a melting point of 182-183.5 °C (lit. mp 184-185 °C).[22]

**9-Methyl-10-methoxyanthracene.** A solution of anthrone, excess potassium hydroxide, and methyl iodide were reacted together according to an original procedure of Meyer and Schlosser[23] as modified by Barnett and Cook.[24] Recrystallization from light petroleum ether yielded a product possessing a melting point of 138-142 °C (lit. mp 141-143 °C).[24]

**9-Methyl-10-cyanoanthracene.** The method of Fieser and Jones[25] was used to react 9-methylanthracene-10-carboxaldehyde with hydroxylamine to give the oxime. This, in turn, was converted to the desired product by the action of acetic anhydride.[26] The compound obtained had a melting point of 208-210 °C (lit. mp 209-210 °C).

**9-Methyl-10-acetylanthracene.** A standard sequence[27] was followed in which 9-methylanthracene, acetyl chloride, and $AlCl_3$ in a benzene solution reacted to yield the desired product. The compound formed melted between 131 and 135 °C (lit. mp 133-135 °C).

**9-Methyl-10-phenylanthracene.** The scheme outlined for preparation of 9,10-dimethylanthracene was utilized to synthesize the present compound from 9-phenylanthracene in two steps.[22] Recrystallization from benzene-ethanol yielded a product with a melting point of 105-107 °C (lit. mp 111-113 °C).

**9-Methyl-10-haloanthracenes.** Both the chlorine- and bromine-containing materials were synthesized via the method of Nonhebel et al.[29] Anhydrous cupric halides were prepared by drying the appropriate halide under reduced (aspirator) pressure and heating until all water was removed. The salt was then immediately transferred to carbon tetrachloride solutions of methylanthracene. The materials were allowed to react at a temperature of 78 °C, that of refluxing carbon tetrachloride, for 12 h. Immediate evolution of hydrogen halide was noted by holding litmus paper over the refluxing solution. The crude products were recrystallized from light petroleum ether. The 9-methyl-10-chloroanthracene obtained melted between 177 and 179.5 °C (lit. mp 180-181 °C) and the bromo analogue between 169 and 171 °C (lit. mp 170-172 °C).

**Kinetics.** Solutions consisting of fluorene, the appropriate anthracene, *p*-di-*tert*-butylbenzene, bromotrichloromethane, and bromobenzene were prepared in approximate ratios of 0.5:1:0.1:30:20. The solutions were each divided among several ampules. After nitrogen flushing during several successive freeze-thaw cycles, the ampules were sealed under a reduced pressure of nitrogen. With an ampule reserved for analysis of starting material concentrations, the remaining samples were immersed in a constant temperature (70.0 ± 0.1 °C) oil bath. An ultraviolet lamp was placed at a distance of 20 cm from the surface of the oil, the ampules being just under the oil's surface. After an appropriate duration of time, ranging from 1 to 4 h depending on a given substrate's proclivity to reaction, the ampules were cooled in a dry ice-acetone bath to quench reaction. The contents were subsequently transferred into NMR tubes and small amounts of $Me_4Si$ were added. Extents of reaction were ascertained by examining the areas of the aliphatic protons corresponding to unreacted fluorene and substituted anthracenes relative to the signal from the internal standard. These areas were converted by a computer program using standard kinetics methodology into relative rates of reaction.[30]

**Registry No.** 10-Methoxy-9-methylanthracene, 21992-33-6; 9,10-dimethylanthracene, 781-43-1; 10-phenyl-9-methylanthracene, 13425-08-6; 9-methylanthracene, 779-02-2; 10-chloro-9-methylanthracene, 19096-07-2; 10-bromo-9-methylanthracene, 23674-17-1; 10-acetyl-9-methylanthracene, 36778-18-4; 10-cyano-9-methylanthracene, 1467-01-2.

(23) L. Meyer and V. Schlosser, *Justus Liebigs Chemie*, **420**, 126 (1920).
(24) L. Barnett and C. Cook, *J. Chem. Soc.*, 2631 (1926)
(25) L. Fieser and S. Jones, *J. Am. Chem. Soc.*, **64**, 1667 (1942).
(26) M. Wawzonek and H. Hallum, *J. Org. Chem.*, **24**, 366 (1959).
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(28) S. Gibson, D. Mosnaim, R. C. Nonhebel, and J. A. Russell, *Tetrahedron*, **25**, 5047 (1969).
(29) D. Mosnaim, D. C. Nonhebel, and J. A. Russell, *Tetrahedron*, **25**, 3485 (1969).
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# α-Lithio-3-indolylacetate Synthons: Generation and Synthetic Utilization

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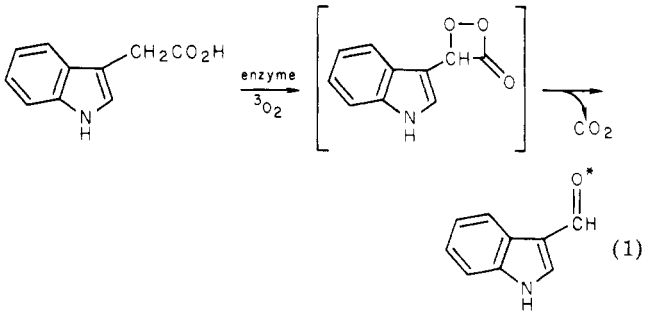
3-Indolyl-, (*N*-methyl-3-indolyl)-, and (*N*-methyl-2-methyl-3-indolyl)acetic acids are quantitatively α-lithiated directly with *n*-BuLi, while methyl (*N*-methyl-3-indolyl)acetate is quantitatively α-lithiated with lithium diisopropylamide (LDA) at -78 °C in THF. These useful synthons react readily with electrophiles such as alkyl halides, chlorosilanes, and ketones to afford the respective α-alkyl derivatives **1**, ketene silyl acetals **2**, and β-hydroxy acids **3**. Photosensitized oxygenation of the ketene silyl acetals **2** affords 1,2-diox-4-ene products through (2 + 4) cycloaddition with singlet oxygen.

Cilento and co-workers recently discovered[2] that in the peroxidase-catalyzed oxygenative decarboxylation of 3-indolylacetic acid the 3-indolecarboxaldehyde product is generated electronically excited and is presumed to be chemienergized through the corresponding α-peroxy lactone[3] (eq 1). This significant discovery enticed us to venture into the synthesis of model compounds of such intriguing dioxetane derivatives. For this purpose we




(1)

decided to employ the synthetic sequence shown in eq 2 which proved successful for the preparation of simple α-peroxy lactones.[4] For the preparation of the essential

(1) NIH Career Development Awardee (1975-1980).
(2) (a) Vidigal, C. C. C.; Zinner, K.; Duran, N.; Bechara, E. J. H.; Cilento, G. *Biochem. Biophys. Res. Commun.* **1975**, *65*, 138. (b) Duran, N.; Zinner, K.; Casadei de Baptista, R.; Vidigal, C. C. C.; Cilento, G. *Photochem. Photobiol.* **1976**, *24*, 383. (c) Vidigal, C. C. C.; Faljoni-Alario, A.; Duran, N.; Zinner, K.; Shimizu, Y.; Cilento, G. *Ibid.*, in press.
(3) Adam, W. *Adv. Heterocycl. Chem.* **1977**, *21*, 437.

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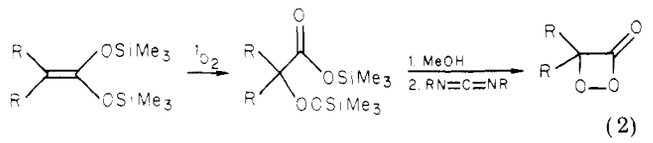
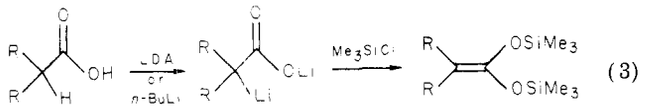


(2)

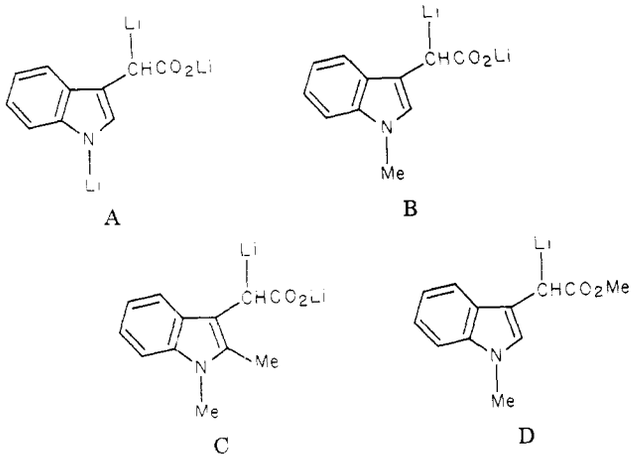
ketene bis(trimethylsilyl) acetals, α-lithiocarboxylates were utilized as a starting point, and are conveniently made by α-lithiation of the corresponding carboxylic acids (eq 3).



(3)

Consequently, we required the corresponding α-lithiocarboxylates derived from 3-indolylacetic acid, a potentially useful class of synthons.

We now report on the generation of the synthons A–D via lithiation of the appropriate derivative of 3-indolylacetic acid and their synthetic utilization.



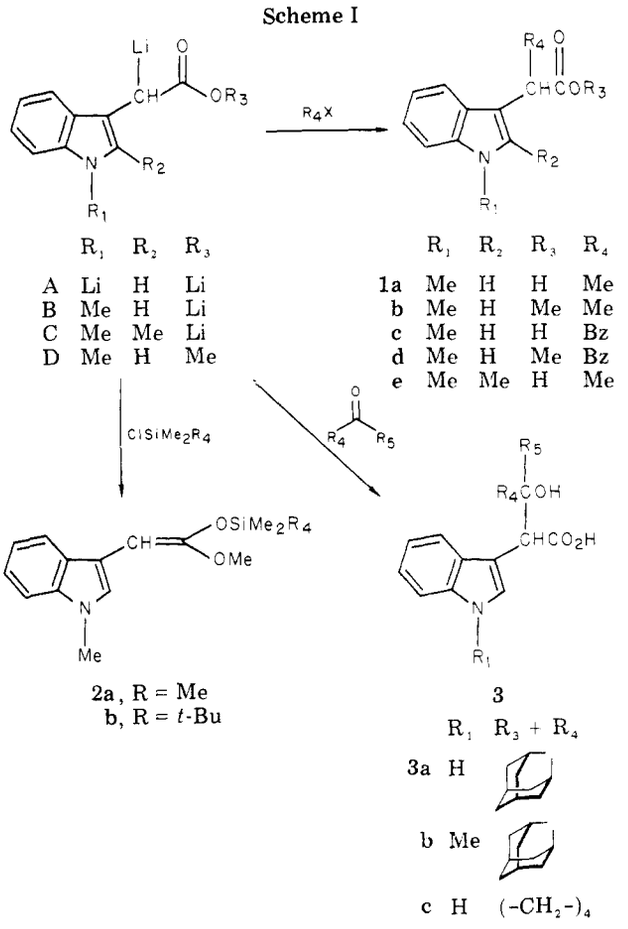
## Results and Discussion

**Generation of Synthons A–D and Electrophilic Substitution.** Treatment of 3-indolylacetic acid, its *N*-methyl derivative, or its 2-methyl-*N*-methyl derivative with the appropriate stoichiometric amounts of *n*-BuLi in THF at −78 °C afforded the respective α-lithiocarboxylates A–C essentially quantitatively, as confirmed by deuteration with excess $D_2O$. The characteristic pale yellow solutions of the α-lithiated substrates immediately discharged, and $^1H$ NMR analysis of the deuterated derivatives indicated that α-lithiation had taken place to better than 98%. These synthons were sufficiently stable even at −20 °C to permit handling at this temperature without deterioration.

Synthon D was generated from methyl (*N*-methyl-3-indolyl)acetate by treatment with lithium diisopropylamide (LDA) in THF at −78 °C. Again deuteration of the pale yellow solution confirmed quantitative formation of D; however, it was critical to handle this synthon at −78 °C since otherwise extensive decomposition would occur.

The synthons A through D were extremely reactive toward electrophiles such as alkyl halides, chlorosilanes, and ketones, and in Scheme I are summarized the respective alkylations, silylations, and ketonations. The yields, physical constants, and characteristic IR and $^1H$ NMR spectral data of the respective alkylated derivatives **1**, the ketene silyl acetals **2**, and α-hydroxy acids **3** are summarized in the Experimental Section. All new compounds exhibited satisfactory elemental analyses after silica gel chromatography and/or recrystallization from the appropriate solvent.

Scheme I



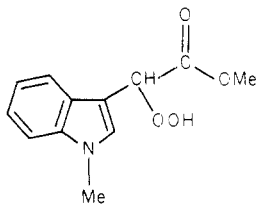
An exception was the ketene trimethylsilyl acetal **2a** derived from synthon D, which could not be distilled without decomposition, even under very high vacuum (ca. $10^{-3}$ torr), chromatographed on silylated silica gel or Florisil without hydrolysis even at −60 °C, or induced to crystallize at low temperatures. However, its characteristic ketene acetal C=C band at 1660 $cm^{-1}$, its $^1H$ NMR spectrum and an analogy to the hydrolytically more stable congener **2b** confirm our structure assignment. Still more problematic were our attempts to prepare the ketene bis(trimethylsilyl) acetals from synthon B. These extremely hydrolytically sensitive products could not be isolated without extensive decomposition even at low temperatures.

**Oxygenations.** Direct oxygenation with molecular oxygen was carried out on methyl α-lithio(*N*-methyl-3-indolyl)acetate (synthon D) since the corresponding α-hydroperoxy ester **8** had the best chance to survive. For example, analogous aliphatic and aromatic α-hydroperoxy esters have been isolated[5] and shown to be considerably more stable than the corresponding α-hydroperoxy acids. Indeed, on oxygenation at −78 °C and workup at subambient conditions, the expected α-hydroperoxy ester **8** was formed, as evidenced by its spectral data and iodometry; however, it proved thermally too labile to permit isolation and purification.

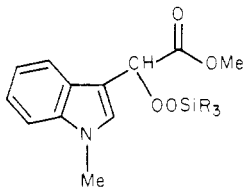
In view of these complications, we decided to employ singlet oxygenation of the ketene silyl acetals **2** as a synthetic route to the silyl-protected derivatives **9**. The latter have been shown to be considerably more stable than **8**.[6]

(4) Adam, W.; Alzerreca, A.; Liu, J.-C.; Yany, F. *J. Am. Chem. Soc.* **1977**, *99*, 5768.

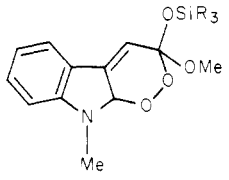
(5) (a) Konen, D. A.; Silbert, L. S.; Pfeffer, P. E. *J. Org. Chem.* **1975**, *40*, 3253. (b) Adam, W.; Cueto, O. *Ibid.* **1977**, *42*, 38. (c) Adam, W.; Cueto, O.; Ehrig, V. *Ibid.* **1976**, *41*, 370.



8



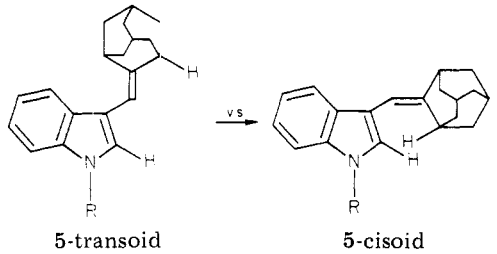
9



6b

Since the trimethyl derivative **2a** already gave insurmountable difficulties in its preparation and purification, we chose the hydrolytically more stable *tert*-butyldimethylsilyl acetal **2b**. On tetraphenylporphyrin-sensitized photooxygenation of **2b** at −78 °C, exclusively (2 + 4) cycloaddition took place to afford the 1,2-dioxene **6b** instead of the desired α-silylperoxy ester **9**. Its IR and $^1$H NMR spectral data confirm the proposed 1,2-diox-4-ene structure; but this material was too unstable to permit purification by low-temperature silica gel chromatography. Analogous cycloaddition behavior involving the indolyl moiety was recently observed[7] in the singlet oxygenation of β-(3-indolyl)styrene derivatives. Our result constitutes another example of the now general behavior of the singlet oxygen dienophile toward activated alkenes bearing aromatic substituents.[8]

To bypass this undesired singlet oxygenation course, we decided to prepare as a model system the 3-indolylalkene **5**, hoping that the bulky group would discourage the **5**-cisoid conformation and thereby prevent (2 + 4) cyclo-

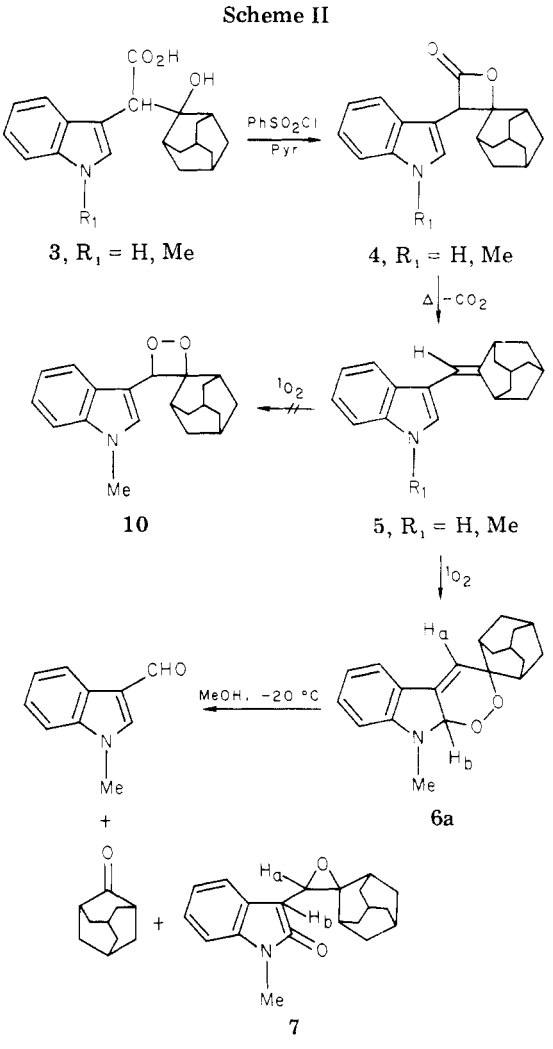


5-transoid 5-cisoid

addition as observed by Kondo et al.[7] for β-(*N*-methyl-3-indolyl)styrene and by us for the ketene silyl acetal **2b**. Fortunately the β-hydroxy acids **3**, which are conveniently accessible through ketonation of A and B, could be converted to the desired 3-indolylalkene **5** by β-lactonization with benzensulfonyl chloride in pyridine[9] and subsequent decarboxylation of the β-lactones **4** (Scheme II) on heating. The yields, physical constants, and spectral data are given in the Experimental Section.

Although inspection of Dreiding models suggested severe crowding between the 2-indolyl and the adamantyl bridgehead hydrogens and thus (2 + 2) cycloaddition to afford the corresponding 1,2-dioxetane **10**, photosensitized singlet oxygenation gave exclusively the (2 + 4) adduct **6a** at −78 °C (Scheme II). This 1,2-diox-4-ene was quite stable

Scheme II



3, $R_1$ = H, Me 4, $R_1$ = H, Me

10 5, $R_1$ = H, Me

6a

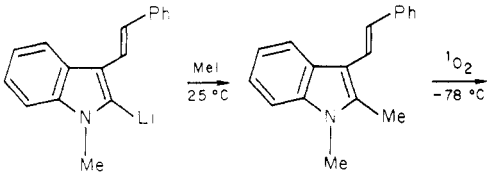
7

and could be fully characterized. However, in MeOH at −20 °C it decomposed into *N*-methyl-3-indolecarboxaldehyde, adamantanone, and the oxindole derivative **7**. Analogous behavior was observed by Kondo.[7] Efforts to rearrange the 1,2-diox-4-ene **6a** into the corresponding 1,2-dioxetane **10** by catalysis with silica gel[10] over a temperature range of −20 to 0 °C led only to the dioxetane cleavage products *N*-methyl-3-indolecarboxaldehyde and adamantanone.

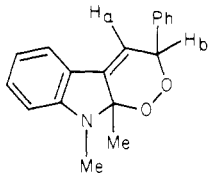
In order to force the prevalence of the transoid conformation, we tried to introduce a methyl substituent at the 2-position of the indolyl moiety of **5b**. While it was possible to lithiate **5b** at the 2-indolyl position, as confirmed through quantitative deuteration with $D_2O$, this lithio derivative resisted all efforts to be methylated with methyl iodide. Presumably, the adamantyl group exercises a considerable steric effect, preventing methylation. This supposition could be confirmed by demonstrating that the synthon E, prepared by lithiation of β-(*N*-methyl-3-indolyl)styrene with *n*-BuLi,[11] could be methylated with methyl iodide to afford alkene **5c**, as shown in eq 4. Photosensitized singlet oxygenation of alkene **5c** gave again the 1,2-diox-4-ene product **6c**. Apparently the methyl and phenyl substituents are not sufficient to suppress the ubiquitous (2 + 4) cycloaddition of singlet oxygen.

Although we have so far been unsuccessful in preparing 3-indolyl-substituted 1,2-dioxetanes, useful synthetic in-

(6) Adam, W.; del Fierro, J. *J. Org. Chem.* **1978**, *43*, 1159.
(7) Matsumoto, M.; Kondo, K. *J. Am. Chem. Soc.* **1977**, *99*, 2393.
(8) Foote, C. S.; Mazur, S.; Burns, P. A.; Lerdal, D. *J. Am. Chem. Soc.* **1973**, *95*, 586.
(9) (a) Adam, W.; Baeza, J.; Liu, J.-C. *J. Am. Chem. Soc.* **1972**, *94*, 2000. (b) Adam, W.; Fick, H.-H. *J. Org. Chem.* **1978**, *43*, 772. (c) *Ibid.* **1979**, *44*, 356. (d) Adam, W.; Arias, L. A. *Synthesis*, **1979**, 388.
(10) Schaap, A. P.; Burns, P. A.; Zaklika, K. A. *J. Am. Chem. Soc.* **1977**, *99*, 1270.
(11) Shirley, D. A.; Roussel, P. A. *J. Am. Chem. Soc.* **1953**, *75*, 375.




6c 5c




E (4)

termediates derived from 3-indolylacetic acid have been generated by direct α-lithiation. These synthons have been exploited for preparative purposes by demonstrating their reactivity toward electrophiles such as alkyl halides, chlorosilanes, and ketones. These results should be of general utility and interest for the synthetic elaboration of the indole skeleton.

## Experimental Section

All melting points and boiling points are uncorrected. Solvents and starting materials, the latter being either purchased from standard chemical suppliers or prepared according to known literature procedures, were purified to match the reported physical constants and spectral data. The infrared spectra were taken on a Perkin-Elmer Model 283 spectrophotometer and the $^1H$ NMR on a Hitachi Perkin-Elmer R-24B spectrometer. Elemental analysis were carried out by Atlantic Analytical Laboratories. Room temperature was ca. 30 °C unless otherwise specified.

**Lithiations. Lithium 1,α-Dilithioindole-3-acetate (A).** A 100-mL, two-necked, round-bottomed flask equipped with a magnetic spinbar and a rubber septum was connected to a nitrogen manifold, evacuated, and subsequently flushed with dry nitrogen. While under a positve nitrogen pressure, the reaction vessel was charged by means of a syringe with indole-3-acetic acid (2.9 mmol, unless otherwise noted) in 50 mL of dry THF (freshly distilled from benzophenone ketyl radical). By means of a dry ice/acetone bath, the reaction flask was cooled to −78 °C, and while the mixture was stirred vigorously, 2 mol of *n*-butyllithium in *n*-hexane was added dropwise with the help of a syringe and the mixture stirred at −78 °C for 1 h. A slightly yellow solution of lithium *N*-lithioindole-3-acetate resulted, which exhibited a methyl iodide assay of better than 99% N-lithiation by NMR. To the *N*-lithiocarboxylate solution was added dropwise 2 mol of *n*-BuLi (100% excess) by means of a syringe, and the mixture was immediately warmed to −40 °C. During this stage the slightly yellow solution turned intense yellow. The mixture was stirred for 80 min at −40 °C to complete the α-lithiation.

A deuterium oxide assay for the α-lithiation was done by allowing the intense yellow solution to warm up to −20 °C and ca. a 200 molar excess of deuterium oxide (99.8% deuterium) was added by means of a syringe. The yellow color immediately disappeared. After the mixture was stirred for 5 min at −20 °C, the solvent was rotoevaporated (25 °C, 30 mm), the residue was acidified with 10% HCl and extracted with ether (3 × 10 mL), and the combined ether extracts were dried over $MgSO_4$. The ether was rotoevaporated (25 °C, 60 mm), and NMR analysis of the crude α-deuterated acid gave better than 98% deuteration.

**Lithium α-lithiocarboxylates B and C** were prepared by a method similar to that described above by using 1-methyl- or 1,2-dimethylindole-3-acetic acid and *n*-butyllithium.

**Methyl α-Lithiocarboxylate D.** A 100-mL, two-necked, round-bottomed flask equipped with a spinbar, a rubber septum, and a nitrogen manifold was evacuated while flame-drying and subsequently flushed with dry nitrogen. While under positive nitrogen pressure, a solution of 6.5 mmol of dry diisopropylamine (freshly distilled from $CaH_2$) in 50 mL of dry THF (freshly distilled from benzophenone ketyl radical) was syringed into the flask and cooled to −78 °C by means of a dry ice/acetone bath. While the mixture was stirred magnetically, 4.8 mL of *n*-butyllithium (1.58 N) was syringed dropwise into the flask. The solution was stirred for an additional 10 min at −78 °C, warmed up to room temperature, and kept at room temperature for 30 min. The lithium diisopropylamide (LDA) solution was again cooled to −78 °C by means of a dry ice/acetone bath, and 5.5 mmol of methyl 1-methylindole-3-acetate in 2 mL of dry THF was syringed dropwise into the LDA solution with stirring. A clear yellow color of α-lithiocarboxylate resulted, which exhibited a deuterium oxide assay of better than 98% α-lithiation.

**β-(*N*-Methyl-2-lithio-3-indolyl)styrene (E).** A 100-mL, two-necked, round-bottomed flask equipped with a spinbar, a rubber septum, and a nitrogen manifold was evacuated while being flame-dried and subsequently flushed with dry nitrogen. While under positive nitrogen pressure, a solution of 1.20 mmol of β-(*N*-methyl-3-indolyl)styrene in 20 mL of dry THF was syringed in, and the flask was surrounded with a water bath. While the mixture was being stirred magnetically, 4.8 mmol of *n*-BuLi in hexane was syringed in dropwise, and the mixture was stirred at 25 °C for 30 min. A dark purple solution of β-(*N*-methyl-2-lithio-3-indolyl)styrene (E) resulted, which exhibited a methyl iodide assay of better than 98% of 2-lithiation by NMR.

**Alkylation. 2-(*N*-Methyl-3-indolyl)propionic Acid (1a) via Methylation of Synthon A.** To the above-prepared 1,α-dilithiocarboxylate A solution in THF was added dropwise, with magnetic stirring and cooling at 0 °C, methyl iodide (tenfold excess based on carboxylate) by means of a syringe, and the mixture was stirred magnetically at 0 °C for 30 min, followed by warm-up to room temperature and stirring for an additional 2 h at room temperature. Afterward the solvent and excess $CH_3I$ were rotoevaporated (25 °C, 80 mm), and the residue was treated with 20 mL of $H_2O$, washed with ether (2 × 5 mL), acidified with 10% HCl, and extracted with ether (4 × 10 mL), and the combined ether extracts were dried over $MgSO_4$. Rotoevaporation (25 °C, 65 mm) of the solvent from the filtrate gave product **1a** in 67% yield; mp 112–113 °C (lit.[12] mp 111–113 °C).

**2-(*N*-Methyl-3-indolyl)propionic Acid (1a) via Methylation of Synthon B.** The above-prepared α-lithiocarboxylate B solution in THF was treated with excess $CH_3I$ as described above, affording product **1a** in 60% yield.

**2-(*N*-Methyl-3-indolyl)-3-phenylpropionic Acid (1c)[13] via Benzylation of Synthon B.** To the above-prepared α-lithiocarboxylate B solution in THF was added dropwise, with magnetic stirring and cooling at −20 °C, freshly distilled benzyl bromide (fivefold excess based on carboxylate) by means of a syringe. After being stirred for 30 min at −20 °C, the mixture was allowed to warm to room temperature and stirred for 1.5 h. The solvent was rotoevaporated (25 °C, 20 mm), the residue was treated with water (20 mL), washed with ether (3 × 5 mL), acidified with 10% HCl, and extracted with ether (3 × 10 mL), and the combined ether extracts were dried over $MgSO_4$. Rotoevaporation of the solvent gave a brown solid which was purified by recrystallization from acetone–hexane: mp 162–163.5 °C; yield 62%; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 2.90–3.42 (2 H, m, $CH_2$), 3.61 (3 H, s, $NCH_3$), 4.08 (1 H, m, CH), 7.01 (5 H, s, $C_6H_5$), 6.80–7.65 (5 H, m, indolyl); IR (KBr) 1690 $cm^{-1}$ (C=O).

**2-(*N*-Methyl-2-methyl-3-indolyl)propionic Acid (1e)[13] via Methylation of Synthon C.** Into the above prepared α-lithiocarboxylate C solution was syringed methyl iodide (tenfold excess based on carboxylate), and the mixture was stirred at −40 °C for 30 min, followed by warm-up to room temperature and stirring for 2 h at room temperature. Workup of the reaction mixture as described above gave the product **1e** in 72% yield: mp 170–170.5 °C ($CH_2Cl_2$–hexane); $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 1.55 (3 H, d, $CH_3CH$), 2.32 (3 H, s, $CH_3$), 3.55 (3 H, s, $NCH_3$), 3.93 (1 H, q, CH), 6.82–7.65 (4 H, m, indolyl), 9.05 (1 H, br s, $CO_2H$); IR (KBr) 1680 $cm^{-1}$ (C=O).

**Methyl 2-(*N*-Methyl-3-indolyl)propionate (1b)[13] via Methylation of Synthon D.** Into the freshly prepared (as described above) α-lithiocarboxylate D solution was syringed methyl iodide (12-fold excess based on carboxylate), and the mixture was stirred at −78 °C for 1 h. After warm-up to room temperature the mixture

(12) Julia, M.; Lenzi, J. *Bull. Soc. Chim. Fr.* **1962**, 1051.
(13) Satisfactory combustion analytical data were obtained for this substance.

was stirred for 1 h. The solvent was rotoevaporated (25 °C, 10 mm), the residue was treated with water (10 mL), neutralized with 10% HCl, and extracted with ether (4 × 10 mL), and the combined ether extracts were dried over $MgSO_4$. Rotoevaporation (25 °C, 20 mm, 1 mm) of the filtrate gave a brown oil, which was purified by column chromatography on silica gel, eluting with benzene: yield 67%; $^1H$ NMR ($CCl_4$, $Me_4Si$) δ 1.47 (3 H, d, $J$ = 7.2 Hz, $CCH_3$), 3.43 (6 H, s, $OCH_3$ and $NCH_3$), 3.60–3.95 (1 H, q, $J$ = 7.2 Hz, CH), 6.61–7.41 (5 H, m, aromatic); IR ($CCl_4$) 1740 $cm^{-1}$ (C=O).

**Methyl 2-(*N*-Methyl-3-indolyl)-3-phenylpropionate (1d)[13] via Benzylation of Synthon D.** Following the above procedure, **1d** was prepared by using benzyl bromide as the electrophile: yield 94%; $^1H$ NMR ($CCl_4$, $Me_4Si$) δ 2.89–3.37 (2 H, m, $CH_2$), 3.40 and 3.49 (6 H, s, $OCH_3$ and $NCH_3$), 3.80–4.05 (1 H, m, CH), 6.91 (5 H, s, $C_6H_5$), 6.25–7.08 and 7.38–7.48 (5 H, m, indolyl); IR ($CCl_4$) 1765 $cm^{-1}$ (C=O).

**β-(*N*-Methyl-2-methyl-3-indolyl)styrene (5c)[13] via Methylation of Synthon E.** To the freshly prepared β-(*N*-methyl-2-lithio-3-indolyl)styrene (E) in THF was added dropwise, with magnetic stirring at 25 °C, methyl iodide (tenfold excess based on E) by means of a syringe, the mixture was stirred at 25 °C for 1 h. The solvent was rotoevaporated (25 °C, 2 mm), the residue was treated with water (20 mL), neutralized with 10% HCl, and extracted with ether (3 × 15 mL), and the combined ether extracts were dried over anhydrous $Na_2SO_4$. Rotoevaporation (25 °C, 2 mm) of the filtrate gave a yellow solid, which was subjected to column chromatography (on silica gel, eluting with $CH_2Cl_2$–hexane, 1:1) followed by purification by recrystallization from $CH_2Cl_2$–hexane: mp 134.5–135 °C; yield 79%; $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 2.40 (3 H, s, $CH_3$), 3.53 (3 H, s, $NCH_3$), 6.95–8.10 (11 H, m, indolyl, phenyl, and vinyl); IR (KBr) 1630 $cm^{-1}$ (C=C).

**Silylations. *N*-Methyl-3-indolylketene Methyl Trimethylsilyl Acetal (2a) via Trimethylsilylation of Synthon D.** Into the freshly prepared α-lithiocarboxylate D solution was syringed within 1 h with stirring at −78 °C the trimethylchlorosilane (twofold excess based on carboxylate), which was previously purged with dry $N_2$ to displace adventitious HCl. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 3 h, and the THF was rotoevaporated (25 °C, 20 mm). The residue was triturated with dry benzene (2 × 20 mL, freshly distilled from benzophenone ketyl radical) and filtered under nitrogen pressure. The combined benzene triturates were rotoevaporated (25 °C, first at 20 mm and subsequently at 1 mm), giving the ketene acetal **2a** in 91% yield. This ketene acetal was extremely hygroscopic, and purification by distillation or low-temperature column chromatography on silica gel or Florisil was unsuccessful: $^1H$ NMR ($CCl_4$, $Me_4Si$ as external standard) δ 0.30 (9 H, s, $Si(CH_3)_3$), 3.50 (6 H, s, $OCH_3$ and $NCH_3$), 4.69 (1 H, s, vinyl), 6.60–6.90 and 7.06–7.32 (5 H, m, indolyl); IR ($CCl_4$) 1660 $cm^{-1}$ (C=C).

***N*-Methyl-3-indolylketene Methyl *tert*-Butyldimethylsilyl Acetal (2b)[13] via *tert*-Butyldimethylsilylation of Synthon D.** The freshly prepared α-lithiocarboxylate D solution was warmed to −40 °C, and with stirring at −40 °C was added dimethyl-*tert*-butylsilyl chloride (50% excess based on carboxylate) in 8 mL of dry THF. The mixture was stirred magnetically at −40 °C for 1 h, followed by warm-up to room temperature and stirring for 1 h. After rotoevaporation (25 °C, 10 mm) of the solvent the residue was worked up as above, and the crude product was purified by distillation at reduced pressure: bp 148 °C (0.02 mm); yield 46%; $^1H$ NMR ($CCl_4$, $Me_4Si$ as external standard) δ 0.28 (6 H, s, $Si(CH_3)_2$), 0.97 (9 H, s, $SiC(CH_3)_3$), 3.43 and 3.53 (6 H, s, $OCH_3$ and $NCH_3$), 4.67 (1 H, s, vinyl), 6.46–7.30 (5 H, m, indolyl); IR ($CCl_4$) 1670 $cm^{-1}$ (C=C).

**Ketonation. β-Hydroxy Acid 3a[13] via Reaction of Adamantanone with Synthon A.** To the freshly prepared α-lithiocarboxylate A solution was added dropwise, with magnetic stirring and cooling at −30 °C, 2-adamantanone (fivefold excess based on carboxylate) in 8 mL of dry THF by means of a syringe. After being stirred for 30 min at −30 °C, the mixture was stirred at 0 °C for 1.5 h. The solvent was rotoevaporated (25 °C, 10 mm), the residue was treated with 20 mL of $H_2O$, washed with ether (3 × 5 mL), acidified with 10% HCl, and extracted with ether (3 × 20 mL), and the combined ether extracts were dried over $MgSO_4$. Rotoevaporation (25 °C, 55 mm) of the filtrate afforded a light brown solid, which was purified by recrystallization from EtOAc–hexane: mp 228–229 °C dec; yield 57%; $^1H$ NMR ($CD_3SOCD_3$, $Me_4Si$) δ 1.10–2.30 (14 H, m, adamantyl), 4.51 (1 H, s, CH), 6.78–7.62 (5 H, m, indolyl), 10.95 (1 H, br s, $CO_2H$); IR (KBr) 1680 $cm^{-1}$ (C=O).

**β-Hydroxy Acid 3b[13] via Reaction of Adamantanone with Synthon B.** To the freshly prepared α-lithiocarboxylate B solution was added dropwise, with magnetic stirring and cooling at −20 °C, 2-adamantanone (fivefold excess based on carboxylate) in 8 mL of dry THF, and the mixture was stirred magnetically at −20 °C for 30 min, followed by warm-up to room temperature and stirring for 16 h. The workup of the reaction mixture was carried out as described above, giving the product **3b** in 63% yield: mp 172–174 °C dec (EtOAc–hexane); $^1H$ NMR ($CD_3SOCD_3$, $Me_4Si$) δ 1.00–2.30 (14 H, m, adamantyl), 3.63 (3 H, s, $NCH_3$), 4.47 (1 H, s, CH), 6.80–7.55 (5 H, m, indolyl); IR (KBr) 1680 $cm^{-1}$ (C=O).

**β-Hydroxy Acid 3c[13] via Reaction of Cyclopentanone with Synthon A.** The β-hydroxy acid **3c** was prepared according to the procedure described above but by using cyclopentanone: yield 57% mp 170–173 °C dec (EtOAc–hexane); $^1H$ NMR ($CD_3SOCD_3$, $Me_4Si$) δ 1.28–1.81 (8 H, m, c-$C_5H_8$), 3.97 (1 H, s, CH), 6.78–7.53 (5 H, m, indolyl), 10.95 (1 H, br s, $CO_2H$); IR (KBr) 1675 $cm^{-1}$ (C=O).

**General Method for the Preparation of β-Lactones 4 via Cyclization of β-Hydroxy Acids 3.** The β-hydroxy acid **3** (1 mmol) in 5 mL of dry pyridine (freshly distilled from $CaH_2$) was syringed into a 50-mL, two-necked, round-bottomed flask under dry nitrogen and cooled to 0 °C, and benzenesulfonyl chloride (2 mmol) was syringed in. The mixture was stirred at 0 °C for 1 h, stored overnight in the freezer, poured onto four volumes of crushed ice, and extracted with methylene chloride (3 × 15 mL). The combined extracts were washed with saturated sodium bicarbonate solution (3 × 15 mL) and with water (3 × 15 mL) and dried over $MgSO_4$. Rotoevaporation (25 °C, first at 30 mm and subsequently at 0.2 mm) gave the crude β-lactone which was recrystallized from the appropriate solvent.

The β-lactone **4a** was prepared in 62% yield:[13] mp 123–124 °C dec (EtOAc–hexane); $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 0.90–2.30 (14 H, m, adamantyl), 4.87 (1 H, s, CH), 6.80–7.50 (5 H, m, indolyl); IR (KBr) 1815 $cm^{-1}$ (C=O).

The β-lactone **4b** was prepared in 81% yield:[13] mp 133 °C dec (EtOAc–hexane); $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 1.00–2.30 (14 H, m, adamantyl), 3.63 (3 H, s, $NCH_3$), 4.47 (1 H, s, CH), 6.80–7.55 (5 H, m, indolyl); IR (KBr) 1815 $cm^{-1}$ (C=O). Mass spectra of both β-lactones **4a** and **4b** showed an M − $CO_2$ peak.

**General Procedure for the Preparation of Olefin 5 via Decarboxylation of β-Lactone 4.** A Pyrex tube (10-cm length, 1-cm diameter), charged with the β-lactone **4** and provided with a gas-outlet tube, was heated to 130–140 °C in an oil bath until cessation of $CO_2$ evolution. The olefin thus obtained was recrystallized from the appropriate solvent.

The olefin **5a** was prepared in 100% yield:[13] mp 159 °C (EtOAc–hexane); $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 1.75–2.00, 2.45–2.70, and 3.00–3.20 (12 H, 1 H, 1 H, m, adamantyl), 6.10 (1 H, s, vinyl), 6.90–7.55 (5 H, m, indolyl).

The olefin **5b** was prepared in 100% yield:[13] mp 97 °C ($CH_3OH$–hexane); $^1H$ NMR ($CDCl_3$, $Me_4Si$) δ 1.70–2.10, 2.32–2.62, and 2.95–3.16 (12 H, 1 H, 1 H, m, adamantyl), 3.62 (3 H, s, $NCH_3$), 6.03 (1 H, s, vinyl), 6.71–7.51 (5 H, m, indolyl).

**Photosensitized Oxygenations. General Photoxygenation Procedure.** A 50-mL, two-necked, round-bottomed flask equipped with a magnetic spinbar and a rubber septum was connected to an oxygen manifold. The flask was flame-dried under reduced pressure while being flushed with dry oxygen and was charged with a solution of 1 mmol of substrate in 5 mL of dry $CH_2Cl_2$ (freshly distilled from $P_2O_5$) containing 1.0 mg of tetraphenylporphyrin (TPP). The solution was cooled to −78 °C with a dry ice/acetone bath, and the contents were irradiated directly with a 400-W sodium lamp (General Electric) while being stirred at −78 °C. The reaction progress was monitored periodically by $^1H$ NMR by following the disappearance of the vinyl protons at δ 6.03 for **5b** and δ 4.67 for **2b**. Usually within 2 h photooxygenation was completed. The solvent was rotoevaporated (0 °C, 2 mm), and the product was submitted to purification.

The 1,2-diox-4-ene **6a** was prepared in 73% yield:[13] mp 105–106 °C ($CH_2Cl_2$–hexane); $^1H$ NMR ($CCl_4$, $Me_4Si$) δ 1.81–2.21 (14 H,

m, adamantyl), 2.78 (3 H, s, $NCH_3$), 5.51 (1 H, d, $J_{ab}$ = 2.1 Hz, $H_a$ or $H_b$), 6.11 (1 H, d, $J_{ab}$ = 2.1 Hz, $H_b$ or $H_a$), 6.20–6.98 (4 H, m, indolyl); IR ($CCl_4$) 1610 (C=C).

The 1,2-diox-4-ene **6b**, prepared in over 90% yield, was too unstable for combustion analysis: $^1H$ NMR ($CCl_4$, $Me_4Si$ as external standard) $\delta$ 0.17 (6 H, s, $Si(CH_3)_2$), 0.88 (9 H, s, $SiC(CH_3)_3$), 2.80 (3 H, s, $NCH_3$), 3.20 (3 H, s, $OCH_3$), 5.27–5.48 (2 H, m, vinyl and CH), 6.16–7.00 (4 H, m, indolyl); IR ($CCl_4$) 1620 $cm^{-1}$ (C=C).

The 1,2-diox-4-ene **6c** was prepared in 30% yield (based on NMR analysis): $^1H$ NMR ($CCl_4$, $Me_4Si$) 1.60 (3 H, s, $CH_3$), 2.68 (3 H, s, $NCH_3$), 5.32 (1 H, d, $J_{ab}$ = 2.0 Hz, $H_a$ or $H_b$), 5.68 (1 H, d, $J_{ab}$ = 2.0 Hz, $H_b$ or $H_a$), 6.20–7.45 (9 H, m, aromatic); IR ($CCl_4$) 1605 $cm^{-1}$ (C=C).

**Methanol Treatment of Dioxane 6a.** A 50-mL, two-necked, round bottomed flask equipped with a spinbar and a rubber septum was charged with 171 mg (0.5 mmol) of dioxene **6a** and connected to a nitrogen manifold. The flask was evacuated, subsequently flushed with nitrogen, and cooled to −10 °C with a dry ice/methanol bath. Dry methanol (35 mL) which had been cooled to −20 °C was syringed in, and the mixture was stirred at −10 °C for 3.5 h. The solvent was rotoevaporated (5 °C, 1 mm), and NMR analysis of the crude product showed that the dioxene **6a** was converted to *N*-methylindole-3-carboxaldehyde (38%), 2-adamantanone (38%), and oxindole compound **7** (62% yield based on dioxene **6a** used). The latter was isolated by silica gel chromatography, eluting with $CH_2Cl_2$–EtOAc, 1:2: mp 222–225 °C ($CHCl_3$–hexane); $^1H$ NMR ($CDCl_3$, $Me_4Si$) $\delta$ 0.88–2.53 (14 H, m, adamantyl), 3.06 (3 H, s, $NCH_3$), 2.90 (1 H, d, $J_{ab}$ = 8.4 Hz, $H_a$ or $H_b$), 3.35 (1 H, d, $J_{ab}$ = 8.4 Hz, $H_b$ or $H_a$), 6.41–7.21 (4 H, m, indolyl); IR ($CHCl_3$) 1700 $cm^{-1}$ (C=O); mass spectrum *m/e* (relative intensity) 309 (M, 43), 159 (100).

**Silica Gel Treatment of Dioxene 6a.** A 50-mL, two-necked, round-bottomed flask equipped with a magnetic spinbar and a rubber septum was charged with 200 mg of silica gel and connected to a nitrogen manifold. The flask was flame-dried under reduced pressure while being flushed with dry nitrogen and was cooled to −20 °C by means of a dry ice/methanol bath. The dioxene **6a** (25 mg) in 10 mL of dry $CH_2Cl_2$ (freshly distilled from $P_2O_5$) was syringed in, and the mixture was stirred at −20 °C for 2 h. The silica gel was filtered off under a nitrogen atmosphere, and the solvent was rotoevaporated (5 °C, 2 mm). NMR analysis of the crude product showed that the dioxene **6a** was converted to *N*-methylindole-3-carboxaldehyde and 2-adamantanone quantitatively.

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# The $\pi$–$\pi$ Interaction between Nitrile and Ethylene Functionalities

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The axial/equatorial free-energy difference for 3-cyano-1-methylenecyclohexane-2,2,4,4,6,6-$d_6$ is 0.26 kcal/mol in $CF_2Cl_2$ and 0.07 kcal/mol in $CHFCl_2$ at −102 °C in favor of the equatorial conformer. The decreased equatorial preference in the polar, hydrogen-bonding solvent results from a less repulsive interaction between the 3-substituent and the 1-*exo*-methylene group. For the low-polarity solvent ($CF_2Cl_2$), the equatorial preference of cyano in the *exo*-methylene system is about the same as that in cyanocyclohexane (0.24 kcal/mol), which lacks the $\pi$–$\pi$ interaction in the axial conformation. These results contrast with polar, lone-pair-containing substituents such as methoxyl, which have dramatically increased equatorial preferences in the *exo*-methylene systems compared to their cyclohexyl counterparts. The $\pi$–$\pi$ interaction between the cyano group and the $C{=}CH_2$ group appears to offer very little repulsion in comparison with the strong electrostatic interactions between methoxyl, hydroxyl, or thiomethyl and the same $C{=}CH_2$ group.

Interactions between functional groups containing $\pi$ electrons have traditionally been studied by their effects on electronic and photoelectronic spectra. In a phenomenological sense, these interactions may also be studied through their influence on conformational equilibria. It is necessary to construct a molecular system with two available conformations, one in which the $\pi$-containing functionalities are forced together and the other in which they are forced apart. The conformational equilibrium constant would be interpreted by reference to similar equilibria lacking the $\pi$ electrons.

We have recently described a system designed for the study of the interaction between the carbon–carbon double bond and either groups that are fully saturated and bonding (e.g., $CH_3$) or groups that contain nonbonding electrons (e.g., $CH_3O$ or $CH_3S$).[2] The $\pi$ electrons are located in an *exo*-methylene group on a cyclohexane ring, and the interacting group is located at the 3-position. The

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