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ENANTIOSELECTIVE SYNTHESIS OF CYCLOHEXENE NITROALDEHYDES

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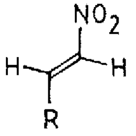
Summary. *An enantioselective synthesis of cyclohexene nitroaldehydes* **2e-5e** *has been effected,* via *Diels-Alder reaction with sugar nitroolefins as chiral dienophiles. Absolute configuration of products has been determined by X-ray crystallographic analysis and chemical correlation.*

Monosaccharides and their derivatives are versatile substrates for the synthesis of optically active target molecules[1]. Among these, the chiral cyclohexene derivatives are useful synthetic intermediates in the preparation of a variety of structures of current interest[2]. In this communication, we describe a simple route for the enantioselective synthesis of chiral cyclohexene nitroaldehydes **2e-5e** by Diels-Alder reactions between 2,3-dimethylbutadiene and carbohydrate-derived nitroalkenes.

The readily available D-*manno*-nitroalkene **1a**[3] reacts (toluene, 105 °C, 40 h) quantitatively with 2,3-dimethyl-1,3-butadiene to give a 65:35 mixture of adducts **2a** and **3a**[4,5]. The relative configurations at C-4 and C-5 were originally defined by a combination of molecular modelling and NMR studies, absolute configurations were later confirmed by X-ray analysis of compound **2a** as 4*R*,5*R*[6] (figure 1); hence, we deduce that **3a** must have the 4*S*,5*S* configuration.



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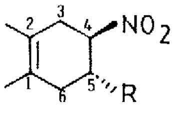

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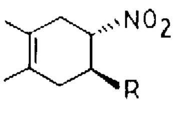

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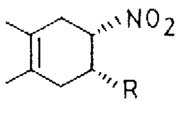

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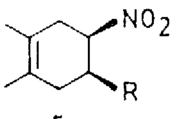

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a), R = D-*manno*-$(CHOAc)_4$-CH_2OAc
b), R = D-*manno*-$(CHOH)_4$-CH_2OH
c), R = D-*galacto*-$(CHOAc)_4$-CH_2OAc
d), R = D-*galacto*-$(CHOH)_4$-CH_2OH
e), R = CHO

Deacetylation of **2a** under basic conditions[7] (potassium carbonate) gave a 68:32 mixture of C-4 epimeric compounds **2b** and **4b**; this was treated with sodium metaperiodate[8], yielding the nitroaldehydes **2e** and **4e** as a mixture that was not separated. However, deacetylation of **2a** with 4 *N* hydrochloric acid[9], followed by sugar-chain degradation led to the pure **2e**[10], $[\alpha]_D^{15}$ −59.4° (*c* 1.25, chloroform).

The preponderance of product **2a** in the cycloaddition agrees with a statement[11] that predicts the 4*R*,5*R* isomer as the major product, taking into account the configuration of the chiral center directly adjacent to the dienophilic double bond. To check the potentiality of this assumption, the reaction was repeated using the D-*galacto*-nitroalkene **1c**[12] (adjacent chiral center opposite), and we obtained a 84:16 mixture of adducts **3c** and **2c**[13], so supporting the validity of the statement.

Acid-catalyzed deacetylation[9] of **3c**, followed by periodate oxidation, afforded (80% yield) nitroaldehyde **3e**, $[\alpha]_D^{15}$ +56.3° (*c* 0.72, chloroform), whose optical rotation is of nearly equal value but opposite sign that of **2e**. This result showed that the adduct **3c** had the 4*S*,5*S* configuration. Deacetylation of **3c** with potassium carbonate[7] led to a 64:36 mixture of **3d** and **5d**, respectively, and the pure compound **5d** (4*R*,5*S*) could be isolated. The latter, when subjected to sugar-chain degradation, yielded **5e**[14].

In conclusion, an efficient synthetic route to the cyclohexene nitroaldehydes **2e**-**5e** has been developed, using readily accesible sugar-nitroalkenes. Further studies dealing with the scope and limitations of the method, and the utility of compounds **2e**-**5e** are now under active investigation.

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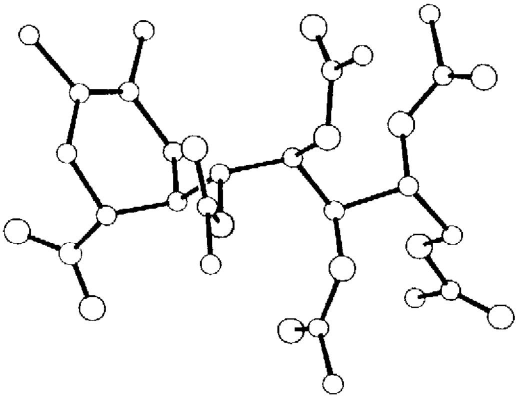

Figure 1.

References and Notes

1. S. Hanessian, *Total Synthesis of Natural Products: The "Chiron" Approach*, Pergamon Press, Oxford, 1983.

2. *a*) W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, 1984, 23, 876.
   b) S. Ogawa, T. Takagaki, *J. Org. Chem.*, 1985, 50, 2356.
   c) N. Ono, A. Kamimura, A. Kaji, *Ibid.*, 1988, 53, 251.

3. J. C. Sowden, R. Schaffer, *J. Am. Chem. Soc.*, 1950, 73, 4662.

4. All new compounds displayed satisfactory analytical and spectral data (IR, NMR 200 MHz). Complete spectroscopic details will be given in our full paper.

5. After evaporation of the crude mixture, major isomer (**2a**) crystallizes from ethanol. Minor isomer (**3a**) remain in the mother liquor and solidifies after pouring on ice-water. Selected data: **2a**; yield, 51%; m. p. 152-3°; $[\alpha]_D^{19}$ +22.5° (*c* 0.72, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) : δ 4.94 (dd, $J_{1',2'}$=5.5, $J_{1',5}$=7.9, H-1'), 4.41 (m, $J_{4,5}$=8.2, H-4), 2.64 (m, H-5); ^{13}C-NMR ($CDCl_3$) : δ 83.1 (C-4), 71.4 (C-1'), 37.0 (C-5). **3a**; yield, 11%; $[\alpha]_D^{15}$ +70°(*c* 0.51, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) : δ 5.02 (d, $J_{1',2'}$=9.7, $J_{1',5}$ ~ 0, H-1'), 4.37 (td, $J_{4,5}$=10.5, H-4); ^{13}C-NMR ($CDCl_3$) : δ 83.2 (C-4), 67.6 (C-1'), 37.7 (C-5).

6. Crystallographic data for compound **2a** ($C_{23}H_{33}NO_{12}$): orthorhombic, space group $P2_12_12_1$, *a*=8.234 (2), *b*=16.898 (5), *c*=19.582 (4) Å, *V*=2724.5 (3) Å, *Z*=4. Data collected on a Siemens AED diffractometer with CuKα graphite monochromated radiation, $\omega : \theta$ scan. Structure determination by direct methods (SHELX86). Full-matrix least squares refinement (fixed isotropic contribution for hydrogen) have converged to R=0.05 for 2060 observed reflections [$I > 4\sigma(I)$, $3° < 2\theta < 122°$]. Figure 1 shows a computer generated view (PLUTO) of **2a**. The final atomic parameters will be deposited with the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U. K. Please give a complete literature citation when ordering.

7. To a solution of the adduct (1.0 g) in 90% methanol was added potassium carbonate (0.62 g), and the mixture was stirred at room temperature. After 18 h, deacetylation was complete.

8. To a solution of the deacetylated adduct (0.14 g) in 30% methanol (27 ml) at 0° was added, dropwise, sodium metaperiodate (0.48 g). After 15 min, the reaction was complete.

9. A solution of the adduct (3.0 g) in 6:1 methanol/4 *N* HCl was boiled for 3.5 h.

10. Yield, 98%, oil; ^{1}H-NMR ($CDCl_3$): δ 9.68 (d, $J_{CHO,5}$=0.7, CHO), 4.89 (ddd, $J_{4,5}$=9.1, H-4), 3.37 (m, H-5); ^{13}C-NMR ($CDCl_3$): δ 199.9 (CHO), 80.2 (C-4), 48.8 (C-5).

11. R. W. Franck, S. Argade, C. S. Subramanian, D. M. Frechet, *Tetrahedron Lett.*, 1985, **26**, 3187.

12. J. C. Sowden, D. R. Strobach, *J. Am. Chem. Soc.*, 1960, **82**, 954.

13. Major isomer (3c) was isolated by fractional crystallization from ethanol of the reaction crude. Yield, 84%; m. p. 150-1°; $[\alpha]_D^{19}$ +51.7° (*c* 0.71, ($CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 4.91 (dd, $J_{1',2'}$=1.5, $J_{1',5}$=9.2, H-1'), 4.44 (td, $J_{4,5}$=6.7, H-4), 2.54 (m, H-5). Minor isomer (2c) was isolated by preparative t.l.c. from the crude mixture (ether-light petroleum, 1:1); m. p. 170-1°; $[\alpha]_D^{19}$ -4.6° (*c* 0.59, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 4.98 (dd, $J_{1',2'}$=2.8, $J_{1',5}$=3.8, H-1'), 4.59 (ddd, $J_{4,5}$=9.5, H-4), 2.66 (m, H-5); ^{13}C-NMR ($CDCl_3$): δ 83.6 (C-4), 69.2 (C-1'), 38.4 (C-5).

14. Yield, 95%; oil; $[\alpha]_D^{15}$ +24.7° (*c* 0.75, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 9.74 (s, CHO), 5.00 (td, $J_{4,5}$=3.1, H-4), 3.05 (td, H-5); ^{13}C-NMR ($CDCl_3$): δ 200.0 (CHO), 79.9 (C-4), 47.4 (C-5).

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