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Chemical reactivity of hydroxymethylnaphthols: hetero-Diels–Alder products of *o*-naphthoquinomethides derived from 2- and 3-hydroxymethylnaphthols

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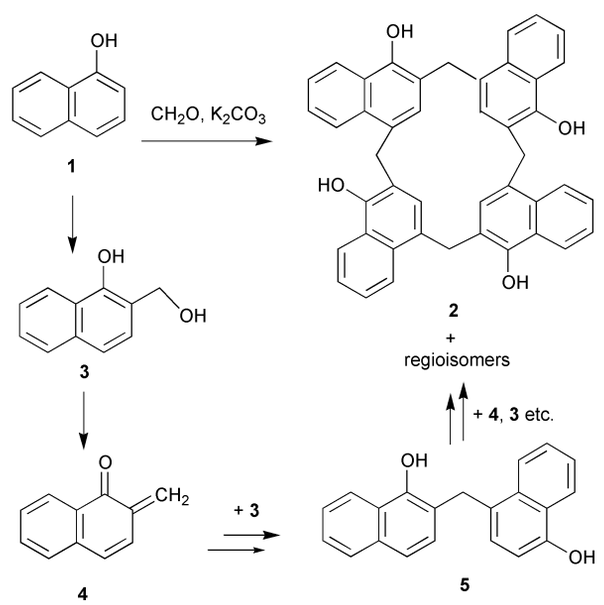
In relation to the syntheses of *exo*- and *endo*-calixnaphthalenes, the chemical reactions of several 2- and 3-hydroxymethylnaphthols, as well as other substituted naphthols, with formaldehyde under a variety of condensation reaction conditions were evaluated. In several instances, *o*-naphthoquinomethides were the putative intermediates which were formed and which resulted in hetero-Diels–Alder [4+2]cyclodimerization spiro products.

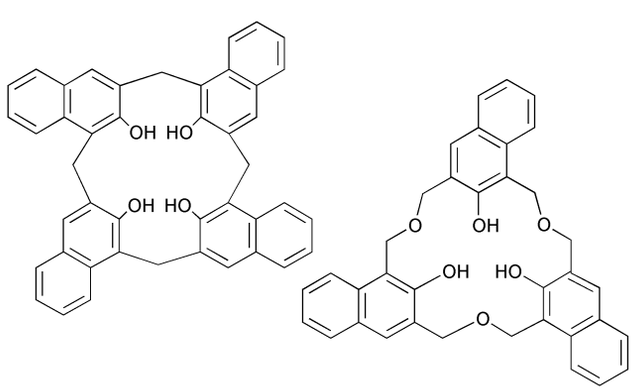
Introduction

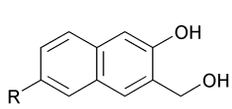
In 1993 we reported that the condensation reaction of 1-naphthol **1** with formaldehyde, under basic conditions in DMF, results in the formation of three regioisomeric *exo*-type calix[4]naphthalenes such as the C_4-symmetrical compound **2**.[1,2] Such *exo*-calix[4]naphthalenes have their hydroxy groups located on the periphery or "upper-rim" of the cyclic structures. A mechanistic scheme was subsequently proposed to account for the formation of all three of these compounds.[3] In this scheme, 2-hydroxymethyl-1-naphthol (**3**) is first formed and then undergoes *in situ* dehydration to form the 1,2-naphthoquino-2-methide intermediate **4** (Scheme 1). This naphthoquinomethide subsequently undergoes a condensation reaction at the *para* position of a second 1-naphthol to give a dinaphthylmethane such as **5** which can then condense sequentially with additional molecules of **4** and **3** to eventually produce a mixture of three *exo*-calix[4]naphthalene regioisomers including **2**.



Scheme 1

In relation to our on-going research into the synthesis and complexation properties of both the *exo*-[1,2] and *endo*-type calix[4]naphthalenes[4,5] *e.g.* **6** and also of the hexahomotrioxacalix[3]naphthalenes[6,7] *e.g.* **7**, we were interested in evaluating the chemistry of 2-hydroxymethyl-1-naphthol (**3**) and its regioisomer, 3-hydroxymethyl-2-naphthol (**8**). These relatively simple naphthol derivatives could, respectively, serve as readily-accessible precursors to compounds such as **6** and **7**. In this report we describe several chemical reactions of these hydroxymethyl naphthols which produce various hetero-Diels–Alder cycloaddition products under different reaction conditions.





8 R = H
8a R = Bu^t

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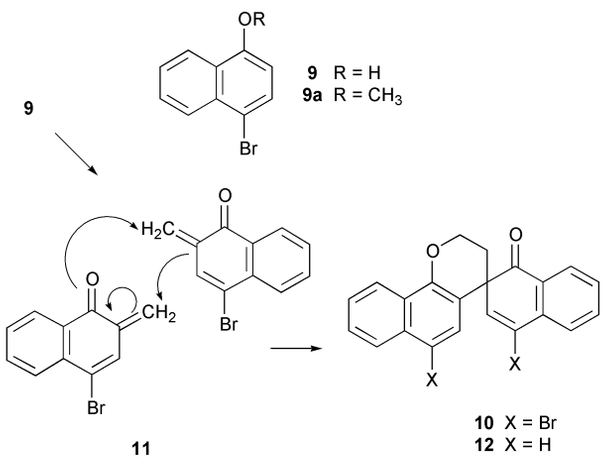
Results and discussion

Reactions of 2-hydroxymethyl-1-naphthols

As described above, 1-naphthol is a precursor for the formation of the three regioisomers of the *exo*-calix[4]naphthalenes such as **2**, in a "one-pot" reaction with formaldehyde under basic conditions in DMF *via* the postulated intermediate, **4**. Further supporting evidence for this intermediate was obtained from the reaction of 4-bromo-1-naphthol (**9**) with formaldehyde and K_2CO_3 in DMF, conditions which were similar to those used with **1**. Since **9** has its 4-position blocked, the reactions which lead to the formation of calix[4]naphthalenes are prevented, but the formation of a naphthoquinomethide is not. A yellow crystalline product was formed with spectral properties which indicated that it was **10**.

This spiroenone can presumably be formed *via* a hetero-Diels–Alder [4+2]cyclodimerization of the naphthoquinomethide intermediate **11**, which is of course, the 4-brominated analogue of **4** (Scheme 2). The structure of the spiroenone **10** was confirmed by X-ray crystallography (Fig. 1).[8,9] Attempts at



Scheme 2

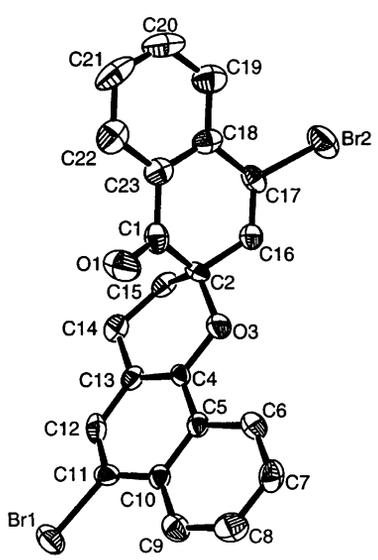
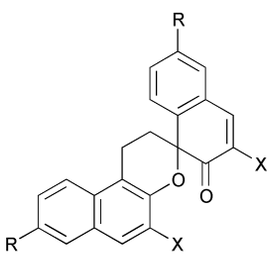


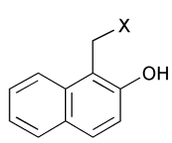
Fig. 1 X-Ray structure of spiroenone **10** showing the numbering used in the data tables.

detecting the corresponding spiroenone product **12** in the analogous reaction of 1-naphthol itself have been unsuccessful.

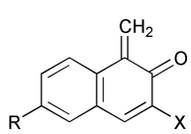
Chaucan *et al.*,[10] reported obtaining a similar hetero-Diels–Alder product, spiroenone **13**, formed from the thermal elimination reactions of the related 1-hydroxymethyl-2-naphthol (**14**) and in particular, two of its derivatives, **14a** and **14b**. They postulated that a 1,2-naphthoquino-1-methide **15** was the intermediate formed, and also found that **13** could be formed most efficiently from the thermal elimination of dimethylamine from the dimethylaminomethyl derivative **14a** in high boiling aprotic solvents. Catterall[11] later reported that with short heating times in decalin† or *n*-dodecane or over a prolonged reaction period in glacial acetic acid at 35 °C, **13** could be obtained in near-quantitative yields from the methoxymethyl derivative **14b**. At the boiling points of these solvents Catterall also found that **13** undergoes isomerization to form **16**. In our own case however, no such behaviour was observed with **12** and it remained unchanged after heating under similar conditions to those described by Catterall (Scheme 3).



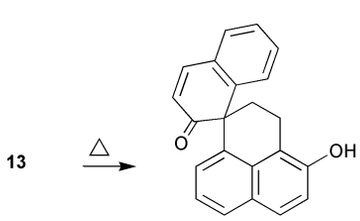
13 R = X = H
27 R = H, X = CH_2Br
27a R = Bu^t, X = CH_2Br



14 X = OH
14a X = $N(CH_3)_2$
14b X = OCH_3



15 R = X = H
28 R = H, X = CH_2Br
28a R = Bu^t, X = CH_2Br



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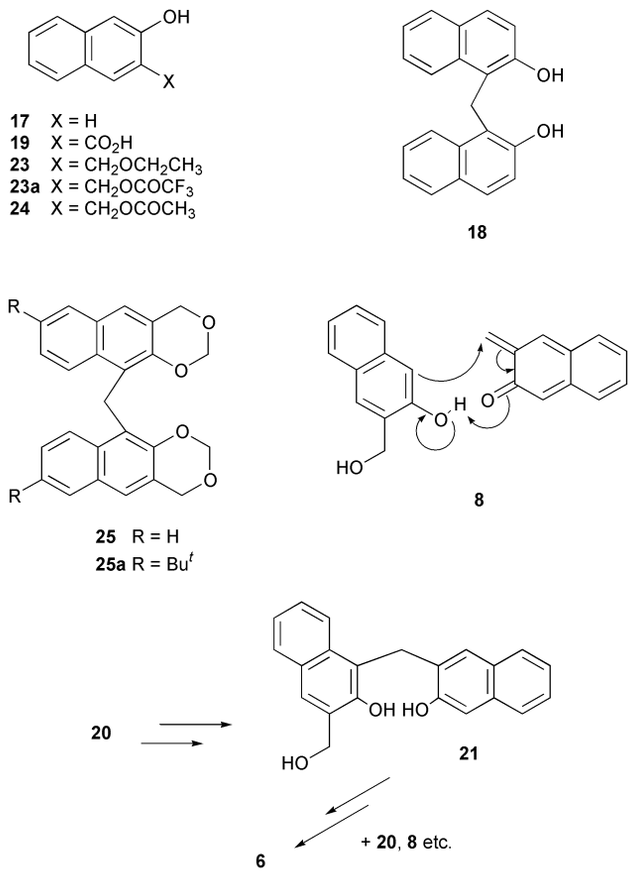
Scheme 3

Reactions of 3-hydroxymethyl-2-naphthols

The hydroxy group in 2-naphthol (**17**) only activates the 1-position in its condensation reactions with formaldehyde under either acid- or base-mediated reactions to form bis-(2-hydroxynaphthyl)methane (**18**). It therefore cannot be used as a direct precursor for the corresponding synthesis of *endo*-calixnaphthalenes such as **6**, in the same way that 1-naphthol was used in a "one-pot" reaction to form compounds such as **2**. *endo*-Calix[4]naphthalenes like **6** have their hydroxy groups located intraannularly within the 16-membered macrocycle, *i.e.* on the "lower rim" and are directly analogous to the better-known and more-widely studied calixarenes.[12]

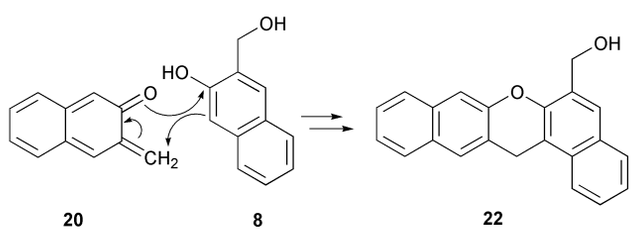
Reduction[13] of 3-hydroxy-2-naphthoic acid (**19**) however, easily gives 3-hydroxymethyl-2-naphthol (**8**) which in principle can undergo cyclocondensation to form **6** as envisioned in Scheme 4, for example, *via* the 2,3-naphthoquino-3-methide (**20**) and the dinaphthylmethane *e.g.* **21**. This intermediate is similar to **5**, one of the putative intermediates which led to the form-

† The IUPAC name for decalin is decahydronaphthalene.



Scheme 4

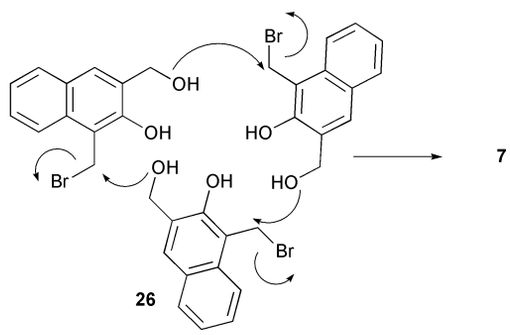
ation of the *exo*-calix[4]naphthalenes obtained from **1**, described earlier in Scheme 1. By analogy with a procedure used to synthesis *p*-*tert*-butylcalix[4]arene,[14] an attempt to synthesize **6** (or a larger calix[*n*]naphthalene) directly by heating **8** with aqueous NaOH in boiling xylene, was conducted. Although no formation of a calixnaphthalene could be detected, the major product formed in 22% yield was isolated from this reaction. Its spectral properties indicated it to be the pyran ring-containing compound **22**. This is presumably formed from a different mode of a [4+2] hetero-Diels–Alder reaction of **8** with **20** (*cf.* **4**) (Scheme 5).



Scheme 5

Using other similar conditions that afford calixarenes with *p*-substituted hydroxymethylphenols, or cyclotriveratrylene with veratryl alcohol, **8** was subjected to refluxing ethanolic HCl, or 5% trifluoroacetic acid (TFA) in $CHCl_3$ at room temperature.[15] Only the corresponding ethyl ether **23** and trifluoroacetate **23a** were formed, respectively.[16] Heating **8** in glacial acetic acid at 70 °C for 48 h produced only the corresponding acetate **24**, with no evidence of any naphthoquinomethide-mediated products being formed. When **8** or its 6-*tert*-butyl derivative **8a**,[4] were treated with paraformaldehyde in a more dilute (0.015 mM) solution of HBr in glacial acetic acid at room temperature, only the dinaphthylmethanes **25** or **25a** respectively, were produced in 19% and 10% yields. The structure of **25a** was confirmed by X-ray crystallography.[9] After considerable experimentation, the only conditions which were found to be effective in producing reasonable amounts (in 10–15% yields) of **6** from **8** (or the corresponding *tert*-butyl substituted derivative of **6** from **8a**) required the use of $TiCl_4$ in refluxing dioxane, as described by Andreetti *et al.*[17] and by us.[4]

In principle, 3-hydroxymethyl-2-naphthol (**8**) can also be envisioned as a suitable precursor for the corresponding bromomethyl derivative **26** which could be used as a precursor for homooxacalixnaphthalenes such as hexahomotrioxacalix[3]naphthalene **7**.[6,7] Scheme 6 envisions a "head-to-tail" Williamson ether cyclization leading to formation of **7**.



Scheme 6

Synthesis of **26** was attempted by reacting **8** with paraformaldehyde in a 0.10 mM solution of HBr in glacial acetic acid at room temperature for 24 h. A dark yellow crystalline product formed in 30% yield was isolated from the reaction mixture which also contained a resinous intractable material of the type that is commonly encountered in reactions of such naphthols. The ^{1}H NMR spectrum revealed a complex pattern of signals centered at δ 2.18, 2.62, 2.87 and 3.17 ppm respectively, in addition to two AB quartets observed between δ 4.0 to 5.0 ppm due to the two methylene groups, and signals in the aromatic region. A carbonyl group was revealed in the IR and ^{13}C NMR spectra. The spectral data was therefore consistent with the hetero-Diels–Alder product spiroenone **27** (*cf.* **13**, Scheme 3) whose structure was confirmed by X-ray crystallography (Fig. 2).[9] Studies suggest that the presence of

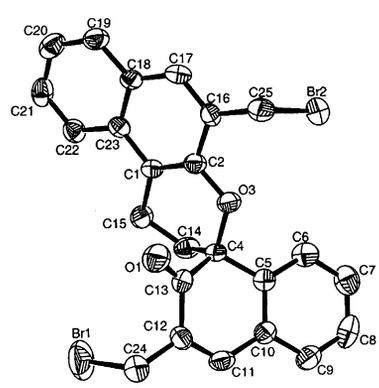
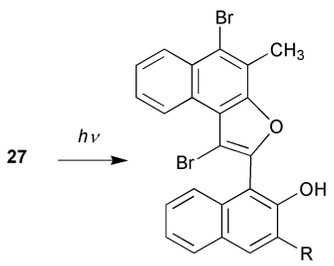


Fig. 2 X-Ray crystal structure of **27** showing numbering labels used in the data tables.

tert-butyl groups on the naphthalene units of **7** (and also on **6**) enhances their complexation with [60]fullerene. These compounds are therefore desirable synthetic targets, and the corresponding reaction using the *tert*-butyl derivative **8a** was also examined. However, only **27a** could be isolated from this reaction. The spiroenones **27** and **27a**, could have been formed *in situ* from the naphthoquinomethides **28** and **28a** respectively, the 3-bromomethyl analogues of **15**. It should be borne in

mind however, that the naphthoquinomethide **15** observed by Chaucan *et al.* and Catterall in their studies referred to above, was generated from 1-hydroxymethyl-2-naphthol (**14**) or its derivatives **14a**,**b**.

The thermal behaviour of **27** (and **27a**) is different from that reported for **13** since, unlike **13**, neither **27** nor **27a** remains unchanged after refluxing in either xylene or dodecane for prolonged periods. On the other hand, when subjected to photolytic conditions in benzene, **27** underwent reproducible rearrangement to produce four new compounds albeit in low yields. The major product, formed in approximately 12% yield was identified mainly by NMR to be the unusual and unexpected bromonaphthofuran, **29** (Scheme 7). Its structure



29 R = CHO
29a R = CH_3

Scheme 7

was confirmed by X-ray crystallography which reveals that its unit cell contains two independent atropisomeric molecules in the asymmetric unit (Fig. 3). The structures of the other crystal-

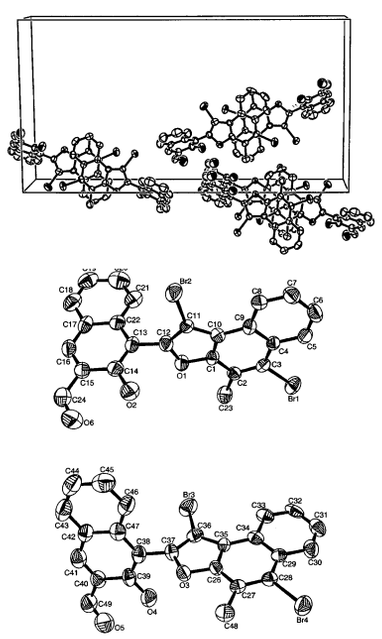
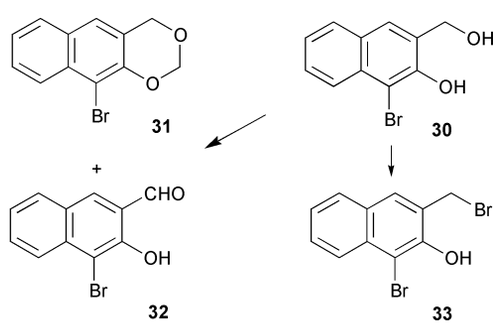


Fig. 3 X-Ray structures of bromonaphthofuran **29** showing the unit cell containing the two atropisomeric molecules and the numbering used in the data tables.

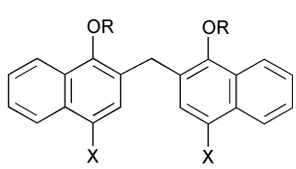
line products obtained in approximately 10% yields however could not be unequivocally assigned. Mass spectroscopic and HMQC and HMBC NMR data were consistent with structure **29a** in which a methyl group exists instead of the aldehyde group that is found in **29**. Its X-ray data however, could not be refined sufficiently to unambiguously confirm the assignment. The mechanism for the formation of these highly unusual brominated naphthofurans can only be conjectured, but in the case of **29** in which an aldehyde is produced, the mechanism clearly requires the involvement of oxygen and could result from photo-assisted oxidation of the corresponding methyl group in **29a**. When steps were taken to exclude atmospheric oxygen from the photolysis solutions by repeated freeze-drying and evacuation under vacuum followed by replacement with argon, **29** was still obtained, although the ratio of **29** to **29a** changed slightly in favour of the latter. The structures of the other two minor components could not be determined.

The presence of a bromine atom at the 1-position in compound **30**[6] instead of an *in situ*-generated bromomethyl group inhibits the formation of the corresponding naphthoquinomethide under similar conditions to those which produced **25** from **26**. Instead, only an intractable resinous product from which none of the corresponding spiroenone [4+2]cycloaddition products could be detected. When the reaction time was reduced to 4 h, only **31** was isolated in 21% yield, together with a small amount of the corresponding naphthaldehyde, **32**, the latter presumably being formed by oxidation of the starting material. With paraformaldehyde in a 0.015 mM solution of HBr in glacial acetic acid, again only **31** and **32** were formed in 36% and 10% yields respectively. With a 0.10 mM solution of HBr in glacial acetic acid, at room temperature for 1 h without any added paraformaldehyde, **30** only produced 71% of the corresponding bromomethylated product **33** (Scheme 8).



Scheme 8

From the foregoing discussion, the reactivity of 2-hydroxymethyl-1-naphthol (**3**) is clearly different to that of 3-hydroxymethyl-2-naphthol (**8**), or that of 1-hydroxymethyl-2-naphthol (**14**) and its derivatives, **14a**–**c**. Apart from the fact that **3** could not be isolated, its corresponding bis(1-hydroxynaphthyl)methane **34** can to date only be synthesized using an indirect method: namely, by the reaction of 4-bromo-1-methoxynaphthalene **9a** using $BF_3{\cdot}Et_2O$–formaldehyde conditions[3] to form **35** which, upon debromination with tri-*n*-butylstannane,[3] forms **36**. Demethylation of **36** with BBr_3 affords **34**. By contrast, bis(2-hydroxy-1-naphthyl)methane (**18**) is very easily formed from **14a** (and also from **17** as mentioned above).



34 R = X = H
35 R = CH_3, X = Br
36 R = CH_3, X = H

In conclusion, the results described here show that the chemistry of the hydroxymethylnaphthols and indeed, the chemistry of naphthols themselves, is exactingly dependent on the conditions employed. In some cases, regioisomeric hetero-Diels–Alder [4+2] dimers are formed from the putative corresponding *o*-naphthoquinomethides. These findings potentially limit their direct application as immediate precursors for the *endo*-calixnaphthalenes.

Experimental

General methods

For general experimental data see references 3 and 4. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75.47 MHz respectively, in $CDCl_3$ unless otherwise indicated. All reactions were carried out under Ar unless otherwise noted. Chromatography was performed using 60-mesh silica gel and preparative layer (1 mm) chromatography (PLC) with standard thin layer chromatography (TLC) grade silica gel. Flash chromatography was conducted using 230–400 mesh silica gel. Where noted, HRMS were conducted on a Quattro 2 spectrometer with APCI in positive or negative mode, as indicated.

Spiroenone compound (10)

To a solution of 4-bromo-1-naphthol (**9**) (395 mg, 1.7 mmol) in DMF (3.0 mL) was added 37% formaldehyde (0.20 mL) and aqueous 10% K_2CO_3 (0.28 mL). The mixture was refluxed, with stirring under N_2, for 30 min. The reaction mixture was then poured into (50 mL) of ice–water and a beige–brown precipitate formed which was collected by suction filtration. The precipitate was purified by TLC using ethyl acetate : petroleum ether (30 : 70) affording **10** (80 mg, 30%) as yellow crystals: mp 130–132 °C; δ_H (C_6D_6) 1.35–1.45 (m, 1H), 1.55–1.65 (m, 1H), 2.00–2.15 (m, 1H), 2.20–2.31 (m, 1H), 6.51 (s, 1H), 6.80–6.85 (td, 1H), 7.00–7.06 (td, 1H), 7.20 (s, 1H), 7.23–7.25 (m, 1H), 7.28–7.30 (m, 1H), 7.46–7.49 (dd, 1H), 7.88–7.91 (dd, 1H), 8.28–8.30 (m, 1H), 8.23–8.35 (dd, 1H); δ_C (C_6D_6) 21.1, 28.8, 81.4, 113.6, 115.4, 121.1, 122.4, 126.4, 126.8, 127.1, 127.7, 128.0, 128.6, 129.1, 129.7, 131.0, 132.1, 134.8, 135.1, 135.5, 148.2, 195.3; *m*/*z* (%): 471 (4), 469 (8), 467 (5), 458 (1), 456 (2), 454 (1), 441 (2), 439 (3), 437 (2), 236 (81), 234 (81), 208 (33), 206 (33); APCI HRMS calcd for $C_{22}H_{14}{}^{79}Br^{81}BrO_2$ 468.9236, found 468.8116.

X-Ray data for 10. $C_{22}H_{14}Br_2O_2$ (crystallized from $CHCl_3$–EtOH) triclinic, space group $P\bar{1}$ (no.2), a = 8.911 (4) Å, b = 12.901 (2) Å, c = 8.346 (8) Å; α = 91.10 (4)°, β = 107.23 (6)°, γ = 106.15 (2)°, Z = 2, D_{calc} = 1.785 g cm^{-3}. Intensity data were measured at 299 ± 1 K on a Rigaku AFC6S diffractometer with graphite–monochromated Mo-Kα radiation (λ = 0.71069 Å) to $2\theta_{max}$ (deg) 50.1°. A total of 3314 reflections were measured of which 3094 (R_{int} = 0.037) were unique. The final cycle of full-matrix least-squares refinement on F was based on 1684 observed reflections ($I > 2.00\sigma(I)$) and 277 variable parameters and converged with unweighted and weighted agreement factors of: R_1 = 0.042, wR_2 = 0.027 and gof = 1.54.

Pyran (22)

To a solution of **8** (1.0 g, 5.75 mmol) in xylene (60 mL) under N_2 was added aqueous NaOH (8 mg, 0.2 mmol in 5 mL water). Upon heating, the colorless emulsion turned light yellow. The reaction mixture was refluxed for 1 week. After cooling to room temperature, the solvent was removed under vacuum. The dark brown residue was extracted with chloroform (250 mL) for 6 h using a Soxhlet extraction apparatus. After evaporating the solvent, the residue was purified by TLC using ethyl acetate : hexane (4 : 6) as solvent. The pyran ring-containing compound **22** was obtained as a colorless solid (400 mg, 22%): mp 140–142 °C; δ_H (CD_2Cl_2) 4.58 (s, 2H), 5.04 (s, 2H), 7.41–7.96 (m, 11H); δ_C (CD_2Cl_2) 24.9, 61.9, 121.0, 122.0, 124.5, 124.6, 126.2, 126.4, 126.7, 126.9, 127.2, 128.2, 128.5, 128.8, 129.1, 129.7, 130.5, 133.3, 145.1, 145.2; *m*/*z* (%): 312 (M^+, 100), 311 ($M^+ - 1$, 79), 294 (16), 282 (22), 281 (89), 265 (12); HRMS calcd for $C_{22}H_{16}O_2$ 312.1149, found 312.1038.

3-(Ethoxymethyl)-2-naphthol (23)

To a solution of **8** [13] (100 mg, 0.53 mmol) in 95% ethanol (20 mL) was added aqueous concentrated HCl (5 mL). The reaction mixture was stirred at rt for 10 h, during which time no further change was observed by TLC. The reaction mixture was heated to 70–75 °C and kept at that temperature for 3 h. After cooling to room temperature, the reaction mixture was poured into crushed ice (25 g). A purple precipitate formed. After filtering the precipitate was washed with water until the washings were neutral to pH paper and then dried under vacuum. The crude product was purified by TLC with dichloromethane as solvent to afford **23** as a colorless solid (395 mg, 68%): mp 80–82 °C; δ_H 1.29 (t, J = 6.9, 3H), 4.86 (s, 2H), 7.25 (s, 1H), 7.30 (m, 1H), 7.40 (m, 1H), 7.53 (s, 1H), 7.64 (q, J = 6.9, 2H), 7.68–7.72 (m, 2H), 7.78 (s, OH); δ_C 15.2, 66.4, 72.5, 111.2, 123.7, 125.1, 126.5, 127.6, 127.5, 127.6, 128.4, 134.9, 154.4; *m*/*z* (%): 202 (M^+, 26), 157 (15), 156 (59), 129 (12), 128 (100), 127 (11), 115 (6); APCI HRMS calcd for $C_{13}H_{14}O_2$ 202.0993, found 201.8080.

3-(Trifluoroacetoxymethyl)-2-naphthol (23a)

To a solution of **7** in $CHCl_3$ (8 mL) was added trifluoroacetic acid (0.4 mL). The reaction mixture was stirred for 14 h at rt. The reaction mixture was washed with water until the washings were neutral to pH paper. After drying with $MgSO_4$, filtering and evaporating the solvent, the crude product was purified by TLC using CH_2Cl_2 as solvent to afford **23a** as a light brown solid (56 mg, 37%): mp 113–115 °C; δ_H 5.58 (s, 2H), 7.16 (s, 1H), 7.36 (m, 1H), 7.46 (m, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.83 (s, 1H); *m*/*z* (%): 270 (M^+, 7), 174 (3), 172 (2), 157(15), 156 (33), 129 (16), 128 (100); APCI HRMS calcd for $C_{13}H_9F_3O_3$ 270.0503, found 270.0142.

Bis(2*H*,4*H*-naphtho[2,3-*d*][1,3]dioxin-10-yl)methane (25)

To a mixture of **8** (260 mg, 1.13 mmol) and paraformaldehyde (70 mg, 2.3 mmol) in 3.5 mL acetic acid was added 0.30 mL of 15% HBr in acetic acid at rt. The reaction was left stirring for 12 h. The reaction solution was worked up by adding 30 mL of $CHCl_3$ and washing several times with H_2O, then with 20 mL of aqueous 10% $NaHCO_3$ and finally with H_2O. After drying and evaporating the solvent, the crude product was purified by TLC using $CHCl_3$ as solvent to give 76 mg of **25** (19%) as a pale yellow solid: mp 229–231 °C; δ_H 4.83 (s, 2H), 5.17 (s, 4H), 5.47 (s, 4H), 7.23 (t, J = 7 Hz, 2H), 7.29 (t, J = 8.5 Hz, 2H), 7.34 (s, 2H), 7.62 (d, J = 8 Hz, 2H), 8.15 (d, J = 8.5, 2H); δ_C 20.4, 67.1, 91.9, 121.8, 122.3,0 123.0, 123.8, 124.4, 125.8, 128.0, 129.1, 132.9, 184.2; *m*/*z* (%): 384 (M^+, 3), 234 (8), 199 (23), 170 (18), 169 (100), 158 (12), 149 (16); APCI HRMS calcd for $C_{25}H_{20}O_4$ 384.1361 found 383.9500.

Bis(7-*tert*-butyl-2*H*,4*H*-naphtho[2,3-*d*][1,3]dioxin-10-yl)methane (25a)

Compound **8a** (260 mg, 1.13 mmol) was subjected to the same reaction conditions as with **25** to afford after TLC purification using $CHCl_3$: petroleum ether (4 : 6) as solvent, **25a** (50 mg, 10%) as a yellow solid: mp 260–261 °C; δ_H 1.32 (s, 18H), 4.78 (s, 2H), 5.19 (s, 4H), 5.52 (s, 4H), 7.28 (s, 2H), 7.35 (d, J = 2.1 Hz, 2H), 7.38 (d, J = 2.4 Hz, 2H), 7.53 (d, J = 1.8 Hz, 2H), 8.10 (d, J = 9 Hz, 2H); δ_C 20.20, 30.95, 34.41, 66.92, 91.77, 121.56, 121.99, 122.74, 122.82, 124.07, 124.70; *m*/*z* (%): 498 (M^+, 6), 496 (78), 450 (12), 437 (33), 436 (94), 421 (8), 321 (8), 295 (11), 265 (8), 237 (21), 225 (15); HRMS calcd for $C_{33}H_{36}O_4$ 496.2612, found 496.1373.

X-Ray data for 25a. $C_{33}H_{36}O_4$, primitive monoclinic, space group $P2_1/n$ (no. 14), a = 6.237 (1) Å, b = 26.725 (2) Å, c = 16.872 (2) Å, β = 96.20 (2)°, Z = 4, D_{calc} = 1.18 g cm^{-3}. Intensity data were measured at 299 ± 1 K on a Rigaku AFC6S diffractometer with graphite-monochromated Cu-Kα radiation (λ = 1.54178 Å) to $2\theta_{max}$ (deg) 120.1°. A total of 4689 reflections were measured of which 4251 (R_{int} = 0.031) were unique. The

final cycle of full-matrix least-squares refinement on F was based on 2008 observed reflections ($I > 2.00\sigma(I)$) and 335 variable parameters and converged with unweighted and weighted agreement factors of: $R_1 = 0.068$, $wR_2 = 0.066$ and gof = 2.18.

Spiro compound (27)

To a solution of **8** (1.17 g, 6.72 mmol) and paraformaldehyde (410 mg, 13 mmol) in acetic acid (20 mL) was added a solution of 15% HBr in acetic acid (20 mL) dropwise under argon. The reaction mixture was stirred at rt for 24 h. The reaction mixture was worked up by adding 70 mL of CH_2Cl_2, and the mixture was washed several times with H_2O and finally with 50 mL of aqueous saturated $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated on a rotary evaporator. The crude product was purified by column chromatography using CH_2Cl_2 : petroleum ether (1 : 1) to give **27** as a yellow crystalline solid (600 mg, 30%). A sample was crystallized from $CHCl_3$: mp 175–180 °C (decomp.); $\nu_{max}(CHCl_3/cm^{-1})$ 1693, 1626, 1507, 1449, 1401, 1246, 1210; δ_H 2.18 (m, 1H), 2.62 (m, 1H), 2.87 (m, 1H), 3.17 (m, 1H), 4.04 (d, J = 9.9 Hz, 1H), 4.56 (d, J = 9.9 Hz, 1H), 4.62 (d, J = 9.6 Hz, 1H), 4.96 (d, J = 9.6 Hz, 1H), 7.39 (m, 3H), 7.46 (s, 1H), 7.49 (m, 2H), 7.76 (s, 2H), 7.95 (d, J = 7.5 Hz, 1H); δ_C 18.4, 27.7, 30.1, 33.1, 83.0, 113.1, 121.9, 123.8, 126.3, 126.6, 126.9, 128.3, 128.4, 128.5, 128.6, 128.9, 129.7, 131.0, 131.6, 132.8, 141.7, 142.3, 145.2, 198.0; *m/z* (%): 500 ($M^+ + 4$, 1), 498 ($M^+ + 2$, 3), 496 (M^+, 1), 336 (1), 250 (18), 249 (38), 248 (3), 170 (9), 169 (63), 142 (5), 141 (32), 139 (12), 115 (17), 78 (100); APCI HRMS calcd for $C_{24}H_{19}{}^{79}Br^{81}BrO_2$ $(M + H)^+$ 498.9688, found 498.7780.

X-Ray data for 27. $C_{24}H_{18}O_2Br_2$, monoclinic, space group $P2_1/n$ (no. 14), a = 9.529 (4) Å, b = 17.524 (8) Å, c = 12.147 (5) Å, β = 98.82 (4)°, Z = 4, D_{calc} = 1.651 g cm^{-3}. Intensity data were measured at 299 ± 1 K on a Rigaku AFC6S diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71069 Å) to $2\theta_{max}$ (deg) 50.1°. A total of 3913 reflections were measured of which 3683 (R_{int} = 0.0440) were unique. The final cycle of full-matrix least-squares refinement on F was based on 1946 observed reflections ($I > 2.00\sigma(I)$) and 308 variable parameters and converged with unweighted and weighted agreement factors of: $R_1 = 0.047$, $wR_2 = 0.032$ and gof = 1.67.

Photolysis of 27. A solution of **27** (80 mg, 0.16 mmol) in 3 mL benzene was photolyzed (λ = 350 nm) under N_2 for 44–48 h. After evaporation of the solvent, the crude product was purified by TLC using $CHCl_3$: petroleum ether (3 : 7) to give **29** (10 mg) as a pale yellow solid: mp 120–121 °C; δ_H 2.51(s, 3H), 2.77 (s, 3H), 5.60 (s, 1H), 7.42–7.53 (m, 3H), 7.70–7.65 (m, 2H), 7.80–7.78 (s + m, 2H), 8.49 (d, J = 10 Hz, 1H), 9.15 (d, J = 9.5 Hz, 1H); δ_C 16.8, 17.1, 100.7, 107.9, 119.3, 122.5, 123.2, 124.2, 124.2, 124.3, 126.7, 126.8, 126.8, 126.9, 127.8, 128.5, 129.0, 130.0, 132.3, 132.5, 147.8, 152.3, 152.8; *m/z* (%): 510 ($M^+ + 2$, 54), 508 (M^+, 28), 432 (50), 418 (30), 416 (31), 279 (14), 277 (14), 276 (23); HRMS calcd for $C_{24}H_{14}{}^{79}Br^{81}BrO_3$ 507.9310, found 507.9321.

X-Ray data for 29. $2{\cdot}C_{24}H_{14}Br_2O_3$, monoclinic, space group $P2_1/n$ (no. 14), a = 7.271 (1) Å, b = 31.618 (1) Å, c = 16.619 (1) Å, β = 92.647 (2)°, Z = 4, D_{calc} = 1.776 g cm^{-3}. Intensity data were measured at 299 ± 1 K on a Rigaku AFC6S diffractometer with graphite-monochromated Cu-Kα radiation (λ = 1.5418 Å) to $2\lambda_{max}$ (deg) 120.1°. A total of 6329 reflections were measured of which 5815 (R_{int} = 0.037) were unique. The final cycle of full-matrix least-squares refinement on F was based on 3282 observed reflections ($I > 2.00\sigma(I)$) and 523 variable parameters and converged with unweighted and weighted agreement factors of: $R_1 = 0.046$, $wR_2 = 0.045$ and gof = 1.36. Also isolated was **29a** (9 mg), as a yellow solid: mp 230–233 °C (decomp.); δ_H 2.78 (s, 3H), 7.67–7.45 (m, 5H), 8.00 (d, J = 5.4 Hz, 1H), 8.38 (s, 1H), 8.51–8.46 (m, 1H), 9.16–9.14 (m, 1H), 10.2 (s, 1H), 10.8 (s, 1H); δ_C 16.8, 29.9, 100.2, 111.3, 119.4, 122.7, 125.3, 126.7, 128.5, 130.5, 131.9, 137.5, 141.0, 147.6, 152.3, 156.4, 196.8; *m/z* (%): 498 (22), 497 (10), 496 (42), 494 (22), 419 (23), 418 (93), 417 (72), 416 (100), 390 (20), 387 (73); HRMS calcd for $C_{24}H_{16}{}^{79}Br^{81}BrO_2$ 495.9495, found 495.9529.

Spiro compound (27a)

Compound **8a** (520 mg, 2.26 mmol) was subjected to the same reaction conditions that produced **27** to afford a crude product that was purified by column chromatography using $CHCl_3$: petroleum ether (1 : 1) to give 130 mg of **27a** as an orange solid: mp 134–136 °C; δ_H 1.38 (s, 9H), 1.42 (s, 9H), 2.17 (m, 1H), 2.61 (m, 1H), 2.85 (m, 1H), 3.15 (m, 1H), 4.05 (d, J = 17.1 Hz, 1H), 4.58 (d, J = 10.2 Hz, 1H), 4.63 (d, J = 9.6 Hz, 1H), 4.98 (d, J = 9.6 Hz, 1H), 5.80 (s, 1H), 7.38 (d, J = 1.8 Hz, 1H), 7.48 (s, 1H), 7.53 (dd, J = 1.8, 10.2 Hz, 1H), 7.59 (dd, J = 2.1, 10.8 Hz, 1H), 7.73 (br, 2H), 7.79 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H); δ_C 8.8, 18.0, 28.0, 30.4, 31.2, 33.0, 34.5, 57.0, 82.9, 112.6, 121.7, 123.6, 125.7, 126.1, 126.2, 126.8, 128.1, 128.9, 130.9, 131.6, 140.4, 142.4, 146.4, 149.6, 151.7, 198.7; *m/z* (%): 612 (1), 610 (2), 306 (3), 226 (19), 225 (100), 210 (12); APCI HRMS calcd for $C_{32}H_{34}{}^{79}Br^{81}BrO_2$ 610.0903, found 610.0308.

3-(Acetoxymethyl)-2-naphthol (24)

A mixture of **8** (300 mg, 1.72 mmol) in 15 mL of acetic acid was heated at 70 °C for 48 h. The reaction mixture was cooled to rt and then 30 mL of chloroform was added. The solution was first washed with several portions of water, then with 30 mL of aqueous 10% $NaHCO_3$. The organic layer was separated, dried and evaporated. The crude product was purified by TLC using ethyl acetate : petroleum ether (3 : 7) to give **24** (165 mg, 45%) as a pale yellow solid: mp 95–96 °C; δ_H 5.31 (s, 3H), 7.28 (s, 1H), 7.32 (t, J = 8 Hz, 1H), 7.38 (s, 1H), 7.42 (t, J = 7 Hz, 1H), 7.68 (d, J = 8.5, 1H), 7.75 (J = 8.5, 1H), 7.80 (s, 1H); δ_C 0.9, 63.3, 112.1, 124.0, 124.1, 126.5, 127.2, 127.9, 128.6, 132.1, 135.5, 152.8, 173.4; *m/z* (%) 216 (M^+, 15), 158 (3), 157 (17), 156 (68), 129 (15), 128 (100); APCI HRMS calcd for $C_{13}H_{11}O_3$ $(M - H)^-$ 215.0785, found 214.9132.

10-Bromo-2*H*,4*H*-naphtho[2,3-*d*][1,3]dioxine (31)

To a mixture of **30** (300 mg, 1.19 mmol) and paraformaldehyde (75 mg, 2.4 mmol) in 4.5 mL of acetic acid was added 4.5 mL of 15% HBr in acetic acid at rt. The reaction was left stirring for 4 h after which time it was worked up in the usual manner. The crude product was purified by TLC using ethyl acetate : petroleum ether (1 : 9) to give **31**, 65 mg (21%): mp 78–80 °C; δ_H 5.10 (s, 2H), 5.44 (s, 2H), 7.39 (t, J = 7 Hz, 1H), 7.42 (s, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.69 (d, J = 8 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H); δ_C 66.7, 92.5, 107.5, 122.8, 123.8, 125.0, 126.1, 127.6, 127.9, 129.5, 132.2, 147.9; *m/z* (%): 266 ($M^+ + 2$, 24), 264 (M^+, 26), 237 (11), 236 (90), 234 (97), 208 (20), 206 (20), 155 (100); APCI HRMS calcd for $C_{12}H_9{}^{79}BrO_2$ 263.9786, found 263.7771. Compound **32** (10 mg, 4%) was also obtained as a yellow solid: mp 114–115 °C; δ_H 7.47 (t, J = 10 Hz, 1H), 7.73 (t, J = 14.5 Hz, 1H), 7.90 (d, J = 14 Hz, 1H), 8.16 (s, 1H), 8.23 (d, J = 14.5 Hz, 1H), 10.02 (s, 1H), 11.09 (s, 1H); δ_C 107.3, 122.0, 123.0, 125.0, 126.2, 128.0, 131.8, 136.3, 137.3, 152.8, 196.3; *m/z* (%): 252 ($M^+ + 2$, 96), 251 (42), 250 (M^+, 100), 249 (35), 195 (15), 193 (16), 125 (11), 114 (44); APCI HRMS calcd for $C_{11}H_6{}^{79}BrO_2$ $(M - H)^-$ 248.9551, found 248.8685. When the reaction was conducted in a 0.015 mM solution of HBr in glacial acetic acid, **31** and **32** were formed in 36% and 10% yields, respectively.

1-Bromo-3-(bromomethyl)-2-naphthol (33)

To a mixture of **30** (300 mg, 1.13 mmol) in 4.5 mL of acetic acid was added 4.5 mL of 15% HBr in acetic acid at rt. The reaction

was left stirring for 1 h. The reaction solution was worked up as usual. The crude product was purified by washing with diethyl ether to give **33** (0.265 g, 71%) as a pale yellow solid: mp 105–106 °C; δ_H 4.75 (s, 2H), 6.20 (s, 1H), 7.41 (t, J = 13.5 Hz, 1H), 7.57 (t, J = 13.5 Hz, 1H), 7.76 (d, J = 13.5 Hz, 1H), 7.81 (s, 1H), 7.99 (d, J = 14 Hz, 1H); δ_C 62.8, 107.4, 120.6, 125.0, 125.8, 126.5, 128.6, 128.7, 129.5, 130.5, 132.7; *m*/*z* (%): 318 ($M^+ + 4$, 10), 316 ($M^+ + 2$, 20), 314 (11), 238 (12), 237 (98), 235 (100), 155 (13), 128 (38), 127 (30), 104 (11); APCI HRMS calcd for $C_{11}H_8{}^{79}Br^{81}BrO$ 315.8921, found 315.8721.

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