Effect of Ortho Substituents on the Direction of 1,2-Migrations in the Rearrangement of 2-*exo*-Arylfenchyl Alcohols

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A series of 2-*exo*-arylfenchyl alcohols (**11a**−**k**) was submitted to acid hydrolysis in EtOH/10 M HCl (2:1−1:1, v/v) or with trifluoromethanesulfonic acid (TfOH) (1 equiv) in $CHCl_3$ under varying conditions. In all cases, initial formation of the cyclofenchene **12** took place, and after prolonged treatment with acid the reaction proceeded along one of two pathways depending on the nature of the aryl substituent. When the aryl substituent was *o*-NH_2 **11b** or *o*-OH **11e**, Wagner−Meerwein rearrangement took place to give a carbocationic intermediate **9** that was trapped by the N or O heteroatom to give (2*R*,4a*R*,9a*R*)-9-aza-2,4a-(10,10-dimethylmethano)-1,2,3,4,4a,9a-hexahydro-9a-methyl-9*H*-fluorene (**3b**) and (3*R*,4a*R*,9b*R*)-3,9b-(10,10-dimethylmethano)-1,2,3,4,4a,9b-hexahydro-4a-methyldibenzofuran (**3c**), respectively. In the case of **3c** bearing an oxygen heteroatom, equilibration to give the thermodynamic product (1*R*,4*S*,4a*R*,9b*R*)-1,2,3,4,4a,9b-hexahydro-1,4-methano-1,4a,9b-trimethyldibenzofuran (**4a**), arising from Nametkin rearrangement, took place via the intermediate 2-fenchyl cation. In contrast, when the aryl substituent was *o*-OCH_3 **11f**, direct conversion of the cyclofenchene to the Nametkin product **4a** occurred with no detectable prior formation of the Wagner−Meerwein product. In the case of *o*-tolylfenchyl alcohol **11k**, cyclofenchene formation was facile, but subsequent conversion to either the Wagner−Meerwein or Nametkin products was highly disfavored. The results indicate that ortho substitution disfavors Wagner−Meerwein rearrangement through adverse steric and electronic effects. However, when the ortho substituent is NH_2 or OH it is proposed that anchimeric assistance provides an intermediate **15a** that is stereoelectronically predisposed to Wagner−Meewein rearrangement.

Introduction

The question of the nature of the norbornyl carbocation **1** represents one of the most thoroughly studied and controversial topics in the history of organic chemistry. The evolution of the concept of nonclassical carbocations and their later detection in superacid media can be considered as milestones in the ensuing discussions promoted by Winstein, Brown, and Olah.[1] The fenchyl carbocation **2** has also been a subject of much interest, and its most notable attribute is the large number of rearrangements that it can undergo as indicated by the characterization of five fenchenes (α−ζ) as well as cyclofenchene.[2] While some work has been carried out to establish the relative energetics of these rearrangements,[2] the complexity of the system has precluded more extensive investigations and certainly limited synthetic application.[3]

1 **2**

While the effect of placing an aryl substituent onto C2 of the norbornyl carbocation serves to delocalize the positive charge onto the aryl ring causing a deviation from nonclassical behavior,[4] the subtle effects of introducing a 2-aryl substituent onto the fenchyl system have not previously been examined. Recently, we found that acid hydrolysis of (1″*S*,2″*S*,4″*R*)-*N*-[4′-chloro-2-(2″-methoxy-1″,3″,3″-trimethylbicyclo[2.2.1]hept-2″-yl)phenyl]-2,2-dimethylpropanamide to the corresponding amino alcohol was followed by dehydration, Wagner−Meerwein rearrangement, and trapping of the resulting carbocation with the free amino group to give an enantiomerically pure hexahydroazafluorene **3** (Z = NH, R = H, R′ = Cl) (Scheme 1, path a). When the hydrolysis was carried out with protected phenols an alternative pathway, Nametkin rearrangement to give **4**, was followed, but the extent to which this occurred appeared to be intrinsically related to the phenol substituent (Scheme 1, path b).[5]

1,2-Migrations are susceptible to a number of influences among which stereoelectronic effects are the most important.[6] A particularly striking example is the rear-

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(1) For an excellent overview see: Schreiner, P. R.; Schleyer, P. v. R.; Schaefer, H. F., III. *J. Org. Chem.* **1997**, *62*, 4216.

(2) Huang, E.; Ranganayakulu, K.; Sorensen, T. S. *J. Am. Chem. Soc.* **1972**, *94*, 1779. Sorensen, T. S. *Acc. Chem. Res.* **1976**, *9*, 257.

(3) For example, see: Yuasa, Y.; Watanabe, T.; Nagakura, A.; Tsuruta, H. King, G. A. III; Sweeny, J. G.; Iacobucci, G. A. *Tetrahedron* **1992**, *48*, 3473.

(4) Brown, H. C.; Takeuchi, K. *J. Am. Chem. Soc.* **1968**, *90*, 2693. arnum, D. G.; Mehta, G. *J. Am. Chem. Soc.* **1969**, *91*, 3256. Brown, H. C.; Takeuchi, K.; Ravindranathan, M. *J. Am. Chem. Soc.* **1977**, *99*, 2684. Substitution by electron-withdrawing groups increases the tendency toward nonclassical stabilization: Farnum, D. G.; Wolf, A. D. *J. Am. Chem. Soc.* **1974**, *96*, 5166.

(5) For preliminary results see: (a) Starling, S. M.; Vonwiller, S. C. *Tetrahedron Lett.* **1997**, *38*, 2159. (b) Starling, S. M. Ph.D. Thesis, University of Sydney, 1997.

(6) Schleyer, P. v. R.; Lam, L. K. M.; Raber, D. J.; Fry, J. L.; McKervey, M. A.; Alford, J. R.; Cuddy, B. D.; Keizer, V. G.; Geluk, H. W.; Schlatmann, J. L. M. A. *J. Am. Chem. Soc.* **1970**, *92*, 5246. Majerski, Z.; Schleyer, P. v. R.; Wolf, A. P. *J. Am. Chem. Soc.* **1970**, *92*, 5731. Nickon, A.; Weglein, R. C. *J. Am. Chem. Soc.* **1975**, *97*, 1271. Paquette, L. A.; Waykole, L.; Jendralla, H.; Cottrell, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 3739. Paquette, L. A.; Lanter, J. C.; Johnston, J. N. *J. Org. Chem.* **1997**, *62*, 1702.

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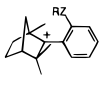
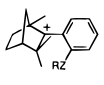
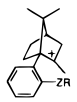
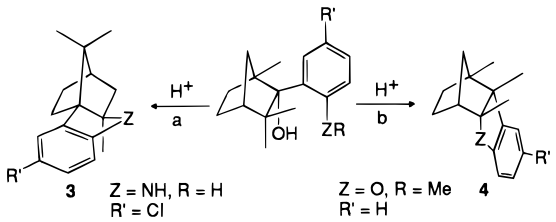
Table 1. Calculated (AM1) Heats of Formation ΔH_f (kcal mol^{-1}) of Carbocation Intermediates and Corresponding Rearrangement Products

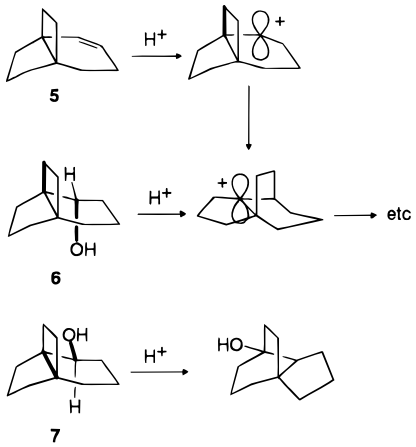
ortho substituent	 **8**	 **8'**	 **9**	 **3**	 **10**	 **10'**	 **4**
Z = NH R = H	188.6 (225.7)[a]	190.9	207.1	39.2	219.5	213.5	29.8
Z = O R = H	153.0 (174.8)[a]	152.9	161.0	-0.36	172.2	166.5	-9.8
Z = O R = Me	158.1 (183.16)[a]	158.2	167.3	-0.36	179.0	173.1	-9.8
RZ = H	198 (220.1)[a]	198	207.2	-	211.8	211.8	-

[a]Calculated by using the MNDO method.

Scheme 1



Scheme 2



rangement of [4.3.2]propellanes **5**−**7** (Scheme 2).[7] In this case, the concertedness or nonconcertedness of the migration and the orientation of the leaving group with respect to the migrating bonds are the key issues.[8] However, to our knowledge, there appear to be no examples in which remote substituents are able so dramatically to influence the direction of 1,2-migrations. Therefore, in this paper we present a full account of our results and a detailed analysis of the origin of the substituent effect.

Results and Discussion

In line with literature results for the treatment of fenchyl alcohol under superacid conditions,[2] AM1 semiempirical calculations on the aryl-substituted carbocations **8**/**8′** and the corresponding migrations show that the heat of formation of the Wagner−Meerwein cationic precursor **9** is lower than that for the Nametkin precursor **10**/**10′** (Table 1). The relative energies of the final products were calculated to follow the opposite trend with the Nametkin products **4** being lower in energy than the Wagner−Meerwein products **3** (Table 1). This suggested that if the reactions are under thermodynamic control then progressively harsher conditions should lead to a greater proportion of Nametkin rearrangement in each case. To delineate the factors affecting the regioselectivity of the migrations, variously substituted 2-*exo*-aryl fenchyl alcohols **11a**−**k** were prepared from fenchone and aryllithium reagents[9,10] and submitted to acid-catalyzed rearrangement. The results are summarized in Table 2.

Rearrangement of the hydroxy pivalamide **11a** in refluxing ethanol/10 M HCl (1:1) led first to deprotection and then loss of water to give the stable cyclofenchene **12a** as a 73:27 mixture of atropisomers.[11−13] Prolonged heating in the presence of acid led to Wagner−Meerwein

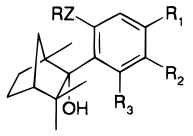
(7) Smith, A. B., III; Wexler, B. A.; Tu, C.-Y.; Konopelski, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1308.

(8) See also: Kočovský, P.; Tureček, F.; Langer, V.; Podhlahová, J.; Podlaha, J. *J. Org. Chem.* **1986**, *51*, 4888.

(9) Exclusive formation of the 2-*exo*-aryl diastereomer in each case was confirmed by NOE experiments. This contrasts with the behavior of phenylmagnesium bromide, which reacts very sluggishly, requiring the assistance of $CeCl_3$, and predominantly from the endo side: Dimitrov, V.; Bratovanov, S.; Simova, S.; Kostova, K. *Tetrahedron Lett.* **1994**, *35*, 6713. The need to activate fenchone with $CeCl_3$ to nucleophilic attack by aryllithium reagents (see ref 10) is not supported by our results.

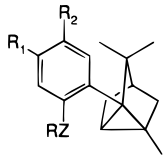
(10) **11c** (1*R*,2*R*,4*S*)-Enantiomer: Genov, M.; Kostova, K.; Dimitrov, V. *Tetrahedron: Asymmetry* **1997**, *8*, 1869.

(11) Our initial assignment of the precursor to the hexahydroazafluorene was incorrect: ref 5a.

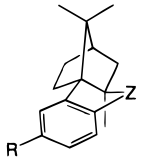


11a: RZ = NH(CO)*t*-Bu; R_1, R_3 = H; R_2 = Cl
11b: RZ = NH_2; R_1, R_2, R_3 = H
11c: RZ = NMe_2; R_1, R_2, R_3 = H
11d: RZ = OTHP; R_1, R_2, R_3 = H
11e: RZ = OH; R_1, R_2, R_3 = H
11f: RZ = OMe; R_1, R_2, R_3 = H
11g: RZ = OMe; R_1, R_2 = H; R_3 = OMe
11h: RZ, R_2, R_3 = H; R_1 = OMe
11i: RZ = CH_2OH; R_1, R_2, R_3 = H
11j: RZ = CH_2OCH_3; R_1, R_2, R_3 = H
11k: RZ = CH_3; R_1, R_2, R_3 = H

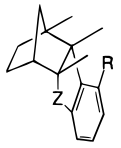
rearrangement and trapping by the amino group to give the final hexahydroazafluorene **3a** in 63% yield after 48 h (Table 2, entry 1). Treatment of the amino alcohol **11b** (Table 2, entry 2) led to the same overall result except that in the absence of a protecting group on nitrogen rearrangement proceeded at a faster rate.[14]



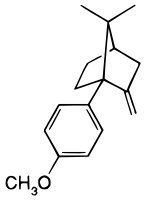
12a: RZ = NH_2; R_1 = H; R_2 = Cl
b: RZ = OCH_3; R_1, R_2 = H
c: RZ, R_2 = H; R_1 = OCH_3
d: RZ = CH_3; R_1, R_2 = H



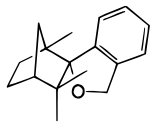
3a: Z = NH, R = Cl
b: Z = NH, R = H
c: Z = O, R = H



4a: Z = O, R = H
b: Z = O, R = OCH_3
c: Z = O, R = OH



13



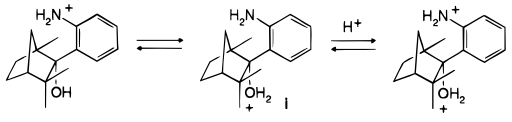
14

Changes to the O-substituent had marked effects on the ensuing 1,2-migrations of the hydroxy phenol derivatives, and whereas *o*-hydroxyl (**11e**) and *o*-tetrahydropyranyloxy (**11d**) groups caused varying degrees of Wagner−

(12) The formation of cyclofenchenes and related compounds is relatively well-known in aprotic solvents: Bartlett, P. D.; Webster, E. R.; Dills, C. E.; Richey, H. G., Jr. *Justus Liebigs Ann. Chem.* **1959**, *623*, 217; Ref: 13.

(13) Fry, J. L.; West, J. W. *J. Org. Chem.* **1981**, *46*, 2177.

(14) The acidic rearrangement conditions would appear to be incompatible with the basic NH_2 group and have a destabilizing effect on carbocation formation. However, under aqueous conditions, the pK_a's of protonated anilines are actually lower than those for carboxylic acids; see: March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1992; p 251. Reichardt, C. *Solvent Effects in Organic Chemistry*; VCH: Weinheim, 1990; pp 89−91. Arnett, E. M. *J. Chem. Educ.* **1985**, *62*, 385. Thus, there will be an equilibrium mixture of the unprotonated, monoprotonated, and diprotonated hydroxy anilines, and it is expected that species **i** will be the only one significant for carbocation formation and subsequent rearrangement. The effect of protonation therefore is simply to decrease the rate of carbocation formation.



i

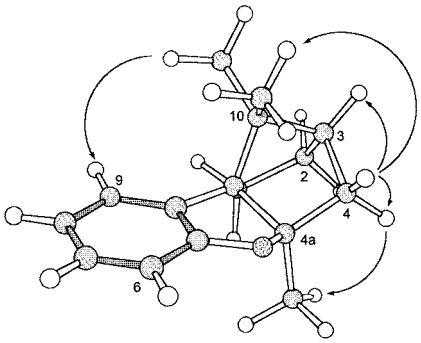


Figure 1. Three-dimensional representation of **3c** with selected NOE results.

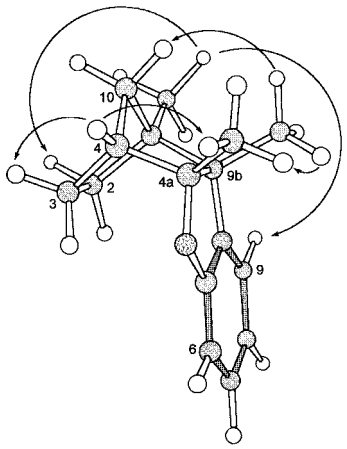


Figure 2. Three-dimensional representation of **4a** with selected NOE results.

Meerwein and Nametkin rearrangement to take place (Table 2, entries 4 and 5), *o*-methoxy groups (**11f**, **11g**) induced exclusive Nametkin rearrangement (Table 2, entries 6 and 7). The structures of **3c** (Figure 1) and **4a** (Figure 2) were unambiguously determined by NMR spectroscopy through a combination of decoupling and NOE experiments. The Wagner−Meerwein products were characterized by a distinctive downfield doublet of doublets of doublets due to H4-*exo* at 2.4−2.6 ppm while the Nametkin products showed a narrow broad doublet at ca. 2.2 ppm due to H4 at the bridgehead. On the basis of the assumption that the energy barrier to Nametkin rearrangement varied in each case due to different degrees of carbocation stabilization, the reactions were run at varying temperatures and reaction times. When the ortho substituent was hydroxyl (Table 2, entry 5) it was found that treatment with acid at 87 °C for 15 min led to complete conversion into the Wagner−Meerwein (**3c**) and Nametkin (**4a**) products in a ratio of 94:6. When this product mixture was resubmitted to the same reaction conditions for 7 h the ratio changed to 60:40, indicating that the reaction was under thermodynamic control, in agreement with the results in Table 1. However, under conditions ranging from stirring at 20 °C to refluxing in acetic acid the preference for Nametkin rearrangement for substrates bearing *o*-methoxy groups (**11f**, **11g**) did not alter, suggesting that somehow the pathway leading to Wagner−Meerwein rearrangement was blocked in these cases.[15]

To test whether the effect of the ortho substituent was electronic or steric in nature, arylfenchyl alcohols bearing a *p*-methoxy group (**11h**) (Table 2, entry 8) or an *o*-methyl

Table 2. Products Arising from Acid Hydrolysis of Substituted 2-*exo*-Arylfenchyl Alcohols

entry	**11**	10 M HCl/ethanol (1:2 v/v) products (% yield), time/*T* (°C)	TfOH (1 equiv)/$CHCl_3$ products (% yield), time/*T* (°C)
1	**a**: RZ = NH(CO)-*t*-Bu R_1, R_3 = H R_2 = Cl	**12a** (45%), **3a** (29%), 24 h/reflux[a] **3a** (63%), 48 h/reflux[a]	
2	**b**: RZ = NH_2 R_1, R_2, R_3 = H	**3b** (68%), 24 h/reflux[a]	
3	**c**: RZ = NMe_2 R_1, R_2, R_3 = H	no reaction, 6 h/reflux[b]	
4	**d**: RZ = OTHP R_1, R_2, R_3 = H	**3c**/**4a** (95:5, 88%), 20 min[c]/refux[b]	
5	**e**: RZ = OH R_1, R_2, R_3 = H	**3c**/**4a** (97:3, 80%), 1.5 h[c]/60 °C (bath) **3c**/**4a** (94:6, 97%), 15 min[c]/reflux[b] **3c**/**4a** (60:40, 93%) 7.25 h/reflux[b]	**3c**/**4a** (93:7, 78%), 5 h[c]/20 °C
6	**f**: RZ = OCH_3 R_1, R_2, R_3 = H	**12b** (65%), 15 min[c]/85 °C (bath) **4a** (86%), 7.5 h[c]/85 °C (bath)	**12b** (74%), **4a** (trace), 1 h[c]/20 °C
7	**g**: RZ = OCH_3 R_1 = H R_3 = OCH_3	**4b** (88%), 1 h[c]/85 °C (bath) **4b** (33%), **4c** (35%), 24 h/reflux[d]	
8	**h**: RZ, R_3 = H R_1 = OCH_3	**12c** (57%), 1 h 40 min[c]/reflux[b]	**13** (83%), 45 min[c]/20 °C
9	**i**: RZ = CH_2OH R_1, R_2, R_3 = H	**14** (98%), 25 min[c]/reflux[b]	
10	**j**: RZ = CH_2OCH_3 R_1, R_2, R_3 = H	**14** (99%), 1 h 50 min[c]/reflux[b]	
11	**k**: RZ = CH_3 R_1, R_2, R_3 = H	**12d** (91%), 40 min[c]/reflux[b] **12d** (84%),[e] other (16%), 3 d/reflux[b] **12d** (64%),[e]other (36%), 24 h/reflux[a]	**12d** (24%), other (39%),[f] 24 h/reflux

[a] EtOH/10 M HCl (1:1 v/v), 93 °C (internal temp). [b] 87 °C (internal temp). [c] Time required to effect complete reaction. [d] 17 M AcOH/48% HBr (4:1, v/v). [e] Yields determined by analytical HPLC. [f] By weight.

group (**11k**) (Table 2, entry 11) were subjected to acid hydrolysis conditions. However, in each case facile formation of the cyclofenchenes **12c** and **12d** (as a 73:27 mixture of atropisomers) took place in refluxing 10 M HCl/ethanol (1:2) within 40 min. This result did not indicate whether the final outcome would be Nametkin rearrangement or Wagner−Meerwein rearrangement as the only other report of this type of tandem sequence involving **11f** by Fry and West,[13] employing diethyl ether as solvent, indicates that the cyclofenchene **12b** is the precursor to the Nametkin product **4a**. It should be noted that the product reported by Fry and West is erroneously depicted as the Wagner−Meerwein product **3c**.[16] To determine what the final products would be, the *o*-methyl- (**11k**), *o*-methoxy- (**11f**), and *p*-methoxy-substituted (**11h**) adducts were subjected to acid-catalyzed dehydration with an acid whose conjugate base is non-nucleophilic, in an aprotic solvent. Thus, each was treated with trifluoromethanesulfonic acid (TfOH) (1.0 equiv) in $CHCl_3$ at 20 °C, and under these conditions the reaction rates were somewhat increased over those observed in 10 M HCl/ethanol (1:2). Surprisingly, while the *o*-methoxy adduct led only to the cyclofenchene within 1 h (Table 2, entry 6), in agreement with the results of Fry and West, the *p*-methoxy adduct underwent facile conversion under the same conditions (entry 8) into the alkene **13** arising from Wagner−Meerwein rearrangement and proton loss. The *o*-methyl adduct **11k** reacted very sluggishly under these conditions and required heating under reflux for 10 min to effect initial conversion into the cyclofenchene **12d**. Extended heating under reflux in either medium resulted in slow conversion into several products slightly more polar and considerably more UV-active than the cyclofenchene (Table 2, entry 11). However, none of these was a Wagner−Meerwein product as indicated by the absence of the characteristic *exo*-methylene signals in the NMR spectrum. Treatment of the *o*-(*N*,*N*-dimethylamino)-substituted adduct **11c** (Table 2, entry 3) in refluxing 10 M HCl/ethanol (1:2) did not result in any change.

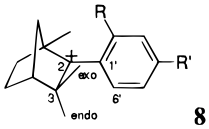
Thus, the effect of an ortho substituent is to inhibit the Wagner−Meerwein migration and the result is that elimination to give the cyclofenchene intermediate **12** is the predominant outcome: the flanking methyl groups make this the only mode of elimination possible. Formation of the cyclofenchene acts as a thermodynamic sink, and reprotonation to provide the reverse reaction to the fenchyl carbocation **8** is required to give access to the 1,2-migration step (Scheme 3). In the presence of a proximate nucleophile, the less stable tertiary alkyl carbocation **9** resulting from 1,2-migration is trapped to give the final product **3**. The possibility of nucleophilic ring opening of the cyclopropane **12** is excluded on the grounds that only a single regioisomeric hexahydroazafluorene is formed when ZR = NH_2, and this corresponds to formation of the tertiary alkyl carbocation rather than the secondary alkyl carbocation intermediate.

To accommodate the occurrence of the Nametkin rearrangement, a competing pathway from the fenchyl carbocation to the tertiary alkyl carbocation **10** resulting from *exo*-methyl migration is set up. The *exo*-methyl group is better aligned with the empty p-orbital than the *endo*-methyl group as indicated by the calculated dihedral angles for 3-Me_{exo}−C_3−C_2−$C_{1'}$ (Table 3),[17] thereby making this reaction stereoelectronically favored.[18] Again, trapping by a proximate nucleophile will give the final Nametkin product **4**.

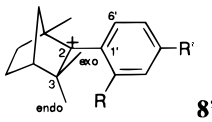
(15) Compounds **4b** and **4c** are of interest because of their structural relationship to the cannabinoids. **4c** can be considered as an analogue of cannabielsoin although the latter shows no CNS activity: Uliss, D. B.; Razdan, R. K.; Dalzell. H. C. *J. Am. Chem. Soc.* **1974**, *96*, 7372.

(16) The reported NMR data are consistent with our data for the Nametkin product (see Experimental Section).

Table 3. Comparison of Dihedral Angles (deg) of Energy-Minimized 2-Arylfenchyl Carbocations Calculated by AM1 and MNDO Methods



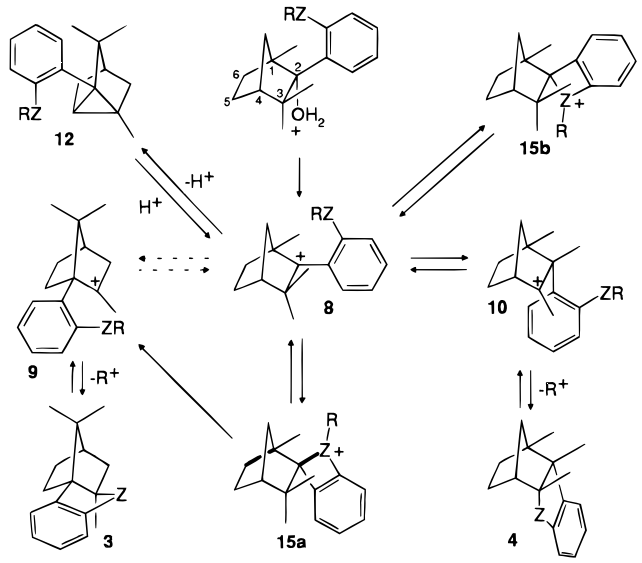
8



8'

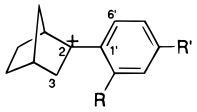
aryl substituent	AM1 $C_3-C_2-C_{1'}-C_{6'}$/3-$Me_{exo}-C_3-C_2-C_{1'}$	MNDO $C_3-C_2-C_{1'}-C_{6'}$/3-$Me_{exo}-C_3-C_2-C_{1'}$	AM1 $C_3-C_2-C_{1'}-C_{6'}$/3-$Me_{exo}-C_3-C_2-C_{1'}$
R = NH_2, R′ = H	19.2/68.6	86.0/68.3	149.2/88.2
R = OH, R′ = H	24.6/74.4	65.0/65.9	155.2/76.9
R = OMe, R′ = H	24.5/74.0	64.6/66.1	154.7/78.1
R = R′ = H	17.6/74.4	34.0/73.7	162.4/74.4
R = H, R′ = OMe	13.2/74.2	27.5/74.2	166.3/74.2

Scheme 3



The manner in which the ortho substituents inhibit subsequent Wagner−Meerwein rearrangement is unclear but is likely to be related to a steric effect of the fenchyl methyl groups, which serves to cause the aryl ring to deviate from being orthogonal to the empty p-orbital. The effect is significant enough that even in the *p*-OMe example where the ortho substituent is hydrogen the reaction is slowed sufficiently in 10 M HCl/ethanol to result in initial formation of the cyclofenchene. This steric interaction would be expected to result in a more localized cation through decreased orbital overlap and decreased electron density at C2[19] and be particularly significant for large substituents. While the large *o*-(*N*,*N*-dimethylamino) substituent (**11c**) completely prevented any reaction from occurring, this is likely to be due mainly to the increased basicity of this group. AM1 results show that each carbocation possesses two energy minima corresponding to conformations in which the aryl ring adopts dihedral angles for $C_3-C_2-C_{1'}-C_{6'}$ ranging from 13.2 to 24.6° (**8**) and 149.2 to 166.3° (**8′**) (Table 3). Thus, according to these calculations, the aryl ring prefers to be as close to orthogonal as possible. This condition appears to be favorable for Wagner−Meerwein rearrangement based on the result of **11h**, but this is contrary to the idea that decreased electron density through disruption of resonance stabilization or increased electron demand provides an unstable carbocation that is susceptible to neighboring group stabilization.[4,19] On the other hand, MNDO calculations suggest that for **8** (Z = NH, R = H) the aryl ring prefers to be in plane with the empty p-orbital (dihedral = 86.0°), a situation that would preclude p-π overlap altogether. Resonance stabilization is removed, leaving the inductive or field effects of the aryl substituent to exert further effects on the carbocation. As all of the substituents are inductively electron-withdrawing,[20] destabilization of the carbocation must result, providing an impetus for migration to occur. Thus, while both methods take into account electronic effects, MNDO is much more sensitive to steric interactions. This is supported by calculations performed on a series of 2-arylnorbornyl carbocations in which both methods afforded energy-minimized structures with $C_3-C_2-C_{1'}-C_{6'}$ dihedral angles approaching 180° (Table 4). It was only in the case of the larger *o*-NH_2 substituent that MNDO afforded a structure with a vastly different dihedral angle of −139.5°. While more direct experiments[19] are required to assess the relative suitability of each method to this problem, in reality it is expected that a combination of steric and electronic factors will come into play in determining the minimum energy conformations of these carbocations. Nevertheless, these observations do not fully address the question of regioselectivity in the 1,2-migration.

Table 4. Comparison of Heats of Formation ΔH_f (kcal mol^{-1}) and Dihedral Angles (deg) of Energy-Minimized 2-Arylnorbornyl Carbocations Calculated by AM1 and MNDO Methods



aryl substituent	AM1 $\Delta H_f/C_3-C_2-C_{1'}-C_{6'}$	MNDO $\Delta H_f/C_3-C_2-C_{1'}-C_{6'}$
R = H, R′ = OMe	157.9/179.8	163.1/178.4
R = R′ = H	203.3/179.6	210.9/178.0
R = OMe, R′ = H	158.8/178.7	167.7/174.4
R = NH_2, R′ = H	191.7/174.7	214.6/−139.5

The calculated rotational barriers for the cyclofenchene atropisomers **12** (Table 5) correlate well with the observed atropisomer ratios and give a good indication of

(17) For X-ray crystallographic data supporting the tendency for *exo*-methyl migration in the Nametkin rearrangement, see: Moews, P. C.; Knox, J. R.; Vaughan, W. R. *J. Am. Chem. Soc.* **1978**, *100*, 260. Cameron, T. S.; Jochem, K.; Morris, D. G.; Maguire, J. *Acta Crystallogr.* **1994**, *C50*, 2085.

(18) Brouwer, D. M.; Hogeveen, H. *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 211.

(19) Heagy, M. D.; Olah, G. A.; Prakash, G. K. S. *J. Org. Chem.* **1995**, *60*, 7355.

(20) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A: Structure and Mechanisms*, Plenum Press: New York, 1990; p 201.

Table 5. Calculated (AM1) Rotational Barriers for Aryl-Substituted Cyclofenchene Atropisomers 12

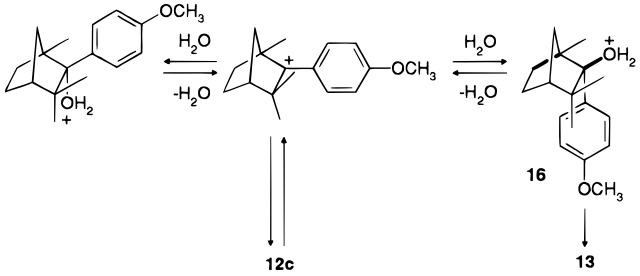
aryl substituent	ΔH_f for lowest energy atropisomer (kcal mol^{-1})	rotational barrier (kcal mol^{-1})	atropisomer ratio (298 K)[a]
2′-CH_3	47.1	17	73:27
2′-NH_2, 5′-Cl	43.7	16.5	73:27
2′-OCH_3	17.4	9.9 (lit.[13] 16.3)	52:48
2′-OH	10.6	9.8	
4′-OCH_3	14.5	4.7	unrestricted rotation

[a] Ratios measured by ^{1}H NMR spectroscopy in $CDCl_3$.

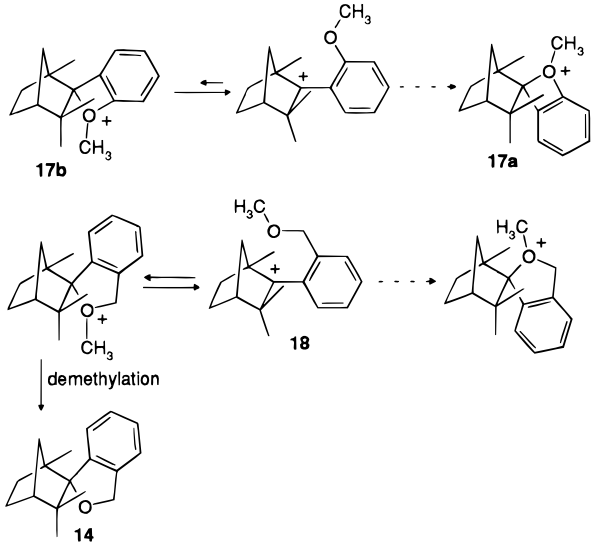
effective steric bulk of the ortho substituents. While the OH and OMe groups would appear to be similar in size, the results in Table 2 indicate that their effect on the 1,2-migration is quite different. Likewise, the effective steric bulk of the NH_2 group is similar to that of CH_3, and yet in the case of the former, Wagner−Meerwein rearrangement proceeds much more readily.

Thus, it is clear that steric bulk alone is insufficient to account for the diverging reaction pathways. However, if the nucleophilicities of the ortho substituents are considered then a correlation with tendency for Wagner−Meerwein migration becomes apparent. This suggests that an alternative pathway may be available that would divert the fenchyl carbocation from the energy well of cyclofenchene formation and assist the otherwise sluggish Wagner−Meerwein rearrangement. It is proposed that the *o*-NH_2 and *o*-OH groups offer anchimeric assistance[21] such that the fenchyl carbocation is transiently trapped to give charged four-membered intermediates **15a** and **15b** (Scheme 3). Four-membered ring formation in anchimerically assisted reactions is uncommon.[22] Nevertheless, when trapping occurs from the exo side the new C−N or C−O bond in this intermediate **15a** is now antiperiplanar to the C1−C6 bond and a concerted Wagner−Meerwein migration becomes stereoelectronically favored[23] through sp^3 alignment.[6,7,24] In this case, stabilization of the incipient cation by p-π overlap is completely removed as the aryl ring is now in plane with the developing empty p-orbital. The result is a species that is more susceptible to stabilization by neighboring groups, this being the C1−C6 bond in this case. While the reactions involving **11a**, **11b** (Z = NH) (Table 2, entries 1 and 2) were difficult to monitor, those involving **11e** (ZR = OH) (Table 2, entry 5) proceeded almost directly to the rearrangement product without significant buildup of the cyclofenchene.[25] By comparison, in 10 M HCl/ethanol, formation of the Wagner−Meerwein product is more facile for **11e** (ZR = OH) than for **11h** (ZR = H) (Table 2, entries 5 and 8) despite the fact that OH is larger than H. When the hydroxyl group is protected as a THP ether **11d** hydrolysis to the phenol occurs immediately in 10 M HCl/ethanol (Table 2, entry 4) and so

Scheme 4



Scheme 5



the reaction outcome is the same as for the phenol **11e**.[5] Trapping of the carbocation **8** from the endo side would lead to a species **15b** with a lower tendency to undergo 1,2-rearrangement.

In light of this, the apparent anomaly with the result of the *p*-anisylfenchyl alcohol **11h** can best be reconciled if the carbocation is considered to be sufficiently resonance-stabilized and sterically unencumbered to allow reversible trapping by water to compete with cyclofenchene formation to give an equilibrium mixture of the protonated endo and exo alcohols (Scheme 4). The protonated exo alcohol **16** will then meet the stereoelectronic requirements for concerted Wagner−Meerwein rearrangement to occur.

In the case of the OMe group the proposed exo four-membered intermediate **17a** is unable to be formed or is too short-lived owing to steric interactions of the methoxymethyl group with the methylene bridge and the flanking methyls of the fenchyl skeleton (Scheme 5). While formation of the endo intermediate **17b** is more likely to occur, this does not lead to Wagner−Meerwein rearrangement. The *o*-OMe group is likely to cause the aryl ring to deviate from being orthogonal to the empty

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(22) Oxygen donor groups: Paquette, L. A.; Scott, M. K. *J. Am. Chem. Soc.* **1972**, *94*, 6760. Gassman, P. G.; Marshall, J. L.; Macmillan: J. G. *J. Am. Chem. Soc.* **1973**, *95*, 6319. Eliel, E. L.; Clawson, L.; Knox, D. E. *J. Org. Chem.* **1985**, *50*, 2707. Sulfur donor groups: Eliel, E. L.; Knox, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2946.

(23) Winstein, S.; Trifan, D. S. *J. Am. Chem. Soc.* **1949**, *71*, 2953.

(24) For other relevant examples of apparently anchimerically assisted Wagner−Meerwein rearrangements, see: (a) McCapra, F.; Beheshti, I. *J. Chem. Soc., Chem. Commun.* **1977**, 517. (b) Kondratenko, M.; El Hafa, H.; Gruselle, M.; Vaissermann, J.; Jaouen, G.; McGlinchey, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6907.

(25) By TLC a faint spot of intermediate polarity is evident throughout the reactions and is likely to be the cyclofenchene, although this was never formed in amounts sufficient for isolation and characterization.

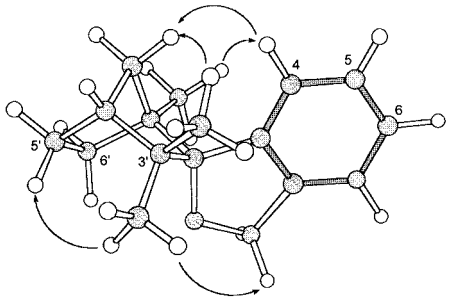

Figure 3. Three-dimensional representation of **14** with selected NOE results.

p-orbital, thereby minimizing resonance stabilization, and this together with the inductively electron-withdrawing effect of the OMe group leads to carbocation destabilization. Although C1−C6 bond migration to a cationic center has a low tendency to occur in the 2-aryl fenchyl system, *exo*-methyl migration takes place instead. When two OMe groups are present as in **11g** the rate of Nametkin rearrangement increases over 7-fold (Table 2, entry 7).

When the ZR group is the more bulky *o*-hydroxymethyl (Table 2, entry 9), internal carbocation trapping is relatively facile from the endo side and the result is formation of the stable phthalan **14**, which does not undergo further reaction under the conditions used. The stereochemistry of **14** was unambiguously determined by NOE experiments (Figure 3). None of the product due to trapping from the exo side was detected despite the well-documented preference for nucleophilic attack of fenchone from the exo side.[9,10] Notably, when ZR is *o*-methoxymethyl, internal carbocation trapping of **18** and demethylation to give **14** are also facile from the endo side, and again, this does not lead to 1,2-migration (Scheme 5).

Thus, there is a narrow margin for the fenchyl skeleton to tolerate the exo approach of *o*-aryl substituents, which in these intramolecular cases have a restricted orientation and trajectory of approach.

Conclusion

In summary, acid hydrolysis of 2-*exo*-arylfenchyl alcohols affords the corresponding cyclofenchenes as the kinetic products that upon prolonged treatment with acid are converted into Wagner−Meerwein products via equilibration with the stabilized fenchyl carbocations. These stabilized, sterically unhindered carbocations are proposed to react with water to give 2-*endo*-arylfenchyl alcohols that are stereoelectronically set up for Wagner−Meerwein rearrangement. The presence of ortho substituents on the aryl ring hinders the Wagner−Meerwein rearrangement through decreased resonance stabilization of the carbocation and steric encumbrance to attack by external nucleophiles and causes the reaction to enter the alternative Nametkin manifold provided that a cation-trapping group is present. However, when the ortho substituent itself is nucleophilic the barrier to Wagner−Meerwein rearrangement is overcome and this is suggested to be due to internal trapping of the carbocation from the exo side to give a reactive intermediate that is stereoelectronically predisposed to concerted bond migration.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200F and AMX-400 spectrometers with samples in $CDCl_3$. Optical rotations were performed on a Perkin-Elmer 241 polarimeter in cells with a path length of 0.5 dm. Flash chromatographic separations employed Merck silica gel 60 (230−400 mesh). Analytical TLC was carried out with Merck precoated aluminum plates coated with silica gel 60 F 254 (0.2 mm), and fractions were visualized by means of UV light (278 nm) and developing the plate in vanillin/sulfuric acid solution followed by heating. Elemental analyses were performed at either the Research School of Chemistry, the Australian National University, or the Campbell Microanalytical laboratory, University of Otago, New Zealand. Melting points were determined on a Reichert micro melting point apparatus and are uncorrected. All solvents and commercially available reagents were purified by standard methods.[26] Butyllithium as a solution in hexanes was standardized by titration against 2,5-dimethoxybenzyl alcohol.[27] Methyllithium as a solution in diethyl ether was standardized by titration against diphenylacetic acid.[28]

Molecular Modeling. All calculations were performed on a Silicon Graphics IRIX workstation with SPARTAN 4.0.[29] The structures of the molecules listed in Table 1 were generated with the Spartan program, minimized using the Sybyl force field and further optimized with the semiempirical methods AM1 or MNDO.

To calculate the rotational barriers of compounds listed in Table 5, the dihedral angle ($C_3-C_2-C_{1'}-C_{2'}$) was forced to rotate 360° (in steps of 10°) using the coordinate driving option within Spartan. The structures were minimized at each step using the Sybyl force field and were further optimized with AM1. The resulting energy-minimized structures were further minimized by using AM1 without constraints, and the energy barriers were calculated by subtracting the minima from the maxima.

Preparation of Arylfenchyl Alcohols. General Method. The lithiated benzene, prepared as described for individual examples, was treated with (+)-fenchone (1 equiv) and added dropwise as a neat liquid, and then the whole was stirred for the stated time and at the stated temperature. The reaction was quenched with saturated ammonium chloride solution, and the product was extracted into ether. The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The pure product was isolated as described for individual examples.

(1′′*S*,2′′*S*,4′′*R*)-*N*-[4′-Chloro-2-(2′′-hydroxy-1′′,3′′,3′′-trimethylbicyclo[2.2.1]hept-2′′-yl)phenyl]-2,2-dimethylpropanamide (11a). Butyllithium (1.6 M, 3.90 mL, 6.24 mmol) was added to a solution of 4-chloropivanilide (656 mg, 3.10 mmol) in THF (10 mL) cooled to −5 °C to give a yellow solution that was stirred at 0 °C for 2 h. The resulting solution was treated with fenchone at room temperature for 3 h. The crude product was purified by flash chromatography (ethyl acetate/hexanes 5:95) to give the amide as colorless prisms (896 mg, 79%): mp 182 °C; $[\alpha]^{20}_D = +43.6°$ (*c* 1.508, EtOAc).

(1*S*,2*S*,4*R*)-2-*exo*-(2′-Aminophenyl)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (11b). (a) (1′*S*,2′*S*,4′*R*)-*N*-[2-(2′-Hydroxy-1′,3′,3′-trimethylbicyclo[2.2.1]hept-2′-yl)phenyl]trifluoroacetamide. 2-Bromo-*N*-trifluoroacetanilide (3.06 g, 0.011 mol) in THF (20 mL) cooled to 0 °C was treated with methyllithium (1.3 M in diethyl ether, 9.0 mL, 0.012 mol) to give a colorless solution. The solution was cooled to −80 °C, and *tert*-butyllithium (1.3 M in pentane, 17.6 mL, 0.023 mol) was added dropwise over 30 min so as to maintain the temperature below −70 °C. The yellow solution was stirred at −80 °C for 1 h and allowed to warm to −30 °C,

(26) Perrin, D. D.; Armarego, W. L. F. K.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1980.
(27) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87.
(28) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.
(29) SPARTAN 4.0, Wavefunction, Inc., 18401 Von Karman, Suite 370, Irvine, CA 92715.

becoming deep red in color. The resulting solution was treated with fenchone at room temperature for 20 h (overnight). The crude product was purified by flash chromatography (ethyl acetate/hexane 10:90) to yield the pure hydroxy amide as colorless prisms (2.79 g, 72%): mp 128−131 °C, $[\alpha]^{20}_D = +9.8°$ (*c* 1.852, EtOAc).

(b) (1*S*,2*S*,4*R*)-2-*exo*-(2′-Aminophenyl)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (11b). A solution of the trifluoroacetamide (3.79 g, 0.011 mol) and sodium hydroxide (12.0 g, 0.30 mol) in ethanol (100 mL) was heated at reflux under nitrogen for 24 h. The ethanol was removed under reduced pressure, the residue was suspended in water, and the product was extracted with ether. The combined ether layers were dried (K_2CO_3), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/hexane, 15:85) and further by distillation [bp 150−160 °C/0.08 mm (Kugelrohr)] to yield the amino alcohol **11b** as colorless prisms (2.17 g, 80%): mp 54−55 °C, $[\alpha]^{20}_D = +181.3°$ (*c* 1.100, hexane).

(1*S*,2*S*,4*R*)-2-*exo*-[2′-(*N*,*N*-Dimethylamino)phenyl]-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (11c). A solution of *N*,*N*-dimethylaniline (0.382 g, 3.16 mmol, 0.400 mL) and TMEDA (0.459 g, 3.95 mmol, 0.459 mL) in diethyl ether (10 mL) was treated with butyllithium (1.88 mL, 3.94 mmol, 2.1 M) at room temperature for 30 min. The reaction mixture was heated under reflux for 3 h and cooled to room temperature. The lithiated aniline was treated with fenchone at room temperature for 1.5 h and then for 30 min under reflux before quenching with water. The crude product was distilled at 60−70 °C (Kugelrohr) to remove the unreacted aniline and fenchone, and the residue was purified by flash chromatography (ether/hexane 10:90) to give the alcohol as a colorless crystalline solid (0.262 g, 30%): mp 61−63 °C (lit.[10] mp 57−60 °C), $[\alpha]^{20}_D = +69.2°$ (*c* 0.338, EtOAc).

(1′′*S*,2′′*S*,4′′*R*)-2-[2′-(2′′-Hydroxy-1′′,3′′,3′′-trimethylbicyclo[2.2.1]hept-2′′-yl)phenyl]tetrahydropyran (11d). A solution of 2′-(phenyloxy)tetrahydropyran (1.96 g, 0.011 mol) in ether (10 mL) was treated with butyllithium (8.0 mL, 0.015 mol, 1.9 M) and the resulting slurry was stirred at room temperature for 24 h. This was then treated with fenchone at room temperature for 3 h. The crude product was purified by flash chromatography (ethyl acetate/light petroleum 10:90) to give the hydroxy THP ether as a colorless solid (2.10 g, 58%) and as a 1:1 mixture of diastereomers: $[\alpha]^{20}_D = +61.5°$ (*c* 1.524, EtOAc).

(1′*S*,2′*S*,4′*R*)-2-(2′-*endo*-Hydroxy-1′,3′,3′-trimethylbicyclo[2.2.1]hept-2′-yl)phenol (11e). A solution of the THP ether **11d** (0.130 g; 0.389 mmol) in THF (8 mL), water (4 mL), and acetic acid (17 M, 1.6 mL) was heated under reflux for 2 h, cooled, and then poured onto water. The mixture was extracted with ether, and the combined extracts were washed with water and brine and dried (Na_2SO_4). The crude product after evaporation of the solvent was purified by flash chromatography (ether/hexane 15:85) to give the hydroxy phenol as a colorless unstable crystalline solid (86 mg, 89%), mp 96−100 °C, $[\alpha]^{20}_D = +110.1°$ (*c* 0.345, EtOAc), which was used immediately in subsequent experiments.

(1*S*,2*S*,4*R*)-2-*exo*-(2′-Methoxyphenyl)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (11f). A solution of anisole (2.52 g, 0.023 mol) in diethyl ether (25 mL) was treated with butyllithium (2.0 M, 14.0 mL, 0.028 mol), and then the reaction mixture was heated at reflux for 22 h. The reaction mixture was treated with fenchone at room temperature for 3 h. The crude product was purified by flash chromatography (ethyl acetate/hexane 5:95) to afford the alcohol as a colorless oil that later solidified as colorless needles (3.85 g, 64%): mp 64−67 °C (lit.[13] mp 65−66 °C); $[\alpha]^{20}_D = +119.2°$ (*c* 0.302, EtOAc) (lit.[13] $[\alpha]^{20}_D = +118.46°$).

(1*S*,2*S*,4*R*)-2-*exo*-(2′,6′-Dimethoxyphenyl)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (11g). A solution of 1,3-dimethoxybenzene (3.04 g, 0.022 mol) in THF (30 mL) was treated with butyllithium (13.2 mL, 2.0 M, 0.026 mol), and then the reaction mixture was heated at 40 °C for 2 h. The reaction mixture was treated with fenchone at room temperature for 2 h. The unreacted 1,3-dimethoxybenzene and excess fenchone were removed by distillation at 100 °C/0.2 mm (Kugelrohr), and the resulting solid was recrystallized from hexane to give the alcohol as colorless needles (4.37 g, 68%); mp 73 °C, $[\alpha]^{20}_D = +81.0°$ (*c* 0.790, EtOAc).

(1*S*,2*S*,4*R*)-2-*exo*-(4′-Methoxyphenyl)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (11h). A solution of *p*-bromoanisole (0.50 g; 2.67 mmol) in diethyl ether (20 mL) was treated with butyllithium (1.59 mL, 3.34 mmol, 2.1 M) slowly at −5 °C. The reaction mixture was stirred at between −5 and 0 °C for 1 h before being treated with fenchone at 0 °C for 5 min and then at room temperature for a further 1 h. Flash chromatography (ether/hexane 5:95) afforded the alcohol as a colorless crystalline solid (0.529 g, 76%): mp 49−51 °C, $[\alpha]^{20}_D = +43.2°$ (*c* 1.51, EtOAc).

(1*S*,2*S*,4*R*)-2-*exo*-[2′-(Hydroxymethyl)phenyl]-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (11i). A solution of benzyl alcohol (0.523 g, 4.83 mmol, 0.500 mL) and TMEDA (1.28 g, 0.011 mol, 1.28 mL) in dry hexane (15 mL) cooled in an ice bath was treated with butyllithium (5.06 mL, 0.011 mol, 2.17 M) to give a pale precipitate. The reaction mixture was heated under reflux for 4 h and cooled, and then diethyl ether (10 mL) was added. This was then treated with fenchone at room temperature for 60 h. Unreacted benzyl alcohol and fenchone were removed by Kugelrohr distillation (70 °C/1 mm) to leave a crystalline residue that was recrystallized from hexane to give the alcohol as acid-sensitive colorless fluffy needles (0.403 g, 32%): mp 115−116 °C, $[\alpha]^{20}_D = +133.8°$ (*c* 0.208, EtOAc).

(1*S*,2*S*,4*R*)-2-*exo*-[2′-(Methoxymethyl)phenyl]-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (11j). A solution of the diol **11i** (96.6 mg, 0.368 mmol) and methyl iodide (52.3 mg, 0.368 mmol, 23 (L) in THF (5 mL) was treated with sodium hydride (60% dispersion in oil) portionwise (5 × 5 mg) at room temperature over a period of 18 h, after which time TLC indicated that the reaction was complete. The reaction was quenched with ammonium chloride solution, and the product was extracted into ether. Flash chromatography (ether/hexane 10:90) of the crude product gave the monomethyl ether as a colorless viscous oil (98.9 mg, 98%): $[\alpha]^{20}_D = +128.8°$ (*c* 0.396, EtOAc).

(1*S*,2*S*,4*R*)-2-*exo*-(2′-Methylphenyl)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (11k). A solution of *o*-bromotoluene (0.711 g, 4.16 mmol, 0.500 mL) in diethyl ether (25 mL) was treated with butyllithium (2.47 mL, 5.20 mmol, 2.1 M) dropwise at −10 °C, whereupon the resulting solution was stirred for 1 h at −10 °C and then at 10 °C for 40 min. The reaction mixture was treated with fenchone at 0 °C, and then the whole was stirred at room temperature for 14 h, after which time a fine precipitate had developed. Flash chromatography (ether/hexane 5:95) afforded the alcohol as a viscous colorless oil (0.825 g, 81%): $[\alpha]^{20}_D = +109.9°$ (*c* 0.626, EtOAc).

Acid Hydrolysis Reactions. Method A. In EtOH/10 M HCl. The arylfenchyl alcohol (0.03−0.05 M) in EtOH/10 M HCl (1:1 or 2:1, v/v) was heated at the temperature indicated in Table 2, and except in the cases of **11a**, **11b**, and **11c** the reaction progress was monitored by TLC. Upon completion, after the reaction time given in Table 2, the reaction mixture was cooled and poured onto water and the product extracted into ether.

Method B. With TfOH in $CHCl_3$. The arylfenchyl alcohol (0.05−0.07 M in $CHCl_3$) was treated with TfOH (1 equiv) as a neat liquid dropwise with cooling in ice and under a nitrogen atmosphere. The reaction mixture was then stirred at the temperature indicated in Table 2. When TLC showed that reaction was complete (time given in Table 2), the mixture was poured onto water and extracted with ether.

(a) (i) 11a in EtOH/10 M HCl (1:1, v/v), 24 h. The pivalamide (0.121 g; 0.333 mmol) was hydrolyzed according to method A (Table 2, entry 1). Prior to ether extraction, the reaction mixture was allowed to cool and treated with a solution of KOH (4 g) in water (30 mL). The product mixture was submittted to flash chromatography on a column protected from light with aluminum foil (ether/hexane 10:90) to give as the first fraction (2*R*,4a*R*,9a*R*)-9-aza-6-chloro-2,4a-(10,10-dimethylmethano)-1,2,3,4,4a,9a-hexahydro-9a-methyl-9*H*-fluo-

rene (**3a**) as colorless plates (26 mg, 29%): mp 134−136 °C, $[\alpha]^{20}_D = -165.5°$ (*c* 0.220, EtOAc); IR ($CHCl_3$) 3388m cm^{-1}; ^1H NMR (400 MHz) δ 0.934 (3H, s, CH_3), 0.946 (3H, s, CH_3), 1.180 (3H, s, CH_3), 1.278 (1H, ddd, J = 12.3, 8.6, 5.3 Hz), 1.366 (1H, d, J = 12.5 Hz), 1.689 (1H, ddd, J = 9.0, 9.0, 2.2 Hz), 1.84−1.94 (2H, m), 1.97−2.04 (1H, m), 2.451 (1H, ddd, J = 12.5, 2.9, 2.9 Hz), 3.523 (1H, br s, $W_{h/2}$ = 23 Hz, NH), 6.467 (1H, d, J = 8.1 Hz), 6.944 (1H, d, J = 2.0 Hz), 6.981 (1H, dd, J = 8.2, 2.2 Hz); ^{13}C NMR (50 MHz) δ 20.40, 20.94, 23.58 (CH_2) 26.14 (CH_2), 27.16, 44.50 (CH_2), 46.37, 53.00 (quaternary), 64.00 (quaternary) 73.22 (quaternary), 110.55, 122.63 (quaternary), 123.64, 127.22, 130.27 (quaternary), 150.36 (quaternary); MS *m*/*z* 261 (M, 40); HRMS *m*/*z* calcd for $C_{16}H_{20}NCl$ M^+ 261.1284, found M^+ 261.1253. Anal. Calcd for $C_{16}H_{20}NCl$: C, 73.41; H, 7.70; N, 5.35. Found: C, 73.40; H, 7.70; N, 5.66.

Next was eluted (1*R*,2*S*,4*R*,6*S*)-2-(2′-amino-5′-chlorophenyl)-1,3,3-trimethyltricyclo[2.2.1.0^{2,6}]heptane (**12a**) as a colorless crystalline solid (41 mg, 45%) and as a 73:27 mixture of atropisomers: IR ($CHCl_3$) 3497w, 3406w cm^{-1}; ^1H NMR (200 MHz) δ (*denotes minor atropisomer) 0.791* (3H, s, CH_3), 0.838 (3H, s, CH_3), 0.878 (3H, s, CH_3), 0.984* (3H, s, CH_3), 1.086 (3H, s, CH_3), 1.130 (1H, br s), 1.237* (1H, br s), 1.285* (1H, br s), 1.352* (1H, br d, J = 11.1 Hz), 1.451 (1H, br d, J = 10.8 Hz), 1.598 (1H, br s, both isomers), 1.826 (1H, br d, J = 10.7 Hz), 1.86−1.93* (2H, m), 1.971 (1H, br d, J = 10.7 Hz), 3.838 (2H, br s, $W_{h/2}$ = 36 Hz, NH_2), 6.55−6.61 (1H, m), 6.90−7.08 (2H, m); ^{13}C NMR (50 MHz) δ (*denotes minor atropisomer) 14.68*, 15.40, 21.63, 21.77, 22.05 (quaternary), 22.57*, 24.73, 26.0 (quaternary), 26.31, 26.38*, 31.83* (CH_2), 32.58 (CH_2), 37.63 (CH_2), 38.42* (CH_2), 41.95, 43.19*, 48.41 (quaternary), 48.90* (quaternary), 116.30*, 116.60, 121.87* (quaternary), 121.98 (quaternary), 127.13, 127.27*, 133.10, 134.23*, 146.12* (quaternary), 146.40 (quaternary); MS *m*/*z* 261 (M, 75); HRMS *m*/*z* calcd for $C_{16}H_{20}NCl$ M^+ 261.1284, found M^+ 261.1282.

(ii) 11a in EtOH/10 M HCl (1:1, v/v), 48 h. Treatment of **11a** (0.152 g, 0.416 mmol) for 48 h resulted in formation of the hexahydroazafluorene **3a** (68.5 mg, 63%).

(b) 11b in EtOH/10 M HCl (1:1, v/v), 24 h. Hydrolysis of the amino alcohol **11b** (78.9 mg, 0.322 mmol) (method A, Table 2, entry 2) and workup as in (a) afforded a solid residue that upon purification by flash chromatography on a column protected from light with aluminum foil (ether/hexane 3:97) gave (2*R*,4a*R*,9a*R*)-9-aza-2,4a-(10,10-dimethylmethano)-1,2,3,4,4a,9a-hexahydro-9a-methyl-9*H*-fluorene (**3b**) as colorless prisms (50 mg, 68%): mp 64−66 °C; $[\alpha]^{20}_D = -248.8°$ (*c* 0.118, EtOAc) and as the only product: IR ($CHCl_3$) 3384m cm^{-1}; ^1H NMR (400 MHz) δ 0.936 (3H, s, CH_3), 1.196 (3H, s, CH_3), 1.288 (1H, ddd, J = 12.5, 8.9, 5.5 Hz), 1.373 (1H, d, J = 12.5 Hz), 1.707 (1H, ddd, J = 12.3, 9.2, 2.8 Hz), 1.84−1.94 (2H, m), 2.01−2.09 (1H, m), 2.465 (1H, ddd, J = 12.5, 3.2, 3.2 Hz), 6.581 (1H, d, J = 7.7 Hz), 6.725 (1H, dd, J = 7.3, 0.9 Hz), 7.00−7.06 (2H, m); ^{13}C NMR (100 MHz) δ 20.46, 21.03, 23.61 (CH_2), 26.23 (CH_2), 27.29, 44.63 (CH_2), 46.41, 52.79 (quaternary), 63.93 (quaternary), 72.53 (quaternary), 109.74, 118.08, 123.44, 127.43, 128.33 (quaternary), 151.97 (quaternary); MS *m*/*z* 227 (M, 18); MS (CI methane) *m*/*z* 228 (M + 1, 100); HRMS *m*/*z* calcd for $C_{16}H_{21}N$ M^+ 227.1674, found M^+ 227.1673. Anal. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.41; H, 9.53; N, 5.96.

(c) 11c in EtOH/10 M HCl (2:1, v/v), 6 h. Hydrolysis of the dimethylamino alcohol **11c** (58 mg, 0.213 mmol) (method A, Table 2, entry 3) and workup as above returned **11c** that by NMR analysis was unchanged, suggesting that dehydration had not occurred.

(d) 11d in EtOH/10 M HCl (2:1, v/v), 20 min. The THP ether **11d** (97.3 mg, 0.292 mmol) was treated according to method A (Table 2, entry 4). TLC indicated immediate hydrolysis to the diol **11e**. Workup, followed by flash chromatography (ether/hexane 1:99), afforded (3*R*,4a*R*,9b*R*)-3,9b-(10,10-dimethylmethano)-1,2,3,4,4a,9b-hexahydro-4a-methyldibenzofuran (**3c**) and **4a** in a ratio of 95:5 as a colorless viscous oil (58.7 mg, 88%), $[\alpha]^{20}_D = -52.5°$ (*c* 0.282, EtOAc). The product ratio was determined by integration of the signals at 2.646 and 2.224 ppm in the ^1H NMR spectrum. **3c**: IR ($CHCl_3$) 1614m, 1233s, 1160s, 1084s cm^{-1}; ^1H NMR (400 MHz) δ 0.763 (3H, s, CH_3), 0.904 (3H, s, CH_3), 1.287 (3H, s, CH_3), 1.26−1.34 (1H, m), 1.549 (1H, d, J = 13.2 Hz), 1.629 (1H, ddd, J = 12.4, 8.8, 2.8 Hz), 1.93−1.97 (2H, m), 2.04−2.11 (1H, m), 2.646 (1H, ddd, J = 13.6, 2.8, 2.8 Hz), 6.729 (1H, br d, J = 8 Hz), 6.854 (1H, ddd, J = 7.2, 7.2, 0.8 Hz), 7.076 (1H, dd, J = 7.2, 1.6 Hz), 7.129 (1H, ddd, J = 7.6, 7.6, 1.2 Hz); ^{13}C NMR (50 MHz) δ 19.97, 20.48, 22.57 (CH_2), 24.30, 26.13 (CH_2), 43.57 (CH_2), 45.92, 52.27 (quaternary), 63.62 (quaternary), 97.64 (quaternary), 110.05, 119.89, 123.46, 128.08, 160.55 (quaternary); MS *m*/*z* 228 (M, 69); HRMS *m*/*z* calcd for $C_{16}H_{20}O$ M^+ 228.1514, found M^+ 228.1521. Data for **4a** are given in section (f) (i).

(e) (i) 11e in EtOH/10 M HCl (2:1, v/v). Hydrolysis of the diol **11e** (35.8 mg; 0.145 mmol) (method A, Table 2, entry 5) (bath 60 °C) for 1.5 h gave complete conversion into a 97:3 mixture of **3c** and **4a** (26.4 mg, 80%). The reaction was extremely slow at room temperature.

When the diol **11e** (31.0 mg, 0.126 mmol) was treated at 87 °C, the reaction was complete after 15 min, giving a 94:6 mixture of **3c** and **4a**. The product mixture thereby obtained was resubmitted to the same reaction conditions, and after 7 h **3c** and **4a** were obtained as a 60:40 mixture (26.7 mg, 93%).

(ii) 11e with TfOH (1 equiv) in $CHCl_3$. Hydrolysis of the diol **11e** (85.7 mg, 0.348 mmol) (method B, Table 2, entry 5) afforded a 93:7 mixture of **3c** and **4a** (72.5 mg, 91%) as a viscous oil.

(f) (i) 11f in EtOH/10 M HCl (2:1, v/v). Hydrolysis of the *o*-anisyl alcohol **11f** (0.143 g; 0.550 mmol) (method A, Table 2, entry 6) at 85 °C (bath) for 15 min gave complete conversion into the cyclofenchene **12b**.[13] This was obtained by flash chromatography (hexane) as a viscous oil (81 mg, 65%) and as a 52:48 mixture of atropisomers.

Treatment of **11f** (58.5 mg, 0.225 mmol) in the same medium at 85 °C led to clean formation of (1*R*,4*S*,4a*R*,9b*R*)-1,2,3,4,4a,9b-hexahydro-1,4-methano-1,4a,9b-trimethyldibenzofuran (**4a**)[13] after 7.5 h. **4a** was obtained as colorless needles (44.3 mg, 86%): mp 74−75 °C; $[\alpha]^{20}_D = -36.8°$ (*c* 0.473, EtOAc); ^1H NMR (400 MHz) δ 0.877 (1H, dddd, J = 12.6, 9.1, 4.5, 2.6 Hz), 1.060 (1H, ddd, J = 12.6, 12.6, 4.9 Hz), 1.180 (3H, s, CH_3), 1.235 (3H, s, CH_3), 1.279 (1H, dd, J = 10.3, 1.6 Hz), 1.20−1.40 (m, 2H), 1.360 (3H, s, CH_3), 1.366 (1H, dddd, J = 12.7, 12.7, 4.5, 4.5 Hz), 1.60−1.71 (2H, m), 2.224 (1H, ddd, J = 4.4, 1.4, 1.4 Hz), 6.727 (1H, ddd, J = 8.0, 0.9, 0.5 Hz), 6.809 (1H, ddd, J = 7.4, 7.4, 1.0 Hz), 6.997 (1H, ddd, J = 7.4, 1.5, 0.5 Hz), 7.116 (1H, ddd, J = 8.0, 7.4, 1.5 Hz); ^{13}C NMR (50 MHz) δ 17.84, 19.48, 21.89, 23.56, 34.01, 42.18, 49.18, 50.81 (quaternary), 55.63 (quaternary), 97.27 (quaternary), 108.89, 119.58, 123.51, 128.01, 133.68 (quaternary), 158.71 (quaternary). NMR data are in agreement with those reported in the literature.[13]

(ii) 11f with TfOH (1 equiv) in $CHCl_3$. Hydrolysis of **11f** (87.2 mg, 0.335 mmol) (method B, Table 2, entry 6) afforded the cyclofenchene **12b** (60.1 mg, 74%) as a viscous oil.

(g) (i) 11g in EtOH/10 M HCl (2:1, v/v), 85 °C. Hydrolysis of the dimethoxyphenyl alcohol **11g** (85 mg; 0.293 mmol) (method A, Table 2, entry 7) afforded (1*R*,4*S*,4a*R*,9b*R*)-4a,9b-dimethyl-1,2,3,4,4a,9b-hexahydro-1,4-methano-9-methoxydibenzofuran (**4b**) after flash chromatography (ether/hexane 1:99) as colorless needles (66.6 mg, 88%): mp 58−61 °C; $[\alpha]^{20}_D = -1.1°$ (*c* 0.460, EtOAc); IR ($CHCl_3$) 1596s, 1254s, 1099s, 1082s cm^{-1}; ^1H NMR (400 MHz) δ 0.998 (1H, dddd, J = 12.1, 7.0, 4.3, 2.6 Hz), 1.115 (1H, ddd, J = 12.2, 12.2, 4.8 Hz), 1.237 (1H, dd, J = 10.4, 1.6 Hz), 1.280 (3H, s, CH_3), 1.301 (3H, s, CH_3), 1.355 (3H, s, CH_3), 1.380 (1H, dddd, J = 12.6, 12.6, 4.4, 4.4 Hz), 1.57−1.65 (2H, m), 2.158 (1H, br d, J = 4.6 Hz), 3.779 (3H, s, CH_3), 6.358 (1H, d, J = 8.8 Hz), 6.379 (1H, d, J = 8.2 Hz), 7.059 (1H, dd, J = 8.2, 8.2 Hz); ^{13}C NMR (50 MHz) δ 16.94, 18.66, 21.87, 23.54, 34.85, 42.47, 48.76, 50.93 (quaternary), 54.92, 56.61 (quaternary), 97.52 (quaternary), 102.33 (quaternary), 102.47 (quaternary), 120.12 (quaternary), 128.83, 157.40 (quaternary), 160.01 (quaternary); MS *m*/*z* 258 (M, 20). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.73; H, 8.71.

Treatment of **11g** as above at 20 °C resulted in slow conversion into **4b** over 6 days.

(ii) 11g in 17 M AcOH/48% HBr (4:1, v/v). A solution of **11g** (1.081 g, 3.72 mmol) in acetic acid (17 M, 40 mL) was treated with hydrobromic acid (48%, 10 mL, 7.15 g, 0.088 mol), and the resulting purple solution was heated at reflux for 24 h. The solution was diluted with water and extracted with ether. The combined organic layers were washed with water and saturated sodium hydrogen carbonate solution and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The products were separated by flash chromatography (ethyl acetate/light petroleum 2:98 grading to 10:90) to give first **4b** (320 mg, 33%) followed by (1*R*,4*S*,4a*R*,9b*R*)-1,2,3,4,4a,9b-hexahydro-9-hydroxy-1,4-methano-1,4a,9b-trimethyldibenzofuran (**4c**) (316 mg, 35%) as colorless needles: mp 191−192 °C; $[\alpha]^{20}_D = -3.7°$ (*c* 0.380, EtOAc); IR ($CHCl_3$) 3595m, 3329br m, 1604s, 1294s, 1022s cm^{-1}; ^1H NMR (400 MHz) δ 1.02−1.09 (1H, m), 1.157 (1H, ddd, J = 12.4, 12.4, 5.1 Hz), 1.262 (1H, dd, J = 10.3, 1.5 Hz), 1.318 (3H, s, CH_3), 1.338 (3H, s, CH_3), 1.366 (3H, s, CH_3), 1.399 (1H, dddd, J = 12.6, 12.6, 4.5, 4.5 Hz), 1.60−1.67 (2H, m), 2.179 (1H, br d, J = 3.6 Hz), 4.72 (1H, br s, $W_{h/2}$ = 59 Hz, OH), 6.188 (1H, dd, J = 8.0, 0.6 Hz), 6.341 (1H, dd, J = 8.0, 0.6 Hz), 6.952 (1H, dd, J = 8.0, 8.0 Hz); ^{13}C NMR (100 MHz) δ 17.03, 18.73, 21.86, 23.55, 34.76, 42.46, 48.83, 50.96 (quaternary), 56.39 (quaternary), 97.73 (quaternary), 102.12, 107.22, 118.84 (quaternary), 128.83, 153.14 (quaternary), 160.68 (quaternary); MS *m*/*z* 244 (M, 40). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.41; H, 8.05.

(h) (i) 11h in EtOH/10 M HCl (2:1, v/v), Reflux. Hydrolysis of the *p*-anisyl alcohol **11h** (0.235 g, 0.901 mmol) (method A, Table 2, entry 8) and flash chromatography (hexane) afforded the cyclofenchene (1*R*,2*S*,4*R*,6*S*)-2-(4′-methoxyphenyl)-1,3,3-trimethyltricyclo[2.2.1.0^{2,6}]heptane (**12c**) as a colorless mobile oil (0.124 g, 57%): $[\alpha]^{20}_D = 0.0°$ (*c* 0.490, EtOAc); IR (thin film) 2955vs, 1609s, 1515s, 1295s, 1244s, 1173s, 1040s cm^{-1}; ^1H NMR (400 MHz) δ 0.738 (3H, s, CH_3), 0.875 (3H, s, CH_3), 0.987 (1H, ddd, J = 1.2, 1.2, 1.2 Hz), 1.069 (3H, s, CH_3), 1.225 (1H, dd, J = 10.6, 1.2 Hz), 1.337 (1H, ddd, J = 10.6, 1.2, 1.2 Hz), 1.568 (1H, ddd, J = 1.5, 1.5, 1.5 Hz), 1.817 (1H, ddd, J = 10.5, 1.5, 1.5 Hz), 1.884 (1H, br d, J = 10.5 Hz), 3.801 (3H, s, CH_3), 6.82−6.85 (2H, m), 7.12−7.15 (2H, m); ^{13}C NMR (50 MHz) δ 15.22, 21.59, 25.19 (quaternary), 25.68, 32.46 (CH_2), 38.14 (CH_2), 40.21 (quaternary), 43.02, 46.79 (quaternary), 55.08 (OCH_3), 113.13 (2 signals), 129.54 (quaternary), 132.62 (2 signals), 158.04 (quaternary); MS *m*/*z* 242 (M, 22); MS (CI methane) *m*/*z* 243 (M + 1, 100). Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.19; H, 9.19.

(ii) 11h with TfOH (1 equiv) in $CHCl_3$. Hydrolysis of the *p*-anisyl alcohol **11h** (76.7 mg; 0.295 mol) (method B, Table 2, entry 8) afforded (1*R*,4*R*)-7,7-dimethyl-1-(4′-methoxyphenyl)-2-methylenebicyclo[2.2.1]heptane (**13**) after flash chromatography (ether/hexane 1:99) as a colorless oil (59.5 mg, 83%): $[\alpha]^{20}_D = +103.8°$ (*c* 0.208, EtOAc); IR (thin film) 1611s, 1289s, 1248s, 1181s, 1041s cm^{-1}; ^1H NMR (400 MHz) δ 0.746 (3H, s, CH_3), 0.976 (3H, s, CH_3), 1.339 (1H, ddd, J = 12.2, 9.4, 4.6 Hz), 1.558 (1H, ddd, J = 12.2, 9.4, 4.0 Hz), 1.853 (1H, dd, J = 4.4, 4.4 Hz), 1.917 (1H, ddddd, J = 12.0, 12.0, 3.8, 3.8, 3.8 Hz), 2.093 (1H, ddd, J = 16.0, 2.4, 2.4 Hz), 2.526 (1H, ddd, J = 11.9, 11.9, 4.4 Hz), 2.654 (1H, ddddd, J = 16.0, 3.1, 3.1, 3.1, 3.1 Hz), 3.810 (1H, s, OCH_3), 4.538 (1H, dd, J = 3.0, 3.0 Hz), 4.796 (1H, dd, J = 2.8, 2.8 Hz), 6.84−6.88 (2H, m), 7.28−7.32 (2H, m); ^{13}C NMR (50 MHz) δ 19.14, 21.66, 27.39 (CH_2), 33.06 (CH_2), 38.06 (CH_2), 43.02 (quaternary), 46.14, 49.91 (quaternary), 55.17 (OCH_3), 105.00 (CH_2), 112.83, 129.88, 131.63 (quaternary), 157.79 (quaternary), 158.92 (quaternary); MS *m*/*z* 242 (M, 91); HRMS *m*/*z* calcd for $C_{17}H_{22}O$ M^+ 242.1671, found M^+ 242.1669.

(i) 11i in EtOH/10 M HCl (2:1, v/v), Reflux. Hydrolysis of the *o*-(hydroxymethyl)phenyl alcohol **11i** (71.2 mg, 0.271 mmol) (method A, Table 2, entry 9) and chromatography (ether/hexane 1:99) afforded (1′*S*,2′*R*,4′*R*)-spiro[phthalan-2,2′-(1′,3′,3′-trimethylbicyclo[2.2.1]heptane) (**14**) as a colorless oil (65.3 mg, 98%): $[\alpha]^{20}_D = +25.0°$ (*c* 0.838, EtOAc); IR (KBr) 1608w, 1057s cm^{-1}; ^1H NMR (400 MHz) δ 0.698 (3H, s, CH_3), 0.766 (3H, s, CH_3), 1.038 (3H, s, CH_3), 1.148 (1H, ddd, J = 12.5, 12.5, 4.1 Hz), 1.289 (1H, dd, J = 10.5, 1.4 Hz), 1.496 (1H, dddd, J = 12.5, 12.5, 5.4, 4.6 Hz), 1.752 (1H, ddd, J = 4.1, 2.2, 2.2 Hz), 1.864 (1H, dddd, J = 12.3, 9.2, 4.5, 2.6 Hz), 2.095 (1H, dddd, J = 10.4, 1.9, 1.9, 1.9 Hz), 2.193 (1H, dddd, J = 11.8, 9.1, 5.3, 2.3 Hz), 4.888 (1H, d, J = 12.2 Hz), 4.953 (1H, d, J = 12.2 Hz), 7.13−7.23 (3H, m), 7.28−7.32 (1H, m); ^{13}C NMR (50 MHz) δ 17.69, 23.01, 25.20 (CH_2), 29.42, 30.59 (CH_2), 41.51 (CH_2), 46.10 (quaternary), 48.59, 52.51 (quaternary), 71.57 (CH_2), 98.85 (quaternary), 120.53, 125.16, 125.78, 126.62, 140.51 (quaternary), 141.65 (quaternary); MS *m*/*z* 242 (M, 25); HRMS *m*/*z* calcd for $C_{17}H_{22}O$ M^+ 242.1671, found M^+ 242.1678. Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.20; H, 9.17.

(j) 11j in EtOH/10 M HCl (2:1, v/v), Reflux. Hydrolysis of the *o*-(methoxymethyl)phenyl alcohol **11j** (41.7 mg, 0.152 mmol) (method A, Table 2, entry10) afforded the phthalan **14** as a colorless oil (36.8 mg, 99%).

(k) (i) 11k in EtOH/10 M HCl (2:1, v/v), Reflux. Hydrolysis of the *o*-tolyl alcohol **11k** (45.6 mg; 0.187 mmol) (method A, Table 2, entry 11) under reflux for 40 min led to complete conversion into the cyclofenchene **12d**. Chromatography (hexane) afforded (1*R*,2*S*,4*R*,6*S*)-2-(2′-methylphenyl)-1,3,3-trimethyltricyclo[2.2.1.0^{2,6}]heptane (**12d**) as a colorless oil (38.3 mg, 91%): IR ($CHCl_3$) 2959vs, 1290m cm^{-1}; ^1H NMR (400 MHz) δ (*denotes minor atropisomer) 0.756* (3H, s, CH_3), 0.821 (3H, s, CH_3), 0.836* (1H, ddd, J = 1.1, 1.1, 1.1 Hz), 0.861 (3H, s, CH_3), 0.923* (3H, s, CH_3), 1.054 (3H, s, CH_3), 1.112 (1H, ddd, J = 1.1, 1.1, 1.1 Hz), 1.192* (3H, s, CH_3), 1.264 (1H, dd, J = 10.4, 1.2 Hz), 1.277* (1H, dd, J = 10.6, 1.2 Hz), 1.366* (1H, ddd, J = 10.6, 1.3, 1.3 Hz), 1.434 (1H, ddd, J = 10.6, 1.4, 1.4 Hz), 1.57−1.60 (1H, m, both isomers), 1.839 (1H, ddd, J = 10.6, 1.6, 1.6 Hz), 1.933* (1H, br d, J = 9.4 Hz), 1.949* (1H, ddd, J = 10.7, 1.6, 1.6 Hz), 2.012 (1H, br d, J = 10.6 Hz), 2.381* (3H, s, CH_3), 2.392 (3H, s, CH_3), 7.06−7.26 (4H, m, both isomers); ^{13}C NMR (50 MHz) δ (*denotes minor atropisomer) 15.03*, 15.75, 20.43, 20.67*, 21.87, 22.07, 22.34*, 25.15 (quaternary), 25.96*, 26.44* (quaternary), 26.95, 32.02* (CH_2), 32.68 (CH_2), 37.95 (CH_2), 38.06 (quaternary), 38.46* (CH_2), 40.23* (quaternary), 42.27, 43.33*, 48.54 (quaternary), 48.98* (quaternary), 124.66, 124.93*, 125.98, 126.09*, 130.15*, 130.59, 133.62, 134.68*, 134.92 (quaternary), 135.99* (quaternary), 139.45* (quaternary), 139.92 (quaternary); MS *m*/*z* 226 (M, 42); MS (CI methane) *m*/*z* 227 (M + 1, 100). Anal. Calcd for $C_{17}H_{22}$: C, 90.20; H, 9.80. Found: C, 90.00; H, 9.93.

When the alcohol **11k** (0.180 g, 0.738 mmol) was treated under the same conditions for 3 d a product mixture (0.117 g) was obtained after workup and chromatography (ether/hexane 1:99) that was found by HPLC analysis (Whatman Partisil 5 column, flow rate 1.5 mL/min, refractive index detector, hexane as solvent) to consist of the cyclofenchene **12d** (84%) (t_R = 4.25 min) and a mixture of 11 unidentified species (16%) (t_R = 5.1−10.1 min).

(ii) 11k in EtOH/10 M HCl (1:1, v/v), Reflux. Hydrolysis of **11k** (0.111 g, 0.453 mmol) (method A, Table 2, entry 11) at 93 °C for 24 h and chromatography (ether/hexane 1:99) afforded a product mixture (75.3 mg) that was found by HPLC analysis to consist of the cyclofenchene (64%) and the same mixture of 11 species as above (36%).

(iii) 11k with TfOH (1 equiv) in $CHCl_3$. Hydrolysis of **11k** (96 mg, 0.393 mol) (method B, Table 2, entry 11) for 10 min resulted in complete conversion into the cyclofenchene **12d** as indicated by TLC analysis. The reaction mixture was heated under reflux for a total of 24 h and afforded after workup and chromatography (hexane) the cyclofenchene **12d** (21.7 mg, 24%) and an inseparable mixture of products (35 mg, 39% based on mass of **12d**).

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Supporting Information Available: Characterization data (IR, ^1H and ^{13}C NMR, MS, and elemental analysis or HRMS) for compounds **11a**−**e**,**g**−**k** and (1′*S*,2′*S*,4′*R*)-*N*-[2-(2′-hydroxy-1′,3′,3′-trimethylbicyclo[2.2.1]hept-2′-yl)phenyl]tri-

fluoroacetamide, ^{1}H NMR data for compound **11f**, tabulated NMR data with assignments for compounds **3c**, **4a**, **13**, and **14**, NOE results for compounds **3c**, **4a**, and **14**, ^{1}H NMR spectra for compounds **3c**, **11e**, **12a**, and **13**, and analytical HPLC chromatogram for hydrolysate from **11k** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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