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One-Pot Diastereoselective Synthesis of 2-Acyl-4-nitrocyclohexanol Derivatives in Aqueous Medium

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Dedicated to Prof. Goffredo Rosini on the occasion of his 60th birthday

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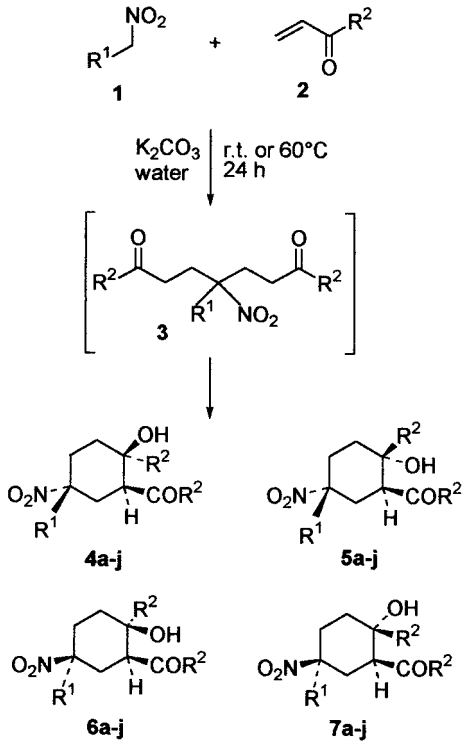
Abstract—The reaction of primary nitroalkanes with conjugated enones, in water and in the presence of K_2CO_3 as base, allows the synthesis of 2-acyl-4-nitrocyclohexanol derivatives in which the diastereoisomer (±)-(1*S**,2*R**,5*R*) is highly predominant. The reaction proceeds by double Michael addition of the nitroalkane to the enone, followed by intramolecular aldol reaction.

Introduction

2-Acyl-4-nitrocyclohexanol derivatives are an interesting class of polyfunctionalized molecules bearing three stereogenic centers. These compounds have already been obtained by Michael addition of nitroalkanes with 2 equiv. of α,β-unsaturated carbonyl compounds, followed by intramolecular aldol reaction of the formed adduct.[123] However, the first two methods reported[1,2] were performed under basic conditions, in an organic solvent, apparently without any diastereoselectivity. Later, ruthenium dihydride, in acetonitrile, was employed for this reaction and a 2:1:1:1 mixture of diastereoisomers was obtained,[3] although the assignment of the relative stereochemistry was not described.

In recent years there has been increasing recognition that organic reactions carried out in aqueous media offer advantages over those occurring in organic solvents. In fact, the aqueous medium is less expensive, less dangerous, environment-friendly and allows a precise control of the pH. In addition, the reactivity and selectivity of the reaction can be dramatically influenced when carried out in water.[4]

Recently we discovered that nitroalkanes exhibit a remarkable reactivity in water,[5] in particular in the formation of C–C bonds via their conjugate addition to electron deficient alkenes.[5a,c] Following these previous results, now we have found that the reaction in water (Scheme 1) of a primary nitroalkane **1** with two equivalents of α,β-unsaturated ketones **2**, in the presence of potassium carbonate as base, provides after 24 h at the appropriate temperature (see Table 1), the 'one-pot' formation of the nitrocyclohexanol derivatives **4**–**7** in excellent chemical and stereochemical yields (Table 1).



Scheme 1. Diastereoselective synthesis of 2-acyl-4-nitrocyclohexanol derivatives **4**–**7**.

Keywords: diastereoselection; nitro compounds; cyclisation; reaction in water.

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Table 1. Synthesis of nitrocyclohexanol derivatives **4**–**7**

	R^1	R^2	Overall yield (%) of **4**–**7**	Ratio of diastereomeric mixture, determined by GC[a]
a	Me	Me	90[b]	5.4:1:1
b	Et	Me	85[b]	12.8:3:1
c	*n*-Pr	Me	93[b]	9:2.2:1
d	*n*-Bu	Me	95[c]	12:5.2:1
e	*n*-C_5H_{11}	Me	95[c]	9:2:1
e	*i*-Pr	Me	75[c]	17:1
g	Ph	Me	70[c]	16.5:1:1
h	Me	Et	77[c]	18.5:4:2:1
i	Et	Et	75[c]	27:5:2:1
j	Me	*n*-Pr	80[c]	17:3.5:1.5:1

[a] The first number refers to the diastereomer **4**.
[b] Reaction performed at room temperature.
[c] Reaction performed at 60°C.

Results and Discussion

The first step of the reaction is the double Michael addition of the nitroalkane to the enone, followed by, in situ, intramolecular aldol reaction of the adduct **3**. The cyclohexanols **4**– **7** are obtained in 70–95% yield and the diastereomer **4** is largely predominant (Table 1). As a model reaction, we take the reaction of nitroethane with methyl vinyl ketone (R^1 and R^2=Me), the GC–MS analysis of the crude mixture showed that all the four diastereoisomers are formed, but one of them (**7a**) is present in a very small amount.

The chromatographic purification gave **4a** and a mixture of **5a** and **6a** which were separated by fractional crystallization (EtOAc–hexane), while **7a** could not be isolated. The three diastereoisomers isolated were in a 5:1.5:1 ratio, very similar to that obtained by GC, showing a significant improvement of the diastereoselectivity of the reaction in water with respect to the previously reported methods. The structures of the three isolated diastereomers, which had hitherto not been assigned, were elucidated on the basis of their NMR spectra.

The COSY spectrum of compound **4a**, the major stereoisomer, showed two isolated spin systems: H-1/H-6 and H-3/H-4 respectively.[6]

The relative position of the two geminal H-6 protons were determined on the basis of their coupling to H-1; the signal at 2.52 ppm, which shows an axial–equatorial coupling constant (3.1 Hz) to H-1, was attributed to equatorial H-6, whereas the signal at 1.91 ppm shows a *trans* diaxial coupling constant (13.2 Hz) and was attributed to axial H-6. The coupling of hydroxyl proton signal (3.86 ppm, J=3.0 Hz) to axial H-3 is due to their sterically fixed '**W**' arrangement[7] (see bold bonds in Fig. 1) that is made possible by the hydrogen bond between the hydroxyl and the acetyl groups. As previously reported,[3] it reveals that the hydroxyl and the acetyl group are *cis* and the assignation of other coupled protons becomes quite easy. The relative stereochemistry of C-1 and C-2 substituents was confirmed by the ROESY spectrum, which revealed the spatial proximity between C-2 methyl and H-1, and between C-2 hydroxyl proton and equatorial H-3. Moreover, the C-5 methyl showed NOE correlation with axial H-6 and axial H-4, confirming its β orientation.

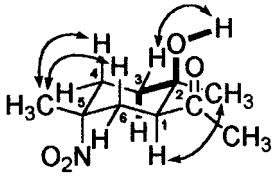

Figure 1. NOE correlations of **4a**.

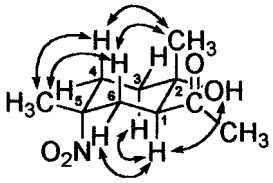

Figure 2. NOE correlations of **5a**.

Analogous considerations permitted the proton signal assignment of compounds **5a** (COSY spectrum) and **6a** (selective decoupling). In both compounds the coupling constants of the H-1 signal (**5a**: J=13.1 and 3.5 Hz. **6a**: J=13.4 and 3.2 Hz) indicate its axial orientation.

The ROESY spectrum of compound **5a** revealed the β orientation of C-2 and C-5 methyls, both showing noe correlation with axial H-6 and axial H-4.

Moreover, irradiation of H-1 enhanced the intensity of the OH, equatorial H-6 and axial H-3 signals, confirming the relative stereochemistry of C-1 and C-2 (Fig. 2).

The ^{1}H NMR spectrum of compound **6a** showed a coupling between OH and axial H-3, revealing the *cis* stereochemistry of the C-2 hydroxyl and acetyl group, which was confirmed by the noe correlation of the C-2 methyl to H-1 and axial H-3 (Fig. 3).

Finally, irradiation of the C-5 methyl enhanced the H-1, equatorial H-6, equatorial H-4 and axial H-3 signals, revealing its α orientation.

It is worth noting that the structure of the major diastereomer is in agreement with the substituent conformational energies,[8] the methyl group having the larger conformational energy value.

The reaction was then extended to different primary nitroalkanes and alkyl vinyl ketones and in each final product the diastereomer **4**, which can be easily obtained by chromatographic purification, is highly predominant

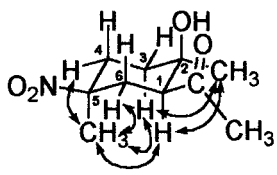

Figure 3. NOE correlations of **6a**.

(Table 1). Since in the ^{1}H NMR spectra of compounds **4b–j** the OH proton is a doublet ($J\sim$2.5–3.0 Hz), we assumed that in each case the OH and the acyl group are *cis*.[3] Moreover, as the C-5 alkyl substituents in the compounds **4b–j** have a greater conformational energy than the methyl group, they were assumed to be equatorial and, as a consequence, the compounds **4b–j** were considered to have the same relative stereochemistry as **4a**. It is worth noting that in the examples reported the diastereoselectivity is much higher if compared to the previously reported synthesis.[3]

Conclusions

In conclusion, we have found that our procedure for the preparation of nitro-substituted cyclohexanol derivatives can be carried out in water and, in addition to the obvious economical and ecological advantages, proceeds with higher diastereoselectivity with respect to the reported methods.

Experimental

All ^{1}H NMR spectra were collected on a 300 MHz NMR spectrometer in $CDCl_3$ or DMSO-d_6. ^{13}C NMR were recorded at 75.4 or 50 MHz with $CDCl_3$ or DMSO-d_6 as reference. All mass spectra were determined on a HP5890 Series II capillary GC operating in split mode with helium carrier gas and fitted with a mass selective detector (MDS). The column used was a HP5 capillary column 30 m×0.25 mm, with 0.25 μm film thickness of 5% phenylmethylsilicone gum. The temperature of 65°C was maintained for 3 min and then ramped at 15°C min^{-1} to 300°C. The products were purified by flash chromatography on Merck silica gel (0.040–0.063 mm). The enones **2** were commercially available; the nitroalkanes **1** (R^1=Me, Et, *n*-Pr, *n*-Bu, *n*-C_5H_{11}) were commercially available or prepared[9,10] (R^1=*i*-Pr, Ph) by standard procedures.

General procedure for the preparation of nitrocyclohexanol derivatives (4–7)

Nitroalkane **1** (2 mmol) and K_2CO_3 (0.138 g, 1 mmol) were dissolved in water (10 ml). The solution was cooled with an ice bath, then conjugated enone **2** (0.42 g, 5 mmol) was added. After stirring at the appropriate temperature (room temperature or 60°C, Table 1) for 24 h, the aqueous medium was extracted with Et_2O (3×15 ml). The organic phase was dried ($MgSO_4$), and the crude product **4–7** was purified by flash chromatography and/or by crystallization (see text).

(±)-1-[(1*S,2*R**,5*R**)-2-Hydroxy-2,5-dimethyl-5-nitrocyclohexyl]-1-ethanone (4a).** White solid (EtOAc–hexane); mp 108–110°C; IR (nujol) ν_{max} 3560, 1700, 1520, 1370, 860 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.22 (dddd, *J*=14.5, 13.8, 4.0, 3.0 Hz, 1H), 1.55 (s, 3H), 1.63 (ddd, *J*=14.5, 4.3, 2.7 Hz, 1H), 1.91 (dd, *J*=14.2, 13.2 Hz, 1H), 2.00 (ddd, *J*=14.6, 13.8, 4.3 Hz, 1H), 2.25 (s, 3H), 2.39 (ddd, *J*=14.7, 4.0, 2.7 Hz, 1H), 2.52 (dt, *J*=14.2, 3.2 Hz, 1H), 2.61 (dd, *J*=13.2, 3.2 Hz, 1H), 3.86 (d, *J*=3.0 Hz, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 28.16, 28.45, 29.91, 29.94, 32.48, 36.00, 55.32, 67.22, 88.11, 210.41; ^{13}C NMR (50 MHz, $CDCl_3$)(δ 28.86, 29.31, 31.09, 31.85, 34.05, 35.28, 53.18, 68.99, 88.48, 215.04; MS (EI) *m/z* 200 $[M-CH_3]^+$, 168 $[M-HNO_2]^+$, 153 $[M-HNO_2-CH_3]^+$, 111, 109, 107, 93, 71, 67, 55, 43 (100). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.69; H, 7.88; N, 6.62.

(±)-1-[(1*S,2*S**,5*R**)-2-Hydroxy-2,5-dimethyl-5-nitrocyclohexyl]-1-ethanone (5a).** White crystals (EtOAc–hexane); mp 127–129°C; IR (nujol) ν_{max} 3565, 1710, 1520, 1365, 850 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96 (s, 3H), 1.42 (ddd, *J*=13.8, 13.5, 3.6 Hz, 1H), 1.52 (s, 3H), 1.56 (ddd, *J*=13.5, 4.1, 3.3 Hz, 1H), 1.70 (ddd, *J*=14.6, 13.8, 4.1 Hz, 1H), 1.86 (dd, *J*=15.5, 13.1 Hz, 1H), 2.20 (s, 3H), 2.24 (dt, *J*=15.5, 3.5 Hz, 1H), 2.38 (ddd, *J*=14.6, 3.6, 3.3 Hz, 1H), 2.66 (dd, *J*=13.1, 3.5 Hz, 1H), 4.90 (s, 1H, OH); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ(21.24, 28.30, 32.47, 33.13, 34.00, 38.61, 55.42, 70.12, 88.55, 211.20; MS (EI) *m/z* 200 $[M-CH_3]^+$, 168 $[M-HNO_2]^+$, 153 $[M-HNO_2-CH_3]^+$, 111, 109, 107, 93, 71, 67, 55, 43 (100). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.69; H, 7.88; N, 6.62.

(±)-1-[(1*S,2*R**,5*S**)-2-Hydroxy-2,5-dimethyl-5-nitrocyclohexyl]-1-ethanone (6a).** White crystals (EtOAc–hexane); mp 112–114°C; IR (nujol) ν_{max} 3570, 1710, 1530, 1375, 855 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.38 (dddd, *J*=14.4, 13.3, 4.1, 2.5 Hz, 1H), 1.64 (s, 3H), 1.79 (ddd, *J*=14.4, 4.4, 3.1 Hz, 1H), 1.89 (m, 1H), 2.03 (dt, *J*=12.6, 2.8 Hz, 1H), 2.24 (s, 3H), 2.42 (dd, *J*=13.4, 12.6 Hz, 1H), 2.45 (ddd, *J*=13.5, 13.3, 4.4 Hz, 1H), 2.58 (dd, *J*=13.4, 3.2 Hz, 1H), 3.82 (d, *J*=2.5 Hz, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 22.97, 28.65, 31.10, 31.56, 34.13, 36.06, 54.03, 69.06, 87.33, 213.69; MS (EI) *m/z* 200 $[M-CH_3]^+$, 168 $[M-HNO_2]^+$, 153 $[M-HNO_2-CH_3]^+$, 111, 109, 107, 93, 71, 67, 55, 43 (100). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.69; H, 7.88; N, 6.62.

(±)-1-[(1*S,2*R**,5*R**)-5-Ethyl-2-hydroxy-2-methyl-5-nitrocyclohexyl]-1-ethanone (4b).** White solid (EtOAc–hexane); mp 87–89°C; IR (nujol) ν_{max} 3550, 1720, 1560, 1365, 860 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.5 Hz, 3H), 1.15 (s, 3H), 1.23 (m, 1H), 1.64 (ddd, *J*=14.5, 4.2, 2.8 Hz, 1H), 1.75–2.05 (m, 4H), 2.26 (s, 3H), 2.38 (m,1H), 2.51 (dt, *J*=14.1, 3.0 Hz, 1H), 2.60 (dd, *J*=13.0, 3.4 Hz, 1H), 3.85 (d, *J*=2.7 Hz, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 7.78, 28.41, 28.86, 31.42, 31.68, 34.72, 34.90, 52.60, 68.81, 91.60, 214.70; MS (EI) *m/z* 214 $[M-CH_3]^+$, 182 $[M-HNO_2]^+$, 167 $[M-HNO_2-CH_3]^+$, 139, 123, 109, 93, 71, 55, 43 (100); Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.70; H, 8.48; N, 5.98.

(±)-1-[(1*S,2*R**,5*R**)-2-Hydroxy-2-methyl-5-nitro-5-propylcyclohexyl]-1-ethanone (4c).** White solid (EtOAc–hexane); mp 98–100°C; IR (nujol) ν_{max} 3650, 1690, 1535, 1375, 855 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.3 Hz, 3H), 1.15 (s, 3H), 1.26 (m, 3H), 1.63 (ddd, *J*=14.6, 4.3, 2.8 Hz, 1H), 1.77 (m, 2H), 1.88 (dd, *J*=14.1, 13.0 Hz, 1H), 1.99 (ddd, *J*=14.6, 13.8, 4.3 Hz, 1H), 2.25 (s, 3H), 2.38 (m,1H), 2.52 (dt, *J*=14.1, 3.0 Hz, 1H), 2.59 (dd,

J=13.0, 3.2 Hz, 1H), 3.85 (d, J=2.6 Hz, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.23, 17.07, 28.81, 29.63, 31.76, 32.42, 35.18, 44.38, 53.03, 69.17, 91.65, 214.95; MS (EI) m/z 228 $[M-CH_3]^+$, 196 $[M-HNO_2]^+$, 181 $[M-CH_3-HNO_2]^+$, 153, 137, 109, 93, 71, 55, 43 (100); Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.15; H, 8.80; N, 5.80.

(±)-1-[(1*S,2*R**,5*R**)-5-Butyl-2-hydroxy-2-methyl-5-nitrocyclohexyl]-1-ethanone (4d).** White solid (EtOAc–hexane); mp 66–68°C; IR (nujol) ν_{max} 3510, 1690, 1545, 1370, 855 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J=6.9 Hz, 3H), 1.15 (s, 3H), 1.23 (m, 5H), 1.63 (ddd, J=14.7, 4.2, 2.7 Hz, 1H), 1.77 (m, 2H), 1.88 (dd, J=14.0, 13.1 Hz, 1H), 2.00 (ddd, J=14.6, 13.8, 4.3 Hz, 1H), 2.25 (s, 3H), 2.38 (m,1H), 2.52 (dt, J=14.1, 3.0 Hz, 1H), 2.60 (dd, J=13.0, 3.3 Hz, 1H), 3.85 (d, J=2.7 Hz, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 13.74, 22.44, 25.34, 28.42, 29.28, 31.42, 32.02, 34.73, 41.64, 52.62, 68.81, 91.30, 214.73; MS (EI) *m/z* 195 $[M-CH_3-HNO_2]^+$, 151, 135, 125, 109, 93, 71, 55, 43 (100); Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.76; H, 8.92; N, 5.57.

(±)-1-[(1*S,2*R**,5*R**)-2-Hydroxy-2-methyl-5-nitro-5-pentylcyclohexyl]-1-ethanone (4e).** Yellow oil; IR (nujol) ν_{max} 3500, 1700, 1540, 1380, 844 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J=6.9 Hz, 3H), 1.15 (s, 3H), 1.24 (m, 7H), 1.64 (ddd, J=14.6, 4.3, 2.8 Hz, 1H), 1.78 (m, 2H), 1.88 (dd, J=13.9, 13.0 Hz, 1H), 2.00 (ddd, J=14.6, 13.7, 4.3 Hz, 1H), 2.26 (s, 3H), 2.38 (m,1H), 2.52 (dt, J=14.1, 3.0 Hz, 1H), 2.60 (dd, J=12.9, 3.3 Hz, 1H), 3.86 (d, J=2.6 Hz, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ(13.87, 22.29 (x2), 22.88, 28.41, 29.27, 31.42, 32.00, 34.72, 41.86, 52.60, 68.79, 91.30, 214.74; MS (EI) *m/z* 256 $[M-CH_3]^+$, 124 $[M-HNO_2]^+$, 209 $[M-CH_3-HNO_2]^+$, 165, 149, 123, 109, 95, 71, 55, 43 (100); Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 62.10; H, 9.22; N, 5.11.

(±)-1-[(1*S,2*R**,5*R**)-2-Hydroxy-5-isopropyl-2-methyl-5-nitrocyclohexyl]-1-ethanone (4f).** White solid (EtOAc–hexane); mp 72–74°C; IR (nujol) ν_{max} 3500, 1695, 1540, 1375, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91(d, J=2.5 Hz, 3H), 0.94(d, J=2.6 Hz, 3H), 1.14 (s, 3H), 1.21 (m, 1H), 1.65 (ddd, J=14.6, 4.3, 2.9 Hz, 1H), 1.92 (dd, J=14.0, 13.0 Hz, 1H), 2.07 (m, 2H), 2.25 (s, 3H), 2.29 (m, 1H), 2.41 (dt, J=14.0, 3.0 Hz, 1H), 2.56 (dd, J=13.0, 3.2 Hz, 1H), 3.84 (d, J=2.6 Hz, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ(17.28, 17.37, 26.22, 28.39, 29.16, 31.47, 34.83, 37.57, 52.64, 68.69, 95.21, 214.91;(MS (EI) *m/z* 228 $[M-CH_3]^+$, 196 $[M-HNO_2]^+$, 181 $[M-(HNO_2+CH_3)]^+$, 159, 137, 121, 109, 95, 81, 71, 55, 43 (100); Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.20; H, 8.77; N, 5.86.

(±)-1-[(1*S,2*R**,5*R**)-2-Hydroxy-2-methyl-5-nitro-5-phenylcyclohexyl]-1-ethanone (4g).** White solid (EtOAc–hexane); mp 119–121°C; IR (nujol) ν_{max} 3505, 1690, 1545, 1385, 850 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.36 (m, 1H), 1.80 (ddd, J=14.6, 4.2, 2.9 Hz, 1H), 2.28 (dd, J=14.1, 13.0 Hz, 1H), 2.30 (s, 3H), 2.47 (ddd, J=14.6, 13.5, 4.2 Hz, 1H), 2.73 (dd, J=13.0, 3.1 Hz, 1H), 2.83 (ddd, J=14.6, 6.3, 3.2 Hz, 1H), 2.95 (dt, J=14.1, 3.1 Hz, 1H), 3.92 (d, J=2.7 Hz, 1H, OH), 7.38 (m,5H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 28.34, 29.75, 31.45, 33.43, 35.21, 53.09, 68.36, 92.94, 124.73 (×2), 128.97, 129.26 (×2), 139.07, 214.28; MS (EI) *m/z* 231 $[M-HNO_2]^+$, 213 $[M-(H_2O+HNO_2)]^+$, 169, 155, 129, 115, 105, 91, 77, 55, 43 (100); Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.90; H, 6.95; N, 5.11.

(±)-1-[(1*S,2*R**,5*R**)-2-Ethyl-2-hydroxy-5-methyl-5-nitrocyclohexyl]-1-propanone (4h).** Yellow oil; IR (nujol) ν_{max} 3505, 1690, 1540, 1375, 845 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, J=7.5 Hz, 3H), 1.05 (t, J=7.2 Hz, 3H), 1.17 (m,1H), 1.30 (dd, J=13.9, 7.5 Hz, 1H), 1.45 (dd, J=13.9, 7.6 Hz, 1H), 1.54 (s, 3H), 1.66 (ddd, J=14.4, 4.1, 2.8 Hz, 1H), 1.96 (dd, J=14.1, 13.0 Hz 1H), 2.00 (ddd, J=14.6, 13.5, 4.1 Hz 1H); 2.34–2.56 (m,5H), 3.82 (d, J=2.7 Hz, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$, DEPT) δ(7.71q, 8.23q, 29.28q, 30.86t, 31.01t, 34.19t, 34.45t, 38.15t, 51.05d, 71.58s, 88.48s, 218.06s; MS (EI) *m/z* 214 $[M-C_2H_5]^+$, 197 $[M-HNO_2]^+$, 167 $[M-(C_2H_5+HNO_2)]^+$, 149, 139, 121, 111, 93, 81, 69, 57 (100), 43; Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.05; H, 8.75; N, 5.85.

(±)-1-[(1*S,2*R**,5*R**)-2,5-Diethyl-2-hydroxy-5-nitrocyclohexyl]-1-propanone (4i).** Yellow oil; IR (nujol) ν_{max} 3495, 1700, 1540, 1375, 845 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, J=7.5 Hz, 3H), 0.86 (t, J=7.5 Hz, 3H), 1.05 (t, J=7.3 Hz, 3H),1.13 (m, 1H), 1.32 (m, 1H), 1.43 (m, 1H), 1.67 (m, 1H), 1.88 (m, 4H), 2.43 (m, 3H), 2.65 (m, 2H), 3.81 (d, J=2.7 Hz, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$, DEPT) δ(7.23q, 7.71q, 7.77q, 28.63t, 30.46t, 32.08t, 33.77t, 34.89t, 37.72t, 50.47d, 71.43s, 89.44s, 217.75s; MS (EI) *m/z* 228 $[M-C_2H_5]^+$, 210 $[M-HNO_2]^+$, 181 $[M-(C_2H_5+HNO_2)]^+$, 163, 135, 121, 107, 95, 79, 67, 57 (100), 43; Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.60; H, 8.95; N, 5.58.

(±)-1-[(1*S,2*R**,5*R**)-2-Hydroxy-5-methyl-5-nitro-2-propylcyclohexyl]-1-butanone (4j).** White solid (EtOAc–hexane); mp 50–52°C; IR (nujol) ν_{max} 3505, 1695, 1545, 1370, 850 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J=6.9 Hz, 3H), 0.92 (t, J=7.5 Hz, 3H), 1.10–1.40 (m, 4H), 1.54 (s, 3H), 1.59 (q, J=7.3 Hz, 2H), 1.66 (ddd, J=14.4, 4.3, 2.7 Hz 1H), 1.94 (dd, J=14.3, 13.4 Hz 1H), 1.99 (ddd, J=14.5, 13.7, 4.3 Hz 1H), 2.42 (m, 3H); 2.54 (t, J=7.5 Hz, 1H), 2.60 (t, J=7.4 Hz, 1H), 2.63 (dd, J=13.0, 3.2 Hz 1H), 3.86 (d, J=2.5 Hz, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$, DEPT) δ(13.60q, 14.55q, 16.54t, 16.71t, 28.83q, 30.44t, 31.21t, 33.80t, 43.65t, 46.30t, 50.99d, 71.01s, 88.02s, 217.186s; MS (EI) *m/z* 228 $[M-C_3H_7]^+$, 224 $[M-HNO_2]^+$, 206 $[M-(H_2O+HNO_2)]^+$, 181 $[M-(C_3H_7+HNO_2)]^+$, 163, 137, 110, 93, 71 (100), 55, 43; Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 62.05; H, 9.32; N, 5.02.

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