Novel Acid-Catalyzed Rearrangement of Tetrahydro-1,2,3,4-tetrazines: Unexpected Formation of Glycosazones

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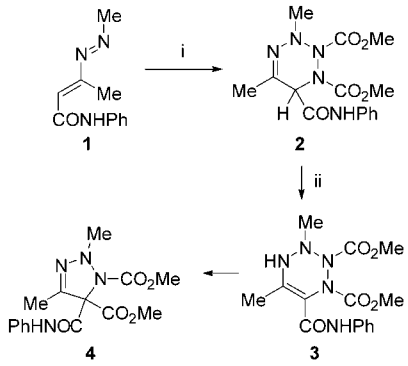
Abstract: The present contribution discloses a simple and unexpected acid-catalyzed cleavage of tetrahydrotetrazines leading to 1,2-bis(hydrazones). Incorporation of a chiral fragment derived from carbohydrates enables the rapid preparation of glycosazones, a family of compounds employed by Emil Fischer to elucidate the configuration of sugars. In addition, a mechanistic proposal accounts for experimental observations.

In 1991, Ferguson and his associates described an interesting rearrangement, accompanied by ring contraction, of 1,2,3,6-tetrahydro-1,2,3,4-tetrazines to afford 2,5-dihydro-1*H*-1,2,3-triazoles, whose structure could be established by X-ray crystallography (Scheme 1).[1]

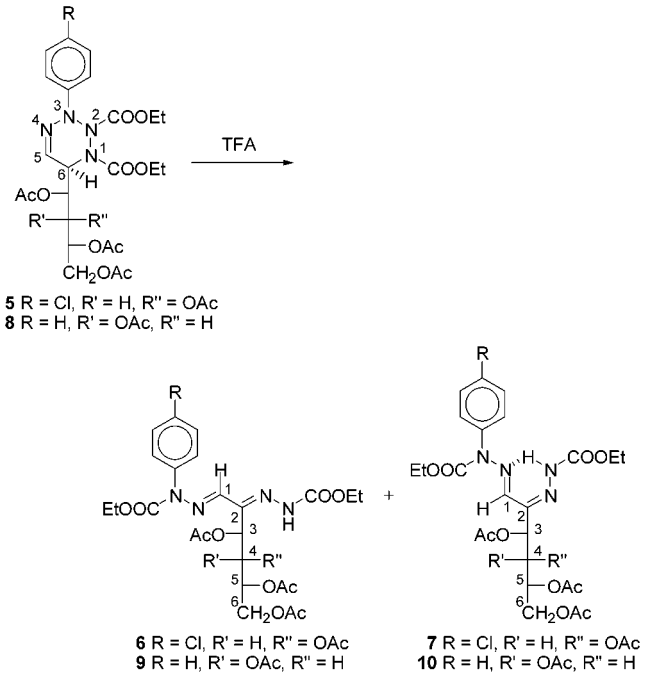
In light of our long held interest in the use of carbohydrate-based 1,2-diazabutadienes for the construction of optically active heterocycles,[2] including tetrazine derivatives,[3] the above-mentioned transformation starting from such heterodienes would be a novel entry into triazole nucleosides. Moreover, the asymmetric version would also aim at ascertaining the stereochemical factors that control this transposition, thus illuminating the mechanistic pathway.[4] As shown herein, however, chiral tetrazines derived from carbohydrates, under the same reaction conditions, do not lead to the expected five-member heterocycles but rather to osazone derivatives, an important family of substances from both historical and conceptual viewpoints in synthetic organic chemistry.

Scheme 1[a]



[a] Reagents: (i) $MeO_2CN{=}NCO_2Me$; (ii) TFA.

Scheme 2



Tetrazine **5**,[3] on exposure to trifluoroacetic acid at room temperature, afforded compounds **6** and **7** having R_f values 0.7 and 0.5, respectively (benzene−acetonitrile, 3:1). Separation by medium-pressure chromatography (benzene−acetonitrile, 12:1) gave pure samples, although only **6** (26% yield) could be crystallized from diethyl ether. Compound **7** was obtained (61%) as a homogeneous amorphous solid. Such products proved to be the 1-(4-chlorophenyl)-1,2-bis(ethoxycarbonyl)-D-glucosazones **6** and **7** with (1*E*,2*Z*)- and (1*E*,2*E*)-configurations, respectively, around the heteroatomic C=N bonds (Scheme 2). These results show a rearrangement distinct from that reported previously.[1]

The structure of compound **6** was confirmed by single-crystal X-ray diffraction[5] (see Supporting Information for

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(4) The mechanism proposed in ref 1 is somewhat confusing as the intermediacy of methoxide and methanol are invoked. Neither, however, was employed in the experimental protocol.

(5) (a) The authors have deposited atomic coordinates for compound **6** with the Cambridge Crystallographic Data Centre (registry number CCDC-164519). X-ray data can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. This material is also available in Supporting Information.

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crystallographic data) evidencing the (1*E*,2*Z*)-geometry of the double bonds, the s-trans disposition of the 1,4-diaza-1,3-butadiene system, and a favored zigzag conformation of the side chain. Furthermore, it is worth noting the existence of a hydrogen bond between the NH of the extended hydrazone moiety and the oxygen of the ester function at C-3 (N−H···O: $d_{N-H} = 0.88$ Å, $d_{H\cdots O} = 2.05$ Å, $d_{N\cdots O} = 2.698$ Å, $\alpha_{N-H\cdots O} = 130.0$).

Assignment of structures **6** and **7** to the isolated products is also supported by analytical and spectroscopic data. Both the IR and NMR spectra show significant differences for these substances. Compound **6** shows a sharp and strong absorption in its IR spectrum at ∼3380 cm^{-1} and a proton signal at δ ∼9.5 ppm, both attributable to the NH proton of the ethoxycarbonylhydrazone group on C-2 (see Scheme 2 for numbering). In stark contrast, a signal for the same NH group of **7** is observed at an unusual downfield shift (δ_{NH} ∼12.6 ppm) and a broad and weak IR band at ∼3180 cm^{-1}. These data suggest a chelated structure for osazone **7** involving an intramolecular hydrogen bonding between the NH group and the imine nitrogen at C-1. This sort of hydrogen bonding is characteristic of osazones derived from monosaccharides[6] and shifts the typical NH stretching modes to longer wavelengths, by about 200 cm^{-1}.[7] Likewise, the NH proton is strongly deshielded ($\Delta\delta$ ∼3 ppm) by hydrogen bonding, a fact observed in glycosazones[6] and other nitrogenated systems featuring a similar chelate ring.[8]

The s-trans conformation adopted by compound **6** places the hydrogen atom on C-3 in the deshielding portions of the C1=N or C2=N bonds (see Supporting Information for location of H-3), leading to a downfield shift of that proton with respect to the same signal for **7** ($\Delta\delta$ ∼0.9 ppm). In contrast, the s-cis geometry of the latter compound is such that the C-3 proton should be shielded as it lies far from the deshielding zone of the C1=N bond. Glycosazones **6** and **7** also show similar ^{13}C NMR spectra, and their C-2 signals, the vinyl carbon of the osazone moiety, appear at a frequency (δ ∼135 ppm) consistent with an unsaturated carbon. The only quaternary and otherwise saturated carbon of the alternative triazoline ring would have been expected to be shifted to a higher field. For both substances, the extended zigzag conformation found in polyacetylated chains with a D-*arabino* configuration can be inferred from the corresponding H−H coupling constants.[9]

Polarimetric studies also evidence that the geometrical disposition of the osazone function for compounds **6** and **7** is very different. The former shows a high and positive optical rotation ($[\alpha]_D = +119$), while compound **7** has a negative value for its optical rotation ($[\alpha]_D = -46$). The large difference should be attributed to the opposite configuration at C-2 (2*Z* in **6** versus 2*E* in **7**) and the conformational restriction of **7** imposed by hydrogen bonding. It is well established that mutarotation of sugar osazones can be associated with the existence of different structures for the initial and final forms involved in this transformation. This phenomenon is largely influenced by acid−base properties of the medium and temperature.[6e]

Further evidence for the origin and evolution of this rearrangement could be obtained by ^1H NMR monitoring of **5**. In $CDCl_3$, this tetrahydrotetrazine is stable, and further addition of a catalytic amount of CF_3COOD does not produce any significant changes after 24 h. However, when CF_3COOD is added in amounts greater than an equimolar ratio, the ^1H NMR spectrum of **5** experiences a sudden and appreciable variation (Figure 1). The signal at δ ∼6.9 ppm, corresponding to H-1, is shifted downfield (δ ∼7.3 ppm), presumably indicating protonation at the imine nitrogen. Likewise, new proton signals appear, and their intensity increases as the rearrangement progresses. After 2.5 h, osazone **6** becomes the major product and disappears slowly to afford the chelated structure **7**. After 8 h, this transformation is almost complete. Elimination of CF_3COOD by extraction with a solution of sodium carbonate in deuterium oxide gives rise to a mixture of **6** and **7**, the latter being prevalent. Glucosazone **6** itself undergoes this acid-catalyzed conversion to **7**, and after 24 h, the mixture containing **6** and **7** is the same as the reaction mixture evolved from **5** (see Supporting Information).

This rearrangement has also been applied to a carbohydrate-based tetrazine bearing a side chain of D-*lyxo* configuration (**8**).[3] Under acid treatment, this compound was equally transformed into glycosazones **9** and **10**. Nevertheless, the former now isomerized rapidly to the chelated structure **10** (see Supporting Information). In fact, only this glycosazone, which displays the NH resonance at δ ∼12 ppm characteristic of a hydrogen bonded structure, could be isolated. All attempts to isolate **9** were unsuccessful as a mixture of compounds **9** and **10** was invariably obtained.

From the foregoing experiments, it is evident that protonated tetrahydrotetrazines are initially converted to osazones of a (1*E*,2*Z*)-configuration, which are then isomerized to their (1*E*,2*E*)-configured derivatives. The rearrangement should most likely involve the initial protonation at the imine nitrogen (Scheme 3).[10] The protonated imine **12** is so strongly electrophilic that a subsequent electronic assistance can be provided by a concerted cleavage of the N2−N3 bond to give **13**, thereby extending the conjugation of the azo group with the aryl substituent (R^1) still further. The resulting species **13** experiences the intramolecular attack of the azo group on the ester function on the nitrogen bonded to C-2 (**14**) to give a six-membered tetrahedral intermediate, which would ultimately evolve to an osazone **15** with a (1*Z*,2*Z*)-configuration. Configurational inversion to the thermodynamically more stable (1*E*,2*E*)-configured osazone **17**

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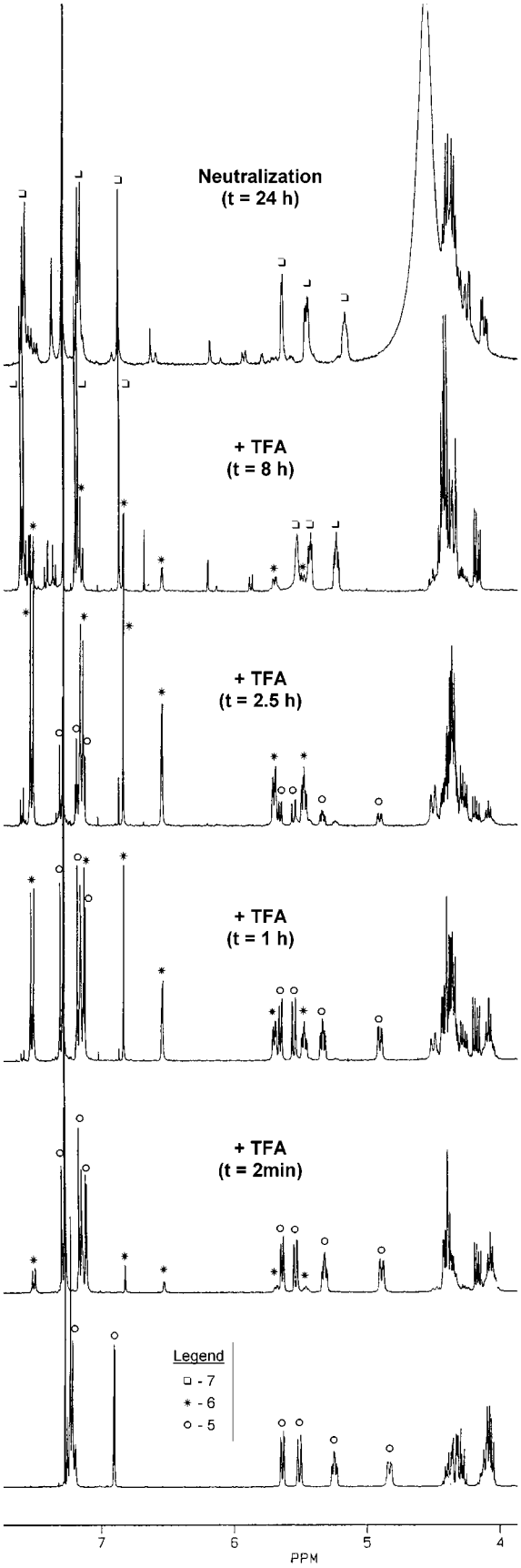
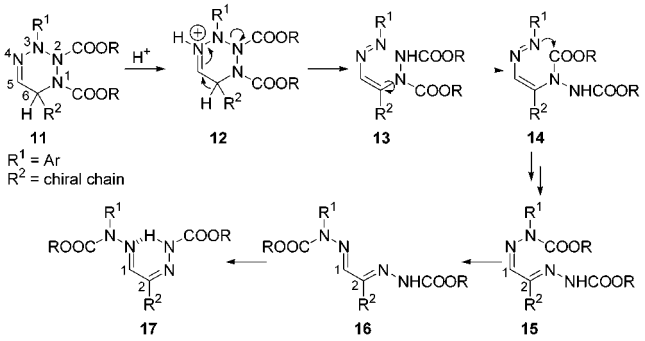
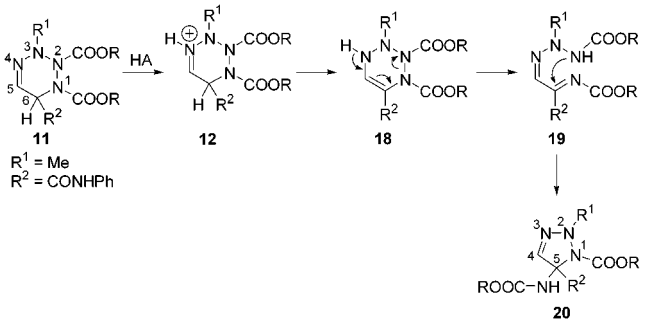


Figure 1. Comparison of the ^{1}H NMR spectra recorded at 400 MHz of the crude reaction mixtures (in $CDCl_3$ solutions) of the products (**6** and **7**) formed by addition of CF_3COOD to tetrazine **5**.

Scheme 3



Scheme 4



would occur through the (1*E*,2*Z*)-isomer **16** by acid catalysis as well.

It should also be noted that osazones with (1*Z*,2*Z*)-configuration (e.g., **15**) would be the primary species generated in this transformation but could not be detected by chromatographic or spectroscopic analyses, as they would likely undergo a rapid isomerization to (1*E*,2*Z*)-osazones such as **16**. The distinctive behavior observed by Ferguson et al.[1] could be rationalized in terms of the mechanistic proposal depicted in Scheme 4. Because of an electron-withdrawing group on C-6 of the starting tetrazine, the hydrogen atom located at that position should exhibit a higher acidity. The protonated imine **12** would thus be equilibrated with its enamine tautomer **18**.[11] In stark contrast with the above-mentioned pathway, fragmentation of the N2−N3 bond is no longer favored as the substituent R^1 (Me) cannot interact with the azo function, while the alternative cleavage of the N1−N2 bond enables a more extended conjugation with two acyl groups (**19**). This ring fragmentation is followed by intramolecular nucleophilic addition affording the dihydrotriazole derivative **20**.

To sum up, we have presented a novel transformation of sugar tetrazines into their osazones. These substances, whose origins date back to the pioneering studies by Emil Fischer,[6e] were once instrumental in elucidating the configuration of carbohydrate molecules. In addition, these bishydrazones can be converted into other heterocyclic compounds. Extensions of these rearrangements to other functionalized systems, as well as their scope and limitations, are currently under investigation.

Experimental Section

Melting points were determined on a capillary apparatus and were uncorrected. Solutions were evaporated under reduced pressure (15−30 mm) with a rotary evaporator, and the residue

(11) Ferguson and associates (ref 1) suggested the existence of such a tautomer on the basis of NMR data.

was chromatographed on a silica gel (400−230 mesh) column or via preparative TLC. Optical rotations were measured using wavelengths at 589 (D line), 578, 546, and 436 nm. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively. Chemical shifts are expressed in parts per million downfield from the signal of internal TMS. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J = (hertz), relative integral, assignment]. For ^{13}C NMR spectra, the data are given as: chemical shift (δ) [relative integral (if higher than 1C), protonicity, assignment] where protonicity is defined as follows: C = quaternary, CH = methine, CH_2 = methylene, CH_3 = methyl. ^{1}H and ^{13}C NMR assignments listed have been confirmed by homo- and heteronuclear two-dimensional correlations and DEPT experiments. FT-IR spectra were recorded on dry KBr pellets. Elemental analyses were recorded by the Servicio de Microanálisis of the University of Extremadura.

Synthesis of (1*E*,2*Z*)- and (1*E*,2*E*)-1-(4-Chlorophenyl)-1,2-bis(ethoxycarbonyl)-D-glucosazones (6 and 7). To a solution of (6*R*)-6-(tetra-*O*-acetyl-D-*arabino*-tetritol-1′-yl)-3-(4-chlorophenyl)-1,2-bis(ethoxycarbonyl)-1,2,3,6-tetrahydro-1,2,3,4-tetrazine (**5**)[3] (1.26 g, 2.0 mmol) in dichloromethane (96 mL) was added TFA (3.2 mL, 42 mmol), and the reaction mixture was kept at room temperature. TLC monitoring (benzene−acetonitrile, 3:1) revealed, after 2 h, the formation of two new products of R_f 0.7 (**6**) and 0.5 (**7**). When the starting material disappeared, the solvent was evaporated, and flash chromatography (benzene−acetonitrile, 12:1) of the residue afforded compounds **6** and **7**. Compound **6** was crystallized from diethyl ether (0.33 g, 26%): mp 150 °C; $[\alpha]_D$ +119, $[\alpha]_{578}$ +125, $[\alpha]_{546}$ +148, $[\alpha]_{436}$ +319 (*c* 0.8, $CHCl_3$, 25 °C); IR (KBr) ν_{max} 3386, 2982, 1763, 1601, 1501, 1373, 1221, 1090, 1044, 932, 756 cm^{-1}; ^{1}H NMR δ 9.48 (br s, 1H, N*H*), 7.46 (d, $J \approx$ 8.5 Hz, 2H, Ar), 7.11 (d, $J \approx$ 8.5 Hz, 2H, Ar), 6.89 (s, 1H, H-1), 6.56 (d, $J \approx$ 2.3 Hz, 1H, H-3), 5.67 (dd, $J \approx$ 2.3, 8.9 Hz, 1H, H-4), 5.39 (ddd, $J \approx$ 2.4, 5.8, 8.9, 1H, H-5), 4.31 (dd, $J \approx$ 2.4, 12.4 Hz, 1H, H-6), 4.29 (q, $J \approx$ 7.2 Hz, 2H, C*H*$_2$CH$_3$), 4.28 (q, $J \approx$ 7.2 Hz, 2H, CH$_2$CH$_3$), 4.17 (dd, $J \approx$ 5.8, 12.4, 1H, H-6′), 2.18 (s, 3H, C*H*$_3$CO), 2.15 (s, 3H, C*H*$_3$CO), 2.06 (s, 3H, C*H*$_3$CO), 2.02 (s, 3H, C*H*$_3$CO), 1.32 (t, $J \approx$ 7.2 Hz, 3H, C*H*$_3$CH$_2$), 1.30 (t, $J \approx$ 7.2 Hz, 3H, C*H*$_3$CH$_2$); ^{13}C NMR δ 170.5 (C, CH$_3$*C*O), 169.9 (C, CH$_3$*C*O), 168.7 (C, CH$_3$*C*O), 168.2 (C, CH$_3$*C*O), 153.2 (C, N*C*OOEt), 152.7 (C, N*C*OOEt), 141.8 (C, C-2), 139.7 (CH, C-1), 135.5 (C, Ar), 134.4 (C, Ar), 130.5 (2C, CH, Ar), 130.3 (2C, CH, Ar), 69.9 (CH, C-4), 69.5 (CH, C-3), 67.6 (CH, C-5), 62.9 (CH$_2$, *C*H$_2$CH$_3$), 62.5 (CH$_2$, C-6), 62.1 (CH$_2$, *C*H$_2$CH$_3$), 20.7 (CH$_3$, *C*H$_3$CO), 20.6 (CH$_3$, *C*H$_3$CO), 20.4 (CH$_3$, *C*H$_3$CO), 20.3 (CH$_3$, *C*H$_3$CO), 14.4 (2C, CH$_3$, *C*H$_3$CH$_2$). Anal. Calcd for $C_{26}H_{33}ClN_4O_{12}$: C, 49.65; H, 5.29; N, 8.92. Found: C, 49.41; H, 5.42; N, 8.91.

Compound **7** was isolated as a homogeneous amorphous solid from diethyl ether: mp 56 °C; $[\alpha]_D$ −46, $[\alpha]_{578}$ −49, $[\alpha]_{546}$ −59, $[\alpha]_{436}$ −150 (*c* 0.5, $CHCl_3$, 25 °C); IR (KBr) ν_{max} 3180, 2988, 1751, 1603, 1491, 1371, 1323, 1219, 1057, 955, 868, 762 cm^{-1}; ^{1}H NMR δ 12.56 (s, 1H, N*H*), 7.56 (d, $J \approx$ 8.5 Hz, 2H, Ar), 7.14 (d, $J \approx$ 8.5 Hz, 2H, Ar), 6.85 (s, 1H, H-1), 5.61 (d, $J \approx$ 3.8 Hz, 1H, H-3), 5.42 (dd, $J \approx$ 3.8, 8.0 Hz, 1H, H-4), 5.13 (ddd, $J \approx$ 2.5, 5.0, 8.0 Hz, 1H, H-5), 4.37 (q, $J \approx$ 7.2 Hz, 2H, CH$_3$C*H*$_2$), 4.32 (q, $J \approx$ 7.2 Hz, 2H, CH$_3$C*H*$_2$), 4.21 (dd, $J \approx$ 2.5, 12.1 Hz, 1H, H-6), 4.07 (dd, $J \approx$ 5.0, 12.1 Hz, 1H, H-6′), 2.03 (s, 6H, C*H*$_3$CO), 1.97 (s, 3H, C*H*$_3$CO), 1.96 (s, 3H, C*H*$_3$CO), 1.39 (t, $J \approx$ 7.2 Hz, 3H, C*H*$_3$CH$_2$), 1.35 (t, $J \approx$ 7.2 Hz, 3H, C*H*$_3$CH$_2$); ^{13}C NMR δ 170.4 (C, CH$_3$*C*O), 169.6 (C, CH$_3$*C*O), 169.1 (C, CH$_3$*C*O), 168.9 (C, CH$_3$*C*O), 153.8 (C, N*C*OOEt), 152.7 (C, N*C*OOEt), 136.1 (C, Ar), 134.4 (C, C-2), 134.0 (CH, C-1), 132.4 (C, Ar), 130.6 (2C, CH, Ar), 130.0 (2C, CH, Ar), 72.0 (CH, C-3), 70.3 (CH, C-4), 68.2 (CH, C-5), 63.8 (CH$_2$, *C*H$_2$CH$_3$C-6), 61.9 (CH$_2$, *C*H$_2$CH$_3$), 61.4 (CH$_2$, C-6), 20.6 (CH$_3$, *C*H$_3$CO), 20.4 (2C, CH$_3$, *C*H$_3$CO), 20.3 (CH$_3$, *C*H$_3$CO), 14.4 (CH$_3$, *C*H$_3$CH$_2$), 14.1 (CH$_3$, *C*H$_3$CH$_2$). Anal. Calcd for $C_{26}H_{33}ClN_4O_{12}$: C, 49.65; H, 5.29; N, 8.91. Found: C, 49.37; H, 5.26; N, 8.79.

Synthesis of (1*E*,2*E*)-1,2-Bis(ethoxycarbonyl)-1-phenyl-D-galactosazone (10). To a solution of (6*R*)-6-(tetra-*O*-acetyl-D-*lyxo*-tetritol-1′-yl)-1,2-bis(ethoxycarbonyl)-3-phenyl-1,2,3,6-tetrahydro-1,2,3,4-tetrazine (**8**)[3] (0.260 g, 0.5 mmol) in dichloromethane (26 mL) was added TFA (0.65 mL, 8.6 mmol), and the reaction mixture was kept at room temperature. TLC monitoring (benzene−acetonitrile, 3:1) revealed the formation of two new products of R_f 0.3 (**9**) and 0.4 (**10**). After 2.5 h, the solution was washed successively with a saturated aqueous solution of sodium hydrogencarbonate (3 × 25 mL), dried with anhydrous sodium sulfate, and evaporated. The crude product was purified by preparative TLC (diethyl ether−*n*-hexane, 12:1) to afford 0.032 g of compound **10** (26%)[12] as a white solid from diethyl ether and 0.063 g of a ∼1.6:1 mixture of compounds **9** and **10** (51%),[12] along with 0.136 g of the starting material **8** (R_f 0.6).

Compound **9** was confirmed on the basis of its NMR data: ^{1}H NMR δ 9.38 (br s, 1H, N*H*), 7.51−7.41 (m, 3H, Ph), 7.15 (d, $J \approx$ 7.4 Hz, 2H, Ph), 6.98 (s, 1H, H-1), 6.43 (d, $J \approx$ 5.5 Hz, 1H, H-3), 5.94 (dd, $J \approx$ 5.5, 4.8 Hz, 1H, H-4), 5.40 (ddd, $J \approx$ 4.8, 5.2, 6.0 Hz, 1H, H-5), 4.39 (dd, $J \approx$ 5.2, 12.4 Hz, 1H, H-6), 4.38 (q, $J \approx$ 7.1 Hz, 2H, CH$_3$C*H*$_2$), 4.29 (q, $J \approx$ 7.1 Hz, 2H, CH$_3$C*H*$_2$), 4.22 (dd, $J \approx$ 6.0, 12.4 Hz, 1H, H-6′), 2.14 (s, 3H, C*H*$_3$CO), 2.11 (s, 3H, C*H*$_3$CO), 2.08 (s, 3H, C*H*$_3$CO), 2.03 (s, 3H, C*H*$_3$CO), 1.31 (t, $J \approx$ 7.1 Hz, 6H, C*H*$_3$CH$_2$).

Compound **10**: mp 64 °C, $[\alpha]_D$ −10, $[\alpha]_{578}$ −11, $[\alpha]_{546}$ −12, $[\alpha]_{436}$ −14 (*c* 0.8, $CHCl_3$, 25 °C); IR (KBr) ν_{max} 3190, 2984, 1761, 1603, 1491, 1371, 1323, 1215, 1059, 868, 762, 700, 602 cm^{-1}; ^{1}H NMR δ 12.68 (s, 1H, N*H*), 7.61−7.52 (m, 3H, Ph), 7.22 (d, $J \approx$ 7.5 Hz, 2H, Ph), 6.89 (s, 1H, H-1), 5.49 (d, $J \approx$ 8.3 Hz, 1H, H-3), 5.29 (ddd, $J \approx$ 3.8, 4.5, 6.8 Hz, 1H, H-5), 5.26 (br d, $J \approx$ 8.3 Hz, 1H, H-4), 4.37 (q, $J \approx$ 7.1 Hz, 2H, CH$_3$C*H*$_2$), 4.33 (q, $J \approx$ 7.1 Hz, 1H, CH$_3$C*H*$_2$), 4.32 (q, $J \approx$ 7.1 Hz, 1H, C*H*$_3$CH$_2$), 4.27 (dd, $J \approx$ 4.5, 11.8 Hz, 1H, H-6), 4.01 (dd, $J \approx$ 6.8, 11.8 Hz, 1H, H-6′), 2.04 (s, 3H, C*H*$_3$CO), 2.02 (s, 3H, C*H*$_3$CO), 1.93 (s, 3H, C*H*$_3$CO), 1.89 (s, 3H, C*H*$_3$CO), 1.40 (t, $J \approx$ 7.1 Hz, 3H, C*H*$_3$CH$_2$), 1.35 (t, $J \approx$ 7.1 Hz, 3H, C*H*$_3$CH$_2$); ^{13}C NMR δ 170.3 (C, CH$_3$*C*O), 170.0 (C, CH$_3$*C*O), 169.6 (C, CH$_3$*C*O), 168.5 (C, CH$_3$*C*O), 153.9 (C, N*C*OOEt), 153.1 (C, N*C*OOEt), 134.9 (C, C-2), 134.1 (2C, CH and C, C-1 and Ph), 130.3 (2C, CH, Ph), 130.1 (CH, Ph), 128.7 (2C, CH, Ph), 71.8 (CH, C-3), 69.8 (CH, C-4), 67.9 (CH, C-5), 63.6 (CH$_2$, *C*H$_2$CH$_3$), 61.9 (2C, CH$_2$, *C*H$_2$CH$_3$, C-6), 20.6 (CH$_3$, *C*H$_3$CO), 20.5 (CH$_3$, *C*H$_3$CO), 20.4 (2C, CH$_3$, *C*H$_3$CO), 14.5 (CH$_3$, *C*H$_3$CH$_2$), 14.3 (CH$_3$, *C*H$_3$CH$_2$). Anal. Calcd for $C_{26}H_{34}N_4O_{12}$: C, 52.52; H, 5.76; N, 9.42. Found: C, 52.05; H, 5.52; N, 9.42.

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Supporting Information Available: ^{1}H NMR spectra are available for compounds **6** (Figure S1), **7** (Figure S2), and **10** (Figure S3), a mixture of compounds **9** and **10** (Figure S4), and transformations of **6** into **7** (Figure S5) and of **8** into **9** and **10** (Figure S6); crystallographic data for compound **6** are presented in Tables S1-S6 and Figures S7-S9 This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Yields are in reference to the converted starting material.