3.1.4.0.0.0. Ionization Constant Determination

NSAIDs should ideally be weak acids that undergo complete absorption, possess a moderate lipophilicity so a high uptake in inflammed tissue occurs and be devoid of GIT irritation or ulcerogenicity. The pK_a of a compound is defined as the negative logarithm of its dissociation constant K_a, and it is a convenient numerical method to compare the relative acidity or basicity of ionizing compounds in aqueous or miscible solvent-aqueous solutions. The higher the pK_a of a compound, the less acidic it is. Since the acidity of NSAIDs is one of the factors implicated in gastric ulcerogenicity, it was of interest to determine the pK_a of one compound from the 3-benzoyl-4-substituted-1,4-dihydropyridyl aceiic acid class of compounds (97-98).

The pK_a of 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acid (98a) was determined using a potentiometric titration method described by Albert and Serjeant.[177] The measurements were carried out in aqueous methanol (H_2O:MeOH = 60:40, v/v) as solvent since compound 98a was insoluble in water. Newton et al.[184] have reported that there was no substantial difference in the precision of pwK_a extrapolated from linear regression plots of psK_a (where pwK_a is the pK_a determined in aqueous medium and psK_a is the pK_a determined in aqueous methanol solutions). All solvents and solutions were properly stored in well-stoppered containers fitted with a Soda-Lime guard tube to exclude carbon dioxide. The pK_a of Ibuprofen was first determined by this procedure to ascertain the precision of the method. Ibuprofen exhibited a pK_a of 5.2 which is the same as the value reported by Davis.[185] From the pH readings and the logarithm of the ratio of the concentrations of acid substrate [HA] and the anion [A$^-$] during the titration, the pK_a values were calculated according to the Henderson-Hasselbach equation as follows:

$$pK_a = pH + \log[HA] - \log[A^-]$$

Some typical titration data are presented in Table 6. The pK_a values shown in Table 6 are the average of the four values obtained for compound **98a**.

3.1.5.0.0.0. Synthesis of Methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydro-pyridyl)methyl]acrylate (111) and Methyl 2-[1-(3,5-diben-zoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (112)

Noyori *et al.*[141c] have reported that ruthenium(II) complexes possessing the 2,2'-bis-(diarylphosphino)-1,1-binaphthyl (BINAP) ligand serve as catalysts for the highly stereo-selective hydrogenation of a range of substituted acrylic acids. For instance, the useful antiinflammatory agent (S)-(+)-Naproxen (**8**) was readily synthesized by the asymmetric hydrogenation of 4-(6-methoxy-2-naphthyl)-2-butenoic acid (**78**) as described in Section 1.1.1.9.3.0.

These reports prompted us to synthesize **111** and **112** which could be subjected to stereoselective hydrogenation to prepare two diastereomers which could be separated (from **111**) or a single enantiomer (from **112**) for evaluation as antiinflammatory agents.

Thus, 3-benzoyylpyridine (**87**, R = H) and 3,5-dibenzoylpyridine (**100**, R = PhCO), were quaternized using methyl 2-(bromomethyl)acrylate by refluxing in acetone for 24 h to yield the respective pyridinium salts (**109**, R = H and **110**, R-PhCO). The subsequent reaction of these pyridinium salts with phenylmagnesium chloride in the presence of 5% CuI, according to the General Procedure A, afforded **111** and **112** in 35% and 21% yield respectively.
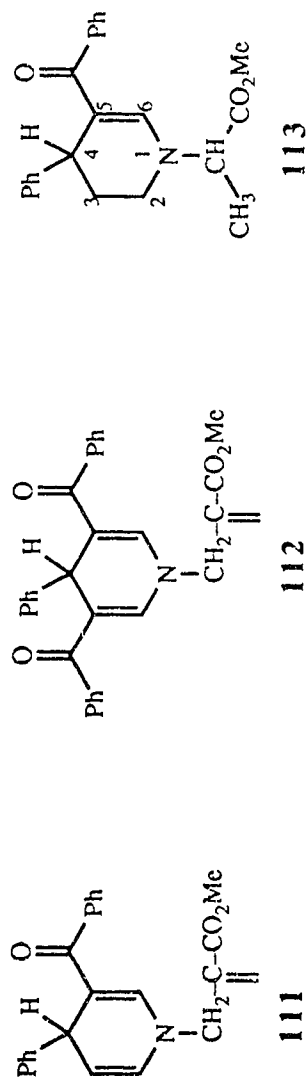
The ^{1}H NMR and IR spectral data for compounds **111** and **112**, which are consistent with their assigned structures, are presented in Table 7 and the physical data in Table 8. The synthetic route used to prepare **111** and **112** is outlined in Scheme 4.

Table 6. Data for the potentiometric titration of a 0.01 M methanolic solution of 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydro-pyridyl)]acetic acid (98a) with a 0.10 M potassium hydroxide solution in water:methanol (60:40, v/v).

Titrant 0.1 M KOH (mL)	pH	[HA] diminished by tenths	[HA] minus Column 3 = [A⁻]	$\dfrac{[HA]}{[A^-]}$	$\log \dfrac{[HA]}{[A^-]}$	$pK_a^* = pH + \log \dfrac{[HA]}{[A^-]}$
0	5.92	0.010	0.			
0.5	8.45	0.009	0.001	9/1	0.95	9.40
1.0	8.58	0.008	0.002	8/2	0.60	9.18
1.5	8.79	0.007	0.003	7/3	0.37	9.16
2.0	8.96	0.006	0.004	6/4	0.18	9.14
2.5	9.17	0.005	0.005	5/5	0	9.17
3.0	9.35	0.004	0.006	4/6	-0.18	9.17
3.5	9.56	0.003	0.007	3/7	-0.37	9.19
4.0	9.74	0.002	0.008	2/8	-0.60	9.14
4.5	9.95	0.001	0.009	1/9	-0.95	9.00
5.0	10.3	0	0.010			

*Result: $pK_a = 9.17 \pm 0.01$.

Table 7. IR and ^{1}H NMR data for methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**111**), methyl-2-[1-(3,5-di-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**112**), and methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetra-hydropyridyl)]acetate (**113**).
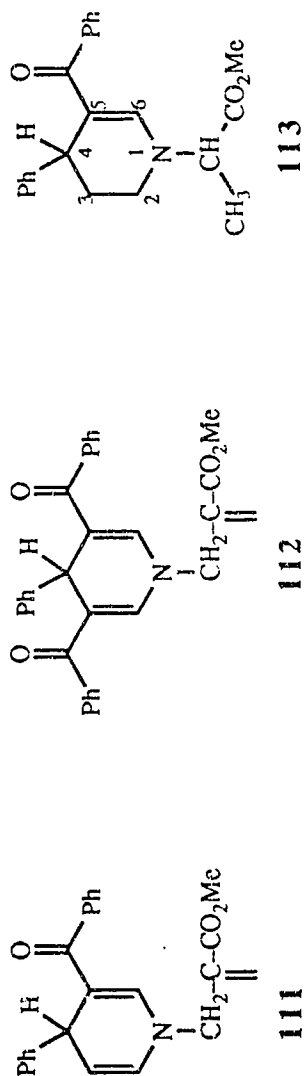

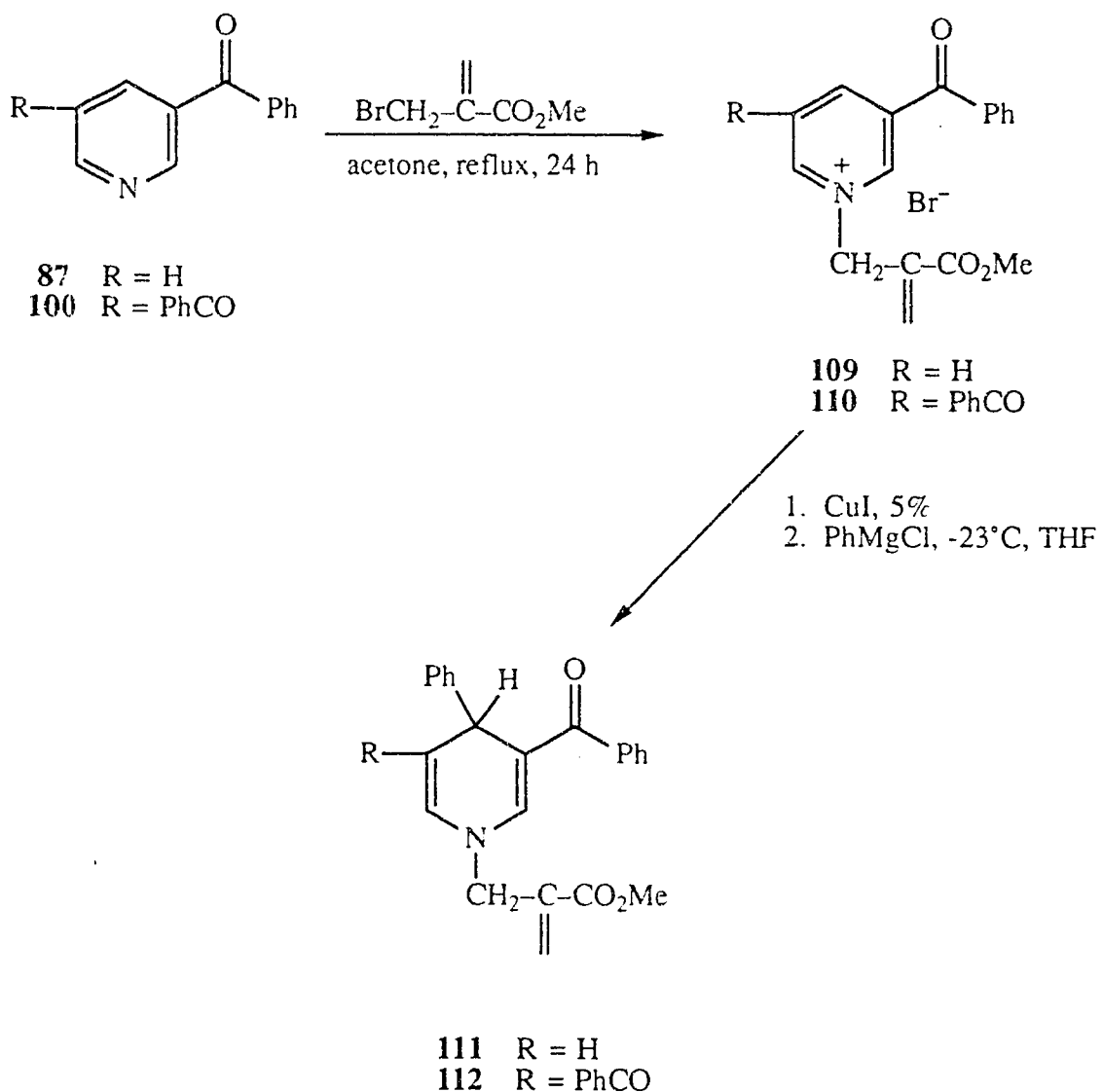| Entry	IR (neat) cm^{-1}	^{1}H NMR (CDCl$_3$) δ
111	1745 (COO); 1679 (CO)	7.1-7.5 (m, 10H, phenyl hydrogens), 6.96 (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.38 (s, 1H, =CHH'), 5.94 (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.5 Hz, 1H, H-6), 5.78 (s, 1H, =CHH'), 5.12 (d, $J_{5,6}$ = 7.5 Hz of d, $J_{4,5}$ = 4.6 Hz, 1H, H-5), 4.9 (d, $J_{4,5}$ = 4.6 Hz, 1H, H-4), 4.08 (s, 2H, NCH$_2$), 3.8 (s, 3H, OCH$_3$)
112	1745 (COO); 1679 (CO)	7.1-7.7 (m, 15H, phenyl hydrogens), 6.88 (s, 2H, H-2, H-6), 6.38 (s, 1H, =CHH'), 5.74 (s, 1H, =CHH'), 5.62 (s, 1H, H-4), 4.12 (s, 2H, NCH$_2$), 3.8 (s, 3H, OCH$_3$)

(Continued)

Entry	IR (neat) cm^{-1}	^{1}H NMR (CDCl$_3$) δ
113	1745 (COO); 1679 (CO)	7.24-7.65 (m, 11H, 9 phenyl hydrogens, H-2, H-6), 7.18 (m, 1H, p-phenyl H), 4.38 (dd, J3,4 = 5.0 Hz, 1H, H-4), 3.88-4.02 (overlapping quartets, J$_{CH,CH_3}$ = 7.2 Hz, 1H, C$\underline{H}$CH$_3$), 3.74 [3.76] (s, 3H total, OCH3), 2.9-3.18 (m, 2H, H-2), 1.9-2.15 (m, 2H, H-3), 1.44 [1.42] (two d, J$_{CH_3CH}$ = 7.2 Hz, 3H total, C$\underline{H}_3$CH)
		Diastereomeric ratio 1:1

Table 8.   Physical data for methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**111**), methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**112**), and methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (**113**).
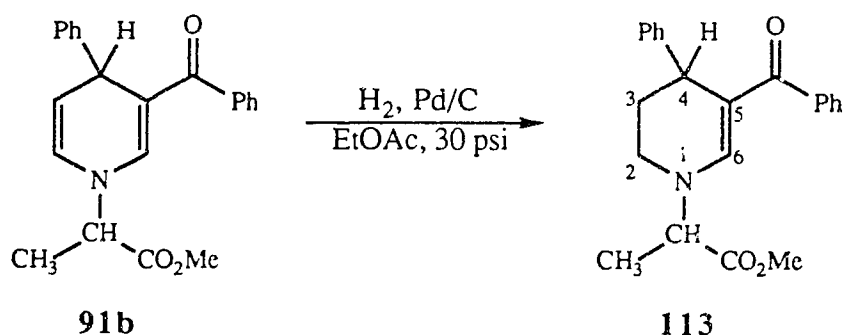

Entry	Yield, %	m.p., °C	Formula	Microanalysis: Calcd. (Found)		
				C	H	N
111	35	oil	$C_{23}H_{21}NO_3 \cdot 3/4H_2O$	74.01 (73.87)	5.61 (5.58)	3.76 (3.92)
112	21	oil	$C_{30}H_{25}NO_4 \cdot H_2O$	74.84 (75.18)	5.20 (5.15)	2.91 (3.01)
113	47	oil	$C_{23}H_{23}NO_3 \cdot 1/2H_2O$	73.65 (73.30)	6.42 (6.36)	3.91 (3.94)

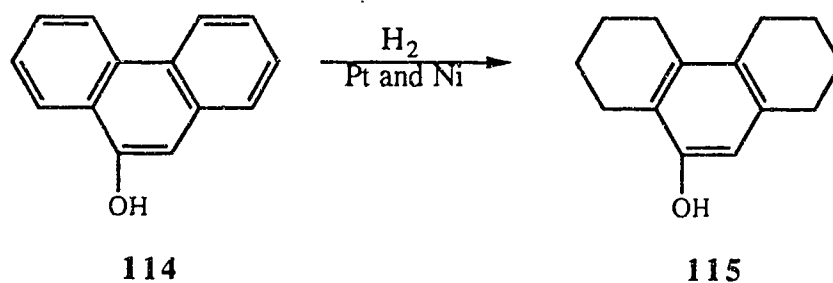Scheme 4. Synthetic route for the preparation of 111 and 112.

3.1.6.0.0.0. Synthesis of Methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (113)

Compound 113 ᵂᵃˢ synthesized in order to investigate the effect of the C5-C6 double bond present in 91 on antiinflammatory and analgesic activity. Thus, compound 91b was subjected to hydrogenation with hydrogen gas at 30 psi in the presence of 10% palladium-on-charcoal in ethyl acetate at 25°C to afford the corresponding tetrahydropyridi... 113 as

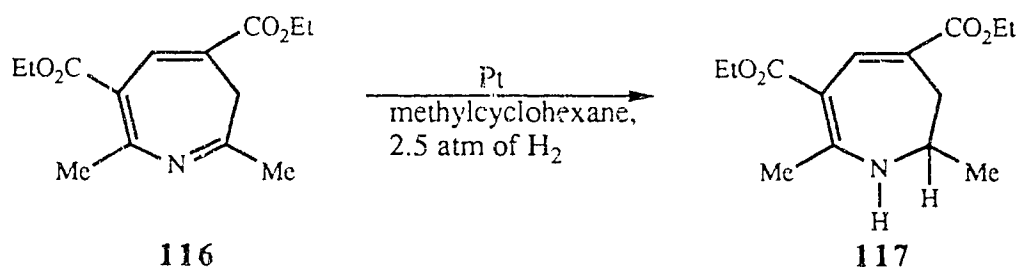Scheme 5. Synthesis of methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (113).

outlined in Scheme 5. The C2-C3 double bond of **91** was not reduced, presumably due to steric factors. As mentioned earlier, compound **91** exists in a flat boat conformation with a C-4 axial phenyl group. Therefore, hydrogen addition occurs preferentially at the less-hindered C5-C6 double bond of **91b**. The effect of steric factors on hydrogenation of C-C double bonds has been studied.[186] Linstead and co-workers,[186] based on studies involving the hydrogenation of phenanthrene and diphenic acid derivatives, concluded that the less-hindered side of an unsaturated molecule is adsorbed on the catalyst surface and this has led to the generalization that catalytic hydrogenation of a multiple bond results in *cis* addition of two hydrogen atoms from the less-hindered site. For example, when 9-phenanthrol **114** was hydrogenated over platinum in acetic acid, the octahydro-9-phenanthrol **115**, was obtained indicating reduction of the non-hindered double bonds (Scheme 6).[186]

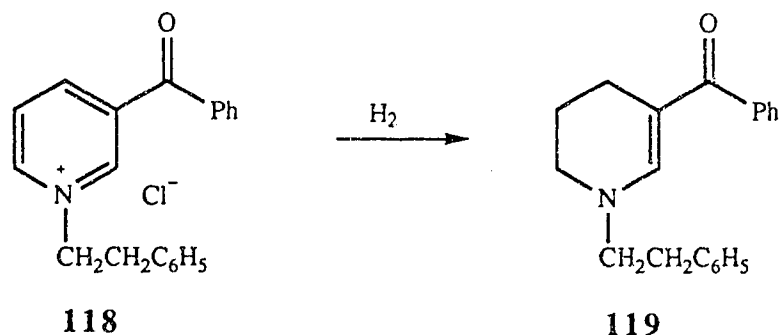Scheme 6. Catalytic hydrogenation of 9-phenanthrol (**114**)

The IR and ^{1}H NMR spectral data, which are consistent with the structure for compound 113, are presented in Table 7 and the physical data in Table 8. The ^{1}H NMR spectrum does not display resonances in the δ 5-6 region indicating the absence of the C5-C6 olefinic bond of 91b. Also, the IR spectrum shows the absence of an isolated olefinic bond in the 1650 cm^{-1} region.

The failure of the N–C=C–C=O moiety to undergo hydrogenation is further illustrated by partial hydrogenation of the azepine (116) to the dihydro derivative (117)[187] as shown in Scheme 7.

Scheme 7. Partial catalytic hydrogenation of the azepine (116).

Furthermore, partial hydrogenation of pyridine rings containing 3-acyl, formyl, keto, cyano, and other functions have been reported.[188,189,190] For example, Lyle and Mallet[188] have described the partial hydrogenation of the 1-alkyl-3-benzoylpyridinium salt 118 to give the corresponding tetrahydropyridine 119 in which the C5-C6 double bond was preferentially reduced (Scheme 8).

Scheme 8. Partial hydrogenation of the 1-alkyl-3-benzoylpyridinium salt (118) to give the tetrahydropyridine (119).

Freidfelder[189] has reported the partial hydrogenation of 3-acetylpyridine (120) to the corresponding tetrahydropyridine (122). It was proposed that the formation of 122 probably takes place by 1,4-addition, giving the intermediate 121. Freidfelder observed that the isolated C5-C6 double bond was reduced preferentially relative to the 2,3-conjugated bond to yield 122 (Scheme 9).

120   **121**   **122**

Scheme 9. Preferential hydrogenation of the isolated C5-C6 double bond of (120) relative to the C2-C3 configurated double bond.

Electronic effects could also be responsible for the reluctance of the C2-C3 olefinic moiety of 91b to undergo hydrogenation. The C2-C3 double bond is conjugated with the carbonyl of the 3-benzoyl group and so resonance can occur, thereby deactivating the C2-C3 double bond. In fact, the C3-CO_2Me bond of the calcium channel antagonist 2,6-dimethyl-3,5-dicarbomethoxy-4-phenyl-1,4-dihydropyridine (123) has been found through X-ray crystallographic studies[191] to be shorter than the C2-C3 bond, suggesting double bond character for the C3-CO_2Me bond (Figure 9).
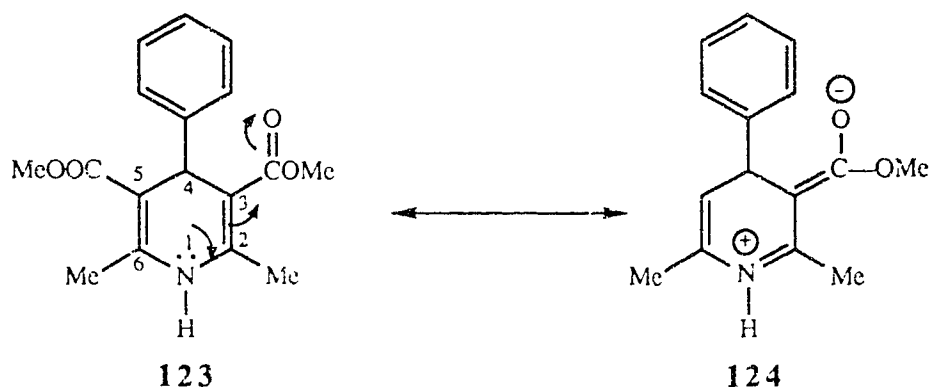
Figure 9. Deactivation of C2-C3 conjugated double bond by resonance.

3.1.7.0.0.0. Synthesis of Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (125-128), Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (129-131), and 2-Methyl-2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicyclo[4.1.0]hept-3-ene)]acetamide (132)

It has been reported that the C-C bonds in cyclopropane rings resemble olefinic double bonds.[192] The hybridization of cyclopropyl bonds is intermediate in character between sigma (σ) and pi (π) bonds. The C-C bonds in cyclopropane mimic a C=C bond in their ability to conjugate with an adjacent olefinic bond,[193] but unlike a C=C bond, it does not transmit electronic effects.[194] Also, the hybridization of the cyclopropane bonds are considered to result in a higher electron density for the C-C bonds. Furthermore, the cyclopropyl moiety interacts with neighbouring π-electron systems and p-electron centers similar to a vinyl group.[195,196] It was therefore anticipated that a cyclopropyl substituent could act as a biological isostere of the C5-C6 double bond present in compound 91b. In addition, the hydrophobic halogen substituents F, Cl, and Br are expected to increase the lipophilicity of these compounds. In fact, some halocyclopropyl analogs of 2'-deoxyuridine have been reported to exhibit antiviral and cytotoxic activity.[197,198]

Thus, dihalocarbene :CX_2, generated *in situ* from the Seyferth reagents[199] $PhHgCX_3$

(X = F, Cl, Br) in refluxing benzene, reacted with **91b** to afford compounds **125-128**.
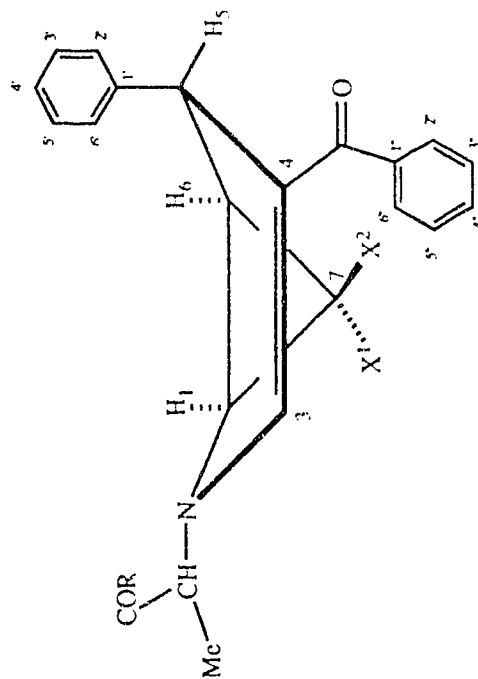
Reactions of **91b** (solid) with phenyl(tribromomethyl)mercury ($PhHgCBr_3$) in dry

benzene at 80°C yielded **125**, whereas compound **126** was synthesized from reaction of

91b with the Seyferth reagent phenyl(bromodichloromethyl)mercury ($PhHgCBrCl_2$). A

similar reaction of **91b** with phenyl(trifluoromethyl)mercury[200] ($PhHgCCF_3$) in dry di-

methoxyethane in the presence of sodium iodide at 90°C afforded **127** whereas reaction of

phenyl(dichlorofluoromethyl)mercury ($PhHgCCl_2F$) with **91b** in refluxing dimethoxy-

ethane yielded **128**.

Monodehalogenation of **125**, **126**, and **128** with tributyltin hydride in the presence of

azobisisobutyronitrile (AIBN) as the initiator of the free radical reaction in refluxing

benzene afforded compounds **129**, **130**, and **131**, respectively. Ammonolysis of **125**,

according to General Procedure C, afforded the corresponding acetamide **132**. These

reactions are schematically outlined in Scheme 10. Spectral data for **125-128**, **129-131**

and **132** are presented in Table 9 and the physical data is summarized in Table 10.

The ^1H NMR spectra of compounds **125-127** indicate that there is no coupling

between H-5 and H-6 which suggests that the dihedral angle between H-5 and H-6 is about

85° based on the Karplus curve.[201]

Carbenes are extremely reactive and give many side reactions, especially insertion

reactions which readily reduce yields.[202] Dihalocarbenes however are less reactive than

carbenes and so there are no insertion reaction products.[203-205] Most carbenes are electro-

philic so electron-withdrawing groups decrease the rate of the reaction,[206,207] as

exemplified by the inertness of the C-2–C-3 double bond of **91** to cyclopropanation.

Carbenes in the singlet state (which is the most common state) react stereospecifically and

syn[208,209] probably by a one-step mechanism.[210] Therefore substituents on the olefin

Table 9. IR and ^{1}H NMR spectral data for methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]-hept-3-ene)]-acetates (**125-128**), methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]-hept-3-ene)]acetates (**129-131**) and acetamide (**132**).

Entry	X^1	X^2	R	IR cm^{-1}	^{1}H NMR, CDCl$_3$ (δ)^a
125	Br	Br	OMe	(KBr): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	7.2-7.5 (m, 10H, phenyl hydrogens), 7.02 (s, 1H, H-3), 4.26 (s, 1H, H-5), 4.14 (q, J$_{CH_2CH_3}$ = 7.2 Hz, 1H, CHCH$_3$), 3.9 (s, 3H, OMe), 3.4 (d, J$_{1,6}$ = 10.9 Hz, 1H, H-1), 2.46 (d, J$_{1,6}$ = 10.9 Hz, 1H, H-6). ^{13}C NMR (CDCl$_3$) δ: 192.45 (benzoyl carbonyl). 171.61 [170.81] (COOMe), 146.44 [144.42] (C-3), 144.69 (phenyl

(Continued)

Entry	X¹	X²	R	IR cm⁻¹	¹H NMR, CDCl₃ (δ)ᵃ
125 (Cont'd)	Br	Br	OMe	(KBr): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	C-1'), 139.96 (benzoyl C-1"), 130.05 [130.19] (benzoyl C-4"), 128.58-126.46 (other phenyl C-5), 112.89 [113.21] (C-4), 62.37 [61.69] (NC$\underline{H}$CH₃), 52.78 (COO$\underline{C}$H₃), 41.83 [43.52] (C-1), 37.76 [38.24] (C-5), 36.14 (C-6), 32.43 [31.80] (C-7), 16.52 [16.44] ($\underline{C}$H₃CH). Diastereomeric ratio is ≅ 2:1
126	Cl	Cl	OMe	(neat): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	7.0-7.42 (m, 10H, phenyl hydrogens), 6.9 (s, 1H, H-3), 4.22 (s, 1H, H-5), 4.02 (q, J_{CH,CH_3} = 7.2 Hz, 1H, C$\underline{H}$CH₃), 3.76 (s, 3H, OMe), 3.26 (d, $J_{1,6}$ = 10.7 Hz, 1H, H-7), 2.24 (d, $J_{1,6}$ = 10.7 Hz, 1H, H-6), 1.56 (d, J_{CH,CH_3} = 7.2 Hz, 3H, CH₃CH). ¹³C NMR (CDCl₃ δ: 171.56 ($\underline{C}$OOMe), 146.35 (C-3), 144.63 (phenyl C-1'), 139.97 (benzoyl C-1"), 130.04 [130.17] (benzoyl C-4"), 126.31-129.03 (other phenyl C"), 112.70 (C-4), 62.35 [62.17] (NC$\underline{H}$CH₃), 52.7 (COO$\underline{C}$H₃), 36.85 [37.87] (C-1), 34.14 [35.13] (C-5), 32.56 [32.43] (C-6), 29.66 (C-7), 16.29 [16.64] (C$\underline{H}$₃CH)

(Continued)

Entry	X^1	X^2	R	IR cm^{-1}	1H NMR, CDCl$_3$ (δ)^a
127	F	F	OMe	(neat): 1745 (COO); 1679 (COO); 3105, 3025 (cyclo-propyl)	7.20-7.50 (m, 10H, phenyl hydrogens), 7.16 [7.04] (s, 1H, H-3), 4.44 (s, 1H, H-5), 4.06 [4.04] (two q, J_{CH,CH_3} = 7.2 Hz, 1H total, C<u>H</u>CH$_3$), 3.80 [3.84] (s, 3H, OCH$_3$), 3.26 [3.38] (d, $J_{1,6}$ = 11.4 Hz, of d $J_{H1,F}$ = 5.1 Hz, 1H, H-1), 2.20-2.36 (m, 1H, H-6), 1.56 (d, $J_{CH_3,CH}$ = 7.2 Hz, 3H, CH$_3$CH). ^{13}C NMR (CDCl$_3$) δ: 192.85 [192.71] (benzoyl CO), 170.33 [171.15] (<u>C</u>OOMe), 146.45 [146.20] (C-3), 144.91 [144.81] (phenyl C-1'), 139.92 [139.84] (benzoyl C-1''), 130.04 [129.92] (benzoyl C-4''), 126.39-127.20 (other phenyl C), 112.49 [112.15] (C-4), 109.73 [109.83] (t, $J_{F,C}$ = 296 Hz, C-7), 62.47 [61.94] (N<u>C</u>HCH$_3$), 52.47 (COO<u>C</u>H$_3$), 35.18-34.88 [34.73-34.43] (C-1), 31.06 (C-5), 29.94 [29.79] (C-6), 15.90 [15.38] (CH<u>C</u>H$_3$) ^{19}F NMR (C$_6$F$_6$) δ: 37.2 (d, J_{F1F2} = 160.7 Hz of d, $J_{H,F}$ (*cis*) = 15.4 Hz, 1F, F-2); [35.8 (d, $J_{F1,F2}$ = 160.7 Hz of d, $J_{H,F}$ (*cis*) = 14.5 Hz, 1F, F-2], 12.88 (d, $J_{F1,F2}$ = 160.7 Hz, 1F, F-1), [13.07 (d, $J_{F1,F2}$ = 160.7 Hz, 1F, F-1)]. Diastereomeric ratio of 5:4.

(Continued)

Entry	X¹	X²	R	IR cm⁻¹	¹H NMR, CDCl₃ (δ)ᵃ
128	Cl	F	OMe	(neat): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	7.2-7.5 (m, 10H, phenyl hydrogens), 7.0 [7.06] (s, 1H, H-3), 4.48 [4.30] (s, 1H, H-5), 4.08 (q, J_{CH,CH_3} = 7.2 Hz, 1H, CHCH₃), 3.90 [3.88] (s, 3H, OCH₃), 3.44 (d, $J_{1,6}$ = 12.6 Hz, of d, $J_{F,1}$ = 7.2 Hz, 1H, H-1), [3.20 (d, $J_{1,6}$ = 12.6 Hz, 1H, H-1)], 2.38 (d, $J_{f,6}$ = 20.4 of d, $J_{6,F}$ = 7.2 Hz, 1H, H-6)], 1.62 [1.56] (d, $J_{CH_c,CH}$ = 7.2 Hz, 3H, CH₃CH). Diastereomeric ratio is 5:4.
129	H	Br	OMe	(neat): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	7.2-7.5 (m, 10H, phenyl hydrogens), 7.0 [6.9] (s, 1H, H-3), 4.46 (s, 1H, H-5), 4.02 (q, J_{CH,CH_3} = 7.0 Hz, 1H, CHCH₃), 3.78 [3.80] (s, 3H, OCH₃), 2.68-2.80 (m, 1H, H-7), 1.45-1.7 (m, 5H, CHCH₃, H-1, H-6). ¹³C NMR (CDCl₃) δ: 193.37 (benzoyl CO), 171.23 (COOCH₃), 147.15 (C-3), 140.58 (benzoyl C-1"), 129.68 (benzoyl C-4"), 125.91-128.48 (other phenyl C's), 113.0 (C-4), 62.35 [62.08] (NCHCH₃), 52.35 (COOMe), 36.17 (C-1), 30.12 (C-5), 21.71 (C-6), 16.52 (CHBr), 15.35 (CHCH₃). Diastereomeric ratio is 4:1.

(Continued)

Entry	X^1	X^2	R	IR cm^{-1}	^{1}H NMR, CDCl$_3$ (δ)^a
130	H	Cl	OMe	(CHCl$_3$): 1745 (COO); 1679 (CO); 3105, 3025 (cyclo-propyl)	7.1-7.5 (m, 10H, phenyl hydrogens), 7.02 (s, 1H, H-3), 4.13 (s, 1H, H-5), 4.08 (q, J_{CH,CH_3} = 7.0 Hz, 1H, C$\underline{H}$CH$_3$), 3.78 [3.74] (s, 3H, OCH$_3$), 3.24 (d, $J_{6,7}$ = 8.5 Hz of d, $J_{1,7}$ = 5.5 Hz, 1H, H-7), 2.92 [2.88] (d, $J_{1,6}$ = 9.9 Hz of d, $J_{1,7}$ = 5.5 Hz, 1H, H-1), 1.8 (d, $J_{1,6}$ = 9.9 Hz of d, $J_{6,7}$ = 8.5 Hz, 1H, H-6), 1.56 [1.48] (d, J_{CH_3CH} = 7.2 Hz, 3H, C$\underline{H_3}$CH). ^{13}C NMR (CDCl$_3$) δ: 193.0 (benzoyl CO), 171.77 ($\underline{C}$OOMe), 148.18 [146.36] (C-3), 146.08 (phenyl C-1'), 140.60 (benzoyl C-1''), 129.83 [129.69] (benzoyl C-4), 128.61-126.04 (other phenyl C's), 113.24 (C-4), 62.65 [61.45] (N$\underline{C}$HCH$_3$), 52.58 (CO$_2$$\underline{Me}$), 38.84 [38.66] (C-1), 33.42 (C-7), 31.65 (C-5), 24.94 [24.61] (C-6), 16.14 [15.82] ($\underline{C}$HCH$_3$). Diastereomeric ratio is 6:1.
131	H	F	OMe	(neat): 1745 (COO); 1679 (CO); 3016, 3025 (cyclo-propyl)	7.18-7.60 (m, 10H, phenyl hydrogens), 7.14 (s, 1H, H-3), 4.64 (d, $J_{F,H7}$ = 6.6 Hz of d, $J_{6,7}$ = 9.2 Hz of d, $J_{1,7}$ = 3.8 Hz, 1H, H-7), 4.38 [4.36] (s, 1H, H-5), 4.1 [4.08] (q, J_{CH,CH_3} = 7.2 Hz,

(Continued)

Entry	X^1	X^2	R	IR cm^{-1}	^{1}H NMR, CDCl$_3$ (δ)^a
131 (Cont'd.)	H	F	OMe	(neat): 1745 (COO); 1679 (CO); 3016, 3025 (cyclopropyl)	1H, C$\underline{H}$CH$_3$), 3.84 [3.80] (s, 3H, OCH$_3$), 2.82 [2.76] (d, $J_{1,6}$ = 12.7 Hz of d, $J_{1,7}$ = 3.8 Hz of d, $J_{1,F}$ = 3.8 Hz, 1H, H-1), 1.5-1.7 (m, $J_{CH_3,CH}$ = 7.2 Hz, 4H, C$\underline{H}$$_3$CH, H-6). Minor diastereomer is listed in brackets. Diastereomeric ratio is 3:1.
132	Br	Br	NH$_2$	(KBr): 1693 (CONH); 1679 (CO); 3322, 3180 (NH$_2$); 3105, 3025 (cyclopropyl)	7.1-7.4 (m, 10H, phenyl), 7.08 [7.10] (s, 1H, H-3), 6.82 [7.52] (s, 2H, NH$_2$), 4.10 [4.20] (q, J_{CH,CH_3} = 7.2 Hz, 1H, C$\underline{H}$CH$_3$), 4.06 (s, 1H, H-5), 3.7 [3.44] (d, $J_{1,6}$ = 10.6 Hz, 1H, H-1), 2.28 [2.26] (d, $J_{1,6}$ = 10.6 Hz, 1H, H-6), 1.56 [1.4] (d, $J_{CH_3,CH}$ = 7.2 Hz, 3H, CH$_3$CH). Diastereomeric ratio is 3:1.

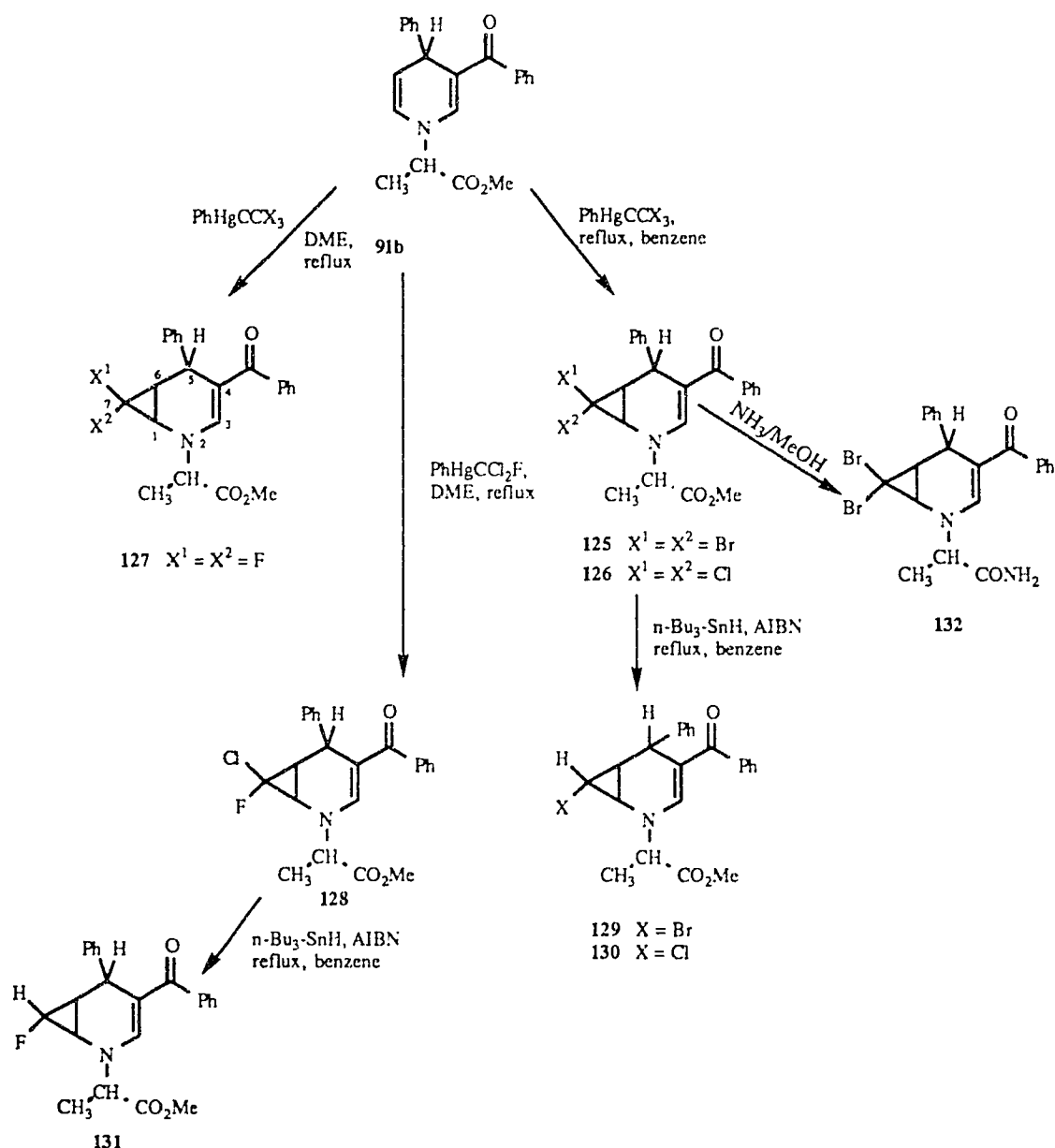^{a}Minor diastereomers shown in brackets.

Table 10. Physical data for methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**125-128**), methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]-hept-3-ene)]acetates (**129-131**) and acetamide (**132**).

Entry	X^1	X^2	R	Yield, %	m.p., °C	Formula	Microanalysis: Calcd. (Found)		
							C	H	N
125	Br	Br	OMe	50	148-150	$C_{23}H_{21}Br_2NO_3$	53.20 (53.49)	4.08 (3.96)	2.70 (2.71)
126	Cl	Cl	OMe	33	142-145	$C_{23}H_{21}Cl_2NO_3 \cdot 1/2H_2O$	63.47 (63.64)	4.92 (4.90)	3.25 (3.27)
128	Cl	F	OMe	64	oil	$C_{23}H_{21}ClFNO_3 \cdot 3/2H_2O$	62.73 (62.80)	4.77 (5.02)	3.18 (3.16)
130	H	Cl	OMe	31	oil	$C_{23}H_{22}ClNO_3 \cdot 2H_2O$	64.04 (63.92)	5.10 (5.37)	3.25 (3.29)
132	Br	Br	NH_2	50	132-135	$C_{22}H_{19}Br_2N_2O_2$	52.41 (52.67)	4.00 (4.01)	5.56 (5.54)

(Continued)

| Entry | X^1 | X^2 | R | Yield, % | m.p., °C | Formula | Exact Mass | |
							Calcd	Found
127	F	F	OMe	53	oil	$C_{23}H_{21}F_2NO_3$	397.1489	397.1484
129	H	Br	OMe	36	oil	$C_{23}H_{22}BrNO_3$	439.0783	439.0889
131	H	F	OMe	45	oil	$C_{23}H_{22}FNO_3$	379.1584	379.1581

Scheme 10. Synthesis of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-di-
halo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (125-128),
methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo-
[4.1.0]hept-3-ene)]acetates (129-131), and 2-methyl 2-methyl-
2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicyclo[4.1.0]hept-
3-ene)]acetamide (132).

should retain their configuration. Dihalocarbenes and carbenoids, which add readily to C=C double bonds, do not generally add to the C=O bond of ordinary aldehydes and lactones.[211] As already discussed in Section 3.1.0.0.0.0, compound **91** exists in a boat shape with the C-4 phenyl axial to the 1,4-dihydropyridyl ring. If addition of the carbenes :CX$_2$ is concerted, then the configuration of the phenyl substituent should not change. When the cyclopropyl is above the plane of the DHP ring there is a strong steric interaction with the axial phenyl substituent (Figure 10).

Attack at the C=C double bond should therefore occur from the lower face of the boat DHP ring if the phenyl substituent is axial since there is much less steric hindrance (Figure 11). Compound **125** synthesized in this way from pure **91b** gave single resonances in both the ^{1}H NMR and ^{13}C NMR spectra. This further supports the theory that :CX$_2$ addition is stereospecific.

The observation that compound **125** does not exhibit a $J_{5,6}$ coupling ($J_{5,6} = 0$ Hz) suggests the H5-H6 dihedral angle is about 85°. When $\phi_{5,6} \cong 85°$, the 1,4-DHP ring exists as a flat boat. H-1 and H-6 must be cis to each other since $J_{1,6} = 10.9$ Hz and the cyclopropane is a fused ring system. For the difluorocyclopropyl compound (**127**), the ^{19}F. NMR spectrum indicated that F$_1$ is shielded, relative to F$_2$, by the DHP 3,4-double bond and possibly by the benzoyl group (Figure 12). F$_1$ must be *trans* to both H-1 and H-6 since $J_{F_{1,1}}$ and $J_{F_{1,6}}$ are both zero hertz.

F$_2$ is at a lower field since it is not shielded by the DHP C-3–C-4 double bond or the benzoyl group. Compound **127** existed as a mixture of two diastereomers in a ratio of 5:4. The ^{19}F NMR spectrum for **127** exhibited two doublets of doublets for F$_2$ [$J_{F_1,F_2} = 160$ Hz; $J_{H,F_1} = 15.4$ Hz (major diastereomer) and $J_{H,F_2} = 14.5$ Hz (minor diastereomer)] at 37.2 and 35.8 δ, respectively. In contrast, F$_1$ appeared as two doublets ($J_{F_1,F_2} = 160$ Hz) at δ 12.8 (major) and 13.07 (minor), respectively. The J_{F_2,H_6} coupling is much larger than the J_{F_2,H_1} coupling constant.
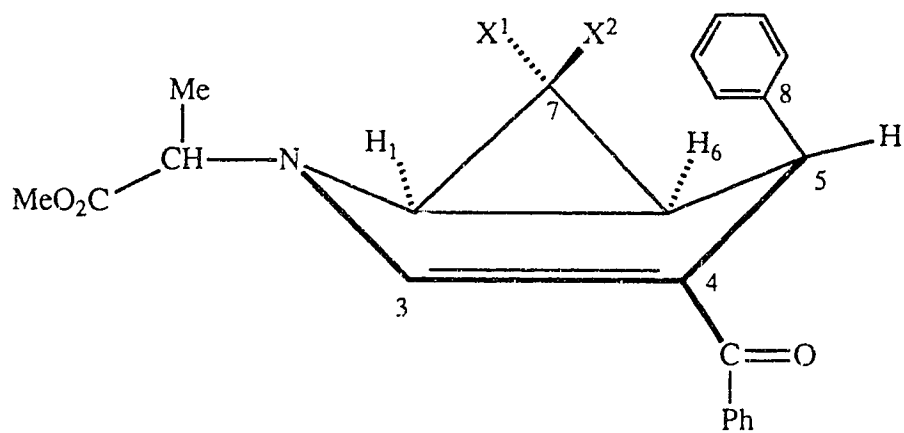
Figure 10. Possible conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (125-128).
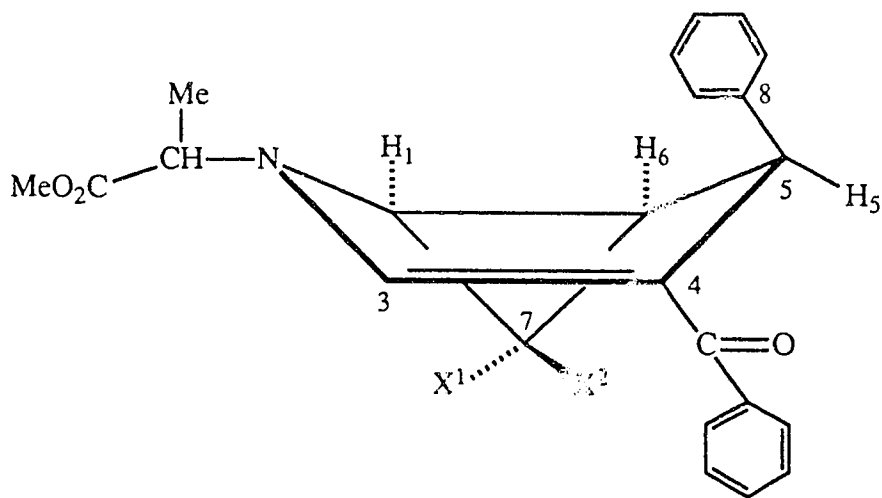

Figure 11. Most stable conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (125-128).
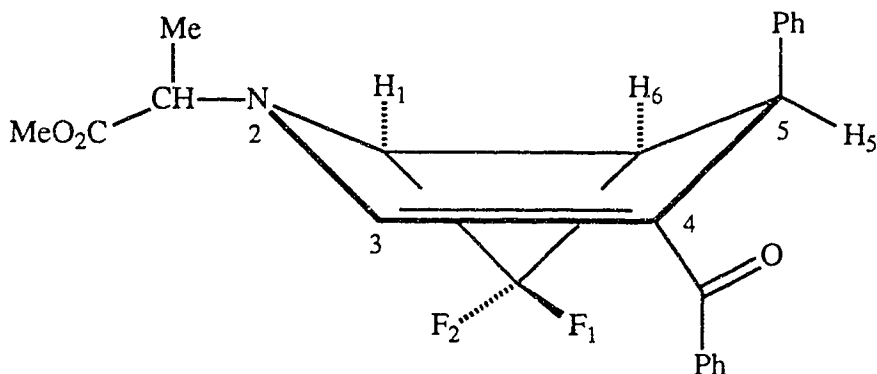
Figure 12. Most probable conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-difluoro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (**127**).

$J_{H_1F} = 0$, $J_{H_6,F} = 7.2$ Hz

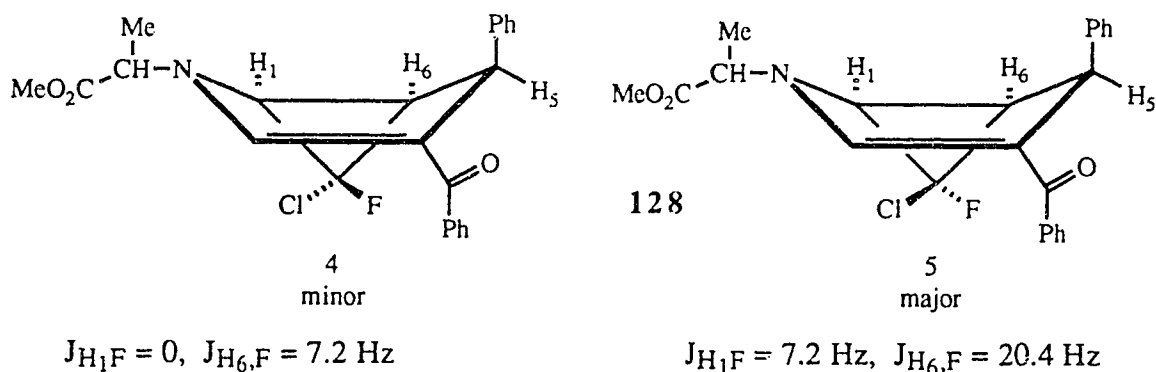$J_{H_1F} = 7.2$ Hz, $J_{H_6,F} = 20.4$ Hz

Figure 13. Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-fluoro-7-chloro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (**128**) diastereomer.

Compound **128**, which contains an additional chiral center at C-7, exhibited dual resonances for H-1, H-3, H-5, H-6, OMe, and MeCH- protons in a diastereomeric ratio of 5:4. The ^{1}H NMR spectrum for compound **128** indicated that $J_{H1,F} = 0$ Hz and $J_{H_6,F} =$ 7.2 Hz in the minor diastereomer suggesting F is *trans* to H-1 and H-6. In the major diastereomer, F must be *cis* to both H1 and H6 as indicated by the coupling constants $J_{H_1,F}$ = 7.2 Hz and $J_{H_6,F}$ = 20.4 Hz (Figure 13).

The stereoselectivity observed in the monodehalogenation reactions of **125, 126,** and **128** is consistent with a reaction mechanism involving preferential attack by the bulky tri-*n*-butyltin radical at the less hindered C-X bond which is *cis* with respect to the cyclopropyl H-1 and H-6 hydrogens, followed by attack by *n*-Bu$_3$SnH on the resulting radical[212a] from the less hindered site[212b] (Figure 14).
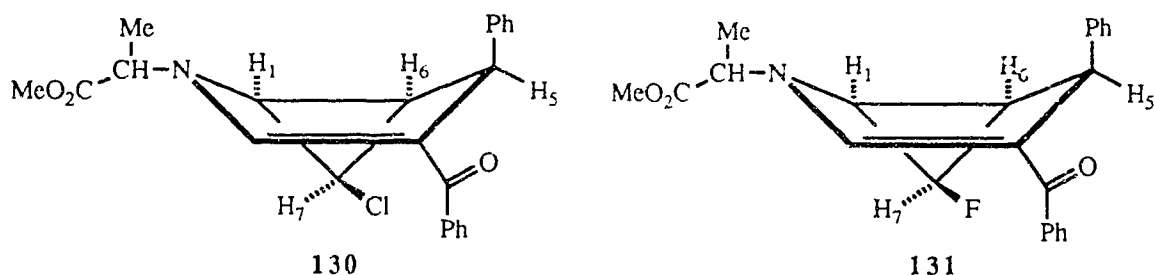

Figure 14. Conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-chloro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (**130**) and methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-fluoro-2-azabicyclo[4.1.0]-hept-3-ene)]acetate (**131**).

H-1 and H-6 must be *cis* to the new H-7 generated for compound **130** due to the magnitude of the coupling constants observed. In compound **131**, the coupling constants were $J_{1,7} = 5.5$ (*cis*), $J_{6,7} = 8.5$ (*cis*) and $J_{1,6} = 9.9$ Hz with respect to the new generated H-7. The magnitude of the coupling constants observed were $J_{F,H7} = 66$ Hz, $J_{6,7} = 9.2$ Hz (*cis*) and $J_{1,7} = 3.8$ Hz (*cis*).

A large number of spectra of substituted cyclopropane derivatives have been reported. The magnitude of the vicinal coupling constant for J_{cis} is always larger than J_{trans} for any given pair of cyclopropyl stereoisomers[213,214] and this was used to assign the orientation, in some cases, of the halogen on the cyclopropane ring. The δ values with respect to each halogen were found to be F > Cl > Br which is consistent with the electronegativity order for F, Cl and Br.

3.1.8.0.0. **Attempted Synthesis of Chiral N-Substituted 1,4-Dihydro-pyridine Analogs**

When a drug exists as a racemate, or a mixture of diastereomers, higher biological activity is often exhibited by one enantiomer or one diastereomer. Therefore, synthetic methodologies[20] that provide the physiologically more active compounds in optically pure form or as a single diastereomer, are advantageous. Several strategies for the synthesis of chiral arylacetic acids in optically pure form have been reported.[215-219] Attempts were made in this investigation to synthesize pure diastereomers, or enantiomers, in anticipation that a single diastereomer, or enantiomer, might exhibit superior antiinflammatory activity. This rationale is based on the well documented SARs for NSAIDs that generally the active (+)-enantiomer has the (S)-configuration.

3.1.9.0.0. **Synthesis of 3-Benzoyl-4-phenyl-1-{1-methyl-2-oxo-2-[(4S)-4-isopropyl-2-oxazolidinonyl]ethyl}-1,4-dihydro-pyridine (135)**

The use of Evans's reagent (4S)-4-isopropyl-2-oxazolidinone as a chiral auxiliary for the synthesis of optically active (S)-Ketoprofen, (S)-Ibuprofen and (S)-Naproxen has been reported.[220] Thus, reaction of (4S)-(-)-4-isopropyl-2-oxazolidinone with n-butyllithium will give the lithio enolate species **133** which should react readily with the activated ester **134**. The activated ester **134** was prepared from the acid **98a** and the coupling reagent 1,1'-bis[6-trifluoromethyl)benzotriazolyl]oxalate (BTBO) according to the procedure reported by Takeda et al.[221] The lithium enolate **133** was then treated with **134** to afford **135** in 33% yield. The reaction pathway and mechanism is outlined in Scheme 11. The diastereomers could not be separated.

Scheme 11. Synthesis of 3-benzoyl-4-phenyl-1-{1-methyl-2-oxo-2-[(4S)-
4-isopropyl-2-oxazolidinonyl]ethyl}-1,4-dihydropyridine
(135).

3.1.10.0.0. Synthesis of N-[(1S)-1-phenethyl]-2-methyl-2-[1-(3,5-di-
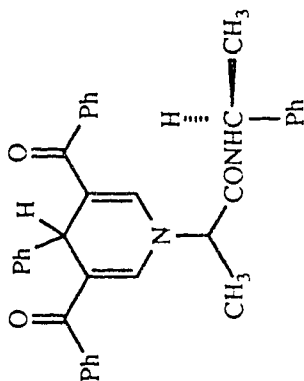
benzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide

Diastereomers (137a and 137b)

The use of (S)-(-)-α-methylbenzylamine as a chiral derivatization agent in the separation of diastereomers of arylpropionic acids has been investigated.[222] Thus, compound **136** was synthesized according to the procedure reported by Takeda et al.[221] with the hope that two diastereomers (SS and SR) could be separated and the amide group hydrolyzed to give the respective enantiomers. Reaction of 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acid (**108**) with BTBO in acetonitrile yielded the activated ester **136**, which on reaction with (S)-(-)-α-methylbenzylamine afforded the diastereomers **137a** and **137b** in 38% total yield. The two diastereomers **137a** and **137b** were separated by preparative silica gel TLC. However, attempts to regenerate the free acids by hydrolysis of the amide moiety in either diastereomer was unsuccessful. The hydrolysis reaction was attempted using triethylamine and trichlorosilane which has been reported by Buckle et al.[223] to be an efficient method for the hydrolysis. The ^{1}H NMR spectrum of the hydrolysis reaction product indicated disappearance of starting DHP material. It is plausible that $HSiCl_3$, which is a strong Lewis acid, protonates the N-1 position of the DHP with subsequent ring cleavage. The reaction is outlined in Scheme 12. The spectral data for **137a** and **137b** are shown in Table 11.

3.1.11.0.0. Synthesis of (S)-Methoxycarbonyl-α-methyl methyl-2-

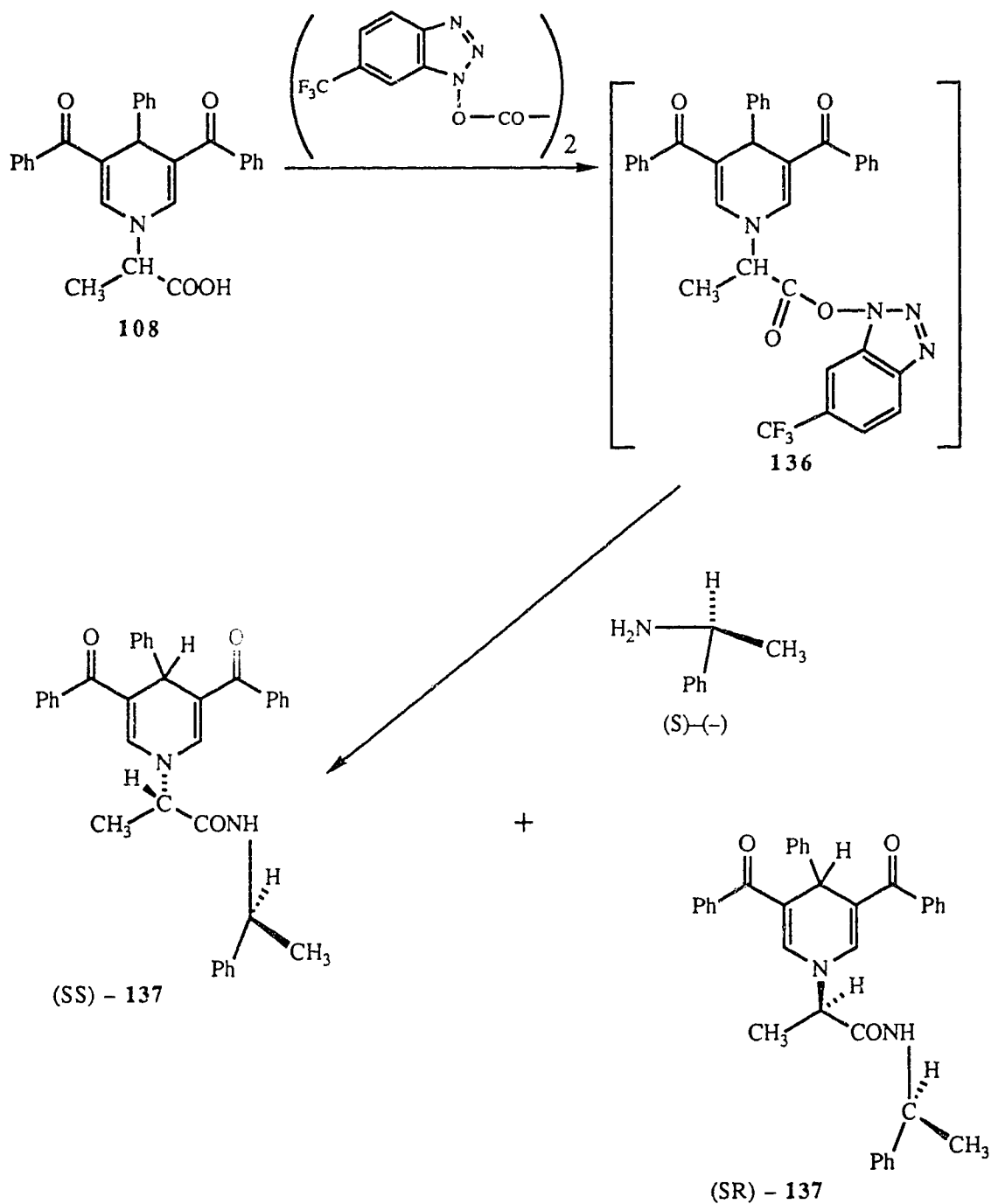methyl-2-{1-[3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl]-

acetate (138)

Further attempts directed towards the synthesis of pure diastereomers possessing a chiral lactate ester led to the synthesis of compound **138**. Thus, using the procedure of Takeda et al.,[221] a solution of 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acid (**108**) was reacted with a suspension of BTBO in acetonitrile to give

Table 11. ^{1}H NMR spectral data for N-[(1S)-1-phenethyl]-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide diastereomers (**137a** and **137b**).

137a and **137b**

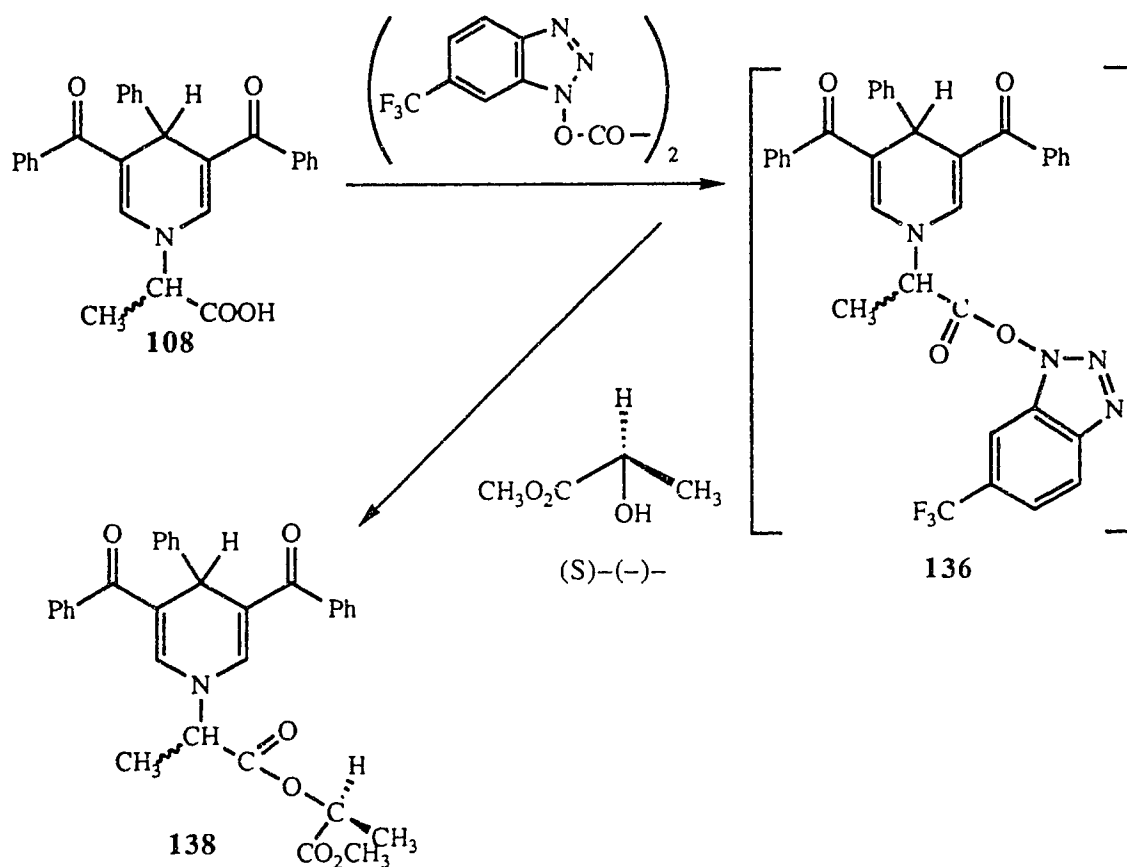| Entry	^{1}H NMR (CDCl$_3$) δ
137a	7.1-7.6 (m, 20H, phenyl hydrogens), 6.90 and 6.96 (two d, J$_{2,6}$ = 1.5 Hz, 1H each, H-2 and H-6), 6.14 (d, J$_{NH,CH}$ = 7.2 Hz, 1H, NH), 5.64 (s, 1H, H-4), 5.1 (q, J$_{CH,CH_3}$ = 7.2 Hz, 1H, C$\underline{H}$(CH$_3$)CO), 1.46 and 1.44 (two d, J$_{CH_3,CH}$ = 7.2 Hz, 6H, two C$\underline{H}_3$CH)
137b	7.1-7.5 (m, 20H, phenyl hydrogens), 6.90 and 6.92 (two d, J$_{2,6}$ = 1.5 Hz, 1H each, H-2 and H-6), 6.22 (d, J$_{NH,CH}$ = 7.2 Hz, 1H, NH), 5.62 (s, 1H, H-4), 5.1 (q, J$_{CH,CH_3}$ = 7.2 Hz, J$_{CH,NH}$ = 7.2 Hz, NHCHC$\underline{H}_3$), 3.9 (q, J$_{CH,CH_3}$ = 7.2 Hz, 1H, C$\underline{H}$(CH$_3$)CO), 1.42 (d, J$_{CH_3,CH}$ = 7.2 Hz, 6H, two C$\underline{H}_3$CH)

Scheme 12. Synthesis of N-[(1S)-1-phenethyl]-2-methyl-2-[1-(3,5-di-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide diastereomers (137a) and (137b).

the activated ester **136** which, without isolation, was reacted with (S)-(-)-methyl lactate.

The resulting mixture was worked up as reported[221] to afford **138** as an oil in 12% yield.

Activated esters have frequently been prepared by reaction of an acid with N-hydroxy

imides[224] or 1-hydroxybenzotriazole[224] in the presence of N,N'-dicyclohexylcarbodiimide

(DCC). However, DCC causes side reactions such as formation of N-acylurea and a

Lossen rearrangement reaction for N-hydroxysuccinimide.[225] BTBO was used in this

investigation since it has been reported that with BTBO, nucleophilic attack by alcohol to

active ester occurs stoichiometrically,[221] while excess alcohols are required with benzotri-

azole[226] and 6-chlorobenzotriazole esters.[227] Furthermore, BTBO is not a skin irritant as

is DCC and BTBO esterifications proceed much faster and produce only three by-products,

carbon monoxide, carbon dioxide, and 1-hydroxy-6-(trifluoromethyl)benzotriazole.[221] It

was expected that the 3,5-dibenzoyl compound **138** could be separated into two pure

diastereomers (SS and SR) which could then be cleaved by hydrolysis to afford the pure S

and R enantiomers. However **138** was a single band on TLC which could not be

separated.

The ^{1}H NMR spectrum of compound **138** indicated a mixture of two diastereomers in

the ratio 5:4 which differ in configuration at the N-C$\underline{H}$(CH$_3$)CO$_2$ chiral carbon. The

spectrum exhibited dual resonances for the H-2, H-6, NC$\underline{H}$CH$_3$ and OMe protons. The

reaction is outlined in Scheme 13.

3.1.12.0.0. Synthesis of (4S)- or (4R)-Methyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (143)

Diisopinocampheylchloroborane, IpC$_2$BCl, **142**), reduces ring and chain substituted

halo or alkyl ketones to the corresponding haloalcohols in excellent enantiomeric excess.[228]

It was therefore anticipated that IpC$_2$BCl could be used to synthesize **143** by stereo-

selective addition to the 3-benzoyl-4-phenyl-N-substituted pyridinium salt **141**. The salt

Scheme 13. Synthesis of (S)-methoxycarbonyl-α-methyl methyl-2-methyl-
2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetate.

141 was prepared by quaternization of 3-benzoyl-4-phenylpyridine (140) in refluxing
anhydrous acetone with methyl DL-2-bromopropionate in acetone for 24 h. To a solution
of IpC₂BCl in THF at -23°C was added 141, suspended in THF under nitrogen and the
mixture was stirred for 7 h prior to work up as reported.[229] Although silica gel TLC
indicated that the starting material 141 was no longer present, the ^{1}H NMR spectrum of the
isolated product was not that of the desired compound. The reaction is outlined in Scheme
14.

Scheme 14. Attempted synthesis of (4S)- or (4R)-methyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (143).

3.1.13.0.0.0. Attempted Synthesis of Methyl 2-methyl-2-[1-(3-phenoxy-4-phenyl-1,4-dihydropyridyl)]acetate (146)

A structural unit common to many useful NSAIDs is the 2-phenylpropionic acid moiety from which the term "profen" drugs is derived. Profen drugs differ in the nature of the substituents on the aromatic ring.[230] Examples include Ibuprofen, Flurbiprofen, Ketoprofen, and Fenoprofen. It was therefore of interest to replace the 2-phenylpropionic

acid moiety with a 1,4-dihydropyridyl acetic acid ester moiety since pyridine and dihydro-

pyridine have been reported to be bioisosteric with phenyl moieties.[40,161,162]

3-Phenoxypyridine (**144**), which was prepared in 84% yield according to the

procedure of Renshaw and Conn,[231] was quaternized with methyl DL-2-bromopropionate

to afford the N-substituted 3-phenoxypyridinium salt (**145**). The copper catalyzed regio-

specific reduction of **145** with phenylmagnesium chloride, as described in General

Procedure A, afforded **146** as a brownish oil. The purification of **146** was attempted

using silica gel and neutral alumina column chromatography but intensive decomposition

occurred. Thus, it was not possible to obtain pure **146**. The instability of compound **146**

could be due to the 3-phenoxy group which has been reported[119] to destabilize dihydro-

pyridines. The synthetic procedure used to prepare **146** is outlined in Scheme 15. The

compound **146** also decomposed on storage both at 0°C and room temperature.

Scheme 15. Syntheis of methyl 2-methyl-2-[1-(3-phenoxy-4-phenyl-1,4-di-
hydropyridyl)]acetate (**146**).

3.1.14.0.0.0. Synthesis of Ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-
1,4-dihydropyridyl)]acetates (149-152), Ethyl 2-methyl-2-
[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]-
acetate (153), and Ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-
1,4-dihydropyridyl)]acetate (154)

The acetic acid side chain of known heteroarylacetic acid NSAIDs is usually attached to an sp^2 hybridized carbon. It has also been established that the pyridine ring and di-hydropyridyl ring systems are bioisosteric with respect to antiinflammatory activity.[40,161,162] Thus, it was of interest to extend the SARs by preparing compounds 149-154 for evaluation as antiinflammatory agents.

Thus, quaternization of ethyl 3-pyridylacetate (147, R^1 = H), or ethyl 2-methyl-3-pyridylacetate (148, R^1 = Me) with phenyl chloroformate (R^2 = Ph) or methylchloro-formate (R^2 = Me) and the subsequent copper-catalyzed Grignard reduction of the N-acyl-pyridinium salts formed, afforded compounds 149-154 in 64 to 96% yield. The reaction procedure is outlined in Scheme 16. The spectral data for 149-154 are shown in Table 12 and the physical data are shown in Table 13.

147 R^1 = H
148 R^1 = Me

149 – 154

Scheme 16. Ethyl 2-[3-[(1-phenoxycarbonyl-4-substituted-1,4-dihydro-pyridyl)]acetates (149-152), Ethyl 2-methyl-2-[3-(1-phenoxy-carbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (153) and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (154).

Table 12. IR and ¹H NMR spectral data for ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (149-152), ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-1,4-dihydropyridyl)]acetate (153), and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (154).

149 – 154
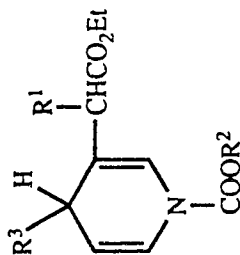
Entry	R¹	R²	R³	IR (neat) cm⁻¹	¹H NMR, CDCl₃ (δ)
149	H	Ph	Ph	1745 (COOEt); 1730 (COOPh)	7.16-7.48 (m, 10H, phenyl hydrogens), 7.0-7.14 (m, 2H, H-2, H-6), 5.05 and 5.12 (two d, $J_{4,5}$ = 4.0 Hz of d, $J_{5,6}$ = 8.6 Hz, 1H total, H-5), 4.26 and 4.36 (two d, $J_{4,5}$ = 4.0 Hz, 1H, H-4), 4.1 (q, J_{CH_2,CH_3} = 7.0 Hz, 2H, CH_2CH_3), 2.72-2.92 (m, 2H, CH_2COO), 1.14-1.32 (m, 3H, CH_3CH)
150	H	Ph	4ClPh	1745 (COOEt); 1730 (COOPh)	6.8-7.45 (m, 9H, phenyl hydrogens), 6.76 and 6.9..., 1H total, H-2), 6.76 (d, $J_{5,6}$ = 8.6 Hz, 1H, H-6), 5.0 and 5.03 (two d, $J_{5,6}$ and 4.30 (two d, $J_{4,5}$ = 4.0 Hz, 1H total, H-), 4.08 (q, J_{CH_2,CH_3} = 7.0 Hz, 2H, CH_2CH_3), 2.7-2.9 (m, 2H, CH_2COO), 1.24 (t, J_{CH_3,CH_2}= 7.0 Hz, 3H, CH_3CH_2)

(Continued)

Entry	R¹	R²	R³	IR (neat) cm⁻¹	¹H NMR, CDCl₃ (δ)
151	H	Ph	n-Bu	1740 (COOEt); 1730 (COOPh)	7.14-7.50 (m, 5H, phenyl hydrogens), 6.86 -7.0 (m, 2H, H-2, H-6), 4.95 and 5.02 (two d, $J_{4,5}$ = 4.9 Hz of d, $J_{5,6}$ = 8.4 Hz, 1H total, H-5), 4.18 (m, 2H, $C\underline{H}_2CH_3$), 3.18-2.92 (m, 3H, $C\underline{H}_2COO$, H-4), 1.2-1.65 (m, 9H, CO_2CH_2, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.88 (t, J = 7 Hz, $CH_2CH_2C\underline{H}_3$)
152	H	Ph	Me	1740 (COOEt); 1730 (COOPh)	7.1-7.45 (m, 5H, phenyl hydrogens), 6.84-6.96 (m, 2H, H-2, H-6), 4.9 and 5.02 (d, $J_{5,6}$ = 8.8 Hz of d, $J_{4,5}$ = 4.3 Hz, 1H total, H-5), 4.19 (q, J_{CH,CH_3} = 7.0 Hz, 2H, $C\underline{H}_2CH_3$), 2.94-3.25 (m, 3H, $C\underline{H}_2CO_2$, H-4), 1.28 (t, 3H, $CH_2C\underline{H}_3$), 1.16 (d, $J_{CH_3,H}$ = 6.9 Hz, 3H, $CHC\underline{H}_3$)
153	Me	Ph	Ph	1742 (COOEt); 1730 (COOPh)	7.1-7.6 (m, 10H, phenyl hydrogens), 6.9-7.1 (m, 2H, H-2, H-6), 5.14 and 5.04 (two d, $J_{5,6}$ = 8.8 Hz of d, $J_{4,5}$ = 4.3 Hz, 1H total, H-5), 4.25 (d, $J_{4,5}$ = 4.3 Hz, 1H, H-4), 4.08 (m, 1H, $C\underline{H}_2CO_2$), 2.9 (q, $J_{CH_3,CH}$ = 7.0 Hz, 1H, $C\underline{H}CH_3$), 1.1-1.45 (m, 6H, $CHC\underline{H}_3$, $CH_2C\underline{H}_3$). Rotameric ratio 1:1.

(Continued)

Entry	R¹	R²	R³	IR (neat) cm⁻¹	¹H NMR, CDCl₃ (δ)
153 (Cont'd.)	Me	Ph	Ph	1742 (COOEt); 1730 (COOPh)	¹H NMR (Me₂SO-d₆) (68°C): 7.2-7.5 (m, 10H, phenyl hydrogens), 6.98-7.10 (m, 2H, H-2, H-6), 5.12 (d, $J_{5,6}$ = 8.8 Hz of d, $J_{4,5}$ = 4.3 Hz, 1H, H-5), 4.20 (d, $J_{4,5}$ = 4.3 Hz, 1H, H-4), 3.98 and 4.02 (two overlapping q, J = 7 Hz, CH₂CH₃), 2.96 and 2.29 (two overlapping q, J = 7.0 Hz, 1H, CHCH₃), 1.06-1.24 (m 6H, CH₂CH₃, CHCH₃)
154	H	Me	Ph	1745 (COOEt); 1740 (COOMe)	7.12-7.3 (m, 5H, phenyl hydrogens), 6.90 and 6.93 (two s, 1H total, H-2), 6.74 and 6.78 (two d, $J_{5,6}$ = 8.6 Hz, 1H total, H-6), 4.85 and 4.95 (two d, $J_{5,6}$ = 8.6 Hz of d, $J_{4,5}$ broadened, 1H total, H-5), 4.16 (broad peak, 1H, H-4), 4.06 (q, J_{CH,CH_3} =7 Hz, 2H, CH₂CH₃), 2.7 (s, 2H, CH₂COO), 1.2 (t, J_{CH,CH_3} = 7.0 Hz, 3H, CH₃CH₂). The rotamer ratio was about 1:1.

Table 13. Physical data for ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (**149-152**), ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-1,4-dihydropyridyl)]acetate (**153**), and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]-acetate (**154**).

Entry	R^1	R^2	R^3	Yield,[a] %	Formula	Microanalysis: Calcd. (Found)		
						C	H	N
149	H	Ph	Ph	96	$C_{22}H_{21}NO_4$	72.71 (72.77)	5.82 (5.85)	3.85 (3.56)
150	H	Ph	4ClPh	75	$C_{22}H_{20}NO_4$	66.42 (66.30)	5.07 (5.30)	3.52 (3.57)
151	H	Ph	n-Br	82	$C_{20}H_{25}NO_4$	69.94 (69.86)	7.33 (7.26)	4.07 (4.04)
152	H	Ph	Me	64	$C_{17}H_{19}NO_4$	67.75 (67.58)	6.35 (6.37)	4.64 (4.32)
153	Me	Ph	Ph	64	$C_{23}H_{23}NO_4 \cdot 1/2H_2O$	71.50 (71.64)	5.96 (6.16)	3.63 (3.26)
154	H	Me	Ph	87	$C_{17}H_{19}NO_4$	67.76 (67.63)	6.36 (6.05)	4.65 (4.59)

[a]All compounds were oils.

^{1}H NMR variable temperature studies for ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (153) indicated that the dual resonances observed for H-2, H-6 and H-5 were due to rotamers in solution. The rotameric ratio was 1:1 for most products at 25°C. The dual resonance peaks for H-5 in compound 153 coalesced at 68°C. The observed rotational isomerism is due to restricted rotation about the nitrogen-to-carbonyl bond of the carbamate moiety present in compounds 149-154 as illustrated in Figure 15 for compound 153.

153

Figure 15. Rotamers of compound 153 as a result of restricted rotation.

The ^{1}H NMR and IR spectra for compounds 149-154 were consistent with their assigned structures.

3.2.0.0.0. PHARMACOLOGICAL SCREENS

3.2.1.0.0.0. Analgesic-Antiinflammatory Structure Activity Relationships (SARs) for Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates (90a-c), Methyl 2-methyl-2-[(1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates (91-93), 2-[1-(3-Benzoyl-4-substituted-1,4-dihydropyridyl)]acetic Acids (97a-c), 2-Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic Acids (98a-e), Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides

(99a-c), and 2-Methyl 2-[1-(3-benzoyl-4-substituted-1,4-di-hydropyridyl)]acetamides (99d-j)

The acetic acid esters (90-93), acetic acids (97-98) and acetamides (99) were synthesized to investigate the effect which replacement of the phenyl ring present in the traditional NSAIDs by a 1,4-dihydropyridyl ring has upon analgesic-antiinflammatory activity. The structures of these 1,4-dihydropyridyl-1-acetic acid esters (90-93), acetic acids (97-98) and acetamides (99) were expected to have some conformational differences relative to the classical aryl acetic acid NSAIDs. For example, the 1,4-dihydropyridine ring system is more puckered than the planar phenyl ring system. While the ene (C=C) moieties of the 1,4-dihydropyridyl ring systems are quasi-planar, there is considerable distortion at the N-1 and C-4 positions. These differences, together with steric effects due to the 1,4-dihydropyridyl N-1 and C-4 substituents were e   ·cted to alter the overall volur·:e of the molecule, the distribution of the drug between hydrophilic and hydrophobic tissues, and the interaction of the drug with the antiinflammatory receptor site.[243]

The acetic acid ester (90-93), acetic acid (97-98) and acetamide (99) classes of compounds were investigated to determine the effect of the α-substituent (R^3 = H or Me), the 1,4-dihydropyridyl ring C-4 substituents (R^2 = phenyl, 4-chlorophenyl, 4-tolyl, benzyl, cyclohexyl, n-butyl, and iso-butyl), the benzoyl substituent (R^1 = H, Cl, CH_3), and the nature of the N-1 substituent (ester, acid or amide), upon analgesic and anti-i..flammatory activities.

In the methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)acetate and methyl 2-methyl-2-[1-(3-benzoyl-4-substituted 1,4-dihydropyridyl)]acetate series (90-93), the analgesic activity potency order with respect to the 1,4-dihydropyridyl C-4 R^3 substituent was phenyl (91) > iso-butyl (91h) > n-butyl (91g) = 4-chlorophenyl (90b) > 4-tolyl (91d) > cyclohexyl (91d) > benzyl (91f). The relative antiinflammatory potency order was phenyl (91) > cyclohexyl (91d) > 4-chlorophenyl (91c) > iso-butyl (91h) > n-butyl

(91g) > benzyl (91f) > 4-tolyl (91d). The phenyl substituent appeared to be the most active in the series.

The relative order of analgesic activity in the 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acid and 2-methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydro-pyridyl)]acetic acid series (97-98) was cyclohexyl (98c) > phenyl (97a) > 4-chlorophenyl (97b) > phenyl (98a) and the antiinflammatory activity order for this series was phenyl (98a) > cyclohexyl (98c) > 4-chlorophenyl (97a) = phenyl (98b).

In the acetamide series, methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]-acetamides (99a-c) and 2-methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]-acetamides (99d-j), the analgesic activity order was cyclohexyl (99g) > phenyl (99d) = benzyl (99h) > 4-tolyl (99f) > 4-chlorophenyl (99e) > 4-chlorophenyl (99b) $\cong$ phenyl (99a).

The α-substituent (R^3 = H or Me) present in the N-1 acetyl moieties of these compounds also influenced analgesic-antiinflammatory activity. In the ester series (R^4 = OMe), those compounds having R^3 = Me substituents were generally more active than the corresponding R^3 = H analogs. A similar correlation was found for the amide group of compounds. For the acid series (R^4 = OH), the relative activity order was generally, but not always, R^3 = H > Me.

The relative analgesic activity order was generally amide (R^4 = NH_2) > ester (R^4 = OMe) > acid (R^4 = OH). This order of activity for the ester, amide and acid analogs could be due to the more lipophilic nature of the ester and amide compounds relative to the acids. The more lipophilic esters may penetrate cell membranes more easily and once inside the cell, hydrolysis to the corresponding acids can occur.

The test results indicate that the R^1 substituent on the benzoyl group influenced analgesic-antiinflammatory activity in the order H = Cl > CH_3 for analgesic activity and H > Cl > CH_3 for antiinflammatory activity. This R^1 substituent activity order could be due to steric factors which might affect drug-receptor interaction.

The pharmacological data for compounds **90-93, 97-98** and **99** are summarized in Table 14. The most active antiinflammatory agent in this series was **91** which reduced inflammation by 50% at 3 hours and 74% at 5 hours after a 100 mg/kg po dose relative to Ibuprofen which reduced inflammation by 44% at 3 hours and 52% at 5 hours at the same dose. The most active analgesic activity was **99g** (96% inhibition at 50 mg/kg sc dose) relative to Aspirin (58% inhibition at the same dose).

3.2.2.0.0.0. Analgesic-Antiinflammatory SARs of Methyl (103) and Methyl 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetates (104), 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (105), 2-Methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (106) and 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]-acetic Acids (107 and 108)

Compounds **103-108** were investigated in order to determine the effect of chirality upon pharmacological activity. Compounds **103, 105,** and **107** are achiral, whereas compounds **104, 106,** and **108** have one chiral center when R^1 = Me.

When the analgesic activities were determined, compounds with R^1 = Me were equiactive to the corresponding analogs with R^1 = H. In contrast, the antiinflammatory activity order was R^1 = Me > H. This latter SAR is consistent with known structure-activity correlations for NSAIDs.[244] In general, the order of activity for the R^2 substituent was ester > amide > acid for both analgesic and antiinflammatory activities.

It appears that chirality is a determinant of antiinflammatory activity. Compound **104**, which is chiral, was considerably more active (80% inhibition at 3 h and 71% inhibition at 5 h for a 100 mg/kg po dose) than compound **103**, which is achiral (10% inhibition at 3 h and 80% inhibition at 5 h) for the same dose. Also, compound **104**, which has only one chiral center at the methine carbon of the N-acetyl moiety had superior antiinflammatory

Table 14. Pharmacological data for methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **90a-90c**; methyl 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **91a-91h, 92a-92d, 93**; *ortho*-methoxyphenyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate **96**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **97a-97c**; 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **98a-98e**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99a-99c**; and 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99d-99j**.

Entry	R^1	R^2	R^3	R^4	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
						3 h	5 h
90a	H	Ph	H	OMe	45.2 ± 5.7	Inactive	12.9 ± 4.0
90b	H	4-ClC$_6$H$_4$	H	OMe	66.0 ± 1.3	44.7 ± 6.5	Inactive
90c	H	4-tolyl	H	OMe	25.5 ± 3.8	18.8 ± 3.8	23.0 ± 5.2
91	H	Ph	H	OMe	94.5 ± 1.5	50.0 ± 7.3	73.6 ± 2.0

(Continued)

Entry	R[1]	R[2]	R[3]	R[4]	Analgesic Act.[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
						3 h	5 h
91a	H	Ph	Me	OMe	NT	54.5 ± 3.6	33.7 ± 1.8
91b	H	Ph	Me	OMe	NT	56.1 ± 5.2	61.4 ± 2.4
91c	H	4-ClC$_6$H$_4$	Me	OMe	57.5 ± 2.0	48.9 ± 4.7	13.57 ± 3.2
91d	H	4-tolyl	Me	OMe	65.4 ± 2.1	13.9 ± 2.4	2.93 ± 3.7
91e	H	cyclohexyl	Me	OMe	62.8 ± 1.8	63.6 ± 2.4	29.3 ± 3.7
91f	H	benzyl	Me	OMe	57.5 ± 3.7	25.6 ± 3.8	7.3 ± 5.2
91g	H	n-Bu	Me	OMe	66.5 ± 1.4	40.4 ± 3.8	52.7 ± 3.2
91h	H	i-Bu	Me	OMe	72.8 ± 3.1	46.1 ± 1.5	26.4 ± 5.3
92a	Cl	Ph	Me	OMe	80.0 ± 2.5	46.9 ± 4.2	48.5 ± 3.1
92b	Cl	4-ClC$_6$H$_4$	Me	OMe	47.6 ± 3.5	Inactive	30.3 ± 2.8
92c	Cl	benzyl	Me	OMe	53.0 ± 2.6	Inactive	38.0 ± 3.0
92d	Cl	cyclohexyl	Me	OMe	51.0 ± 5.3	3.0 ± 2.9	32.0 ± 5.2
93	CH$_3$	Ph	Me	OMe	62.7 ± 1.7	12.1 ± 2.3	Inactive
96	H	Ph	Me		83.0 ± 4.8	45.5 ± 3.9	50.0 ± 3.6

(Continued)

Entry	R^1	R^2	R^3	R^4	Analgesic Act.^{a} % Inhibition	Antiinflammatory Act.^{b}, % Inhibition	
						3 h	5 h
97a	H	Ph	H	OH	45.1 ± 0.2	Inactive	Inactive
97b	H	4-ClC$_6$H$_4$	H	OH	43.4 ± 2.1	29.7 ± 4.7	Inactive
97c	H	4-tolyl	H	OH	NT	NT	NT
98a	H	Ph	Me	OH	30.1 ± 4.7	14.20 ± 1.3	68.5 ± 0.8
98b	H	4-ClC$_6$H$_4$	Me	OH	43.4 ± 2.1	29.7 ± 4.7	Inactive
98c	H	cyclohexyl	Me	OH	62.8 ± 1.8	63.6 ± 5.4	41.9 ± 2.6
98d	H	benzyl	Me	OH	NT	NT	NT
98e	H	n-Bu	Me	OH	NT	NT	NT
98f	H	i-Bu	Me	OH	NT	NT	NT
99a	H	Ph	H	NH$_2$	33.3 ± 3.2	Inactive	16.0 ± 3.6
99b	H	4-ClC$_6$H$_4$	H	NH$_2$	34.2 ± 5.2	40.4 ± 2.3	Inactive
99c	H	4-tolyl	H	NH$_2$	NT	NT	NT
99d	H	Ph	Me	NH$_2$	75.9 ± 2.3	14.3 ± 2.5	68.6 ± 3.0
99e	H	4-ClC$_6$C$_4$	Me	NH$_2$	59.3 ± 2.7	31.2 ± 2.6	Inactive

(Continued)

Entry	R[1]	R[2]	R[3]	R[4]	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.,[b] % Inhibition	
						3 h	5 h
99f	H	4-tolyl	Me	NH$_2$	62.5 ± 5.7	8.3 ± 4.6	60.9 ± 3.5
99g	H	cyclohexyl	Me	NH$_2$	95.6 ± 3.6	Inactive	Inactive
99h	H	benzyl	Me	NH$_2$	75.5 ± 2.9	25.0 ± 4.8	18.4 ± 3.9
99i	H	n-Bu	Me	NH$_2$	NT	NT	NT
99j	H	i-Bu	Me	NH$_2$	NT	NT	NT
Ibuprofen					–	43.8 ± 2.3	51.7 ± 3.6
Aspirin					57.8 ± 2.8	–	–

NT = Not tested

[a]The result is the mean value ± SEM (n = 5) for a 50 mg/kg sc dose in the 4% NaCl-induced writhing test.

[b]The result is the mean value ± SEM (n = 4) for a 100 mg/kg po dose in the carrageenan-induced edema test.

[c]Tested as a mixture of the oil **91a** and solid **91b**.

[d]Tested as an oil.

[e]Tested as a solid.

activity relative to compound **91** which has two chiral centers at C-4 and the methine carbon.
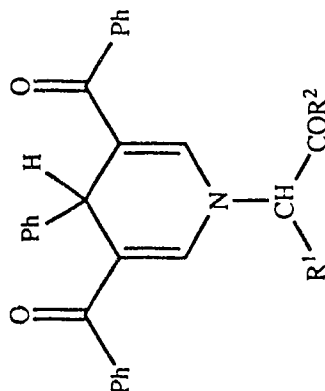
The pharmacological data for compounds **103-108** are summarized in Table 15. The most active analgesic agent in this series was **104** (75% inhibition at 50 mg/kg sc dose relative to Aspirin (58% inhibition at the same dose). Compound **104** was also the most potent antiinflammatory agent (80% inhibition at 3 h and 71% inhibition at 5 h at 100 mg/kg po dose) relative to Ibuprofen (44% inhibition at 3 h and 52% inhibition at 5 h at the same dose).

3.2.3.0.0.0. Analgesic-Antiinflammatory Activity of Methyl 2-methyl-2-(1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl))]acetate (113)

The effect of the bioisosteric replacement of a 1,4-dihydropyridyl ring system by a tetrahydropyridyl group was investigated. The tetrahydropyridyl compound (**113**) was more active (78% inhibition at 3 h for a 100 mg/kg po dose) than its 1,4-dihydropyridyl analog (**91**) (50% inhibition at 3 h) when evaluated for antiinflammatory activity. However, compound **91** was more active as an analgesic agent (95% inhibition at 50 mg/kg sc dose) than its tetrahydropyridyl analog (**125**) (69% inhibition at 50 mg/kg sc dose).

The test results suggest that compound **113** may have a rapid onset of antiinflammatory activity and shorter duration of action since antiinflammatory activity was considerably higher at 3 h relative to 5 h, compared to compound **91** which may have a slower onset of action and a longer duration of action. The pharmacological data for compound **113** is presented in Table 16.

Table 15. Pharmacological data for methyl (103) and methyl 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetates (104), 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (105), 2 methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-di-hydropyridyl)]acetamide (106) and 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acids (107 and 108).

Entry	R^1	R^2	Analgesic Act.[a] % Inhibition	Antiinflammatory Act.[b] % Inhibition	
				3 h	5 h
103	H	OMe	74.0 ± 6.2	10.0 ± 2.5	8.0 ± 3.5
104	Me	OMe	75.0 ± 2.5	80.0 ± 3.5	70.7 ± 4.8
105	H	NH_2	59.8 ± 13.7	23.5 ± 4.0	26.9 ± 5.0
106	Me	NH_2	52.0 ± 3.8	60.4 ± 2.2	68.2 ± 1.5
107	H	OH	34.6 ± 7.4	22.2 ± 3.04	21.9 ± 2.7
108	Me	OH	48.0 ± 3.9	56.3 ± 5.3	51.2 ± 4.5

[a]The result is the mean value ± SEM (n = 5) for a 50 mg/kg sc dose in the 4% NaCl-induced writhing test.

[b]The result is the mean value ± SEM (n = 4) for a 100 g/kg po dose in the carrageenan-induced edema test.

Table 16. Pharmacological data for methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (111), methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (112), and methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (113).

Entry	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.,[b] % Inhibition	
		3 h	5 h
111	60.0 ± 3.8	30.0 ± 5.6	10.5 ± 4.2
112	48.0 ± 2.3	15.3 ± 3.5	28.0 ± 3.8
113	68.6 ± 5.0	78.0 ± 4.8	23.0 ± 4.2

[a]The result is the mean ± SEM (n = 5) for a 50 mg/kg sc dose (n = 5) determined using the NaCl-induced writhing test.

[b]The result is the mean ± SEM (n = 4) for a 100 mg/kg po dose (n = 4) determined using the carrageenan-induced edema test.

3.2.4.0.0.0. Analgesic-Antiinflammatory Activity of Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (125-128)
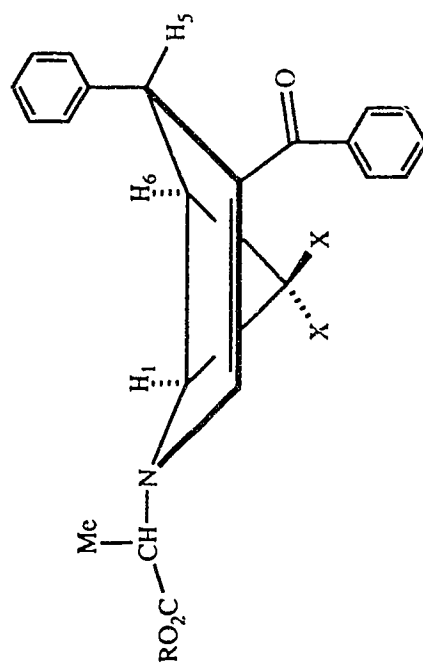
The effect which replacement of the C5-C6 double bond of 91 with a dihalocyclopropyl moiety has upon biological activity was investigated (Table 17). With respect to the halogen substituents, the antiinflammatory potency order was $Br_2 > Cl_2 > F_2 > ClF$, whereas the analgesic activity order was $Cl_2 > Br_2 > F_2 > ClF$. The cyclopropyl moiety in general reduced analgesic-antiinflammatory compared to the corresponding dihydropyridyl analog. This reduced activity could be due to the change in the overall volume of the cyclopropyl compounds with respect to interaction at the receptor site.

3.2.5.0.0.0. Analgesic-Antiinflammatory SARs for Ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (151-152), Ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (153) and Ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (154)

The analgesic activity test results (Table 18) indicated that the order of activity for the R^3 substituent was Ph (149) > Me (152) > n-Bu (151) > 4-chlorophenyl (150). The α-methyl substituent also had an effect on analgesic activity with R^1 = H exhibiting superior activity to a R^1 = Me substituent. The R^2 substituent was also a determinant of analgesic activity with R^2 = Ph (149) > Me (154) [149 (R^2 = Ph) > 154 (R^2 = Me)]. The antiinflammatory activity order for the R^3 substituent was n-Bu (151) > Me (152) > phenyl (149) > p-chlorophenyl (150) whereas the R^1 substituent potency order was R^1 = Me (153) > H (149).

The most active analgesic agent in this series was 149 (83% inhibition at 50 mg/kg sc dose) relative to Aspirin (58% inhibition at the same dose) whereas the most potent anti

Table 17. Pharmacological data for methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (125-128), methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]-hept-3-ene)]acetates (129-131) and acetamide (132).

Entry	X^1	X^2	R	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
					3 h	5 h
125	Br	Br	OMe	68.3 ± 2.9	62.5 ± 3.2	41.0 ± 1.6
126	Cl	Cl	OMe	75.2 ± 1.8	50.3 ± 6.5	35.6 ± 2.3
127	F	F	OMe	56.5 ± 2.1	42.3 ± 1.5	28.5 ± 3.3
128	Cl	F	OMe	36.9 ± 1.8	32.9 ± 2.5	30.6 ± 2.5

(Continued)

Entry	X^1	X^2	R	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
					3 h	5 h
130	H	Cl	OMe	–	–	–
131	H	F	OMe	–	–	–
132	Br	Br	NH_2	82.5 ± 2.8	48.5 ± 2.8	68.2 ± 1.6

[a]The result is the mean $\pm$ SEM (n = 5) for a 50 mg/kg sc dose in the NaCl-induced writhing test.

[b]The result is the mean $\pm$ SEM (n = 4) for a 100 mg/kg po dose in the carrageenan-induced edema test.

Table 18. Pharmacological data for ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (**149-152**), ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-1,4-dihydropyridyl)]acetate (**153**), and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**154**).

Entry	R^1	R^2	R^3	Analgesic Act.[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
					3 h	5 h
149	H	Ph	Ph	83.1 ± 3.8	50.2 ± 3.5	31.7 ± 1.5
150	H	Ph	4ClPh	62.4 ± 5.2	7.3 ± 4.8	6.0 ± 2.8
151	H	Ph	n-Bu	73.2 ± 2.6	62.3 ± 2.3	35.4 ± 1.8
152	H	Ph	Me	80.2 ± 2.4	60.3 ± 3.2	37.3 ± 4.5
153	Me	Ph	Ph	68.0 ± 1.5	70.5 ± 3.5	45.8 ± 1.6
154	H	Me	Ph	58.0 ± 2.5	46.0 ± 1.5	38.0 ± 2.8

[a]The result is the mean ± SEM (n = 5) for a 50 mg/kg sc dose in the NaCl-induced writhing test.

[b]The result is the mean ± SEM (n = 4) for a 100 mg/kg po dose in the carrageenan-induced edema test.

inflammatory agent in the series was (153) which reduced inflammation by 76% at 3 h and 46% at 5 h for a 100 mg/kg po dose relative to Ibuprofen which reduced inflammation by 44% at 3 h and 52% at 5 h at the same dose.

3.3.0.0.0.0. ANALGESIC ACTIVITY EVALUATION

A variety of analgesic tests are used which differ from each other by the nature of the stimuli, parameters, sites of application, nature of responses, quantitation, and apparatus. These tests can be classified into chemical, electrical, mechanical, and thermal methods. Chemically induced animal writhing assays are common protocols used for analgesic activity evaluation. A variety of chemical agents have been used to produce pain, including acetic acid,[232] acetylcholine,[233] hypertonic saline,[234] phenylquinone,[235] serotonin,[236] and bradykinin.[237] The intraperitoneal administration of a noxious chemical substance to mice and rats produces peritoneal irritation, which elicits a writhing response characterized by internal rotation of the feet, sucking in of the stomach, elongation of the body, arching of the back, rolling on one side, and circling the cage.[238]

The phenylquinone-induced writhing test in mice is the most extensively used writhing assay, but it gives false positive results for some compounds.[237] In addition, repeated challenge using phenylquinone at short time intervals is not possible. Therefore, the time course of drug action cannot be determined using this assay. Chronic phenylquinone challenges may also cause damage to abdominal organs.

The NaCl-induced writhing assay used in this investigation, described by Fukawa et al.[239] is reported to be highly specific with no incidence of false positives. Hypertonic sodium chloride solution (4%, w/w, 1 M) was found to be the most reliable agent from a number of noxious irritants evaluated in rats.[234] The 4% sodium chloride-induced writhing assay also has advantages that repeated challenges at short intervals (15 minutes) are possible and chronic challenges do not cause damage to abdominal organs.[239]

Analgesic activity was determined as the reduction in writhing responses (expressed as % inhibition) caused by the test compound as compared to control responses. The analgesic activity results for the test compounds were compared to the reference drugs Aspirin and Ibuprofen.

3.4.0.0.0.0. ANTIINFLAMMATORY ACTIVITY EVALUATION

The complexity of the inflammatory process and the diversity of the drugs that have been found effective in modifying this process have resulted in the development of numerous assay methods capable of detecting antiinflammatory substances. A few of these methods have achieved popularity due to their simplicity, economic feasibility, and relative accuracy. Screening procedures that have been used in an attempt to assess the antiinflammatory potential of drugs include: (i) interference with the manifestation of one of the cardinal signs of inflammation, (ii) modification of one of the events occurring during the inflammatory process, (iii) a biological or chemical characteristic of a class of known antiinflammatory drugs, or (iv) modification of those syndromes in laboratory animals which are believed to represent models for various rheumatoid disease states.[240]

Methods based on the inhibition of an induced swelling of the rat's paw have been the most popular and the method described by Winter et al.[241] was used in this investigation. Test compounds suspended in gum acacia were administered orally at a dose of 100 mg/kg, one hour prior to subcutaneous injection of 0.1 mL of a 1% suspension of carrageenanan into the plantar tissue of the right hind paw and the size of the paw was measured at this time by determining the magnitude of swelling by volume displacement of mercury. Three hours and 5 hours later the size of the injected paw was again measured. Control experiments were identical except the vehicle did not contain a test compound.

Antiinflammatory activity was determined as the reduction of edema (expressed as per cent inhibition) caused by test compound with respect to a control group. The results

obtained were compared to the antiinflammatory activity exhibited by the reference drug Ibuprofen.

3.5.0.0.0.0. ULCEROGENIC LIABILITY DETERMINATION

Gastric upset and irritation are a major obstacle to patient compliance with a prescribed dosage regimen of NSAIDs. Several attempts have been made to improve gastric tolerance of NSAIDs which have met with varying degrees of success. For example, buffered, sustained-release, or enteric-coated tablets, chemical manipulation such as esterification[42] and co-administration of agents have been employed in attempts to protect the stomach.[242] Endoscopic studies, to evaluate GI injury caused by NSAIDs, have shown that 23% of patients taking NSAIDs on a regular basis, regardless of whether or not they presented GI symptoms, were found to have a significant degree of mucosal inflammation and ulceration.[159] In addition, 41% of patients with significant gastric lesions were asymptomatic.[159] NSAIDs often mask the pain associated with GI ulceration. Therefore many patients suffer dangerous complications without clinical symptoms being manifested until the problem has reached a critical stage.

It was therefore considered important to assess the ulcerogenic liability of methyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (91a), 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acid (98a), and 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (99d). The ulcerogenic liability of these compounds was determined according to a modified procedure reported by Nagai et al.[178] The results obtained for three compounds 91a, 98a, and 99d were compared to that of the reference drug Ibuprofen. The results indicate that compounds 91a, 98a, and 99d were completely devoid of any ulcerogenic effects at a dose of 1200 mg/kg po for a single oral dose 8 h after administration. A subsequent rat chronic study showed that 98a, administered at a 600 mg/kg po dose, twice a day for 6 days was also completely devoid of any gastric irritation or ulcerogenicity, whereas Ibuprofen exhibited ulcerogenicity effects

in rat (UD_{50} = 250 mg/kg po). The UD_{50} for Ibuprofen was 124.6 mg/kg po dose as reported in the literature. However a different procedure was used for the determination of UD_{50} of Ibuprofen in this study.

4.0.0.0.0.0. EXPERIMENTAL

4.1.0.0.0.0. PHYSICAL CONSTANTS AND SPECTROSCOPY

Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined for solutions in deutero-chloroform ($CDCl_3$) or dimethylsulfoxide-d_6 (DMSO-d_6), with a Bruker AM-300 spectrometer using tetramethylsilane (Me_4Si) as internal standard. High resolution mass (exact mass) spectra (HRMS) were recorded with an AEI MS-50 spectrometer and, in most cases, these exact mass determinations are used in lieu of elemental analyses. Infrared (IR) spectra were taken either neat, or as KBr pellets, on a Nicolet 5DX FT spectrophotometer. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of Alberta. pH measurements were performed using an Orion Model SA520 digital pH meter.

4.2.0.0.0.0. CHROMATOGRAPHY

Column chromatography was performed using silica gel (Merck type 7734, 100-200 mesh). Preparative thin layer chromatography (TLC) was performed with Camag Kieselgel DF-5 plates, 1.00 mm in thickness, activated at 120°C overnight prior to use. The purity of products and monitoring of reaction progress were determined using E. Merck precoated silica gel "G" microslides (250 μm in thickness). The spots were detected by shortwave ultraviolet light and/or iodine vapor visualization.

4.3.0.0.0.0. SOLVENTS AND REAGENTS

Tetrahydrofuran (THF) and diethyl ether were dried over sodium-benzophenone and distilled immediately prior to use. Benzene and acetonitrile were dried by distillation from calcium hydride. All organometallic reagents were purchased in "sure-sealed" containers from the Aldrich Chemical Company. 3-Benzoylpyridine, ethyl 3-pyridylacetate, methyl 2-

bromoacetate, methyl DL 2-bromopropionate and Evan's reagent (4S)-(-)-4-isopropyl-2-oxazolidinone were also obtained from Aldrich.

4.4.0.0.0.0. SYNTHETIC CHEMISTRY

4.4.1.0.0.0. Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]-acetates and Methyl 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates (90-93). General Procedure A

A solution of 3-benzoylpyridine (2.0 g, 10.9 mmol, 87) and either methyl bromo-acetate (2.5 g, 16.4 mmol) or methyl DL-2-bromopropionate (2.6 g, 16.4 mmol) in anhydrous acetone (20 mL) was refluxed for 8 h to afford the respective N-substituted 3-benzoylpyridinium salts (2.6 g, 71%, 88) and (2.8 g, 73%, 89). A solution of 88 (1 g, 3 mmol) or 89 (1.5 g, 4.3 mmol) in dry THF (50 mL) and cuprous iodide (0.06 g, 0.3 mmol) was stirred under a nitrogen atmosphere until the solution became homogeneous. The reaction mixture was cooled to -23°C using a dry ice-CCl_4 bath. A solution of the respective Grignard reagent (phenyl, p-chlorophenyl, benzyl, p-tolyl, cyclohexyl, n-butyl, or iso-butylmagnesium chloride or bromide (9.6 mmol) in THF (2 M) was added dropwise and the reaction mixture was maintained at -23°C for 30 min. The reaction mixture was allowed to warm to 25°C, the mixture was stirred for 1.5 h and then a saturated aqueous solution of NH_4Cl (5 mL) was added to quench the reaction. Diethyl ether (30 mL) was added, the organic phase was separated and washed successively with solutions of 30% NH_4OH; saturated aqueous NH_4Cl (3:1 v/v, 20 mL), water (2 × 10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The respective products 90-93 were purified by elution from a silica gel column using an EtOAc:hexane gradient going from 5:95 to 15:85 v/v as eluent. The IR and ^{1}H NMR spectral data for compounds 90-93 are presented in Table 2, the physical and pharmacological data are presented in Tables 3 and 4 respectively.

4.4.1.1.0.0. o-Methoxyphenyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (96)

Sodium hydride (0.024 g, 1 mmol), washed wi·h hexane to remove the mineral oil, was add·d slowly with stirring to a solution of guaiacol (0.98 g, 8 mmol) in dry THF (15 mL) at 20°C under a nitrogen atmosphere and the mixture was stirred for 45 min. To the resulting solution, a solution of 2-bromopropionyl bromide (1.7 g, 8.0 mmol) in dry THF (2 mL) was added dropwise and the reaction was allowed to proceed for 30 min prior to addition of ice water (10 mL). Diethyl ether (20 mL) was added, the organic phase separated and dried with anhydrous magnesium sulphate. Removal of the solvent in vacuo afforded the guaiacol ester 94 (1.9 g, 95%). A solution of 3-benzoylpyridine (1 g, 5.4 mmol, 87) in acetone (25 mL) and 94 (1.0 g, 3.9 mmol) was refluxed for 24 h to give the quaternary salt 95 (1.6 g, 67%). A solution of 95 (1.6 g, 3.6 mmol) in dry THF (25 mL) and cuprous iodide (0.32 g, 1.7 mmol) was stirred under a nitrogen atmosphere at 25°C for 30 min, and the reaction mixture was cooled to -23°C using a dry ice-CCl_4 bath. A solution of phenylmagnesium chloride (0.5 g, 3.7 mmol) in THF (2.2 mL of a 2 M solution) was added dropwise and the reaction mixture was maintained at -23°C for 30 min. The reaction mixture was allowed to warm to 25°C, stirred 1.5 h, after which saturated aqueous NH_4Cl (10 mL) was added to quench the reaction. Diethyl ether (20 mL) was added, the organic phase was separated, and washed successively with solutions of 30% NH_4OH:saturated aqueous NH_4Cl (3:1 v/v, 20 mL), water (2 × 20 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo to afford an oil which was purified by silica gel column chromatography using EtOAc:hexane (15:85, v/v) as eluent to afford 96 as an oil (0.48 g, 30%). The IR and ^{1}H NMR spectral data for 96 are presented in Table 2.

4.4.2.0.0.0. 2-[1-(3-Benzoyl-4-substituted-1,4-dihydropyridyl)]acetic

Acids and 2-Methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic Acids (97-98). General Procedure B

Aqueous sodium hydroxide (10 mL, 1% w/v, 0.75 mmol) was added dropwise to a solution of the respective methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)acetates (0.75 mmol) (90-91) in ethanol:water (4:1 v/v, 12.5 mL) at 25°C with stirring. The reaction was allowed to proceed with stirring until micro TLC indicated that the reaction was complete (2 h). Removal of the solvent *in vacuo*, addition of water (10 mL) to the solution and acidification with 5 N HCl afforded a yellow solid which was filtered and dried in a drying pistol to afford the acids.

These acids (97-98) were characterized as their methyl ester derivatives by addition of a solution of excess diazomethane in methanol at 25°C with stirring. The respective methyl ester products were obtained in quantitative yield. The ^{1}H NMR spectra of the esters prepared in this way were identical to the corresponding esters synthesized using General Procedure A. The IR and ^{1}H NMR spectral data for compounds 97-98 are summarized in Table 2 and the physical data are presented in Table 3.

4.4.3.0.0.0. 2-Methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)ac-etamides (99). General Procedure C

A saturated solution of ammonia in methanol (10 mL) was added to a solution of 90-91 (2.7 mmol) in methanol (20 mL), the reaction flask was sealed with a rubber septum and the reaction was allowed to proceed for 48 h at 25°C with stirring. Removal of the solvent *in vacuo* gave the respective product which was purified by preparative TLC using EtOAc:hexane (3:1 v/v) as development solvent. Extraction of the band containing the product using EtOAc and removal of the solvent *in vacuo* afforded the respective product 99a-j as solids. The spectral data are summarized in Table 2 and the physical data are presented in Table 3.

4.4.3.1.0.0. 3,5-Dibenzoylpyridine (100)

A mixture of 3,5-pyridinedicarboxylic acid (10 g, 59.9 mmol) and thionyl chloride (48.9 g, 411 mmol, 30 mL) was refluxed for 16 h. Excess thionyl chloride was removed by evaporation under reduced pressure. Dry benzene (2 × 10 mL) was added and evaporated to remove the last traces of the thionyl chloride. The residual acid chloride was dissolved in anhydrous benzene (60 mL) and to this solution, cooled to 5 to 10° (ice-NaCl bath), was added anhydrous aluminum chloride (40 g, 300 mmol) with stirring. The reaction mixture was allowed to warm to room temperature and then refluxed for 6 h. The dark brown mixture was poured cautiously onto ice and 5 N HCl (20 mL), and the solid 3,5-dibenzoylpyridine which was formed was collected by filtration (12.5 g, 73%) and dried in a drying pistol, m.p. 121.5-123.5°C (lit.[245] m.p. 123°C).

4.4.4.0.0.0. Methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]-acetate (103). General Procedure D

A solution of 3,5-dibenzoylpyridine (1 g, 3.5 mmol, 100) in anhydrous acetone (10 mL) was refluxed with methyl bromoacetate (0.80 g, 5.2 mmol) for 48 h to give the pyridinium salt (0.44 g, 29.4%, 101). A solution of 101 (0.4 g, 1.1 mmol) in dry THF (20 mL) and cuprous iodide (0.02 g, 0.10 mmol) was stirred under nitrogen until the solution became homogeneous. The reaction mixture was cooled to -23°C using a dry ice-CCl$_4$ bath. A solution of phenylmagnesium chloride (0.48 g, 3.5 mmol) in THF (2 M solution) was added dropwise and the reaction mixture was maintained at -23°C for 30 min prior to warming to 25°C. The reaction mixture was stirred for 1.5 h and then a saturated aqueous solution of NH$_4$Cl (5 mL) was added to quench the reaction. Diethyl ether (20· mL) was added, the organic phase was separated and washed successively with solutions of 30% NH$_4$OH:saturated NH$_4$Cl (3:1 v/v, 10 mL), water (2 × 10 mL) and then brine (10 mL). The organic phase was dried (MgSO$_4$) and the solvent was removed *in vacuo* to give

a brownish oil which was purified by silica gel column chromatography using ether:hexane (30:70 v/v) as eluent to afford 103 as a yellow solid after recrystallization from ether (0.320 g, 66.6%).

A similar procedure was used to prepare methyl 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (104) by Grignard reduction of the 3,5-dibenzoyl-pyridinium salt 102 (0.3 g, 0.7 mmol). Compound 104 was purified by silica gel column chromatography using ether:hexane (30:70 v/v) as eluent to afford a yellow solid (0.10 g, 31.7%) after recrystallization from ether. The IR and ^{1}H NMR spectral data are summarized in Table 4 and the physical data are presented in Table 5.

4.4.4.1.0.0. 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamides (105 and 106)

A solution of 103 (0.1 g, 0.2 mmol) in methanol (10 mL) was subjected to ammonolysis according to General Procedure C to afford a yellow oil. The oil was purified on preparative silica gel TLC using EtOAc:hexane (3:1 v/v). Extraction of the band containing the product using ethyl acetate (2 × 10 mL) and removal of the solvent *in vacuo* afforded compound 105 as a yellow solid (0.08 g, 100%).

A similar procedure was used to synthesize compound 106 which was purified on silica gel preparative TLC using EtOAc:hexane (3:1 v/v) as development solvent to give a yellow solid in 85% yield.

The IR and ^{1}H NMR spectral data for 107 and 108 are summarized in Table 4 and the physical data are presented in Table 5.

4.4.4.2.0.0. 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic Acids (107 and 108)

Compounds 107 and 108 were synthesized from 103 and 104 respectively according to General Procedure B and were obtained in 72% and 55% yields. The IR and

^{1}H NMR spectral data for **107** and **108** are summarized in Table 4 and the physical data are presented inTable 5.

4.4.4.4.3.0. Methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)-methyl]acrylate (111) and Methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (112)

A solution of 3-benzoylpyridine (1.0 g, 5.5 mmol) and methyl 2-(bromomethyl)-acrylate (1.25 g, 7 mmol) in dry acetone (20 mL) was refluxed for 24 h to give the pyridinium salt **109** which was washed with ether after evaporation of the acetone *in vacuo* (0.76 g, 49%). To a solution of **109** (0.6 g, 2.1 mmol) in dry THF (20 mL), cuprous iodide (0.03 g, 0.2 mmol) was added and the mixture was stirred under a nitrogen atmosphere for 30 min. The reaction mixture was cooled to -23°C using a dry ice-CCl$_4$ bath, a solution of phenylmagnesium chloride (5.6 mmol of a 2 M solution) in THF was added dropwise and the reaction was carried out according to General Procedure A for 1 h to afford a brownish oil. Purification of this oil by preparative TLC using EtOAc:hexane (1:3, v/v) as development solvent afforded **111** as a yellow oil (R$_f$ 0.6, 0.320 g, 42%).

Similarly, 3,5-dibenzoylpyridine (1.5 g, 5.2 mmol, **100**) was quaternized with methyl 2-(bromomethyl)acrylate (1.25 g, 7 mmol) to give the corresponding 3,5-dibenzoyl-pyridinium salt **110** which was washed with ether (20 mL) after evaporation of acetone *in vacuo* (0.9 g, 45%). To a solution of **110** (0.6 g, 1.6 mmol) in dry THF (20 mL), cuprous iodide (0.03 g, 0.2 mmol) was added and the mixture was stirred for 30 min. The reaction mixture was cooled to -23°C, a solution of phenylmagnesium chloride (5.6 mmol of a 2 M solution) in THF was added dropwise and the reaction was continued according to General Procedure A for 1 h to give a brownish oil. This oil was purified by preparative TLC using EtOAc:hexane (1:3, v/v) as the development solvent to afford **112** as a yellow oil (R$_f$ 0.4, 0.28 g, 39%). The spectral data for **113** are presented in Table 7 and the physical data are presented in Table 8.

4.4.4.4.0.0. Methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahy-dropyridyl)acetate (113)

To a solution of 91b (0.5 g, 1.4 mmol) in ethyl acetate (10 mL) in a pressure bottle, 20 mg of % Pd/C was cautiously added and the reaction was allowed to proceed in the presence of hydrogen gas at a pressure of 30 psi with shaking, for 24 h at 25°C until hydrogen uptake ceased. Filtration and then removal of the solvent *in vacuo* afforded a yellow oil which was purified by preparative silica gel TLC using EtOAc:hexane (1:1, v/v) as development solvent to afford 113 as an oil ($R_f = 0.65$, 200 mg, 47%). The spectral data for 113 are presented in Table 7 and the physical data are presented in Table 8.

4.4.4.5.0.0. Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicyclo[4.1.0]hept-3-ene]acetate (125) and Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dichloro-2-azabicy-clo[4.1.0]hept-3-ene]acetate (126)

Phenyl(tribromomethyl)mercury (1.3 g, 2.6 mmol) was added to a stirred solution of 91b (0.9 g, 2.6 mmol) in dry benzene (20 mL) under a nitrogen atmosphere, and the mixture was refluxed for 8 h. Additional aliquots of PhHgCCBr₃ (1.3 g, 2.6 mmol) were added to the reaction mixture at 2, 4, and 6 h. The reaction mixture was then cooled to 25°C and the PhHgBr which precipitated during the reaction was removed by filtration. Evaporation of the solvent *in vacuo* gave a brownish oil which was purified by preparative TLC on silica gel plates using EtOAc:hexane (1:3, v/v) as development solvent to give 125 as an oil ($R_f = 0.5$, 0.46 g, 50%). The oil was crystallized from hexane:ether (4:1, v/v).

Compound 126 was synthesized employing the same procedure using phenyl(bromo-dichloromethyl)mercury (PhHgCBrCl₂) and 91a. The product obtained was purified by preparative TLC using EtOAc:hexane (1:3, v/v) as development solvent to afford an oil which was crystallized from hexane:ether (3:1, v/v) to give 126 as a solid ($R_f = 0.3$, 0.15

g, 33%). The spectral data for **125** and **126** are presented in Table 9 and the physical data is summarized in Table 10.

4.4.4.6.0.0. Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-difluoro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (127) and Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-chloro-7-fluoro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (128)

Phenyl(trifluoromethyl)mercury (1.0 g, 1.1 mmol) was added to a mixture of **91a** and **91b** (0.5 g, 1.1 mmol) and dry NaI (0.65 g, 4.3 mmol) in dry dimethoxyethane (20 mL) under a nitrogen atmosphere with stirring, and the mixture was heated at 85-90°C for 2 h. Additional aliquots of $PhHgCCF_3$ (1.0 g, 1.1 mmol) were added to the reaction mixture at 2 and 4 h after initiation of the reaction which was allowed to proceed for 6 h in total reaction time. The reaction mixture was then cooled to 25°C, and the solids (PhHgI, NaF and unreacted NaI) were removed by filtration. Removal of the solvent *in vacuo* and separation of the mixture by preparative silica gel TLC using EtOAc:hexane (1:3, v/v) as developing solvent afforded **127** as a brown oil (R_f = 0.35, 0.230 g, 53%).

Similarly, compound **128** was synthesized by refluxing $PhHgCCl_2F$ (1.0 g, 2.6 mmol) with **91b** (0.5 g, 1.1 mmol) in dimethoxyethane (20 mL). The product was isolated by preparative TLC using EtOAc:hexane (1:3, v/v) as development solvent to afford **128** as an oil (Rf = 0.55, 0.260 g, 64%). The spectral data for **127** and **128** are presented in Table 9 and the physical data is summarized in Table 10.

4.4.4.7.0.0. Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (129, 7-Br; 130, 7-Cl; 131, 7-F)

To a stirred solution of **125** (0.2 g, 0.4 mmol) and a catalytic amount of azobisisobutyronitrile (AIBN), tri-*n*-butyltin hydride (0.12 g, 0.44 mmol) in benzene (20 mL) was

added in aliquots over 8 h and the reaction mixture was refluxed at 90°C overnight to afford

an oil after removal of solvent *in vacuo*. The residue obtained was washed with pentane (5

× 20 mL) to remove any remaining *n*-Bu₃SnH. The product was purified by silica gel

column chromatography using hexane:ether (70:30, v/v) as eluent to afford **129** in 35%

yield as an oil ($R_f = 0.55$)

Similar reactions employing **126** and **128** afforded **130** ($R_f = 0.62$, 31%) and **131**

($R_f = 0.7$, 45%) respectively as oils. The spectral data for **129-131** are presented in Table

9 and the physical data is presented in Table 10.

4.4.4.8.0.0. 2-Methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicy-clo[4.1.0]hept-3-ene)]acetamide (132)

To a solution of **125** (0.3 g, 0.6 mmol) in methanol (10 mL), a saturated solution of

ammonia in methanol (5 mL) was added and the reaction carried out according to General

Procedure C. A brownish oil was obtained which was purified by preparative silica gel

TLC using EtOAc:hexane (3:1, v/v) as development solvent. The band having $R_f = 0.3$

was extracted with ethyl acetate (20 mL) to give a yellow oil which crystallized from

hexane:ether to give **132** as a solid (0.15 g, 50%). The spectral data for compound **132** is

presented in Table 9 and the physical data is presented in Table 10.

4.4.4.9.0.0. 3-Benzoyl-4-phenyl-1-{1-methyl-2-oxo-2-[(4S)-4-iso-propyl-2-oxazolidinonyl]ethyl}-1,4-dihydropyridine (135)

To a solution of (4S)-(-)-4-isopropyl-2-oxazolidinone (2.71 g, 21 mmol) in dry THF

(30 mL), stirred at -78°C under a nitrogen atmosphere, was added a solution of *n*-butyl-

lithium (1.34 g, 21 mmol). The reaction mixture was stirred for 30 min at -78°C prior to

the addition of **133** which was prepared from **98a** (0.5 g, 1.5 mmol) and BTBO,

according to the procedure reported by Takeda *et al.*[221] Suspended BTBO (460 mg, 1

mmol) in acetonitrile (10 mL) was added to a solution of **98a** (0.5 g, 1.5 mmol) and the

reaction mixture was stirred for 1 h at room temperature, after which it was added dropwise to 134 and the resulting mixture stirred for 4 h. After evaporation of the solvent under reduced pressure, the residue was extracted with ethyl acetate. The organic layer was successively washed with 4% aqueous $NaHCO_3$, HCl, water, and brine, and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residual brownish oil was purified by silica gel preparative TLC using EtOAc:hexane (1:1, v/v). The band having $R_f = 0.6$ was isolated by extraction with ethyl acetate (30 mL) and removal of the solvent *in vacuo* afforded **135** as an oil (0.2 g, 33%). ^1H NMR (CDCl$_3$) δ: 7.2-7.6 (m, 10H, phenyl hydrogens), 7.08 [7.06] (d, $J_{2,6} = 1.5$ Hz, 1H, H-2), 6.04 (d, $J_{2,6} = 1.5$ Hz of d, $J_{5,6} = 7.7$ Hz, 1H, H-6), 5.28 (two overlapping q, $J_{CH,CH_3} = 7.1$ Hz, 1H, CH$_3$C$\underline{H}$), 5.1 (two d, $J_{5,6} = 7.7$ Hz of d, $J_{4,5} = 4.9$ Hz, 1H total, H-5), 4.88 (d, $J_{4,5} = 4.9$ Hz, 1H, H-4), 4.2-4.5 (m, 3H, oxazolidinone, -C$\underline{H}$H, -CH$\underline{H}$, -NC$\underline{H}$), 2.28-2.44 (m, 1H, (CH$_3$)$_2$C$\underline{H}$), 1.54 [1.56] (d, $J_{CH_3CH} = 7.1$ Hz, 3H, CH$_3$CH), 0.8-1.0 (m, 6H, (CH$_3$)$_2$CH). Absorptions of the minor diastereomers are indicated in brackets.

4.4.4.10.0.0. N-[(1S)-1-phenethyl]-2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide Diastereomers (137a and 137b)

A suspension of BTBO (0.46 g, 1 mmol) in acetonitrile (10 mL) was added to a solution of **108** (0.43 g, 1 mmol) and pyridine (0.079 g, 1 mmol) in acetonitrile (20 mL) and the resulting solution was stirred at 25°C for 1 h. A solution of (S)-(-)-α-methyl-benzylamine (0.138 g, 1 mmol) and triethylamine (0.15 g, 1 mmol) in acetonitrile (10 mL) was added. The reaction mixture was stirred for 4 h, the solvent removed *in vacuo* and the residue was extracted with ethyl acetate (15 mL). The organic layer was succesively washed with 4% aqueous $NaHCO_3$ (10 mL), 1 N HCl (10 mL), water (10 mL), and brine (10 mL) prior to drying with Na_2SO_4. The solvent was removed *in vacuo* and the residue obtained was purified by preparative silica gel TLC using hexane:EtOAc (1:1, v/v) as

development solvent. Extraction of the two bands having R_f 0.65 and 0.5 afforded **137a** and **137b** respectively as gummy solids. ^{1}H NMR data for **137a** and **137b** are presented in Table 11.

4.4.4.11.0.0. (S)-Methoxycarbonyl-α-methyl methyl 2-{1-[3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl]}acetate (138)

A suspension of BTBO (0.46 g, 1 mmol) in acetonitrile (10 mL) was added to a solution of **101** (0.436 g, 1 mmol) and pyridine (0.079 g, 1 mmol) in acetonitrile (10 mL) and the reaction mixture was stirred for 1 h at 25°C. A solution of (S)-(-)-methyl lactate (0.104 g, 1 mmol) and DMAP (0.134 g, 1 mmol) in acetonitrile (10 mL) was added. The reaction mixture was allowed to proceed for 8 h at 25°C prior to addition of water (10 mL). Extraction with ethyl acetate (3 × 20 mL) and isolation of the product, as described for compound **137**, gave a residue which was purified by preparative silica gel TLC using EtOAc:hexane (1:1, v/v) as development solvent. Isolation of the band having $R_f = 0.63$, extraction with ethyl acetate (20 mL) and evaporation of the solvent afforded **138** (0.08 g, 12%) as an oil. ^{1}H NMR (CDCl$_3$) δ: 7.1-7.6 (m, 15H, phenyl hydrogens), 6.94 and 6.98 (two d, $J_{2,6}$ = 1.5 Hz, 1H each, H-2, H-6), 5.69 (s, 1H, H-4), 5.24 (q, $J_{CH_3,C4}$ = 7.2 Hz, 1H, -OC$\underline{H}$(CH$_3$)CO$_2$CH$_3$), 4.2 (q, J_{CH,CH_3} = 7.2 Hz, 1H, NC$\underline{H}$CH$_3$), 3.76 and 3.74 (two s, 3H total, OCH$_3$), 1.55-1.65 (m, 6H, NCHC$\underline{H}_3$ and -OCHC$\underline{H}_3$).

4.4.4.12.0.0. 3-Benzoyl-4-phenylpyridine (140)

A solution of 3-benzoylpyridine (2 g, 10.9 mmol, **87**) and cuprous iodide (0.3 g, 1.6 mmol) in dry THF (60 mL) was cooled to -78°C (dry ice/acetone). Methyl chloroformate (1.02 g, 10.9 mmol) was added dropwise to the vigorously stirred solution under nitrogen. After 30 min a solution of phenylmagnesium chloride (8 mmol) in dry THF (10 mL) was added dropwise and the mixture was stirred for 30 min at -78°C, allowed to come to room temperature, and quenched with aqueous NH$_4$Cl solution (10 mL). Diethylether (20 mL)

was added and the organic layer was washed with 10 mL portions of 20% NH_4Cl/NH_4OH (50:50, v/v), water and brine. After drying with anhydrous magnesium sulphate, the solution was concentrated to give the crude dihydropyridine (**139**) as a viscous oil, R_f = 0.45 (1.3 g, 38.9%).

The crude dihydropyridine **139** (1.3 g, 4.1 mmol) was refluxed in toluene (50 mL) with o-chloranil (1.02 g, 4.2 mmol) for 5 h, the solvent was evaporated and the brownish oil obtained was chromatographed on a silica gel column using EtOAc:hexane (15:85, v/v) as eluant to afford **140** as a yellow oil (0.9 g, 83%).

^{1}H NMR (CDCl$_3$) δ 8.76 (d, $J_{5,6}$ = 5 Hz, 1H, H-6), 8.7 (s, 1H, H-2), 7.64 (d, $J_{5,6}$ = 5 Hz, 1H, H-5), 7.2-7.46 (m, 10H, phenyl hydrogens).

4.4.4.13.0.0. Attempted Synthesis of (4S)- or (4R)-Methyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (143)

To a solution of diisopinocampheylchloroborane (**142**) (0.45 g, 1.4 mmol) prepared according to the reported procedure,[209] in dry THF (10 mL) was added **141** (0.55 g, 1.3 mmol) under a nitrogen atmosphere. The reaction, which was monitored by TLC, was finished in 18 h. The solvent was removed *in vacuo* and the residue obtained was chromatographed using a silica gel column using EtOAc:hexane (30:70, v/v) as eluent to afford a gummy oil (0.2 g, 35%). The ^{1}H NMR spectrum of the isolated product indicated that it was not the desired compound **143**.

4.4.4.14.0.0. Methyl 2-methyl-2-[1-(3-phenoxy-4-phenyl-1,4-dihydropyridyl)acetate (146)

A solution of 3-phenoxypyridine (1 g, 5.8 mmol; **144**) and methyl DL-2-bromopropionate (1.2 g, 7.6 mmol) in anhydrous acetone (20 mL) was refluxed for 24 h to give a brown solid which was washed with ether (3 × 20 mL) to afford the 3-phenoxypyridinium salt **145** (1.1 g, 80%). A solution of **145** (1.0 g, 4.2 mmol) in dry THF (20 mL) and

cuprous iodide (0.05 g, 0.3 mmol) was stirred under a nitrogen atmosphere until the solution became homogeneous. The reaction mixture was cooled to -23°C using a dry ice-CCl4 bath. Phenylmagnesium chloride (7.6 mmol) in THF (5 mL) was added dropwise and the reaction mixture was maintained at -23°C for 30 min. The reaction mixture was allowed to warm to 25°C, the mixture was stirred for 1.5 h and then a saturated aqueous solution of NH4Cl (5 mL) was added to quench the reaction. Diethyl ether (20 mL) was added, the organic phase was separated and washed successively with a solution of 30% NH4OH:saturated aqueous NH4Cl (3:1, v/v) (10 mL). The organic phase was dried (MgSO4) and the solvent was removed *in vacuo*. Purification of the brownish oil obtained was carried out using both silica gel and neutral alumina column chromatography during which the compound underwent extensive decomposition. The ^{1}H NMR spectrum of the impure product obtained exhibited the following spectrum: ^{1}H NMR (CDCl3) δ 6.8-7.3 (m, 11H, phenyl hydrogens, H-6), 6.02 (s, 1H, H-2), 4.65-4.72 (m, 1H, H-5), 4.46 (d, $J_{4,5}$ = 4.8 Hz, 1H, H-4), 3.82-4.02 (m, 1H, C$\underline{H}$-Me), 3.78 (s, 3H, OMe), 1.44 and 1.46 (two d, J_{CH,CH_3} = 7.2 Hz, 3H, CH$\underline{Me}$).

4.4.5.0.0.0. Ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydro-pyridyl)]acetates (149-152), Ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (146) and Ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (147). General Procedure D

Ethyl 3-pyridylacetate (0.55 g, 3.15 mmol, R^1 = H, 147) in dry THF (30 mL) was stirred at 25°C under a nitrogen atmosphere, CuI (0.028 g, 0.2 mmol) was added, followed by the addition of phenyl chloroformate (0.57 g, 3.7 mmol). The reaction mixture was cooled to -23°C using a dry ice-CCl4 bath and phenylmagnesium chloride (0.47 g, 3.46 mmol) in THF (0.65 mL) was added dropwise with stirring over a period of 10 min. The reaction mixture was stirred for 15 minutes more at the same temperature and

the reaction mixture was allowed to warm to 25°C with continued stirring for 1 h. A saturated solution of NH₄Cl (5 mL) was added to quench the reaction, followed by addition of ether (30 mL). This mixture was washed with 20% NH₄Cl-NH₄OH (50:50, v/v, 2 × 20 mL), water (2 × 10 mL) and then brine (10 mL). The organic fraction was dried (MgSO₄), filtered and the solvent was removed *in vacuo* to give a crude oily product which was purified by silica gel column chromatography using EtOAc:hexane (15:85, v/v) as eluent to afford **149** (1.1 g, 96%) as an oil. The spectral data are presented in Table 12 and the physical data are presented in Table 13.

Similarly, compounds **150**, **151**, and **152** were synthesized in yields of 75%, 82%, and 64%, respectively as oils after purification by silica gel column chromatography using EtOAc:hexane (15:85, v/v) as eluent.

Ethyl 2-methyl-3-pyridylacetate (0.55 g, 3.7 mmol, R^1 = Me, **148**) was quaternized with phenyl chloroformate (0.57 g, 3.7 mmol) and reduced with phenylmagnesium chloride (3.46 mmol) to give a brownish oil after work-up (General Procedure D). The oil was purified by silica gel column chromatography using EtOAc:hexane (15:85, v/v) as eluent to afford **153**, R_f = 0.45 (0.9 g, 64%) as an oil.

Compound **154** was synthesized from ethyl 3-pyridylacetate (0.55 g, 3.15 mmol), methyl chloroformate (0.3 g, 3.15 mmol) and phenylmagnesium chloride (3.46 mmol) according to General Procedure D. The product was purified by silica gel column chromatography using EtOAc:hexane (15:85, v/v) as eluent to afford **154** as an oil, R_f = 0.48 (0.85 g, 87%).

4.5.0.0.0.0. DETERMINATION OF THE pKₐ VALUE FOR 2-METHYL-2-[1-(3-BENZOYL-4-PHENYL-1,4-DIHYDROPYRIDYL)]-ACETIC ACID (98a)

Compound **98a** (0.33 g, 1 mmol) was dissolved in methanol (40 mL) and the volume was adjusted to 100 mL with doubly distilled water to give a 0.01 M solution. A 50 mL

aliquot of this solution was placed in a 100 mL beaker, which in turn was placed in a constant temperature circulating water bath at $25.0 \pm 0.5°C$. The beaker was then covered with a rubber cork fitted with a thermometer, pH microelectrode, burette, and nitrogen inlet and outlet tubes.

Purified nitrogen (freed from oxygen and carbon dioxide by passage through an alkaline solution of pyrogallol) was continuously passed through the solution to be titrated to maintain an inert atmosphere. To this solution was added carbonate-free 0.10 M methanolic potassium hydroxide (as the titrant, obtained from Anderson Laboratories, Inc., USA) in ten equal portions, each a tenth of an equivalent and the pH was recorded as soon as equilibrium was reached after each addition. The pH meter was equipped with a combined microelectrode which was calibrated before use each time, with two buffer solutions of pH 4.00 and 10.00 ± 0.01 (from BHD Chemicals). The pK_a was calculated using the Henderson-Hasselbach equation and the results are presented in Table 8.

4.6.0.0.0.0. ANALGESIC ACTIVITY ASSAY

Analgesic activity was determined using the method described by Fukawa et al.[239] Five male Sprague-Dawley rats, weighing between 120-150 g, were used for each test dose. The number of writhing responses induced in each rat after injection of a 4% w/v sodium chloride solution at a dose of 1 mL/kg ip were recorded two hours prior to administration of the test compound. The test compound was administered as a solution in physiological saline solution (0.9%, w/v aqueous NaCl) solubilized with 10% v/v Tween 80.

After administration of the test dose, each rat was again injected with 4% sodium chloride (1 mL/kg ip) at intervals of 30 and 60 minutes from the time the test compound was administered. The number of writhing responses elicited at each time was recorded. The lower of the two responses at the 30 or 60 minute interval was subtracted from the initial number of control writhing responses and the percentage inhibition, which is a

measure of analgesic activity, was calculated using the formula shown below. Single dose test results are reported as the mean % inhibition ± standard error of the mean (SEM) for five animals.

$$\% \text{ Inhibition } = \frac{W_1 - W_2}{W_1} \times 100$$

Where W_1 is the number of initial (control) writhing responses and W_2 is the lower of the numbers of writhing responses at either 30 or 60 minutes.

4.7.0.0.0.0. ANTIINFLAMMATORY ACTIVITY ASSAY

Antiinflammatory activity was measured using the carrageenan-induced rat paw edema assay described by Winter et al.[241] Four male Sprague-Dawley rats weighing 100-120 g were used in each group. Test compounds were administered as suspensions in water, using gum accaia as the suspending agent. The test compound was administered orally at a dose of 100 mg/kg one hour prior to subcutaneous injection of carrageenanan (0.1 mL, 1%) in physiological saline under the plantar skin of the right-hand paw. Control experiments were identical except the vehicle did not contain a test compound. The volume of the injected paw was measured immediately (V^1) and at 3 h and 5 h (V^2) and the % inhibition of inflammation, which is a measure of antiinflammatory activity, was calculated using the formula shown below.

$$\% \text{ Inhibition } = \frac{V^2 - V^1}{V^1} \times 100$$

4.8.0.0.0.0. ULCEROGENIC LIABILITY ASSAY

Six male Sprague-Dawley rats weighing 100-120 g, fasted for 24 h, were sacrificed 8 h after oral administration of the selected test compounds 91a, 98a or 99d at doses of 300 mg/kg, 600 mg/kg and 1200 mg/kg. The stomach, sternum and duodenum were removed and macroscopically and microscopically assessed for the presence or absence of lesions which were used to calculate the UD_{50} (the dose of compound causing lesions in 50% of

the animals). A chronic ulcerogenesis assay was also performed on compound **98a** by

administration of 600 mg/kg po twice daily for six days. The ulcerogenic liability assay

was also used to determine the UD_{50} for the reference drug Ibuprofen.

5.0.0.0.0.0. REFERENCES

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3.1.4.0.0.0. Ionization Constant Determination

NSAIDs should ideally be weak acids that undergo complete absorption, possess a moderate lipophilicity so a high uptake in inflammed tissue occurs and be devoid of GIT irritation or ulcerogenicity. The pK_a of a compound is defined as the negative logarithm of its dissociation constant K_a, and it is a convenient numerical method to compare the relative acidity or basicity of ionizing compounds in aqueous or miscible solvent-aqueous solutions. The higher the pK_a of a compound, the less acidic it is. Since the acidity of NSAIDs is one of the factors implicated in gastric ulcerogenicity, it was of interest to determine the pK_a of one compound from the 3-benzoyl-4-substituted 1,4-dihydropyridyl acetic acid class of compounds (97-98).

The pK_a of 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acid (98a) was determined using a potentiometric titration method described by Albert and Serjeant.[177] The measurements were carried out in aqueous methanol (H_2O:MeOH = 60:40, v/v) as solvent since compound 98a was insoluble in water. Newton *et al.*[184] have reported that there was no substantial difference in the precision of pwK_a extrapolated from linear regression plots of psK_a (where pwK_a is the pK_a determined in aqueous medium and psK_a is the pK_a determined in aqueous methanol solutions). All solvents and solutions were properly stored in well-stoppered containers fitted with a Soda-Lime guard tube to exclude carbon dioxide. The pK_a of Ibuprofen was first determined by this procedure to ascertain the precision of the method. Ibuprofen exhibited a pK_a of 5.2 which is the same as the value reported by Davis.[185] From the pH readings and the logarithm of the ratio of the concentrations of acid substrate [HA] and the anion [A⁻] during the titration, the pK_a values were calculated according to the Henderson-Hasselbach equation as follows:

$$pK_a = pH + \log[HA] - \log[A^-]$$

Some typical titration data are presented in Table 6. The pK_a values shown in Table 6 are the average of the four values obtained for compound 98a.

3.1.5.0.0.0. Synthesis of Methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydro-pyridyl)methyl]acrylate (111) and Methyl 2-[1-(3,5-diben-zoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (112)

Noyori et al.[141c] have reported that ruthenium(II) complexes possessing the 2,2'-bis-(diarylphosphino)-1,1-binaphthyl (BINAP) ligand serve as catalysts for the highly stereo-selective hydrogenation of a range of substituted acrylic acids. For instance, the useful antiinflammatory agent (S)-(+)-Naproxen (8) was readily synthesized by the asymmetric hydrogenation of 4-(6-methoxy-2-naphthyl)-2-butenoic acid (78) as described in Section 1.1.1.9.3.0.

These reports prompted us to synthesize 111 and 112 which could be subjected to stereoselective hydrogenation to prepare two diastereomers which could be separated (from 111) or a single enantiomer (from 112) for evaluation as antiinflammatory agents.

Thus, 3-benzoyylpyridine (87, R = H) and 3,5-dibenzoylpyridine (100, R = PhCO), were quaternized using methyl 2-(bromomethyl)acrylate by refluxing in acetone for 24 h to yield the respective pyridinium salts (109, R = H and 110, R-PhCO). The subsequent reaction of these pyridinium salts with phenylmagnesium chloride in the presence of 5% CuI, according to the General Procedure A, afforded 111 and 112 in 35% and 21% yield respectively.

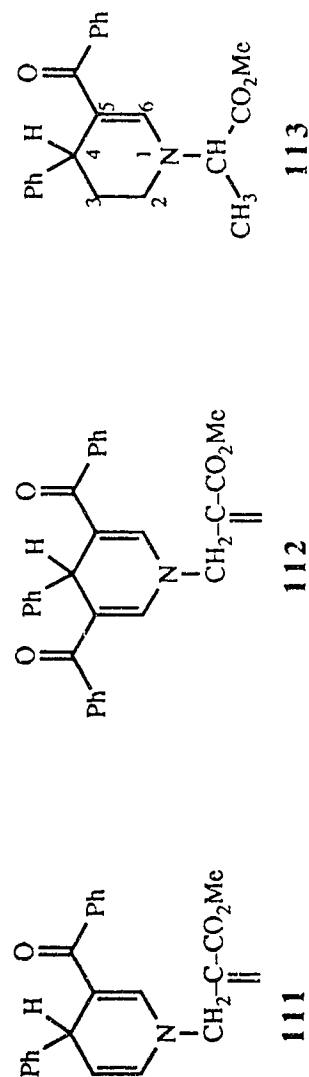The ^1H NMR and IR spectral data for compounds 111 and 112, which are consistent with their assigned structures, are presented in Table 7 and the physical data in Table 8. The synthetic route used to prepare 111 and 112 is outlined in Scheme 4.

Table 6. Data for the potentiometric titration of a 0.01 M methanolic solution of 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydro-pyridyl)]acetic acid (98a) with a 0.10 M potassium hydroxide solution in water:methanol (60:40, v/v).

Titrant 0.1 M KOH (mL)	pH	[HA] diminished by tenths	[HA] minus Column 3 = [A⁻]	$\frac{[HA]}{[A^-]}$	$\log\frac{[HA]}{[A^-]}$	$pK_a{}^* = pH + \log\frac{[HA]}{[A^-]}$
0	5.92	0.010	0.			
0.5	8.45	0.009	0.001	9/1	0.95	9.40
1.0	8.58	0.008	0.002	8/2	0.60	9.18
1.5	8.79	0.007	0.003	7/3	0.37	9.16
2.0	8.96	0.006	0.004	6/4	0.18	9.14
2.5	9.17	0.005	0.005	5/5	0	9.17
3.0	9.35	0.004	0.006	4/6	-0.18	9.17
3.5	9.56	0.003	0.007	3/7	-0.37	9.19
4.0	9.74	0.002	0.008	2/8	-0.60	9.14
4.5	9.95	0.001	0.009	1/9	-0.95	9.00
5.0	10.3	0	0.010			

*Result: $pK_a = 9.17 \pm 0.01$.

Table 7. IR and ^{1}H NMR data for methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**111**), methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**112**), and methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetra-hydropyridyl)]acetate (**113**).
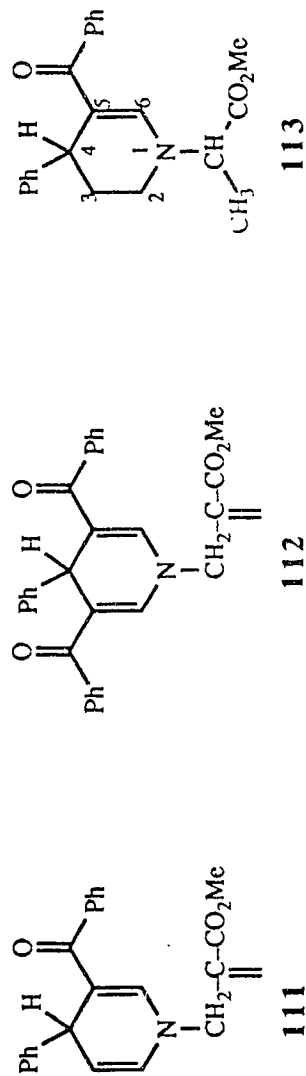

111

112

113

Entry	IR (neat) cm^{-1}	^{1}H NMR (CDCl$_3$) δ
111	1745 (COO); 1679 (CO)	7.1–7.5 (m, 10H, phenyl hydrogens), 6.96 (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.38 (s, 1H, =C$\underline{H}$H'), 5.94 (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.5 Hz, 1H, H-6), 5.78 (s, 1H, =CH$\underline{H}$'), 5.12 (d, $J_{5,6}$ = 7.5 Hz of d, $J_{4,5}$ = 4.6 Hz, 1H, H-5), 4.9 (d, $J_{4,5}$ = 4.6 Hz, 1H, H-4), 4.08 (s, 2H, NCH$_2$), 3.8 (s, 3H, OCH$_3$)
112	1745 (COO); 1679 (CO)	7.1–7.7 (m, 15H, phenyl hydrogens), 6.88 (s, 2H, H-2, H-6), 6.38 (s, 1H, =C$\underline{H}$H'), 5.74 (s, 1H, =CH$\underline{H}$'), 5.62 (s, 1H, H-4), 4.12 (s, 2H, NCH$_2$), 3.8 (s, 3H, OCH$_3$)

(Continued)

Entry	IR (neat) cm⁻¹	¹H NMR (CDCl₃) δ
113	1745 (COO); 1679 (CO)	7.24-7.65 (m, 11H, 9 phenyl hydrogens, H-2, H-6), 7.18 (m, 1H, p-phenyl H), 4.38 (dd, J3,4 = 5.0 Hz, 1H, H-4), 3.88-4.02 (overlapping quartets, J_{CH,CH_3} = 7.2 Hz, 1H, C$\underline{H}$CH₃), 3.74 [3.76] (s, 3H total, OCH3), 2.9-3.18 (m, 2H, H-2), 1.9-2.15 (m, 2H, H-3), 1.44 [1.42] (two d, J_{CH_3CH} = 7.2 Hz, 3H total, C$\underline{H}$₃CH)
		Diastereomeric ratio 1:1

Table 8. Physical data for methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (111), methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (112), and methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydro-pyridyl)]acetate (113).
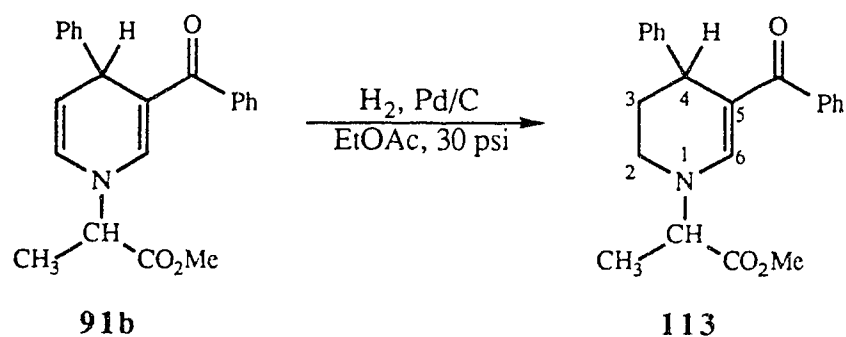

Entry	Yield, %	m.p., °C	Formula	Microanalysis: Calcd. (Found)		
				C	H	N
111	35	oil	$C_{23}H_{21}NO_3 \cdot 3/4 H_2O$	74.01 (73.87)	5.61 (5.58)	3.76 (3.92)
112	21	oil	$C_{30}H_{25}NO_4 \cdot H_2O$	74.84 (75.18)	5.20 (5.15)	2.91 (3.01)
113	47	oil	$C_{23}H_{23}NO_3 \cdot 1/2 H_2O$	73.65 (73.30)	6.42 (6.36)	3.91 (3.94)

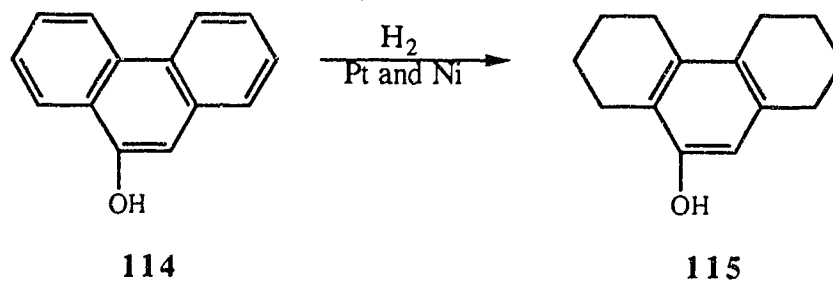Scheme 4. Synthetic route for the preparation of 111 and 112.

3.1.6.0.0.0. Synthesis of Methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (113)

Compound 113 was synthesized in order to investigate the effect of the C5-C6 double bond present in 91 on antiinflammatory and analgesic activity. Thus, compound 91b was subjected to hydrogenation with hydrogen gas at 30 psi in the presence of 10% palladium-on-charcoal in ethyl acetate at 25°C to afford the corresponding tetrahydropyridine 113 as

Scheme 5. Synthesis of methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (113).

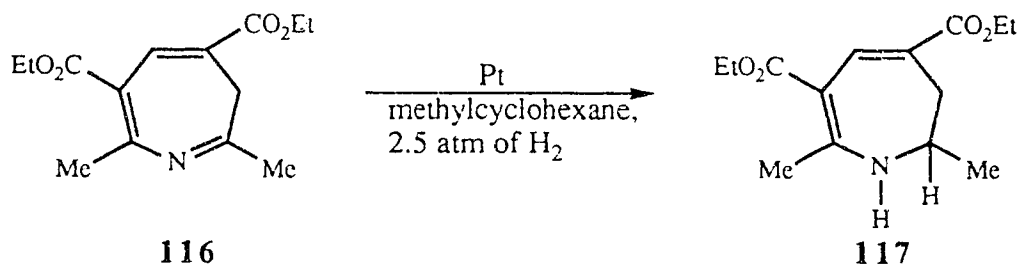outlined in Scheme 5. The C2-C3 double bond of 91 was not reduced, presumably due to steric factors. As mentioned earlier, compound 91 exists in a flat boat conformation with a C-4 axial phenyl group. Therefore, hydrogen addition occurs preferentially at the less-hindered C5-C6 double bond of 91b. The effect of steric factors on hydrogenation of C-C double bonds has been studied.[186] Linstead and co-workers,[186] based on studies involving the hydrogenation of phenanthrene and diphenic acid derivatives, concluded that the less-hindered side of an unsaturated molecule is adsorbed on the catalyst surface and this has led to the generalization that catalytic hydrogenation of a multiple bond results in cis addition of two hydrogen atoms from the less-hindered site. For example, when 9-phenanthrol 114 was hydrogenated over platinum in acetic acid, the octahydro-9-phenanthrol 115, was obtained indicating reduction of the non-hindered double bonds (Scheme 6).[186]
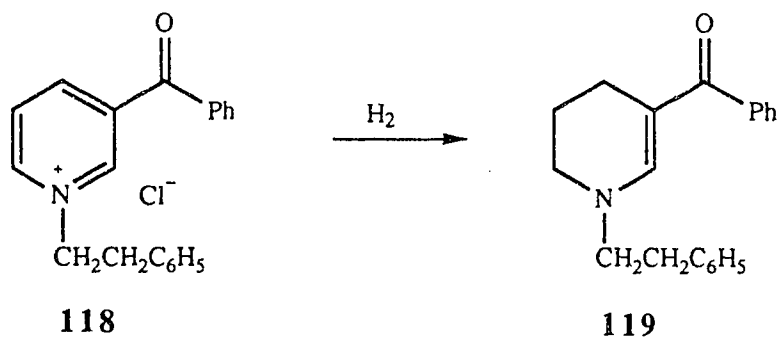

Scheme 6. Catalytic hydrogenation of 9-phenanthrol (114)

The IR and ^{1}H NMR spectral data, which are consistent with the structure for compound 113, are presented in Table 7 and the physical data in Table 8. The ^{1}H NMR spectrum does not display resonances in the δ 5-6 region indicating the absence of the C5-C6 olefinic bond of 91b. Also, the IR spectrum shows the absence of an isolated olefinic bond in the 1650 cm^{-1} region.

The failure of the N–C=C–C=O moiety to undergo hydrogenation is further illustrated by partial hydrogenation of the azepine (116) to the dihydro derivative (117)[187] as shown in Scheme 7.

Scheme 7. Partial catalytic hydrogenation of the azepine (116).

Furthermore, partial hydrogenation of pyridine rings containing 3-acyl, formyl, keto, cyano, and other functions have been reported.[188,189,190] For example, Lyle and Mallet[188] have described the partial hydrogenation of the 1-alkyl-3-benzoylpyridinium salt 118 to give the corresponding tetrahydropyridine 119 in which the C5-C6 double bond was preferentially reduced (Scheme 8).

Scheme 8. Partial hydrogenation of the 1-alkyl-3-benzoylpyridinium salt (118) to give the tetrahydropyridine (119).

Freidfelder[189] has reported the partial hydrogenation of 3-acetylpyridine (120) to the corresponding tetrahydropyridine (122). It was proposed that the formation of 122 probably takes place by 1,4-addition, giving the intermediate 121. Freidfelder observed that the isolated C5-C6 double bond was reduced preferentially relative to the 2,3-conjugated bond to yield 122 (Scheme 9).

120   **121**   **122**

Scheme 9. Preferential hydrogenation of the isolated C5-C6 double bond of
(120) relative to the C2-C3 configurated double bond.

Electronic effects could also be responsible for the reluctance of the C2-C3 olefinic moiety of 91b to undergo hydrogenation. The C2-C3 double bond is conjugated with the carbonyl of the 3-benzoyl group and so resonance can occur, thereby deactivating the C2-C3 double bond. In fact, the C3-CO$_2$Me bond of the calcium channel antagonist 2,6-dimethyl-3,$\stackrel{\text{\tiny 5}}{\text{-}}$-dicarbomethoxy-4-phenyl-1,4-dihydropyridine (123) has been found through X-ray crystallographic studies[191] to be shorter than the C2-C3 bond, suggesting double bond character for the C3-CO$_2$Me bond (Figure 9).
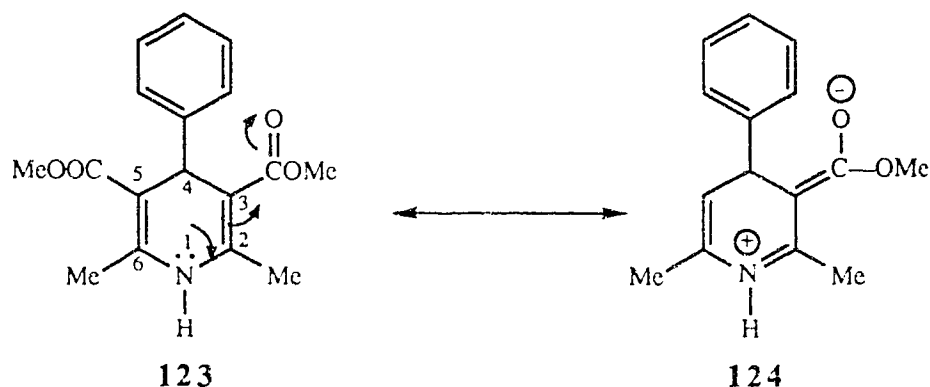
Figure 9. Deactivation of C2-C3 conjugated double bond by resonance.

3.1.7.0.0. Synthesis of Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (125-128), Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (129-131), and 2-Methyl-2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicyclo-[4.1.0]hept-3-ene)]acetamide (132)

It has been reported that the C-C bonds in cyclopropane rings resemble olefinic double bonds.[192] The hybridization of cyclopropyl bonds is intermediate in character between sigma (σ) and pi (π) bonds. The C-C bonds in cyclopropane mimic a C=C bond in their ability to conjugate with an adjacent olefinic bond,[193] but unlike a C=C bond, it does not transmit electronic effects.[194] Also, the hybridization of the cyclopropane bonds are considered to result in a higher electron density for the C-C bonds. Furthermore, the cyclopropyl moiety interacts with neighbouring π-electron systems and p-electron centers similar to a vinyl group.[195,196] It was therefore anticipated that a cyclopropyl substituent could act as a biological isostere of the C5-C6 double bond present in compound 91b. In addition, the hydrophobic halogen substituents F, Cl, and Br are expected to increase the lipophilicity of these compounds. In fact, some halocyclopropyl analogs of 2'-deoxyuridine have been reported to exhibit antiviral and cytotoxic activity.[197,198]

Thus, dihalocarbene :CX$_2$, generated *in situ* from the Seyferth reagents[199] PhHgCX$_3$ (X = F, Cl, Br) in refluxing benzene, reacted with **91b** to afford compounds **125-128**.
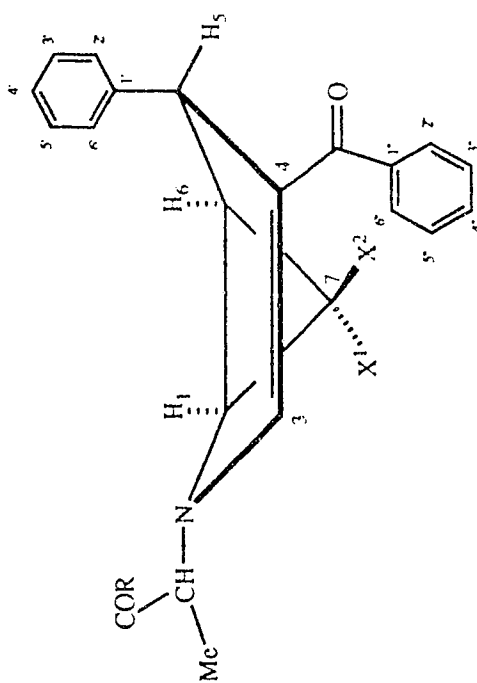
Reactions of **91b** (solid) with phenyl(tribromomethyl)mercury (PhHgCBr$_3$) in dry benzene at 80°C yielded **125**, whereas compound **126** was synthesized from reaction of **91b** with the Seyferth reagent phenyl(bromodichloromethyl)mercury (PhHgCBrCl$_2$). A similar reaction of **91b** with phenyl(trifluoromethyl)mercury[200] (PhHgCCF$_3$) in dry di-methoxyethane in the presence of sodium iodide at 90°C afforded **127** whereas reaction of phenyl(dichlorofluoromethyl)mercury (PhHgCCl$_2$F) with **91b** in refluxing dimethoxy-ethane yielded **128**.

Monodehalogenation of **125**, **126**, and **128** with tributyltin hydride in the presence of azobisisobutyronitrile (AIBN) as the initiator of the free radical reaction in refluxing benzene afforded compounds **129**, **130**, and **131**, respectively. Ammonolysis of **125**, according to General Procedure C, afforded the corresponding acetamide **132**. These reactions are schematically outlined in Scheme 10. Spectral data for **125-128**, **129-131** and **132** are presented in Table 9 and the physical data is summarized in Table 10.

The ^{1}H NMR spectra of compounds **125-127** indicate that there is no coupling between H-5 and H-6 which suggests that the dihedral angle between H-5 and H-6 is about 85° based on the Karplus curve.[201]

Carbenes are extremely reactive and give many side reactions, especially insertion reactions which readily reduce yields.[202] Dihalocarbenes however are less reactive than carbenes and so there are no insertion reaction products.[203-205] Most carbenes are electro-philic so electron-withdrawing groups decrease the rate of the reaction,[206,207] as exemplified by the inertness of the C-2–C-3 double bond of **91** to cyclopropanation. Carbenes in the singlet state (which is the most common state) react stereospecifically and syn[208,209] probably by a one-step mechanism.[210] Therefore substituents on the olefin

Table 9. IR and ^{1}H NMR spectral data for methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]-hept-3-ene)]-acetates (**125-128**), methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]-hept-3-ene)]acetates (**129-131**) and acetamide (**132**).

Entry	X^1	X^2	R	IR cm^{-1}	^{1}H NMR, CDCl$_3$ (δ)^a
125	Br	Br	OMe	(KBr): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	7.2-7.5 (m, 10H, phenyl hydrogens), 7.02 (s, 1H, H-3), 4.26 (s, 1H, H-5), 4.14 (q, J_{CH,CH_3} = 7.2 Hz, 1H, Cl$\underline{C}$H$_3$), 3.9 (s, 3H, OMe), 3.4 (d, $J_{1,6}$ = 10.9 Hz, 1H, H-1), 2.46 (d, $J_{1,6}$ = 10.9 Hz, 1H, H-6). ^{13}C NMR (CDCl$_3$) δ: 192.45 (benzoyl carbonyl), 171.61 [170.81] (C─ ─), 146.44 [144.42] (C-3), 144.69 (phenyl

(Continued)

Entry	X^1	X^2	R	IR cm^{-1}	^{1}H NMR, CDCl$_3$ (δ)^a
125 (Cont'd)	Br	Br	OMe	(KBr): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	C-1'), 139.96 (benzoyl C-1"), 130.05 [130.19] (benzoyl C-4"), 128.58-126.46 (other phenyl C-5), 112.89 [113.21] (C-4), 62.37 [61.69] (NC$\underline{H}$CH$_3$), 52.78 (COOC$\underline{H}_3$), 41.83 [43.52] (C-1), 37.76 [38.24] (C-5), 36.14 (C-6), 32.43 [31.80] (C-7), 16.52 [16.44] (C$\underline{H}_3$CH). Diastereomeric ratio is $\cong$ 2:1
126	Cl	Cl	OMe	(neat): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	7.0-7.42 (m, 10H, phenyl hydrogens), 6.9 (s, 1H, H-3), 4.22 (s, 1H, H-5), 4.02 (q, J$_{CH,CH_3}$ = 7.2 Hz, 1H, C$\underline{H}$CH$_3$), 3.76 (s, 3H, OMe), 3.26 (d, J$_{1,6}$ = 10.7 Hz, 1H, H-7), 2.24 (d, J$_{1,6}$ = 10.7 Hz, 1H, H-6), 1.56 (d, J$_{CH,CH_3}$ = 7.2 Hz, 3H, C$\underline{H}_3$CH). ^{13}C NMR (CDCl$_3$ δ: 171.56 ($\underline{C}$OOMe), 146.35 (C-3), 144.63 (phenyl C-1'), 139.97 (benzoyl C-1"), 130.04 [130.17] (benzoyl C-4"), 126.31-129.03 (other phenyl C"), 112.70 (C-4), 62.35 [62.17] (NC$\underline{H}$CH$_3$), 52.7 (COOC$\underline{H}_3$), 36.85 [37.87] (C-1), 34.14 [35.13] (C-5), 32.56 [32.43] (C-6), 29.66 (C-7), 16.29 [16.64] (C$\underline{H}_3$CH)

(Continued)

Entry	X¹	X²	R	IR cm⁻¹	1H NMR, CDCl₃ (δ)ᵃ
127	F	F	OMe	(neat): 1745 (COO); 1679 (COO); 3105, 3025 (cyclo-propyl)	7.20-7.50 (m, 10H, phenyl hydrogens), 7.16 [7.04] (s, 1H, H-3), 4.44 (s, 1H, H-5), 4.06 [4.04] (two q, $J_{CH_2CH_3}$ = 7.2 Hz, 1H total, $CHCH_3$), 3.80 [3.84] (s, 3H, OCH_3), 3.26 [3.38] (d, $J_{1,6}$ = 11.4 Hz, of d $J_{H1,F}$ = 5.1 Hz, 1H, H-1), 2.20-2.36 (m, 1H, H-6), 1.56 (d, $J_{CH_3,CH}$ = 7.2 Hz, 3H, CH_3CH). ¹³C NMR (CDCl₃) δ: 192.85 [192.71] (benzoyl CO), 170.33 [171.15] ($\underline{C}$OOMe), 146.45 [146.20] (C-3), 144.91 [144.81] (phenyl C-1'), 139.92 [139.84] (benzoyl C-1''), 130.04 [129.92] (benzoyl C-4''), 126.39-127.20 (other phenyl C), 112.49 [112.15] (C-4), 109.73 [109.83] (t, $J_{F,C}$ = 296 Hz, C-7), 62.47 [61.94] ($N\underline{C}HCH_3$), 52.47 (COO$\underline{C}H_3$), 35.18-34.88 [34.73-34.43] (C-1), 31.06 (C-5), 29.94 [29.79] (C-6), 15.90 [15.38] (CH$\underline{C}H_3$) ¹⁹F NMR (C_6F_6) δ: 37.2 (d, J_{F1F2} = 160.7 Hz of d, $J_{H,F}$ (*cis*) = 15.4 Hz, 1F, F-2); [35.8 (d, $J_{F1,F2}$ = 160.7 Hz of d, $J_{H,F}$ (*cis*) = 14.5 Hz, 1F, F-2], 12.88 (d, $J_{F1,F2}$ = 160.7 Hz, 1F, F-1), [13.07 (d, $J_{F1,F2}$ = 160.7 Hz, 1F, F-1)]. Diastereomeric ratio of 5:4.

(Continued)

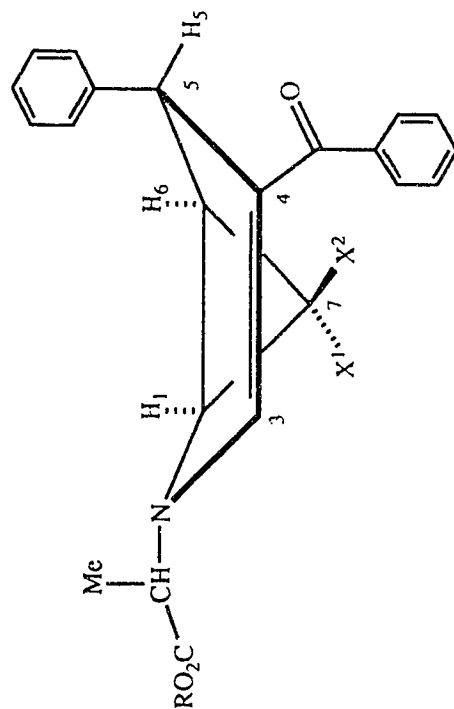| Entry	X¹	X²	R	IR cm⁻¹	¹H NMR, CDCl₃ (δ)ᵃ
128	Cl	F	OMe	(neat): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	7.2-7.5 (m, 10H, phenyl hydrogens), 7.0 [7.06] (s, 1H, H-3), 4.48 [4.30] (s, 1H, H-5), 4.08 (q, J_{CH,CH_3} = 7.2 Hz, 1H, CHCH₃), 3.90 [3.88] (s, 3H, OCH₃), 3.44 (d, $J_{1,6}$ = 12.6 Hz, of d, $J_{F,1}$ = 7.2 Hz, 1H, H-1), [3.20 (d, $J_{1,6}$ = 12.6 Hz, 1H, H-1)], 2.38 (d, $J_{f,6}$ = 20.4 of d, $J_{6,F}$ = 7.2 Hz, 1H, H-6), 1.62 [1.56] (d, $J_{CHe,CH}$ = 7.2 Hz, 3H, CH₃CH). Diastereomeric ratio is 5:4.
129	H	Br	OMe	(neat): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	7.2-7.5 (m, 10H, phenyl hydrogens), 7.0 [6.9] (s, 1H, H-3), 4.46 (s, 1H, H-5), 4.02 (q, J_{CH,CH_3} = 7.0 Hz, 1H, CHCH₃), 3.78 [3.80] (s, 3H, OCH₃), 2.68-2.80 (m, 1H, H-7), 1.45-1.7 (m, 5H, CHCH₃, H-1, H-6). ¹³C NMR (CDCl₃) δ: 193.37 (benzoyl CO), 171.23 (COOCH₃), 147.15 (C-3), 140.58 (benzoyl C-1"), 129.68 (benzoyl C-4"), 125.91-128.48 (other phenyl C's), 113.0 (C-4), 62.35 [62.08] (NCHCH₃), 52.35 (COOMe), 36.17 (C-1), 30.12 (C-5), 21.71 (C-6), 16.52 (CHBr), 15.35 (CHCH₃). Diastereomeric ratio is 4:1.

Entry	X^1	X^2	R	IR cm^{-1}	1H NMR, CDCl$_3$ (δ)^a
130	H	Cl	OMe	(CHCl$_3$): 1745 (COO); 1679 (CO); 3105, 3025 (cyclopropyl)	7.1-7.5 (m, 10H, phenyl hydrogens), 7.02 (s, 1H, H-3), 4.13 (s, 1H, H-5), 4.08 (q, J_{CH,CH_3} = 7.0 Hz, 1H, C$\underline{H}$CH$_3$), 3.78 [3.74] (s, 3H, OCH$_3$), 3.24 (d, $J_{6,7}$ = 8.5 Hz of d, $J_{1,7}$ = 5.5 Hz, 1H, H-7), 2.92 [2.88] (d, $J_{1,6}$ = 9.9 Hz of d, $J_{1,7}$ = 5.5 Hz, 1H, H-1), 1.8 (d, $J_{1,6}$ = 9.9 Hz of d, $J_{6,7}$ = 8.5 Hz, 1H, H-6), 1.56 [1.48] (d, J_{CH_3CH} = 7.2 Hz, 3H, C$\underline{H_3}$CH). ^{13}C NMR (CDCl$_3$) δ: 193.0 (benzoyl CO), 171.77 ($\underline{C}$OOMe), 148.18 [146.36] (C-3), 146.08 (phenyl C-1'), 140.60 (benzoyl C-1''), 129.83 [129.69] (benzoyl C-4), 128.61-126.04 (other phenyl C's), 113.24 (C-4), 62.65 [61.45] (N$\underline{C}$HCH$_3$), 52.58 (CO$_2$Me), 38.84 [38.66] (C-1), 33.42 (C-7), 31.65 (C-5), 24.94 [24.61] (C-6), 16.14 [15.82] ($\underline{C}$HCH$_3$). Diastereomeric ratio is 6:1.
131	H	F	OMe	(neat): 1745 (COO); 1679 (CO); 3016, 3025 (cyclopropyl)	7.18-7.60 (m, 10H, phenyl hydrogens), 7.14 (s, 1H, H-3), 4.64 (d, $J_{F,H7}$ = 6.6 Hz of d, $J_{6,7}$ = 9.2 Hz of d, $J_{1,7}$ = 3.8 Hz, 1H, H-7), 4.38 [4.36] (s, 1H, H-5), 4.1 [4.08] (q, J_{CH,CH_3} = 7.2 Hz,

(Continued)

Entry	X^1	X^2	R	IR cm^{-1}	1H NMR, CDCl$_3$ (δ)[a]
131 (Cont'd.)	H	F	OMe	(neat): 1745 (COO); 1679 (CO); 3016, 3025 (cyclopropyl)	1H, CHCH$_3$), 3.84 [3.80] (s, 3H, OCH$_3$), 2.82 [2.76] (d, $J_{1,6}$ = 12.7 Hz of d, $J_{1,7}$ = 3.8 Hz of d, $J_{1,F}$ = 3.8 Hz, 1H, H-1), 1.5-1.7 (m, $J_{CH_3,CH}$ = 7.2 Hz, 4H, C$\underline{H}_3$CH, H-6). Minor diastereomer is listed in brackets. Diastereomeric ratio is 3:1.
132	Br	Br	NH$_2$	(KBr): 1693 (CONH); 1679 (CO); 3322, 3180 (NH$_2$); 3105, 3025 (cyclopropyl)	7.1-7.4 (m, 10H, phenyl), 7.08 [7.10] (s, 1H, H-3), 6.82 [7.52] (s, 2H, NH$_2$), 4.10 [4.20] (q, J_{CH,CH_3} = 7.2 Hz, 1H, C$\underline{H}$CH$_3$), 4.06 (s, 1H, H-5), 3.7 [3.44] (d, $J_{1,6}$ = 10.6 Hz, 1H, H-1), 2.28 [2.26] (d, $J_{1,6}$ = 10.6 Hz, 1H, H-6), 1.56 [1.4] (d, $J_{CH_3,CH}$ = 7.2 Hz, 3H, CH$_3$CH). Diastereomeric ratio is 3:1.

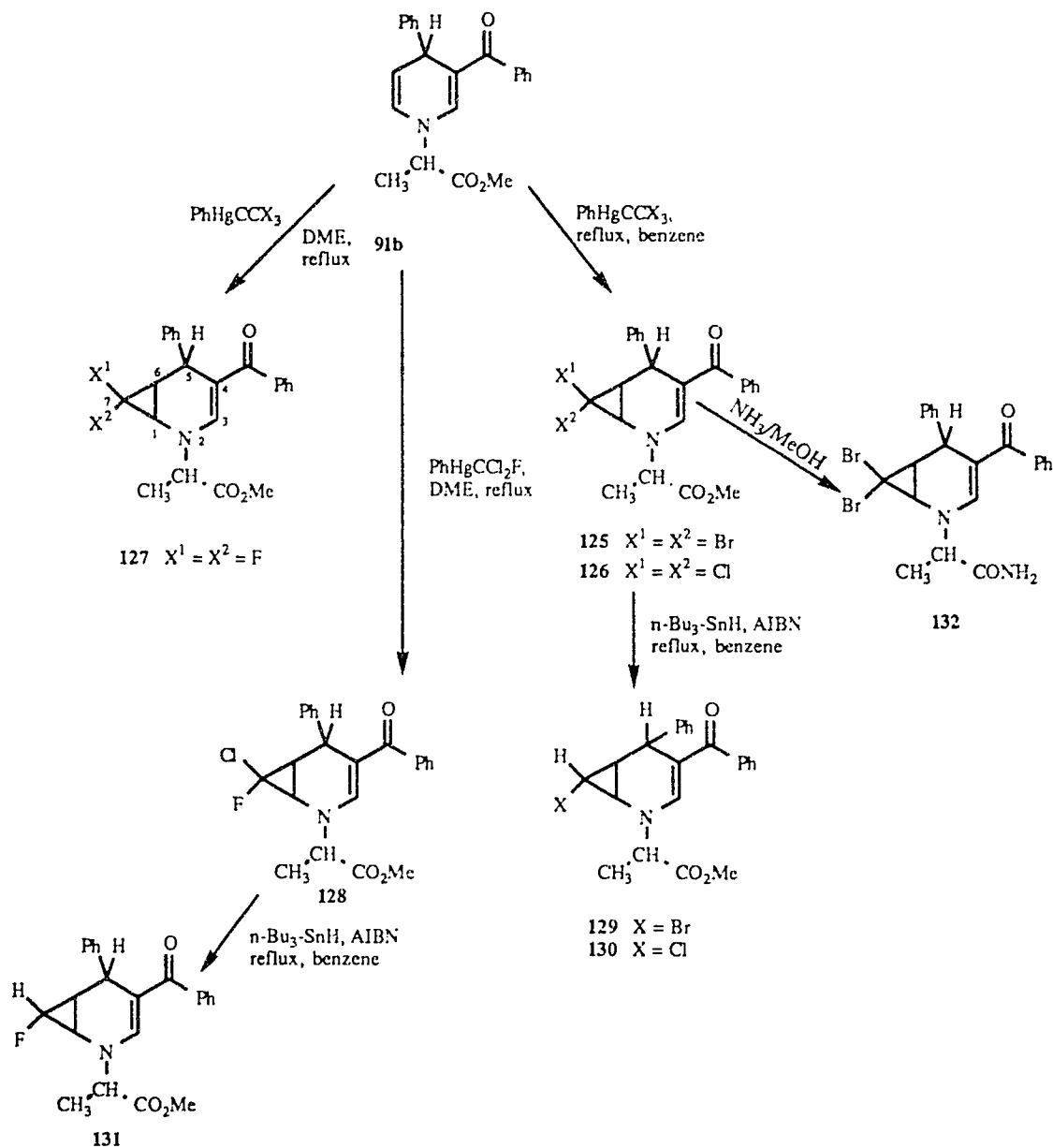[a]Minor diastereomers shown in brackets.

Table 10. Physical data for methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (**125-128**), methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]-hept-3-ene)]acetates (**129-131**) and acetamide (**132**).

Entry	X^1	X^2	R	Yield, %	m.p., °C	Formula	Microanalysis: Calcd. (Found)		
							C	H	N
125	Br	Br	OMe	50	148-150	$C_{23}H_{21}Br_2NO_3$	53.20 (53.49)	4.08 (3.96)	2.70 (2.71)
126	Cl	Cl	OMe	33	142-145	$C_{23}H_{21}Cl_2NO_3 \cdot 1/2H_2O$	63.47 (63.64)	4.92 (4.90)	3.25 (3.27)
128	Cl	F	OMe	64	oil	$C_{23}H_{21}ClFNO_3 \cdot 3/2H_2O$	62.73 (62.80)	4.77 (5.02)	3.18 (3.16)
130	H	Cl	OMe	31	oil	$C_{23}H_{22}ClNO_3 \cdot 2H_2O$	64.04 (63.92)	5.10 (5.37)	3.25 (3.29)
132	Br	Br	NH_2	50	132-135	$C_{22}H_{19}Br_2N_2O_2$	52.41 (52.67)	4.00 (4.01)	5.56 (5.54)

(Continued)

| Entry | X^1 | X^2 | R | Yield, % | m.p., °C | Formula | Exact Mass | |
							Calcd	Found
127	F	F	OMe	53	oil	C$_{23}$H$_{21}$F$_2$NO$_3$	397.1489	397.1484
129	H	Br	OMe	36	oil	C$_{23}$H$_{22}$BrNO$_3$	439.0783	439.0889
131	H	F	OMe	45	oil	C$_{23}$H$_{22}$FNO$_3$	379.1584	379.1581

Scheme 10. Synthesis of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-di-
halo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (125-128),
methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo-
[4.1.0]hept-3-ene)]acetates (129-131), and 2-methyl 2-methyl-
2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicyclo[4.1.0]hept-
3-ene)]acetamide (132).

should retain their configuration. Dihalocarbenes and carbenoids, which add readily to C=C double bonds, do not generally add to the C=O bond of ordinary aldehydes and lactones.[211] As already discussed in Section 3.1.0.0.0.0, compound **91** exists in a boat shape with the C-4 phenyl axial to the 1,4-dihydropyridyl ring. If addition of the carbenes :CX_2 is concerted, then the configuration of the phenyl substituent should not change. When the cyclopropyl is above the plane of the DHP ring there is a strong steric interaction with the axial phenyl substituent (Figure 10).

Attack at the C=C double bond should therefore occur from the lower face of the boat DHP ring if the phenyl substituent is axial since there is much less steric hindrance (Figure 11). Compound **125** synthesized in this way from pure **91b** gave single resonances in both the ^1H NMR and ^{13}C NMR spectra. This further supports the theory that :CX_2 addition is stereospecific.

The observation that compound **125** does not exhibit a $J_{5,6}$ coupling ($J_{5,6}$ = 0 Hz) suggests the H5-H6 dihedral angle is about 85°. When $\phi_{5,6} \cong 85°$, the 1,4-DHP ring exists as a flat boat. H-1 and H-6 must be cis to each other since $J_{1,6}$ = 10.3 Hz and the cyclopropane is a fused ring system. For the difluorocyclopropyl compound (**127**), the ^{19}F NMR spectrum indicated that F_1 is shielded, relative to F_2, by the DHP 3,4-double bond and possibly by the benzoyl group (Figure 12). F_1 must be *trans* to both H-1 and H-6 since $J_{F_{1,1}}$ and $J_{F_{1,6}}$ are both zero hertz.

F_2 is at a lower field since it is not shielded by the DHP C-3–C-4 double bond or the benzoyl group. Compound **127** existed as a mixture of two diastereomers in a ratio of 5:4. The ^{19}F NMR spectrum for **127** exhibited two doublets of doublets for F_2 [J_{F_1,F_2} = 160 Hz; J_{H,F_1} = 15.4 Hz (major diastereomer) and J_{H,F_2} = 14.5 Hz (minor diastereomer)] at 37.2 and 35.8 δ, respectively. In contrast, F_1 appeared as two doublets (J_{F_1,F_2} = 160 Hz) at δ 12.8 (major) and 13.07 (minor), respectively. The J_{F_2,H_6} coupling is much larger than the J_{F_2,H_1} coupling constant.
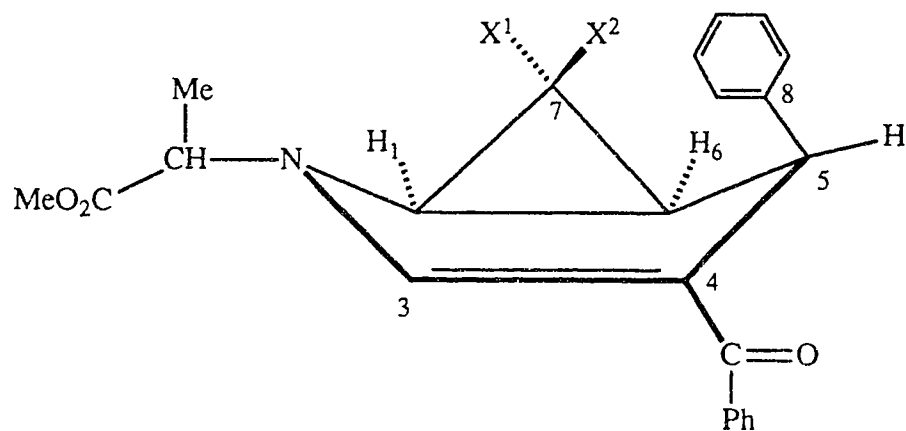
Figure 10. Possible conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (125-128).
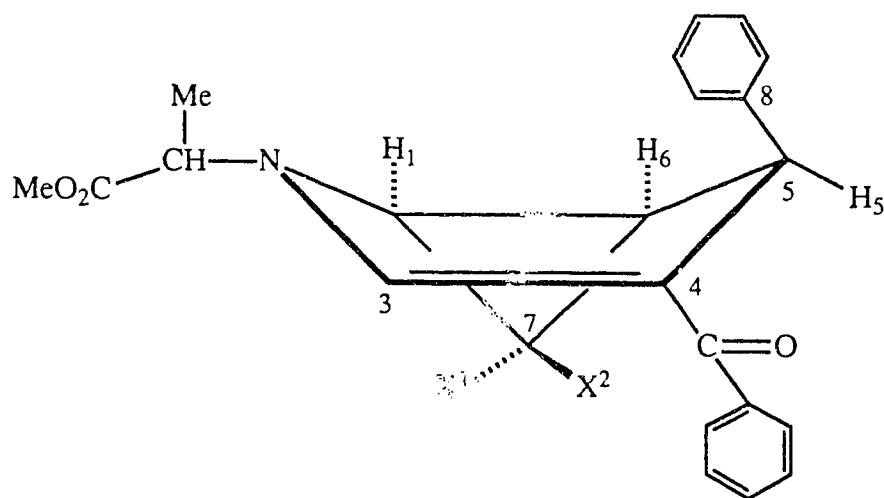

Figure 11. Most stable conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (125-128).
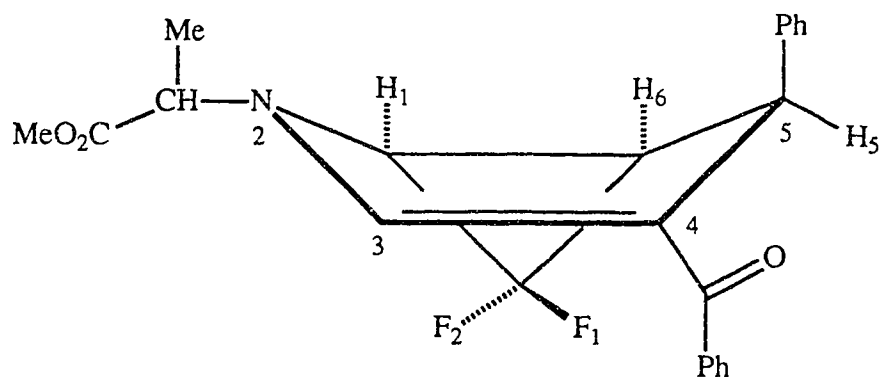
Figure 12. Most probable conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-difluoro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (**127**).

$J_{H_1F} = 0$, $J_{H_6,F} = 7.2$ Hz

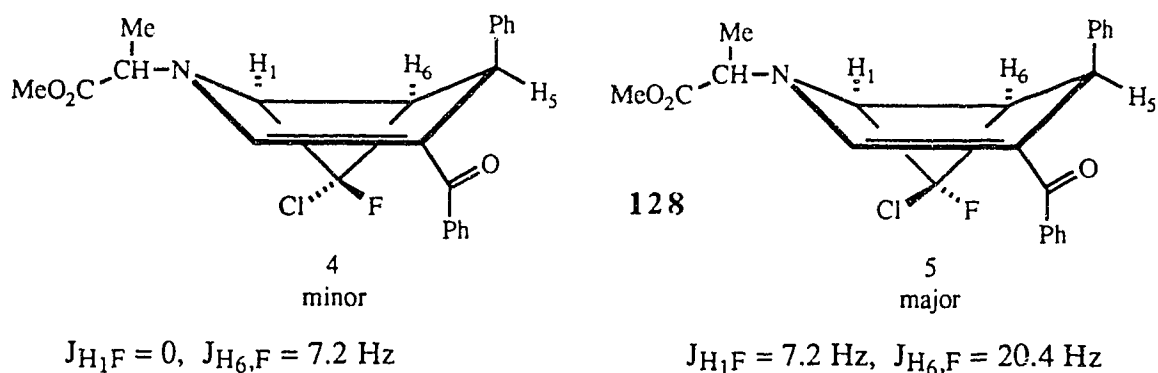$J_{H_1F} = 7.2$ Hz, $J_{H_6,F} = 20.4$ Hz

Figure 13. Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-fluoro-7-chloro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (**128**) diastereomer.

Compound **128**, which contains an additional chiral center at C-7, exhibited dual resonances for H-1, H-3, H-5, H-6, OMe, and MeCH- protons in a diastereomeric ratio of 5:4. The ^{1}H NMR spectrum for compound **128** indicated that $J_{H1,F} = 0$ Hz and $J_{H_6,F} = 7.2$ Hz in the minor diastereomer suggesting F is *trans* to H-1 and H-6. In the major diastereomer, F must be *cis* to both H1 and H6 as indicated by the coupling constants $J_{H_1,F} = 7.2$ Hz and $J_{H_6,F} = 20.4$ Hz (Figure 13).

The stereoselectivity observed in the monodehalogenation reactions of **125**, **126**, and **128** is consistent with a reaction mechanism involving preferential attack by the bulky tri-n-butyltin radical at the less hindered C-X bond which is *cis* with respect to the cyclopropyl H-1 and H-6 hydrogens, followed by attack by n-Bu3SnH on the resulting radical[212a] from the less hindered site[212b] (Figure 14).
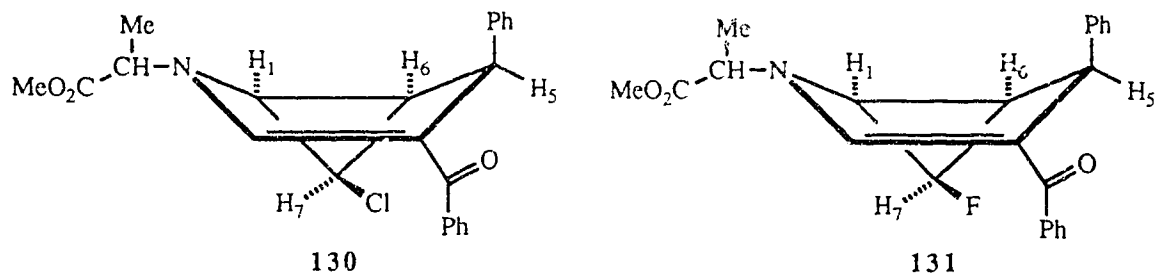

Figure 14. Conformation of methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-chloro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (**130**) and methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-fluoro-2-azabicyclo[4.1.0]-hept-3-ene)]acetate (**131**).

H-1 and H-6 must be *cis* to the new H-7 generated for compound **130** due to the magnitude of the coupling constants observed. In compound **131**, the coupling constants were $J_{1,7} = 5.5$ (*cis*), $J_{6,7} = 8.5$ (*cis*) and $J_{1,6} = 9.9$ Hz with respect to the new generated H-7. The magnitude of the coupling constants observed were $J_{F,H7} = 66$ Hz, $J_{6,7} = 9.2$ Hz (*cis*) and $J_{1,7} = 3.8$ Hz (*cis*).

A large number of spectra of substituted cyclopropane derivatives have been reported. The magnitude of the vicinal coupling constant for J_{cis} is always larger than J_{trans} for any given pair of cyclopropyl stereoisomers[213,214] and this was used to assign the orientation, in some cases, of the halogen on the cyclopropane ring. The δ values with respect to each halogen were found to be F > Cl > Br which is consistent with the electronegativity order for F, Cl and Br.

3.1.8.0.0.0. Attempted Synthesis of Chiral N-Substituted 1,4-Dihydro-pyridine Analogs

When a drug exists as a racemate, or a mixture of diastereomers, higher biological activity is often exhibited by one enantiomer or one diastereomer. Therefore, synthetic methodologies[20] that provide the physiologically more active compounds in optically pure form or as a single diastereomer, are advantageous. Several strategies for the synthesis of chiral arylacetic acids in optically pure form have been reported.[215-219] Attempts were made in this investigation to synthesize pure diastereomers, or enantiomers, in anticipation that a single diastereomer, or enantiomer, might exhibit superior antiinflammatory activity. This rationale is based on the well documented SARs for NSAIDs that generally the active (+)-enantiomer has the (S)-configuration.

3.1.9.0.0.0. Synthesis of 3-Benzoyl-4-phenyl-1-{1-methyl-2-oxo-2-[(4S)-4-isopropyl-2-oxazolidinonyl]ethyl}-1,4-dihydro-pyridine (135)

The use of Evans's reagent (4S)-4-isopropyl-2-oxazolidinone as a chiral auxiliary for the synthesis of optically active (S)-Ketoprofen, (S)-Ibuprofen and (S)-Naproxen has been reported.[220] Thus, reaction of (4S)-(-)-4-isopropyl-2-oxazolidinone with n-butyllithium will give the lithio enolate species 133 which should react readily with the activated ester 134. The activated ester 134 was prepared from the acid 98a and the coupling reagent 1,1'-bis[6-trifluoromethyl)benzotriazolyl]oxalate (BTBO) according to the procedure reported by Takeda et al.[221] The lithium enolate 133 was then treated with 134 to afford 135 in 33% yield. The reaction pathway and mechanism is outlined in Scheme 11. The diastereomers could not be separated.

Scheme 11. Synthesis of 3-benzoyl-4-phenyl-1-{1-methyl-2-oxo-2-[(4S)-
            4-isopropyl-2-oxazolidinonyl]ethyl}-1,4-dihydropyridine
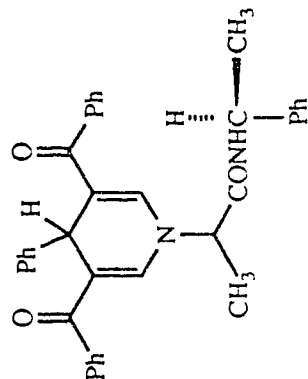   (135).

3.1.10.0.0.0. Synthesis of N-[(1S)-1-phenethyl]-2-methyl-2-[1-(3,5-di-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide Diastereomers (137a and 137b)

The use of (S)-(-)-α-methylbenzylamine as a chiral derivatization agent in the separation of diastereomers of arylpropionic acids has been investigated.[222] Thus, compound **136** was synthesized according to the procedure reported by Takeda *et al*.[221] with the hope that two diastereomers (SS and SR) could be separated and the amide group hydrolyzed to give the respective enantiomers. Reaction of 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acid (**108**) with BTBO in acetonitrile yielded the activated ester **136**, which on reaction with (S)-(-)-α-methylbenzylamine afforded the diastereomers **137a** and **137b** in 38% total yield. The two diastereomers **137a** and **137b** were separated by preparative silica gel TLC. However, attempts to regenerate the free acids by hydrolysis of the amide moiety in either diastereomer was unsuccessful. The hydrolysis reaction was attempted using triethylamine and trichlorosilane which has been reported by Buckle *et al*.[223] to be an efficient method for the hydrolysis. The ^{1}H NMR spectrum of the hydrolysis reaction product indicated disappearance of starting DHP material. It is plausible that HSiCl$_3$, which is a strong Lewis acid, protonates the N-1 position of the DHP with subsequent ring cleavage. The reaction is outlined in Scheme 12. The spectral data for **137a** and **137b** are shown in Table 11.

3.1.11.0.0.0. Synthesis of (S)-Methoxycarbonyl-α-methyl methyl-2-methyl-2-{1-[3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl]-acetate (138)
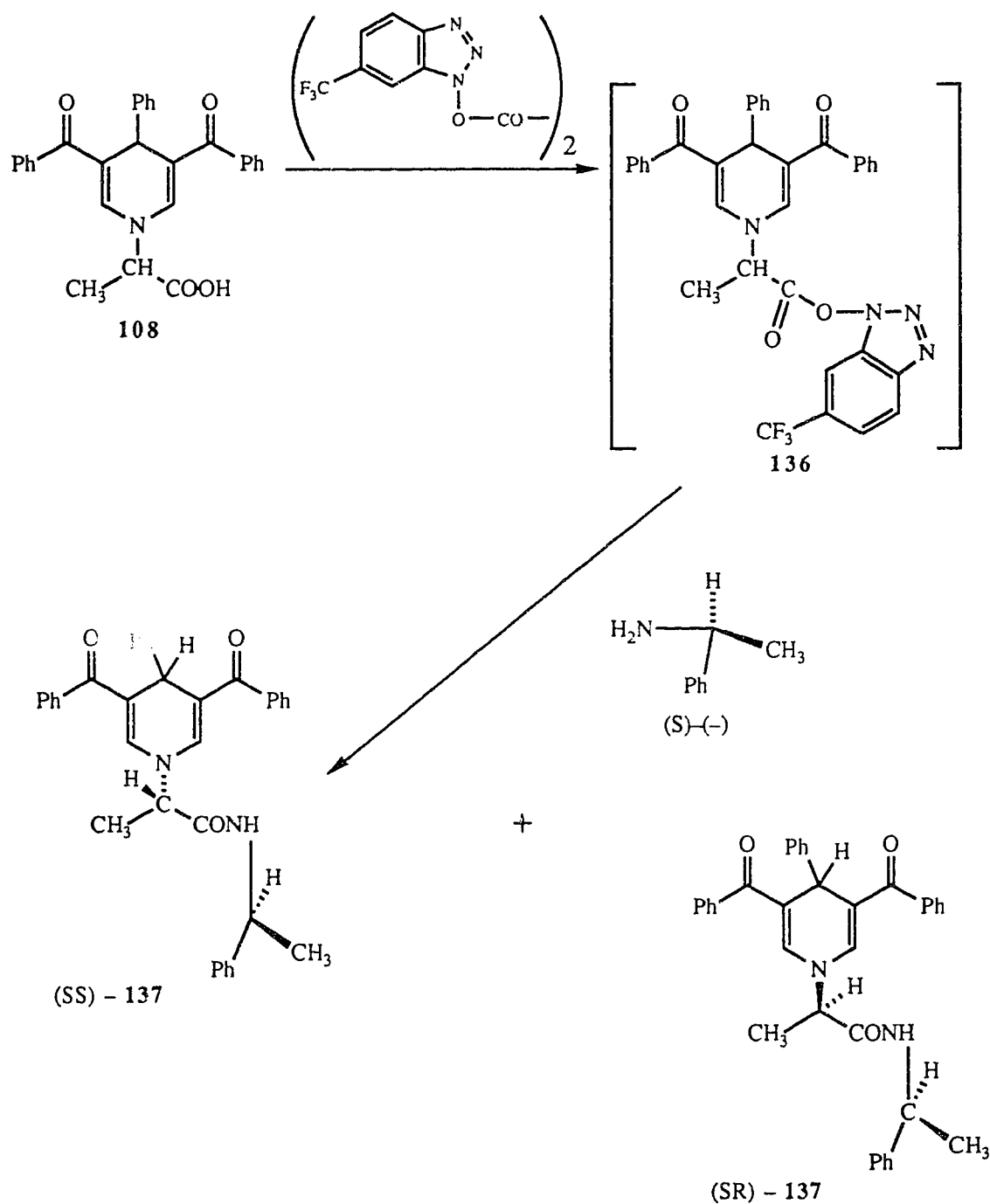
Further attempts directed towards the synthesis of pure diastereomers possessing a chiral lactate ester led to the synthesis of compound **138**. Thus, using the procedure of Takeda *et al*.,[221] a solution of 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydro-pyridyl)]acetic acid (**108**) was reacted with a suspension of BTBO in acetonitrile to give

Table 11. ^{1}H NMR spectral data for N-[(1S)-1-phenethyl]-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide diastereomers (**137a** and **137b**).

137a and **137b**

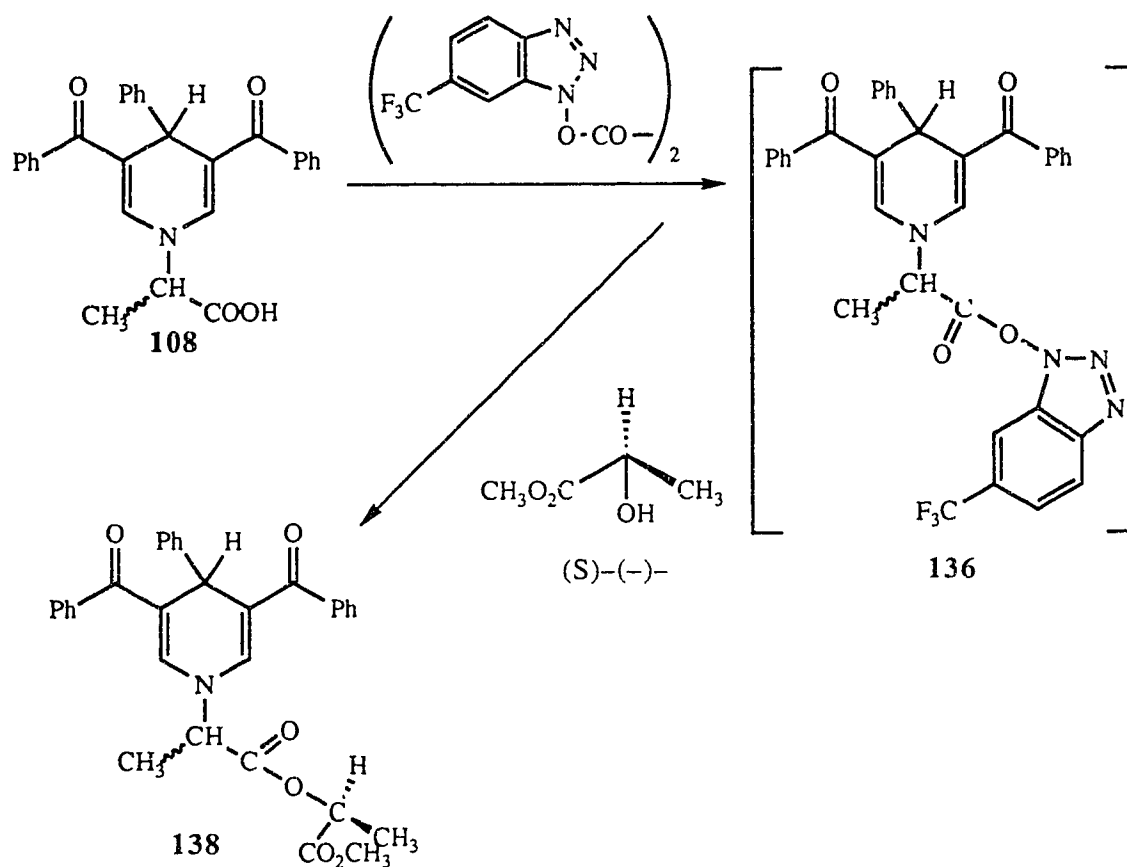| Entry	^{1}H NMR (CDCl$_3$) δ
137a	7.1-7.6 (m, 20H, phenyl hydrogens), 6.90 and 6.96 (two d, $J_{2,6}$ = 1.5 Hz, 1H each, H-2 and H-6), 6.14 (d, $J_{NH,CH}$ = 7.2 Hz, 1H, NH), 5.64 (s, 1H, H-4), 5.1 (q, J_{CH,CH_3} =7.2 Hz, 1H, C$\underline{H}$(CH$_3$)CO), 1.46 and 1.44 (two d, $J_{CH_3,CH}$ =7.2 Hz, 6H, two C$\underline{H}_3$CH)
137b	7.1-7.5 (m, 20H, phenyl hydrogens), 6.90 and 6.92 (two d, $J_{2,6}$ = 1.5 Hz, 1H each, H-2 and H-6), 6.22 (d, $J_{NH,CH}$ = 7.2 Hz, 1H, NH), 5.62 (s, 1H, H-4), 5.1 (q, J_{CH,CH_3} = 7.2 Hz, $J_{CH,NH}$ = 7.2 Hz, NHC$\underline{H}$CH$_3$), 3.9 (q, J_{CH,CH_3} = 7.2 Hz, 1H, C$\underline{H}$(CH$_3$)CO), 1.42 (d, $J_{CH_3,CH}$ = 7.2 Hz, 6H, two C$\underline{H}_3$CH)

Scheme 12. Synthesis of N-[(1S)-1-phenethyl]-2-methyl-2-[1-(3,5-di-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide diastereomers (137a) and (137b).

the activated ester **136** which, without isolation, was reacted with (S)-(-)-methyl lactate. The resulting mixture was worked up as reported[221] to afford **138** as an oil in 12% yield. Activated esters have frequently been prepared by reaction of an acid with N-hydroxy imides[224] or 1-hydroxybenzotriazole[224] in the presence of N,N'-dicyclohexylcarbodiimide (DCC). However, DCC causes side reactions such as formation of N-acylurea and a Lossen rearrangement reaction for N-hydroxysuccinimide.[225] BTBO was used in this investigation since it has been reported that with BTBO, nucleophilic attack by alcohol to active ester occurs stoichiometrically,[221] while excess alcohols are required with benzotriazole[226] and 6-chlorobenzotriazole esters.[227] Furthermore, BTBO is not a skin irritant as is DCC and BTBO esterifications proceed much faster and produce only three by-products, carbon monoxide, carbon dioxide, and 1-hydroxy-6-(trifluoromethyl)benzotriazole.[221] It was expected that the 3,5-dibenzoyl compound **138** could be separated into two pure diastereomers (SS and SR) which could then be cleaved by hydrolysis to afford the pure S and R enantiomers. However **138** was a single band on TLC which could not be separated.

The ^{1}H NMR spectrum of compound **138** indicated a mixture of two diastereomers in the ratio 5:4 which differ in configuration at the N-C$\underline{\text{H}}$(CH$_3$)CO$_2$ chiral carbon. The spectrum exhibited dual resonances for the H-2, H-6, NC$\underline{\text{H}}$CH$_3$ and OMe protons. The reaction is outlined in Scheme 13.

3.1.12.0.0.0. Synthesis of (4S)- or (4R)-Methyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (143)

Diisopinocampheylchloroborane, IpC$_2$BCl, **142**), reduces ring and chain substituted halo or alkyl ketones to the corresponding haloalcohols in excellent enantiomeric excess.[228] It was therefore anticipated that IpC$_2$BCl could be used to synthesize **143** by stereoselective addition to the 3-benzoyl-4-phenyl-N-substituted pyridinium salt **141**. The salt

Scheme 13. Synthesis of (S)-methoxycarbonyl-α-methyl methyl-2-methyl-
2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetate.

141 was prepared by quaternization of 3-benzoyl-4-phenylpyridine (**140**) in refluxing anhydrous acetone with methyl DL-2-bromopropionate in acetone for 24 h. To a solution of IpC₂BCl in THF at -23°C was added **141**, suspended in THF under nitrogen and the mixture was stirred for 7 h prior to work up as reported.[229] Although silica gel TLC indicated that the starting material **141** was no longer present, the ^{1}H NMR spectrum of the isolated product was not that of the desired compound. The reaction is outlined in Scheme 14.

Scheme 14. Attempted synthesis of (4S)- or (4R)-methyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (143).

3.1.13.0.0.0. Attempted Synthesis of Methyl 2-methyl-2-[1-(3-phenoxy-4-phenyl-1,4-dihydropyridyl)]acetate (146)

A structural unit common to many useful NSAIDs is the 2-phenylpropionic acid moiety from which the term "profen" drugs is derived. Profen drugs differ in the nature of the substituents on the aromatic ring.[230] Examples include Ibuprofen, Flurbiprofen, Ketoprofen, and Fenoprofen. It was therefore of interest to replace the 2-phenylpropionic

acid moiety with a 1,4-dihydropyridyl acetic acid ester moiety since pyridine and dihydro-pyridine have been reported to be bioisosteric with phenyl moieties.[40,161,162]

3-Phenoxypyridine (144), which was prepared in 84% yield according to the procedure of Renshaw and Conn,[231] was quaternized with methyl DL-2-bromopropionate to afford the N-substituted 3-phenoxypyridinium salt (145). The copper catalyzed regio-specific reduction of 145 with phenylmagnesium chloride, as described in General Procedure A, afforded 146 as a brownish oil. The purification of 146 was attempted using silica gel and neutral alumina column chromatography but intensive decomposition occurred. Thus, it was not possible to obtain pure 146. The instability of compound 146 could be due to the 3-phenoxy group which has been reported[119] to destabilize dihydro-pyridines. The synthetic procedure used to prepare 146 is outlined in Scheme 15. The compound 146 also decomposed on storage both at 0°C and room temperature.

$CH_3CH(Br)CO_2CH_3$

acetone, reflux, 24 h

144

145

1. 5% CuI
2. PhMgCl, THF, -23°C

146

Scheme 15. Syntheis of methyl 2-methyl-2-[1-(3-phenoxy-4-phenyl-1,4-di-hydropyridyl)]acetate (146).

3.1.14.0.0. Synthesis of Ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (149-152), Ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]-acetate (153), and Ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (154)

The acetic acid side chain of known heteroarylacetic acid NSAIDs is usually attached to an sp^2 hybridized carbon. It has also been established that the pyridine ring and di-hydropyridyl ring systems are bioisosteric with respect to antiinflammatory activity.[40,161,162] Thus, it was of interest to extend the SARs by preparing compounds 149-154 for evaluation as antiinflammatory agents.

Thus, quaternization of ethyl 3-pyridylacetate (147, R^1 = H), or ethyl 2-methyl-3-pyridylacetate (148, R^1 = Me) with phenyl chloroformate (R^2 = Ph) or methylchloro-formate (R^2 = Me) and the subsequent copper-catalyzed Grignard reduction of the N-acyl-pyridinium salts formed, afforded compounds 149-154 in 64 to 96% yield. The reaction procedure is outlined in Scheme 16. The spectral data for 149-154 are shown in Table 12 and the physical data are shown in Table 13.

Scheme 16. Ethyl 2-[3-[(1-phenoxycarbonyl-4-substituted-1,4-dihydro-pyridyl)]acetates (149-152), Ethyl 2-methyl-2-[3-(1-phenoxy-carbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (153) and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (154).

Table 12. IR and ^{1}H NMR spectral data for ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (**149-152**), ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-1,4-dihydropyridyl)]acetate (**153**), and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**154**).
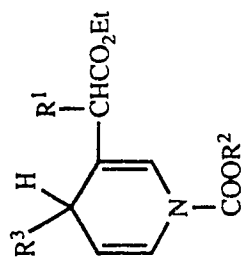

149 – 154

Entry	R^1	R^2	R^3	IR (neat) cm^{-1}	^{1}H NMR, CDCl$_3$ (δ)
149	H	Ph	Ph	1745 (COOEt); 1730 (COOPh)	7.16-7.48 (m, 10H, phenyl hydrogens), 7.0-7.14 (m, 2H, H-2, H-6), 5.05 and 5.12 (two d, J$_{4,5}$ = 4.0 Hz of d, J$_{5,6}$ = 8.6 Hz, 1H total, H-5), 4.26 and 4.36 (two d, J$_{4,5}$ = 4.0 Hz, 1H, H-4), 4.1 (q, J$_{CH_2,CH_3}$ = 7.0 Hz, 2H, C$\underline{H}_2$CH$_3$), 2.7?——3.? (m, 2H, C$\underline{H}_2$COO), 1.14-1.32 (m, 3H, C$\underline{H}_3$CH)
150	H	Ph	4ClPh	1745 (COOEt); 1730 (COOPh)	6.8-7.45 (m, 9H, phenyl hydrogens), 6.76 and 6.8? (two s, 1H total, H-2), 6.76 (d, J$_{5,6}$ = 8.6 Hz, 1H, H-6), 5.0 and 5.0? (two d, J$_{5,6}$ and 4.30 (two d, J$_{4,5}$ = 4.0 Hz, 1H total, H-4), 4.08 (q, J$_{CH_2,CH_3}$ = 7.0 Hz, 2H, C$\underline{H}_2$CH$_3$), 2.7-2.9 (m, 2H, C$\underline{H}_2$COO), 1.24 (t, J$_{CH_3,CH_2}$ = 7.0 Hz, 3H, C$\underline{H}_3$CH$_2$)

(Continued)

Entry	R^1	R^2	R^3	IR (neat) cm^{-1}	^{1}H NMR, CDCl$_3$ (δ)
151	H	Ph	n-Bu	1740 (COOEt); 1730 (COOPh)	7.14-7.50 (m, 5H, phenyl hydrogens), 6.86 -7.0 (m, 2H, H-2, H-6), 4.95 and 5.02 (two d, J$_{4,5}$ = 4.9 Hz of d, J$_{5,6}$ = 8.4 Hz, 1H total, H-5), 4.18 (m, 2H, C$\underline{H}_2$CH$_3$), 3.18-2.92 (m, 3H, C$\underline{H}_2$COO, H-4), 1.2-1.65 (m, 9H, CO$_2$CH$_2$, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CH$_3$), 0.88 (t, J = 7 Hz, CH$_2$CH$_2$C$\underline{H}_3$)
152	H	Ph	Me	1740 (COOEt); 1730 (COOPh)	7.1-7.45 (m, 5H, phenyl hydrogens), 6.84-6.96 (m, 2H, H-2, H-6), 4.9 and 5.02 (d, J$_{5,6}$ = 8.8 Hz of d, J$_{4,5}$ = 4.3 Hz, 1H total, H-5), 4.19 (q, J$_{CH,CH_3}$ = 7.0 Hz, 2H, C$\underline{H}_2$CH$_3$), 2.94-3.25 (m, 3H, C$\underline{H}_2$CO$_2$, H-4), 1.28 (t, 3H, CH$_2$C$\underline{H}_3$), 1.16 (d, J$_{CH_3,H}$ = 6.9 Hz, 3H, CHC$\underline{H}_3$)
153	Me	Ph	Ph	1742 (COOEt); 1730 (COOPh)	7.1-7.6 (m, 10H, phenyl hydrogens), 6.9-7.1 (m, 2H, H-2, H-6), 5.14 and 5.04 (two d, J$_{5,6}$ = 8.8 Hz of d, J$_{4,5}$ = 4.3 Hz, 1H total, H-5), 4.25 (d, J$_{4,5}$ = 4.3 Hz, 1H, H-4), 4.08 (m, 1H, CH$_2$CO$_2$), 2.9 (q, J$_{CH_3,CH}$ = 7.0 Hz, 1H, C$\underline{H}$CH$_3$), 1.1-1.45 (m, 6H, CHC$\underline{H}_3$, CH$_2$C$\underline{H}_3$). Rotameric ratio 1:1.

(Continued)

Entry	R^1	R^2	R^3	IR (neat) cm^{-1}	^{1}H NMR, CDCl$_3$ (δ)
153 (Cont'd.)	Me	Ph	Ph	1742 (COOEt); 1730 (COOPh)	^{1}H NMR (Me$_2$SO-d$_6$) (68°C): 7.2-7.5 (m, 10H, phenyl hydrogens), 6.98-7.10 (m, 2H, H-2, H-6), 5.12 (d, $J_{5,6}$ = 8.8 Hz of d, $J_{4,5}$ = 4.3 Hz, 1H, H-5), 4.20 (d, $J_{4,5}$ = 4.3 Hz, 1H, H-4), 3.98 and 4.02 (two overlapping q, J = 7 Hz, CH$_2$CH$_3$), 2.96 and 2.29 (two overlapping q, J = 7.0 Hz, 1H, CHCH$_3$). 1.06-1.24 (m, 6H, CH$_2$CH$_3$, CHCH$_3$)
154	H	Me	Ph	1745 (COOEt); 1740 (COOMe)	7.12-7.3 (m, 5H, phenyl hydrogens), 6.90 and 6.93 (two s, 1H total, H-2), 6.74 and 6.78 (two d, $J_{5,6}$ = 8.6 Hz, 1H total, H-6), 4.85 and 4.95 (two d, $J_{5,6}$ = 8.6 Hz of d, $J_{4,5}$ broadened, 1H total, H-5), 4.16 (broad peak, 1H, H-4), 4.06 (q, J_{CH,CH_3} =7 Hz, 2H, CH$_2$CH$_3$), 3.8 (s, 3H, OCH$_3$), 2.7 (s, 2H, CH$_2$COO), 1.2 (t, J_{CH,CH_3} =7.0 Hz, 3H, CH$_3$CH$_2$). The rotamer ratio was about 1:1.

Table 13. Physical data for ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (**149-152**), ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-1,4-dihydropyridyl)]acetate (**153**), and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]-acetate (**154**).

Entry	R^1	R^2	R^3	Yield,[a] %	Formula	Microanalysis: Calcd. (Found)		
						C	H	N
149	H	Ph	Ph	96	$C_{22}H_{21}NO_4$	72.71 (72.77)	5.82 (5.85)	3.85 (3.56)
150	H	Ph	4ClPh	75	$C_{22}H_{20}NO_4$	66.42 (66.30)	5.07 (5.30)	3.52 (3.57)
151	H	Ph	n-Br	82	$C_{20}H_{25}NO_4$	69.94 (69.86)	7.33 (7.26)	4.07 (4.04)
152	H	Ph	Me	64	$C_{17}H_{19}NO_4$	67.75 (67.58)	6.35 (6.37)	4.64 (4.32)
153	Me	Ph	Ph	64	$C_{23}H_{23}NO_4 \cdot 1/2H_2O$	71.50 (71.64)	5.96 (6.16)	3.63 (3.26)
154	H	Me	Ph	87	$C_{17}H_{19}NO_4$	67.76 (67.63)	6.36 (6.05)	4.65 (4.59)

[a]All compounds were oils.

^{1}H NMR variable temperature studies for ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (153) indicated that the dual resonances observed for H-2, H-6 and H-5 were due to rotamers in solution. The rotameric ratio was 1:1 for most products at 25°C. The dual resonance peaks for H-5 in compound 153 coalesced at 68°C. The observed rotational isomerism is due to restricted rotation about the nitrogen-to-carbonyl bond of the carbamate moiety present in compounds 149-154 as illustrated in Figure 15 for compound 153.

Figure 15. Rotamers of compound 153 as a result of restricted rotation.

The ^{1}H NMR and IR spectra for compounds 149-154 were consistent with their assigned structures.

3.2.0.0.0. PHARMACOLOGICAL SCREENS

3.2.1.0.0.0. Analgesic-Antiinflammatory Structure Activity Relationships (SARs) for Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates (90a-c), Methyl 2-methyl-2-[(1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates (91-93), 2-[1-(3-Benzoyl-4-substituted-1,4-dihydropyridyl)]acetic Acids (97a-c), 2-Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic Acids (98a-e), Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides

(99a-c), and 2-Methyl 2-[1-(3-benzoyl-4-substituted-1,4-di-hydropyridyl)]acetamides (99d-j)

The acetic acid esters (90-93), acetic acids (97-98) and acetamides (99) were synthesized to investigate the effect which replacement of the phenyl ring present in the traditional NSAIDs by a 1,4-dihydropyridyl ring has upon analgesic-antiinflammatory activity. The structures of these 1,4-dihydropyridyl-1-acetic acid esters (90-93), acetic acids (97-98) and acetamides (99) were expected to have some conformational differences relative to the classical aryl acetic acid NSAIDs. For example, the 1,4-dihydropyridine ring system is more puckered than the planar phenyl ring system. While the ene (C=C) moieties of the 1,4-dihydropyridyl ring systems are quasi-planar, there is considerable distortion at the N-1 and C-4 positions. These differences, together with steric effects due to the 1,4-dihydropyridyl N-1 and C-4 substituer˙ were expected to alter the overall volume of the molecule, the distribution of the drug between hydrophilic and hydrophobic tissues, and the interaction of the drug with the antiinflammatory receptor site.[243]

The acetic acid ester (90-93), acetic acid (97-98) and acetamide (99) classes of compounds were investigated to determine the effect of the α-substituent (R^3 = H or Me), the 1,4-dihydropyridyl ring C-4 substituents (R^2 = phenyl, 4-chlorophenyl, 4-tolyl, benzyl, cyclohexyl, n-butyl, and iso-butyl), the benzoyl substituent (R^1 = H, Cl, CH_3), and the nature of the N-1 substituent (ester, acid or amide), upon analgesic and anti-inflammatory activities.

In the methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)acetate and methyl 2-methyl-2-[1-(3-benzoyl-4-substituted 1,4-dihydropyridyl)]acetate series (90-93), the analgesic activity potency order with respect to the 1,4-dihydropyridyl C-4 R^3 substituent was phenyl (91) > iso-butyl (91h) > n-butyl (91g) = 4-chlorophenyl (90b) > 4-tolyl (91d) > cyclohexyl (91d) > benzyl (91f). The relative antiinflammatory potency order was phenyl (91) > cyclohexyl (91d) > 4-chlorophenyl (91c) > iso-butyl (91h) > n-butyl

(91g) > benzyl (91f) > 4-tolyl (91d). The phenyl substituent appeared to be the most active in the series.

The relative order of analgesic activity in the 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acid and 2-methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acid series (97-98) was cyclohexyl (98c) > phenyl (97a) > 4-chlorophenyl (97b) > phenyl (98a) and the antiinflammatory activity order for this series was phenyl (98a) > cyclohexyl (98c) > 4-chlorophenyl (97a) = phenyl (98b).

In the acetamide series, methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]-acetamides (99a-c) and 2-methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]-acetamides (99d-j), the analgesic activity order was cyclohexyl (99g) > phenyl (99d) = benzyl (99h) > 4-tolyl (99f) > 4-chlorophenyl (99e) > 4-chlorophenyl (99b) ≅ phenyl (99a).

The α-substituent (R^3 = H or Me) present in the N-1 acetyl moieties of these compounds also influenced analgesic-antiinflammatory activity. In the ester series (R^4 = OMe), those compounds having R^3 = Me substituents were generally more active than the corresponding R^3 = H analogs. A similar correlation was found for the amide group of compounds. For the acid series (R^4 = OH), the relative activity order was generally, but not always, R^3 = H > Me.

The relative analgesic activity order was generally amide (R^4 = NH_2) > ester (R^4 = OMe) > acid (R^4 = OH). This order of activity for the ester, amide and acid analogs could be due to the more lipophilic nature of the ester and amide compounds relative to the acids. The more lipophilic esters may penetrate cell membranes more easily and once inside the cell, hydrolysis to the corresponding acids can occur.

The test results indicate that the R^1 substituent on the benzoyl group influenced analgesic-antiinflammatory activity in the order H = Cl > CH_3 for analgesic activity and H > Cl > CH_3 for antiinflammatory activity. This R^1 substituent activity order could be due to steric factors which might affect drug-receptor interaction.

The pharmacological data for compounds **90-93, 97-98** and **99** are summarized in Table 14. The most active antiinflammatory agent in this series was **91** which reduced inflammation by 50% at 3 hours and 74% at 5 hours after a 100 mg/kg po dose relative to Ibuprofen which reduced inflammation by 44% at 3 hours and 52% at 5 hours at the same dose. The most active analgesic activity was **99g** (96% inhibition at 50 mg/kg sc dose) relative to Aspirin (58% inhibition at the same dose).

3.2.2.0.0.0. **Analgesic-Antiinflammatory SARs of Methyl (103) and Methyl 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydro-pyridyl)]acetates (104), 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (105), 2-Methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (106) and 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]-acetic Acids (107 and 108)**

Compounds **103-108** were investigated in order to determine the effect of chirality upon pharmacological activity. Compounds **103, 105**, and **107** are achiral, whereas compounds **104, 106**, and **108** have one chiral center when R^1 = Me.

When the analgesic activities were determined, compounds with R^1 = Me were equiactive to the corresponding analogs with R^1 = H. In contrast, the antiinflammatory activity order was R^1 = Me > H. This latter SAR is consistent with known structure-activity correlations for NSAIDs.[244] In general, the order of activity for the R^2 substituent was ester > amide > acid for both analgesic and antiinflammatory activities.

It appears that chirality is a determinant of antiinflammatory activity. Compound **104**, which is chiral, was considerably more active (80% inhibition at 3 h and 71% inhibition at 5 h for a 100 mg/kg po dose) than compound **103**, which is achiral (10% inhibition at 3 h and 80% inhibition at 5 h) for the same dose. Also, compound **104**, which has only one chiral center at the methine carbon of the N-acetyl moiety had superior antiinflammatory

---

Table 14. Pharmacological data for methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **90a-90c**; methyl 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates **91a-91h**, **92a-92d**, **93**; *ortho*-methoxyphenyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate **96**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **97a-97c**; 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetic acids **98a-98e**; 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99a-99c**; and 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetamides **99d-99j**.

Entry	R^1	R^2	R^3	R^4	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
						3 h	5 h
90a	H	Ph	H	OMe	45.2 ± 5.7	Inactive	12.9 ± 4.0
90b	H	4-ClC$_6$H$_4$	H	OMe	66.0 ± 1.3	44.7 ± 6.5	Inactive
90c	H	4-tolyl	H	OMe	25.5 ± 3.8	18.8 ± 3.8	23.0 ± 5.2
91	H	Ph	H	OMe	94.5 ± 1.5	50.0 ± 7.3	73.6 ± 2.0

(Continued)

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Entry	R[1]	R[2]	R[3]	R[4]	Analgesic Act.[a] % Inhibition	Antiinflammatory Act.[b] % Inhibition	
						3 h	5 h
91a	H	Ph	Me	OMe	NT	54.5 ± 3.6	33.7 ± 1.8
91b	H	Ph	Me	OMe	NT	56.1 ± 5.2	61.4 ± 2.4
91c	H	4-ClC$_6$H$_4$	Me	OMe	57.5 ± 2.0	48.9 ± 4.7	13.57 ± 3.2
91d	H	4-tolyl	Me	OMe	65.4 ± 2.1	13.9 ± 2.4	2.93 ± 3.7
91e	H	cyclohexyl	Me	OMe	62.8 ± 1.8	63.6 ± 2.4	29.3 ± 3.7
91f	H	benzyl	Me	OMe	57.5 ± 3.7	25.6 ± 3.8	7.3 ± 5.2
91g	H	n-Bu	Me	OMe	66.5 ± 1.4	40.4 ± 3.8	52.7 ± 3.2
91h	H	i-Bu	Me	OMe	72.8 ± 3.1	46.1 ± 1.5	26.4 ± 5.3
92a	Cl	Ph	Me	OMe	80.0 ± 2.5	46.9 ± 4.2	48.5 ± 3.1
92b	Cl	4-ClC$_6$H$_4$	Me	OMe	47.6 ± 3.5	Inactive	30.3 ± 2.8
92c	Cl	benzyl	Me	OMe	53.0 ± 2.6	Inactive	38.0 ± 3.0
92d	Cl	cyclohexyl	Me	OMe	51.0 ± 5.3	3.0 ± 2.9	32.0 ± 5.2
93	CH$_3$	Ph	Me	OMe	62.7 ± 1.7	12.1 ± 2.3	Inactive
96	H	Ph	Me	(structure, CH$_3$)	83.0 ± 4.8	45.5 ± 3.9	50.0 ± 3.6

(Continued)

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Entry	R^1	R^2	R^3	R^4	Analgesic Act.[a] % Inhibition	Antiinflammatory Act.[b] % Inhibition	
						3 h	5 h
97a	H	Ph	H	OH	45.1 ± 0.2	Inactive	Inactive
97b	H	4-ClC$_6$H$_4$	H	OH	43.4 ± 2.1	29.7 ± 4.7	Inactive
97c	H	4-tolyl	H	OH	NT	NT	NT
98a	H	Ph	Me	OH	30.1 ± 4.7	14.20 ± 1.3	68.5 ± 0.8
98b	H	4-ClC$_6$H$_4$	Me	OH	43.4 ± 2.1	29.7 ± 4.7	Inactive
98c	H	cyclohexyl	Me	OH	62.8 ± 1.8	63.6 ± 5.4	41.9 ± 2.6
98d	H	benzyl	Me	OH	NT	NT	NT
98e	H	n-Bu	Me	OH	NT	NT	NT
98f	H	i-Bu	Me	OH	NT	NT	NT
99a	H	Ph	H	NH$_2$	33.3 ± 3.2	Inactive	16.0 ± 3.6
99b	H	4-ClC$_6$H$_4$	H	NH$_2$	34.2 ± 5.2	40.4 ± 2.3	Inactive
99c	H	4-tolyl	H	NH$_2$	NT	NT	NT
99d	H	Ph	Me	NH$_2$	75.9 ± 2.3	14.3 ± 2.5	68.6 ± 3.0
99e	H	4-ClC$_6$C$_4$	Me	NH$_2$	59.3 ± 2.7	31.2 ± 2.6	Inactive

(Continued)

Entry	R^1	R^2	R^3	R^4	Analgesic Act.^{a} % Inhibition	Antiinflammatory Act.^{b} % Inhibition	
						3 h	5 h
99f	H	4-tolyl	Me	NH$_2$	62.5 ± 5.7	8.3 ± 4.6	60.9 ± 3.5
99g	H	cyclohexyl	Me	NH$_2$	95.6 ± 3.6	Inactive	Inactive
99h	H	benzyl	Me	NH$_2$	75.5 ± 2.9	25.0 ± 4.8	18.4 ± 3.9
99i	H	n-Bu	Me	NH$_2$	NT	NT	NT
99j	H	i-Bu	Me	NH$_2$	NT	NT	NT
Ibuprofen					–	43.8 ± 2.3	51.7 ± 3.6
Aspirin					57.8 ± 2.8	–	–

NT = Not tested

^{a}The result is the mean value ± SEM (n = 5) for a 50 mg/kg sc dose in the 4% NaCl-induced writhing test.

^{b}The result is the mean value ± SEM (n = 4) for a 100 mg/kg po dose in the carrageenan-induced edema test.

^{c}Tested as a mixture of the oil **91a** and solid **91b**.

^{d}Tested as an oil.

^{e}Tested as a solid.

activity relative to compound **91** which has two chiral centers at C-4 and the methine carbon.
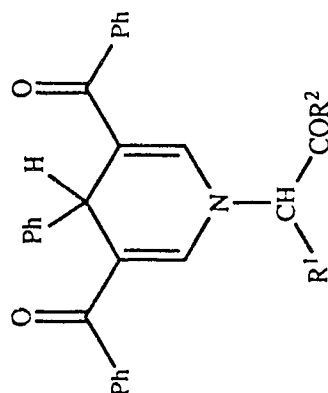
The pharmacological data for compounds **103-108** are summarized in Table 15. The most active analgesic agent in this series was **104** (75% inhibition at 50 mg/kg sc dose relative to Aspirin (58% inhibition at the same dose). Compound **104** was also the most potent antiinflammatory agent (80% inhibition at 3 h and 71% inhibition at 5 h at 100 mg/kg po dose) relative to Ibuprofen (44% inhibition at 3 h and 52% inhibition at 5 h at the same dose).

3.2.3.0.0.0. Analgesic-Antiinflammatory Activity of Methyl 2-methyl-2-(1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahydropyridyl)]acetate (113)

The effect of the bioisosteric replacement of a 1,4-dihydropyridyl ring system by a tetrahydropyridyl group was investigated. The tetrahydropyridyl compound (**113**) was more active (78% inhibition at 3 h for a 100 mg/kg po dose) than its 1,4-dihydropyridyl analog (**91**) (50% inhibition at 3 h) when evaluated for antiinflammatory activity. However, compound **91** was more active as an analgesic agent (95% inhibition at 50 mg/kg sc dose) than its tetrahydropyridyl analog (**125**) (69% inhibition at 50 mg/kg sc dose).

The test results suggest that compound **113** may have a rapid onset of antiinflammatory activity and shorter duration of action since antiinflammatory activity was considerably higher at 3 h relative to 5 h, compared to compound **91** which may have a slower onset of action and a longer duration of action. The pharmacological data for compound **113** is presented in Table 16.

Table 15. Pharmacological data for methyl (103) and methyl 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetates (104), 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (105), 2 methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-di-hydropyridyl)]acetamide (106) and 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acids (107 and 108).

Entry	R^1	R^2	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
				3 h	5 h
103	H	OMe	74.0 ± 6.2	10.0 ± 2.5	8.0 ± 3.5
104	Me	OMe	75.0 ± 2.5	80.0 ± 3.5	70.7 ± 4.8
105	H	NH$_2$	59.8 ± 13.7	23.5 ± 4.0	26.9 ± 5.0
106	Me	NH$_2$	52.0 ± 3.8	60.4 ± 2.2	68.2 ± 1.5
107	H	OH	34.6 ± 7.4	22.2 ± 3.04	21.9 ± 2.7
108	Me	OH	48.0 ± 3.9	56.3 ± 5.3	51.2 ± 4.5

[a]The result is the mean value ± SEM (n = 5) for a 50 mg/kg sc dose in the 4% NaCl-induced writhing test.

[b]The result is the mean value ± SEM (n = 4) for a 100 g/kg po dose in the carrageenan-induced edema test.

Table 16. Pharmacological data for methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**111**), methyl 2-[1-(3,5-di-benzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (**112**), and methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetra-hydropyridyl)]acetate (**113**).

Entry	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.[b], % Inhibition	
		3 h	5 h
111	60.0 ± 3.8	30.0 ± 5.6	10.5 ± 4.2
112	48.0 ± 2.3	15.3 ± 3.5	28.0 ± 3.8
113	68.6 ± 5.0	78.0 ± 4.8	23.0 ± 4.2

[a]The result is the mean ± SEM (n = 5) for a 50 mg/kg sc dose (n = 5) determined using the NaCl-induced writhing test.

[b]The result is the mean ± SEM (n = 4) for a 100 mg/kg po dose (n = 4) determined using the carrageenan-induced edema test.

3.2.4.0.0.0. Analgesic-Antiinflammatory Activity of Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (125-128)
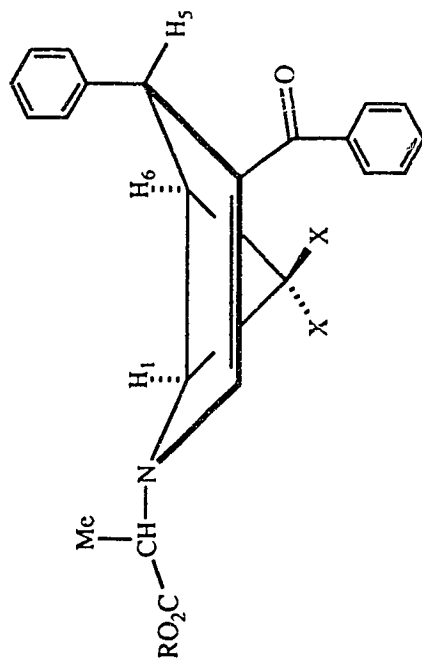
The effect which replacement of the C5-C6 double bond of 91 with a dihalocyclopropyl moiety has upon biological activity was investigated (Table 17). With respect to the halogen substituents, the antiinflammatory potency order was $Br_2 > Cl_2 > F_2 > ClF$, whereas the analgesic activity order was $Cl_2 > Br_2 > F_2 > ClF$. The cyclopropyl moiety in general reduced analgesic-antiinflammatory compared to the corresponding dihydropyridyl analog. This reduced activity could be due to the change in the overall volume of the cyclopropyl compounds with respect to interaction at the receptor site.

3.2.5.0.0.0. Analgesic-Antiinflammatory SARs for Ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (151-152), Ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (153) and Ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (154)

The analgesic activity test results (Table 18) indicated that the order of activity for the R^3 substituent was Ph (149) > Me (152) > n-Bu (151) > 4-chlorophenyl (150). The α-methyl substituent also had an effect on analgesic activity with R^1 = H exhibiting superior activity to a R^1 = Me substituent. The R^2 substituent was also a determinant of analgesic activity with R^2 = Ph (149) > Me (154) [149 (R^2 = Ph) > 154 (R^2 = Me)]. The antiinflammatory activity order for the R^3 substituent was n-Bu (151) > Me (152) > phenyl (149) > p-chlorophenyl (150) whereas the R^1 substituent potency order was R^1 = Me (153) > H (149).

The most active analgesic agent in this series was 149 (83% inhibition at 50 mg/kg sc dose) relative to Aspirin (58% inhibition at the same dose) whereas the most potent anti

Table 17. Pharmacological data for methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dihalo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (125-128), methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]-hept-3-ene)]acetates (129-131) and acetamide (132).

Entry	X^1	X^2	R	Analgesic Act.,[a] % Inhibition	Antiinflammatory Act.,[b] % Inhibition	
					3 h	5 h
125	Br	Br	OMe	68.3 ± 2.9	62.5 ± 3.2	41.0 ± 1.6
126	Cl	Cl	OMe	75.2 ± 1.8	50.3 ± 6.5	35.6 ± 2.3
127	F	F	OMe	56.5 ± 2.1	42.3 ± 1.5	28.5 ± 3.3
128	Cl	F	OMe	36.9 ± 1.8	32.9 ± 2.5	30.6 ± 2.5

(Continued)

Entry	X^1	X^2	R	Analgesic Act.[a], % Inhibition	Antiinflammatory Act.[b], % Inhibition	
					3 h	5 h
130	H	Cl	OMe	–	–	–
131	H	F	OMe	–	–	–
132	Br	Br	NH_2	82.5 ± 2.8	48.5 ± 2.8	68.2 ± 1.6

[a]The result is the mean ± SEM (n = 5) for a 50 mg/kg sc dose in the NaCl-induced writhing test.

[b]The result is the mean ± SEM (n = 4) for a 100 mg/kg po dose in the carrageenan-induced edema test.

Table 18. Pharmacological data for ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (**149-152**), ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-1,4-dihydropyridyl)]acetate (**153**), and ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-di-hydropyridyl)]acetate (**154**).

Entry	R^1	R^2	R^3	Analgesic Act.[a] % Inhibition	Antiinflammatory Act.[b] % Inhibition	
					3 h	5 h
149	H	Ph	Ph	83.1 ± 3.8	50.2 ± 3.5	31.7 ± 1.5
150	H	Ph	4ClPh	62.4 ± 5.2	7.3 ± 4.8	6.0 ± 2.8
151	H	Ph	n-Bu	73.2 ± 2.6	62.3 ± 2.3	35.4 ± 1.8
152	H	Ph	Me	80.2 ± 2.4	60.3 ± 3.2	37.3 ± 4.5
153	Me	Ph	Ph	68.0 ± 1.5	70.5 ± 3.5	45.8 ± 1.6
154	H	Me	Ph	58.0 ± 2.5	46.0 ± 1.5	38.0 ± 2.8

[a]The result is the mean ± SEM (n = 5) for a 50 mg/kg sc dose in the NaCl-induced writhing test.

[b]The result is the mean ± SEM (n = 4) for a 100 mg/kg po dose in the carrageenan-induced edema test.

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inflammatory agent in the series was (153) which reduced inflammation by 76% at 3 h and 46% at 5 h for a 100 mg/kg po dose relative to Ibuprofen which reduced inflammation by 44% at 3 h and 52% at 5 h at the same dose.

3.3.0.0.0.0. ANALGESIC ACTIVITY EVALUATION

A variety of analgesic tests are used which differ from each other by the nature of the stimuli, parameters, sites of application, nature of responses, quantitation, and apparatus. These tests can be classified into chemical, electrical, mechanical, and thermal methods. Chemically induced animal writhing assays are common protocols used for analgesic activity evaluation. A variety of chemical agents have been used to produce pain, including acetic acid,[232] acetylcholine,[233] hypertonic saline,[234] phenylquinone,[235] serotonin,[236] and bradykinin.[237] The intraperitoneal administration of a noxious chemical substance to mice and rats produces peritoneal irritation, which elicits a writhing response characterized by internal rotation of the feet, sucking in of the stomach, elongation of the body, arching of the back, rolling on one side, and circling the cage.[238]

The phenylquinone-induced writhing test in mice is the most extensively used writhing assay, but it gives false positive results for some compounds.[237] In addition, repeated challenge using phenylquinone at short time intervals is not possible. Therefore, the time course of drug action cannot be determined using this assay. Chronic phenylquinone challenges may also cause damage to abdominal organs.

The NaCl-induced writhing assay used in this investigation, described by Fukawa et al.[239] is reported to be highly specific with no incidence of false positives. Hypertonic sodium chloride solution (4%, w/w, 1 M) was found to be the most reliable agent from a number of noxious irritants evaluated in rats.[234] The 4% sodium chloride-induced writhing assay also has advantages that repeated challenges at short intervals (15 minutes) are possible and chronic challenges do not cause damage to abdominal organs.[239]

Analgesic activity was determined as the reduction in writhing responses (expressed as % inhibition) caused by the test compound as compared to control responses. The analgesic activity results for the test compounds were compared to the reference drugs Aspirin and Ibuprofen.

3.4.0.0.0.0. ANTIINFLAMMATORY ACTIVITY EVALUATION

The complexity of the inflammatory process and the diversity of the drugs that have been found effective in modifying this process have resulted in the development of numerous assay methods capable of detecting antiinflammatory substances. A few of these methods have achieved popularity due to their simplicity, economic feasibility, and relative accuracy. Screening procedures that have been used in an attempt to assess the antiinflammatory potential of drugs include: (i) interference with the manifestation of one of the cardinal signs of inflammation, (ii) modification of one of the events occurring during the inflammatory process, (iii) a biological or chemical characteristic of a class of known antiinflammatory drugs, or (iv) modification of those syndromes in laboratory animals which are believed to represent models for various rheumatoid disease states.[240]

Methods based on the inhibition of an induced swelling of the rat's paw have been the most popular and the method described by Winter et al.[241] was used in this investigation. Test compounds suspended in gum acacia were administered orally at a dose of 100 mg/kg, one hour prior to subcutaneous injection of 0.1 mL of a 1% suspension of carrageenanan into the plantar tissue of the right hind paw and the size of the paw was measured at this time by determining the magnitude of swelling by volume displacement of mercury. Three hours and 5 hours later the size of the injected paw was again measured. Control experiments were identical except the vehicle did not contain a test compound.

Antiinflammatory activity was determined as the reduction of edema (expressed as per cent inhibition) caused by test compound with respect to a control group. The results

obtained were compared to the antiinflammatory activity exhibited by the reference drug Ibuprofen.

3.5.0.0.0.0. ULCEROGENIC LIABILITY DETERMINATION

Gastric upset and irritation are a major obstacle to patient compliance with a prescribed dosage regimen of NSAIDs. Several attempts have been made to improve gastric tolerance of NSAIDs which have met with varying degrees of success. For example, buffered, sustained-release, or enteric-coated tablets, chemical manipulation such as esterification[42] and co-administration of agents have been employed in attempts to protect the stomach.[242] Endoscopic studies, to evaluate GI injury caused by NSAIDs, have shown that 23% of patients taking NSAIDs on a regular basis, regardless of whether or not they presented GI symptoms, were found to have a significant degree of mucosal inflammation and ulceration.[159] In addition, 41% of patients with significant gastric lesions were asymptomatic.[159] NSAIDs often mask the pain associated with GI ulceration. Therefore many patients suffer dangerous complications without clinical symptoms being manifested until the problem has reached a critical stage.

It was therefore considered important to assess the ulcerogenic liability of methyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (91a), 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetic acid (98a), and 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide (99d). The ulcerogenic liability of these compounds was determined according to a modified procedure reported by Nagai et al.[178] The results obtained for three compounds 91a, 98a, and 99d were compared to that of the reference drug Ibuprofen. The results indicate that compounds 91a, 98a, and 99d were completely devoid of any ulcerogenic effects at a dose of 1200 mg/kg po for a single oral dose 8 h after administration. A subsequent rat chronic study showed that 98a, administered at a 600 mg/kg po dose, twice a day for 6 days was also completely devoid of any gastric irritation or ulcerogenicity, whereas Ibuprofen exhibited ulcerogenicity effects

in rat (UD_{50} = 250 mg/kg po). The UD_{50} for Ibuprofen was 124.6 mg/kg po dose as reported in the literature. However a different procedure was used for the determination of UD_{50} of Ibuprofen in this study.

4.0.0.0.0.0. EXPERIMENTAL

4.1.0.0.0.0. PHYSICAL CONSTANTS AND SPECTROSCOPY

Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined for solutions in deutero-chloroform (CDCl$_3$) or dimethylsulfoxide-d$_6$ (DMSO-d$_6$), with a Bruker AM-300 spectrometer using tetramethylsilane (Me$_4$Si) as internal standard. High resolution mass (exact mass) spectra (HRMS) were recorded with an AEI MS-50 spectrometer and, in most cases, these exact mass determinations are used in lieu of elemental analyses. Infrared (IR) spectra were taken either neat, or as KBr pellets, on a Nicolet 5DX FT spectrophotometer. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of Alberta. pH measurements were performed using an Orion Model SA520 digital pH meter.

4.2.0.0.0.0. CHROMATOGRAPHY

Column chromatography was performed using silica gel (Merck type 7734, 100-200 mesh). Preparative thin layer chromatography (TLC) was performed with Camag Kieselgel DF-5 plates, 1.00 mm in thickness, activated at 120°C overnight prior to use. The purity of products and monitoring of reaction progress were determined using E. Merck precoated silica gel "G" microslides (250 μm in thickness). The spots were detected by shortwave ultraviolet light and/or iodine vapor visualization.

4.3.0.0.0.0. SOLVENTS AND REAGENTS

Tetrahydrofuran (THF) and diethyl ether were dried over sodium-benzophenone and distilled immediately prior to use. Benzene and acetonitrile were dried by distillation from calcium hydride. All organometallic reagents were purchased in "sure-sealed" containers from the Aldrich Chemical Company. 3-Benzoylpyridine, ethyl 3-pyridylacetate, methyl 2-

bromoacetate, methyl DL 2-bromopropionate and Evan's reagent (4S)-(-)-4-isopropyl-2-oxazolidinone were also obtained from Aldrich.

4.4.0.0.0.0. SYNTHETIC CHEMISTRY

4.4.1.0.0.0. Methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]-acetates and Methyl 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)]acetates (90-93). General Procedure A

A solution of 3-benzoylpyridine (2.0 g, 10.9 mmol, **87**) and either methyl bromo-acetate (2.5 g, 16.4 mmol) or methyl DL-2-bromopropionate (2.6 g, 16.4 mmol) in anhydrous acetone (20 mL) was refluxed for 8 h to afford the respective N-substituted 3-benzoylpyridinium salts (2.6 g, 71%, **88**) and (2.8 g, 73%, **89**). A solution of **88** (1 g, 3 mmol) or **89** (1.5 g, 4.3 mmol) in dry THF (50 mL) and cuprous iodide (0.06 g, 0.3 mmol) was stirred under a nitrogen atmosphere until the solution became homogeneous. The reaction mixture was cooled to -23°C using a dry ice-CCl$_4$ bath. A solution of the respective Grignard reagent (phenyl, p-chlorophenyl, benzyl, p-tolyl, cyclohexyl, n-butyl, or iso-butylmagnesium chloride or bromide (9.6 mmol) in THF (2 M) was added dropwise and the reaction mixture was maintained at -23°C for 30 min. The reaction mixture was allowed to warm to 25°C, the mixture was stirred for 1.5 h and then a saturated aqueous solution of NH$_4$Cl (5 mL) was added to quench the reaction. Diethyl ether (30 mL) was added, the organic phase was separated and washed successively with solutions of 30% NH$_4$OH; saturated aqueous NH$_4$Cl (3:1 v/v, 20 mL), water (2 × 10 mL) and brine (10 mL). The organic phase was dried (MgSO$_4$) and the solvent was removed *in vacuo*. The respective products **90-93** were purified by elution from a silica gel column using an EtOAc:hexane gradient going from 5:95 to 15:85 v/v as eluent. The IR and ¹H NMR spectral data for compounds **90-93** are presented in Table 2, the physical and pharmacological data are presented in Tables 3 and 4 respectively.

4.4.1.1.0.0. o-Methoxyphenyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (96)

Sodium hydride (0.024 g, 1 mmol), washed with hexane to remove the mineral oil, was added slowly with stirring to a solution of guaiacol (0.98 g, 8 mmol) in dry THF ⟨ ⟩5 mL) at 20°C under a nitrogen atmosphere and the mixture was stirred for 45 min. To the resulting solution, a solution of 2-bromopropionyl bromide (1.7 g, 8.0 mmol) in dry THF (2 mL) was added dropwise and the reaction was allowed to proceed for 30 min prior to addition of ice water (10 mL). Diethyl ether (20 mL) was added, the organic phase separated and dried with anhydrous magnesium sulphate. Removal of the solvent *in vacuo* afforded the guaiacol ester **94** (1.9 g, 95%). A solution of 3-benzoylpyridine (1 g, 5.4 mmol, **87**) in acetone (25 mL) and **94** (1.0 g, 3.9 mmol) was refluxed for 24 h to give the quaternary salt **95** (1.6 g, 67%). A solution of **95** (1.6 g, 3.6 mmol) in dry THF (25 mL) and cuprous iodide (0.32 g, 1.7 mmol) was stirred under a nitrogen atmosphere at 25°C for 30 min, and the reaction mixture was cooled to -23°C using a dry ice-CCl_4 bath. A solution of phenylmagnesium chloride (0.5 g, 3.7 mmol) in THF (2.2 mL of a 2 M solution) was added dropwise and the reaction mixture was maintained at -23°C for 30 min. The reaction mixture was allowed to warm to 25°C, stirred 1.5 h, after which saturated aqueous NH_4Cl (10 mL) was added to quench the reaction. Diethyl ether (20 mL) was added, the organic phase was separated, and washed successively with solutions of 30% NH_4OH:saturated aqueous NH_4Cl (3:1 v/v, 20 mL), water (2 × 20 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to afford an oil which was purified by silica gel column chromatography using EtOAc:hexane (15:85, v/v) as eluent to afford **96** as an oil (0.48 g, 30%). The IR and ^1H NMR spectral data for **96** are presented in Table 2.

4.4.2.0.0.0. **2-[1-(3-Benzoyl-4-substituted-1,4-dihydropyridyl)]acetic**

Acids and 2-Methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihy-

dropyridyl)]acetic Acids (97-98). General Procedure B

Aqueous sodium hydroxide (10 mL, 1% w/v, 0.75 mmol) was added dropwise to a

solution of the respective methyl 2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)acetates

(0.75 mmol) (90-91) in ethanol:water (4:1 v/v, 12.5 mL) at 25°C with stirring. The

reaction was allowed to proceed with stirring until micro TLC indicated that the reaction

was complete (2 h). Removal of the solvent *in vacuo*, addition of water (10 mL) to the

solution and acidification with 5 N HCl afforded a yellow solid which was filtered and

dried in a drying pistol to afford the acids.

These acids (97-98) were characterized as their methyl ester derivatives by addition of

a solution of excess diazomethane in methanol at 25°C with stirring. The respective methyl

ester products were obtained in quantitative yield. The ^{1}H NMR spectra of the esters

prepared in this way were identical to the corresponding esters synthesized using General

Procedure A. The IR and ^{1}H NMR spectral data for compounds 97-98 are summarized in

Table 2 and the physical data are presented in Table 3.

4.4.3.0.0.0. **2-Methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)ac-**

etamides (99). General Procedure C

A saturated solution of ammonia in methanol (10 mL) was added to a solution of

90-91 (2.7 mmol) in methanol (20 mL), the reaction flask was sealed with a rubber

septum and the reaction was allowed to proceed for 48 h at 25°C with stirring. Removal of

the solvent *in vacuo* gave the respective product which was purified by preparative TLC

using EtOAc:hexane (3:1 v/v) as development solvent. Extraction of the band containing

the product using EtOAc and removal of the solvent *in vacuo* afforded the respective

product 99a-j as solids. The spectral data are summarized in Table 2 and the physical data

are presented in Table 3.

4.4.3.1.0.0. 3,5-Dibenzoylpyridine (100)

A mixture of 3,5-pyridinedicarboxylic acid (10 g, 59.9 mmol) and thionyl chloride (48.9 g, 411 mmol, 30 mL) was refluxed for 16 h. Excess thionyl chloride was removed by evaporation under reduced pressure. Dry benzene (2 × 10 mL) was added and evaporated to remove the last traces of the thionyl chloride. The residual acid chloride was dissolved in anhydrous benzene (60 mL) and to this solution, cooled to 5 to 10° (ice-NaCl bath), was added anhydrous aluminum chloride (40 g, 300 mmol) with stirring. The reaction mixture was allowed to warm to room temperature and then refluxed for 6 h. The dark brown mixture was poured cautiously onto ice and 5 N HCl (20 mL), and the solid 3,5-dibenzoylpyridine which was formed was collected by filtration (12.5 g, 73%) and dried in a drying pistol, m.p. 121.5-123.5°C (lit.[245] m.p. 123°C).

4.4.4.0.0.0. Methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]-acetate (103). General Procedure D

A solution of 3,5-dibenzoylpyridine (1 g, 3.5 mmol, 100) in anhydrous acetone (10 mL) was refluxed with methyl bromoacetate (0.80 g, 5.2 mmol) for 48 h to give the pyridinium salt (0.44 g, 29.4%, 101). A solution of 101 (0.4 g, 1.1 mmol) in dry THF (20 mL) and cuprous iodide (0.02 g, 0.10 mmol) was stirred under nitrogen until the solution became homogeneous. The reaction mixture was cooled to -23°C using a dry ice-CCl₄ bath. A solution of phenylmagnesium chloride (0.48 g, 3.5 mmol) in THF (2 M solution) was added dropwise and the reaction mixture was maintained at -23°C for 30 min prior to warming to 25°C. The reaction mixture was stirred for 1.5 h and then a saturated aqueous solution of NH₄Cl (5 mL) was added to quench the reaction. Diethyl ether (20· mL) was added, the organic phase was separated and washed successively with solutions of 30% NH₄OH:saturated NH₄Cl (3:1 v/v, 10 mL), water (2 × 10 mL) and then brine (10 mL). The organic phase was dried (MgSO₄) and the solvent was removed *in vacuo* to give

a brownish oil which was purified by silica gel column chromatography using ether:hexane (30:70 v/v) as eluent to afford **103** as a yellow solid after recrystallization from ether (0.320 g, 66.6%).

A similar procedure was used to prepare methyl 2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]ace... (104) by Grignard reduction of the 3,5-dibenzoyl-pyridinium salt **102** (0.3 g, 0.7 mmol). Compound **104** was purified by silica gel column chromatography using ether:hexane (30:70 v/v) as eluent to afford a yellow solid (0.10 g, 31.7%) after recrystallization from ether. The IR and ^{1}H NMR spectral data are summarized in Table 4 and the physical data are presented in Table 5.

4.4.4.1.0.0. 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]ac-
etamides (105 and 106)

A solution of **103** (0.1 g, 0.2 mmol) in methanol (10 mL) was subjected to ammonolysis according to General Procedure C to afford a yellow oil. The oil was purified on preparative silica gel TLC using EtOAc:hexane (3:1 v/v). Extraction of the band containing the product using ethyl acetate (2 × 10 mL) and removal of the solvent *in vacuo* afforded compound **105** as a yellow solid (0.08 g, 100%).

A similar procedure was used to synthesize compound **106** which was purified on silica gel preparative TLC using EtOAc:hexane (3:1 v/v) as development solvent to give a yellow solid in 85% yield.

The IR and ^{1}H NMR spectral data for **107** and **108** are summarized in Table 4 and the physical data are presented in Table 5.

4.4.4.2.0.0. 2-[1-(3,5-Dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetic
Acids (107 and 108)

Compounds **107** and **108** were synthesized from **103** and **104** respectively according to General Procedure B and were obtained in 72% and 55% yields. The IR and

^{1}H NMR spectral data for **107** and **108** are summarized in Table 4 and the physical data are presented inTable 5.

4.4.4.4.3.0. Methyl 2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)-methyl]acrylate (111) and Methyl 2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)methyl]acrylate (112)

A solution of 3-benzoylpyridine (1.0 g, 5.5 mmol) and methyl 2-(bromomethyl)-acrylate (1.25 g, 7 mmol) in dry acetone (20 mL) was refluxed for 24 h to give the pyridinium salt **109** which was washed with ether after evaporation of the acetone *in vacuo* (0.76 g, 49%). To a solution of **109** (0.6 g, 2.1 mmol) in dry THF (20 mL), cuprous iodide (0.03 g, 0.2 mmol) was added and the mixture was stirred under a nitrogen atmosphere for 30 min. The reaction mixture was cooled to -23°C using a dry ice-CCl$_4$ bath, a solution of phenylmagnesium chloride (5.6 mmol of a 2 M solution) in THF was added dropwise and the reaction was carried out according to General Procedure A for 1 h to afford a brownish oil. Purification of this oil by preparative TLC using EtOAc:hexane (1:3, v/v) as development solvent afforded **111** as a yellow oil (R$_f$ 0.6, 0.320 g, 42%).

Similarly, 3,5-dibenzoylpyridine (1.5 g, 5.2 mmol, **100**) was quaternized with methyl 2-(bromomethyl)acrylate (1.25 g, 7 mmol) to give the corresponding 3,5-dibenzoyl-pyridinium salt **110** which was washed with ether (20 mL) after evaporation of acetone *in vacuo* (0.9 g, 45%). To a solution of **110** (0.6 g, 1.6 mmol) in dry THF (20 mL), cuprous iodide (0.03 g, 0.2 mmol) was added and the mixture was stirred for 30 min. The reaction mixture was cooled to -23°C, a solution of phenylmagnesium chloride (5.6 mmol of a 2 M solution) in THF was added dropwise and the reaction was continued according to General Procedure A for 1 h to give a brownish oil. This oil was purified by preparative TLC using EtOAc:hexane (1:3, v/v) as the development solvent to afford **112** as a yellow oil (R$_f$ 0.4, 0.28 g, 39%). The spectral data for **113** are presented in Table 7 and the physical data are presented in Table 8.

4.4.4.4.0.0. Methyl 2-methyl-2-[1-(4-phenyl-5-benzoyl-1,2,3,4-tetrahy-dropyridyl)acetate (113)

To a solution of **91b** (0.5 g, 1.4 mmol) in ethyl acetate (10 mL) in a pressure bottle, 20 mg of % Pd/C was cautiously added and the reaction was allowed to proceed in the presence of hydrogen gas at a pressure of 30 psi with shaking, for 24 h at 25°C until hydrogen uptake ceased. Filtration and then removal of the solvent *in vacuo* afforded a yellow oil which was purified by preparative silica gel TLC using EtOAc:hexane (1:1, v/v) as development solvent to afford **113** as an oil (R_f = 0.65, 200 mg, 47%). The spectral data for **113** are presented in Table 7 and the physical data are presented in Table 8.

4.4.4.5.0.0. Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicyclo[4.1.0]hept-3-ene]acetate (125) and Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dichloro-2-azabicy-clo[4.1.0]hept-3-ene]acetate (126)

Phenyl(tribromomethyl)mercury (1.3 g, 2.6 mmol) was added to a stirred solution of **91b** (0.9 g, 2.6 mmol) in dry benzene (20 mL) under a nitrogen atmosphere, and the mixture was refluxed for 8 h. Additional aliquots of PhHgCCBr3 (1.3 g, 2.6 mmol) were added to the reaction mixture at 2, 4, and 6 h. The reaction mixture was then cooled to 25°C and the PhHgBr which precipitated during the reaction was removed by filtration. Evaporation of the solvent *in vacuo* gave a brownish oil which was purified by preparative TLC on silica gel plates using EtOAc:hexane (1:3, v/v) as development solvent to give **125** as an oil (R_f = 0.5, 0.46 g, 50%). The oil was crystallized from hexane:ether (4:1, v/v).

Compound **126** was synthesized employing the same procedure using phenyl(bromo-dichloromethyl)mercury (PhHgCBrCl2) and **91a**. The product obtained was purified by preparative TLC using EtOAc:hexane (1:3, v/v) as development solvent to afford an oil which was crystallized from hexane:ether (3:1, v/v) to give **126** as a solid (R_f = 0.3, 0.15

g, 33%). The spectral data for **125** and **126** are presented in Table 9 and the physical data is summarized in Table 10.

4.4.4.6.0.0. Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7,7-difluoro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (127) and Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-chloro-7-fluoro-2-azabicyclo[4.1.0]hept-3-ene)]acetate (128)

Phenyl(trifluoromethyl)mercury (1.0 g, 1.1 mmol) was added to a mixture of **91a** and **91b** (0.5 g, 1.1 mmol) and dry NaI (0.65 g, 4.3 mmol) in dry dimethoxyethane (20 mL) under a nitrogen atmosphere with stirring, and the mixture was heated at 85-90°C for 2 h. Additional aliquots of PhHgCCF$_3$ (1.0 g, 1.1 mmol) were added to the reaction mixture at 2 and 4 h after initiation of the reaction which was allowed to proceed for 6 h in total reaction time. The reaction mixture was then cooled to 25°C, and the solids (PhHgI, NaF and unreacted NaI) were removed by filtration. Removal of the solvent *in vacuo* and separation of the mixture by preparative silica gel TLC using EtOAc:hexane (1:3, v/v) as developing solvent afforded **127** as a brown oil (R$_f$ = 0.35, 0.230 g, 53%).

Similarly, compound **128** was synthesized by refluxing PhHgCCl$_2$F (1.0 g, 2.6 mmol) with **91b** (0.5 g, 1.1 mmol) in dimethoxyethane (20 mL). The product was isolated by preparative TLC using EtOAc:hexane (1:3, v/v) as development solvent to afford **128** as an oil (Rf = 0.55, 0.260 g, 64%). The spectral data for **127** and **128** are presented in Table 9 and the physical data is summarized in Table 10.

4.4.4.7.0.0. Methyl 2-methyl-2-[2-(4-benzoyl-5-phenyl-7-halo-2-azabicyclo[4.1.0]hept-3-ene)]acetates (129, 7-Br; 130, 7-Cl; 131, 7-F)

To a stirred solution of **125** (0.2 g, 0.4 mmol) and a catalytic amount of azobisisobutyronitrile (AIBN), tri-*n*-butyltin hydride (0.12 g, 0.44 mmol) in benzene (20 mL) was

added in aliquots over 8 h and the reaction mixture was refluxed at 90°C overnight to afford an oil after removal of solvent *in vacuo*. The residue obtained was washed with pentane (5 × 20 mL) to remove any remaining n-Bu$_3$SnH. The product was purified by silica gel column chromatography using hexane:ether (70:30, v/v) as eluent to afford **129** in 35% yield as an oil (R$_f$ = 0.55)

Similar reactions employing **126** and **128** afforded **130** (R$_f$ = 0.62, 31%) and **131** (R$_f$ = 0.7, 45%) respectively as oils. The spectral data for **129-131** are presented in Table 9 and the physical data is presented in Table 10.

4.4.4.8.0.0. 2-Methyl-2-[2-(4-benzoyl-5-phenyl-7,7-dibromo-2-azabicy-clo[4.1.0]hept-3-ene)]acetamide (132)

To a solution of **125** (0.3 g, 0.6 mmol) in methanol (10 mL), a saturated solution of ammonia in methanol (5 mL) was added and the reaction carried out according to General Procedure C. A brownish oil was obtained which was purified by preparative silica gel TLC using EtOAc:hexane (3:1, v/v) as development solvent. The band having R$_f$ = 0.3 was extracted with ethyl acetate (20 mL) to give a yellow oil which crystallized from hexane:ether to give **132** as a solid (0.15 g, 50%). The spectral data for compound **132** is presented in Table 9 and the physical data is presented in Table 10.

4.4.4.9.0.0. 3-Benzoyl-4-phenyl-1-{1-methyl-2-oxo-2-[(4S)-4-iso-propyl-2-oxazolidinonyl]ethyl}-1,4-dihydropyridine (135)

To a solution of (4S)-(-)-4-isopropyl-2-oxazolidinone (2.71 g, 21 mmol) in dry THF (30 mL), stirred at -78°C under a nitrogen atmosphere, was added a solution of n-butyl-lithium (1.34 g, 21 mmol). The reaction mixture was stirred for 30 min at -78°C prior to the addition of **133** which was prepared from **98a** (0.5 g, 1.5 mmol) and BTBO, according to the procedure reported by Takeda *et al.*[221] Suspended BTBO (460 mg, 1 mmol) in acetonitrile (10 mL) was added to a solution of **98a** (0.5 g, 1.5 mmol) and the

reaction mixture was stirred for 1 h at room temperature, after which it was added dropwise to 134 and the resulting mixture stirred for 4 h. After evaporation of the solvent under reduced pressure, the residue was extracted with ethyl acetate. The organic layer was successively washed with 4% aqueous $NaHCO_3$, HCl, water, and brine, and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residual brownish oil was purified by silica gel preparative TLC using EtOAc:hexane (1:1, v/v). The band having R_f = 0.6 was isolated by extraction with ethyl acetate (30 mL) and removal of the solvent in vacuo afforded 135 as an oil (0.2 g, 33%). ^{1}H NMR (CDCl$_3$) δ: 7.2-7.6 (m, 10H, phenyl hydrogens), 7.08 [7.06] (d, $J_{2,6}$ = 1.5 Hz, 1H, H-2), 6.04 (d, $J_{2,6}$ = 1.5 Hz of d, $J_{5,6}$ = 7.7 Hz, 1H, H-6), 5.28 (two overlapping q, J_{CH,CH_3} = 7.1 Hz, 1H, CH$_3$C$\underline{H}$), 5.1 (two d, $J_{5,6}$ = 7.7 Hz of d, $J_{4,5}$ = 4.9 Hz, 1H total, H-5), 4.88 (d, $J_{4,5}$ = 4.9 Hz, 1H, H-4), 4.2-4.5 (m, 3H, oxazolidinone, -C$\underline{H}$H, -CH$\underline{H}$, -NC$\underline{H}$), 2.28-2.44 (m, 1H, (CH$_3$)$_2$C$\underline{H}$), 1.54 [1.56] (d, $J_{CH_3,CH}$ = 7.1 Hz, 3H, CH$_3$CH), 0.8-1.0 (m, 6H, (CH$_3$)$_2$CH). Absorptions of the minor diastereomers are indicated in brackets.

4.4.4.10.0.0. N-[(1S)-1-phenethyl]-2-methyl-2-[1-(3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl)]acetamide Diastereomers (137a and 137b)

A suspension of BTBO (0.46 g, 1 mmol) in acetonitrile (10 mL) was added to a solution of 108 (0.43 g, 1 mmol) and pyridine (0.079 g, 1 mmol) in acetonitrile (20 mL) and the resulting solution was stirred at 25°C for 1 h. A solution of (S)-(-)-α-methyl-benzylamine (0.138 g, 1 mmol) and triethylamine (0.15 g, 1 mmol) in acetonitrile (10 mL) was added. The reaction mixture was stirred for 4 h, the solvent removed in vacuo and the residue was extracted with ethyl acetate (15 mL). The organic layer was succesively washed with 4% aqueous $NaHCO_3$ (10 mL), 1 N HCl (10 mL), water (10 mL), and brine (10 mL) prior to drying with Na_2SO_4. The solvent was removed in vacuo and the residue obtained was purified by preparative silica gel TLC using hexane:EtOAc (1:1, v/v) as

development solvent. Extraction of the two bands having R_f 0.65 and 0.5 afforded **137a** and **137b** respectively as gummy solids. ^{1}H NMR data for **137a** and **137b** are presented in Table 11.

4.4.4.11.0.0. (S)-Methoxycarbonyl-α-methyl methyl 2-{1-[3,5-dibenzoyl-4-phenyl-1,4-dihydropyridyl]}acetate (138)

A suspension of BTBO (0.46 g, 1 mmol) in acetonitrile (10 mL) was added to a solution of **101** (0.436 g, 1 mmol) and pyridine (0.079 g, 1 mmol) in acetonitrile (10 mL) and the reaction mixture was stirred for 1 h at 25°C. A solution of (S)-(-)-methyl lactate (0.104 g, 1 mmol) and DMAP (0.134 g, 1 mmol) in acetonitrile (10 mL) was added. The reaction mixture was allowed to proceed for 8 h at 25°C prior to addition of water (10 mL). Extraction with ethyl acetate (3 × 20 mL) and isolation of the product, as described for compound **137**, gave a residue which was purified by preparative silica gel TLC using EtOAc:hexane (1:1, v/v) as development solvent. Isolation of the band having $R_f = 0.63$, extraction with ethyl acetate (20 mL) and evaporation of the solvent afforded **138** (0.08 g, 12%) as an oil. ^{1}H NMR (CDCl$_3$) δ: 7.1-7.6 (m, 15H, phenyl hydrogens), 6.94 and 6.98 (two d, $J_{2,6} = 1.5$ Hz, 1H each, H-2, H-6), 5.69 (s, 1H, H-4), 5.24 (q, $J_{CH_3,C4} = 7.2$ Hz, 1H, -OCH(CH$_3$)CO$_2$CH$_3$), 4.2 (q, $J_{CH,CH_3} = 7.2$ Hz, 1H, NCHCH$_3$), 3.76 and 3.74 (two s, 3H total, OCH$_3$), 1.55-1.65 (m, 6H, NCHCH$_3$ and -OCHCH$_3$).

4.4.4.12.0.0. 3-Benzoyl-4-phenylpyridine (140)

A solution of 3-benzoylpyridine (2 g, 10.9 mmol, **87**) and cuprous iodide (0.3 g, 1.6 mmol) in dry THF (60 mL) was cooled to -78°C (dry ice/acetone). Methyl chloroformate (1.02 g, 10.9 mmol) was added dropwise to the vigorously stirred solution under nitrogen. After 30 min a solution of phenylmagnesium chloride (8 mmol) in dry THF (10 mL) was

was added and the organic layer was washed with 10 mL portions of 20% NH4Cl/NH4OH (50:50, v/v), water and brine. After drying with anhydrous magnesium sulphate, the solution was concentrated to give the crude dihydropyridine (139) as a viscous oil, R_f = 0.45 (1.3 g, 38.9%).

The crude dihydropyridine 139 (1.3 g, 4.1 mmol) was refluxed in toluene (50 mL) with o-chloranil (1.02 g, 4.2 mmol) for 5 h, the solvent was evaporated and the brownish oil obtained was chromatographed on a silica gel column using EtOAc:hexane (15:85, v/v) as eluant to afford 140 as a yellow oil (0.9 g, 83%).

^{1}H NMR (CDCl3) δ 8.76 (d, $J_{5,6}$ = 5 Hz, 1H, H-6), 8.7 (s, 1H, H-2), 7.64 (d, $J_{5,6}$ = 5 Hz, 1H, H-5), 7.2-7.46 (m, 10H, phenyl hydrogens).

4.4.4.13.0.0. Attempted Synthesis of (4S)- or (4R)-Methyl 2-methyl-2-[1-(3-benzoyl-4-phenyl-1,4-dihydropyridyl)]acetate (143)

To a solution of diisopinocampheylchloroborane (142) (0.45 g, 1.4 mmol) prepared according to the reported procedure,[209] in dry THF (10 mL) was added 141 (0.55 g, 1.3 mmol) under a nitrogen atmosphere. The reaction, which was monitored by TLC, was finished in 18 h. The solvent was removed *in vacuo* and the residue obtained was chromatographed using a silica gel column using EtOAc:hexane (30:70, v/v) as eluent to afford a gummy oil (0.2 g, 35%). The ^{1}H NMR spectrum of the isolated product indicated that it was not the desired compound 143.

4.4.4.14.0.0. Methyl 2-methyl-2-[1-(3-phenoxy-4-phenyl-1,4-dihydropyridyl)acetate (146)

A solution of 3-phenoxypyridine (1 g, 5.8 mmol; 144) and methyl DL-2-bromopropionate (1.2 g, 7.6 mmol) in anhydrous acetone (20 mL) was refluxed for 24 h to give a brown solid which was washed with ether (3 × 20 mL) to afford the 3-phenoxypyridinium salt 145 (1.1 g, 80%). A solution of 145 (1.0 g, 4.2 mmol) in dry THF (20 mL) and

cuprous iodide (0.05 g, 0.3 mmol) was stirred under a nitrogen atmosphere until the solution became homogeneous. The reaction mixture was cooled to -23°C using a dry ice-CCl4 bath. Phenylmagnesium chloride (7.6 mmol) in THF (5 mL) was added dropwise and the reaction mixture was retained at -23°C for 30 min. The reaction mixture was allowed to warm to 25°C, the mixture was stirred for 1.5 h and then a saturated aqueous solution of NH4Cl (5 mL) was added to quench the reaction. Diethyl ether (20 mL) was added, the organic phase was separated and washed successively with a solution of 30% NH4OH:saturated aqueous NH4Cl (3:1, v/v) (10 mL). The organic phase was dried (MgSO4) and the solvent was removed *in vacuo*. Purification of the brownish oil obtained was carried out using both silica gel and neutral alumina column chromatography during which the compound underwent extensive decomposition. The ^{1}H NMR spectrum of the impure product obtained exhibited the following spectrum: ^{1}H NMR (CDCl3) δ 6.8-7.3 (m, 11H, phenyl hydrogens, H-6), 6.02 (s, 1H, H-2), 4.65-4.72 (m, 1H, H-5), 4.46 (d, $J_{4,5}$ = 4.8 Hz, 1H, H-4), 3.82-4.02 (m, 1H, CH-Me), 3.78 (s, 3H, OMe), 1.44 and 1.46 (two d, J_{CH,CH_3} = 7.2 Hz, 3H, CHMe).

4.4.5.0.0.0. **Ethyl 2-[3-(1-phenoxycarbonyl-4-substituted-1,4-dihydropyridyl)]acetates (149-152), Ethyl 2-methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (146) and Ethyl 2-[3-(1-methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (147). General Procedure D**

Ethyl 3-pyridylacetate (0.55 g, 3.15 mmol, R^1 = H, 147) in dry THF (30 mL) was stirred at 25°C under a nitrogen atmosphere, CuI (0.028 g, 0.2 mmol) was added, followed by the addition of phenyl chloroformate (0.57 g, 3.7 mmol). The reaction mixture was cooled to -23°C using a dry ice-CCl4 bath and phenylmagnesium chloride (0.47 g, 3.46 mmol) in THF (0.65 mL) was added dropwise with stirring over a period of 10 min. The reaction mixture was stirred for 15 minutes more at the same temperature and

the reaction mixture was allowed to warm to 25°C with continued stirring for 1 h. A saturated solution of NH₄Cl (5 mL) was added to quench the reaction, followed by addition of ether (30 mL). This mixture was washed with 20% NH₄Cl-NH₄OH (50:50, v/v, 2 × 20 mL), water (2 × 10 mL) and then brine (10 mL). The organic fraction was dried (MgSO₄), filtered and the solvent was removed *in vacuo* to give a crude oily product which was purified by silica gel column chromatography using EtOAc:hexane (15:85, v/v) as eluent to afford **149** (1.1 g, 96%) as an oil. The spectral data are presented in Table 12 and the physical data are presented in Table 13.

Similarly, compounds **150**, **151**, and **152** were synthesized in yields of 75%, 82%, and 64%, respectively as oils after purification by silica gel column chromatography using EtOAc:hexane (15:85, v/v) as eluent.

Ethyl 2-methyl-3-pyridylacetate (0.55 g, 3.7 mmol, R¹ = Me, **148**) was quaternized with phenyl chloroformate (0.57 g, 3.7 mmol) and reduced with phenylmagnesium chloride (3.46 mmol) to give a brownish oil after work-up (General Procedure D). The oil was purified by silica gel column chromatography using EtOAc:hexane (15:85, v/v) as eluent to afford **153**, Rf = 0.45 (0.9 g, 64%) as an oil.

Compound **154** was synthesized from ethyl 3-pyridylacetate (0.55 g, 3.15 mmol), methyl chloroformate (0.3 g, 3.15 mmol) and phenylmagnesium chloride (3.46 mmol) according to General Procedure D. The product was purified by silica gel column chromatography using EtOAc:hexane (15:85, v/v) as eluent to afford **154** as an oil, Rf = 0.48 (0.85 g, 87%).

4.5.0.0.0.0. DETERMINATION OF THE pKₐ VALUE FOR 2-METHYL-2-[1-(3-BENZOYL-4-PHENYL-1,4-DIHYDROPYRIDYL)]-ACETIC ACID (98a)

aliquot of this solution was placed in a 100 mL beaker, which in turn was placed in a constant temperature circulating water bath at 25.0 ± 0.5°C. The beaker was then covered with a rubber cork fitted with a thermometer, pH microelectrode, burette, and nitrogen inlet and outlet tubes.

Purified nitrogen (freed from oxygen and carbon dioxide by passage through an alkaline solution of pyrogallol) was continuously passed through the solution to be titrated to maintain an inert atmosphere. To this solution was added carbonate-free 0.10 M methanolic potassium hydroxide (as the titrant, obtained from Anderson Laboratories, Inc., USA) in ter equal portions, each a tenth of an equivalent and the pH was recorded as soon as equilibrium was reached after each addition. The pH meter was equipped with a combined microelectrode which was calibrated before use each time, with two buffer solutions of pH 4.00 and 10.00 ± 0.01 (from BHD Chemicals). The pKa was calculated using the Henderson-Hasselbach equation and the results are presented in Table 8.

4.6.0.0.0.0. ANALGESIC ACTIVITY ASSAY

Analgesic activity was determined using the method described by Fukawa et al.[239] Five male Sprague-Dawley rats, weighing between 120-150 g, were used for each test dose. The number of writhing responses induced in each rat after injection of a 4% w/v sodium chloride solution at a dose of 1 mL/kg ip were recorded two hours prior to administration of the test compound. The test compound was administered as a solution in physiological saline solution (0.9%, w/v aqueous NaCl) solubilized with 10% v/v Tween 80.

After administration of the test dose, each rat was again injected with 4% sodium chloride (1 mL/kg ip) at intervals of 30 and 60 minutes from the time the test compound was administered. The number of writhing responses elicited at each time was recorded. The lower of the two responses at the 30 or 60 minute interval was subtracted from the initial number of control writhing responses and the percentage inhibition, which is a

measure of analgesic activity, was calculated using the formula shown below. Single dose test results are reported as the mean % inhibition ± standard error of the mean (SEM) for five animals.

$$\% \text{ Inhibition } = \frac{W_1 - W_2}{W_1} \times 100$$

Where W_1 is the number of initial (control) writhing responses and W_2 is the lower of the numbers of writhing responses at either 30 or 60 minutes.

4.7.0.0.0.0. ANTIINFLAMMATORY ACTIVITY ASSAY

Antiinflammatory activity was measured using the carrageenan-induced rat paw edema assay described by Winter et al.[241] Four male Sprague-Dawley rats weighing 100-120 g were used in each group. Test compounds were administered as suspensions in water, using gum accaia as the suspending agent. The test compound was administered orally at a dose of 100 mg/kg one hour prior to subcutaneous injection of carrageenanan (0.1 mL, 1%) in physiological saline under the plantar skin of the right-hand paw. Control experiments were identical except the vehicle did not contain a test compound. The volume of the injected paw was measured immediately (V^1) and at 3 h and 5 h (V^2) and the % inhibition of inflammation, which is a measure of antiinflammatory activity, was calculated using the formula shown below.

$$\% \text{ Inhibition } = \frac{V^2 - V^1}{V^1} \times 100$$

4.8.0.0.0.0. ULCEROGENIC LIABILITY ASSAY

Six male Sprague-Dawley rats weighing 100-120 g, fasted for 24 h, were sacrificed 8 h after oral administration of the selected test compounds 91a, 98a or 99d at doses of 300 mg/kg, 600 mg/kg and 1200 mg/kg. The stomach, sternum and duodenum were removed and macroscopically and microscopically assessed for the presence or absence of lesions

the animals). A chronic ulcerogenesis assay was also performed on compound **98a** by administration of 600 mg/kg po twice daily for six days. The ulcerogenic liability assay was also used to determine the UD_{50} for the reference drug Ibuprofen.

5.0.0.0.0.0. REFERENCES

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