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Stereoselective Michael Addition Reactions of 5-Glyco-4-nitrocyclohex-1-enes

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Abstract

Michael additions of 5-glyco-4-nitrocyclohex-1-enes (2 and 3) proceeded in a stereoselective way, leading in each case to single adducts in which the electron-deficient alkenes add on the C-4 of the cyclohexene rings, in a *trans* mode to the adjacent, sterically demanding, sugar side-chain. When dimethyl maleate or dimethyl fumarate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were used, there was *in situ* elimination of nitrous acid, and the product consisted in a 1:1 mixture of the epimeric α,β-unsaturated esters 7. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Michael reactions; Nitro compounds; Stereoselectvity; Cyclohexenes

The Michael addition reaction constitutes one of the most important preparative methods in organic chemistry. Among the plethora of nucleophiles that can be used in those carbon-carbon bond-forming processes [1], aliphatic nitro compounds are of increasing importance because of their remarkable versatility, since the nitro group can be transformed into various functionalities [2]. Moreover, in recent years considerable efforts have been made in the development of highly diastereo- and even enantio-selective methods, allowing the control of absolute stereochemistry [3]. In this sense, the easy availability of chiral nitro compounds should increase the synthetic usefulness of this methodology.

In previous papers [4], we reported on the preparation of stereochemically pure 5-glyco-4-nitrocyclohex-1-enes (2 and 3), which were obtained by Diels-Alder reactions between the sugar-derived nitroalkenes **1a** or **1b** and 2,3-dimethylbuta-1,3-diene (Scheme 1).

We present here our results of stereoselective Michael additions between chiral nitro compounds 2 or 3 and several electron-deficient alkenes. In all cases, the reactions were carried out at room temperature for 12-24 h, with acetonitrile as the solvent, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,1,3,3-tetramethylguanidine (TMG) or triethylamine (TEA) as the basic catalysts (see Table I).

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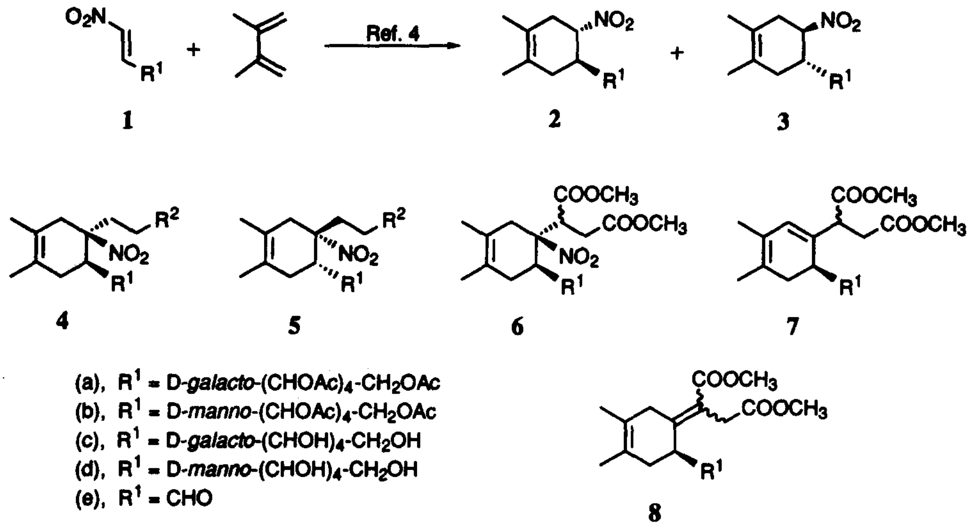


(a), R^1 = D-*galacto*-$(CHOAc)_4$-CH_2OAc
(b), R^1 = D-*manno*-$(CHOAc)_4$-CH_2OAc
(c), R^1 = D-*galacto*-$(CHOH)_4$-CH_2OH
(d), R^1 = D-*manno*-$(CHOH)_4$-CH_2OH
(e), R^1 = CHO

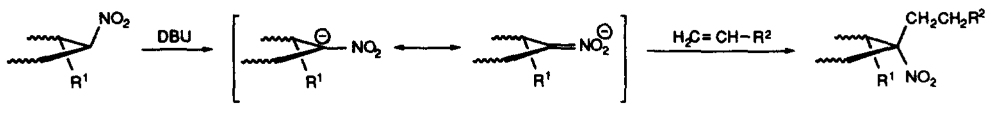
Scheme 1

Table I. Michael additions with 5-glyco-4-nitrocyclohex-1-enes **2** and **3**.

Compound[a]	R^2	Base (equiv.)	Yield (%)[b]
4a	$COOCH_3$	DBU (1.15)	60
4a	$COCH_3$	TMG (0.09)	82
4a	CHO	TMG (0.09)	44 (*)
4a	CN	TMG (0.09)	60
5b	$COOCH_3$	DBU (1.15)	89
5b	$COOCH_3$	TMG (0.09)	54
5b	$COOCH_3$	TMG (1.15)	91
5b	$COCH_3$	TMG (0.09)	65
5b	CHO	TEA (1.60)	36 (*)
5b	CN	TMG (0.09)	85
4b	$COOCH_3$	DBU (1.15)	35 (*)
4b	$COCH_3$	TMG (0.09)	44 (*)
4b	CHO	TMG (0.09)	43 (*)
4b	CN	TMG (0.09)	50 (*)
6a	-	TMG (1.15)	91
7a	-	DBU (2.0)	88

[a] All compounds were crystalline except for those marked (*), which were isolated as amorphous solids. [b] Yields refer to pure isolated products.

The crucial point to be studied for the above processes was the stereoselectivity of the Michael additions; in this way, the NMR spectra of the crude mixtures showed that only one of the two possible diastereomers was formed in each case. Thus, the Diels-Alder adducts **2a** and **2b** led exclusively to products of the type **4** (or **6**), whereas the Diels-Alder adduct **3b** yielded exclusively compounds of the **5** series. Hence, the Michael reactions were completely stereoselective, the products being the result of the addition of the electron-deficient alkenes on the less-hindered face of the intermediate carbanion; i.e. the opposite to that is occupied by the sugar side-chain (Scheme 2).



Scheme 2

The structures of the new compounds (**4**-**7**) are based on elemental analyses and spectroscopic data (IR, ^1H and ^{13}C NMR). For compound **4a** (R^2 = $COOCH_3$), the absolute configuration at C-4 was unambiguously determined by single crystal X-ray crystallographic analysis [5], the result of which is shown in Fig. 1. The opposite configurations at C-4 for compounds **4a** (R^2 = $COOCH_3$) and **5b** (R^2 = $COOCH_3$) were deduced from data of their respective nitro aldehydes [6] **4e** and **5e**, which showed spectral identity and nearly equal and opposite values for their optical rotations. For all the remaining products we have obtained, the configuration at C-4 is based on the close resemblance between the ^1H NMR spectra within each series; thus, the ranges in which the H-5 proton appears are: (a) 2.67-2.78 ppm, (b) 2.93-2.99 ppm, and (c) 2.43-2.44 ppm for compounds in the series **4a**, **5b**, and **4b**, respectively.

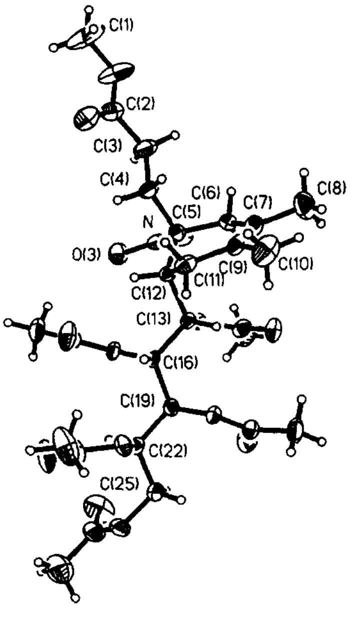


Figure 1. X-ray crystal structure of compound **4a** (R^2 = $COOCH_3$).

On the other hand, we have also studied the Michael reactions of **2a** and dimethyl maleate or dimethyl fumarate. The results we found were identical for these two alkenes and, although the stereochemistry at C-4 in the products is only tentatively assigned, we suppose that it is the same as above cited (see Scheme 2). The compounds we obtained depended on the basic catalyst and temperature; thus, with TMG (1.15 mol) at 0 °C, a 1:1 mixture of the epimers **6** was formed quantitatively, whereas with DBU (2.0 mol) at room temperature, the product consisted in a quantitative 1:1 mixture of the epimers **7**. These same elimination products **7** were obtained when the addition compounds **6** were treated with 2.0 mol of DBU. As described by Ballini et al. [7] for reactions between achiral nitroalkanes and dimethyl maleate by using DBU, formation of compounds **7** should occur *via* the adducts **6**, through nitrous acid elimination induced by the presence of an electron withdrawing group at the β position to the nitro group. For the not isolated compound **8**, the new exocyclic double bond should isomerize to the more-stable, endocyclic conjugated diene **7**. In this sense, we have performed semiempirical calculations [8] for simplified model compounds of **7** and **8** (R^1 = $-CHOH-CH_2OH$), finding that the former was more stable by about 9.2 Kcal/mol.

Acknowledgements

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[5] Crystal data for **4a** (R^2 = $COOCH_3$): Data were acquired with a Siemens P4 diffractometer and graphite monochromatized Mo-K_α radiation (λ = 0.71073 Å). $C_{27}H_{39}NO_{14}$ (601.61), crystal size 0.48 x 0.34 x 0.30 mm, monoclinic, space group $P2_1$, 298 K, a = 9.880(1), b = 16.916(1), c = 10.006(1) Å, β = 107.99 (1)° ,V = 1590.5(5) $Å^3$, Z = 2; D_c = 1.256 Mg/m^3, F(000) = 640, μ = 0.102 mm^{-1}. A total of 5863 reflections were collected in the $2° < 2\theta < 60°$ range using variable speed (3-45°/m) $\omega/2\theta$-scan mode, and of these 5066 were independent (R_{int} = 0.021). Three standard reflections monitored every 97 reflections indicated no significant intensity variation.

The structure was solved by direct methods and subsequent Fourier differences and refined by full-matrix least-squares using anisotropic thermal parameters for non-hydrogen atoms. The hydrogen atoms were located from a differential Fourier synthesis and placed in idealized positions (C-H = 0.96 Å) riding on their respective bonded atoms. The final refinement was carried out with a weighting scheme of $w^{-1} = \sigma^2(F_o) + 0.0015F_o^2$ and converged to $R(F) = 0.061$ and $R_w(F) = 0.072$ for 2402 reflections with $F_o > 4\sigma(F_o)$ and 378 refined parameters. The goodness of fit on F^2 was 1.27. The largest negative and positive peaks in the final difference map were 0.27 and -0.22 $eÅ^{-3}$. All calculations were performed on a Silicon Graphics Iris Indigo XS24 computer using the SHELXTL-IRIS program package.

Complete details of the structure investigation are available at request from the Cambridge Crystal Data Centre, 12 Union Road, Cambridge CB2 1EZ, England.

[6] **4e**: $[\alpha]_D$ -2.61 (c 0.52, $CHCl_3$); **5e**: $[\alpha]_D$ +2.40 (c 0.50, $CHCl_3$). Nitroaldehydes **4e** and **5e** were prepared by oxidative cleavage with sodium metaperiodate of pentitols **4c** and **5d**, which were obtained by sodium methoxide deacetylation of **4a** and **5b**.

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