and Gibson[15b] have also recently shown that a 5-(propargylamino)-2'-deoxyuridine can be incorporated into an oligonucleotide hybridization probe and labeled with a fluorescent dye or a photoactivable cross-linking agent.

In summary, alkynylamino linkers can be easily attached to a variety of nucleotides in a manner compatible either with enzymatic incorporation into DNA or with chemical synthesis of hybridization probes. The alkynylamino group, therefore, can be considered to serve as a "universal linker" for attaching reporters to nucleic acids.

Acknowledgment. The assistance of my colleagues G. L. Trainor, A. J. Cocuzza, M. A. Jensen, W. A. Nugent, and P. N. Confalone and the technical assistance of L. A. DeAngelis is gratefully acknowledged.

Registry No. 1 (R^1 = I, R^2 = R^3 = H), 105784-83-6; 1 (R^1 = I, R^2 = H, R^3 = OH), 54-42-2; 1 (R^1 = I, R^2 = R^3 = OH), 1024-99-3; **1a**, 114748-60-6; **1b**, 115899-42-8; **1c**, 115899-44-0; **1d**, 115899-46-2; **1e**, 115899-45-1; **1f**, 115899-40-6; **1g**, 120609-05-4; **2** (R^1 = I, R^2 = R^3 = H), 114748-57-1; **2** (R^1 = I, R^2 = H, R^3 = OH), 611-53-0; **2a**, 114748-58-2; **2b**, 115899-38-2; **3**, 114748-71-9; **3** (R^1 = I, R^2 = R^3 = H), 114748-70-8; **4**, 114748-68-4; **4** (R^1 = I, R^2 = R^3 = H), 114748-67-3; $HC{\equiv}CCH_2NHCOCF_3$, 14719-21-2; $HC{\equiv}C(CH_2)_3NHCOCF_3$, 115899-41-7; $HC{\equiv}C(CH_2)_{10}NHCOCF_3$, 115899-43-9; $HC{\equiv}CCH_2NH_2$, 2450-71-7; $HC{\equiv}C(CH_2)_3NH_2$, 15252-44-5; CuI, 7681-65-4; $Pd(PPh_3)_4$, 14221-01-3.

Synthesis of γ-Spirolactones and γ-Spirolactams. Diels–Alder Adducts Based on a 9,10-Dihydro-9,10-ethanoanthracene Structure

William H. Pirkle* and James V. Gruber

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

Received January 18, 1989

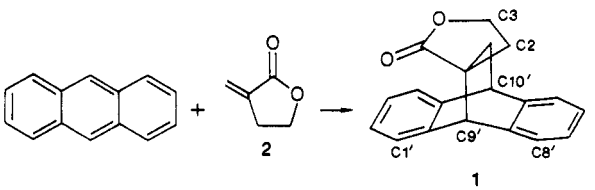
Syntheses of a variety of γ-spirolactones and γ-spirolactams derived from Diels–Alder adducts of anthracene are described. Alkylation of the anion of nitrile 8 with a variety of electrophilic agents affords either C2,C3-substituted γ-spirolactones or C2- or C2,C3-substituted γ-spirolactams. Hydrogenation of 8 affords C2-substituted γ-spirolactams. Changes in relative stereochemistry occur during synthesis of the spirolactones, product stereochemistry being dependent upon temperature and reaction time. A sequence of reactions involving aldol-like condensations and reversible ring closures is suggested to account for the observed stereoselectivities.

Introduction

Spirolactones and spirolactams having the spiro conjunction at the ene terminus of a Diels–Alder adduct are of interest because, as masked exocyclic double bonds,[1] they allow selective protection and deprotection of the latent and possibly labile ene during synthetic manipulation. In addition, the chiral recognition properties of these relatively rigid compounds are of interest in other contexts, for we earlier noted that the enantiomers of **1** are separable on the (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine stationary phase.[2] It was this observation that prompted our initial interest in these compounds. Originally, racemic **1** was prepared by treatment of anthracene with α-methylene-γ-butyrolactone, **2** (Scheme I). The yield of this adduct is low, with polymeric materials being the major products. *exo*-Methylene lactones such as **2** are relatively unavailable, so this synthetic approach to spirolactones or spirolactams is unattractive.

Thebtaranonth's synthesis of spirolactones from the Diels–Alder adduct of anthracene and methacrylate provides the basic strategy for the synthesis of the spirolactones and spirolactams used in this study.[3] Owing to the greater basicity of the carbonyl oxygen and the presence of the NH, which might serve as an additional site for hydrogen bonding, we suspected that spirolactams would resolve more readily on CSP **1** then the corresponding spirolactone. Accordingly, our initial efforts were directed at the synthesis of spirolactams.[4]

Scheme I



Results and Discussion

Spirolactam Synthesis. Thebtaranonth et al. alkylated the enolate of ester **3** with epoxides; the initial adducts close spontaneously to afford spirolactones. Attempts to alkylate this enolate with aziridine led to acylaziridines instead of the desired spirolactams. Alkylation of the enolate (LDA, THF, −78 °C) with ethylene dibromide affords adduct **4** in high yield (Scheme II).[5] Treatment of a methanolic solution of **4** with gaseous ammonia in a sealed glass tube affords γ-spirolactam **5** in 50% yield. In a similar fashion, alkylation with 1,3-dibromopropane followed by amination affords δ-spirolactam **7** in 70% yield. The methylene groups of **4** and **6** are not amenable to further substitutions, so only unsubstituted lactams such

(1) For recent reviews on the application of the retro-Diels–Alder reaction to organic synthesis, see: (a) Ichihara, A. *Synthesis* **1987**, 207. (b) Ripoll, J.; Lasne, M. *Synthesis* **1985**, 121. (c) Wiersum, U. E. *Aldrichimica Acta* **1984**, 17, 31. (d) Brown, R. F. C. *Pyrolytic Methods in Organic Chemistry*; Organic Chemistry Monographs; Academic Press: New York, 1980; Vol. 41. (e) Pirkle, W. H.; Gruber, J. V. *Abstracts of Papers*; 20th Great Lakes Regional Meeting of the American Chemical Society, Milwaukee, WI; American Chemical Society: Washington, DC, 1986; Abstract 283. (f) Flash vacuum pyrolysis of several of the Diels–Alder adducts described herein will be described subsequently.

(2) (a) Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1981**, *46*, 2935. (b) Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1982**, *47*, 4037. (c) Pirkle, W. H.; Finn, J. M.; Hamper, B. C.; Schreiner, J. L.; Pribish, J. *ACS Symp. Ser.* **1982**, No. 185, 245.

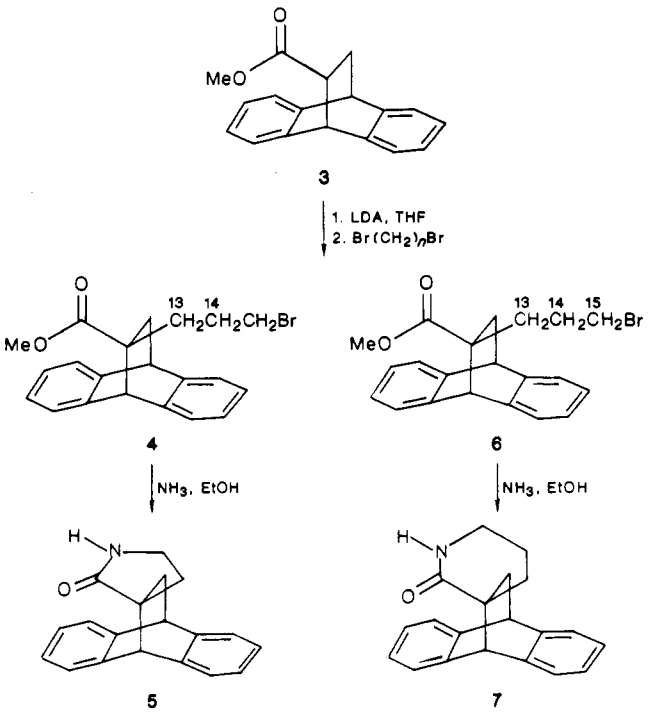
(3) Thebtaranonth, Y.; Jenkitkasemwong, Y.; Wajirum, N. *Tetrahedron Lett.* **1979**, 1615.

(4) Gruber, J. V.; Pirkle, W. H. *Abstracts of Papers*; 19th Midwest Chemical Society, Springfield, MO; American Chemical Society: Washington, DC, 1984; Abstract 622.

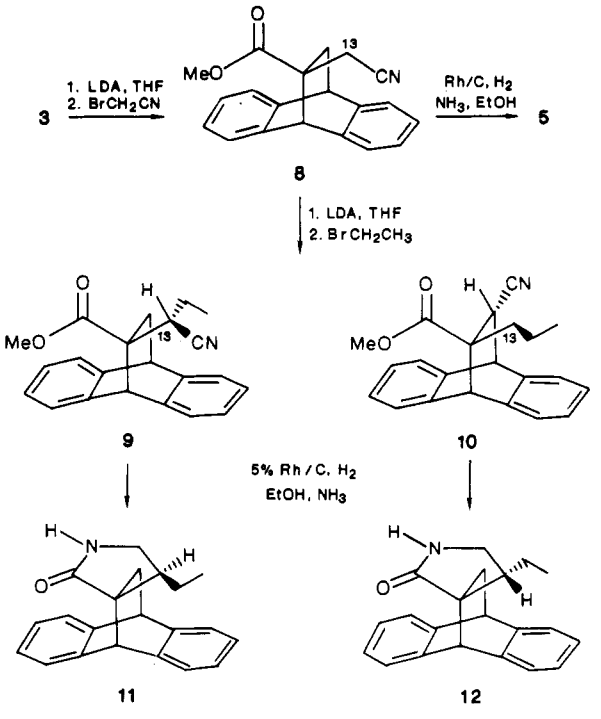
(5) Ichihara, A.; Nio, N.; Sakamura, S. *Tetrahedron Lett.* **1980**, *21*, 4467.

0022-3263/89/1954-3422$01.50/0

Scheme II



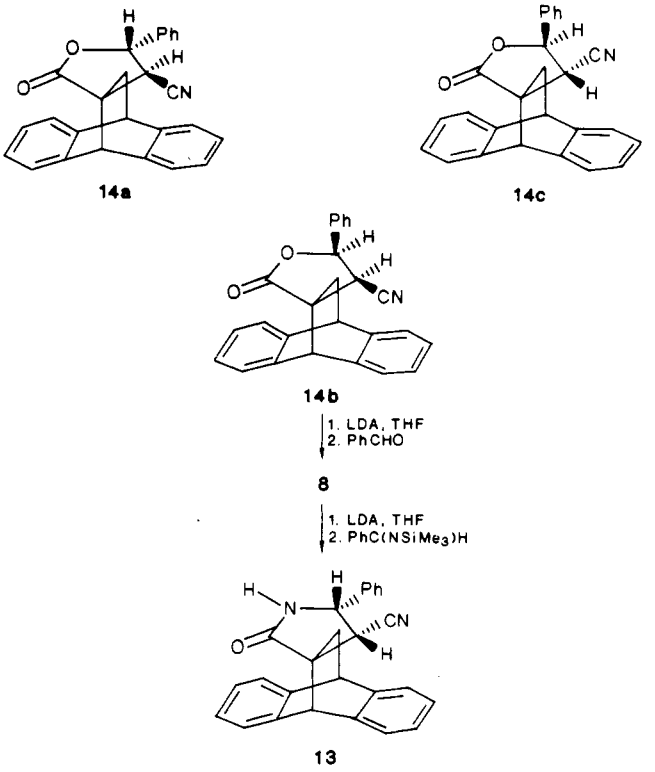
Scheme III



as **5** and **7** are readily generated by this sequence. Attempts to produce ring-substituted analogues by the use of more highly substituted dihalides (e.g. 1,2-dibromocyclohexane or 2,3-dibromopropane) failed. Similarly, use of acrylonitrile, nitroethene, and chloracetylaldehyde diethyl acetal proved unsuccessful. However, treatment of the enolate of **3** with bromoacetonitrile affords a dark reaction mixture from which **8** was ultimately obtained in 80% yield (Scheme III). Compound **8** is useful in that it allows considerable elaboration of the final lactam ring and is the focus of the remaining discussion.

Hydrogenation of **8** using a 5% Rh/C catalyst affords the amino ester, which, under the reaction conditions, cyclizes to afford γ-spirolactam **5** in 70% yield. Additionally, nitrile **8** can be deprotonated and alkylated with a variety of electrophilic agents. For example, treatment of **8** with 1 equiv of LDA (THF, −78 °C) followed by bromoethane affords diastereomers **9** and **10** in a 3:2 ratio, these being separable by silica gel chromatography.

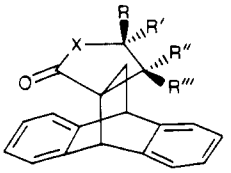
Scheme IV



The relative stereochemistry of diastereomers **9** and **10** was assigned from the results of nuclear Overhauser enhancement experiments and is consistent with the chromatographic behavior of each diastereomer on silica gel. It is suggested that diastereomers **9** and **10** preferentially populate conformations in which the methine hydrogen adjacent to the nitrile resides near the ester carbonyl, as shown in Scheme III. This is consistent with the downfield shift noted for this proton in both diastereomers (**9**, δ 2.80, and **10**, δ 2.79) relative to the methine hydrogen of isobutyronitrile (δ 2.67). A weak interaction between this weakly acidic methine hydrogen and the proximate ester carbonyl oxygen might promote the population of these conformations. In these conformations, the nitrile group of **9** is presumably less accessible to silica gel then is the nitrile group of **10**. It is observed that **9** elutes from silica before **10**. In the aforementioned conformation, H8, one of the aromatic protons, resides in the deshielding region of the nitrile group. This causes a distinctive downfield shift of the NMR signal of H8, placing this signal approximately 0.2 ppm away from the other aromatic protons. This downfield shift is noted in several of the compounds to be discussed and aids in the establishment of relative stereochemistry for a number of the lactones and lactams. Finally, nitrile **10** is found to undergo catalytic reduction more rapidly than nitrile **9**, presumably because of the greater accessibility of the nitrile group to the rhodium catalyst. Reduction of **9** and **10** leads to spirolactams **11** and **12**, respectively.

The enolate of **8** can be alkylated with *N*-(trimethylsilyl)imines. These adducts then undergo ring closure to *N*-trimethylsilyl γ-spirolactams (Scheme IV). These are not isolated for they hydrolyze during workup to afford

Table I. Product Spirolactones and Spirolactams



compd no.	X	R	R′	R″	R‴
1	O	H	H	H	H
5	NH	H	H	H	H
11	NH	H	H	H	Et
12	NH	H	H	Et	H
13	NH	H	Ph	CN	H
14a	O	H	Ph	CN	H
14b	O	Ph	H	H	CN
14c	O	Ph	H	CN	H
15a	O	Me	Me	CN	H
15b	O	Me	Me	H	CN
16a	O	Ph	Ph	H	CN
16b	O	Ph	PH	CN	H
17a	O	H	Me	CN	H
17b	O	Me	H	H	CN
17c	O	Me	H	CN	H
18a	O	H	$(CH_2)_{12}CH_3$	CN	H
18b	O	$(CH_2)_{12}CH_3$	H	H	CN

γ-spirolactams. The reaction of the enolate of **8** with *N*-(trimethylsilyl)benzaldimine could conceivably afford four racemic diastereomers. However, only spirolactam **13** was detected and isolated. Formation of but one racemic diastereomer from a reaction which potentially might afford four is of some interest.

Spirolactone Synthesis. In a reaction analogous to the preceding imine alkylation, alkylation with benzaldehyde affords γ-spirolactone diastereomers **14a**, **14b**, and **14c** as the ultimate products, the fourth diastereomer being undetected. Closer examination of this reaction has demonstrated that diastereomers **14a**, **14b**, and **14c** are formed sequentially. Similar sequential formations of diastereomers have been encountered when other ketones or aldehydes have been utilized as electrophiles in these reactions, (Table I).[6,7] The relative stereochemistry of all of the products in Table I was determined by NOE experiments and, in some instances, is supported by vicinal coupling constants and by the downfield shift of the aromatic H8 signal described earlier.

The nature of the substituents on the electrophilic carbonyl can have a significant effect on the stereochemical outcome of the reaction. If R and R′ are equivalent, two racemic diastereomers may result. If the two substituents are nonequivalent, four racemic diastereomers may result. Acetone, benzophenone, acetaldehyde, benzaldehyde, and tetradecyl aldehyde were used as electrophilic trapping agents for the enolate of **8**. Sequential changes in the relative stereochemistry of the various products have been observed and seem to be dependent on both temperature and reaction time. Thus, treatment of the enolate of **8** with acetone at −78 °C followed by a water quench after 5 min affords a mixture of **15a** and **15b**, **15a** being the major isomer present. However, if the reaction is kept at 24 °C for 24 h before quenching, only diastereomer **15b** is isolable. Similar observations are made for the formation of **16a** and **16b** from the enolate of **8** and benzophenone. However, the relative stereochemistry of **16a**, the major diastereomer isolated after reaction at −78 °C for 15 min, does not correspond to that of **15a**, there being a difference in relative configuration at the cyano-bearing carbon.

Isolation of spirolactones **14a**, **14b**, and **14c** from benzaldehyde, **17a**, **17b**, and **17c** from acetaldehyde, and **18a** and **18b** from tetradecyl aldehyde requires a more complex reaction sequence. As mentioned, alkylation with aldehydes potentially can afford four racemic diastereomers as products. Three racemic diastereomers were detected and isolated in the first two instances, tetradecyl aldehyde leading to but two detectable diastereomers.

The sequential formation of **14a**, **14b**, and **14c** is easily demonstrated by following the reaction by proton NMR and HPLC. Quenching of the reaction mixture at −35 °C after 90 min gives **14a** as the predominant diastereomer. This diastereomer gives a clear doublet at δ 5.94 for the vicinal C3 proton, the coupling constant being 5.3 Hz. When the product is chromatographed on a racemic *N*-(2-naphthyl)alanine undecenyl ester stationary phase,[8] **14a** is found to be the major product with small quantities of **14b** and **14c** being detected. If a second identical reaction mixture is allowed to slowly warm to 22 °C and allowed to stand for 5 h before workup, the predominant diastereomer is now **14b**, which has its vicinal C3 proton signal at δ 5.42 with a coupling constant of 5.3 Hz. Chromatographically, **14b** is the major diastereomer, a diminishing quantity of **14a** is apparent as is an increasing amount of **14c**. The latter compound is the first of the three diastereomers to elute from the racemic column; **14b** elutes last. After 24 h at 24 °C, a third reaction mixture contains primarily diastereomer **14c**, which has its vicinal C3 proton signal at δ 5.05 with a vicinal coupling constant of 8.8 Hz.

The sequential formation of lactones **17a**, **17b**, and **17c** when acetaldehyde is used as the electrophile occurs in a similar fashion but is still more complicated. Quenching the reaction mixture at −72 °C after 15 min affords **17a** as the major product, a small amount of **17c** being present as well. After 165 min at 3 °C the fraction of **17c** present remains unaffected, but the relative amounts of **17a** and

(6) For some examples involving spontaneous formation of spirolactones by addition of an aldehyde to an anionic equivalent, see: (a) Carlson, R. M.; Oyler, H. R. *J. Org. Chem.* **1976**, *41*, 4065. (b) Semmelhack, M. F.; Wu, E. S. C. *J. Am. Chem. Soc.* **1976**, *98*, 3384.

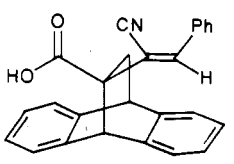
(7) Gruber, J. V.; Pirkle, W. H. *Abstracts of Papers*; 3rd Chemical Congress of North America and 195th National Meeting of the American Chemical Society, Toronto, Ontario, Canada; American Chemical Society: Washington, DC, 1988; Org. Abstract 386.

(8) Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 352.

17b change, both being present in almost equal amounts. If the reaction is conducted at 24 °C for 24 h prior to quenching, **17b** becomes the major isomer although a considerable amount of **17a** remains. Only a small amount of **17c** is found. This trend is even more pronounced when tetradecyl aldehyde is employed to afford **18a** and **18b**. Indeed, no trans product analogous to **17c** could be detected in the reaction mixture.

The conversion of **15a** to **15b** and **16a** to **16b** could occur by epimerization of the groups at C2 under the basic reaction conditions, **15b** and **16b** being the thermodynamically more stable products. However, the restructuring of diastereomer **14a** to diastereomer **14b** involves changes at two stereogenic centers and requires a more complex sequence to explain the observed results. Obviously, lactone **14a** is kinetically favored. As the temperature is increased, the methoxide ion present may facilitate ring opening of **14a**, followed by the retro-aldol with subsequent recondensation to give the thermodynamically more stable **14b**, which may then epimerize at C2 to afford the yet more stable **14c**.

It was thought that if pure **14a** were treated with 1 equiv of LiOMe in THF at −78 °C and the reaction mixture was slowly warmed, then the conversion of **14a** to **14b** to **14c** might possibly be observed. This was not the case. Instead, a new product was isolated and identified spectroscopically as **19**. Compound **19** may form by deprotonation at C2 by methoxide ion and subsequent eliminative ring opening to afford the highly conjugated ene carboxylate anion. Isolation of **19** instead of either **14b** or **14c** suggests that other factors (excess aldehyde present in the reaction, the availability of the diisopropylamine, or both) may be required to cause the observed changes in relative stereochemistry.



19

In conclusion, a general approach to both C2- or C3-substituted γ-spirolactams and C2- or C3-substituted γ-spirolactones has been described. These are formally Diels–Alder adducts of anthracene and either *exo*-methylene lactams or lactones. Synthesis of the spirolactones proceeds through an aldollike condensation and reversible ring closure. Final product composition is dependent upon reaction time and temperature. The product lactams and lactones which are formed with substituents at both C2 and C3 of the lactone or lactam ring seem to favor relative conformations in which these substituents reside in a cis arrangement to one another. Only in isolated cases (e.g. compounds **14c** and **17c**) are the corresponding trans isomers detected, and they are rarely the major products (e.g. **14c**).

Experimental Section

Microanalysis were performed in the microanalytical laboratory by J. Nemeth and T. McCarthy. Proton NMR spectra were recorded on a Varian XL 200 (200 MHz) spectrometer. Tetramethylsilane was used as a standard. IR spectra were recorded on either an IBM IR-32 FT-IR or a Nicolet 7000 FT-IR spectrometer. Melting points were obtained on a Büchi apparatus and are uncorrected.

Analytical high-performance liquid chromatography was performed by using either (1) an Altex 100 pump, Altex 210 injector, and an Altex Model 253 detector operating at 254 nm or (2) a Rainin HPX or Anspec pump, Rheodyne injector, and Milton Roy LDC fixed-wavelength detector. All chromatograms were recorded using a Kipp-Zonen BD 41 chart recorder. Semipreparative resolutions were performed using commercially available CSP's using an Altex 100 A pump, Altex 210 injector with a 250-μL loop, and a Beckman Model 153 detector.

General Procedure for the Generation of the Enolate of 3 and Subsequent Alkylation with a Dibromide. In a three-necked round-bottom flask purged with nitrogen was placed **3**[9] (3.20 g, 12.12 mmol) in 60 mL of dry THF. This mixture was cooled to −78 °C, and LDA (1.1 equiv), formed by addition of (1.1 equiv) *n*-butyllithium to (1.1 equiv) *N,N*-diisopropylamine in 40 mL of anhydrous THF was added. After 30 min, the appropriate alkyl dihalide (2 equiv of 1,2-dibromoethane affords **4**; 1,3-dibromopropane affords **6**) was added, and the mixture was warmed slowly to room temperature and stirred for 24 h. The mixture was diluted with 50 mL of ether and washed well with water and brine. The ethereal layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the crude product.

(±)-9,10-Dihydro-11-(13-bromoethyl)-11-carbomethoxy-9,10-ethanoanthracene (4). Product **4** was isolated in 80% yield (white needles from methanol): mp 128–131 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 6.33–6.45 (m, 8 H) aromatics); 4.41 (s, 1 H, H9), 4.25 (t, 1 H, J = 2.5 Hz, H10, 3.48 (s, 3 H, OCH_3), 3.00–3.26 (m, 2 H, H15, H16), 2.78 (dd, 1 H, J = 12.0, 3.0 Hz, H12), 2.04–2.40 (m, 1 H), H13), 1.45 (dd, 1 H, J = 12.0, 3.0 Hz, H11), 1.42–1.72 (m, 1 H, H14); IR (KBr) 2920, 1728, 1640, 1450, 1310, 1250, 1220, 1190, 1150, 1050, 965, 770 cm^{-1}. Anal. Calcd for $C_{20}H_{19}O_2Br$: C, 64.70; H, 5.16. Found: C, 64.62; H, 5.42.

(±)-9,10-Dihydro-11-(15-bromopropyl)-11-carbomethoxy-9,10-ethanoanthracene (6). Compound **6** was isolated in 83% yield as white plates from absolute MeOH: mp 103–105 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 6.94–7.35 (m, 8 H, aromatics), 4.46 (s, 1 H, H9), 4.28 (t, 1 H, J = 2.8 Hz, H10), 3.54 (s, 3 H, O-CH_3), 3.13–3.24 (m, 2 H, CH_2Br), 2.65 (dd, 1 H, J = 12.3, 2.8 Hz, H11), 1.60–1.97 (m, 2 H, H15, H16), 1.60–1.97 (m, 1 H, H13), 1.43 dd, 1 H, J = 12.3, 2.8 Hz, H12), 1.00–1.15 (m, 1 H, H14); IR (KBr) 2944, 1731, 1460, 1432, 1320, 1305, 1249, 1230, 1195, 1180, 1150, 769 cm^{-1}. Anal. Calcd for $C_{21}H_{21}O_2Br$: C, 65.46; H, 5.49; Br, 20.74 Found: C, 65.77; H, 5.72; Br, 20.98.

General Procedure for the Synthesis of Spiropyrrolidinones via Amination. Esters **4** (1.00 g, 2.70 mmol) and **6** (2.17 g, 5.63 mmol) from above were placed into Carius tubes (1.0 cm × 15 cm), which were partially filled with MeOH, and cooled in a dry ice/isopropyl alcohol bath, and anhydrous ammonia was passed into the tubes until a weight increase of ca. 0.5 g was noted. The tube contents were frozen using liquid N_2, and the tubes were sealed and heated on a steam bath for ca. 8 h. The progress of the reactions could be estimated by the gradual dissolution of the starting materials. The tubes were cooled in liquid nitrogen and cautiously opened. The retrieved contents were taken up in ether, and the organics were washed well with H_2O and brine. The ethereal layers were dried over $MgSO_4$, filtered, and evaporated in vacuo to afford crude products. Chromatography through silica using ethyl acetate removes a number of impurities.

(±)-9′,10′-Dihydrospiro[pyrrolidine-1,11′-9′,10′-ethanoanthracen]-5-one (5). Compound **5** was formed through the treatment of **4** with ammonia. The product was obtained as white flakes in 53% yield after recrystallization from toluene: mp 217–218.5 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 6.95–7.45 (m, 8 H, aromatics), 6.00 (s, broad, 1 H, NH), 4.34 (t, 1 H, J = 2.0 Hz, H10′), 4.15 (s, 1 H, H9′), 3.12–3.55 (m, 2 H, H3, H4), 2.33 (dd, 1 H, J = 12.0, 2.0 Hz, H12′), 1.60–1.97 (m, 2 H, H1, H2), 1.54 (dd, 1 H, J = 12.0, 2.0 Hz, H11′); IR (KBr) 2940, 1695, 1460, 1365, 1280, 1250, 1060, 760, 740 cm^{-1}. Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.76; H, 6.15; N, 5.02.

(±)-9′,10′-Dihydrospiro[piperdine-1,11′-9′,10′-ethanoanthracen]-6-one (7). Spirolactam **7** was formed from **6** by the action of ammonia and was isolated as white needles from benzene in 52% yield: mp 194–196 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.00–7.36 (m, 8 H, aromatics), 5.41 (s, broad, 1 H, NH), 4.41 (s, 1 H, H9′), 4.32 (t, 1 H, J = 2.8 Hz, H10′), 3.21–3.54 (m, 2 H, H5, H6), 2.69 (dd, 1 H, J = 12.3, 2.8 Hz, H11′), 2.05–2.31 (m, 1 H, H4), 1.30 (dd, 1 H, J = 12.3, 2.8 Hz, H12′), 1.17–1.75 (m, 3 H,

(9) Bartlett, P. D.; Tate, F. A. *J. Am. Chem. Soc.* **1953**, *75*, 91.

H1, H2, H3); IR (KBr) 3060, 2935, 2860, 1670, 1492, 1485, 1410, 1360, 1320, 1275, 1220, 1110, 760 cm^{-1}. Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.06; H, 6.55; N, 4.80.

General Procedure for the Synthesis of Spirolactams via Reduction of Nitriles. (±)-9,10-Dihydro-11-carbomethoxy-11-(13-cyanomethyl)-9,10-ethanoanthracene (8). In a three-necked round-bottomed flask purged with nitrogen was placed ester **3** (13.3 g, 50.12 mmol) in 150 mL of dry THF. This mixture was chilled to −78 °C and 1.0 equiv of LDA in 100 mL of dry THF was added. After 0.5 h, bromoacetonitrile (2.0 equiv) was added to the mixture which was stirred for 4 h and brought slowly to room temperature. The reaction mixture was quenched with H_2O, and the organics were removed by extraction with ether. The dark ethereal layer was dried with brine and $MgSO_4$, filtered, and evaporated in vacuo to afford the crude product as a tan solid. Two recrystallizations from absolute MeOH afforded colorless **8**. The mother liquors were chromatographed on silica (activity 1) with CH_2Cl_2 to give a second portion of **8**. The overall yield was 70%: mp 145–148 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.20–7.39 (m, 8 H, aromatics), 4.53 (s, 1 H, H9), 4.34 (t, 1 H, H10), 3.59 (s, 3 H, OCH_3), 2.75 (dd, 1 H, J = 13.7, 3.5 Hz, H11), 2.44 (d, 1 H, J = 19.6 Hz, H13), 2.14 (d, 1 H, J = 19.6 Hz, H14), 1.54 (dd, 1 H, J = 13.7, 3.5 Hz, H12); IR (KBr) 3022, 2951, 2250, 1738, 1481, 1458, 1433, 1306, 1292, 1253, 1199, 1176, 1113, 1086, 1061, 787 cm^{-1}. Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.36; H, 5.79; N, 4.60.

To **8** (2.00 g, 6.59 mmol) in 60 mL of dry nitrogen purged THF at −78 °C was added LDA (1.0 equiv). The mixture was stirred for 0.5 h, ethyl bromide (2.0 equiv) was added, and the reaction mixture was slowly warmed to room temperature and stirred for 24 h. The reaction was quenched with H_2O, and the organics were removed by extraction with ether, dried with brine and $MgSO_4$, and filtered, and the solvent was removed by evaporation in vacuo. The crude product was obtained as a mixture of diastereomers **9** and **10** in a 3:2 ratio in 72% overall yield. The diastereomers were separated by chromatography on silica with ethyl acetate–benzene–hexane, 1:4:5, with **9** eluting first.

(±)-9,10-Dihydro-11-(*cis*-13-cyanopropyl)-11-carbomethoxy-9,10-ethanoanthracene (9). Pure **9** was obtained as white needles by recrystallization from absolute methanol: mp 155–157 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.50–7.59 (m, 1 H, aromatic H1), 7.03–7.38 (m, 7 H, aromatics), 4.97 (s, 1 H, H9), 4.32 (t, 1 H, J = 3.5 Hz, H10), 3.64 (s, 3 H, OCH_3), 2.80 (dd, 1 H, J = 13.8, 3.1 Hz, H13), 1.73 (dd, 1 H, J = 12.3, 3.5 Hz, H11), 1.40–1.63 (m, 1 H, H14), 1.34 (dd, 1 H, J = 12.3, 2.7 Hz, H12), 1.12–1.38 (m, 1 H, H15), 0.95 (t, 3 H, J = 7.3 Hz, H16, H17, H18); IR (KBr) 2972, 2250, 1738, 1460, 1435, 1306, 1250, 1209, 1194, 1178, 768, 752 cm^{-1}. Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.60; H, 6.38; N, 4.13.

(±)-9,10-Dihydro-11-(*trans*-13-cyanopropyl)-11-carbomethoxy-9,10-ethanoanthracene (10). Recrystallization from absolute methanol afforded **10** as white flakes: mp 133–136 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.05–7.36 (m, 8 H, aromatics), 4.65 (s, 1 H, H9), 3.34 (t, 1 H, J = 3.1 Hz, H10), 3.58 (s, 1 H, OCH_3), 2.79 (dd, 1 H, J = 15.0, 3.1 Hz, H13), 2.14 (dd, 1 H, J = 11.9, 3.8 Hz, H11), 1.79–2.00 (m, 1 H, H14), 1.85 (dd, 1 H, J = 11.9, 3.8 Hz, H12), 1.46–1.68 (m, 1 H, H15), 1.00 (t, 3 H, J = 7.3 Hz, H16, H17, H18); IR (KBr) 3027, 2970, 2250, 1734, 1458, 1309, 1255, 1215, 1181, 1120, 976, 767, 752 cm^{-1}. Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.36; N, 4.23. Found: C, 79.67; H, 6.28; N, 4.18.

Diastereomers **9** and **10** (0.71 g, 2.14 mmol) present as a 3:2 mixture were taken up in 70 mL of absolute EtOH and placed in a Parr hydrogenation bottle and hydrogenated over 5% Rh/C (1.0 mol %) at 50 psi until no starting material was detected by TLC on silica (ethyl acetate). Usually, the reaction requires about 3 days to go to completion. The crude product was filtered through Celite, and the solvent was removed by evaporation in vacuo to afford the crude product. Reduction of **8** directly gives **5**, identical with that afforded via amination.

(±)-9′,10′-Dihydro-*cis*-2-ethylspiro[pyrrolidine-1,11′-9′,10′-ethanoanthracen]-5-one (11). Spirolactam **11** was isolated from the reduction of ester **9**. Compound **11** was contaminated with spirolactam **12**, which was removed by HPLC chromatography on a racemic *N*-(3,5-dinitrobenzoyl)phenylglycine stationary phase with a 1:1 CH_2Cl_2–hexane mobile phase; **11** is most retained: mp 166–167 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.03–7.35 (m, 8 H, aromatics); 5.42 (s, broad, 1 H, NH); 4.38 (t, 1 H, J = 3.0 Hz, H10′), 4.19 (s, 1 H, H9′), 3.74 (dd, 1 H, J = 10.4, 7.4 Hz, H7), 3.00 (dd, 1 H, J = 1.04, 2.5 Hz, H8), 2.30 (dd, 1 H, J = 13.3, 3.0 Hz, H11′), 1.82–1.99 (m, 1 H, H1), 1.82 (dd, 1 H, J = 13.3, 3.0 Hz, H12′), 0.80–1.11 (m, 2 H, H2), 0.69 (t, 3 H, J = 6.7 Hz, CH_3); IR (KBr) 3210, 2934, 2872, 1700, 1455, 1290, 1260, 1025 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO$: C, 82.74; H, 6.85; N, 4.49.

(±)-9′,10′-Dihydro-*trans*-2-ethylspiro[pyrrolidine-1,11′-9′,10′-ethanoanthracen]-5-one (12). Spirolactam **12** was isolated as described for **11**: mp 183–187 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 6.92–7.32 (m, 8 H, aromatics), 5.44 (s, broad, 1 H, NH); 4.20–4.35 (m, 2 H, H9′, H10′), 3.30 (dd, 1 H, J = 11.1, 5.6 Hz, H7), 3.08 (dd, 1 H, J = 11.1, 5.6 Hz, H8), 2.22 (dd, 1 H, J = 11.9, 3.0 Hz, H11′), 1.72 (dd, 1 H, J = 11.9, 3.0 Hz, H12′), 1.60–1.73 (m, 1 H, H1), 1.00–1.42 (m, 2 H, H2, H3), 0.67 (t, 3 H, J = 6.7 Hz, CH_3); IR (KBr) 3200, 2920, 2857, 1698, 1452, 1280, 1249, 1018 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 82.93; H, 6.97; N, 4.62.

General Procedure for the Synthesis of Spirolactams Using *N*-(Trimethylsilyl)imines. (±)-9′,10′-Dihydro-*trans*-2-cyano-*trans*-3-phenylspiro[pyrrolidine-1,11′-9′,10′-ethanoanthracen]-5-one (13). To **8** (3.00 g, 9.89 mmol) in 60 mL of dry nitrogen purged THF at −78 °C, was added LDA (1.1 equiv). After 0.5 h, 2.0 equiv of *N*-(trimethylsilyl)benzaldimine, formed as described by Hart,[10] was added, and the mixture was stirred for 24 h by which time it had come to room temperature. The dark reaction mixture was taken up in ether and washed sequentially with 1 M HCl, H_2O, and brine. The solution was dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo to yield the product lactam. The product was isolated as a single diastereomer and was purified by chromatography on silica (activity 1) with CH_2Cl_2 followed by ethyl acetate. Recrystallization in absolute EtOH afforded **13** in 50% yield as tan prisms: mp 270–272 °C; ^{1}NMR (200 MHz, $CDCl_3$) δ 6.90–7.50 (m, 13 H, aromatics), 5.89 (s, broad, 1 H, NH), 4.62 (d, 1 H, J = 7.7 Hz, H2), 4.48 (t, 1 H, J = 3.5 Hz, H10′), 4.15 (s, 1 H, H9′), 2.98 (d, 1 H, J = 7.7 Hz, H1), 2.40 (dd, 1 H, J = 13.5, 3.5 Hz, H11′), 2.11 (dd, 1 H, J = 13.5, 2.7 Hz, H12′); IR (KBr) 3235, 3067, 2940, 2250, 1715, 1458, 1369, 1337, 1279, 1205, 1173, 783, 760 cm^{-1}. Anal. Calcd for $C_{26}H_{20}N_2O$: C, 82.95; H, 5.36; N, 7.44. Found: C, 82.70; H, 5.21; N, 7.33.

General Procedure for the Synthesis of Spirofuranones. The syntheses of **15a** and **15b** will be used to represent the general method for synthesis of all the reported spirolactones although reaction times and reaction temperatures for individual reactions did vary. To **8** (1.00 g, 3.30 mmol) in 50 mL of dry nitrogen purged THF at −78 °C was added LDA (1.1 equiv) in 40 mL of anhydrous THF. After 0.5 h, the enolate of **8** was trapped with acetone (2.0 equiv). An aliquot of the reaction mixture was diluted with ether after 5 min at −78 °C, washed sequentially with 1 M HCl, H_2O, and brine, and dried over $MgSO_4$. Evaporation of the solvent affords a 1:1 mixture of **15a** and **15b**. If the reaction mixture was allowed to warm to 24 °C and stir for 24 h before workup, only **15b** could be detected and isolated. Diastereomers **15a** and **15b** were obtained in a yield of 84%. Separation of the diastereomers was accomplished on a racemic *N*-(3,5-dinitrobenzoyl)phenylglycine stationary phase with 5% isopropyl alcohol/hexane as the mobile phase; **15a** elutes first.

(±)-9′,10′-Dihydro-*cis*-2-cyano-3,3-dimethylspiro[furan-1,11′-9′,10′-ethanoanthracen]-5-one (15a).[11] Lactone **15a** was isolated as white needles from hexane: mp 244–245 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.46–7.56 (m, 1 H, H8′), 7.00–7.38 (m, 7 H, aromatics), 4.73 (s, 1 H, H9′), 4.35 (t, 1 H, J = 3.5 Hz, H10′), 2.58 (s, 1 H, H1), 2.36 (dd, 1 H, J = 13.0, 2.5 Hz, H11′), 2.00 (dd, 1 H, J = 13.0, 2.5 Hz, H12′), 1.62 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3); IR (KBr) 3020, 2945, 2240, 1780, 1470, 1460, 1375, 1285, 1268, 1250, 1150, 765 cm^{-1}. Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.01; H, 5.87; N, 4.17.

(±)-9′,10′-Dihydro-*trans*-2-cyano-3,3-dimethylspiro[furan-1,11′-9′,10′-ethanoanthracen]-5-one (15b). The crude product was recrystallized from absolute MeOH to give pure **15**: mp 210–213 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.08–7.46 (m, 8

(10) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T. *J. Org. Chem.* **1983**, *48*, 289.

(11) The standard numbering for pyrrolidine and furan is not followed.

H, aromatics), 4.49 (t, 1 H, J = 1.5 Hz, H10′), 4.22 (s, 1 H, H9′), 3.16 (s, 1 H, H1), δ 2.45 (dd, 1 H, J = 13.7, 3.4 Hz, H11′), 2.19 (dd, 1 H, J = 13.7, 1.5 Hz, H12′), 1.58 (s, 3 H), CH_3), 1.41 (s, 3 H, CH_3); IR (KBr) 3022, 2984, 2943, 2258, 1778, 1460, 1379, 1296, 1263, 1213, 1172, 1128, 1032, 949, 762 cm^{-1}. Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.25; H, 5.87; N, 4.18.

(±)-9′,10′-Dihydro-*trans*-2-cyano-*trans*-3-phenylspiro-[furan-1,11′-9′,10′-ethanoanthracen]-5-one (14a). This compound was formed by alkylating the enolate of **8** with benzaldehyde freshly distilled from molecular sieves. Quenching of the reaction mixture with H_2O at −78 °C after 0.5 h gives predominantly **14a** as crude product, small amounts of **14b** and **14c** being present as well. Pure **14a** was obtained by repeated recrystallizations from either hexane/ethyl acetate or ethanol, or by chromatography on silica (activity 1) with 1:1 CH_2Cl_2–benzene. Diastereomer **14a** elutes second: mp 207–209 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.05–7.50 (m, 13 H, aromatics), 5.94 (d, 1 H, J = 5.3 Hz, H2), 4.48 (m, 2 H, H9′, H10′), δ 3.42 (d, 1 H, J = 5.3 Hz, H1), 2.52 (dd, 1 H, J = 13.5, 2.6 Hz, H11′), 2.16 (dd, 1 H, J = 13.5, 3.39 Hz, H12′); IR (KBr) 3030, 2941, 2250, 1782, 1626, 1458, 1294, 1209, 1147, 1022, 765, 584 cm^{-1}. Anal. Calcd for $C_{28}H_{19}NO_2$: C, 82.74; H, 5.07; N, 3.71. Found: C, 82.76; H, 5.20; N, 3.63.

(±)-9′,10′-Dihydro-*cis*-2-cyano-*cis*-3-phenylspiro[furan-1,11′-9′,10′-ethanoanthracen]-5-one (14b). Diastereomer **14b** was isolated by quenching the preceding reaction mixture after the temperature had increased from −78 °C to 22 °C over a period of 4 h; **14b** was the predominant stereoisomer present but was contaminated with a small amount of **14c**. This impurity was removed by chromatography on silica with 1:1 CH_2Cl_2–benzene and recrystallization of the major component from either ethyl acetate/hexane or ethanol to give **14b** as a white powder: mp 303–304 °C dec; ^1H NMR (200 MHz, $CDCl_3$) δ 7.10–7.56 (m, 13 H, aromatics), 5.42 (d, 1 H, J = 5.3 Hz, H2), δ 4.83 (s, 1 H, H9′), 4.50 (t, 1 H, J = 3.0 Hz, H10′), 2.69 (d, 1 H, J = 5.3 Hz, H1), 2.30 (dd, 1 H, J = 12.4, 3.0 Hz, H11′), 2.13 (dd, 1 H, J = 12.4, 3.0 Hz, H12′); IR (KBr) 3040, 2953, 2256, 1790, 1624, 1458, 1296, 1209, 1145, 1020, 769, 588 cm^{-1}. Anal. Calcd for $C_{28}H_{19}NO_2$: C, 82.74; H, 5.07; N, 3.71. Found: C, 82.40; H, 5.12; N, 3.60.

(±)-9′,10′-Dihydro-*trans*-2-cyano-*cis*-3-phenylspiro[furan-1,11′-9′,10′-ethanoanthracen]-5-one (14c). Diastereomer **14c** was isolated from the aforementioned reaction mixture after it had stood for 24 °C at 24 h. Isomer **14c** predominates but was contaminated with a small amount of **14b**. Pure **14c** was obtained as a white solid by repeated recrystallizations in absolute ethanol: mp 192–195 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.00–7.68 (m, 13 H, aromatics), 5.05 (d, 1 H, J = 8.8 Hz, H2), 4.54 (t, 1 H, J = 3.1 Hz, H10′), 4.22 (s, 1 H, H9′), 3.20 (d, 1 H, J = 8.8 Hz, H1), 2.51 (dd, 1 H, J = 13.1, 3.1 Hz, H11′), 2.22 (dd, 1 H, J = 13.1, 3.1 Hz, H12′); IR (KBr) 3027, 2950, 2240, 1785, 1469, 1459, 1247, 1158, 1025, 765, 745 cm^{-1}. Anal. Calcd for $C_{28}H_{19}NO_2$: C, 82.74; H, 5.07; N, 3.71. Found: C, 82.72; H, 5.10; N, 3.72.

(±)-9′,10′-Dihydro-*trans*-2-cyano-3,3-diphenylspiro[furan-1,11′-9′,10′-ethanoanthracen]-5-one (16a). Compound **16a** was isolated from a crude reaction mixture in which benzophenone was added as a solid to the enolate of **8**. The reaction was quenched at 0 °C after 3 h. The reaction mixture also contained diastereomer **16b**. The ratio of **16a**:**16b** was 2:1 with the reaction giving the mixed isomers in an overall yield of **64%**. The resulting diastereomers are separable on racemic *N*-(3,5-dinitrobenzoyl)-phenylglycine chiral stationary phase using 5% isopropyl alcohol/hexane as an eluent. Diastereomer **16a** elutes first: mp 223–225 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.00–7.66 (m, 18 H, aromatics), 4.29 (t, 1 H, J = 3.08 Hz, H10′), 4.05 (s, 1 H, H9′), 3.93 (s, 1 H, H1), 2.15 (dd, 1 H, J = 14.2, 3.1 Hz, H11′), 1.90 (dd, 1 H, J = 14.2, 3.5 Hz, H12′); IR (KBr) 3063, 2254, 1780, 1493, 1460, 1448, 1273, 1228, 1167, 1118, 1086, 1062, 1018, 981, 787 cm^{-1}. Anal. Calcd for $C_{32}H_{23}NO_2$: C, 84.74; H, 5.11; N, 3.09. Found: C, 84.50; H, 5.32; N, 2.89.

(±)-9′,10′-Dihydro-*cis*-2-cyano-3,3-diphenylspiro[furan-1,11′-9′,10′-ethanoanthracen]-5-one (16b). Compound **16b** was the only isomer isolated (as a white solid) from the aforementioned reaction mixture after it had been allowed to stand at 24 °C and stir for 24 h: mp 199–200 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.84 (d, 1 H, J = 7.4 Hz, aromatic), 6.79–7.42 (m, 18 H, aromatics, H1); 5.3 (s, 1 H, H9′), 4.11 (t, 1 H, J = 3.5 Hz, H10′), 2.10 (dd, 1 H, J = 14.1, 3.1 Hz, H11′), 1.40 (dd, 1 H, J = 14.1, 2.5 Hz, H12′); IR (KBr) 3040, 2943, 2215, 1710, 1489, 1470, 1468, 1440, 1288, 1260, 1075, 768 cm^{-1}. Anal. Calcd for $C_{32}H_{23}NO_2$: C, 84.74; H, 5.11; N, 3.09. Found: C, 84.48; H, 5.24; N, 2.98.

(±)-9′,10′-Dihydro-*trans*-2-cyano-*trans*-3-methylspiro-[furan-1,11′-9′,10′-ethanoanthracen]-5-one (17a). Diastereomer **17a** was isolated from a reaction using acetaldehyde to alkylate the enolate of **8**. This material was the major diastereomer isolated after a reaction period of 15 min at −72 °C. A small quantity of diastereomer **17c** is also produced. Pure **17a** was obtained as a white solid by chromatography on a racemic *N*-(3,5-dinitrobenzoyl)phenylglycine stationary phase using 5% isopropyl alcohol/hexane as the mobile phase: mp 205–208 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.08–7.44 (m, 8 H, aromatics), 4.95 (qt, 1 H, J = 5.6 H, H2), 4.49 (t, 1 H, J = 3.5 Hz, H9′), 4.29 (s, 1 H, H10′), 3.15 (d, 1 H, J = 5.6 Hz, H1), δ 2.48 (dd, 1 H, J = 13.0, 3.0 Hz, H11′), 2.18 (dd, 1 H, J = 13.0, 3.0 Hz, H12′), 1.62 (dd, 1 H, J = 5.6 Hz, CH_3); IR (KBr) 2945, 2928, 2240, 1788, 1470, 1460, 1395, 1182, 1172, 1131, 1125, 945, 765 cm^{-1}. Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.71; H, 5.67; N, 4.16.

(±)-9′,10′-Dihydro-*cis*-2-cyano-*cis*-3-methylspiro[furan-1,11′-9′,10′-ethanoanthracen]-5-one (17b). Diastereomer **17b** was isolated as the major product of the preceding reaction when the reaction mixture was kept at 24 °C for 24 h prior to workup. This material was isolated in pure form (white flakes) by chromatography on silica with 7:1 cyclohexane–ethyl acetate as a mobile phase. Isomer **17b** elutes after **17a**: mp 228–229 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48–7.59 (m, 1 H, aromatics), 7.12–7.36 (m, 7 H, aromatics), 4.77 (s, 1 H, H9′), 4.39–4.52 (m, 2 H, H2, H10′), 2.43 (d, 1 H, J = 4.8 Hz, H1), 2.17 (dd, 1 H, J = 12.6, 3.0 Hz, H11′), 1.94 (dd, 1 H, J = 12.6, 3.3 Hz, H12′), 1.57 (d, 3 H, J = 6.7 Hz, CH_3); IR (KBr) 3020, 2942, 2235, 1783, 1462, 1451, 1390, 1300, 1179, 1125, 948 cm^{-1}. Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 80.10; H, 5.55; N, 4.22.

(±)-9′,10′-Dihydro-*trans*-2-cyano-*cis*-3-methylspiro[furan-1,11′-9′,10′-ethanoanthracen]-5-one (17c). Diastereomer **17c** was isolated as a white solid by HPLC chromatograpy on a cyanopropyl column with a 5% isopropyl alcohol/hexane as a mobile phase from the same reaction mixture that afforded **17a** as the major product: mp 226–227 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.08–7.49 (m, 8 H, aromatics), 4.51 (t, 1 H, J = 3.2 Hz, H10′), 4.28–4.41 (m, 1 H, H2), 4.26 (s, 1 H, H9′), 3.91 (d, 1 H, J = 10.0 Hz, H1), 2.40 (dd, 1 H, J = 11.5, 3.3 Hz, H11′), 2.07 (dd, 1 H, J = 11.5, 2.3 Hz, H12′), 1.55 (d, 3 H, J = 6.0 Hz, CH_3); IR (KBr) 3075, 2960, 2240, 1780, 1455, 1385, 1310, 1181, 1088, 1067, 960 cm^{-1}. Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.58; H, 5.44; N, 4.49.

(±)-9′,10′-Dihydro-*trans*-2-cyano-*trans*-3-tridecylspiro-[furan-1,11′-9′,10′-ethanoanthracen]-5-one (18a). This diastereomer, formed by addition of tetradecylaldehyde to the enolate of **8**, was isolated as the major product by working up a reaction conducted at −72 °C for 15 min. The reaction also afforded a small amount of diastereomer **18b**. The overall yield of both products was 40%. Pure **18a** was isolated by chromatography on silica with 7:1 cyclohexane–ethyl acetate (**18a** elutes first) and recrystallization from hexane: mp 79–81° C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.08–7.42 (m, 8 H, aromatics), 4.70–4.84 (m, 1 H, H3), 4.48 (t, 1 H, J = 3.0 Hz, H10′), 4.30 (s, 1 H, H9′), 3.10 (d, 1 H, J = 5.6 Hz, H1), 2.46 (dd, 1 H, J = 13.5, 3.3 Hz, H11′), 2.15 (dd, 1 H, J = 13.5, 3.7 H, H12′), 1.80–2.09 (m, 1 H, H3), 1.67–1.88 (m, 1 H, H4), 1.40–1.65 (m, 1 H, H5), 1.29 (s, 21 H, alkyls), 0.90 (t, 3 H, J = 7.4 Hz, CH_3); IR (KBr) 2912, 2840, 2231, 1780, 1462, 1452, 1165, 1110, 760 cm^{-1}. Anal. Calcd for $C_{33}H_{41}NO_2$: C, 81.94; H, 8.54; N, 2.90. Found: C, 82.04; H, 8.54; N, 2.86.

(±)-9′,10′-Dihydro-*cis*-2-cyano-*cis*-3-tridecylspiro[furan-1,11′-9′,10′-ethanoanthracen]-5-one (18b). Diastereomer **18b** was isolated as the major product from the reaction as described for **18a** except that the reaction mixture was allowed to stand for 24 h at 24 °C. The minor amount of **18a** remaining was removed by chromatography as described above. Pure **18b** was recrystallized in heane and isolated as white flakes: mp 250–251 °C dec; ^1H NMR (200 MHz, $CDCl_3$) δ 7.46–7.59 (m, 2 H, aromatics), 7.05–7.38 (m, 6 H, aromatics), 4.75 (s, 1 H, H9′), 4.40 (t, 1 H, J = 3.2 Hz, H10′), 4.17–4.30 (m, 1 H, H2), 2.40 (d, 1 H, J = 4.8 Hz, H1), 2.16 (dd, 1 H, J = 11.5, 2.6 Hz, H11′), 1.93 (dd, 1 H, J = 11.5, 3.0 Hz, H12′), 1.93–2.13 (m, 1 H, H3), 1.60–1.79 (m, 1 H, H4), 1.24

(s, 22 H, alkyls), 0.88 (t, 3 H, J = 6.7 Hz, CH_3); IR (KBr) 2920, 2850, 2240, 1798, 1469, 1459, 1170, 765, 750 cm^{-1}. Anal. Calcd for $C_{33}H_{41}NO_2$: C, 81.94; H, 8.54; N, 2.90. Found: C, 81.85; H, 8.46; N, 2.95.

(±)-9,10-Dihydro-11-(*cis*-1-cyano-2-phenylvinyl)-9,10-ethanoanthracenecarboxylic Acid (19). To 0.14 g (0.37 mmol) of **14a** in 10 mL of anhydrous nitrogen purged THF was added a mixture of 0.39 mmol of LiOMe (formed by addition of 0.28 mL of 1.40 M *n*-BuLi to 0.39 mmol of anhydrous MeOH) in 10 mL of dry THF at −78 °C. The reaction was slowly warmed to −10 °C over 3 h whereupon a 10-mL aliquot was removed and worked up as described for **14a**. NMR examination of the crude product from this aliquot revealed the presence of **19**, a small amount of **14a** being detected as well. Pure **19** was obtained by allowing the remainder of the reaction mixture to warm slowly to 24 °C and to stand for 24 h. After isolation and workup, **19** was recrystallized from hexane to afford a white powder: mp 190–193 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 6.97–7.69 (m, 14 H, aromatics, H13), 5.11 (s, 1 H, H9), 4.38 (t, 1 H, J = 3.3 Hz, H10), 2.97 (dd, 1 H, J = 13.0, 3.3 Hz, H11), 2.20 (dd, 1 H, J = 13.0, 3.3 Hz, H12), IR (KBr) 3030, 2960, 2210, 1700, 1465, 1455, 1440, 1255, 1235, 740 cm^{-1}; mass calcd for $C_{26}H_{19}NO_2$ 377.1416, observed 377.1425. Anal. Calcd for $C_{26}H_{19}NO_2$: C, 82.74; H, 5.07; N, 3.71. Found: C, 82.34; H, 5.22; N, 3.60.

Acknowledgment. This work has been supported by grants from the National Science Foundation and from Eli Lilly and Co.

Phospholipid Studies of Marine Organisms. 22.[1] Structure and Biosynthesis of a Novel Brominated Fatty Acid from a Hymeniacidonid Sponge[†]

Wai-kwan Lam, Soonkap Hahn, Eser Ayanoglu, and Carl Djerassi*

Department of Chemistry, Stanford University, Stanford, California 94305

Received February 10, 1989

A new long-chain fatty acid, (5*E*,9*Z*)-6-bromo-5,9-hexacosadienoic acid (**1a**), was isolated from the phospholipids of a marine sponge of the family Hymeniacidonidae. Structure elucidation was accomplished by means of mass spectrometry and 2D-homonuclear (COSY-45) ^1H NMR spectroscopy. The configuration of the bromo-substituted double bond was established by lithiation followed by protonolysis. Incorporation experiments with radiolabeled precursors revealed that biological bromination was the terminal step in the biosynthesis of this unusual acid.

Introduction

Since the original studies of Litchfield and collaborators,[2] numerous unusual fatty acids have been isolated from marine sponges featuring exceptionally long carbon chains (C_{24}–C_{30}) with novel branching, unsaturation, and substituent patterns.[3] It is assumed[4-7] that phospholipids with such acyl components serve special biological functions in modulating the membrane properties of the organism. The recent discoveries[8-11] of brominated fatty acids in marine sponges are of particular interest, as the number of halogenated fatty acids found in marine organisms[8-12] is extremely small in comparison with the wide spectrum of halometabolites from the same source.[13] Unique physiological properties may, therefore, be associated with such acids.

The earliest report[12] of halogenated long-chain fatty acids in marine organisms dates back to 1977 when several chlorohydrins of palmitic and stearic acids were found in the total lipids of a jellyfish. Subsequently a dibrominated straight-chain C_{16} acetylenic acid—the first recorded representative of this class—was found in the marine sponge *Xestospongia muta*.[8] This was followed by the discovery of a monobrominated straight-chain C_{18} bisacetylenic acid from *Xestospongia testudinaria*[9] and six mono- and dibrominated straight-chain unsaturated C_9, C_{16}, and C_{18} acids from the same genus.[10] However, there was so far only one report[11] of brominated demospongic acids existing in the phospholipids of living organisms. Two C_{27} acids with the unique 5,9-diene pattern, iso/anteiso methyl branching, and the bromovinyl functionality were isolated from the marine sponges *Petrosia ficiformis* and *Petrosia hebes*, which appeared to contain also traces of the C_{28} homologues of the above two acids. It is significant that all marine brominated fatty acids identified to date contain a bromovinyl or dibromovinyl moiety.

Despite a growing list of around 1000 isolated marine halometabolites, the mechanisms whereby halogens (mainly chlorine and bromine) are incorporated into these molecules have received attention only in recent years,[14-21]

[†] Dedicated with respect and affection to the memory of Professor Edgar Lederer—a pioneer in the lipid field.

(1) Part 21: Gillan, F. T.; Stoilov, I. L.; Thompson, J. E.; Hogg, R. W.; Wilkinson, C. R.; Djerassi, C. *Lipids* **1988**, *23*(12), 1139–1145.
(2) (a) Jefferts, E.; Morales, R. W.; Litchfield, C. *Lipids* **1974**, *9*, 244–247. (b) Morales, R. W.; Litchfield, C. *Biochim. Biophys. Acta* **1976**, *431*, 206–216.
(3) Ayanoglu, E.; Kurtz, K.; Kornprobst, J. M.; Djerassi, C. *Lipids* **1985**, *20*, 141–144 and preceding papers in the series "Phospholipid Studies of Marine Organisms".
(4) Litchfield, C. In *Aspects of Sponge Biology*; Harrison, F. W., Cowden, R. R., Eds.; Academic Press: New York, 1976; pp 183–200.
(5) (a) Ayanoglu, E.; Duzgunes, N.; Wijekoon, W. M. D.; Djerassi, C. *Biochim. Biophys. Acta* **1986**, *863*, 110–114. (b) Ayanoglu, E.; Li, H.; Djerassi, C.; Duzgunes, N. *Chem. Phys. Lipids* **1988**, *47*, 165–175. (c) Li, H.; Duzgunes, N.; Ayanoglu, E.; Djerassi, C. *Chem. Phys. Lipids* **1988**, *48*, 109–117.
(6) Lawson, M. P.; Thompson, J. E.; Djerassi, C. *Lipids* **1988**, *23*, 741–749.
(7) Jain, M. K. *Introduction to Biological Membranes*; John Wiley & Sons: New York, 1988.
(8) Schmitz, F. J.; Gopichand, Y. *Tetrahedron Lett.* **1978**, 3637–3640.
(9) Quinn, R. J.; Tucker, D. J. *Tetrahedron Lett.* **1985**, *26*, 1671–1672.
(10) Hirsh, S.; Carmely, S.; Kashman, Y. *Tetrahedron* **1987**, *43*, 3257–3261.
(11) Wijekoon, W. M. D.; Ayanoglu, E.; Djerassi, C. *Tetrahedron Lett.* **1984**, *25*, 3285–3288.
(12) White, R. H.; Hager, L. P. *Biochemistry* **1977**, *16*, 4944–4948.
(13) Faulkner, D. J. *Nat. Prod. Rep.* **1987**, *4*, 539 and preceding reviews in the series.
(14) Neidleman, S. L.; Geigert, J. *Biohalogenation: Principles, Basic Roles and Applications*; Ellis Horwood: Chichester, 1986.

0022-3263/89/1954-3428$01.50/0