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NEW FUNCTIONALIZATIONS OF OXANORBORNENIC SYSTEMS VIA 1,3-DIPOLAR CYCLOADDITIONS WITH C,N-DIPHENYLNITRONE

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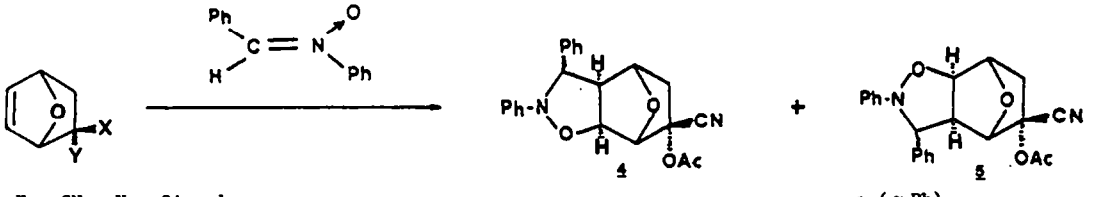
Abstract- The regio- and stereoselectivity of the cycloaddition between C,N-diphenylnitrone and 2-endo-acetoxy-7-oxabicyclo[2.2.1]hept-5-ene-2-exo-carbonitrile has been studied. Subsequent fragmentation of the isoxazolidine ring with mCPBA followed by acidic hydrolysis yields highly functionalized oxanorbornenic hydroxyketones.

The regioselectivity of electrophilic additions to 7-oxanorbornenic systems can be controlled by the substituents at C-2[1]. These substrates are now readily available optically pure[2] and they have assumed an increasingly important role in synthetic chemistry[3]. During the course of our investigation on new methods to functionalize C-5 and C-6 of 7-oxanorbornenic systems, we studied the regioselectivity of the 1,3-dipolar cycloaddition of benzonitrile oxide to 1-3[4]. In this paper, we wish to report the outcome of the reaction between C,N-diphenylnitrone and oxanorbornenic substrates 1 and 2[5], as well as some subsequent synthetic transformations which led to functionalized intermediates.

Scheme 1



X = CN, Y = OAc 1
X = Y = O 2
X, Y = OCH_2CH_2O 3

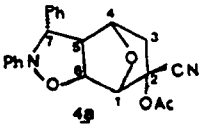
a (α Ph)
b (β Ph)

The cycloaddition of C,N-diphenylnitrone to cyanoacetoxy derivative 1 was carried out in benzene to afford a 1:1 mixture of regioisomers 4 and 5 (Scheme 1), both exo relative to the bridge[5,6] in excellent yield. Trituration of the mixture with diethyl ether allowed for the

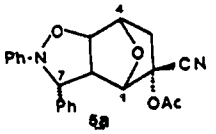
isolation of a 1:1 mixture of diastereomers 4a and 5a (67%); these were later separated by column chromatography. Fractional recrystallization of the portion of crude reaction mixture soluble in ether (28%) led to the isolation of 4b. Finally, 5b was obtained by column chromatography of the mother liquors of 4b.

The stereochemical elucidation of the cycloaddition adducts was based on the analysis of their ^{1}H-NMR spectra. Table I summarizes the spectroscopic data for adducts 4 and 5. The splitting pattern of H-1 (s) and H-4 (d) in all cases allows for the conclusive assignment of the exo stereochemistry of all adducts with respect to the oxanorbornenic moiety. The regio- and stereochemistry relative to C-7 was assigned as follows. For the major isomers, 4a and 5a, the bridgehead protons (H-1 or H-4) were found to be more shielded when the -CH-Ph moiety is in a 1,2 disposition than when the isoxazolidinic oxygen is in a 1,2 disposition. This is in good agreement with literature precedents[5a]. Furthermore, a NOE effect was encountered between H-7 and H-4 in isomer 4a while isomer 5a displayed a similar NOE enhancement between H-1 and H-7. These results are consistent with the regio- and stereochemistry proposed.

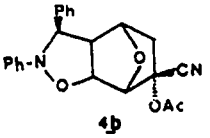
Table I ^{1}H-NMR Spectral Data for Oxanorbornenic Isoxazolidines 4a, 5a, 4b and 5b[a,b]



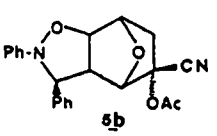
4a



5a



4b



5b

	4a	5a	4b	5b
H-1	5.21 (s)	5.08 (s)	5.16 (s)	4.42 (s)
H-4	4.71 (d, 6.4)	4.87 (d, 6.3)	4.03 (d, 6.0)	4.75 (d, 6.5)
H-7	4.00 (d, 7.3)	4.08 (d, 7.3)	4.66 (d, 9.0)	4.90 (d, 9.0)
H-6	4.83 (d, 7.3)	3.14 (t, 7.3)	4.80 (d, 7.0)	3.27 (dd, 7.0, 9.0)
H-5	2.98 (t, 7.3)	4.56 (d, 7.3)	3.05 (dd, 7.0, 9.0)	4.57 (d, 7.0)

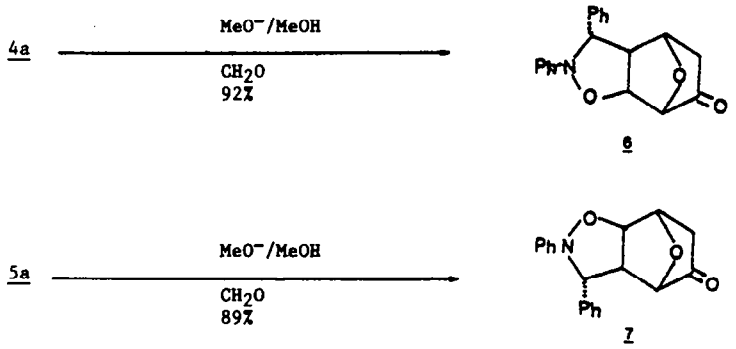
[a] Chemical shifts in δ units downfield from TMS and, in parentheses, coupling constants in Hertzs.
[b] The numbering system is arbitrary and it has been utilized to facilitate comparison of the data.

It should also be pointed out that our adducts display an upfield shift of the protons vicinal to C-7 (H-5 and H-6) when the phenyl group is cis. For the minor isomers, 4b and 5b, the anisotropy of the phenyl ring introduces dramatic changes in the chemical shifts of the bridgehead protons. These changes secure both the regio- and stereochemistry of these adducts. However, the values of the coupling constants $J_{5,7}$ (4a, 4b) and $J_{6,7}$ (5a, 5b) measured by us (7.3 Hz for J_{trans} for major isomers 4a and 5a and 9.0 Hz for J_{cis} for minor isomers 4b and 5b) clearly disagree with those reported by Fisera[5b] (6.0 Hz for J_{cis} and 0.0 Hz for J_{trans}) for related cycloadducts. In order to unequivocally prove our assignments, adduct 5a was characterized by X-ray difraction analysis[7], and the proposed structure was thus secured. It should be mentioned that there are some precedents in the literature of isoxazolidines presenting coupling constants as large as those found by us[8].

In conclusion, the reaction between C,N-diphenylnitrone and 2-endo-acetoxy-7-oxabicyclo[2.2.1]hept-5-ene-2-exo-carbonitrile occurs with high exo-selectivity relative to the oxygen bridge, without any regioselectivity and with moderate endo diastereoselectivity (67:28) relative to the isoxazolidinic proton [5b].

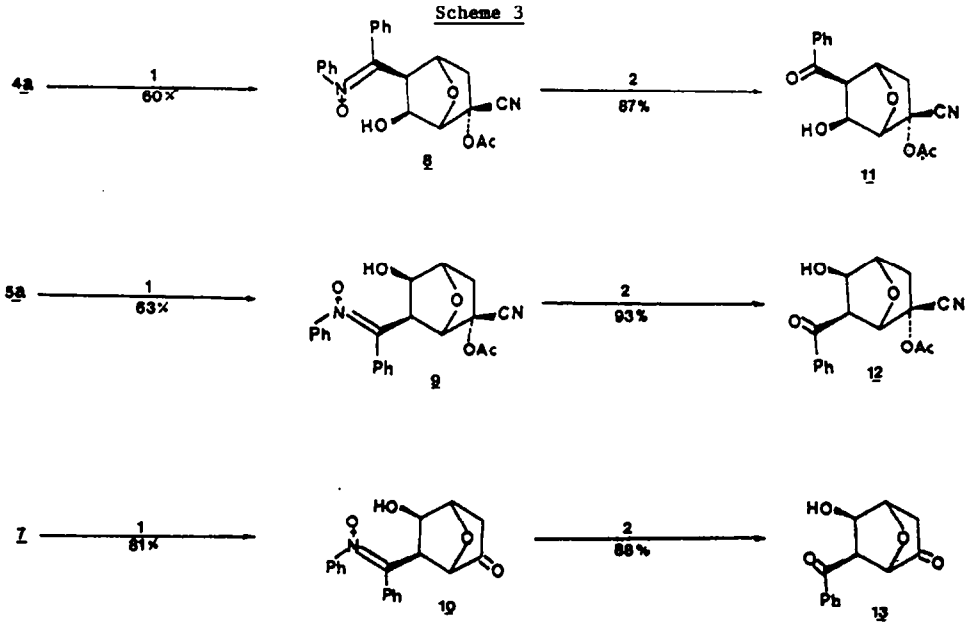
From a synthetic point of view, the first transformation explored was the hydrolysis of the cyanoacetoxy functionality of these cycloadducts to produce the corresponding ketones (Scheme 2). In this manner we were able to circumvent the experimental problems associated with the direct cycloaddition to oxanorbornenone 2, which led to inseparable mixtures of cycloadducts. This transformation was effected on the pure cycloadducts 4a and 5a to yield ketones 6 and 7 respectively in excellent yields.

Scheme 2



Another transformation studied was the fragmentation of the isoxazolidine ring of adducts 4a, 5a and 7 by treatment with mCPBA, to generate the corresponding oxanorbornenic hydroxynitrones 8-10 in fair yields [10] (Scheme 3). It should be pointed out that this oxidative

Scheme 3



Reagents:1) mCPBA, CH_2Cl_2, 0ºC, 15 min; 2) p-TsOH (cat), THF:H_2O (9:1), reflux, 8 h.

fragmentation could be carried out on the crude cycloaddition mixture (4 + 5) to afford exclusively a 1:1 mixture of 8 and 9, which were separated by column chromatography. The configuration of the nitrone moiety is tentatively assigned as E based on the observation of a strong intramolecular hydrogen bond[11]. In the case of ketoisoxazolidine, 7, we did not detect any products derived from Baeyer-Villiger rearrangement of the ketone functionality[12]. Hydroxynitrones, 8-10, were hydrolyzed in mild conditions with a catalytic amount of p-TsOH in aqueus THF, to afford good yields of the highly functionalized oxanorbornenic hydroxyketones 11-13.

EXPERIMENTAL

General

All reactions were conducted under a positive pressure of dry nitrogen using freshly distilled solvents under anhydrous conditions unless otherwise stated. Diethyl ether and tetrahydrofuran were distilled from lithium aluminum hydride; benzene, hexane and ethyl acetate from phosphorus pentoxide and methylene chloride from calcium hydride. All other commercially available reagents were used without further purification unless otherwise noted.

Analytical TLC was carried out on 0.20 mm E. Merck precoated silica gel plates (60 F-254), using UV light, iodine or acidic vanillin solution as visualizing agents. Column chromatography was performed using E. Merck 230-400 mesh or 70-230 mesh silica gel.

Infrared spectra were recorded on either a Perkin-Elmer 781 or 257 grating spectrophotometers; band positions are indicated in wavenumbers.

^{1}H-NMR spectra were recorded on a Varian T-60 A or on a Brüker WH-360 FT spectrometer, using $CDCl_3$ or DMSO-d_6 as solvent. ^{13}C-NMR spectra were measured on a Varian FT-80 A. In both, ^{1}H-NMR and ^{13}C-NMR, chemical shifts are reported in δ units downfield from tetramethylsilane. The following abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Melting points were recorded on a Büchi 512 apparatus and are uncorrected. Mass spectra were recorded on a Varian MAT-711 instrument.

Cycloaddition between C,N-Diphenylnitrone and 2-endo-Acetoxy-7-oxabicyclo[2.2.1]hept-5-en-2-exo-carbonitrile (1)

A round-bottomed flask fitted with a magnetic stirring bar was charged with 1 (1.79 g, 10 mmol), C,N-diphenylnitrone (1.05 equiv, 2.00 g) and benzene (20 ml). The reaction mixture was stirred at room temperature in the dark for 6 days after which time the solvent was removed in vacuo. Trituration of the crude product with warm ether (10 ml) followed by filtration of the cold mixture, afforded 2.60 g of a 1:1 mixture (determined by integration of the ^{1}H-NMR spectra) of the major products 4a and 5a (67%). These adducts were separated by column chromatography (chloroform:ethyl acetate, 40:1, R_f = 0.24 (4a) and 0.17 (5a)). Minor isomer 4b was purified by fractional recrystallization with ethanol of the mixture of 4b and 5b (obtained by evaporation of the mother liquours of 4a and 5a). Minor isomer 5b was purified by column chromatography (chloroform:ethyl acetate, 40:1 R_f = 0.34) of the residue obtained by concentration of the mother liquours of 4b.

4a: mp: 221-223 ºC. ^{1}H-NMR ($CDCl_3$): 1.82 (1H, d, J = 14.0 Hz, H-3 endo), 2.20 (3H, s, CH_3), 2.76 (1H, dd, J = 14.0, 6.4 Hz, H-3 exo), 2.98 (1H, t, J = 7.3 Hz, H-5), 4.00 (1H, d, J = 7.3 Hz, H-7), 4.71 (1H, d, J = 6.4 Hz, H-4), 4.83 (1H, d, J = 7.3 Hz, H-6), 5.21 (1H, s, H-1), 6.70-7.23 (10H, m , H-Ar). ^{13}C-NMR ($CDCl_3$): 20.2, 42.5, 63.2, 72.3, 74.6, 77.8, 77.9, 83.0, 119.2, 127.4, 128.4, 129.0, 138.5, 148.1, 168.6. IR (KBr): 1190, 1215, 1490, 1750.

5a: mp: 179-181 ºC. ^{1}H-NMR ($CDCl_3$): 1.86 (1H, d, J = 14.0 Hz, H-3 endo), 2.08 (3H, s, CH_3), 2.79 (1H, dd, J = 14.0, 6.3 Hz, H-3 exo), 3.14 (1H, t, J = 7.3 Hz, H-6), 4.08 (1H, d, J = 7.3 Hz, H-7), 4.56 (1H, d, J = 7.3 Hz, H-5), 4.87 (1H, d, J = 6.3 Hz, H-4), 5.08 (1H, s, H-1), 6.93-7.23 (10H, m, H-Ar). ^{13}C-NMR ($CDCl_3$): 20.2, 39.2, 57.5, 73.0, 73.5, 79.1, 81.4, 83.4, 118.0, 119.1, 124.3, 127.2, 128.4, 129.0, 138.4, 148.2, 168.6. IR (KBr): 1210, 1490, 1760.

4b: mp: 145-149 ºC. ^{1}H-NMR ($CDCl_3$): 1.63 (1H, d, J = 14.0 Hz, H-3 endo), 2.12 (3H, s, CH_3), 2.49 (1H, dd, J = 14.0, 6.0 Hz, H-3 exo), 3.05 (1H, dd, J = 9.0, 7.0 Hz, H-5), 4.03 (1H, d, J = 6.0 Hz, H-4), 4.66 (1H, d, J = 9.0 Hz, H-7), 4.80 (1H, d, J = 7.0 Hz, H-6), 5.16 (1H, s, H-1), 6.66-7.60 (10H, m, H-Ar). ^{13}C-NMR ($CDCl_3$): 20.2, 42.6, 57.4, 71.4, 72.7, 78.8, 83.7, 116.2, 122.6, 127.8, 128.4, 128.5, 136.8, 149.7, 168.6. IR (KBr): 1215, 1370, 1450, 1485, 1595, 1750.

5b: ^{1}H-NMR($CDCl_3$): 1.66 (1H, d, J = 14.0 Hz, H-3 endo), 2.10 (3H, s, CH_3), 2.65 (1H, dd, J = 14.0, 6.5 Hz, H-3 exo), 3.27 (1H, dd, J = 7.0, 9.0 Hz, H-6), 4.42 (1H, s, H-1), 4.57 (1H,d, J =

7.0 Hz, H-5), 4.75 (1H, d, J = 6.5 Hz, H-4), 4.90 (1H, d, J = 9.0 Hz, H-7), 6.77-7.60 (10H, m, H-Ar). ^{13}C-NMR ($CDCl_3$): 20.4, 40.0, 51.0, 71.4, 73.1, 81.4, 83.4, 115.6, 118.2, 122.5, 127.9, 128.6, 128.9, 137.0, 150.3, 168.7. IR ($CHCl_3$): 1370, 1485, 1595, 1755, 2920, 3010.

General Procedure for Hydrolysis of the Cyanoacetoxy Functionality in Oxanorbornenic Isoxazolidines

To a solution of isoxazolidine in anhydrous methanol (5 ml/mmol) was added sodium methoxide (0.05 equivalents). The mixture was stirred for 2 h at room temperature after which time formaline (4 equivalents) was added and the solution was stirred for 1 h. To the crude reaction mixture was added water (2 ml/mmol), brine (2 ml/mmol) and dichloromethane (1.5 ml/mmol) and the layers were separated. The aqueous portion was extracted with dichloromethane (7x1.5 ml/mmol) and the combined organic extracts were washed with brine (4x1.5 ml/mmol) and dried over magnesium sulfate. The solvent was removed in vacuo and the crude ketone was purified by flash chromatography on silica gel.

Hydrolysis of 4a, (6).

From 753 mg (2 mmol) of 4a was obtained 564 mg of 6 (92%) as a yellowish solid (mp = 140-144 ºC) after chromatography (chloroform, R_f = 0.26). ^{1}H-NMR ($CDCl_3$): 1.75 (1H, d, J = 18.0 Hz, H-3 endo), 2.40 (1H, dd, J = 18.0, 6.0 Hz, H-3 exo), 3.07 (1H, t, J = 7.0 Hz, H-5), 4.05 (1H, d, J = 7.0 Hz, H-7), 4.42 (1H, s, H-1), 4.72 (1H, d, J = 7.0 Hz, H-6), 4.87 (1H, d, J = 6.0 Hz, H-4), 6.75-7.45 (10H, m, H-Ar). ^{13}C-NMR ($CDCl_3$): 41.3, 63.7, 74.4, 78.2, 78.9, 83.3, 119.1, 124.2, 127.4, 128.3, 129.0, 138.6, 148.2, 208.4. IR ($CHCl_3$): 1455, 1495, 1600, 1765.

Hydrolysis of 5a, (7)

From 690 mg (1.83 mmol) of 5a was obtained 500 mg of 7 (89%) as a yellowish solid (mp = 152-156 ºC) after chromatograhy (chloroform, R_f = 0.21). ^{1}H-NMR ($CDCl_3$): 1.88 (1H, d, J = 18.0 Hz, H-3 endo), 2.46 (1H, dd, J = 18.0, 6.0 Hz, H-3 exo), 3.03 (1H, t, J = 7.0 Hz, H-6), 4.05 (1H, d, J = 7.0 Hz, H-7), 4.33 (1H, s, H-1), 4.77 (1H, d, J = 7.0 Hz, H-5), 4.93 (1H, d, J = 6.0 Hz, H-4), 6.75-7.26 (10H, m, H-Ar). ^{13}C-NMR ($CDCl_3$): 37.5, 58.0, 73.5, 78.8, 80.6, 82.0, 119.1, 124.2, 127.4, 128.2, 128.9, 148.1, 208.3. IR ($CHCl_3$): 1440, 1485, 1595, 1765.

General Procedure for the Reaction of Oxanorbornenic Isoxazolidines with m-Chloroperbenzoic Acid

To a cold (0ºC) solution of 1 equivalent of isoxazolidine in dry dichloromethane (10 ml/mmol), was added 1.1 equivalent of mCPBA. The mixture was stirred for 15 min at 0ºC after which time the solution was washed with 5% sodium bicarbonate (3x10 ml/mmol) and then with brine (3x10 ml/mmol). The combined aqueous portions were washed with dichloromethane (3x10 ml/mmol). The combined organic extracts were dried over magnesium sulfate. The solvent was removed in vacuo affording the crude product which was purified by chromatography unless otherwise noted.

Fragmentation of 4a, (8)

From 376 mg (1 mmol) of 4a was obtained 235 mg of 8 (60%) after chromatography (ethyl acetate:ethanol, 8:1, R_f = 0.31). ^{1}H-NMR (DMSO-d_6): 2.00-2.70 (5H, m), 3.93-4.36 (2H, m), 4.76-5.10 (2H, m), 5.93 (1H, d, J = 5.0 Hz), 7.00-7.45 (10H, m). ^{13}C-NMR (DMSO-d_6): 20.4, 52.2, 70.4, 72.6, 77.2, 86.5, 119.0, 124.6, 127.6, 128.2, 128.3, 128.4. IR ($CHCl_3$): 1065, 1370, 1755, 2950-3080, 3180.

Fragmentation of 5a, (9)

From 376 mg (1 mmol) of 5a was obtained 249 mg of 9 (63%) after chromatography (ethyl acetate:ethanol, 8:1, R_f = 0.24). ^{1}H-NMR (DMSO-d_6): 2.02 (1H, d, J = 14.0 Hz), 2.20 (3H, s), 2.63 (1H, dd, J = 14.0, 6.0 Hz), 4.17-4.83 (4H, m), 5.97 (1H, d, J = 5.0 Hz), 7.10-7.50 (10H, m). ^{13}C-NMR (DMSO-d_6): 20.6, 46.2, 73.1, 74.3, 80.8, 82.1, 119.2, 124.7, 127.9, 128.3, 128.5, 130.5, 132.6, 147.1, 148.6, 169.4. IR (film): 1065, 1185, 1210, 1755, 2900-3400.

Fragmentation of 7, (10)

From 460 mg of 7 (1.5 mmol) was obtained 410 mg (85%) of 10 as a yellowish solid (mp = 117-118 ºC) after trituration of the crude reaction mixture with 15 ml of ether. ^{1}H-NMR (DMSO-d_6): 2.20-2.46 (2H, m), 3.73 (1H, s), 4.03 (1H, d, J = 7.0 Hz), 4.57-5.00 (2H, m), 5.90 (1H, d, J = 5.0 Hz), 7.00-7.57 (10H, m). ^{13}C-NMR (DMSO-d_6): 47.0, 74.2, 79.4, 82.2, 124.7, 127.7, 128.2, 128.5, 130.7, 132.7, 147.1, 148.4, 209.7. IR (KBr): 700, 775, 1230, 1240, 1760, 3020, 3130. Mass spectrum, m/e 305, 304, 297, 260, 106, 93, 77 (base), 44, 28.

General Procedure for the Hydrolysis of Oxanorbornenic Hydroxynitrones

To a solution of hydroxynitrone in tetrahydrofuran/water, 9:1, (10 ml/mmol) was added a catalytic amount of p-toluenesulfonic acid and the mixture was stirred under reflux for 8h. Ethyl acetate (20 ml/mmol) was then added and the layers were separated. The organic portion was washed with 5% sodium bicarbonate (3x10 ml/mmol) and brine (3x10 ml/mmol). The combined aqueous extracts were washed with ethyl acetate (3x15 ml/mmol). The combined organic extracts were dried over magnesium sulfate. The solvent was removed in vacuo and the crude product was purified by flash chromatography.

2-endo-Acetoxy-5-exo-benzoyl-6-exo-hydroxy-7-oxabicyclo[2.2.1]heptane-2-exo-carbonitrile, (11)

From 240 mg of 8 (0.61 mmol) was obtained 160 mg (87%) of 11 after chromatography (hexane:ethyl acetate, 1:1, R_f = 0.21). ^{1}H-NMR (DMSO-d_6): 1.98 (1H, d, J = 14.0 Hz), 2.22 (3H, s), 2.50 (1H, dd, J = 14.0, 6.0 Hz), 3.93 (1H, d, J = 8.0 Hz), 4.73 (1H, s), 4.85 (1H, d, J = 8.0 Hz), 5.03 (1H, d, J = 6.0 Hz), 7.07-7.37 (1H, m), 7.43-7.70 (2H, m), 7.80-8.10 (2H, m). ^{13}C-NMR (DMSO-d_6): 20.5, 55.3, 70.4, 72.6, 77.0, 86.8, 119.1, 128.2, 128.5, 132.7, 137.6, 169.7, 195.3. IR (film): 800, 1255, 1670, 1755, 3400.

2-endo-Acetoxy-6-exo-benzoyl-5-exo-hydroxy-7-oxabicyclo[2.2.1]heptane-2-exo-carbonitrile, (12).

From 200 mg of 9 (0.5 mmol) was obtained 140 mg (93%) of 12 after chromatography (hexane:ethyl acetate, 1:1, R_f = 0.19). ^{1}H-NMR ($CDCl_3$): 2.20 (3H, s), 2.20-2.77 (2H, m), 3.60-3.80 (1H, m), 4.17-4.77 (2H, m), 5.23 (1H, s), 7.00-7.33 (1H, m), 7.43-7.77 (2H, m), 7.87-8.20 (2H, m). ^{13}C-NMR ($CDCl_3$): 20.5, 35.7, 51.7, 72.7, 74.4, 79.3, 83.7, 118.3, 128.7, 133.6, 135.0, 168.8, 196.0. IR (film): 700, 1075, 1675, 1750, 3400.

6-exo-Benzoyl-5-exo-hydroxy-7-oxabicyclo[2.2.1]heptan-2-one, (13)

From 540 mg of 10 (1.7 mmol) was obtained 347 mg (88%) of 13 after chromatography (hexane:ethyl acetate, 1:1, R_f = 0.26): ^{1}H-NMR ($CDCl_3$): 1.97-2.63 (2H, m), 3.40 (1H, br s), 4.03 (1H, dd, J = 7.0, 2.0 Hz), 4.40-4.63 (2H, m), 4.73 (1H, dd, J = 6.0, 2.0 Hz), 7.17-7.67 (3H, m), 7.80-8.10 (2H, m). ^{13}C-NMR ($CDCl_3$): 38.3, 58.5, 76.5, 81.1, 83.5, 128.3, 128.8, 133.9, 136.0, 196.5, 206.7. IR ($CHCl_3$): 900, 1210, 1450, 1590, 1675, 1760, 2900-3030, 3420.

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6. It is well known that 1,3-dipolar cycloadditions to norbornene and norbornadiene derivatives as well as their heterocyclic analogues lead exclusively to exo-adducts. See, for example: a) R.Huisgen, P.H.J.Ooms, M.Mungin and N.L.Allinger, J. Am. Chem. Soc., (1980), 102, 3951. b) D.N.Reinhondt and C.G.Konwenhoven, Rec. Trav. Chim. Pays-Bas, (1976), 95, 67.

7. We thank Dr. E.Gutiérrez Puebla, Dr. A.Monge and Dr. C.Ruiz Valero for carrying out the X-ray difraction analysis of 5a. These data will be published elsewhere.

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10. To our knowledge, this is the first report of oxanorbornenic hydroxynitrones. We have not explored the reactivity of these systems, aside from their acid-catalyzed hydrolysis.

11. The hydroxylic proton resonates downfield from 5.90 ppm in the ^{1}H-NMR spectra (DMSO-d_6) of these nitrones. After ca. 15 days in solution, a substantial disappearance of this proton was observed, this may be attributed a slow exchange with the solvent.

12. It has been reported that oxanorbornenic ketones undergo a facile Baeyer-Villiger rearrangement. See ref. 3.