Stereoselective Synthesis and Biological Evaluation of Anisomycin and 2-Substituted Analogues[1]

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Abstract: The naturally occurring pyrrolidine anisomycin **1**, its deacetyl derivative **9k**, and some previously unknown analogues were prepared from 2-*O*-benzyl-3,4-*O*-isopropylidene-L-threose **2**, via the *N*-benzylimine **3**, using highly *threo*-selective additions of organolithium and Grignard compounds and subsequent cyclization as key steps. Anisomycin **1** was obtained in 8 steps/44% total yield from L-threose **2** (12 steps/23% from diethyl L-tartrate). The overall yields for deacetylanisomycin **9k** were 54% (5 steps from L-threose **2**) and 28% (9 steps from diethyl L-tartrate), respectively. The compounds **1**, **8i**, **8k**, **9k**, **18**, **20,** and **23** showed good to high cytotoxic activity towards three tumour and non-tumour cell lines.

Key words: threose imine, diastereoselective 1,2-addition, 1,4-amino alcohol cyclization, dihydroxypyrrolidine, anisomycin, cytotoxicity

There is considerable interest in the synthesis of optically active cyclic amino alcohols, e.g. iminopolyols, imino sugars, and cyclic amino acids since many representatives have been reported to exhibit diverse, strong physiological effects.[2,3] One of these classes of compounds we are concerned with is that of 2-alkyl- and 2-aryl- hydroxypyrrolidines. Representative examples are the antibiotic preussin **A**,[4] the hypertensive alkaloid codonopsine **B**,[5] and the antibiotic anisomycin **1**,[6–11] a fermentation product of various species of *Streptomyces*, known for its marked, but not outstanding activity towards some pathogenic protozoa and fungi[6a] (Figure 1).

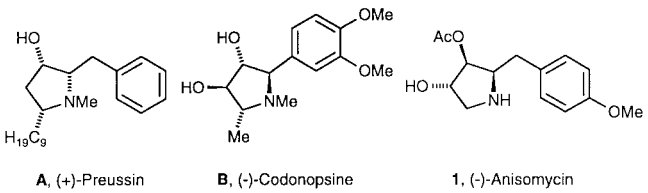


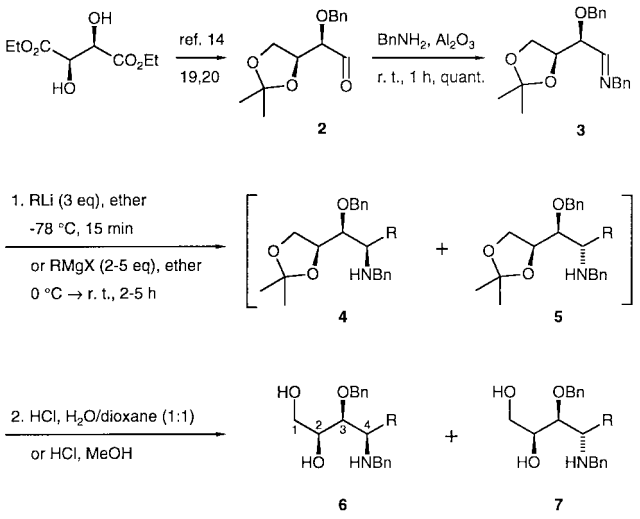
Figure 1

Practical syntheses of the latter have met with increased interest when high anti-tumour activity in vitro, with IC_{50} values in the nanomolar range, was reported for the parent **1** and some analogues in 1993.[12a] Further, in 1995 some anisomycin derivatives with 3-*O*-carbamoyl- or 3-*O*-alkyl groups have been patented due to their improved in vivo stability and activity.[12b]

Since these derivatives were all obtained semi-synthetically starting from anisomycin produced by fermentation, short alternative approaches to **1** and the family of derivatives and analogues deemed worthwhile to be sought. In the literature, about 15 syntheses of **1** or the precursor, deacetylanisomycin (**9k**), are found.[6–11] Most impressive is the route shown by Yoda and Takabe, starting from tri-*O*-benzyl-L-arabinose.[7d] The anisylmethyl side-chain was introduced into the *N*,*O*-acetal by imine addition[7d] (vide infra); after 7 steps a 34% overall yield of *N*-*Z*-deacetylanisomycin was reported. Similarly, in our preliminary paper **9k** was obtained in 7 steps/34% total yield from 2-*O*-benzylthreitol, with *N*,2-*O*-dibenzyl-3,4-*O*-isopropylidene-L-threose imine **3** as the key intermediate.[1a] In many syntheses, deacetylanisomycin (**9k**) was the final product, since its transformation into **1** in a sequence of 5 steps/45% yield[8c] is known. Actually, a shorter, more efficient, and regioselective introduction of the 3-*O*-acetyl group presented another challenge to be dealt with.

In earlier work, we investigated the synthesis of aminodiols and -polyols as key intermediates, e.g. in the preparation of dipeptide isosteres (statine family), inter alia by addition of organometallic reagents to imines[13] of 2-*O*-benzylglyceraldehyde.[14–17] It was shown that the dia-stereoselectivity in this kind of reaction is greatly influenced by the solvent, the metal counterion, and, notably, by introducing a chiral auxiliary at the imine nitrogen.[15b,c] This was applied also to reactions of Grignard and organolithium compounds with Schiff bases of tetroses.[1,18] Subsequent cyclization of such addition products should give access to dihydroxypyrrolidines. While earlier attempts at practicable syntheses of anisomycin **1** had failed, both using a furoisoxazoline derivative[2d] and via nitroaldol addition,[17a,c] we now report on a new, highly efficient, and diastereoselective synthesis of anisomycin **1** and of previously unknown analogues. This details and extends our preliminary communication on a "concise synthesis of deacetylanisomycin and analogues". The highly *threo*-selective addition of organolithium or Grignard reagents to the L-threose imine **3** forms the key step of these syntheses (Scheme 1). The starting material, 2-*O*-benzyl-3,4-*O*-isopropylidene-L-threose **2**, is easily available in four steps from diethyl L-tartrate via 2-*O*-benzyl-L-threitol,[14b] according to ref.[14c,19,20] (50% overall yield). Condensation[21] of **2**, with benzylamine quantitatively yielded the *N*-benzylimine **3**,[1,18] which was then treated with 3 equivalents

of organolithium compound at –78 °C or with 2 to 5 equivalents of Grignard reagent at 0 °C to room temperature in diethyl ether. Use of less, that is 1–1.5 equivalents of organolithium or Grignard reagent, gave a considerable amount (10–20%) of unidentified byproducts. Alkyl Grignard compounds could not be employed due to decomposition of the starting material. The aminotriols **6/7** were obtained pure and in higher yield by subsequent hydrolysis of the acetal group, without isolation of the intermediates **4**/**5**.[22] The results are summarized in Table 1.



Scheme 1

In accord with results observed with other α-alkoxy-,[23] α-aminoaldimines,[24] or 2-*O*-benzyllactaldimines,[15a,b] but in contrast to our observations with 2-*O*-benzylglyceraldimines,[15] the reactions of **3** with organolithium compounds (Table 1, entries 1–6) showed excellent 3,4-*threo*-selectivity (1,2-asymmetric induction). In all cases except one (MeLi, entry 1), a single isomer with D-*xylo* configuration was found by ^{1}H and ^{13}C NMR analysis of the crude acetonide-protected material **4/5**. Yields were in the range of 37–70% after chromatography on silica. The addition of Grignard reagents (entries 7–10) gave comparable results concerning diastereoselectivity and yield (65–78%). In one case, that of allylmagnesium bromide (entry 8), the *erythro*-adduct (L-*arabino* isomer) was also detected. The aminotriol adducts **6** were assigned the D-*xylo* (3,4-*threo*) configuration based on analogies in ^{1}H and ^{13}C NMR spectroscopic data (see Tables 2 and 3). Thus, all the major products **6a–i** showed a small coupling constant for $J_{3,4}$ 1.4–1.8 Hz, whereas a value of 6.0 Hz was found for **7h**. Shift differences of ^{13}C NMR recordings for these free aminodiols **6/7** proved too small and inconsistent for safe assignment (see Table 3), as was the case with the ^{1}H and ^{13}C NMR data of the acetonide precursors **4/5**.[18] The configurations shown were established notably by a crystal structure analysis[25] of the cyclization product **8b**, and complete agreement of all data of **1** and deacetylanisomycin **9k** with the published ones.

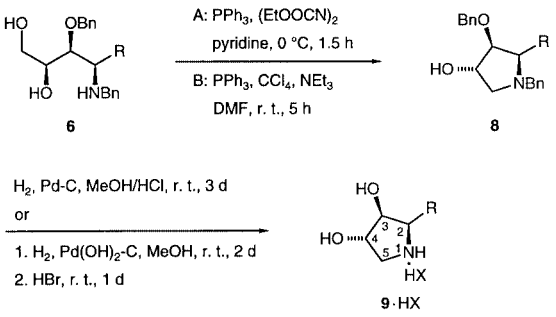
We attribute the high 3,4-*threo*-selectivity of these additions to prior formation of a five-membered chelate (Cram-chelate) with the 2-benzyloxy group, due both to the coordinative ability of OBn[26] and to the Lewis basicity of the imine nitrogen atom (cf. high *threo*-selectivity of like additions to 2-*O*-benzyllactaldimines[15a,b]). The respective ground and transition states of the competing pathways are assumed to correspond closely to the ones given for analogous additions of RM to imines of 2-*O*-benzylglyceraldehyde.[15a–c]

Several of the pure D-*xylo* diastereomers **6** were transformed into 2-substituted *trans*-dihydroxypyrrolidines **8** in good to high yield (62–84%; Table 4), either by intramolecular Mitsunobu reaction according to the procedure of Vogel and Chen[27] (Scheme 2; Method A), or by cyclization using the Appel reaction[28] (alcohol to chloride transformation, Method B). The Mitsunobu reaction failed for the cyclization of the vinyl compound **6g**, but the Appel procedure served well (entry 6): The dihydroxypyrrolidine **8g** was isolated in 63% yield after chromatographic purification.

Table 1 Addition of Organometallic Reagents RM to the *N*-Benzylthreose imine **3** to give **4/5** and Hydrolysis to Aminotriols **6/7**

Entry	RM	**4:5**[a] D-*xylo*/ L-*arabino*	Product **6**/**7**	Yield[b] [%]
1	MeLi	89:11[c]	**6a**/**7a**	52[c]
2	BuLi	>95:5	**6b**/**7b**	59
3	*t*-BuLi	>95:5	**6c**/**7c**	70
4	Me_3SiCH_2Li	>95:5	**6d**/**7d**	67
5	PhLi	>95:5	**6e**/**7e**	66
6	2-C_4H_3SLi	>95:5	**6f**/**7f**	37
7	VinylMgBr	>95:5	**6g**/**7g**	65
8	AllylMgBr	85:15	**6h**/**7h**	75
9	$PhCH_2MgBr$	>95:5	**6i**/**7i**	78
10	$AnCH_2MgCl$[d]	>95:5	**6k**/**7k**	71

[a] Diastereomer ratio (dr) from ^{1}H and ^{13}C NMR analyses of crude addition products **4**/**5**.
[b] Yield based on **3** after chromatography on silica.
[c] Only **6a** was isolated after chromatography.
[d] An = 4-anisyl.



Scheme 2 Cyclization of D-*xylo*-Aminotriols **6**

Table 2 ^{1}H NMR Data of Compounds **6** and **7** Prepared

Compound	Chemical Shifts, δ						
	1-H_A	1-H_B	2-H	3-H	4-H	5-H	Others
6a	3.49–3.70	3.81–3.88		3.49–3.70	3.08	1.27	3.63, 3.90 (NCH_2Ph), 4.55, 4.64 (OCH_2Ph), 7.25–7.38 (2 C_6H_5)
6b	3.57	3.82–3.88		3.63	2.81	1.63, 1.74	0.89 (8-H), 1.16–1.38 (6-H, 7-H), 3.66, 3.88 (NCH_2Ph), 4.51, 4.65 (OCH_2Ph), 7.22–7.38 (2 C_6H_5)
6c	3.66	3.71	3.80	3.74	2.51	–	1.05 [$C(CH_3)_3$], 3.90, 3.97 (NCH_2Ph), 4.65 (OCH_2Ph), 7.23–7.34 (2 C_6H_5)
6d	3.56	3.86	3.87	3.53	3.04	0.96, 1.01	0.03 [$Si(CH_3)_3$], 3.62, 3.83 (NCH_2Ph), 4.54, 4.65 (OCH_2Ph), 7.25–7.37 (2 C_6H_5)
6e	3.54	3.90	3.82	3.65	3.99	–	3.48, 3.63 (NCH_2Ph), 4.16, 4.30 (OCH_2Ph), 7.13–7.45 (3 C_6H_5)
6f	3.52	3.91	3.86	3.77	4.20	–	3.50, 3.65 (NCH_2Ph), 4.46, 4.51 (OCH_2Ph), 7.01–7.04, 7.19–7.37 (2 C_6H_5, C_4H_3S)
6g	3.51	3.81–3.88		3.63	3.36	5.87	3.55, 3.81 (NCH_2Ph), 4.55, 4.61 (OCH_2Ph), 5.23 (6-HE), 5.31 (6-HZ), 7.23–7.37 (2 C_6H_5)
6h[b]	3.54	3.85	3.84	3.66	2.96	2.36, 2.57	3.70, 3.90 (NCH_2Ph), 4.54, 4.63 (OCH_2Ph), 5.04–5.17 (7-H), 5.72 (6-H), 7.24–7.35 (2 C_6H_5)
7h[c]	3.62	–	4.06	3.43	3.18	–	3.71, 3.91 (NCH_2Ph), 4.54, 4.63 (OCH_2Ph)
6i	3.53	3.83	3.82	3.52	3.18	2.81, 3.13	3.75, 3.88 (NCH_2Ph), 4.52, 4.63 (OCH_2Ph), 7.05–7.07, 7.23–7.40 (3 C_6H_5)
6k	3.52	3.76–3.88		3.49	3.11	2.77, 3.07	3.75, 3.89 (NCH_2Ph), 3.80 (OCH_3), 4.51, 4.63 (OCH_2Ph), 6.81–6.98, 7.21–7.37 (C_6H_4, 2 C_6H_5)
	Coupling Constants *J* (Hz)						
	$J_{1A,1B}$	$J_{1A,2}$	$J_{1B,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	Others
6a	–[d]	–[d]	–[d]	–[d]	1.4	6.5	J_{NCH_2Ph} = 12.4, J_{OCH_2Ph} = 11.3
6b	12.3	5.9	–[d]	4.7	1.4	8.4, 4.6	$J_{7,8}$ = 6.8, J_{NCH_2Ph} = 12.3, J_{OCH_2Ph} = 11.4
6c	11.2	4.6	5.6	4.5	1.8	–	J_{NCH_2Ph} = 12.4
6d	12.2	5.8	3.0	5.0	1.5	8.8, 4.6	$J_{5A,5B}$ = 14.7, J_{NCH_2Ph} = 12.3, J_{OCH_2Ph} = 11.3
6e	11.6	4.6	2.7	4.1	1.5	–	J_{NCH_2Ph} = 12.4, J_{OCH_2Ph} = 11.0
6f	11.3	4.3	2.6	4.1	1.8	–	J_{NCH_2Ph} = 12.4, J_{OCH_2Ph} = 10.9
6g	10.6	4.6	–[d]	4.4	1.8	8.8	$J_{5,6E}$ = 17.3, $J_{5,6Z}$ = 10.2, $J_{6E,6Z}$ = 1.1, J_{NCH_2Ph} = 12.7, J_{OCH_2Ph} = 11.3
6h[b]	12.3	5.9	3.1	4.7	1.4	8.1, 5.2	J_{NCH_2Ph} = 12.4, J_{OCH_2Ph} = 11.3
7h[c]	11.1	5.0	6.2	3.0	6.0	–[d]	J_{NCH_2Ph} = 12.6, J_{OCH_2Ph} = 11.2
6i	12.3	6.1	3.4	4.9	1.5	6.7, 6.1	$J_{5A,5B}$ = 12.2, J_{NCH_2Ph} = 12.6, J_{OCH_2Ph} = 11.4
6k	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]	J_{NCH_2Ph} = 12.4, J_{OCH_2Ph} = 11.4

[a] Recorded in $CDCl_3$ at 250.1 MHz (**6a**, **6b**, **6e**, **6f**, **6k**), at 300.1 MHz (**6g**, **6h/7h**), or at 500.1 MHz (**6c**, **6d**).
[b] Major isomer of the 83:17 mixture **6h**/**7h**.
[c] Minor isomer of the 83:17 mixture; signals in part not identified due to overlap with respective signals of **6h**.
[d] *J* not resolved.

Table 3 ^{13}C NMR Chemical Shifts, δ of Compounds **6** and **7**[a]

Compound	C-1	C-2	C-3	C-4	C-5	Others
6a	61.3	71.6	82.7	52.1	17.0	50.4 (N*C*H$_2$Ph), 74.3 (O*C*H$_2$Ph), 127.3, 127.8, 128.0, 128.3, 128.5, 137.9, 138.6 (2 C$_6$H$_5$)
6b	61.8	72.1	78.8	57.3	29.3	13.9 (C-8), 22.7 (C-7), 28.8 (C-6), 50.6 (N*C*H$_2$Ph), 73.9 (O*C*H$_2$Ph), 127.3, 127.8, 127.9, 128.3, 128.4, 128.5, 137.9, 138.7 (2 C$_6$H$_5$)
6c	63.8	74.8	78.2	67.5	36.1	28.1 [C(*C*H$_3$)$_3$], 55.1 (N*C*H$_2$Ph), 73.8 (O*C*H$_2$Ph), 127.1, 127.6, 127.7, 128.3, 128.4, 138.0, 140.5 (2 C$_6$H$_5$)
6d	61.6	71.4	81.7	53.8	17.7	–0.9 [Si(*C*H$_3$)$_3$], 50.7 (N*C*H$_2$Ph), 73.8 (O*C*H$_2$Ph), 127.4, 127.9, 128.4, 128.5, 128.6, 137.9, 138.5 (2 C$_6$H$_5$)
6e	61.0	71.3	83.6	60.6	–	50.6 (N*C*H$_2$Ph), 74.7 (O*C*H$_2$Ph), 127.4, 127.5, 127.9, 128.1, 128.3, 128.6, 128.7, 137.6, 138.4, 140.6 (3 C$_6$H$_5$)
6f	60.7	70.5	83.5	56.4	–	50.7 (N*C*H$_2$Ph), 74.5 (O*C*H$_2$Ph), 125.1, 126.0, 126.3, 144.6 (C$_4$H$_3$S), 127.5, 128.0, 128.1, 128.4, 128.6, 128.7, 137.6, 138.3 (2 C$_6$H$_5$)
6g	60.8	71.2	82.3	60.0	137.6	50.4 (N*C*H$_2$Ph), 74.4 (O*C*H$_2$Ph), 118.0 (C-6), 127.3, 127.9, 128.4, 128.5, 137.8, 138.5 (2 C$_6$H$_5$)
6h[b]	61.7	71.7	79.3	56.5	34.5	50.6 (N*C*H$_2$Ph), 73.7 (O*C*H$_2$Ph), 117.9 (C-7), 127.4, 127.8, 128.3, 128.4, 128.5, 128.6, 137.9, 138.5 (2 C$_6$H$_5$), 135.2 (d, C-6)
7h[c]	63.8	71.7	78.6	56.9	34.7	51.9 (N*C*H$_2$Ph), 72.1 (O*C*H$_2$Ph), 119.0 (t, C-7), 127.4, 130.0, 137.6, 138.9 (2 C$_6$H$_5$), 133.8 (d, C-6)
6i	61.9	71.5	79.2	58.4	36.1	50.9 (N*C*H$_2$Ph), 73.7 (O*C*H$_2$Ph), 126.5, 127.5, 127.9, 128.0, 128.5, 128.7, 128.7, 129.0, 129.2, 138.0, 138.3, 138.8 (3 C$_6$H$_5$)
6k	61.9	71.6	78.9	58.6	35.1	50.8 (N*C*H$_2$Ph), 55.1 (O*C*H$_3$), 73.6 (O*C*H$_2$Ph), 127.4, 127.8, 127.8, 128.4, 128.6, 129.8, 138.0, 138.3 (2 C$_6$H$_5$), 114.1, 130.6, 158.1 (C$_6$H$_4$OMe)

[a] Recorded in $CDCl_3$ at 62.9 MHz. (**6a-f**, **6k**) or at 75.5 MHz (**6g**, **6h/7h**, **6i**).
[b] Major isomer **6h** of the 83:17 mixture.
[c] Minor isomer **7h** of the 83:17 mixture, signals in part not identified due to overlap with respective signal of **6h**.

In order to obtain the free iminopolyols, several of the *N*,3-*O*-dibenzyldihydroxypyrrolidines **8** were deprotected by hydrogenation at 4 bar using palladium or palladium hydroxide on charcoal as catalyst. The 2-alkyl- or 2-aryl-substituted *trans*-dihydroxypyrrolidines **9** were obtained in almost quantitative yield in (95–99%), in the form of the hydrochloride or -bromide. The hydrogenation of the anisylmethyl derivative **8k** afforded the known (+)-deacetylanisomycin **9k** as its hydrobromide, whose spectral data in all respects were identical to those reported for the corresponding hydrochloride.[6a,7c,29] Thus, deacetylanisomycin **9k** was obtained in somewhat improved yield as compared to our preliminary report,[1a] i.e. in 7 steps/39% overall yield from commercially available 2-*O*-benzylthreitol[30] [9 steps/28% total yield from (+)-diethyl L-tartrate]. The ^1H and ^{13}C NMR data of dihydroxypyrrolidines **8** and **9** are summarized in Tables 5 and 6.

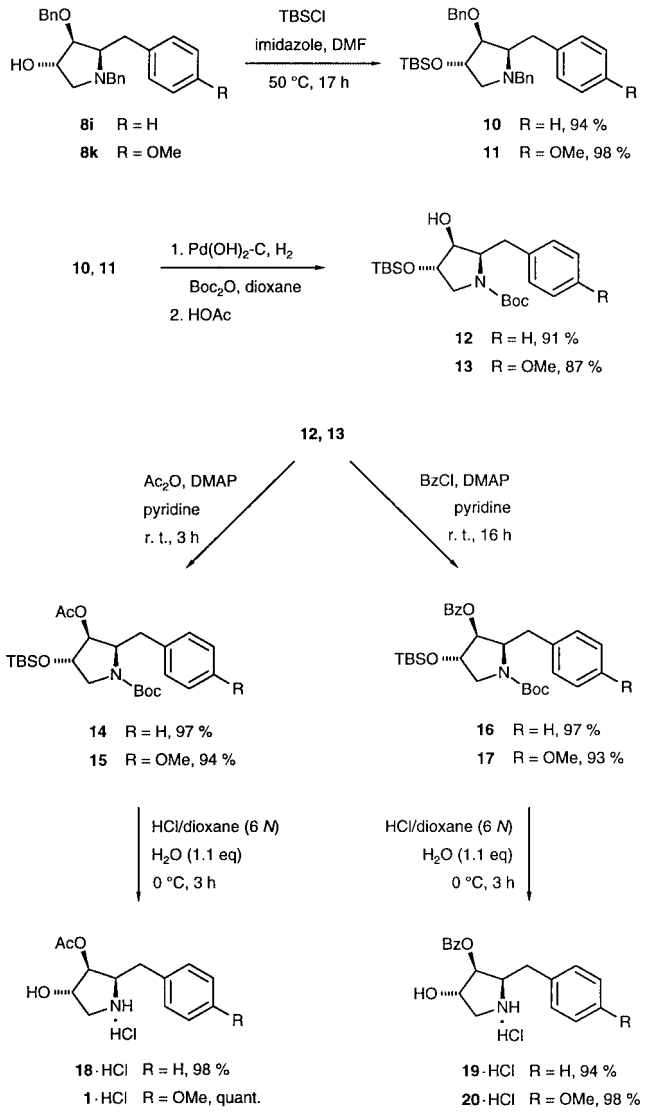
Table 4 Hydroxypyrrolidines **8** and **9** from Cyclization of Aminotriols **6** and Catalytic *N*,*O*-Debenzylation, Respectively

Entry	R	Method[a]	Product **8**	Yield [%][b]	Product **9** (X)	Yield [%][c]
1	Me	A	**8a**	62		
2	Bu	A	**8b**	76	**9b** (Cl)	95
3	*t*-Bu	A	**8c**	84	**9c** (Br)	96
4	CH_2SiMe_3	A	**8d**	74	**9d** (Cl)	96
5	Ph	A	**8e**	82		
6	Vinyl	B	**8g**	63		
7	CH_2Ph	A	**8i**	79	**9i** (Br)	95
8	CH_2An	A	**8k**	77	**9k** (Br)	99

[a] Method of cyclization., A. Mitsunobu, B. Appel, see text.
[b] After chromatography on silica.
[c] After crystallization.

The synthesis of anisomycin **1** was attempted next, in view of elaborating a shorter completing sequence from **9k**, for which, so far, 4 to 5 steps had been required.[6c,8c] In order to solve this problem of regioselective *O*-acetylation of the (more hindered) 3-OH group in **9k**, enzymatic ap-

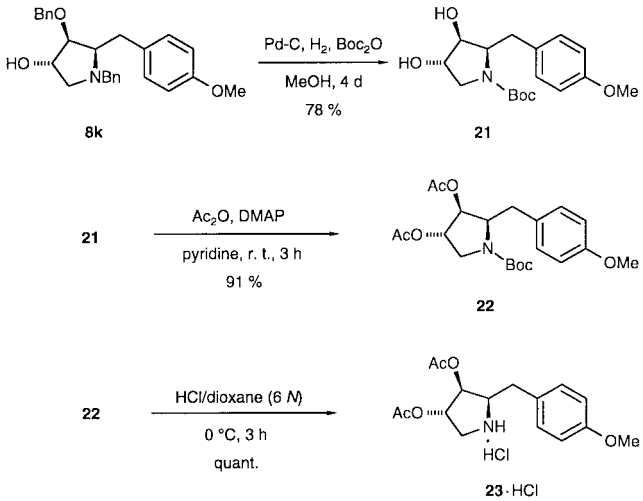
proaches were studied. The acetylation of **9k** with isopropenyl acetate and *Pseudomonas cepacia* as a catalyst[18c,31] proceeded rather slowly, and, after 6 d, led to a mixture of starting, mono-, and di-*O*-acetylated material (**9k/1/23**). Likewise, selective hydrolysis of the less hindered 4-acetoxy group from 4-*O*-acetylanisomycin **23** by means of *Chromobacterium viscosum*[18c,31] failed, producing similar mixtures only. Advantage was then taken of the fact that differentiation of 3-OH vs. 4-OH was already at hand with the 3-*O*-benzyl derivatives **8**. Thus, from **8i** and **8k** the target compound anisomycin **1** as well as demethoxyanisomycin **18** and the 3-*O*-benzoyl derivatives **19** and **20** were secured in four steps (Scheme 3).



Scheme 3

Silylation of **8i** and **8k** with *tert*-butyldimethylsilyl chloride (TBSCl, 1.5 eq) under standard conditions gave the silyl ethers **10** and **11** in 94 and 98% yield, respectively. Subsequent debenzylation at 4 bar hydrogen pressure with palladium hydroxide on charcoal serving as catalyst in the presence of Boc_2O (1.5 eq)[18a,32] afforded the silylated *N*-Boc derivatives **12** and **13** in 86 and 85% yield, respectively. Acetylation with acetic anhydride in pyridine with a catalytic amount of DMAP at room temperature gave pyrrolidines **14** and **15** in 97 and 94%. After removal of TBS and Boc groups at 0 °C with anhydrous 6 *M* HCl in dioxane with 1.1 eq of water added at the end (after some experimentation), anisomycin **1** and demethoxyanisomycin **18** were isolated almost quantitatively as hydrochloride salts. The 3-*O*-benzoyl analogues **19** and **20** were prepared in a similar way, by reaction of **12** and **13**, respectively, with benzoyl chloride and subsequent deprotection with HCl-dioxane.

Finally, 4-*O*-acetylanisomycin **23**, one of the substrates for attempted enzyme-catalyzed hydrolysis (vide supra) and also of interest for screening assays, was obtained in three steps starting from the 2-anisylmethylpyrrolidine **8k** (Scheme 4), using the same principle: Catalytic hydrogenation of **8k** in the presence of Boc_2O (vide infra) gave 78% of the *N*-Boc derivative **21** with a free diol function. After peracetylation with Ac_2O in pyridine (91%) and quantitative cleavage of the Boc group with anhydrous HCl in dioxane (6 M), 4-*O*-acetylanisomycin hydrochloride (23•HCl) was isolated in analytically pure form. Tables 7 and 8 show the ^1H and ^{13}C NMR spectroscopic data of the dihydroxypyrrolidines **1** and **10–23**.



Scheme 4

To our knowledge, the above approach offers superior[6–11] access to anisomycin **1** (8 steps from **2** with 44% and 12 steps from diethyl L-tartrate with 23% overall yield) and a wide range of 2- and 3-*O*-substituted analogues. Also, the route to deacetylanisomycin **9k** is improved (54% from **2**) which may be important for the preparation of non-differentiated, 3-*O*- and 4-*O*-substituted derivatives[12b] in view of potential anti-tumour activity (vide infra).

In Vitro Cytotoxicity of Anisomycin 1 and Some Derivatives

Some of the dihydroxypyrrolidines prepared, as well as four relatives **C–F** with other configurations (Figure 2) which had been obtained in our group either by addition of Grignard reagents to imines of 2,4-*O*-ethylidene-D-erythrose (**C** and **D**)[18c] or via nitroaldol addition (**E** and **F**),[33] were tested with respect to in vitro-cytotoxic activity against human cell lines KB, HBL 100 RAS A, and HBL 100 (as reference, non-tumour cell line). For comparison the reported values of anisomycin **1**[7] are cited: LU99 IC_{50} = 0.082 μM,[12a] MCF7 0.074 μM,[12a] FM3A 0.066 μM[12b]).

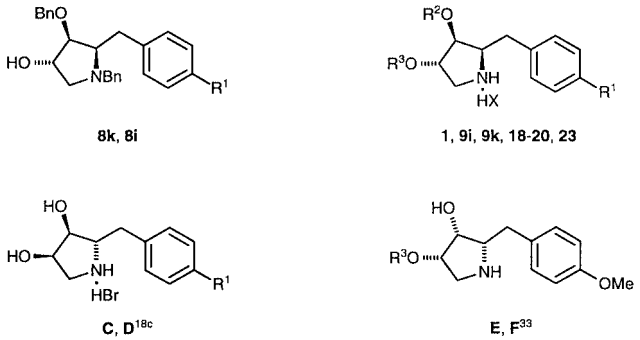


Figure 2

Table 9 In vitro-Cytotoxicity of Anisomycin **1** and Analogues

Compound	R^1	R^2	R^3	IC_{50} [μM] KB[a]	HBL 100 RAS A[b]	HBL 100[c]
8k	H			14	51	79
8i	OMe			20	45	55
9i	H	H	H	–[d]	–[d]	–[d]
9k	OMe	H	H	19	50	29
18	H	Ac	H	0.40	0.094	0.079
1	OMe	Ac	H	0.01	0.05	0.05
19	H	Bz	H	–[d]	–[d]	–[d]
20	OMe	Bz	H	24	9	18
23	OMe	Ac	Ac	0.1	0.3	0.2
C	H			–[d]	–[d]	–[d]
D	OMe			–[d]	–[d]	–[d]
E			H	–[d]	–[d]	–[d]
F			Bn	–[d]	–[d]	–[d]

[a] Human epidermoid carcinoma.
[b] Human mammary cell line converted to a tumorigenic phenotype.
[c] Human mammary cell line.
[d] No inhibition at 100 μM.

As seen from Table 9, with the three new cell lines the results for anisomycin **1** itself again show IC_{50} values in the nanomolar range. Omission of the methoxy group of the aromatic ring of **1**, see compound **18**, causes only a slight decrease of cytotoxicity against HBL 100 cells, but reduces activity towards KB cells by a factor of 40. Acetylation of the second hydroxy function, as seen with 4-*O*-acetylanisomycin **23**, leads to somewhat lower (1/10), yet still considerable activity. It is important to note here that this derivative synthetically is much better available than anisomycin itself because the two hydroxy groups need not be differentiated. Deacetylation of the 3-*O*-Ac function in **1**, i.e. with deacetylanisomycin (**9k**), results in strong reduction of activity, and the additional demethoxylation of the aromatic ring (with **9i**) causes complete loss thereof. The 3-*O*-benzoyl derivative **20** and, interestingly, the two *N*,*O*-dibenzyl compounds **8i** and **8k** also showed approximately the same effect as deacetylanisomycin **9k**, with IC_{50} values in the micromolar range. The 3-*O*-benzoyl-demethoxy derivative **19**, all compounds with a 2-alkyl side-chain, and the samples of **C–F** with differing configuration turned out to be wholly inactive.

Concerning the requirements for high cytotoxic activity of this class of compounds, the following conclusions may be drawn: (i) activity is found only with D-*xylo* compounds, i.e. the configuration of natural (–)-anisomycin **1**; (ii) the presence of the *p*-methoxy group is beneficial (factor 1.6 to 40); (iii) other substituents on the (indispensable) aromatic ring might be even more favourable; (iv) a (small) 3-*O*-acyl group is essential (cf. ref.[12]); (v) additional 4-*O*-substituents may be tolerated (with 4-*O*-Ac decrease of activity by a factor of 4 to 10 only).

Solvents were purified and dried according to standard procedures. MeLi (1.6 M in Et_2O), BuLi (1.6 M in hexane), *t*-BuLi (1.6 M in pentane), diethyl azodicarboxylate (DEAD, Merck), trimethylsilylmethyllithium (1.0 M in pentane), phenyllithium (2.0 M in benzene/Et_2O 7:3), vinylmagnesium bromide (1.0 M in THF), allylmagnesium bromide (2.0 M in Et_2O), thiophene (Aldrich), benzyl bromide, *p*-methoxybenzyl chloride, Boc_2O, and PPh_3 (Fluka) were purchased and used without further purification. 2-*O*-Benzyl-3,4-*O*-isopropylidene-L-threose **2** was prepared in four steps from diethyl L-tartrate according to ref.[14,19,20] (50% overall yield); $[\alpha]_D^{20}$ +34.6 (*c* = 1.51, $CHCl_3$). TLC was performed on silica F_{254}-coated aluminium sheets (E. Merck) using mixtures of EtOAc/petroleum ether (bp 30–75 °C), with detection by UV at 254 nm or by heating with a solution of cerium(IV) sulfate (1 g), ammonium molybdate (2.1 g), and concd H_2SO_4 (31 mL) in H_2O (500 mL).[34] Products were purified by chromatography on silica (Merck, 32–63 μm). Mps were determined on a Fisher-Johns apparatus and are uncorrected. The optical rotations were measured on a Perkin-Elmer 241 MC polarimeter using the Drude method to calculate $[\alpha]_D$ from the values found at 546 and 579 nm. IR spectra were recorded on a Bruker IFS 28 spectrometer. NMR spectra were obtained from Bruker AC 250, ABX 300, and ABX 500 spectrometers (^{1}H: 250.1, 300.1, or 500.1 MHz; ^{13}C: 62.9, 75.5, or 125.8 MHz) with TMS as internal standard; evaluation of ^{1}H NMR spectra according to 1st order interpretation; multiplicity of ^{13}C NMR signals from broad band decoupled or DEPT spectra. The in vitro-cytotoxicity tests were carried out at the Institut de Chimie des Substances Naturelles (ICSN-CNRS) in Gif-sur-Yvette (Essonne, France).

(2*S*,3*S*)-*N*,2-*O*-Dibenzyl-3,4-*O*-isopropylidene-L-threose imine (3)

According to lit.[21] L-threose **2** (2.08 g, 8.31 mmol), Al_2O_3 (neutral, type 90/activity I; 63–200 μm; 1.83 g, 18.0 mmol), benzylamine (890 mg, 8.31 mmol), and CH_2Cl_2 (0.5 mL) were stirred at r. t. for 1 h. To the mixture was added CH_2Cl_2 (10 mL) and stirring was continued for 10 min. The suspension was filtered, the residue washed with CH_2Cl_2 (2 × 5 mL), and the filtrate was dried

($MgSO_4$). Removal of the solvent in vacuo (1 mbar) gave the imine **3** as an analytically pure, colourless oil; yield 2.82 g (quant); $[\alpha]_D^{20}$ +31.1 (*c* = 1.50, $CHCl_3$).

IR (film): ν = 3078, 3057, 3023, 2981, 2932, 2878, 1662 (C=N), 1596, 1490, 1449, 1377, 1368, 1258, 1213, 1156, 1070, 1030, 908, 851, 740, 702 cm^{-1}.

^1H NMR ($CDCl_3$, 250.1 MHz): δ = 1.36, 1.39 [2 s, 6 H, $C(CH_3)_2$], 3.91 (dd, $^3J_{3,4a}$ = 6.5, $^2J_{4a,4b}$ = 8.7 Hz, 1 H, 4-H_a), 3.99 (dd, $^3J_{3,4b}$ = 6.5, $^2J_{4a,4b}$ = 8.7 Hz, 1 H, 4-H_b), 4.02 (dd, $^3J_{1,2}$ = 5.6, $^3J_{2,3}$ = 6.0 Hz, 1 H, 2-H), 4.35 (m, 1 H, 3-H), 4.61 (s, 2 H, NCH_2Ph), 4.61, 4.70 (A, B of AB, ^2J = 12.1 Hz, 2 H, OCH_AH_BPh), 7.22–7.43 (m, 10 H, 2 C_6H_5), 7.72 (dt, $^3J_{1,2}$ = 5.6, $^4J_{1,3}$ = 1.4 Hz, 1 H, 1-H).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 25.2, 26.3 [2 q, $C(CH_3)_2$], 64.6 (t, C-4), 65.5 (t, NCH_2Ph), 71.9 (t, OCH_2Ph), 76.5 (d, C-3), 80.7 (d, C-2), 109.6 [s, $C(CH_3)_2$], 127.0, 127.7, 127.9, 128.0, 128.3, 128.4 (6 d; *o*-, *m*-, *p*-C of 2 C_6H_5), 137.8, 138.5 (2 s, *i*-C of 2 C_6H_5), 160.9 (d, C-1).

$C_{21}H_{25}NO_3$	calc.	C 74.31	H 7.42	N 4.13
(339.4)	found	C 74.08	H 7.65	N 4.07

(2*S*,3*S*,4*R*)-4-(Benzylamino)-3-(benzyloxy)pentane-1,2-diol (6a); Typical Procedure A

To a mixture of MeLi (1.6 M in Et_2O, 4.2 mL, 6.7 mmol) and anhyd Et_2O (10 mL) at –78 °C under N_2 was slowly (10 min) added a solution of the imine **3** (759 mg, 2.24 mmol) in anhyd Et_2O (5 mL). The reddish mixture was stirred at –78 °C for 15 min and then quenched at this temperature with sat. aq NH_4Cl (10 mL). After warming to r. t., the mixture was extracted with Et_2O (3 × 40 mL), washed with sat. aq $NaHCO_3$ (40 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo (20 mbar) to furnish the acetonide-protected amino alcohols **4a/5a** as a yellow oil (693 mg, dr 89:11 from ^{13}C NMR). The crude product was dissolved in dioxane/H_2O (1:1, 20 mL), then concd HCl (0.5 mL) was added and the mixture stirred for 16 h at 50 °C. After removal of the solvent under reduced pressure, the residue was suspended in sat. aq $NaHCO_3$ (20 mL), extracted with EtOAc (4 × 40 mL), and the solutes were dried (Na_2SO_4). Concentration in vacuo (20 mbar) afforded a brown crude product (561 mg) which was purified by flash chromatography (silica gel, 21 g, column 3.5 cm × 6 cm, petroleum ether/EtOAc 1:1 + 1% Et_3N) to give **6a** (**6a/7a** >95:5 from ^{13}C NMR) as an analytically pure, pale-yellow oil; 350 mg (52%); $[\alpha]_D^{20}$–16 (*c* = 0.52, $CHCl_3$).

IR (film): ν = 3317 (OH, NH), 3062, 3029, 2924, 1655, 1495, 1453, 1373, 1260, 1208, 1068, 1027, 788, 735, 698 cm^{-1}.

$C_{19}H_{25}NO_3$	calc.	C 72.35	H 7.99	N 4.44
(315.4)	found	C 72.20	H 8.13	N 4.54

(2*S*,3*S*,4*R*)-4-(Benzylamino)-3-(benzyloxy)octane-1,2-diol (6b)

According to the Typical Procedure A; imine **3** (1.12 g, 3.30 mmol), Et_2O (5 mL), BuLi (1.6 M in hexane, 6.2 mL, 9.9 mmol), Et_2O (10 mL), 15 min at –78 °C. After workup, the protected amino alcohol **4b** was obtained as a yellow oil (1.22 g, dr >95:5 from ^{13}C NMR). Treatment of the crude product with dioxane/H_2O (1:1, 20 mL)/concd HCl (0.5 mL) as above afforded a brown oil (1.04 g) which was purified by flash chromatography (silica gel, 40 g, column 3 cm × 12 cm, petroleum ether/EtOAc 1:1+1% Et_3N) to give analytically pure **6b** (**6b/7b** >95:5 from ^{13}C NMR) as a pale yellow oil; yield 699 mg (59%); $[\alpha]_D^{20}$ –23.0 (*c* = 1.47, $CHCl_3$).

IR (film): ν = 3322 (OH, NH), 3062, 3029, 2927, 2858, 1604, 1495, 1453, 1209, 1069, 1028, 813, 800, 736, 698 cm^{-1}.

$C_{22}H_{31}NO_3$	calc.	C 73.92	H 8.74	N 3.92
(357.5)	found	C 73.66	H 8.91	N 3.81

(2*S*,3*S*,4*R*)-4-(Benzylamino)-3-(benzyloxy)-5,5-dimethylhexane-1,2-diol (6c)

According to the Typical Procedure A; imine **3** (1.31 g, 3.85 mmol), Et_2O (5 mL), *t*-BuLi (1.6 M in pentane, 7.2 mL, 11.5 mmol), Et_2O (10 mL), 15 min at –78 °C. After workup, the crude amino alcohol **4c** was obtained as a yellow oil (1.38 g, dr >95:5 from ^{13}C NMR). The crude product was dissolved in MeOH (25 mL), then concd HCl (0.5 mL) was added and the mixture stirred for 2 d at r. t. Workup analogous to the Typical Procedure A afforded a brown crude product (1.30 g) which was purified by flash chromatography (silica gel, 30 g, column 3.5 cm × 9 cm, petroleum ether/EtOAc 1:1 + 1% Et_3N) to furnish **6c** (**6c/7c** >95:5 from ^{13}C NMR) as an analytically pure, colourless oil; yield 966 mg (70%); $[\alpha]_D^{21}$ +26 (*c* = 0.54, $CHCl_3$).

IR (film): ν = 3360 (OH; NH), 3087, 3063, 3030, 2953, 2905, 2869, 1658, 1604, 1494, 1454, 1394, 1363, 1211, 1071, 1031, 912, 869, 734, 699 cm^{-1}.

$C_{22}H_{31}NO_3$	calc.	C 73.92	H 8.74	N 3.92
(357.5)	found	C 73.85	H 8.86	N 3.91

(2*S*,3*S*,4*S*)-4-(Benzylamino)-3-(benzyloxy)-5-(trimethylsilyl)pentane-1,2-diol (6d)

According to the Typical Procedure A; imine **3** (1.50 g, 4.42 mmol), Et_2O (5 mL), trimethylsilylmethyllithium (1.0 M in pentane, 13.3 mL, 13.3 mmol), Et_2O (10 mL), 15 min at –78 °C. After workup, the crude amino alcohol **4d** was obtained as a yellow oil (1.89 g, dr >95:5 from ^{13}C NMR). Treatment of the crude product as above with dioxane/H_2O (1:1, 30 mL)/concd HCl (0.5 mL) afforded a brown oil (1.51 g) which was purified by flash chromatography (silica, 31 g, column 3.5 cm × 9 cm, petroleum ether/EtOAc 1:1 + 1% Et_3N) to give analytically pure **6d** (**6d/7d** >95:5 from ^{13}C NMR) as a pale yellow oil; yield 1.15 g (67%); $[\alpha]_D$ –9.40 (*c* = 1.57, $CHCl_3$).

IR (film): ν = 3656, 3321 (OH, NH), 3087, 3063, 3030, 2950, 2891, 1604, 1496, 1453, 1435, 1360, 1305, 1248, 1208, 1154, 1069, 1032, 985, 910, 858, 843, 735, 699 cm^{-1}.

$C_{22}H_{33}NO_3Si$	calc.	C 68.18	H 8.58	N 3.61
(387.6)	found	C 68.02	H 8.65	N 3.51

(2*S*,3*S*,4*R*)-4-(Benzylamino)-3-(benzyloxy)-4-phenylbutane-1,2-diol (6e)

According to the Typical Procedure A; imine **3** (500 mg, 1.47 mmol), Et_2O (5 mL), PhLi (2.0 M in benzene/Et_2O 7:3, 2.2 ml, 4.4 mmol), Et_2O (10 mL), 15 min at –78 °C. After workup, the crude amino alcohol **4e** was obtained as a yellow oil (542 mg, dr >95:5 from ^{13}C NMR). The crude product was dissolved in MeOH (20 mL), then concd HCl (0.5 mL) was added and the mixture stirred for 4 d at r. t. Workup analogous to the Typical Procedure A afforded a brown oil (527 mg) which was purified by flash chromatography (silica, 22 g, column 3.5 cm × 8 cm, petroleum ether/EtOAc 1:1 + 1% Et_3N) to give analytically pure **6e** (**6e/7e** >95:5 from ^{13}C NMR) as a pale yellow solid; yield 362 mg (66%); mp 89–91 °C; $[\alpha]_D^{20}$ –74.1 (*c* = 1.00, $CHCl_3$).

IR (film/CH_2Cl_2): ν = 3480, 3330 (OH; NH), 3062, 3029, 2922, 1603, 1495, 1453, 1399, 1353, 1261, 1210, 1066, 1028, 911, 874, 750, 699 cm^{-1}.

$C_{24}H_{27}NO_3$	calc.	C 76.36	H 7.21	N 3.71
(377.5)	found	C 76.12	H 7.20	N 3.63

(2*S*,3*S*,4*S*)-4-(Benzylamino)-3-(benzyloxy)-4-(thien-2-yl)butane-1,2-diol (6f)

2-Thienyllithium was prepared according to lit.[35] To a solution of thiophene (283 µL, 3.54 mmol) in anhyd Et_2O (5 mL) under N_2 was added (5 min) BuLi (1.6 M in hexane, 2.2 mL, 3.5 mmol). After 1 h at –20 °C and 15 min at r. t. the yellow mixture was cooled to –70 °C. A solution of the imine **3** (300 mg, 0.884 mmol) in anhyd Et_2O (3 mL) was slowly added (10 min). The reddish mixture was stirred at –70 °C for 1 h and then quenched with sat. aq NH_4Cl (10 mL). Workup according to the Typical Procedure A furnished the protected aminotriol **4f** as a brown oil (343 mg, dr >95:5 from ^{13}C NMR). The crude product was dissolved in MeOH (10 mL), then concd HCl (0.2 mL) was added and the mixture stirred for 2 d at r. t. Workup analogous to the Typical Procedure A afforded a brown crude product (309 mg) which was purified by flash chromatography (silica gel, 15 g, column 2.5 cm × 8 cm, petroleum ether/EtOAc 1:1 + 1% Et_3N) to give analytically pure **6f** (**6f/7f** >95:5 from ^{13}C NMR) as a pale yellow solid; yield 123 mg (37%); mp 69–70 °C; $[\alpha]_D^{20}$ –62.5 (*c* = 1.42, $CHCl_3$).

IR (film/CH_2Cl_2): ν = 3331 (OH; NH), 3063, 3029, 2961, 2918, 2850, 1604, 1496, 1453, 1353, 1261, 1208, 1066, 1027, 800, 733, 698 cm^{-1}.

$C_{22}H_{25}NO_3S$	calc.	C 68.90	H 6.57	N 3.65
(383.5)	found	C 68.96	H 6.67	N 3.61

(2*S*,3*S*,4*R*)-4-(Benzylamino)-3-(benzyloxy)hex-5-ene-1,2-diol (6g)

To vinylmagnesium bromide (1.0 M in THF, 8.5 mL, 8.5 mmol) under N_2 at 0 °C a solution of the imine **3** (1.45 g, 4.27 mmol) in anhyd Et_2O (11 mL) was slowly (15 min) added. The yellow mixture was stirred at r. t. for 5 h and then quenched at 0 °C with sat. aq NH_4Cl (20 mL). Workup analogous to the Typical Procedure A furnished the amino alcohol **4g** as a yellow oil (1.51 g, dr >95:5 from ^{13}C NMR). The crude product was dissolved in MeOH (20 mL), then concd HCl (0.5 mL) was added and the mixture stirred for 18 h at r. t. Workup analogous to the Typical Procedure A afforded a brown crude product (1.33 g) which was purified by flash chromatography (silica gel, 45 g, column 3.5 cm × 10 cm, petroleum ether/EtOAc 1:1 + 1% Et_3N) to give analytically pure **6g** (**6g/7g** >95:5 from ^{13}C NMR) as a pale yellow oil; yield 901 mg (65%); $[\alpha]_D^{20}$ –10.4 (*c* = 1.43, $CHCl_3$).

IR (film): ν = 3386 (OH, NH), 3063, 3028, 2867, 1639, 1605, 1586, 1496, 1453, 1352, 1210, 1066, 1028, 1000, 869, 825, 804, 734, 698 cm^{-1}.

$C_{20}H_{25}NO_3$	calc.	C 73.37	H 7.70	N 4.28
(327.4)	found	C 73.07	H 7.83	N 4.24

(2*S*,3*S*,4*R*)-4-(Benzylamino)-3-(benzyloxy)hept-6-ene-1,2-diol (6h/7h)

To allylmagnesium bromide (1.0 M in Et_2O, 4.6 mL, 4.6 mmol) under N_2 at 0 °C a solution of the imine **3** (780 mg, 2.30 mmol) in Et_2O (4 mL) was slowly (15 min) added. The yellow mixture was stirred at r. t. for 4 h and then quenched at 0 °C with sat. aq NH_4Cl (20 mL). Workup as described in the Typical Procedure A furnished the protected amino alcohols **4h/5h** as a yellow oil (998 mg, dr 85:15 from ^{13}C NMR). The crude product was dissolved in MeOH (20 mL), then concd HCl (0.5 mL) was added, and the mixture was stirred for 21 h at r. t. Workup analogous to the Typical Procedure A afforded a light brown crude product (794 mg) which was purified by flash chromatography (silica gel, 35 g, column 3 cm × 10 cm, petroleum ether/EtOAc 1:1 + 1% Et_3N) to give a mixture of **6h/7h** (83:17 from ^{13}C NMR) as an analytically pure, pale yellow oil; yield 590 mg (75%); $[\alpha]_D^{20}$ –13.2 (*c* = 1.50, $CHCl_3$).

IR (film): ν = 3380 (OH, NH), 3063, 3028, 2917, 2865, 1638, 1604, 1496, 1453, 1399, 1353, 1209, 1072, 1028, 1000, 915, 801, 737, 699 cm^{-1}.

$C_{21}H_{27}NO_3$		calc.	C 73.87	H 7.97	N 4.10
(341.5)	**6h/7h** (83:17)	found	C 73.54	H 8.16	N 4.09

(2*S*,3*S*,4*R*)-4-(Benzylamino)-3-(benzyloxy)-5-phenylpentane-1,2-diol (6i)

Under N_2 a solution of benzyl bromide (1.39 mL, 11.5 mmol) in anhyd Et_2O (11 mL) was added dropwise to a vigorously stirred suspension of magnesium turnings (288 mg, 11.8 mmol) in anhyd Et_2O (4 mL). The mixture was then refluxed for 15 min. A solution of the imine **3** (1.35 g, 3.83 mmol) in anhyd Et_2O (8 mL) was slowly (15 min) added at 0 °C. The yellow mixture was stirred at r. t. for 3 h and then quenched at 0 °C with sat. aq NH_4Cl (20 mL). Workup analogous to the Typical Procedure A furnished the protected aminotriol **4i** as a yellow oil (1.83 g, dr >95:5 from ^{13}C NMR). Treatment of the crude product with dioxane/H_2O (1:1, 20 mL)/concd HCl (0.5 mL) according to the Typical Procedure A afforded a brown oil (1.47 g) which was purified by flash chromatography (silica gel, 50 g, column 3 cm × 14 cm, petroleum ether/EtOAc 1:1 + 1% Et_3N) to give analytically pure **6i** (**6i/7i** >95:5 from ^{13}C NMR) as a pale yellow oil; yield 1.17 g (78%); $[\alpha]_D^{20}$ –37.3 (*c* = 1.15, $CHCl_3$).

IR (film): ν = 3320 (OH, NH), 3085, 3062, 3027, 2864, 1603, 1495, 1453, 1396, 1351, 1260, 1207, 1177, 1155, 1071, 1029, 912, 802, 735, 698 cm^{-1}.

$C_{25}H_{29}NO_3$	calc.	C 76.70	H 7.47	N 3.58
(391.5)	found	C 76.70	H 7.47	N 3.50

(2*S*,3*S*,4*R*)-4-(Benzylamino)-3-(benzyloxy)-5-(4-methoxyphenyl)pentane-1,2-diol (6k)

Under N_2 magnesium turnings (17.4 g, 711 mmol) were suspended in anhyd Et_2O (20 mL), then 0.5 mL (0.58 g, 3.7 mmol) of 4-methoxybenzyl chloride and a few grains of iodine were added. The mixture was stirred vigorously and heated to reflux until the reaction started. The rest of 4-methoxybenzyl chloride (3.86 g, 24.7 mmol) in anhyd Et_2O (12 mL) was added dropwise under vigorous stirring. The mixture was refluxed for 15 min, then at 0 °C a solution of the imine **3** (1.93 g, 5.68 mmol) in anhyd Et_2O (5 mL) was slowly (10 min) added. The yellow mixture was stirred at r. t. for 3 h and quenched at 0 °C with sat. aq NH_4Cl (20 mL). Workup analogous to the Typical Procedure A furnished the impure amino alcohol **4k** as a yellow oil (4.78 g, dr >95:5 from ^{13}C NMR). Treatment of the crude product with dioxane/H_2O (1:1, 30 mL)/concd HCl (0.5 mL) according to the Typical Procedure A afforded a brown oil (3.94 g) which was purified by flash chromatography (silica gel, 60 g, column 3 cm × 15 cm, petroleum ether/EtOAc 1:1 + 1% Et_3N) to furnish **6k** (**6k/7k** >95:5 from ^{13}C NMR) as an analytically pure, pale yellow oil; yield 1.70 g (71%); $[\alpha]_D^{20}$ –39.8 (*c* = 1.39, $CHCl_3$).

IR (film): ν = 3320 (OH, NH), 3062, 3029, 3004, 2926, 1611, 1512, 1496, 1453, 1397, 1352, 1301, 1246, 1209, 1178, 1070, 1030, 922, 736, 698 cm^{-1}.

$C_{26}H_{31}NO_4$	calc.	C 74.08	H 7.41	N 3.32
(421.5)	found	C 74.08	H 7.43	N 3.16

(2*R*,3*S*,4*S*)-1-Benzyl-3-(benzyloxy)-4-hydroxy-2-methylpyrrolidine (8a); Typical Procedure B (Mitsunobu Cyclization)

According to lit.[27b] diethyl azodicarboxylate (DEAD; 75 µL, 58 mg, 0.48 mmol) at 0 °C under N_2 was added slowly to a solution of the aminotriol **6a** (126 mg, 0.400 mmol) and PPh_3 (126 mg,

0.480 mmol) in anhyd pyridine (2.2 mL). The mixture was stirred at 0 °C for 90 min and then quenched with ice-water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL) and the combined solutes were evaporated (20 mbar) to leave a yellow oil. The crude product was dissolved in dioxane/H_2O (1:1, 5 mL) and LiOH monohydrate (168 mg, 4.00 mmol) was added (for destruction of the byproduct diethyl hydrazinedicarboxylate). The mixture was stirred at 80 °C for 20 h and then extracted with Et_2O (4 × 30 mL). The combined ether layers were dried (Na_2SO_4), filtered, and evaporated in vacuo. The yellowish residue was purified by flash chromatography (silica gel, 12 g, column 2 cm × 8 cm, petroleum ether/Et_2O 3:7) to obtain spectroscopically pure **8a** as a colourless oil; yield 74 mg (62%); $[\alpha]_D^{20}$ –42.5 (*c* = 1.53, $CHCl_3$).

IR (film): ν = 3385 (OH), 3062, 3029, 2965, 2925, 1603, 1495, 1452, 1376, 1347, 1260, 1208, 1126, 1069, 1028, 911, 798, 736, 698 cm^{-1}.

$C_{19}H_{23}NO_2$	calc.	C 76.74	H 7.79	N 4.71
(297.4)	found	C 76.11	H 7.95	N 4.73

(2*R*,3*S*,4*S*)-1-Benzyl-3-(benzyloxy)-2-butyl-4-hydroxypyrrolidine (8b)

According to the Typical Procedure B; aminotriol **6b** (190 mg, 0.532 mmol), PPh_3 (167 mg, 0.638 mmol), DEAD (99 µL, 72 mg, 0.64 mmol), pyridine (3.0 mL), 90 min at 0 °C. After workup treatment of the residue with dioxane/H_2O (1:1, 6 mL)/LiOH•H_2O (223 mg, 5.32 mmol) as above. Flash chromatography (silica gel, 15 g, column 2 cm × 11 cm, petroleum ether/ ether 3:7) furnished a colourless solid; after crystallization from heptane/Et_2O **8b**, analytically pure, colourless needles; yield 137 mg (76%) mp 68–69 °C; $[\alpha]_D^{20}$ –103 (*c* = 0.76, $CHCl_3$).

IR (CCl_4): ν = 3620 (OH), 3087, 3065, 3031, 2957, 2929, 2860, 2793, 1571, 1559 (CCl_4), 1548, 1496, 1454, 1342, 1252, 1207, 1115, 1070, 1028, 1007, 911, 807 (CCl_4), 699 cm^{-1}.

$C_{22}H_{29}NO_2$	calc.	C 77.84	H 8.61	N 4.13
(339.5)	found	C 77.72	H 8.67	N 4.10

(2*R*,3*S*,4*S*)-1-Benzyl-3-(benzyloxy)-2-*tert*-butyl-4-hydroxypyrrolidine (8c)

According to the Typical Procedure B; aminotriol **6c** (420 mg, 1.17 mmol), PPh_3 (371 mg, 1.41 mmol), DEAD (221 µL, 161 mg, 1.41 mmol), pyridine (6.5 mL), 90 min at 0 °C. After workup treatment of the residue with dioxane/H_2O (1:1, 10 mL)/LiOH•H_2O (491 mg, 11.7 mmol) as above. Flash chromatography (silica gel, 16 g, column 2 cm × 12 cm, petroleum ether/Et_2O 3:7) furnished **8c**; analytically pure, colourless oil; yield 336 mg (84%); $[\alpha]_D^{20}$ –18 (*c* = 0.77, $CHCl_3$).

IR (film): ν = 3319 (OH), 3085, 3062, 3029, 2953, 2905, 2865, 1603, 1495, 1484, 1453, 1387, 1356, 1214, 1164, 1121, 1062, 1039, 1028, 1002, 914, 735, 697 cm^{-1}.

$C_{22}H_{29}NO_2$	calc.	C 77.84	H 8.61	N 4.13
(339.5)	found	C 77.72	H 8.63	N 4.07

(2*S*,3*S*,4*S*)-1-Benzyl-3-(benzyloxy)-4-hydroxy-2-(trimethylsilyl)pyrrolidine (8d)

According to the Typical Procedure B; aminotriol **6d** (303 mg, 0.782 mmol), PPh_3 (245 mg, 0.938 mmol), DEAD (145 µL, 106 mg, 0.938 mmol), pyridine (4.4 mL), 90 min at 0 °C. After workup treatment of the residue with dioxane/H_2O (1:1, 8 mL)/LiOH•H_2O (328 mg, 7.82 mmol) as above. Yellowish crude product, purified by flash chromatography (silica gel, 15 g, column 2 cm × 11 cm, petroleum ether/Et_2O 3:7) and crystallization from heptane/Et_2O; **8d**, analytically pure, colourless needles; yield 212 mg (74%); mp 121–122 °C; $[\alpha]_D^{20}$ –96.4 (*c* = 1.50, $CHCl_3$).

IR (CCl_4): ν = 3066 (OH), 3032, 2953, 2791, 1654, 1545 (CCl_4), 1511, 1497, 1459, 1249, 1216, 1115, 1070, 1006, 979, 861, 783 (CCl_4), 699 cm^{-1}.

$C_{22}H_{31}NO_2Si$	calc.	C 71.50	H 8.45	N 3.79
(369.6)	found	C 71.70	H 8.55	N 3.75

(2*S*,3*S*,4*R*)-1-Benzyl-3-(benzyloxy)-4-hydroxy-2-phenylpyrrolidine (8e)

According to the Typical Procedure B; aminotriol **6e** (225 mg, 0.596 mmol), PPh_3 (188 mg, 0.715 mmol), DEAD (112 µL, 81.7 mg, 0.715 mmol), pyridine (3.3 mL), 90 min at 0 °C. After workup treatment of the residue with dioxane/H_2O (1:1, 6 mL)/LiOH•H_2O (250 mg, 5.96 mmol) as above. Flash chromatography (silica gel, 13 g, column 2 cm × 9 cm, petroleum ether/ether 3:7) furnished a colourless solid; after crystallization from heptane/Et_2O **8e**, analytically pure, colourless needles; yield 175 mg (82%); mp 82 °C; $[\alpha]_D^{20}$ +37 (*c* = 0.90, $CHCl_3$).

IR (film/CH_2Cl_2): ν = 3420 (OH), 3086, 3063, 3029, 2922, 2793, 1640, 1603, 1494, 1453, 1373, 1348, 1208, 1156, 1100, 1072, 1028, 920, 787, 759, 699 cm^{-1}.

$C_{24}H_{25}NO_2$	calc.	C 80.19	H 7.01	N 3.90
(359.5)	found	C 80.24	H 6.93	N 3.88

(2*R*,3*S*,4*S*)-1-Benzyl-3-(benzyloxy)-4-hydroxy-2-vinylpyrrolidine (8g) by Appel Cyclization

According to lit.[28b] to a solution of the aminotriol **6g** (500 mg, 1.53 mmol) in anhyd DMF (5.3 ml) under N_2 in the dark was added PPh_3 (797 mg, 3.05 mmol), CCl_4 (294 µl, 3.05 mmol), and Et_3N (413 µl, 3.00 mmol). The mixture was stirred in the dark for 5 h at r. t., then MeOH (5 mL) was added and stirring continued for 30 min. The solvents were removed (20 mbar, 40 °C) and the brown residue was purified by flash chromatography (silica gel, 20 g, column 2 cm × 12 cm, petroleum ether/Et_2O 3:7) to give **8g** as an analytically pure, pale yellow oil; yield 300 mg (63%); $[\alpha]_D^{20}$ –42 (*c* = 0.50, $CHCl_3$).

IR (film): ν = 3405 (OH), 3063, 3029, 2978, 2919, 2796, 1743, 1640, 1604, 1586, 1495, 1453, 1423, 1370, 1349, 1314, 1209, 1111, 1071, 1029, 995, 924, 852, 774, 735, 697 cm^{-1}.

$C_{20}H_{23}NO_2$	calc.	C 77.64	H 7.49	N 4.53
(309.4)	found	C 77.75	H 7.52	N 4.31

(2*R*,3*S*,4*S*)-1,2-Dibenzyl-3-(benzyloxy)-4-hydroxypyrrolidine (8i)

According to Typical Procedure B; aminotriol **6i** (1.05 g, 2.68 mmol), PPh_3 (835 mg, 3.17 mmol), DEAD (499 µL, 364 mg, 3.17 mmol), pyridine (15.6 mL), 90 min at 0 °C. After workup treatment of the residue with dioxane/H_2O (1:1, 30 mL), LiOH monohydrate (1.10 g, 31.7 mmol), 17 h at 80 °C. Yellowish crude product, purified by flash chromatography (silica gel, 20 g, column 3 cm × 7 cm, petroleum ether/Et_2O 3:7) and crystallization from heptane/Et_2O; **8i**, analytically pure, colourless needles; yield 792 mg (79%); mp 97–98 °C; $[\alpha]_D^{20}$ –72.7 (*c* = 1.30, $CHCl_3$).

IR (KBr): ν = 3190 (OH), 3043, 3015, 2825, 2801, 1487, 1443, 1430, 1398, 1342, 1331, 1208, 1187, 1169, 1094, 1059, 1048, 1014, 1002, 903, 889, 836, 748, 720, 692, 679, 613 cm^{-1}.

$C_{25}H_{27}NO_2$	calc.	C 80.40	H 7.29	N 3.75
(373.5)	found	C 80.33	H 7.35	N 3.76

Table 5 ^{1}H NMR Data of Compounds **8** and **9** Prepared[a]

Compound	Chemical Shifts, δ						
	2-H	3-H	4-H	5-H_A	5-H_B	1'-H	Others
8a	2.75	3.65	4.06	2.01	3.03	1.15	3.07, 3.78 (NCH_2Ph), 4.37, 4.51 (OCH_2Ph), 7.08–7.23, 7.30–7.34 (2 C_6H_5)
8b	2.63	3.69	4.04	1.96	3.19	1.53, 1.92	0.93 (4'-H), 1.20–1.46 (2'-H, 3'-H), 3.08, 3.97 (NCH_2Ph), 4.34, 4.56 (OCH_2Ph), 7.06–7.23, 7.32–7.37 (2 C_6H_5)
8c	2.74	3.76	3.96	2.21	3.13	–	1.20 [C(CH_3)$_3$], 3.65, 4.06 (NCH_2Ph), 4.34, 4.39 (OCH_2Ph), 7.08–7.34, 7.43–7.46 (2 C_6H_5)
8d	2.78	3.67	4.01	1.89	3.16	0.87, 1.42	0.06 [Si(CH_3)$_3$], 2.97, 4.01 (NCH_2Ph), 4.34, 4.95 (OCH_2Ph), 7.08–7.24, 7.34–7.37 (2 C_6H_5)
8e	3.66–3.71		4.16	2.03	3.30	–	2.95, 3.82 (NCH_2Ph), 3.93, 4.08 (OCH_2Ph), 6.94–7.26, 7.56–7.59 (3 C_6H_5)
8g	3.16	3.80	4.17	2.08	3.15	6.19	3.09, 3.96 (NCH_2Ph), 4.45, 4.50 (OCH_2Ph), 5.17 (2'-H_E), 5.18 (2'-H_Z), 7.11–7.25, 7.31–7.38 (2 C_6H_5)
8i	3.10	3.54	3.99	2.08	3.26	2.91, 3.29	3.18, 3.95 (NCH_2Ph), 4.25, 4.41 (OCH_2Ph), 7.10–7.38 (3 C_6H_5)
8k	3.10	3.59	4.01	2.10	3.29	2.91, 3.28	3.22, 4.00 (NCH_2Ph), 3.38 (OCH_3), 4.30, 4.46 (OCH_2Ph), 6.83–6.87, 7.12–7.40 (C_6H_4, 2 C_6H_5)
9b	3.69	4.07	4.28	3.15	3.58	1.76–1.92	1.02 (4'-H), 1.32–1.54 (2'-H, 3'-H)
9c	3.43	4.23	4.25	3.20	3.69	–	1.22 [C(CH_3)$_3$]
9d	3.85	3.98	4.29	3.10	3.58	1.02, 1.36	0.17 [Si(CH_3)$_3$]
9i	3.96	4.03	4.30	3.14	3.67	3.06, 3.27	7.32–7.42 (C_6H_5)
9k	3.91	4.02	4.30	3.14	3.66	3.00, 3.20	3.82 (OCH_3), 6.95, 7.32 (C_6H_4)

	Coupling Constants *J* (Hz)						
	$J_{2,3}$	$J_{3,4}$	$J_{4,5A}$	$J_{4,5B}$	$J_{5A,5B}$	$J_{2,1'}$	Others
8a	6.8	3.6	6.3	6.8	9.6	6.5	J_{NCH_2Ph} = 13.0, J_{OCH_2Ph} = 12.2
8b	6.3	2.8	6.1	6.4	9.9	9.4, 3.6	$J_{3',4'}$ = 6.8, J_{NCH_2Ph} = 13.1, J_{OCH_2Ph} = 12.0
8c	6.9	4.3	4.4	4.8	11.1	–	$J_{3,5A}$ = 0.9, J_{NCH_2Ph} = 13.9, J_{OCH_2Ph} = 11.9
8d	6.3	2.2	6.3	6.7	9.8	2.7, 11.5	$J_{1'A,1'B}$ = 14.2, J_{NCH_2Ph} = 13.0, J_{OCH_2Ph} = 11.9
8e	–[b]	1.7	6.5	6.5	9.7	–	J_{NCH_2Ph} = 13.1, J_{OCH_2Ph} = 11.9
8g	6.6	3.5	6.4	6.6	9.6	8.9	$J_{1',2'E}$ = 16.1, $J_{1',2'Z}$ = 11.3, $J_{2'E,2'Z}$ = 2.0, J_{NCH_2Ph} = 13.2, J_{OCH_2Ph} = 12.2
8i	5.8	2.7	5.3	6.1	10.2	4.6, 9.0	$J_{1'A,1'B}$ = 13.1, J_{NCH_2Ph} = 13.2, J_{OCH_2Ph} = 11.9
8k	5.8	2.6	5.3	6.1	10.2	4.7, 9.0	$J_{1'A,1'B}$ = 13.2, J_{NCH_2Ph} = 12.9, J_{OCH_2Ph} = 11.9
9b	2.9	1.6	0	4.3	12.4	7.5, 7.5	$J_{3',4'}$ = 7.0
9c	2.5	1.6	0	4.2	12.3	–	–
9d	2.9	1.5	0	4.5	12.4	4.4, 11.7	$J_{1'A,1'B}$ = 13.7
9i	2.8	1.7	0	4.4	12.5	8.2, 7.0	$J_{1'A,1'B}$ = 13.9
9k	2.8	1.5	0	4.4	12.4	8.2, 7.1	$J_{1'A,1'B}$ = 14.0, $J_{3',4'}$ = 8.6 (*o*-, *m*-H of C_6H_4)

[a] Recorded at 250.1 MHz. (**8a–e**, **8i** in C_6D_6 and **9c**, **9i**, **9k** in CD_3OD) or at 300.1 MHz (**8g**, **8k** in C_6D_6 and **9b**, **9d** in CD_3OD).
[b] *J* not resolved.

(2*R*,3*S*,4*S*)-1-Benzyl-3-(benzyloxy)-4-hydroxy-2-(4-methoxybenzyl)pyrrolidine (8k)

According to the Typical Procedure B; aminotriol **6k** (400 mg, 0.952 mmol), PPh_3 (295 mg, 1.12 mmol), DEAD (175 µL, 128 mg, 1.12 mmol), pyridine (5.5 mL), 90 min at 0 °C. After workup treatment of the residue with dioxane/H_2O (1:1, 20 mL), LiOH•H_2O (423 mg, 9.52 mmol), 18 h at 80 °C as above. Flash chromatography (silica gel, 16 g, column 2 cm × 10 cm, petroleum ether/Et_2O 3:7) furnished a colourless solid; after crystallization from hexane/Et_2O **8k**, analytically pure, colourless needles; yield 293 mg (77%); mp 84–85 °C; $[\alpha]_D^{20}$ –84.9 (*c* = 1.16, $CHCl_3$)

IR (KBr): ν = 3195 (OH), 3009, 2915, 2818, 1606, 1503, 1453, 1441, 1432, 1391, 1380, 1290, 1237, 1199, 1162, 1092, 1074, 1045, 1017, 902, 838, 803, 777, 740, 709, 686, 674 cm^{-1}.

$C_{26}H_{29}NO_3$	calc.	C 77.39	H 7.24	N 3.47
(403.5)	found	C 77.42	H 7.17	N 3.70

(2*R*,3*S*,4*S*)-2-Butyl-3,4-dihydroxypyrrolidine Hydrochloride (9b•HCl)

The dihydroxypyrrolidine hydrochloride **9b•** HCl was prepared by hydrogenation of **8b** (220 mg, 0.648 mmol) with concd HCl (0.5 mL) on 10% Pd/C (50 mg) under H_2 (4 bar) in MeOH (5 mL) at r. t. for 3 d. The mixture was passed through a column filled with Celite and the solvents were removed in vacuo (20 mbar). Crystallization of the resulting material from MeOH/EtOAc afforded **9b•**HCl as a colourless solid; yield 119 mg (95%); mp 155–158 °C; $[\alpha]_D^{20}$ –5.5 (*c* = 0.53, MeOH).

IR (KBr): ν = 3395 (OH, NH), 2980, 2840, 1595, 1460, 1453, 1445, 1413, 1368, 1349, 1300, 1269, 1239, 1208, 1190, 1123, 1070, 1017, 951, 920, 808, 778, 741, 712, 677 cm^{-1}.

$C_8H_{18}ClNO_2$	calc.	C 49.10	H 9.27	N 7.16
(195.7)	found	C 49.22	H 9.33	N 7.15

(2*R*,3*S*,4*S*)-2-*tert*-Butyl-3,4-dihydroxypyrrolidine Hydrobromide (9c•HBr)

The hydrobromide **9c•**HBr was prepared by hydrogenation of **8c** (250 mg, 0.736 mmol) on 20% $Pd(OH)_2$/C (120 mg) under H_2 (4 bar) in MeOH (5 mL) at r. t. After 2 d, concd HBr (1 mL) was added and the hydrogenation continued for 3 d. The mixture was then passed through a column filled with Celite and the solvents were removed in vacuo (40 °C/20 mbar). Crystallization of the remainders from MeOH/EtOAc afforded **9c•**HBr, colourless solid; yield 170 mg (96%); mp 232–233 °C; $[\alpha]_D^{21}$ –28 (*c* = 0.50, MeOH).

IR (KBr): ν = 3410 (OH, NH), 3085, 2950, 2858, 2662, 2505, 2492, 2207, 1574, 1471, 1442, 1397, 1368, 1336, 1285, 1238, 1193, 1102, 1081, 1028, 1011, 970, 953, 919, 889, 686 cm^{-1}.

$C_8H_{18}BrNO_2$	calc.	C 40.01	H 7.56	N 5.83
(240.1)	found	C 39.98	H 7.49	N 5.62

Table 6 ^{13}C NMR Chemical Shifts, δ of Compounds **8** and **9**[a]

Compound	C-2	C-3	C-4	C-5	C-1'	Others
8a	61.3	87.4	75.7	59.5	12.6	58.2 (NCH_2Ph), 71.7 (OCH_2Ph), 127.1, 127.6, 127.7, 128.3, 128.5, 129.1, 139.4, 139.7 (2 C_6H_5)
8b	67.1	86.2	75.2	60.5	29.2	14.4 (C-4'), 23.6 (C-3'), 27.8 (C-2'), 59.3 (NCH_2Ph), 71.6 (OCH_2Ph), 127.1, 127.6, 127.9, 128.3, 128.5, 129.0, 139.2, 140.0 (2 C_6H_5)
8c	73.6	88.1	75.1	64.5	35.9	28.6 [$C(CH_3)_3$], 58.7 (NCH_2Ph), 73.0 (OCH_2Ph), 126.9, 127.6, 128.0, 128.3, 128.4, 128.6, 139.1, 141.3 (2 C_6H_5)
8d	64.6	87.2	75.2	60.4	14.5	-0.5 [$Si(CH_3)_3$], 58.4 (NCH_2Ph), 70.8 (OCH_2Ph), 127.1, 127.6, 127.7, 128.3, 128.5, 129.2, 139.2, 139.7 (2 C_6H_5)
8e	72.1	88.0	76.3	59.1	–	58.5 (NCH_2Ph), 72.2 (OCH_2Ph), 127.1, 127.5, 127.6, 127.7, 128.2, 128.3, 128.4, 129.1, 130.2, 138.6, 138.9, 139.3 (3 C_6H_5)
8g	70.5	88.0	75.9	59.0	136.6	57.9 (NCH_2Ph), 71.9 (OCH_2Ph), 118.4 (C-2'), 127.1, 127.6, 127.7, 128.3, 128.5, 129.1, 139.2, 139.6 (2 C_6H_5)
8i	68.1	85.4	74.0	59.8	34.3	59.2 (NCH_2Ph), 71.3 (OCH_2Ph), 125.6, 126.7, 127.2, 127.4, 127.8, 128.0, 128.1, 128.7, 129.3, 138.6, 139.3, 140.3 (3 C_6H_5)
8k	68.9	86.0	74.6	60.5	33.9	54.7 (OCH_3), 59.7 (NCH_2Ph), 71.7 (OCH_2Ph), 127.1, 127.7, 127.8, 128.3, 128.5, 129.1, 139.2, 140.0 (2 C_6H_5), 114.0, 130.6, 132.6, 158.5 (C_6H_4)
9b	64.0	76.4[b]	76.2[b]	52.5	30.2	14.5 (C-4'), 23.9 (C-3'), 27.0 (C-2')
9c	71.1	77.0	75.9	52.9	33.0	28.5 [$C(CH_3)_3$]
9d	60.3	75.2[b]	75.1[b]	50.8	13.5	–2.4 [$Si(CH_3)_3$]
9i	65.3	76.1[b]	75.8[b]	52.8	33.1	128.4, 130.2, 130.3, 138.3 (C_6H_5)
9k	65.5	76.0[b]	75.9[b]	52.7	32.3	56.0 (OCH_3), 115.5, 130.1, 131.4, 160.4 (C_6H_4)

[a] Recorded at 62.9 MHz (**8a–e**, **8i** in C_6D_6, **9b**, **9d**, **9i** in CD_3OD) or at 75.5 MHz (**8g**, **8k** in C_6D_6, **9c**, **9k** in CD_3OD).
[b] Tentative assignments, eventually to be reversed.

(2*S*,3*S*,4*S*)-3,4-Dihydroxy-2-(trimethylsilymethyl)pyrrolidine Hydrochloride (9d•HCl)

The dihydroxypyrrolidine hydrochloride **9d**•HCl was prepared as described for **9b**•HCl: from **8d** (172 mg, 0.466 mmol) with concd HCl (0.5 mL), 10% Pd/C (50 mg), H_2 (4 bar), MeOH (5 mL), r. t., 5 d. Workup as above, then crystallization of the residue from MeOH/CH_2Cl_2 afforded **9d**•HCl as a colourless solid; yield 103 mg (98%); mp 221–224 °C (dec); $[\alpha]_D^{20}$ –25 (*c* = 0.30, MeOH).

IR (KBr): ν = 3379 (OH, NH), 2985, 2542, 2470, 1590, 1416, 1356, 1308, 1242, 1200, 1181, 1149, 1108, 1071, 1038, 1021, 962, 923, 891, 837, 749, 737, 701, 689, 633 cm^{-1}.

$C_8H_{20}ClNO_2Si$	calc.	C 42.56	H 8.93	N 6.20
(225.8)	found	C 42.22	H 8.73	N 5.99

(2*R*,3*S*,4*S*)-2-Benzyl-3,4-dihydroxypyrrolidine Hydrobromide (9i•HBr)

The hydrobromide **9i**•HBr was prepared as described for **9c**•HBr: **8i** (150 mg, 0.402 mmol), 20% $Pd(OH)_2/C$ (100 mg), H_2 (4 bar), MeOH (4 mL), r. t., 4 d. Then concd HBr (1 mL) was added and hydrogenation continued for 1 d. Workup as above, then crystallization of the residue from MeOH/Et_2O; **9i**•HBr, colourless solid; yield 105 mg (95%); mp 202–203 °C; $[\alpha]_D^{20}$ +6.7 (*c* = 0.56, MeOH).

IR (KBr): ν = 3238 (OH, NH), 2928, 2901, 2510, 1572, 1488, 1425, 1386, 1352, 1292, 1262, 1194, 1082, 1009, 951, 906, 891, 758, 730, 687 cm^{-1}.

$C_{11}H_{16}BrNO_2$	calc.	C 48.19	H 5.88	N 5.11
(274.2)	found	C 48.06	H 5.88	N 5.08

(2*R*,3*S*,4*S*)-3,4-Dihydroxy-2-(4-methoxybenzyl)pyrrolidine Hydrobromide [(+)-Deacetylanisomycin Hydrobromide] (9k•HBr)

The dihydroxypyrrolidine hydrobromide **9k**•HBr was prepared as described for **9c**•HBr: **8k** (200 mg, 0.496 mmol), 20% $Pd(OH)_2/C$ (100 mg), H_2 (4 bar), MeOH (5 mL), r. t., 2 d. Then concd HBr (1 mL) was added and hydrogenation continued for 3 d. Workup as above, then crystallization[36] of the remainders from MeOH/Et_2O afforded **9k**•HBr as a colourless solid; yield 150 mg (99%); mp 222–224 °C (dec; for hydrochloride: ref.[7c] 227–229 °C, ref.[29] 224–226 °C); $[\alpha]_D^{20}$ +7.2 (*c* = 1.00, MeOH) {for hydrochloride: ref.[7c] $[\alpha]_D^{20}$ +6 (*c* = 0.7, MeOH)}.

IR (KBr): ν = 3410 (OH, NH), 2948, 1605, 1578, 1503, 1431, 1391, 1370, 1296, 1283, 1236, 1169, 1089, 1073, 1020, 953, 890, 830, 818, 802, 789, 743 cm^{-1}.

$C_{12}H_{18}BrNO_3$	calc.	C 47.38	H 5.96	N 4.60
(304.2)	found	C 47.65	H 6.10	N 4.43

(2*R*,3*S*,4*S*)-1,2-Dibenzyl-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)pyrrolidine (10)

To a solution of **8i** (750 mg, 2.01 mmol) and imidazole (274 mg, 4.01 mmol) in DMF (10 mL) under N_2 was added TBSCl (453 mg, 3.02 mmol) at 0 °C. The mixture was stirred for 20 h at 50 °C, then quenched with H_2O (10 mL) and extracted with Et_2O (4 × 30 mL). The organic layers were combined and dried (Na_2SO_4). The filtrate was concentrated (40 °C, 20 mbar) to afford a yellow oil, which was purified by flash chromatography on silica gel (20 g, column 3 cm × 6 cm, petroleum ether/EtOAc 5:1); yield 918 mg (94%); colourless oil; $[\alpha]_D^{20}$ –48.2 (*c* = 1.30, $CHCl_3$).

IR (film): ν = 3063, 3029, 2955, 2928, 2857, 2798, 1603, 1495, 1471, 1454, 1361, 1342, 1256, 1125, 1091, 1074, 1029, 1007, 982, 915, 837, 777, 734, 698 cm^{-1}.

$C_{31}H_{41}NO_2Si$	calc.	C 76.34	H 8.47	N 2.87
(487.8)	found	C 76.47	H 8.62	N 2.87

(2*R*,3*S*,4*S*)-1-Benzyl-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzyl)pyrrolidine (11)

As described for **10**, a mixture of **8k** (370 mg, 0.917 mmol), imidazole (125 mg, 1.83 mmol), and TBSCl (207 mg, 1.38 mmol) in DMF (5 mL) under N_2 was stirred for 17 h at 50 °C. After workup as above the yellowish crude product was purified by flash chromatography on silica (10 g, column 2 cm × 5 cm, petroleum ether/EtOAc 5:1); yield 465 mg (98%); colourless oil; $[\alpha]_D^{20}$ –50.6 (*c* = 1.10, $CHCl_3$).

IR (film): ν = 3062, 3029, 2953, 2928, 2856, 2797, 1612, 1512, 1496, 1463, 1454, 1300, 1247, 1177, 1126, 1080, 1039, 1007, 982, 914, 836, 777, 736, 699 cm^{-1}.

$C_{32}H_{43}NO_3Si$	calc.	C 74.23	H 8.37	N 2.71
(517.8)	found	C 74.12	H 8.35	N 2.64

(2*R*,3*S*,4*S*)-2-Benzyl-1-(*tert*-butoxycarbonyl)-4--(*tert*-butyldimethylsilyloxy)-3-hydroxypyrrolidine (12)

A solution of **10** (270 mg, 0.554 mmol) and $(Boc)_2O$ (181 mg, 0.830 mmol) in dioxane (5 mL) was hydrogenated on 10% $Pd(OH)_2/C$ (150 mg) under H_2 (4 bar) at r. t. for 6 d. Concd HOAc (0.5 mL) was added and hydrogenation was continued for 1 d. The mixture was then passed through a column filled with Celite, and the solvents were removed in vacuo (40 °C/ 20 mbar). The yellowish crude product was purified by flash chromatography (silica gel, 12 g, column 2 cm × 6 cm, petroleum ether/EtOAc 5:1) to furnish **12** as an analytically pure, colourless solid; yield 205 mg (91%); mp 89–91 °C; $[\alpha]_D^{20}$ + 8.8 (*c* = 0.48, $CHCl_3$).

IR (film): ν = 3425 (OH), 3029, 2928, 2855, 1655 (C=O), 1495, 1454, 1404, 1366, 1252, 1210, 1164, 1127, 1090, 1042, 1001, 919, 834, 776, 736, 700 cm^{-1}.

$C_{22}H_{37}NO_4Si$	calc.	C 64.82	H 9.15	N 3.44
(407.6)	found	C 64.97	H 9.09	N 3.38

(2*R*,3*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)-3-hydroxy-2-(4-methoxybenzylpyrrolidine (13)

As described for **12** a mixture of **11** (310 mg, 0.599 mmol) and $(Boc)_2O$ (198 mg, 0.899 mmol) in dioxane (6 mL) was hydrogenated on 10% $Pd(OH)_2/C$ (150 mg) under H_2 (4 bar) at r. t. for 3 d. Concd HOAc (0.5 mL) was added and hydrogenation was continued for 1 d. After workup as above the yellowish crude product was purified by flash chromatography (silica gel, 12 g, column 2 cm × 6 cm, petroleum ether/EtOAc 5:1) to furnish **13** as an analytically pure, colourless oil; yield 228 mg (87%); $[\alpha]_D^{20}$ +7.1 (*c* = 0.48, $CHCl_3$).

IR (film): ν = 3427 (OH), 2930, 2857, 1695, 1667 (C=O), 1613, 1584, 1513, 1463, 1410, 1366, 1300, 1248, 1174, 1124, 1040, 1002, 949, 914, 834, 776 cm^{-1}.

$C_{23}H_{39}NO_5Si$	calc.	C 63.12	H 8.98	N 3.20
(437.7)	found	C 62.93	H 8.78	N 3.12

Table 7 ^{1}H NMR Data of Compounds **1** and **10–23** Prepared[a]

Compound	Chemical Shifts, δ							
	2-H	3-H	4-H	5-H_A	5-H_B	1'-H_A	1'-H_B	Others
1	4.21	5.10	4.40	3.24	3.65	3.02	3.13	2.23 ($COCH_3$), 3.82 (OCH_3), 6.96, 7.28 (C_6H_4)
10	3.15	3.60	4.17	2.24	3.25	2.85	3.04	–0.03, –0.01 [$Si(CH_3)_2$], 0.84 [$SiC(CH_3)_3$], 3.42, 3.92 (NCH_2Ph), 4.38, 4.56 (OCH_2Ph), 7.16–7.34 (3 C_6H_5)
11	3.09	3.58	4.16	2.23	3.24	2.78	2.97	–0.03, –0.01 [$Si(CH_3)_2$], 0.84 [$SiC(CH_3)_3$], 3.42, 3.93 (NCH_2Ph), 3.78 (OCH_3), 4.39, 4.57 (OCH_2Ph), 6.77, 7.11, 7.23–7.35 (C_6H_4, 2 C_6H_5)
12	4.22	3.68–3.74		3.46–3.51		3.04	3.30	–0.06, –0.05 [$Si(CH_3)_2$], 0.85 [$SiC(CH_3)_3$], 1.48 [$OC(CH_3)_3$], 7.01–7.13, 7.30–7.33 (C_6H_5)
13	4.26	3.79	3.83	3.49	3.55	3.08	3.33	0.01 [$Si(CH_3)_2$], 0.91 [$SiC(CH_3)_3$], 1.54 [$OC(CH_3)_3$], 3.44 (OCH_3), 6.82, 7.30 (C_6H_4)
14	4.57	5.02	3.96	3.42	3.49	2.94	3.26	–0.03, –0.02 [$Si(CH_3)_2$], 0.84 [$SiC(CH_3)_3$], 1.47 [$OC(CH_3)_3$], 1.67 ($COCH_3$), 7.01–7.22 (C_6H_5)
15	4.55	5.04	3.96	3.43	3.49	2.95	3.22	–0.03, –0.02 [$Si(CH_3)_2$], 0.85 [$SiC(CH_3)_3$], 1.48 [$OC(CH_3)_3$], 1.71 ($COCH_3$), 3.36 (OCH_3), 6.75, 7.14 (C_6H_4)
16	4.69	5.29	4.08	3.51	3.64	3.10	3.45	–0.03, 0.01 [$Si(CH_3)_2$], 0.84 [$SiC(CH_3)_3$], 1.50 [$OC(CH_3)_3$], 6.93–7.23, 8.08–8.12 (2 C_6H_5)
17	4.68	5.32	4.10	3.52	3.65	3.09	3.42	0.01, 0.02 [$Si(CH_3)_2$], 0.85 [$SiC(CH_3)_3$], 1.51 [$OC(CH_3)_3$], 3.29 (OCH_3), 6.63–6.67, 6.98–7.21, 7.96, 8.10–8.14 (C_6H_4, C_6H_5)
18	4.17	5.03	4.31	3.16	3.56	2.99	3.11	2.14 ($COCH_3$), 7.25–7.36 (C_6H_5)
19	4.30	5.25	4.44	3.25	3.67	3.09	3.22	7.20–7.32, 7.50–7.55, 7.65, 8.11–8.14 (2 C_6H_5)
20	4.19	5.18	4.36	3.19	3.61	2.99	3.08	3.64 (OCH_3), 6.76, 7.09, 7.45, 7.58, 8.07 (C_6H_4, C_6H_5)
21	4.13	3.20	3.56	3.31	3.41–3.48	2.96	3.41–3.48	1.47 [$OC(CH_3)_3$], 3.40 (OCH_3), 6.78, 7.21 (C_6H_4)
22	4.58	5.34	5.14	3.52	3.68	2.91	3.11	1.47 [$OC(CH_3)_3$], 1.58, 1.67 ($COCH_3$), 3.41 (OCH_3), 6.81, 7.31 (C_6H_4)
23	4.01	5.08	5.10	3.33	3.79	3.11	3.21	2.06, 2.22 ($COCH_3$), 3.72 (OCH_3), 6.81, 7.13 (C_6H_4)
	Coupling Constants *J* (Hz)							
	$J_{2,3}$	$J_{3,4}$	$J_{4,5A}$	$J_{4,5B}$	$J_{5A,5B}$	$J_{2,1'A}$	$J_{2,1'B}$	Others
1	3.4	0	0	4.5	12.7	8.7	6.9	$J_{1'A,1'B}$ = 14.2, $J_{3',4'}$ = 8.5 (*o*-, *m*-H of C_6H_4)
10	5.5	2.6	4.6	5.5	10.4	5.1	8.8	$J_{1'A,1'B}$ = 13.3, J_{NCH_2Ph} = 13.2, J_{OCH_2Ph} = 11.8
11	5.5	2.4	4.5	5.5	10.4	5.1	8.9	$J_{1'A,1'B}$ = 13.6, J_{NCH_2Ph} = 13.2, J_{OCH_2Ph} = 11.8, $J_{3',4'}$ = 8.5 (*o*-, *m*-H of C_6H_4)
12	5.1	–[b]	–[b]	–[b]	–[b]	8.9	4.0	$J_{1'A,1'B}$ = 13.4
13	5.7	4.3	6.5	4.9	11.2	8.8	4.0	$J_{1'A,1'B}$ = 13.5, $J_{3',4'}$ = 8.6 (*o*-, *m*-H of C_6H_4)
14	6.2	5.1	5.4	4.7	11.3	9.1	4.1	$J_{1'A,1'B}$ = 13.6
15	6.4	5.0	5.4	3.9	11.2	8.9	4.0	$J_{1'A,1'B}$ = 13.7, $J_{3',4'}$ = 8.6 (*o*-, *m*-H of C_6H_4)
16	5.7	4.2	4.7	3.4	11.5	9.3	4.2	$J_{1'A,1'B}$ = 13.4
17	5.6	4.2	4.7	3.5	11.5	9.4	4.0	$J_{1'A,1'B}$ = 13.5
18	3.4	1.3	1.0	4.5	12.7	8.8	6.7	$J_{3,5a}$ = 0.9, $J_{1'A,1'B}$ = 14.2
19	3.4	1.4	0.8	4.4	12.8	8.5	7.1	$J_{3,5a}$ = 0.8, $J_{1'A,1'B}$ = 14.0

Table 7 (continued)

	Coupling Constants *J* (Hz)							
	$J_{2,3}$	$J_{3,4}$	$J_{4,5A}$	$J_{4,5B}$	$J_{5A,5B}$	$J_{2,1'A}$	$J_{2,1'B}$	Others
20	3.5	1.7	0	4.2	12.9	8.5	7.2	$J_{1'A,1'B}$ = 14.1, $J_{3',4'}$ = 8.3 (*o*-, *m*-H of C_6H_4)
21	5.9	4.2	3.6	6.1	11.2	9.0	4.1	$J_{1'A,1'B}$ = 13.5, $J_{3',4'}$ = 8.6 (*o*-, *m*-H of C_6H_4)
22	6.8	5.8	4.2	6.5	12.2	8.2	4.3	$J_{1'A,1'B}$ = 13.9, $J_{3',4'}$ = 8.6 (*o*-, *m*-H of C_6H_4)
23	4.5	1.2	0	4.7	13.4	9.0	6.3	$J_{1'A,1'B}$ = 14.1, $J_{3',4'}$ = 8.5 (*o*-, *m*-H of C_6H_4)

[a] Recorded at 300.1 MHz (**10**, **23** in $CDCl_3$, **1**, **18**, **19** in CD_3OD, and **12–17**, **21**, **22** in C_6D_6 at 343 K) or at 500.1 MHz (**11** in $CDCl_3$ and **20** in CD_3OD).
[b] *J* not resolved.

(2*R*,3*S*,4*S*)-3-Acetoxy-2-benzyl-1-(*tert*-butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)pyrrolidine (14)
To a solution of **12** (200 mg, 0.491 mmol) in anhyd pyridine (4 mL) under N_2 was slowly added Ac_2O (92.6 µL, 0.981 mmol) and DMAP (10 mg) at 0 °C. After stirring the mixture at r. t. for 3 h, the solvent was removed in vacuo (40 °C, 20 mbar). The residue was purified by flash chromatography (silica gel, 12 g, column 2 cm × 6 cm, petroleum ether/EtOAc 5:1) to give **14** as an analytically pure, colourless oil; yield 215 mg (97%); $[\alpha]_D^{20}$ +23.5 (*c* = 1.01, $CHCl_3$).

IR (film): ν = 2955, 2931, 2887, 2858, 1748 (C=O), 1697 (C=O), 1497, 1473, 1455, 1393, 1367, 1332, 1251, 1232, 1167, 1123, 1076, 1042, 955, 937, 918, 837, 778, 670 cm^{-1}.

$C_{24}H_{39}NO_5Si$	calc.	C 64.11	H 8.74	N 3.12
(449.7)	found	C 63.87	H 8.70	N 3.10

(2*R*,3*S*,4*S*)-3-Acetoxy-1-(*tert*-butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzyl)pyrrolidine (15)
As described for the preparation of **14**, a solution of **13** (100 mg, 0.229 mmol), Ac_2O (43.2 µL, 0.458 mmol), and DMAP (10 mg) in anhyd pyridine (2 mL) under N_2 was stirred for 3 h at r. t. After workup as above and purification by flash chromatography (silica gel, 10 g, column 2 cm × 5 cm, petroleum ether/EtOAc 5:1) a colourless oil was isolated; yield 103 mg (94%); $[\alpha]_D^{20}$ +21 (*c* = 0.67, $CHCl_3$).

IR (film): ν = 2955, 2932, 2858, 1747 (C=O), 1696 (C=O), 1613, 1513, 1464, 1393, 1367, 1300, 1249, 1176, 1124, 1067, 1042, 956, 917, 836, 778 cm^{-1}.

$C_{25}H_{41}NO_6Si$	calc.	C 62.60	H 8.61	N 2.92
(479.7)	found	C 62.77	H 8.66	N 2.90

(2*R*,3*S*,4*S*)-3-Benzoyloxy-2-benzyl-1-(*tert*-butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)pyrrolidine (16)
To a solution of **12** (160 mg, 0.393 mmol) in anhyd pyridine (4 mL) under N_2 was slowly added PhCOCl (182 µL, 1.57 mmol) and DMAP (10 mg) at 0 °C. After stirring the mixture at r. t. for 23 h, the solvent was removed in vacuo (40 °C, 20 mbar). The residue was purified by flash chromatography (silica gel, 18 g, column 2 cm × 12 cm, petroleum ether/EtOAc 10:1) to give **16** as an analytically pure, colourless oil; yield 195 mg (97%); $[\alpha]_D^{20}$ –7.87 (*c* = 1.22, $CHCl_3$).

IR (film): ν = 3087, 3030, 2954, 2930, 2886, 2857, 1726 (C=O), 1696 (C=O), 1602, 1495, 1472, 1453, 1391, 1366, 1333, 1317, 1266, 1166, 1108, 1071, 1028, 918, 835, 778, 711 cm^{-1}.

$C_{29}H_{41}NO_5Si$	calc.	C 68.07	H 8.08	N 2.74
(511.7)	found	C 67.89	H 7.98	N 2.72

(2*R*,3*S*,4*S*)-3-*O*-Benzoyloxy-1-(*tert*-butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzyl)pyrrolidine (17)
As described for **16**, a solution of **13** (80.0 mg, 0.183 mmol), PhCOCl (92.4 µL, 0.734 mmol), and DMAP (10 mg) in anhyd pyridine (2 mL) under N_2 was stirred for 21 h at r. t. After workup as above and purification by flash chromatography (silica, 10 g, column 2 cm × 5 cm, petroleum ether/EtOAc 6:1) a slightly impure (NMR: ca. 5% pyridinium benzoate) colourless oil was isolated; yield 92.0 mg (93%); $[\alpha]_D^{20}$ –8.1 (*c* = 0.56, $CHCl_3$).

IR (film): ν = 2954, 2930, 2856, 1792, 1724 (C=O), 1697 (C=O), 1612, 1512, 1452, 1391, 1366, 1268, 1250, 1212, 1173, 1109, 1070, 1035, 834, 778, 710 cm^{-1}.

$C_{30}H_{43}NO_6Si$	calc.	C 66.51	H 8.00	N 2.59
(541.8)	found	C 67.26	H 7.81	N 2.46

(2*R*,3*S*,4*S*)-3-Acetoxy-2-benzyl-4-hydroxypyrrolidine Hydrochloride (Demethoxyanisomycin Hydrochloride) (18•HCl); Typical Procedure C
A solution of **14** (210 mg, 0.467 mmol) in anhyd. HCl/dioxane (6 M, 5 mL) under N_2 was stirred for 3 h at 0 °C. H_2O (10 µL, 0.555 mmol) was added and stirring continued at 0 °C for 15 min. The solvent was evaporated (20 mbar, 25 °C) and the solid residue crystallized from MeOH/Et_2O; yield 124 mg (98%); colourless needles; mp 159–161 °C (subl.; ref[7b] 242 °C); $[\alpha]_D^{20}$ +7.03 (*c* = 1.02, MeOH).

IR (KBr): ν = 3275 (OH, NH), 2870, 2739, 2655, 2530, 2440, 2418, 1749 (C=O), 1386, 1489, 1448, 1398, 1365, 1320, 1210, 1075, 1061, 1019, 956, 921, 869, 760, 728, 693, 681 cm^{-1}.

$C_{13}H_{18}NO_3Cl$	calc.	C 57.46	H 6.68	N 5.15
(271.7)	found	C 57.24	H 6.63	N 5.14

(2*R*,3*S*,4*S*)-3-Acetoxy-4-hydroxy-2-(4-methoxybenzyl)pyrrolidine Hydrochloride (Anisomycin Hydrochloride) (1•HCl)
Typical Procedure C; **15** (85.0 mg, 0.177 mmol), anhyd HCl/dioxane (6 M, 2.5 mL), 3 h at 0 °C, water (4.0 µL, 0.22 mmol), 30 min at 0 °C; colourless solid, recrystallized from MeOH/ether; yield 53.0 mg of **1**. HCl (quant.); colourless needles; mp 187–188 °C (ref.[6a] 187–188 °C); $[\alpha]_D^{20}$ +4.2 (*c* = 0.51, MeOH) {ref.[6b] +3.9 (*c* = 1, MeOH), ref.[7a] $[\alpha]_D^{20}$ +3.5 (*c* = 1, MeOH)}.

Table 8 ^{13}C NMR Chemical Shifts, δ of Compounds **1** and **10–23**[a]

Compound	C-2	C-3	C-4	C-5	C-1'	Others
1	63.9	78.5	73.7	52.9	33.4	21.0 ($CO\mathit{C}H_3$), 56.0 (OCH_3), 115.7, 129.3, 131.3, 160.8 (C_6H_4), 171.1 ($\mathit{C}OCH_3$)
10	67.6	85.8	75.0	60.0	34.7	–4.9, –4.6 [$Si(CH_3)_2$], 17.8 [$Si\mathit{C}(CH_3)_3$], 25.7 [$SiC(\mathit{C}H_3)_3$], 59.7 ($N\mathit{C}H_2Ph$), 72.0 ($O\mathit{C}H_2Ph$), 125.7, 126.8, 127.5, 127.8, 128.1, 128.3, 128.9, 129.3, 138.4, 139.2, 140.4 (3 C_6H_5)
11	67.8	85.8	74.9	60.0	33.7	–4.9, –4.6 [$Si(CH_3)_2$], 17.8 [$Si\mathit{C}(CH_3)_3$], 25.7 [$SiC(\mathit{C}H_3)_3$], 55.1 (OCH_3), 59.7 ($N\mathit{C}H_2Ph$), 71.9 ($O\mathit{C}H_2Ph$), 126.8, 127.5, 127.7, 128.1, 128.2, 128.9, 138.4, 139.2 (2 C_6H_5), 113.5, 130.1, 132.3, 157.7 (C_6H_4)
12	61.6	77.4	75.4	52.4	34.5	–4.7, –4.6 [$Si(CH_3)_2$], 18.1 [$Si\mathit{C}(CH_3)_3$], 26.0 [$SiC(\mathit{C}H_3)_3$], 28.7 [$OC(\mathit{C}H_3)_3$], 79.3 [$O\mathit{C}(CH_3)_3$], 126.4, 128.6, 130.2, 140.1 (C_6H_5), 155.3 (NCO_2)
13	61.6	77.5	75.3	52.3	33.6	–4.7, –4.6 [$Si(CH_3)_2$], 18.1 [$Si\mathit{C}(CH_3)_3$], 25.9 [$SiC(\mathit{C}H_3)_3$], 28.7 [$OC(\mathit{C}H_3)_3$], 54.9 (OCH_3), 79.1 [$O\mathit{C}(CH_3)_3$], 114.5, 131.1, 130.9, 159.1 (C_6H_4), 155.2 (NCO_2)
14	59.5	78.7	72.9	52.2	35.2	–4.9, –4.7 [$Si(CH_3)_2$], 18.1 [$Si\mathit{C}(CH_3)_3$], 20.2 ($CO\mathit{C}H_3$), 25.8 [$SiC(\mathit{C}H_3)_3$], 28.6 [$OC(\mathit{C}H_3)_3$], 79.4 [$O\mathit{C}(CH_3)_3$], 126.5, 128.6, 129.8, 139.2 (C_6H_5), 155.0 (NCO_2), 168.9 ($\mathit{C}OCH_3$)
15	59.6	78.8	72.9	52.2	34.2	–4.9, –4.7 [$Si(CH_3)_2$], 18.1 [$Si\mathit{C}(CH_3)_3$], 20.3 ($CO\mathit{C}H_3$), 25.8 [$SiC(\mathit{C}H_3)_3$], 28.6 [$OC(\mathit{C}H_3)_3$], 55.0 (OCH_3), 79.4 [$O\mathit{C}(CH_3)_3$], 114.4, 130.7, 131.1, 159.1 (C_6H_4), 155.0 (NCO_2), 169.0 ($\mathit{C}OCH_3$)
16	60.5	79.3	73.1	53.1	35.1	–4.9, –4.7 [$Si(CH_3)_2$], 18.1 [$Si\mathit{C}(CH_3)_3$], 25.9 [$SiC(\mathit{C}H_3)_3$], 28.6 [$OC(\mathit{C}H_3)_3$], 79.5 [$O\mathit{C}(CH_3)_3$], 126.6, 128.6, 128.7, 129.7, 130.0, 130.7, 133.2, 139.1 (2 C_6H_5), 155.4 (NCO_2), 165.3 ($\mathit{C}OPh$)
17	60.7	79.3	73.1	53.1	34.2	–4.9, –4.6 [$Si(CH_3)_2$], 18.1 [$Si\mathit{C}(CH_3)_3$], 25.9 [$SiC(\mathit{C}H_3)_3$], 28.7 [$OC(\mathit{C}H_3)_3$], 54.9 (OCH_3), 79.5 [$O\mathit{C}(CH_3)_3$], 114.5, 128.9, 130.0, 130.6, 130.7, 131.0, 159.1 (C_6H_5, C_6H_4), 155.4 (NCO_2), 165.4 ($\mathit{C}OPh$)
18	63.5	78.3	73.4	52.6	33.0	20.8 ($CO\mathit{C}H_3$), 128.6, 130.0, 130.2, 137.3 (C_6H_5), 171.0 ($\mathit{C}OCH_3$)
19	63.8	78.8	73.6	52.8	33.2	128.6, 130.0, 130.2, 131.1, 135.1, 137.2 (2 C_6H_5), 166.2 ($\mathit{C}OPh$)
20	64.0	78.8	73.6	52.8	32.4	55.8 (OCH_3), 115.5, 128.9, 131.1, 160.6 (C_6H_4), 130.0, 130.3, 131.0, 135.2 (C_6H_5), 166.2 ($\mathit{C}OPh$)
21	61.0	76.5	73.7	50.7	33.3	28.4 [$OC(\mathit{C}H_3)_3$], 55.2 (OCH_3), 80.2 [$O\mathit{C}(CH_3)_3$], 113.7, 130.6, 130.9, 157.9 (C_6H_4), 155.3 (NCO_2)
22	59.4	75.9	74.2	49.3	34.3	20.0, 20.1 (2 $CO\mathit{C}H_3$), 28.5 [$OC(\mathit{C}H_3)_3$], 54.9 (OCH_3), 79.7 [$O\mathit{C}(CH_3)_3$], 114.5, 130.5, 130.8, 159.2 (C_6H_4), 154.3 (NCO_2), 168.9, 169.3 ($\mathit{C}OCH_3$)
23	62.5	73.8[b]	73.7[b]	48.9	31.1	20.7, 20.7 (2 $CO\underline{C}H_3$), 55.1 (OCH_3), 114.4, 126.8, 129.8, 158.9 (C_6H_4), 169.0, 169.2 (2 $\mathit{C}OCH_3$)

[a] Recorded at 75.5 MHz (**8**, **23** in $CDCl_3$; **12-17**, **22** in C_6D_6 at 343 K; **1**, **18–20** in CD_3OD) or at 125.8 MHz (**11**, **21** in $CDCl_3$).
[b] Tentative assignments, eventually to be reversed.

IR (KBr): ν = 3370 (OH, NH), 3235, 2890, 2815, 2726, 1742 (C=O), 1603, 1502, 1432, 1388, 1359, 1316, 1291, 1240, 1213, 1162, 1084, 1065, 1015, 953, 866, 818, 796, 741, 620 cm^{-1}.

$C_{14}H_{20}NO_4Cl$	calc.	C 55.72	H 6.68	N 4.64
(301.8)	found	C 55.86	H 6.74	N 4.56

(2*R*,3*S*,4*S*)-3-Benzoyloxy-2-benzyl-4-hydroxypyrrolidine Hydrochloride (19•HCl)

Preparation according to Typical Procedure C; **16** (190 mg, 0.371 mmol), anhyd HCl/dioxane (6 M, 4 mL), stirred for 3 h at 0 °C, H_2O (7.5 µL, 0.41 mmol), 20 min at 0 °C; solid residue, recrystallized from MeOH/Et_2O; yield 106 mg of **19**•HCl (94%); colourless needles; mp 150–155 °C (subl.); $[\alpha]_D^{20}$ –45 (*c* = 0.52, MeOH).

IR (KBr): ν = 3280 (OH, NH), 3039, 3005, 2930, 2900, 2840, 1723 (C=O), 1591, 1576, 1484, 1440, 1402, 1372, 1333, 1251, 1165, 1092, 1056, 1009, 960, 820, 806, 787, 730, 688 cm^{-1}.

$C_{18}H_{20}NO_3Cl$	calc.	C 64.77	H 6.04	N 4.20
(333.8)	found	C 64.38	H 6.13	N 4.09

(2*R*,3*S*,4*S*)-3-Benzoyloxy-4-hydroxy-2-(4-methoxybenzyl)pyrrolidine Hydrochloride (20•HCl)

Typical Procedure C; **17** (90.0 mg, 0.166 mmol), anhyd HCl/dioxane (6 M, 3 mL), 3 h at 0 °C, water (4.0 µL, 0.22 mmol), 30 min at 0 °C; solid residue, recrystallized from MeOH/Et_2O; yield 59.4 mg (98%); colourless needles; mp 203–204 °C; $[\alpha]_D^{20}$ –46 (*c* = 0.53, MeOH).

IR (KBr): ν = 3290 (OH, NH), 2932, 2905, 2805, 1720 (C=O), 1603, 1591, 1578, 1503, 1441, 1332, 1305, 1289, 1238, 1164, 1090, 1054, 1009, 960, 818, 790, 740, 691, 663 cm^{-1}.

$C_{19}H_{22}NO_4Cl$	calc.	C 62.72	H 6.09	N 3.85
(363.8)	found	C 62.70	H 6.15	N 3.80

(2*R*,3*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-3,4-dihydroxy-2-(4-methoxybenzyl)pyrrolidine (21)

A solution of **8k** (300 mg, 0.744 mmol) and $(Boc)_2O$ (324 mg, 1.49 mmol) in MeOH (6 mL) was hydrogenated with 10% Pd/C (150 mg)/H_2 (4 bar) at r. t. for 4 d. The mixture was passed through a column filled with Celite and the solvents were removed in vacuo (30 °C/20 mbar). The crude product was purified by flash chromatography (silica gel, 15 g, column 2 cm × 7 cm, petroleum ether/EtOAc 1:3) to furnish a colourless solid. Crystallization from MeOH/Et_2O afforded **21** as colourless needles; yield 186 mg (78%); mp 142 °C; $[\alpha]_D^{20}$ –6.80 (*c* = 1.02, MeOH).

IR (film/CH_2Cl_2): ν = 3426 (OH), 2927, 1663 (C=O), 1512, 1412, 1366, 1301, 1248, 1175, 1125, 1102, 1076, 1035, 749 cm^{-1}.

$C_{17}H_{25}NO_5$	calc.	C 63.14	H 7.79	N 4.33
(322.4)	found	C 63.21	H 7.94	N 4.32

(2*R*,3*S*,4*S*)-3,4-Diacetoxy-1-(*tert*-butoxycarbonyl)-2-(4-methoxybenzyl)pyrrolidine (22)

To a solution of the *N*-Boc-pyrrolidinediol **21** (175 mg, 0.541 mmol) in anhyd pyridine (2 mL) under N_2 was slowly added Ac_2O (2.04 mL, 21.6 mmol)/DMAP (10 mg) at 0 °C. After stirring the mixture at r. t. for 3 h, the solvents were removed in vacuo (40 °C, 20 mbar) and the residue purified by flash chromatography (silica gel, 12 g, column 2 cm × 6 cm, petroleum ether/ EtOAc 5:1) to give **22** as an analytically pure, colourless oil; yield 201 mg (91%); $[\alpha]_D^{20}$ +54 (*c* = 0.73, $CHCl_3$).

IR (film): ν = 2975, 2935, 2837, 1717 (C=O), 1694 (C=O), 1613, 1584, 1513, 1455, 1393, 1333, 1301, 1216, 1166, 1120, 1043, 960, 904, 857, 771 cm^{-1}.

$C_{21}H_{29}NO_7$	calc.	C 61.90	H 7.17	N 3.44
(407.5)	found	C 61.84	H 7.17	N 3.16

(2*R*,3*S*,4*S*)-3,4-*O*-Diacetyl-3,4-dihydroxy-2-(4-methoxybenzyl)pyrrolidine Hydrochloride (4-*O*-Acetylanisomycin Hydrochloride) (23•HCl)

A solution of **22** (125 mg, 0.307 mmol) in anhyd HCl/dioxane (6 *M*, 3 mL) under N_2 was stirred for 3 h at 0 °C, then the solvent was evaporated (20 mbar, 25 °C), affording a colourless solid which was crystallized from MeOH/Et_2O; yield 106 mg of **23**•HCl (quant.); colourless needles; mp 82–83 °C; $[\alpha]_D^{20}$ +25.1 (*c* = 1.00, MeOH).

IR (film/CH_2Cl_2): ν = 3423 (NH), 2933, 2756, 1751 (C=O), 1613, 1585, 1514, 1443, 1372, 1301, 1245, 1182, 1058, 1033, 964, 893, 820, 734 cm^{-1}.

$C_{16}H_{22}NO_5Cl$	calc.	C 55.90	H 6.45	N 4.07
(343.8)	found	C 55.93	H 6.58	N 3.80

In Vitro Cytotoxicity Tests Against Human Cancer Cells; General Procedure[37]

The cells (3.5×10^4 cells/mL) were suspended in medium 199 (KB cells) or EMEM (HBL 100 cells) containing 5% newborn calf serum together with penicillin, streptomycin, and gentamycin as antibacterial agents. The cell suspension was inoculated on 12-well Costar plates in 2 mL/well, followed by addition of serial dilutions of the sample in EtOH (from 10^{-4} mol/L to 10^{-10} mol/L). The plates were then incubated at 37 °C in a 95% air/5% CO_2 humidified incubator for 3 d. This was followed by overnight incubation in medium containing 0.002% neutral red,[38] extraction of the absorbed vital dye with sodium dodecylsulfate, and photometric determination at 540 nm. The IC_{50} was expressed as the dilution concentration causing 50% cell mortality in comparison with uninoculated control cell cultures.

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