UNIVERSITY OF ILLINOIS

May 12 1990

THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

Lori L. Buntrom

ENTITLED Molecular Tweezers and Chiral Reagents: Synthesis of Novel Disubstituted 5,6,8,9-Tetrahydrodibenzi[a,j]anthracenes

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF Bachelor of Science in Chemistry

Instructor in Charge

APPROVED:

HEAD OF DEPARTMENT OF Chemistry

O-1364

Molecular Tweezers and Chiral Reagents:

Synthesis of Novel Disubstituted 5,6,8,9-Tetrahydrodibenz[*a,j*]anthracenes

By

Lori L. Bostrom

Thesis

for the
Degree of Bachelor of Science
in
Chemistry

College of Liberal Arts and Sciences
University of Illinois
Urbana, Illinois

1990

Table of Contents

Introduction	1
Results and Discussion	4
Experimental	8
Figures & Schemes	12
References	18

Introduction

Rigid molecular spacers have found widespread utility in bioorganic chemistry. They have proved useful in such diverse areas as polymer chemistry,[1] porphyrin[2a] and crown ether linkage,[2b] and in the creation of a variety of rigid molecular clefts.[3] Zimmerman and coworkers have described the use of the rigid dibenzacridine and dibenzanthracene spacers to form the basis of molecules known as "molecular tweezers."[4-6] When these spacers are substituted at C-2 and C-12 with two aromatic chromophores, they are capable of

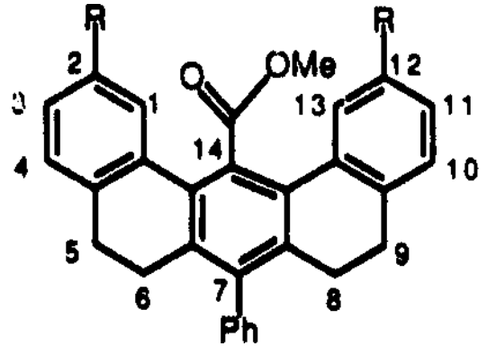


Figure 1: Numbering Scheme for dibenzanthracene

complexing small aromatic guest molecules in a double π-stacking interaction described as a π-sandwich.[4] The rigidity of the spacer and the position of the chromophores can greatly enhance the π-sandwich interaction by forcing the chromophores to maintain a syn cofacial orientation with a separation of ca. 7 Å.[5] Zimmerman and Wu have discovered that guest complexation can be improved

further by introducing a carboxylic acid functional group into the host cleft to provide hydrogen bonding interactions.[7] In this paper, the synthesis of a new molecular tweezer **13b** is described, which is one of a series of four tweezers (see **Figure 2**) designed to investigate the importance of interchromophore distance in determining the host-guest binding constant. The four spacers have C-2 to C-12 distances ranging from 7.52Å for tweezer **19** to 8.20Å for tweezer **17**.[6,8] All four will be substituted with identical methylanthracene chromophores. Thus, any discrepancies in the binding constants should be due to the spacing of the chromophores.

As a precedent to a second project, X-ray crystallography has revealed that the presence of an ester functionality at C-14 in the cleft of the dibenzanthracene spacer induces the aromatic system to twist 43° from end to end.[6] It was proposed that the inherent chiral nature of the helical twist could be further enhanced by the substitution of bulky groups at C-2 and C-12. This would provide a greater barrier to interconversion of the right- and left-handed helices in solution. It was also proposed that, if the bulky groups were themselves chiral, the resulting molecular cavity would provide an environment capable of inducing chirality on other small molecules. Replacement of the ester functionality in the cleft of the molecule with an acid or a peroxyacid would facilitate the possibility of performing asymmetric protonations or epoxidations on small molecules entering the cleft. Structures **1a** and **1b** (see Scheme 2) were proposed as possible protonation and epoxidizing reagents,

respectively, and progress towards the synthesis of these molecules is presented in this paper.

As a third and final project, molecular tweezer **16** (Figure 3) was proposed which would be capable of forming both a π-sandwich and as many as four hydrogen bonds with guest molecules. Previous studies have shown that the presence of two hydrogen bonding interactions greatly enhances the binding constant of small molecules with the Zimmerman tweezer.[7] It was thus expected that additional hydrogen bonding interactions should enhance binding to an even greater degree. Thus, the synthesis of tweezer **16** was pursued.

Results and Discussion

The synthesis of dibenzanthracene spacer **7a** followed previous work in our laboratory (Scheme 1). Bromotetralone **4** was synthesized as previously described.[9] Bromobenzene was reacted with with succinic anhydride to form the phenylketobutyric acid **2**. Wolff-Kishner reduction of the ketone followed by cyclization with polyphosphoric acid yielded 7-bromotetralone **4** in overall 43% yield from succinic anhydride. Aldol condensation of **4** with benzaldehyde yielded the corresponding benzylidine **5** in 78% yield.[10] Tetralone **4** and benzylidine **5** were coupled in $BF_3 \cdot Et_2O$ to give the crude pyrylium salt **6**,[10] which was then condensed with trimethylphosphonoacetate to produce the desired spacer **7a** in 25% overall yield from bromotetralone.[11]

At this point it was necessary to effect the substitution of the dibromide **7a** at C-2 and C-12. Previously, substitutions involving related spacers were carried out according to Scheme 3.[5] According to this method, the acridine chromophores were added to the ketal-protected bromotetralone **9** before conversion to the benzylidine **11** and coupling to form the pyrylium salt. This method involved several steps and had the added disadvantage of requiring a uniquely substituted tetralone for each desired tweezer. If the substitution could be effected simultaneously at both positions of the dibromide **7a**, this would facilitate the use of Scheme 1 for the

large-scale synthesis of a common spacer, which could then be substituted with a variety of groups. Scheme 2 shows the procedure developed to effect the disubstitution, which proceeded in a similar overall yield to Scheme 3. Treatment of dibromide **7a** with t-BuLi[12] followed by a deuterium quench yielded the dideuterated spacer **7b** in 95% yield, evidence that the lithium-halogen exchange did proceed with high efficiency to yield the dianion. However, when either benzaldehyde or pivaldehyde was used to quench the dianion, the diadduct was obtained in only 37% and 60% yield, respectively. Since it has already been shown that the dianion is formed nearly quantitatively, it is likely that the lower yield of the aldehyde adducts was due to steric interactions with the new carbon centers. Additional evidence to this effect is given by the fact that no starting material was recovered, and the monoprotio/monoadduct was isolated in both cases.

At this point in the synthesis it was desirable to resolve the mixture of stereoisomers of **8a** and **8b**, before completing the conversion to the more reactive acid **1a** and peracid **1b**. Attempts at selective recrystallization of the stereoisomers were unsuccessful. Therefore, separation by chiral HPLC was investigated. Although no resolution was obtained for the benzaldehyde adduct **8a**, the pivaldehyde adduct did show some separation as the alpha-napthyl urethane derivative on a chiral Pirkle column.[13] However, the separation was not sufficient to warrant the cost of scale-up, and the

synthesis of the chiral acid and peracid reagents was ended at this point.

The synthesis of tweezer **13a** was accomplished by Grignard addition of methyl bromoanthracene to spacer **7a** (Scheme 4).[14] 9-Bromo-10-metaylanthracene was obtained from 9,10-dibromoanthracene by monolithiation with n-BuLi followed by addition of methyl iodide.[14a] The Grignard **12** was formed in the presence of magnesium metal with I_2 and dibromoethane catalysts in refluxing ether. This was added to spacer **7a** in the presence of $Ni(acac)_2$ as catalyst.[14b] The tweezer **13a** was thus obtained in >50% yield. Conversion to the carboxylic acid with boron trichloride[15] is currently in progress. After tweezer **13b** is thus obtained, its binding constant with small aromatic guests will be determined and compared to the binding constants of tweezers **17**, **18**, and **19**.

Synthesis of macrocyclic tweezer **16** began with the conversion of spacer **7a** to the diamine **15** (Scheme 5). Several methods for the conversion of aromatic bromides to aromatic amines have precedent in the literature.[16,17] Treatment of the dibromide with n-BuLi followed by a methoxylamine/methyllithium quench[16] yielded a complex mixture of products from which the amine could not be isolated. In a second attempt, the method of Shioiri *et. al.*,[17] was attempted. Scheme 5 shows the conversion of the dibromide **7a** to the dicarboxylic acid **14** by formation of the dianion with n-BuLi and

quenching with CO_2.[18] Schmidt rearrangement of the diacid with diphenylphosphorylazide was expected to yield the diamine,[17] but once again the result was a complex mixture of products. A new method for this conversion is presently being sought. Once the diamine is obtained, it will be condensed with a variety of dianhydrides (Scheme 5) to yield the corresponding macrocycles shown in Figure 3. An appropriate guest molecule will be selected, which will be capable of interacting with the tweezer in four hydrogen bonding interactions and an aromatic π-stacking interaction. The binding constant of this molecule will then be compared with the binding constant of the Wu tweezer[7] to determine the contribution of the new hydrogen bonds.

Experimental

Methyl 2,12-dideutero-7-phenyl-5,6,8,9-tetrahydrodibenz[*a,j*]anthracene-14-carboxylate(7b). A solution of 43.5 mg (0.076 mmol) dibromide **7a** in 1.0 mL THF under a dry N_2 atmosphere was cooled to -65°C. t-BuLi (180 µL, 0.31 mmol) was added and stirred at -65°C for 5 minutes. The reaction was quenched with 300 µL CH_3OD and warmed slowly to room temperature. The reaction mixture was concentrated under reduced pressure, redissolved in $CHCl_3$, and filtered through glass wool. The clear solution was then partitioned between CH_2Cl_2 and 50% saturated NaCl. The aqueous layer was washed once with CH_2Cl_2, the organic layers were combined, and the solvent was removed under reduced pressure to yield 30.0 mg (94.7%) of **7b** as a creamy white solid: mp >240°C; ^1H NMR: (300 MHz, $CDCl_3$) δ 7.47 (m, 5H, H-2', H-3', H-4', H-5', H-6'), 7.22 (m, 6H, H-1, H-3, H-4, H-10, H-11, H-13), 3.80 (s, 3H, methyl ester), 2.68 (t, 4H, H-6, H-8), 2.47 (t, 4H, H-5, H-9). MS (EI, 70eV) *m/e* 418.

Methyl 2,12-bis(1-hydroxy-1-phenylmethyl)-7-phenyl-5,6,8,9 - tetrahydrodibenz[*a,j*]anthracene - 14 - carboxylate (8a). To a solution of 50.0 mg (0.087 mmol) of dibromide **7a** in 2.0 mL THF at -60°C under a dry N_2 atmosphere was added 150 µL (0.23 mmol) n-BuLi. After stirring 30 minutes at -60°C the reaction

was quenched with 200 µL benzaldehyde and allowed to warm slowly to room temperature. The solvent was removed under reduced pressure, and the salts were removed by passing through a plug of silica eluted with EtOAc. The eluent was flash chromatographed (35% EtOAc/petroleum ether) to yield 20.0 mg (36.7%) of **8a** as a white solid: ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.47-7.15 (m, 22H, H-1, H-3, H-4, H-10, H-11, H-13, H-2', H-3', H-4', H-5', H-6', H-2", H-3", H-4", H-5", H-6", H-2'", H-3'", H-4'", H-5'", H-6'"), 5.80 (s, 2H, methine), 3.39 (d, 3H, methyl ester), 2.64 (t, 4H, H-6, H-8), 2.43 (t, 4H, H-5, H-9), 2.31 (s, 2H, hydroxyl).

Methyl 2,12-bis(1-hydroxy-2,2-dimethylpropyl)-7-phenyl-5,6,8,9 - tetrahydrodibenz[*a,j*]anthracene - 14 - carboxylate (8b). To a solution of 60.0 mg (0.104 mmol) dibromide **7a** in 3.0 mL THF at -54°C under a dry nitrogen atmosphere were added 200 µL (0.313 mmol) n-BuLi. After stirring 70 minutes at -50°C, the reaction was quenched with 200 µL pivaldehyde and allowed to warm slowly to room temperature. The solvent was evaporated under reduced pressure, and the salts were removed by elution with EtOAc through a plug of silica. The eluent was flash chromatographed (15% EtOAc/petroleum ether followed by 25% EtOAc/petroleum ether) to provide 36.9 mg (60.1%) of **8b** as a yellowish solid: mp >170°C; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.42 (m, 5H, H-2', H-3', H-4', H-5', H-6'), 7.18 (m, 6H, H-1, H-3, H-4, H-10, H-11, H-13), 4.37 (s, 2H, methine), 3.87 (d, 3H, methyl ester), 2.65 (t, 4H, H-6,

H-8), 2.47 (t, 4H, H-5, H-9), 1.87 (s, 2H, hydroxyl), 0.93 (s, 18H, t-Bu). MS (EI, 70eV) *m/e* 588.

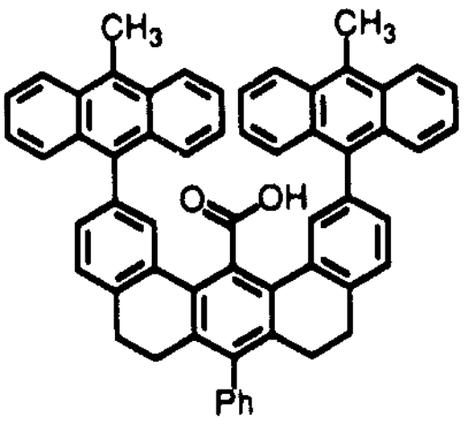
Methyl 2,12-bis[9-(10-methylanthracenyl)]-7-phenyl-5,6,8,9 - tetrahydrodibenz[*a,j*]anthracene - 14 - carboxylate (13a). Et_2O (25 mL) was added to 240 mg (0.89 mmol) 9-methyl-10-bromoanthracene, 417 mg (17.2 mmol) Mg metal, a few crystals I_2, and 4 drops 1,2-dibromoethane under a dry N_2 atmosphere, and the resultant slurry was heated to 65°C. After stirring 5.5 hours at 60-65°C, the reaction mixture was cooled to 0°C and added via cannula to a cooled (0°C) solution of 100 mg (0.174 mmol) **7a** and 7.0 mg $Ni(acac)_2$ in 40 mL benzene. The resultant mixture was warmed to room temperature for 1 hour before heating to 65°C. The reaction was allowed to stir overnight (15 hours) before quenching with 1N HCl. The reaction mixture was partitioned between CH_2Cl_2 and 50% saturated $NaHCO_3$. The aqueous layer was washed twice with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The mixture was flash chromatographed (50% CH_2Cl_2/hexane) and recromatographed (20% CH_2Cl_2/hexane followed by 25% CH_2Cl_2/hexane) to yield approximately 100 mg (95%) **13a** as a yellow solid: mp >200°C; ^1H NMR: (200 MHz, $CDCl_3$) δ 8.31 (d, 2H, H-1, H-13), 7.62 (d, 2H, H-3, H-11), 7.55-7.13 (m, 23H, H-4, H-10, H-2', H-3', H-4', H-5', H-6', H-1", H-2", H-3", H-4", H-5", H-6", H-7", H-8", H-1'", H-2'", H-3'", H-4'", H-5'",

H-6''', H-7''', H-8'''), 3.16 (s, 6H, methyl), 2.80 (m, 4H, H-6, H-8), 2.74 (s, 3H, methyl ester), 2.66 (m, 4H, H-5, H-9). MS (EI, 70eV) *m/e* 797.

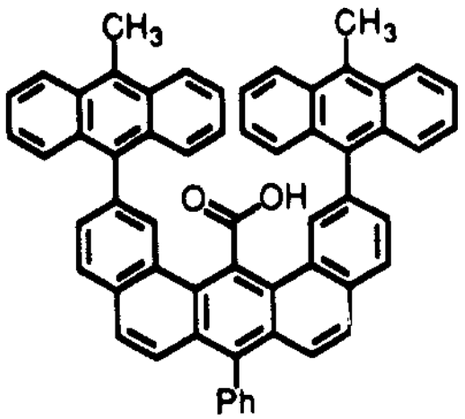
Methyl 2,12-carboxyl-7-phenyl-5,6,8,9-tetrahydro-dibenz[*a*,*j*]anthracene-14-carboxylate(14). Dibromide **7a** (500 mg, 0.871 mmol) was dissolved in 15 mL THF under a dry nitrogen atmosphere and cooled to -76°C. n-BuLi (1.65 mL, 2.61 mmol) was added and the reaction was stirred at -76°C for 1 hour. Dry ice (2.0 g.) was added and the reaction was stirred overnight (17 hours) while warming to room temperature. After quenching with water, the reaction mixture was made basic with 2N NaOH and extracted twice with Et_2O. The aqueous layer was acidified with 2N HCl and extracted twice with 10% i-PrOH/$CHCl_3$. The organic layers were combined and the solvent was removed to yield 402 mg (91.5%) pure **14** as a white powder: ^{1}H NMR (200 MHz, DMSO) δ 8.04 (s, 2H, H-1, H-13), 7.83 (dd, 2H, H-3, H-11), 7.47 (m, 4H, H-4, H-10, H-2', H-6'), 7.30 (d, 3H, H-3', H-4', H-5'), 3.76 (s, 3H, methyl ester), 2.70 (t, 4H, H-6, H-8), 2.43 (t, 4H, H-5, H-9).

Figures and Schemes

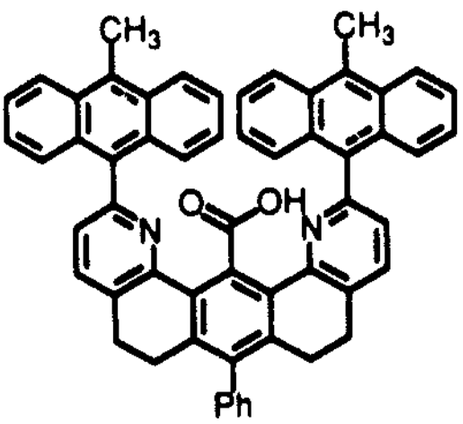
Figure 2



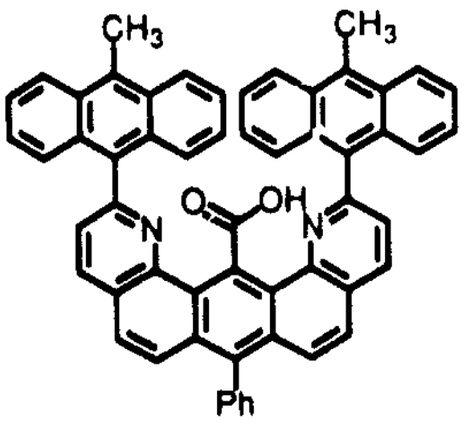
13b



17

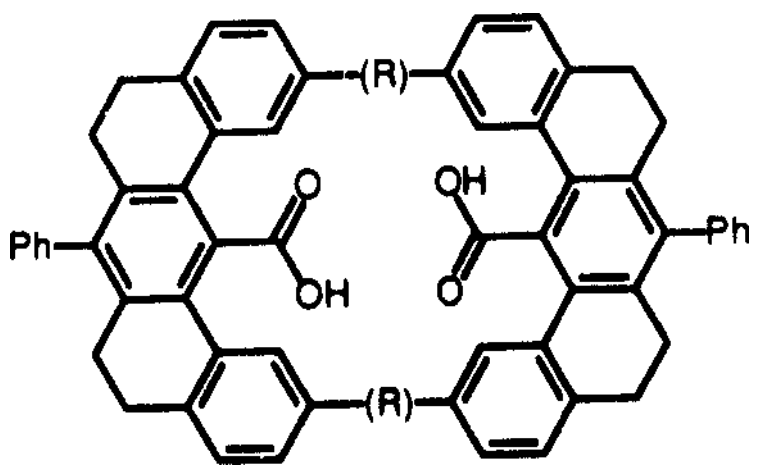


18

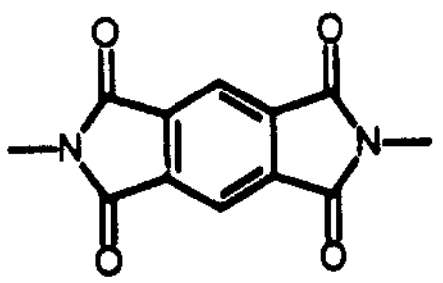


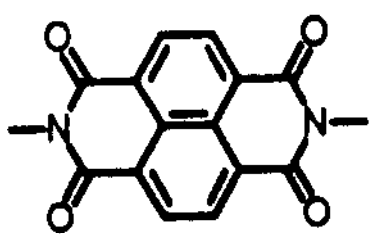
19

Figure 3

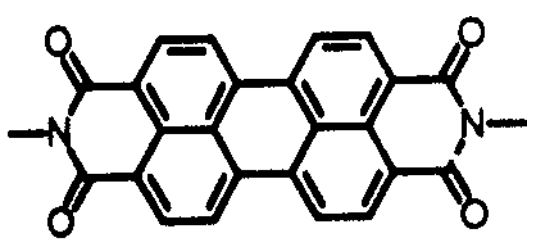


16a: R=



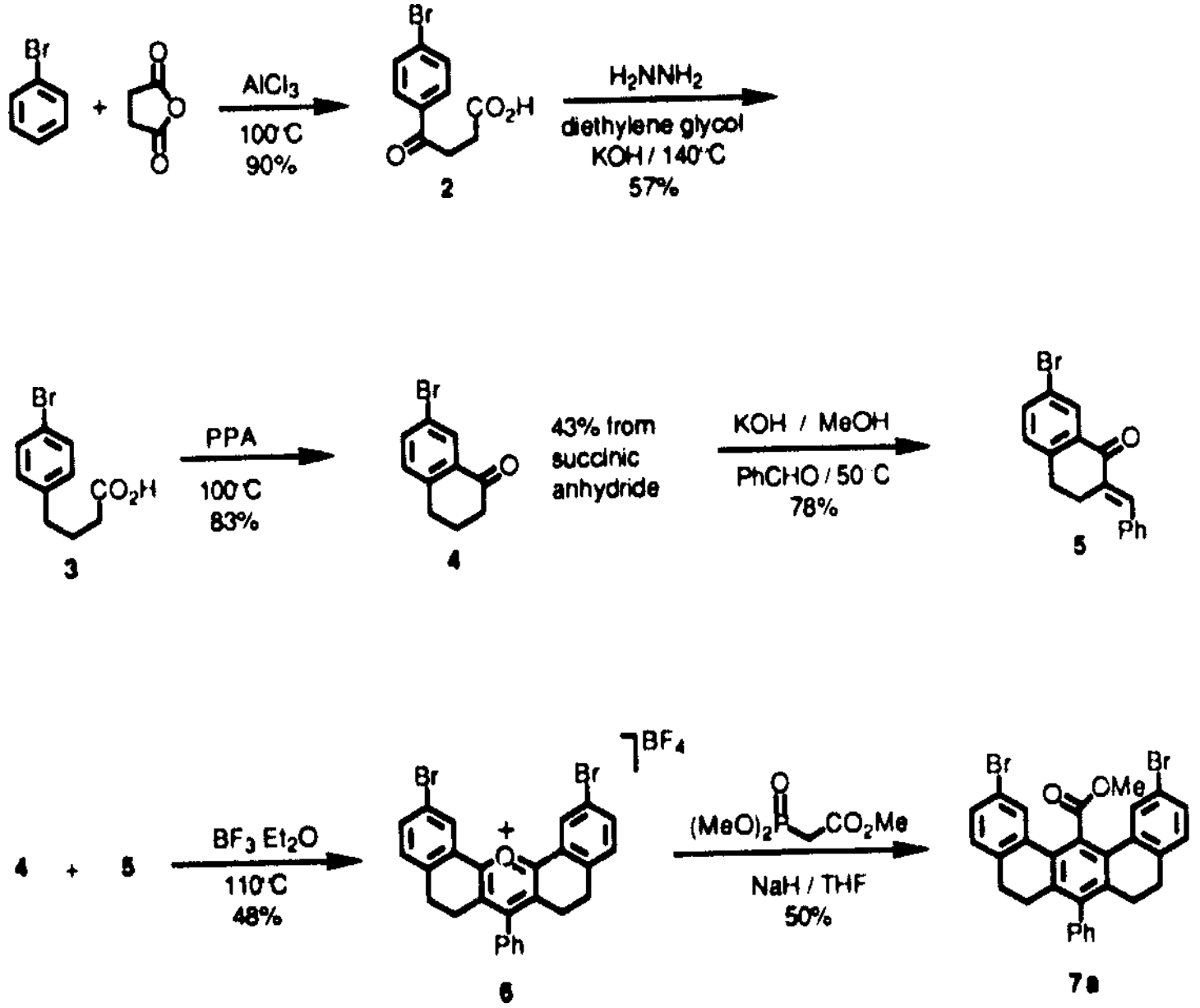


16b

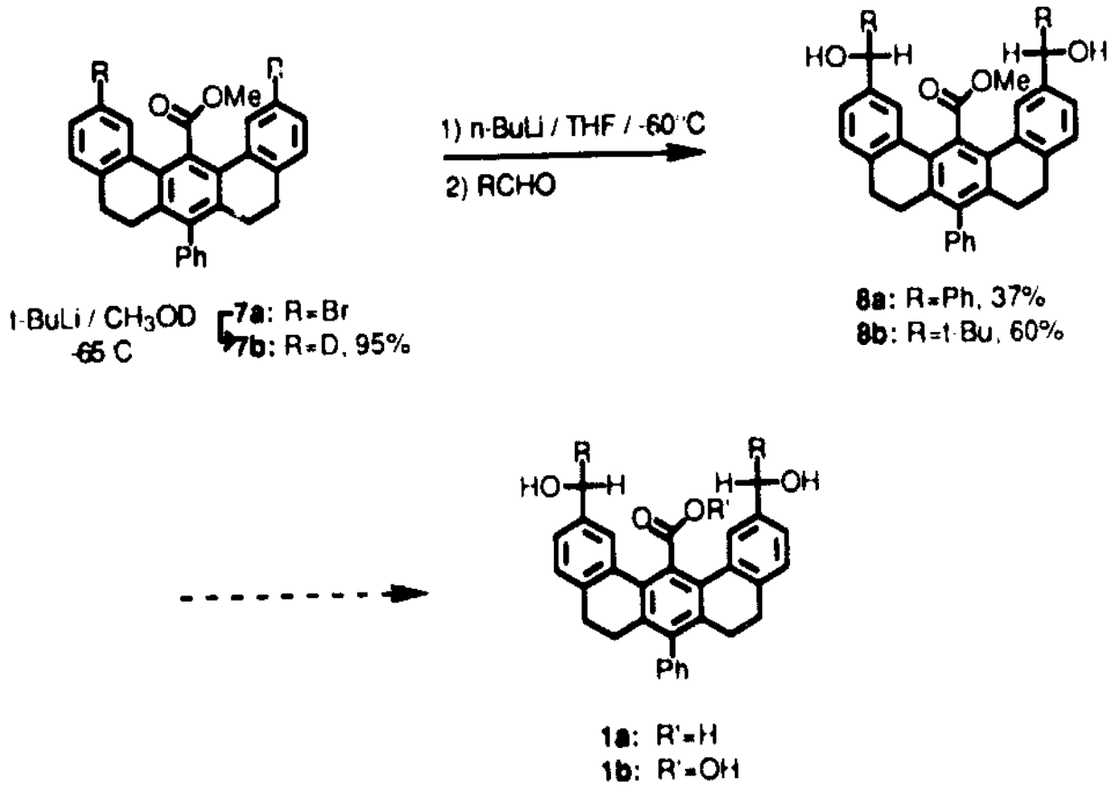


16c

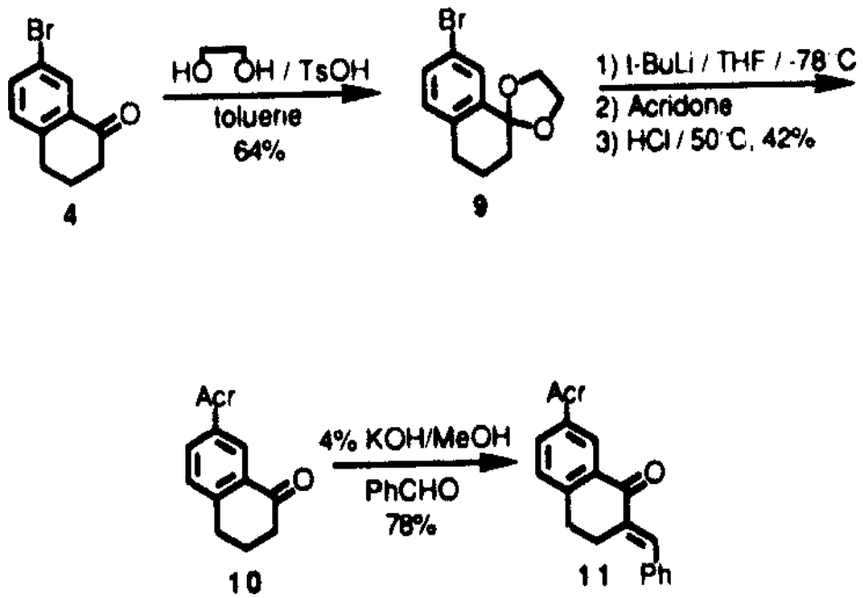
Scheme 1


Br
AlCl3
100°C
90%
CO2H
2
H2NNH2
diethylene glycol
KOH / 140°C
57%
3
PPA
100°C
83%
4
43% from
succinic
anhydride
KOH / MeOH
PhCHO / 50°C
78%
5
Ph
4 + 5
BF3 Et2O
110°C
48%
BF4
6
(MeO)2P
CO2Me
NaH / THF
50%
OMe
7a

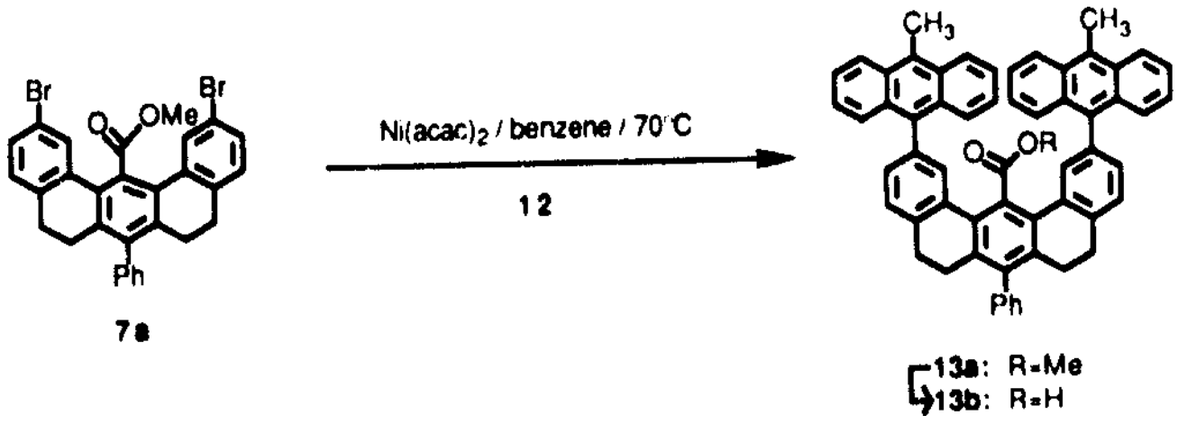
Scheme 2

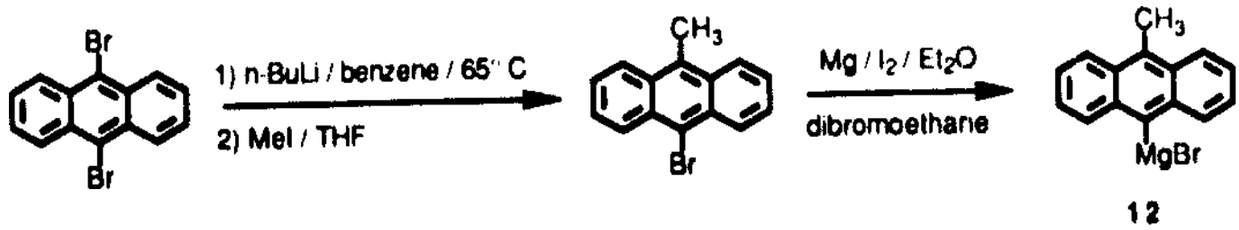


Scheme 3

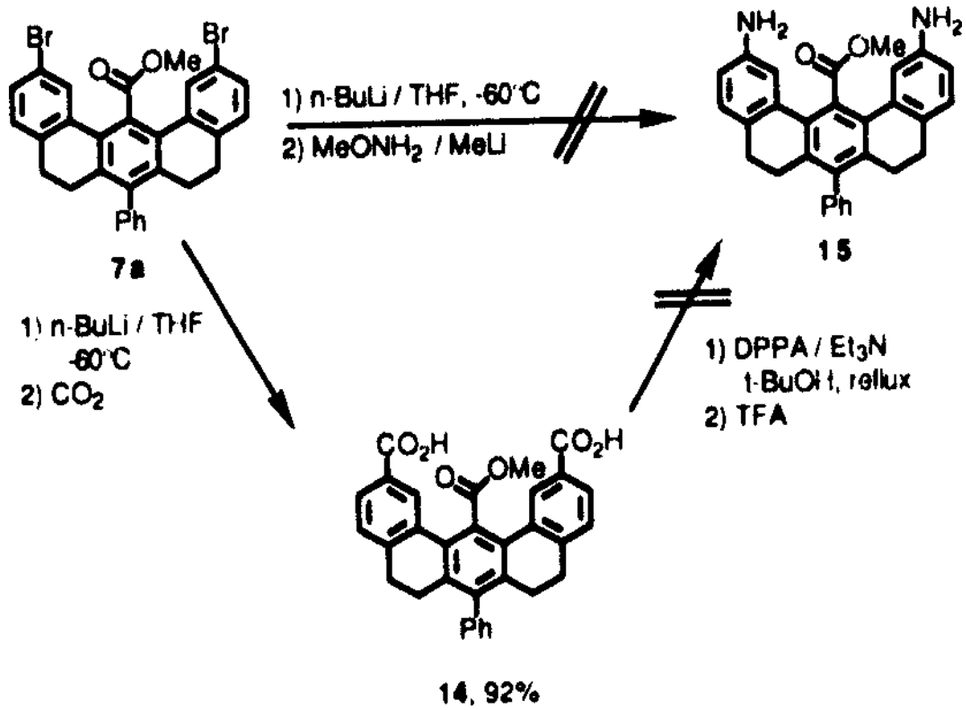


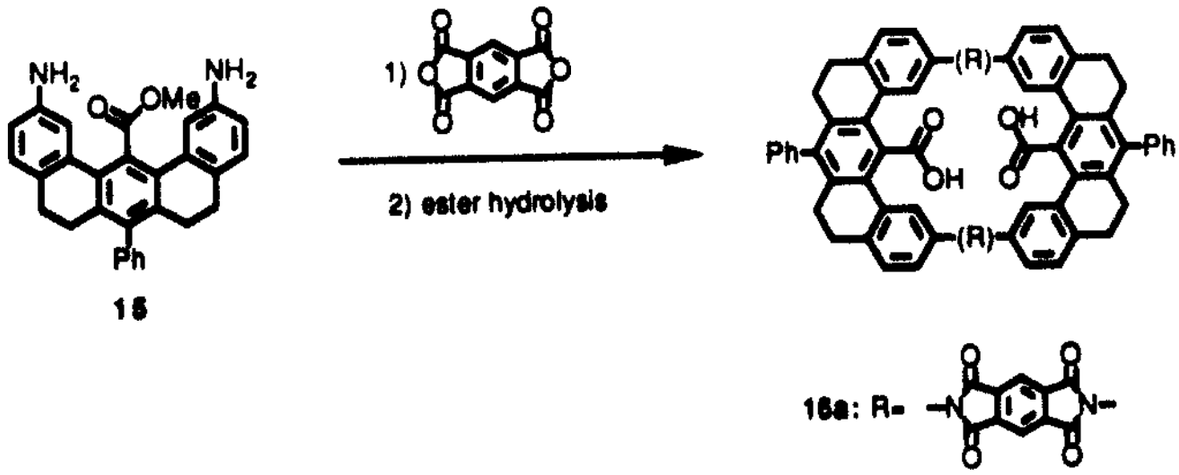
Scheme 4


Br
Br
O
OMe
Ph
7a
Ni(acac)2 / benzene / 70°C
12
CH3
CH3
O
OR
Ph
13a: R=Me
13b: R=H


Br
Br
1) n-BuLi / benzene / 65° C
2) MeI / THF
CH3
Br
Mg / I2 / Et2O
dibromoethane
CH3
MgBr
12

Scheme 5


Br
Br
OMe
Ph
7a
1) n-BuLi / THF, -60°C
2) MeONH2 / MeLi
NH2
NH2
OMe
Ph
15
1) n-BuLi / THF
-60°C
2) CO2
1) DPPA / Et3N
t-BuOH, reflux
2) TFA
CO2H
CO2H
OMe
Ph
14, 92%


NH2
NH2
OMe
Ph
16
1)
2) ester hydrolysis
(R)
(R)
Ph
Ph
OH
OH
16a: R=

References

1. Feldman, K. S.; Lee, Y. B. *J. Am. Chem. Soc.* **1987**, *109*, 5850.
2. (a) Fillers, J. P.; Ravichandran, K. G.; Abalmuhdi, I.; Tulinksy, A.; Chang, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 417. (b) Johnson, M. R.; Sutherland, I. O.; Newton, R. F. *J. Chem. Soc., Chem. Commun.* **1979**, 309. Kotzyba-Hilbert, F.; Lehn, J. M.; Vierling, P. *Tetrahedron Letters* **1980**, 941.
3. Rebek, J., Jr. *Science* **1987**, *235*, 1478.
4. Zimmerman, S. C.; VanZyl, C. M.; Hamilton, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1373.
5. Zimmerman, S. C.; VanZyl, C. M. *J. Am. Chem. Soc.* **1987**, *109*, 7894.
6. Zimmerman, S. C. *Tetrahedron Letters* **1988**, 983.
7. Zimmerman, S. C.; Wu, W. *J. Am. Chem. Soc.* **1989**, *111*, 8054.
8. No data has yet been obtained for structures **13b** and **18**. Work is in progress.
9. Newman, M. S.; Seshardi, S. *J. Org. Chem.* **1962**, *27*, 76. Fieser, L. F.; Seligman, A. M. *J. Am. Chem. Soc.* **1938**, *60*, 170.
10. Katritzky, A. R.; Thind, S. S. *J. Chem. Soc., Perkin Trans.* **1980**, *1*, 1895.
11. Griffin, D. A.; Staunton, J. *J. Chem. Soc., Chem. Commun.* **1975**, 675.

12. Modification of a procedure developed by Lehmstedt. See Lehmstedt, K.; Dostal, F. *Chem. Ber.* **1939**, *72*, 804.

13. Separations run by Andy Burke. Column = JEM 001 #501; eluted in methanol at 2 mL/min; detected at 254 nm.

14. (a) Reaction conditions adapted from Trepka, W. J.; Sonnenfeld, R. J. *J. Organometal. Chem.* **1969**, *16*, 317. (b) Ibuki, E.; Ozasa, O.; Fujioka, Y.; Yanagihara, Y. *J. Chem. Pharm. Bull.* **1982**, *30*, 802.

15. Marchand, P. S. *Chem. Comm.* **1971**, 667.

16. Beak, P.; Kokko, B. J. *J. Org. Chem.* **1982**, *47*, 2823.

17. Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203. Baumgarten, H. E.; Staklis, A. *J. Am. Chem. Soc.* **1965**, *87*, 1141.

18. *Organic Synthesis Vol. III* **1955**, p. 413, 553.