An Expeditious Synthesis of Optically Pure 1,4,5,6-Tetrahydro-*as*-Triazines, Fused to the Carbohydrate Skeleton

Muhammad Saeed, Raid J. Abdel-Jalil, Wolfgang Voelter,* and Mustafa M. El-Abadelah
Abteilung für Physikalische Biochemie, Physiologisch-Chemisches Institut der Universität Tübingen, Hoppe-Seyler Straße 4, D-72076-Tübingen, Germany

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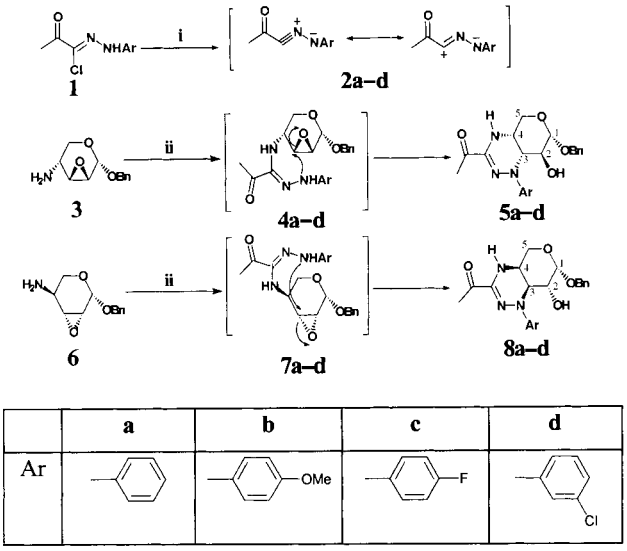
An easy and high yield one pot reaction to enantiomerically pure 1,4,5,6-tetrahydro-*as*-triazines **5a–d** and **8a–d** is described, starting from benzyl 4-amino-2,3-anhydro-4-deoxy-β-L-lyxopyranoside (**3**) and benzyl 4-amino-2,3-anhydro-4-deoxy-α-D-lyxopyranoside (**6**).

Carbohydrates provide an important source for the synthesis of optically pure targets in organic and medicinal chemistry. The defined topology and stereochemistry of the carbohydrate framework permits an array of new strategies with unique synthetic properties to design artificial as well as natural materials.[1,2] Quite some time ago, we became interested in developing new methodologies for the synthesis of sugar-fused heterocycles.[3] Despite the achievements in the earlier described areas, we intended to expand the versatility and specificity of our strategies to other important targets.

Substituted 1,4,5,6-tetrahydro-*as*-triazines have been reported in the literature[4–9] showing insecticidal, herbicidal and fungicidal activities.[4] They can also prolong the hypnotic effects of barbiturates,[5] act as analgesics,[6,7] and possess anticonvulsant properties.[7] However, these syntheses suffer from the formation of a mixture of products,[8,9] or involving hard reaction conditions.[5,6] In this communication we would like to present the syntheses of representative examples of such *as*-triazines, fused to the carbohydrate skeleton, which are, to the best of our knowledge, unknown so far.

Recently, we have demonstrated that benzyl 4-amino-2,3-anhydro-4-deoxy-β-L-lyxopyranoside (**3**) and benzyl 4-amino-2,3-anhydro-4-deoxy-α–D-lyxopyranoside (**6**), with an amino group adjacent to an oxirane ring, display electrophilic and nucleophic reactivity which upon reaction with *p*-substituted phenylisothiocyanate afforded the corresponding thiazoline ring in one step.[10] Extending the potentials of these novel aminodeoxy sugars, we planned to exploit the 1,3-dipole-like nitrile imine **2**, generated in situ from the reaction of triethylamine with the hydrazonoyl chlorides **1**.[11] The primary amine of **3** adds readily on to the nitrile imines **2a–d,** to yield the intermediate (*Z*)-amidrazone adducts **4a–d**[12] as the kinetically-controlled products. The latter transient acyclic adducts undergo cyclization by opening the epoxide ring to yield pyrano[4,3-e][1,2,4]triazines **5a–d** in good to excellent yields in a one step reaction. In a similar fashion, **6** reacted with the generated nitrile imines **2a–d** to produce the isomeric 1,2,4-triazines **8a–d** (Scheme 1). The general procedure involved addition of the hydrazonoyl chloride **1a–d** (2 equiv) to a stirred solution of **3** or **6** (200 mg) in methanol (10 mL) at 0 °C. Et_3N (2 mL) was added dropwise within 10 min and the temperature was allowed to raise slowly to room temperature, followed by stirring for 4–6 h. Normal work up and purification on a silica gel column with 5% ethyl acetate in dichloromethane gave the desired triazines in excellent yields (Table 1).



i) Et_3N, MeOH, 0 °C; ii) **1**,Et_3N, MeOH, 0 °C and then at rt, 4–6 h.

Scheme 1.

Table 1. Yields, melting points and optical rotations of triazines **5a-d** and **8a-d.**

Entry	Product	Yield[a] (%)	mp (°)	$[\alpha]_D$[b] degree/g/cm^3
1	**5a**	85	115	+606.4° (c = 0.04)
2	**5b**	80	145	+690.6° (c = 0.13)
3	**5c**	78	112	+617.0° (c = 0.10)
4	**5d**	72	oil	+457.4° (c = 0.10)
5	**8a**	79	99	-476.6° (c = 0.16)
6	**8b**	85	170	-442.5° (c = 0.10)
7	**8c**	77	oil	-295.2° (c = 0.16)
8	**8d**	70	oil	-303.2° (c = 0.20)

[a]Yields are given after chromatographic purification. [b]Optical rotation values are measured in dichloromethane at 25 °C.

^1H and ^{13}C NMR, mass spectrometry and elemental analysis were used to establish the structures of these compounds.[13,14] All compounds show a prominent molecular ion peak in their FAB-MS spectra. The ^{13}C NMR spectra exhibit a quaternary carbon resonance at about 150 ppm, indicative for the imine bond (C = N). Signals for C-3 and C-4 arise at 54–56

and 46–48 ppm, respectively. Extensive ^{1}H NMR studies enabled to diagnose the conformation of the pyranose ring in the final compounds. A salient feature of the ^{1}H NMR spectra of the series **5a–d** are the chemical shifts and the coupling constants of H-1 (δ = 4.33–4.42 ppm; J ~7.9 Hz), indicating an axial–axial relationships between H-1 and H-2. The coupling interaction between H-2 and H-3 were found to be large in the range of 9–10 Hz, and thus showing that $^1C_4$ is the predominant conformation in these compounds. For the other series **8a–d**, small $J_{1,2}$ coupling constants were determined (3.36 Hz), indicating quasi-equatorial–axial relationships between the respective protons. In addition, large $J_{2,3}$ (around 10 Hz), confirmed $^4C_1$ as the predominant conformation in this series.

Figure 1 shows the ORTEP diagram of compound **5a** with selected bond lengths and angles. C(4)–N(19) and C(3)–N(16) are found to have bond length values of 1.439(3) and 1.461(3) Å, respectively. A shorter bond length of the bond N(17)–C(18) is found with a value of 1.303(3) Å, indicating C=N bond.

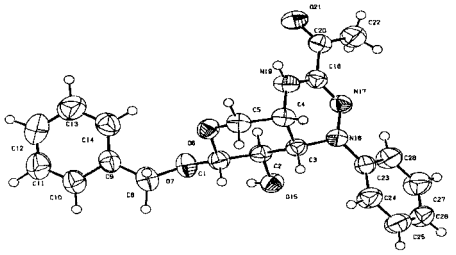


Figure 1. The molecular structure of **5a.** Selected bond lengths (Å) and bond angles (°): C(4)-N(19) 1.439(3); N (19)-C(18) 1.352(3); C(18)-N(17) 1.303(3); N(17)-N(16) 1.369 (3); N(16)-C(3) 1.461 (3); C(3)-C(4) 1.527 (3); C(5)-C(4)-N(19) 111.1 (2); C(4)-N(19)-C(18) 120.2(2); N(19)-C(18)-N(17) 126.1 (2); C(18)-N(17)-N(16) 116.03 (19); N(17)-N(16)-C(3)118.12 (18); N(16)-C(3)-C(4) 109.34 (19); C(3)-C(4)-N(19)107.1 (2).

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13 ^{1}H NMR (250 MHz, $CDCl_3$) data of **5a:** δ (ppm) 7.40–7.44 (2H, m, Ph*H*), 7.26–7.32 (7H, m, Ph*H*), 6.90 (1H, m, Ph*H*), 5.54 (1H, s, NH), 4.88 (1H, d, J = 11.5 Hz, PhC*H*H), 4.59 (1H, d, J = 11.5 Hz, PhCH*H*), 4.42 (1H, d, J = 7.77 Hz, H-1), 3.84 (1H, dd, J = 3.35 and 9.7 Hz, H-3), 4.07 (1H, dd, J = 1.5 and 13.13 Hz, H-5), 3.76 (1H, dd, J = 1.5 and 13.13 Hz, H-5'), 3.55 (1H, dd, J = 7.9 and 9.7 Hz, H-2), 3.43 (1H, br s, H-4), 2.5 (3H, s, OMe); **5b**: 7.33 (7H, m, Ph*H*), 6.86 (2H, m, Ph*H*), 5.50 (1H, s, NH), 5.29 (3H, s, OMe), 4.90 (1H, d, J = 11.6 Hz, PhC*H*H), 4.62 (1H, d, J = 11.6 Hz, PhCH*H*), 4.41 (1H, d, J = 9.7 Hz, H-1), 4.08 (1H, d, J = 12.8 Hz, H-5), 3.77 (3H, m, H-2, H-3, H-5'), 2.5 (3H, s, OMe); **5c:** 7.25–7.37 (2H, m, Ph*H*), 7.29 (5H, m, Ph*H*), 6.98 (2H, m, Ph*H*), 5.55 (1H, s, NH), 4.87 (1H, d, J = 11.6 Hz, PhC*H*H), 4.57 (1H, d, J = 11.6 Hz, PhCH*H*), 4.40 (1H, d, J = 7.63 Hz, H-1), 4.22 (1H, dd, J = 3.36 and 9.76 Hz, H-3), 4.06 (1H, dd, J = 1.53 and 13.12 Hz, H-5), 3.75 (1H, dd, J = 1.53 and 13.12 Hz, H-5'), 3.52 (1H, dd, J = 7.63 and 9.76 Hz, H-2), 3.42 (1H, m, H-4), 2.5 (3H, s, OMe); **5d**: 7.42-7.43 (2H, m, Ph*H*), 7.13–7.42 (5H, m, Ph*H*), 6.83-6.86 (2H, m, Ph*H*), 5.73 (1H, s, NH), 4.81 (1H, d, J = 11.3 Hz, PhC*H*H), 4.50 (1H, d, J = 11.3 Hz, PhCH*H*), 4.37 (1H, d, J = 7.94 Hz, H-1), 4.24 (1H, dd, J = 2.74 and 9.76 Hz, H-3), 4.02 (1H, d, J = 13.12 Hz, H-5), 3.69 (1H, d, 13.12 Hz, H-5'), 3.54 (2H, m, H-2, H-4), 2.5 (3H, s, OMe).

14 ^{1}H NMR (250 MHz, $CDCl_3$) data of **8a:** δ (ppm) 6.82–7.42 (10H, m, Ph*H*), 5.43 (1H, s, NH), 4.97 (1H, d, J = 3.36 Hz, H-1), 4.81 (1H, d, J = 11.9 Hz, PhC*H*H), 4.64 (1H, m, H-4), 4.60 (1H, d, J = 11.8 Hz, PhCH*H*), 4.11 (1H, dd, J = 0.8 and, 12.0 Hz, H-5), 3.70 (1H, m, H-2), 3.68 (1H, dd, J = 0.8 and 12.0 Hz, H-5'), 2.52 (1H, br s, H-3), 2.5 (3H, s, CH_3); **8b**: 6.83–6.92, 7.16–7.40 (9H, m, Ph*H*), 5.38 (1H, s, NH), 4.98 (1H, d, J = 3.6 Hz, H-1), 4.81 (1H, d, J = 11.8 Hz, PhC*H*H), 4.59 (1H, d, J = 11.8 Hz, PhCH*H*), 4.52 (1H, m, H-4), 4.11 (1H, dd, J = 1.5 and, 12.8 Hz, H-5), 3.80 (1H, m, H-2), 3.77 (3H, s, OMe), 3.70 (1H, dd, J = 1.5 and 12.8 Hz, H-5'), 2.5 (3H, s, CH_3); **8c**: 6.95–7.01, 7.16–7.41 (9H, m, Ph*H*), 5.45 (1H, s, NH), 4.98 (1H, d, J = 3.6 Hz, H-1), 4.82 (1H, d, J = 11.6 Hz, PhC*H*H), 4.60 (1H, d, J = 11.6 Hz, PhCH*H*), 4.54 (1H, m, H-4), 4.12 (1H, dd, J = 1.8 and, 12.81 Hz, H-5), 3.68–3.79 (2H, m, H-2, H-5'), 3.54 (1H, brs, H-3), 2.5 (3H, s, CH_3); **8d**: 6.82–7.41 (9H, m, Ph*H*), 5.52 (1H, s, NH), 4.98 (1H, d, J = 3.6 Hz, H-1), 4.83 (1H, d, J = 11.7 Hz, PhC*H*H), 4.59 (2H, m, H-4, PhCH*H*), 4.12 (1H, dd, J = 1.5 and, 12.8 Hz, H-5), 3.71 (2H, m, H-2, H-5'), 3.55 (1H, brs, H-3), 2.5 (3H, s, CH_3).