Conformationally Rigid Analogues of Aldose Reductase Inhibitor, Tolrestat. Novel Syntheses of Naphthalene-Fused γ-, δ-, and ε-Lactams

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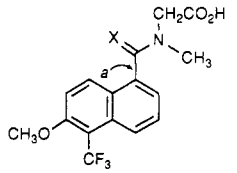
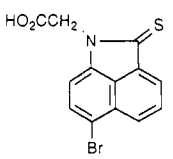
Cyclic analogues (**4–6**) of tolrestat (**1**) and oxotolrestat (**2**) were prepared by employing novel synthesis routes for the formation of the required γ-, δ-, and ε-lactams. In this regard 2,3,4,5-tetrahydro-9-methoxy-1*H*-naphth[1,2-*c*]azepin-1-one, **7**, and 3,4-dihydro-8-methoxybenz[*h*]isoquinolin-1(2*H*)-one, **8**, were prepared from a common precursor, namely 2,3-dihydro-7-methoxy-4(1*H*)-phenanthrenone, **13**, and further elaborated to compounds **4a–b** and **5a–d**, respectively. Compounds **6a–b** were prepared from a tolrestat precursor, 5-methyl-2-methoxy-1-(trifluoromethyl)naphthalene, **35**. Six- and seven-membered lactam acetic acid methyl esters, **29**, resisted vigorous thioamidation conditions; therefore, the corresponding thiolactam analogues of **4** and **5** could not be prepared. However, thioamidation was achieved in the five-membered ring series, leading to thiolactam **6b**. Lactams in the series **4** or **5** were considerably weaker than **1** or **2** as inhibitors of bovine lens aldose reductase although thiolactam **6b** had high inhibitory activity.

Tolrestat (**1**)[1] is an orally effective aldose reductase inhibitor which is currently marketed under the proprietary trade name Alredase for the treatment of diabetic complications.[2,3a] The amide analogue **2** of tolrestat (referred to as oxotolrestat) is also a potent aldose reductase inhibitor, albeit less active orally than tolrestat.[4] These compounds exist in solution as pairs of rotamers; however, it is believed that the biologically active rotamers have their acetic acid side chains cis to their respective carbonyl moieties. The basis of this belief stems from the conformationally fixed thionaphthostyrils, for example **3**,[3] which were also shown to have strong aldose reductase inhibitory properties. The cis rotamer is the one observed in the X-ray crystal structure of the 5-((trifluoromethyl)thio) analogue of tolrestat.[5]

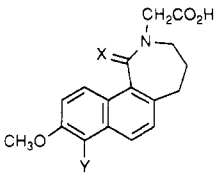


1, X=S, Tolrestat
2, X=O, Oxo-tolrestat

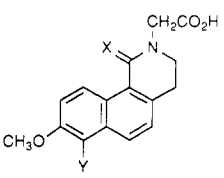


3

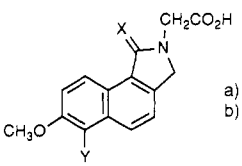
We wished to prepare cyclic analogues of **1** and **2** as shown by **4–6** (X = O, S; Y = CF_3) in which the amide nitrogen is tethered to the 2-position of the naphthalene ring by an alkyl chain of varying length. Although the new lactam ring of derivatives **4–6** would preclude the formation of rotamers, it would also severely restrict the rotation of the carbonyl–naphthalene bond (bond a of **1**). In fact, compound **6** with a lactam ring size of five atoms would force the amide moiety to be nearly coplanar with the naphthalene nucleus and/or distort this nucleus from planarity. By comparison, the amide side chain of **1** or **2** prefers an orientation that is nearly perpendicular to the naphthalene nucleus.[5] The ring constraints imposed upon cyclic analouges **4–6** could therefore have a dramatic effect on the aldose reductase inhibitory activity.



4
a) X = O, Y = H
b) X = O, Y = Br



5
a) X = O, Y = H
b) X = O, Y = Br
c) X = O, Y = I
d) X = O, Y = CF_3



6
a) X = O, Y = CF_3
b) X = S, Y = CF_3

Although there were scattered reports on the preparation of the tetrahydro-2*H*-naphth[1,2-*c*]azepines[6] related to **4**, tetrahydrobenz[*h*]isoquinolines[7] related to **5**, and dihydro-1*H*-benz[*e*]isoindoles[8] related to **6**, none of the synthesis were general or easily amenable to the type of substituted derivatives we required. We therefore needed to develop and implement new synthesis strategies in order to prepare our target compounds. We report here novel syntheses of the above mentioned heterocyclic ring systems

(1) Sestanj, K.; Bellini, F.; Fung, S.; Abraham, N.; Treasurywala, A.; Humber, L.; Simard-Duquesne, N.; Dvornik, D. *J. Med. Chem.* **1984**, *27*, 255.

(2) For recent reviews on aldose reductase, the polyol pathway hypothesis and their role in diabetic complications, see: (a) Kador, P. F.; Robinson, W. G.; Kinoshita, J. H. *Annu. Rev. Pharmacol. Toxicol.* **1985**, *25*, 691. (b) Kador, P. F.; Kinoshita, J. H.; Sharpless, N. E. *J. Med. Chem.* **1985**, *28*, 841. (c) Benfield, P. *Drugs* **1986**, *32*(Suppl. 2), 43. (d) Sarges, R. *Trends in Medicinal Chemistry, Proceedings of the 9th International Symposium on Medical Chemistry*; Berlin, 1986; Mutschler, E., Winterfeldt, E., Eds.; VCH: Weinheim, 1987; pp 551–564. (e) Dvornik, D. *Aldose Reductase Inhibition. An Approach to the Prevention of Diabetic Complications*; Porte, D., Ed.; McGraw-Hill: New York, 1987.

(3) (a) Humber, L. G. *Prog. Med. Chem.* **1987**, *24*, 299. (b) Sestanj, K. U.S. Patent 4 369 188, 1983; *Chem. Abstr.* **1983**, *98*, 179217z.

(4) Wrobel, J.; Millen, J.; Sredy, J.; Dietrich, A.; Kelly, J. M.; Gorham, B. J.; Sestanj, K. *J. Med. Chem.* **1989**, *32*, 2493.

(5) Vargughese, K. I.; Przybylska, M.; Sestanj, K.; Bellini, F.; Humber, L. G. *Can. J. Chem.* **1983**, *61*, 2137.

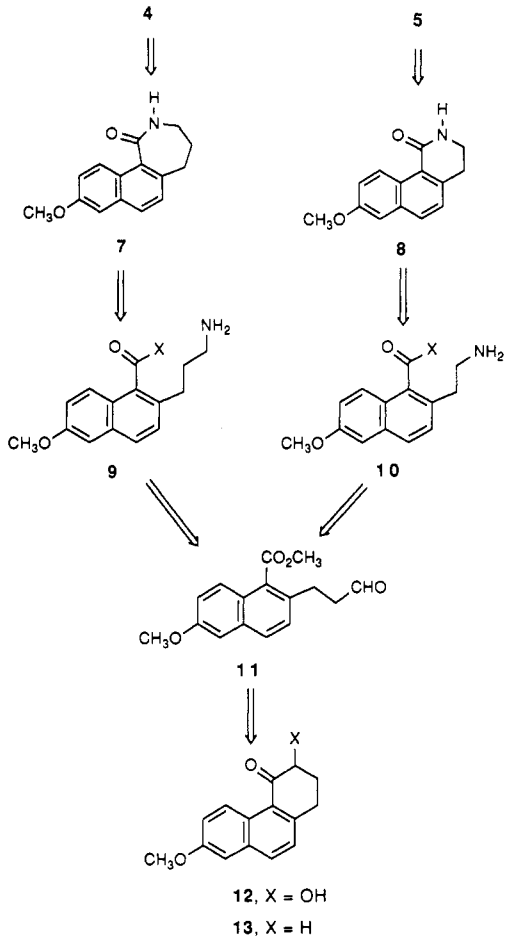
(6) Photochemical additions of alkenes to *N*-methyl-1,2-naphthalenedicarboxamide. (a) Kubo, Y.; Mihara, M.; Araki, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 241. (b) Kubo, Y.; Toda, R.; Araki, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 429.

(7) (a) Zee-Cheng, K. Y.; Nyberg, W. H.; Cheng, C. C. *J. Heterocycl. Chem.* **1972**, *9*, 805. (b) Beaumont, D.; Waigh, R. D. *J. Chem. Res. Synop.* **1979**, 332. (c) Bobowski, G.; Gottlieb, J. M.; West, B. *J. Heterocycl. Chem.* **1980**, *17*, 1563. (d) Schwann, T. J. *Heterocycles* **1981**, *15*, 469. (e) Gellert, E.; Kumar, N.; Tober, D. *Aust. J. Chem.* **1983**, *36*, 157. (f) Gellert, E.; Kumar, N. *Aust. J. Chem.* **1984**, *37*, 812. (g) Fleishhacken, W.; Richter, B. *Arch. Pharm.* **1984**, *317*, 840.

(8) Reid, W.; Grabosch, J. *Chem. Ber.* **1958**, *91*, 2485. (b) Brewster, J. H.; Fusco, A. M. *J. Org. Chem.* **1963**, *28*, 501. (c) Rosenthal, A.; Weir, M. R. S. *J. Org. Chem.* **1963**, *28*, 3025. (d) Jones, D. W.; Kneen, G. *J. Chem. Soc., Perkin Trans. 1* **1975**, 175. (e) Aziz, G.; Sakla, A. B.; El-Sayed, S.; Aziz, A.; Aziz, S. I. *Indian J. Chem.* **1976**, *14B*, 43. (f) Sakla, A. B.; Aziz, G.; Aziz, S. I. *Indian J. Chem.* **1977**, *15B*, 800. (g) Rufer, C.; Bahlmann, F.; Kapp, J. F. *Eur. J. Med. Chem.* **1978**, *13*, 193.

0022-3263/90/1955-2694$02.50/0

Scheme I



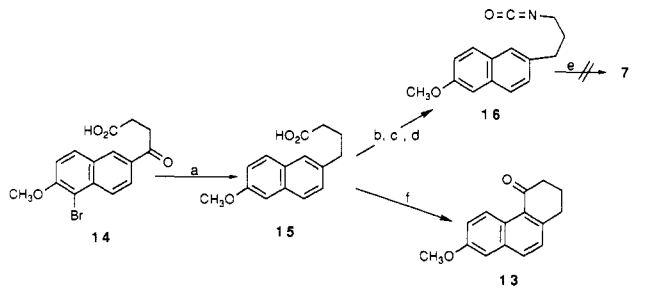
and tolrestat analogues **4a–b**, **5a–d**, and **6a–b**.

Results and Discussion

A. Syntheses of Naphthazepinones 4 and Benzisoquinolinones 5 from a Common Intermediate. Lactams **7** and **8** were obvious intermediate targets toward our goal of **4** and **5**, respectively (Scheme I). We were confident we could effect the remaining steps of incorporating an *N*-acetic acid moiety, thioamidation, naphthalene halogenation, and trifluoromethylation since we had experience with these transformations in syntheses leading to the thionaphthostyrils[3] and tolrestat analogues.[1,3,4] Logically, the lactam ring of **7** or **8** could arise from the appropriate amino acid derivative **9** or **10**. It occurred to us that these latter intermediates could be obtained from a common precursor, ester aldehyde **11**. Reductive amination of **11** would provide **9**. The lower homologue amine **10** could be obtained by oxidation of the aldehyde group in **11** to the carboxylic acid, conversion to the acyl azide or primary amide, followed by Curtius or Hofmann rearrangement, respectively. The known 2,3-dihydro-7-methoxy-4(1*H*)-phenanthrenone (**13**)[9] appeared to be a plausible starting material for the preparation of **11** via conversion of **13** to the hydroxy ketone **12** followed by oxidative ring opening.

We modified a literature procedure[9b] to prepare **13** (Scheme II). Under the original procedure, the highly insoluble keto acid **14** (obtained from Friedel–Crafts acylation of 1-bromo-2-methoxynaphthalene with succinic anhydride) was converted to the more soluble ethyl ester

Scheme II[a]



[a] (a) Et_3SiH/TFA; (b) $(COCl)_2$/DMF/CH_2Cl_2; (c) NaN_3/H_2O/acetone/0 °C; (d) benzene/reflux; (e) see text; (f) polyphosphoric acid/80 °C.

using Fisher esterification conditions. Clemensen reduction of the keto ester effected the ketone to methylene transformation as well as naphthalene debromination. Ethyl ester saponification afforded acid **15**. We found, however, that the **14** to **15** conversion could be accomplished directly and efficiently in one step by use of 3–4 equiv of triethylsilane in trifluoroacetic acid.[10] Simultaneous debromination and ketone reduction occurred with yields ranging from 83 to 94%. Intramolecular Friedel–Crafts cyclization then provided the desired ketone **13**.[11]

We made several attempts to prepare the naphth[1,2-*c*]azepinone, **7**, from **15** via the isocyanate **16**. This isocyanate was prepared under standard conditions of the Curtius rearrangement from the acyl azide of **15**. Attempted cyclization of **16** failed, utilizing several different Lewis acid catalysts including $AlCl_3$, $BF_3{\cdot}OEt_2$, and $SnCl_4$. A subsequent report noted that intramolecular cyclizations of isocyanates are difficult unless the aromatic ring of the presursor is highly activated.[12]

We again turned our attention to transformations involving ketone **13** (Scheme III). This compound was converted to the trimethylsilyl enol ether with TMS-triflate,[13] and the resultant compound was treated with MCPBA followed by desilylation of the alcohol moiety with aqueous acid[14] to provide α-hydroxy ketone **12** in 90% overall yield. Oxidative cleavage of **12** ($NaIO_4$) led to a high yield of acid–aldehyde **17**. However, efforts to reductively aminate this compound with ammonium acetate or glycine methyl ester hydrochloride using the Borch sodium cyanoborohydride procedure[15] were not fruitful. Mixtures of products were obtained in these reactions.

Further work with **17** was abandoned when our efforts with ester–aldehyde **11** were more successful. This latter compound was obtained in 76–86% yields by the reaction of **12** with periodic acid in anhydrous methanol followed by aqueous acid hydrolysis of the intermediate methyl acetal of **11**. Reductive amination[15] of **11** with glycine methyl ester hydrochloride led to 40–50% yields of **18**. However, various attempts to cyclize this product to **19** either thermally or by deprotonation of the amine group with strong base were unsuccessful.

(9) (a) Ghosal, M. *J. Org. Chem.* **1960**, *25*, 1856. (b) Roa, G. R. R. S.; Shyamasundar, N. *Indian J. Chem.* **1976**, *14B*, 26.

(10) West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* **1973**, *38*, 2675.

(11) We were unable to effect this cyclization under the conditions described in ref 9b ($POCl_3$/polyphosphoric acid/room temperature). However heating **15** at 80 °C in polyphosphoric acid or other standard methods ($PCl_5/SnCl_4$ or $AlCl_3$ treatment of the acid chloride of **15**) provided **13** in good yields.

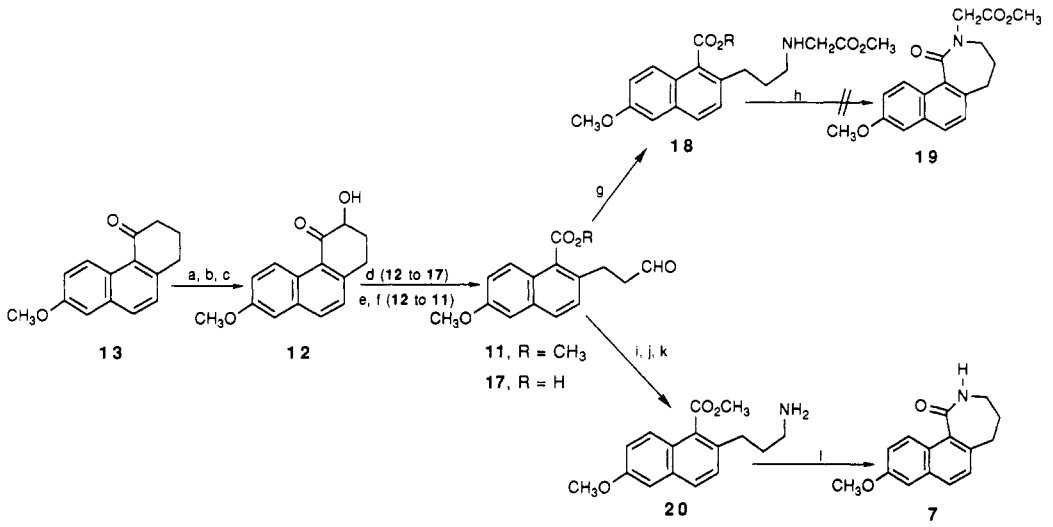
(12) See ref 7 in Jahanger; Fisher, L. E.; Clark, R. D.; Muchowski, J. M. *J. Org. Chem.* **1989**, *54*, 2992.

(13) Simchen, G.; Kober, W. *Synthesis* **1976**, 259.

(14) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319.

(15) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

Scheme III[a]



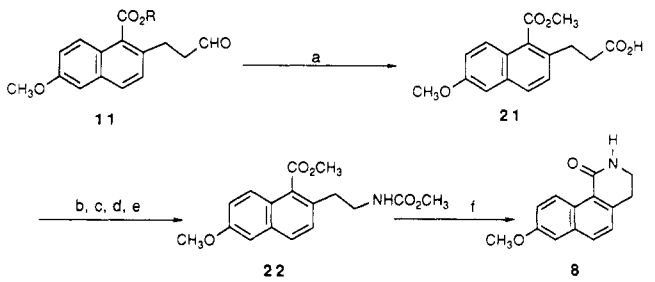
[a] (a) $CF_3SO_2SiMe_3$/TEA/benzene/0 °C; (b) MCPBA/hexane/−30 °C; (c) 1.5 N HCl/ether; (d) $NaIO_4$/HOAc/acetone/H_2O; (e) H_5IO_6/MeOH; (f) 10% HCl/THF; (g) $NaBH_3CN/CH_3O_2CCH_2NH_3Cl$/MeOH; (h) see text; (i) $NH_2OH{\cdot}H_2O$/NaOAc/MeOH/H_2O; (j) H_2/PtO_2/$CHCl_3$/EtOH; (k) aqueous NaOH; (l) KOtBu/THF.

Although reductive amination of **11** with ammonium acetate led to only a very low yield of the primary amine **20**, a more satisfactory synthesis of **20** was realized from the oxime of **11** via catalytic hydrogenation (H_2/PtO_2/$CHCl_3$/ethanol)[16] followed by basification of the resultant amine hydrochloride (75% yield from **11**). Amino ester **20** would not cyclize to the desired lactam **7** even upon subjection to toluene reflux temperatures. We therefore decided to convert the ester to the acid and attempt to cyclize the resultant amino acid using standard methods. However, under basic or acidic hydrolysis conditions that normally hydrolyze 1-naphthoic acid esters, no reaction was observed for **20**. Apparently the combination of the naphthalene peri-effect[17] and the presence of a naphthalene 2-substituent made this ester very hindered and resistant to nucleophilic attack.

We sorted to Gassman's procedure for the hydrolysis of hindered esters.[18] Thus compound **20**, potassium *tert*-butoxide (7.8 equiv), and water (2 equiv) were stirred in dry THF at ambient temperature. Although after several hours all starting material was consumed, little or no amino acid was detected and to our surprise the desired lactam **7** was the only observable product. We believed that the potassium *tert*-butoxide promoted the direct cyclization of amino ester **20** without prior hydrolysis of the ester moiety. Our hypothesis was reinforced when we found that the water was not necessary to effect this reaction. Using this procedure we typically obtained 50–60% yields of **20** after chromatography.

With a good synthesis of the naphthazepine **7** in hand, we turned our attention to the preparation of tetrahydrobenzisoquinoline **8** (Scheme IV). In this regard, Jones oxidation of aldehyde **11** provided the carboxylic acid **21** in 86% yield. Subsequent acyl azide formation and Curtius rearrangement, followed by trapping the intermediate isocyanate with methanol, went without event to afford an 87% yield of carbamate ester **22**. Upon generation of the anion of **22** with sodium hydride in THF at 0 °C and warming the reaction mixture to room temperature for 30 min, lactam **8** was produced in 96% yield after

Scheme IV[a]



[a] (a) Jones oxidation; (b) $(COCl)_2$/DMF/CH_2Cl_2; (c) NaN_3/acetone/0 °C; (d) toluene/reflux; (e) MeOH; (f) NaH/THF.

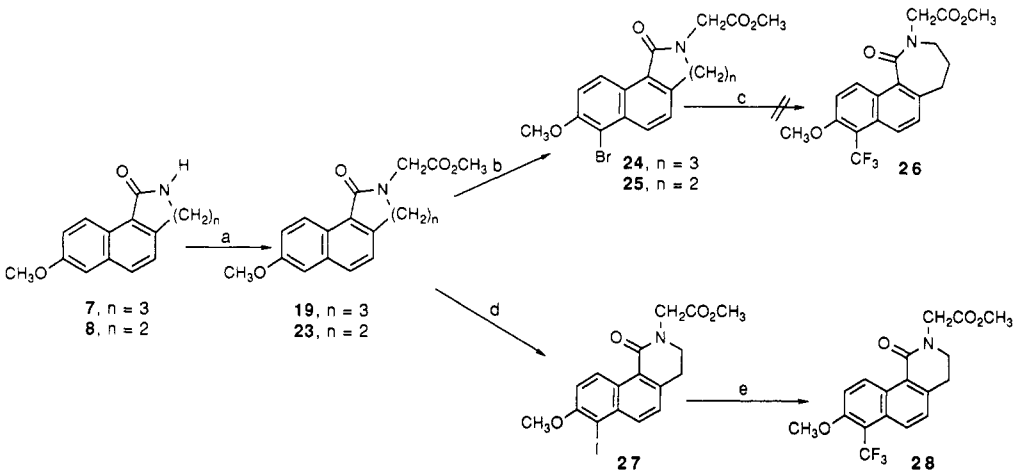
workup. Not only had cyclization occurred but the adventitious methoxide further eliminated the *N*-carbomethoxy group of the cyclized product.

Compounds **7** and **8** were thereafter elaborated to the corresponding *N*-acetic acid derivatives (Scheme V). Deprotonation of **7** or **8** with lithium bis(trimethylsilyl)-amide in THF followed by alkylation of the amide anion with methyl bromoacetate afforded 94 and 96% yields of the *N*-acetic acid methyl esters **19** and **23**, respectively.[19] Facile bromination of **19** or **23** with bromine in acetic acid gave the corresponding bromides **24** and **25**. Trifluoromethylation of **24** (CF_3CO_2Na/CuI/*N*-methylpyrrolidinone/140–180 °C)[20] provided the trifluoromethyl analogue **26** only in low yield contaminated with an inseparable amount of the corresponding 8-iodonaphthazepine (as confirmed by MS and NMR analyses).

Trifluoromethylation could be accomplished more readily from the corresponding aryl iodide. Thus reaction of **23** with iodine and iodic acid in 80% aqueous acetic acid and sulfuric acid at 50–60 °C provided iodide **27** (97%). This iodide was then converted to the desired trifluoromethyl analogue **28** in 76% yield using the procedure of Matsui et al. (CF_3CO_2Na/CuI).[20] However, the mass spectrum indicated that the samples was contaminated by a small amount of the heptafluoroethyl analogue, which

(16) Secrist, J. A.; Logue, M. W. *J. Org. Chem.* **1972**, *37*, 335.
(17) See Balasubramaniyan, V. *Chem. Rev.* **1966**, *66*, 567 for a discussion of the naphthalene peri-effect.
(18) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918.
(19) Reaction of **7** with sodium hydride/DMF followed by methyl bromoacetate provided a 46% yield of **19** along with 10% of the O-alkylated product.
(20) Matsui, K.; Tobita, E; Ando, M; Kondo, K *Chem. Lett.* **1981**, *12*, 1719.

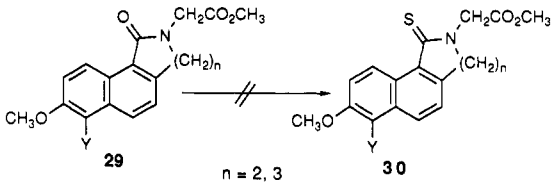
Scheme V[a]

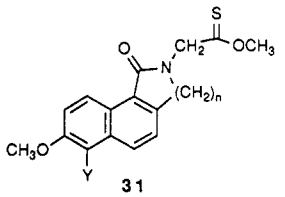


[a] (a) $LiNTMS_2/BrCH_2CO_2CH_3/THF/0$ °C to room temperature; (b) $Br_2/HOAc$; (c) see text; (d) $I_2/HIO_3/H_2SO_4/HOAc/H_2O/50$ °C; (e) $(CF_3)_2Hg/Cu^0/DMA/140$ °C.

presumably arose from a second trifluoromethylation of the product **28**. We resorted to a different procedure and found that **28** could be obtained in near quantitative yield, uncontaminated with the heptafluoroethyl analogue, by reaction of the iodide **27** with bis(trifluoromethylmercury) and activated copper powder in dimethylacetamide at 155 °C.[21] To complete the synthesis of our target compounds, methyl esters **19**, **23–25**, and **27–28** were hydrolyzed with aqueous NaOH to their corresponding *N*-acetic acid derivatives (**4a–b**, **5a–d**).

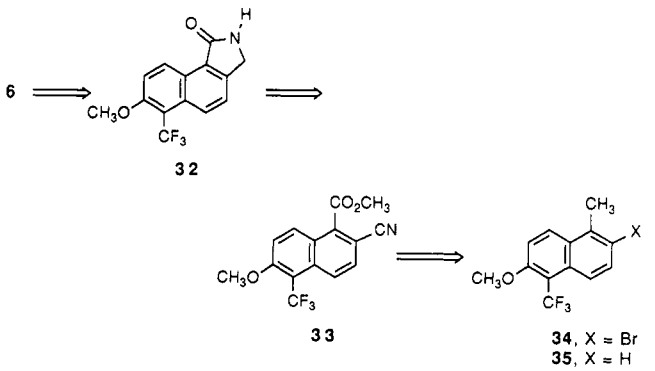
Unfortunately we were unable to convert any of the lactam *N*-acetic acid methyl esters (**29**) to the corresponding thiolactams (**30**). Under the conditions normal for conversion of the methyl ester of **2** to tolrestat methyl ester (P_4S_{10}/pyridine/reflux/2 h or Lawesson's reagent[22]/toluene/reflux/3 h) only starting materials were observed. Prolonged reaction times (12–20 h) still left most of the starting material intact, although in several cases the thioester **31** was isolated in ~20% yields. We believe the combination of the naphthalene peri-effect[17] and the bridging alkyl chain of **29** sterically impedes the thioamidation reaction.





B. Syntheses of Benzisoindolones 6. We had in hand an abundant supply of a tolrestat intermediate, **35**,[23] which

Scheme VI

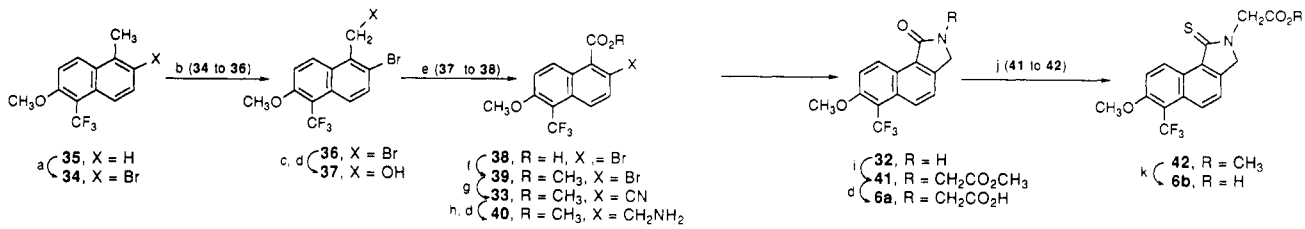


appeared to be a convenient precursor for benzisoindolone **6** (Scheme VI). Retrosynthetic analysis of **6** led to lactam **32**, which in turn could be prepared from nitrile ester **33** via reduction in the primary amine followed by cyclization. Compound **33** could be feasibly prepared from **34** by oxidation of the methyl group to a carboxylic acid derivative followed by cyanation of the bromide. Compound **34** might be obtained by the bromination of the naphthalene **35**.[23]

Indeed, treatment of **35** with bromine in acetic acid or CCl_4 afforded **34** in near quantitative yield (Scheme VII). We attempted to directly oxidize the methyl group of **34** to an aldehyde moiety using cerric ammonium nitrate.[24] However this was not successful,[25] so more conventional methods were sought. In this regard benzylic bromination with NBS provided **36** in 100% yield. We later found that the **35** to **36** transformation could be done in one pot (98% yield) by use of CCl_4 as solvent and sequential treatment of **35** with bromine followed by NBS/benzoyl peroxide after the consumption of starting material. Conversion of dibromide **36** to the bromo alcohol **37**, Jones oxidation, and esterification led to bromo methyl ester **39**. Reaction of **39** with copper(I) cyanide in DMF at reflux temperatures provided nitrile ester **33** in 53% overall yield from naphthalene **35**.

(21) Kondratenko, N. V.; Vechirko, E. P.; Yagupolskii, L. M. *Synthesis* **1980**, 932.
(22) (a) For a review on the thionation reaction with Lawesson's reagent, see: Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5087. (b) Mechanistic study: Rauchfuss, T. B.; Zank, G. A. *Tetrahedron Lett.* **1986**, 3445.
(23) Fung, S.; Abraham, N. A.; Bellini, F.; Sestanj, K. *Can. J. Chem.* **1983**, *61*, 368.
(24) Keay, B. A.; Rodrigo, R. *J. Am. Chem. Soc.* **1982**, *104*, 4725.
(25) By using much higher temperatures and longer reaction times than those described in ref 24, the only discernable product we were able to isolate, in low yield, was the nitrate ester of alcohol **37**.

Scheme VII[a]



[a] (a) Br_2/CCl_4; (b) NBS/$(PhCO_2)_2/CCl_4$/reflux; (c) $NaO_2CH/EtOH/H_2O$/reflux; (d) NaOH; (e) Jones oxidation; (f) CH_3I/K_2CO_3/DMF; (g) CuCN/DMF/reflux; (h) $H_2/PtO_2/CHCl_3/EtOH$; (i) $LiNTMS_2/BrCH_2CO_2CH_3$/THF/0 °C to room temperature; (j) Lawesson's reagent/toluene/reflux; (k) 6 N HCl/reflux.

Catalytic hydrogenation[16] gave the corresponding amino ester hydrochloride. Basification to the amine **40** caused spontaneous cyclization to lactam **32** (76% yield from **33**). This was in sharp contrast to the results obtained for higher homologue amino ester **20** (Scheme III), which would not cyclize to the seven-membered lactam **7** even at high temperatures. The kinetic preference for five-membered ring closure over seven-membered ring closure is well documented and probably explains the difference in reactivity of **40** versus **20**. Also, the electrophilicity of the ester carbonyl of **40** is enhanced relative to that of **20** by the electron-withdrawing inductive effect of the trifluoromethyl group. To complete the synthesis of target lactam **6a**, **32** was alkylated with methyl bromoacetate. Saponification of the resultant *N*-acetic acid methyl ester **41** afforded lactam **6a**.

In contrast to the naphthazepine and benzisoquinoline lactams, benzisoindole ester **41** readily reacted with Lawesson's reagent to provide the corresponding thiolactam **42** in 60% yield after chromatography. This selective reactivity apparently is due to the planar nature of the ring system of **41**. The amide moieties of the higher homologue lactams such as **24** or **28** are twisted relative to the naphthalene plane.[26] The flanking peri-hydrogen atom and the bridging methylene groups of **24** or **28** could impede the formation of a Wittig-type four-membered ring tetrahedral intermediate between the amide moiety and the dithiophosphinic anhydride reagent derived from Lawesson's reagent.[22b] On the other hand, the formation of this tetrahedral intermediate between the planar **41** and the Lawesson's derived reagent should be facile since unfavorable interactions between the amide carbonyl oxygen atom and the peri-hydrogen atom would be relieved.

Surprisingly **42** was unstable in base, and attempted methyl ester hydrolysis with aqueous NaOH did not provide any discernable products. Likewise treatment of **42** with trimethylsilyl iodide/CCl_4[27] or lithium iodide/DMF/Δ failed to effect the demethylation to lactam *N*-acetic acid **6b** and only intractable materials were observed. We were able to complete the synthesis of **6b**, however, by hydrolysis of **42** in 6 N aqueous HCl (15 h/reflux), although only low yields of **6b** were obtained after recrystallization.

The naphthazepine *N*-acetic acids **4a–b**, the benzisoquinoline *N*-acetic acids **5a–d**, and the benzisoindole *N*-acetic acids **6a–b** were tested for their ability to inhibit glyceraldehyde reduction by bovine lens aldose reductase.[4] Interestingly, compounds **4** and **5** were 2 orders of magnitude weaker as aldose reductase inhibitors compared to tolrestat (**1**) and oxotolrestat (**2**). While the in vitro activity improved marginally with γ-lactam **6a**, there was a dramatic increase in activity with γ-thiolactam **6b**, which was nearly as active as **1** and **2**.

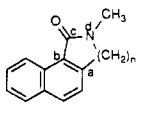
The Kador–Sharpless aldose reductase inhibitor site model[2b,28] proposes that aldose reductase inhibitors (ARIs) inhibit aldose reductase through a reversible charge-transfer interaction in which an enzyme nucleophile interacts with a participating acceptor group on the ARI, usually a carbonyl or thiocarbonyl. For tolrestat, the thioamide carbonyl moiety is thought to serve this electron-acceptor function. The high enzyme inhibition activities for **1**, **3**, and **6b** suggest that the directionality of the thiocarbonyl sulfur atom is unimportant as long as the carbonyl carbon atom is available for binding and/or charge transfer.

Conclusions

We have prepared several cyclic analogues of tolrestat (**1**) and oxotolrestat (**2**) shown by **4–6**, in which the amide nitrogen of **1** or **2** was tethered to the naphthalene ring by an alkyl chain of one to three carbon atoms. Because little information was available on the preparation of tetrahydro-2*H*-naphth[1,2-*c*]azepines related to **4**, tetrahydrobenz[*h*]isoquinolines related to **5**, and dihydro-1*H*-benz[*e*]isoindoles related to **6**, we developed novel routes to these ring systems and compounds **4–6**.

In this regard we synthesized 2,3,4,5-tetrahydro-9-methoxy-1*H*-naphth[1,2-*c*]azepin-1-one, **7**, in seven steps, 30% overall yield, and 3,4-dihydro-8-methoxybenz[*h*]isoquinolin-1(2*H*)-one, **8** in nine steps, 52% overall yield, from a common precursor, 2,3-dihydro-7-methoxy-4(1*H*)-phenanthrenone, **13**. Compounds **7** and **8** were then elaborated to the targets **4** and **5**, respectively. Since the unsubstituted and several substituted 2,3-dihydro-4-(1*H*)-phenanthrenones are readily available,[29] the synthetic

(26) Molecular mechanics[31] and AM1[32] calculations done on simpler *N*-methyl derivatives **43–45** suggest that torsion angle abcd for **43** is nearly 0°, while the same torsion angles for **44** and **45** are approximately 30° and 60°, respectively.



43, n = 1
44, n = 2
45, n = 3

(27) Jung, M. E.; Lyster, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 968.

(28) (a) Kador, P. F.; Sharpless, N. E. *Mol. Pharm.* **1983**, *24*, 521. (b) Kador, P. F.; Nakayama, T.; Sato, S.; Smar, M.; Miller, D. D. Enzymology and Molecular Biology of Carbonyl Metabolism 2. *Progress in Clinical and Biological Research, Volume 290*; Weiner, H., Flynn, T. G., Ed.; Alan R. Liss, Inc.: New York, 1989; pp 237–250.

(29) For example: (a) Unsubstituted: Hunlin, B.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 207. (b) 7-Methyl: Buu-Hoi, N. P.; Saint-Ruf, G. *J. Chem. Soc.* **1965**, 2642. (c) 10-Methyl: Moyle, M.; Ritchie, E. *Aust. J. Chem.* **1958**, *11*, 211. (d) 10-Methoxy: Yamamoto, K.; Fukushima, H.; Yumioka, H.; Nakazaki, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3633. (e) 1,1-Dimethyl: Forrester, A. R.; Gill, M.; Napier, R. J.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 632. (f) 6,7-Dimethoxy: Buu-Hoi, N. P.; Saint-Ruf, G. *Compt. Rend.* **1965**, *260*, 593. (g) 7,10-Dimethoxy: Buu-Hoi, N. P.; Saint-Ruf, G. *Bull. Soc. Chim. Fr.* **1970**, 2225. (h) 6,7,10-Trimethyl: Carruthers, W.; Gray, J. D. *J. Chem. Soc.* **1957**, 2422.

procedures used for **7** and **8** can potentially be extended to provide tetrahydro-2*H*-naphth[1,2-*c*]azepines and tetrahydrobenz[*h*]isoquinolines with substitution patterns differing from **7** or **8**. Unfortunately we were able to prepare thiolactams in the series **4** or **5** because the corresponding lactam precursors **29** resisted vigorous thioamidation conditions with P_4S_{10} or Lawesson's reagent. Compounds **6** were prepared from a tolrestat intermediate, naphthalene **35**. In this series, the thioamidation reaction, **41** to **42**, was successful. While the naphthazepine-*N*-acetic acids **4a–b** and benzisoquinoline-*N*-acetic acids **5a–d** were considerably weaker than **1** or **2** as inhibitors of bovine lens aldose reductase, thiolactam **6b** had high inhibitory activity.

Experimental Section

Melting points were determined on an Electrothermal capillary melting point apparatus and are not corrected. Proton magnetic resonance (^{1}H NMR) spectra were recorded at 200 MHz (Varian XL-200), 400 MHz (Bruker AM-400), or 80 MHz (Varian CFT-20). Infrared spectra were obtained on either a Beckman Accu Lab 2 or a Perkin-Elmer Model 781 spectrophotometer as KBr pellets, thin films on sodium chloride plates, or as solutions in chloroform and are reported as reciprocal centimeters (cm^{-1}). Mass spectra were recorded on either a Finnigan Model 8230 or a Hewlett-Packard Model 5995A spectrometer. Analyses (C, H, N) were carried out on a modified Perkin-Elmer Model 240 CHN analyzer. Analytical results for elements were within ±0.4% of the theoretical values. Flash chromatography was carried out according to the procedure of Still.[30] Thin-layer analyses were done on E. Merck silica gel 60 F-254 plates of 2.5-mm thickness.

6-Methoxy-2-naphthalenebutanoic Acid (15). Triethylsilane (100 mL, 0.628 mmol) was added dropwise over a period of 1 h to a stirred suspension of 5-bromo-6-methoxy-γ-oxo-2-naphthalenebutanoic acid[9b] (61.6 g, 0.183 mol) in CF_3CO_2H (130 mL) at room temperature under an Ar atmosphere. The reaction exotherm heated the solution to reflux temperatures. The reaction mixture was then stirred an additional 2.5 h. The reaction mixture was basified with 20% aqueous NaOH (350 mL), and the insoluble white solid was collected by filtration, washed well with Et_2O, suspended in water (500 mL), and acidified with concentrated HCl to pH 0. Filtration gave **15** (41.9 g, 94%): mp 166–168 °C (EtOH); NMR (DMSO-d_6, 200 MHz) δ 1.88 (quintet, 2 H, *J* = 7 Hz, $CH_2CH_2CH_2$), 2.23 (t, 2 H, *J* = 7 Hz, CH_2COOH), 2.70 (t, 2 H, *J* = 8 Hz, $ArCH_2$), 3.84 (s, 3 H, OCH_3), 7.11 (dd, 1 H, Ar*H*), 7.26 (d, 1 H, Ar*H*), 7.32 (d, 1 H), 7.59 (s, 1 H, Ar*H*), 7.73 (m, 2 H, Ar*H*); IR (KBr) 1690 (C=O); M_r 244.1123 (calcd for $C_{15}H_{16}O_3$ 244.1100).

2,3-Dihydro-3-hydroxy-7-methoxy-4(1*H*)-phenanthrenone (12). Trimethylsilyltriflate (10.4 mL, 53.70 mmol) was added to a cold (0–10 °C), stirred solution of **13**[9b] (11.25 g, 49.72 mmol) and Et_3N (9.8 mL, 70.60 mmol) in benzene (56 mL) under a dry N_2 atmosphere over a 15-min period. After 1 h at 0–10 °C and 10 min at room temperature, Et_2O (110 mL) was added. The reaction mixture was washed with water (4 × 100 mL), saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl (100 mL). The organic phase was diluted with CH_2Cl_2 (200 mL) and dried (Na_2SO_4). The organic phase was concentrated to provide an oil (14.4 g, 48.24 mmol of enol silyl ether, 97%).

A solution of the oil in hexane (60 mL) was added to a stirred suspension of *m*-CPBA (11.48 g, 53.06 mmol) in hexane (530 mL) at −30 °C (dry ice–methanol) over a 30-min period under a dry N_2 atmosphere. The reaction mixture was warmed to 0 °C and stirred for an additional 10 min. The suspension was filtered, and the solids were washed well with hexane. The combined hexane filtrates were concentrated. Ether (300 mL) and 1.5 N HCl (200 mL) were added to the resulting oil, and the biphasic mixture was stirred at room temperature for 17 h. The aqueous layer was removed, and the ether layer was washed with water (3 × 100 mL), saturated aqueous $NaHCO_3$ (2 × 100 mL), and saturated aqueous NaCl (2 × 100 mL). Silica gel (200 mL) was added to the ether solution, and the solvent was removed. The silica gel absorbate was flash chromatographed (7:3 petroleum ether–ethyl acetate) to provide **12** as a light orange solid product (9.46 g, 90%): mp 109.5–111 °C (hexane–$CHCl_3$); NMR ($CDCl_3$, 400 MHz) δ 2.12 (ddd, 1 H), 2.57 (dtd, 1 H), 3.14 (ddd, 1 H), 3.31 (ddd, 1 H), 7.12 (d, 1 H, Ar*H*), 7.28 (m, 2 H, Ar*H*), 7.86 (d, 1 H, Ar*H*), 9.26 (d, 1 H, Ar*H*); IR ($CHCl_3$) 3490 (OH), 1670 (C=O). Anal. ($C_{15}H_{14}O$) C, H.

6-Methoxy-2-(3-oxopropyl)-1-naphthalenecarboxylic Acid Methyl Ester (11). Periodic acid (35.68 g, 0.156 mmol) was added to a stirred, room temperature suspension of **12** (30.5 g, 0.126 mol) in anhydrous CH_3OH (610 mL) under a dry N_2 atmosphere. Dissolution occurred within 10 min. After 1.3 h the reaction was quenched with saturated aqueous $NaHCO_3$ (260 mL). The methanol was removed. Water (400 mL) was added, and the suspension was extracted with ether (3 × 750 mL). The ether was removed from the combined extracts and 2:1 THF–10% aqueous HCl (660 mL) was added. This solution was stirred at room temperature for 1 h in order to hydrolyze the intermediate methyl acetal. The THF was removed, and the aqueous phase was extracted with ether (3 × 400 mL). The solvent was removed to provide **11** as a brown solid: mp 77–79 °C (hexane–$CHCl_3$); NMR ($CDCl_3$, 400 MHz) δ 2.84 (t, 2 H, *J* = 7.4 Hz, CH_2), 3.03 (t, 2 H, *J* = 7.4 Hz, CH_2), 3.90 (s, 3 H, CO_2CH_3), 4.01 (s, 3 H, OCH_3), 7.10 (d, 1 H, *J* = 2.6 Hz, Ar*H*), 7.17 (dd, 1 H, *J* = 2.6, 9.2 Hz, Ar*H*), 7.29 (d, 1 H, *J* = 8.5 Hz, Ar*H*), 7.69 (d, 1 H, *J* = 9.2 Hz, Ar*H*), 7.73 (d, 1 H, *J* = 8.5 Hz, Ar*H*) 9.81 (d, 1 H, C*H*O); IR ($CHCl_3$) 2740 (CHO), 1740 (CHO). Anal. ($C_{16}H_{16}O_4$) C, H.

2,3,4,5-Tetrahydro-9-methoxy-1*H*-naphth[1,2-*c*]azepin-1-one (7). A solution of NH_2OH·HCl (4.33 g, 62.31 mmol) and NaOAc (6.94 g, 84.60 mmol) in water (145 mL) was added to a stirred solution of **11** (13.59 g, 49.90 mmol) in methanol (145 mL) at room temperature. An oil separated. After 30 min the methanol was removed, and the oil was extracted with ether (500 mL). The ether was removed, and the resulting oil was triturated with petroleum ether. The resulting solid was broken up, filtered, washed with petroleum ether, and dried in vacuo to provide the oxime of **11** as a tan solid (13.4 g, 94%): mp 107–109 °C; Anal. (Calcd for $C_{16}H_{17}NO_4$) C, H, N. A suspension containing the oxime (13.2 g, 45.94 mmol), PtO_2 (1.15 g), $CHCl_3$ (23 mL), and absolute EtOH (1.15 L) was hydrogenated at 40 psi for 6 h. The reaction mixture was filtered through sulka floc, and the sulka floc was washed with generous amounts of EtOH. The aqueous phase was extracted with EtOAc, and these extracts were discarded. The aqueous solution was basified with 10% aqueous NaOH and then saturated with solid NaCl. The aqueous phase was extracted with ether (3 × 300 mL). This ether phase was dried (K_2CO_3), and the solvent was removed to provide amine **20** as a tan solid (9.95 g, 79%).

To a stirred, cold (0–10 °C) solution of **20** (9.72 g, 35.56 mmol) in dry THF (70 mL) was added t-BuOK (34.16 g, 0.280 mol), and the reaction mixture was immediately warmed to room temperature. After 1.75 h the reaction mixture was quenched with saturated aqueous NH_4Cl. The reaction mixture was filtered, and the solids were washed with water and EtOAc. The layers of the filtrate were separated, and the water was extracted twice more with EtOAc. Silica gel (100 mL) was added to the combined extracts, and the solvent was removed. The silica gel absorbate was flash chromatographed (EtOAc) to provide **7** (4.75 g, 55%): mp 178–180 °C; NMR ($CDCl_3$, 200 MHz) δ 2.05 (m, 2 H, $CH_2CH_2CH_2$), 2.97 and 3.12 (2 m, 4 H, $CH_2CH_2CH_2$), 3.95 (s, 3 H, OCH_3), 6.71 (m, 1 H, N*H*), 7.10–7.35 (m, 3 H, Ar*H*), 7.78 (d, 1 H, Ar*H*), 8.32 (d, 1 H, Ar*H*); IR ($CHCl_3$) 3440, 3300, 3200 (NH), 1645 (C=O); MS (*m/e*) 241 (96), 224 (70), 211 (100), 198 (23). Anal. ($C_{15}H_{15}NO_2$) C, H, N.

1-(Methoxycarbonyl)-6-methoxy-2-naphthalenepropanoic Acid (21). Jones reagent (29 mL) was added dropwise over a 2-min period to a stirred, 0–10 °C solution of **11** (29 g, 0.106 mol) in acetone (370 mL). After 30 min, more Jones reagent (10 mL) was added. After an additional 10 min the reaction was quenched with iPrOH (30 mL). The solvents were removed, and the resulting sludge was triturated with ether (2 × 750 mL). The sludge was taken up in water (300 mL) and extracted with ether (1 ×

(30) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(31) Molecular mechanics calculations were done using Allinger's MM2 force field as found in the MODEL program (Version K.S.-2.92) written by Prof. Clark Still.
(32) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

400 mL). The ether phases were combined and extracted with 0.3 N aqueous NaOH. The aqueous phase was acidified with 10% HCl, and the resulting solid was filtered and washed well with water. The solid was taken up in $CHCl_3$ (600 mL) and dried ($MgSO_4$). The solvent was removed to provide **21** (26.5 g, 86%): mp 129–130 °C (EtOH–water); NMR ($CDCl_3$, 200 MHz) δ 2.73, 3.06 (2 t, 4 H, CH_2CH_2), 3.91, 4.02 (2 s, 6 H, OCH_3, CO_2CH_3), 7.11 (d, 1 H, J = 2.5 Hz, Ar*H*), 7.18 (dd, 1 H, J = 2.5, 9.1 Hz, Ar*H*), 7.32 (d, 1 H, J = 8.6 Hz, Ar*H*), 7.73 (d, 1 H, J = 9.1 Hz, Ar*H*), 7.74 (d, 1 H, J = 8.6 Hz, Ar*H*); IR (KBr) 3500–2400 (COOH), 1730, 1710 (C=O). Anal. ($C_{16}H_{16}O_5$) C, H, N.

6-Methoxy-2-[2-[(methoxycarbonyl)amino]ethyl]-1-naphthalenecarboxylic Acid Methyl Ester (22). Oxalyl chloride (9.7 mL, 0.111 mol) was added to a stirred, 0–10 °C solution of **21** (26.0 g, 90.18 mmol) and DMF (0.39 mL) in CH_2Cl_2 (390 mL) under a dry N_2 atmosphere. The reaction mixture was warmed to room temperature and after 1 h and 20 min the solvent was removed. Acetone (100 mL) was added, and the stirred solution was cooled to 0–10 °C. A solution of NaN_3 (6.4 g, 98.30 mmol; **caution**: NaN_3 is highly toxic and explodes when heated) in water (40 mL) was added. After 30 min the acetone was removed and water (50 mL) was added. The reaction mixture was extracted with ether (600 mL), and this ether extract was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed, and the resulting oil was dissolved in toluene (195 mL) and heated in a 80 °C oil bath under a dry N_2 atmosphere. Gas evolution was noted, and after 50 min the reaction mixture was cooled to room temperature. The toluene was removed and anhydrous CH_3OH (200 mL) was added. The reaction mixture was heated in a 75 °C oil bath for 1.5 h. Silica gel (500 mL) was added to the cooled reaction mixture, and the solvent was removed. The silica gel absorbate was flash chromatographed (1:1 petroleum ether–EtOAc) to provide **22** as an oil (25.0 g, 87%). A small portion of this oil was triturated in hexane to provide a white solid: mp 75–76 °C; NMR ($CDCl_3$, 200 MHz) δ 2.92 (t, 2 H, $ArCH_2$), 3.50 (q, 2 H, $ArCH_2CH_2$) 3.62 (s, 3 H, $NHCO_2CH_3$), 3.91 and 4.03 (2 s, 6 H, CO_2CH_3, OCH_3), 5.16 (m, 1 H, N*H*), 7.12 (d, 1 H, J = 2.5 Hz, Ar*H*), 7.18 (dd, 1 H, J = 2.5, 9.3 Hz, Ar*H*), 7.30 (d, 1 H, J = 8.4 Hz, Ar*H*), 7.68 (d, 1 H, J = 9.3 Hz, Ar*H*), 7.75 (d, 1 H, J = 8.4 Hz, Ar*H*); IR ($CHCl_3$) 3470, 3390 (NH), 1720 (C=O). Anal. ($C_{17}H_{19}NO_5$) C, H, N.

3,4-Dihydro-8-methoxybenz[*h*]isoquinolin-1(2*H*)-one (8). Sodium hydride (4.14 g, 86.31 mmol, 50% dispersion in mineral oil) was added to a stirred solution of **22** (24.9, 78.46 mmol) in anhydrous THF (414 mL) at 0–10 °C under a dry N_2 atmosphere. After 5 min the reaction mixture was allowed to warm to room temperature. After 40 min the reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL), and the THF was removed. Water (300 mL) was added, and the solid was filtered. The solid was washed with water (2 × 100 mL), triturated with hexane (2 × 150 mL), and dried in vacuo to provide **8** (16.99 g, 95%): mp 170–172 °C; NMR ($CDCl_3$, 200 MHz) δ 3.07 (t, 2 H, $ArCH_2$), 3.52 (m, 2 H, $NHCH_2$), 3.92 (s, 3 H, OCH_3), 6.40 (broad, s, H, N*H*), 7.11 (d, 1 H, J = 2.9 Hz, Ar*H*), 7.26 (m, 2 H, Ar*H*), 7.80 (d, 1 H, J = 8.2 Hz, Ar*H*), 9.33 (d, 1 H, J = 9.6 Hz, Ar*H*); IR (KBr) 3300, 3200, 3140 (NH), 1660 (CON). Anal. ($C_{14}H_{13}NO_2$) C, H, N.

2,3,4,5-Tetrahydro-9-methoxy-1-oxo-1*H*-naphth[1,2-*c*]azepine-2-acetic Acid Methyl Ester (19). Lithium bis(trimethylsilyl)amide (1.0 N in THF, 24 mL, 24.02 mmol) was added to a cold (0–10 °C), stirred suspension of **7** (4.46 g, 18.48 mmol) in THF (45 mL) under a dry Ar atmosphere. Dissolution occurred immediately. After 15 min methyl bromoacetate (2.6 mL, 27.72 mmol) was added. After an additional 20 min at 0–10 °C and 5 min at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL). The THF was removed and more water (50 mL) was added. The reaction mixture was extracted with EtOAc (2 × 200 mL). Silica gel (50 mL) was added to the EtOAc extracts, and the solvent was removed. The silica gel absorbate was flash chromatographed (3:2 petroleum ether–EtOAc) to provide **19** (5.59 g, 99%) as a white solid: mp 139–141 °C (EtOH); NMR (DMSO-d_6, 400 MHz) δ 1.7, 2.3, 2.8, 3.0, 3.1, 3.3 (6 m, 6 H, $(CH_2)_3$), 3.71, 3.86 (2 s, 6 H, 2 OCH_3), 4.4 (m, 2 H, NCH_2), 7.16 (dd, 1 H, J = 2.7, 9.3 Hz, Ar*H*), 7.33 (d, 1 H, J = 2.7 Hz, Ar*H*), 7.35 (d, 1 H, J = 8.3 Hz, Ar*H*), 7.86 (d, 1 H, J = 8.3 Hz, Ar*H*), 7.98 (d, 1 H, J = 9.3 Hz, Ar*H*); IR ($CHCl_3$) 1745 (CO_2CH_3), 1630 (CON). Anal. ($C_{18}H_{19}NO_4$) C, H, N.

3,4-Dihydro-8-methoxy-1-oxo-2*H*-benz[*h*]isoquinoline-2-acetic Acid Methyl Ester (23). Compound **23** was prepared from **8** using the conditions described for compound **19** (yield 98%): mp 74–76 °C; NMR ($CDCl_3$, 200 MHz) δ 3.13 (t, 2 H, J = 6.7 Hz, $ArCH_2$) 3.65 (t, 2 H, J = 6.7 Hz, NCH_2CH_2), 3.77 (s, 3 H, CO_2CH_3), 3.91 (s, 3 H, OCH_3), 4.41 (s, 2 H, NCH_2CO_2) 7.10 (d, 1 H, J = 2.3 Hz, Ar*H*), 7.21 (m, 2 H, Ar*H*), 7.79 (d, 1 H, J = 8.2 Hz, Ar*H*), 9.28 (d, 1 H, J = 9.1 Hz, Ar*H*); IR ($CHCl_3$) 1745 (CO_2CH_3), 1645 (CON). Anal. ($C_{17}H_{17}NO_4$) C, H, N.

8-Bromo-2,3,4,5-tetrahydro-9-methoxy-1-oxo-1*H*-naphth[1,2-*c*]azepine-2-acetic Acid Methyl Ester (24). Bromine (0.46 mL, 8.89 mmol) was added dropwise to a stirred solution of **19** (2.53 g, 8.07 mmol) in glacial HOAc (40 mL) at room temperature under a dry N_2 atmosphere. After addition, a precipitate appeared and more acetic acid (10 mL) failed to solubilize this precipitate. After an additional 1 h, the reaction mixture was added to dilute aqueous $NaHSO_3$. The resulting solid was filtered, washed with water, and dried in vacuo to provide **24** (3.02 g, 94%): mp 153–155 °C; NMR $CDCl_3$, 200 MHz) δ 1.80, 2.35, 2.85, 3.20, 3.35 (4 m, 6 H, $(CH_2)_3$), 3.81, 4.02 (2 s, 6 H, 2 OCH_3), 4.44 (s, 2 H, NCH_2), 7.31 (m, 2 H, Ar*H*), 8.29 (m, 2 H, Ar*H*); IR ($CHCl_3$) 1750 (CO_2CH_3), 1640 (CON). Anal. ($C_{18}H_{18}BrNO_4$) C, H, N.

7-Bromo-3,4-dihydro-8-methoxy-1-oxo-2*H*-benz[*h*]isoquinoline-2-acetic Acid Methyl Ester (25). Compound **25** was prepared from **23** using the conditions described for compound **24** (yield 85%): mp 148–149 °C; NMR ($CDCl_3$, 200 MHz) δ 3.16 (t, 1 H, J = 6.7 Hz, $ArCH_2$), 3.66 (t, 1 H, J = 6.7 Hz, NCH_2CH_2), 3.77 (s, 3 H, CO_2CH_3), 4.02 (s, 3 H, OCH_3), 4.41 (s, 2 H, NCH_2CO_2), 7.34 (m, 2 H, Ar*H*), 8.38 (d, 1 H, J = 7.9 Hz, Ar*H*), 9.40 (d, 1 H, J = 9.4 Hz, Ar*H*); IR ($CHCl_3$) 1740 (CO_2CH_3), 1640 (CON). Anal. ($C_{17}H_{16}BrNO_4$) C, H, N.

3,4-Dihydro-7-iodo-8-methoxy-1-oxo-2*H*-benz[*h*]isoquinoline-2-acetic Acid Methyl Ester (27). Concentrated H_2SO_4 (0.74 mL), I_2 (8.98 g, 34.38 mmol), and HIO_3 (2.22 g, 12.73 mmol) were added to a stirred suspension of **23** (14.66 g, 48.97 mmol) in 80% aqueous HOAc (82 mL) at room temperature. The suspension was heated at 50–60 °C for 30 min, cooled to room temperature, and added to dilute aqueous $NaHSO_3$ (1.5 L). More solid $NaHSO_3$ was added, and the suspension was stirred for 15 min to remove solid I_2. The solid was filtered, washed well with water, and dried in vacuo (20.17 g, 97%). A small portion was purified by flash chromatography (EtOAc): mp 153–156 °C; NMR ($CDCl_3$, 200 MHz) δ 3.16 (t, 2 H, J = 6.7 Hz, $ArCH_2$), 3.66 (t, 2 H, J = 6.7 Hz, NCH_2CH_2), 3.78 (s, 3 H, CO_2CH_3), 4.02 (s, 3 H, OCH_3), 4.42 (s, 2 H, NCH_2CO_2), 7.25 (d, 1 H, J = 9.5 Hz, Ar*H*), 7.33 (d, 1 H, J = 8.8 Hz, Ar*H*), 8.31 (d, 1 H, J = 8.8 Hz, Ar*H*), 9.42 (d, 1 H, J = 9.5 Hz, Ar*H*); IR ($CHCl_3$) 1745 (CO_2H), 1645 (CON). Anal. ($C_{17}H_{16}INO_4$) C, H, N.

3,4-Dihydro-7-(trifluoromethyl)-8-methoxy-1-oxo-2*H*-benz[*h*]isoquinoline-2-acetic Acid Methyl Ester (28). A stirred mixture of $(CF_3)_2Hg$[33] (2.43 g, 7.40 mmol) and activated Cu^0[34] (1.84 g, 28.94 mmol) in dimethyl acetamide (16 mL) was heated to 145 °C under a dry N_2 atmosphere. After 2 h a suspension of **27** (5.10 g, 12.00 mmol) in dimethylacetamide (26 mL) was added dropwise over a 5-min period. The stirred reaction mixture was heated at 150–155 °C for 1 h, cooled to room temperature, and added to rapidly stirred water (650 mL). The resulting solid was filtered and washed well with water. The solid was then triturated with EtOAc (700 mL). The EtOAc phase was dried ($MgSO_4$) and concentrated to provide **28** as a yellow solid (4.40 g, 99%): mp 154–156 °C (hexane, $CHCl_3$); NMR ($CDCl_3$, 200 MHz) δ 3.14 (t, 2 H, J = 6.7 Hz, $ArCH_2$), 3.66 (t, 2 H, J = 6.7 Hz, NCH_2CH_2), 3.77 (s, 3 H, CO_2CH_3), 3.99 (s, 3 H, OCH_3), 4.40 (s, 2 H, NCH_2CO_2), 7.34 (d, 2 H, J = 9.2 Hz, Ar*H*), 8.26 (dm, 1 H, Ar*H*), 9.58 (d, 1 H, J = 9.9 Hz, Ar*H*); IR ($CHCl_3$) 1745 ($COOCH_3$), 1645 (CON); MS (m/e) 367 (83), 308 (100). Anal. ($C_{18}H_{16}F_3NO_4$) C, H, N.

3,4-Dihydro-7-(trifluoromethyl)-8-methoxy-1-oxo-2*H*-benz[*h*]isoquinoline-2-acetic Acid (5d). Aqueous NaOH (2.5

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N, 4.2 mL, 10.5 mmol) was added to a stirred solution of **28** (2.97 g, 8.08 mmol) in 4:1 THF–CH_3OH (30 mL) at room temperature. After 20 min the reaction mixture was added to water (500 mL). This solution was acidified, and the white solid was collected and washed well with water. The white solid was recrystallized from EtOH to provide **5d** (2.27 g, 79%): mp 227–229 °C (EtOH); NMR (DMSO-d_6, 400 MHz) δ 3.09 (t, 2 H, J = 6.4 Hz, ArCH_2), 3.63 (t, 2 H, J = 6.4 Hz, NCH_2CH_2), 3.99 (s, 3 H, OCH_3), 4.30 (s, 2 H, NCH_2CO_2), 7.57 (d, 1 H, J = 9.0 Hz, ArH), 7.66 (d, 1 H, J = 9.9 Hz, ArH), 8.15 (dm, 1 H, ArH), 9.55 (d, 1 H, J = 9.9 Hz, ArH); IR (KBr) 3650–2400 (COOH), 1740 (COOH), 1645 (CON); MS (m/e) 353 (43), 309 (41), 308 (42), 266 (100). Anal. ($C_{17}H_{14}F_3NO_4$) C, H, N.

2,3,4,5-Tetrahydro-9-methoxy-1-oxo-1*H*-naphth[1,2-*c*]azepine-2-acetic Acid (4a). Compound **4a** was prepared from **19** using the conditions described for **5d** (yield 89%): mp 157–158 °C (EtOH–water); NMR (DMSO-d_6, 400 MHz) δ 1.70, 2.30 2.80, 3.00, 3.10, 3.30 (6 m, 6 H, (CH_2)$_3$), 3.86 (s, 3 H, OCH_3), 4.30 (m, 2 H, NCH_2), 7.16 (dd, 1 H, J = 2.7, 9.3 Hz, ArH), 7.33 (d, 1 H, J = 2.7 Hz, ArH), 7.35 (d, 1 H, J = 8.3 Hz, ArH), 7.85 (d, 1 H, J = 8.3 Hz, ArH), 8.00 (d, 1 H, J = 9.3 Hz, ArH); IR (KBr) 3650–2500 (COOh), 1760 (COOH), 1615 (CON); MS (m/e) 299 (100), 255 (14), 254 (11), 226 (30), 224 (11), 212 (91) 211 (95). Anal. ($C_{17}H_{17}NO_4$) C, H, N.

8-Bromo-2,3,4,5-tetrahydro-9-methoxy-1-oxo-1*H*-naphth[1,2-*c*]azepine-2-acetic Acid (4b). Compound **4b** was prepared from **24** using the conditions described for **5d** (yield 88%): mp 270–272 °C (EtOH–water); NMR (DMSO-d_6, 400 MHz) δ 1.68 (1 H), 2.29 (1 H), 2.85 (1 H), 3.07 (2 H), 3.33 (1 H) [5 m, (CH_2)$_3$], 3.97 (s, 3 H, OCH_3), 4.32 (q, 2 H, NCH_2), 7.51 (d, 1 H, J = 8.6 Hz, ArH), 7.54 (d, 1 H, J = 9.5 Hz, ArH), 8.14 (d, 1 H, J = 8.6 Hz, ArH), 8.15 (d, 1 H, J = 9.5 Hz, ArH); IR (KBr) 3650–2800 (COOH), 1765 (COOH), 1635 (CON); MS (m/e) 379 (48), 377 (50), 306 (10), 304 (13), 292 (33), 291 (30), 290 (34), 289 (26). Anal. ($C_{17}H_{16}BrNO_4$) C, H, N.

3,4-Dihydro-8-methoxy-1-oxo-2*H*-benz[*h*]isoquinoline-2-acetic Acid (5a). Compound **5a** was prepared from **23** using the conditions described for **5d** (yield 79%): mp 107–109.5 °C (EtOH–water); NMR (DMSO-d_6, 400 MHz) δ 3.07 (t, 2 H, J = 6.5 Hz, ArCH_2), 3.61 (t, 2 H, J = 6.5 Hz, NCH_2CH_2), 3.87 (s, 3 H, OCH_3), 4.28 (s, 2 H, NCH_2CO_2), 7.20 (dd, 1 H, J = 2.8, 9.5 Hz, ArH), 7.34 (d, 1 H, J = 2.8 Hz, ArH), 7.39 (d, 1 H, J = 8.4 Hz, ArH), 7.94 (d, 1 H, J = 8.4 Hz, ArH), 9.18 (d, 1 H, J = 9.5 Hz, ArH), 10.35 (s, 1 H, OH); IR (KBr) 3650–2750 (COOH), 1750 (COOH), 1615 (CON); MS (m/e): 285 (100), 241 (45), 240 (41), 212 (21), 198 (100). Anal. ($C_{16}H_{15}NO_4$) C, H, N.

7-Bromo-3,4-dihydro-8-methoxy-1-oxo-2*H*-benz[*h*]isoquinoline-2-acetic Acid (5b). Compound **5b** was prepared from **25** using the conditions described for **5d** (yield 74%): mp 233–234 °C (EtOH); NMR (DMSO-d_6, 400 MHz) δ 3.10 (t, 2 H, J = 6.5 Hz, ArCH_2), 3.62 (t, 2 H, J = 6.5 Hz, NCH_2CH_2), 3.99 (s, 3 H, OCH_3), 4.29 (s, 2 H, NCH_2CO_2), 7.55 (d, 1 H, J = 8.7 Hz, ArH), 7.77 (d, 1 H, J = 9.7 Hz, ArH), 8.26 (d, 1 H, J = 8.7 Hz, ArH), 9.34 (d, 1 H, J = 9.7 Hz, ArH); IR (KBr) 3650–2400 (COOH), 1745 (COOH), 1610 (CON); MS (CI) 366, 364 (M + 1), 320, 318. Anal. ($C_{16}H_{14}BrNO_4$) C, H, N.

3,4-Dihydro-7-iodo-8-methoxy-1-oxo-2*H*-benz[*h*]isoquinoline-2-acetic Acid (5c). Compound **5c** was prepared from **27** using the conditions described for **5d** (yield 50%): mp 215–216 °C (EtOH); NMR (DMSO-d_6, 400 MHz) δ 3.10 (t, 2 H, J = 6.5 Hz, ArCH_2), 3.62 (t, 2 H, J = 6.5 Hz, NCH_2CH_2), 3.97 (s, 3 H, OCH_3), 4.30 (s, 2 H, NCH_2CO_2), 7.47 (d, 1 H, J = 9.6 Hz, ArH), 7.51 (d, 1 H, J = 8.8 Hz, ArH), 8.21 (d, 1 H, J = 8.8 Hz, ArH), 9.33 (d, 1 H, J = 9.6 Hz, ArH); IR (KBr) 3600–2400 (COOH), 1740 (COOH), 1620 (CON). Anal. ($C_{16}H_{14}INO_4$) C, H, N.

2-Bromo-1-(bromomethyl)-5-(trifluoromethyl)-6-methoxynaphthalene (36). Bromine (12.80 mL, 0.250 mol) was added dropwise over a 10-min period to a solution of 5-methyl-2-methoxy-1-(trifluoromethyl)naphthalene (**35**) (50.00 g, 0.208 mol) in CCl_4 (750 mL) at room temperature under a dry N_2 atmosphere. After the mixture was stirred for 20 h, NBS (55.53 g, 0.312 mol) and benzoyl peroxide (0.252 g, 1.04 mmol) were added. The reaction mixture was heated to reflux, and, after 6 h, more NBS (5.50 g, 20.8 mmol) and benzoyl peroxide (0.252 g, 1.04 mmol) were added. After an additional 21 h at reflux, the reaction mixture was filtered hot and the filtrate was washed with dilute aqueous $NaHSO_3$ (500 mL) and saturated aqueous $NaHCO_3$ (300 mL), dried ($MgSO_4$), and concentrated to give **36** as a yellow solid (80.0 g, 98%): mp 141.5–143 °C; NMR ($CDCl_3$, 200 MHz) δ 4.02 (s, 3 H, OCH_3), 5.09 (s, 2 H, CH_2Br), 7.46 (d, 1 H, J = 9.5 Hz, ArH), 7.66 (d, 1 H, J = 9.5 Hz, ArH), 8.06 (dm, 1 H, ArH), 8.30 (d, 1 H, J = 9.5 Hz, ArH). Anal. ($C_{13}H_9Br_2F_3O$) C, H.

2-Bromo-5-(trifluoromethyl)-6-methoxy-1-naphthalenemethanol (37). A stirred suspension of **36** (32.4 g, 78 mmol), sodium formate (13.95 g, 0.203 mol), EtOH (160 mL), and water (42 mL) was heated to reflux. Dissolution occurred within 20 min. After 3 h the heating source was removed, 2.5 N NaOH (31 mL) was added, and the reaction mixture was cooled to room temperature. The EtOH was removed, water (100 mL) was added, and the solid was filtered. The solid was washed with water (2 × 30 mL), triturated with $CHCl_3$ (2 × 25 mL), and dried ($MgSO_4$) to provide **37** as a light yellow solid (23.10 g, 87%). A small sample was flash chromatographed (gradient, 7:3 to 3:2 petroleum ether–EtOAc) to provide a white solid: mp 171–173 °C; NMR (DMSO-d_6, 200 MHz) δ 4.01 (s, 3 H, OCH_3), 5.07 (d, 2 H, J = 4.4 Hz, CH_2), 5.44 (t, 1 H, J = 5.2 Hz, OH), 7.70 (d, 1 H, J = 9.5 Hz, ArH), 8.56 (d, 1 H, J = 10.2 Hz, ArH); IR (KBr) 3318 (OH). Anal. ($C_{13}H_{10}BrF_3O$) C, H.

2-Bromo-5-(trifluoromethyl)-6-methoxy-1-naphthalenecarboxylic Acid (38). Jones reagent (45 mL) was added slowly to a stirred solution of **37** (30.1 g, 89.7 mmol) in acetone (540 mL) at 0 °C. After 5 min, the reaction was warmed to room temperature. After 1 h the reaction was quenched with iPrOH (10 mL) and diluted with water (1.4 L). The aqueous phase was extracted with EtOAc (3 × 400 mL). The combined extracts were quickly washed with 5 N NaOH (3 × 350 mL). The combined basic phase was acidified to pH 1 with concentration HCl, and the aqueous suspension was stirred overnight at room temperature. The solid was collected by suction filtration, washed with water (25 mL), and dried to provide **38** as a beige solid (16.05 g, 78%): mp 221–222.5 °C; NMR (DMSO-d_6, 400 MHz) δ 4.02 (s, 3 H, ArOCH_3), 7.77 (d, 1 H, J = 9.7 Hz, ArH), 7.84 (d, 1 H, J = 9.4 Hz, ArH), 8.02 (d, 2 H, J = 9.3 Hz, ArH); IR (KBr) 1710 (C=O); MS (m/e) 350 (99), 348 (100), 333 (20), 331 (20), 307 (24), 305 (26). Anal. ($C_{13}H_8BrF_3O_3$) C, H.

2-Bromo-5-(trifluoromethyl)-6-methoxy-1-naphthalenecarboxylic Acid Methyl Ester (39). Iodomethane (4.55 mL, 73.0 mmol) was added to a stirred suspension of anhydrous K_2CO_3 (11.65 g, 84.3 mmol) and **38** (19.63 g, 56.2 mmol) in anhydrous DMF (45 mL) at room temperature under a dry N_2 atmosphere. After 50 min, more CH_3I (0.70 mL, 11.2 mmol) was added. After 1 h, the reaction mixture was diluted with water (1.3 L) and extracted with Et_2O (3 × 350 mL). The combined extracts were washed with saturated aqueous NaCl (200 mL), dried ($MgSO_4$), and concentrated to provide **39** as a pink solid (19.13 g, 94%): mp 96.5–97.5 °C; NMR ($CDCl_3$, 200 MHz) δ 3.99 (s, 3 H, CO_2CH_3), 4.05 (s, 3 H, ArOCH_3), 7.36 (d, 1 H, J = 9.1 Hz, ArH), 7.65 (d, 1 H, J = 9.6 Hz, ArH), 7.86 (d, 1 H, J = 9.1 Hz, ArH), 8.12 (d, 1 H, J = 9.6 Hz, ArH); IR ($CHCl_3$) 1730 (C=O). Anal. ($C_{14}H_{10}BrF_3O_3$) C, H.

2-Cyano-5-(trifluoromethyl)-6-methoxy-1-naphthalenecarboxylic Acid Methyl Ester (33). Copper(I) cyanide (5.19 g, 58.0 mmol) was added to a stirred suspension of **39** (19.13 g, 52.7 mmol) in anhydrous DMF (30 mL) at room temperature under a dry N_2 atmosphere. The reaction was heated at reflux for 30 min. The cooled reaction mixture was diluted with water (300 mL), and the solid was collected by suction filtration and washed with water (3 × 25 mL). The solid was suspended in a solution of NaCN (30 g) in water (1.0 L). The suspension was warmed on a hot plate with rapid stirring for 20 min. The aqueous suspension was then extracted with EtOAc (3 × 300 mL). The combined extracts were washed with water (2 × 100 mL), dried ($MgSO_4$), and concentrated. The crude product was recrystallized in 1:3 $CHCl_3$–hexane to provide **33** as a beige solid (13.87 g, 85%): mp 158–159.5 °C; NMR ($CDCl_3$, 200 MHz) δ 4.05 (s, 3 H, ArOCH_3), 4.11 (s, 3 H, CO_2CH_3) 7.48 (d, 1 H, J = 9.5 Hz, ArH), 7.71 (d, 1 H, J = 9.2 Hz, ArH), 8.38 (t, 2 H, J = 9.2 Hz, ArH); IR ($CHCl_3$) 2240 (CN), 1728 (C=O). Anal. ($C_{15}H_{10}F_3NO_3$) C, H, N.

2,3-Dihydro-6-(trifluoromethyl)-7-methoxy-1*H*-benz[*e*]isoindol-1-one (32). A suspension of **33** (13.87 g, 44.9 mmol), PtO_2 (2.04 g, 9.00 mmol), and $CHCl_3$ (23.3 mL) in absolute EtOH

(1.17 L) was shaken in a Parr hydrogenator at 40 psi for 17.5 h. The reaction mixture was filtered through sulka floc, and the solid was rinsed with absolute EtOH (2 × 15 mL). The reaction mixture was concentrated, and the resultant solid was dissolved in water (1.4 L). The aqueous solution was basified to pH 9 with 10% aqueous NaOH. The precipitate was collected by suction filtration and washed with water (2 × 100 mL). The solid was recrystallized in 1:1 EtOH–water to provide **32** as amber needles (9.57 g, 76%). A small portion of this latter solid was recrystallized from 1:1 petroleum ether–CH_2Cl_2: mp 214–216 °C; NMR (DMSO-d_6, 200 MHz) δ 4.02 (s, 3 H, ArOCH_3), 4.46 (s, 2 H, NCH_2), 7.80 (t, 2 H, J = 8.8 Hz, ArH), 8.26 (d, 1 H, J = 9.0 Hz, ArH), 8.78 (s, 1 H, NH), 9.48 (d, 1 H, J = 9.1 Hz, ArH); IR (KBr) 3190 and 3080 (NH), 1676 (C=O); MS (m/e) 281 (100), 253 (76), 212 (33). Anal. ($C_{14}H_{10}F_3NO_2$) C, H, N.

2,3-Dihydro-6-(trifluoromethyl)-7-methoxy-1-oxo-1*H*-benz[*e*]isoindole-2-acetic Acid Methyl Ester (41). Compound **41** was prepared from **32** using the conditions described for **19** (yield 46%): mp 190–192 °C (2:1 hexane–$CHCl_3$); NMR ($CDCl_3$, 200 MHz) δ 3.76 (s, 3 H, CO_2CH_3), 4.02 (s, 3 H, ArOCH_3), 4.46 (s, 2 H, NCH_2), 4.57 (s, 2 H, NCH_2CO_2), 7.48 (d, 1 H, J = 9.5 Hz, ArH), 7.60 (d, 1 H, J = 9.3 Hz, ArH), 8.42 (d, 1 H, J = 9.3 Hz, ArH), 9.49 (d, 1 H, J = 9.5 Hz, ArH); IR ($CHCl_3$) 1748 (C=O), 1681 (C=O), 1602 (C=O). Anal. ($C_{17}H_{14}F_3NO_4$) C, H, N.

2,3-Dihydro-6-(trifluoromethyl)-7-methoxy-1-thioxo-1*H*-benz[*e*]isoindole-2-acetic Acid Methyl Ester (42). Lawesson's reagent (5.37 g, 13.32 mmol) was added to a stirred suspension of lactam **41** (3.91 g, 11.1 mmol) in toluene (40 mL) at room temperature under a dry N_2 atmosphere. The reaction was heated at reflux for 2.5 H, and the cooled reaction mixture was diluted with EtOAC (100 mL), preabsorbed onto silica gel, and flash chromatographed (7:3 to 3:7 petroleum ether–EtOAc, gradient elution, silica) to priovide **42** as a beige solid (2.44 g, 60%): mp 187–188.5 °C (2:1 $CHCl_3$–petroleum ether); NMR ($CDCl_3$, 200 MHz) δ 3.79 (s, 3 H, CO_2CH_3), 4.02 (s, 3 H, ArOCH_3), 4.93 (s, 2 H, NCH_2), 5.04 (s, 2 H, NCH_2CO_2), 7.39 (d, 1 H, J = 9.4 Hz, ArH), 7.92 (d, 1 H, J = 9.3 Hz, ArH), 8.08 (d, 1 H, J = 9.2 Hz, ArH), 8.29 (d, 1 H, J = 9.6 Hz, ArH); IR ($CHCl_3$) 2990 and 2960 (CH), 1746 (C=O), 1622 (C=C); MS (m/e) 369 (99), 337 (11), 310 (58), 309 (100), 282 (68). Anal. ($C_{17}H_{14}F_3NO_3S$) C, H, N.

2,3-Dihydro-6-(trifluoromethyl)-7-methoxy-1-oxo-1*H*-benz[*e*]isoindole-2-acetic Acid (6a). Compound **6a** was prepared from **41** using the conditions described for **5d** (yield 48%): mp 264–265 °C (2:1 EtOH–water); NMR (DMSO-d_6, 400 MHz) δ 4.03 (s, 3 H, ArOCH_3), 4.36 (s, 2 H, NCH_2), 4.61 (s, 2 H, CH_2CO_2), 7.82 (d, 1 H, J = 9.5 Hz, ArH), 7.86 (d, 1 H, J = 9.0 Hz, ArH), 8.29 (d, 1 H, J = 7.8 Hz, ArH), 9.42 (d, 1 H, J = 9.4 Hz, ArH); IR (KBr) 1735 (C=O), 1651 (C=O); MS (m/e) 339 (56), 294 (100), 266 (36), 251 (27), 239 (29). Anal. ($C_{16}H_{12}F_3NO_4$) C, H, N.

2,3-Dihydro-6-(trifluoromethyl)-7-methoxy-1-thioxo-1*H*-benz[*e*]isoindole-2-acetic Acid (6b). A suspension of **42** (2.08 g, 5.63 mmol) in 6 N HCl (80 mL) was heated at reflux for 15 h, with more 6 N HCl (40 mL) added after 3 h. The reaction was cooled to room temperature and diluted with water (100 mL). The acidic suspension was filtered, and the solid was washed with water (2 × 30 mL) and triturated with 1:1 EtOAc–petroleum ether (2 × 40 mL). Recrystallization (EtOAc) provided **6b** as a light yellow solid (0.50 g, 25%): mp 253–255.5 °C dec; NMR (DMSO-d_6, 400 MHz) δ 4.05 (s, 3 H, ArOCH_3), 4.86 (s, 2 H, NCH_2), 5.30 (s, 2 H, NCH_2CO_2), 7.78 (d, 1 H, J = 9.3 Hz, ArH), 7.99 (d, 1 H, J = 9.1 Hz, ArH), 8.20 (d, 1 H, J = 7.7 Hz, ArH), 8.36 (d, 1 H, J = 9.3 Hz, ArH); IR (KBr) 1722 (C=O); MS (m/e) 355 (100), 310 (45), 309 (78), 296 (24), 282 (77). Anal. ($C_{16}H_{12}F_3NO_3S$) C, H, N.

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Evidence for Electron Transfer in Reactions of Thianthrene Cation Radical with Dialkylmercurials

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Reactions of dialkylmercurials (R_2Hg) with thianthrene cation radical perchlorate ($Th^{\bullet+}ClO_4^-$) in acetonitrile solution have been studied in quantitative detail. Evidence was obtained from reactions of MeHgR (R = Et, *i*-Pr, *t*-Bu) that reaction begins with electron transfer rather than with electrophilic cleavage of an alkyl–mercury bond. That is, each reaction gave $MeHg^+$ and $R^\bullet$, diagnostic of the formation and decomposition of $MeHgR^{\bullet+}$, rather than 5-methylthianthreniumyl perchlorate (**1a**), which would have been diagnostic of electrophilic displacement of the least hindered group (Me). The radicals $R^\bullet$ either were trapped at the sulfur atom of $Th^{\bullet+}$ to form a 5-alkylthianthreniumyl perchlorate (Et$^\bullet$, **1b**) and at the ring positions of $Th^{\bullet+}$ to form 1- and 2-alkylthianthrenes and dialkylthianthrenes (Et$^\bullet$, *i*-Pr$^\bullet$) or were oxidized to the cations R^+ (Et$^\bullet$, *i*-Pr$^\bullet$, and *t*-Bu$^\bullet$). Products of R^+ were then obtained, after workup with 4 M aqueous LiCl, as alkene, ROH, $RNHCOCH_3$, and RCl. These reactions had the stoichiometric ratio of reactants $2Th^{\bullet+}ClO_4^-$/MeHgR. Reactions of symmetrical R_2Hg sometimes followed this stoichiometry (R = Me, Et, Bu) and led to RHg^+ and 5-R-thianthreniumyl perchlorates (**1a,b,e**). Other R_2Hg (R = *t*-Bu, benzyl, allyl) underwent oxidation by 4 equiv of $Th^{\bullet+}ClO_4^-$. Di-*tert*-butyl- and dibenzylmercury gave products derived entirely from the respective cation, R^+. Diallylmercury gave some of the sulfonium product, 5-allylthianthreniumyl perchlorate (**1g**). None of the reactions with R = *i*-Pr, *t*-Br, and benzyl led to the isolation of a thianthreniumyl perchlorate (i.e., **1c,d,f**). Oxidations at the 4:1 molar ratio produced $Hg(ClO_4)_2$, which formed a partly insoluble complex (**2**) with thianthrene having the composition $Th_3Hg(ClO_4)_2$. This product could be isolated if removed before workup treatment with aqueous 4 M LiCl, which, otherwise caused its decomposition into its components. The complex **2** was also prepared directly from reaction of Th with $Hg(ClO_4)_2$ in acetonitrile. Oxidation of benzylmercuric chloride by $Th^{\bullet+}ClO_4^-$ in methylene chloride solution also occurred quantitatively, giving benzyl chloride, 1- and 2-benzylthianthrene, and a mixture of dibenzylthianthrenes. Oxidation of *t*-BuHgCl in acetonitrile solution led to a quantitative mixture of isobutene, *t*-BuOH, and *t*-BuNHAc. $Th^{\bullet+}ClO_4^-$ also oxidized metallic Hg to either Hg^+ or Hg^{2+}, depending on the amount of oxidant used.

Some years ago it was found that the thianthrene ($Th^{\bullet+}$) and phenoxathiin cation radicals reacted with some diarylmercurials and with dimethyl- and diethylmercury according to eq 1.[2] In this equation, R represented then

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