Direct Synthesis of Keto Nitroaliphatics via Retro-Henry Reaction of Cyclic 2-Nitroalcohols by Anhydrous Copper Sulfate Adsorbed on Silica Gel. A Short Synthesis of (±)-Phoracantholide I

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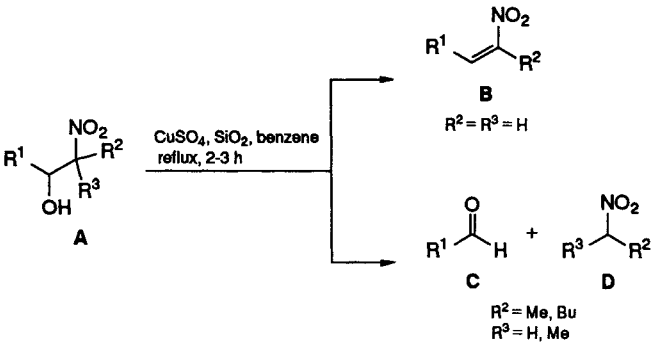
Dedicated to Prof. R.R. Schmidt on the occasion of his 60th birthday

It has been observed that anhydrous $CuSO_4$ adsorbed on silica gel effects the C–C bond cleavage between the hydroxy group and the nitro group of 2-nitroalcohols. In the case of 2-nitrocyclohexanols, the products are $RCO(CH_2)_4CH_2NO_2$ where R is alkyl, aryl, etc. This strategy has been applied for a short synthesis of (±)-phoracantholide I.

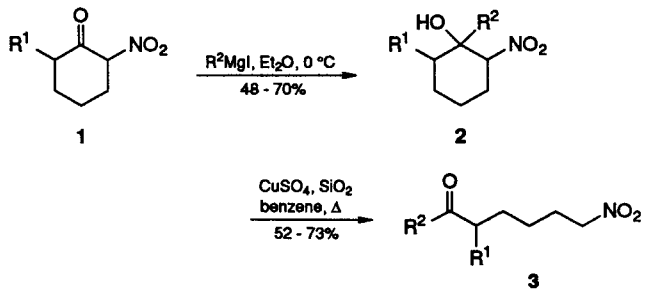
Aliphatic nitro compounds have emerged, in recent years, as versatile intermediates and building blocks in organic synthesis.[1] In particular, nitroalkenes readily undergo addition reactions with a variety of nucleophiles;[2] they are powerful dienophiles and undergo Diels–Alder reactions and the vinyl nitro group can be converted into a variety of functional groups. Reagents adsorbed on solid supports are becoming increasingly more popular in comparison with homogenous reagents among organic chemists. This is due to the fact that solid supported reagents are often milder, operationally simpler and are selective.[3–6] Anhydrous copper sulfate is known to dehydrate alcohols[7] under rather drastic conditions,[6,8] but the same dehydration process proceeds rapidly, selectively and under mild conditions when anhydrous copper sulfate is adsorbed on silica gel.[5]

In continuation of our interest in nitroaliphatic compounds,[9,10] we needed a high-yielding simple method for synthesis of nitroalkenes which are normally prepared by dehydration of 2-nitroalcohols **A**.[11] During our studies, we found that when anhydrous $CuSO_4$ adsorbed on silica gel is used as the dehydrating agent, the products were not the nitroalkenes **B** but carbonyl compounds **C** and nitroaliphatics **D**, produced as a result of a retro-Henry reaction (Scheme 1). Subsequently, while exploring the utility of this cleavage reaction, we found that when 1-alkyl-2-nitrocyclohexanols **2**, prepared by reacting 2-nitrocyclohexanones **1** with two equivalents of Grignard reagents,[12] are treated with anhydrous $CuSO_4$/SiO_2 in anhydrous benzene or toluene under reflux, ω-ketonitroaliphatics **3** were obtained in good yields (52–73%). This type of nitroalkane with a carbonyl group in a remote position is normally synthesised by a multistep process.[13] This novel ring-cleavage reaction has been generalised and is presented in Scheme 2. The same cleavage reaction has also been observed with other cyclic nitroalcohols such as 1-methyl-2-nitrocyclododecanol **(2m)** (Experimental). In the case of open chain nitroalcohols where the nitro group is in the primary position, the products are the nitroalkenes and with nitroalcohols having the nitro group in the tertiary position, the retro-Henry products are formed (Scheme 1). The cyclic nitroalcohols were prepared by reacting two equivalents of the corresponding Grignard reagents with 2-nitrocyclohexanones **1** and 2-nitrocyclododecanone.



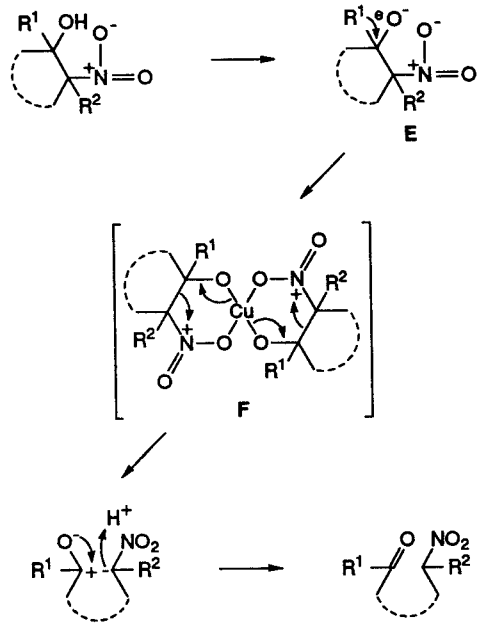
Scheme 1

As for the mechanism of this reaction, no definite statement can be made at present. Initially we thought that such a retro-Henry reaction might take place when cyclic nitroalcohols are treated with a catalytic amount of base like KF or Et_3N in a protic solvent like isopropanol; however, to our surprise we found that when **2a** was refluxed with KF or Et_3N in isopropanol for 5 hours, only isomerization from *trans*-nitroalcohol **2a** to its *cis* isomer[12] was observed and there was no retro-Henry reaction. A pathway via alkoxy radical is also eliminated due to the fact that less than the stoichiometric amount of the reagent is not enough for the cleavage. Another possibility may be the fact that the C–C bond between the carbons carrying the hydroxy and the nitro group is under high strain in the case of cyclic 2-nitroalcohols and the cleavage is favoured just to release the strain. But this fails to explain the cleavage in the case of open chain 2-nitroalcohols (Scheme 1). Considering these points, we anticipate a pathway analogous to the one proposed by Ballini et al.[14] The cleavage most probably proceeds via a d^9-tetracoordinated square planar copper complex. The copper environment in anhydrous $CuSO_4$ is coordinatively unsaturated; on the other hand, an electron-rich substituent 'R' may facilitate to give a species **E** and H^+ ions and both these species will favour formation of a labile d^9-tetracoordinated square planar copper complex of type **F** which satisfies $16e^-$ electron count. On heating, the complex breaks down and ring opens in a concerted manner (Scheme 3). This argument is supported by the fact that the pH of the reaction mixture changes from 4.02 to 3.74 immediately after addition of 2-nitroalkanols, and after refluxing for 15 minutes changes to 5.20. The instability of the complex may be due to the fact that copper is linked to silicon by electrostatic forces and therefore attempts to isolate the complex were not successful.



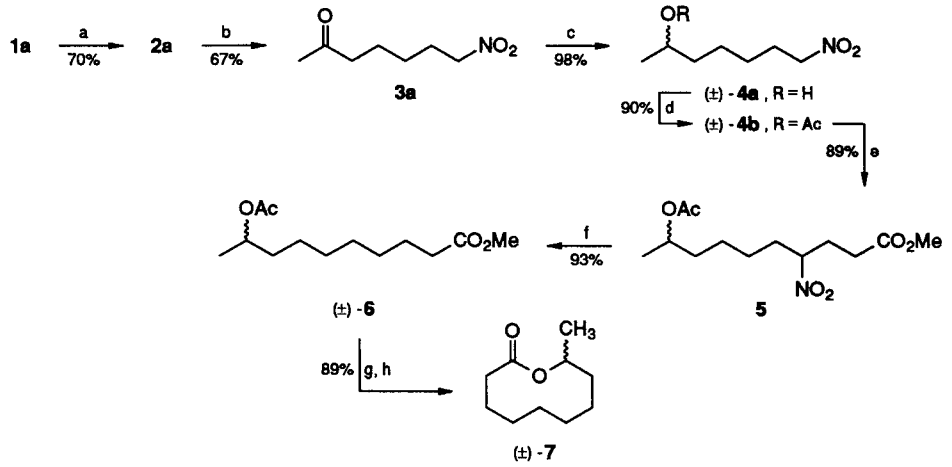
2, 3	R^1	R^2
a	H	Me
b	Me	Me
c	H	Et
d	Me	Et
e	H	Bu
f	Me	Bu
g	H	Ph
h	Me	Ph
i	H	C_5H_9
j	Me	C_5H_9
k	H	*i*-Pr
l	Me	*i*-Pr

Scheme 2



Scheme 3

The utility of this cleavage of 2-nitroalcohols has been demonstrated by achieving a short synthesis of (±)-phoracantholide I [(±)-decen-9-olide] (Scheme 4) the metabolite isolated by Moore et al.[15] from the metasternal gland of the eucalypt longicorn *Phoracantha synonyma*. The synthesis of phoracantholide I has been achieved previously.[16] Treatment of 2-nitrocyclohexanone **(1a)** with 2 equivalents of freshly prepared methylmagnesium iodide gave crystalline 1-methyl-2-nitrocyclohexanol **(2a)**, mp 66 °C in 70% yield which on treatment with anhydrous copper sulfate adsorbed on silica gel as in the general procedure gave 7-nitroheptan-2-one **(3a)** in 67% yield as a gum. Treatment of **3a** with sodium borohydride in methanol gave (±)-**4a** as a gum in 98% yield. The acetate (±)-**4b** on treatment with methyl acrylate in the presence of Amberlyst A-21 resin without any solvent gave the Michael adduct **5** as a gum. Treatment of the nitroester **5** with tributyltin hydride and AIBN[17] in anhydrous benzene under reflux gave the denitrated product **6** which on hydrolysis with 40% NaOH in MeOH and subsequent acidification with dilute HCl to pH 1 gave (±)-phoracantholide I, (±)-**7** in 89% yield.



(a) $MeMgI/Et_2O$ (2 equiv.); NH_4Cl/H_2O; (b) anhydrous $CuSO_4 \cdot SiO_2$, benzene, reflux; (c) $NaBH_4$/MeOH/r.t.; (d) Ac_2O/Py; (e) Amberlyst A-21, methyl acrylate, r.t. 8 h; (f) Bu_3SnH, AIBN, Bz, reflux, 2 h; (g) 40% NaOH/MeOH; (h) HCl.

Scheme 4

Melting and boiling points reported were uncorrected. Mass spectra were obtained by EI at 70 eV using a INCOS 50 GC-MS instrument. ^{1}H NMR spectra were recorded in $CDCl_3$ solutions at 60 MHz using TMS as the internal standard and shift values are expressed in ppm. IR spectra were recorded as thin films unless otherwise stated. All chemicals used were purified before use and literature methods were followed for the syntheses of 2-nitrocyclohexanone,[18] 6-methyl-2-nitrocyclohexanone[18] and organometallic reagents.[19]

Preparation of Cyclic 2-Nitroalcohols; Typical Procedure:

1-Methyl-2-nitrocyclohexanol (**2a**):

To a stirred solution of MeMgI (15.66 mmol) in Et_2O (20 mL) was added an ethereal solution of 2-nitrocyclohexanone (**1a**; 1.12 g, 7.83 mmol) dropwise at 0 °C. The mixture was stirred for 30 min at 0 °C, the temperature raised to r.t. and stirring continued for an additional 30 min. The mixture was then quenched with sat. aq NH_4Cl, extracted with Et_2O and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the crude product was purified by preparative TLC using EtOAc/petroleum ether bp 40–60 °C (1:10) solvent system to afford **2a** as white solid; yield: 0.78 g (70%); mp 66 °C (Lit.[12] mp 68 °C).

Other 2-nitrocyclohexanols **2b**, **2c**,[12] **2d**, **2e**,[12] **2f**, **2g**,[12] **2h**, **2i**, **2j**, **2k**, **2l** and 2-nitrocyclododecanol **2m** were similarly prepared.

1,6-Dimethyl-2-nitrocyclohexanol (**2b**): Yield: 65%; oil.

IR (neat): $\nu = 3400, 1550\ cm^{-1}$.

^{1}H NMR: $\delta = 0.86$ (d, $J = 6.8$ Hz, 3H, CH_3), 1.19 (s, 3H), 1.46–2.00 (m, 7H), 3.33 (br s, 1H, OH), 4.34 (dd, $J = 11.5, 4.4$ Hz, 1H, $CHNO_2$).

MS: $m/z = 174$ ($[M+1]^+$), 127, 109.

Analysis calculated for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09; found: C, 55.46; H, 8.73; N, 8.06.

1-Ethyl-6-methyl-2-nitrocyclohexanol (**2d**): Yield: 54%; oil.

IR (neat): $\nu = 3400$ (OH), $1550\ cm^{-1}$.

^{1}H NMR: $\delta = 0.88$ (d, $J = 6.9$ Hz, CH_3), 0.95 (t, $J = 7$ Hz, 3H), 2.20 (m, 10H), 2.95 (s, 1H, OH), 4.45 (dd, $J = 11.7, 4.4$ Hz, 1H, $-CHNO_2$).

MS: $m/z = 187$ (M^+), 172, 141.

Analysis calculated for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48; found: C, 57.25; H, 9.35; N, 7.63.

1-Butyl-6-methyl-2-nitrocyclohexanol (**2f**): Yield: 48%; gum.

IR ($CHCl_3$): $\nu = 3337, 1540\ cm^{-1}$.

^{1}H NMR: $\delta = 0.86$ (t, $J = 6.5$ Hz, 3H, CH_3), 0.90 (d, $J = 6.8$ Hz, 3H, CH_3), 1.0–2.0 (m, 13H, CH_2, CH), 3.6 (br s, 1H, OH), 4.1 (dd, $J = 10.5, 4.4$ Hz, 1H, $CHNO_2$).

MS: $m/z = 216$ ($[M+1]^+$), 198, 169, 158, 112, 95.

Analysis calculated for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51; found: C, 61.12; H, 9.88; N, 6.49.

6-Methyl-2-nitro-1-phenylcyclohexanol (**2h**): Yield: 48%; mp 101 °C.

IR ($CHCl_3$): $\nu = 3450, 1540\ cm^{-1}$.

^{1}H NMR: $\delta = 0.86$ (d, $J = 6.8$ Hz, 3H, CH_3), 1.00 (m, 7H, CH_2, CH), 2.86 (br s, 1H, OH), 4.39 (dd, $J = 10.4, 4.0$ Hz, 1H, $CHNO_2$), 7.00–7.60 (m, 5H, aromatic).

MS: $m/z = 236$ ($[M+1]^+$), 188, 159, 112, 105.

Analysis calculated for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95; found: C, 66.30; H, 7.23; N, 5.90.

1-Cyclopentyl-1-nitrocyclohexanol (**2i**): Yield: 58%; gum.

IR (neat): $\nu = 3440, 1530\ cm^{-1}$.

^{1}H NMR: $\delta = 1.20$–2.19 (m, 17H, CH_2, CH), 3.0 (br s, 1H, OH), 4.36 (dd, $J = 10.4, 4$ Hz).

MS: $m/z = 214$ ($[M+1]^+$), 195, 149, 144, 125, 98.

Analysis calculated for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57; found: C, 61.89; H, 8.78; N, 6.49.

1-Cyclopentyl-2-methyl-2-nitrocyclohexanol (**2j**): Yield: 61%; gum.

IR ($CHCl_3$): $\nu = 3440, 1542\ cm^{-1}$.

^{1}H NMR: $\delta = 0.91$ (d, $J = 6.9$ Hz, 3H, CH_3), 1.1 (m, 16H, CH_2, CH), 3.2 (br s, 1H, OH), 4.37 (dd, $J = 10.5, 4.0$ Hz).

MS: $m/z = 228$ ($[M+1]^+$), 209, 194, 113, 98.

Analysis calculated for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16; found: C, 63.52; H, 9.27; N, 6.37.

1-Isopropyl-2-nitrocyclohexanol (**2k**): Yield: 50%; oil.

IR (neat): $\nu = 3300, 1550\ cm^{-1}$.

^{1}H NMR: $\delta = 0.89$ (d, $J = 7$ Hz, 6H), 1.35–2.33 (m, 9H, CH_2, CH), 2.90 (br s, 1H, OH), 4.5 (dd, $J = 11.7, 4.4$ Hz; 1H, $CHNO_2$).

MS: $m/z = 188$ ($[M+1]^+$), 169, 144.

Analysis calculated for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48, found: C, 57.68; H, 9.09; N, 7.43.

1-Isopropyl-6-methyl-2-nitrocyclohexanol (**2l**): Yield: 48%.

IR (neat): $\nu = 3310, 1548\ cm^{-1}$.

^{1}H NMR: $\delta = 0.90$ (d, $J = 7$ Hz), 0.94 (d, $J = 7$ Hz, 6H, CH_3), 1.3–2.4 (m, 7H, CH_2, CH), 2.96 (br s, 1H, OH), 4.52 (dd, $J = 11.7, 4.4$ Hz, 1H, $CHNO_2$).

MS: $m/z = 202$ ($[M+1]^+$), 186, 155.

Analysis calculated for $C_{10}H_{19}NO_3$: C, 59.68, H, 9.45; N, 6.96; found: C, 59.59; H, 9.55; N, 6.87.

1-Methyl-2-nitrododecanol (**2m**): Yield: 63%; gum.

IR (neat): $\nu = 3300, 1550\ cm^{-1}$.

^{1}H NMR: $\delta = 1.0$ (s, 3H, CH_3), 1.1–1.6 (m, 20H, CH_2), 2.3 (br s, 1H, OH), 4.2 (t, $J = 7$ Hz, 1H, $CHNO_2$).

MS: $m/z = 244$ ($[M+1]^+$), 197.

Analysis calculated for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76; found: C, 64.57; H, 10.15; N, 5.82.

Cleavage of 2-Nitroalkanols Catalysed by Anhydrous Copper Sulfate Adsorbed on Silica Gel; General Procedure:

The catalyst anhyd copper(II) sulfate adsorbed on silica gel was prepared as in the procedure described by Nishiguchi et al.[5]

A mixture of 2-nitroalcohol (1 equiv), catalyst (1 equiv) and the substrate in anhyd benzene (25 mL/gm) was refluxed while monitoring the reaction on TLC. For workup, the catalyst was filtered off and washed with a polar solvent such as acetone. The combined filtrate was evaporated and the products were purified by chromatography. Reaction of 2-nitrocyclohexanols **2a–l** and 2-nitrocyclododecanol **2m** were carried out as in the general procedure given above.

7-Nitroheptan-2-one (**3a**): Yield: 67%; oil.

IR (neat): $\nu = 1700, 1550\ cm^{-1}$.

^{1}H NMR: $\delta = 1.33$–1.69 (m, 6H), 2.00 (s, 3H, $COCH_3$), 2.33 (t, $J = 7$ Hz, 2H, CH_2), 4.20 (t, $J = 7$ Hz, 2H, $-CH_2NO_2$).

MS: $m/z = 160$ ($[M+1]^+$), 113, 69.

Analysis calculated for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80; found: C, 52.78; H, 8.15; N, 8.76.

3-Methyl-7-nitroheptan-2-one (**3b**): Yield: 54%; oil.

IR (neat): $\nu = 1700, 1550\ cm^{-1}$.

^{1}H NMR: $\delta = 0.81$ (m, 6H), 1.17 (d, $J = 6.8$ Hz, 3H), 1.43–1.73 (m, 1H), 1.98 (s, 3H), 4.16 (t, $J = 7$ Hz, 2H, CH_2NO_2).

MS: $m/z = 174$ ($[M+1]^+$), 158, 112, 85.

Analysis calculated for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09; found: C, 55.43; H, 8.66; N, 8.12.

8-Nitrooctan-3-one (**3c**): Yield: 73%; oil.

IR (neat): $\nu = 1700, 1550\ cm^{-1}$.

^{1}H NMR: $\delta = 0.09$ (t, $J = 7$ Hz, 3H), 1.03–1.59 (m, 6H), 1.74 (q, $J = 7$ Hz, 2H, CH_2), 1.69–2.00 (m, 1H, CH), 4.80 (t, $J = 7$ Hz, 2H, CH_2NO_2).

MS: $m/z = 174$ ($[M+1]^+$), 127, 115, 69.

Analysis calculated for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09; found: C, 55.40; H, 8.70; N, 8.12.

4-Methyl-8-nitrooctan-3-one (**3d**): Yield: 69%; gum.

IR (neat): $\nu = 1700, 1545\ cm^{-1}$.

^1H NMR: $\delta = 0.92$ (t, $J = 7$ Hz, 3H, CH_3), 1.04–1.60 (m, 6H, CH_2), 1.15 (d, $J = 7$ Hz, 3H, CH_3), 1.62–1.80 (m, 3H), 4.2 (t, $J = 7$ Hz, 2H, CH_2NO_2).

MS: $m/z = 188$ ($[M+1]^+$), 141, 127.

Analysis calculated for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48; found: C, 57.65; H, 9.36, N, 7.32.

10-Nitrodecan-5-one (**3e**): Yield: 69%; bp 170–172°C.

IR (neat): $\nu = 1700, 1545\ cm^{-1}$.

^1H NMR: $\delta = 0.73$–0.96 (m, 3H), 1.00–1.66 (m, 10H), 2.06–2.41 (m, 4H), 4.18 (t, $J = 6$ Hz, 2H, CH_2NO_2).

MS: $m/z = 202$ ($[M+1]^+$), 155, 127.

Analysis calculated for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10; found: C, 60.59; H, 7.45; N, 7.29.

6-Methyl-10-nitrodecan-5-one (**3f**): Yield: 64%; gum.

IR (neat): $\nu = 1700, 1550\ cm^{-1}$.

^1H NMR: $\delta = 0.77$–1.03 (m, 6H), 1.10–1.66 (m, 10H), 2.06–2.33 (m, 3H), 4.16 (t, $J = 7$ Hz, 2H, CH_2NO_2).

MS: $m/z = 216$ ($[M+1]^+$), 197, 169, 85.

Analysis calculated for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51; found: C, 61.35; H, 9.78; N, 6.45.

6-Nitro-1-phenylhexan-1-one (**3g**): Yield: 62%; mp 44°C.

IR KBr (neat): $\nu = 1670, 1550\ cm^{-1}$.

^1H NMR: $\delta = 1.08$–2.03 (m, 6H), 2.78 (t, $J = 7$ Hz, 2H), 4.14 (t, $J = 7$ Hz, 2H, CH_2NO_2), 6.93–7.33 (m, 3H), 7.49–7.79 (m, 2H).

MS: $m/z = 222$ ($[M+1]^+$), 165, 135, 98.

Analysis calculated for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33; found: C, 65.10; H, 6.78; N, 6.25.

2-Methyl-6-nitro-1-phenylhexan-1-one (**3h**): Yield: 65%.

IR (neat): $\nu = 1670, 1545\ cm^{-1}$.

^1H NMR: $\delta = 0.82$ (d, $J = 6$ Hz, 3H), 1.00–1.98 (m, 6H), 2.10–2.83 (m, 1H), 4.00 (t, $J = 7$ Hz, 2H, CH_2NO_2), 6.16–7.26 (m, 3H), 7.36–7.69 (m, 2H).

MS: $m/z = 236$ ($[M+1]^+$), 189, 120, 105, 77.

Analysis calculated for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95; found: C, 66.23; H, 7.32; N, 5.90.

1-Cyclopentyl-6-nitrohexan-1-one (**3i**): Yield: 59%; oil.

IR (neat): $\nu = 1665, 1540\ cm^{-1}$.

^1H NMR: $\delta = 1.33$–1.89 (m, 14H), 2.03 (m, 3H), 4.19 (t, $J = 7$ Hz, 2H, CH_2NO_2).

MS: $m/z = 214$ ($[M+1]^+$), 167, 144, 97.

Analysis calculated for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57; found: C, 61.89; H, 8.94; N, 6.49.

1-Cyclopentyl-2-methyl-6-nitrohexan-1-one (**3j**): Yield: 52%; gum.

IR ($CHCl_3$): $\nu = 1700, 1545\ cm^{-1}$.

^1H NMR: $\delta = 0.91$ (d, $J = 7$ Hz, CH_3), 1.28–1.86 (m, 14H, CH_2), 2.03–2.3 (m, 2H, $-CH-$), 4.21 (t, $J = 7$ Hz, CH_2NO_2).

MS: $m/z = 228$ ($[M+1]^+$), 181, 158.

Analysis calculated for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16; found: C, 63.45; H, 9.42, N, 6.09.

2-Methyl-8-nitroheptan-3-one (**3k**): Yield: 59%; oil.

IR (neat): $\nu = 1770, 1550\ cm^{-1}$.

^1H NMR: $\delta = 0.96$ (d, $J = 6$ Hz, 6H), 1.2–1.9 (m, 6H, CH_2), 2.29 (d, $J = 6$ Hz, 2H), 4.13 (t, $J = 7$ Hz, 2H, CH_2NO_2).

MS: $m/z = 188$ ($[M+1]^+$), 141, 128, 97.

Analysis calculated for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48; found: C, 57.69; H, 9.10; N, 7.52.

2,4-Dimethyl-8-nitroheptan-3-one (**3l**): Yield: 61%; gum.

IR ($CHCl_3$): $\nu = 1700, 1555\ cm^{-1}$.

^1H NMR: $\delta = 0.95$ (d, $J = 6$ Hz, 6H), 1.2 (d, $J = 6.9$ Hz, 3H, CH_3), 1.25–1.89 (m, 6H, CH_2), 2.30 (m, 2H, CH), 4.22 (t, $J = 6.8$ Hz, 2H, CH_2NO_2).

MS: $m/z = 202$ ($[M+1]^+$), 155.

Analysis calculated for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96; found: C, 59.52, H, 9.68; N, 6.75.

13-Nitrotridecan-2-one (**3m**): Yield: 57%; mp 82–83°C.

IR (neat): $\nu = 1700, 1550\ cm^{-1}$.

^1H NMR: $\delta = 1.2$ (m, 18H, CH_2), 2.0 (s, 3H, $COCH_3$), 2.3 (t, $J = 7$ Hz, 2H, CH_2CO), 4.2 (t, $J = 7$ Hz, 2H, CH_2NO_2).

MS: $m/z = 244$ ($[M+1]^+$), 197, 183.

Analysis calculated for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76; found: C, 64.24; H, 10.25; N, 5.10.

Sodium Borohydride Reduction of 7-Nitroheptan-2-one (3a):

A solution of **3a** (0.57 g, 3.57 mmol) in MeOH (5 mL) was treated with $NaBH_4$ (0.14 g, 3.57 mmol) at 0–5°C. The mixture was stirred for 1 h while monitoring it on TLC and to this was added 5% HCl (5 mL) to neutralise the excess $NaBH_4$. It was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (20 mL). The extract was dried (anhyd Na_2SO_4) and evaporated to yield a gummy residue which was purified by preparative TLC (1:4, EtOAc/hexane) to give 5.58 g (98%) (±)-7-nitroheptan-2-ol, (±)-**4a**.

IR (neat): $\nu = 3375, 1550, 1380\ cm^{-1}$.

^1H NMR: $\delta = 1.04$ (d, $J = 6.0$ Hz, 3H), 1.19–1.79 (m, 8H), 1.66–2.23 (m, 1H), 3.33–3.83 (m, 1H, OH), 4.33 (t, $J = 6.5$ Hz, CH_2NO_2).

MS: $m/z = 162$ ($[M+1]^+$), 115.

Analysis calculated for $C_7H_{15}NO_3$: C, 52.16; H, 9.38; N, 8.69; found: C, 52.30, H, 9.15; N, 8.55.

(±)-Nitroheptan-6-ol Acetate [(±)-4b]:

A solution of (±)-**4a** (0.3 g, 1.83 mmol) in pyridine (1 mL) is treated with Ac_2O (2 mL) and left at r.t. overnight. Usual workup followed by purification gave (±)-**4b**, 0.27 g (90%) as a gum.

IR ($CHCl_3$): $\nu = 1735, 1550\ cm^{-1}$.

^1H NMR: $\delta = 1.07$ (d, $J = 7.2$ Hz, 3H), 1.16–1.46 (m, 6H, CH_2), 1.96 (s, 3H, $-COCH_3$), 4.15 (t, $J = 7$ Hz, 2H, $-CH_2NO_2$), 4.5 (m, 1H, CH).

MS: $m/z = 204$ ($M^+ + 1$), 160, 157.

Analysis calculated for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48; found: C, 57.32; H, 9.52; N, 7.57.

Reaction of (±)-4b with Methyl Acrylate:

A solution of (±)-**4b** (0.25 g, 1.2 mmol) and methyl acrylate (0.09 g, 1.2 mmol) was mixed with Amberlyst A-21 resin (0.9 gm) and left overnight at r.t. The resin was then washed with CH_2Cl_2 and the washings evaporated to yield a residue which was purified by chromatography [EtOAc/petroleum ether (1:3)] to yield **5** as a gum; yield: 0.3 g (89%).

IR ($CHCl_3$): $\nu = 1725, 1645, 1550\ cm^{-1}$.

^1H NMR: $\delta = 4.7$ (m, 2H, $CHNO_2$, $-CHOAc$), 3.5 (s, 3H, $COOCH_3$), 2.0 (s, 3H, $-OCOCH_3$), 2.15 (t, $J = 6.5$ Hz, 2H, $-CH_2COOCH_3$), 1.4 (m, 10H, CH_2), 1.1 (d, $J = 7$ Hz, 3H, CH_3CHOAc).

MS: $m/z = 290$ ($[M+1]^+$), 243.

Analysis calculated for $C_{13}H_{23}NO_6$: C, 53.97; H, 8.01; N, 4.84; found: C, 53.50; H, 8.20; N, 4.67.

Methyl (±)-9-Acetoxydecanoate [(±)-6]:

A solution containing **5** (0.28 g, 0.94 mmol), tributyltin hydride (0.15 g, 0.5 mmol) and AIBN (0.01 g) in anhyd benzene was refluxed at 80°C under N_2 for 2 h while monitoring the reaction by TLC. The mixture was evaporated under reduced pressure and the residue was washed with aq $NaHCO_3$, extracted with CH_2Cl_2, dried

(Na_2SO_4) and evaporated. The residue was purified furthur by preparative TLC to yield (±)-**6** as a colourless gum (93%).

IR ($CHCl_3$): ν = 2900, 1720, 1375, 1250 cm^{-1}.

^1H NMR: δ = 4.65 (m, 1H, C*H*OAc), 3.4 (s, 3H, $COOCH_3$), 2.00 (t, J = 6.5 Hz, 2H, $CH_2{=}COOCH_3$), 1.95 (s, 3H, $OCOCH_3$), 0.9–1.6 (m, 12H, CH_2), 0.88 (d, J = 7 Hz, 3H, CH_3CHOAc).

MS: m/z = 244 (M^+), 201.

Analysis calculated for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90; found: C, 63.76; H, 9.85.

(±)-Phoracantholide I [(±)-7]:

A solution of 0.25 g of the (±)-**6** in MeOH (4 mL) and 40% aq NaOH (0.5 mL) was stirred under N_2, the reaction being monitored by TLC. After the disappearance of all starting material the solution was diluted with H_2O, acidified with dil HCl, and extracted thoroughly with $CHCl_3$. Evaporation of the washed and dried extract yielded 0.22 g (89%) of (±)-phoracantholide I [(±)-**7**] as a gum.

IR ($CHCl_3$): ν = 2925, 1710, 1250 cm^{-1}.

^1H NMR: δ = 5.15 (m, 1H), 2.55–1.15 (m, 14H, CH_2), 1.27 (d, J = 6.8 Hz, 3H, CH_3).

MS: m/z = 170 (M^+), 155, 98.

Analysis calculated for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66; found: C, 70.27; H, 10.81.

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