Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1673–1675

TETRAHEDRON: *ASYMMETRY*

Stereoselective denitrohydrogenation reactions of 4-alkyl-5-glyco-4-nitrocyclohex-1-enes

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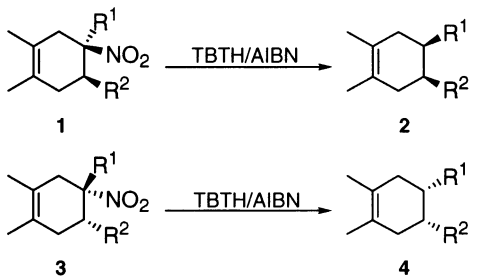
Received 13 June 2001; accepted 29 June 2001

Abstract—The denitrohydrogenation of chiral 4-alkyl-5-glyco-4-nitrocyclohex-1-enes (**1** and **3**) with tri-*n*-butyltin hydride and azobisisobutironitrile proceeded in a completely stereoselective way. In each case, the hydrogen atom provided by tri-*n*-butyltin hydride adds to a free radical intermediate in a *trans* mode to the adjacent, sterically demanding, sugar side-chain. Attempts to perform denitroalkylation reactions of **1a**, **3a** or **8** with electron-deficient alkenes yielded only denitrohydrogenated products.

The replacement of a nitro group by hydrogen constitutes a useful process in synthetic organic chemistry. This type of reaction was first reported in 1978 by Kornblum et al.[1] who utilized tertiary nitro compounds and the sodium salt of methanethiol as a denitrating agent. Since them, many other reagents have been discovered,[2] the most extensively used being tri-*n*-butyltin hydride (TBTH) in the presence of a radical initiator as benzoyl peroxide[3] or azobis(isobutyrylnitrile) (AIBN);[4] this metal hydride has been shown to effect selective and clean denitrohydrogenation of tertiary and even some secondary nitro compounds without affecting other functional groups. Furthermore, as these reactions with TBTH are known to proceed through alkyl free radical intermediates, tertiary and secondary nitro compounds can also be used as adequate substrates for intra- or intermolecular radical C–C bond-forming reactions.[5]

Nevertheless, given the importance and potential applications of the denitration reaction, surprisingly few reports have been focused on studying the stereochemical outcome;[6] to our knowledge, apart from the works of Sinou[7] and Barco,[8] in which stereoselective denitrohydrogenations were effected, this problem has only been treated in radical cyclizations of certain nitroalkanes.[5a,5c,5d,9] Herein, we report our preliminary findings in the denitrohydrogenation reactions of tertiary nitrocyclohexenes **1a**, **3b**, **3c** and **3d** (Scheme 1) in which a sugar side-chain, that is adjacent to the nitro functionality, works as the stereodifferentiating element. The configuration at C(4) and C(5) of these starting compounds is a consequence of their provenance from either D-*galacto*- or D-*manno*-1-nitroalkenes, that yielded the above cited nitrocyclohexenes through cycloaddition with 2,3-dimethylbuta-1,3-diene, followed by Michael reaction of the resulting Diels–Alder adduct with methyl acrylate, acrylonitrile or methyl vinyl ketone.[10] Attempts at radical denitroalkylations between these substrates and olefins are also described.



a, R^1= $CH_2CH_2COOCH_3$, R^2= D-*galacto*-$(CHOAc)_4$-CH_2OAc
b, R^1= $CH_2CH_2COOCH_3$, R^2= D-*manno*-$(CHOAc)_4$-CH_2OAc
c, R^1= CH_2CH_2CN, R^2= D-*manno*-$(CHOAc)_4$-CH_2OAc
d, R^1= $CH_2CH_2COCH_3$, R^2= D-*manno*-$(CHOAc)_4$-CH_2OAc
e, R^1= $CH_2CH_2COOCH_3$, R^2= D-*galacto*-$(CHOH)_4$-CH_2OH
f, R^1= $CH_2CH_2COOCH_3$, R^2= D-*manno*-$(CHOH)_4$-CH_2OH
g, R^1= $CH_2CH_2COOCH_3$, R^2= CHO

Scheme 1.

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0957-4166/01/$ - see front matter
PII: S0957-4166(01)00304-4

Treatment of 1,2,3,4,5-penta-*O*-acetyl-1-*C*-[(4*R*,5*S*)-1,2-dimethyl-4-(2-methoxycarbonylethyl)-4-nitrocyclohex-1-en-5-yl]-D-*galacto*-pentitol **1a**[10] with 2 equivalent of TBTH in refluxing benzene (2 h.) in the presence of AIBN (0.5 equivalent) led, after evaporation of the solvent and crystallization (MeOH) of the resulting oil, to 1,2,3,4,5-penta-*O*-acetyl-1-*C*-[(4*S*,5*S*)-1,2-dimethyl-4-(2-methoxycarbonylethyl)cyclohex-1-en-5-yl]-D-*galacto*-pentitol **2a**.

The ^{1}H NMR spectrum of the crude mixture at the end of the reaction time indicated a single denitrohydrogenated product, thus the process was completely stereoselective. The structure of the new compound **2a** is supported by elemental analysis and spectroscopic data (IR, ^{1}H and ^{13}C NMR);[11] the absolute configuration at C(4) being unambiguously established by X-ray single crystal structure analysis.[12] The result of this (see Fig. 1), showed that both chains on the cyclohexene ring, i.e. the sugar side-chain at C(5) (C(1′)–C(5′)) and the other at C(4) (C(1″)–C(4″)) adopt roughly planar, zig–zag conformations. The torsion angles C(1″)–C(4)–C(5)–C(1′) = 66.9° and C(4)H–C(4)–C(5)–C(5)H = 64.6° indicate a *cis*-relationship between substituents at C(4) and C(5).

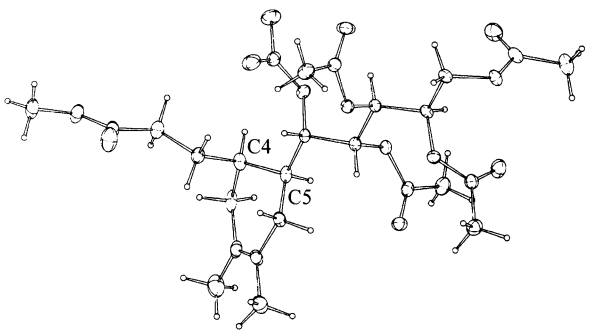
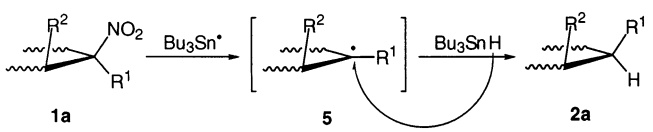


Figure 1. ORTEP view of compound **2a**.

Since a free radical intermediate **5** (Scheme 2) would be involved in denitration of **1a**, it is noteworthy that only one of the possible stereoisomeric products was formed. This completely stereoselective process could be rationalized by supposing that the hydrogen atom, provided by tri-*n*-butyltin hydride, adds to the less-hindered face of **5**; i.e. the opposite to that occupied by the sterically demanding sugar side-chain.

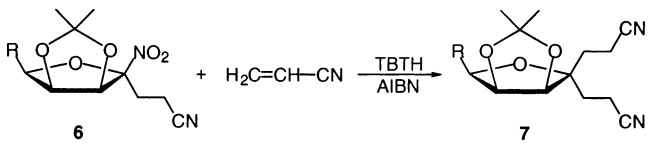


Scheme 2.

In order to check our above results, we carried out reactions starting from **3b**, **3c** and **3d**, and using the same conditions described for the preparation of **2a**. Although in each one of the respective reaction mixtures only one denitrohydrogenated product was detected, the reactions yielded non-crystallizable oils, that had to be purified by column chromatography on silica gel. In addition to the expected **4b** (40%), **4c** (65%) and **4d** (54% yield), we found fractions that contained mixtures of partially deacetylated compounds,[13,14] which probably arise through silica gel promoted catalytic processes.

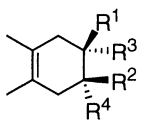
The opposite configurations at C(4) and C(5) for **2a** and **4b** were deduced from data of their respective aldehyde derivatives **2g** and **4g**, which showed spectral identity and nearly equal and opposite values for their optical rotations.[15] These aldehydes were prepared by a two-step sequence, in which treatment of pure pentaacetates **2a** or **4b** (or their denitrohydrogenation reaction mixtures) with sodium methoxide afforded pentitols **2e** (67%) and **4f** (64%); then, oxidative cleavage of their deacetylated sugar side-chains with sodium metaperiodate yielded quantitatively aldehydes **2g** and **4g**. Based on the proposed pathway for denitrohydrogenation showed in Scheme 2, and also taking into account the close resemblance of ^{1}H and ^{13}C NMR spectra between compounds **4b**, **4c** and **4d**, we propose that they must present identical configurations at their stereogenic centers, C(4) and C(5).

As pointed out above, the free radical intermediates arising in denitrohydrogenation reactions could participate in C–C bond-forming processes when they are treated with electron-deficient alkenes. For example, Dupuis et al.[5b] reported on the reaction of nitro sugar **6** and a large excess of acrylonitrile in the presence of TBTH/AIBN, yielding product **7** in 55% yield (Scheme 3).



Scheme 3.

By using the same methodology, we reacted tertiary nitro compounds **1a** and **3b** (and even the secondary **8**) with either methyl acrylate or acrylonitrile; however, we found that only the respective denitrohydrogenated compounds **2a** (55%), **4b** (38%) and **9** (27% isolated yield) were formed, with any evidence of hypothetical 4,4-dialkyl-5-glycocyclohexenes, as for example **10**. This result, that indicates severe steric crowding in the radical intermediate **5**, could support the complete stereoselection observed in the denitrohydrogenation reaction.



8, $R^1 = NO_2$, $R^2 = R^3 = H$, R^4 = D-*manno*-$(CHOAc)_4$-CH_2OAc

9, $R^1 = R^2 = R^3 = H$, R^4 = D-*manno*-$(CHOAc)_4$-CH_2OAc

10, $R^1 = R^3 = CH_2CH_2CN$, $R^2 = H$, R^4 = D-*manno*-$(CHOAc)_4$-CH_2OAc

Acknowledgements

This work was supported by the Spanish Ministerio de Educación y Cultura (CICYT, PB98-0997) and the Junta de Extremadura-Fondo Social Europeo through grant IPR98A066. We also thank the Junta de Extremadura for a fellowship to M. V. Gil.

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11. Analytical data for the representative compound **2a**: white solid; yield (unoptimized) 57%; mp 128–130°C; R_f 0.64 (hexane:EtOAc, 1:1); $[\alpha]_D$ = +69.5 (*c* 0.51; $CHCl_3$); IR (KBr, cm^{-1}): 2980, 2920, 2840, 1730, 1630, 1210, 1020; ^1H NMR (400 MHz, $CDCl_3$, ppm): 5.33 (d, 1H, $J_{2',3'}$ 9.6, H-2′), 5.16 (m, 1H, H-4′), 5.13 (dd, 1H, $J_{3',4'}$ 1.6, H-3′), 5.06 (d, 1H, $J_{1',5}$ 9.2, H-1′), 4.32 (dd, 1H, $J_{4',5'}$ 4.4, $J_{5',5''}$ 11.7, H-5′), 3.78 (dd, 1H, $J_{4',5''}$ 7.3, H-5″), 3.63 (s, 3H, $COOCH_3$), 2.3–2.1 (m, 2H, H-2″a, H-2″b), 2.11 (s, 3H, $OCOCH_3$), 2.09 (s, 6H, 2×$OCOCH_3$), 2.08 (s, 3H, $OCOCH_3$), 2.00 (s, 3H, $OCOCH_3$), 1.94 (m, 1H, $J_{5,6a}$ 10.0, H-6a), 1.9–1.45 (m, 4H, H-1″a, H-1″b, H-3a, H-6b), 1.72 (m, 1H, H-5), 1.56 (s, 6H, CH_3-1, CH_3-2), 1.48 (m, 1H, H-3b), 1.37 (m, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 174.3 (C-3″), 170.5, 170.4, 170.3, 170.0 ($OCOCH_3$), 123.8, 123.2 (C-1, C-2), 71.0 (C-1′), 68.2 (C-2′, C-3′), 68.1 (C-4′), 62.7 (C-5′), 38.4 (C-5), 35.5 (C-6), 32.5 (C-3, C-2″), 31.7 (C-4), 30.1 (C-1″), 21.0, 20.9, 20.8, 20.7 ($OCOCH_3$), 19.3, 18.9 (CH_3-1, CH_3-2). Anal. calcd for $C_{27}H_{40}O_{12}$: C, 58.26; H, 7.24. Found: C, 58.28; H, 7.21%. All the other new compounds were fully characterized by spectroscopic means (^1H, ^{13}C NMR, IR) and analytical or HRMS data.
12. A single crystal of **2a**, crystallizing from methanol by slow evaporation of the solvent, with approximate size of 0.30×0.20×0.10 mm was employed. The compound crystallized in the monoclinic space group *P*2 with *a* = 5.8425(5), *b* = 18.5242(18), *c* = 13.2751(7) Å, β = 90.885(4)°, *V* = 1436.6(2) Å^3, *Z* = 2, D_c = 1.280 Mg/m^3, μ = 0.101 mm. The intensities were measured on an Enraf Nonius Kappa CCD area detector diffractometer (ϕ and ω scans to fill the Ewald sphere). A total of 8586 reflections were collected in the range θ 3.07–75° utilizing Mo Kα radiation (λ = 0.71073 Å), and of these 4544 were independent (R_{int} = 0.0726). The structure was solved by direct methods with SHELXS-86 (Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467) and refined by full matrix least squares using SHELXL-97 (Sheldrick, G. M. Program for Crystal Structure Refinement; University of Göttingen: Germany, 1997). X-Ray crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 165154), which are available free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
13. From the reaction mixture of **3b**, the C(4′) deacetylated product (5% yield) was isolated in addition to **4b**. This showed C(4′)H at 3.69 ppm, coupled with OH (D_2O exchangeable signal, 3.33 ppm).
14. Probably due to partial deacetylation, the yields of **4b** and **4d** were only moderate. In fact, when the crude denitrohydrogenation mixture from **3b** was treated with sodium metaperiodate, deacetylated derivative **4f** was isolated in 64% yield.
15. Compound **2g**: $[\alpha]_D$ = −3.0 (*c* 2.0, $CHCl_3$); **4g**: $[\alpha]_D$ = +3.0 (*c* 2.0, $CHCl_3$). These enantiomeric compounds were oils, showing the following spectroscopic data: IR (film, cm^{-1}): 2900, 2840, 2820, 2700, 1700, 1190, 1150; ^1H NMR (400 MHz, $CDCl_3$, ppm): 9.72 (d, 1H, $J_{5,CHO}$ 1.2, C*H*O), 3.67 (s, 3H, H-4″), 2.54 (m, 1H, $J_{4,5} = J_{5,6a} = J_{5,6b}$ 4.0, H-5), 2.38 (m, 2H, H-2″a, H-2″b), 2.21 (m, 2H, H-6a, H-6b), 2.13 (d, 1H, $J_{3a,4}$ 5.2, H-3a), 2.06 (m, 1H, H-4), 1.90 (dd, 1H, $J_{3a,3b}$ 16.6, $J_{3b,4}$ 7.3, H-3a), 1.70 (m, 2H, H-1″a, H-1″b), 1.65 and 1.61 (each s, each 3H, CH_3-1, CH_3-2); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 205.0 (*C*HO), 173.7 (C-3″), 124.7, 123.4 (C-1, C-2), 51.5, 49.5 (C-4″, C-5), 33.9 (C-4), 35.2, 32.0, 30.2 (C-3, C-6, C-1″, C-2″), 19.0, 18.8 (CH_3-1, CH_3-2).