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Stereochemistry of Reactions Involving Rotationally Restricted, Sterically Hindered Cations, Radicals, and Anions: 9-Fluorenyl Systems†

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Received July 28, 2003

A study of the stereochemical pathways of reactions involving rotationally restricted, sterically hindered cations, radicals, and anions has been undertaken utilizing chiral 9-(*o*-*tert*-butylphenyl)-fluorenes. Previous reports of studies with these or related achiral compounds contained erroneous or equivocal conclusions. This study shows that (+)-*sp*-9-(*o*-*tert*-butylphenyl)-9-methoxy-2-methylfluorene, treated with $Tf_2O-CHCl_3$ to form 100% of the 9-cation, then with NaOMe−MeOH, provided 29% of re-formed substrate (configurational retention) and 71% of the (−)-*sp* enantiomer (inversion). The same substrate treated with $HI-CHCl_3$ was converted into the 9-radical, which was rapidly reduced, affording 100% isolation of (−)-*sp*-9-(*o*-*tert*-butylphenyl)-2-methylfluorene (inversion). Treatment of the latter with *n*-BuLi−THF provided the 9-anion which, on acidification, yielded 100% of the enantiomeric (+)-*sp*-9-(*o*-*tert*-butylphenyl)-2-methylfluorene (inversion). The substrates in these reactions were the thermodynamically favored *sp* rotamers. Inversion directly produced the higher energy nonenantiomeric *ap* rotamers, which rapidly rotated into the *sp* products that were enantiomeric with the substrates. These results are explained by the rotational restriction and partial steric hindrance by the *tert*-butyl group to the original face of the sp^3 antiaromatic 9-cation ($4n\ \pi$ electrons), and the rotational restriction and extensive blockage to the original face of the sp^2 nonaromatic 9-radical ($4n + 1\ \pi$ electrons) and aromatic ($4n + 2\ \pi$ electrons) 9-anion. The barrier to rotation in some of the ortho-substituted 9-arylfluorenes is great enough to allow their *sp* and *ap* rotamers to be detected coexisting in solution, although their crystals were composed exclusively of one. Rotational restriction and steric hindrance at the 9-position have a large influence on the pK_a values of these fluorenes and can offset the classic electronic effects of the substituents.

Introduction

In a series of earlier reports we described our studies of the properties, crystal structures, and reactions of *sp* and *ap*[1a,b] 9-acylfluorenes[2] and 9-(alkylphenyl)fluorenes,[3] some of whose C-9 substituents were rotationally restricting and sterically hindering to attack at that position. However, the question of the stereochemical consequences of reactions involving the C-9 cation, radical, and anion of such fluorenes was not addressed. Cram et al.[4] found that chiral 9-substituted fluorenes that were neither sterically hindered nor rotationally restricted underwent varying degrees of retention and racemization during base-catalyzed 9-D/H exchange, which were associated with the type of base, solvent, and concentration used. Ford et al.[5] provided strong evidence of hindered rotation around the aryl−C-9 bond of a variety of 9-(2,6-disubstituted-phenyl)fluorenes and 9-(2-substituted-1-naphthyl)fluorenes, but they did not explore the combined effects of steric hindrance and restricted rotation on the stereochemistry of reactions at C-9. Oki and co-

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† This paper is dedicated to the late Professor Frederick G. Bordwell, whose contributions in the field of physical organic chemistry inspired so many others.

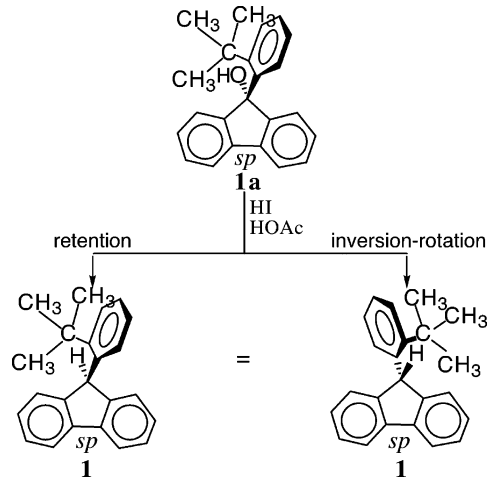
‡ Ph.D. Dissertation, Southern Illinois University, Carbondale, IL, 1997.

(1) (a) The designations *sp* (syn periplanar) and *ap* (anti periplanar) for the conformations discussed here are in accord with Rule E-6.6, IUPAC Tentative Rules, Section E, Fundamental Stereochemistry (*J. Org. Chem*. **1970**, *35*, 2861). (b) The *ap* and *sp* stereochemistry of a number of crystalline 9-acylfluorenes and 9-(*o*-alkylphenyl)fluorenes has been unequivocally determined by X-ray diffraction, and in solution they are effectively characterized by ^{1}H NMR spectroscopy (refs 2 and 3). In the latter, the most striking differences emanate from the *tert*-butyl protons in 9-(*o*-*tert*-butylphenyl)fluorenes. In the *ap* rotamers these protons are shielded by the fluorene-ring π electrons and resonate upfield in the 0.7-ppm region, while in the *sp* rotomers they are correspondingly deshielded and resonate downfield in the 1.8-ppm region. Differences are also observed in the resonances of the *o*-H of *ap* vs *sp* rotamers, and of H-9 of these rotamers of 9-(*o*-*tert*-butylphenyl)fluorene itself.

(2) (a) Meyers, C. Y.; Chan-Yu-King, R.; Wahner, A. P.; Manohar, S. K.; Carr, S. E.; Robinson, P. D. *Acta Crystallogr*. **1991**, C*47*, 1236−1239. (b) Meyers, C. Y.; Tunnell, J. L.; Robinson, P. D.; Hua, D. H.; Saha, S. *Acta Crystallogr*. **1992**, C*48*, 1815−1818. (c) Robinson, P. D.; Lutfi, H. G.; Lim, L. W.; Meyers, C. Y. *Acta Crystallogr*. **1994**, C*50*, 1728−1732. (d) Meyers, C. Y.; Lutfi, H. G. A.; Robinson, P. D. *Acta Crystallogr*. **2000**, C*56*, IUC0000220, e418−e419. (e) Robinson, P. D.; Lutfi, H. G.; Hou, Y.; Meyers, C. Y. *Acta Crystallogr*. **2000**, C*56*, 1380−1382. (f) Robinson, P. D.; Lutfi, H. G.; Hou, Y.; Meyers, C. Y. *Acta Crystallogr*. **2001**, C*57*, 428−430. (g) Meyers, C. Y.; Lutfi, H. G.; Hou, Y.; Robinson, P. D. *Acta Crystallogr*. **2001**, C*57*, 580−581. (h) Robinson, P. D.; Lutfi, H. G.; Hou, Y.; Meyers, C. Y. *Acta Crystallogr*. **2001**, C*57*, 582−584.

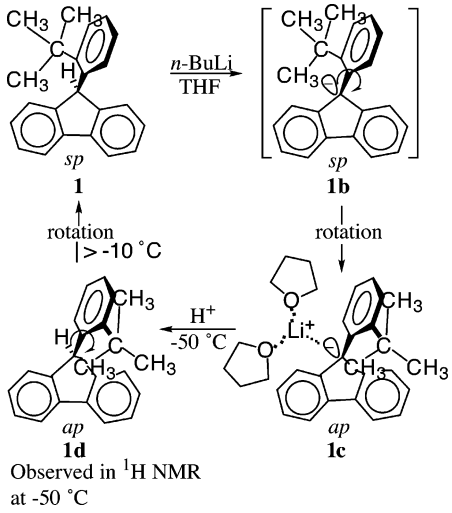
10.1021/jo0351015 CCC: $27.50
Published on Web 01/15/2004

SCHEME 1. Conversion of 1a to 1 (Stereochemical Pathway Not Noted)[6]

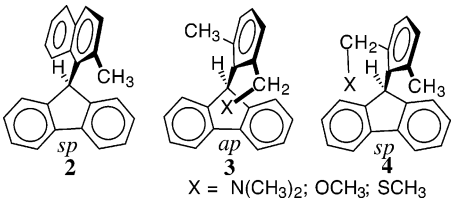


workers[6] subsequently studied reactions at C-9 of achiral fluorenes whose C-9 substituent concurrently sterically hindered C-9 and was rotationally restricted. In the absence of chirality, conversion of *sp*-9-fluorenol **1a** to *sp*-fluorene **1** by treatment with HI−HOAc provided no information regarding the stereochemical pathway—retention or inversion−rotation—as illustrated in Scheme 1. In a related study, they deprotonated *sp*-**1** with *n*-BuLi−THF; the lithiated anion solution was then cooled to −50 °C and acidified. Dynamic ^{1}H NMR at this temperature showed that the *ap* rotamer, **1d**, had been formed exclusively, which, when the solution was slowly warmed above ca. −10 °C, underwent rotation to *sp*-**1**.

SCHEME 2. Deprotonation−Reprotonation of *sp*-1: Anion Rotation−Protonation−Rotation Proposed[6]



The Oki group suggested that the initially formed anion *sp*-**1b** was tetrahedral and retained the *sp* conformation, but it *rotated* to the *ap*-**1c** anion, which offered less hindrance to solvation, and it was direcly protonated into fluorene *ap*-**1**, which rotated to the thermodynamically favored *sp*-**1** (Scheme 2). Again, in the absence of studies with chiral substrates, the Oki group's explanation of this stereochemical pathway as well as that with rotationally restricted 9-α-naphthylfluorenes (e.g. **2**) appeared reasonable.



In related studies, their results with achiral fluorenes *ap*-**3** and *sp*-**4** suggested that the stereochemistry resulting from deprotonation−reprotonation could be controlled by the intramolecular association of the metalated carbanion with a polar substituent. However, in the absence of chirality, whether the intramolecular association directed this conversion via a rotation or inversion mechanism could not be ascertained (Scheme 3). A recent report by Baker et al.[7] provided a partial answer by studies with related rotationally restricted chiral substrates. They found that chiral *ap*-**5**, via reprotonation of its anion, provided chiral *sp*-**6**, the *inverted* product, thereby ruling out a rotation pathway. The inversion mechanism in this case was explained by the intramolecular assistance derived from intramolecular ion pairing (**5a**) (Scheme 4). However, this explanation and what stereochemical pathway this reaction would have taken in the absence of such ion pairing required further study.

In reviewing the earlier studies, it seemed reasonable to us that the stereochemistry of reactions at C-9 of fluorenes even without intramolecular assistance, but

(3) (a) Meyers, C. Y.; Hou, Y.; Scott, D.; Robinson, P. D. *Acta Crystallogr.* **1997**, *C53*, 1149−1151.(b) Robinson, P. D.; Hou, Y.; Lutfi, H. G.; Meyers, C. Y. *Acta Crystallogr.* **1998**, *C54*, 73−77. (c) Hou, Y.; Meyers, C. Y.; Robinson, P. D. *Acta Crystallogr.* **1998**, *C54*, 1013−1016. (d) Robinson, P. D.; Hou, Y.; Meyers, C. Y. *Acta Crystallogr.* **1998**, *C54*, 1173−1175. (e) Robinson, P. D.; Hou, Y.; Meyers, C. Y. *Acta Crystallogr.* **1998**, *C54*, CIF Access paper, DVN IUC9800051. (f) Meyers, C. Y.; Hou, Y.; Robinson, P. D. *Acta Crystallogr.* **1999**, *C55*, 626−628. (g) Hou, Y.; Meyers, C. Y. *Can. J. Chem*, **1999**, *77*, 960−966. (h) Meyers, C. Y.; Hou, Y.; Lutfi, H. G.; Saft, H. L. *J. Org. Chem.* **1999**, *64*, 9444−9449. (i) Hou, Y.; Robinson, P. D.; Meyers, C. Y. *Acta Crystallogr.* **1999**, *C55*, CIF Access, Data Validation No. IUC9900144, November issue. (j) Robinson, P. D.; Hou, Y.; Meyers, C. Y. *Acta Crystallogr.* **1999**, *C55*, CIF Access, Data Validation No. IUC9900147, November issue. (k) McLean, A. W.; Meyers, C. Y.; Robinson, P. D. *Acta Crystallogr.* **2003**, *E59*, o891−o893. (l) Meyers, C. Y.; McLean, A. W.; Robinson, P. D. *Acta Crystallogr.* **2003**, *E59*, o978−o980. (m) Robinson, P. D.; McLean, A. W.; Meyers, C. Y. *Acta Crystallogr.* **2003**, *C59*, o539−o540. (n) McLean, A. W.; Meyers, C. Y.; Robinson, P. D. *Acta Crystallogr.* **2003**, *E59*, o1228−o1230. (o) Robinson, P. D.; McLean, A. W.; Meyers, C. Y, *Acta Crystallogr.* **2003**, *E59*, o1915−o1917. (p) Meyers, C. Y.; Robinson, P. D.; McLean, A. W. *Acta Crystallogr.* **2003**, *C59*, o712−o714. (q) McLean, A. W.; Meyers, C. Y.; Robinson, P. D. *Acta Crystallogr.* **2003**, *E59*, accepted for publication. (r) Meyers, C. Y.; Robinson, P. D.; McLean, A. W. *Acta Crystallogr.* Submitted for publication.

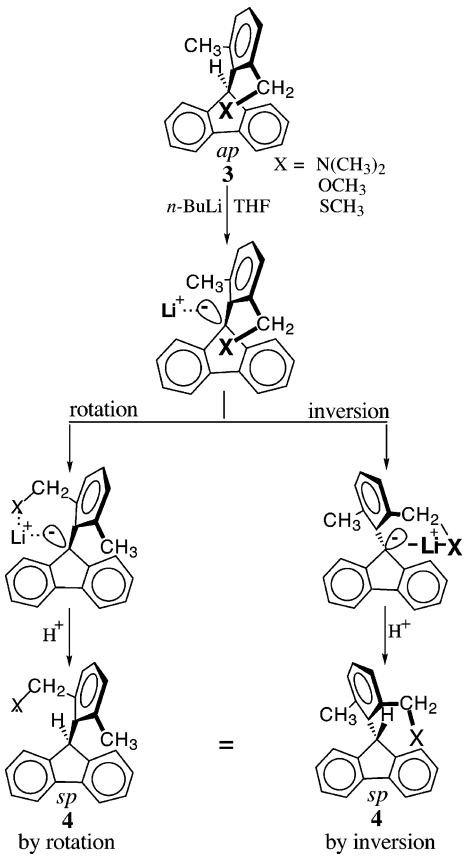
(4) (a) Cram, D. J. Fundamentals of Carbanion Chemistry. In *Organic Chemistry−A Series of Monographs*; Blomquist, A. L., Ed; Academic Press: New York, 1965; Vol. 4, Chapter 3 and references therein. (b) Ford, W. T.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 2612−2622 and references therein.

(5) Ford, W. T.; Thompson, T. B.; Snoble, K. A. J.; Timko, J. M. *J. Am. Chem. Soc.* **1975**, *97*, 95−101.

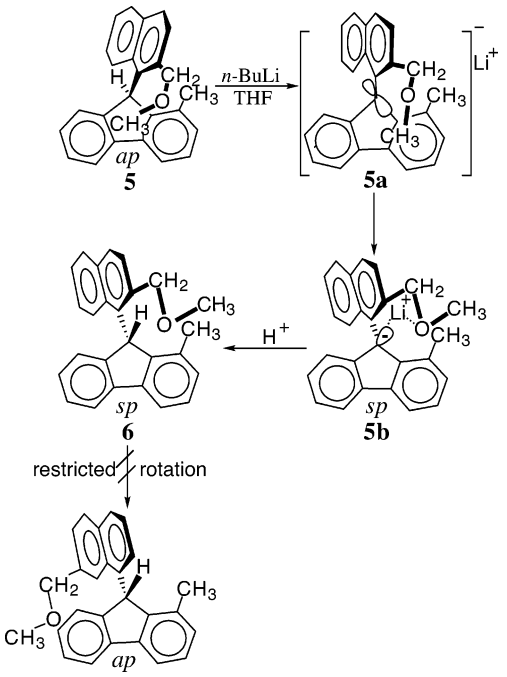
(6) (a) Oki, M. The Chemistry of Rotational Isomers. In *Reactivity and Structure Concepts in Organic Chemistry*; Hafner, K., Lehn, J.-M., Rees, C. W., Schleyer, P. v. R., Trost, B. M., Zahradník, R., Eds; Springer-Verlag: New York, 1993; Vol. 30, Chapter 4. (b) Moriyama, K.; Nakamura, M.; Nakamura, N.; Oki, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 485−489. (c) Nakamura, M.; Suzuki, Y.; Oki, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2370−2375. (d) Nakamura, M.; Nakamura, N.; Oki, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2986−2990.

(7) Baker, R. W.; Hambley, T. W.; Turner, P. *J. Chem. Soc., Chem. Commun.* **1995**, 2509−2510.

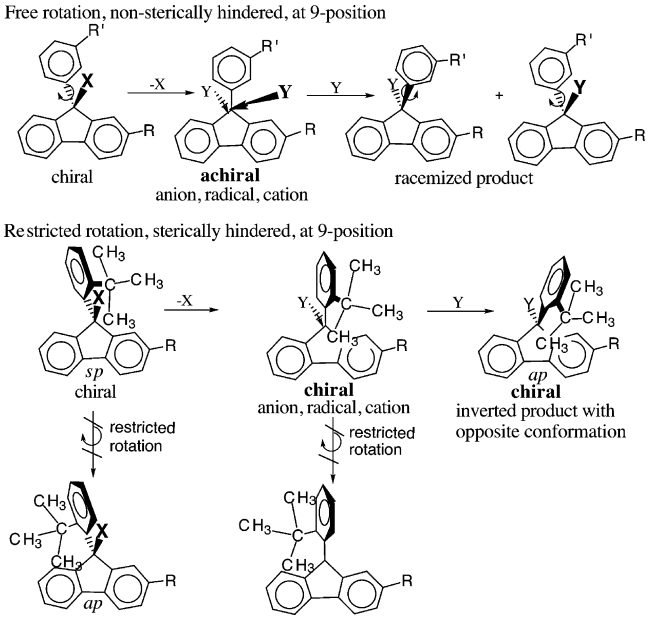
SCHEME 3. Probe of Intramolecularly Assisted Deprotonation−Reprotonation of Achiral *ap*-3 to *sp*-4:[6] Rotation or Inversion?



SCHEME 4. Stereochemical Probe of Intramolecularly Assisted Reprotonation of a Chiral 9-Fluorenyl Anion: Inversion of *ap*-5 to *sp*-6



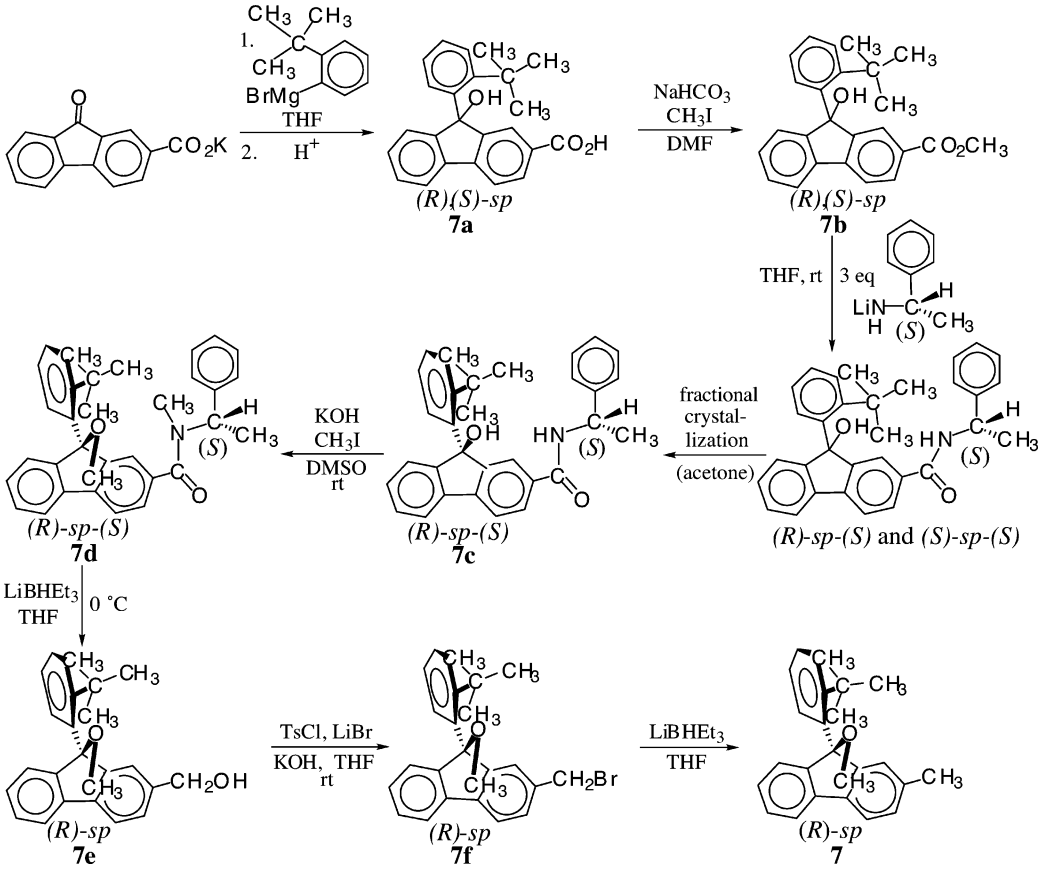
with rotationally restricted, sterically hindering C-9 substituents, would differ from that of counterpart fluorenes without such substituents. It was reasoned that a simple chiral 9-arylfluorene without these constraints would be converted into its *achiral* 9-anion, -cation, and -radical and subsequent attack on either face would be equally favored, leading to racemization. This reasoning was partly supported by a related example in which Cram et al. reported 100% *racemization* of a chiral 9-deuteriofluorene via 9-D/H exchange by treatment with *t*-BuOK−*t*-BuOH.[4] In contrast, a chiral 9-arylfluorene rotationally restricted and sterically hindered at C-9 would be converted into its 9-anion, -cation, and -radical, respectively, which would also be chiral, rotationally restricted, and sterically hindered. In the case of *sp* rotamers, subsequent attack at the unhindered face is favored, leading directly to the *ap* rotamer via *inversion* of configuration. The difference between these two types of fluorenes is apparent from a comparison of their chiral stereochemistry, illustrated here.



Results and Discussion

We have now determined the mechanistic stereochemistry of reactions of sterically hindered, rotationally restricted fluorenyl 9-cations, -radicals, and -anions utilizing chiral fluorenes *unencumbered by the possibility of intramolecular assistance*. These results could not have been predicted on the basis of the previously published reports and, in some cases, contradict the proposed stereochemical pathways. Most of our studies described here with chiral fluorenes either directly utilized (*R*)-(+)-*sp*-9-(*o*-*tert*-butylphenyl)-9-methoxy-2-methylfluorene (**7**) or chiral compounds prepared from it. The first step in our planned synthesis of **7** required the preparation of racemic *sp*-9-(*o*-*tert*-butylphenyl)-9-hydroxyfluorenecarboxylic acid (**7a**), which was accomplished via the reaction of *o*-*tert*-butylphenylmagnesium bromide with the potassium salt of commercially available fluorenone-2-carboxylic acid. Although **7a** was then successfully converted into its two diastereomeric L-cinchonidine salts, they were essentially indistinguishable by ^{1}H NMR. However, via the racemic methyl esters (**7b**), the epimeric *R* and *S* *sp*-9-(*o*-*tert*-butylphenyl)-9-hydroxyfluorene-2-(*S*)-*N*-α-methylbenzylcarboamides were prepared, from which the *R*

SCHEME 5. Preparation of 7



epimer (**7c**) was successfully isolated and purified, and was unequivocally chracterized by X-ray diffraction.[3c] On treatment of **7c** with KOH−MeI, methylation of 9-OH as well as NH occurred, providing **7d**. *N*-Methylation was required; otherwise formation of the amide anion in the subsequent reaction with $LiBHEt_3$ would have prevented the desired reductive cleavage of the *N*-methyl-*N*-α-methylbenzylamido group. Thus, reductive cleavage of **7d** into chiral (*R*)-*sp*-9-(*o*-*tert*-butylphenyl)-2-hydroxymethyl-9-methoxylfluorene (**7e**) was successful. Treatment with TsCl−LiBr−KOH converted **7e** into the corresponding 2-bromomethyl compound (**7f**) which, in turn, was reductively debrominated with $LiBHEt_3$ to the desired chiral **7**. This series of transformations is illustrated in Scheme 5. The 2-methyl substituent was chosen because it imparted chirality without imposing intramolecular association or additional steric or rotational hindrance in the reactions of the 9-cation, -radical, or -anion. Thus, the stereochemistry of the reactions unequivocally determined with chiral **7** or its derivatives would serve as an excellent model to ascertain the stereochemistry of these reactions followed by achiral **1** and related achiral fluorenes via their 9-cation, -radical, and -anion.

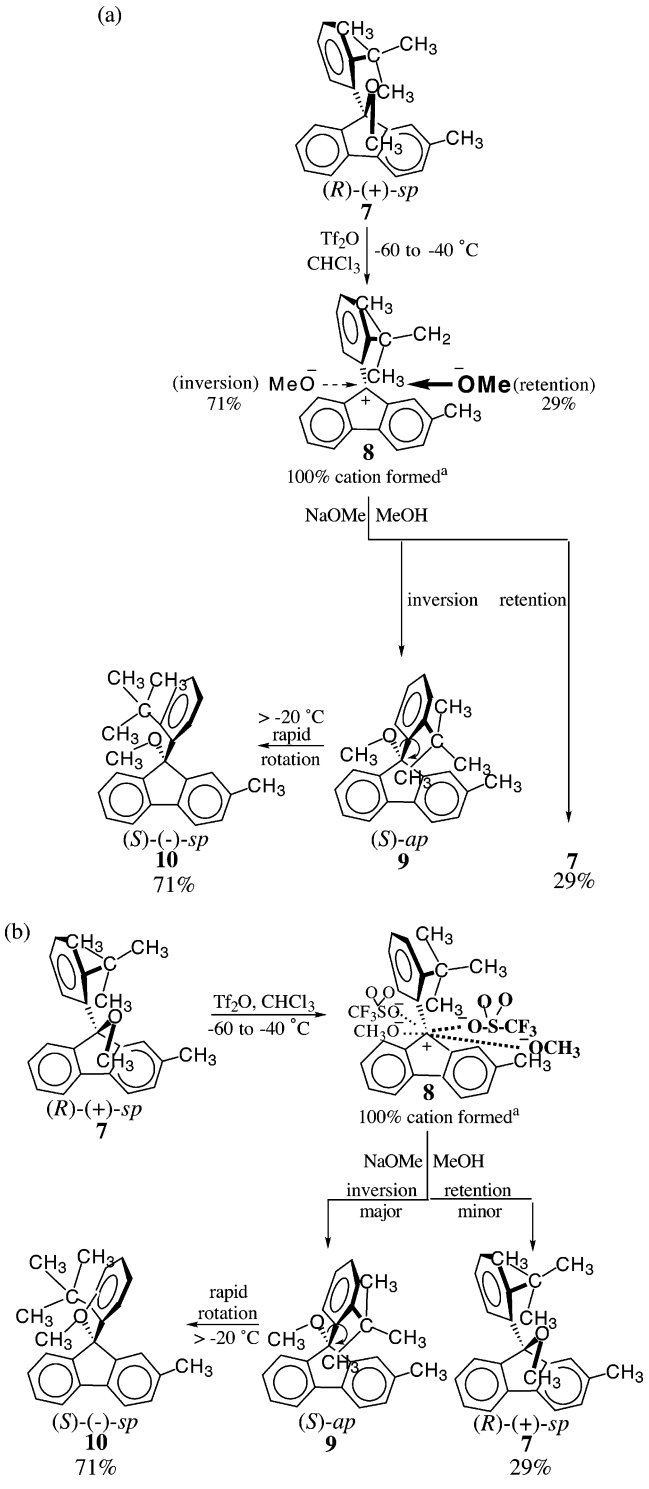
Reactions via the 9-Fluorenyl Cation. Via a cationic mechanism, treatment of (*R*)-(+)-*sp*-**7** at −60 to −40 °C with Tf_2O−$CHCl_3$ followed by MeONa−MeOH, then warming the mixture above −20 °C, produced 71% of the *inverted* enantiomer, (*S*)-(−)-s*p*-**10**, along with 29% of reformed (*R*)-(+)-*sp*-**7**. Oki et al.[6] reported that *ap*-9-(*tert*-butylphenyl)fluorene (**1d**) rapidly rotates to the *sp* rotamer (**1**) above −10 °C, and our studies showed that **1** as well as the corresponding *sp*-9-fluorenol (**1a**) exist *exclusively* in their *sp* rotameric conformations in solution (NMR) at room temperature as well as their crystalline states.[3b,g,h,8] The fact that the reaction via the 9-fluorenyl cation **8** occurred with 29% *retention*−*71% inversion* of configuration while the reactions via the corresponding 9-fluorenyl carbanion and radical (described below) proceeded with *exclusive inversion* reasonably may be explained on the basis of the 9-fluorenyl cation's antiaromaticity (4*n* π electrons).

The antiaromaticity of the 9-fluorenyl cation, which has been experimentally supported,[9a] is derived from its cyclopentadienyl cation moiety, whose antiaromatic character has been extensively investigated.[9b] The antiaromatic nature of boracyclopentadienes, counterparts of cyclopentadienyl cations, has likewise been investigated,[9c] and that of 9-borafluorenes, electronically related to the 9-fluorenyl cation, was recently reported.[9d] The antiaromatic nature of cation **8** promotes a distorted trigonal

(8) It should be noted that, based on NMR and X-ray analysis of the large number of C-9-substituted fluorenes, the thermodynamically favored conformation can be either the *sp* or *ap* rotamer, depending on the C-9 substituents (see refs 2 and 3).

(9) (a) Jiao, H.; Schleyer, P. v. R.; Mo, Y.; McAllister, M. A.; Tidwell, T. T. *J. Am. Chem. Soc.* **1997**, *119*, 7075−7083. Amyes, T. L.; Richard, J. P.; Novak, M. *J. Am. Chem. Soc.* **1992**, *114*, 8032−8041. Olah, G. A.; Prakash, G. K. S.; Liang, G.; Westerman, P. W.; Kunde, K.; Chandrasekar, J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1980**, *102*, 4485−4492. (b) Lambert, J. B.; Lin, L.; Rassolov, V. *Angew. Chem., Int. Ed.* **2002**, *41*, 1429−1431. Otto, M.; Scheschkewitz, D.; Kato, T.; Midland, M.; Lambert, J. B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 2275−2276. Müller, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 2276−2278. Allen, A. D.; Sumonja, M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1997**, *119*, 2371−2375. (c) Eisch, J. J.; Galle, J. E.; Kozima, S. *J. Am. Chem. Soc.* **1986**, *108*, 379−385. (d) Wehmschulte, R. J.; Diaz, A. A.; Khan, M. A. *Organometallics* **2003**, *22*, 83−92.

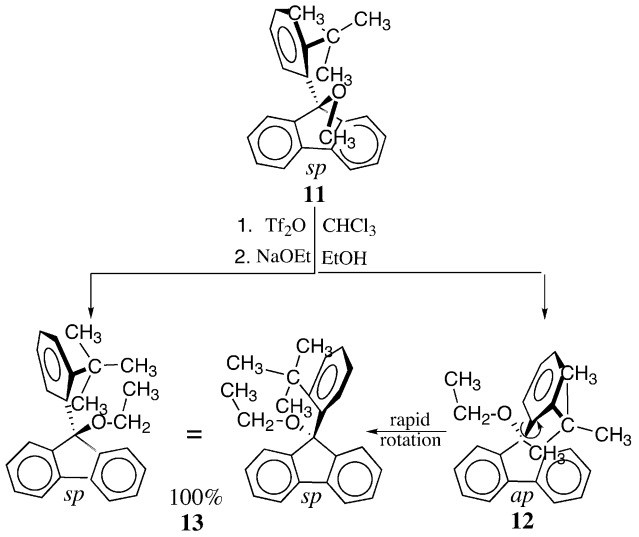
SCHEME 6.[a] Reaction of 7 via Chiral 9-Fluorenyl Cation 8 (71% Inversion and 29% Retention)



[a] See reaction with EtONa−EtOH under identical conditions, Scheme 7.

character to C-9$^+$ (see structure **8**),[9] affording a geometry in which attack leading to inversion is favored over the *o-tert*-butyl-hindered frontal attack resulting in retention (Scheme 6, a). A related explanation for the relative amounts of inversion vs retention products involves the participation of two cationic species ion-paired with triflate anion (**8**): the more hindered, minor ion pair re-

SCHEME 7. 100% Conversion of *sp*-9−MeO−Fluorene 11 to *sp*-9−EtO−Fluorene 13 via 9-Fluorenyl Cations 1b and 1b

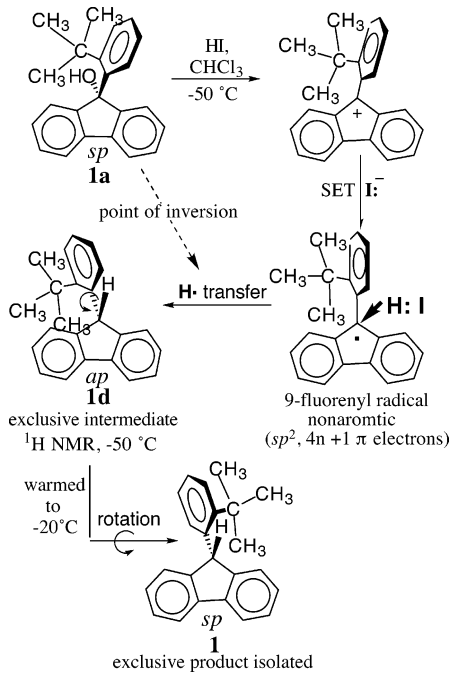


forms (*R*)-(+)-*sp*-**7** on reaction with MeONa, and the less hindered, major ion pair provides the inverted product, *ap*-9 (Scheme 6, b). In either case, the initially formed inversion product, **9**, rotates to the thermodynamically favored, isolated conformer, (*S*)-(−)-sp-**10**, the enantiomer of **7**. The percentages of products **7** and **10** were calculated from the specific rotation of the isolated mixture, $[\alpha]^{20}_D$ −19.2 (*c* 0.106, acetone); ee of **10** = 42.2%. That isolated **7** did not contain any unchanged *starting material* **7** was determined from the *quantitative* exchange of 9-methoxy by ethoxy on converting the related *sp*-9-*o-tert*-butylphenyl-9-methoxyfluorene (**11**) to *sp*-9-(*o-tert*-butylphenyl)-9-ethoxyfluorene (**13**) by similar treatment with triflic anhydride in $CHCl_3$ followed by NaOEt−EtOH (Scheme 7). Thus, **7**, with only one asymmetric center, offers an example wherein inversion at that center does not directly provide the enantiomeric structure. A similar result was reported by Baker et al.[7] (shown in Scheme 4). Both of these observations are rare examples of this phenomenon.

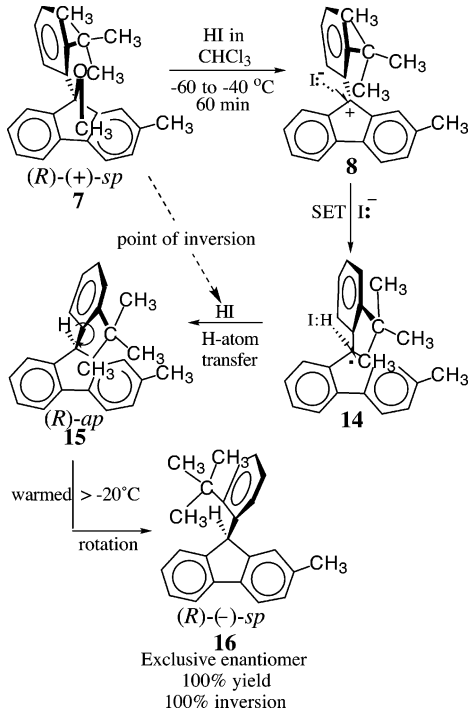
Reactions via the 9-Fluorenyl Radical. As shown in Scheme 1, Oki et al.[6] reported that achiral *sp*-9-(*o-tert*-butylphenyl)-9-fluorenol (**1a**), treated with HI−HOAc, was converted into *sp*-9-(*o-tert*-butylphenyl)fluorene (**1**), but neither the mechanistic nor stereochemical aspects of the reaction were noted.

We recently reported on our effort to examine these aspects via a dynamic NMR study also involving achiral **1a**.[3h] In that radical-reduction study, carried out with HI in $CDCl_3$ at −50 °C in an NMR tube, *sp*-**1a** was initially converted into the 9-cation, which was reduced via single-electron transfer from I^- into the 9-radical, which, in turn, underwent hydrogen atom transfer. Complete replacement of the 9-OH by H was signaled by the exclusive formation of *ap*-9-(*o-tert*-butylphenyl)fluorene (**1d**). As the temperature was warmed from −50 to −20 °C, rotation of the *o-tert*-butylphenyl group of *ap*-**1d** slowly and irreversibly converted it into its thermodynamically favored *sp*-**1** rotamer, the isolated product**.** We have already shown by ^{1}H NMR ($CDCl_3$) that the *sp* rotamers **1a** and **1** show no tendency to undergo rotation

SCHEME 8. Illustration of the Conversion of Achiral *sp* 1a to *sp* 1 via *ap* 1d with HI−$CHCl_3$ by a Free-Radical Inversion Pathway



SCHEME 9. 100% Inversion via Chiral Radical 14: Conversion of 7 into 16 with HI−$CHCl_3$



to their *ap* rotamers in solution, their spectra respectively exhibiting a *sharp downfield singlet* of nine hydrogens for their deshielded *sp t*-Bu group but no sign of any corresponding *upfield* resonance for the *shielded t*-Bu hydrogens of their *ap* rotamers; moreover, they crystallize exclusively as their *sp* rotamers.[3b] Under identical NMR conditions, equilibration of the *sp* and *ap* rotamers of the less rotationally restricted 9-(*o*-isopropylphenyl)-fluorene does occur, both rotamers being readily observed.[3a] Thus, the initial formation of *ap*-**1d** in this reaction proceeding through the rotationally restricted, sterically hindered 9-fluorenyl radical, together with the inversion mechanism substantiated in the reactions involving the corresponding 9-fluorenyl cations (and anions; see below), strongly supported an inversion mechanism in the reactions with HI involving these 9-fluorenyl radicals (Scheme 8).

The mechanistic stereochemistry involving the 9-radical was further investigated by repeating the reaction in HI in $CHCl_3$ with a corresponding chiral substrate, *R*-(+)-(*sp*)-9-(*o-tert*-butylphenyl)-9-methoxy-2-methylfluorene (**7**), $[\alpha]^{20}_D$ +45.5 (*c* 0.2, acetone). At −60 to −40 °C, chiral *sp* **7** was converted *exclusively* into the *ap* reduction product, (*R*)-*ap*-9-(*o-tert*-butylphenyl)-2-methylfluorene (**15**), via chiral cation **8** and chiral radical **14**, the latter subsequently undergoing hydrogen atom transfer from HI.[3h,10] This free-radical reduction mechanism is supported by our related studies.[11] H-atom transfer from HI occurred exclusively via kinetic control from the less hindered face, the large iodine atom enhancing the effect of steric hindrance, to provide only the *ap* product (**15**), i.e., 100% kinetically controlled *inversion*, discussed above. The complete blockage to attack on the original face strongly suggests an sp^2 geometry on C-9 of the radical **14**, although it is nonaromatic, having $4n + 1$ π electrons. Warming the solution >−20 °C effected rotation of *ap*-**15** to the thermodynamically favored (−)-*sp* product, **16**, $[\alpha]^{20}_D$ −33.5 (*c* 0.2, acetone), which is configurationally enantiomeric with substrate **7**. These transformations from (+)-*sp*-**7** to (−)-*sp*-**16** are illustrated in Scheme 9.

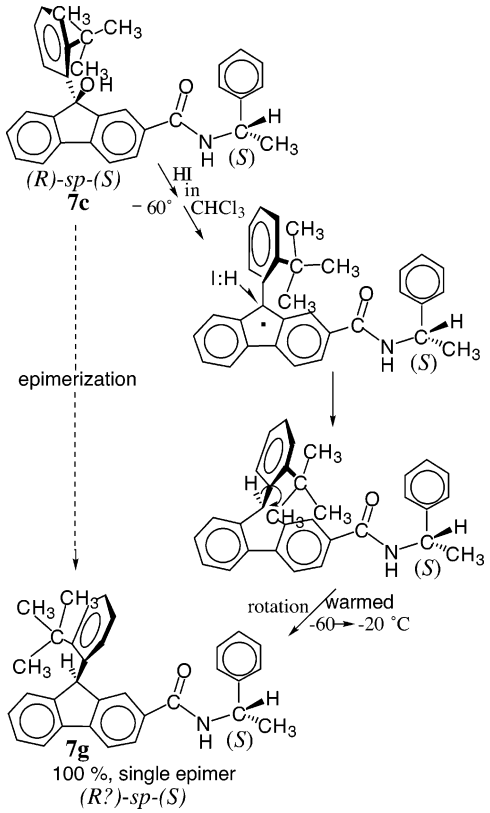
We intended to carry out a parallel study of the stereochemistry of these C-9 radical reactions by X-ray crystallographic examination of the absolute structures of the epimeric products formed from HI reductions of diastereomeric substrates related to the chiral 2-methylfluorenes discussed above. In our first attempt we utilized chiral diastereomer **7c**, whose absolute stereochemical structure we had determined by X-ray analysis.[3c] As expected, treatment of **7c** with HI in $CHCl_3$ at −60 °C provided a reddish-brown solution, as in the related reductions, indicative of the generation of I_2 from I^- by transfer of an electron to the fluorenyl cation, forming the fluorenyl radical.[3i,j,11] Workup afforded an off-white solid (ca. 100% yield) shown by NMR to be an almost pure, single epimer. Unfortunately, this product resisted all attempts at crystallization, thereby precluding X-ray analysis.

However, based on the indication that it was a single epimer and that the related radical reductions appeared

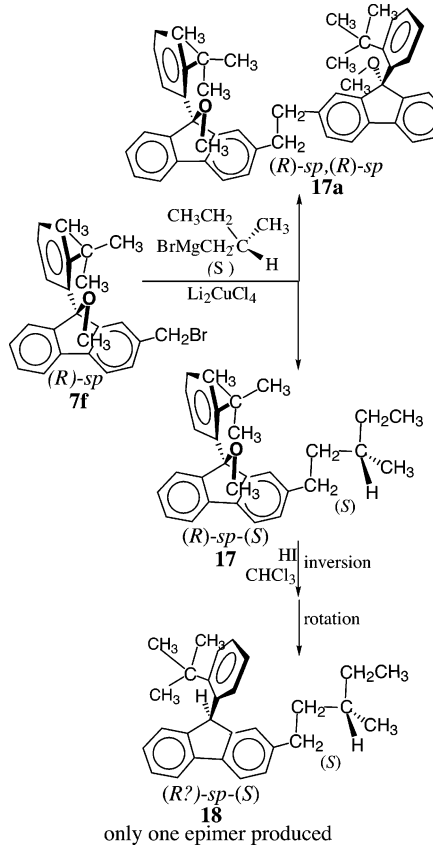
(10) Aside from our report[3h] and that of Oki et al.,[6] there are only a few reports of HI as a reducing agent for organic compounds: (a) Gordon, P. E.; Fry, A. J. *Tetrahedron Lett.* **2001**, *42*, 831−833 and references therein. (b) Penso, M.; Mottadelli, S.; Albanese, D. *Synth. Commun.* **1993**, *23*, 1385. (c) Gemal, A. L.; Luche, J. L. *Tetrahedron Lett.* **1980**, *21*, 3195.

(11) The purple-brown coloration of I_2 was indicative of free-radical formation. The related conversion of 9-hydroxy-9-(*o*-isopropylphenyl)-fluorene into 9-(*o*-isopropylphenyl)fluorene by treatment with HI−$CHCl_3$ likewise produced this coloration. Moreover, formation of the free-radical intermediate in the latter transformation was verified by the isolation of its air-oxidation product, *ap*-9-(*o*-isopropylphenyl)-9-fluorenyl peroxide, which was unequivocally characterized by X-ray analysis.[3i,j] Under the same conditions, the corresponding peroxide from radical **14** was not observed, most likely for steric reasons.

SCHEME 10. Reduction of Diastereomer 7c with Epimerization via C-9 Radical: Conversion of 7g



SCHEME 11. Reductive Epimerization by Inversion via C-9 Radical: Conversion of 17 to 18 with HI−$CHCl_3$

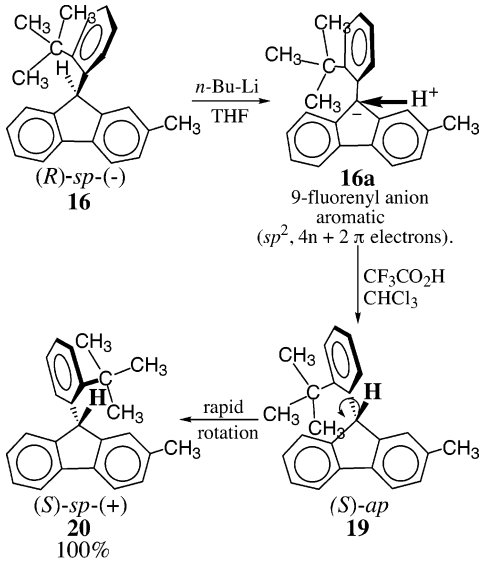


to proceed via inversion, it is reasonable to presume that this reaction likewise proceeded via C-9 inversion, providing the single epimeric product **7g**. This reaction sequence is illustrated in Scheme 10.

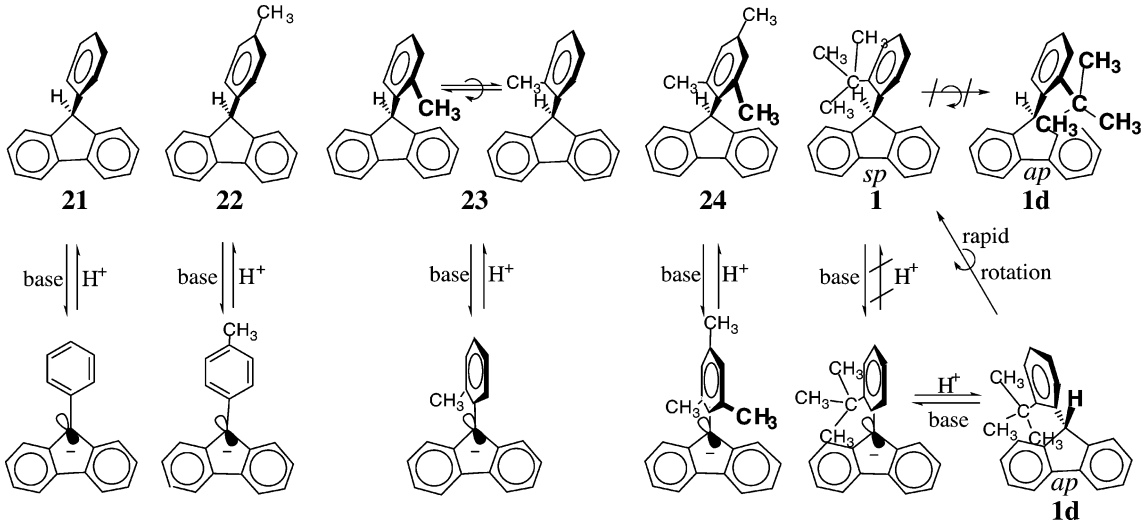
In our second attempt to utilize X-ray analysis of the product to confirm the stereochemistry of the radical reduction, we used (*R*)-*sp*-9-(*o*-*tert*-butylphenyl)-9-methoxy-2-(*S*)-(3-methyl-1-pentyl)fluorene (**17**) as the substrate. Diastereomer (*R*)-*sp*-(*S*) **17** was prepared from the reaction of (*R*)-*sp*-**7f** with (*S*)-2-methyl-1-butylMgBr, which also provided the dimer (*R*)-*sp*,(*R*)-*sp* **17a**. Chromatographic separation afforded (*R*)-*sp*-(*S*) **17**, an oil, identified and shown to be pure by ^{1}H and ^{13}C NMR. Bubbling HI gas into a solution of **17** in $CHCl_3$ at −60 °C for 30 min, followed by the usual workup and chromatographic purification, afforded a colorless oil identified by NMR to be the reduction product, a single epimer, telling us that the reaction was stereospecific**.** Crystallization was unsuccessful from a variety of solvents which, again, precluded X-ray identification of its absolute stereochemistry. On the basis of the observations discussed above, it is strongly indicated that this reduction via the 9-fluorenyl radical, which provided a single epimer, **18**, proceeded via inversion (Scheme 11).

Reactions via the 9-Fluorenyl Anion. After (*R*)-*sp*-(−)-9-(*o*-*tert*-butylphenyl)-2-methylfluorene (**16**) was treated with *n*-BuLi in THF for 6 h at 25 °C, a small sample was removed, treated with excess D_2O, and worked up. ^{1}H NMR showed that the 9-position of the compound isolated contained 9.6% H and 90.4% D, indicating that almost all of **16** was converted into its anion. Acidification of the remainder of the solution produced colorless crystals whose optical rotation, $[\alpha]^{20}_D$ +28.0 (*c* 0.093, acetone), indicated a composition of 8.2% **16** and 91.8% of its (*S*)-*sp*-(+)-enantiomer, **20**. This result supports the D/H exchange result, confirming that **16** was almost all converted into its aromatic 9-fluorenyl anion (**16a**) (sp^2, $4n + 2\ \pi$ electrons). Reprotonation exclusively from the less hindered face produced the (*S*)-*ap* rotamer, **19**, i.e., 100% inversion associated with kinetic control, which underwent rapid rotation to the thermodynami-

SCHEME 12. 100% Inversion via Chiral Anion 16a: Quantitative Conversion of 16 to 20 by Deprotonation−Reprotonation



SCHEME 13. [a] **Effect of Rotational Restriction and Steric Hindrance on the pK_a of 9-Arylfluorenes**



[a] pK_a values (DMSO, 25 °C): fluorene, 22.6; **21**, 17.92; **22**, 18.32; **23**, 18.78; **24**, 18.55;[12a,b] and **1**, 20.20.[13]

cally favored rotamer, *sp*-(+)-**20**, the enantiomer of **16** (Scheme 12).

In their study with related but achiral **1**, Oki et al.[6] found that reprotonation of its lithiated anion at −50 °C indeed produced the *ap* rotamer, which rotated to the *sp* substrate on warming. However, in the absence of chiral information, they erroneously ascribed their results to rotation of the *o*-*tert*-butylphenyl group of an sp^3-hybridized anion/Li^+ pair *prior* to reprotonation which, in turn, would also erroneously indicate retention of configuration (see Scheme 2). In our studies of the stereochemistry of various reactions of thermodynamically favored *sp* fluorene rotamers, inversions directly produced the thermodynamically less favored *ap* rotamers which underwent rapid rotation to the *sp* rotamer product, which was enantiomeric with the substrate. In comparison, deprotonation of the *ap* rotamer **5** was followed by intramolecularly assisted reprotonation with inversion, directly providing *sp* rotamer **6**. Because of the high barrier to rotation, conversion of **6** into its *ap* rotamer, the enantiomer of **5**, did not occur (see Scheme 4).[7]

Bordwell et al.[12a,b] determined the pK_a values of a very large number of fluorenes and correlated them mainly with the resonance, inductive, and polarizability effects of the substituents. However, some of the changes in pK_a values could not be explained on this basis. For example, in going from 9-phenylfluorene (**21**) to 9-*p*-tolylfluorene (**22**) the acidity is reduced, but it is substantially further reduced in 9-*o*-tolylfluorene (**23**); yet 9-mesitylfluorene (**24**) is *more* acidic than **23**. They related these unexpected observations to the restricted rotation of the 9-(*o*-methylphenyl) and 9-(*o*,*o*′-dimethylphenyl), respectively, in **23** and **24** and their 9-anions, and their relative anion vs ground-state stabilities.[12a] We recently verified the rotational restriction in **23** in solution (25 °C), NMR showing 60% *sp* and 40% *ap*, although the crystalline state is composed exclusively of the former.[3r] Our results suggest that the reduction in the acidity of **1** compared to **23** by 1.42 pK_a units[13] simply by replacing the *o*-methyl with an *o*-*tert*-butyl (**1**, *sp*), emanates from the enhanced rotational restriction in *sp*-**1** and its anion[14] and the *additional* effects engendered by the *o*-*tert*-butyl group found in this study, viz. steric hindrance to deprotonation, and reprotonation with inversion, leading directly to the geometrically different *ap* rotamer, **1d**. The effects of these structural features are illustrated in Scheme 13. In view of these observations, the question arises: Can constants be assigned to these rotational restriction and steric hindrance effects, like resonance and inductive effects, to correlate with their contribution to pK_a values? We are currently addressing this question.

Experimental Section

General Methods. Unless stated otherwise, melting points are corrected and ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ at 300 and 75 MHz, respectively.

Resolution of 7a via the Diastereomeric (*S*)-*N*-α-Methylbenzylcarboamides. Formation of (*R*)-*sp*-9-(*o*-*tert*-Butylphenyl)-2-hydroxymethyl-9-methoxyfluorene (7e). (a) *sp*-Methyl 9-(*o*-*tert*-Butylphenyl)-9-fluorenol-2-carboxylate (7b). A mixture of **7a** (0.62 g, 1.73 mmol) and 10 mL of DMF was stirred, forming a light yellow solution. Iodomethane (0.5 mL, 8.0 mmol) and anhyd $NaHCO_3$ (3 g, 36 mmol) were added, the flask was flushed with argon, and the reaction mixture was stirred at 25 °C for12 h, after which time TLC indicated the absence of starting material. The mixture was extracted with ether and the extracts were washed with water, dried, and evaporated in vacuo, leaving a light blue solid, 0.70 g, shown by ^{1}H NMR to be almost pure **7b** (100% yield). Recrystallization (hexanes) provided a colorless solid, mp 172−173 °C. ^{1}H NMR δ 1.82 (s, 9 H), 2.48 (br s, 1 H), 3.83

(12) (a) Bordwell, F. G.; Drucker, G. E.; McCollum, G. J. *J. Org. Chem.* **1982**, 2504−2510. (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463. (c) Structural and solvent effects evaluated from acidities in DMSO and in the gas phase are described by: Taft, R. W.; Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 463−469.

(13) The determination of the pK_a of **1** by the standard method, using 4-chloro-2-nitroaniline as indicator, required a full day to get a stable reading: Meyers, C. Y.; Hou, Y.; Lutfi, H. G.; Robinson, P. D. *Abstracts of Papers*; 210th National Meeting of the American Chemical Society, Chicago, IL, Aug 20−24, 1995; American Chemical Society: Washington, DC, 1995; ORGN 297.

(14) *sp*-**1** is the exclusive rotamer in solution as well as the crystalline state,[3b] while 9-(*o*-isopropylphenyl)fluorene exists in an *sp*:*ap* rotamer ratio of 70:30 in $CDCl_3$, and 58:42 in CD_3OD, but 100% as the *sp* rotamer in the crystalline state,[3a] and 9-(*m*-*tert*-butylphenyl)-fluorene rotates rapidly in solution showing no conformational preference, but crystallizes as its *ap* rotamer exclusively.[3m]

(s, 3 H), 6.37 (dd, J = 8.1, 1.5 Hz, 1 H), 6.74 (ddd, J = 7.5, 1.2 Hz, 1 H), 7.06 (ddd, J = 7.5, 1.5 Hz, 1 H), 7.33 (m, 3 H), 7.59 (dd, J = 8.1, 1.5 Hz, 1 H), 7.71 (dd, J = 7.8, 0.9 Hz, 2 H), 7.92 (s, 1 H), 8.03 (d, J = 7.8 Hz, 1 H); ^{13}C NMR δ 34.0, 37.1, 52.1, 87.2, 119.9, 120.9, 125.1, 125.2, 126.1, 126.4, 127.7, 128.9, 130.0, 130.2, 130.6, 131.9, 137.4, 138.5, 143.3, 149.6, 154.6, 155.3, 166.6. Anal. Calcd for $C_{25}H_{24}O_3$: C, 80.62; H, 6.49. Found: C, 80.58; H, 6.41.

(b) (*R*)-*sp*-9-(*o*-*tert*-Butylphenyl)-9-fluorenol-2-(*S*)-*N*-α-methylbenzylcarboamide (7c). A stirred solution of (*S*)-(−)-α-methylbenzylamine (1 mL, 7.7 mmol) in THF (5 mL) was cooled in an ice−water bath, *n*-BuLi−hexane (3.0 mL, 1.6 M, 4.8 mmol) was added, stirring was continued for 10 min, and **7b** (0.569 g, 1.42 mmol) was added. After the mixture was stirred under argon at 25 °C for 17 h, TLC indicated the absence of **7b,** but exhibited two very close spots after the TLC plate was developed in hexanes−ether (2:1) three times. This mixture was extracted with ether, and the extracts were washed successively with dil HCl, $NaHCO_3$, and water, dried, and evaporated in vacuo, leaving a tan product (0.717 g). Purification by dry column chromatography afforded a light yellow solid, 0.658 g (100% yield). ^{1}H NMR showed the product to be a mixture of equal amounts of diastereomeric (*R*)- and (*S*)-*sp*-9-(*o*-*tert*-butylphenyl)-9-fluorenol-2-(*S*)-*N*-α-methylbenzylcarboamide.

Over a 12-h period at 25 °C, an acetone solution of the two diastereomers gave rise to a mass of colorless crystals formed from an acetone solution containing the two diastereomers. The liquid was decanted off and the crystalline residue (0.23 g) was washed with hexanes. TLC (silica gel, hexanes:ether 3:2) indicated that only the more polar diastereomer was present. ^{1}H NMR likewise exhibited the presence of a single diastereomer, which was unequivocally identified by X-ray crystallography[3c] as the (*R*)-*sp*-(*S*) isomer, **7c**; mp 194−195 °C (crystals became brown). ^{1}H NMR δ 1.55 (d, J = 7.2 Hz, 3 H), 1.80 (s, 9 H), 2.61 (br s, 1 H), 5.24 (dq, J = 6.6 Hz, 1 H), 6.26 (d, J = 6.9 Hz, 1 H), 6.37 (dd, J = 8.1, 1.5 Hz, 1 H), 6.75 (ddd, J = 7.5, 1.2 Hz, 1 H), 7.06 (ddd, J = 7.8, 1.5 Hz, 1 H), 7.30 (m, 8 H), 7.58 (dd, J = 7.8, 1.2 Hz, 1 H), 7.68 (m, 3 H), 7.75 (dd, J = 8.1, 1.2 Hz, 1 H); ^{13}C NMR δ 21.7, 33.9, 37.1, 49.3, 87.3, 120.1, 120.8, 123.6, 125.2, 126.3, 126.5, 127.4, 127.9, 128.1, 128.7, 128.9, 129.8, 132.1, 134.8, 137.6, 142.1, 143.1, 149.7, 154.9, 155.3, 166.2. On standing, the mother liquor gave rise to more crystals, somewhat enriched in one diastereomer.

After the second crystallization, the mother liquor was highly enriched in the other diastereomer, (*S*)-*sp*-(*S*), which separated as crystals upon evaporation of the solvent and was purified by column chromatography (silica gel; hexanes:ether 3:2) as white crystals (0.12 g). After being washed with hexanes their mp was 179.5−181 °C (became brown). ^{1}H NMR δ 1.57 (d, J = 6.9 Hz, 3 H), 1.81 (s, 9 H), 2.43 (br s, 1 H), 5.28 (dq, J = 6.9 Hz, 1 H), 6.23 (d, J = 7.2 Hz, 1 H), 6.38 (dd, J = 8.1, 1.5 Hz, 1 H), 6.75 (ddd, J = 7.5 Hz, 1 H), 7.06 (ddd, J = 7.8, 1.5 Hz, 1 H), 7.31 (m, 8 H), 7.58 (dd, J = 8.1, 1.2 Hz, 1 H), 7.68 (m, 3 H), 7.75 (dd, J = 8.1, 1.2 Hz, 1 H); ^{13}C NMR δ 21.8, 34.0, 37.1, 49.3, 87.3, 105.6, 120.1, 120.7, 123.6, 125.1, 126.2, 126.4, 127.4, 127.8, 127.8, 128.6, 128.9, 129.7, 132.0, 134.8, 142.0, 142.9, 149.5, 154.8, 155.1, 166.0.

(c) (*R*)-*sp*-9-(*o*-*tert*-Butylphenyl)-9-methoxy-2-(*S*)-*N*-methyl-α-methybenzylcarboamide (7d). Freshly powdered KOH (2.0 g, 35.7 mmol) and iodomethane (2 mL, 32 mmol) were added to a solution of **7c** (1.655 g, 3.59 mmol) and DMSO (10 mL), the suspension was stirred at 25 °C for 5 h, and water was added. The mixture was extracted with ether, the extracts were washed with water, dried (anhyd $MgSO_4$), and evaporated in vacuo, leaving a light yellow sticky oil (1.77 g, 100% yield). Crystals formed over a period of several weeks, mp 87−88.5 °C, which were identified as **7d** by NMR. ^{1}H NMR δ 1.33 (br s, 2 H), 1.56 (br s, 1 H), 1.73 (s, 9 H), 2.54 (br s, 0.6 H), 2.73 (br s, 5.4 H), 4.82 (br s, 0.62 H), 6.1 (br s, 0.37 H), 6.38 (d, J = 8.1 Hz, 1 H), 6.68 (dd, J = 7.8 Hz, 1 H), 7.00 (ddd, J = 7.5, 1.5 Hz, 1 H), 7.3 (m, H), 7.49 (dd, J = 7.5, 1.5 Hz, 1 H), 7.55 (dd, J = 8.4, 1.2 Hz, 1 H), 7.70 (d, J = 7.8 Hz, 1 H), 7.73 (d, J = 7.8 Hz, 1 H); ^{13}C NMR δ 17.0 (br), 27.8 (br), 31.8 (br), 33.9, 37.6, 49.7, 50.8 (br), 56.5 (br), 92.9, 120.0, 126.6 (br), 124.9, 125.6, 126.1, 126.4, 127.3, 127.8, 128.5, 128.7, 129.0, 131.7, 136.3, 139.6, 139.6, 139.8 (br), 143.6 (br), 149.1, 150.4 (br). MS (HR, FAB, m/z) calcd for $C_{34}H_{36}NO_2$ $(M + H)^+$ 490.2746, obsd 490.2742.

(d) (*R*)-*sp*-9-(*o*-*tert*-Butylphenyl)-2-hydroxymethyl-9-methoxyfluorene (7e). A solution of $LiBHEt_3$ in THF (10 mL, 1.0 M, 10 mmol) was injected into a septum-sealed, argon-flushed flask containing **7d** (1.70 g, 3.48 mmol) and maintained in an ice bath. The mixture, which became light blue, was stirred for 30 min at 0 °C, then for 30 min at 25 °C, and the reaction was quenched by the addition of dil aq NaOH−ethanol and 30% H_2O_2. This mixture was stirred at 25 °C for 10 h and extracted with ether; the extracts were washed with water, dried (anhyd $MgSO_4$), and evaporated in vacuo, leaving a colorless thick oil (1.22 g, 97.9% yield) that crystallized from hexanes solution; mp 118−119 °C. The product was characterized as **7e**. ^{1}H NMR δ 1.64 (br s, 1 H), 1.76 (s, 9 H), 2.76 (s, 3 H), 4.63 (s, 2 H), 6.42 (dd, J = 8.1, 1.5 Hz, 1 H), 6.71 (ddd, J = 8.1, 1.5 Hz, 1 H), 7.01 (ddd, J = 8.4, 1.5 Hz, 1 H), 7.17−7.26 (m, 3 H), 7.31−7.38 (m, 2 H), 7.56 (dd, J = 8.4, 1.5 Hz, 1 H), 7.66 (d, J = 7.8 Hz, 2 H); ^{13}C NMR δ 34.0, 37.7, 49.7, 65.4, 93.0, 119.6, 119.7, 124.1, 124.9, 125.6, 126.0, 127.5, 127.8, 128.4, 128.6, 131.9, 140.1, 140.2, 140.3, 141.2, 149.2, 150.4, 150.7. Anal. Calcd for $C_{25}H_{26}O_2$: C, 83.76; H, 7.31. Found: C, 83.21; H, 7.32.

Conversion of 7e to (*R*)-*sp*-9-(*o*-*tert*-Butylphenyl)-2-methylfluorene (7). (a) (*R*)-*sp*-2-Bromomethyl-9-(*o*-*tert*-butylphenyl)-9-methoxyfluorene (7f). After a mixture of powdered KOH (1.0 g, 17.8 mmol), freshly recrystallized *p*-toluenesulfonyl chloride (1.07 g, 5.6 mmol), and **7e** (1.0 g, 2.79 mmol) in THF (10 mL) was stirred at 25 °C for 5 min, powdered anhydrous lithium bromide (4.0 g, 46.2 mmol) was added. The mixture became hot and stirring was continued without external heating for 6 h, after which the reaction was quenched with water, the mixture was extracted with hexanes, and the extracts were washed with water, dried, and evaporated in vacuo, yielding a colorless oil, shown by NMR to contain **7e** along with product **7f** and some *sp*-(*R*)-2-chloromethyl-9-(*o*-*tert*-butylphenyl)-9-methoxyfluorene. Purification by dry column chromatography (silica gel, hexanes) provided a colorless solid. It was dissolved in acetone (30 mL) and lithium bromide (10 g) was added while the solution was stirred at 25 °C for 10 h, then concentrated in vacuo. The solid residue was triturated with ether and the ether washings were evaporated, leaving colorless crystals, 0.98 g (87.1% yield), mp 113−114 °C, identified as **7f** by NMR. ^{1}H NMR δ 1.77 (s, 9 H), 2.77 (s, 3 H), 4.44 (s, 2 H), 6.41 (dd, J = 8.1, 1.5 Hz, 1 H), 6.72 (ddd, J = 1.2, 6.9, 8.1 Hz, 1 H), 7.03 (ddd, J = 6.9, 1.5 Hz, 1 H), 7.22 (m, J = 7.2 Hz, 3 H), 7.34 (ddd, J = 7.5, 2.1 Hz, 1 H), 7.40 (dd, J = 7.8, 1.8 Hz, 1 H), 7.57 (dd, J = 8.1, 1.5 Hz, 1 H), 7.64 (d, J = 7.8 Hz, 1 H), 7.66 (dd, J = 7.5, 0.9 Hz, 1 H); ^{13}C NMR δ 34.0, 37.7, 49.8, 92.9, 119.8, 120.0, 124.9, 125.6, 125.9, 126.1, 127.8, 128.7, 128.7, 129.8, 131.8, 138.0, 139.8, 139.9, 140.9, 149.2, 150.5, 150.9.

(b) (*R*)-*sp*-(+)-9-(*o*-*tert*-Butylphenyl)-9-methoxy-2-methylfluorene (7). A solution of **7f** (0.457 g, 1.12 mmol) in freshly distilled dry THF (5 mL) was added to a solution of $LiBHEt_3$ in THF (1.0 M, 10 mL, 10 mmol) in a flask sealed with a rubber septum and flushed with argon, and immersed in an ice−water bath. After the mixture was stirred at 25 °C under argon for 2 h, TLC indicated the absence of **7f** and the presence of a single spot chracteristic of a compound less polar than **7f**. After residual $LiBHEt_3$ was decomposed by the addition of water, the mixture was extracted with hexanes and worked up as usual, leaving a colorless oil. Column chromatography (silica gel, hexanes) provided a colorless sticky oil (0.36 g, 97.7% yield) that crystallized overnight in the freezer. Recrystallization (ethanol) yielded colorless crystals of **7**, mp 106−107 °C. ^{1}H NMR δ 1.77 (s, 9 H), 2.30 (s, 3 H), 2.76 (s, 3 H), 6.44 (dd, J =

8.1, 1.5 Hz, 1 H), 6.73 (ddd, J = 8.1, 1.5 Hz, 1 H), 7.02 (ddd, J = 8.4, 1.5, Hz, 1 H), 7.04 (d, J = 0.9 Hz, 1 H), 7.13−7.24 (m, 3 H), 7.32 (ddd, J = 6.9, 1.5 Hz, 1 H), 7.55 (d, J = 7.8 Hz, 1 H), 7.56 (dd, J = 8.1, 1.5 Hz, 1 H), 7.63 (dd, J = 7.5, 1.2 Hz, 1 H); ^{13}C NMR δ 21.8, 34.0, 37.6, 49.6, 93.0, 119.3, 119.3, 124.9, 125.5, 125.9, 126.1, 127.6, 127.9, 128.4, 129.3, 132.1, 138.0, 138.38, 140.6, 149.1, 150.2, 150.5. Anal. Calcd for $C_{25}H_{26}O$: C, 87.68; H, 7.65. Found: C, 87.77; H, 7.71. The optical rotation was measured from a 25-mL solution of 50.0 mg of **7** in acetone: $[\alpha]^{20}_D$ +45.5 (*c* 0.2, acetone).

Major Inversion of 7 via Chiral Cation 8. Treatment with Triflic Anhydride followed by NaOCH$_3$−CH$_3$OH. Formation of (*S*)-*sp*-(−)-9-(*o*-*tert*-Butylphenyl)-9-methoxy-2-methylfluorene (9). Triflic anhydride (0.5 mL, 6 mmol) was added to a stirred solution of **7** (55 mg) in chloroform (2 mL) in a flask sealed with a rubber septum, flushed with argon, and cooled in a liquid nitrogen−acetone bath (−60 °C). The blood-red mixture, maintained at −60 to −40 °C, was stirred for 30 min. A suspension of NaOMe−MeOH [43.5 mmol (1.0 g of sodium metal in 25 mL of anhyd MeOH)] was added, which immediately discharged the red color, and the mixture was extracted with hexanes. The extracts, worked up as usual, provided a pale yellow sticky oil, 49 mg (89.1% of substrate weight), whose ^{1}H NMR spectrum matched that of substrate **7**. However, recrystallization (ethanol) afforded colorless crystals, mp 114−115.5 °C, with an optical rotation (determined from a 25-mL solution of 26.5 mg in acetone) of $[\alpha]^{20}_D$ −19.2 (*c* 0.106, acetone), corresponding to a mixture of 71.1% **10** (inversion) and 28.9% **7** (retention); ee 42.2%. It was convincingly shown that isolated **7** was not unreacted substrate but was formed in the reaction (see below).

Quantitative Conversion of *sp*-9-(*o*-*tert*-Butylphenyl)-9-methoxyfluorene (11) via Its Cation 1b to *sp*-9-(*o*-*tert*-Butylphenyl)-9-ethoxyfluorene (13) by Treatment with Triflic Anhydride Followed by NaOEt−EtOH. The procedure described in the preceding reaction was repeated with the same amounts of triflic anhydride and chloroform, but with **11 (**50 mg) and NaOEt in ethanol (43.5 mmol; prepared by dissolving 1.0 g of sodium metal into 25 mL of absolute ethanol). The product was a slightly yellow sticky oil, 48 mg (ca. 100% yield), characterized by ^{1}H NMR to be exclusively *sp*-9-(*o*-*tert*-butylphenyl)-9-ethoxyfluorene (*sp*-**13**).[3g] This product was not purified further.

Exclusive Inversion of 7 via Chiral Radical 14. Reduction with HI (g) in CHCl$_3$. Formation of (*R*)-*sp*-(−)-9-(*o*-*tert*-Butylphenyl)-2-methylfluorene (16). Hydrogen iodide gas was bubbled into a colorless solution of **7** (145 mg, 0.29 mmol) in chloroform (2 mL) in a flask sealed with a rubber septum, flushed with argon, and immersed in liquid nitrogen−acetone bath (−60 °C). The mixture, which turned dark brown very rapidly, was stirred at −60 to −40 °C for 60 min. TLC exhibited a spot very close to that of the starting material. The reaction was quenched by the addition of aq $NaHCO_3$, the mixture was extracted with ether, and the extracts were washed with aq $Na_2S_2O_3$, then water, and worked up as usual, providing a yellow solid, 0.129 g (yield 97.2%). Recrystallization (hexanes) afforded colorless crystals, mp 194−195 °C, characterized as **16**. ^{1}H NMR δ 1.71 (s, 9 H), 2.32 (s, 3 H), 5.82 (s, 1 H), 6.34 (dd, J = 7.8, 1.5 Hz, 1 H), 6.88 (ddd, J = 7.8, 1.5 Hz, 1 H), 7.03 (s, 1 H), 7.11 (ddd, J = 8.1, 1.5 Hz, 1 H), 7.18 (m, 3 H), 7.35 (m, 1 H), 7.49 (dd, J = 8.1, 1.2 Hz, 1 H), 7.71 (d, J = 7.8 Hz, 1 H), 7.77 (d, J = 7.8 Hz, 1 H); ^{13}C NMR δ 21.8, 32.7, 35.7, 50.9, 119.4, 119.5, 120.2, 125.6, 125.7, 126.1, 126.3, 126.8, 127.9, 130.9, 137.2, 138.4, 140.1, 141.0, 148.0, 149.8, 150.1. Anal. Calcd for $C_{24}H_{24}$: C, 92.26; H, 7.74. Found: C, 92.48; H, 7.65. Optical rotation was determined on a 25-mL solution of 50.0 mg of product in acetone; $[\alpha]^{20}_D$ −33.5 (*c* 0.2, acetone).

Reduction of 17 via Its 9-Fluorenyl Radical. Formation of a Single Epimer: (*R*?)-*sp*-9-(*o*-*tert*-butylphenyl)-2-(*S*)-(3-methylpentyl)fluorene (18). A colorless solution of **17** (0.175 g, mmol) and $CHCl_3$ (5 mL) in a flask sealed with a rubber septum was cooled in a liquid nitrogen−acetone bath (−60 °C) and then stirred while HI gas (prepared by refluxing a mixture of I_2 and tetralin) was bubbled in for 30 min. The reaction was stopped by removing the solvent and HI in vacuo. The black oil residue was purified by dry column chromatography (silica gel, hexanes) to a brownish oil, which was dissolved in hexanes, and the solution washed with aq $Na_2S_2O_3$. The organic layer was dried and evaporated in vacuo, leaving a colorless oil shown by NMR to be a single epimer of (*R*?)-*sp*-9-(*o*-*tert*-butylphenyl)-2-(*S*)-(3-methylpentyl)fluorene (**18**). Crystallization was unsuccessful from a variety of solvents. Attempts to obtain crystals by forming a complex with picric acid in 95% ethanol or benzene also failed. ^{1}H NMR δ 0.82 (t, J = 7.5 Hz, 3 H), 0.87 (d, J = 6.3 Hz, 3 H), 1.15 (m, 1 H), 1.34 (m, 3 H), 1.58 (m, 1 H), 1.72 (s, 9 H), 2.57 (m, 2 H), 5.82 (s, 1 H), 6.25 (dd, J = 7.5, 1.5 Hz, 1 H), 6.88 (ddd, J = 7.5, 1.2 Hz, 1 H), 7.03 (s, 1 H), 7.11 (ddd, J = 7.5, 1.5 Hz, 1 H), 7.19 (m, 3 H), 7.34 (m, 1 H), 7.49 (dd, J = 8.1, 1.5 Hz, 1 H), 7.72 (d, J = 7.8 Hz, 1 H), 7.77(d, J = 7.5 Hz, 1 H); ^{13}C NMR δ 11.4, 19.2, 29.4, 32.7, 33.8, 34.2, 35.7, 38.7, 51.0, 119.4, 119.5, 125.0, 125.6, 126.1, 126.3, 126.8, 126.9, 127.1, 131.0, 138.6, 140.14, 140.08, 142.8, 148.0, 149.8, 150.1.

Exclusive Inversion of (*R*)-*sp*-(−)-16 via Chiral Anion 16a. Quantitative Deprotonation−Reprotonation of 16 Leading to (*S*)-*sp*-(+)-9-(*o*-*tert*-Butylphenyl)-2-methylfluorene (20). A solution of *n*-BuLi in hexanes (2.2 M, 2 mL, 4.4 mmol) in THF was added to **16** (60 mg, 0.19 mmol) in a septum-sealed flask. The mixture became red immediately and was stirred at 25 °C under argon for 6 h, during which time substantial precipitation occurred. A 0.5-mL sample of the suspension was removed and diluted with D_2O, while the major part of the suspension was diluted with $CHCl_3$ containing CF_3CO_2H, the red color of the anion being quickly discharged in both cases, giving way to a light tan color. The sample was diluted with D_2O and extracted with hexanes and the extracts were washed with water and worked up as usual, leaving light tan crystals, 13 mg, shown by ^{1}H NMR to be *sp*-9-(*o*-*tert*-butylphenyl)-2-methylfluorene containing 90.4% D and 9.6% H at C-9. The portion of the suspension treated with CF_3CO_2H−$CHCl_3$ was worked up similarly, except that the extracts were washed with aq $NaHCO_3$ before being worked up to provide light tan crystals, 44 mg, shown by ^{1}H NMR to be 100% *sp*-9-(*o*-*tert*-butylphenyl)-2-methylfluorene. Recrystallization (ethanol) provided colorless crystals, mp 157−170 °C; optical rotation (measured on a 25-mL solution of 23.2 mg in acetone), $[\alpha]^{20}_D$ +28.0 (*c* 0.093, acetone), corresponding to a mixture of 8.2% (*R*)-*sp*-(−) substrate (**16**) and 91.8% of its (*S*)-*sp*-(+) enantiomer, product **20**; ee 83.6%. The 9.6% residual hydrogen on C-9 of the sample diluted with D_2O corresponded well with the determination of 8.2% unreacted substrate **16**, showing an inversion of virtually 100%.

Supporting Information Available: Synthesis, ^{1}H and ^{13}C NMR spectra, and elemental analysis of *sp*-9-(*o*-*tert*-butylphenyl)-9-fluorenol-2-carboxylic acid (**7a**), attempted resolution of *sp*-9-(*o*-*tert*-butylphenyl)-9-fluorenol-2-carboxylic acid (**7a**) through its diastereomeric L-cinchonidine salts, and attempted enantiomeric identification via X-ray analysis, reduction of (*R*)-*sp*-9-(*o*-*tert*-butylphenyl)-9-fluorenol-2-(*S*)-*N*-α-methylbenzylcarboamide **(7c)** via its 9-fluorenyl radical; formation of a single epimer *N*-(*S*)-α-methylbenzyl (*R*?)-*sp*-9-(*o*-*tert*-butylphenyl)fluorene-2-carboamide (**7g**), conversion of (*R*)-*sp*-2-bromomethyl-9-(*o*-*tert*-butylphenyl)-9-methoxyfluorene (**7f**) to (*R*)-*sp*-9-(*o*-*tert*-butylphenyl)-9-methoxy-2-(*S*)-(3-methylpentyl)fluorene (**17**) and (*R*)-*sp*,(*R*)-*sp*-1,2-bis[9-(*o*-*tert*-butylphenyl)-9-methoxy-2-fluorenyl]ethane (**17a**). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0351015