Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

CrossMark click for updates

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 8593

Received 12th July 2014,
Accepted 11th September 2014

DOI: 10.1039/c4ob01468e

www.rsc.org/obc

Preparation of indium nitronates and their Henry reactions†

Raquel G. Soengas,* Rita Acúrcio and Artur M. S. Silva*

Indium nitronates were readily prepared from commercially available nitroalkanes by transmetallation of the corresponding lithium nitronates with indium salts. The Henry reaction of this indium organometallics with aldehydes afforded β-nitroalkanols in moderate to high yields. The use of chiral sugar aldehydes furnished the corresponding carbohydrate-derived β-nitroalkanols with excellent stereoselectivity.

Introduction

The nitro-aldol reaction, often known as the Henry reaction, is a powerful carbon–carbon bond-forming reaction.[1] The classical Henry reaction, which involves the base-catalysed reaction of nitroalkanes and aldehydes, has been widely used in synthesis.[2] Nevertheless, the classical nitro-aldol reaction does suffer from some important drawbacks:[3] (1) poor stereochemical control, due to the reversibility of the reaction;[4] (2) low yields, mainly when either the starting carbonyl compound or the resulting 2-nitro alcohols are base-sensitive; (3) sensitiveness to steric factors, causing sterically hindered nitro alkanes to be less reactive, usually failing to give the desired nitro-aldol products in good yields.[5] Hence, the nitroaldol condensation of α,α-dialkylnitroalkanes[6] has not been widely used in organic synthesis, despite the usefulness of the resulting 1,1-alkyl-1-nitroalkan-2-ols.[7]

In order to circumvent these limitations, there is recent interest in the development of alternative procedures for the preparation of 2-nitroalkan-1-ols that obviate the use of bases.[8] Our group reported a promising and convenient alternative to the classical nitroaldol (Henry) reaction, consisting of the addition of indium nitronates to aldehydes where indium nitronates were generated *in situ* from α-bromonitroalkanes and indium powder.[9] The approach is very simple from the experimental point of view and, as bases are not required, it is not subject to the limitations of the classical Henry reaction. In addition, reaction of aldehydes and hindered α,α-dialkyl-bromonitro alkanes afforded the corresponding 1,1-alkyl-1-nitroalkan-2-ols in good yields. However, the application of this methodology is limited by the difficult access to α-bromonitroalkanes: just a few are commercially available and they are considerably more expensive than nitroalkanes.

The preparation of organoindium reagents has attracted the attention of organic chemists, due to their low toxicity[10] and their synthetic utility for carbon–carbon bond formation.[11] The synthesis of organoindium reagents can be achieved not only by reaction between an organic halide and an indium metal[12] but also by reaction of aluminum,[13] magnesium,[14] or lithium[15] organometallics with indium halides. In this paper we report a new and straightforward preparation of indium nitronates from nitroalkanes *via* reaction of the corresponding lithium nitronates with indium trichloride and their Henry reactions with carbonyl compounds.

Results and discussion

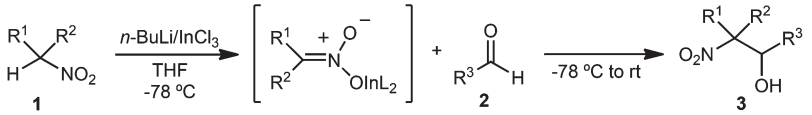
In our preliminary studies, the reaction of nitromethane **1a** with benzaldehyde **2a** was assessed. Thus, the lithium nitronate generated by the reaction of nitromethane **1a** and *n*-BuLi was readily transmetalated with indium trichloride in THF at −78 °C to give the corresponding indium nitronate. Further reaction with benzaldehyde gave the β-nitroalkanol **3a** in 71% yield (Table 1, entry 1).[16]

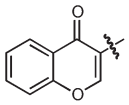
As shown by the results compiled in Table 1, under the above conditions, aromatic aldehydes **2b–d**, linear aldehydes **2e–f** and alicyclic aldehyde **2g** were efficiently converted into their corresponding β-nitroalkanols (Table 1, entries 2–7). High yields were obtained, except for the electron-rich aryl aldehyde **1b**, which, as expected, proved to be substantially less reactive and yielded the corresponding adduct **3c** in only 39% yield (Table 1, entry 2). This process tolerates a broad

Department of Chemistry & QOPNA, University of Aveiro, 3810-193 Aveiro, Portugal. E-mail: artur.silva@ua.pt, rsoengas@ua.pt; Fax: +351 234 370084; Tel: +351 234 370714

† Electronic supplementary information (ESI) available: Full experimental details and NMR spectra for compounds **3**. See DOI: 10.1039/c4ob01468e

Table 1 Synthesis of β-nitroalkanols[a]

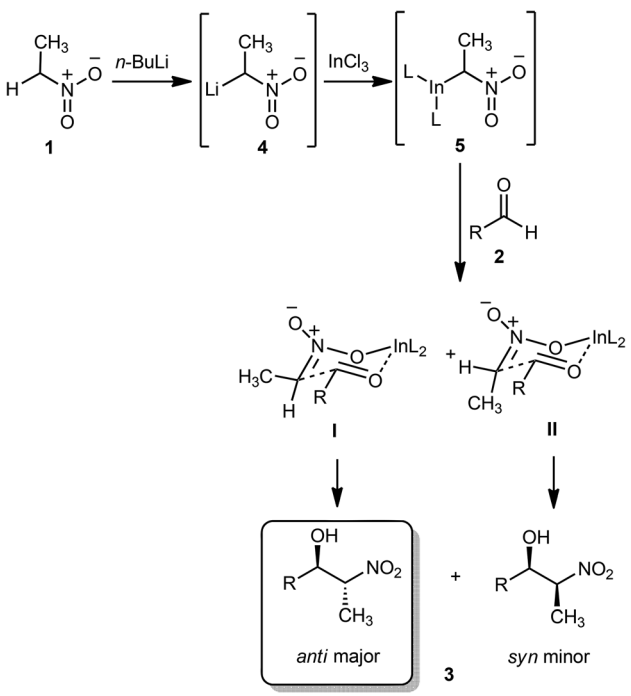


Entry	1	R^1	R^2	2	R^3	3	*syn*/*anti*[b]	Yield[c] (%)
1	**1a**	H	H	**2a**	Ph	**3a**	—	71
2	**1a**	H	H	**2b**	4-MeO-C_6H_4	**3b**	—	39
3	**1a**	H	H	**2c**	4-CN-C_6H_4	**3c**	—	81
4	**1a**	H	H	**2d**	2-NO_2-C_6H_4	**3d**	—	75
5	**1a**	H	H	**2e**	*n*-C_7H_{15}	**3e**	—	85
6	**1a**	H	H	**2f**	CO_2Et	**3f**	—	69
7	**1a**	H	H	**2g**	*c*-C_6H_{12}	**3g**	—	83
8	**1a**	H	H	**2h**		**3h**	—	63
9	**1b**	CH_3	CH_3	**2a**	Ph	**3i**	—	58
10	**1c**			**2e**	*n*-C_7H_{15}	**3j**	—	55
11	**1d**			**2i**	H	**3k**	—	71
12	**1e**	CH_3	H	**2a**	Ph	**3l**	33/67	60
13	**1e**[d]	CH_3	H	**2a**	Ph	**3l**	33/67	59
14	**1e**	CH_3	H	**2g**	*c*-C_6H_{12}	**3m**	27/73	79
15	**1f**	CH_2OBn	H	**2a**	Ph	**3n**	30/70	61

[a] Reactions were carried out with the appropriate nitroalkane (3 mmol), indium trichloride (1 mmol), *n*-butyllithium (3 mmol), and the aldehyde (2 mmol) overnight at room temperature. [b] Determined by ^1H NMR. [c] Isolated yield. [d] Ethanol was added (3 mmol) before the coupling with the aldehydes.

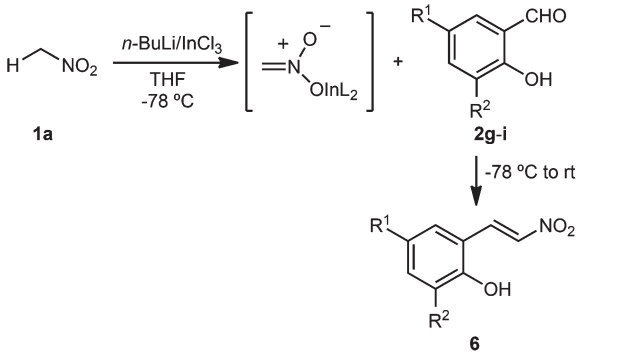
scope of functional groups, including a cyano group (Table 1, entry 3), a nitro group (Table 1, entry 4) or an ester group (Table 1, entry 6). Moreover, the reaction of nitromethane and formyl chromone **2h** afforded exclusively the corresponding Henry adduct in good yield, and the 1,4-addition product was not detected in the crude reaction mixture (Table 1, entry 8).[17] In subsequent experiments aimed at extending these studies to include other nitroalkanes, hindered 1,1′-dialkylnitroalkanes were considered first. Thus, the reaction of 2-nitropropane **1b** and nitrocyclopentane **1c** with benzaldehyde **2a** and octanal **2e**, respectively, afforded the corresponding β-nitroalkanols **3i** and **3j** in good yields (Table 1, entries 9 and 10). It is also worth mentioning the good results obtained by the reaction of nitrocyclohexane **1d** with solid paraformaldehyde. Under these conditions, the hydroxymethylated product **3k** was obtained in 71% yield (Table 1, entry 11).

The addition of nitroethane **1e** to aldehydes resulted in moderate *anti*-selectivity (Table 1, entries 12 and 14), identical to those obtained when nitroethane indium nitronate was generated from bromonitroalkanes and indium(0).[9c] Similarly, the reaction of indium nitronate, derived from ethyl *O*-benzylnitroethanol **1f**, with benzaldehyde **2a** afforded the corresponding nitroalkanol **3k** in good yield and moderate *anti*-selectivity (Table 1, entry 15).[18]



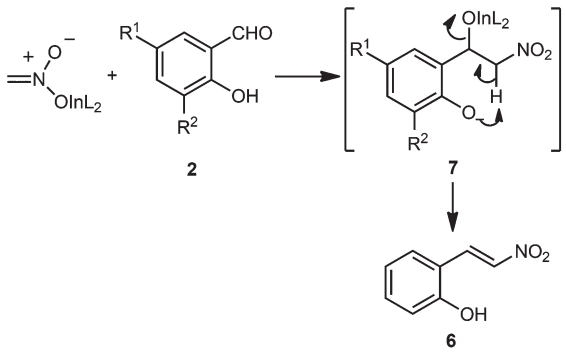
Scheme 1 Proposed mechanism for the synthesis of β-nitroalkanols **3**.

Table 2 Synthesis of (*E*)-2-(2-nitrovinyl)phenols



Entry	2	R^1	R^2	6	*E*/*Z*	Yield[a] (%)
1	**2j**	H	H	**6a**	>98 : 2	73
2	**2k**	Cl	H	**6b**	>98 : 2	78
3	**2l**	H	OMe	**6c**	>98 : 2	62

[a] Isolated yield.



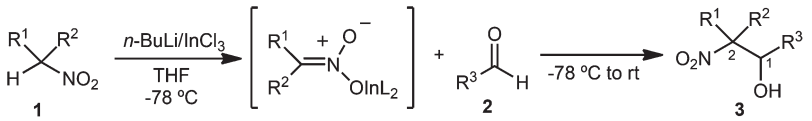
Scheme 2 Proposed mechanism for the synthesis of (*E*)-2-(2-nitrovinyl)phenols **6**.

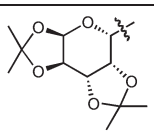
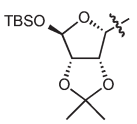
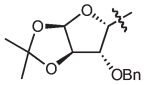
The observed *anti*-selectivity could be explained according to a chelation-control model. According to our proposition, indium metallation of intermediate lithium nitronate **4**, readily generated from nitroalkene **1** and *n*-butyllithium, renders specie **5** (Scheme 1). For the reaction of intermediate **5** with aldehydes, we suggest intramolecular chelation of the metallic centre producing a rigid chair-like state.

The predominant formation of the *anti*-isomers over the *syn*-isomers could be explained based on the higher stability of the pseudochair transition state **I** leading to the *anti*-isomer.[19]

In contrast to lithium organometallics, organoindium reagents are known to be tolerable to active hydrogen. In order to demonstrate the intermediacy of indium nitronates, ethanol was added to the reaction mixture before the coupling with the aldehyde. In this case, neither the yield nor the diastereoselectivity decreased (Table 1, entry 13). In a further experiment aimed to confirm the intermediacy of indium nitronates and their stability to active hydrogen, the reaction of nitromethane **1a** and hydroxyaldehydes was investigated. Unexpectedly, the reaction of nitromethane **1a** with salicylaldehyde **2j** afforded (*E*)-2-(2-nitrovinyl)phenol **6a** in a 73% yield (Table 2, entry 1). The extension of this reaction to 2-hydroxybenzaldehydes **2k** and **2l** gave the corresponding (*E*)-2-(2-nitrovinyl) phenols **6b** and **6c**, respectively (Table 2, entries 2 and 3). 2-(2-Nitrovinyl)phenols have been used as substrates in sequential Michael and acetalization reactions for the preparation of 4-nitromethylchromans, which have wide range of uses in pharmaceutical chemistry.[20] However, the methods described for their synthesis to date only gave low to moderate yields, limiting their usefulness as starting materials in the synthesis of drug intermediates. The present methodology is a convenient alternative to the diastereoselective synthesis of (*E*)-2-(2-nitrovinyl)phenols in good yields.

Table 3 Synthesis of chiral sugar-derived β-nitroalkanols



Entry	1	R^1	R^2	2	R^3	3	1*R*/1*S*[a]	2*R*/2*S*[a]	Yield[b] (%)
1	**1a**	H	H	**2m**		**3o**	89/11	—	71
2	**1a**	H	H	**2n**		**3p**	87/13	—	75
3	**1c**			**2o**		**3q**	90/10	—	52
4	**1e**	CH_3	H			**3r**	96/4	15/85	67

[a] Determined by ^{1}H NMR. [b] Isolated yield.

A plausible mechanism would involve elimination of the intermediate indium alcoholate 7 by the action of the 2-alkoxy group, producing (*E*)-nitroalkene **6a** (Scheme 2).

The satisfactory results obtained in the synthesis of racemic nitro alcohols **3** prompted us to test the usefulness of this methodology for the synthesis of enantiopure 1-nitroalkan-2-ols. Our studies were carried out with chiral sugar aldehydes **2m–o**, which upon reaction with indium nitronates of nitroalkanes **1** under the same reaction conditions as above, provided the corresponding 1-nitroalkan-2-ols **3o–r** in moderate to good yields and good diastereomeric ratios (see Table 3).[21]

The major diastereomers were always those predicted by the Felkin–Anh model. Upon addition of nitroethane **1e**, the *anti* diastereoselectivity is also excellent (Table 3, entry 4).

In conclusion, we have developed a new route to form indium nitronates directly from nitroalkanes by deprotonation with *n*-BuLi followed by transmetalation with indium trichloride. This method provides easier access to indium nitronates compared with the existing procedures that need α-bromonitroalkanes. The Henry reaction of this indium organometallics with aldehydes afforded β-nitroalkanols in moderate to high yields and *anti*-diastereoselectivity.

The use of chiral sugar aldehydes afforded the corresponding carbohydrate-derived β-nitroalkanols with excellent stereoselectivity. The use of 2-hydroxybenzaldehydes allows establishment of a new diastereoselective synthesis of (*E*)-2-(2-nitrovinyl)phenols in good yields.

Notes and references

1 L. Henry, *Bull. Soc. Chim. Fr.*, 1895, **13**, 999–1004.
2 (*a*) F. A. Luzzio, *Tetrahedron*, 2001, **57**, 915–1138; (*b*) C. Palomo, M. Oiarbide and A. Laso, *Eur. J. Org. Chem.*, 2007, 2561–2574; (*c*) P. P. Bora and G. Bez, *Eur. J. Org. Chem.*, 2013, 2922–2929.
3 (*a*) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, 2001; (*b*) *Organic Nitro Chemistry Series*, ed. H. Feuer, Wiley-VCH, 2001, ch. 2.
4 (*a*) V. Jäger and R. Ohrlein, *Tetrahedron Lett.*, 1988, **29**, 6083–6086; (*b*) A. G. M. Barret, C. Robyr and C. D. Spilling, *J. Org. Chem.*, 1989, **54**, 1233–1234; (*c*) A. Gómez-Sánchez, R. Fernández, C. Gasch and J. E. Vílchez, *Tetrahedron Lett.*, 1991, **32**, 3225–3228.
5 D. Seebach and F. Lehr, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 505–506.
6 (*a*) G. Rosini, R. Ballini, P. Sorrenti and M. Petrini, *Synthesis*, 1984, 607–608; (*b*) J.-M. Melot, F. Texier-Boullet and A. Foucaud, *Tetrahedron Lett.*, 1986, **27**, 493–496; (*c*) Y. J. Chen and W. Y. Lin, *Tetrahedron*, 1993, **49**, 10263–10270; (*d*) T. Kolter, G. van Echten-Deckert and K. Sandhoff, *Tetrahedron*, 1994, **50**, 13425–13432; (*e*) R. Ballini, G. Bosica and P. Forconi, *Tetrahedron*, 1996, **52**, 1677–1684; (*f*) V. J. Bulbule, V. H. Deshpande, S. Velu, A. Sudalai, S. Sivasankar and V. T. Sathe, *Tetrahedron*, 1999, **55**, 9325–9332; (*g*) K. Akutu, H. Kabashima, T. Seki and H. Hattori, *Appl. Catal., A*, 2003, **247**, 65–74; (*h*) R. Ballini, D. Fiorini, M. V. Gil and A. Palmieri, *Tetrahedron*, 2004, **60**, 2799–2804.
7 (*a*) D. Crich, K. Ranganathan, S. Rumthao and M. Shirai, *J. Org. Chem.*, 2003, **68**, 2034–2037; (*b*) F. A. Luzzio, J. P. Ott and D. Y. Duveau, *J. Org. Chem.*, 2006, **71**, 5027–5030; (*c*) D. Crich, M. Shirai, F. Brebion and S. Rumthao, *Tetrahedron*, 2006, **62**, 6501–6518.
8 (*a*) J. M. Concellón, H. Rodríguez-Solla and C. Concellón, *J. Org. Chem.*, 2006, **71**, 7919–7922; (*b*) A. S. Mahasneh, *Z. Naturforsch.*, 2005, **60**, 416–418.
9 (*a*) R. G. Soengas and A. M. Estévez, *Eur. J. Org. Chem.*, 2010, 5190–5196; (*b*) H. Rodríguez-Solla, N. Alvaredo and R. G. Soengas, *Synlett*, 2012, 2083–2086; (*c*) R. G. Soengas and A. M. Estévez, *Tetrahedron Lett.*, 2012, **53**, 570–574; (*d*) R. G. Soengas and A. M. Estévez, *Synlett*, 2010, 2625–2627; (*e*) R. G. Soengas and A. M. S. Silva, *Synlett*, 2012, 873–876; (*f*) R. G. Soengas and A. M. S. Silva, *Tetrahedron*, 2013, **69**, 3425–3431.
10 (*a*) K. Wade and A. J. Banister, in *Comprehensive Inorganic Chemistry*, ed. J. C. Bailar Jr., H. J. Emeléus, R. Nyholm and A. E. Trotman-Dikenson, Pergamon, Oxford, UK, 1973, vol. 1, ch. 12, p. 1072; (*b*) I. J. Worrall and J. D. Smith, in *Organometallic Compounds of Aluminum, Gallium, Indium and Thallium*, ed. A. McKillop, J. D. Smith and I. J. Worrall, Chapman and Hall, London, UK, 1985, p. 137.
11 (*a*) Z.-L. Shen, S.-Y. Wang, Y.-K. Chok, Y.-H. Xu and T.-P. Loh, *Chem. Rev.*, 2013, **113**, 271–401; (*b*) P. Cintas, *Synlett*, 1995, 1087–1096; (*c*) C.-J. Li, *Tetrahedron*, 1996, **52**, 5643–5668; (*d*) C.-J. Li and T. H. Chan, *Tetrahedron*, 1999, **55**, 11149–11176; (*e*) K. K. Chauhan and C. G. Frost, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3015–3019; (*f*) B. C. Ranu, *Eur. J. Org. Chem.*, 2000, 2347–2356; (*g*) J. Podelech and T. C. Maier, *Synthesis*, 2003, 633–655; (*h*) V. Nair, S. Ros, C. N. Jayan and B. S. Pillai, *Tetrahedron*, 2004, **68**, 1959–1982.
12 (*a*) G. B. Deacon and J. C. Parrot, *Aust. J. Chem.*, 1971, **24**, 1771–1779; (*b*) M. J. S. Gynane, L. G. Waterworth and I. J. Worrall, *J. Organomet. Chem.*, 1972, **40**, C9–C10.
13 J. J. Eisch, *J. Am. Chem. Soc.*, 1962, **84**, 3605–3610.
14 (*a*) F. Runge, W. Zimmermann, H. Pfeiffer and I. Pfeiffer, *Z. Anorg. Allg. Chem.*, 1952, **267**, 39–48; (*b*) J. L. W. Pohlmann and F. E. Brinckmann, *Z. Naturforsch.*, 1965, **20b**, 5–11.
15 (*a*) T. Hirashita, K. Kinoshita, H. Yamamura, M. Kawai and S. Araki, *J. Chem. Soc., Perkin Trans. 1*, 2000, 825–828; (*b*) I. Perez, J. Perez Sestelo and L. A. Sarandeses, *Org. Lett.*, 1999, **1**, 1267; (*c*) H. C. Clark and A. L. Pickard, *J. Organomet. Chem.*, 1967, **8**, 427–434.
16 **General Procedure for the reaction of indium nitronates and aldehydes**. *n*-Butyllithium (1.6 M in hexane, 2.0 mL, 3.1 mmol) was added to a stirred solution of anhydrous indium trichloride (221 mg, 1.0 mmol) and nitroalkane **1** (3.0 mmol) in THF (4 mL) at −78 °C. The mixture was stirred for 10 min, after which time aldehyde **2** (2.0 mmol) was added. The reaction mixture was warmed to room

temperature and left overnight. The reaction was quenched with 1 M HCl (10 mL), and the product was extracted with diethyl ether (3 × 20 mL). The organic extracts were washed with water and brine, and concentrated. The residue was purified by flash column chromatography in mixtures of ethyl acetate–hexane when necessary to obtain pure nitroalkanols **3**. The products **3a**,[9a] **3b**,[9a] **3c**,[9e] **3d**,[8a] **3e**,[9a] **3f**,[2c] **3g**,[9a] **3i**,[9a] **3k**,[9d] **3l**,[9c] **3m**[9c] and **3n**[18] are known compounds. **2-(1-Nitrocyclopentyl)octan-1-ol (3j):** clear oil. ^{1}H NMR ($CDCl_3$, ppm): 0.81 (t, J = 6.9 Hz, 3 H, –CH_3), 1.16–1.20 (m, 12 H), 1.62–1.76 (m, 5 H), 2.02–2.12 (m, 1 H), 2.24–2.38 (m, 1 H), 2.46–2.58 (m, 1 H), 3.75 (d, 1 H, J = 10.3 Hz, H-1). ^{13}C NMR ($CDCl_3$, ppm): 14.1 (CH_3), 22.6, 24.6, 24.8, 26.3, 29.2, 31.8, 32.5, 33.7, 35.6 (10 × CH_2), 75.9 (CH), 103.6 (C). MS (ESI^+) m/z (%) 244 ($[M + H]^+$, 40); HRMS (ESI^+) calc. for $[C_{13}H_{26}NO_3]^+$ $[M + H]^+$ 244.1907, found: 244.1925.

17 J. M. Rodríguez and M. D. Pujol, *Tetrahedron Lett.*, 2011, **52**, 2629–2632.
18 T. Nitabaru, A. Nojiri, M. Kobayashi, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 13860–13869.
19 B. Lecea, A. Arrieta, I. Morao and F. P. Cossio, *Chem. – Eur. J.*, 1997, **3**, 20–28.
20 D. B. Ramachary and R. Sakthidevi, *Org. Biomol. Chem.*, 2010, **8**, 4259–4265.

21 The products **3o**[9a] and **3p**[9a] are known compounds. **3-*O*-Benzyl-1,2-*O*-isopropylidene-5-(1-nitrocyclopentanyl)-α-D-xylofuranose (3q):** clear oil. ^{1}H-NMR ($CDCl_3$, ppm): 1.23 (s, 3 H, CH_3, *anti*), 1.26 (s, 3 H, CH_3, *syn*), 1.38 (s, 3 H, CH_3, *anti*), 1.40 (s, 3 H, CH_3, *syn*), 1.54–1.67 (m, 8 H, *syn* + *anti*), 1.85–1.96 (m, 2 H, *syn* + *anti*), 2.10–2.20 (m, 2 H, *syn* + *anti*), 2.35–2.42 (m, 2 H, *syn* + *anti*), 2.54–2.62 (m, 2 H, *syn* + *anti*), 3.96–4.50 (m, 4 H, *syn* + *anti*), 4.25–4.28 (m, 2 H, *syn* + *anti*), 4.36–4.66 (m, 6 H, *syn* + *anti*), 5.84 (d, J = 3.8 Hz, 1 H, H-1, *anti*), 5.90 (d, J = 3.8 Hz, 1 H, H-1, *syn*), 7.16–7.32 (m, 10 H, Ar–H, *syn* + *anti*). ^{13}C NMR ($CDCl_3$, ppm) major isomer: 23.8, 24.5 (2 × CH_2), 26.4, 26.8 (2 × CH_3), 33.4, 35.9 (2 × CH_2), 72.2 (CH_2), 72.8, 79.6, 81.4, 82.6 (4 × CH), 102.6 (C), 105.3 (CH), 112.0 (C), 128.0 (2 × CH), 128.4 (CH), 128.8 (2 × CH), 136.9 (C). MS (ESI^+) m/z (%) 394 ($[M + H]^+$, 19); HRMS (ESI^+) calc. for $[C_{20}H_{28}NO_7]^+$ $[M + H]^+$ 394, 1860, found: 394, 1852. **3-*O*-Benzyl-1,2-*O*-isopropylidene-5-(1-nitroethyl)-α-D-xylofuranose (3r):** clear oil. ^{1}H-NMR ($CDCl_3$, ppm): 1.24 (s, 6 H, 2 × CH_3, *syn* + *anti*), 1.38 (s, 6 H, 2 × CH_3, *syn* + *anti*), 1.48 (d, J = 6.8 Hz, 3 H, CH_3, *anti*), 1.55 (d, J = 6.8 Hz, 3 H, CH_3, *syn*), 3.88–3.94 (m, 2 H, *syn* + *anti*), 4.02–4.07 (m, 2 H, *syn* + *anti*), 4.37–4.72 (m, 6 H, *syn* + *anti*), 5.82 (d, J = 3.7 Hz, 1 H, H-1, *anti*), 5.91 (d, J = 3.7 Hz, 1 H, H-1, *syn*), 7.18–7.32 (m, 10 H, Ar–H, *syn* + *anti*). ^{13}C NMR ($CDCl_3$, ppm) major isomer *anti*: 11.4, 26.3, 26.9 (3 × CH_3), 65.8 (CH), 72.3 (CH_2), 68.5, 79.1, 80.9, 82.1, 83.8, 105.2 (6 × CH), 112.0 (C), 128.0 (2 × CH), 128.4 (CH), 128.8 (2 × CH), 137.1 (C). MS (ESI^+) m/z (%) 354 ($[M + H]^+$, 22); HRMS (ESI^+) calc. for $[C_{17}H_{24}NO_7]^+$ $[M + H]^+$ 354, 1547, found: 354, 1552.