D-Glucosamine trimethylene dithioacetal derivatives: formation of six- and seven-membered ring amino carbasugars. Synthesis of (−)-calystegine B_3†,‡

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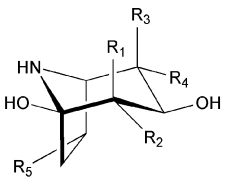
By virtue of carefully chosen protecting groups, D-glucosamine trimethylene dithioacetal derivatives were successfully oxidized to the corresponding 6-aldehydes. This methodology reverses the donor and acceptor position on a normal open chain sugar and changes the relative position of the *N*-substituent. From the 6-aldehydes, heptose epoxide derivatives were prepared by a Corey–Chaykovsky reaction, and cyclized by the Corey–Seebach method. Depending on the designed protecting groups, the orthogonally protected six- and seven-membered ring amino carbasugars can be produced selectively and efficiently. (−)-Calystegine B_3 was synthesized from one of those products with high yield. This is the first anionic cyclization pathway to calystegine type structures.

Introduction

Iminosugars (also known as azasugars) and amino carbasugars as selective and efficient glycosidase inhibitors are presently the two most attractive categories[1] in the field of *N*-containing carbohydrates. The compounds are mainly five- or six-membered (or fused) ring systems. Some of them are used as chemotherapeutic agents against diabetes or viral infections. The interest in larger rings (seven or even eight-membered) has recently increased significantly. Despite the difficulties, syntheses of iminosugars,[1a,b,2] as well as amino carbasugars,[2a,3] have been investigated and reviewed extensively. Versatile, low cost, and concise synthetic methodologies are of high interest.

A representative example is the calystegine family isolated from Solanaceae and other plants[4] (Fig. 1). These compounds, typically constructed by a seven-membered carbocycle with a nitrogen bridge, are considered as conformationally restricted 6-membered ring iminosugars; this explains their selective and strong activities. Since they are regarded as lead compounds for new bioactive structures and even drugs, calystegine (±)-A_3,[5] (±)-B_2,[6] (+)-B_3,[7] (+)-B_4[7] and their analogues[8] have been synthesized. More calystegine type structures, especially their homomorphous analogues,[9] which are believed to possess biological activities, too, are still requested.

In contrast to most of the traditional synthetic methodologies where the nitrogen has to be introduced into the molecules at a later synthesis stage, we recently demonstrated[10] that the trimethylene dithioacetal derivatives, which are readily prepared from D-glucosamine as an abundant natural source, serve as cheap and versatile starting materials for *N*-containing carbohydrates, especially iminosugars and amino carbasugars (*via* a stabilized dilithiated dithiane-imidate intermediate without 1,2-elimination) by use of 6-*O*-Ts derivatives.[10b] Another attractive step of conceptual importance would be oxidizing the 6-OH derivative to the corresponding aldehyde. It reverses the donor and acceptor position of a normal open chain sugar, switches the relative stereochemistry from D-*gluco* to L-*gulo* according to the established concept,[11] and changes the relative substituting position of the nitrogen. In general, this allows for many further interesting conversions, for example, elongating the chain at the side rather than the dithiane end.



calystegine

(-)-A_3, R_2=OH, R_1=R_3=R_4=R_5=H, (+)-A_5, R_4=OH, R_1=R_2=R_3=R_5=H,
(-)-B_1, R_2=R_5=OH, R_1=R_3=R_4=H, (+)-B_2, R_2=R_4=OH, R_1=R_3=R_5=H,
(+)-B_3, R_1=R_4=OH, R_2=R_3=R_5=H, (+)-C_1, R_2=R_4=R_5=OH, R_1=R_3=H.

Fig. 1 Some calystegines discovered in nature.

In the work reported here, we have synthesized such aldehydes. From the aldehydes bearing carefully designed protecting groups of different types, the corresponding epoxides are produced by one carbon elongation *via* an anionic cyclization[10b] of the epoxides according to the Corey–Seebach method;[12] depending on the protecting groups,[13] divergent syntheses of seven-membered ring amino carbasugars as well as a six-membered ring fully functionalized amino carbasugar bearing orthogonal protections can be conducted efficiently. All products are valuable precursors for iminosugar and amino carbasugar synthesis. Subsequently, the power of this synthetic methodology is demonstrated by the first synthesis of (−)-calystegine B_3 from one of the cyclization products, which is also the first anionic pathway to the calystegine family, while the ring expansions,[5a,6b,c] the enzymatical resolution,[5b] the cycloadditions,[6a,d,e] the ring closure metathesis,[6f,g,7] and the radical cyclization[6g] have been explored.

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† Dedicated to Prof. Dr Hans Paulsen on the occasion of his 85th birthday.

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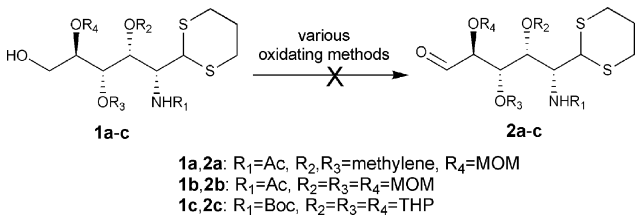
Results and discussion

For the success of the entire plan, it was essential to be able to oxidize efficiently the non-reducing ends of properly protected D-glucosamine trimethylene dithioacetals to aldehydes. However, an oxidation reaction on densely functionalized compounds, especially those with sulfur and amide functional groups, is generally a difficult task. Various known typical oxidation methods[14] (*e.g.* most of the DMSO based oxidations, chromium based oxidations, hypervalent iodine based oxidations, manganese based oxidations, TEMPO based oxidations, Ley oxidation, Oppenauer oxidation and some other reported oxidation methods) were applied to the *N*-acetyl (Ac) protected model compounds **1a** and **1b**. However, the results were either no reaction or decomposition of the starting material. Modification of these oxidation conditions did not give any improvement. Similarly, the *N*-*tert*-butoxycarbonyl (Boc) protected compound **1c** failed to give the desired aldehydo group, too (Scheme 1).

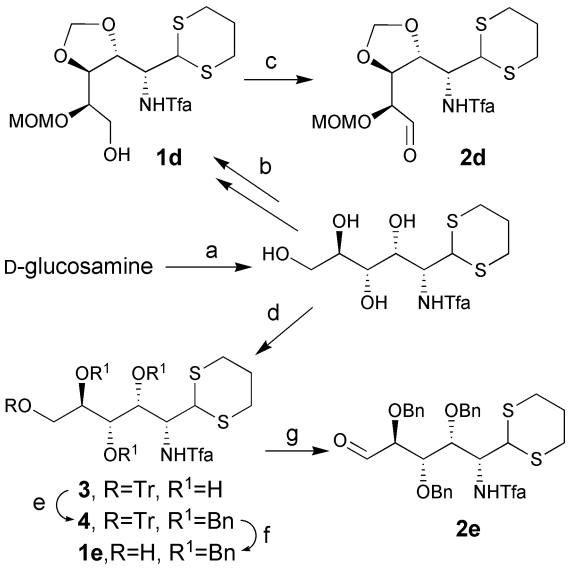


Scheme 1 The preliminary exploration of the oxidation.

Surprisingly, we found that when the free amino group was protected by an *N*-trifluoroacetyl (Tfa) group, the oxidations worked excellently even with different protection patterns for the secondary hydroxyls in the molecule. When the *N*-Tfa protection was used, the corresponding alcohols could be oxidized smoothly to the desired aldehydes with typical methods, *i.e.*, Dess–Martin reagent (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one)[15] or Parikh–Doering oxidation (SO_3·Py, triethylamine and DMSO).[16] According to the experimental results, the dominant factor for the successful oxidation of the hydroxyl in the presence of the dithiane functional group is the *N*-protection. It can be deduced from the results that an *N*-protection of strong electron withdrawing capability enables the desired oxidation.

In another aspect, hydroxyl protections are crucial for further reactions, though they do not strongly affect the oxidation as observed in this particular case. We designed two series of compounds with different types of *O*-protecting groups suitable for the later cyclization reactions. One of the two types has the *O*-acetal (an *O*-MOM and a cyclic formaldehyde acetal) protections, while the other one has non-cyclic *O*-Bn protecting groups. They are expected to induce diverse stereochemistry outcomes in different stages.

Experimentally, from *N*-trifluoroacetyl D-glucosamine dithiane, which was prepared readily[10a,b] by protecting D-glucosamine, *O*-acetal-*N*-Tfa derivative **1d** was produced in three steps and in 25% yield.[10b] The subsequent oxidation of compound **1d** with Dess–Martin reagent gave the corresponding aldehyde **2d** in a satisfying 83% yield after isolation. Also, starting from *N*-trifluoroacetyl D-glucosamine dithiane, *via* regioselective 6-*O* tritylation, per-*O*-benzylation, and de-*O*-tritylation, the *O*-Bn-*N*-Tfa derivative **1e** was prepared in a high yield. Compound **1e** was oxidized to aldehyde **2e** with the Dess–Martin reagent in 63% isolated yield (Scheme 2).



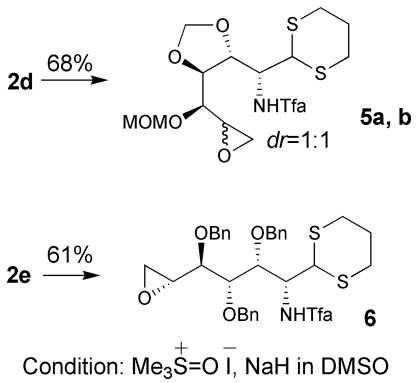
Scheme 2 The preparation of the aldehydes. *Reaction conditions and yields:* (a) reported procedures;[10a,b] (b) 3 steps,[10b] 25%; (c) Dess–Martin reagent, 83%; (d) TrCl, Py, DMAP, 95%; (e) BnCl, NaH, *n*-Bu_4NI, THF, 99%; (f) MeOH, EtOAc, *p*-TsOH hydrate, 78%; (g) Dess–Martin reagent, 63%.

By oxidating the 6-hydroxy to an *a*-synthon, along with the established dithiane group, the donor and the acceptor position in a normal open chain sugar is reversed. The relative position of the *N*-substituent is also changed. In the extensively investigated field of the so-called dithiane route, this is the first time that such a manipulation is realized on a nitrogen containing sugar dithiane. It is of great conceptual importance because a full utilization of carbohydrate type intermediates in many natural product or bioactive structure syntheses is enabled by this methodology.

The following epoxidation on compounds **2d** and **2e** could be realized by the Corey–Chaykovsky method[17] (using the ylide formed from trimethyl sulfoxonium iodide and sodium hydride). As a comparison, the halomethyllithium methods[18] led to significant decomposition of the aldehyde due to its strong basicity, which probably interferes with the dithiane functional group or induces side reactions on the aldehydo group.

In this epoxidation, the two different *O*-protecting patterns gave distinct stereochemical outcomes. The tri-*O*-acetal protected compound **2d** gave a 1 : 1 mixture (by NMR) of the two diastereoisomers **5a** and **5b**, which are inseparable by silica gel chromatography. As an interesting comparison, the tri-*O*-Bn derivative **2e** gave only one diastereoisomer **6** (by NMR) with the D-*gluco*-D-*glycero* configuration out of the two possible diastereoisomers (Scheme 3). This absolute configuration was decided by its cyclized derivatives, as the following describes.

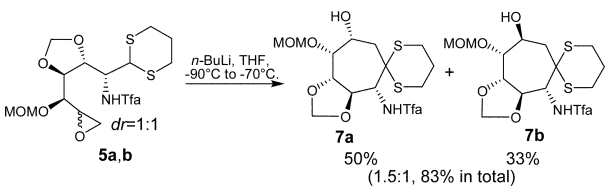
The results can be understood by conformational analysis. The rigid cyclic protection on compound **2d** separates the main chain as two substituents above and below the dioxolane ring. Therefore, the epoxidation was performed without being strongly affected by the chiral substituents. The nucleophilic reagent can attack the carbonyl group of compound **2d** from both the *Re* and *Si* face



Scheme 3 Corey–Chaykovsky epoxidation.

to produce the 1 : 1 diastereomeric mixture. On the contrary, the epoxidation on compound **2e** took place on a molecule with the natural *sickle* conformation.[19] The *Si* face of the carbonyl group of compound **2e** is shielded most probably by the 3,4-hydroxyl protections, while the *Re* face is left open to nucleophilic attack. As a result, perfect diastereoselectivity is observed. Computer modeling supported this idea, too.[20]

Scheme 4 illustrates the intramolecular anionic cyclization according to the Corey–Seebach method.[12] When the above-produced tri-*O*-acetal protected epoxides **5a** and **5b** as a 1 : 1 mixture were deprotonated with *n*-BuLi at −90 °C, the stabilized dilithiated dithiane-imidate intermediate was formed according to our former report.[10b,c] An anionic cyclization from this intermediate took place immediately. Warming up to −70 °C in one hour completed the reaction, and gave the *carba*-analogue of a 1-amino-1-deoxy-α-D-altro-septanose derivative (**7a**) and the *carba*-analogue of a 1-amino-1-deoxy-β-L-galacto-septanose derivative (**7b**), which are readily separated by silica gel chromatography, with yields of 50% and 33% respectively (*ca.* 1.5 : 1, 83% in total). No six-membered ring was obtained under such conditions. The high cyclization yield to seven-membered rings could be expected for compounds with *trans*-3,4-*O*-cyclic acetal protection, again due to the separated reaction centers. The ratio of products **7a** and **7b** indicates that the anionic cyclization is accompanied by a slight kinetic resolution process for the adducts **5a** and **5b** as a 1 : 1 diastereoisomeric pair, though the adduct related to the low yield product **5b** was not recovered. The kinetic resolution process can be understood, for the dithiane anion of compound **7b** attacks the epoxide ring from a more hindered face than that of compound **7a**.



Scheme 4 Anionic cyclization of the *O*-acetal epoxides **5a,b**.

The stereochemistry at C-6 and the conformations of both diastereomers **7a** (in $CDCl_3$) and **7b** (in C_6D_6) have been assigned unambiguously by the corresponding coupling constants and the NOE (see experimental section for detail).

A crystal structure of compound **7b** is also available for further confirmation of the stereochemistry (Fig. 2).[21]

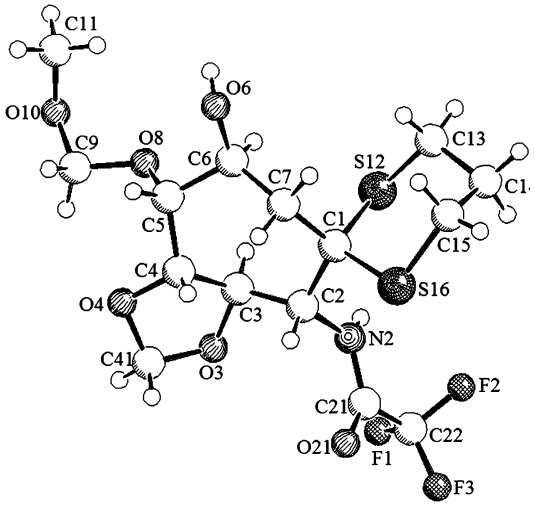
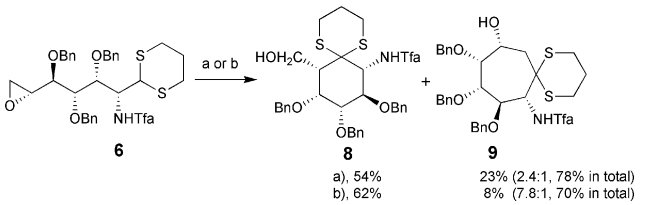


Fig. 2 Crystal structure of compound **7b**.

The tri-*O*-Bn counterpart **6** was cyclized under similar conditions using 2.5 eq. of *n*-BuLi as the base and THF as the solvent. Contrary to the last cyclization, a *carba*-analogue of 1-amino-1-deoxy-β-L-*galacto*-pyranose derivative (**8**) was obtained as the main product, accompanied by a certain amount of the *carba*-analogue of a 1-amino-1-deoxy-α-D-*altro*-septanose derivative (**9**). As illustrated in Scheme 5, in the last cyclization, under standard Corey–Seebach conditions (at −10 °C due to the slow cyclization rate), compounds **8** and **9** were obtained in 54% and 23% yield respectively (*ca.* 2.4 : 1, 78% in total). However, when LiBr was added, the cyclization was speeded up (therefore the reaction was started from −90 °C and quenched at −50 °C) and the ratio of the six-membered ring product to seven-membered ring product was increased significantly, probably *via* a Li-chelated intermediate, to give 62% yield for compound **8** and 8% yield for compound **9** (*ca.* 7.8 : 1, 70% in total). Clearly, the latter LiBr condition is ideal for selective preparation of a fully functionalized branched six-membered ring amino carbasugar **8**.



Scheme 5 Anionic cyclization of the *O*-Bn epoxide **6**. *Reaction conditions and yields:* (a) *n*-BuLi, THF, −10 °C; (b) *n*-BuLi, THF, 1 eq. LiBr, −90 °C to −50 °C.

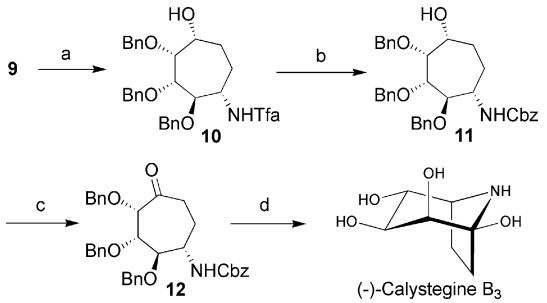
Furthermore, in various optimization experiments, it was found[22] that with the Corey–Seebach method, a preference of cyclization to a six-membered ring over a seven-membered ring is a strong intrinsic nature of the epoxide **6**, independent of the conditions tested, because the six-membered ring formation benefits from both geometrical and energetical factors, while the formation of the seven-membered ring results only from the more reactive C-7 of the epoxide.

The stereochemistry at C-6 and conformations of six-membered ring **8** and seven-membered ring **9** have been assigned unambiguously by the corresponding coupling constants and the NOE. Both the stereochemistry at C-6 on compound **8** and compound **9** match each other and the configuration of C-6 on the epoxide **6** was deduced readily (see experimental section for detail).

Several points from the above described cyclizations are worth discussing here. Side reactions, such as deprotonation of the *O*-Bn protecting group and the subsequent Wittig rearrangement[23] did not occur when epoxide **6** was treated with *n*-BuLi. Besides, it has been well known conceptually that the cyclization can depend strongly on the protecting groups. However, the successful application of such a concept is rare.[13] As described above, by generating a proper conformation with different protecting groups, the fast reaction and strong preference for 7-*endo*-cyclization of the tri-*O*-acetal epoxides **5a**,**b**, as well as the rare preference[13a,b] of the 6-*exo*-cyclization of the tri-*O*-Bn epoxide **6**, were achieved divergently. This demonstrates a successful application of a protection controlled cyclization concept.

In a practical aspect, the resulting orthogonally protected seven-membered ring amino carbasugars **7a**,**b** from the epoxides **5a**,**b** as well as the fully functionalized six-membered ring amino carbasugar **8** from epoxide **6** are useful precursors for many bioactive structures. For example, from compound **8**, the *carba*-analogue of 1-amino-1-deoxy-β-L-*galacto*-pyranose is readily available. From compounds **7a**,**b** and **9**, calystegine type structures could be produced as well. Experimentally, the deprotections for compounds **7a**, **b**, **8** and **9** are possible by our previously reported methods[10b] or standard conditions.[24] As an example, we decided to apply the resulting seven-membered ring product in the synthesis of an enantiomer of naturally discovered (+)-calystegine B_3. For simplicity of deprotection and purification, compound **9** was used as the starting material.

The dithiane ring of compound **9** was cleaved by hydrogenolysis with Raney-Ni. Without significant deprotection of *O*-Bn, compound **10** was obtained in 71% isolated yield. The *N*-Tfa protection[25] of the resulting compound **10** was then removed by heating with $Ba(OH)_2$ octahydrate in a water–methanol mixture. $NaHCO_3$ and CbzCl were added to the above reaction mixture to achieve an interesting one-pot protection group switching reaction and produced the crude compound **11** (indicated by HRMS-ESI$^+$) mixed with inseparable impurities introduced by CbzCl.[26] The crude compound **11** was directly oxidized with Dess–Martin reagent[15] to the corresponding ketone **12**, which is readily purified by silica gel chromatography. The isolated yield based on compound **10** is 58%. Hydrogenolysis of ketone **12** with 10% Pd-C in a THF–water mixture cleaved *N*-Cbz completely without significant deprotection of *O*-Bn (according to the HRMS-ESI$^+$). The following hydrogenolytic de-*O*-benzylation under acidic conditions led to (−)-calystegine B_3 (81% isolated yield), which shows a correct HRMS(ESI$^+$) peak, a reversed specific rotation signal and parallel NMR data as those from the reported (+)-calystegine B_3 (Scheme 6).[27]



Scheme 6 The synthesis of (−)-calystegine B_3. *Reaction conditions and yields:* (a) R-Ni, EtOH, reflux, 71%; (b) i. $Ba(OH)_2$ octahydrate, MeOH, water, 80 °C; ii. CbzCl, $NaHCO_3$; (c) Dess–Martin reagent, 58% for steps b and c; (d) 1 atm H_2, 10% Pd/C, THF, water, RT, overnight, followed by addition of excessive 1 N HCl, 3 more days, 81%.

Conclusions

In summary, we used D-glucosamine trimethylene dithioacetal as a cheap and versatile starting material and established a methodology for the first time that switches the sugar carbonyl reaction center from head to tail as well as the relative position of the *N*-substituent to yield valuable *N*-containing carbohydrate dithiane synthetic intermediates. By virtue of carefully selected protecting groups, the aldehydes **2d** and **2e** as very useful *N*-containing carbohydrate building blocks were produced. The following Corey–Chaykovsky method yielded the *N*-containing heptose epoxide derivatives **5a**, **b** and **6**. The stereochemistry of this epoxidation can be controlled to a certain extent by the hydroxy protecting groups. Depending on the protecting groups, *via* the stabilized dilithiate dithiane-imidate intermediate, the anionic cyclizations of those epoxides according to the Corey–Seebach method achieved either highly functionalized seven-membered ring amino carbasugars **7a**,**b** and **9** or six-membered ring amino carbasugar **8** with defined stereochemistry and high yields. From compound **9**, we accomplished the first synthesis of (−)-calystegine B_3 as an interesting enantiomer, also a possible homomorphous analogue of the naturally discovered calystegines. As the first realization of an anionic cyclization pathway to calystegine type structures, the strategy described above has a high potential for the syntheses of various structural analogues of calystegines. The bioactivity of (−)-calystegine B_3 will be tested in due course.

Experimental

Thin layer chromatography (TLC) was conducted on silica gel aluminium sheets (Kieselgel 60 F254, Merck). The spots were visualized by UV light or heating after being dipped into a mixture of two solutions (500 mg 1,3-dihydroxy naphthalin in 250 mL ethanol and 250 mL 2 N H_2SO_4) or a mixture of 25 g phosphomolybdic acid, 10 g $Ce(SO_4)_2$, 60 mL conc. H_2SO_4 and 940 mL water. All solvents used were dried as a standard method or as indicated in the procedures when an anhydrous condition was required. All reagents are commercially available and were used without further purification. Air or moisture sensitive reactions were performed under an argon atmosphere (Argon 4.8 of Messer Griesheim, without further drying) with standard Schlenk techniques. The specific rotation was measured on a polarimeter 341 (Perkin-Elmer) with 1 dm cuvettes. Nuclear magnetic resonance spectra were recorded on a Bruker AMX 400 spectrometer, a Varian 500 INOVA, or a Varian Unity Plus 600. The chemical shift is specified as δ in ppm and the signal of the solvent was used as the internal standard. Electrospray ionisation mass spectra (MS-ESI)

were recorded on a Quattro LCZ or a MicroTof. Medium pressure chromatography (MPLC) was performed on silica gel 60 (230–400 mesh, Merck). Melting points were measured on an uncorrected Buchi B-540 apparatus. Elementary analysis was performed on CHN-O-RAPID (Heraeus) and refers to the stoichiometric mass. The elementary analysis results for most compounds were not presented due to the large data deviation caused by the several additional hetero elements in the system.

2-Deoxy-3,4-*O*-methylene-5-*O*-methoxymethyl-2-trifluoracetamido-D-*gluco*-hexodialdose-1,1-trimethylene dithioacetal, 2d

Under argon, alcohol **1d**[10b] (4.0 g, 9.5 mmol, dried by coevaporation with toluene) was dissolved in dichloromethane (40 mL). To this solution at RT, 1,1,1-triacetoxy-1,1-dihydro-1,2-benzodioxol-3-(1*H*)-one (Dess–Martin periodinane, 15% wt., from Acros, 28 mL, 9.9 mmol, 1.04 eq.) in dichloromethane was added. The mixture was stirred at RT for 2 h (monitored by TLC). Then triethylamine (1.5 mL) was added and the resulting mixture was stirred for another 10 min at RT. All the volatile components were removed under vacuum (bath temperature should be lower than 40 °C) and the residue was purified by MPLC (cyclohexane–ethyl acetate 5 : 1) to yield product **2d** (3.3 g, 83%) as a light yellow oil; $[\alpha]_D$ −1.7 (*c* 1.00, MeOH); δ_H (CD_2Cl_2, 400 MHz): 9.74 (d, *J* 1.6 Hz, 1H, H-6), 6.79 (m, 1H, NH), 5.14 (s, 1H, 3,4-*O*-methylene-Ha), 5.01 (s, 1H, 3,4-*O*-methylene-Hb), 4.82 (dd, 1H, *J* 1.5 Hz, *J* 6.2 Hz, H-3), 4.81 (s, 2H, CH_2-MOM), 4.60 (dt, *J* 1.5 Hz, *J* 9.7 Hz, 1H, H-2), 4.23 (dd, *J* 1.6 Hz, *J* 6.1 Hz, 1H, H-5), 4.02 (pseudo-t, *J* 6.1 Hz, 1H, H-4), 3.95 (d, *J* 9.7 Hz, 1H, H-1), 3.47 (s, 3H, CH_3-MOM), 3.06–2.95 (m, 2H, dithiane), 2.75–2.66 (m, 2H, dithiane), 2.05–2.03 (m, 2H, dithiane); δ_C (CD_2Cl_2, 100 MHz): 200.4 (C-6), 157.9 (q, *J* 37.4, 1C, CO-Tfa), 116.2 (q, *J* 287.9, 1 C, CF_3-Tfa), 97.8 (CH_2-MOM), 96.6 (3,4-*O*-methylene), 81.7 (C-5), 76.8 (C-3), 76.7 (C-4), 56.6 (CH_3-MOM), 52.2 (C-2), 46.2 (C-1), 27.6 (dithiane), 27.1 (dithiane), 25.5 (dithiane); HRMS-ESI$^+$: *m*/*z* [M + MeOH + Na]$^+$ 474.0837, $C_{15}H_{24}F_3NNaO_7S_2$ requires 474.0838.

2-Deoxy-2-trifluoracetamido-6-*O*-trityl-D-glucose-1,1-trimethylene dithioacetal, 3

In dry pyridine (400 mL, over MS 4 Å), *N*-trifluoroacetamido-D-glucose-1,1-trimethylene dithioacetal[10b] (20.0 g, 0.055 mol) was dissolved. To this solution at RT, TrCl (28.0 g, 0.1 mmol) and DMAP (0.5 g) were added. The clear solution was then stirred at RT for 2 days. For quenching the reaction, MeOH (20 mL) was added. Then all volatile components were removed under vacuum. The residue was distributed in ethyl acetate (1 L) and HCl (1 N, 500 mL). The organic phase was separated and washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL) in turn. The resulting solution was then evaporated to yield a syrup, which was triturated with cyclohexane several times and coevaporated to dryness with toluene. The resulting crude syrup can be used directly for the next step of the reaction. Otherwise it can be purified by MPLC (*n*-pentane–ethyl acetate 5 : 1) to yield compound **3** (31.8 g, 95%) as a white solid; mp: 96–98 °C; $[\alpha]_D$ −12.7 (*c* 1.00, MeOH); δ_H ($CDCl_3$, 400 MHz): 7.36–7.17 (m, 15H, H_{aryl}-Tr), 6.87 (d, *J* 9.4 Hz, 1H, NH), 4.46 (m, 1H, H-2), 4.27 (brd, *J* 2.4 Hz, 1H, H-3), 3.97 (d, *J* 8.4 Hz, 1H, H-1), 3.73 (brd, *J* 4.1 Hz, 1H, H-5), 3.56 (brs, 1H, H-4), 3.33 (dd, *J* 4.4 Hz, *J* 9.8 Hz, 1H, H-6a), 3.25 (dd, *J* 3.3 Hz, *J* 9.8 Hz, 1H, H-6b), 2.89–2.49 (m, 6H, dithiane and 3 × OH), 1.95–1.85 (m, 2H, dithiane); δ_C ($CDCl_3$, 100 MHz): 157.3 (q, *J* 36.4 Hz, 1C, *C*OCF$_3$), 146.8 ($C_{q,aryl}$-Tr), 128.5–127.1 (m, 15C, CH_{aryl}-Ph), 116.1 (q, *J* 288.0 Hz, 1C, CO*C*F$_3$), 87.4 ($C_{q,alkyl}$-Tr), 72.8 (C-4), 71.5 (C-5), 69.3 (C-3), 64.3 (C-6), 53.5 (C-2), 46.1 (C-1), 27.6 (dithiane), 27.3 (dithiane), 25.2 (dithiane); HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ 630.1549, $C_{30}H_{32}F_3NNaO_5S_2$ requires 630.1566.

2-Deoxy-3,4,5-tri-*O*-benzyl-2-trifluoracetamido-6-*O*-trityl-D-glucose-1,1-trimethylene dithioacetal, 4

Purified starting material **3** (30.0 g, 0.049 mol, crude product from last step can be used too) was dissolved in THF (500 mL) and immersed in an ice-water bath. To this solution, NaH (17.0 g, 60% in oil, 0.71 mol) was added portion-wise followed by BnCl (80 mL, 0.7 mol) and *n*-Bu_4NI (1.0 g). The resulting suspension was then stirred at RT for 2 days and poured into a mixture of ethyl acetate (1 L), ice cold water (1 L), and the necessary amount of HOAc for keeping the mixture neutral. The two phases were separated and the water phase was washed with ethyl acetate several times. Combined organic layers were washed with HCl (1 N, 100 mL), sat. aqueous $NaHCO_3$ (100 mL), and brine (100 mL) in turn. Finally the solvent was evaporated and the residue was coevaporated with toluene several times to dryness. The resulting crude product can be used directly for the next reaction or purified by MPLC (cyclohexane–ethyl acetate 10 : 1) to yield compound **4** (42.5 g, 99%) as a colorless syrup; $[\alpha]_D$ −4.0 (*c* 1.00, benzene); δ_H (C_6D_6, 600 MHz): 7.57–6.94 (m, 15H, H_{aryl}-Bn), 6.86 (d, *J* 9.8 Hz, 1H, NH), 4.85 (t, *J* 9.8 Hz, 1H, H-2), 4.76 (d, *J* 11.0 Hz, 1H, H_{alkyl}-Bn), 4.65 (d, *J* 12.0 Hz, 1H, H_{alkyl}-Bn), 4.61 (d, *J* 11.0 Hz, 1H, H_{alkyl}-Bn), 4.51–4.47 (m, 3H, H-3 and 2 × H_{alkyl}-Bn), 4.43 (d, *J* 12.0 Hz, 1H, H_{alkyl}-Bn), 3.99 (dd, *J* 5.1 Hz, *J* 8.1 Hz, 1H, H-4), 3.74 (dd, *J* 4.3 Hz, *J* 8.1 Hz, 1H, H-5), 3.60 (br-d, *J* 3.6 Hz, 2H, H-6a,b), 3.53 (d, *J* 9.6 Hz, 1H, H-1), 2.77–2.72 (m, 1H, dithiane), 2.26–2.21 (m, 1H, dithiane), 2.00–1.96 (m, 1H, dithiane), 1.71–1.67 (m, 1H, dithiane), 1.45–1.39 (m, 1H, dithiane), 1.22–1.17 (m, 1H, dithiane); δ_C (C_6D_6, 150 MHz): δ 157.4 (q, *J* 36.7 Hz, 1C, *C*OCF$_3$), 144.47 (3C, $C_{q,aryl}$-Tr), 138.7 ($C_{q,aryl}$-Bn), 138.6 ($C_{q,aryl}$-Bn), 138.2 ($C_{q,aryl}$-Bn), 129.2–127.2 (30 C, CH_{aryl}-Bn and CH_{aryl}-Tr), 116.7 (q, *J* 288.3 Hz, 1C, CO*C*F$_3$), 87.3 (3C, C_{alkyl}-Tr), 80.8 (C-5), 79.6 (C-4), 77.6 (C-3), 75.4 (C_{alkyl}-Bn), 74.6 (C_{alkyl}-Bn), 72.0 (C_{alkyl}-Bn), 62.8 (C-6), 53.2 (C-2), 45.8 (C-1), 26.5 (dithiane), 25.2 (dithiane), 23.3 (dithiane); HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ 900.2978, $C_{51}H_{50}F_3NNaO_5S_2$ requires 900.2975.

2-Deoxy-3,4,5-tri-*O*-benzyl-2-trifluoracetamido-D-glucose-1,1-trimethylene dithioacetal, 1e

In a flask, purified starting material **4** (39.0 g, 0.044 mol, crude product from last step can be used too) was dissolved in ethyl acetate (400 mL) and MeOH (400 mL) followed by addition of *p*-TsOH monohydrate (45.0 g, 0.237 mol). The reaction mixture was stirred at RT for 2 days and poured into a mixture of water (1 L) and ethyl acetate (1 L) with excessive $NaHCO_3$ for keeping the mixture slightly basic. The biphasic mixture was separated and the water phase was washed several times with ethyl acetate. Combined organic phases were washed with brine and evaporated

to dryness. The residue was purified by MPLC (cyclohexane–ethyl acetate 4 : 1) to yield compound **1e** (21.8 g, 78%) as a light yellow solid; mp: 150–151 °C; $[\alpha]_D$ −19.6 (*c* 1.00, MeOH); δ_H ($CDCl_3$, 500 MHz): δ 7.42–7.27 (m, 15H, H_{aryl}-Bn), 6.84 (d, *J* 9.8 Hz, 1H, NH), 4.96–4.64 (m, 3H, H_{alkyl}-Bn), 4.58 (t, *J* 9.8 Hz, 1H, H-2), 4.45 (d, *J* 8.6 Hz, 1H, H-3), 3.89 (d, *J* 4.7 Hz, 2H, H-6), 3.85–3.82 (m, 1H, H-4), 3.72–3.69 (m, 1H, H-5), 3.63 (d, *J* 9.6 Hz, 1H, H-1), 3.01–2.95 (m, 1H, dithiane), 2.75–2.70 (m, 1H, dithiane), 2.57–2.52 (m, 1H, dithiane), 2.44–2.39 (m, 1H, dithiane), 2.21–2.08 (brs, OH), 1.98–1.86 (m, 2H, dithiane); δ_C ($CDCl_3$, 125 MHz): 157.4 (q, *J* 37.1 Hz, 1C, *C*OCF_3), 137.7 (2C, $C_{q,aryl}$-Bn), 138.5 ($C_{q,aryl}$-Bn), 128.6–127.7 (15C, CH_{aryl}-Bn), 115.8 (q, *J* 288.0 Hz, 1C, CO*C*F_3), 80.2 (C-5), 80.1 (C-4), 77.2 (C-3), 75.3 (C_{alkyl}-Bn), 75.0 (C_{alkyl}-Bn), 71.7 (C_{alkyl}-Bn), 60.8 (C-6), 52.3 (C-2), 45.6 (C-1), 26.9 (dithiane), 26.2 (dithiane), 25.0 (dithiane); HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ 658.1871, $C_{32}H_{36}F_3NNaO_5S_2$ requires 658.1879.

2-Deoxy-3,4,5-tri-*O*-benzyl-2-trifluoracetamido-D-*gluco*-hexodialdose-1,1-trimethylene dithioacetal, 2e

Alcohol **1e** (16.0 g, 25.2 mmol, dried by coevaporation with toluene) was dissolved in dichloromethane (80 mL). To this solution, Dess–Martin periodinane (75.0 mL, 15% wt, from Acros, 26.5 mmol, 1.05 eq.) was added *via* syringe at RT. The mixture was then stirred at RT for 1 h followed by addition of TEA (6.0 mL). The dark mixture was stirred for 10 min and quenched by addition of saturated aqueous $Na_2S_2O_3$ (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The biphasic mixture was separated and the water phase was washed with dichloromethane several times. Combined organic phases were then evaporated and purified by MPLC (cyclohexane–ethyl acetate 50 : 1–20 : 1) to yield aldehyde **2e** (10.1 g, 63%) as a light yellow oil; $[\alpha]_D$ −16.3 (*c* 1.00, benzene); δ_H (C_6D_6, 600 MHz): 9.60 (s, 1H, H-6), 7.19–6.97 (m, 15H, H_{aryl}-Bn), 6.91 (d, *J* 9.7 Hz, 1H, NH), 4.87 (t, *J* 9.2 Hz, 1H, H-2), 4.60–4.58 (m, 2H, H-3 and H_{alkyl}-Bn), 4.49–4.34 (m, 5H, H_{alkyl}-Bn), 3.95–3.92 (m, 2H, H-4 and H-5), 3.63 (d, *J* 8.8 Hz, 1H, H-1), 2.73–2.70 (m, 1H, dithiane), 2.56–2.52 (m, 1H, dithiane), 2.04–2.00 (m, 1H, dithiane), 1.94–1.90 (m, 1H, dithiane), 1.44–1.40 (m, 1H, dithiane), 1.33–1.28 (m, 1H, dithiane); δ_C (C_6D_6, 150 MHz): 202.0 (C-6), 157.1 (q, *J* 36.7 Hz, 1C, *C*OCF_3), 137.7 ($C_{q,aryl}$-Bn), 137.4 ($C_{q,aryl}$ -Bn), 136.9 ($C_{q,aryl}$-Bn), 128.4–127.5 (15C, CH_{aryl}-Bn), 116.3 (q, *J* 288.3 Hz, 1C, CO*C*F_3), 83.3 (C-5), 81.6 (C-4), 76.4 (C-3), 74.4 (C_{alkyl}-Bn), 73.7 (C_{alkyl}-Bn), 72.9 (C_{alkyl}-Bn), 51.1 (C-2), 46.4 (C-1), 26.7 (dithiane), 26.0 (dithiane), 24.9 (dithiane); HRMS-ESI$^+$: *m*/*z* [M + MeOH + Na]$^+$ 688.1978, $C_{33}H_{38}F_3NNaO_6S_2$ requires 688.1985.

6,7-Anhydro-2-deoxy-3,4-*O*-methylene-5-*O*-methoxymethyl-2-trifluoracetamido-D-*gluco*-D-*glycero*-heptose-1,1-trimethylene dithioacetal and 6,7-anhydro-2-deoxy-3,4-*O*-methylene-5-*O*-methoxy-methyl-2-tri-fluoracetamido-D-*gluco*-L-*glycero*-heptose-1,1-trimethylene dithioacetal, 5a,b

A solution of trimethylsulfoxonium iodide (97 mg, 0.4 mmol) in DMSO (1.0 mL) was added to a suspension of NaH (60% dispersion in oil, 18 mg, 0.4 mmol) in DMSO (1 mL) at RT. The suspension was stirred at room temperature for 30 min. A solution of aldehyde **2d** (40 mg, 0.1 mmol, dried by coevaporation with toluene) in DMSO (1 mL) was added to the above suspension, and the resulting mixture was stirred for 1 h at RT. The reaction mixture was then poured into ice-cold water (20 mL) and extracted with ethyl acetate several times. Combined organic phases were evaporated and purified by MPLC (cyclohexane–ethyl acetate 5 : 1) to yield inseparable diastereomeric epoxides **5a**,**b** (28 mg, 68%) as a colorless oil; $[\alpha]_D$ −16.2 (*c* 1.00, MeOH). The NMR spectra are listed as separated compounds: diastereomer 1, δ_H (CD_2Cl_2, 600 MHz): 6.80 (m, 1H, NH), 5.07 (s, 1H, 3,4-*O*-methylene-Ha), 4.96 (s, 1H, 3,4-*O*-methylene-Hb), 4.84 (dd, *J* 1.1 Hz, *J* 6.3 Hz, 1H, H-3), 4.75 (s, 1H, CH_2-MOM-Ha), 4.66 (s, 1H, CH_2-MOM-Hb), 4.60–4.56 (m, 1H, H-2), 3.96 (d, *J* 9.6 Hz, 1H, H-1), 3.85 (t, *J* 4.6 Hz, 1H, H-5), 3.77–3.73 (m, 1H, H-4), 3.40 (s, 3H, CH_3-MOM), 3.10–3.08 (m, 1H, H-6), 3.02–2.95 (m, 2H, dithiane), 2.83–2.78 (m, 2H, H-7), 2.72–2.61 (m, 2H, dithiane), 2.02–1.95 (m, 2H, dithiane); δ_C (CD_2Cl_2, 150 MHz): 157.86 (q, *J* 37.3, 1C, CO-Tfa), 116.2 (q, *J* 287.8, 1C, CF_3-Tfa), 97.0 (CH_2-MOM), 96.4 (3,4-*O*-methylene), 78.4 (C-4), 75.9 (C-3), 75.7 (C-5), 56.4 (CH_3-MOM), 52.3 (C-2), 51.3 (C-6), 46.4 (C-1), 44.8 (C-7), 27.7 (dithiane), 27.3 (dithiane), 25.5 (dithiane); diastereomer 2, δ_H (CD_2Cl_2, 600 MHz): 6.80 (m, 1H, NH), 5.05 (s, 1H, 3,4-*O*-methylene-Ha), 4.90 (s, 1H, 3,4-*O*-methylene-Hb), 4.88 (s, 1H, CH_2-MOM-Ha), 4.79 (dd, *J* 1.1 Hz, *J* 6.5 Hz, 1H, H-3), 4.71 (s, 1H, CH_2-MOM-Hb), 4.68–4.66 (m, 1H, H-2), 3.92 (d, *J* 9.8 Hz, 1H, H-1), 3.77–3.73 (m, 1H, H-4), 3.59 (t, *J* 6.3 Hz, 1H, H-5), 3.37 (s, 3H, CH_3-MOM), 3.06–3.02 (m, 1H, H-6), 2.82 (t, *J* 4.6 Hz, 1H, H-7a), 3.02–2.95 (m, 2H, dithiane), 2.72–2.61 (m, 1H, H-7b), 2.72–2.61 (m, 2H, dithiane), 2.02–1.95 (m, 2H, dithiane); δ_C (CD_2Cl_2, 150 MHz): 157.89 (q, *J* 37.3, 1C, CO-Tfa), 116.2 (q, *J* 288.0, 1C, CF_3-Tfa), 96.2 (3,4-*O*-methylene), 96.0 (CH_2-MOM), 78.0 (C-4), 76.8 (C-5), 76.7 (C-3), 56.4 (CH_3-MOM), 52.5 (C-6), 52.3 (C-2), 46.2 (C-1), 43.8 (C-7), 27.4 (dithiane), 27.0 (dithiane), 25.5 (dithiane); HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ 456.0725, $C_{15}H_{22}F_3NNaO_6S_2$ requires 456.0733.

6,7-Anhydro-2-deoxy-3,4,5-tri-*O*-benzyl-2-trifluoracetamido-D-*gluco*-D-*glycero*-heptose-1,1-trimethylene dithioacetal, 6

To a suspension of NaH (1.69 g, 60% in oil, 42.2 mmol) in dry DMSO (20.0 mL, dried over MS 4 Å), a solution of trimethylsulfoxonium iodide (9.21 g, 41.9 mmol) in dry DMSO (100 mL) was added at RT. The mixture was stirred for 1 h at RT, to which a solution of aldehyde **2e** (8.0 g, 12.6 mmol, dried by coevaporation with toluene) in dry DMSO (80 mL, dried over MS 4 Å) was added *via* syringe. The resulting dark red solution was stirred at RT for 1 h and poured into ice-cold saturated aqueous ammonium chloride solution (200 mL). The water phase was then extracted with ethyl acetate several times. Combined organic phases were washed with brine and evaporated. The crude product was purified by MPLC (cyclohexane–ethyl acetate 20 : 1) to yield epoxide **6** (5.0 g, 61%) as a light yellow oil; $[\alpha]_D$ −14.3 (*c* 1.00, MeOH); δ_H (C_6D_6, 600 MHz): 7.28–7.01 (m, 15H, H_{aryl}-Bn), 6.78 (d, *J* 10.1 Hz, 1H, NH), 4.94 (d, *J* 11.0 Hz, 1H, H_{alkyl}-Bn), 4.84 (d, *J* 11.0 Hz, 1H, H_{alkyl}-Bn), 4.82 (t, *J* 10.1 Hz, 1H, H-2), 4.78 (dd, *J* 1.5 Hz, *J* 8.6 Hz, 1H, H-4), 4.66 (d, *J* 11.1 Hz, 1H, H_{alkyl}-Bn), 4.62 (d, *J* 11.1 Hz, 1H, H_{alkyl}-Bn), 4.44 (s, 2H, H_{alkyl}-Bn), 3.94 (dd, *J* 1.9 Hz, *J* 8.6 Hz, 1H, H-5), 3.65 (d, *J* 10.1 Hz, 1H, H-1), 3.49 (dd, *J* 1.5 Hz, *J* 8.6 Hz, 1H, H-3), 3.32–3.29 (m, 1H, H-6), 2.82–2.75 (m, 2H, dithiane), 2.33–2.20 (m, 1H, H-7), 2.33–1.96 (m, 2H, dithiane), 1.52–1.48 (m, 1H, dithiane), 1.35–1.32 (m, 1H, dithiane); δ_C (C_6D_6, 150 MHz): 157.7 (q, *J* 36.7 Hz,

1C, *C*OCF$_3$), 138.9 (C$_{q,aryl}$-Bn), 138.6 (C$_{q,aryl}$-Bn), 138.5 (C$_{q,aryl}$-Bn), 128.7–127.8 (15C, CH$_{aryl}$-Bn), 117.0 (q, *J* 288.3 Hz, 1C, CO*C*F$_3$), 84.2 (C-5), 81.1 (C-3), 77.9 (C-4), 76.1 (C$_{alkyl}$-Bn), 75.3 (C$_{alkyl}$-Bn), 72.7 (C$_{alkyl}$-Bn), 52.4 (C-2), 48.9 (C-6), 46.1 (C-7), 45.4 (C-1), 26.6 (dithiane), 25.9 (dithiane), 25.3 (dithiane); HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ 670.1886, $C_{33}H_{36}F_3NNaO_5S_2$ requires 670.1879.

(2*R*,3*R*,4*S*,5*R*,6*R*)-6-Hydroxy-3,4-methylenedioxy-5-methoxymethoxy-2-trifluoracetamido-cycloheptanone trimethylene dithioacetal, 7a and (2*R*,3*R*,4*S*,5*R*,6*S*)-6-hydroxy-3,4-methylenedioxy-5-methoxymethoxy-2-trifluoracetamido-cycloheptanone trimethylene dithioacetal, 7b

Under argon, epoxides **5a**,**b** as a 1 : 1 mixture (1.2 g, 2.8 mmol, dried by coevaporation with toluene) were dissolved in THF (12 mL) and cooled down to −90 °C. *n*-BuLi (6.5 mL, 1.6 M in hexane, 10.4 mmol, 3.7 eq.) was added to the stirred solution. The reaction mixture was then warmed up to −70 °C in 2 h and saturated aqueous ammonium chloride was added to quench the reaction. The resulting mixture was extracted by ethyl acetate. The organic layer was then evaporated and purified by MPLC (cyclohexane–ethyl acetate 3 : 1–2 : 1) to yield the faster moving component as compound **7a** (0.6 g, 50%) and the slower moving component as compound **7b** (0.4 g, 33%). Compound **7a** as an amorphous solid can be crystallized from a cyclohexane and ethyl acetate mixture. Compound **7b** was initially a light yellow oil that turned into a solid after storage.

Compound **7a** (the faster moving component), mp: 61–63 °C; $[\alpha]_D$ −48.8 (*c* 1.00, MeOH); δ_H ($CDCl_3$, 600 MHz): 7.28–7.19 (brs, 1H, NH), 5.01 (d, *J* 8.7 Hz, 1H, 3,4-*O*-methylene-Ha), 4.96 (d, *J* 8.7 Hz, 1H, 3,4-*O*-methylene-Hb), 4.82 (d, *J* 6.4 Hz, 1H, CH$_2$-MOM-Ha), 4.76 (d, *J* 6.4 Hz, 1H, CH$_2$-MOM-Hb), 4.49 (t, *J* 9.8 Hz, *J* 9.8 Hz, 1H, H-2), 4.25 (s, 1H, H-5), 4.14–4.10 (m, 2H, H-6 and H-3), 4.02 (m, 1H, H-4), 3.65–3.62 (m, 1H, OH), 3.46 (s, 3H, H-CH$_3$-MOM), 2.96–2.90 (m, 1H, dithiane), 2.85–2.77 (m, 3H, dithiane), 2.53 (dd, *J* 15.1 Hz, *J* 10.5 Hz, 1H, H-7$_{ax}$), 2.36 (d, *J* 15.1 Hz, 1H, H-7$_{eq}$), 2.04–1.95 (m, 2H, dithiane); δ_C ($CDCl_3$, 150 MHz): 156.7 (q, *J* 37.3 Hz, 1C, *C*OCF$_3$), 115.9 (q, *J* 288.2 Hz, 1C, CO*C*F$_3$), 98.5 (C-8), 95.2 (C-10), 78.3 (C-5), 78.1 (C-4), 74.0 (C-3), 66.3 (C-6), 58.1 (C-2), 56.1 (C-9), 53.3 (C-1), 40.4 (C-7), 27.3 (dithiane), 26.0 (dithiane), 23.7 (dithiane); HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ 456.0733, $C_{15}H_{22}F_3NNaO_6S_2$ requires 456.0733; Anal. Calcd. for $C_{15}H_{22}F_3NO_6S_2$: C 41.56, H 5.12, N 3.23%. Found: C 42.18, H 5.35, N, 3.13%.

Compound **7b** (the slower moving component), mp: 128–129 °C; $[\alpha]_D$ +25.2° (*c* 1.00, MeOH); δ_H (C_6D_6, 600 MHz): 7.19 (d, *J* 9.8 Hz, 1H, NH), 4.74 (s, 1H, 3,4-*O*-methylene-Ha), 4.72 (s, 1H, 3,4-*O*-methylene-Hb), 4.57 (d, *J* 6.6 Hz, 1H, CH$_2$-MOM-Ha), 4.46 (d, *J* 6.6 Hz, 1H, CH$_2$-MOM-Hb), 4.30 (t, *J* 10.2 Hz, *J* 10.2 Hz, 1H, H-2), 4.18 (dd, *J* 10.6 Hz, *J* 5.4 Hz, 1H, H-6), 3.94 (dd, *J* 10.2 Hz, *J* 8.6 Hz, 1H, H-3), 3.73 (t, *J* 5.4 Hz, *J* 5.1 Hz, 1H, H-5), 3.29 (dd, *J* 8.6 Hz, *J* 5.1 Hz, 1H, H-4), 3.21 (brs, 1H, OH), 3.04 (s, 3H, H-CH$_3$-MOM), 2.58 (d, *J* 15.8 Hz, 1H, H-7$_{eq}$), 2.43–2.38 (m, 1H, dithiane), 2.34–2.29 (m, 1H, dithiane), 2.00–1.90 (m, 3H, 2 × dithiane and H-7$_{ax}$), 1.20–1.07 (m, 2H, dithiane); δ_C (C_6D_6, 150 MHz): 157.3 (q, *J* 37.1 Hz, 1C, *C*OCF$_3$), 116.9 (q, *J* 288.5 Hz, 1C, CO*C*F$_3$), 98.1 (C-8), 95.4 (C-10), 81.5 (C-5), 79.1 (C-4), 73.3 (C-3), 73.1 (C-6), 60.8 (C-2), 55.7 (C-1), 55.3 (C-9), 40.3 (C-7), 25.8 (dithiane), 24.9 (dithiane), 24.1 (dithiane); HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ 456.0728, $C_{15}H_{22}F_3NNaO_6S_2$ requires 456.0733.

Fig. 3 shows selected NOE effects on compounds **7a**,**b**, which confirmed their absolute stereochemistry along with the single crystal structure[21] of compound **7b**.§

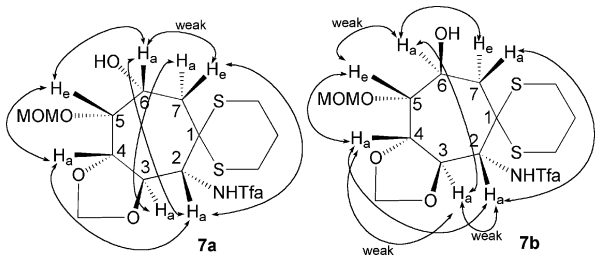


Fig. 3 The NOE observed from the protons on the seven-membered ring skeletons of compounds **7a**,**b**.

(2*R*,3*R*,4*R*,5*R*,6*S*)-3,4,5-Tris(benzyloxy)-6-hydroxymethyl-2-trifluoracetamido-cyclohexanone trimethylene dithioacetal, 8 and (2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-hydroxy-2-trifluoracetamido-cycloheptanone trimethylene dithioacetal, 9

The salt free procedure:

Epoxide **6** (250 mg, 0.467 mmol, dried by coevaporation with toluene) was dissolved in THF (10.0 mL) and cooled to −90 °C. To this solution, *n*-BuLi (0.73 mL, 1.6 M in hexane, 2.5 eq.) was added and the mixture was then warmed up to −10 °C immediately. The reaction mixture was stirred at this temperature for 3 h followed by addition of 3 mL saturated aqueous ammonium chloride. The resulting mixture was then warmed to RT and extracted by ethyl acetate (50 mL). The organic layer was washed with brine, evaporated and purified by MPLC (cyclohexane–ethyl acetate 10 : 1) to yield the faster moving component as the seven-membered ring **9** (57 mg, 23%, colorless oil) and the slower moving component as the six-membered ring **8** (135 mg, 54%, colorless oil, but can be crystallized from ethanol).

The procedure with LiBr:

Epoxide **6** (50 mg, 0.094 mmol, dried by coevaporation with toluene) and anhydrous LiBr (8 mg, 0.09 mmol, 1 eq.) were dissolved in THF (1.0 mL) and cooled to −90 °C. At this temperature, *n*-BuLi (0.13 mL, 1.6 M in hexane, 2.2 eq.) was added to the resulting solution. The reaction mixture was then warmed up to −50 °C in 2 h followed by addition of saturated aqueous ammonium chloride (3 mL). The resulting mixture was then warmed to RT and extracted by ethyl acetate (30 mL). The organic layer was washed with brine, evaporated and purified by MPLC to yield seven-membered ring **9** (4 mg, 8%) and six-membered ring **8** (31 mg, 62%).

Compound **8**, mp: 128–129 °C; $[\alpha]_D$ +19.0 (*c* 1.00, MeOH); δ_H (C_6D_6, 600 MHz): 7.36–7.01 (m, 15H, H$_{aryl}$-Bn), 7.18 (d, *J* 2.7 Hz, 1H, NH), 5.03 (dd, *J* 9.0 Hz, *J* 2.7 Hz, 1H, H-2), 4.80 (d, *J* 11.9 Hz, 1H, H$_{alkyl}$-Bn), 4.59–4.58 (m, 1H, H-5), 4.52 (d, *J* 11.9 Hz, 1H, H$_{alkyl}$-Bn), 4.31–4.16 (m, 4H, H$_{alkyl}$-Bn), 4.12 (dd, *J* 10.3 Hz, *J* 2.0 Hz, 1H, H-7a), 3.98–3.91 (m, 2H, H-3 and H-7b), 3.71 (m, 1H, H-4), 2.43–2.40 (brs, 1H, H-6), 2.36–2.29 (m, 2H, dithiane),

§ CCDC reference number 648111. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b711112f

2.24–2.20 (m, 1H, dithiane), 2.04–2.00 (m, 1H, dithiane), 1.39–1.34 (m, 2H, dithiane); δ_C (C_6D_6, 150 MHz): 156.3 (q, *J* 37.0 Hz, 1C, *C*OCF$_3$), 138.3 ($C_{q,aryl}$-Bn), 137.9 ($C_{q,aryl}$-Bn), 136.5 ($C_{q,aryl}$-Bn), 128.4–127.4 (15C, CH_{aryl}-Bn), 116.7 (q, *J* 288.0 Hz, 1C, CO*C*F$_3$), 77.8 (C-3), 77.7 (C-4), 73.1 (C_{alkyl}-Bn), 72.7 (C-5), 72.4 (C_{alkyl}-Bn), 71.8 (C_{alkyl}-Bn), 57.0 (C-7), 54.2 (C-1), 51.8 (C-2), 47.7 (C-6), 27.0 (dithiane), 25.6 (dithiane), 23.8 (dithiane); HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ 670.1879, $C_{33}H_{36}F_3NNaO_5S_2$ requires 670.1879.

Compound **9**, $[\alpha]_D$ −72.4 (*c* 1.00, MeOH); δ_H (C_6D_6, 600 MHz): 8.32 (d, *J* 10.6 Hz, 1H, NH), 7.28–7.03 (m, 15H, H_{aryl}-Bn), 5.33 (d, *J* 10.6 Hz, 1H, H-2), 4.76 (d, *J* 11.4 Hz, 1H, H_{alkyl}-Bn), 4.68 (d, *J* 11.4 Hz, 1H, H_{alkyl}-Bn), 4.57 (d, *J* 11.4 Hz, 1H, H_{alkyl}-Bn), 4.47 (d, *J* 11.4 Hz, 1H, H_{alkyl}-Bn), 4.40 (d, *J* 11.4 Hz, 1H, H_{alkyl}-Bn), 4.31 (d, *J* 7.7 Hz, 1H, H-4), 4.25 (d, *J* 11.4 Hz, 1H, H_{alkyl}-Bn), 3.95 (m, 1H, H-5), 3.94–3.87 (m, 1H, H-6), 3.88 (m, 1H, H-3), 3.27–3.23 (m, 1H, dithiane), 2.93–2.88 (m, 1H, dithiane), 2.16–1.93 (m, 4H, H-7$_{ax}$, H-7$_{eq}$ and 2 × dithiane), 1.48–1.41 (m, 1H, dithiane), 1.31–1.28 (m, 1H, dithiane); δ_C (C_6D_6, 150 MHz): 156.2 (q, *J* 36.5 Hz, 1C, *C*OCF$_3$), 138.6 ($C_{q,aryl}$-Bn), 137.8 ($C_{q,aryl}$-Bn), 136.9 ($C_{q,aryl}$-Bn), 128.6–127.4 (15C, CH_{aryl}-Bn), 116.4 (q, *J* 288.5 Hz, 1C, CO*C*F$_3$), 86.8 (C-3), 83.7 (C-5), 82.9 (C-4), 75.7 (C_{alkyl}-Bn), 73.1 (C_{alkyl}-Bn), 73.0 (C_{alkyl}-Bn), 68.2 (C-6), 51.1 (C-2), 51.0 (C-1), 38.9 (C-7), 27.4 (dithiane), 26.0 (dithiane), 24.3 (dithiane); HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ 670.1890, $C_{33}H_{36}F_3NNaO_5S_2$ requires 670.1879.

Fig. 4 shows selected NOE effects on compounds **8** and **9**, which confirmed their absolute stereochemistry

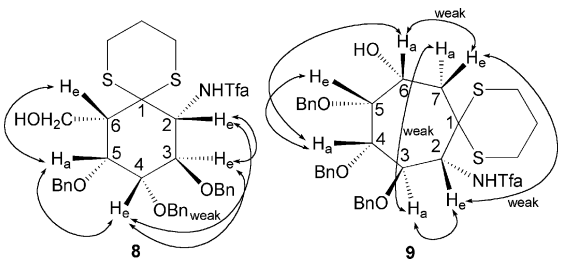


Fig. 4 The NOE observed from the protons on the six-membered ring (compound **8**) and seven-membered ring (compound **9**) skeletons.

(1*S*,2*R*,3*S*,4*R*,5*R*)-2,3,4-Tris(benzyloxy)-5-hydroxy-1-trifluoracetamido-cycloheptane, 10

Under air, compound **9** (200 mg, 0.309 mmol) was dissolved in EtOH (10.0 mL) followed by addition of Raney-Ni suspension in EtOH (4 mL, containing *ca.* 3 g W-2 Raney-Ni, purchased from Aldrich as a water slurry). The mixture was then refluxed for 1 h, cooled to RT, and filtered through a Celite® 512 medium (Fluka) pad. The filtrate was evaporated to dryness and purified by MPLC (cyclohexane–ethyl acetate 10 : 1–5 : 1) to yield compound **10** (119 mg, 71%) as a colorless oil; $[\alpha]_D$ −43.0 (*c* 1.00, MeOH); δ_H (C_6D_6, 600 MHz): 8.06 (brs, 1H, NH), 7.22–7.07 (m, 15H, H_{aryl}-Bn), 4.63–4.53 (m, 3H, 2 × H_{alkyl}-Bn and H-1), 4.50–4.25 (m, 4H, H_{alkyl}-Bn), 3.89 (brs, 1H, H-4), 3.57 (d, *J* 6.7 Hz, 1H, H-2), 3.43 (d, *J* 6.7 Hz, 1H, H-3), 3.66 (s, 1H, H-5), 1.66–1.29 (m, 4H, H-6a,b and H-7a,b); δ_C (C_6D_6, 150 MHz): 156.1 (q, *J* 36.5 Hz, 1C, *C*OCF$_3$), 138.6 ($C_{q,aryl}$-Bn), 138.2 ($C_{q,aryl}$-Bn), 137.6 ($C_{q,aryl}$-Bn), 128.8–127.8 (m, 15C, CH_{aryl}-Bn), 116.7 (q, *J* 288.4 Hz, 1C, CO*C*F$_3$), 83.9 (C-2), 83.7 (C-3), 83.0 (C-4), 74.8 (C_{alkyl}-Bn), 73.5 (C_{alkyl}-Bn), 72.2 (C_{alkyl}-Bn), 71.9 (C-5), 48.5 (C-1), 26.2 (C-6), 22.3 (C-7); HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ 566.2131, $C_{30}H_{32}F_3NNaO_5$ requires 566.2125.

(1*S*,2*R*,3*S*,4*R*,5*R*)-1-(*N*-Benzyloxycarbonyl)-amino-5-hydroxy-2,3,4-tris(benzyloxy)-cycloheptane, 11

In a sealed tube, starting material **10** (200 mg, 0.368 mmol) was dissolved in MeOH (15.0 mL) and water (2.0 mL) followed by addition of Ba(OH)$_2$ octahydrate (1.5 g, 4.7 mmol). The mixture was stirred at 80 °C for 1 h, cooled to RT, to which NaHCO$_3$ (3.0 g) and CbzCl (1.0 mL) were added in turn. The resulting mixture was stirred at RT for 2 h with the addition of two batches of CbzCl (1.0 mL) at an interval of 1 h. Then the reaction mixture was stirred overnight, to which Celite® 512 medium (Fluka) was added followed by filtration through a Celite® 512 medium (Fluka) pad. The clear filtrate was evaporated and purified by MPLC (cyclohexane–ethyl acetate 5 : 1) to yield crude product **11** (which was mixed with an inseparable impurity introduced by CbzCl) as a colorless oil. In HRMS, the desired peak accompanied by other impurity peaks can be observed: HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ 604.2663, $C_{36}H_{39}NNaO_6$ requires 604.2670.

(2*S*,3*S*,4*R*,5*S*)-5-(*N*-Benzyloxycarbonyl)-amino-2,3,4-tris(benzyloxy)-cycloheptanone, 12

Under argon, the crude product **11** from the last step (dried by coevaporation with toluene) was dissolved in dichloromethane (5.0 mL) followed by addition of Dess–Martin periodinane (1.5 mL, 15% wt., from Acros, 0.53 mmol). The mixture was stirred at RT for 1 h, to which TEA (1 mL) was then added. The resulting mixture was stirred for 10 min, and quenched by addition of saturated aqueous $Na_2S_2O_3$ (20 mL), saturated aqueous NaHCO$_3$ (20 mL) and ethyl acetate (30 mL). The biphasic mixture was separated and the water phase was washed with ethyl acetate several times. The combined organic phases were then evaporated and the residue was purified by MPLC (cyclohexane–ethyl acetate 10 : 1) to yield ketone **12** (149 mg) as a colorless syrup. The total yield of the 2 steps is 58%; $[\alpha]_D$ −3.5 (*c* 1.00, $CHCl_3$); δ_H (C_6D_6, 600 MHz): 7.34–7.02 (m, 20H, H_{aryl}-Bn), 6.13 (d, *J* 9.0 Hz, 1H, NH), 5.15–4.78 (m, 4H, H_{alkyl}-Bn), 4.75 (s, 1H, H-2), 4.51–4.48 (m, 1H, H-5), 4.36–4.05 (m, 4H, H_{alkyl}-Bn), 4.04 (s, 1H, H-3), 3.56–3.54 (m, 1H, H-4), 2.51–2.05 (m, 1H, H-7a), 2.02–1.98 (m, 1H, H-7b), 1.98–1.75 (m, 2H, H-6a and 6b); δ_C (C_6D_6, 150 MHz): 205.5 (CO_{ketone}), 155.7 (N*C*OOBn), 138.7 ($C_{q,aryl}$-Bn), 138.1 ($C_{q,aryl}$-Bn), 137.8 ($C_{q,aryl}$-Bn), 137.4 ($C_{q,aryl}$-Bn), 128.6–127.6 (20C, CH_{aryl}-Bn), 83.4 (C-2), 82.4 (C-3), 76.7 (C-4), 73.8 (C_{alkyl}-Bn), 72.6 (C_{alkyl}-Bn), 71.8 (C_{alkyl}-Bn), 66.6 (C_{alkyl}-Bn), 50.7 (C-5), 34.6 (C-7), 30.2 (C-6); HRMS-ESI$^+$: *m*/*z* [M + Na]$^+$ 602.2511, $C_{36}H_{37}NNaO_6$ requires 602.2513.

(−)-Calystegine B$_3$

In THF (4.5 mL) and water (0.5 mL), ketone **12** (98 mg, 0.169 mmol) was dissolved. Then 10% Pd-C (20 mg) was added to the solution. This suspension was hydrogenated at RT by a balloon charged with hydrogen overnight. HRMS-ESI$^+$ showed a complete deprotection of *N*-Cbz, but no deprotection of *O*-Bn was observed. Therefore HCl (1 N, 1.0 mL) was added and the mixture was hydrogenated under the same conditions for 3 more days. The resulting suspension was neutralized with Amberlite 400 OH$^-$

(Fluka), and filtered over a pad of silica gel. The filter cake was washed with distilled water (10 × 15 mL). Combined filtrates were washed with dichloromethane (5 × 20 mL), evaporated, and coevaporated with toluene to dryness. This resulting white solid is relatively pure according to NMR. But it can be further purified by MPLC (*ca.* 25 × 2 cm) filled with Sephadex LH-20 (Sigma-Aldrich) using ethanol as an eluent (*ca.* 2 mL for each fraction) to yield (24 mg, 81%) (−)-calystegine B_3 as an amorphous white solid; $[\alpha]_D$ −59.1 (*c* 1.00, water) {as a reference: for (+)-calystegine B_3, $[\alpha]_D$ +76.8 (*c* 0.88, water),[7b] or $[\alpha]_D$ +82.8 (*c* 0.50, water)[27]}; δ_H (D_2O, 600 MHz): 3.70 (d, *J* 4.0 Hz, 1H, H-2), 3.54 (dd, *J* 3.9 Hz, *J* 9.4 Hz, 1H, H-4), 3.47 (dd, *J* 4.0 Hz, *J* 9.4 Hz, 1H, H-3), 3.21 (dd, *J* 3.9 Hz, *J* 6.4 Hz, 1H, H-5), 1.85–1.75 (m, 1H, H-6a), 1.74–1.63 (m, 3H, H-6b and H-7a,b); δ_C (D_2O, 150 MHz): 95.7 (C-1), 79.0 (C-2), 76.5 (C-4), 74.9 (C-3), 60.3 (C-5), 35.7 (C-7), 24.9 (C-6). The NMR data are in full accordance with those reported for (+)-calystegine B_3;[7b,27] HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ 176.0924, $C_7H_{14}NO_4$ requires 176.0917.

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21 X-Ray crystal structure analysis for compound **7b**: formula $C_{15}H_{22}F_3NO_6S_2$, $M = 433.46$, colorless crystal 0.35 × 0.30 × 0.15 mm, $a = 9.905(1)$, $c = 39.488(1)$ Å, $V = 3874.1(6)$ Å^3, $\rho_{calc} = 1.486$ g cm^{-3}, $\mu = 3.055$ mm^{-1}, empirical absorption correction ($0.414 \leq T \leq 0.657$), $Z = 8$, tetragonal, space group $P4_12_12$ (no. 92), $\lambda = 1.54178$ Å, $T = 293$ K, ω and φ scans, 24194 reflections collected ($\pm h, \pm k, \pm l$), $[(\sin\theta)/\lambda] = 0.59$ Å^{-1}, 2937 independent ($R_{int} = 0.047$) and 2803 observed reflections [$I \geq 2\sigma(I)$], 249 refined parameters, $R = 0.048$, $wR^2 = 0.141$, Flack parameter 0.02(3), max. residual electron density 0.93 (−0.28) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms. Data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT (Nonius B.V., 1998), data reduction Denzo-SMN (Z. Otwinowski and W. Minor, *Methods Enzymol.*, 1997, **276**, 307–326), absorption correction Denzo (Z. Otwinowski, D. Borek, W. Majewski and W. Minor, *Acta Crystallogr.* 2003, **A59**, 228–234), structure solution SHELXS-97 (G. M. Sheldrick, *Acta Crystallogr.* 1990, **A46**, 467–473), structure refinement SHELXL-97 (G. M. Sheldrick, Universität Göttingen, 1997), graphics SCHAKAL (E. Keller, Universität Freiburg, 1997).§.

22 The reaction was started from −90 °C, and it was found that the reaction is rather slow, and the 6-*exo*-cyclization of the epoxide was preferred at this temperature. A prolonged reaction time (more than 8 h) at −90 °C to −50 °C did not increase the cyclization yield significantly, while more side products were observed. Increasing the reaction temperature to −10 °C immediately after adding the *n*-BuLi improved the cyclization yield significantly. Also, at this temperature, the ratio of the 6-*exo*- *vs.* 7-*endo*-cyclization of the epoxide was decreased and compounds **8** and **9** were obtained with yields of 54% and 23% respectively (*ca.* 2.4 : 1, 78% in total). Changing the solvent to diethyl ether led to slower cyclization, while using toluene as the solvent led to significant decomposition. Addition of various Lewis acids (for example, $CeCl_3$, $MgBr_2$ etherate or BF_3 etherate, *etc.*, still with *n*-BuLi as the base and THF as the solvent) increased the ratio of 6-*exo*- *vs.* 7-*endo*-cyclization or led to side reactions. Enhancing the basicity by addition of HMPA or *t*-BuOK led to significant decomposition or a slight increase of the 6-*exo*-cyclization of the epoxide, respectively. Different salts including LiBr and LiI were tested too. In general, they caused a faster cyclization, and consequently the reaction can be performed at a temperature range of −90 °C to −50 °C. The 6-*exo*-cyclization of the epoxide is also favored in such cases probably due to a Li-chelated intermediate. As a typical example, with a stoichiometric amount of LiBr, the six-membered ring **8** was obtained in 62% yield and the yield of seven-membered ring **9** decreased to 8% (*ca.* 7.8 : 1, 70% in total) accompanied by slight decomposition.

23 G. Wittig, *Angew. Chem.*, 1954, **66**, 10.

24 Y.-L. Chen and H. Redlich, unpublished work.
25 Generally, the *N*-Tfa protection is readily removed under very mild conditions. However, in this special case, it was unusually stable. See, for example: T. W. Green, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, London, 3rd edn, 1999.
26 Fully protected ketone compound **8** can be sensitive to acid or base treatment. Hence, once the ketone is produced the *O*- and *N*-protections have to be removed under very mild conditions, which is not compatible with the vigorous basic conditions for deprotecting *N*-Tfa. Therefore *N*-Tfa protection has to be removed and reprotected with *N*-Cbz before the free hydroxy is oxidized. Also leaving the hydrogenolysis as the last step for cleveage of all protections offers further benefit in purifiction.
27 N. Asano, A. Kato, K. Oseki, H. Kizu and K. Matsui, *Eur. J. Biochem.*, 1995, **229**, 369.