(2R,3S)-26, 116264-00-7; (2S,3S)-26, 116264-36-9; (2R,3R)-27, 116264-01-8; (2S,3R)-27 (free acid), 116264-45-0; (2S,3R)-27, 116264-37-0; (2S,3R)-27 (free acid), 116264-45-0; (2R,3R)-28, 116264-02-9; (2S,3R)-28, 116264-38-1; (2R,3S)-29, 103542-90-1; (2S,3S)-29, 103542-91-2; (2R,3S)-31, 116264-03-0; (2S,3S)-31, 116264-04-1; (2R,3R)-33, 116264-05-2; (2S,3R)-33, 116264-06-3; (2R,3R)-35, 116264-07-4; (2S,3R)-35, 116264-08-5; (2R,3S)-37, 103542-92-3; (2S,3S)-37, 103542-93-4; (2R,3S)-39, 116264-09-6; (2S,3S)-39, 116264-10-9; (2R,3R)-41, 116264-11-0; (2S,3R)-41, 116264-12-1; (2R,3R)-43, 116264-13-2; (2S,3R)-43, 116264-16-5; (2R,3S)-47, 116264-17-6; (2S,3S)-47, 116264-18-7; (2R,3R)-49, 116264-19-8; (2S,3R)-49, 116264-20-1; (2R,3R)-51, 116264-21-2; (2S,3R)-51, 116264-22-3; (2R,3S)-53·2HCl, 116278-41-2; (2R,3S)-53 (free base), 116264-46-1; (2S,3S)-53·2HCl, 116264-23-4; (2S,3S)-53 (free base), 116264-47-2; (2R,3S)-55·2HCl, 116264-24-5; (2R,3S)-55 (free base), 116264-48-3; (2S,3S)-55·2HCl, 116264-25-6; (2S,3S)-55 (free base), 116264-49-4; (2R,3R)-57·2HCl, 116264-26-7; (2R,3R)-57 (free base), 116264-50-7; (2S,3R)-57·2HiCl, 116264-27-8; (2S,3R)-57 (free base), 116264-51-8; (2R,3R)-59·2HCl, 116264-28-9; (2R,3R)-59 (free base), 116264-52-9; (2S,3R)-59·2HCl, 116264-29-0; (2S,3R)-59 (free base), 116264-53-0; (2R)-61, 103542-94-5; (2S)-61, 103618-11-7; (2R)-62·2HCl, 116300-01-7; (2R)-62 (free base), 103542-95-6; 3-(2S)-62·2HCl, 116300-20-0; (2S)-62 (free base), 103618-12-8; 63, 6258-60-2; 64, 35378-93-9; 65, 85301-93-5; 66·HCl, 116264-30-3; 66 (free base), 81110-01-2; 67, 116264-31-4; 68, 116264-32-5; 69, 116264-33-6; (2R)-70·2HCl, 116346-47-5; (2R)-70 (free base), 116300-11-9; (2S)-70·2HCl, 116346-48-6; (2S[-70 (free base), 116300-12-0; (2R)-72·2HCl, 116346-49-7; (2R)-72 (free base), 116300-13-1; (2R)-72 (N-BOC-protected), 116264-41-6; (2S)-72·2HCl, 116346-51-1; (2S)-72 (free base), 116300-14-2; 1(2S)-72 (N-BOC-protected), 116300-06-2; (2R)-73·2HCl, 116264-34-7; (2R)-73 (free base), 116300-15-3; (2R)-73 (N-BOC-protected), 116264-42-7; (2S)-73·2HCl, 116300-09-5; (2S)-73 (free base), 116346-53-3; (2S)-73 (N-BOC-protected), 116300-07-3; (2R)-74·2HCl, 116346-50-0; (2R)-74 (free base), 116300-16-4; (2R)-74 (N-BOC-protected), 116264-43-8; (2S)-74·2HCl, 116346-52-2; (2S)-74 (free base), 116300-17-5; (2S)-74 (N-BOC-protected), 116300-08-4; (2R)-75, 116300-02-8; (2S)-75, 116300-19-7; (2R)-76, 115362-76-0; (2S)-76, 115362-75-9; (2R)-78·HCl, 114926-90-8; (2R)-78 (free base), 116346-77-1; (2S)-78·HCl, 114886-46-3; (2S)-78 (free base), 116300-18-6; (2R)-80, 116300-03-9; (2S)-80, 116300-10-8; (2R)-81·HCl, 116300-04-0; (2R)-81 (free base), 116346-54-4; (2S)-81·HCl, 116403-21-5; (2S)-81 (free base), 116346-55-5; [(4-MeO)$C_6H_4CH_2S]_2$, 17004-42-1; $H_2NCH_2CH_2CH_2CH(CH_3)_2$, 107-85-7; H-Phe-Leu-OBu-t, 28635-78-1; $ClCH_2CH_2OH$, 107-07-3; (4-MeO)$C_6H_4CH_2SCH_2CH_2$-Phe-Leu-OBu-t, 116264-39-2; H-Leu-OBu-t, 21691-53-2; (2R,3S)-(BOC)NHCH(CH_2Ph)CH(S$CH_2C_6H_4$-p-OMe)CH_2-Leu-OBu-t, 116264-40-5; (2S,3S)-(BOC)NHCH(CH_2Ph)CHu(S$CH_2C_6H_4$-p-OMe)CH_2-Leu-OBu-t, 116300-05-1; H-Leu-NHz, 687-51-4; aminopeptidase, 9031-94-1.

Structure–Activity Relationships among Analogues of Pemedolac, *cis*-1-Ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)pyrano[3,4-*b*]indole-1-acetic acid, a Potent Analgesic Agent

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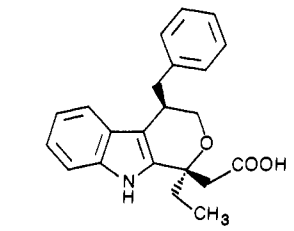
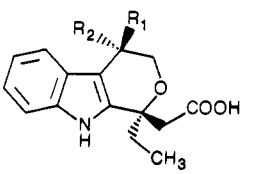
The syntheses of analogues of pemedolac (*cis*-1-ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)pyrano[3,4-*b*]indole-1-acetic acid), a potent analgesic, are described. They were tested for analgesic and antiinflammatory effects in vivo and for inhibition of prostaglandin production in vitro. Analysis of structure–activity relationships shows that analgesic activity in this series is associated with 1*S*-cis stereochemistry, the presence of a π-system (allyl or benzyl) at position 4, and a log *P* value greater than 4.0.

Recent reports from our laboratories[1,2] describe the synthesis, structure, and pharmacological properties of *cis*-1-ethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)pyrano-[3,4-*b*]indole-1-acetic acid, AY-30,715, pemedolac (USAN), **1**, a new potent analgesic agent that is currently being evaluated in humans. Herein we describe the syntheses, analgesic, and antiinflammatory screening data and structure–activity relationships for a series of pemedolac analogues.

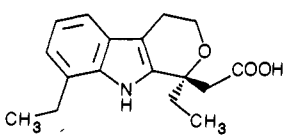
The choice of targets for synthesis was dictated by two independent observations made during the study of structure–activity relationships among analogues of the antiinflammatory–analgesic agent etodolac, **5**.[3,4] First, of the diastereomeric pair of 4-methylpyrano[3,4-*b*]indole-1-acetic acids **2** and **3**, the cis diastereomer **2**[5] is twice as potent as the corresponding 4-desmethyl analogue, while the trans diastereomer **3**, as well as the 4,4-dimethyl analogue **4**, was almost devoid of activity.[6] Second, replacing the pyrano oxygen of etodolac by a methylene group gives the tetrahydrocarbazole **6**, which is almost equipotent to etodolac in the rat adjuvant arthritis model.[7]



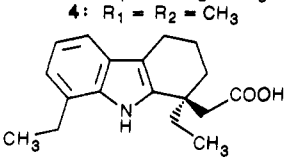
1



2: $R_1 = CH_3$; $R_2 = H$
3: $R_1 = H$; $R_2 = CH_3$
4: $R_1 = R_2 = CH_3$



5



6

These observations suggested that it might be profitable to synthesize and test a series of 4-substituted pyrano-

† Ayerst Laboratories.
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§ University of Waterloo.

(1) Katz, A.; Demerson, C. A.; Shaw, C. C.; Asselin, A. A.; Humber, L. G.; Conway, K.; Gavin, G.; Jensen, N. P.; Noureldin, R.; Schmid, J.; Shah, U.; Van Engen, D.; Chau, T.; Weichman, B. *J. Med. Chem.* **1988**, *31*, 1244.
(2) Chau, T. T.; Weichman, B. M. *J. Pharmacol. Exp. Ther.*, in press.

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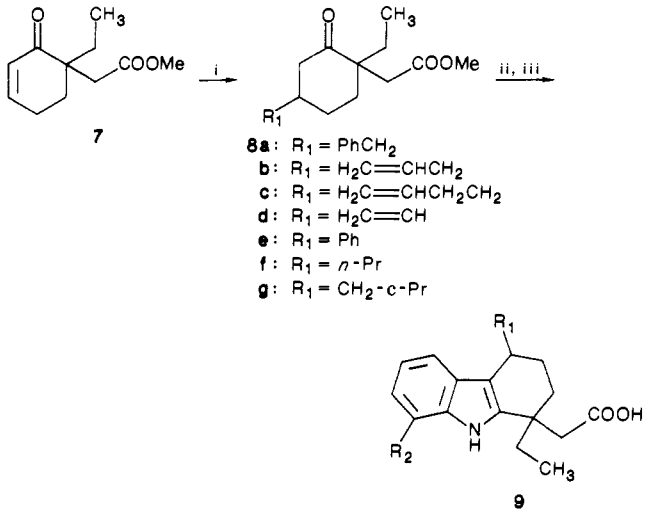
Scheme I[a]



[a] (i) $R^1MgX/CuBr\cdot Me_2S/THF/Me_2S$. (ii) (a) $ArNHNH_2$/MeOH/Δ; (b) HCl/Δ. (iii) K_2CO_3/MeOH/Δ.

[3,4-*b*]indole and tetrahydrocarbazole-1-acetic acids as probes for exploring the characteristics of the region in space on the "receptor" for these agents, that is, the enzyme arachidonic acid cyclooxygenase (see below), that is occupied by the 4-cis substituent.

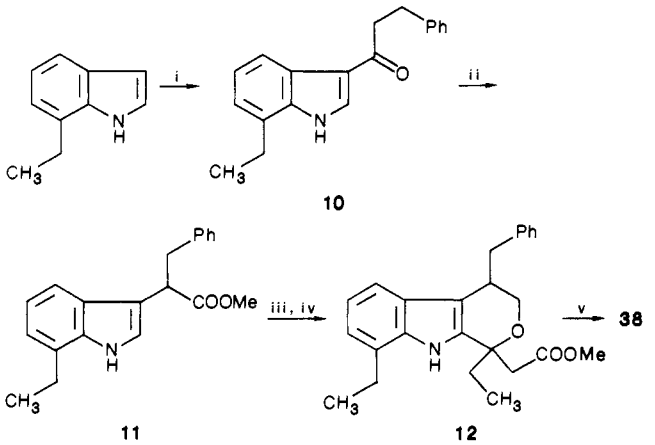
Chemistry

The 4-substituted tetrahydrocarbazoles **13**, **14**, and **20–29** were prepared as outlined in Scheme I. Copper-catalyzed conjugate addition of Grignard reagents to enone **7** gave ketones **8**. Hydrazone formation, Fischer indole cyclization, and ester hydrolysis then afforded tetrahydrocarbazoles **9**. In the case of *cis*-4-allylcarbazoles **15** and **30–32**, ketone **8b** (cis) was prepared stereoselectively as described elsewhere[8] and then converted to carbazoles **9** via the same Fischer indole sequence. Propyl compound **19** was prepared by catalytic hydrogenation of the 4-allyl compound **15**. Resolution of compound **15** was accomplished by classical recrystallization techniques using brucine as the resolving agent. Catalytic hydrogenation of the 1*R* enantiomer followed by derivatization with 2,4′-dibromoacetophenone giving **47**, or salt formation with (*R*)-α-methylbenzylamine giving **48**, produced crystalline compounds, which were used for X-ray crystallography. The trans isomer **18** was prepared by chromatographic separation of a mixture of ketones **8b**[8] followed by Fischer indole cyclization and ester hydrolysis. Cyclopropylmethyl compound **33** was prepared by cyclopropanation of ketone **8b** (cis) followed by the Fischer indole sequence.

Except for **38**, the 4-substituted pyranoindoles **1**, **34–37**, and **39–46** were prepared from the corresponding 7-substituted isatins as described recently.[1]

In the case of **38**, indoleacetic acid **11** was prepared via thallium(III) rearrangement[9] of 3-acylindole **10** (Scheme II).

Scheme II[a]



[a] (i) (a) $EtMgBr/Et_2O$; (b) $PhCH_2CH_2COCl$. (ii) $Th^{III}(NO_3)_3\cdot 3H_2O/(MeO)_3CH/MeOH$. (iii) LAH. (iv) $EtCOCH_2COOMe$/TsOH/PhH. (v) $NaOH/EtOH/H_2O$.

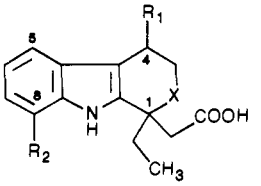
Acylation of 7-ethylindole with dihydrocinnamoyl chloride produced **10**. Treatment of **10** with thallium(III) nitrate trihydrate in 1:1 methanol–trimethyl orthoformate resulted in indole ester **11**. Reduction with lithium aluminum hydride then gave the 7-ethyltryptophol, which was cyclized and hydrolyzed to **38** as described recently.[1]

Results and Discussion

The compounds studied are collected in Table I along with their analgesic and antiinflammatory activities in comparison with those of etodolac, indomethacin, and pemedolac, **1**. The most striking facet of the structure–activity relationships (SAR) to emerge is that, in both the pyrano[3,4-*b*]indole and the tetrahydrocarbazole series, high analgesic potency is associated with the presence of a π-system comprising at least two sp^2 hybridized carbon atoms attached to position 4 through a methylene group and oriented cis (see below) to the acetic acid moiety. Thus, 4-allyl analogues (**15**, **16**, **30–32**, **43**, and **45**) and 4-benzyl analogues (**1**, **24**, **26**, **28**, and **36**) have ED50s in the range of 1.2–28.7 mg/kg in the mouse writhing assay. The virtually complete absence of analgesic activity with **19**, the dihydro derivative of the 4-allyl analogue **15**, suggests that, on binding with its receptor, the allyl group is not involved in a purely hydrophobic interaction since the π-values for allyl and *n*-propyl, 1.1 and 1.5, respectively, are similar.[10] The location of the π-system with respect to the nuclei is of critical importance since both members of the diastereomeric pairs with vinyl (**13**, **14**), homoallyl (**20**, **21**), phenyl (**22**, **23**), and phenylethyl (**34**, **35**) substituents at position 4 result in compounds with only marginal analgesic activity. The dependence of high analgesic activity on the presence of a precisely localized π-system suggests that the nature of its interaction with its receptor should be of the charge transfer or dispersive variety.[11,12] However, the difference in the ionization potential between a monosubstituted phenyl ring and an olefin (8.78 and 10.01 eV, respectively) is sufficiently large that charge-transfer interactions, at least at the same site,

(3) ULTRADOL, LODINE; trademark names, Ayerst Laboratories Inc., New York, New York.
(4) For a review on etodolac, see: Humber, L. G. *Med. Res. Rev.* **1987**, *7*, 1.
(5) The relative stereochemistries of **2** and **3** were assigned on the basis of a crystallographic study of **2** (see Table II). Details of this study are available as supplementary material.
(6) Demerson, C. A.; Humber, L. G.; Dobson, T. A.; Martel, R. R. *J. Med. Chem.* **1975**, *18*, 189.
(7) Asselin, A.; Humber, L. G.; Dobson, T.; Martel, R. *J. Med. Chem.* **1976**, *19*, 787.
(8) Mobilio, D.; DeLange, B. *Tetrahedron Lett.* **1987**, *28*, 1483.
(9) McKillop, A.; Taylor, E. C. *Comprehensive Organometallic Chemistry*, Wilkinson, G., Stone, F. G., Abel, E. W., Eds.; Pergamon: New York, 1983; Vol. 7, pp 465–513.
(10) Hansch, C.; Leo, A. *Sustituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1974.
(11) Kollman, P. A. *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; Wiley: New York, 1980; Part 1, pp 313–329.
(12) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969, Chapter 9.

Table I. Chemical, Pharmacological, and Biochemical Data on Substituted Tetrahydrocarbazole- and Pyrano[3,4-*b*]indole-1-acetic Acids



no.	config[a]	R_1	R_2	X	mp, °C	crystn solvent[b]	mouse writhing assay[c]	preventative adjuvant edema assay[c]	log P[d]	chondrocyte assay, $IC_{50} \times 10^{-8}$ M
1	cis	$CH_2C_6H_5$	H	O	145–147	A, B	2.0 (0.5–8.3)[e]	37%	4.4	2.3
6		H	Et	CH_2	*f*		16%	*i*	5.3	2
13	cis/trans pair	$CH=CH_2$	Et	CH_2	144–147	A, B	21%	30%		
14		$CH=CH_2$	Et	CH_2	100–101	A, B	0%	62%		
15	cis; (±)	$CH_2CH=CH_2$	Et	CH_2	120.5–122	A, B	10.6 (3–38)[e]	44%	6.3	1.5
16	(+)-(1*S*-*cis*)[g]	$CH_2CH=CH_2$	Et	CH_2	133–134	C	94%	54%		1.5
17	(−)-(1*R*-*cis*)[g]	$CH_2CH=CH_2$	Et	CH_2	133.5–134	C	5%	0%		400
18	trans	$CH_2CH=CH_2$	Et	CH_2	127–129.5	C, D	23%[h]	35%		
19	cis	*n*-Pr	Et	CH_2	109–110	A, B	15%	*i*		
20	cis/trans pair	$(CH_2)_2CH=CH_2$	Et	CH_2	107–108.5	A, B	2%	43%		
21		$(CH_2)_2CH=CH_2$	Et	CH_2	101–102.5	A, B	0%	16%		
22	cis/trans pair	C_6H_5	Et	CH_2	140–142.5	A, B	17%	12%		
23		C_6H_5	Et	CH_2	118–121	A, B	28%	37%		
24	cis	$CH_2C_6H_5$	H	CH_2	155–157	E	1.2 (0.4–3.8)[e]	49%	6.2	1.1
25	trans	$CH_2C_6H_5$	H	CH_2	115–116.5	A, B	4%	42%		
26	cis	$CH_2C_6H_5$	Me	CH_2	179–181	E	3.4 (2.1–5.8)[e]	43%	6.9	
27	trans	$CH_2C_6H_5$	Me	CH_2	121–123	E	5%[j]	24%		
28	cis	$CH_2C_6H_5$	Et	CH_2	181–184	A, B	22.3 (12.2–41)[e]	38%	7.4	
29	trans	$CH_2C_6H_5$	Et	CH_2	185–186	A, B	15%	6%		
30	cis	$CH_2CH=CH_2$	H	CH_2	103–105	A, B	19.6 (9.6–40.6)[e]	11.1 (7–18)[e]	5.2	5
31	cis	$CH_2CH=CH_2$	Me	CH_2	142–143	A, B	8.3 (4.2–16.3)[e]	8.5 (4.1–16.6)[e]	5.8	5
32	cis	$CH_2CH=CH_2$	*n*-Pr	CH_2	140–142	A, B	28.7 (16.3–50.5)[e]	39%	6.9	
33	cis	CH_2-c-Pr	Et	CH_2	100–102	A, B	0%	19%		
34	cis/trans pair	$(CH_2)_2C_6H_5$	H	O	104–106	A, B	0%	0%		
35		$(CH_2)_2C_6H_5$	H	O	136–138	A, B	0%	20%		
36	cis	$CH_2C_6H_5$	Me	O	141–143	B, F	4.7 (2.4–9.0)[e]	47%	5.0	
37	trans	$CH_2C_6H_5$	Me	O	174–176	B, F	11%	40%		
38	cis[k]	$CH_2C_6H_5$	Et	O	147–148.5	A, B	86%	15%	5.6	
39	cis	$CH_2CH=CH_2$	H	O	133–138	A, B	21%	46%	3.3	12
40	trans	$CH_2CH=CH_2$	H	O	136–141	A, B	25%	30%		>1000
41	cis	$CH_2CH=CH_2$	Me	O	135–137	D	10%[j]	54%[l]	4.0	20
42	trans	$CH_2CH=CH_2$	Me	O	138–139	B, F	15%[j]	31%		>1000
43	cis	$CH_2CH=CH_2$	Et	O	96–97	B, C	6.2 (3–13.5)[e]	7.8 (1.8–34.8)[e]	4.5	30
44	trans	$CH_2CH=CH_2$	Et	O	118–119.5	B, C	33%[m]	55%		
45	cis	$CH_2CH=CH_2$	*n*-Pr	O	99.5–101.5	A, B	9.5 (4.9–18.3)[e]	32%[l]		
46	trans	$CH_2CH=CH_2$	*n*-Pr	O	117–120	A, B	2%	36%		
etodolac							168 (117–241)[e]	11.2 (4.4–29)[e]	3.5	2.3
indomethacin							1.5 (0.9–2.8)[e]	1.0 (0.4–2.7)[e]		1.1

[a] All compounds, except 16 and 17, are racemates. [b] A = benzene, B = petroleum ether, C = ether, D = hexane, E = heptane, F = toluene. [c] Inhibition of phenylbenzoquinone-induced writhing, or of adjuvant-induced paw edema at 25 mg/kg, po unless indicated otherwise; see Experimental Section for details. [d] Calculated log P values using the CLOGP3 Program in MEDCHEM, version 3.51, distributed by the Medicinal Chemistry Project, Pomona College, Claremont, CA. A correlation coefficient of 0.87 was found between calculated log P values and experimentally determined log K' values (see Experimental Section) for a series of 51 pyrano[3,4-*b*]indole- and tetrahydrocarbazole-1-acetic acids. [e] ED_{50} value (mg/kg) with 95% confidence limits. [f] See ref 7. [g] Tested as benzylamine salts. Doses used were calculated as the free acid. [h] Tested at 200 mg/kg. [i] Not tested. [j] Tested at 10 mg/kg. [k] Only one diastereomer was tested; it was assigned a cis configuration on the basis of its potency in the mouse writhing assay. [l] Tested at 3 mg/kg. [m] Tested at 100 mg/kg.

can be ruled out.[13] Therefore, it is likely that the interaction between the allyl and benzyl substituents of these ligands with their receptor is due predominately to dispersion forces.

The above SAR describing the role of the 4-substituent are in marked contrast to that observed with the opiate antagonists where *N*-allyl, *N*-*n*-propyl, and *N*-cyclopropylmethyl substituents lead to potent antagonists,[14] while *N*-benzyl derivatives do not.[15] In this instance, it is likely that these former groups participate in hydrophobic interactions with the opiate receptor. Although the cyclopropyl ring and the olefinic bond have many reactivity parameters in common,[16] the absence of analgesic activity with the 4-cyclopropylmethyl derivative **33** described herein may be due to its high ionization potential, 11.0 eV, which would prevent it from participating in charge transfer or dispersion interactions.

In summary, the findings discussed above suggest the following: (1) that there exists on the receptor with which these drugs interact a uniquely located binding site that recognizes the π-system present in the allyl and benzyl groups, and (2) that the normal function of the binding

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(14) Clark, R. L.; Pessolano, A. A.; Weijlard, J.; Pfister, K., 3rd *J. Am. Chem. Soc.* **1953**, *75*, 4963.
(15) Winter, C. A.; Orahovats, P. D.; Lehman, E. G. *Arch. Int. Pharmacodyn.* **1957**, CX, 186, 16.
(16) For a summary of data on this similarity, see footnote 7 In Gates, M.; Montzka, T. A. *J. Med. Chem.* **1964**, *7*, 127.

site is to recognize one of the double bonds of arachidonic acid, the substrate for cyclooxygenase, the presumed receptor with which these ligands interact (see below).

The stereochemical features associated with analgesic activity have been elucidated in detail by single-crystal X-ray analyses (see Table II and ref 1). On the basis of these studies,[1,17] both **16** and the active enantiomer of **1** were shown to possess cis-1*S*,4*R* relative and absolute configurations. A cis relative configuration was assigned for racemates **19** and **30–33** on the basis of the stereochemical controls operative during their syntheses. In the other entries in Table I, the relative configurations are unknown; however, compounds that were active in vivo or in vitro (**24**, **26**, **28**, **36**, **38**, **39**, **41**, **43**, **45**) were assumed to have cis relative configurations based on the crystallographically determined configurational requirements associated with the activity of **1** and **16** in the writhing and chondrocyte assays.

The prototype of this series, etodolac, has been resolved,[18] and its antiinflammatory activity is known to be associated exclusively with the 1*S* enantiomer.[19] The common absolute configurational requirements between the biologically active enantiomers of these structurally similar drugs, etodolac, **1**, and **16**, suggest that they may act at a common receptor by a like mechanism. Indeed, etodolac has been shown to inhibit prostaglandin biosynthesis in a sheep seminal vesicle preparation[18] and in various cell types including the chondrocyte.[20] The inhibitory activities in the chondrocyte assay of **1**, **16**, and selected other analogues are shown in Table I. Thus, it is likely that etodolac, as well as the active compounds described herein, exert their antiinflammatory and analgesic activities via inhibition of cyclooxygenase. However, even for compounds such as etodolac, **1**, **16**, **24**, **30**, and **31**, which are demonstrated to be virtually equipotent in the chondrocyte assay (IC50s between 1.1 and 5.0 × 10^{-8} M; see Table I), markedly different balances between antiinflammatory and analgesic potencies are observed (see Table I). Particularly striking is the fact that the most potent analgesics described herein, **1** and **24**, are respectively 84 and 140 times more potent than etodolac in the mouse writhing assay.

As discussed above, high analgesic potency is dependent on the presence of a π-system attached at position 4; however, that does not appear to be the sole prerequisite for activity. Thus, the most potent analgesics described herein are markedly more lipophilic (log P = 4.4–7.4)[21] than etodolac (log P = 3.5), and the only 4-allyl or 4-benzyl derivatives that are inactive as analgesics are **39**/**40** and **41**/**42**, which have log P values of 3.3 and 4.0, respectively. While **39** and **41** are inactive as analgesics, they nevertheless possess levels of activity in the chondrocyte assay (IC_{50} = (12–20) × 10^{-8} M) similar to that of the active analgesic analogue **43** (ED_{50} = 7.0 mg/kg in the writhing assay; IC_{50} = 30 × 10^{-8} M). The major difference between inactive **39** and **41** and analgesically active **43** is that the latter has a log P value of 4.5 while **39** and **41** have values of less than 4.0 (see above), and the failure of **39** and **41** to manifest analgesic activity may be due to their possession of subthreshold lipophilicity levels. It thus appears that the presence of a π-system, as well as a log P value greater than ~4.0, is required for potent analgesic activity. Consistent with this suggestion is the profile of **6**, the tetrahydrocarbazole analogue of etodolac. Compound **6** is equipotent to etodolac in vitro in the chondrocyte assay and in the curative adjuvant arthritis assay,[7,22] and has a log P value of 5.3, but shows only weak analgesic activity in the mouse writhing assay (16% inhibition at 25 mg/kg). This lack of activity is ascribed to the absence of a π-binding group at position 4 in **6**.

While the requisites for high analgesic potency can be rationalized in terms of the presence of the π-system at position 4 and a log P value greater than 4, the requirements for high antiinflammatory potency are not obvious. High antiinflammatory potency is seen both in the absence (e.g. etodolac, **6**[7]) and in the presence (e.g. **30**, **31**, **43**) of a π-system at position 4, and analogues that are equipotent as analgesics and antiinflammatory agents (**30**, **31**, **43**) have log P values encompassing that of pemedolac, which, in turn, has only marginal antiinflammatory activity. Etodolac, a potent antiinflammatory agent with weak analgesic activity has a log P value of 3.5, well below the threshold value associated with potent analgesia.

We have presented evidence above for the existence of a π-binding site on cyclooxygenase; the occupancy of and the binding to this site by the ligands described herein should, theoretically, endow them with a higher affinity for the enzyme, in comparison with ligands such as etodolac and **6**, which do not utilize that site. However, this is not evident from an inspection of IC50s in the chondrocyte assay (Table I), where various ligands have virtually identical potencies whether or not they possess allyl or benzyl groups. The chondrocyte assay comprises a cellular system and therefore does not provide a measure of intrinsic affinity for cyclooxygenase. If the analgesics described in this work do indeed possess higher affinities for cyclooxygenase than 4-unsubstituted pyrano[3,4-*b*]-indoles and tetrahydrocarbazoles, it will be possible to provide evidence only by measuring binding constants in a purified cyclooxygenase preparation.

In conclusion, from an analysis of SAR data in this series of potent analgesic agents, it appears that high activity is dependent on the presence of a uniquely located π-system and that a threshold lipophilicity value needs to be achieved before analgesic activity can be expressed. Very little is known about the anatomical location of the prostaglandin pool that mediates nociception in the animal model used; however, its accessibility, at least for the present series of analgesics, appears to be dependent on a relatively high lipophilicity.

Experimental Section

The animal and cell assays described above were carried out according to the following procedures.

Phenylbenzoquinone Writhing Assay. Analgesic activity was quantitated in male Swiss albino mice (15–25 g; Charles River, Kingston, NY) as the inhibition of writhing elicited by intra-

(17) Crystallographic studies were carried out on the dihydro derivative of **17**, the biologically inactive enantiomer of **16**; thus, **47**, the *p*-bromophenacyl ester, and **48**, the (*R*)-α-methylbenzylamine salt, were both observed to have cis-1*R*,4*R* relative and absolute configurations (see Table **II** and supplementary material for details). Taking into account the change in priorities consequent to reduction of the double bond in **17**, it follows that **16** possesses cis-1*S*,4*R* relative and absolute configurations. A single-crystal X-ray analysis done on the racemate **15** (see Table **II** and supplementary material) showed that it possesses a cis relative configuration, thus confirming the above cis assignment.

(18) Demerson, C.; Humber, L.; Abraham, N.; Schilling, G.; Martel, R.; Pace-Asciak, C. *J. Med. Chem.* **1983**, *26*, 1778.

(19) Humber, L.; Demerson, C.; Swaminathan, P.; Bird, P. *J. Med. Chem.* **1986**, *29*, 871.

(20) Neuman, G. R.; Wilson, B. D.; Barkley, M.; Kimball, E. S.; Weichman, B. M.; Wood, D. D. *Agents Actions* **1987**, *21*, 160.

(21) log P values were calculated. See footnote *d*, Table I.

(22) Demerson, C. A.; Humber, L. G.; Philipp, A. H.; Martel, R. R. *J. Med. Chem.* **1976**, *19*, 391.

peritoneal injection of 2-phenyl-1,4-benzoquinone (PBQ) by using a modification of the method of Siegmund et al.[23] Groups of 10 mice were fasted overnight and then either the indicated drug or the vehicle control (0.5% Tween 80 in distilled water) was administered by gastric gavage. One hour later, the mice were injected ip with PBQ (0.15 mL of 0.02% PBQ/10 g body weight). The mice were placed in individual observation boxes, and the number of writhes or abdominal squirming movements made by each mouse was determined for the 15-min period following PBQ. The percent inhibition of writhing relative to the control vehicle treated group was calculated, and where appropriate, the ED_{50} and its 95% confidence limits were determined by the method of Litchfield and Wilcoxon.[24]

Preventative Adjuvant Edema. Male Sprague–Dawley rats (180–200 g) were injected intradermally in the left hindpaw with 0.1 mL of Freund's complete adjuvant (FCA). The indicated compound or vehicle control was administered by gastric gavage immediately before the FCA injection (day 0) and 24 and 48 h after the FCA (days 1 and 2). The volume of the injected hindpaw was measured both before the FCA injection and 24 h after the last compound administration (day 3) by means of a plethysmometer (Buxco Electronics, Sharon, CT). The mean hindpaw volume was calculated for each group, and the mean edema volume represents the difference between the volumes on days 0 and 3.

In Vitro IC_{50} Determinations. The method for determining IC50s in stimulated chondrocyte cultures has been described in detail elsewhere.[20]

Chemistry. All chemicals were obtained from Aldrich Chemical Co. and were used as received, except lithium diisopropylamide (LDA), which was purchased as a cyclohexane solution from Lithco, and methyl 4-pentenoate, which was purchased from Bedoukian Research Inc. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under nitrogen. (2-Ethyl-, 2-propyl-, and 3-chloro-2-methylphenyl)hydrazine were prepared as described in the literature.[7]

Flash chromatography was carried out according to the procedure of Still.[25] Thin-layer analyses were done on E. Merck silica gel 60 F-254 plates of 2.5-mm thickness.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. Proton magnetic resonance (^1H NMR) spectra were recorded at 60 MHz (Varian EM 360) or at 200 MHz (Varian XL-200) as solutions in chloroform-*d* with added tetramethylsilane or chloroform (7.25 ppm) serving as the internal standard. 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. Mass spectra were recorded on either a Finnigan Model 8230 or Hewlett-Packard Model 5995A mass spectrometer. All rotations were measured as 1% solutions in $CHCl_3$. Analyses were carried out by the Chemistry Department of Ayerst Laboratories Research Inc., on a modified Perkin-Elmer Model 240 CHN analyzer. Analytical results for elements indicated were within ±0.4% of the theoretical values. Gas chromatography was performed on a Varian 3300 gas chromatograph using a Chrompak wall coated fused silica 51 m × 0.23 mm capillary column with a Cp Sil 5 CB liquid phase. X-Ray crystallography was carried out on **2**, **15**, **47**, and **48**, and a partial listing of the data can be found in Table II. Complete details are provided as supplementary material.

Determination of log *k'*. log *k'* data were generated by using the following HPLC component system: Knauer Type 64 pump, Waters Model 710b WISP autosampler, Waters Model 481 Lambda-Max variable-wavelength absorbance detector, Spectra Physics Model SP 4200 integrator, Jones Chromatography Model 7931 column heater.

A 0.03 mg/mL sample of each compound (10 μL) was injected onto a Waters Novapak C18 column (150 × 3.9 mm). The flow rate was 1 mL/min and the column was maintained at 25 °C. Samples were monitored at a wavelength of 280 nm. The eluent was made up to an initial concentration of 42.5% acetonitrile/57.5% 0.001 M KH_2PO_4, pH 3, and then adjusted so that, for any Novapak C18 column, the log *k'* of the standard (etodolac) was 0.96 ± 0.02. Capacity factors (*k'*) were calculated by the equation: $t_R - V_o/V_o = k'$, where t_R is the retention time of the compound and the retention time of $NaNO_2$ under the experimental conditions was used as V_o.

Each sample was injected twice and after every one to six injections (depending on length of run) the standard was reinjected. Deviation of the values of the standard sample log *k'* during an experiment was <0.5%.

Table II. Crystallographic Data[a]

	47	48	15	2[b]
molecular formula	$C_{29}H_{34}BrNO_3$	$C_{29}H_{40}N_2O_2$	$C_{21}H_{27}NO_2$	$C_{16}H_{19}NO_3$
formula weight	524.5	448.65	325.5	273.33
a (Å)	12.339 (4)	6.081 (2)	12.119 (4)	8.557 (1)
b (Å)	12.339 (4)	15.850 (5)	12.711 (4)	8.756 (1)
c (Å)	35.495 (13)	27.919 (8)	15.702 (4)	20.363 (3)
α			113.38 (2)	
β			90.48	108.32 (1)
δ			116.48 (2)	
V (Å^3)	5404 (3)	2691	1936 (1)	1448.4 (4)
Z	8	4	4	4
space group	$P4_12_12$	$P2_12_12_1$	P_1	$P2_1/n$
ρ_c (g cm^{-3})		1.107	1.12	1.253
R	0.096	0.058	0.0865	0.038
R_w	0.085	0.068	0.097	0.045
program	SHELXTL	MULTAN 80	SHELXTL	MULTAN 80

[a] Full details of the crystallographic analyses are available as supplementary material. [b] See ref 7 for the synthesis of this compound.

General Procedure for the Synthesis of 4-Substituted 2-Oxocyclohexaneacetic Acid Methyl Esters (8). Except for **8b**, which is described elsewhere,[8] the synthesis of the ketones was carried out as described below for **8a**. In the case of **8c–e**, the diastereomeric mixture was separated at the ketone stage by chromatography on silica gel. In the case of **8a**, separation of the diastereomers was carried out by reverse-phase chromatography on C18 gel at the indoleacetic acid stage.

1-Ethyl-2-oxo-4-(phenylmethyl)cyclohexaneacetic Acid Methyl Esters (8a). Enone **7** (56.26 mmol, 11.04 g), Me_2S (11.25 mL), and $CuBr{\cdot}Me_2S$ (5.63 mmol, 1.15 g) were stirred in 166 mL of THF at −40 °C under nitrogen and treated with 56.3 mmol (28.1 mL of 2 M in THF) of $PhCH_2MgCl$ added dropwise. The reaction was then quenched with 150 mL of 1 M HCl and extracted with 4 × 100 mL of petroleum ether. The organic phases were dried over Na_2SO_4 and concentrated. Flash chromatography (95 mm diameter column, 12% ethyl acetate/petroleum ether eluent) afforded **8a** (11.20 g, 38.84 mmol, 69%, yellow oil) as a mixture of isomers: ^1H NMR ($CDCl_3$, 60 MHz) δ 0.8 (2 t, 3 H, *J* = 7 Hz), 1.2–2.8 (m, 11 H), 2.6 (s, 2 H), 3.6 and 3.7 (2 s, 3 H), 7.3 (s, 5 H); IR (neat) 1745, 1710 cm^{-1}.

***cis*-4-(Cyclopropylmethyl)-1-ethyl-2-oxocyclohexaneacetic Acid Methyl Ester (8g).** Diazald (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, 40 g) was dissolved in 360 mL of ether and dripped into a solution of potassium hydroxide (40 g) in 64 mL of water and 80 mL of ethanol at 65 °C. The ethereal diazomethane was distilled and collected at 0 °C. To the ethereal solution were then added 2.0 g (8.39 mmol) of olefin **8b** followed by 10 mg of $Pd(OAc_2)$. After the bubbling had subsided, a few more portions of $Pd(OAc_2)$ were added until no additional bubbling was observed. The reaction was then filtered through basic alumina and concentrated in vacuo. Gas chromatography showed that the product was a 70:26 mixture of cyclopropanation product/starting material. The product was combined with material from two other reactions, one done on 715 mg of olefin and one done on 2.86 g of olefin, and chromatographed on silver nitrate impregnated silica gel. The gel was made by mixing 296 g of flash chromatography gel with 29.6 g of silver nitrate in 266 mL of water. The suspension was diluted with 2.6 L of acetone and solvent was then removed on a rotary evaporator. The gel was dried at 110 °C for 16 h and stored in the dark. Flash chromatography (50-mm column, 10% ethyl acetate in petroleum ether eluent, 5.5 in. of gel) afforded 4.07 g (16.1 mmol, 67%) of product which contained

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(24) Litchfield, J. T.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99.
(25) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

no starting material: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0 (m, 2 H), 0.4 (m, 2 H), 0.6 (m, 1 H) 0.81 (t, 3 H, J = 7.62 Hz), 1.1–2.6 (m, 13 H), 3.61 (s, 3 H); IR (neat) 3000–2850, 1730, 1690 cm^{-1}.

General Procedure for the Synthesis of 4-Substituted Tetrahydrocarbazole-1-acetic Acids (9). The synthesis of the carbazoles **13** to **34** was carried out as described for **28** and **29** except that in the cases of **13**, **14**, and **20–23**, the diastereomers were separated before the Fischer indole reaction. In the cases of **15**, **19**, and **30–34**, no diastereomer separation was necessary as only a single diastereomeric ketone was formed.

1,8-Diethyl-2,3,4,9-tetrahydro-4-(phenylmethyl)-1*H*-carbazole-1-acetic Acid (28 and 29). Ketone **8a** (74.56 mmol, 17.78 g, a mixture of diastereomers) and (2-ethylphenyl)hydrazine (74.56 mmol, 10.16 g) were refluxed in 320 mL of MeOH under nitrogen for 112 h. The reaction was cooled to 0 °C, treated with 112 mmol (8.78 g, 8 mL) of AcCl, and refluxed an additional 45 min. Concentration in vacuo and flash chromatography (95 mm diameter column, 12% EtOAc/petroleum ether eluent) afforded 8.92 g (22.9 mmol, 31%) of a yellow oil. This material and K_2CO_3 27.5 mmol, 3.80 g) were heated at reflux under nitrogen in 183 mL of MeOH and 23 mL of water for 26.5 h. Most of the MeOH was removed in vacuo and the residue was dissolved in 50 mL of water. The solution was acidified to pH 1 with 3 M HCl (aqueous), extractd with 4 × 50 mL of ether, dried over $MgSO_4$, and concentrated. Flash chromatography (75 mm diameter column, 50% EtOAc/petroleum ether eluent) afforded 6.77 g (18.0 mmol, 79%) of yellow oil. About 1 g of each isomer was isolated by reverse-phase chromatography (Waters Associates C18, Prep 500, 60:40 CH_3CN/H_2O with 0.001 M KH_2PO_4) and each was recrystallized from ~2/1 petroleum ether/benzene. Both isomers were dried in vacuo (72 °C, silica gel desiccant) for 8 h. The first isomer eluted on reverse phase was designated **29** and the second eluted isomer was designated **28**. Compound **29**: mp 185–186 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.9 (t, 3 H, J = 9 Hz), 1.36 (t, 3 H, J = 9 Hz), 1.5–2.3 (m, 7 H), 2.6–3.6 (m, 6 H), 7.0–7.6 (m, 8 H), 8.9 (s, 1 H); IR (KBr) 3440, 3600–3000, 3060, 3000–2880, 1710 cm^{-1}. Anal. ($C_{25}H_{29}NO_2$) C, H, N. Compound **28**: mp 181–184 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 0.88 (t, 3 H, J = 9 Hz), 1.36 (t, 3 H, J = 9 Hz), 1.6–2.2 (m, 7 H), 2.7–3.5 (m, 6 H), 6.9–7.6 (m, 8 H), 9.0 (s, 1 H); IR (KBr) 3600–2500, 3420, 1700 cm^{-1}. Anal. ($C_{25}H_{29}NO_2$) C, H, N.

***cis*-1,8-Diethyl-2,3,4,9-tetrahydro-4-propyl-1*H*-carbazole-1-acetic Acid (19).** A solution of **15** (3.0 g, 9.2 mmol) in 25 mL of methanol containing 300 mg of 10% palladium on carbon was hydrogenated (balloon pressure) for 4 h. Filtering through Celite and concentration in vacuo afforded 3.0 g (9.2 mmol, 100%) of **19** as a yellow oil. Crystallization from benzene–petroleum ether gave 2.0 g of white flakes: mp 109–110 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (t, 3 H, J = 7.6 Hz), 1.35 (t, 3 H, J = 7.6 Hz), 1.2–2.1 (m, 10 H), 1.35 (t, 3 H, J = 7.6 Hz), 2.74 (s, 2 H), 2.84 (q, 2 H, J = 7.5 Hz), 2.95 (m, 1 H), 7 (m, 2 H), 7.42 (d, 1 H, J = 7.0 Hz), 9.03 (s, 1 H); IR (KBr) 3400, 3060–2860, 1690 cm^{-1}. Anal. ($C_{21}H_{29}NO_2$) C, H, N.

1-(7-Ethyl-1*H*-indol-3-yl)-3-phenylpropanone (10). To a vigorously stirred solution of ethylmagnesium bromide (2.85 M in ether, 0.07 mol, 24.6 mL) in anhydrous ether (50 mL) was added a solution of 7-ethyl-1*H*-indole (7.25 g, 0.05 mol) in benzene (25 mL), dropwise over the course of 10 min. The resulting pale green mixture was heated at reflux for 2 h and then cooled to −10 °C with a dry ice/methanol bath. A solution of hydrocinnamoyl chloride (8.43 g, 0.05 mol) in benzene (20 mL) was added dropwise over 45 min. The reaction mixture was allowed to warm to room temperature, and after an additional 2 h, no starting material was detected by TLC analysis. Aqueous ammonium chloride (10%, 30 mL) was added to the reaction mixture and a white precipitate formed, which was collected by filtration, washed with ether, and dried in vacuo to yield 7.78 g (56%) of **10**: mp 140–145 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.39 (s, 1 H), 8.30 (d, 1 H), 7.80 (d, 1 H), 3.12 (s, 4 H), 2.88 (q, 2 H), 1.32 (t, 3 H); IR ($CHCl_3$) 3465, 1645 cm^{-1}.

7-Ethyl-α-(phenylmethyl)-1*H*-indole-3-acetic Acid Methyl Ester (11). A solution of **10** (2.77 g, 10 mmol) in a 1:1 mixture of methanol and trimethyl orthoformate (25 mL) was added to thallium(III) nitrate trihydrate (4.88 g, 11 mmol), and the mixture was heated under reflux until precipitation of thallium(I) nitrate was complete (about 3 h). The dark brown mixture was diluted with 25 mL of ether, and the thallium(I) nitrate was removed by filtration. The filtrate was washed successively with 1 × 50 mL portions of water, 5% aqueous sodium bicarbonate, and water and was then dried over $MgSO_4$. Concentration of the filtrate and flash chromatography of the crude product (20% ethyl acetate/hexane, silica gel) gave **11** as a red-brown oil (0.98 g, 31.9%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.35 (s, 1 H), 7.70 (dd, 1 H), 7.15 (m, 3 H), 4.28 (m, 1 H), 3.75 (s, 3 H), 3.35 (s, 3 H), 2.80 (q, 2 H), 1.25 (m, 3 H); IR ($CHCl_3$) 3485, 1735 cm^{-1}.

1,8-Diethyl-1,3,4,9-tetrahydro-4-(phenylmethyl)-pyrano[3,4-*b*]indole-1-acetic Acid (38). To a stirred suspension of lithium aluminum hydride (0.702 g, 18.5 mmol) in 80 mL of anhydrous tetrahydrofuran under nitrogen at 0 °C was slowly added (about 1.5 h) a solution of 7-ethyl-α-(phenylmethyl)-1*H*-indole-3-acetic acid methyl ester (5.17 g, 16.8 mmol) in 30 mL of anhydrous tetrahydrofuran. The resulting dark red mixture was heated under reflux for 2 h. It was cooled to 0 °C and quenched by the dropwise addition of 40 mL of water. The precipitated aluminum salts were removed by filtration and washed with ether. The layers of the filtrate were separated, and the aqueous layer was washed with ether. The combined ether layers were washed with saturated sodium chloride, dried over magnesium sulfate, and concentrated to give the desired alcohol as a brown oil (4.51 g, 96%). This material and methyl propionyl acetate (3.61 g, 27.7 mmol) and *p*-toluenesulfonic acid (0.38 g, 2.0 mmol) were dissolved in 135 mL of benzene and heated at reflux for 5 h as water was collected with a Dean–Stark receiver. The mixture was washed with saturated sodium bicarbonate (2 × 50 mL), dried ($MgSO_4$), filtered, and evaporated to give the crude methyl ester **12**. This material was dissolved in a mixture of 125 mL of ethanol and 125 mL of 10% aqueous sodium hydroxide, and the mixture was heated at reflux for 2.5 h. It was then concentrated to dryness, and a mixture of 100 mL of ether and 50 mL of 10% aqueous sodium hydroxide was added to the residue. The layers were separated, and the aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether (2 × 100 mL). The combined ether extracts were dried ($MgSO_4$), filtered, and evaporated to give the crude product as a tan solid (44% yield). The diastereomers were partially separated by flash chromatography (30% ethyl acetate/hexane, H_3PO_4-treated silica gel), and a portion of the mixed fractions from the column was separated by HPLC (Waters Associates C18, Prep 500). The isomer which eluted first on the C18 column was **38**. The other isomer could not be isolated in sufficient quantities for testing. Compound **38** was recrystallized from 1:3 benzene/petroleum ether: mp 147–148.5 °C; IR (KBr) 3600–2600, 3330, 1740 cm^{-1}. Anal. ($C_{24}H_{27}NO_3$) C, H, N.

Resolution of *cis*-1,8-Diethyl-2,3,4,9-tetrahydro-4-(2-propenyl)-1*H*-carbazole-1-acetic Acid (15). (1*R*-*cis*)-1,8-Diethyl-2,3,4,9-tetrahydro-4-(2-propenyl)-1*H*-carbazole-1-acetic Acid Compound with Benzenemethanamine (1:1) (17). Racemic **15** (1.947 g, 6.0 mmol) and brucine dihydrate (2.583 g, 6.0 mmol) were dissolved in hot ethanol (25 mL). To the resultant clear solution was added water (6.25 mL) and the new solution was left standing at room temperature overnight. The white crystalline salt was collected by filtration and washed with a 1:1 ethanol/water mixture (5 mL). This salt (1.94 g) was taken up in hot ethanol (14 mL), and water (3.5 mL) was added dropwise while the solution was kept hot. It was left standing overnight at room temperature. The (−) brucine salt thus prepared (1.73 g, 80%) was collected by filtration, washed with a 1:1 ethanol/water mixture (5 mL), and dried under vacuum overnight (mp 128–180 °C). Analysis of the methyl ester of the free acid on a covalent (*R*)-*N*-(3,5-dinitrobenzoylphenyl)glycine (DNBPG) HPLC column (5 μM, 7.5% EtOAc in hexane) showed an ee of >99%.

The salt (1.73 g) was suspended in ether (100 mL). To this was added 1 N hydrochloric acid with stirring. The aqueous layer was then separated. The organic layer was washed with a saturated sodium chloride solution, dried over sodium sulfate, and evaporated to give a colorless oil (765 mg, 99%). To this material dissolved in ether (5 mL) was added a solution of benzylamine (255 mg) in ether (2 mL) to give a clear solution. Upon standing at room temperature for 2 h, a crystalline product precipitated and the solution was stored in the refrigerator overnight. The crystals were collected by filtration, washed with a small amount

of ether, and dried under vacuum at room temperature to give analytically pure **17** (715 mg, 71%), >99.9% ee by HPLC of the methyl ester on a DNBPG column: mp 133.5–134 °C; $[\alpha]_D$ −93.0°. Anal. ($C_{28}H_{36}N_2O_2$) C, H, N.

(1***S-cis***)-1,8-**Diethyl-2,3,4,9-tetrahydro-4-(2-propenyl)-1*H*-carbazole-1-acetic Acid Compound with Benzenemethanamine** (1:1) (**16**). The mother liquor from the first crystallization of the brucine salt above was saturated with water (5 mL) and put in a refrigerator overnight. The crystals were collected by filtration and washed with a 1:1 mixture of ethanol/water (10 mL) to give an enriched mixture of the (+) salt (1.9 g). This material was dissolved in hot ethanol (10 mL) and water (1 mL) was added. The solution was seeded with the (−) salt from the preceding step and left at room temperature overnight to remove the remaining amount of the (−) isomer. Crystals (385 mg, (±) salt, 50%) were filtered off, and the mother liquor was saturated with water (30 mL). The precipitate (1.5 g, yield 70%, 96% chirally pure by HPLC analysis of the methyl ester on a DNBPG column) was taken back in hot ethanol (8 mL) and water (3 mL) was added and the solution was left at room temperature overnight. Crystals (50 mg) were filtered off, and more water (5 mL) was added to the hot filtrate. Upon crystallization overnight in the refrigerator, a white crystalline compound (1.1 g, 51%) was obtained. Recrystallization twice from hot ethanol (3 mL) and water (1.5 mL) at room temperature (first, overnight; second, 5 h) afforded the (+) brucine salt (600 mg, yield 28%, >99.9% ee by HPLC analysis of the methyl ester on a DNBPG column). This was suspended in ether and treated with 1 N hydrochloric acid. The aqueous layer was then separated. The organic layer was washed with a saturated sodium chloride solution, dried over sodium sulfate, and evaporated to give a colorless oil (265 mg, yield 99%). To this material dissolved in ether (1.5 mL) was added a solution of benzylamine (88 mg) in ether (0.5 mL) to give a clear solution. Upon standing at room temperature for 2 h and in the refrigerator overnight, a crystalline product precipitated out. The crystals were collected by filtration, washed with a small amount of ether, and dried under vacuum at room temperature to give analytically pure **16** (248 mg, 70% yield, >99.9% ee by HPLC analysis of the methyl ester on a DNBPG column): mp 133–134 °C; $[\alpha]_D$ +91.5°. Anal. ($C_{28}H_{36}N_2O_2$) C, H, N.

(1***R-cis***)-1,8-**Diethyl-2,3,4,9-tetrahydro-4-propyl-1*H*-carbazole-1-acetic Acid 2-(4-Bromophenyl)-2-oxoethyl Ester** (**47**). The brucine salt of **17** (330 mg) was dissolved in 5 mL of 0.1 M HCl (aqueous) and extracted with ether. The ether was dried over $MgSO_4$ and concentrated. The resulting 120 mg of acid (0.368 mmol) was stirred with 15 mg of 10% Pd/C in 3 mL of MeOH under balloon pressure of hydrogen. After 1.5 h, the mixture was filtered through Celite. Concentration afforded 115 mg (0.351 mmol, 95%) of product. Of this, 100 mg (0.305 mmol) and 2,4′-dibromoacetophenone (85 mg, 0.31 mmol) were stirred in 600 μL of dry DMF under nitrogen and treated with 0.40 mmol (40 mg, 55 μL) of triethylamine. After 5 h, the reaction was diluted with 3 mL of 1:1 ether/petroleum ether and washed with 3 × 2 mL of water. Drying ($MgSO_4$) and concentration in vacuo afforded 132 mg (0.252 mmol, 83%) of **47** as a white foam. X-ray crystallography (supplementary material) on a crystal grown from ethanol demonstrated that the propyl group was cis to the acetic acid group and that the absolute configuration at the 1-position was *R*; mp 134.5–135 °C. Anal. ($C_{29}H_{34}BrNO_3$) C, H, N.

(1***R-cis***)-1,8-**Diethyl-2,3,4,9-tetrahydro-4-propyl-1*H*-carbazole-1-acetic Acid (*R*)-α-Methylbenzenemethanamine Salt** (1:1) (**48**). The brucine salt of **17** (330 mg) was dissolved in 5 mL of 0.1 M HCl (aqueous) and extracted with ether. The ether was dried over $MgSO_4$ and concentrated. The resulting 120 mg of acid (0.368 mmol) was stirred with 15 mg of 10% Pd/C in 3 mL of MeOH under balloon pressure of hydrogen. After 1.5 h, the mixture was filtered through Celite. Concentration afforded 115 mg (0.351 mmol, 95%) of product. A solution of this product and material from another reaction (300 mg total, 0.916 mmol) in 4 mL of ether was treated with 0.916 mmol (111 mg, 118 μL) of (*R*)-(+)-α-methylbenzylamine. After 10 min, 10 mL of petroleum ether was added to precipitate the salt, but this did not occur. The reaction was rotovaped down to an oil, which was then crystallized from acetone/water. Collected were 260 mg of **48** (wet weight). The relative and absolute configurations were determined by X-ray crystallography: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.84 (t, 3 H, *J* = 7.5 Hz), 0.97 (t, 3 H, *J* = 7.0 Hz), 1.32 (t, 3 H, *J* = 7.5 Hz), 1.47 (d, 3 H, *J* = 6.7 Hz), 1.4–2.2 (m, 10 H), 2.5 (br s, 2 H), 2.82 (q, 2 H, *J* = 7.6 Hz), 2.98 (br s, NH and OH and water), 4.1 (br s, 1 H), 7 (m, 2 H), 7.30 (s, 5 H), 7.40 (d, 1 H, *J* = 6.7 Hz), 9.93 (br s, 1 H).

Registry No. (±)-**1**, 103024-44-8; (±)-**2**, 116350-80-2; (±)-**3**, 116350-81-3; (±)-**4**, 116350-82-4; (±)-**5**, 41340-25-4; (±)-**6**, 116350-83-5; (±)-**7**, 116350-84-6; (±)-*cis*-**8a**, 116091-46-4; (±)-*trans*-**8a**, 116091-47-5; (±)-*cis*-**8b**, 116091-44-2; (±)-*trans*-**8b**, 116091-45-3; (±)-*cis*-**8c**, 116351-08-7; (±)-*trans*-**8c**, 116351-09-8; (±)-*cis*-**8d**, 116351-10-1; (±)-*trans*-**8d**, 116351-11-2; (±)-*cis*-**8e**, 116351-12-3; (±)-*trans*-**8e**, 116351-13-4; (±)-*cis*-**8g**, 116351-14-5; **10**, 109832-38-4; (±)-**11**, 116350-85-7; (±)-**11** (alcohol), 116351-17-8; (±)-*cis*-**12**, 116350-86-8; (±)-*trans*-**12**, 116351-16-7; (±)-cis-**13**, 116350-87-9; (±)-*trans*-**13**, 116350-88-0; (±)-**15**, 116404-32-1; **16**, 106500-00-9; **16**·$PhCH_2NH_2$, 106500-03-2; **16**·brucine, 106500-02-1; **17**, 106500-01-0; **17**·$PhCH_2NH_2$, 106564-94-7; **17**·brucine, 106564-95-8; (±)-**18**, 116404-33-2; (±)-**19**, 116350-89-1; (±)-*cis*-**20**, 116350-90-4; (±)-*trans*-**20**, 116350-91-5; (±)-*cis*-**22**, 116350-92-6; (±)-*trans*-**22**, 116350-93-7; (±)-**24**, 116350-94-8; (±)-**25**, 116350-95-9; (±)-**26**, 116350-96-0; (±)-**27**, 116350-97-1; (±)-**28**, 116350-98-2; (±)-**28** (methyl ester), 116351-15-6; (±)-**29**, 116350-99-3; (±)-**29** (methyl ester), 116374-58-4; (±)-**30**, 116351-00-9; (±)-**31**, 116351-01-0; (±)-**32**, 116351-02-1; (±)-**33**, 116351-03-2; (±)-**34**, 116351-04-3; (±)-**35**, 116351-05-4; (±)-**36**, 114895-72-6; (±)-**37**, 114895-73-7; (±)-**38**, 114895-60-2; (±)-*trans*-**38**, 114895-61-3; (±)-**39**, 114895-66-8; (±)-**40**, 114895-67-9; (±)-**41**, 114895-86-2; (±)-**42**, 114895-87-3; (±)-**43**, 116351-06-5; (±)-**44**, 116351-07-6; (±)-**45**, 114895-64-6; (±)-**46**, 114895-65-7; **47**, 116404-34-3; **48**, 116497-03-1; **48** (base), 116404-35-4; $PhCH_2MgCl$, 6921-34-2; CH_2=$CH(CH_2)_2MgBr$, 7103-09-5; CH_2=$CHMgBr$, 1826-67-1; $PhMgBr$, 100-58-3; $Ph(CH_2)_2COCl$, 645-45-4; $EtCOCH_2COOMe$, 30414-53-0; 2-$EtC_6H_4NHNH_2$, 19275-55-9; $PhNHNH_2$, 100-63-0; 2-$MeC_6H_4NHNH_2$, 529-27-1; 2-$PrC_6H_4NHNH_2$, 58711-27-6; $PhCH_2NH_2$, 100-46-9; $BrCH_2COC_6H_4$-4-Br, 99-73-0; (*R*)-$PhCH(CH_3)NH_2$, 3886-69-9; 7-ethylindole, 22867-74-9; brucine, 357-57-3.

Supplementary Material Available: Listings of bond lengths, bond angles, and atomic coordinates and thermal parameters for **47**, **48**, **15**, and **2** (40 pages); tables of calculated and observed structure factors for **47**, **48**, **15**, and **2** (43 pages). Ordering information is given on any current masthead page.