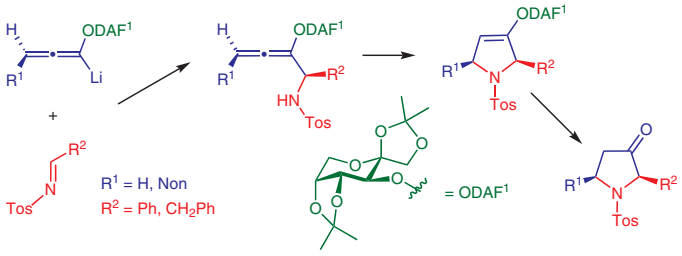
Synthesis A. Hausherr et al. Paper

Additions of Carbohydrate-Derived Alkoxyallenes to Imines and Subsequent Reactions to Enantiopure 2,5-Dihydropyrrole Derivatives

Arndt Hausherr
Reinhold Zimmer
Hans-Ulrich Reissig*

Institut für Chemie und Biochemie, Freie Universität Berlin,
Takustr. 3, 14195 Berlin, Germany
hans.reissig@chemie.fu-berlin.de



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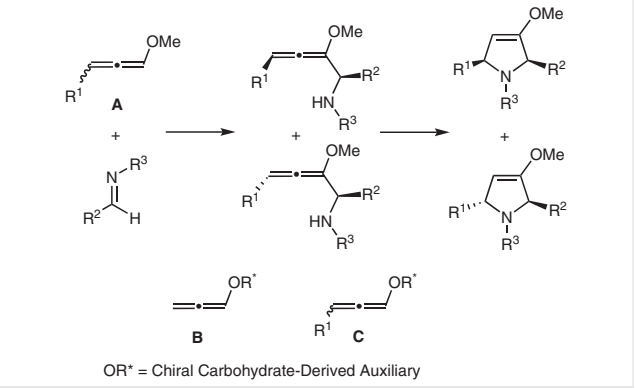
Abstract The additions of six alkoxyallenes bearing carbohydrate-derived chiral auxiliaries to imines were systematically studied. The reactions of three lithiated 1-alkoxypropa-1,2-dienes with an *N*-tosyl imine revealed that the diacetone fructose-derived auxiliary provided the highest diastereoselectivity of 91:9. The preferred absolute configuration of the newly formed stereogenic center was determined by subsequent ozonolysis of the allene moiety, transesterification and comparison with literature data. The analogous reactions of three axially chiral 3-nonyl-substituted 1-alkoxyallenes with these auxiliaries confirm these results and also prove that the configuration of the generated stereogenic center was only steered by the auxiliaries, whereas the chiral axis has essentially no influence. In general, four diastereomers were obtained in various portions, depending on the ratio of the two precursor allene diastereomers and on the auxiliary employed. The obtained diastereomeric allenyl amines were cyclized under different conditions. As expected, under basic conditions, a stereospecific cyclization occurred, whereas under silver nitrate catalysis partial isomerization at the allene stage was observed. Under both conditions the 2,5-*cis*-disubstituted dihydropyrroles were formed faster than the *trans*-isomers. Several of the 2-substituted or 2,5-disubstituted dihydropyrrole derivatives could be isolated in diastereomerically pure form and were subsequently converted into the expected pyrrolidin-3-ones by removal of the carbohydrate-derived auxiliary under acidic conditions. The desired products were obtained in good yield and with high enantiopurity. They are suitable starting materials for the synthesis of enantiopure pyrrolidine natural products.

Key words alkoxyallenes, axial chirality, carbohydrate derivatives, imines, lithiation, nitrogen heterocycles, pyrrolidines

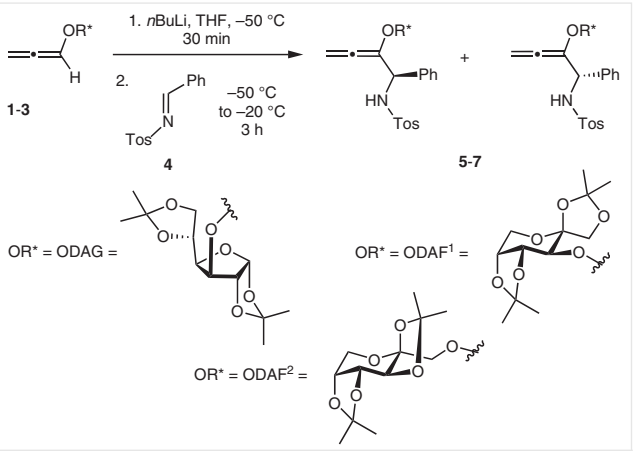
Axially chiral 1,3-disubstituted alkoxyallenes such as **A** have rarely been studied in organic synthesis.[1] Considering the preparative potential[2] of simple alkoxyallenes such as methoxyallene, a broad variety of compounds should be available if additional substituents are installed at the C-3 terminus of these cumulenes. We recently described the synthesis of racemic 3-alkyl-substituted alkoxyallenes **A**[3] and also reported on their addition to imines,[4] which provided allenyl amines (Scheme 1). Unfortunately, the diastereoselectivities of the addition reactions studied were low.



Scheme 1 Synthesis of 2,5-disubstituted dihydropyrroles starting from 3-alkyl-substituted methoxyallenes **A** and general structure of alkoxyallenes **B** and **C**, bearing chiral auxiliaries

The prepared allenyl amines undergo a 5-*endo*-*trig* cyclization under appropriate conditions and delivered 2,5-dihydropyrrole derivatives. These heterocycles are suitable intermediates for further synthetic elaboration and for the synthesis of natural products with a pyrrolidine substructure.[5] Alkoxyallenes **B**, bearing carbohydrate-derived auxiliaries, are known and have been employed in hetero-Diels–Alder reactions[6] or, after lithiation, in additions to electrophiles.[7] We also described methods to prepare similar 3-alkyl-substituted alkoxyallenes **C**.[8] In this report, we present our results on the additions of lithiated **B** and **C** to imines followed by cyclization and other transformations. The influence of the axial chirality and of the carbohydrate auxiliary on the diastereoselectivity of addition was of particular interest. Experiments were also performed to set up an enantioselective synthesis of the natural product preussin and analogues thereof.[9]

The preparation of alkoxyallenes **1–3** has been published.[8] The selectively protected carbohydrate-derived auxiliaries were efficiently alkylated at their free hydroxyl group by propargyl bromide and the subsequent base-catalyzed isomerizations furnished the corresponding allenes connected to the oxygen of the auxiliaries (at C-3 for diacetone glucose derivative **1** and diacetone fructose derivative **2**, and at C-1 for the regioisomeric diacetone fructose derivative **3**, see Scheme 2). The lithiation of the three alkoxyallenes with *n*-butyllithium in tetrahydrofuran under standard conditions and subsequent treatment with *N*-tosyl imine **4** provided, after aqueous work-up, the allenyl imines **5–7** in moderate to good yields and with differing diastereoselectivities (Table 1). Whereas the diacetone glucose derived alkoxyallene gave a 70:30 ratio of the two diastereomeric allenyl imines **5** (entry 1), this ratio was enhanced to very good 91:9 for **6**, when diacetone fructose derivative **2** was used as precursor (entry 2). The isomeric diacetone fructose-derived allene **3** gave only a 40:60 ratio of the two diastereomers of **7**, but with inverted preference.



Scheme 2 Synthesis of allenyl amines **5–7** by lithiation of alkoxyallenes **1–3** and additions to *N*-tosyl imine **4** (for details see Table 1)

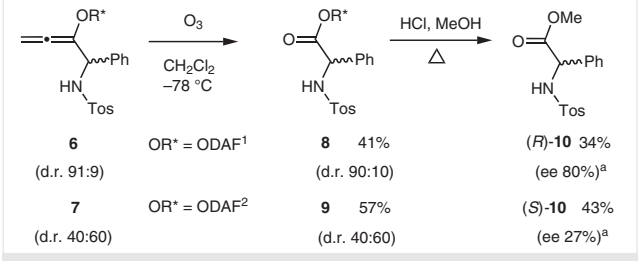
Table 1 Additions of Alkoxyallenes **1–3**, Bearing Carbohydrate-Derived O-Substituents, to *N*-Tosyl Imine **4** Leading to Allenyl Amines **5–7**

Entry	Allene	OR*[a]	Imine	Product	d.r.[b] (*R*/*S*)[c]	Yield (%)[d]
1	**1**	ODAG	**4**	**5**	70:30	69
2[e]	**2**	ODAF[1]	**4**	**6**	91:9	85
3	**3**	ODAF[2]	**4**	**7**	40:60	44[f]

[a] For definition of OR* see Scheme 2.
[b] Ratio determined by HPLC or NMR analysis of the crude product.
[c] Assignment by subsequent reactions.
[d] Yield of purified product.
[e] Slight modification: addition of imine **4** at –80 °C (30 min), then warmed to –30 °C within 3 h and stirring at this temperature for 12 h.
[f] Precursor **3** (30%) was reisolated.

For the determination of the predominating absolute configuration at the newly formed stereogenic center, we converted allenyl imines **6** and **7** into the corresponding esters **8** and **9** and finally into the known protected phenylglycine derivative **10** (Scheme 3). Ozonolysis of allenyl alcohols and amines has been employed earlier in our group to convert these into the corresponding ester.[10] This oxidative removal of two carbon atoms proves that lithiated alkoxyallenes are also synthetic equivalents of acyl anions and some years ago we used this capacity in a synthesis of neuraminic acid.[11] Under standard conditions of ozonolysis, the esters **8** and **9**, still containing the carbohydrate-derived auxiliaries, were obtained in moderate yields, but with essentially unchanged diastereomeric ratios. An acid-catalyzed transesterification was then performed to convert the two intermediates into a compound with known absolute configuration. Although the yields under fairly harsh conditions were only moderate, the stereogenic center was not touched since **8** provided (*R*)-**10** with an ee of 80%, whereas **9** furnished (*S*)-**10** with a lower ee of 27%. These values were calculated from the observed optical rotations and from the reported value of enantiopure (*R*)-**10**.[12] More importantly, the shown sequences reveal that the two carbohydrate-derived auxiliaries used induce opposite directions of asymmetry, as indicated in Table 1.

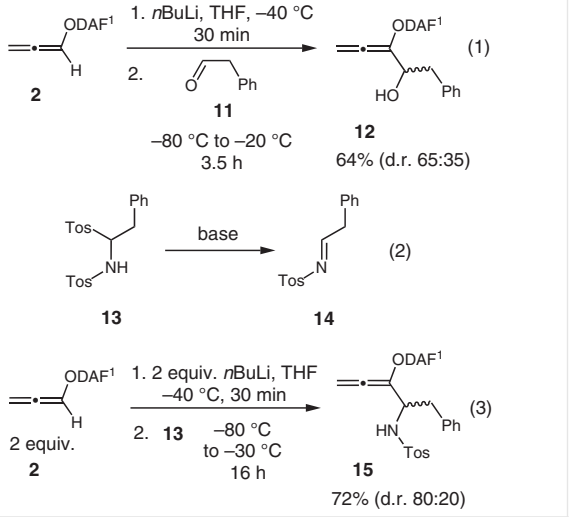
Given the number of stereogenic centers and the large number of oxygen atoms as potential coordination partners for the lithium cation,[13] it is not possible to propose a serious mechanistic model for the observed diastereoselectivities. We can just state that diacetone fructose-derived substituent DAF[1] is a reasonably good, though not perfect, auxiliary attached to alkoxyallenes. As an additional benefit, the very low cost and simple methodology for the synthesis of alkoxyallene **2** should be emphasized here.



Scheme 3 Ozonolysis of allenyl amines **6** and **7** to esters **8** and **9** followed by transesterification to give (*R*)-**10** and (*S*)-**10**, respectively (for substituents OR* see Scheme 2). [a] Calculated by comparison of the optical rotation with literature data.

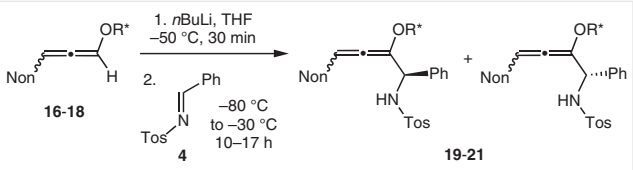
Two additional reactions were performed with lithiated alkoxyallene **2** to gain information for the planned synthesis of preussin. Given that a benzyl group has to be installed at C-2 of the pyrrolidine skeleton of this natural product, we studied additions of lithiated **2** to phenylethanal (**11**) and to its *N*-tosyl imine congener **14** (Scheme 4). From **2** and **11** we obtained the expected allenyl alcohol **12** in good yield

as a 65:35 mixture of diastereomers (Equation 1). The corresponding imine **14** is not stable due to its easy tautomerization to the corresponding *N*-tosyl-substituted enamine. Fortunately, the *C*,*N*-ditosyl amine **13** is an excellent alternative because it easily undergoes elimination to **14** by treatment with base (Equation 2), which is efficiently trapped by a suitable nucleophile to give the corresponding addition products.[14] Hence, we examined this option to generate imine **14** by adding two equivalents of lithiated alkoxyallene **2** to its precursor **13**; gratifyingly, we obtained the expected allenyl amine **15** in good yield (Equation 3). The diastereoselectivity of ca. 80:20 lies between the ratio observed in additions of lithiated **2** to imine **4** and to aldehyde **11**, respectively.



Scheme 4 Additions of lithiated alkoxyallene **2** to aldehyde **11** and to imine **14** leading to allenyl alcohol **12** and allenyl amine **15** (for substituent ODAF[1] see Scheme 2)

We then investigated the axially chiral 3-nonyl-substituted alkoxyallenes **16–18**, which — depending on the method applied for their synthesis — are available in differing diastereomeric ratios.[8] We already knew from the model reactions with racemic compounds that the chirality of the allene axis has almost no influence on the (relative) configuration of the newly formed stereogenic center.[4] This was fully confirmed by the results obtained with **16–18** and *N*-tosyl imine **4** as model electrophile (Scheme 5, Table 2). Starting with the DAG-substituted alkoxyallene **16** (d.r. 50:50), we could confirm that this auxiliary induces only moderate diastereoselectivity (entry 1). The four diastereomers of allenyl amine **19** were obtained in a ratio of 37:37:13:13 and were assigned to the configurations as depicted, assuming that the axial chirality has no influence on the selectivity. This hypothesis was substantiated by converting diastereomers into subsequent products with known configuration (see below). As expected from the reactions of alkoxyallene **2**, the addition of its 3-nonyl-substituted congener **17** provided the highest *R*/*S*-selectivity (entry 2). On the other hand, alkoxyallene **18** furnished a product mixture with the *S*-configured allenyl amines in slight excess (entry 3).



Scheme 5 Synthesis of allenyl amines **19–21** by addition of lithiated alkoxyallenes **16–18** to *N*-tosyl imine **4** (for details see Table 2, for substituents OR* see Scheme 2)

Table 2 Additions of 3-Nonyl-Substituted Alkoxyallenes **16–18**, Bearing Carbohydrate-Derived O-Substituents, to *N*-Tosyl Imine **4** Leading to Allenyl Amines **19–21**

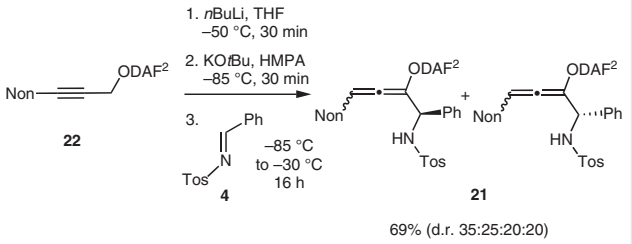
Entry	Allene *R*:*aS*	OR*	Product	d.r.[a] *R*,*aR*/*R*,*aS*/*S*,*aR*/*S*,*aS*[b]	Yield (%)[c]
1	**16** 50:50	ODAG	**19**	37:37:13:13 (*R*/*S* = 74:26; *aR*/*aS* = 50:50)	88[d]
2	**17** 75:25	ODAF[1]	**20**	69:21:6:4 (*R*/*S* = 90:10; *aR*/*aS* = 75:25)	99[e]
3	**18** 55:45	ODAF[2]	**21**	20:14:35:31[f] (*R*/*S* = 34:66; *aR*/*aS* = 55:45)[g]	76

[a] Determined by HPLC analysis of the crude product.
[b] Assignment of the configurations by subsequent reactions (see text).
[c] Yield of purified product.
[d] Major fraction (66%, *R*,*aR*/*R*,*aS* = 50:50), minor fraction (22%, *S*,*aR*/*S*,*aS* = 50:50).
[e] All four diastereomers; after HPLC separation: major fraction (68%, *R*,*aR*/*S*,*aR*/*S*,*aS* = 87:9:4), minor fraction (23%, *R*,*aS*).
[f] No assignment possible.
[g] Assignments and ratios assuming that axial chirality of **18** has no influence on the newly formed stereogenic center.

The isolated major fraction of allenyl amine **19** was also subjected to the ozonolysis/transesterification sequence, which provided phenylglycine derivative (*R*)-**10** in 27% overall yield and with an ee of 86%. This confirms that in this fraction both diastereomers have identical *R*-configuration at the stereogenic center, but that the chiral axis has different configurations. It also shows that the diacetone glucose-derived auxiliary DAG, like the fructose-derived auxiliary DAF[1] (Scheme 3), preferentially induces *R*-configuration at the newly formed stereogenic center, but with considerably lower selectivity. The assignments given for entries 2 and 3 of Table 2 are based on this experiment and on subsequent cyclization reactions of allenyl amines **20** and **21**.

As an alternative, we also examined a method based on a study of the Brandsma group.[15] Nonyl-substituted propargyl ether **22** with DAF[2] as auxiliary was deprotonated and potassium *tert*-butoxide and hexamethylphosphoramide (HMPA) were added. The reaction of the in situ generated

metallated allene to imine **4** was unselective and afforded 24% of allene **18** (d.r. 60:40) and 69% of all four diastereomers of **21** (d.r. 35:25:20:20) (Scheme 6). Given this moderate selectivity, we did not study this method in additional cases.



Scheme 6 Synthesis of allenyl amines **21** starting from propargyl ether **22** (for substituent ODAF[2] see Scheme 2)

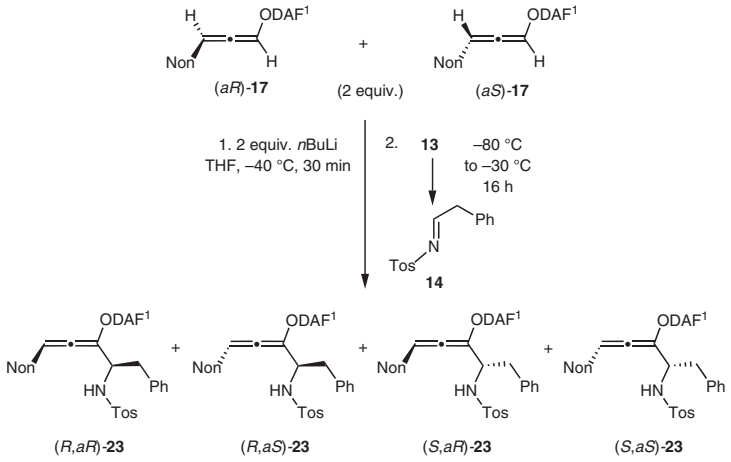
For the synthesis of preussin, we planned to combine a 3-nonyl-substituted alkoxyallene with *N*-tosyl imine (**14**). As auxiliary we selected the DAF[1] group, which provided the highest diastereoselectivities in the model reactions presented above, and as a reliable imine source we again employed the bis-tosylated compound **13**. The precursor allene **17** was available with different ratios of diastereomers[3] and hence two cases are presented (Scheme 7, Table 3). In entry 1, **17** with an *aR*/*aS* ratio of 15:85 was combined with in situ generated **14**, whereas in entry 2 a 75:25 mixture was used. In both cases, two equivalents of the lithiated allene were employed because one equivalent is lost by the conversion of **13** into **14**; the excess of **17** could be partially regained. For reisolated alkoxyallene **17** of entry 1 (69% yield) a diastereomeric ratio of 15:85 was determined, which was identical to that of the starting material. This observation suggests that the intermediate lithiated **17** is configurationally stable under the reaction conditions employed. The second equivalent of lithiated allene **17** efficiently adds to **14** and furnished allenyl amine **23** in 81% and 85% yield, respectively, after chromatographic purification. The ratios of the four diastereomers were determined by HPLC analysis of the crude product. These ratios agree well with the calculated ratios if it is assumed that the diastereoselectivity is identical to that observed in the addition of allene **2** to **14** (80:20, see Scheme 4) and that the chirality of the allene axis has negligible influence. This last assumption is based on our reported reactions with racemic model compounds.[4]

Table 3 Synthesis of Allenyl Amine **23** by Addition of Lithiated 3-Nonyl-Substituted Alkoxyallene **17** to *N*-Tosyl Imine **14**

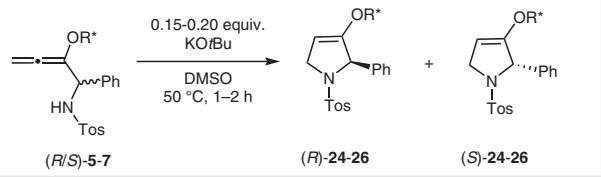
Entry	Allene **17** *aR*/*aS*	Allenyl Amine **23** *R*,*aR*/*R*,*aS*/*S*,*aR*,*S*/*S*,*aS*	Yield (%)[a]
1	15:85	11:68:0:21[b] (*R*/*S* = 79:21; *aR*/*aS* = 11:89) (12:68:3:17)[c]	81
2	75:25	54:22:21:3[b] (*R*/*S* = 76:24; *aR*/*aS* = 75:25) (60:20:15:5)[c]	85

[a] Yield of purified product.
[b] Determined by HPLC analysis.
[c] Calculated ratios (see text).

After these addition reactions and the (partial) configurational assignments, we studied the cyclizations of the allenyl amines.[16] Treatment with ca. 0.2 equiv of potassium *tert*-butoxide in dimethyl sulfoxide at 50 °C converted allenyl amines **5**–**7** into the dihydropyrrole derivatives **24**–**26** (Scheme 8, Table 4). The yields of purified products were in general very good and, in the case of (*R*/*S*)-**26** (entry 3), we separated the two diastereomers by HPLC. Most importantly, the three entries show that the diastereomeric ratios did not change under the basic reaction conditions applied.



Scheme 7 Synthesis of allenyl amine **23** by addition of lithiated alkoxyallene **17** to *N*-tosyl imine **14** generated in situ from **13** (for details see Table 3, for substituent ODAF[1] see Scheme 2)



(*R*/*S*)-**5-7** (*R*)-**24-26** (*S*)-**24-26**

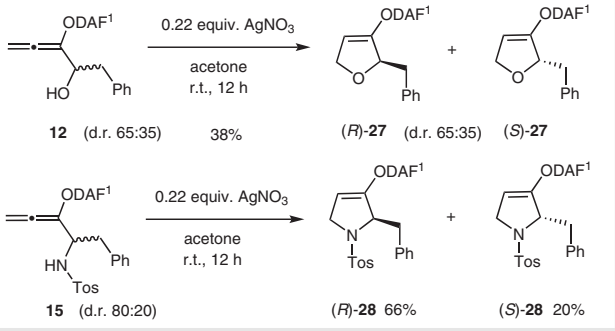
Scheme 8 Cyclizations of allenyl amines (*R*/*S*)-**5–7** under basic conditions to dihydropyrrole derivatives (*R*/*S*)-**24–26** (for details see Table 4, for substituents OR* see Scheme 2)

Table 4 Potassium *tert*-Butoxide-Promoted Cyclizations of Allenyl Amines (*R*/*S*)-**5–7** to Dihydropyrrole Derivatives (*R*/*S*)-**24–26**

Entry	Allenyl amine, *R*/*S*	OR*	Product, *R*/*S*[a]	Yield (%)[b]
1	**5**, 70:30	ODAG	**24**, 70:30	68
2	**6**, 91:9	ODAF[1]	**25**, 90:10	75
3	**7**, 40:60	ODAF[2]	**26**, 40:60	84[c]

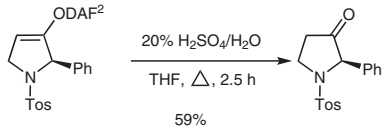
[a] Determined by ^{1}H NMR spectroscopy.
[b] Yield of purified product.
[c] The two isomers were separated by HPLC to provide 31% of (*R*)-**26** and 53% of (*S*)-**26**.

As an alternative to the basic cyclization conditions, we also examined the known silver nitrate catalysis.[17,18] The allenyl alcohols (*R*/*S*)-**12** furnished the dihydrofuran derivatives (*R*)-**27** and (*S*)-**27** in low yield and unchanged diastereomeric ratio (Scheme 9). This method also converted the analogous allenyl amines (*R*/*S*)-**15** into the expected dihydropyrrole derivative (*R*)-**28** and (*S*)-**28**, isolated after separation in 66% and 20% yield, respectively.



Scheme 9 Silver nitrate-catalyzed cyclizations of (*R*/*S*)-**12** and (*R*/*S*)-**15** providing dihydrofuran and dihydropyrrole derivatives (*R*/*S*)-**27** and (*R*/*S*)-**28**, respectively (for substituent ODAF[1] see Scheme 2)

Removal of the chiral auxiliary of diastereomerically pure dihydropyrrole derivative (*R*)-**26** by hydrolysis of the enol ether moiety under strongly acidic conditions gave the 2-phenyl-substituted pyrrolidin-3-one (*R*)-**29** in 59% yield (Scheme 10). This compound was carefully analyzed by ^{1}H NMR spectroscopy in the presence of the chiral shift reagent europium(III) tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorate] and no splitting of the signals was observed. A control experiment with racemic **29**[16a,c] revealed that already 3% of the shift reagent was sufficient to induce signal splitting. We can therefore assume that our sample of (*R*)-**29** has an enantiomeric purity of >95:5 and that even the harsh hydrolysis conditions did not induce racemization at the C–H acidic position C-2 of the compound. The absolute configuration of (*R*)-**29** and its precursor (*R*)-**26** is based on the ozonolysis and transesterification experiments with its precursor **7** (see Scheme 3). A similar approach to enantiopure 2-substituted pyrrolidin-3-one derivatives has been reported by Liu.[7e]

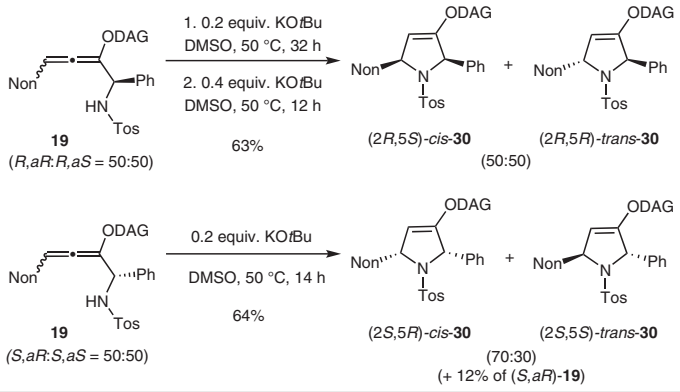


(*R*)-**26** (*R*)-**29**

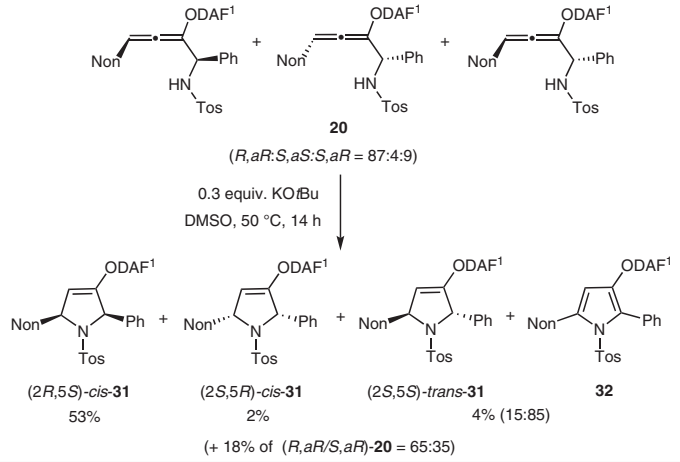
Scheme 10 Hydrolysis of minor diastereomer (*R*)-**26** to enantiopure pyrrolidin-3-one (*R*)-**29** with sulfuric acid (for substituent ODAF[2] see Scheme 2)

The cyclization results of allenyl amines with 3-nonyl substituents such as **19**, **20** or **23** are more complex due to existence of four diastereomers caused by the chiral axis. When a 50:50 mixture of DAG-substituted (*R*,*aR*/*R*,*aS*)-**19** was cyclized under the approved basic conditions with potassium *tert*-butoxide, longer reaction times were required (Scheme 11). The 3-alkyl substituent considerably retards the cyclization, as already observed with the model compounds.[4] Hence, **19** was heated in total for 44 h to achieve full conversion into (2*R*,5*S*)-*cis*-**30** and (2*R*,5*R*)-*trans*-**30**. The cyclization under basic conditions is stereospecific and therefore the two compounds were formed as a 50:50 mixture. The second pair of diastereomers (*S*,*aR*/*S*,*aS*)-**19** afforded the two diastereomers (2*S*,5*R*)-*cis*-**30** and (2*S*,5*S*)-*trans*-**30** in 64% yield, proving that no cross-over to the other diastereomers occurred. Since the base-promoted cyclization was already stopped after 14 h, 12% of the precursor (*S*,*aR*)-**19** were re-isolated and (2*S*,5*R*)-*cis*-**30** was formed in excess. This confirms our results in the racemic series where the pro-*trans*-precursors cyclized considerably slower than pro-*cis*-diastereomers.

Similar results were observed with the DAF[1]-substituted allenyl amine **20** under basic conditions (Scheme 12). Starting with a 87:4:9 mixture of three diastereomers, the expected cyclization products (2*R*,5*S*)-*cis*-**31** and (2*S*,5*R*)-*cis*-**31** were formed and separated from the crude product mixture. The third diastereomer (2*S*,5*S*)-*trans*-**31** was isolated only as a minor component in a mixture together with pyrrole **32**, which was apparently generated by oxidation of the dihydropyrroles. In addition, 18% of the precursor (*R*,*aR*)- and (*S*,*aR*)-**20** was re-isolated as a 65:35) mixture, again showing the slowness of the cyclization.



Scheme 11 Cyclizations of diastereomers of **19** under basic conditions to dihydropyrrole derivatives **30** (for substituent ODAG see Scheme 2)

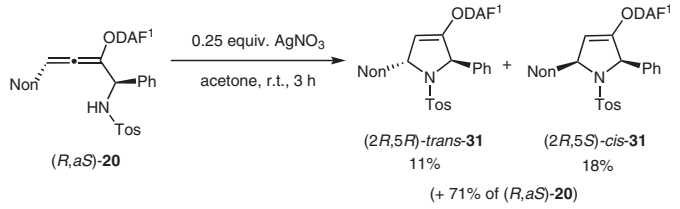


Scheme 12 Base-promoted cyclization of allenyl amine **20** to dihydropyrrole derivative **31** (for substituent ODAF[1] see Scheme 2)

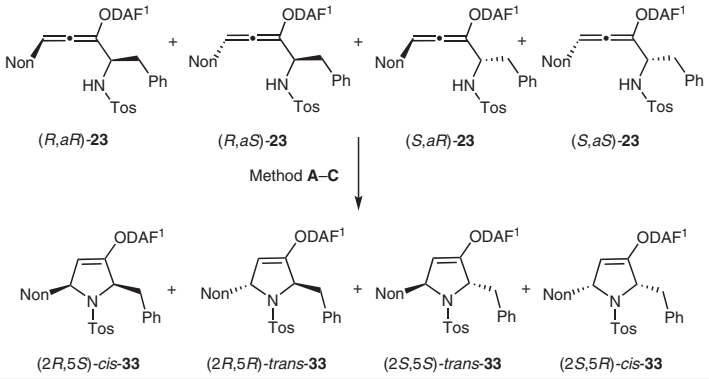
With diastereomerically pure (*R*,*aS*)-**20**, the silver nitrate-catalyzed cyclization was examined. After 3 h the majority of the precursor was recovered unchanged and (2*R*,5*R*)-*trans*-**31** was isolated together with (2*R*,5*S*)-*cis*-**31** (Scheme 13). This experiment again shows that cyclizations in the presence of silver nitrate are not stereospecific due to partial isomerization of the chiral axis at the allenyl amine stage.[4] Again, the formation of *cis*-compounds is kinetically favored, hence leading to a slight excess of (2*R*,5*S*)-*cis*-**31**.

With the DAF[2]-substituted allenyl amines **21** very similar results were obtained, confirming the stereospecificity of the cyclization under basic conditions.[9a]

The diastereomers of allenyl amine **23** were prepared as potential precursors of preussin and its stereoisomers. Hence their cyclizations to dihydropyrroles **33** were systematically investigated employing methods **A**–**C** (Scheme 14, Table 5). In entry 1, a 12:68:3:17 mixture was used in a silver nitrate-promoted cyclization (method **A**) and the four conceivable dihydropyrroles **33** were formed in a 68:12:3:17 ratio as analyzed by HPLC of the crude product



Scheme 13 Partial silver nitrate-promoted cyclization of (*R*,*aS*)-**20** to dihydropyrrole **31** (for substituent ODAF[1] see Scheme 2)



Scheme 14 Cyclizations of allenyl amine **23** to dihydropyrrole derivative **33** under different conditions (for details see Table 5, for substituent ODAF[1] see Scheme 2)

mixture. Three fractions were obtained by preparative HPLC consisting of (2*R*,5*S*)-*cis*-**33** together with (2*S*,5*S*)-*trans*-**33** (49% yield, ratio 95:5), (2*R*,5*R*)-*trans*-**33** (11%) and (2*S*,5*R*)-*cis*-**33** (14% yield). The shifted ratio of products again shows that the silver nitrate-promoted cyclization is accompanied by an isomerization of the allene axis and that the formation of *cis*-configured products is generally favored. This result was confirmed by the data shown in entry 2, where a 54:22:21:3 mixture was employed under slightly modified[19] silver nitrate catalysis (method **B**). In entry 3 the approved basic conditions were used (method **C**) to convert a 54:22:21:3 mixture of allenyl amines **23** into the two dihydropyrroles (2*R*,5*S*)-*cis*-**33** and (2*S*,5*R*)-*cis*-**33** in 61% yield (ratio 90:10); the two allenyl amine diastereomers (*R*,*aS*)-**23** and (*S*,*aR*)-**23**, that would have led to the *trans*-configured products, were isolated unchanged in this experiment in 33% yield. This result again demonstrates the stereospecificity of the base-promoted cyclization and the lower reactivity of pro-*trans* allenyl amines such as (*R*,*aS*)-**23** and (*S*,*aR*)-**23**.[4]

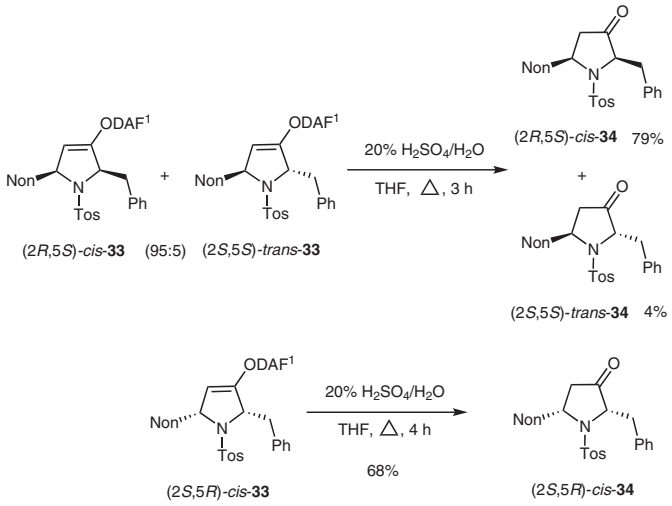
Gore et al.[20] reported the addition of simple lithiated alkoxyallenes to hydrazones, including SAMP- or RAMP-derived hydrazones.[21] The primary addition products cyclized under the reaction conditions to furnish the expected dihydropyrrole derivatives with the chiral auxiliaries linked to the pyrrole nitrogen. Given that this method provided excellent diastereoselectivities, we also briefly investigated the addition of racemic 3-nonyl-substituted methoxyallene to the benzaldehyde derived SAMP-hydrazone. The lithiated allene provided the two expected diastereomeric dihydropyrroles in 22% and 3% yield.[9a] Although in this unoptimized reaction the yield was low, it demonstrated the potential of this method. However, the corresponding phenylethanal-derived RAMP-hydrazone, required to approach preussin, did not furnish the expected addition and cyclization products. Apparently, this electrophile is not suitable for lithiated alkoxyallene additions.[22]

Table 5 Cyclizations of Allenyl Amine **23** with Silver Nitrate (Methods **A** or **B**) or with Potassium *tert*-Butoxide (Method **C**) Leading to Diastereomers of Dihydropyrrole **33** (see Scheme 14)

Entry	Allenyl Amine **23** *R*,*aR*/*R*,*aS*/*S*,*aR*/*S*,*aS*[a]	Method[b]	Dihydropyrrole **33** 2*R*,5*S*/2*R*,5*R*/2*S*,5*S*/2*S*,5*R*[c] (yields of separated diastereomers)
1	12:68:3:17	**A**	68:12:3:17 (47%,[d] 11%, 2%,[d] 14%)
2	54:22:21:3	**B**	54:24:14:8 (38%, 18%, 8%, 8%)
3	54:22:21:3	**C**	90:0:0:10[e] (61%)

[a] Ratio determined by HPLC analysis (Table 3), in the case of entry 1 the calculated ratio is listed.
[b] Method **A**: $AgNO_3$ (0.2 equiv), acetone, r.t., 16 h; Method **B**: $AgNO_3$ (0.2 equiv), K_2CO_3 (2.2 equiv), acetonitrile, r.t., 14 h; Method **C**: KO*t*Bu (0.1 equiv), DMSO, 50 °C, 12 h.
[c] Ratio of diastereomers in the crude product determined by HPLC.
[d] Obtained as 95:5 mixture of (2*R*,5*S*)- and (2*S*,5*S*)-diastereomers.
[e] Ratio determined by ^{1}H NMR analysis of the purified products; in addition, 33% of a mixture of (*R*,*aS*)-**23** and (*S*,*aR*)-**23** were recovered.

With diastereomerically highly enriched or pure samples of **33** in hand, the removal of the auxiliary was examined (Scheme 15). Hydrolysis of the enol ether moiety of a (2*R*,5*S*)-*cis*/(2*S*,5*S*)-*trans*-**33** mixture (95:5) furnished the two pyrrolidin-3-ones (2*R*,5*S*)-*cis*-**34** and (2*S*,5*S*)-*trans*-**34**, which could be separated by column chromatography and were isolated in 79% and 4%, respectively. Diastereomerically pure (2*S*,5*R*)-*cis*-**33** analogously provided the corresponding pyrrolidinone (2*S*,5*R*)-*cis*-**34** in good yield. The samples of the two enantiomers (2*R*,5*S*)-*cis*-**34** and (2*S*,5*R*)-*cis*-**34** showed optical rotations $[\alpha]_D^{20}$ of –39.4 and of +41.5, respectively. This already indicates that our assignments are correct and that these pyrrolidinones are enantiomerically pure as already shown above for compound (*R*)-**29**. An unequivocal confirmation of the high enantiopurity and the assigned absolute configuration of (2*R*,5*S*)-*cis*-**34** was obtained by its conversion into the unnatural enantiomer of preussin.[9] The recorded optical rotation of the final product



Scheme 15 Removal of the auxiliary DAF[1] by acidic hydrolysis converting the dihydropyrrole derivatives **33** into pyrrolidin-3-one derivatives **34** (for substituent ODAF[1] see Scheme 2)

nicely matched the reported literature data. The syntheses of racemic preussin, enantiopure (–)-preussin and analogues thereof as well as their biological evaluation will be reported in a subsequent publication.[9b]

In conclusion, we could demonstrate that the diacetone fructose-derived auxiliary DAF[1] steers the additions of the corresponding lithiated alkoxyallenes to imines with reasonably good selectivities.[23] The primarily obtained allenyl amines **6**, **15**, **20** and **23** were formed with preferential *R*-configuration at the newly formed stereogenic center (d.r. 76:24 to 91:9). Addition of the axially chiral 3-nonyl-substituted alkoxyallene **17** showed that the chirality of the axis has no influence on the diastereoselectivity of the reaction. Hence, four diastereomeric allenyl imines were isolated, the proportion of which depends on the ratio of the two precursor alkoxyallene stereoisomers. The obtained allenyl amines were cyclized under basic conditions to stereospecifically furnish dihydropyrrole derivatives, whereas the silver nitrate-promoted cyclizations proceed with partial stereochemical cross-over as observed earlier.[4] Dihydropyrrole derivatives such as (*R*)-**26** or (2*R*,5*S*)-*cis*-**33** were converted into the expected 2-substituted or 2,5-disubstituted pyrrolidin-3-one derivatives (*R*)-**29** or (2*R*,5*S*)-*cis*-**34** without racemization or epimerization. The enol ether moiety of dihydropyrroles such as **26** or **33** should also allow the introduction of other functional groups at C-4, for example by electrophilic halogenation or hydroboration. Overall, the sequence of reactions developed in the current study shows the potential of auxiliary-derived enantiopure alkoxyallenes as key C3-building blocks in stereoselective synthesis.

Reactions were generally performed under argon in flame-dried flasks, and the components were added by using a syringe. Reagents were purchased and used without further purification. Potassium *t*-butoxide was freshly sublimed in vacuo before use. Products were purified by flash chromatography on neutral aluminum oxide (6% water, activity III, Merck-Schuchardt or Fluka) or on silica gel (32–63 µm, Merck-Schuchardt or Fluka). HPLC was performed with nucleosil 50–5 columns (dimensions: analytical, 4 × 245 mm; preparative, 16 × 244 mm or 32 × 237 mm). Detection by Knauer variable UV detector (λ = 255 nm) and Knauer refractometer. Unless otherwise stated, yields refer to analytically pure samples.

^{1}H NMR [$CHCl_3$ (δ = 7.26 ppm), TMS (δ = 0.00 ppm) as internal standard] and ^{13}C NMR spectra [$CDCl_3$ (δ = 77.0 ppm) as internal standard] were recorded with Bruker AC 250, WH 270, AC 300 and DRX 500 instruments in $CDCl_3$ solutions. Integrals are in accordance with assignments; coupling constants are given in Hz. The signals of the carbohydrate auxiliaries are very similar and are given only once for compounds **5**–**7**. A complete data set can be obtained from the authors.[9a] ^{1}H/^{13}C-correlated spectra (HSQC, HMBC) and ^{1}H/^{1}H-correlated spectra (COSY, NOESY) were recorded for assignments. IR spectra were measured with Nicolet 5 SXC FTIR or Nicolet 205 FTIR spectrometers. Optical rotations ($[\alpha]_D$) were measured with a Perkin Elmer 241 polarimeter in a 1 mL microcuvette at the temperature given. MS analyses were performed with MAT 711, MAT 112 S and with HP 5890 II instruments. The elemental analyses were recorded with 'Elemental-Analyzers' (Perkin–Elmer or Carlo Erba). Melting points were measured with a Reichert apparatus (Thermovar) or a Gallenkamp apparatus (MPD 350) and are uncorrected.

Alkoxyallenes **1**,[8] **2**,[8] **3**,[8] **16**,[8] **17**,[8,3] **18**[8] and propargyl ether **22**[3] were prepared according to the cited literature procedures. Imine **2a**[24] and imine precursor **13**[14] are known compounds.

Addition of Lithiated Alkoxyallenes to Imines; General Procedure GP1

For generation of lithiated alkoxyallene, the corresponding alkoxyallene was dissolved in THF and *n*-butyllithium (ca. 2.4 M in hexanes) was added at –50 °C or at –40 °C. After 30 min, a solution of the corresponding imine (dissolved in a small amount of THF) was added within 5 min. The mixture was allowed to warm to –20 °C or to –30 °C for the time given. After quenching with saturated aqueous $NaHCO_3$ solution, the organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 15 mL/mmol of alkoxyallene). The combined

organic phases were dried (Na_2SO_4), filtered and evaporated in vacuo to provide the crude product, which was purified by column chromatography on aluminum oxide (activity III). The given yields refer to the amount of imine used.

1,2:4,5-Di-*O*-isopropylidene-3-*O*-[1-phenyl-1-(*p*-toluenesulfonamido)buta-2,3-dien-2-yl]-β-D-fructopyranose (6)

According to **GP1**, alkoxyallene **2** (0.500 g, 1.68 mmol) was treated with *n*-butyllithium (0.70 mL, 1.68 mmol of 2.27 M in hexanes) in THF (35 mL). After 30 min the mixture was cooled to –80 °C and imine **4** (0.413 g, 1.59 mmol) was added. After stirring at this temperature for 1 h the mixture was allowed to warm to –30 °C within 3 h and stirred at this temperature for 12 h. Crude product **6** (d.r. 91:9) was purified by column chromatography (alumina III, hexanes/EtOAc 2:1) to afford pure allene **2** (0.060 g, 12%) and pure **6** (0.757 g, 85%, d.r. 91:9) as viscous colorless oils. A separation of the diastereomers was not possible at this stage. Subsequent reactions show that the major diastereomer is *R*-configured.

$[\alpha]_D^{20}$ = –73.9 (*c* = 1.2, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 2.41 (s, 3 H, Tos-Me), 5.04 (d, *J* = 7.8 Hz, 1 H, 1-H), 5.25, 5.34 (AB system, J_{AB} = 8.5 Hz, 2 H, 4-H), 5.57 (d, *J* = 7.8 Hz, 1 H, NH), 7.18–7.30 (m, 5 H, Ph, Tos), 7.37 (d, *J* = 7.3 Hz, 2 H, Ph), 7.70 (d, *J* = 8.3 Hz, 2 H, Tos); DAF^1-auxiliary: δ = 1.02, 1.35, 1.40, 1.44 (4 s, 3 H each, Me), 3.59, 3.74 (AB system, J_{AB} = 8.8 Hz, 2 H, 1-H), 3.74 (d, *J* = 7.5 Hz, 1 H, 3-H), 3.93, 4.02 (AB part of ABX system, J_{AB} = 13.3 Hz, $J_{A,5}$ = 2.2 Hz, 2 H, 6-H), 4.08–4.16 (m, 1 H, 5-H), 4.20 (dd, *J* = 7.5 Hz, *J* = 5.4 Hz, 1 H, 4-H); distinguishable signals of the minor isomer, allene part: δ = 5.70 (d, *J* = 7.8 Hz, 1 H, NH); DAF^1-auxiliary: δ = 3.50 (d, *J* = 9.3 Hz, 1 H, 1-H), 3.81 (d, *J* = 7.8 Hz, 1 H, 3-H), 5.13 (d, *J* = 7.8 Hz, 1 H, 1-H).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 21.5 (q, Tos-Me), 58.4 (d, C-1), 93.8 (t, C-4), 127.1, 127.4, 127.6, 128.2, 129.3 (5 d, Ph, Tos), 133.1 (s, C-2), 137.5, 138.1, 143.0 (3 s, Tos, Ph), 196.7 (s, C-3); DAF^1-auxiliary: δ = 25.5, 26.2, 26.7, 27.8 (4 q, Me), 60.3 (t, C-6), 71.3 (t, C-1), 73.7, 75.4, 76.1 (3 d, C-3, C-4, C-5), 103.6 (s, C-2), 109.1, 112.0 (2 s, CMe_2); minor diastereomer, allene part: δ = 21.0 (q, Tos-Me), 58.8 (d, C-1), 93.5 (t, C-4), 127.1, 127.4, 127.6, 128.2, 129.3 (5 d, Ph, Tos), 133.1 (s, C-2), 137.5, 138.1, 143.0 (3 s, Tos, Ph), 196.7 (s, C-3); DAF^1-auxiliary: δ = 25.5, 25.9, 26.5, 27.3 (4 q, Me), 60.7 (t, C-6), 71.4 (t, C-1), 72.6, 75.7, 76.7 (3 d, C-3, C-4, C-5), 103.6 (s, C-2), 109.0, 111.9 (2 s, CMe_2).

IR (film): 3285 (N–H), 2985, 2935 (C–H), 1965 (C=C=C), 1375, 1160 (TosN) cm^{-1}.

MS (EI, 80 eV): *m*/*z* (%) = 557 (8) [M$^+$], 542 (2) [M$^+$ – Me], 402 (4) [M$^+$ – Tos], 260 (100) [$C_{12}H_{20}O_6$], 185 (50).

HRMS (EI, 80 eV): *m*/*z* [M]$^+$ calcd for $C_{29}H_{35}NO_8S$: 557.2083; found: 557.2082.

Ozonolysis of Allenyl Amines; General Procedure GP2

The corresponding allenyl amine was dissolved in anhydrous dichloromethane and cooled to –78 °C and the solution was saturated with oxygen. Ozone was bubbled through the solution until the blue color remained (ca. 1 h). The mixture was allowed to warm to r.t. and quenched with saturated aqueous $NaHCO_3$ solution. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and evaporated in vacuo to provide the crude product, which was purified either by recrystallization from hexanes/dichloromethane or by column chromatography.

1,2:4,5-Di-*O*-isopropylidene-3-*O*-[2-phenyl-2-(*p*-toluenesulfonamido)acetyl]-β-D-fructopyranose (8)

According to **GP2**, allenyl amine **6** (0.520 g, 0.93 mmol, d.r. 91:9) in dichloromethane (10 mL) provided crude **8** (0.500 g) as a light-yellow oil. Purification by column chromatography (silica gel, hexanes/EtOAc 1:1) provided pure **8** (0.210 g, 41%, d.r. 90:10) as colorless crystals (m.p. 172–174 °C). The diastereomers were not separated.

$[\alpha]_D^{20}$ = –155.1 (*c* = 0.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 2.40 (s, 3 H, Tos-Me), 5.07 (d, *J* = 8.3 Hz, 1 H, 2-H), 5.66 (d, *J* = 8.3 Hz, 1 H, NH), 7.21–7.30 (m, 7 H, Ph, Tos), 7.69 (d, *J* = 8.3 Hz, 2 H, Tos); signal of the minor diastereomer: δ = 2.43 (s, 3 H, Tos-Me).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 21.5 (q, Tos-Me), 59.2 (d, C-2), 127.2, 127.3, 128.5, 128.7, 129.7 (5 d, Ph, Tos), 135.0, 137.1, 143.7 (3 s, Ph, Tos), 170.0 (s, C-1); due to the low content of the minor diastereomer no signals could be detected.

IR (KBr): 3430 (N–H), 2990, 2935 (C–H), 1760 (C = O), 1335, 1160 (TosN) cm^{-1}.

MS (EI, 80 eV): *m*/*z* (%) = 547 (0.1) [M$^+$], 532 (2) [M$^+$ – Me], 260 (100) [$C_{12}H_{20}O_6^+$].

HRMS (EI, 80 eV): *m*/*z* [M$^+$ – Me] calcd for $C_{26}H_{30}NO_9S$: 532.1641; found: 532.1644.

Transesterification; General Procedure GP3

The corresponding ester bearing the auxiliary was dissolved in anhydrous MeOH (4 mL) and a saturated solution of HCl in MeOH (1 mL) was added at r.t. The mixture was heated to reflux for 1.5 h, cooled to r.t., and neutralized with solid potassium carbonate. The solid was filtered off and the solvent was removed in vacuo. The crude product was purified either by recrystallization or by HPLC.

Methyl (*R*)-*N*-(*p*-Tosyl)-2-phenylglycinate (10)

According to **GP3**, DAF^1-ester **8** (0.152 g, 0.28 mmol, d.r. 90:10) in MeOH (4 mL) provided crude **10** (0.070 g) as a brownish oil. Purification by column chromatography (silica gel, hexanes/EtOAc 1:1) and HPLC (hexanes/EtOAc 4:1) provided pure **10** (0.030 g, 34%) as colorless crystals (m.p. 127–130 °C, reported value for racemic **10** m.p. 111 °C[25]). By comparison with literature[12] the predominating configuration at C-2 was determined to be *R*.

$[\alpha]_D^{20}$ = –90.0 (*c* = 1.2, $CHCl_3$); reported value: $[\alpha]_D^{20}$ = –113.6 (*c* = 2.33, $CHCl_3$).[12] Enantiomeric excess of the sample according to these values: 80%.

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 2.37 (s, 3 H, Tos-Me), 3.55 (s, 3 H, OMe), 5.06 (d, *J* = 8.1 Hz, 1 H, 2-H), 5.88 (d, *J* = 8.1 Hz, 1 H, NH), 7.10–7.35 (m, 7 H, Ph, Tos), 7.62 (d, *J* = 8.3 Hz, 2 H, Tos); these data agree with those of the literature.[26]

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 21.4 (q, Tos-Me), 52.9 (q, OMe), 59.3 (d, C-2), 127.0, 127.1, 128.5, 128.7, 129.4 (5 d, Ph, Tos), 135.1, 136.8, 143.5 (3 s, Tos, Ph), 170.5 (s, C-1); no literature data available.

1,2:4,5-Di-*O*-isopropylidene-3-*O*-[1-phenyl-2-(*p*-toluenesulfonamido)penta-3,4-dien-3-yl]-β-D-fructopyranose (15)

According to **GP1**, alkoxyallene **2** (0.260 g, 0.87 mmol), *n*-butyllithium (0.36 mL, 0.87 mmol of 2.42 M in hexanes) in THF (35 mL) and **13** (0.188 g, 0.44 mmol) provided, after 1 h at –80 °C and warm-up to –30 °C within 3 h and stirring at –30 °C for 12 h, the crude product mixture (0.470 g) as a light-yellow oil. Purification by column chromatography (alumina III, hexanes/EtOAc 3:1) afforded allene **2** (0.110

g, 42%) as yellow oil and **15** (0.180 g, 72%, d.r. 80:20) as light-yellow oil. A separation of the diastereomers was not possible at this stage. Preferred *R*-configuration is assumed by analogy.

$[\alpha]_D^{20}$ = –45.4 (*c* = 0.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 2.38 (s, 3 H, Tos-Me), 3.02, 3.09 (AB part of ABX system, J_{AB} = 13.8 Hz, J_{AX} = 6.5 Hz, J_{BX} = 5.2 Hz, 2 H, 1-H), 4.02–4.15 (m, 1 H, 2-H), 4.69 (d, *J* = 9.6 Hz, 1 H, NH), 5.03, 5.06 (AB system, J_{AB} = 11.8 Hz, $J_{A,CH}$ = 2.1 Hz, $J_{B,CH}$ = 2.1 Hz, 2 H, 5-H), 7.15–7.25 (m, 7 H, Ph, Tos), 7.64 (d, *J* = 8.3 Hz, 2 H, Tos); minor diastereomer: δ = 2.38 (s, 3 H, Tos-Me), 2.98, 3.10 (AB part of ABX system, J_{AB} = 13.2 Hz, J_{AX} = 5.9 Hz, J_{BX} = 8.1 Hz, 2 H, 1-H), 4.02–4.15 (m, 1 H, 2-H), 5.01 (s, 2 H, 5-H), 5.39 (d, *J* = 8.7 Hz, 1 H, NH), 7.15–7.25 (m, 7 H, Ph, Tos), 7.66 (d, *J* = 8.3 Hz, 2 H, Tos).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 20.9 (q, Tos-Me), 39.4 (t, C-1), 54.8 (d, C-2), 94.5 (t, C-5), 126.6, 127.1, 127.9, 129.4, 130.2 (5 d, Ph, Tos), 133.5 (s, C-3), 135.7, 137.6, 143.1 (3 s, Ph, Tos), 196.6 (s, C-4); minor diastereomer: δ = 20.9 (q, Tos-Me), 40.5 (t, C-1), 57.9 (d, C-2), 92.4 (t, C-5), 126.3, 127.2, 127.9, 129.2, 129.7 (5 d, Ph, Tos), 131.1 (s, C-3), 135.7, 137.0, 143.1 (3 s, Ph, Tos), 196.2 (s, C-4).

IR (film): 3430 (N–H), 3030, 2990, 2935 (C–H), 1965 (C=C=C), 1385, 1160 (TosN) cm^{-1}.

MS (EI, 80 eV): *m*/*z* (%) = 571 (0.8) [M^+], 570 (2) [M^+ – H], 479 (5) [M^+ – H – Bn], 326 (9), [M^+ – Bn – Tos], 155 (31) [Tos^+], 91 (100) [Bn^+].

1,2:4,5-Di-*O*-isopropylidene-3-*O*-[1-(*p*-toluenesulfonamido)-1-phenyltrideca-2,3-dien-2-yl]-β-D-fructopyranose (20)

According to **GP1**, alkoxyallene **17** (0.930 g, 2.19 mmol, d.r. 75:25), *n*-butyllithium (0.86 mL, 2.08 mmol of 2.42 M in hexanes) in THF (40 mL) and **4** (0.511 g, 1.97 mmol) provided, after 1 h at –80 °C and warm-up to –30 °C within 1.5 h and stirring at –30 °C for 8 h, the crude product mixture (1.84 g, d.r. 69:21:6:4) as a light-yellow oil. Purification by column chromatography (alumina III, hexanes/EtOAc 4.5:1) afforded allene **17** (0.087 g, 9%) as colorless oil and **20** (1.35 g, 99%, all four diastereomers) as a light-yellow oil.

Data obtained from this mixture:

IR (film): 3280 (N–H), 3030–2855 (C–H), 1965 (C=C=C) cm^{-1}.

MS (EI, 80 eV): *m*/*z* (%) = 683 (3) [M^+], 668 (10) [M^+ – Me], 556 (16) [$M^+ - C_9H_{19}$], 260 (46) [$C_{12}H_{20}O_6^+$], 185 (74), 91 (100) [Bn^+].

HRMS (EI, 80 eV): *m*/*z* [M^+] calcd for $C_{38}H_{53}NO_8S$: 683.3492; found: 683.3447.

The four diastereomers of **20** were partially separated by HPLC (hexanes/EtOAc 4:1).

Fraction 1: (*R*,a*R*/*S*,a*R*/*S*,a*S*)-**20** (0.922 g, 68%, d.r. 87:9:4, determined by HPLC) as a colorless oil.

Optical rotation: $[\alpha]_D^{20}$ = –72.4 (*c* = 0.9, $CHCl_3$).

Fraction 2: (*R*,a*S*)-**20** (0.308 g, 23%) as a light-yellow oil.

Optical rotation: $[\alpha]_D^{20}$ = –42.7 (*c* = 1.2, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 270 MHz): δ [(*R*,a*R*)-**20**] = 0.90 (t, *J* = 6.4 Hz, 3 H, Me), 1.15–1.40, 1.80–1.90 (2 m, 14 H, 2 H, CH_2), 2.39 (s, 3 H, Tos-Me), 5.02 (d, *J* = 7.7 Hz, 1 H, 1-H), 5.61 (d, *J* = 7.7 Hz, 1 H, NH), 5.73 (dt, *J* = 6.6 Hz, *J* = 1.0 Hz, 1 H, 4-H), 7.18–7.26, 7.32–7.38 (2 m, 7 H, Ph, Tos), 7.69 (d, *J* = 8.1 Hz, 2 H, Tos); δ [(*S*,a*R*)-**20**] = 0.90 (t, *J* = 6.4 Hz, 3 H, Me), 1.15–1.40, 1.80–1.90 (2 m, 14 H, 2 H, CH_2), 2.41 (s, 3 H, Tos-Me), 5.07 (d, *J* = 7.5 Hz, 1 H, 1-H), 5.59 (t, *J* = 6.6 Hz, 1 H, 4-H), 5.83 (d, *J* = 7.5 Hz, 1 H, NH), 7.16–7.43 (m, 7 H, Ph, Tos), 7.68 (d, *J* = 8.3 Hz, 2 H, Tos); δ [(*R*,a*S*)-**20**] = 0.88 (t, *J* = 6.6 Hz, 3 H, Me), 1.15–1.40, 1.90–2.00 (2 m, 14 H, 2 H, CH_2), 2.40 (s, 3 H, Tos-Me), 5.00 (d, *J* = 7.4 Hz, 1 H, 1-H), 5.56 (t, *J* = 6.3 Hz, 1 H, 4-H), 5.67 (d, *J* = 7.4 Hz, 1 H, NH), 7.16–7.26 (m, 5 H, Ph, Tos), 7.35 (d, *J* = 6.6 Hz, 2 H, Ph), 7.69 (d, *J* = 8.1 Hz, 2 H, Tos).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ [(*R*,a*R*)-**20**] = 14.0 (q, Me), 21.4 (q, Tos-Me), 22.6, 28.6, 29.1, 29.2, 29.3, 29.4, 31.3, 31.8 (8 t, CH_2), 58.4 (d, C-1), 111.7 (d, C-4), 127.2, 127.3, 127.5, 128.0, 129.3 (5 d, Ph, Tos), 132.7 (s, C-2), 137.7, 138.5, 142.9 (3 s, Ph, Tos), 188.6 (s, C-3); δ [(*S*,a*R*)-**20**] = 14.0 (q, Me), 21.4 (q, Tos-Me), 22.6, 28.8, 29.1, 29.2, 29.3, 29.4, 31.3, 31.8 (8 t, CH_2), 59.5 (d, C-1), 111.7 (d, C-4), 127.2, 127.3, 127.5, 128.0, 129.3 (5 d, Ph, Tos), 132.7 (s, C-2), 137.7, 138.6, 142.9 (3 s, Ph, Tos), 188.6 (s, C-3); δ [(*R*,a*S*)-**20**] = 14.1 (q, Me), 21.5 (q, Tos-Me), 22.6, 28.7, 29.2, 29.3, 29.4, 29.5, 31.3, 31.8 (8 t, CH_2), 59.2 (d, C-1), 110.2 (d, C-4), 127.0, 127.3, 127.4, 128.1, 129.3 (5 d, Ph, Tos), 132.1 (s, C-2), 137.6, 138.4, 142.9 (3 s, Ph, Tos), 188.5 (s, C-3).

Although (*S*,a*S*)-**20** could not be detected unambiguously in the major fraction by ^{1}H- and ^{13}C NMR spectroscopy, its presence was proven by the subsequent base-catalyzed cyclization to (2*S*,2*R*)-*cis*-**31** of this mixture (see below).

1,2:4,5-Di-*O*-isopropylidene-3-*O*-[1-phenyl-2-(*p*-toluenesulfonamido)tetradeca-3,4-dien-3-yl]-β-D-fructopyranose (23)

According to **GP1**, alkoxyallene **17** (0.960 g, 3.20 mmol, d.r. 15:85), *n*-butyllithium (1.37 mL, 3.20 mmol of 2.34 M in hexanes) in THF (60 mL) and **13** (0.688 g, 1.60 mmol) provided (after 1 h at –80 °C, warm-up to –30 °C within 3 h and stirring at –30 °C for 12 h) the crude product mixture. Purification by column chromatography (alumina III, hexanes/EtOAc 3:1) afforded allene **17** (0.666 g, 69%, d.r. 15:85) as a yellow oil and **23** (0.907 g, 81%, d.r. 11:68:0:21) as a light-yellow oil. The ratio of diastereomers was determined by analytical HPLC. $[\alpha]_D^{20}$ = –45.4 (*c* = 0.5, $CHCl_3$).

According to **GP1**, alkoxyallene **17** (1.40 g, 3.30 mmol, d.r. 75:25), *n*-butyllithium (1.36 mL, 3.30 mmol of 2.43 M in hexanes) in THF (60 mL) and **13** (0.708 g, 1.65 mmol) provided (after 1 h at –80 °C and warm-up to –30 °C within 3 h and stirring at –30 °C for 12 h) the crude product mixture. Purification by column chromatography (alumina III, hexanes/EtOAc 3:1) afforded allene **17** (0.768 g, 55%) as a yellow oil and **23** (0.972 g, 85%, d.r. 54:22:21:3) as a light-yellow oil. The ratio of diastereomers was determined by analytical HPLC.

^{1}H NMR ($CDCl_3$, 270 MHz): δ [(*R*,a*S*)-**23**] = 0.89 (t, *J* = 6.6 Hz, 3 H, Me), 0.95–1.60 (m, 16 H, CH_2), 2.40 (s, 3 H, Tos-Me), 3.02–3.10 (m, 2 H, 1-H), 3.95–4.10 (m, 1 H, 2-H), 5.07 (d, *J* = 8.6 Hz, 1 H, NH), 5.40 (td, *J* = 6.7 Hz, *J* = 0.8 Hz, 1 H, 5-H), 7.15–7.25 (m, 7 H, Ph, Tos), 7.70 (d, *J* = 8.3 Hz, 2 H, Tos); distinguishable signals of the other isomers, δ [(*S*,a*R*)-**23**] = 5.24 (t, *J* = 6.6 Hz, 1 H, 5-H), 5.56 (d, *J* = 8.8 Hz, 1 H, NH), δ [(*R*,a*R*)-**23**] = 2.38 (s, 3 H, Tos-Me), 4.41 (d, *J* = 9.6 Hz, 1 H, NH), 5.32 (t, *J* = 6.7 Hz, 1 H, 5-H), 7.64, 7.69 (2 d, *J* = 8.4 Hz, 2 H each, Tos); the signals of (*S*,a*S*)-**23** are hidden by those of the other diastereomers.

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ [(*R*,a*S*)-**23**] = 14.1 (q, Me), 21.4 (q, Tos-Me), 22.6, 29.2, 29.3, 29.5, 30.9, 31.0, 31.1, 31.8 (8 t, CH_2), 40.1 (t, C-1), 56.9 (d, C-2), 110.1 (d, C-5), 126.4, 127.0, 127.9, 129.4, 129.9 (5 d, Ph, Tos), 131.3 (s, C-3), 136.6, 137.9, 142.9 (3 s, Ph, Tos), 188.6 (s, C-4); distinguishable signals of the other isomers, δ [(*R*,a*R*)-**23**] = 39.1 (t, C-1), 53.9 (d, C-2), 111.5 (d, C-5), 126.8, 127.1, 129.2, 129.6, 130.5 (5 d, Ph, Tos), 132.1 (s, C-3), 135.3, 137.4, 142.6 (3 s, Ph, Tos), 187.8 (s, C-4); δ [(*S*,a*R*)-**23** and (*S*,a*S*)-**23**] = 40.1, 40.6 (2 t, C-1), 111.1, 111.3 (2 d, C-5).

IR (film): 3285 (N–H), 3060–2855 (C–H), 1965 (C=C=C), 1380, 1160 (TosN) cm^{-1}.

MS (EI, 80 eV): *m*/*z* (%) = 697 (4) [M$^+$], 696 (4) [M$^+$ – H], 682 (4) [M$^+$ – Me], 606 (32) [M$^+$ – Bn], 548 (16), 274 (53), 243 (100), 185 (65), 91 (93) [Bn$^+$].

HRMS (EI, 80 eV): *m*/*z* [M$^+$] calcd for $C_{39}H_{55}NO_8S$: 697.3648; found: 697.3682.

Potassium *tert*-Butoxide Promoted Cyclization; General Procedure GP4

The corresponding allenyl amine was dissolved in anhydrous dimethyl sulfoxide and, under a stream of argon, at 50 °C sublimed potassium *tert*-butoxide was added via a funnel. The mixture was stirred at this temperature for the time given in the individual experiments. After cooling to r.t., the mixture was hydrolyzed with saturated aqueous $NaHCO_3$ solution (20 mL) and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with aqueous $NaHCO_3$ solution (2 × 20 mL) to remove DMSO, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography.

3-*O*-(2-Phenyl-1-tosyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (25)

According to **GP4**, allenyl amine **6** (0.120 g, 0.22 mmol, *R*/*S* 91:9) and KO*t*Bu (5 mg, 0.05 mmol) in DMSO (5 mL) gave, after 2 h heating to 50 °C, the crude product (0.200 g) as a yellow oil. Purification by column chromatography (alumina III, hexanes/EtOAc 3:1) afforded **25** (0.091 g, 75%, *R*/*S* 90:10) as a light-yellow oil. The ratio of diastereomers was determined by ^{1}H NMR spectroscopy.

$[\alpha]_D^{20}$ = –124.5 (*c* = 0.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 270 MHz): δ [(*R*)-**25**] = 2.37 (s, 3 H, Tos-Me), 3.85–4.05 (m, 1 H, 5-H), 4.83 (s_{br}, 1 H, 4-H), 5.27 (s_{br}, 1 H, 2-H), 7.18 (d, *J* = 8.3 Hz, 2 H, Tos), 7.20–7.36 (m, 5 H, Ph), 7.50 (d, *J* = 8.3 Hz, 2 H, Tos); distinguishable signals of (*S*)-**25**: δ = 4.86 (s, 1 H, 4-H), 7.43 (d, *J* = 8.3 Hz, 2 H, Tos).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ [(*R*)-**25**] = 21.3 (q, Tos-Me), 51.8 (t, C-5), 67.2 (d, C-2), 92.8 (d, C-4), 127.1, 127.7, 128.1, 128.8, 129.3 (5 d, Tos, Ph), 135.2, 138.5, 143.1 (3 s, Tos, Ph), 154.9 (s, C-3); distinguishable signals of (*S*)-**25**: δ = 155.4 (s, C-3).

IR (film): 3065–2880 (C–H), 1665 (C=C), 1385, 1160 (TosN) cm^{-1}.

MS (EI, 80 eV): *m*/*z* (%) = 557 (2) [M$^+$], 542 (4) [M$^+$ – Me], 402 (15) [M$^+$ – Tos], 260 (5) [$C_{12}H_{20}O_6^+$], 243 (70), 185 (100).

HRMS (EI, 80 eV): *m*/*z* [M$^+$ – Me] calcd for $C_{28}H_{32}NO_8S$: 542.1849; found: 542.1874.

Anal. Calcd. for $C_{29}H_{35}NO_8S$ (557.7): C 62.46, H 6.33, N 2.51; found: C 62.83, H 6.44, N 2.25.

Silver Nitrate-Promoted Cyclization; General Procedure GP5

To a solution of the corresponding allenyl alcohol or amine in anhydrous acetone was added silver nitrate under a stream of argon via a funnel. The resulting mixture was stirred at r.t. under light exclusion for 3–16 h and then evaporated in vacuo. EtOAc (ca. 5 mL) was added to the residue and the mixture was filtered through a pad of Celite (elution with EtOAc). After removal of the solvents in vacuo, the crude product was purified as indicated in the individual experiments.

3-*O*-(2-Benzyl-1-tosyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (28)

According to **GP5**, allenyl amine **15** (0.151 g, 0.26 mmol, *R*/*S* 80:20) and $AgNO_3$ (10 mg, 0.06 mmol) in acetone (10 mL) gave, after 12 h, the crude product (0.300 g) as a brown oil. Purification by column chromatography (alumina III, hexanes/EtOAc 2:1) and separation by HPLC (hexanes/EtOAc 2:1) afforded (*R*)-**28** (0.100 g, 66%) and (*S*)-**28** (0.030 g, 20%) as colorless oils.

Data for (*R*)-**28**

$[\alpha]_D^{20}$ = –139.0 (*c* = 0.4, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.40 (s, 3 H, Tos-Me), 3.07, 3.20 (AB part of ABX system, J_{AB} = 13.5 Hz, J_{AX} = 2.2 Hz, J_{BX} = 5.3 Hz, 2 H, PhCH_2), 3.25 (dd, *J* = 13.8 Hz, *J* = 4.0 Hz, 1 H, 5-H), 3.79 (dd, *J* = 13.8 Hz, *J* = 1.8 Hz, 1 H, 5-H), 4.20 (s_{br}, 1 H, 4-H), 4.40–4.44 (m, 1 H, 2-H), 7.15–7.24 (m, 3 H, Ph), 7.28 (d, *J* = 8.2 Hz, 2 H, Tos), 7.41 (d, *J* = 7.3 Hz, 2 H, Ph), 7.68 (d, *J* = 8.2 Hz, 2 H, Tos).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 21.4 (q, Tos-Me), 39.0 (t, PhCH_2), 52.3 (t, C-5), 64.9 (d, C-2), 91.6 (d, C-4), 126.2, 127.0, 127.4, 129.7, 131.0 (5 d, Ph, Tos), 134.1, 135.7, 143.7 (3 s, Ph, Tos), 154.1 (s, C-3).

IR (film): 3030, 2985, 2930, 2875 (C–H), 1665 (C=C), 1385, 1165 (TosN) cm^{-1}.

MS (EI, 80 eV): *m*/*z* (%) = 571 (4) [M$^+$], 556 (9) [M$^+$ – Me], 480 (100) [M$^+$ – Bn], 155 (40) [Tos$^+$], 91 (75) [Bn$^+$].

HRMS (EI, 80 eV): *m*/*z* [M$^+$] calcd for $C_{30}H_{37}NO_8S$: 571.2240; found: 571.2288; *m*/*z* [M$^+$ – Me] calcd for $C_{29}H_{34}NO_8S$: 556.2005; found: 556.2036.

Anal. calcd. for $C_{30}H_{37}NO_8S$ (571.7): C 63.03, H 6.52, N 2.45; found: C 63.01, H 6.35, N 2.20.

Data for (*S*)-**28**

$[\alpha]_D^{20}$ = –41.6 (*c* = 0.4, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 2.42 (s, 3 H, Tos-Me), 3.02, 3.31 (AB part of ABX system, J_{AB} = 13.9 Hz, J_{AX} = 2.6 Hz, J_{BX} = 4.6 Hz, 2 H, PhCH_2), 3.48 (ddd, *J* = 13.3 Hz, *J* = 5.1 Hz, *J* = 2.4 Hz, 1 H, 5-H), 3.82 (ddd, *J* = 13.3 Hz, *J* = 2.6 Hz, *J* = 1.4 Hz, 1 H, 5-H), 4.32 (s_{br}, 1 H, 4-H), 4.57–4.65 (m, 1 H, 2-H), 7.18–7.25 (m, 3 H, Ph), 7.30 (d, *J* = 8.3 Hz, 2 H, Tos), 7.38 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 2 H, Ph), 7.72 (d, *J* = 8.3 Hz, 2 H, Tos).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 21.5 (q, Tos-Me), 38.7 (t, PhCH_2), 52.2 (t, C-5), 65.0 (d, C-2), 93.5 (d, C-4), 126.3, 127.4, 127.7, 129.6, 130.6 (5 d, Ph, Tos), 134.7, 136.3, 143.2 (3 s, Ph, Tos), 154.5 (s, C-3).

IR (film): 3030, 2990, 2930, 2875 (C–H), 1665 (C=C), 1385, 1165 (TosN) cm^{-1}.

MS (EI, 80 eV): *m*/*z* (%) = 571 (2) [M$^+$], 556 (6) [M$^+$ – Me], 480 (58) [M$^+$ – Bn], 155 (47) [Tos$^+$], 91 (100) [Bn$^+$].

HRMS (EI, 80 eV): *m*/*z* [M$^+$] calcd for $C_{30}H_{37}NO_8S$: 571.2240; found: 571.2266; *m*/*z* [M$^+$ – Me] calcd for $C_{29}H_{34}NO_8S$: 556.2005; found: 556.2037.

Anal. Calcd. for $C_{30}H_{37}NO_8S$ (571.7): C 63.03, H 6.52, N 2.45; found: C 63.00, H 6.41, N 2.25.

3-*O*-(2,5-Dihydro-5-nonyl-2-phenyl-1-tosyl-1*H*-pyrrol-3-yl)-1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (31)

According to **GP4**, allenyl amine **20** (0.894 g, 1.31 mmol, *R*,*aR*/*S*,*aR*/*S*,*aS* = 87:9:4) and KO*t*Bu (47 mg, 0.42 mmol) in DMSO (20 mL) gave after 14 h heating to 50 °C the crude product (0.980 g) as brown oil. Purification by column chromatography (alumina III, hexanes/EtOAc 9:2) afforded **31** (0.627 g, 70%) as a light-yellow oil and allenyl amine **20** (0.165 g, 18%, *R*,*aR*/*S*,*aR* = 65:35) as a light-yellow oil. Product **31** was separated by HPLC (hexanes/EtOAc 6:1) to provide a mixture of (2*S*,5*S*)-*trans*-**31** and pyrrole **32** (0.030 g, 4%, 15:85), (2*R*,5*S*)-*cis*-**31** (0.470 g, 53%) as colorless crystals (m.p. 85 °C) and (2*S*,5*R*)-*cis*-**31** (0.018 g, 2%) as a light-yellow oil.

Data for (2*R*,5*S*)-*cis*-**31**

$[\alpha]_D^{20}$ = –109.0 (*c* = 1.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.89 (t, *J* = 6.8 Hz, 3 H, Me), 1.21–1.35, 1.52–1.59, 1.84–1.92 (3 m, 14 H, 1 H each, CH_2), 2.40 (s, 3 H, Tos-Me), 4.37–4.42 (m, 1 H, 5-H), 4.81 (s, 1 H, 4-H), 5.23 (s, 1 H, 2-H), 7.25–7.35 (m, 5 H, Ph, Tos), 7.49 (d, *J* = 7.1 Hz, 2 H, Ph), 7.65 (d, *J* = 8.3 Hz, 2 H, Tos).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 14.1 (q, Me), 21.4 (q, Tos-Me), 22.7, 29.2, 29.3, 29.4, 29.5, 31.5, 31.8, 38.3 (8 t, CH_2), 65.0 (d, C-5), 67.2 (d, C-2), 97.2 (d, C-4), 127.4, 127.7, 127.8, 128.1, 129.5 (5 d, Ph, Tos), 134.8, 139.0, 143.5 (3 s, Ph, Tos), 154.3 (s, C-3).

IR (KBr): 3030–2855 (C–H), 1665 (C=C), 1350, 1165 cm^{-1} (TosN).

MS (EI, 80 eV): *m*/*z* (%) = 683 (0.2) [M^+], 668 (6) [M^+ – Me], 556 (100) [$M^+ - C_9H_{19}$], 314 (39), 243 (30), 185 (14).

HRMS (EI, 80 eV): *m*/*z* [M^+ – Me] calcd for $C_{37}H_{50}NO_8S$: 668.3257; found: 668.3279.

Anal. Calcd. for $C_{38}H_{53}NO_8S$ (683.3): C 66.74, H 7.81, N 2.05; found: C 66.68, H 7.74, N 2.21.

Data for (2*S*,5*R*)-*cis*-**31**

$[\alpha]_D^{20}$ = –4.8 (*c* = 0.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.89 (t, *J* = 6.8 Hz, 3 H, Me), 1.20–1.70, 2.05–2.25 (2 m, 14 H, 2 H, CH_2), 2.39 (s, 3 H, Tos-Me), 4.48–4.57 (m, 1 H, 5-H), 4.95 (s, 1 H, 4-H), 5.29 (s, 1 H, 2-H), 7.17 (d, *J* = 8.3 Hz, 2 H, Tos), 7.21–7.35 (m, 5 H, Ph), 7.54 (d, *J* = 8.3 Hz, 2 H, Tos).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.1 (q, Me), 21.4 (q, Tos-Me), 22.7, 26.1, 29.3, 29.5, 29.6,* 31.9, 38.7 (7 t, CH_2), 64.6 (d, C-5), 68.4 (d, C-2), 96.5 (d, C-4), 127.6, 127.9, 128.0, 128.4, 129.4 (5 d, Ph, Tos), 135.9, 139.7, 143.1 (3 s, Ph, Tos), 154.6 (s, C-3); * higher intensity.

IR (film): 3035–2855 (C–H), 1665 (C=C), 1350, 1165 (TosN) cm^{-1}.

MS (EI, 80 eV): *m*/*z* (%) = 683 (0.2) [M^+], 668 (3) [M^+ – Me], 556 (100) [$M^+ - C_9H_{19}$], 314 (71), 243 (86), 185 (63).

HRMS (EI, 80 eV): *m*/*z* [M^+ – Me] calcd for $C_{37}H_{50}NO_8S$: 668.3257; found: 668.3289.

Data for **32** and (2*S*,5*S*)-*cis*-**31**

^{1}H NMR ($CDCl_3$, 270 MHz): δ (**32**) = 0.88 (t, *J* = 7.0 Hz, 3 H, Me), 1.10–1.35, 1.65–1.82 (2 m, 14 H, 2 H, CH_2), 2.38 (s, 3 H, Tos-Me), 5.95 (d, *J* = 1.7 Hz, 1 H, 4-H), 7.17 (d, *J* = 8.2 Hz, 2 H, Tos), 7.32–7.38, 7.40–7.45 (2 m, 5 H, Ph), 7.55 (d, *J* = 8.2 Hz, 2 H, Tos); the following signals could be assigned to (2*S*,5*S*)-**31**: δ = 2.32 (s, 3 H, Tos-Me), 4.66 –4.75 (m, 1 H, 5-H), 4.80 (s, 1 H, 4-H), 5.37 (d, *J* = 5.2 Hz, 1 H, 2-H).

Due to the very low amount available no further characterization was possible.

According to **GP5**, diastereomerically pure allenyl amine (*R*,*aS*)-**20** (0.170 g, 0.25 mmol) and $AgNO_3$ (10 mg, 0.06 mmol) in acetone (8 mL) gave, after 3 h, the crude product (0.300 g) as a brown oil. Purification and separation by column chromatography (alumina III, hexanes/EtOAc 2:1) afforded (2*R*,5*R*)-*trans*-**31** (0.019 g, 11%) and (2*R*,5*S*)-*cis*-**31** (0.030 g, 18%) as colorless oils and (*R*,a*S*)-**20** (0.120 g, 71%) as a light-yellow oil.

Data for (2*R*,5*R*)-*trans*-**31**

$[\alpha]_D^{20}$ = –116.5 (*c* = 0.9, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.89 (t, *J* = 6.6 Hz, 3 H, Me), 1.20–1.43, 1.93–2.06 (2 m, 14 H, 2 H, CH_2), 2.31 (s, 3 H, Tos-Me), 4.64–4.71 (m, 1 H, 5-H), 4.97 (s, 1 H, 4-H), 5.39 (d, *J* = 5.1 Hz, 1 H, 2-H), 6.91, 6.98 (2 d, *J* = 8.8 Hz, 2 H each, Tos), 7.05–7.30 (m, 5 H, Ph).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.1 (q, Me), 21.3 (q, Tos-Me), 22.3, 27.9, 29.3, 29.6,* 29.8, 31.9, 36.0 (7 t, CH_2), 64.8 (d, C-5), 68.8 (d, C-2), 98.8 (d, C-4), 126.6, 127.8, 127.9, 128.7, 129.3 (5 d, Ph, Tos), 136.6, 140.0, 141.9 (3 s, Ph, Tos), 154.5 (s, C-3); * higher intensity.

MS (EI, 80 eV): *m*/*z* (%) = 683 (0.05) [M^+], 668 (2) [M^+ – Me], 667 (3) [M^+ – H – Me], 556 (51) [$M^+ - C_9H_{19}$], 555 (72) [M^+ – H – C_9H_{19}], 313 (47), 243 (51), 185 (41), 57 (100).

HRMS (EI, 80 eV): *m*/*z* [M^+ – Me] calcd for $C_{37}H_{50}NO_8S$: 668.3257; found: 668.3275.

3-*O*-(2,5-Dihydro-2-benzyl-5-nonyl-1-tosyl-1*H*-pyrrol-3-yl)-1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (33)

Method A: According to **GP5**, allenyl amine **23** (0.960 g, 1.30 mmol, *R*,*aR*/*R*,*aS*/*S*,*aR*/*S*,*aS* = 12:68:3:17) and $AgNO_3$ (44 mg, 0.26 mmol) in acetone (35 mL) gave, after 16 h, the crude product mixture, which was pre-purified by column chromatography (alumina III, hexanes/EtOAc 6:1). The obtained product mixture (0.970 g) was separated by HPLC (hexanes/EtOAc 9:1) to afford (2*R*,5*R*)-*trans*-**33** (0.099 g, 11%) as colorless crystals (m.p. 103–106 °C), (2*R*,5*S*)-*cis*-**33** (0.445 g, 49%, containing ca. 5% of (2*S*,5*S*)-*trans*-**33**) as a colorless foam and (2*S*,5*R*)-*cis*-**33** (0.130 g, 14%) as colorless crystals (m.p. 96–99 °C).

Data for (2*R*,5*R*)-*trans*-**33**

$[\alpha]_D^{20}$ = –127.1 (*c* = 0.4, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.87 (t, *J* = 7.2 Hz, 3 H, Me), 0.90–1.30, 1.75–1.85 (2 m, 15 H, 1 H, CH_2), 2.41 (s, 3 H, Tos-Me), 3.15, 3.55 (AB part of ABX system, J_{AB} = 13.7 Hz, J_{AX} = 1.5 Hz, J_{BX} = 5.2 Hz, 2 H, PhCH_2), 3.88–3.94 (m, 1 H, 5-H), 4.49 (s_{br}, 1 H, 4-H), 4.69–4.74 (m, 1 H, 2-H), 7.17–7.28 (m, 5 H, Ph, Tos), 7.48 (d, *J* = 7.0 Hz, 2 H, Ph), 7.71 (d, *J* = 8.3 Hz, 2 H, Tos).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 14.1 (q, Me), 21.4 (q, Tos-Me), 22.6, 25.1, 29.2, 29.3, 29.4, 29.5, 31.8, 33.8 (8 t, CH_2), 38.6 (t, PhCH_2), 65.1 (d, C-5), 66.3 (d, C-2), 96.8 (d, C-4), 126.2, 126.5, 127.6, 129.4, 131.0 (5 d, Ph, Tos), 136.2, 140.3, 142.7 (3 s, Ph, Tos), 153.2 (s, C-3).

IR (KBr): 3060–2855 (C–H), 1670 (C=C), 1380, 1160 (TosN) cm^{-1}.

MS (EI, 80 eV): *m*/*z* (%) = 697 (1.4) [M^+], 683 (4.4) [M^+ – Me], 606 (100) [M^+ – Bn], 570 (8) [$M^+ - C_9H_{19}$], 364 (67), 91 (76) [Bn^+].

HRMS (EI, 80 eV): *m*/*z* [M^+] calcd for $C_{39}H_{55}NO_8S$: 697.3648; found: 697.3684.

Anal. Calcd for $C_{39}H_{55}NO_8S$ (697.4): C 67.12, H 7.94, N 2.01; found: C 67.42, H 7.80, N 1.76.

(2*R*,5*S*)-*cis*-**33**

$[\alpha]_D^{20}$ = –55.4 (*c* = 0.4, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.89 (t, *J* = 6.8 Hz, 3 H, Me), 0.75–1.40 (m, 16 H, CH_2), 2.41 (s, 3 H, Tos-Me), 3.08–3.15 (m, 2 H, PhCH_2), 3.92–4.05 (m, 1 H, 5-H), 4.20–4.30 (m, 2 H, 2-H, 4-H), 7.15–7.32 (m, 5 H, Ph, Tos), 7.35 (d, *J* = 7.6 Hz, 2 H, Ph), 7.68 (d, *J* = 8.2 Hz, 2 H, Tos).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.0 (q, Me), 21.3 (q, Tos-Me), 22.5, 25.5, 29.1, 29.2,* 29.3, 31.7, 37.2, 38.9 (8 t, PhCH_2, CH_2), 65.0, 65.3 (2 d, C-2, C-5), 95.4 (d, C-4), 126.2, 127.2, 127.4, 129.5, 131.3 (5 d, Ph, Tos), 133.8, 136.1, 143.5 (3 s, Ph, Tos), 153.5 (s, C-3); * higher intensity.

IR (film): 3060, 3030, 2985, 2925, 2855 (C–H), 1665 (C=C), 1380, 1165 (TosN) cm^{-1}.

MS (EI, 80 eV): *m*/*z* (%) = 697 (0.9) [M^+], 682 (7) [M^+ – Me], 606 (100) [M^+ – Bn], 364 (65), 155 (23) [Tos^+], 91 (48) [Bn^+].

HRMS (EI, 80 eV): *m*/*z* [M^+] calcd for $C_{39}H_{55}NO_8S$: 697.3648; found: 697.3673.

Data for (2*S*,5*S*)-*trans*-**33**

The compound was isolated as mixture with (2*R*,5*S*)-*cis*-**33**.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.88 (t, *J* = 6.9 Hz, 3 H, Me), 0.90–1.30, 1.79–1.87 (2 m, 15 H, 1 H, CH_2), 2.40 (s, 3 H, Tos-Me), 3.06 (dd, *J* = 14.4 Hz, *J* = 2.0 Hz, 1 H, PhC*H*$_2$), 3.71 (dd, *J* = 14.4 Hz, *J* = 4.8 Hz, 1 H, PhC*H*$_2$), 4.06–4.11 (m, 1 H, 5-H), 4.52 (s, 1 H, 4-H), 4.76 (s_{br}, 1 H, 2-H), 7.17–7.28 (m, 5 H, Ph, Tos), 7.45 (d, *J* = 7.2 Hz, 2 H, Ph), 7.69 (d, *J* = 8.3 Hz, 2 H, Tos).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 14.1 (q, Me), 21.4 (q, Tos-Me), 22.6, 29.2, 29.3, 29.5, 29.7, 31.5, 31.8, 34.0 (8 t, CH_2), 37.9 (t, PhCH_2), 65.4, 66.0 (2 d, C-2, C-5), 98.4 (d, C-4), 126.2, 126.7, 127.8, 129.3, 130.5 (5 d, Ph, Tos), 136.8, 140.0, 142.6 (3 s, Ph, Tos), 153.3 (s, C-3).

(2*S*,5*R*)-*cis*-**33**

$[\alpha]_D^{20}$ = –81.3 (*c* = 0.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.87 (t, *J* = 7.2 Hz, 3 H, Me), 0.80–1.40 (m, 16 H, CH_2), 2.39 (s, 3 H, Tos-Me), 3.05, 3.19 (AB part of ABX system, J_{AB} = 13.6 Hz, J_{AX} = 2.8 Hz, J_{BX} = 5.2 Hz, 2 H, PhC*H*$_2$), 4.39 (s_{br}, 1 H, 4-H), 4.48–4.53 (m, 1 H, 2-H), 7.10–7.36 (m, 7 H, Ph, Tos), 7.69 (d, *J* = 8.2 Hz, 2 H, Tos); signal of 5-H is hidden by those of the auxiliary.

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 14.0 (q, Me), 21.4 (q, Tos-Me), 22.6, 25.7, 29.2, 29.3, 29.4, 31.5, 31.8, 37.6, 38.7 (9 t, PhCH_2, CH_2), 64.9, 65.7 (2 d, C-2, C-5), 97.5 (d, C-4), 126.3, 127.6*, 129.5, 131.1 (4 d, Ph, Tos), 134.5, 136.3, 143.0 (3 s, Ph, Tos), 154.1 (s, C-3); * signal with double intensity.

IR (KBr): 3060, 3030, 2990, 2925, 2855 (C–H), 1665 (C=C), 1380, 1165 (TosN) cm^{-1}.

MS (EI, 80 eV): *m*/*z* (%) = 697 (1.3) [M$^+$], 682 (7) [M$^+$ – Me], 606 (99) [M$^+$ – Bn], 364 (77), 155 (44) [Tos$^+$], 91 (100) [Bn$^+$].

HRMS (EI, 80 eV): *m*/*z* [M$^+$ – Me] calcd for $C_{38}H_{52}NO_8S$: 682.3414; found: 682.3456.

Method ***B***: Analogously to **GP5**, allenyl amine **23** (0.311 g, 0.45 mmol, *R*,*aR*/*R*,*aS*/*S*,*aR*/*aS*,*S* = 54:22:21:3) and $AgNO_3$ (17 mg, 0.10 mmol), K_2CO_3 (0.135 g, 0.98 mmol) in acetonitrile (10 mL) gave, after 14 h, the crude product mixture, which was pre-purified by column chromatography (alumina III, hexanes/EtOAc 7:1). The obtained product mixture (0.270 g) was separated by HPLC (hexanes/EtOAc 9:1) to afford (2*R*,5*R*)-*trans*-**33** (0.060 g, 18%), (2*S*,5*S*)-*trans*-**33** (0.027 g, 8%), (2*R*,5*S*)-*cis*-**33** (0.130 g, 38%) and (2*S*,5*R*)-*cis*-**32** (0.026 g, 8%) as colorless oils.

Method ***C***: According to **GP4**, allenyl amine **23** (0.972 g, 1.39 mmol, *R*,*aR*/*R*,*aS*/*S*,*aR*/*S*,*aS* = 54:22:21:3) and KO*t*Bu (32 mg, 0.14 mmol) in DMSO (20 mL) gave, after 12 h heating to 50 °C, the crude product. Purification by column chromatography (alumina III, hexanes/EtOAc 5:1) afforded a mixture of (2*R*,5*S*)-*cis*-**33** and (2*S*,5*R*)-*cis*-**33** (0.634 g, 61%, d.r. 90:10) as a colorless yellow oil and allenyl amine **23** (0.343 g, 33%, *R*,*aS*/*S*,*aR* = 55:45) as a light-yellow oil.

(2*R*,5*S*)- and (2*S*,5*S*)-2-Benzyl-5-nonyl-1-tosylpyrrolidin-3-one (34)

A solution of **33** (0.320 g, 0.46 mmol, 2*R*,5*S*/2*S*,5*S* = 95:5) in THF (20 mL) and 20% aqueous sulfuric acid (12 mL) was heated to reflux for 3 h. After cooling to r.t., the mixture was cautiously neutralized with saturated aqueous $NaHCO_3$ solution and the organic phase was separated. The aqueous phase was extracted with diethyl ether (2 × 15 mL), the combined organic phases were dried (Na_2SO_4), filtered and evaporated in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 5:1) to give pure (2*R*,5*S*)-*cis*-**34** (0.165 g, 79%) as a colorless wax (m.p. 32–33 °C) and (2*S*,5*S*)-*trans*-**34** (8 mg, 4%) as colorless crystals (m.p. 76–78 °C).

Data of (2*R*,5*S*)-*cis*-**34**

$[\alpha]_D^{20}$ = –39.4 (*c* = 0.3, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.90 (t, *J* = 6.7 Hz, 3 H, Me), 0.90–1.40 (m, 16 H, CH_2), 1.76, 2.14 (AB part of ABX system, J_{AB} = 18.2 Hz, J_{AX} = 3.0 Hz, J_{BX} = 9.3 Hz, $J_{A,CH}$ = 1.3 Hz, 2 H, 4-H), 2.43 (s, 3 H, Tos-Me), 3.22, 3.27, 3.93 (ABX system, J_{AB} = 13.5 Hz, J_{AX} = 5.7 Hz, J_{BX} = 4.0 Hz, 1 H each, PhC*H*$_2$, 2-H), 3.77–3.88 (m, 1 H, 5-H), 7.20–7.30 (m, 5 H, Ph), 7.33, 7.73 (2 d, *J* = 8.3 Hz, 2 H each, Tos).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.1 (q, Me), 21.5 (q, Tos-Me), 22.6, 25.8, 29.0, 29.2, 29.3, 29.4, 31.8, 37.0, 37.9, 42.2 (10 t, CH_2, PhCH_2, C-4), 56.8, 65.4 (2 d, C-2, C-5), 126.9, 127.5, 128.2, 130.0, 130.9 (5 d, Ph, Tos), 134.1, 136.2, 144.1 (3 s, Ph, Tos), 211.3 (s, C-3).

IR (film): 3060, 3030, 2925, 2855 (C–H), 1760 (C=O), 1355, 1155 (TosN) cm^{-1}.

MS (EI, 80 eV): *m*/*z* (%) = 455 (1.5) [M$^+$], 364 (100) [M$^+$ – Bn], 155 (89) [Tos$^+$], 91 (91) [Bn$^+$].

HRMS (EI, 80 eV): *m*/*z* [M$^+$] calcd for $C_{27}H_{37}NO_3S$: 455.2494; found: 455.2473.

Anal. Calcd. for $C_{27}H_{37}NO_3S$ (455.6): C 71.17, H 8.18, N 3.07; found: C 71.19, H 7.96, N 2.95.

Data of (2*S*,5*S*)-*trans*-**34**

^{1}H NMR ($CDCl_3$, 270 MHz): δ = 0.87 (t, *J* = 6.8 Hz, 3 H, Me), 0.90–1.35, 1.60–1.70 (2 m, 15 H, 1 H, CH_2), 1.65, 1.99 (AB system, J_{AB} = 17.2 Hz, $J_{A,5}$ = 9.0 Hz, $J_{B,5}$ = 1.0 Hz, 2 H, 4-H), 2.44 (s, 3 H, Tos-Me), 3.12 (dd, *J* = 13.7 Hz, *J* = 3.2 Hz, 1 H, PhC*H*$_2$), 3.64 (dd, *J* = 13.7 Hz, *J* = 5.1 Hz, 1 H, PhC*H*$_2$), 3.94 (dd, *J* = 5.1 Hz, *J* = 3.2 Hz, 1 H, 2-H), 4.00–4.10 (m, 1 H, 5-H), 7.20–7.30 (m, 7 H, Ph, Tos), 7.77 (d, *J* = 8.3 Hz, 2 H, Tos).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 14.1 (q, Me), 21.5 (q, Tos-Me), 22.6, 24.6, 27.4, 29.3*, 29.4, 31.8, 33.2, 37.9, 42.8 (9 t, CH_2, PhCH_2, C-4), 57.6, 64.8 (2 d, C-2, C-5), 127.0, 127.2, 128.3, 129.7, 130.6 (5 d, Ph, Tos), 135.3, 137.8, 143.6 (3 s, Ph, Tos), 210.9 (s, C-3); * double intensity.

Due to the low amount available, further characterization was not possible.

(2*S*,5*R*)-2-Benzyl-5-nonyl-1-tosylpyrrolidin-3-one (*cis*-34)

A solution of (2*S*,5*R*)-*cis*-**33** (0.045 g, 0.065 mmol) in THF (5 mL) and 20% aqueous sulfuric acid (4 mL) was heated to reflux for 4 h. After cooling to r.t., the mixture was cautiously neutralized with saturated aqueous $NaHCO_3$ solution and the organic phase was separated. The aqueous phase was extracted with diethyl ether (2 × 10 mL), the combined organic phases were dried (Na_2SO_4), filtered and evaporated in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 5:1) to give pure (2*S*,5*R*)-*cis*-**34** (0.020 g, 68%) as a colorless wax (m.p. 30–31 °C).

Data of (2*S*,5*R*)-*cis*-**34**

$[\alpha]_D^{20}$ = +41.5 (*c* = 1.1, $CHCl_3$).

The NMR data agree with those of enantiomer (2*R*,5*S*)-*cis*-**34**.

IR (film): 3060–2855 (C–H), 1760 (C=O), 1355, 1165 (TosN) cm^{-1}.

Anal. Calcd. for $C_{27}H_{37}NO_3S$ (455.6): C 71.17, H 8.18, N 3.07; found: C 71.20, H 8.11, N 2.94.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609942.

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