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Tetrahedron 60 (2004) 3825–3830
Tetrahedron

The reaction of spiroepoxycyclohexadienones towards cyanide nucleophiles

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Received 12 January 2004; revised 8 February 2004; accepted 2 March 2004

Abstract—The reaction of spiroepoxycyclohexadienones **1** with TMSCN in the presence of catalytic amounts of Bu_4NCN results in the formation of two diastereomeric cyanohydrins. Alternatively, the reaction of **1** with equimolecular amounts of Bu_4NCN gave rise to products arising from two other different reaction paths.

1. Introduction

Spiroepoxycyclohexadienones **1** (Fig. 1) have attracted attention in the context of their reactivity as dienes in Diels–Alder reactions.[1] On the other hand, their use as synthetic intermediates has also been reported by considering the reactivity of the carbonyl group towards organolithium reagents.[2] Additionally, differently substituted spiroepoxycyclohexadienones **1** have been synthesised and evaluated as irreversible inhibitors of neutral sphingomyelinase.[3]

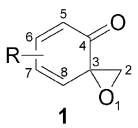

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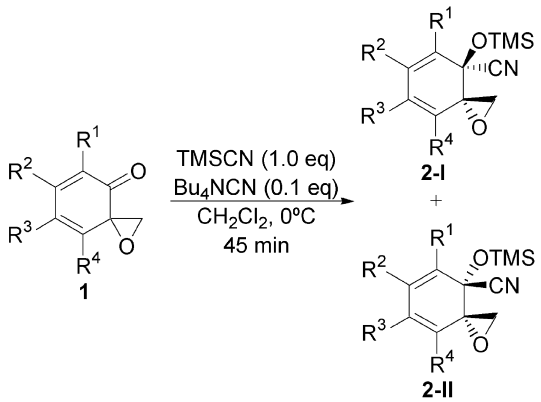
Figure 1.

Taking into account that compounds **1** show up to five possible electrophilic reaction centres, this densely functionalized structure may be considered as a suitable model to test the site-selectivity of the attack of a single nucleophilic agent. Considering that this type of process has not been previously studied on compounds such as **1**, with the exception of two isolated reports,[4] we decided to explore the behaviour against **1** of a nucleophilic reagent, the cyanide anion, arising from two different sources: TMSCN or Bu_4NCN.

2. Results and discussion

The reaction of spiroepoxycyclohexadienones **1** with TMSCN (1.0 equiv.) in the presence[5] of catalytic amounts of Bu_4NCN (0.1 equiv.) in CH_2Cl_2 at 0 °C for 45 min. afforded cyanohydrins **2** in yields between 35 and 70% as almost equimolecular mixtures of diastereomers (Scheme 1, Table 1).



Scheme 1.

Keywords: Epoxides; Catalysis; Cyanides.
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doi:10.1016/j.tet.2004.03.007

Table 1. Reaction of compound **1** with TMSCN (1.0 equiv.) and Bu_4NCN (0.1 equiv.)

No.	1	R^1	R^2	R^3	R^4	2 (%) [a]	dr[b]
1	**1a**	Br	MeO	Br	H	**2a** (71)	1.0:1.3
2	**1b**	Br	MeO	Br	MeO	**2b** (55)	1.0:1.0
3	**1c**	H	H	Br	H	**2c** (50)	1.0:1.4
4	**1d**	H	MeO	H	H	**2d** (55)	1.0:1.6

[a] Percent yield in the pure isolated mixture of diastereomeric **2**. The remaining starting material was recovered unchanged.
[b] Diastereomer ratio, evaluated by GC–MS. See Section 3.

The structural assignment of cyanohydrins **2** was possible by NOE measurements on the ^1H NMR spectra of the mixture of diastereomers (Fig. 2): selective irradiation (experiments carried out in toluene-d_8 and $CDCl_3$ at 500 MHz) of the methyl signal of the TMS group of the major isomer **2a-I** (9H, s, δ=0.22 ppm in toluene-d_8, δ=0.32 ppm in $CDCl_3$) gave an enhancement of one of the diastereotopic hydrogen atoms of the epoxide moiety (1H, d, ^3J=5.0 Hz, δ=2.98 ppm in toluene-d_8, δ=3.46 ppm in $CDCl_3$). This puts forward the *cis* stereochemical relationship between the OTMS group and the epoxidic CH_2 in **2a-I**. On the other hand, no NOE effect was observed upon irradiation of the methyl signal of the TMS group of the minor isomer **2a-II** (9H, s, δ=0.28 ppm in toluene-d_8, δ=0.29 ppm in $CDCl_3$).

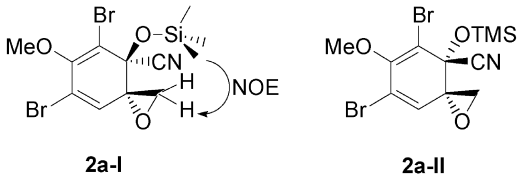
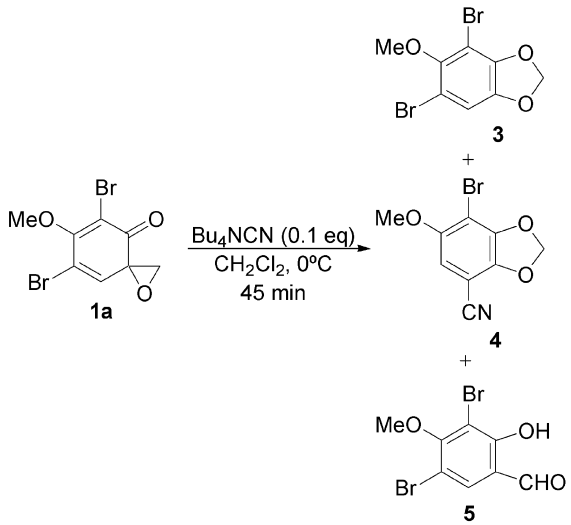


Figure 2.

Efforts to achieve the chromatographic separation of these diastereomers at preparative scale were unsuccessful. However, treatment of the mixture of compounds **2a** with TsOH (1.0 equiv.) in MeOH (0 °C, 2 h) resulted in a clean transformation of the minor isomer **2a-II** back into **1a**, whereas the major isomer **2a-I** remained unaltered[6] under these reaction conditions.

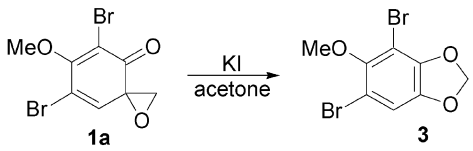
In order to gain more information on this process, we submitted compound **1a** to reaction, in two independent experiments, with either equimolecular amounts of TMSCN or Bu_4NCN. Whereas the reaction of **1a** with TMSCN under these new reaction conditions gave rise to the full recovery of the starting material, the reaction with Bu_4NCN (1.0 equiv., CH_2Cl_2, 0 °C, 45 min) afforded a mixture of compounds **3**, **4** and **5**, which were obtained in a ratio **3**:**4**:**5**=5.5:1.0:3.5 (evaluated by GC–MS) in 75% overall yield (Scheme 2).

The formation of benzodioxole **3** from **1a** has been previously reported under different experimental conditions: (a) by a 1,3-sigmatropic shift analogous to the rearrangement of vinylcyclopropanes to cyclopentenes;[4b] (b) by reaction with NaCN in DMSO or Et_2AlCN in toluene, albeit in low yield (20%);[4b] (c) by reaction with $^tBuMe_2SiCl$ in the presence of Et_3N in DMF.[4a,7] In an additional experiment, we have observed that the reaction of **1a** with



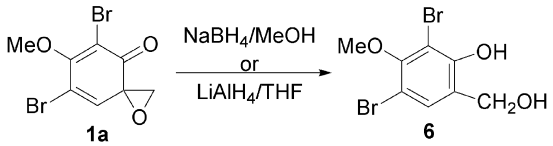
Scheme 2.

KI in acetone (24 h, rt) also affords **3** in 79% isolated yield (Scheme 3).



Scheme 3.

With respect to compounds **4** and **5**, they have not been observed in nucleophilic addition reactions to these kind of spiroepoxycyclohexadienones, although the related alcohol **6** (Scheme 4) is the main product in the reactions of **1a** both with $NaBH_4/CeCl_3$ in MeOH[4b] (70%) or $LiAlH_4$ in THF (70%), which indicates that also in these cases compound **5** may be formed and overreduced to **6**.



Scheme 4.

In an attempt to gain more insight into the factors that control the outcome of these reactions, we decided to carry out an ab initio MO study of compound **1a**. The determination of atomic coefficients in the frontier molecular orbitals, particularly in the LUMO, along with the atomic charges, should give a better idea of the sites more amenable to suffer nucleophilic attack. The data obtained from the HF/6-31G calculation of the most stable conformer of **1a** are shown in Table 2.

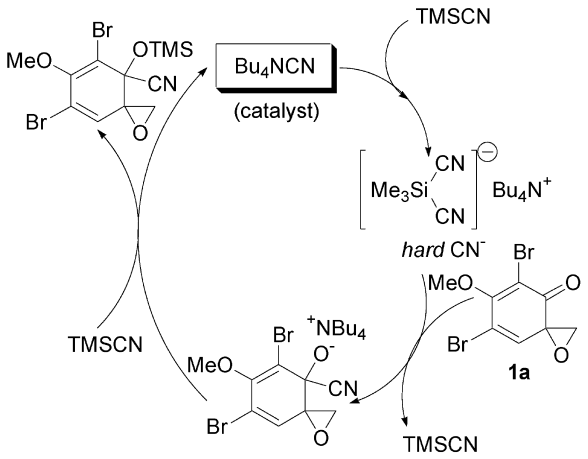
These results indicate that: (a) the epoxide moiety should not be reactive towards nucleophilic reagents, as both charges and LUMO-coefficients at C_2 and C_3 are smaller than the same parameters on C_4 and C_8; (b) for a charge-controlled reaction, the carbonyl carbon C_4 is clearly the preferred centre for nucleophilic attack; (c) for an orbital-controlled reaction, C_8 is the preferred centre for nucleophilic attack.

Table 2. HF/6-31G** calculations of energies (eV) and coefficients[a] of the frontier molecular orbitals, and charge distribution, of compound **1a**[b]

C_i	HOMO E=−9.1763	LUMO E=1.1404	Charges[b]
C_2	−0.0760	−0.1276	0.060
C_3	−0.0627	0.0194	0.077
C_4	−0.0237	0.1875	0.594
C_8	0.2497	0.2410	−0.050

[a] Values of the p_z coefficients. The relative p_z^1 contributions and their ΔC_i are analogues.
[b] Mülliken.

Therefore, the experimental outcome when **1a** was made to react with TMSCN (1.0 equiv.) in the presence of Bu_4NCN as catalyst (Scheme 5) may be explained on the basis of the formation of an hypervalent silicon intermediate[8] (note that no reaction took place with TMSCN alone, vide supra) which delivers a hard cyanide species that preferentially attacks the C=O group, giving rise to an intermediate ammonium salt plus TMSCN. Trapping of the ammonium salt with TMSCN affords the final product **2** and regenerates the catalyst.

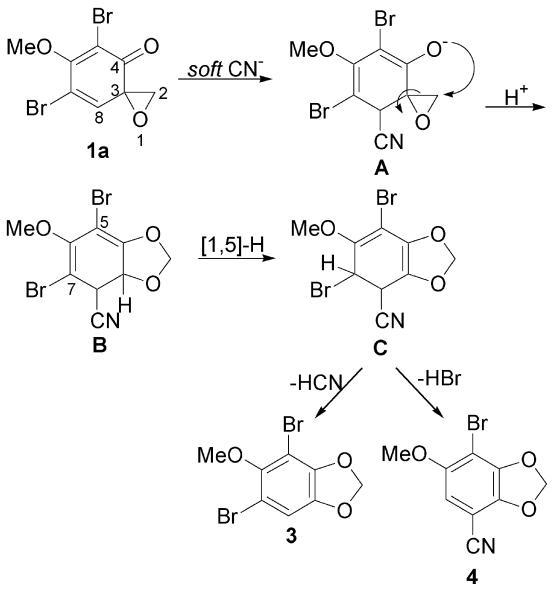


Scheme 5.

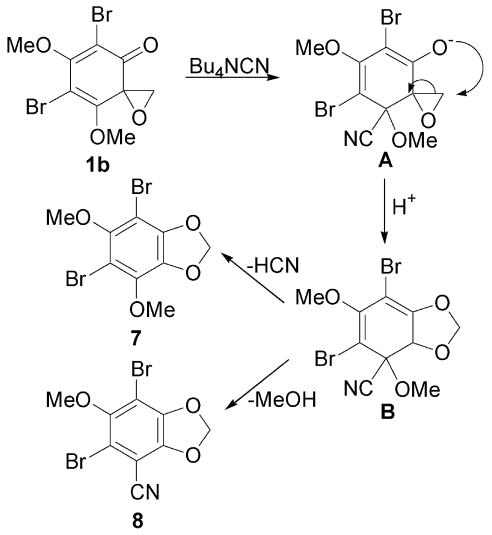
On the other hand, when the reaction was carried out with equimolecular amounts of Bu_4NCN (Scheme 6), a soft cyanide species is delivered, which attacks on C_8 affording an intermediate **A**. Intramolecular nucleophilic attack on C_2 takes place with cleavage of the C_2–C_3 bond instead of the expected C_2–O bond due to the formation a delocalized pentadienyl carbanion which is protonated on workup to give **B**, which finally aromatises by [1,5]-H shift[9] followed by loss of either HCN or HBr, affording the final products **3** and **4** respectively.

A similar reaction pathway may also account for the formation of **3** with I^- as nucleophile, when **1a** was treated with KI in acetone (Scheme 3). That the attack to C_8 by CN^- is the initial event of the reaction with equimolecular amounts of Bu_4NCN can also be deduced from the results obtained using **1b** as starting material (Scheme 7). In this case, a mixture of compounds **7** and **8** was obtained in a ratio **7**:**8**=1:3 (evaluated by GC–MS) and 72% overall yield.

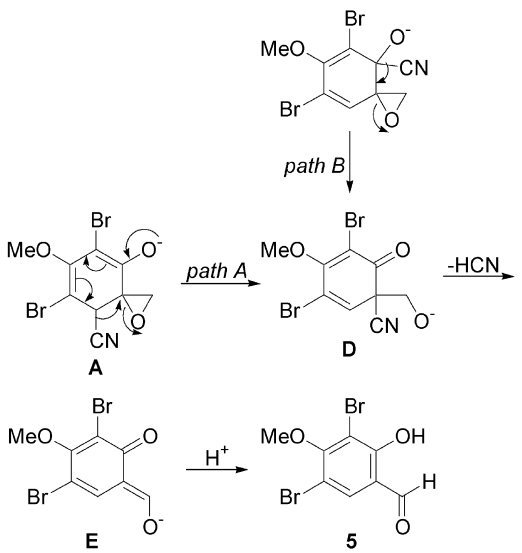
Finally, the formation of aldehyde **5** may be interpreted by two different reaction paths: (i) by initial CN attack on C_8



Scheme 6.



Scheme 7.



Scheme 8.

(Scheme 8, path A) followed by CN migration to afford intermediate **D**, which upon loss of HCN to give intermediate **E** and final aromatization affords **5**; or (ii) by initial CN attack on C_4 (Scheme 8, path B) followed by CN migration to afford intermediate **D**, which evolves to the final product as previously stated.

However, the path B can be ruled out because, in an independent essay, cyanohydrins **2** did not afford compounds **5** after reaction with Bu_4NCN or TMSCN–Bu_4NCN (2.5 h, 0 °C).

In summary in this paper the different behaviour of the epoxide moiety of spiroepoxycyclohexadienone towards cyanide nucleophiles has been described. A competitive reaction pathway was proposed in order to account for the different results obtained.

3. Experimental

3.1. General

All reactions were carried out under argon atmosphere. Column chromatography was performed on silica gel Merck 230–400 mesh. NMR spectra were recorded on Bruker 200-AM (200 MHz), Bruker AM300 (300 MHz) and on a Bruker AM500 (500 MHz) instruments, using $CDCl_3$ and toluene-d_8 as solvents. Chemical shifts are in ppm relative to TMS. Mass spectra were recorded on a mass spectrometer HP 5890. GC/MS analyses were performed with a capillary column 95% dimethyl 5% diphenylpolysiloxane, using a gradient of temperature 45–290 °C. Ab initio calculations were carried out using the Gaussian 94 program package[10] in personal computers running under the Linux operating system. The initial structure of **1a** was optimized using the semiempirical AM1 model, and the resulting geometry was employed as the starting structure for optimisation at the HF/6-31G** level. The 6-31G** atomic orbitals for bromine, as implemented in Gaussian 94, are incomplete, and they were supplemented with a *d* polarization function formed by a single gaussian primitive with a scale factor of 1.00, an exponent of 0.389, and a contraction factor of 1.00, giving a total of 30 basis functions.[11] Additional optimisations were carried out in order to locate the most stable conformer of **1a**, with respect to the methoxy group. This conformer turned out to be that with the MeO group *syn* to the epoxide oxygen, and perpendicular to the plane of the six-membered ring. Spiroepoxycyclohexadienone **1a** was synthesized using the method described by K. Hinterding et al.[4b] Compound **1c** was obtained using the method described by V. Bonnarme et al.[1b] Spiroepoxycyclohexadienone **1d** was synthesized using the method described by E. J. Corey et al.[2] Compound **1b** was obtained following the analogous synthetic route used by K. Hinterding et al.[4b] to synthesize **1a**, in a four step sequence using 2,4,6-trimethoxybenzaldehyde as the starting material. Compounds **3**, **5** and **6** have been previously described by K. Hinterding et al.[4b]The rest of chemicals were obtained from commercial sources and were used without further purification. Solvents were distilled and dried over molecular sieves.

3.2. Typical procedure for the cyanosilylation of 6-spiroepoxycyclohexadienones

To a solution of the carbonyl compound (0.37 mmol) in dry CH_2Cl_2 (0.5 mL) was added, under argon and at 0 °C, TMSCN (0.046 mL, 0.37 mmol) followed by a solution of the ammonium salt (10 mg, 0.037 mmol) in dry CH_2Cl_2 (0.5 mL). The mixture was stirred at 0 °C for 15 min. A saturated solution of $NaHCO_3$ (3 mL) was added and the mixture was extracted with CH_2Cl_2. Drying of the combined organic phases with $MgSO_4$ was followed by evaporation of the solvent under vacuum. The products were purified by chromatography on silica gel (ethyl acetate/hexane).

3.2.1. 5,7-Dibromo-6-methoxy-4-trimethylsilanyloxy-1-oxaspiro[2.5]octa-5,7-diene-4-carbonitriles, 2a. Data for **2a-I**, ^{1}H NMR: ($CDCl_3$, 500 MHz) δ 0.32 (s, 9H, $3CH_3$–Si), 2.92 (d, J=5.0 Hz, 1H, CH_2–O), 3.46 (d, J=5.0 Hz, 1H, CH_2–O), 3.81 (s, 3H, OCH_3), 6.19 (s, 1H, CH) ppm; ^{1}H NMR: (toluene-d_8, 500 MHz) δ 0.22 (s, 9H, $3CH_3$–Si), 2.01 (d, J=5.0 Hz, 1H, CH_2–O), 2.98 (d, J=5.0 Hz, 1H, CH_2–O), 3.30 (s, 3H, OCH_3), 5.58 (s, 1H, CH) ppm; ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 0.00 ($3CH_3$–Si), 50.16 (CH_2–CN), 58.87 (OCH_3), 59.46 (O–C–CH_2), 73.70 (O–C–CN), 109.10 (CBr), 114.68 (CN), 119.27 (CBr), 129.01 (CH), 148.87 (C–OCH_3) ppm; MS (70 eV, EI) *m/z* (%): 407/409/411 (5/10/5) [$M^{+\cdot}$], 362/364/366 (11/22/11) [M−45], 352/354/356 (5/8/4) [M−55], 347/349/351 (3/7/4) [M−60], 337/339/341 (4/6/3) [M−70], 229/231 (18/18), 201/203 (7/7), 137/139 (5/5), 122 (5), 103 (6), 89 (8), 75 (34), 74 (10), 73 (100), 59 (9), 45 (30), 44 (5), 43 (10). Data for **2a-II**: ^{1}H NMR: ($CDCl_3$, 500 MHz) δ 0.29 (s, 9H, $3CH_3$–Si), 3.06 (d, J=5.0 Hz, 1H, CH_2–O), 3.45 (d, J=5.0 Hz, 1H, CH_2–O), 3.81 (s, 3H, OCH_3), 6.12 (s, 1H, CH) ppm; ^{1}H NMR: (toluene-d_8, 500 MHz) δ 0.28 (s, 9H, $3CH_3$–Si), 2.05 (d, J=5.0 Hz, 1H, CH_2–O), 2.95 (d, J=5.0 Hz, 1H, CH_2–O), 3.35 (s, 3H, OCH_3), 5.50 (s, 1H, CH) ppm; ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 0.00 ($3CH_3$–Si), 51.75 (CH_2–CN), 58.00 (O–C–CH_2), 58.87 (OCH_3), 74.28 (O–C–CN), 108.50 (CBr), 115.27 (CN), 118.93 (CBr), 128.72 (CH), 148.87 (C– OCH_3) ppm; MS (70 eV, EI) *m/z* (%): 407/409/411 (7/15/8) [$M^{+\cdot}$], 363/365/367 (11/15/9) [M−44], 362/364/366 (39/78/40) [M−45], 352/354/356 (7/12/6) [M−55], 347/349/351 (6/13/8) [M−60], 229/231 (14/14), 201/203 (7/8), 137/139 (10/9), 103 (13), 89 (8), 75 (32), 74 (11), 73 (100), 59 (14), 47 (11), 45 (32), 43 (12). Anal. calcd for $C_{12}H_{15}Br_2NO_3Si$: C, 35.23; H, 3.70; N, 3.42. Found: C, 35.35; H, 3.75; N, 3.61.

3.2.2. 5,7-Dibromo-6,8-dimethoxy-4-trimethylsilanyloxy-1-oxaspiro[2.5]octa-5,7-diene-4-carbonitriles, 2b. Data for **2b-I**: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.14 (s, 9H, $3CH_3$–Si), 3.09 (d, 1H, J=5.4 Hz, CH_2–O), 3.22 (d, 1H, J=5.4 Hz, CH_2–O), 3.61 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3) ppm; MS (70 eV, EI) *m/z* (%): 437/439/481 (20/40/21) [$M^{+\cdot}$], 392/394/396 (10/18/11) [M−45], 377/379/381 (10/21/12) [M−60], 358/360 (47/47) [M−Br], 335/337/339 (12/20/12) [M−104], 259/261 (49/50) [M−Br–TMSCN], 231/233 (22/21), 75 (46), 73 (100), 59 (27), 45 (25), 43 (26). Data for **2b-II**: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.15 (s, 9H, $3CH_3$–Si), 3.05 (d, 1H, J=5.6 Hz, CH_2–O), 3.22 (d, 1H, J=5.6 Hz, CH_2–O), 3.61 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3) ppm; MS (70 eV, EI) *m/z* (%): 437/439/481

(22/47/23) [$M^{+\cdot}$], 392/394/396 (24/48/96) [M−45], 377/379/381 (17/34/16) [M−60], 358/360 (34/34) [M−Br], 335/337/339 (16/32/15) [M−104], 259/261 (52/50) [M−Br−TMSCN], 231/233 (21/19), 75 (28), 73 (100), 59 (28), 45 (32). Anal. calcd for $C_{13}H_{17}Br_2NO_4Si$: C, 35.55; H, 3.90; N, 3.19. Found: C, 35.71; H, 3.99; N, 3.27.

3.2.3. 7-Bromo-4-trimethylsilanyloxy-1-oxaspiro[2.5]-octa-5,7-diene-4-carbonitriles, 2c. Data for **2c-I**: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.19 (s, 9H, $3CH_3$−Si), 2.89 (d, 1H, J=5.0 Hz, CH_2−O), 3.25 (d, 1H, J=4.9 Hz, CH_2−O), 5.70−5.90 (m, 2H, H-5, H-8), 6.21 (dd, 1H, J=9.8 Hz, J=1.5 Hz, H-6) ppm; MS (70 eV, EI) *m/z* (%): 254/256 (79/81) [M−45], 103 (25), 75 (26), 73 (100), 45 (32). Data for **2c-II**: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.20 (s, 9H, $3CH_3$−Si), 2.83 (d, 1H, J=4.9 Hz, CH_2−O), 3.28 (d, 1H, J=4.9 Hz, CH_2−O), 5.70−5.90 (m, 2H, H-5, H-8), 6.21 (dd, 1H, J=9.8 Hz, J=1.5 Hz, H-6) ppm; MS (70 eV, EI) *m/z* (%): 254/256 (18/19) [M−45], 244/246 (10/10) [M−55], 103 (17), 75 (20), 73 (100), 45 (66). Anal. calcd for $C_{11}H_{14}BrNO_2Si$: C, 44.01; H, 4.70; N, 4.67. Found: C, 44.09; H, 4.81; N, 4.83.

3.2.4. 6-Methoxy-4-trimethylsilanyloxy-1-oxaspiro-[2.5]octa-5,7-diene-4-carbonitriles, 2d. Data for **2d-I**: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.18 (s, 9H, $3CH_3$−Si), 2.93 (d, 1H, J=4.9 Hz, CH_2−O), 3.50 (d, 1H, J=4.9 Hz, CH_2−O), 4.81 (d, 1H, J=2.5 Hz, H-2), 5.55 (d, 1H, J=10.1 Hz, H-5), 6.08 (dd, 1H, J=10.1, 2.5 Hz, H-4) ppm. Data for **2d-II**: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.02 (s, 9H, $3CH_3$−Si), 2.94 (d, 1H, J=4.9 Hz, CH_2−O), 3.45 (d, 1H, J=4.9 Hz, CH_2−O), 4.87 (d, 1H, J=2.5 Hz, H-5), 5.55 (d, 1H, J=10.1 Hz, H-8), 6.05 (dd, 1H, J=10.1, 2.5 Hz, H-7) ppm. Anal. calcd for $C_{12}H_{17}NO_3Si$: C, 57.34; H, 6.82; N, 5.57. Found: C, 57.25; H, 6.71; N, 5.65.

3.3. Typical procedure for the addition of Bu_4NCN to 6-spiroepoxycyclohexadienones 1

To a solution of the spiroepoxycyclohexadienone **1** (0.22 mmol) in dry CH_2Cl_2 (1.1 mL) was added, under argon and at 0 °C, a solution of Bu_4NCN (0.22 mmol) in dry CH_2Cl_2 (1.1 mL). The mixture was stirred at 0 °C for 45 min. A saturated solution of $NaHCO_3$ (5 mL) was added and the mixture was extracted with CH_2Cl_2. Drying of the combined organic phases with $MgSO_4$ was followed by evaporation of the solvent under vacuum. The products were purified by chromatography on silica gel (ethyl acetate/hexane).

3.3.1. 7-Bromo-6-methoxy-benzo[1,3]dioxole-4-carbonitrile, 4. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.98 (s, 3H, OCH_3), 6.09 (s, 2H, O−CH_2−O), 6.83 (s, 1H, CH) ppm; MS (70 eV, EI) *m/z* (%): 255/257 (100/97) [$M^{+\cdot}$], 240/242 (59/60) [M−15], 227/229 (19/19) [M−28], 210/212 (7/7), 182/184 (6/9), 131/133 (5/6), 75 (15), 53 (9), 29 (14).

3.3.2. 4,6-Dibromo-5,7-dimethoxy-benzo[1,3]dioxole, 7. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3. 82 (s, 3H, OMe), 3.84 (s, 3H, OMe), 5.99 (s, 2H, O−CH_2−O) ppm; MS (70 eV) *m/z* (%): 333/335/337 (47/95/46) [$M^{+\cdot}$], 318/320/322 (50/100/47) [M−CH_3], 262/264/266 (7/9/5) [M−71], 131/133 (9/9), 102 (7), 86 (7), 78 (7), 74 (7).

3.3.3. 5,7-Dibromo-6-methoxy-benzo[1,3]dioxole-4-carbonitrile, 8. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.79 (s, 3H, OMe), 6.15 (s, 2H, O−CH_2−O) ppm; MS (70 eV) *m/z* (%): 338/340/342 (51/100/48) [$M^{+\cdot}$], 323/325/327 (41/83/39) [M−CH_3], 293/295/297 (3/9/6) [M−45], 267/269/271 (7/9/4) [M−71], 244/246 (4/4), 131/133 (5/5), 92 (5), 59 (16).

3.4. Addition of KI to spiroepoxycyclohexadienone 1a

To a solution of **1a** (19 mg, 0.06 mmol) in dry acetone (10 mL) was added potassium iodide (100 mg, 0.60 mmol). The reaction was stirred for 72 h at room temperature. The residue was diluted with acetone and filtered to eliminate the excess of salt. Drying with $MgSO_4$ was followed by evaporation of the solvent under vacuum. The crude product was purified by chromatography on silica gel (ethyl acetate/hexane) to yield compound **3**[4b] (15 mg, 0.05 mmol) as a white solid.

3.5. Addition of $LiAlH_4$ to spiroepoxycyclohexadienone 1a

A solution of **1a** (100 mg, 0.32 mmol) in THF (0.5 mL) was added, dropwise, to a solution of $LiAlH_4$ (13 mg, 0.32 mmol) in THF (1 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. The reaction was quenched by the dropwise addition of water, and the mixture was extracted with Et_2O. Drying of the combined organic phases with $MgSO_4$ was followed by evaporation of the solvent under vacuum. The products were purified by chromatography on silica gel (ethyl acetate/hexane) and characterized by ^{1}H NMR and mass spectrometry. The reaction yielded compound **6** as the major product (70 mg, 0.22 mmol) and 2,4-dibromo-3-methoxy-phenol as a minor product (13 mg, 0.05 mmol).

Acknowledgements

Ministerio de Educación, Cultura y Deporte, Project BQU 2000-0653 is gratefully thanked for financial support.

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