Syntheses of Enantiomerically Pure 2-Substituted Pyrrolidin-3-ones *via* Lithiated Alkoxyallenes – An Auxiliary-Based Synthesis of both Enantiomers of the Antibiotic Anisomycin

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Dedicated to Professor *Rolf Huisgen* on the occasion of his 85th birthday

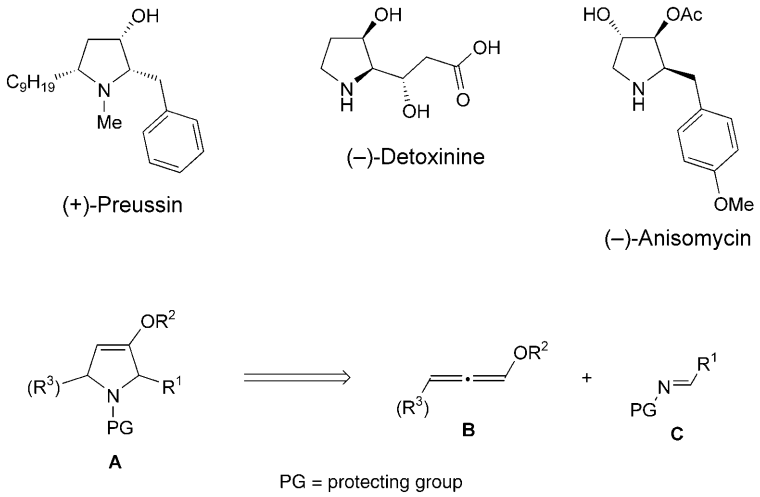
The hydrochlorides of both enantiomers of the antibiotic anisomycin were prepared starting with the 'diacetone-fructose'-substituted allene **1** and the *N*-Boc-protected imine precursor **2a**. Addition of an excess of lithiated **1** to **2a** provided a 2:1 mixture **3a** of diastereoisomers, which were cyclized to **4a** under base promotion (*Scheme 2*). The two diastereoisomers of **4a** were separated and converted into enantiomerically pure pyrrolidin-3-ones (2*R*)-**5a** and (2*S*)-**5a**. A similar sequence yielded the *N*-Tos-protected compounds (2*R*)-**5b** and (2*S*)-**5b**. Compounds **5a** were converted into silyl enol ethers **6** and by subsequent regio- and stereoselective hydroboration into pyrrolidine derivatives **7** (*Scheme 3*). Straightforward functional-group transformations led to the hydrochlorides **9** of anisomycin (*Scheme 3*). The (2*R*) series provided the hydrochloride (2*R*)-**9** of the natural occurring enantiomer, whereas the (2*S*) series furnished the antipode (2*S*)-**9**. The overall sequence to the natural product involved ten steps with eight purified intermediates and afforded an overall yield of 8%. Our stereochemically divergent approach to this type of hydroxylated pyrrolidines is highly flexible and should easily allow preparation of many analogues.

Introduction. – A variety of interesting biologically active natural products contain configurationally defined pyrrolidine substructures among which many bear 3-hydroxy substituents or related functional groups. As a consequence, their synthesis and that of analogues has attracted much attention[1]). Typical examples of these pyrrolidinol derivatives are (+)-preussin, (−)-detoxinine, and (−)-anisomycin (*Scheme 1*), which display interesting biological activities. We have earlier prepared (−)-preussin and (−)-detoxinine by constructing their pyrrolidine core **A** from alkoxyallenes **B** and *N*-protected imines **C**. Lithiation of **B** at C(1) and addition of these strong nucleophiles to imines **C** followed by ring closure of the primary adducts provided the required dihydropyrrole derivatives **A** by an efficient [3+2] cyclization mode [2]. Whereas the stereochemical control of the synthesis of (−)-detoxinine was easily achieved with a chiral side chain R^1 of imine **C** [3], the preparation of (−)-preussin exploited a chiral auxiliary R^2 at the alkoxyallene building block **B**. In this synthesis [4], the most-difficult problem was control of the configuration at C(5) of the pyrrolidine. In this report, we demonstrate that a suitable auxiliary also allows the synthesis of both enantiomers of anisomycin.

(−)-Anisomycin – a compound with a 4-methoxyphenyl substituent – is a secondary metabolite of streptomyces species (*Streptomyces grisoleaus* and *S. roseochromo-*

[1]) For selected recent stereoselective syntheses of highly substituted pyrrolidin-3-ols, see [1].

Scheme 1. *Structures of (+)-Preussin, (−)-Detoxinine, and (−)-Anisomycin and Retrosynthetic Analysis of Their Potential Precursors* **A**



genes). It was first described in 1954 by *Sobin* and *Tanner* [5], and its constitution was elucidated by *Beereboom et al.* [6]. Later relative and absolute configurations of this compound were established by spectroscopy [7] and finally by chemical correlation [8] with compounds of known absolute configuration. This natural product shows antibacterial and fungicide activity [9], and more recently it has been found that (−)-anisomycin displays high *in vitro* antitumor activity [10]. Quite a number of enantioselective syntheses of this relatively simple natural product containing only three stereogenic centers have been reported since 1970; however, despite this apparent simplicity, all synthesis involve many steps and are usually not very flexible due to the reliance on chiral starting materials [10b][2]). A characteristic structural feature of anisomycin, which often causes the low efficacy of its preparation, is the existence of two OH functions in *trans* arrangement, one being acetylated. Therefore, more-efficient and potentially flexible approaches to this bioactive compound also allowing preparation of analogues are of continuing interest.

Results. – Preliminary studies motivated us to select 'diacetone-fructose' (=1,2:4,5-di-*O*-isopropylidenefructose)-substituted allene **1** as chiral C_3 building block **B** for our anisomycin synthesis. This compound is easily available on a multigram scale from 3-bromoprop-1-yne and the corresponding protected fructose derivative; the resulting prop-2-ynyl ether is then smoothly isomerized to the more-stable allene **1** [12][3]). The required imine **C** has to be derived from 4-methoxybenzeneacetaldehyde, but this kind

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[2]) For syntheses of racemic anisomycin, see [11a–d]. For syntheses (including formal total syntheses) of enantiomerically pure anisomycin based on the chiral pool approach, see [11e–s]. For syntheses (including formal total syntheses) of enantiomerically pure anisomycin based on chiral auxiliaries or catalysts, see [11t–x].

[3]) For diastereoselective hetero-*Diels–Alder* reactions of these carbohydrate-derived alkoxyallenes, see [12b].

of imine is known to rapidly isomerize giving the corresponding enamine tautomer [13]. It has, however, successfully been demonstrated that sulfonyl derivatives such as **2a** and **2b** are suitable precursors for this type of imine. By treatment with base, these compounds smoothly suffer deprotonation at the protected N-atom followed by elimination of sulfinate to deliver the corresponding *N*-protected imines which then can be trapped by the desired nucleophile [14]. Very often, the base employed is identical with the nucleophile to be introduced. We followed this promising protocol for the crucial C–C connecting step of our synthesis (*Scheme 2*).

DAF-Allene **1** was deprotonated under standard conditions with BuLi, and 3 (series **a**) or 2 (series **b**) equiv. of the resulting lithiated allene were combined with 1 equiv. of **2a** and **2b**, respectively (*Scheme 2*). The *in situ* generated *N*-protected imines were immediately trapped by the excess of lithiated **1** and afforded the expected primary addition products **3a** and **3b** in moderate to good yields. Since the excess of **1**, generated by reprotonation with **2** or during aqueous workup, could easily be recovered by column chromatography and re-used, the protocol is fairly efficient with respect to the chiral allene derivative **1**.

The diastereoselectivities of the additions of lithiated **1** to the *N*-protected imines were surprisingly low[4]), and *ca.* 2:1 mixtures of diastereoisomers of allenylamines **3** were isolated, which were not separated at this stage. Additions of lithiated alkoxyallenes with carbohydrate-derived auxiliaries to aldehydes were considerably more stereoselective [4][15]. A few other auxiliaries examined at the alkoxyallene moiety did not dramatically improve the asymmetric induction[5]). Since we planned to prepare both enantiomers of anisomycin, we proceeded with these 2:1 mixtures of **3** and did not continue to optimize the diastereoselectivity of the addition reaction.

It was found that *N*-Boc-protected allenylamine **3a** cyclized to **4a** most reproducibly under strongly basic conditions. Employment of ^{t}BuOK in DMSO [2][16] provided a mixture of the two diastereoisomers of **4a** in 65% yield. No change of the ratio of diastereoisomers was observed during the cyclization. The isomers were easily separated by prep. HPLC to furnish the pure diastereoisomers (2*R*)-**4a** and (2*S*)-**4a** in 38 and 14% overall yield (based on **3a**), respectively. The assignments of configuration at C(2) of these compounds are based on the successful conversion of the major isomer (2*R*)-**4a** into (–)-anisomycin hydrochloride (see below). In the case of *N*-Tos-protected allenylamine **3b**, $AgNO_3$-promoted cyclization (in $MeCN/K_2CO_3$) afforded good results [17]. The desired dihydropyrrole derivative **4b** was obtained in 68% yield. Subsequent HPLC separation supplied us with two pure diastereoisomers (2*R*)-**4b** and (2*S*)-**4b** in 46 and 14% overall yield (based on **3b**), respectively[6]). Compound **3a** could also be cyclized to **4a** with this $AgNO_3$ protocol; however, the

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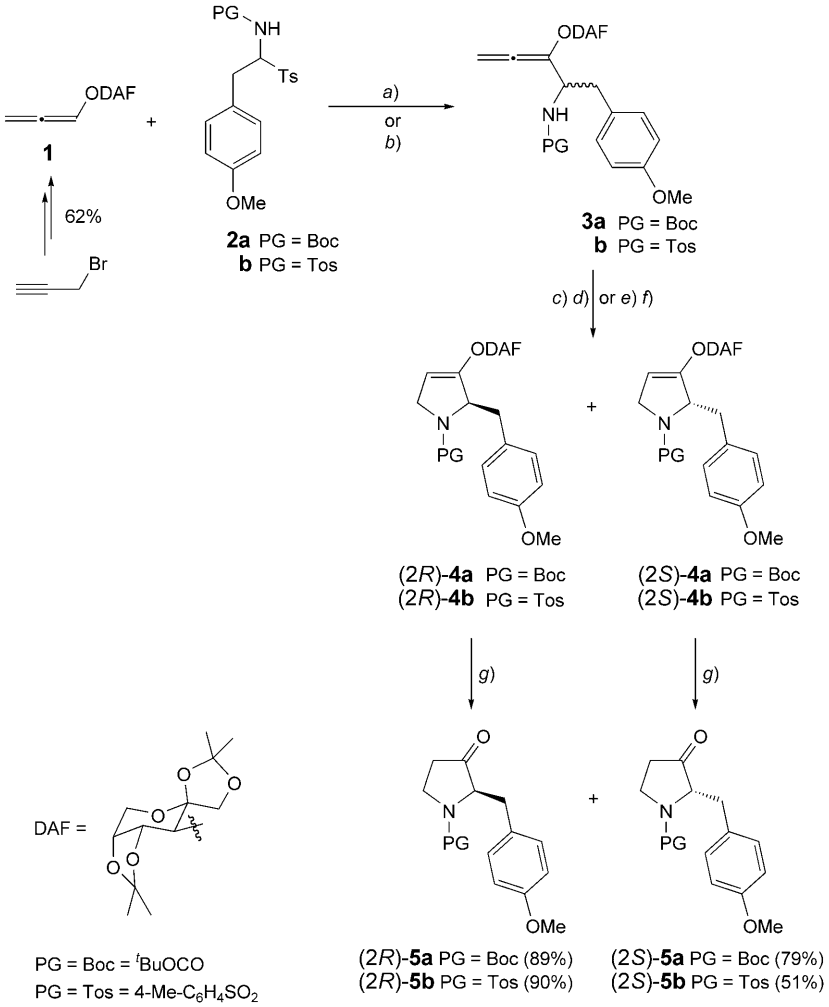
[4]) Additions of lithiated DAF-allene **1** to other *N*-Tos-protected imines proceeded with diastereoselectivities in the range of 4:1 up to 9:1; see [4].

[5]) Similar reactions of a lithiated alkoxyallene derived from D-mannose also gave diastereoselectivities of *ca.* 2:1; *S. Kaden*, unpublished results.

[6]) The assignments for the *N*-Tos-protected compounds is essentially based on analogy: it is unlikely that the switch of the *N*-protective group from Boc to Tos will change the preferred attack of lithiated **1** to the corresponding imines. This is supported by the fact that the optical rotations of the *N*-Tos-protected compounds (2*R*)-**5b** and (2*S*)-**5b** have the same sign as those of the corresponding Boc-protected pyrrolidinones (2*R*)-**5a** and (2*S*)-**5a**.

Scheme 2

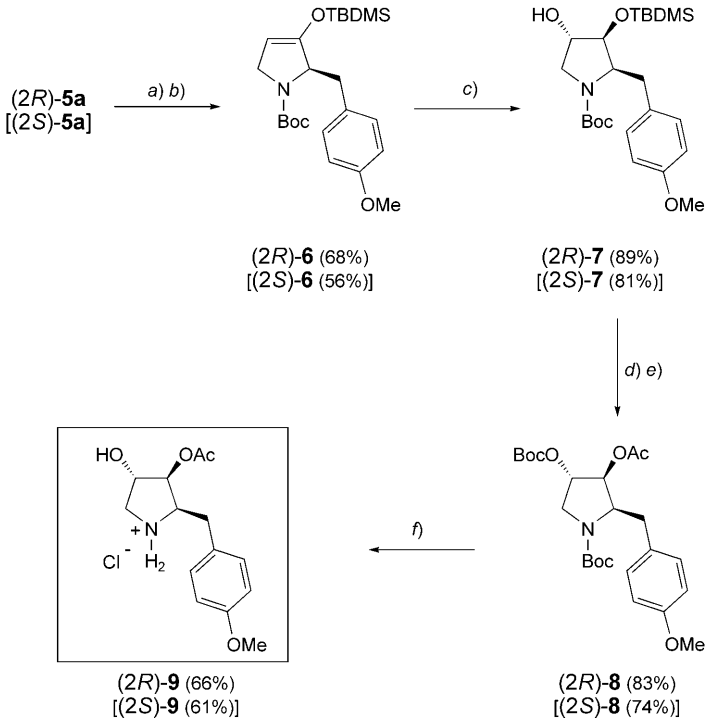


a) PG = Boc: **1** (3 equiv.), BuLi (3 equiv.), THF, −78°, 20 min; then **2a** (1 equiv.), −50 to −20°, 4 h; 73%. *b*) PG = Tos: **1** (2 equiv.), BuLi (2 equiv.), THF, −50°, 20 min; then **2b** (1 equiv.), −50 to −20°, 4 h; 41%. *c*) PG = Boc: KO^{t}Bu, DMSO, 50°, 8 h; 65%. *d*) PG = Boc: prep. HPLC; major diastereoisomer 38%, minor diastereoisomer 14%. *e*) PG = Tos: $AgNO_3$, K_2CO_3, MeCN, 16 h, r.t., light exclusion; 68%. *f*) PG = Tos: prep. HPLC; major isomer 46%, minor isomer 18%. *g*) PG = Boc or Tos: 6N HCl, THF, 2–3 h, r.t.

base-catalyzed reaction was more reliable on a larger scale. *N*-Tos-protected dihydropyrroles such as **4b** can undergo elimination of sulfinate and provide pyrroles [2], which deterred us from applying the base-promoted method to **3b**. By treatment with aqueous hydrochloric acid, all four dihydropyrroles **4a**,**b** were smoothly converted into the required enantiomerically pure 2-substituted *N*-protected pyrrolidinones (2*R*)-**5a**, (2*S*)-**5a**, (2*R*)-**5b**, and (2*S*)-**5b** in good yields.

After preliminary experiments with **5b** [18], we decided to continue the synthesis of anisomycin employing the *N*-Boc-protected pyrrolidine derivatives **5a** which seem to allow more-efficient conversions. Both enantiomers of **5a** were transformed into the (*tert*-butyl)dimethylsilyl-substituted enol ethers **6**. Although we tried to optimize this apparent standard reaction, we could not obtain more than 68% yield (*Scheme 3*). Gratifyingly, the subsequent hydroborations of **6**, which were supposed to generate the two missing stereogenic centers of the target compound, not only proceeded with excellent diastereofacial selectivity but also with high efficacy. Employment of borane in THF followed by oxidative workup with H_2O_2 and NaOH afforded the desired monoprotected diol derivatives (2*R*)-**7** and (2*S*)-**7** as single isomers in 89 and 81% yield, respectively. The substituent at C(2) very efficiently shields one face of the enol ether C=C bond of **6** leading to the observed high diastereoselectivity of borane addition. It should also be noted that the hydroboration is highly regioselective [19].

Scheme 3[a])



TBDMS = ^{t}BuMe$_2$Si, Boc = ^{t}BuOCO

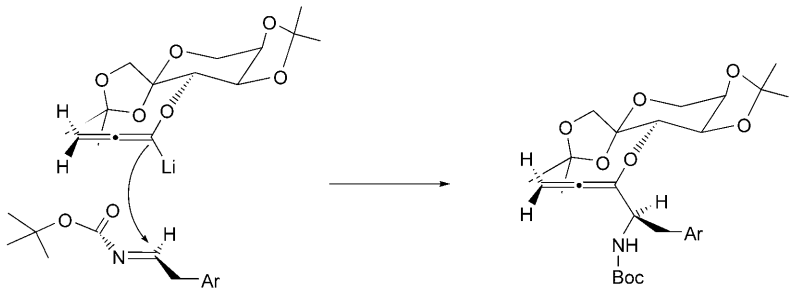
a) LDA, THF, 45 min, −78°. *b*) ^{t}BuMe$_2$SiCl, DMPU (= 3,4,5,6-tetrahydro-1,3-dimethylpyrimidin-2(1*H*)-one), 30 min, −78° to r.t. *c*) $BH_3 \cdot$ THF, THF, −30° to r.t., 3 h; then NaOH, H_2O_2, −10° to r.t., 12 h. *d*) Boc_2O, pyridine, 4-(*N*,*N*-dimethylamino)pyridine (DMAP), 12 h, r.t. *e*) Bu_4NF, THF, 12 h, r.t.; then Ac_2O, CH_2Cl_2, Et_3N, 0° to r.t., 12 h. *f*) HCl/dioxane, 0°, 3.5 h.

[a]) The yields of the enantiomers leading to (+)-anisomycin hydrochloride – (2*S*)-series – are presented in brackets.

Conversions of compounds **7** into **8** were essentially one-pot procedures. The free OH group of **7** was Boc-protected, and the resulting intermediate was desilylated with Bu_4NF and finally *O*-acetylated employing Ac_2O. Again these transformations to (2*R*)-**8** or (2*S*)-**8** occurred with good overall efficacies. The end game of our anisomycin synthesis was performed according to *Jäger* and *Schwardt* [10b] and also proceeded without problems. Concomitant O- and N-deprotection employing HCl in dioxane and recrystallization furnished the two enantiomeric hydrochlorides of anisomycin (2*R*)-**9** and (2*S*)-**9**, in 66 and 61%, respectively. Having these compounds in hand, we could finally confirm the assumed configurations at C(2) of all our intermediates in *Schemes 2* and *3*. The positive optical rotation of (2*R*)-**9** established that this isomer was the hydrochloride of the naturally occurring enantiomer [10b][20]. The major diastereoisomer of **3a** and all subsequent derivatives finally leading to (−)-anisomycin hydrochloride have the drawn (2*R*)-configuration. The enantiomeric purity of our sample appears to be high (ee > 95%) since we obtained fairly similar values of the optical rotation as those reported in the literature. We have earlier established that pyrrolidin-3-ones such as **5** are configurationally fairly stable [4] and, therefore, a (partial) racemization at this stage is rather unlikely.

The high conformational flexibility of lithiated DAF-allene **1** and the possibility of the lithium cation to coordinate to a manifold of O-atoms of the auxiliary make interpretations of its addition reactions highly speculative. However, a transition structure as depicted in *Scheme 4* may operate to explain the (moderately) preferred formation of the observed major diastereoisomer of **3a**. In our model, the bulky DAF group shields the back side of lithiated **1**, and the *N*-protected imine approaches the nucleophilic allene C(1) center with the sterically less-demanding C−H moiety pointing into this direction. This attack to the *Si* face of the *N*-protected imine provides (*R*)-configuration at the newly generated stereogenic center as observed. It should be mentioned again that the modest diastereoselectivity recorded is evidence that alternative transition structures either adding to the *Re*- or to the *Si*-face of the *N*-protected imine may be involved.

Scheme 4. *Possible Transition Structure for the Addition of Lithiated* **1** *to the* N-*Boc-Protected Imine*



Conclusions. – Based on easily available 'diacetone-fructose'-derived allene **1**, (−)-anisomycin hydrochloride (2*R*)-**9** was synthesized in ten steps (involving eight purified

intermediates) in *ca.* 8% overall yield. Although this seems not to be particularly efficient, this compares well to the best-known syntheses of this natural product [11]. The drawbacks of our approach are the moderate diastereoselectivity of the crucial addition of lithiated **1** to the corresponding *in situ* generated *N*-protected imine delivering compounds **3a** and **3b** only as *ca.* 2 : 1 mixtures of isomers. However, this fact allowed us to synthesize both enantiomers starting with one single compound. The separation of diastereoisomers **4a** was achieved by prep. HPLC but could also be performed by standard column chromatography. A second step with disappointingly low efficacy concerns formation of silyl enol ethers **6**. Although we tried to improve this process, not all conceivable alternative methods have been examined.

An important advantage of our synthetic approach to pyrrolidine derivatives *via* lithiated allenes and *N*-protected imines is certainly its high flexibility. Instead of imine precursors **2**, analogues thereof or stable *N*-protected imines **C** could be introduced to the synthesis. They will lead to other substituents at the N-atom or at C(2) of the pyrrolidinol target. The allene building block **B**, providing three C-atoms of the pyrrolidine core, may be substituted at C(3) (*Scheme 1*) and as consequence furnish C(5)-substituted pyrrolidine derivatives as demonstrated in our synthesis of (−)-preussin. Furthermore, the enol ether functionality as present in intermediates **4** or **6** may be exploited by introducing other functional groups at C(4). All these options should smoothly allow the preparation of analogues of anisomycin, which may be of importance for screening the biological activity of this type of compounds. In a more general view, pyrrolidin-3-one derivatives such as (2*R*)-**5a**, (2*S*)-**5a**, (2*R*)-**5b**, and (2*S*)-**5b** should be valuable intermediates for the preparation of a variety of enantiomerically pure natural products or pharmaceuticals. Here, as well as in other applications, lithiated alkoxyallenes served as versatile and useful C_3 building block for the stereoselective construction of the required heterocyclic core[7]).

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Experimental Part

General. Starting materials 4-methoxybenzeneacetaldehyde [22], 1,2 : 4,5-di-*O*-isopropylidene-3-*O*-(prop-2-ynyl)-*β*-D-fructopyranose [12a], and 1,2 : 4,5-di-*O*-isopropylidene-3-*O*-(propa-1,2-diene)-*β*-D-fructopyranose [12a] were prepared by known procedures. All other chemicals were commercially available and used as received. Unless otherwise stated, all reactions were performed under Ar in flame-dried flasks by adding the components *via* syringes. All solvents were dried by using standard procedures. Column chromatography (CC): neutral aluminium oxide (act. III, *Fluka* or *Merck*) or silica gel (0.040 – 0.063 mm, *Fluka*). HPLC: *Nucleosil 50-5* (*Macherey & Nagel*). M.p.: *Reichert Thermopan*; uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter. IR Spectra: *Perkin-Elmer* FT-IR spectrometer *Nicolet 5 SXC* with *DTGS* detector. ^{1}H- and ^{13}C-NMR Spectra: *Bruker* instruments (*WH 270*, *AC 250*, *AC 500*) and *Joel Eclipse 500*; δ(H) in ppm rel. to $SiMe_4$ (= 0.00 ppm) or to $CHCl_3$ (= 7.26 ppm), and δ(C) rel. to $CDCl_3$ (= 77.0 ppm), higher-order spectra are approximately interpreted as first-order spectra if possible.

tert-*Butyl {2-(4-Methoxyphenyl)-1-[(4-methylphenyl)sulfonyl]ethyl}carbamate* (**2a**). A well-stirred soln. of *tert*-butyl carbamate (1.13 g, 9.60 mmol) in H_2O (10.5 ml), formic acid (2.94 ml), and MeOH (2.22 ml) was treated with the sodium salt of 4-methylbenzenesulfinic acid (1.71 g, 9.60 mmol). Freshly distilled 4-methoxybenzeneacetaldehyde (1.59 g, 10.6 mmol) was added dropwise, and the soln. was stirred at 70° for

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7) For reviews, see [21a – d]. For recently published results, see [21e – j].

10 min. After cooling to r.t., the suspension was filtered, and the residue was washed with H_2O, 1N HCl, and pentane. Evaporation of the solvents gave product **2a** (3.00 g, 77%). Colorless solid. M.p. 152–153°. IR (KBr): 3380 (N–H), 3010 (=C–H), 2980–2835 (C–H), 1710 (C=O), 1305, 1150 (SO_2). ^{1}H-NMR ($CDCl_3$; several doubled signals due to the occurrence of rotamers, the minor one being marked with *): 0.97* (*s*, 1.8 H, ^{t}Bu); 1.13 (*s*, 7.2 H, ^{t}Bu); 2.41, 2.43* (2*s*, 3 H, *Me*C_6H_4); 2.78–2.88* (*m*, 0.2 H, H–C(2)); 2.97 (*dd*, *J* = 15.1, 9.9, 0.8 H, H–C(2)); 3.51–3.63 (*m*, H–C(2)); 3.77 (*s*, MeO); 4.77–4.85* (*m*, 0.4 H, 1 H, NH); 4.97–5.12 (*m*, 1.6 H, 1 H, NH); 6.83, 7.13 (2*d*, *J* = 8.8, 2 arom. H each); 7.32, 7.80 (2*d*, *J* = 8.1, 2 arom. H each). ^{13}C-NMR ($CDCl_3$): 21.4 (*q*, *Me*C_6H_4); 27.3*, 27.7 (2*q*, ^{t}Bu); 31.6, 31.9* (2*t*, C(2)); 55.1 (*q*, MeO); 71.4, 73.5* (2*d*, C(1)); 80.3, 80.8* (2*s*, ^{t}Bu); 113.9, 129.2*, 129.4, 129.5, 130.1 (5*d*, arom. C); 126.7, 133.7, 144.8, 153.6, 158.5 (5*s*, arom. C, C=O). EI-MS (80 eV): 406 (1, $[M+H]^+$), 250 (21, $[M-\text{Tos}]^+$), 194 (60, $[M-\text{Tos}-C_4H_8]^+$), 150 (100, $[M-\text{Tos}-\text{Boc}]^+$), 121 (8, Tos^+), 57 (84, $^t\text{Bu}^+$). Anal. calc. for $C_{21}H_{27}NO_5S$ (405.5): C 62.20, H 6.71, N 3.45; found: C 62.20, H 6.50, N 3.28.

N-*{2-(4-Methoxyphenyl)-1-[(4-methylphenyl)sulfonyl]ethyl}-4-methylbenzenesulfonamide* (**2b**). A well-stirred soln. of 4-methylbenzenesulfonamide (2.02 g, 11.8 mmol) in H_2O (18 ml) and formic acid (18 ml) was treated with sodium 4-methylbenzenesulfinite (2.10 g, 11.8 mmol). Freshly distilled 4-methoxybenzeneacetaldehyde (1.78 g, 11.8 mmol) was added dropwise, and the soln. was stirred overnight at r.t. The suspension was filtered, and the residue was washed with H_2O and pentane and then dissolved in AcOEt (150 ml). The org. phase was extracted with 1N HCl, dried (Na_2SO_4), and evaporated at 20°. Drying at 1 mbar gave **2b** (3.03 g, 56%). Colorless solid. M.p. 118–119°. IR (KBr): 3255 (N–H), 3030 (=C–H), 2955–2835 (C–H), 1335, 1160 (SO_2). ^{1}H-NMR ($CDCl_3$): 2.31, 2.45 (2*s*, 3 H each, *Me*C_6H_4); 2.95 (*dd*, *J* = 14.0, 10.5, H–C(2)); 3.52 (*dd*, *J* = 14.0, 3.7, H–C(2)); 3.70 (*s*, MeO); 4.80 (*td*, *J* = 10.5, 3.7, H–C(1)); 6.01 (*d*, *J* = 10.5, NH); 6.49, 7.15 (2*d*, *J* = 8.8, 2 H each, Ar); 6.91 (*m*, 4 H, Tos, Ar), 7.38, 7.89 (2*d*, *J* = 8.1, 2 H each, Tos). ^{13}C-NMR ($CDCl_3$): 21.2, 21.7 (2*q*, *Me*C_6H_4); 32.5 (*t*, C(2)), 54.9 (*q*, MeO); 75.6 (*d*, C(1)); 113.9 (*d*, Ar); 126.1, 129.2, 129.7, 130.0, 130.5 (5*d*, Tos, Ar); 125.9, 132.5, 137.6, 142.7, 145.4 (5*s*, Tos, Ar); 158.6 (*s*, Ar). FAB-MS (pos.): 304 (100, $[M-\text{Tos}]^+$), 155 (37, Tos^+), 149 (33), 148 (44, $[M-2\,\text{Tos}-\text{H}]^+$), 139 (21), 121 (31, MeOBn^+), 91 (61, PhCH_2^+), 77 (16). Anal. calc. for $C_{23}H_{25}NO_5S_2$ (459.6): C 60.11, H 5.48, N 3.05; found: C 60.47, H 5.15, N 2.75.

3-O-*{2-{[(*tert*-Butoxy)carbonyl]amino}-1-ethenylidene-3-(4-methoxyphenyl)propyl}-1,2 : 4,5-di*-O-*isopropylidene-β*-D-*fructopyranose* (**3a**). To a soln. of **1** (3.37 g, 11.3 mmol) in dry THF (70 ml), 2.4M BuLi in hexanes (4.70 ml, 10.9 mmol) was slowly added at −78° under Ar. After stirring for 15 min, a soln. of **2a** (1.52 g, 3.76 mmol) in dry THF (10 ml) was added over 5 min. The mixture was stirred for 4 h and allowed to warm from −78 to −20°. After addition of sat. $NaHCO_3$ soln. (70 ml), the aq. layer was extracted with AcOEt, the combined extract dried ($MgSO_4$) and evaporated, and the crude product purified by CC (aluminium oxide, hexane/AcOEt 4 : 1): starting material **1** (2.61 g; yellow oil) and **3a** (1.50 g, 73%; colorless solid) as a mixture of two diastereoisomers (d.r. 2 : 1, by ^{13}C-NMR). The separation of the diastereoisomers was achieved after cyclization to **4a**. **3a**: IR (KBr): 3365 (N–H); 2985, 2935 (C–H); 1955 (C=C=C); 1690 (C=O). ^{1}H-NMR ($CDCl_3$): 1.38–1.53 (*m*, 21 H, 4 Me, ^{t}Bu); 2.94–2.98 (*m*, 2 H–C(3)); 3.79 (*s*, MeO); 3.88–4.17 (*m*, 2 H–C(6′), H–C(3′), 2 H–C(1′), H–C(2)); 4.24 (*dd*, *J* = 5.2, 2.2, H–C(5′)); 4.36–4.44 (*m*, 1.4 H, NH, H–C(4′)); 4.81 (*d*, *J* = 8.8, 0.6 H, NH); 5.10–5.15, 5.32–5.35 (2*m*, CH_2=C=C(1)); 6.79, 7.18 (2*d*, *J* = 8.8, 2 arom. H each). ^{13}C-NMR ($CDCl_3$; the signals of the minor diastereoisomer marked with *): 26.0, 26.3, 26.6*, 26.9, 28.0 (5*q*, Me); 28.3 (*q*, ^{t}Bu); 37.3, 38.6* (2*t*, C(3)); 52.8 (*d*, C(2)); 55.2 (*q*, MeO); 60.2, 60.4* (*t*, C(6′)); 71.4, 71.6* (*t*, C(1′)); 73.9*, 74.0, 75.5*, 75.9, 76.1* (5*d*, C(3′), C(4′), C(5′)); 79.2 (*s*, ^{t}Bu); 92.5*, 93.5 (2*t*, *C*H_2=C=C(1)); 104.1 (*s*, C(2′)); 109.1, 112.0 (2*s*, Me_2C); 129.9, 130.8 (2*s*, arom. C, C(3)); 113.4, 130.9 (2*d*, arom. C); 154.9, 158.2 (2*s*, C=O, arom. C); 197.3 (*s*, CH_2=*C*=C(1)). EI-MS (80 eV): 547 (1, M^+), 491 (4, $[M-C_4H_8]^+$), 430 (4, $[M-O^t\text{Bu}]^+$), 370 (11, $[M-\text{MeOBn}-C_4H_8]^+$), 326 (9, $[M-\text{MeOBn}-\text{Boc}]^+$), 268 (16), 243 (14), 185 (15), 121 (100, MeOBn^+), 57 (83, $^t\text{Bu}^+$), 43 (32, $C_2H_3O^+$). HR-MS: 547.2747 (M^+, $C_{29}H_{41}NO_9$; calc. 547.2781).

3-O-*{1-Ethenylidene-3-(4-methoxyphenyl)-2-{[(4-methylphenyl)sulfonyl]amino}propyl}-1,2 : 4,5-di*-O-*isopropylidene-β*-D-*fructopyranose* (**3b**). As described for **3a**, with **1** (1.39 g, 4.66 mmol) THF (40 ml), 2.39M BuLi in hexanes (1.87 ml, 4.40 mmol), **2b** (1.01 g, 2.20 mmol), and THF (5 ml), all at −50° instead of −78°, then warming up to −20°. Workup with sat. $NaHCO_3$ soln. (60 ml) and AcOEt (3 × 30 ml) followed by CC (aluminium oxide, hexane/AcOEt 2 : 1) yielded **1** (0.855 g, 61%; yellow oil) and **3b** (0.546 g, 41%; yellow oil) as a mixture of two diastereoisomers (d.r. 72 : 28, by ^{1}H-NMR). The separation of the diastereoisomers was achieved after cyclization to **4b**. **3b**: ^{1}H-NMR ($CDCl_3$; the minor diastereoisomer is marked with *): 1.37, 1.42, 1.47, 1.51 (4*s*, 3 H each, Me); 2.40 (*s*, *Me*C_6H_4); 3.01 (*dd*, *J* = 8.8, 5.9, 2 H–C(3)); 3.47–4.36 (*m*, 2 H–C(1′), H–C(3′), H–C(4′), H–C(5′), 2 H–C(6′), H–C(2)); 3.79 (*s*, MeO); 4.59, 5.33* (2*d*, *J* = 8.8, 0.28 H and 0.72 H, NH); 5.01–5.11 (*m*, CH_2=C=C(1)); 6.75 (*d*, *J* = 8.6, 2 arom. H); 7.12–7.29 (*m*, 4 arom. H); 7.65, 7.66* (2*d*, *J* = 8.6, 2 arom. H).

3-O-*{[1-(*tert-*Butoxy)carbonyl]-2,5-dihydro-2-(4-methoxybenzyl)-1*H*-pyrrol-3-yl}-1,2:4,5-di*-O-*isopropylidene-β-*D*-fructopyranose* (**4a**). To a soln. of **3a** (1.00 g, 1.82 mmol) in dry DMSO (30 ml), freshly sublimated KO*t*Bu (57 mg, 0.48 mmol) was added. The dark brown mixture was stirred for 16 h at 50°. The soln. was quenched with sat. $NaHCO_3$ soln. (30 ml), the aq. layer extracted with AcOEt (3 × 15 ml), the combined org. layer washed with sat. NaCl soln., dried (Na_2SO_4), and evaporated, and the crude product purified by CC (aluminium oxide, hexane/AcOEt 5:1): **4a** (0.65 g, 65%) as light yellow oil. Separation of the two diastereoisomers by HPLC (hexane/AcOEt 4:1) gave major isomer (2*R*)-**4a** (0.37 g, 37%) as colorless foam and minor isomer (2*S*)-**4a** (0.14 g, 14%) as colorless resin.

*Data of (2*R*)-***4a***:* $[\alpha]_D^{20} = -163.7$ ($c = 0.61$, $CHCl_3$). IR (KBr): 3100–2835 (=C−H, C−H), 1700 (C=O), 1660 (C=C). ^{1}H-NMR ($CDCl_3$; several doubled signals due to the occurrence of rotamers): 1.37, 1.40, 1.42, 1.43, 1.49, 1.51, 1.57 (7*s*, 21 H, *t*Bu, Me_2C); 2.91 (br. *d*, $J = 13.2$, 1 H, ArCH_2); 3.03–3.24 (*m*, 1.5 H, H−C(5), ArCH_2); 3.37 (*dd*, $J = 13.2$, 5.2, 0.5 H, ArCH_2); 3.77, 3.79 (2*s*, each 1.5 H, MeO); 3.84 (br. *d*, $J = 13.5$, 0.5 H, H−C(5)); 3.90–4.21 (*m*, 5.5 H, H−C(4), H−C(5), H−C(1′), H−C(3′), H−C(6′)); 4.30 (*dd*, $J = 5.5$, 2.6, 1 H, H−C(5′)); 4.39–4.48 (*m*, 2.5 H, H−C(2), H−C(4′), H−C(6′)); 4.57–4.61 (*m*, 0.5 H, H−C(2)); 6.73, 6.74, 7.15, 7.19 (4*d*, $J = 8.8$, 2 arom. H each). ^{13}C-NMR ($CDCl_3$): 25.7, 25.9, 26.2, 26.7, 26.9, 28.2, 28.5, 28.6 (8*q*, Me, *t*Bu); 34.1, 35.6 (2*t*, ArCH_2); 50.0, 50.4 (2*t*, C(5)); 55.1 (*q*, MeO); 62.3, 62.5 (2*d*, C(2)); 60.2, 60.4, 71.4, 71.7 (4*t*, C(1′), C(6′)); 73.8, 75.8, 77.5 (3*d*, C(3′), C(4′), C(5′)); 79.1, 79.7 (2*s*, *t*Bu); 91.3, 91.8 (2*d*, C(4)); 104.0, 109.0, 112.3 (3*s*, C(2′), Me_2C); 112.8, 113.0, 131.3, 131.5 (4*d*, arom. C); 128.7, 153.6, 154.1, 154.4, 158.0 (5*s*, arom. C, C(3), C=O). EI-MS (80 eV): 547 (32, M^+), 532 (6, $[M - Me]^+$), 426 (31, $[M - MeOBn]^+$), 370 (1, $[M - MeOBn - C_4H_8]^+$), 243 (20), 185 (12, $[M - MeOBn - DAF]^+$), 121 (38, $MeOBn^+$), 57 (100, $C_4H_9^+$). HR-MS: 547.2763 (M^+, $C_{29}H_{41}NO_9^+$; calc. 547.2781). Anal. calc. for $C_{29}H_{41}NO_9$ (547.6): C 63.60, H 7.55, N 2.56; found: C 63.23, H 7.20, N 2.26.

*Data of (2*S*)-***4a***:* $[\alpha]_D^{20} = +4.3$ ($c = 0.48$, $CHCl_3$). IR (neat): 2985–2935 (=C−H, C−H), 1700 (C=O), 1660 (C=C). ^{1}H-NMR ($CDCl_3$; several doubled signals due to the occurrence of rotamers): 1.36, 1.43, 1.49, 1.51, 1.54 (5*s*, 21 H, *t*Bu, Me_2C); 2.77–2.85, 3.20–3.28 (2*m*, 1 H each, $ArCH_2$); 3.38 (*dd*, $J = 13.0$, 4.8, 0.5 H, H−C(5)); 3.43 (*dd*, $J = 13.0$, 5.2, 0.5 H, H−C(5)); 3.76 (*s*, MeO); 3.86–4.26 (*m*, 7 H, H−C(1′) H−C(3′), H−C(6′), H−C(4), H−C(5)); 4.34 (*d*, $J = 7.4$, 0.5 H, H−C(5′)); 4.36 (*d*, $J = 5.2$, 0.5 H, H−C(5′)); 4.50 (*m*, 1 H, H−C(4′)); 4.62–4.68 (*m*, 1 H, H−C(2)); 6.76 (*d*, $J = 8.5$, 2 arom. H); 7.10 (*d*, $J = 8.5$, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 25.9, 26.2, 26.6, 27.9, 28.2, 28.4 (6*q*, Me, *t*Bu); 34.0, 35.7, 50.0, 50.4 (4*t*, C(5), ArCH_2); 55.0 (*q*, MeO); 62.3, 62.7 (2*d*, C(2)); 60.2, 60.6, 72.5, 72.6 (4*t*, C(1′), C(6′)); 73.6, 76.3, 77.5 (3*d*, C(3′), C(4′), C(5′)); 78.9, 79.5 (2*s*, *t*Bu); 92.3, 92.5 (2*d*, C(4)); 104.0, 109.2, 112.3 (3*s*, C(2′), Me_2C); 113.0, 113.2, 130.8, 131.0 (4*d*, arom. C); 128.9, 153.8, 154.1, 154.3, 158.0, 158.1 (6*s*, arom. C, C(3), C=O). EI-MS (80 eV): 547 (16, M^+), 426 (21, $[M - MeOBn]^+$), 370 (53, $[M - MeOBn - C_4H_8]^+$), 243 (18), 185 (12, $[M - MeOBn - DAF]^+$), 121 (41, $MeOBn^+$), 117 (12), 84 (25), 69 (13), 59 (11), 57 (100, $C_4H_9^+$), 43 (28). HR-MS: 547.2753 (M^+, $C_{29}H_{41}NO_9^+$; calc. 547.2781).

3-O-*{2,5-Dihydro-2-(4-methoxybenzyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl}-1,2:4,5-di*-O-*isopropylidene-β-*D*-fructopyranose* (**4b**). To a soln. of **3b** (0.542 g, 0.90 mmol) in dry MeCN, K_2CO_3 (249 mg, 1.80 mmol) and $AgNO_3$ (31 mg, 0.180 mmol) were added. The soln. was stirred for 16 h at r.t. in the dark. The soln. was filtered over *Celite*, the filtrate evaporated, and the crude product purified by CC (aluminium oxide, hexane/AcOEt 2:1): **4b** (370 mg, 68%) as yellow oil. Separation of the two diastereoisomers by HPLC (hexane/^{i}PrOH 97:3) gave major isomer (2*R*)-**4b** (252 mg, 46%) as colorless foam and minor isomer (2*S*)-**4b** (96 mg, 18%) as light yellow crystals.

*Data of (2*R*)-***4b***:* M.p. 158–160°. $[\alpha]_D^{20} = -109.8$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3090–3035 (=C−H), 2990–2835 (C−H), 1670 (C=C), 1345, 1165 (RSO_2N). ^{1}H-NMR ($CDCl_3$): 1.25, 1.39, 1.47, 1.48 (4*s*, 12 H, Me_2C); 2.41 (*s*, *Me*C_6H_4); 3.01, 3.14 (*AB* of *ABX*, $J_{AB} = 13.8$, $J_{AX} = 2.4$, $J_{BX} = 5.0$, ArCH_2); 3.27 (*ddd*, $J = 13.6$, 4.6, 1.4, 1 H−C(5)); 3.21, 3.61 (2*d*, $J = 8.9$, 2 H−C(1′)); 3.79 (*s*, MeO); 3.76–3.83 (*m*, 1 H−C(5), H−C(3′)); 3.99 (br. *d*, $J = 13.4$, 1 H−C(6′)); 4.10 (*dd*, $J = 13.4$, 2.6, 1 H−C(6′)); 4.22–4.26 (*m*, H−C(4), H−C(5′)); 4.33 (*dd*, $J = 7.4$, 5.9, 1 H, H−C(4′)); 4.39 (*m*, H−C(2)); 6.76 (*d*, $J = 8.8$, 2 arom. H); 7.26–7.31 (*m*, 4 arom. H); 7.68 (*d*, $J = 8.1$, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 21.4 (*q*, *Me*C_6H_4); 25.7, 26.1, 26.8, 28.2 (4*q*, *Me*$_2$C); 38.1 (*t*, ArCH_2); 52.4 (*t*, C(5)); 55.1 (*q*, MeO), 60.2 (*t*, C(6′)); 65.1 (*d*, C(2)); 73.7 (*t*, C(1′)); 71.0, 75.4, 76.5 (3*d*, C(3′), C(4′), C(5′)); 91.7 (*d*, C(4)); 103.7 (*s*, C(2′)); 109.0, 112.1 (2*s*, Me_2C); 112.9, 127.1, 129.7, 132.0 (4*d*, arom. C); 127.8, 134.4, 143.6, 154.3, 158.2 (5*s*, arom. C, C(3)). EI-MS (80 eV): 601 (22, M^+), 480 (97, $[M - MeOBn]^+$), 274 (34), 243 (34), 185 (44), 155 (56, Tos^+), 131 (45), 127 (17), 121 (100, $MeOBn^+$), 91 (65, $PhCH_2^+$), 69 (41), 59 (30), 43 (32). Anal. calc. for $C_{31}H_{39}NO_9S$ (601.7): C 61.88, H 6.53, N 2.33; found: C 61.84, H 6.37, N 2.14.

*Data of (2*S*)-***4b***:* M.p. 200° (dec.). $[\alpha]_D^{20} = -47.8$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3105–3000 (=C−H), 2990–2875 (C−H), 1665 (C=C), 1345, 1160 (RSO_2N). ^{1}H-NMR ($CDCl_3$): 1.17, 1.27, 1.51 (3*s* (2:1:1), 12 H, Me_2C); 2.42 (*s*, *Me*C_6H_4); 2.97 (*dd*, $J = 13.9$, 1.1, 1 H, ArCH_2); 3.25 (*dd*, $J = 13.9$, 4.4, 1 H, ArCH_2), 3.48 (*ddd*, $J = 13.2$,

5.2, 1.5, 1 H–C(5)); 3.77 (*s*, MeO); 3.81 (*m*, H–C(3′), 1 H–C(5)); 3.93 (*m*, 2 H–C(1′)); 4.09 (*m*, 2 H–C(6′), H–C(4), H–C(5′)); 4.32 (br. *s*, H–C(4′)); 4.55–4.56 (*m*, H–C(2)); 6.79 (*d*, $J = 8.1$, 2 arom. H); 7.27–7.31 (*m*, 4 arom. H); 7.71 (*d*, $J = 8.1$, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 21.4 (*q*, *Me*C_6H_4); 26.0, 26.2, 26.6, 27.5 (4*q*, *Me*$_2$C); 37.7, 52.2 (2*t*, C(5), Ar*C*H$_2$); 55.1 (*q*, MeO); 60.5 (*t*, C(6′)); 65.1 (*d*, C(2)); 73.6 (*t*, C(1′)); 72.3, 75.8, 78.7 (3*d*, C(3′), C(4′), C(5′)); 93.4 (*d*, C(4)); 103.9 (*s*, C(2′)); 108.9, 112.2 (2*s*, Me$_2$*C*); 112.9, 127.3, 129.6, 131.5 (4*d*, arom. C); 128.2, 134.7, 143.1, 154.5, 158.2 (5*s*, arom. C, C(3)). EI-MS (80 eV): 601 (26, M^+), 480 (100, [M – MeOBn]$^+$), 274 (23), 243 (27), 185 (34), 155 (40, Tos$^+$), 131 (32), 127 (14), 121 (76, MeOBn$^+$), 91 (48, PhCH$_2$), 69 (34), 59 (27), 43 (43). Anal. calc. for $C_{31}H_{39}NO_9S$ (601.7): C 61.88, H 6.53, N 2.33; found: C 61.72, H 6.44, N 2.20.

tert-*Butyl (2*R*)-2-(4-Methoxybenzyl)-3-oxopyrrolidine-1-carboxylate* ((2*R*)-**5a**). To a soln. of (2*R*)-**4a** (0.350 g, 0.639 mmol) in THF (13 ml), 6N aq. HCl (4.7 ml) was added. The mixture was stirred (TLC control) for 2 h at r.t. The soln. was diluted with Et_2O and neutralized with sat. $NaHCO_3$ soln. (15 ml). The aq. layer was extracted with Et_2O (3 × 10 ml), the combined extract dried (Na_2SO_4) and evaporated and the crude product purified by CC (silica gel, hexane/AcOEt 4:1): (2*R*)-**5a** (0.175 g, 89%). Yellow oil. $[\alpha]_D^{20} = -192.4$ ($c = 0.58$, $CHCl_3$).

tert-*Butyl (2*S*)-2-(4-Methoxybenzyl)-3-oxopyrrolidine-1-carboxylate* ((2*S*)-**5a**). As described for (2*R*)-**5a**, with (2*S*)-**4a** (0.240 g, 0.438 mmol), THF (9 ml), and 6N aq. HCl (2.5 ml) (neutralized with sat. $NaHCO_3$ soln. (10 ml)): (2*S*)-**5a** (88 mg, 66%). Yellow oil. $[\alpha]_D^{20} = +184.8$ ($c = 0.56$, $CHCl_3$). IR (neat): 2975–2840 (=C–H, C–H), 1755 (C=O), 1700 (C=O). ^{1}H-NMR ($CDCl_3$; several doubled signals due to the occurrence of rotamers): 1.54 (*s*, ^{t}Bu); 1.89 (*ddd*, $J = 18.8, 9.2, 4.4$, 1 H–C(4)); 2.31–2.45 (*m*, 1 H–C(4)); 2.77 (*m*, 1 H–C(5)); 3.03 (*dd*, $J = 13.6, 2.6$, 1 H, ArCH_2); 3.16, 3.37, 3.64, 3.71 (4*m*, 0.5 H each, H–C(5), ArCH_2); 3.78 (*s*, MeO); 4.11–4.14 (*m*, H–C(2)); 6.79 (*d*, $J = 8.5$, 2 arom. H); 6.98 (*d*, $J = 8.5$, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 28.5 (*q*, ^{t}Bu); 35.9, 36.1, 36.6, 41.5 (4*t*, C(4), C(5), Ar*C*H$_2$); 55.2 (*q*, MeO); 63.3, 63.6 (2*d*, C(2)); 80.4, (*s*, ^{t}Bu); 114.0, 130.8 (2*d*, arom. C); 128.0, 154.3, 158.5 (3*s*, C=O, arom. C); 214.2 (*s*, C(3)). EI-MS (80 eV): 305 (24, M^+), 249 (4, [$M - C_4H_8$]$^+$), 232 (10, [M – O^{t}Bu]$^+$), 121 (100, MeOBn$^+$), 83 (23), 57 (68, ^{t}Bu$^+$). HR-MS: 305.1644 (M^+, $C_{17}H_{23}NO_4$; calc. 305.1627).

*(2*R*)-2-(4-Methoxybenzyl)-1-[(4-methylphenyl)sulfonyl]pyrrolidin-3-one* ((2*R*)-**5b**). As described for (2*R*)-**5a**, with (2*R*)-**4b** (0.249 g, 0.414 mmol), THF (8.5 ml), and 6N aq. HCl (2.1 ml) (neutralized with sat. $NaHCO_3$ soln. (10 ml)). CC (silica gel; hexane/AcOEt 1:1) yielded (2*R*)-**5b** (0.134 g, 90%). Colorless solid. M.p. 147°. $[\alpha]_D^{20} = -64.5$ ($c = 1.0$, $CHCl_3$).

*(2*S*)-2-(4-Methoxybenzyl)-1-[(4-methylphenyl)sulfonyl]pyrrolidin-3-one* ((2*S*)-**5b**). As described for (2*R*)-**5a**, with (2*S*)-**4b** (0.184 g, 0.306 mmol), THF (6 ml) and 6N aq. HCl (1.5 ml) (neutralized with sat. $NaHCO_3$ soln. (10 ml)). CC (silica gel; hexane/AcOEt 1:1) yielded (2*S*)-**5b** (56 mg, 51%). Colorless solid. M.p. 142–144°. $[\alpha]_D^{20} = +55.6$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3060–3015 (=C–H), 2935–2870 (C–H), 1755 (C=O), 1345, 1160 (RSO_2N). ^{1}H-NMR ($CDCl_3$): 1.66–1.80, 1.98–2.11 (2*m*, 2 H–C(4)); 2.44 (*s*, *Me*C_6H_4); 3.12 (*dd*, $J = 13.9, 2.9$, 1 H, ArCH_2); 3.18–3.36 (*m*, 3 H, H–C(5), ArCH_2); 3.75 (*m*, H–C(2)); 3.77 (*s*, MeO); 7.34 (*d*, $J = 8.1$, 2 H, Ar); 6.80, 7.16, 7.72 (3*d*, $J = 8.8$, 2 H each, Ar, Tos). ^{13}C-NMR ($CDCl_3$): 21.4 (*q*, *Me*C_6H_4); 36.3, 37.0, 44.1 (3*t*, C(4), C(5), Ar*C*H$_2$); 55.0 (*q*, MeO); 64.6 (*d*, C(2)); 113.6, 127.5, 129.9, 131.4 (4*d*, arom. C); 127.3, 133.4, 144.2, 158.5 (4*s*, arom. C); 211.7 (*s*, C(3)). EI-MS (80 eV): 359 (14, M^+), 238 (10, [M – MeOBn]$^+$), 155 (24, Tos$^+$), 121 (100, MeOBn$^+$), 91 (27, PhCH$_2^+$). HR-MS: 359.1183 (M^+, $C_{19}H_{21}NO_4S^+$; calc. 359.1191).

tert-*Butyl (2*R*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-2,5-dihydro-2-(4-methoxybenzyl)-1*H*-pyrrol-1-carboxylate* ((2*R*)-**6**). For the preparation of LDA, 2.46M BuLi in hexanes (0.76 ml, 1.87 mmol) was dissolved in dry THF (25 ml) at −78° and treated with ^{i}Pr$_2$NH (0.260 ml, 0.189 g, 1.87 mmol). The mixture was stirred at 0° for 30 min and then cooled to −78°, and (2*R*)-**5a** (0.519 g, 1.70 mmol) in dry THF (5 ml) was slowly added. The mixture was stirred for further 20 min. ^{t}BuMe$_2$SiCl (0.641 g, 4.25 mmol) and DMPU (0.410 ml, 0.435 g, 3.40 mmol) were added. The resulting soln. was stirred for 45 min at −78°, allowed to warm to r.t., and stirred for additional 2.5 h. The solvent was evaporated, the residue dissolved with Et_2O, the soln. washed with sat. Na_2CO_3 soln. (30 ml), the aq. layer extracted with Et_2O (4 × 20 ml), the combined org. layer washed with brine, dried (Na_2SO_4), and evaporated and the crude product purified by CC (aluminium oxide, hexane/AcOEt 7:1): (2*R*)-**6** (0.480 g, 68%). Yellow oil. $[\alpha]_D^{20} = -68.3$ ($c = 0.5$, $CHCl_3$).

tert-*Butyl (2*S*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-2,5-dihydro-2-(4-methoxybenzyl)-1*H*-pyrrole-1-carboxylate* ((2*S*)-**6**). As described for (2*R*)-**6**, with 2.3M BuLi in hexanes (0.14 ml, 0.31 mmol), THF (5 ml), and ^{i}Pr$_2$NH (45 µl, 32 mg, 0.31 mmol) (stirring at −78° instead of 0° for 30 min), then (2*S*)-**5a** (88 mg, 0.29 mmol) in THF (1 ml), and finally ^{t}BuMe$_2$SiCl (108 mg, 0.72 mmol) and DMPU (70 µl, 0.58 mmol). Extraction with Et_2O (4 × 5 ml) and CC (silica gel, hexane/AcOEt 4:1) yielded (2*S*)-**6** (67 mg, 56%). Yellow oil. $[\alpha]_D^{20} = +52.0$ ($c = 1.3$, $CHCl_3$). IR (neat): 3100–3035 (=C–H), 2955–2835 (C–H), 1700 (C=O), 1660 (C=C). ^{1}H-NMR ($CDCl_3$;

several doubled signals due to rotamers): 0.17, 0.19 (2*s*, 3 H each, Me_2Si); 0.97 (*s*, ^{t}BuSi); 1.49, 1.55 (2*s*, 5 H, 4 H, ^{t}BuO); 2.77–2.84 (*m*, 1 H, ArCH_2); 3.16 (*dd*, *J* = 13.6, 4.8, 1 H, ArCH_2); 3.24–3.39 (*m*, 1 H–C(5)); 3.76, 3.78 (2*s*, 1.3 H, 1.7 H, MeO); 3.84–3.91 (*m*, 1 H–C(5)); 4.37 (br. *d*, *J* = 7.0, H–C(4)); 4.43 (*m*, H–C(2)); 6.75, 7.01, 7.02 (3*d*, *J* = 8.8, 1 H, 1 H, 2 H, arom. H). ^{13}C-NMR ($CDCl_3$): −5.1, −4.8, −4.7 (3*q*, Me_2Si); 18.0 (*s*, ^{t}BuSi); 25.5, 28.5, 28.6 (3*q*, ^{t}Bu); 33.8, 35.3, 50.0, 50.3 (4*t*, C(5), ArCH_2); 55.1 (*q*, MeO); 63.0, 63.3 (2*d*, C(2)); 78.8, 79.5 (2*s*, ^{t}Bu); 96.4, 96.9 (2*d*, C(4)); 112.9, 113.2, 130.8, 131.0 (4*d*, Ar); 129.0, 129.2, 149.7, 153.8, 158.0 (5*s*, Ar, C=O, C(3)). EI-MS (80 eV): 419 (11, M^+), 363 (2, $[M - C_4H_8]^+$), 346 (4, $[M - O^tBu]^+$), 298 (15, $[M - MeOBn]^+$), 242 (100, $[M - MeOBn - C_4H_8]^+$), 198 (46), 121 (30, $MeOBn^+$), 73 (20, $^tBuO^+$), 57 (67, $^tBu^+$). HR-MS: 419.2476 (M^+, $C_{23}H_{37}NO_4Si^+$; calc. 419.2492).

tert-*Butyl (2*R*,3*S*,4*S*)-3-[[(*tert*-Butyl)dimethylsilyl]oxy]-4-hydroxy-2-(4-methoxybenzyl)pyrrolidine-1-carboxylate* ((2*R*)-**7**). To a soln. of (2*R*)-**6** (0.334 g, 0.795 mmol) in dry THF (16 ml), 1M $BH_3 \cdot$THF in THF (3.2 ml, 3.2 mmol) was added at −30°. The mixture was allowed to warm up to r.t. and stirred for further 3 h. After cooling the soln. to −10°, 1N NaOH (4.8 ml) and 30% aq. H_2O_2 soln. (1.6 ml) were added. After stirring for 16 h at r.t., sat. $Na_2S_2O_3$ soln. (20 ml) was added. The aq. layer was extracted with Et_2O (3 × 20 ml), the combined extract dried ($MgSO_4$) and evaporated, and the crude product purified by CC (silica gel, hexane/AcOEt 2:1): (2*R*)-**7a** (0.311 g, 89%). Colorless oil. Only one diastereoisomer was obtained (d.r. > 95:5, by NMR). $[\alpha]_D^{20} = -6.4$ (*c* = 0.90, $CHCl_3$).

tert-*Butyl (2*S*,3*R*,4*R*)-3-[[(*tert*-Butyl)dimethylsilyl]oxy]-4-hydroxy-2-(4-methoxybenzyl)pyrrolidine-1-carboxylate* ((2*S*)-**7**). As described for (2*R*)-**7**, with (2*S*)-**6** (60 mg, 0.14 mmol), dry THF (3 ml), 1M $BH_3 \cdot$THF in THF (0.6 ml, 0.6 mmol), 1N NaOH (0.86 ml), 30% aq. H_2O_2 soln. (0.30 ml). Workup with sat. $Na_2S_2O_3$ soln. (5 ml) and Et_2O (3 × 5 ml): (2*S*)-**7** (50 mg, 81%). Colorless oil. Only one diastereoisomer was obtained (d.r. > 95:5, by NMR). $[\alpha]_D^{20} = +7.5$ (*c* = 0.90, $CHCl_3$). IR (neat): 3430 (OH), 3060 (=C–H), 2955–2835 (C–H), 1695 (C=O). ^{1}H-NMR ($CDCl_3$): 0.08, 0.11 (2*s*, each 3 H, Me_2Si); 0.96 (*s*, ^{t}BuSi); 1.43 (*s*, ^{t}Bu); 1.85 (br. *s*, OH); 2.82–3.32 (*m*, H–C(2), 2 H–C(5), ArCH_2); 3.72 (*m*, H–C(4)); 3.77 (*s*, MeO); 4.06 (*t*, *J* = 6.8, H–C(3)); 6.78, 7.11 (2*d*, *J* = 8.6, 2 arom. H each). ^{13}C-NMR ($CDCl_3$; one signal for aryl not detected): −4.8, −4.5 (2*q*, Me_2Si); 18.2 (*s*, ^{t}BuSi); 26.0, 28.5 (2*q*, ^{t}Bu); 32.9 (*t*, ArCH_2); 50.2 (*t*, C(5)); 55.3 (*q*, MeO); 60.7 (*d*, C(2)); 74.3, 78.2 (2*d*, C(3), C(4)); 79.5 (*s*, ^{t}Bu); 113.7, 131.1 (2*d*, Ar); 154.6, 158.2 (2*s*, C=O, arom. C). EI-MS (80 eV): 437 (6, M^+), 364 (5, $[M - O^tBu]^+$), 316 (24, $[M - MeOBn]^+$), 260 (53, $[M - MeOBn - C_4H_8]^+$), 242 (11), 216 (61), 121 (41, $MeOBn^+$), 75 (70), 57 (100, $^tBuO^+$). HR-MS: 437.2575 (M^+, $C_{23}H_{39}NO_5Si^+$; calc. 437.2598).

tert-*Butyl (2*R*,3*S*,4*S*)-4-[[(*tert*-Butoxy)carbonyl]oxy]-3-[[(*tert*-butyl)dimethylsilyl]oxy]-2-(4-methoxybenzyl)pyrrolidine-1-carboxylate*. To a soln. of (2*R*)-**7** (0.387 g, 0.884 mmol) in dry pyridine (20 ml), DMAP (0.108 g, 0.884 mmol) and di(*tert*-butyl) carbonate (0.289 g, 1.32 mmol) were added at r.t. The mixture was stirred for 12 h, and the soln. was diluted with CH_2Cl_2 and extracted with sat. $NaHCO_3$ soln. (25 ml). The aq. layer was extracted with CH_2Cl_2 (3 × 20 ml), the combined extract dried ($MgSO_4$) and evaporated, and the crude product purified by CC (silica gel, hexane/AcOEt 6:1): Colorless oil (0.428 g, 90%). $[\alpha]_D^{20} = +21.4$ (*c* = 0.93, $CHCl_3$).

tert-*Butyl (2*S*,3*R*,4*R*)-4-[[(*tert*-Butoxy)carbonyl]oxy]-3-[[(*tert*-butyl)dimethylsilyl]oxy]pyrrolidine-1-carboxylate*. As described above, with (2*S*)-**7** (0.127 g, 0.290 mmol), dry pyridine (5 ml), DMAP (35 mg, 0.29 mmol), and di(*tert*-butyl) carbonate (95 mg, 0.44 mmol). Workup with sat. $NaHCO_3$ soln. (10 ml) and CH_2Cl_2 (3 × 10 ml) and CC (silica gel, hexane/AcOEt 5:1) yielded a colorless oil (147 mg, 95%). $[\alpha]_D^{20} = -17.6$ (*c* = 0.46, $CHCl_3$). IR (neat): 3020–2860 (=C–H, C–H), 1745, 1700 (C=O). ^{1}H-NMR ($CDCl_3$): 0.05, 0.10 (2*s*, Me_2Si); 0.94 (*s*, ^{t}BuSi); 1.37–1.44 (*m*, 2 ^{t}Bu); 2.80–3.53 (*m*, 2 H–C(5), ArCH_2); 3.77 (*s*, MeO); 4.04–4.19 (*m*, 1 H–C(2)); 4.26 (br. *t*, *J* ≈ 6.3, H–C(3)); 4.61–4.66 (*m*, 1 H–C(4)); 6.80 (*d*, *J* = 8.4, 2 arom. H); 7.13–7.17 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$): −5.0, −4.7 (2*q*, Me_2Si); 18.1 (*s*, ^{t}BuSi); 25.6, 25.9, 27.8, 27.9, 28.4, 28.6 (6*q*, ^{t}Bu); 31.6 (*t*, ArCH_2); 48.4 (*t*, C(5)); 55.3 (*q*, MeO); 60.6, 75.2, 79.0 (3*d*, C(2), C(3), C(4)); 79.6, 82.3 (2*s*, ^{t}Bu); 113.8, 130.8 (2*d*, arom. C); 128.2, 152.8, 154.4, 158.3 (4*s*, C=O, arom. C). EI-MS (80 eV): 537 (3, M^+), 424 (8, $[M - C_4H_8 - {}^tBu]^+$), 416 (11, $[M - MeOBn]^+$), 360 (12, $[M - C_4H_8 - MeOBn]^+$), 304 (40), 260 (16), 242 (24), 198 (30), 121 (36, $MeOBn^+$), 75 (12), 73 (16), 57 (100, $^tBu^+$). HR-MS: 537.3154 (M^+, $C_{28}H_{47}NO_7Si^+$; calc. 537.3122).

tert-*Butyl (2*R*,3*S*,4*S*-3-(Acetyloxy)-4-[[(*tert*-butoxy)carbonyl]oxy]-2-(4-methoxybenzyl)pyrrolidine-1-carboxylate* ((2*R*)-**8**). To a soln. of intermediate silyl ether (0.428 g, 0.795 mmol) in dry THF (9 ml), 1M Bu_4NF in THF (1.0 ml, 1.0 mmol) was added, and the mixture was stirred for 16 h at r.t. The soln. was diluted with CH_2Cl_2 (50 ml), and Et_3N (0.15 ml, 104 mg, 1.03 mmol) and DMAP (6.4 mg, 0.52 mmol) were added. After cooling to 0°, Ac_2O (0.097 ml, 105 mg, 1.03 mmol) was added, and the resulting soln. was stirred for 12 h. The mixture was diluted with CH_2Cl_2, the aq. layer extracted with CH_2Cl_2 (4 × 20 ml), the combined org. layer washed with sat.

$NaHCO_3$ and NaCl soln., dried ($MgSO_4$), and evaporated. The crude product was purified by CC (silica gel, hexane/AcOEt 2:1): (2*R*)-**8** (0.342 g, 92%). Pale yellow oil. $[\alpha]_D^{20} = +35.6$ ($c = 1.05$, $CHCl_3$).

tert-*Butyl (2*S*,3*R*,4*R*)-3-(Acetyloxy)-4-{[(*tert*-butoxy)carbonyl]oxy}-2-(4-methoxybenzyl)pyrrolidine-1-carboxylate* ((2*S*)-**8**). As described for (2*R*)-**8**, with intermediate silyl ether (50 mg, 0.092 mmol), dry THF (1 ml), 1M Bu_4NF in THF (0.12 ml, 0.12 mmol), then CH_2Cl_2 (4 ml), Et_3N (17 µl, 13 mg, 0.130 mmol), and DMAP (*ca.* 1 mg, 8 µmol), followed by Ac_2O (11 µl, 13 mg, 0.13 mmol): (2*S*)-**8** (34 mg, 79%). Pale yellow oil. $[\alpha]_D^{20} = -29.6$ ($c = 0.41$, $CHCl_3$). IR (neat): 3030–2835 (=C–H, C–H); 1745, 1700 (C=O). ^{1}H-NMR ($CDCl_3$): 1.46–1.52 (*m*, 2 ^{t}Bu); 2.04 (*s*, Ac); 2.79–3.62 (*m*, 2 H–C(5), ArCH_2); 3.77 (*s*, MeO); 4.38–4.46 (*m*, H–C(2)); 4.84 (*m*, H–C(4)); 5.13 (*dd*, $J = 6.6$, 5.9, H–C(3)); 6.81 (br. *d*, $J \approx 7.5$, 2 arom. H); 7.07 (*d*, $J \approx 7.5$, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 20.6 (*q*, *Me*CO); 27.6, 28.3 (2*q*, ^{t}Bu); 33.8 (*t*, Ar*C*H$_2$); 48.4 (*t*, C(5)); 55.2 (*q*, MeO); 58.4 (*d*, C(2)); 74.6, 75.8 (*d*, br. *d*, C(3), C(4)); 80.1, 83.0 (2*s*, ^{t}Bu); 113.9, 130.3 (2*d*, arom. C); 129.5, 152.4, 154.1, 158.2 (4*s*, *C*O^{t}Bu, arom. C); 169.6 (*s*, *C*OMe). EI-MS (80 eV): 465 (17, M^+), 344 (35, $[M - MeOBn]^+$), 336 (10), 288 (25, $[M - MeOBn - C_4H_8]^+$), 244 (15), 232 (100, $[M - MeOBn - C_4H_8 - C_4H_8]^+$), 188 (34), 170 (16), 128 (20), 126 (25), 121 (51, $MeOBn^+$), 84 (16), 57 (30, $^tBu_8^+$). HR-MS: 465.2400 (M^+, $C_{24}H_{35}NO_8^+$; calc. 465.2363).

*(2*R*,3*S*,4*S*)-3-(Acetyloxy)-4-hydroxy-2-(4-methoxybenzyl)pyrrolidinium Chloride* (*=(−)-Anisomycin Hydrochloride* [10b]; (2*R*)-**9**). A soln. of (2*R*)-**8** (0.230 g, 0.494 mmol) in 4M HCl in dioxane (10 ml) was stirred for 5 h at 0°. H_2O (11 µl, 0.59 mmol) was added, and the mixture was stirred for further 30 min at 0°. After evaporation, the residue was recrystallized from MeOH/Et_2O: (2*R*)-**9** (99 mg, 66%). Colorless crystals. M.p. 178–186° ([10b][20]: m.p. 187–188°). $[\alpha]_D^{20} = +3.95$ ($c = 0.96$, MeOH) ([10b]: $[\alpha]_D^{20} = +4.2$ ($c = 0.51$, MeOH); [20]: $[\alpha]_D^{20} = +4.0$ ($c = 0.28$, MeOH)). ^{1}H-NMR (CD_3OD): 2.20 (*s*, Ac); 2.96, 3.06 (*AB* of *ABX*, $J_{AB} = 14.1$, $J_{AX} = 8.3$, $J_{BX} = 7.1$, ArCH_2); 3.14 (*d*, $J = 12.5$, 1 H–C(5)); 3.58 (*dd*, $J = 2.5$, 4.8, 1 H–C(5)); 3.81 (*s*, MeO); 4.07 (*ddd*, $J = 8.3$, 7.1, 3.3, H–C(2)); 4.34 (br. *d*, $J \approx 4.8$, H–C(4)); 5.04 (br. *d*, $J \approx 3.3$, H–C(3)); 6.94, 7.24 (2*d*, $J = 8.7$, 2 arom. H each). ^{13}C-NMR (CD_3OD): 17.0 (*q*, *Me*CO); 28.6 (*t*, Ar*C*H$_2$); 49.0 (*t*, C(5)); 52.1 (*q*, MeO); 60.1 (*d*, C(2)); 69.8 (*d*, C(4)); 74.6 (*d*, C(3)); 112.0, 127.4 (2*d*, arom. C); 125.4, 157.0 (2*s*, arom. C), 167.2 (*s*, C=O). FAB-MS (pos.): 266 (100, $[M - Cl]^+$), 206 (5, $[M - Cl - AcOH]^+$), 121 (28, $MeOBn^+$), 89 (11), 84 (11), 77 (12). Anal. calc. for $C_{14}H_{20}ClNO_4$ (301.8): C 55.72, H 6.68, N 4.64; found: C 55.10, H 6.39, N 4.49.

*(2*S*,3*R*,4*R*)-3-(Acetyloxy)-4-hydroxy-2-(4-methoxybenzyl)pyrrolidinium Chloride* (*=(+)-Anisomycin Hydrochloride*; (2*S*)-**9**). As described for (2*R*)-**9**, with (2*S*)-**8** (33 mg, 0.071 mmol), 4M HCl in dioxane (1.50 ml), and H_2O (2 µl, 0.11 mmol): (2*S*)-**9** (13 mg, 61%). Colorless crystals. M.p. 179–187°; because of the small amount of product the low optical rotation, a specific value could not be unambiguously determined.

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