis*(*trans*)-benzene trioxides], diepoxycyclohexanes **2** [dianhydro-*cis*(*epi, muco*)-inositols], and **3** [dianhydro-deoxy-*cis*(*epi*)-inositols] has induced a systematic study of their applicability to the synthesis of aminocyclitols, which function in various forms as building blocks of aminoglycoside antibiotics[2]. With a selection of enantiopure aminocyclitol-type glycosyl acceptors now at hand[3–8] and with the parallel elaboration of efficient routes to a considerable number of enantiopure purpurosamine-type glycosyl donors[9], combinations nearly at will in the construction of antibiotic-type glycosides have become possible. In the following paper[10] a glycosylation study directed toward sannamycin-analogous glycosides with natural and non-natural configurations will be presented.



In preceding papers, the potential of the epoxycyclohexanes **1**–**3** for the preparation of *cis*-1,3(1,4)-(deoxy)inosadiamines[3,4] such as streptamines[5], fortamines[6], and, of particular relevance in this paper, of sannamines[7] and sporamines[8] has been demonstrated. The route to the respective glycosyl acceptors **C** and **D** (Scheme 1) – suitably protected forms of sannamine [(–)-**4**] and sporamine [(+)-**5**][*] – starts from prochiral *anti*-**3** as common intermediate; the β-methylamino group is regiospecifically introduced by 5-*exo*-cyclization of the methylurethane derived from *anti*-**3** (**A** → **B**), the β-primary amino group by regiospecific epoxide opening (C-1) with azide ion (N_3^-) (**B** → **C**).



The 6-epimeric acceptors **D** are obtained by addition of a potent leaving group to **B** (at C-1) and subsequent replacement by azide ion. The products **C** and **D**, with the azide functionality as "protected" primary amine, are ready for glycosylation at the free 1-OH group. Attempts to achieve asymmetric cyclizations **A** → **B** (chiral bases, chiral carbamates) have not proved rewarding (low ee). Yet, optical resolution of diastereomers has been effected both in the sannamine series obtained from intermediates **B** and (+)(1*R*)-(1-phenylethyl)amine[7] and in the sporamine series obtained from hydroxy iodide intermediates of step **B** → **D** with (–)-camphanic acid[8].

Given the impact which fluorination or epimerization in the aglycon part of aminoglycoside antibiotics can have upon antibacterial activity and toxicity[11] [e.g. fluorinated kanamycins[12], (*epi*) sporaricins[13]], we became interested in extending Scheme 1 to the preparation of glycosyl acceptors of type **E** and **F**, in which the 4α-OCH_3 group of the

[*] As in preceding publications, cyclohexane nomenclature is used throughout this paper (antibiotics numbering is given in parentheses).

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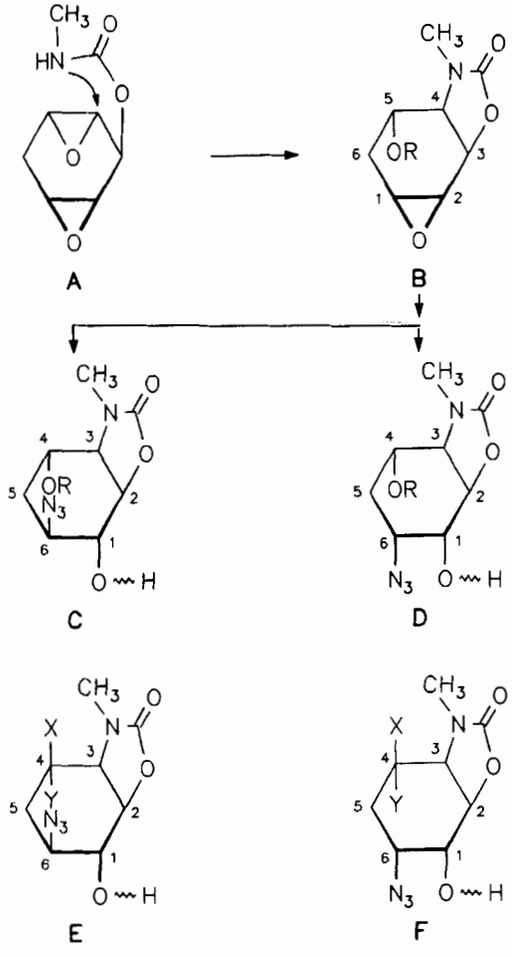
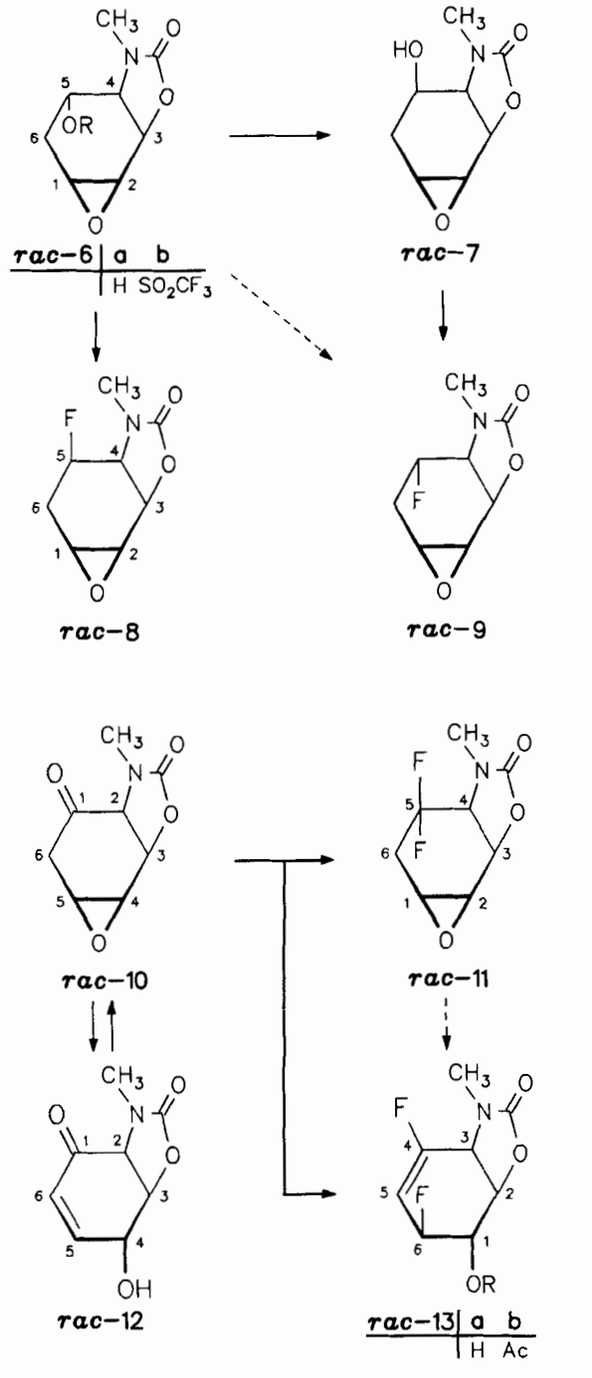
C and **D** compounds is either replaced by α(β)-positioned fluorine atoms (**14**, **16**, **18**; **21**, **23**, **26**) or is introduced into β-position (**31**; **34**). Exploitation of enzymatic methodologies for optical resolution at various stages of Scheme 1 has been an additional aspect of this project[14].

Scheme 1

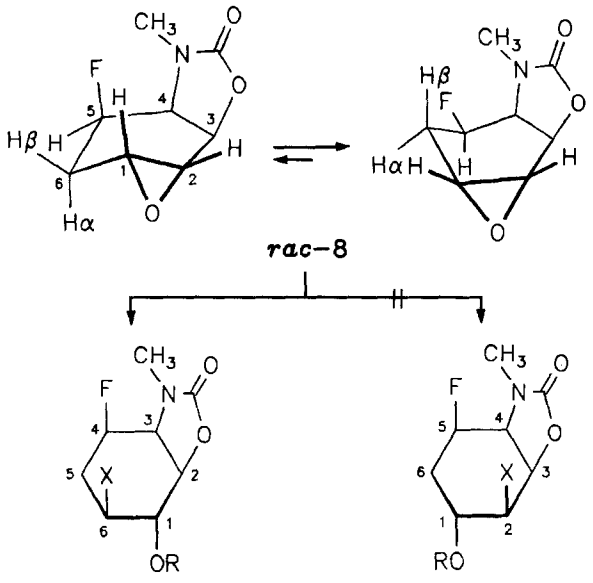


Fluorination of Epoxyurethanes B

5α-Alcohol *rac*-**6a** (**B**) serves as common precursor of the three fluorides *rac*-**8**, *rac*-**9**, and *rac*-**11** utilized in this study. In exploratory experiments[7] with *rac*-**6a** and DAST [(diethylamino)sulfur trifluoride][15] the inverted 5β-fluoride *rac*-**8** has been obtained in only low yield (ca. 10%) besides 39% of the olefin resulting from β-elimination. Treatment of triflate *rac*-**6b** with tetrabutylammonium fluoride on silica leads to an increase of the yield to ca. 40%. Still, separation from comparable amounts of olefin causes a considerable loss of material. It has now been found that the elimination caused by the F^- base can be reduced to a few percent, if not totally, by executing the substitution in *rac*-**6b** with $NEt_3 \cdot 3HF$ as described by Picq et al.[16]. The use of CH_2Cl_2 as solvent has proven to be mandatory whereas in CH_3CN as solvent elimination dominates again. Yields up to 67% of crystalline *rac*-**8** have become reproducible up to a 50-mmolar scale; potential small amounts of olefin (5%) can be conveniently extracted with aqueous $KMnO_4$ solution. 5α-Fluoride *rac*-**9** has originally been prepared by first epimerizing 5α-alcohol *rac*-**6a** to 5β-alcohol *rac*-**7** and then exposing the latter alcohol to DAST. A shorter access now resulted from a systematic investigation of the reactions of *rac*-**6a** with DAST in solvents of varying polarity. In CH_3CN an aspired goal has been achieved in that substitution takes place only with retention of configuration, the yield increasing with an excess of DAST and with decreasing temperature. Thus, from experiments with six equivalents of reagent and at −40°C, an average of 63% of 5β-fluoride *rac*-**9** is isolated (based on conversion, mmol scale).

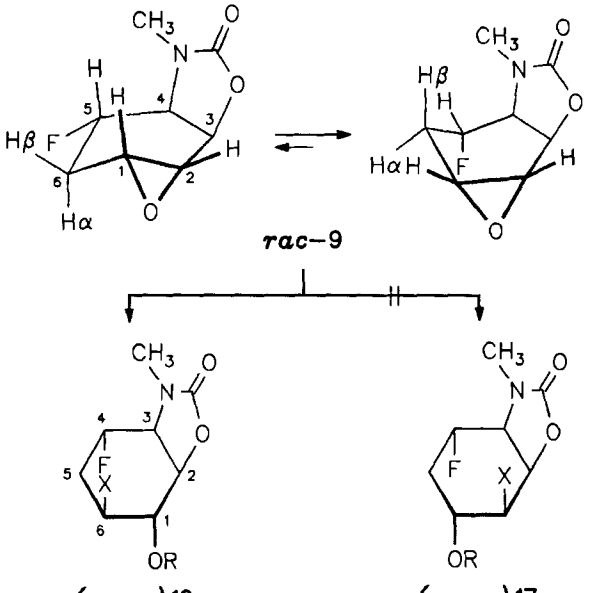


Geminal difluoride *rac*-**11** is generated by the reaction of ketone *rac*-**10** with DAST[15]. Oxidation of alcohol *rac*-**6a** to ketone *rac*-**10**, however, poses a problem. Presumably as a consequence of the high tendency of the latter toward isomerization, out of several oxidants used (MnO_2; CrO_3/pyridine[17], PDC[18], PCC[19], $NaBrO_4$/CAN[20], DMSO/acetic anhydride[21], DMSO/trifluoroacetic anhydride[22]) only the use of RuO_4[23] has provided *rac*-**10** in sufficiently high yield (84%, higher than 90% on conversion). On standing or during crystallization/chromatography, β-epoxy ketone *rac*-**10** isomerizes to highly labile and therefore only spectroscopically characterized γ-hydroxy enone *rac*-**12**. Therefore, unpurified, crude, oily *rac*-**10** is treated with 2.2 equivalents of DAST in CH_2Cl_2; after a very slow transformation a 73% yield (not optimized) of colorless oily *rac*-**11** [DL-(1α,2α,3β,4β)-1,2-Anhydro-3-*O*,4-*N*-carbonyl-5,5-difluoro-4-(methylamino)cyclohexane-1,2,3-triol] is obtained. On a gram-scale, a trace of a byproduct (2%) has been identified spectroscopically as *rac*-**13a** (and as *rac*-**13b**). Addition of fluoride to the epoxide and β-elimination are indeed pathways that must be taken into account in substrates like *rac*-**10**[15]. For *rac*-**11** vicinal and long-range coupling constants ($CDCl_3$, room temp.; i.a. $J_{1,2}$ = 3.8, $J_{2,3}$ < 1, $J_{3,4}$ = 8.3, $J_{6\alpha,6\beta}$ = 15.8, $J_{6\alpha,1}$ = 4, $J_{6,\beta,1}$ < 1, $J_{3,F\alpha}$ = $J_{3,F\beta}$ = 1, $J_{4,F\alpha}$ = 13.5, $J_{4,F\beta}$ = 1, $J_{6\alpha,F\beta}$ = 11.3, $J_{6\beta,F\alpha}$ = 21.8; $J_{NCH_3,F\beta}$ = 1.5 Hz) reveal equilibrating half-chair-like conformations, the conformation with F_β (F_α) with quasi-equatorial (axial) orientation predominating.



	a	b	c	d	e	f
X	N_3	N_3	NHR*	NHR*	N_3	N_3
R	H	Ac	H	Ac	R**	R***

R* = (+)-1-phenylethyl
R** = (−)-camphanoyl
R*** = (+)-MTPC



	a	b	c	d
X	N_3	N_3	NHR*	NHR*
R	H	Ac	H	Ac

R* = (+)-1-phenylethyl

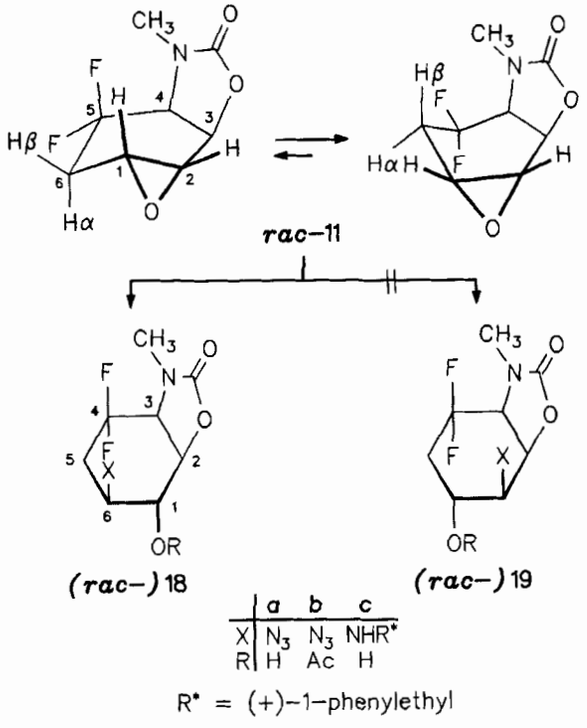
Fluorinated Glycosyl Acceptors of Type E

5β-Fluoride *rac*-**8** (i.a. $J_{5,6\alpha}$ = 4.5, $J_{5,6\beta}$ = 10.0, $J_{4,6\alpha}$ = 1.0 Hz)[24], when exposed to the azidation conditions used in the case of several 5-OR analogs[7,8] – ca. tenfold excess of NaN_3, $MgSO_4$, methanol, reflux temperature – reacts only sluggishly, requiring a reflux time of ca. 18 h for complete conversion. A low equilibrium concentration of the 5-F_{axial} half-chair, at which opening at C-1 should occur, and steric/electronic 1,3-diaxial interference between the axial F and the axially incoming N_3^- nucleophile are reasonable explanations. This pathway, nevertheless, is exclusively operative: Besides azido alcohol *rac*-**14a** [DL-(1α,2β,3β,4β,6β)-6-Azido-2-*O*,3-*N*-carbonyl-4-fluoro-3-(methylamino)cyclohexane-1,2-diol], practically quantitatively isolated in crystalline form and for higher reliability analyzed also as better soluble acetate *rac*-**14b**, not even trace amounts (< 2%) of the isomers **15a,b** have been detected by careful TLC and ^{1}H-NMR control measurements.

5α-Fluoride *rac*-**9** ($J_{5,6\alpha}$ = 6.0; $J_{5,6\beta}$ = 5.0 Hz; higher proportion of the 5-$F_{equatorial}$ half-chair conformer) is completely converted into the hydroxy azide **16a** under the above mentioned reaction conditions already after 3 h at reflux temperature (97% isolated in crystalline form). TLC and ^{1}H-NMR analyses of the crude reaction product again and with the same reliability exclude the presence of the isomer **17a**.

Difluoride *rac*-**11** ($J_{6\beta,F\alpha}$ = 21.8, $J_{6\alpha,F\alpha}$ = 17.3, $J_{6\beta,F\beta}$ = 9.0, $J_{6\alpha,F\beta}$ = 11.3 Hz) with its pronounced preference for the half-chair with 5β-F (6β-H) being oriented equatorially (axially) adds N_3^- even more reluctantly than *rac*-**8**. With the necessarily prolonged reflux time (48 h totally) decomposition becomes significant. For that reason, only 80% of crystalline hydroxy azide *rac*-**18a** is obtained. Again no

other monomeric component is present (< 2%, TLC, ^{1}H-NMR) before and after acetylation (*rac*-**18b**).



	a	b	c
X	N_3	N_3	NHR*
R	H	Ac	H

In Figure 1 the ^{1}H-NMR assignments and approximate major conformations for **14a**, **16a**, and **18a** are shown. As discussed at length for previous cases[7], the distinction between isomeric structures (**15a**, **17a**, **19a**) primarily and reliably rests on the vicinal H/H coupling constants and H/H interconnectivities. On this basis, *rac*-**16a** and *rac*-**18a** closely resemble the $4_{\alpha\text{-OH}}$ analog (c.f. Table 2 in ref.[7]) for which the equilibrium between 1e,4a,6e and 1a,4e,6a half-chair conformations has favored the former one. *rac*-**14a** differs from *rac*-**16a** and *rac*-**18a** by its large $J_{3,F}/J_{5\alpha,F}$ and $J_{1,2}/J_{6,1}$ values, suggesting predominance of a nearly boat-like conformation with axially positioned fluorine. For the aminocyclitol portion of 3-*epi*-3-fluoro-de(methoxy)sporaricin A, conformations with equatorial fluorine have been similarly excluded[13]. A recent X-ray structural analysis of a glycoside of **14a** has provided more detailed informations[10,25].

Three pathways to the enantiopure 4β-fluoro acceptors **14a** and *ent*-**14a** have been tried: Separation of diastereomers produced by esterification of *rac*-**14a** with (−)-camphanoyl chloride (**14e**/**14'e**)[7,8], addition of (+)-(1-phenylethyl)amine to *rac*-**8** (**14c**/**14'c**), and enzymatic hydrolysis/esterification of *rac*-**14b**/*rac*-**14a**[14].

Separation of a mixture of diastereomers **14e**/**14'e**, quantitatively obtained on a gram-scale, has proved preparatively useful when a larger portion of **14'e** crystallizes from ethyl acetate in pure form (m.p. 249°C), and rapid chromatography of the mother liquor ($CHCl_3/CH_3OH$ 25:1) allows clean separation of the rest of **14'e** from **14e** (m.p. 212°C). After saponification, pure alcohols **14a** and *ent*-**14a** are extracted with CH_2Cl_2 from the alkaline aqueous

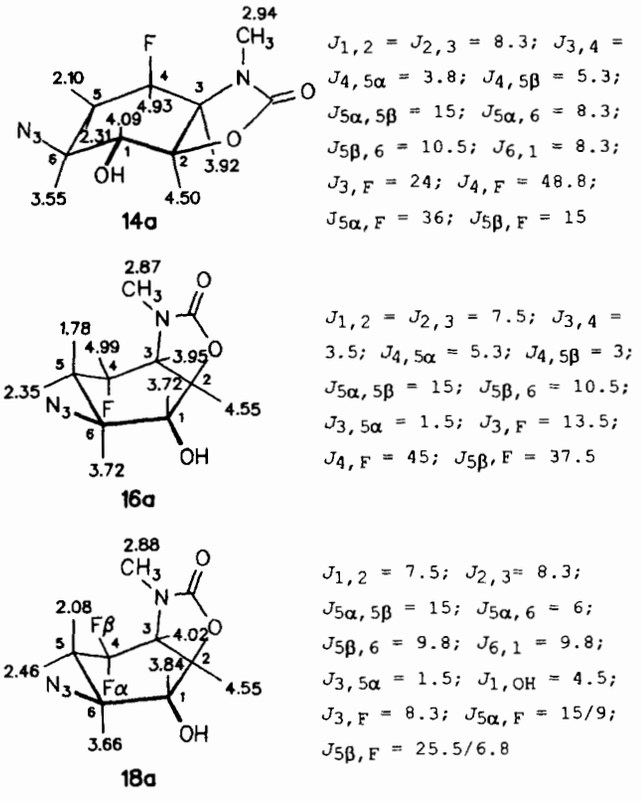
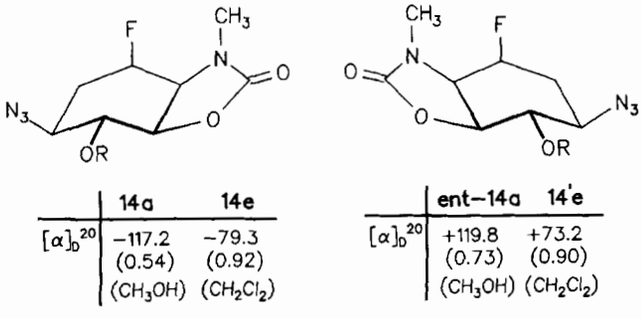


Figure 1. ^{1}H-NMR assignments (δ) and selected coupling constants (Hz) for *rac*-**14a**, *rac*-**16a**, and *rac*-**18a**

solution; by acidification of the latter, the chiral auxiliary [(−)-camphanic acid] is quantitatively regained. For the optical rotation measurements (Figure 2), samples of the nearly quantitatively isolated crystalline **14a**/*ent*-**14a** are repeatedly crystallized from chloroform.



	14a	14e
$[\alpha]_D^{20}$	−117.2	−79.3
	(0.54)	(0.92)
	(CH_3OH)	(CH_2Cl_2)

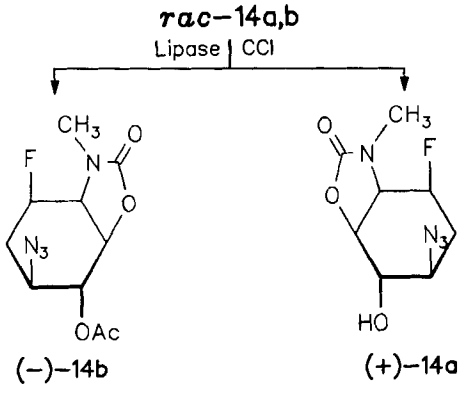
	ent-14a	14'e
$[\alpha]_D^{20}$	+119.8	+73.2
	(0.73)	(0.90)
	(CH_3OH)	(CH_2Cl_2)

Figure 2. Optical rotations for **14a**/*ent*-**14a** and **14e**/**14'e**

The reaction between *rac*-**8** and (+)-(1-phenylethyl)amine proceeding too slowly in boiling methanol and being completed even in boiling *n*-propanol only after 47 h, proceeds again regiospecifically within the limits of the ^{1}H-NMR/TLC analysis. Isolation of pure diastereomers benefited from the fact that during crystallization from ethyl acetate in the case of the alcohols **14c**/**14'c** the non-natural (**14'c**) and in the case of their acetates **14d**/**14'd** the natural component (**14d**) separate nearly completely and in pure form. Since the R*-protected 6-amines like **14c** have later been found not to be applicable to the glycosylation method-

ology ultimately applied[10], total spectral analysis is limited to the better soluble **14c** and **14'c**, and the assignment to the natural and non-natural series is provisionally based on a TLC comparison[26]. It should be noticed that the structural modifications introduced with the chiral groups in **14c, d** have no consequence as to the preference for a boat-like conformation.

To achieve enzymatic resolutions at the stages of tricyclic (**B**) and bicyclic intermediates (**C**) (Scheme 1), lipase-catalyzed esterification of **14a** and hydrolysis of **14b** have been studied. In a test series with **14a** and fifteen lipases/esterases[27] in vinyl acetate as solvent and in the presence of an acetyl transfer agent under varied conditions (room temp., 45°C), no catalysis has been realized. In contrast, from a test series with acetate **14b** and the same set of enzymes in pH 7 phosphate buffer/*n*-hexane solution/suspension, the lipase CCL has emerged as the reagent of choice: The alcohol isolated after ca. 50% conversion is highly enriched (+)-**14a** (and as such directly subjected to glycosylation). In contrast to the camphanic esters **14e/14'e**, the Mosher esters **14f/14'f** exhibit clearly separated signals in their high-field ^{1}H-NMR spectra; the derived ee value of 89% has been confirmed by HPLC analysis on a Merck LiChrosorb Si 100 column.



Similarly expeditious biocatalytic routes to enantiopure 4α-fluoro and difluoro acceptors, **16a**/*ent*-**16a** and **18a**/*ent*-**18a**, are not yet available. In explorative experiments, the separability of the diastereomers **16c/16'c** and **18c/18'c** has been established in principle. In the latter case, however, the necessity for even more rigorous conditions for their formation – as compared to **16c** – and hence greater material loss exclude practical applications.

Fluorinated Glycosyl Acceptors of Type F

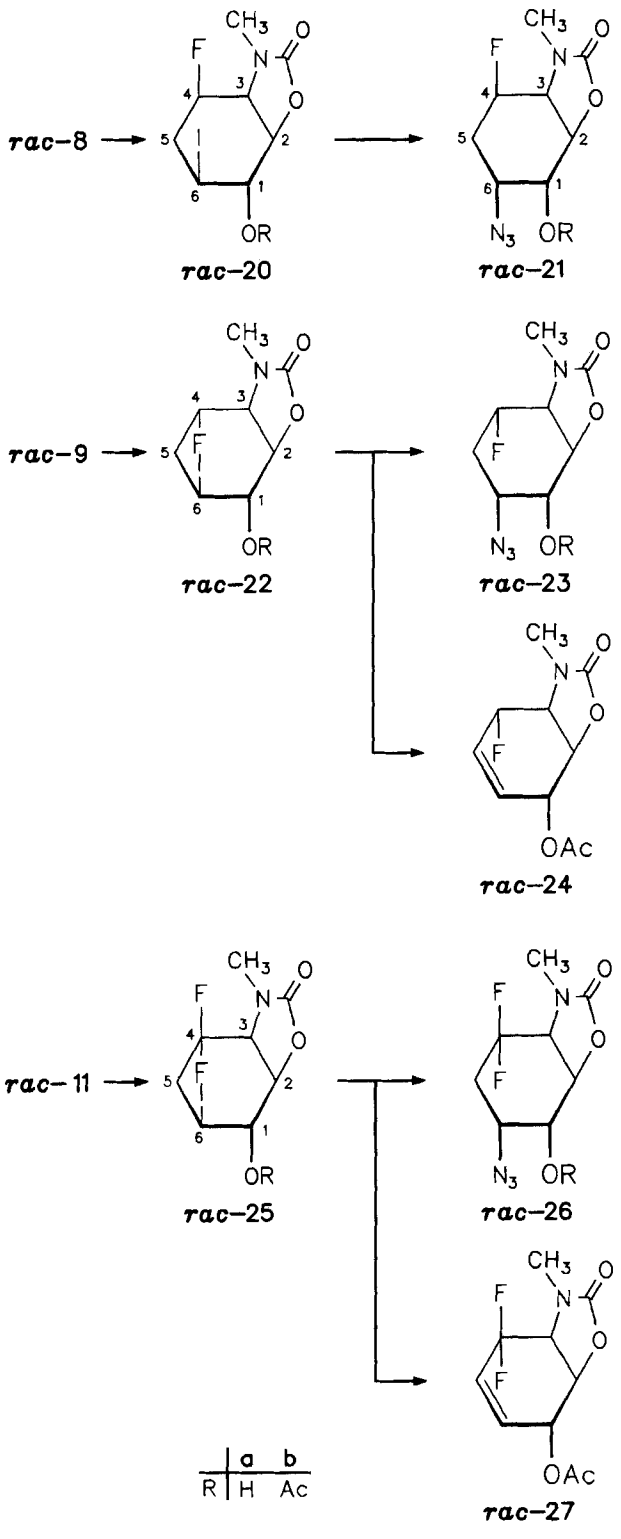
The efficiency in prior preparations of sporamine-type glycosyl acceptors **D** via intermediates **B** (Scheme 1) is closely connected with the highly regioselective addition of iodide ion (C-1) and with only minor if not insignificant competition (β-elimination) in the S_N2 substitution of azide for iodide ion performed after protection of the 1-OH group (to prevent epoxide reformation). There are, however, some uncertainties as to what extent the different functionalization in the substrates *rac*-**8**, *rac*-**9**, and *rac*-**11** would influence ease and selectivity of the respective transformations leading to *rac*-**21a**, *rac*-**23a**, and *rac*-**26a** as glycosyl acceptors of type F.

The reaction between 4β-fluoro epoxide *rac*-**8** and potassium iodide under otherwise proven conditions (ca. tenfold excess, 80% aqueous acetic acid, 50°C)[8] is sluggish and not optimal. After completion (ca. 5 h) of the reaction ^{1}H-NMR and TLC analysis of the crude solid product indicate 1α-hydroxy-6β-iodide *rac*-**20a** to be the preponderant component (79% isolated) accompagnied by one or even two other compounds (not definitely characterized but must probably not the regioisomer of *rac*-**20a**). With iodo trimethylsilane (NaI/TMSCl, CH_3CN)[28] the product isolated after hydrolysis, conventional workup, and crystallization has been found to consist uniformely of *rac*-**20a** (isolated yield 96%, $J_{6,1}$ = 11.3 Hz). After nearly quantitative acetylation, the carefully dried solution of *rac*-**20b** ($J_{6,1}$ = 12 Hz) and tetramethylguanidinium azide (TMGA) in CH_3CN is only moderately heated (50°C), indicating a relatively long reaction time of ca. 18 h for completion. In this way, β-elimination is totally avoided; the crude solid product consisting mainly of 6α-azide **21a** (TLC, ^{1}H-NMR, 84%) is crystallized from ethyl acetate/cyclohexane (84%). Under controlled conditions, hydrolysis affording the 4β-fluoro acceptor *rac*-**21a** (99% after crystallization from ethyl acetate/cyclohexane, 1:1) faced no competition by cleavage of the carbamate ring.

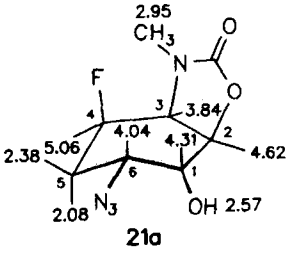
On the way from *rac*-**9** to acceptor *rac*-**23a** the generation of the hydroxyiodide by treatment with KI/aqueous acetic acid provides *rac*-**22a** in moderate (67%) yield as colorless crystals ($J_{5\beta,6}$ = $J_{6,1}$ = 11.3 Hz); it should be replaced by the TMSI variant. After esterification (nearly quantitative yield of *rac*-**22b**; $J_{6,1}$ = 10.5 Hz) and complete conversion with TMGA under the conditions applied to *rac*-**20b**, ^{1}H-NMR and TLC analysis reveal the presence of olefin **24** as a trace impurity (< 2.5%) in oily *rac*-**23b** (90%). After saponification acceptor *rac*-**23a** is isolated in crystalline form from ethyl acetate (94%).

4,4-Difluoro epoxide *rac*-**11** resists reaction with KI/acetic acid up to temperatures causing largely decomposition but is rapidly attacked by TMSI under the conditions applied to *rac*-**8** to provide after hydrolysis 94% of crystalline iodo alcohol *rac*-**25a** ($J_{6,1}$ = 11, $J_{5\beta,F\alpha}$ = 30.5 Hz). The outcome of the reaction of acetate *rac*-**25b** (98%) with TMGA, executed as in the synthesis of **20b** and complete after 20 h, differed in that besides 86% of *rac*-**26b** up to 13% of olefin *rac*-**27** is present. For their characterization the two components are separated chromatographically; for the subsequent isolation of *rac*-**26a** it is sufficient to separate the olefin from the crude reaction mixture before saponification by a short treatment of the CH_2Cl_2 solution of the mixture with aqueous $KMnO_4$ solution.

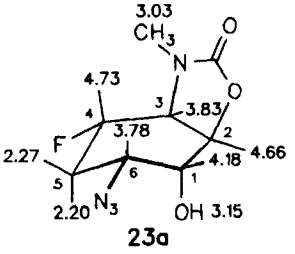
The analytical data confirming structures **20**–**27** are collected in the experimental section. The conformational representations for *rac*-**21a**, *rac*-**23a**, and *rac*-**26a** in Figure 3 are once more approximative. When compared with Figure 1, the change in configuration at C-6 is expressed in the small $J_{6,1}$ values (3.8 vs. 8.3–9.1 Hz) in line with the quasi-equatorial (axial) position for the N_3 (OH) group. Com-



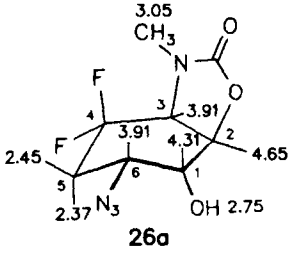
pound **21a** additionally differs from epimer **14a** with otherwise close correspondence within the sets of H,H (H,F) coupling constants by an appreciable high-field shift of the 5α-H signal ascribed to a shielding effect by the neighboring 6α-azide function. The large $J_{F,5\alpha}$ (**21a**, **26a**) and $J_{4,5\alpha}$ (**23a**) values are in line with *trans*-diaxial relationships, the relatively large $J_{5\alpha,6}$ value for **23a** with a 1a,4e,6e half-chair. The smaller $J_{5\alpha,6}$ values for **21a** and **26a** suggest conformations with more equatorial alignment of the 1-OH group.



$J_{1,2}$ = 4.5; $J_{2,3}$ = 7.5; $J_{3,4}$ = $J_{4,5\alpha}$ = $J_{4,5\beta}$ = 3.8; $J_{5\alpha,5\beta}$ = 15; $J_{5\alpha,6}$ = 7.5; $J_{5\beta,6}$ = 5.3; $J_{6,1}$ = 3.8; $J_{3,F}$ = 22.5; $J_{4,F}$ = 48.8; $J_{5\alpha,F}$ = 36; $J_{5\beta,F}$ = 15



$J_{1,2}$ = 2.3; $J_{2,3}$ = $J_{3,4}$ = 7.5; $J_{4,5\alpha}$ = 10.5; $J_{4,5\beta}$ = 6; $J_{5\alpha,5\beta}$ = 13.5; $J_{5\alpha,6}$ = 9.8; $J_{5\beta,6}$ = $J_{6,1}$ = 3.8; $J_{2,F}$ = 4.5; $J_{3,F}$ = 16.5; $J_{4,F}$ = 49; $J_{5\alpha,F}$ = 20.3; $J_{5\beta,F}$ = 18; $J_{NCH3,F}$ = 1.5



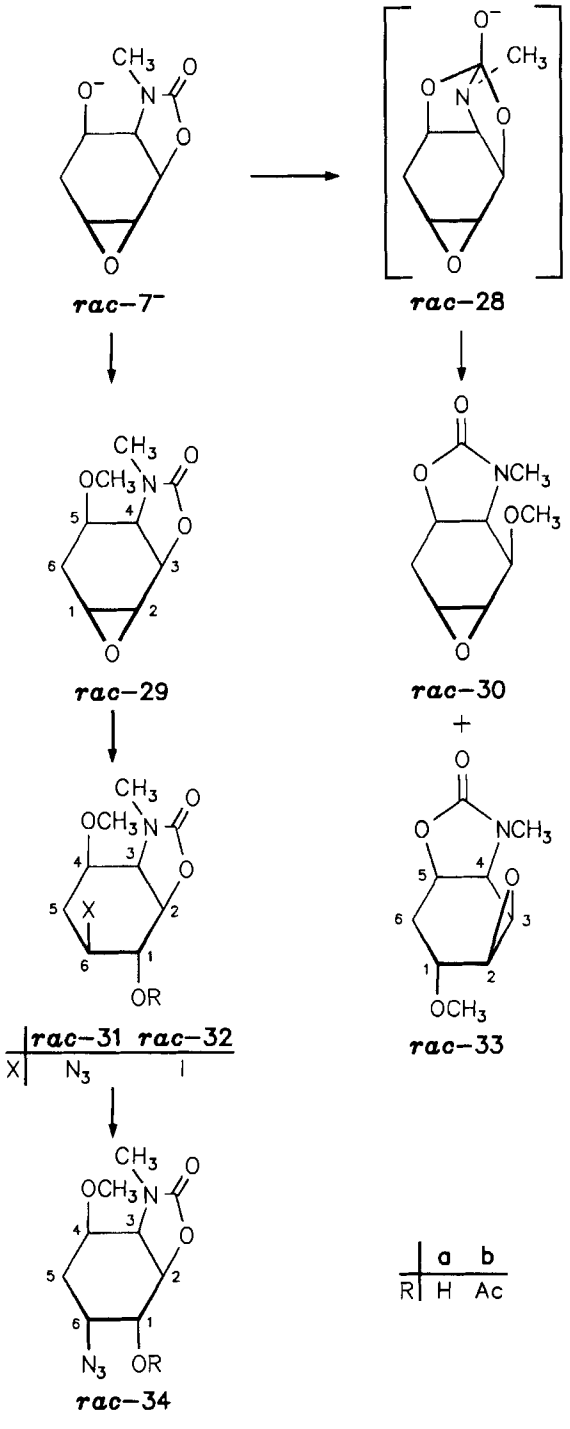
$J_{1,2}$ = 3.5; $J_{2,3}$ = 7; $J_{5\alpha,5\beta}$ = 14.5; $J_{5\alpha,6}$ = 4.5; $J_{5\beta,6}$ = 5; $J_{1,OH}$ = 3.5; $J_{2,F}$ = 2/3.5; $J_{3,F}$ = 7/16; $J_{5\alpha,F}$ = 33/10; $J_{5\beta,F}$ = 14.5/5; $J_{NCH3,F}$ = 1

Figure 3. ^{1}H-NMR assignments (δ) and selected coupling constants (Hz) for *rac*-**21a**, *rac*-**23a**, and *rac*-**26a**

4β-Methoxy Glycosyl Acceptors of Type E/F

Ready access to 4-epimeric, protected sannamines and sporamines *rac*-**31** and *rac*-**34** seems guaranteed with the rapid three-step epimerization of 5α-alcohol *rac*-**6a** to 5β-alcohol *rac*-**7** (84%). In fact, except the seemingly trivial alkylation *rac*-**7**$^-$ → *rac*-**29**, all steps – introduction of azide and iodide ion into *rac*-**29** (*rac*-**31a**, *rac*-**32a**) as well as the substitution reaction *rac*-**32b** → *rac*-**34b** – take the expected selective course. The complication arising in the methylation of *rac*-**7**$^-$ is caused by the proximity-assisted intramolecular addition of the 5β-hydroxide to the carbamate ring (*rac*-**28**), giving rise to transamidation and subsequent epoxide migration. Thus, after treatment of *rac*-**7** with NaH/DMF/CH_3I (25°C), besides ca. 40% of desired *rac*-**29**, a comparable amount of a non-separable mixture of the two isomeric methyl ethers *rac*-**30** and *rac*-**33** is obtained. Yet, with a more reactive alkylating agent in a less polar medium [$(CH_3)_2SO_4$/DMF/glyme, 1:2, 25°C], *rac*-**7**$^-$ is much more efficiently captured, and the yield of isolated (oily) *rac*-**29** is raised to non-optimized 90%. After the expectedly slow azidation (36 h in refluxing methanol for completion) the exclusively formed 4-*epi*-sannamine-type acceptor *rac*-**31a** (TLC) is isolated after crystallization

(ethyl acetate) in 88% yield and derivatized as *rac*-**31b**. Addition of iodide to *rac*-**29** (82% *rac*-**32a**), acetylation (94% *rac*-**32b**), replacement by N_3^- (89% *rac*-**34b**), and hydrolysis provide the crude, oily and so far not crystallizable sporamine-type acceptor *rac*-**34a**.



Structural distinction of the three isomeric methyl ethers *rac*-**29**, *rac*-**30**, and *rac*-**33**, the configurational details of the 4β-functionalized products *rac*-**31**, *rac*-**32**, and *rac*-**34** as well as conformational preference are primarily based on ^{1}H-NMR spectral comparison. $J_{6,1}$ = 10.2(3.0) Hz for *rac*-**31a** and *rac*-**34a** (Figure 4) are typical of sannamines/sporamines in highly populated approximate 1e,4e,6e and 1e,4a,6e half-chair-like conformations.

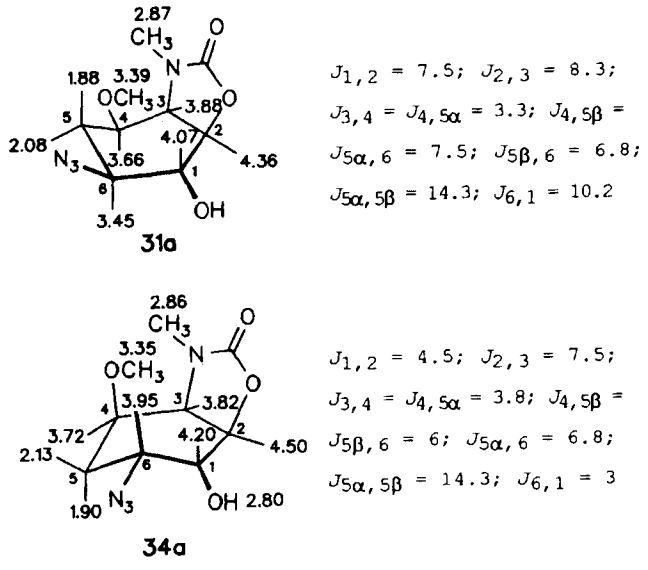


Figure 4. ^{1}H-NMR assignments (δ) and selected coupling constants (Hz) for *rac*-**31a** and *rac*-**34a**

Conclusion

High selectivity in the transformations **B** → **C** and **B** → **D** – as essential feature of this route to protected (*epi*)sannamine- and (*epi*)sporamine-related glycosyl donors – is retained for the 5-fluorinated and 5-epimeric substrates of type **B**. With the fluorination as limiting step, overall yields of 49–61 and 38–48% for the 6β- (**14a**, **16a**, **18a**, **31a**) and 6α-azides (**21a**, **23a**, **26a**, **34a**) are not optimal, yet satisfactory enough to go ahead with the project. Optical resolution has been demonstrated for exemplary cases; work is in progress to make all aglyca presented in this paper available as pure enantiomers. Thus, with several aglycon-building blocks of type **E** and **F**, the scope of our approach to (protected) diaminodeoxycyclitols of various configurations at C-4 and C-6 – five stereogenic centers are ultimately generated on the benzene ring via *anti*-**3** – has been significantly extended.

Financial support by the *Fonds der Chemischen Industrie*, the *Deutsche Forschungsgemeinschaft*, the *BASF AG*, and the *Ministerium für Wissenschaft und Forschung des Landes Baden-Württemberg* (Schwerpunkt "Synthese – Enzyme") is gratefully acknowledged. We thank Prof. Dr. *H. Fritz*, Dr. *D. Hunkler*, and Dr. *J. Wörth* for extensive NMR and MS measurements, Dr. *L. Knothe* and Dr. *C. Ludin* for help with the manuscript, Fa. *Amano & Co* for generous gifts of enzymes.

Experimental

Melting points (m.p.): Bock Monoscop M. – Analytical TLC: Merck silica gel plates with F_{254} indicator. – Optical rotation data: Perkin Elmer 241 polarimeter, cell 10 cm. – IR: Perkin Elmer 457, Philips PU 9706. – UV: Perkin Elmer Lambda 15. – ^{1}H NMR: Bruker AC 250, AM 400. – ^{13}C NMR: AM 400. Chemical shifts relative to TMS (δ = 0), coupling constants in Hz; if not specified otherwise, the 250-MHz (^{1}H) and 100.6-MHz (^{13}C) spectra in $CDCl_3$ are given; assignments marked by an asterisk (*) can be interchanged. – MS: Finnigan MAT 44S, EI 70 eV, if not specified differently.

DL-(1a,2a,3β,4β,5a)-1,2-Anhydro-3-O,4-N-carbonyl-5-fluoro-4-(methylamino)cyclohexane-1,2,3-triol (*rac*-**8**): To a solution of *rac*-**6b** (560 mg, 1.77 mmol) and NEt_3 (286 mg, 2.83 mmol) in CH_2Cl_2 (20 ml, N_2) $NEt_3 \cdot 3$ HF (855 mg, 5.31 mmol) was added. After stirring at room temp. for 20 h [total conversion, TLC, cyclohexane/ethyl acetate, 1:3, R_f (*rac*-**8**) = 0.31] an aqueous $NaHCO_3$ solution was added and the organic phase extracted twice with 2 N H_2SO_4, with water, and with 1% $KMnO_4$ solution. After conventional workup and concentration in vacuo colorless crystals were obtained (200 mg, 67%)[7].

DL-(1a,2a,3β,4β,5a)-1,2-Anhydro-3-O,4-N-carbonyl-5-fluoro-4-(methylamino)cyclohexane-1,2,3-triol (*rac*-**9**): To a solution of *rac*-**6a** (110 mg, 0.59 mmol) in dry acetonitrile (N_2) at −40°C DAST (574 mg, 3.57 mmol) was added dropwise. After 3 h it was concentrated in vacuo, the residue was dissolved in $CHCl_3$ and the resulting solution washed with a saturated aqueous $NaHCO_3$ solution. After extraction with $CHCl_3$, the organic phase was dried ($MgSO_4$) and concentrated in vacuo. After chromatographic purification of the residue on silica gel ($CHCl_3/CH_3OH$, 10:1) colorless crystals (70 mg, 63% yield based on conversion)[7] were obtained.

DL-(2a,3a,4β,5β)-4,5-Anhydro-3-O,2-N-carbonyl-2-(methylamino)-3,4,5-trihydroxycyclohexanone (*rac*-**10**): To a solution of $NaIO_4$ (4.50 g, 21.0 mmol) in water (8 ml) containing a catalytic amount of $RuCl_3$ and adjusted to pH 3 by the addition of 2 N H_2SO_4 a solution of *rac*-**6a** (1.00 g, 5.4 mmol) in acetonitrile (4 ml)/ethyl acetate (4 ml) was added. After stirring at room temp. for 20 h [total conversion, TLC, cyclohexane/ethyl acetate, 1:3, R_f (*rac*-**10**) = 0.38], 2-propanol (1 ml) was added. After 5 min ethyl acetate (20 ml) and water were added. After extraction with ethyl acetate, the organic phase was dried ($MgSO_4$) and concentrated in vacuo to give an air-sensitive colorless oil (830 mg, 84%), which on standing or in solution slowly rearranged into the equally sensitive *rac*-**12**. – ^{1}H NMR ($CDCl_3$): δ = 5.21 (ddd, 3-H), 3.85 (dd, 4-H), 3.60 (ddd, 1-H), 3.52 (dd, 2-H), 3.15 (dd, 6α-H), 2.98 (ddd, 6β-H), 2.95 (s, NCH_3); $J_{1,2} = J_{2,3} = 9$, $J_{3,4} = 9$, $J_{4,5} = 3$, $J_{5,6\beta} = 4.5$, $J_{6\alpha,6\beta} = 15.8$, $J_{6\alpha,1} = 1.5$, $J_{6\beta,1} = 4.5$.

DL-(1a,2a,3β,4β)-1,2-Anhydro-3-O,4-N-carbonyl-5,5-difluoro-4-(methylamino)cyclohexane-1,2,3-triol (*rac*-**11**): To a solution of *rac*-**10** (830 mg, 4.5 mmol) in dry CH_2Cl_2 (20 ml, N_2) (diethylamino)sulfur trifluoride (DAST)[15] (1.88 g, 11.7 mmol) was added dropwise at 0°C. After stirring at room temp. for 20 h CH_2Cl_2 (10 ml) was added and the solution worked up as described above. After chromatographic separation on silica gel [cyclohexane/ethyl acetate, 1:3, R_f (*rac*-**11**) = 0.47] *rac*-**11** (680 mg, 73%) and *rac*-**13a** (20 mg, 2%) were obtained, both as a colorless oil. – IR (film): $\tilde{\nu}$ = 1764 cm^{-1} (s, C=O), 1109 (m, CF). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.99 (ddd, 3-H), 3.80 (dddd, 4-H), 3.45 (m, 1-H), 3.41 (d, 2-H), 3.00 (dd, NCH_3), 2.58 (dddd, 6α-H), 2.38 (ddd, 6β-H); $J_{1,2} = 3.8$, $J_{2,3} < 1$, $J_{3,4} = 8.3$, $J_{6\alpha,6\beta} = 15.8$, $J_{6\alpha,1} = 4$, $J_{6\beta,1} < 1$, $J_{3,F\alpha} = J_{3,F\beta} = 1$, $J_{4,F\alpha} = 13.5$, $J_{4,F\beta} = 1$, $J_{6\alpha,F\alpha} = 17.3$, $J_{6\alpha,F\beta} = 11.3$, $J_{6\beta,F\alpha} = 21.8$, $J_{6\beta,F\beta} = 9$, $J_{NCH_3,F\alpha} = J_{NCH_3,F\beta} = 1.5$. – MS, *m/z* (%): 205 (23) [M^+], 177 (9) [$M^+ - CO$], 148 (7) [$M^+ - CO - NCH_3$].

DL-(2a,3a,4β)-3-O,2-N-Carbonyl-3,4-dihydroxy-2-(methylamino)cyclohex-5-en-1-one (*rac*-**12**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.05 (ddd, 5-H), 6.23 (ddd, 6-H), 4.89 (ddd, 3-H), 4.66 (ddd, 4-H), 4.08 (dd, 2-H), 3.00 (s, NCH_3); $J_{2,3} = 8.3$, $J_{3,4} = 5.3$, $J_{4,5} = 3$, $J_{5,6} = 10.5$, $J_{2,6} = 0.5$, $J_{3,5} = 0.8$, $J_{4,6} = 1.8$.

DL-(1a,2β,3β,6β)-2-O,3-N-Carbonyl-4,6-difluoro-3-(methylamino)-cyclohex-4-ene-1,2-diol (*rac*-**13a**): R_f (ethyl acetate/cyclohexane, 3:1) = 0.35. – IR (film): $\tilde{\nu}$ = 3402 cm^{-1} (m, OH), 1767 cm^{-1} (s, C=O), 1109 (m, CF). – ^{1}H NMR ($CDCl_3$): δ = 5.69 (ddd, 5-H), 5.08 (ddddd, 6-H), 4.62 (ddd, 2-H), 4.35 (dddd, 3-H), 4.10 (ddd, 1-H), 3.56 (m, OH), 3.00 (d, NCH_3); $J_{1,2} = 7$, $J_{2,3} = 8.5$, $J_{5,6} = 3$, $J_{6,1} = 7$, $J_{1,F} = 14.5$, $J_{2,F} = 0.8$, $J_{3,F} = 1/3.5$, $J_{5,F} = 10.5/13.5$, $J_{6,F} = 6.5/50$, $J_{3,6} = 1$, $J_{NCH_3,F} = 1.8$. – ^{13}C NMR ($CDCl_3$): δ = 157.5/154.7 (d, C-4), 157.4/157.2 (d, C=O), 106.6/106.5/106.3/106.2 (dd, C-5), 87.9/87.8/86.1/86.0 (dd, C-6), 73.9/73.8/73.7 (t, C-2), 70.8, 70.6 (d, C-1), 55.5/55.2 (d, C-3), 31.2/31.1 (d, NCH_3); $^2J_{1,F} = 20$, $^3J_{2,F} = 9/9$, $^2J_{3,F} = 27$, $^1J_{6,F} = 174$, $^3J_{4,F} = 12$, $^2J_{5,F} = 17/25$, $^1J_{4,F} = 278$, $^4J_{NCH_3,F} = 15$.

DL-(1a,2β,3β,6β)-2-O,3-N-Carbonyl-4,6-difluoro-2-hydroxy-3-(methylamino)cyclohex-4-en-1-yl Acetate (*rac*-**13b**): ^{1}H NMR ($CDCl_3$): δ = 5.75 (ddd, 5-H), 5.44 (ddd, 1-H), 5.14 (ddd, 6-H), 4.69 (ddd, 2-H), 4.34 (ddd, 3-H), 3.02 (d, NCH_3), 2.15 (s, $COCH_3$); $J_{1,2} = 6$, $J_{2,3} = 8.3$, $J_{5,6} = 3.8$, $J_{6,1} = 6$, $J_{1,F} = 11.7$, $J_{2,F} = 1.5$, $J_{3,F} = 2.7/2.7$, $J_{6,F} = 6/48.8$, $J_{NCH_3,F} = 1.8$.

DL-(1a,2β,3β,4β,6β)-6-Azido-2-O,3-N-carbonyl-4-fluoro-3-(methylamino)-cyclohexane-1,2-diol (*rac*-**14a**): A solution of *rac*-**8** (60 mg, 0.32 mmol), NaN_3 (240 mg, 3.7 mmol), and $MgSO_4$ (440 mg, 3.7 mmol) in CH_3OH (10 ml) was refluxed for 18 h [total conversion, TLC, cyclohexane/ethyl acetate, 1:3, R_f (*rac*-**14a**) = 0.15]. After filtration and concentration of the filtrate in vacuo the residue was extracted with hot ethyl acetate. After evporation colorless crystals (71 mg, 97%), m.p. 133°C ($CHCl_3$) were obtained. – IR (KBr): $\tilde{\nu}$ = 3338 cm^{-1} (s, OH), 2912 (m, CH_2), 2090 (s, N_3), 1729 (s, C=O), 1084 (s, CF). – ^{1}H NMR ($CDCl_3$, 400 MHz): see Figure 1. – $C_8H_{11}FN_4O_3$ (230.2): calcd. C 41.74, H 4.82, N 24.34; found C 41.62, H 4.77, N 24.06.

DL-(1a,2β,3β,4β,6β)-6-Azido-2-O,3-N-carbonyl-4-fluoro-2-hydroxy-3-(methylamino)cyclohexyl Acetate (*rac*-**14b**): *rac*-**14a** (20 mg, 0.09 mmol) was acetylated under standard conditions. After conventional workup colorless crystals (24 mg, 99%), m.p. 149°C (ethyl acetate/cyclohexane, 1:1) were obtained. R_f ($CHCl_3/CH_3OH$, 10:1) = 0.33. – IR (KBr): $\tilde{\nu}$ = 2978 cm^{-1} (w, CH_3), 2098 (s, N_3), 1761 (s, C=O), 1122 (s, CF). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.44 (ddd, 1-H), 4.97 (dddd, 4-H), 4.52 (t, 2-H), 3.90 (ddd, 3-H), 3.57 (ddd, 6-H), 2.94 (s, NCH_3), 2.37 (dddd, 5α-H), 2.19 (dddd, 5β-H), 2.15 (s, $COCH_3$); $J_{1,2} = 8$, $J_{2,3} = 9$, $J_{3,4} = 3$, $J_{4,5\alpha} = 4$, $J_{4,5\beta} = 5$, $J_{5\alpha,5\beta} = 15.5$, $J_{5\alpha,6} = 7.5$, $J_{5\beta,6} = 7.5$, $J_{6,1} = 11$, $J_{1,F} = 3.5$, $J_{3,F} = 23.5$, $J_{4,F} = 48.5$, $J_{5\alpha,F} = 35$, $J_{5\beta,F} = 16$. – ^{13}C NMR ($CDCl_3$): δ = 169.2 (N,O−C=O), 157.1 [C=O(Ac)], 85.6/83.7 (d, C-4), 73.3/73.3 (d, C-2), 72.7/72.7 (d, C-1), 58.5/58.3 (d, C-3), 55.4/55.4 (d, C-6), 30.9/30.7 (d, C-5), 29.83/29.81 [d, CH_3(Ac)], 20.7 (NCH_3); $^4J_{1,F} = 3$, $^3J_{2,F} = 2.4$, $^2J_{3,F} = 19$, $^1J_{4,F} = 182.5$, $^2J_{5,F} = 20.8$, $^3J_{6,F} = 3$, $^4J_{[CH_3(Ac)],F} = 2.4$. – $C_{10}H_{13}FN_4O_4$ (272.7): calcd. C 44.12, H 4.81, N 20.58; found C 43.86, H 4.79, N 20.18.

Enzymatic Resolution of rac-**14b**: A suspension of *rac*-**14b** (100 mg, 0.37 mmol) and lipase CCL (100 mg) in distilled water (100 ml) and *n*-hexane (10 ml) was stirred extensively (an autotitrator was used to monitor the reaction, pH 7, by addition of aqueous 0.01 N NaOH, 0.5 eq., within **6d**). After removal of the solvent the residue was suspended in CH_3OH and the suspension adsorbed on silica gel. Flash chromatographic separation gave (−)-**14b** (48 mg, 48%) and (+)-**14a** (38 mg, 46%, ee 89%).

A small portion of the alcoholic fraction was used for ee determination via the Mosher ester (see **14f**). 12 other lipases (and PLE) were tested[14]. The following enzymes showed good conversion but only greatly reduced enantioselectivity: lipase HLL (42%, 3.5 d, ee 8%), lipase ROL (46%, 2.5 d, ee 18%), and PLE (44%, 4.5 h, ee 0%).

L- and D-(1a,2β,3β,4β,6β)-2-O,3-N-Carbonyl-4-fluoro-3-(methylamino)-6-[(1R)-(1-phenylethyl)amino]cyclohexane-1,2-diol (**14c** and **14'c**): A solution of *rac*-**8** (200 mg, 1.60 mmol), [(1*R*)-1-phenylethyl]amine (255 mg, 2.11 mmol) and $MgSO_4$ (153 mg, 1.30 mmol) in *n*-propanol (20 ml) was refluxed for 47 h (total conversion, TLC, ethyl acetate/cyclohexane, 3:1). After concentration in vacuo the crude oil was crystallized (ethyl acetate, 50 ml, room temp.) to give **14'c** (150 mg, 46%) as colorless crystals. Compound **14c** (150 mg, 46%) was isolated from the mother liquor (ethyl acetate, 30 ml, room temp.) as colorless crystals, m.p. 190°C (ethyl acetate). **14c**: IR (KBr): $\tilde{\nu}$ = 3396 cm^{-1} (s, OH), 2956 (w, CH), 1720 (s, C=O), 1141 (m, CF). – ^{1}H NMR ($CDCl_3$): δ = 7.28 (m, 5H), 4.76 (dddd, 4-H), 4.43 (dd, 2-H), 3.89 (q, 1''-H), 3.80 (m, 1-H, 3-H), 2.86 (s, NCH_3), 2.59 (ddd, 6-H), 1.89 (dddd, 5α-H), 1.68 (dddd, 5β-H), 1.39 (d, 2''-H); $J_{1,2} = 8.3$, $J_{2,3} = 8.3$, $J_{3,4} = 3$, $J_{4,5\alpha} = 4.5$, $J_{4,5\beta} = 4.5$, $J_{5\alpha,5\beta} = 15$, $J_{5\alpha,6} = 8.3$, $J_{5\beta,6} = 8.3$, $J_{6,1} = 10.5$, $J_{4,F} = 49.5$, $J_{5\alpha,F} = 35.3$, $J_{5\beta,F} = 19.5$. – $C_{16}H_{21}FN_2O_3$ (308.4): calcd. C 62.32, H 6.86, N 9.08; found C 62.12, H 6.93, N 9.01.

L- and D-(1a,2β,3β,4β,6β)-6-Azido-2-O,3-N-carbonyl-4-fluoro-3-(methylamino)cyclohexane-1,2-diol (**14a** and *ent*-**14a**): A solution of **14c** (**14c'**) (620 mg, 1.51 mmol) in 3% methanolic NaOH solution (10 ml) was stirred for 10 min. After addition of CH_2Cl_2 and water the organic phase was conventionally worked up to give **14a** (*ent*-**14a**) (370 mg, 92%) (optical rotations see Figure 2).

L-(1a,2β,3β,4β,6β)-2-O,3-N-Carbonyl-4-fluoro-2-hydroxy-3-(methylamino)-6-[(1R)-(1-phenylethyl)amino]cyclohexyl Acetate (**14'd**): Compound **14'c** (20 mg, 0.065 mmol) was acetylated under standard conditions (1 d): Colorless crystals (22 mg, 99%), m.p. 187°C (ethyl acetate/cyclohexane, 1:1). – ^{1}H NMR ($CDCl_3$): δ = 7.27 (m, 5H), 5.24 (ddd, 1-H), 4.85 (dddd, 4-H), 4.38 (dd, 2-H), 3.87 (q, 1''-H), 3.74 (ddd, 3-H), 2.88 (s, NCH_3), 2.51 (ddd, 6-H), 2.31−1.85 (m, 5-H), 2.10 (s, $COCH_3$), 1.27 (d, 2''-H); $J_{1,2} = 7.5$, $J_{2,3} = 9$, $J_{3,4} = 3$, $J_{4,5\alpha} = 3$, $J_{4,5\beta} = 1.5$, $J_{5\alpha,6} = 7$, $J_{5\beta,6} = 7$, $J_{6,1} = 10.5$, $J_{1,F} = 3.5$, $J_{3,F} = 21.8$, $J_{4,F} = 48.8$. – $C_{18}H_{23}FN_2O_4$ (350.4): calcd. C 61.70, H 6.62, N 7.99; found C 60.86, H 6.66, N 7.88.

L- and D-(1'a,2'β,3'β,4'β,6'β)-6'-Azido-2'-O,3'-N-carbonyl-4'-fluoro-2'-hydroxy-3'-(methylamino)cyclohexyl (1S)-3-Oxo-4,7,7-trimethyl-2-oxabicyclo[2.2.1]heptane-1-carboxylate (**14e**/**14'e**): To a solution of *rac*-**14a** (1.40 g, 6.0 mmol) in pyridine (17 ml) at 0°C (−)-camphanoyl chloride (1.67 g, 7.7 mmol) was added (N_2). After total conversion (30 min at room temp., TLC, $CHCl_3/CH_3OH$, 10:1) the mixture was concentrated in vacuo. The solid residue was dissolved in CH_2Cl_2 (20 ml), the solution washed with 2 N H_2SO_4, aqueous $NaHCO_3$ solution, and water. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give 2.43 g (99%). After crystallization (ethyl acetate) and rapid chromatography **14e** (1.10 g, 90%), m.p. 212°C (ethyl acetate), and **14'e** (1.13 g, 93%), m.p. 249°C (ethyl acetate), were obtained. – **14e**: R_f ($CHCl_3/CH_3OH$, 25:1) = 0.21. $[\alpha]_D^{20}$ = −79.3 (*c* = 0.92, CH_2Cl_2). – IR (KBr): $\tilde{\nu}$ = 2966 cm^{-1} (w, CH_3), 2106 (s, N_3), 1785, 1753, 1739 (s, C=O), 1100 (m, CF). – ^{1}H NMR ($CDCl_3/CD_3CN$, 1:1, 400 MHz): δ = 5.50 (ddd, 1'-H), 5.07 (dddd, 4'-H), 4.66 (dd, 2-H), 3.98 (ddd, 3'-H), 3.75 (ddd, 6'-H), 2.89 (s, NCH_3), 2.52 (m, 6-H), 2.42 (ddd, 5'α-H), 2.20 (dddd, 5'β-H), 2.06 (ddd, 5-H), 2.01 (ddd, 6-H), 1.70 (m, 6-H), 1.08/

1.00 (s, 7-CH_3), 0.87 (s, 4-CH_3); $J_{1',2'} = J_{2',3'} = 9$, $J_{3',4'} = J_{4',5'\alpha} = 3$, $J_{4',5'\beta} = 3$, $J_{5'\alpha,5'\beta} = 16.5$, $J_{5'\alpha,6'} = 9$, $J_{5'\beta,6} = 6$, $J_{6',1'} = 10.5$, $J_{1',F} = 4$, $J_{3',F} = 27.8$, $J_{4',F} = 49.5$, $J_{5'\alpha,F} = 18$. – **14'e**: R_f ($CHCl_3/CH_3OH$, 25:1) = 0.19. $[\alpha]_D^{20}$ = +73.2 (*c* = 0.90, CH_2Cl_2). – IR (KBr): $\tilde{\nu}$ = 2970 cm^{-1} (w, CH_3), 2100 (s, N_3), 1780/1755 (s, C=O), 1107 (m, CF). – ^1H NMR (CD_3CN, 250 MHz): δ = 5.43 (ddd, 1'-H), 5.09 (dddd, 4'-H), 4.68 (dd, 2'-H), 3.98 (ddd, 3'-H), 3.83 (ddd, 6'-H), 2.84 (s, NCH_3), 2.53 (m, 6-H), 2.39 (ddd, 5'α-H), 2.15 (dddd, 5'β-H), 2.11–1.85 (m, 5-H, 6-H), 1.66 (m, 5-H), 1.12/1.08 (s, 7-CH_3), 0.97 (s, 4-CH_3); $J_{1',2'} = J_{2',3'} = 9$, $J_{3',4'} = J_{4',5'\alpha} = J_{4',5'\beta} = 3$, $J_{5'\alpha,5'\beta} = 9$, $J_{5'\alpha,6'} = 9$, $J_{5'\beta,6'} = 6$, $J_{6',1'} = 10.5$, $J_{1',F} = 4$, $J_{3',F} = 27.8$, $J_{4',F} = 49.5$, $J_{5'\alpha,F} = 18$. – $C_{18}H_{23}FN_4O_6$ (410.4): calcd. C 52.68, H 5.65, N 13.65; **14e**: found C 52.31, H 5.08, N 13.29; **14'e**: found C 52.61, H 5.71, N 13.51.

L-(1'α,2'β,3'β,4'β,6'β)-6'-Azido-2'-O,3'-N-carbonyl-4'-fluoro-2'-hydroxy-3'-(methylamino)cyclohexyl (S)-α-Methoxy-α-(trifluoromethyl)phenylacetate (**14f**): To a solution of **14a** (10 mg, 0.04 mmol) in CH_2Cl_2/pyridine (1 ml) were added a catalytic amount of DMAP and 0.08 mmol of (*S*)(+)-Mosher acyl chloride. The solution was stirred at room temp. for 24 h (total conversion, TLC, $CHCl_3/CH_3OH$, 10:1, R_f = 0.41), then extracted with 2 N HCl and a saturated $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a colorless oil. – ^1H NMR ($CDCl_3$): δ = 7.60/7.41 (m, 5H), 5.59 (ddd, 1-H), 4.97 (dddd, 4-H), 4.61 (dd, 2-H), 3.86 (ddd, 3-H), 3.63 (s, OCH_3), 3.46 (dt, 6-H), 2.95 (s, NCH_3), 2.41 (m, 5α-H), 2.35 (m, 5β-H); $J_{1,2}$ = 8.4, $J_{2,3}$ = 9, $J_{3,4}$ = 3, $J_{6,1}$ = 10.5, $J_{1,F}$ = 3.4, $J_{3,F}$ = 24, $J_{4,F}$ = 48 Hz. – IR (film): $\tilde{\nu}$ = 2952 cm^{-1} (CH), 2848 (m, CH), 2106 (s, N_3), 1760 (s, C=O), 1257 (CO), 1180 (CF). – $[\alpha]_D^{20}$ = –6.8 (*c* = 1.20, $CHCl_3$). – MS, *m/z* (%): i.a. 446 (7) [M^+], 360 (8) [$M^+ - N_3 - CO_2$], 189 (100) [$C_9H_8OF_3^+$].

D-(1'α,2'β,3'β,4'β,6'β)-6'-Azido-2'-O,3'-N-carbonyl-4'-fluoro-2'-hydroxy-3-(methylamino)cyclohexyl (S)-α-Methoxy-α-(trifluoromethyl)phenylacetate (**14'f**): From *ent*-**14a** analogously to **14f**, colorless crystals, m.p. 148°C. – ^1H NMR ($CDCl_3$): δ = 7.58/7.43 (m, 5H), 5.57 (ddd, 1H), 4.98 (dddd, 4-H), 4.48 (dd, 2-H), 3.86 (ddd, 3-H), 3.60/3.57 (m, OCH_3, 6-H), 2.95 (s, NCH_3), 2.53 (dddd, 5α-H), 2.38 (m, 5β-H); $J_{1,2}$ = 8.3, $J_{2,3}$ = 9, $J_{3,4}$ = 3, $J_{4,5\alpha}$ = 3.8, $J_{4,5\beta}$ = 7.5, $J_{5\alpha,5\beta}$ = 15, $J_{1,F}$ = 3.4, $J_{3,F}$ = 24, $J_{4,F}$ = 48 Hz. – IR (film): $\tilde{\nu}$ = 2956 cm^{-1} (arom. CH), 2788 (m, CH), 2106 (s, N_3), 1753 (s, C=O), 1257 (CO), 1180 (CF). – $[\alpha]_D^{20}$ = +79.2 (*c* = 0.85, $CHCl_3$). – $C_{18}H_{18}F_4N_4O_5$ (446.4): calcd. C 48.44, H 4.06, N 12.05; found C 49.12, H 4.45, N 11.70.

For the determination of the ee (Figure 2) a mixture of the Mosher esters was separated by analytical HPLC (Merck LiChrosorb Si 100, 3.9 × 300 m, flow speed 2 ml/min, room temp. **14f**: 1.48 min, **14'f**: 1.96 min).

DL-(1α,2β,3β,4α,6β)-6-Azido-2-O,3-N-carbonyl-4-fluoro-3-(methylamino)-cyclohexane-1,2-diol (*rac*-**16a**): A solution of *rac*-**9** (70 mg, 0.37 mmol), NaN_3 (247 mg, 3.70 mmol), and $MgSO_4$ (440 mg, 3.70 mmol) in dry CH_3OH (9 ml) was refluxed for 3 h [total conversion, TLC, $CHCl_3/CH_3OH$, 10:1, R_f (*rac*-**16a**) = 0.53]. After filtration and concentration of the filtrate in vacuo the solid residue was extracted with hot ethyl acetate. After concentration in vacuo colorless crystals (83 mg, 97%), m.p. 159°C (ethyl acetate), were obtained. – IR (KBr): $\tilde{\nu}$ = 3382 cm^{-1} (s, OH), 2974 (m, CH_3), 2930 (m, CH_2), 2886 (m, CH), 2094 (s, N_3), 1763 (s, C=O), 1106 (s, CF). – ^1H NMR ($CDCl_3$, 400 MHz): see Figure 1. – $C_8H_{11}FN_4O_3$ (230.2): calcd. C 41.74, H 4.82, N 24.34; found C 41.48, H 4.76, N 23.92.

L- and D-(1α,2β,3β,4α,6β)-2-O,3-N-Carbonyl-4-fluoro-3-(methylamino)-6-[(1R)-1-(phenylethyl)amino]cyclohexane-1,2-diol (**16c** and **16'c**): A solution of *rac*-**9** (320 mg, 1.60 mmol) and [(1*R*)-1-phenylethyl]amine (410 mg, 3.40 mmol) in *n*-propanol (20 ml) was refluxed for 4 h (total conversion, TLC, ethyl acetate/cyclohexane, 3:1). After concentration in vacuo the crude oil was purified by chromatography (ethyl acetate/cyclohexane, 3:1) to give **16c** (240 mg, 49% based on conversion) as colorless crystals, m.p. 113°C (ethyl acetate/cyclohexane, 1:1) and **16'c** (240 mg, 49% based on conversion) as colorless crystals, m.p. 113°C (ethyl acetate/cyclohexane, 1:1). – **16c**: IR (KBr): $\tilde{\nu}$ = 3400 cm^{-1} (s, OH), 2960 (w, CH_3), 1745 (s, C=O), 1075 (s, CF). – ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.33 (m, 5H), 4.94 (dddd, 4-H), 4.34 (t, 2-H), 3.90 (q, 1''-H), 3.80 (ddddd, 3-H), 3.57 (dd, 1-H), 2.84 (s, NCH_3), 2.56 (m, 6-H), 2.20 (m, 5α-H), 1.70 (m, 5β-H), 1.38 (d, 2''-H); $J_{1,2}$ = 8.5, $J_{2,3}$ = 8.5, $J_{3,4}$ = 4.5, $J_{4,5\alpha}$ = 6, $J_{4,5\beta}$ = 3.5, $J_{5\alpha,5\beta}$ = 14, $J_{5\alpha,6}$ = 5, $J_{5\beta,6}$ = 9, $J_{6,1}$ = 10, $J_{3,F}$ = 14, $J_{4,F}$ = 46, $J_{5\alpha,F}$ = 15, $J_{5\beta,F}$ = 30. – ^{13}C NMR ($CDCl_3$): δ = 158.3 (C=O), 144.1–126.4 (6 C), 87.8 (C-4), 77.4 (C-2), 73.0 (C-1), 60.6 (C-3), 54.5 (C-1''), 49.6 (C-6), 30.5 (C-5), 30.4 (NCH_3), 24.9 (C-2''); $^3J_{2,F}$ = 2, $^2J_{3,F}$ = 31, $^1J_{4,F}$ = 171, $^2J_{5,F}$ = 21, $^3J_{6,F}$ = 5.5. – $C_{16}H_{22}FN_2O_3$ (308.4): calcd. C 62.32, H 6.86, N 9.08; found C 61.79, H 6.87, N 8.90. – **16'c**: IR (KBr): $\tilde{\nu}$ = 3480 cm^{-1} (s, OH), 2975 (w, CH_3), 1750 (s, C=O), 1085 (s, CF). – ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.33 (m, 5H), 4.85 (dddd, 4-H), 4.51 (t, 2-H), 3.88 (q, 1''-H), 3.87 (ddddd, 3-H), 3.48 (dd, 1-H), 2.89 (m, 6-H), 2.82 (s, NCH_3), 1.98 (m, 5α-H), 1.39 (m, 5β-H), 1.39 (d, 2''-H); $J_{1,2}$ = 8, $J_{2,3}$ = 8, $J_{3,4}$ = 3.5, $J_{4,5\alpha}$ = 5, $J_{4,5\beta}$ = 3.5, $J_{5\alpha,5\beta}$ = 14, $J_{5\alpha,6}$ = 4.5, $J_{5\beta,6}$ = 10, $J_{6,1}$ = 10, $J_{3,F}$ = 14, $J_{4,F}$ = 45.5, $J_{5\alpha,F}$ = 13.5, $J_{5\beta,F}$ = 36. – ^{13}C NMR ($CDCl_3$): δ = 157.4 (C=O), 146.0–126.4 (6 C), 87.4 (C-4), 77.5 (C-2), 74.0 (C-1), 60.4 (C-3), 56.8 (C-1''), 52.0 (C-6), 31.6 (C-5), 30.4 (NCH_3), 24.0 (C-2''); $^2J_{3,F}$ = 32, $^1J_{4,F}$ = 170, $^2J_{5,F}$ = 20, $^3J_{6,F}$ = 3. – $C_{16}H_{21}FN_2O_3$ (308.4): calcd. C 62.32, H 6.86, N 9.08; found C 61.68, H 6.97, N 8.91.

DL-(1α,2β,3β,6β)-6-Azido-2-O,3-N-carbonyl-4,4-difluoro-3-(methylamino)cyclohexane-1,2-diol (*rac*-**18a**): A solution of *rac*-**11** (80 mg, 0.4 mmol), NaN_3 (80 mg, 1.2 mmol), and $MgSO_4$ (120 mg, 1.0 mmol) in dry CH_3OH (5 ml) was refluxed for 48 h [total conversion, TLC, $CHCl_3/CH_3OH$, 10:1, R_f (*rac*-**18a**) = 0.32]. After filtration, concentration of the filtrate, and chromatography of the residue on silica gel ($CHCl_3/CH_3OH$, 10:1) colorless crystals (75 mg, 80%), m.p. 86°C (ethyl acetate), were obtained. – IR (KBr): $\tilde{\nu}$ = 3408 cm^{-1} (s, OH), 2890 (w, CH_2), 2094 (s, N_3), 1744 (s, C=O), 1124 (m, CF). – ^1H NMR ($CDCl_3$): see Figure 1. – $C_8H_{10}F_2N_4O_3$ (248.2): calcd. C 38.72, H 4.06, N 22.57; found C 38.79, H 4.10, N 22.18.

DL-(1α,2β,3β,6β)-6-Azido-2-O,3-N-carbonyl-4,4-difluoro-2-hydroxy-3-(methylamino)cyclohexyl Acetate (*rac*-**18b**): *rac*-**18a** (10 mg, 0.04 mmol) was acetylated under standard conditions (1 d): Colorless crystals (11 mg, 99%), m.p. 110°C (ethyl acetate). – IR (KBr): $\tilde{\nu}$ = 2890 cm^{-1} (w, CH_2), 2094 (s, N_3), 1744 (s, C=O), 1124 (m, CF). – ^1H NMR ($CDCl_3$): δ = 5.21 (ddd, 1-H), 4.57 (ddd, 2-H), 3.99 (dddd, 3-H), 3.72 (ddd, 6-H), 2.97 (dd, NCH_3), 2.52 (ddddd, 5α-H), 2.19 (dddd, 5β-H), 2.19 (s, $COCH_3$); $J_{1,2}$ = $J_{2,3}$ = 7.5, $J_{5\alpha,5\beta}$ = 14.7, $J_{5\alpha,6}$ = 5.3, $J_{5\beta,6}$ = 10.5, $J_{6,1}$ = 10.5, $J_{3,5\alpha}$ = 1.5, $J_{1,F}$ = 1.5, $J_{2,F}$ = 1.5, $J_{3,F}$ = 7.5/7.5, $J_{5\alpha,F}$ = 14.7/9, $J_{5\beta,F}$ = 27.5/5.7, $J_{NCH_3,F}$ = 2.3/0.8.

DL-(1α,2β,3β,4β,6β)-2-O,3-N-Carbonyl-4-fluoro-6-iodo-3-(methylamino)-cyclohexane-1,2-diol (*rac*-**20a**): To a suspension of *rac*-**8** (200 mg, 1.1 mmol) and NaI (825 mg, 5.5 mmol) in dry CH_3CN a 0.1 M TMSCl solution in CH_3CN (11 ml) was slowly added. After stirring for 30 min [total conversion, TLC, cyclohexane/ethyl acetate, 1:3, R_f (*rac*-**20a**) = 0.20] a saturated aqueous Na_2S solution was added (20 ml). After concentration of the mixture in vacuo and crystallization of the residue colorless crystals (332 mg, 96%), m.p. 143°C (ethyl acetate/cyclohexane, 1:1), were obtained. – IR (KBr): $\tilde{\nu}$ = 3454 cm^{-1} (s, OH), 2952 (w, CH_2), 2922 (w, CH), 1722 (s, C=O), 1040 (s, CF). – ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.79 (dddd, 4-H), 4.45 (t, 2-H), 4.14 (ddd, 1-H), 4.03 (ddd, 3-H), 3.93 (ddd, 6-H), 3.21 (d, OH), 2.96 (s, NCH_3), 2.79 (ddd, 5β-H), 2.70 (ddd, 5α-H); $J_{1,2}$ = $J_{2,3}$ = 7.5, $J_{3,4}$ = 3, $J_{4,5\alpha}$ = 4.5, $J_{4,5\beta}$ = 6, $J_{5\alpha,5\beta}$ = 15, $J_{5\alpha,6}$ = 7.5, $J_{5\beta,6}$ = 9.3, $J_{6,1}$ = 11.3, $J_{3,F}$ = 18.8, $J_{4,F}$ = 47.3, $J_{NCH_3,F}$ = 1.5, $J_{1,OH}$ = 3.8. – $C_8H_{11}FINO_3$ (315.1): calcd. C 30.50, H 3.52, N 4.45; found C 30.57, H 3.51, N 4.45.

DL-(1α,2β,3β,4β,6β)-2-O,3-N-Carbonyl-4-fluoro-2-hydroxy-6-iodo-3-(methylamino)cyclohexyl Acetate (*rac*-**20b**): *rac*-**20a** (220 mg, 0.70 mmol) was acetylated under standard conditions (1 d): Colorless needles (250 mg, 99%), m.p. 155°C (ethyl acetate/cyclohexane, 1:1). – R_f ($CHCl_3/CH_3OH$, 10:1) = 0.44. – IR (KBr): $\tilde{\nu}$ = 2974 cm^{-1} (w, CH_3), 1762 (s, C=O), 1110 (s, CF). – ^1H NMR ($CDCl_3$): δ = 5.53 (ddd, 1-H), 4.84 (dddd, 4-H), 4.55 (t, 2-H), 4.02 (ddd, 3-H), 3.94 (ddd, 6-H), 2.97 (s, NCH_3), 2.84 (ddd, 5β-H), 2.71 (ddd, 5α-H), 2.16 (s, $COCH_3$); $J_{1,2}$ = $J_{2,3}$ = 8.3, $J_{3,4}$ = 3, $J_{4,5\alpha}$ = 4.5, $J_{4,5\beta}$ = 6, $J_{5\alpha,5\beta}$ = 15.8, $J_{5\alpha,6}$ = 7.5, $J_{5\beta,6}$ = 9.8, $J_{6,1}$ = 12, $J_{1,F}$ = 3, $J_{3,F}$ = 19.5, $J_{4,F}$ = 47.3. – $C_{10}H_{13}FINO_4$ (357.1): calcd. C 33.63, H 3.67, N 3.92; found C 33.84, H 3.70, N 3.93.

DL-(1α,2β,3β,4β,6α)-6-Azido-2-O,3-N-carbonyl-4-fluoro-2-hydroxy-3-(methylamino)cyclohexyl Acetate (*rac*-**21b**): A carefully dried solution of *rac*-**20b** (110 mg, 0.31 mmol) and TMGA (100 mg, 0.62 mmol) in acetonitrile (5 ml) was stirred at 50°C for 18 h [total conversion, TLC, cyclohexane/ethyl acetate, 1:3, R_f (*rac*-**21b**) = 0.25]. Concentration, filtration of the residue through a short pad of silica gel ($CHCl_3/CH_3OH$, 10:1) and concentration of the filtrate in vacuo furnished colorless, practically pure solid (70 mg, 84%), m.p. 123°C (ethyl acetate/cyclohexane, 1:1). – IR (KBr): $\tilde{\nu}$ = 2964 cm^{-1} (w, CH_3), 2094 (s, N_3), 1752 (s, C=O), 1127 (s, CF). – ^1H NMR ($CDCl_3$): δ = 5.38 (ddd, 1H), 5.03 (dddd, 4-H), 4.76 (dd, 2-H), 4.15 (ddd, 6-H), 3.93 (ddd, 3-H), 2.95 (s, NCH_3), 2.52 (dddd, 5β-H), 2.17 (s, $COCH_3$), 2.07 (dddd, 5α-H); $J_{1,2}$ = 6.8, $J_{2,3}$ = 7.5, $J_{3,4}$ = 3, $J_{4,5\alpha}$ = 3.8, $J_{4,5\beta}$ = 4.5, $J_{5\alpha,5\beta}$ = 15.8, $J_{5\alpha,6}$ = 4.5, $J_{5\beta,6}$ = 6, $J_{6,1}$ = 3, $J_{1,F}$ = 1.5, $J_{3,F}$ = 24.8, $J_{4,F}$ = 48.8, $J_{5\alpha,F}$ = 20.3, $J_{5\beta,F}$ = 18. – $C_{10}H_{13}FN_4O_4$ (272.7): calcd. C 44.12, H 4.81, N 20.58; found C 44.00, H 4.75, N 20.06.

DL-(1α,2β,3β,4β,6α)-6-Azido-2-O,3-N-carbonyl-4-fluoro-3-(methylamino)-cyclohexane-1,2-diol (*rac*-**21a**): A solution of *rac*-**21b** (70 mg, 0.26 mmol) in 3% methanolic NaOH (2 ml) was kept at room temp. for 10 min [total conversion, TLC, $CHCl_3/CH_3OH$, 10:1, R_f (*rac*-**21a**) = 0.26]. After neutralization and standard workup colorless crystals (60 mg, 99%), m.p. 179°C (ethyl acetate/cyclohexane, 1:1), were obtained. – IR (KBr): $\tilde{\nu}$ = 3362 cm^{-1} (s, OH), 2950 (w, CH_3), 2100 (s, N_3), 1723 (s, C=O), 1082 (s, CF). – ^1H NMR ($CDCl_3$, 400 MHz): see Figure 3. – $C_8H_{11}FN_4O_3$ (230.2): calcd. C 41.74, H 4.82, N 24.34; found C 41.72, H 4.80, N 24.23.

DL-(1α,2β,3β,4α,6β)-2-O,3-N-Carbonyl-4-fluoro-6-iodo-3-(methylamino)-cyclohexane-1,2-diol (*rac*-**22a**): A solution of *rac*-**9** (90 mg, 0.48 mmol) and KI (700 mg, 4.0 mmol) in 80% aqueous acetic acid (5 ml) was stirred at

room temp. for 6 h [total conversion, TLC, $CHCl_3/CH_3OH$, 10:1, R_f (*rac*-**22a**) = 0.51]. After addition of water it was carefully extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. After filtration of the residue through a short pad of silica gel ($CHCl_3/CH_3OH$, 10:1) colorless crystals (100 mg, 67%), m.p. 178°C (ethyl acetate), were obtained. – IR (KBr): $\tilde{\nu}$ = 3400 cm^{-1} (s, OH), 2972 (m, CH_3), 2952 (m, CH_2), 2888 (m, CH), 1754 (s, C=O), 1112 (s, CF). – ^1H NMR ($CDCl_3$): δ = 4.78 (ddt, 4-H), 4.56 (t, 2-H), 4.20 (dt, 6-H), 4.04 (dddd, 3-H), 3.88 (ddd, 1-H), 2.91 (d, OH), 2.87 (s, NCH_3), 2.82 (ddddd, 5α-H), 2.38 (dddd, 5β-H); $J_{1,2} = J_{2,3}$ = 7.5, $J_{3,4}$ = 2.3, $J_{4,5\alpha}$ = 4.5, $J_{4,5\beta}$ = 2.3, $J_{5\alpha,5\beta}$ = 15, $J_{5\alpha,6}$ = 3.8, $J_{5\beta,6}$ = 11.3, $J_{6,1}$ = 11.3, $J_{3,5\alpha}$ = 1.5, $J_{3,F}$ = 12, $J_{4,F}$ = 44.3, $J_{5\alpha,F}$ = 19.5, $J_{5\beta,F}$ = 39.8, $J_{1,OH}$ = 3.8. – $C_8H_{11}FINO_3$ (315.1): calcd. C 30.50, H 3.52, N 4.45; found C 30.67, H 3.55, N 4.17.

DL-(1a,2β,3β,4β,6β)-2-O,3-N-Carbonyl-4-fluoro-2-hydroxy-6-iodo-3-(methylamino)cyclohexyl Acetate (*rac*-**22b**): *rac*-**22a** (70 mg, 0.22 mmol) was acetylated under standard conditions [2 d, TLC, $CHCl_3/CH_3OH$, 10:1, R_f (*rac*-**22b**) = 0.59]: Colorless crystals (78 mg, 99%), m.p. 180°C (ethyl acetate). – IR (KBr): $\tilde{\nu}$ = 3478 cm^{-1} (m, OH), 2954 (m, CH_3), 1762 (s, C=O), 1108 (s, CF). – ^1H NMR ($CDCl_3$): δ = 5.31 (dd, 1-H), 4.86 (ddt, 4-H), 4.57 (t, 2-H), 4.21 (dt, 6-H), 4.01 (dddd, 3-H), 2.91 (s, NCH_3), 2.76 (m, 5α-H), 2.43 (dddd, 5β-H), 2.15 (s, $COCH_3$); $J_{1,2} = J_{2,3}$ = 7.2, $J_{3,4}$ = 3, $J_{4,5\alpha}$ = 5.3, $J_{4,5\beta}$ = 3, $J_{5\alpha,5\beta}$ = 15, $J_{5\alpha,6}$ = 3.8, $J_{5\beta,6}$ = 11.3, $J_{6,1}$ = 10.5, $J_{3,5\alpha}$ = 1, $J_{3,F}$ = 12.8, $J_{4,F}$ = 45, $J_{5,F}$ = 36. – $C_{10}H_{13}FINO_4$ (357.1): calcd. C 33.63, H 3.67, N 3.92; found C 33.97, H 3.69, N 3.87.

DL-(1a,2β,3β,4a,6a)-6-Azido-2-O,3-N-carbonyl-4-fluoro-2-hydroxy-3-(methylamino)cyclohexyl Acetate (*rac*-**23b**): cf. *rac*-**21b**. A solution of *rac*-**22b** (140 mg, 0.39 mmol) and TMGA (123 mg, 0.78 mmol) in dry acetonitrile (5 ml, N_2) was kept at 50°C for 60 h [total conversion, TLC, $CHCl_3/CH_3OH$, 10:1, R_f (*rac*-**23b**) = 0.69]. After workup as described a colorless oil (96 mg, 90%) was obtained. – ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.24 (ddd, 1-H), 4.83 (dddd, 4-H), 4.73 (ddd, 2-H), 3.93 (ddd, 6-H), 3.90 (ddd, 3-H), 3.00 (d, NCH_3), 2.39 (dddt, 5β-H), 2.18 (s, $COCH_3$), 2.15 (dddd, 5α-H); $J_{1,2}$ = 6, $J_{2,3}$ = 7.5, $J_{3,4}$ = 6, $J_{4,5\alpha}$ = 9, $J_{4,5\beta}$ = 6, $J_{5\alpha,5\beta}$ = 14.3, $J_{5\alpha,6}$ = 8.3, $J_{5\beta,6}$ = 5.3, $J_{6,1}$ = 3, $J_{5\beta,1}$ < 1, $J_{3,F}$ = 7.5, $J_{4,F}$ = 48.8, $J_{5\alpha,F} = J_{5\beta,F}$ = 14.3, $J_{NCH_3,F}$ = 1.5.

DL-(1a,2β,3β,4a,6a)-6-Azido-2-O,3-N-carbonyl-4-fluoro-3-(methylamino)-cyclohexane-1,2-diol (*rac*-**23a**): A solution of *rac*-**23b** (90 mg, 0.33 mmol) in 3% methanolic NaOH (2 ml) was kept at room temp. for 10 min [total conversion, TLC, $CHCl_3/CH_3OH$, 10:1, R_f (*rac*-**23a**) = 0.45]. After neutralization and conventional workup colorless crystals (70 mg, 94%), m.p. 144°C (ethyl acetate/cyclohexane, 1:1) were obtained. – IR (KBr): $\tilde{\nu}$ = 3298 cm^{-1} (s, OH), 2932 (m, CH_2), 2886 (m, CH), 2094 (s, N_3), 1727 (s, C=O), 1223, 1117 (s, CF). – ^1H NMR ($CDCl_3$, 400 MHz): see Figure 3. – $C_8H_{11}FN_4O_3$ (230.2): calcd. C 41.74, H 4.82, N 24.34; found C 41.74, H 4.80, N 23.53.

DL-(1a,2β,3β,6β)-2-O,3-N-Carbonyl-4,4-difluoro-6-iodo-3-(methylamino)-cyclohexane-1,2-diol (*rac*-**25a**): To a solution of *rac*-**11** (270 mg, 1.31 mmol) in dry CH_2Cl_2 (5 ml, N_2) at −78°C idotrimethylsilane (290 mg, 1.45 mmol) was added dropwise. After 40 min CH_2Cl_2 and water were added, the organic phase was dried ($MgSO_4$) and concentrated in vacuo to give colorless crystals (410 mg, 94%), m.p. 131°C (ethyl acetate/cyclohexane, 1:1). R_f (ethyl acetate/cyclohexane, 3:1) = 0.48. – IR (KBr): $\tilde{\nu}$ = 3372 cm^{-1} (s, OH), 2944 (w, CH_2), 1771 (s, C=O), 1117 (m, CF). – ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.53 (ddd, 2-H), 4.08–4.00 (m, 3-H, 6-H), 3.92 (ddd, 1-H), 3.56 (d, OH), 2.95 (d, NCH_3), 2.87 (ddddd, 5α-H), 2.72 (dddd, 5β-H); $J_{1,2}$ = 7, $J_{2,3}$ = 7, $J_{5\alpha,5\beta}$ = 14.5, $J_{5\alpha,6}$ = 4.5, $J_{5\beta,6}$ = 4, $J_{6,1}$ = 11, $J_{3,5\alpha}$ = 2, $J_{1,OH}$ = 4, $J_{2,F}$ = 0.5, $J_{5\alpha,F}$ = 9.5/9.5, $J_{5\beta,F}$ = 30.5/12. – $C_8H_{10}F_2INO_3$ (333.1): calcd. C 28.85, H 3.03, N 4.21; found C 28.96, H 3.05, N 4.15.

DL-(1a,2β,3β,6β)-2-O,3-N-Carbonyl-4,4-difluoro-2-hydroxy-6-iodo-3-(methylamino)cyclohexyl Acetate (*rac*-**25b**): *rac*-**25a** (210 mg, 0.63 mmol) was acetylated under standard conditions (20 h): Colorless crystals (230 mg, 98%), m.p. 111°C (ether). R_f (cyclohexane/ethyl acetate, 1:3) = 0.57. – IR (KBr): $\tilde{\nu}$ = 2984 cm^{-1} (w, CH_3), 1761/1735 (s, C=O), 1114 (s, CF). – ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.33 (dd, 1-H), 4.57 (dd, 2-H), 4.10–4.01 (m, 3-H, 6-H), 2.97 (d, NCH_3), 2.89 (ddddd, 5α-H), 2.76 (dddd, 5β-H), 2.18 (s, $COCH_3$); $J_{1,2}$ = 7.5, $J_{2,3}$ = 7.5, $J_{5\alpha,5\beta}$ = 14.3, $J_{5\alpha,6}$ = 4.5, $J_{5\beta,6}$ = 12, $J_{6,1}$ = 11.7, $J_{3,5\alpha}$ = 2, $J_{2,F}$ = 0.8, $J_{5\alpha,F}$ = 9.8/9.8, $J_{5\beta,F}$ = 30.8/3.8, $J_{NCH_3,F}$ = 2.3. – $C_{10}H_{12}F_2INO_4$ (375.1): calcd. C 32.02, H 3.22, N 3.73; found C 32.24, H 3.26, N 3.67.

DL-(1a,2β,3β,6a)-6-Azido-2-O,3-N-carbonyl-4,4-difluoro-2-hydroxy-3-(methylamino)cyclohexyl Acetate (*rac*-**26b**): cf. *rac*-**21b**. A carefully dried solution of *rac*-**25b** (100 mg, 0.27 mmol) and TMGA (90 mg, 0.57 mmol) in acetonitrile (5 ml, N_2) was stirred at 50°C for 20 h (total conversion). After workup as described the solid residue was dissolved in CH_2Cl_2 (10 ml) and the solution treated with 1% aqueous $KMnO_4$ solution. The organic phase was washed, dried ($MgSO_4$), and concentrated in vacuo to give pure *rac*-**26b**. For characterization of the olefinic component the solid residue was chromatographed [silica gel, cyclohexane/ethyl acetate, 1:3, R_f (*rac*-**26b**) = 0.57] to give *rac*-**26b** (66 mg, 86%) and *rac*-**27** (9 mg, 13%) as colorless oils. *rac*-**26b**: IR (KBr): $\tilde{\nu}$ = 2984 cm^{-1} (w, CH_3), 2094 (s, N_3), 1761 (s, C=O), 1114 (s, CF). – ^1H NMR ($CDCl_3$): δ = 5.41 (m, 1-H), 4.68 (dddd, 2-H), 4.04–3.89 (m, 3-H, 6-H), 3.03 (s, NCH_3), 2.56 (dt, 5β-H), 2.27 (dddd, 5α-H), 2.16 (s, $COCH_3$); $J_{1,2}$ = 4.5, $J_{2,3}$ = 8, $J_{5\alpha,5\beta}$ = 15, $J_{5\alpha,6}$ = 8.5, $J_{5\beta,6}$ = 5.5, $J_{2,F}$ = 1.5/3, $J_{5\alpha,F}$ = 31/7, $J_{5\beta,F}$ = 15/5.5.

DL-(1a,2β,3β,6a)-6-Azido-2-O,3-N-carbonyl-4,4-difluoro-3-(methylamino)-cyclohexane-1,2-diol (*rac*-**26a**): *rac*-**26b** (60 mg, 0.21 mmol) was saponified (10 min) in a 3% methanolic NaOH solution (2 ml). After standard workup colorless crystals (50 mg, 98%), m.p. 130°C (ether/cyclohexane, 1:1), were obtained. R_f (cyclohexane/ethyl acetate 1:3) = 0.44. – IR (KBr): $\tilde{\nu}$ = 3378 cm^{-1} (s, OH), 2982 (w, CH_3), 2100 (s, N_3), 1746 (s, C=O), 1087 (s, CF). – ^1H NMR ($CDCl_3$, 400 MHz): see Figure 3. – $C_8H_{10}F_2N_4O_3$ (248.2): calcd. C 38.72, H 4.06, N 22.57; found C 39.00, H 4.08, N 22.29.

DL-(1a,2β,3β)-2-O,3-N-Carbonyl-4,4-difluoro-2-hydroxy-3-(methylamino)-cyclohex-5-en-1-yl Acetate (*rac*-**27**): R_f (cyclohexane/ethyl acetate, 1:3) = 0.44. – IR (KBr): $\tilde{\nu}$ = 2980 cm^{-1} (w, CH_3), 1761 (s, C=O), 1114 (s, CF). – ^1H NMR ($CDCl_3$): δ = 6.24 (ddd, 5-H), 6.13 (dddd, 6-H), 5.48 (dddd, 1-H), 4.83 (dd, 2-H), 4.13 (ddd, 3-H), 3.05 (s, NCH_3), 2.14 (s, $COCH_3$); $J_{1,2}$ = 5, $J_{2,3}$ = 10, $J_{5,6}$ = 10, $J_{6,1}$ = 4, $J_{1,F}$ = 2.5, $J_{2,F}$ < 1, $J_{3,F}$ = 8/12, $J_{5,F}$ = 2/2, $J_{6,F}$ = 2/8.5.

DL-(1a,2a,3β,4β,5β)-1,2-Anhydro-3-O,4-N-carbonyl-5-O-methyl-4-(methylamino)cyclohexane-1,2,3,5-tetrol (*rac*-**29**): To a solution of *rac*-**7a** (50 mg, 0.27 mmol) in a mixture of glyme/DMF (2:1, 5 ml) (N_2) was added at 0°C NaH (13 mg, 1.00 mmol) in portions with intensive stirring. After 30 min dimethyl sulfate (68 mg, 0.50 mmol) was added by means of a syringe and the mixture stirred at room temp. for 1 h. Excess NaH was destroyed with *n*-butanol (2 ml). After concentration in vacuo the residue was dissolved in CH_2Cl_2 (100 ml) and the solution washed with water (3 × 30 ml). The organic phase was dried ($MgSO_4$), concentrated in vacuo, and the residue purified by chromatography (ethyl acetate/cyclohexane, 3:1) to give *rac*-**29** (39 mg, 90% based on conversion), colorless oil. – R_f ($CHCl_3/CH_3OH$, 10:1) = 0.56. – IR (KBr): $\tilde{\nu}$ = 2982 cm^{-1} (w, CH_3), 1746 (s, C=O). – ^1H NMR ($CDCl_3$): δ = 4.82 (d, 3-H), 3.95 (dd, 4-H), 3.63 (ddd, 5-H), 3.38 (s, OCH_3), 3.36 (dd, 1-H), 3.15 (d, 2-H), 2.93 (s, NCH_3), 2.43 (ddd, 6α-H), 1.95 (ddd, 6β-H); $J_{1,2}$ = 3.8, $J_{2,3}$ < 1, $J_{3,4}$ = 8.3, $J_{4,5}$ = 2.3, $J_{5,6\alpha}$ = 4.2, $J_{5,6\beta}$ = 11.3, $J_{6\alpha,6\beta}$ = 14.3, $J_{6\alpha,1}$ < 1, $J_{6\beta,1}$ = 1.5. – MS, *m/z* (%): 199 (9) [M^+], 155 (30) [$M^+ - CO_2$], 140 (9) [$M^+ - CO_2 - NCH_3$].

DL-(1a,2a,3β,4β,5β)-1,2-Anhydro-4-N,5-O-carbonyl-3-O-methyl-4-(methylamino)cyclohexane-1,2,3,5-tetrol (*rac*-**30**): R_f ($CHCl_3/CH_3OH$, 10:1) = 0.49. – IR (KBr): $\tilde{\nu}$ = 2984 cm^{-1} (w, CH_3), 1764 (s, C=O). – ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.62 (ddd, 5-H), 3.86 (dd, 3-H), 3.74 (dd, 4-H), 3.50 (s, OCH_3), 3.42 (dd, 2-H), 3.28 (ddd, 1-H), 2.84 (s, NCH_3), 2.46 (ddd, 6α-H), 2.35 (ddd, 6β-H); $J_{1,2}$ = 3.5, $J_{2,3} = J_{3,4}$ = 4, $J_{4,5}$ = 9, $J_{5,6\alpha}$ = 6.5, $J_{5,6\beta}$ = 8, $J_{6\alpha,6\beta}$ = 15, $J_{1,6\alpha}$ = 4, $J_{1,6\beta}$ = 1.5. – ^{13}C NMR ($CDCl_3$): δ = 158.0 (C=O), 74.3 (C-3), 70.3 (C-5), 58.6 (OCH_3), 57.1 (C-4), 50.2 (C-2), 49.2 (C-1), 29.4 (NCH_3), 27.6 (C-6). – MS, *m/z* (%): 199 (3) [M^+].

DL-(1a,2β,3β,4β,6β)-6-Azido-2-O,3-N-carbonyl-4-O-methyl-3-(methylamino)cyclohexane-1,2,4-triol (*rac*-**31a**): A solution of *rac*-**29** (50 mg, 0.25 mmol), NaN_3 (3 mg, 0.50 mmol), and $MgSO_4$ (60 mg, 0.50 mmol) in CH_3OH (5 ml) was heated to reflux for 36 h [total conversion, TLC, $CHCl_3/CH_3OH$, 10:1, R_f (*rac*-**31a**) = 0.24].The mixture was filtrated, and the filtrate was concentrated in vacuo. The residue was treated with hot ethyl acetate (3 × 10 ml), the mixture filtrated, and the filtrate concentrated in vacuo to give colorless crystals (53 mg, 88%), m.p. 134°C (ethyl acetate). – IR (KBr): $\tilde{\nu}$ = 3422 cm^{-1} (s, OH), 2972 (m, CH_3), 2930 (m, CH_2), 2818 (m, OCH_3), 2088 (s, N_3), 1732 (s, C=O). – ^1H NMR ($CDCl_3$, 400 MHz): see Figure 4. – $C_9H_{14}N_4O_4$ (242.2): calcd. C 44.63, H 5.83, N 23.13; found C 44.33, H 5.77, N 22.66.

DL-(1a,2β,3β,4β,6β)-6-Azido-2-O,3-N-carbonyl-2-hydroxy-4-methoxy-3-(methylamino)cyclohexyl Acetate (*rac*-**31b**): *rac*-**31a** (30 mg, 0.12 mmol) was acetylated under standard conditions (1 d). Concentration in vacuo gave colorless crystals (34 mg, 97%), m.p. 131°C (ethyl acetate/cyclohexane, 1:1). R_f ($CHCl_3/CH_3OH$, 10:1) = 0.42. – IR (KBr): $\tilde{\nu}$ = 2984 cm^{-1} (m, CH_3), 2930 (m, CH_2), 2822 (m, OCH_3), 2094 (s, N_3), 1759 (s, C=O). – ^1H NMR ($CDCl_3$): δ = 5.48 (dd, 1-H), 4.47 (dd, 2-H), 3.88 (dd, 3-H), 3.62 (ddd, 4-H), 3.50 (ddd, 6-H), 3.43 (s, OCH_3), 2.89 (s, NCH_3), 2.20 (ddd, 5α-H), 2.15 (s, CH_3), 2.00 (ddd, 5β-H); $J_{1,2} = J_{4,5\beta} = J_{5\alpha,6}$ = 7.5, $J_{2,3}$ = 8.8, $J_{3,4} = J_{4,5\alpha}$ = 3.5, $J_{5\beta,6}$ = 8.5, $J_{5\alpha,5\beta}$ = 14.8, $J_{6,1}$ = 10.5. – $C_{11}H_{16}N_4O_5$ (284.3): calcd. C 46.48, H 5.67, N 19.71; found C 46.52, H 5.68, N 19.79.

DL-(1a,2β,3β,4β,6β)-2-O,3-N-Carbonyl-6-iodo-4-O-methyl-3-(methylamino)cyclohexane-1,2,4-triol (*rac*-**32a**): A solution of *rac*-**29** (176 mg, 0.38 mmol) and KI (190 mg, 1.10 mmol) in acetic acid/water (3:1, 6 ml) was stirred at room temp. for 48 h [red color, total conversion, TLC, $CHCl_3/CH_3OH$, 10:1, R_f (*rac*-**32a**) = 0.35]. It was subsequently concentrated in

vacuo, the residue dissolved in CH_2Cl_2 (100 ml), the solution washed with water (3 × 50 ml), dried ($MgSO_4$), and concentrated in vacuo to give yellowish crystals (102 mg, 82%), m.p. 135°C (ethyl acetate). – IR (KBr): $\tilde{\nu}$ = 3324 cm^{-1} (s, OH), 2976 (m, CH_3), 2950 (m, CH_2), 2906 (m, CH), 2870 (m, OCH_3), 1762 (s, C=O), 674 (m, CI). – ^1H NMR ($CDCl_3$): δ = 4.33 (t, 2-H), 4.10 (dd, 3-H), 4.02 (ddd, 1-H), 3.88 (ddd, 6-H), 3.42 (ddd, 4-H), 3.39 (s, OCH_3), 3.35 (d, OH), 2.88 (s, NCH_3), 2.56 (ddd, 5α-H), 2.42 (ddd, 5β-H); $J_{1,2}$ = $J_{2,3}$ = 7.5, $J_{3,4}$ = $J_{4,5\alpha}$ = 3.8, $J_{4,5\beta}$ = 9, $J_{5\alpha,6}$ = 6, $J_{5\beta,6}$ = 10.5, $J_{5\alpha,5\beta}$ = 14.3, $J_{6,1}$ = 6, $J_{1,OH}$ = 4.5. – $C_9H_{14}INO_4$ (327.1): calcd. C 33.05, H 4.31, N 4.28; found C 32.82, H 4.28, N 4.19.

DL-(1α,2β,3β,4β,6β)-2-O,3-N-Carbonyl-2-hydroxy-6-iodo-4-methoxy-3-(methylamino)cyclohexyl Acetate (*rac*-**32b**): *rac*-**32a** (70 mg, 0.12 mmol) was acetylated under standard conditions (12 h). Concentration in vacuo gave colorless crystals (74 mg, 94%), m.p. 132°C (ethyl acetate/cyclohexane, 1:1). R_f ($CHCl_3/CH_3OH$, 10:1) = 0.47. – IR (KBr): $\tilde{\nu}$ = 2970 cm^{-1} (m, CH_3), 2952 (m, CH_2), 2924 (m, CH), 2884 (m, OCH_3), 1762 (s, C=O), 632 (m, CI). – ^1H NMR ($CDCl_3$): δ = 5.48 (dd, 1-H), 4.42 (t, 2-H), 4.00 (dd, 3-H), 3.95 (ddd, 6-H), 3.48 (ddd, 4-H), 3.40 (s, OCH_3), 2.92 (s, NCH_3), 2.62 (ddd, 5α-H), 2.53 (ddd, 5β-H), 2.14 (s, CH_3); $J_{1,2}$ = $J_{2,3}$ = $J_{4,5\beta}$ = 7.5, $J_{3,4}$ = 3.5, $J_{4,5\alpha}$ = 4.2, $J_{5\alpha,6}$ = 6.8, $J_{5\beta,6}$ = 9.8, $J_{5\alpha,5\beta}$ = 14.3, $J_{6,1}$ = 11.5. – $C_{11}H_{16}INO_5$ (369.2): calcd. C 35.79, H 4.37, N 3.79; found C 35.79, H 4.35, N 3.74.

DL-(1α,2β,3β,4β,5β)-2,3-Anhydro-4-N,5-O-carbonyl-1-O-methyl-4-(methylamino)cyclohexane-1,2,3,5-tetrol (*rac*-**33**): To a solution of *rac*-**7** (120 mg, 0.65 mmol) in DMF (10 ml) (N_2) was added at 0°C with intensive stirring NaH (32 mg, 1.30 mmol) in portions, and the mixture was heated to 60°C for 30 min. Then dimethyl sulfate (170 mg, 1.40 mmol) was added by means of a syringe and the mixture stirred at 60°C for 1 h. Excess NaH was destroyed with *n*-butanol (3 ml). The mixture was concentrated in vacuo, dissolved in CH_2Cl_2 (150 ml), and the solution washed with water (3 × 50 ml). The organic phase was dried ($MgSO_4$), concentrated in vacuo and the residue purified by rapid chromatography (ethyl acetate/cyclohexane, 3:1) to give *rac*-**29** (21 mg, 16%) and a mixture (85 mg, 66%) of *rac*-**33** and *rac*-**30** as a nonseparable yellowish oil (*rac*-**33**/*rac*-**30** ca. 2:1, ^1H NMR). – *rac*-**33**: R_f ($CHCl_3/CH_3OH$, 10:1) = 0.49. – IR (KBr): $\tilde{\nu}$ = 2981 cm^{-1} (w, CH_3), 1761 (s, C=O). – ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.57 (ddd, 5-H), 4.05 (dd, 4-H), 3.95 (ddd, 1-H), 3.44 (s, OCH_3), 3.42 (dd, 3-H), 3.31 (dd, 2-H), 2.95 (s, NCH_3), 2.13 (ddd, 6α-H), 1.80 (ddd, 6β-H); $J_{1,2}$ = $J_{2,3}$ = $J_{3,4}$ = 3.5, $J_{4,5}$ = 9, $J_{5,6\alpha}$ = 4.5, $J_{5,6\beta}$ = 10, $J_{6\alpha,6\beta}$ = 14, $J_{6\alpha,1}$ = 4.5, $J_{6\beta,1}$ = 2.5. – ^{13}C NMR ($CDCl_3$): δ = 157.6 (C=O), 73.3 (C-1), 68.1 (C-5), 57.7 (OCH_3), 54.2 (C-4), 52.4 (C-3), 48.9 (C-2), 28.9 (NCH_3), 26.3 (C-6). – MS, *m/z* (%): 199 (5) [M^+], 167 (3) [$M^+ - OCH_3$], 125 (8) [$M^+ - CO_2 - OCH_3$].

DL-(1α,2β,3β,4β,6α)-6-Azido-2-O,3-N-carbonyl-2-hydroxy-4-methoxy-3-(methylamino)cyclohexyl Acetate (*rac*-**34b**): A solution of *rac*-**32b** (35 mg, 0.10 mmol) and TMGA (31 mg, 0.20 mmol) in dry acetonitrile (5 ml) was stirred at 45°C for 20 h [total conversion, TLC, ethyl acetate/cyclohexane, 3:1, R_f (*rac*-**34b**) = 0.25]. It was subsequently concentrated in vacuo and the residue filtrated over silica gel (ethyl acetate/cyclohexane, 3:1). Concentration of the filtrate in vacuo gave colorless crystals (24 mg, 89%), m.p. 112°C (ether/cyclohexane, 1:1). – IR (KBr): $\tilde{\nu}$ = 2934 cm^{-1} (m, CH_3), 2102 (s, N_3), 1750 (s, C=O). – ^1H NMR ($CDCl_3$): δ = 5.34 (dd, 1-H), 4.65 (dd, 2-H), 4.11 (ddd, 6-H), 3.90 (dd, 3-H), 3.70 (ddd, 4-H), 3.40 (s, OCH_3), 2.90 (s, NCH_3), 2.27 (ddd, 5β-H), 2.15 (s, $COCH_3$), 1.86 (ddd, 5α-H); $J_{1,2}$ = 6.8, $J_{2,3}$ = 7.5, $J_{3,4}$ = $J_{4,5\alpha}$ = 3.8, $J_{4,5\beta}$ = 5.3, $J_{5\alpha,6}$ = 4.5, $J_{5\beta,6}$ = 6, $J_{5\alpha,5\beta}$ = 14.5, $J_{6,1}$ = 3. – $C_{11}H_{16}N_4O_5$ (284.3): calcd. C 46.48, H 5.67, N 19.71; found C 47.52, H 5.81, N 19.34.

DL-(1α,2β,3β,4β,6α)-6-Azido-2-O,3-N-carbonyl-4-O-methyl-3-(methylamino)cyclohexane-1,2,4-triol (*rac*-**34a**): A solution of *rac*-**34b** (12 mg, 0.042 mmol) in 3% methanolic NaOH (2 ml) was kept at room temp. for 10 min, then neutralized with 2 N HCl, concentrated in vacuo, and the residue dissolved in CH_2Cl_2. Drying ($MgSO_4$) of the solution and concentration in vacuo gave a colorless oil (10 mg, 98%). R_f ($CHCl_3/CH_3OH$, 10:1) = 0.32. – IR (film): $\tilde{\nu}$ = 3380 cm^{-1} (s, OH), 2920 (s, CH_2), 2092 (s, N_3), 1744 (s, C=O). – ^1H NMR ($CDCl_3$): see Figure 4. – MS (CI), *m/z* (%): 260 (100) [MNH_4^+].

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