Development of a Stereoselective and Chemoselective Approach to *trans*-2,3-Disubstituted-4-chromanones

R. J. Chambers* and A. Marfat

Department of Medicinal Chemistry, Pfizer Central Research, Groton, CT 06340

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A direct synthesis of chromanones **10** and **11** was achieved in five steps from acetophenone **1** in an overall yield of 37% and 53% respectively. The requisite 2,3-*trans* stereochemistry in chromanone **10** and **11** was set by a chemoselective and stereoselective conjugate reduction of chromones **8** and **9**.

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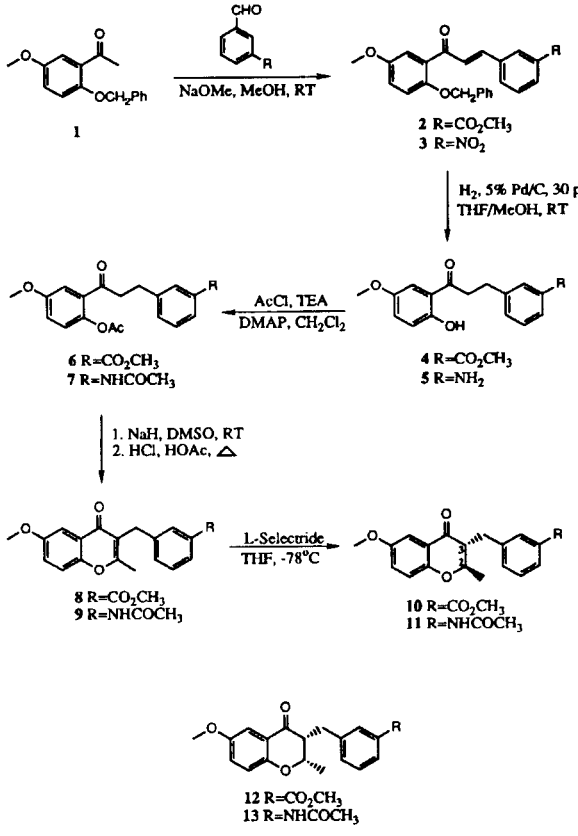
During the course of preparing analogs for biological evaluation in a series of 6-methoxy-4-chromanones, we sought to prepare analogs in which a 2-methyl and a 3-benzyl group were *trans* disposed. Furthermore, we required that the benzyl group would bear either an ester or amide function in the meta position as in chromanones **10** and **11** (Scheme 1). We therefore sought a synthesis which would be direct, chemoselective and stereoselective, characteristics which established routes lack [1]. Such an approach could potentially be extended to natural products possessing a *trans*-2,3-dimethylchromanone structure such as tomentolide-A and Inophyllolide which show anti-inflammatory and anticonvulsant activity respectively [2].

The *2,3-trans* stereochemistry in **10** and **11** might be achieved by a stereoselective conjugate hydride reduction of chromones **8** and **9** since reduction of a 2-methyl-3-phenyl-4-chromone with diisobutylaluminum hydride affords the corresponding 4-chromanone as a 1:2 *cis/trans* mixture [3]. The presence of an ester or amide function as in 4-chromones **8** and **9** would preclude the use of diisobutylaluminum hydride, since esters and amides undergo reduction with this reagent [4]. Lithium tri-*sec*-butylborohydride (L-Selectride®) has been shown to be a highly stereoselective reducing agent [5] and affects chemoselective conjugate reduction of enones in the presence of esters [6]. The requisite chromones **8** and **9** could result from a Claisen condensation of keto esters **6** and **7** followed by cyclization of their respective β-diketone intermediates since condensation of 2-acetoxy propiophenone and subsequent cyclization has been shown to afford 2,3-dimethyl-4-chromone [7]. Keto esters **6** and **7** were to be secured in a straightforward alkylation and acylation sequence from acetophenone **1** [8].

Scheme 1



Aldol condensation of acetophenone **1** with 3-carbomethoxybenzaldehyde [9] or 3-nitrobenzaldehyde in the presence of sodium methoxide in methanol at ambient temperature afforded enones **2** (90%) and **3** (98%) respectively. Hydrogenation of **2** or **3** at 30 psi over 5% palladium on charcoal catalyst in methanol/tetrahydrofuran (1:1) at ambient temperature gave the corresponding hydroxy ketones **4** (80%) and **5** (90%). Acetylation of **4** or **5** with acetyl chloride in the presence of triethylamine and catalytic dimethylaminopyridine in methylene chloride at 0° yielded keto esters **6** (97%) and **7** (88%) respectively. Claisen condensation of **6** or **7** with sodium hydride in dimethyl sulfoxide at ambient temperature and subsequent cyclization with hydrochloric acid in refluxing glacial acetic acid afforded the corresponding chromones **8** (67%) and **9** (85%). Reduction of **8** or **9** with L-Selectride® in tetrahydrofuran at -78° gave chromanones **10** (79%) and **11** (80%) respectively.

The stereochemistry in chromanones **10** and **11** were assigned as *trans* since their nmr spectra showed their C-2 and C-3 protons possessing a large coupling constant ($J_{2,3}$ =13 Hz) in accordance with other *trans*-2,3-disubstituted-4-chromanones [10]. The stereochemistry in chromanone **11** was definitively shown to be *trans* by single crystal X-ray crystallography (Figure 1).

A semiempirical molecular orbital calculation [11] comparing the ground state energy of *trans*-chromanone

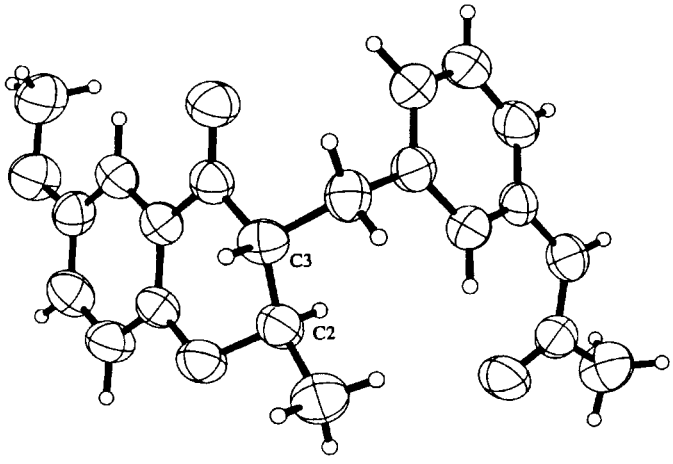


Figure 1. Molecular Structure of 11.

Table 1

Single Crystal X-Ray Crystallographic Analysis of 11

A. Crystal Parameters	
formula	$C_{20}H_{21}NO_4$(339.4)
crystallization medium	acetone
crystal size, mm	0.12 X 0.14 X 0.16
cell dimensions	a = 5.114 (2) Å
	b = 35.382 (8) Å
	c= 9.803 (3)
	α = 90.0°
	β = 104.27 (2)°
	γ = 90.0°
	V = 1719.2 (7) Å^3
space group	$P2_1/c$
molecules/unit cell	4
density calcd, g/cm^3	1.311
linear absorption factor, mm^{-1}	0.745
B. Refinement Parameters	
number of reflections	1758
nonzero reflections (I>3.0σ)	1249
R-index[a]	5.68%
GOF[b]	1.39
secondary extinction factor[C], χ	NONE

a R-index = Σ||Fol-|Fcll/Σ1Fol

b GOF = $[\Sigma w(Fo^2-Fc^2)^2/(m-s)]^{1/2}$
where $w = [\sigma^2(F) + |g|F2]^{-1}$ g = 0.0010

c $F^* = F[1+0.002\chi F^2/\sin(2\theta)]^{-1/4}$

Table 2

Bond Lengths (Å) and Bond Angles (°)

O(1)-C(2)	1.444 (6)	O(1)-C(8A)	1.365 (7)
C(2)-C(2A)	1.509 (8)	C(2)-C(3)	1.509 (6)
C(3)-C(4)	1.512 (7)	C(3)-C(9)	1.539 (6)
C(4)-O(4)	1.220 (6)	C(4)-C(4A)	1.462 (7)
C(4A)-C(5)	1.406 (7)	C(4A)-C(8A)	1.371 (7)
C(5)-C(6)	1.374 (7)	C(6)-C(7)	1.383 (8)
C(6)-O(19)	1.370 (7)	C(7)-C(8)	1.374 (8)
C(8)-C(8A)	1.390 (7)	C(9)-C(10)	1.510 (8)
C(10)-C(11)	1.400 (7)	C(10)-C(15)	1 392 (8)
C(11)-C(12)	1.378 (8)	C(12)-C(13)	1.386 (8)
C(12)-N(16)	1.409 (7)	C(13)-C(14)	1.375 (8)
C(14)-C(15)	1.380 (9)	N(16)-C(17)	1.354 (7)
C(17)-O(17)	1.217 (8)	C(17)-C(18)	1.493 (8)
O(19)-C(20)	1.390 (7)		

Table 2 (continued)

C(2)-O(1)-C(8A)	114.6 (4)	O(1)-C(2)-C(2A)	104.9 (4)
O(1)-C(2)-C(3)	111.3 (4)	C(2A)-C(2)-C(3)	114.4 (4)
C(2)-C(3)-C(4)	111.8 (4)	C(2)-C(3)-C(9)	115.3 (4)
C(4)-C(3)-C(9)	112.2 (4)	C(3)-C(4)-O(4)	121.5 (4)
C(3)-C(4)-C(4A)	115.7 (4)	O(4)-C(4)-C(4A)	122.8 (5)
C(4)-C(4A)-C(5)	119.9 (4)	C(4)-C(4A)-C(8A)	120.6 (5)
C(5)-C(4A)-C(8A)	119.4 (4)	C(4A)-C(5)-C(6)	120.1 (5)
C(5)-C(6)-C(7)	119.5 (5)	C(5)-C(6)-O(19)	125.4 (5)
C(7)-C(6)-O(19)	115.1 (4)	C(6)-C(7)-C(8)	121.0 (5)
C(7)-C(8)-C(8A)	119.3 (5)	O(1)-C(8A)-C(4A)	122.8 (4)
O(1)-C(8A)-C(8)	116.6 (4)	C(4A)-C(8A)-C(8)	120.6 (5)
C(3)-C(9)-C(10)	115.0 (4)	C(9)-C(10)-C(11)	121.9 (5)
C(9)-C(10)-C(15)	119.9 (4)	C(11)-C(10)-C(15)	118.1 (5)
C(10)-C(11)-C(12)	121.4 (5)	C(11)-C(12)-C(13)	119.3 (5)
C(11)-C(12)-N(16)	123.1 (5)	C(13)-C(12)-N(16)	117.5 (5)
C(12)-C(13)-C(14)	120.1 (6)	C(13)-C(14)-C(15)	120.6 (5)
C(10-C(15)-C(14)	120.4 (5)	C(12)-N(16)-C(17)	128.4 (5)
N(16)-C(17)-O(17)	123.5 (5)	N(16)-C(17)-C(18)	114.2 (6)
O(17)-C(17)-C(18)	122.2 (5)	C(6)-O(19)-C(20)	118.4 (4)

Table 3

Atomic Coordinates (x10^4) and Equivalent Isotropic Displacement Coefficients (Å^{2}x10^3)

	x	y	z	U (eq)
O(1)	3240 (7)	6145 (1)	957 (3)	61 (2)
C(2)	4689 (11)	6353 (1)	2178 (5)	57 (2)
C(2A)	6061 (12)	6670 (2)	1595 (6)	78 (3)
C(3)	6585 (10)	6099 (1)	3203 (5)	52 (2)
C(4)	5168 (10)	5751 (1)	3555 (6)	51 (2)
O(4)	6059 (7)	5573 (1)	4635 (4)	68 (2)
C(4A)	2744 (10)	5637 (1)	2499 (5)	47 (2)
C(5)	1284 (10)	5317 (1)	2731 (5)	53 (2)
C(6)	-947 (11)	5202 (2)	1723 (6)	58 (2)
C(7)	-1705 (11)	5399 (2)	469 (6)	68 (3)
C(8)	-284 (12)	5710 (2)	221 (6)	65 (2)
C(8A)	1939 (11)	5830 (2)	1255 (5)	51 (2)
C(9)	8270 (10)	6297 (1)	4529 (5)	54 (2)
C(10)	6661 (10)	6456 (1)	5498 (5)	51 (2)
C(11)	5282 (10)	6800 (1)	5219 (5)	54 (2)
C(12)	3724 (10)	6935 (1)	6076 (5)	50 (2)
C(13)	3534 (11)	6727 (2)	7245 (5)	63 (2)
C(14)	4914 (13)	6391 (2)	7550 (6)	71 (3)
C(15)	6417 (12)	6251 (2)	6672 (6)	65 (2)
N(16)	2223 (9)	7272 (1)	5801 (5)	60 (2)
C(17)	1162 (11)	7439 (2)	4543 (7)	58 (2)
O(17)	1632 (8)	7335 (1)	3444 (4)	77 (2)
C(18)	-774 (12)	7751 (2)	4599 (6)	80 (3)
O(19)	-2556 (8)	4900 (1)	1840 (4)	77 (2)
C(20)	-2073 (13)	4711 (2)	3119 (6)	88 (3)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

10 to *cis*-chromanone **12** showed an energy difference of less than 1 Kcal./mole. This result was borne out in the reduction of chromone **8** with L-Selectride® in tetrahydrofuran at 0° affording *trans*-chromanone **10** and *cis*-chromanone **12** in a 3:2 ratio respectively. Similarly, epimerization of *trans*-chromanones **10** or **11** with sodium methoxide in methanol at ambient temperature also yielded a mixture of chromanones **10** and **12** or **11** and **13**

in a 3:2 ratio respectively. However, reduction of chromones **8** or **9** with L-Selectride® in tetrahydrofuran at -78° gave exclusively *trans*-chromanones **10** or **11** respectively. The C-2 proton at δ 4.62 (dq, $J_{2,3}$ = 4 Hz) of the *cis*-chromanones **12** or **13** [12] could not be detected in the nmr spectra of the crude reaction mixture. Thus the high stereoselectivity in the conjugate reduction of chromones **8** or **9** presumably arises from the kinetic protonation of the intermediate enolate.

A direct route to chromanones **10** and **11** has been secured in five steps from acetophenone **1** in an overall yield of 37% and 53% respectively, utilizing a chemoselective and stereoselective conjugate reduction of chromones **8** or **9** to set the requisite *2,3-trans* stereochemistry. The extension of this methodology to natural products possessing a *trans*-2,3-disubstituted chromanone structure is anticipated.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker AC-300 spectrometer. Mass spectra were determined on a Hewlett-Packard 5989A mass spectrometer. Infrared spectra were acquired using either a Nicolet 510 FT spectrometer or a Perkin Elmer 283B spectrophotometer. Elemental analysis was performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

3-[3-(2-Benzyloxy-5-methoxyphenyl)-3-oxopropenyl]benzoic Acid Methyl Ester (**2**).

To a mechanically stirred solution of 19.5 g (0.076 mole) of **1** in 150 ml of absolute methanol at ambient temperature was added 4.1 g (0.076 mole) of sodium methoxide. After 20 minutes, 12.5 g (0.076 mole) of 3-carbomethoxybenzaldehyde was added and the reaction mixture was stirred at ambient temperature for 18 hours. The resulting yellow precipitate was filtered, washed with absolute methanol, then dried *in vacuo* to yield 27.4 g (90%) of **2**, mp 98-100°; ^{1}H-nmr (deuteriochloroform): δ 3.80 (s, 3H), 3.90 (s, 3H), 5.10 (s, 2H), 7.05 (m, 2H), 7.25 (m, 4H), 7.40 (m, 3H), 7.55 (d, J = 8 Hz, 1H), 7.65 (dd, J = 16 Hz, 2H), 8.05 (d, J = 8 Hz, 1H), 8.15 (s, 1H); ms: (chemical ionization) m/z 403 (M^++1, 100); ir (potassium bromide): 1710, 1660 (CO) cm^{-1}

Anal. Calcd. for $C_{25}H_{22}O_5$: C, 74.61; H, 5.51. Found: C, 74.16; H, 5.29.

1-(2-Benzyloxy-5-methoxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-one (**3**).

To a mechanically stirred solution of 13.5 g (0.053 mole) of **1** in 100 ml of absolute methanol at ambient temperature was added 2.84 g (0.053 mole) of sodium methoxide. After 20 minutes, 8.0 g (0.053 mole) of 3-nitrobenzaldehyde was added and the reaction mixture was stirred at ambient temperature for 18 hours. The resulting precipitate yellow was filtered, washed with absolute methanol, then dried *in vacuo* to afford 20.2 g (98%) of **3**, mp 108-110°; ^{1}H-nmr (deuteriochloroform): δ 3.83 (s, 3H), 5.11 (s, 2H), 7.05 (m, 2H), 7.25 (m, 3H), 7.40 (m, 4H), 7.57 (d, J = 7 Hz, 1H), 7.63 (s, 2H), 8.15 (d, J = 8 Hz, 1H), 8.23 (s, 1H); ms: (chemical ionization) m/z 390 (M^++1, 100); ir (potassium bromide): 1660 (CO) cm^{-1}.

Anal. Calcd. for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60. Found: C, 71.07; H, 4.47; N, 3.46.

3-[3-(2-Hydroxy-5-methoxyphenyl)-3-oxopropyl]benzoic Acid Methyl Ester (**4**).

A mixture of 27.4 g (0.068 mole) of **2** and 5.5 g of 5% palladium on charcoal in 300 ml of tetrahydrofuran and 300 ml absolute methanol was shaken in a Parr apparatus under 20 psi hydrogen at ambient temperature for 3 hours. The reaction mixture was filtered through celite and filtrate was evaporated *in vacuo* to give an oil. Column chromatography of the oil on silica gel eluting with ethyl acetate:hexanes (1:4, v/v) afforded a solid which was recrystallized from ether:hexanes to yield 17.1 g (80%) of **4**, mp 77-79°; ^{1}H-nmr (deuteriochloroform): δ 3.12 (t, J = 8 Hz, 1H) 3.35 (t, J = 8 Hz, 2H), 3.77 (s, 3H), 3.92 (s, 3H), 6.94 (d, J = 9 Hz, 1H), 7.10 (m, 2H), 7.26 (s, 1H), 7.38 (t, J = 8 Hz, 1H), 7.46 (d, J = 8 Hz, 1H), 7.90 (d, J = 8 Hz, 1H), 7.94 (s, 1H), 11.85 (s, 1H); ms: (chemical ionization) m/z 332 (M^++18, 100); ir (potassium bromide): 3400, 3240 (OH), 1710, 1640, 1610 (CO) cm^{-1}.

Anal. Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.70; H, 5.74.

3-(3-Aminophenyl)-1-(2-hydroxy-5-methoxyphenyl)propan-1-one (**5**).

A mixture of 15.0 g (0.039 mole) of **3** and 1.5 g of 5% palladium on charcoal in 300 ml of tetrahydrofuran and 200 ml of absolute methanol was shaken in a Parr apparatus under 10 psi hydrogen at ambient temperature for 3 hours. The reaction mixture was filtered through celite and the filtrate was evaporated *in vacuo* to yield an oil. Column chromatography of the oil on silica gel eluting with ethyl acetate:hexanes (1:2, v/v) gave 9.42 g (90%) of **5** as an oil; ^{1}H-nmr (deuteriochloroform): δ 2.98 (t, J = 8 Hz, 2H), 3.28 (t, J = 8 Hz, 2H), 3.65 (s, br, 2H), 3.77 (s, 3H), 6.65 (m, 3H), 6.93 (d, J = 9 Hz, 1H), 7.10 (m, 3H), 11.95 (s, 1H); ms: (chemical ionization) m/z 289 (M^++18, 38), 272 (M^++1, 100); ir (chloroform): 3671 (NH), 3460, 3373 (OH), 1642, 1616 (CO) cm^{-1}.

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.51; H, 6.30; N, 4.97.

3-[3-(2-Acetoxy-5-methoxyphenyl)-3-oxopropyl]benzoic Acid Methyl Ester (**6**).

To a stirred solution of 29.0 g (0.092 mole) of **4**, 28 ml (0.200 mole) of triethylamine and 1.12 g (0.009 mole) of dimethylaminopyridine in 450 ml of methylene chloride at 0° was added dropwise 7.2 ml (0.101 mmole) of acetyl chloride. The reaction mixture was allowed to warm to ambient temperature over 1 hour, then the volume was reduced *in vacuo*. The concentrate was diluted with ethyl acetate and washed successively with 1*N* hydrochloric acid, water, brine then dried (magnesium sulfate) and evaporated *in vacuo* to give an oil. Column chromatography of the oil on silica gel eluting with ethyl acetate: hexanes (1:3, v/v) afforded 31.7 g (97%) of **6**, mp 76-78"; ^{1}H-nmr (deuteriochloroform): δ 2.28 (s, 3H), 3.06 (t, J = 8 Hz, 2H), 3.21 (t, J = 8 Hz, 2H), 3.81 (s, 3H), 3.91 (s, 3H), 7.02 (s, 2H), 7.21 (s, 1H), 7.40 (m, 2H), 7.90 (m, 2H); ms: (chemical ionization) m/z 374 (M^++18, 100); ir (potassium bromide): 1760, 1720, 1690 (CO) cm^{-1}.

Anal. Calcd. for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66. Found: C, 67.62; H, 5.42.

Acetic Acid 4-Methoxy-2-[3-(3-nitrophenyl)propionyl]phenyl Ester (**7**).

To a stirred solution of 16.5 g (0.061 mole) of **5**, 43 ml (0.305 mole) of triethylamine and 0.7 g (0.006 mole) of dimethylaminopyridine in 200 ml of methylene chloride at 0° was added dropwise 10.8 ml (0.152 mole) of acetyl chloride. The reaction mixture was allowed to warm to ambient temperature over 1 hour, then the volume was reduced *in vacuo*. The concentrate was diluted with ethyl acetate and washed successively with 1*N* hydrochloric acid, water, brine then dried (magnesium sulfate) and evaporated *in vacuo* to give an oil. Column chromatography of the oil on silica gel eluting with methanol:methylene chloride (1:40, v/v) afforded 19.0 g (88%) of **7** as an oil; ^{1}H-nmr (deuteriochloroform): δ 2.13 (s, 3H), 2.27 (s, 3H), 2.97 (t, J = 7 Hz, 2H), 3.17 (t, J = 8 Hz, 2H), 3.80 (s, 3H) 6.94 (d, J = 8 Hz, 1H), 7.02 (s, 2H), 7.25 (m, 3H), 7.38 (d, J = 8 Hz, 1H), 7.46 (s, br, 1H); ms: (chemical ionization) m/z 373 (M^+18, 12), 356 (M^+1,100); ir (chloroform): 3431 (NH), 1761, 1688 (CO) cm^{-1}.

Anal. Calcd. for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.28, H, 5.83; N, 3.54.

3-(6-Methoxy-2-methyl-4-oxo-4*H*-chromen-3-yl methyl)-benzoic Acid Methyl Ester (**8**).

To a stirred suspension of 5.5 g (0.138 mole) of 60% sodium hydride in 20 of ml dimethyl sulfoxide at 20° was added dropwise a solution of 16.3 g (0.046 mole) of **6** in 50 ml of dimethyl sulfoxide. The reaction mixture was stirred at 20° for 1 hour, then slowly poured into a stirred slurry of ice in an oxalic acid solution. The aqueous mixture was extracted with ethyl acetate which in turn was successively washed with water, brine then dried (magnesium sulfate) and evaporated *in vacuo* to give an oil. The oil was dissolved in 50 ml of glacial acetic acid and 1 ml of hydrochloric acid then refluxed for 30 minutes. The reaction mixture was poured into water, then extracted with ethyl acetate which in turn was successively washed with water, brine then dried (magnesium sulfate) and evaporated *in vacuo* to afford an oil. Column chromatography of the oil on silica gel eluting with ethyl acetate:hexanes (1:2, v/v) yielded 10.7 g (67%) of **8**, mp 117-119°; ^{1}H-nmr (deuteriochloroform): δ 2.42 (s, 3H), 3.90 (s, 6H), 4.00 (s, 2H), 7.25 (m, 1H), 7.35 (m, 2H), 7.50 (d, J = 8 Hz,1H), 7.60 (d, J = 2 Hz, 1H), 7.85 (d, J = 8 Hz, 1H), 7.90 (s, 1H); ms:(chemical ionization) m/z 356 (M^++ 18, 20), 339 (M^++1, 100); ir (potassium bromide): 1720, 1640, 1620 (CO) cm^{-1}.

Anal. Calcd. for $C_{20}H_{18}O_5$: C, 71.00; H, 5.36. Found: C, 71.05; H, 4.96.

N-[3-(6-Methoxy-2-methyl-4-oxo-4*H*-chromen-3-yl methyl)-phenyl]acetamide (**9**).

To a stirred suspension of 3.8 g (0.095 mole) of 60% sodium hydride in 50 ml of dimethyl sulfoxide at 20° was added dropwise to a solution of 9.6 g (0.027 mole) of **7** in 100 of ml dimethyl sulfoxide. The reaction mixture was stirred at 20° for 1 hour, then slowly poured into a slurry of ice in an oxalic acid solution. The aqueous mixture was extracted with ethyl acetate which in turn was successively washed with water, brine then dried (magnesium sulfate) and evaporated *in vacuo* to afford an oil. The oil was dissolved in 50 ml of glacial acetic acid and 1 ml of hydrochloric acid then refluxed for 30 minutes. The reaction mixture was poured into water, then extracted with ethyl acetate which in turn was successively washed with water, brine then dried (magnesium sulfate) and evaporated *in vacuo* to afford an oil. Column chromatography of the oil on silica gel eluting with methanol:methylene chloride (1:40, v/v) yielded 7.7 g (85%) of **9**, mp 176-178°; ^{1}H-nmr (deuteriochloroform): δ 2.11 (s, 3H), 2.40 (s, 3H), 3.74 (s, 3H), 3.90 (s, 2H), 7.00 (d, J = 8 Hz, 1H), 7.25 (m, 4H), 7.46 (d, J = 3 Hz, 1H), 7.55 (d, J = 8 Hz, 1H), 7.71 (s, br, 1H); ms: (chemical ionization) m/z 355 (M^++18, 70), 338 (M^++1, 100); ir (potassium bromide): 3320 (NH), 1680, 1620, 1590 (CO) cm^{-1}.

Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.22; H, 5.48; N, 4.22.

trans-3-(6-Methoxy-2-methyl-4-oxochroman-3-ylmethyl)-benzoic Acid Methyl Ester (**10**).

To a stirred solution of 1.30 g (3.80 mmoles) of **8** in 40 ml of dry tetrahydrofuran at -78° was added dropwise 4.2 ml (4.20 mmoles) of 1.0 *M* L-Selectride® in tetrahydrofuran. The reaction mixture was stirred at -78° for 30 minutes then quenched by the dropwise addition of an ammonium chloride solution. The mixture was poured into water and extracted with ethyl acetate which was in turn successively washed with water, brine then dried (magnesium sulfate) and evaporated *in vacuo* to give an oil. Column chromatography of the oil on silica gel eluting with ethyl acetate:hexanes (1:4, v/v) afforded 1.03 g (79%) of **10**, mp 94-97°; ^{1}H-nmr (deuteriochloroform): δ 1.37 (d, J = 7 Hz, 3H), 2.74 (dd, J = 7, 13 Hz, 1H), 3.10 (m, 2H), 3.79 (s, 3H), 3.90 (s, 3H), 4.37 (q, J = 7, 13 Hz, 1H), 6.88 (d, J = 9 Hz, 1H), 7.09 (dd, J = 3, 9 Hz, 1H), 7.30 (d, J = 3 Hz, 1H), 7.36 (t, J = 8 Hz, 1H), 7.45 (d, J = 8 Hz, 1H), 7.90 (m, 2H); ms: (chemical ionization) m/z 358 (M^++18, 100); ir (potassium bromide): 1710, 1680 (CO) cm^{-1}.

Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.58; H, 5.92. Found: C, 70.28; H, 5.77.

trans-N-[3-(6-Methoxy-2-methyl-4-oxo-chroman-3-ylmethyl)-phenyl]acetamide (**11**).

To a stirred solution of 500 mg (1.48 mmoles) of **9** in 20 ml of dry tetrahydrofuran at -78° was added dropwise 3.1 ml (3.11 moles) of 1.0 *M* L-Selectride® in tetrahydrofuran. The mixture was stirred at -78° for 30 minutes, then quenched by the dropwise addition of an ammonium chloride solution. The mixture was poured into water and extracted with ethyl acetate which was in turn successively washed with water, brine then dried (magnesium sulfate) and evaporated *in vacuo* to give an oil. Column chromatography on silica gel eluting with methanol:methylene chloride (1:40, v/v) afforded 400 mg (80%) of **11**, mp 139-141°; ^{1}H-nmr (deuteriochloroform): δ 1.37 (d, J = 7 Hz, 3H), 2.16 (s, 3H), 2.70 (dd, J = 7, 13 Hz, 1H), 3.01 (d, J = 7 Hz, 2H), 3.80 (s, 3H), 4.40 (q, J = 7, 13 Hz, 1H), 6.88 (d, J = 9 Hz, 1H), 6.98 (d, J = 8 Hz, 1H), 7.09 (dd, J = 3, 9 Hz, 1H) 7.35 (m, 5H); ms: (chemical ionization) m/z 357 (M^++18, 100); ir (potassium bromide): 3300 (NH), 1680, 1660 (CO) cm^{-1}.

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.38; H, 5.99; N, 4.07.

Single Crystal X-ray Crystallographic Analysis for **11**.

A representative crystal was surveyed and a 1 Å data set (maximum sin θ/λ = 0.5) was collected on a Siemens R3RA/v diffractometer. Atomic scattering factors were taken from the International Tables for X-ray Crystallography [13]. All crystallographic calculations were facilitated by the SHELXTL system [14]. All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are

summarized in Table 1. A trial structure was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens and the hydrogen on nitrogen were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R-index was 5.68%. A final difference Fourier revealed no missing or misplaced electron density. The refined structure was plotted using the SHELXTL plotting package (Figure 1). Coordinates, anisotropic temperature factors, distances and angles are available as supplementary material (Tables 2 and 3).

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REFERENCES AND NOTES

[1] M. McKervey and T. Ye, *J. Chem. Soc., Chem. Commun.*, 823 (1992); T. Wallace and S. Saengchantara, *Tetrahedron*, **46**, 3029 (1990); G. Hofle, B. Kunze, C. Zorzin and H. Reichenbach, *Liebigs Ann. Chem.*, 1883 (1984).

[2] S. Parmar, A. Chaturvedi, S. Bhatnagar, G. Misra and S. Nigam, *Res. Commun. Chem. Pathol. Pharmacol.*, **9**, 11 (1974).

[3] S. Antus, A. Gottsegen and N. Nogradi, *Synthesis*, 574 (1981).

[4] E. Winterfeldt, *Synthesis*, 617 (1975).

[5] H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972).

[6] J. Fortunato and B. Ganem, *J. Org. Chem.*, **41**, 2194 (1976).

[7] I. Hirao, M. Yamaguchi and M. Hamada, *Synthesis*, 1076 (1984).

[8] L. Briggs and T. Cebalo, *Tetrahedron*, **19**, 2301 (1963).

[9] F. Irreverre, H. Kag, S. Asen, J. Thompson and C. Morris, *J. Biol., Chem.*, **236**,1093 (1961).

[10] T. Wallace and S. Saengchantara, *Tetrahedron*, **46** 3029 (1990); S. Antus, A. Gottsegen and M. Nogradi, *Synthesis* 574 (1981); S. Gunasekera, G. Jayatilake, S. Selliah and M. Sultanbawa, *J. Chem. Soc., Perkin Trans 1*, 1505 (1977).

[11] M. Dewar, E. Zoebisch, E. Healy and J. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).

[12] A. Gunatilaka, A. Jasmin de Silva, S. Sotheeswaran, S. Balasubramiam and M. Wazeer, *Phytochemistry*, **23**, 323 (1984).

[13] International Tables for X-ray Crystallography, Vol **IV**, Birmingham, Kynoch Press,1974, pp 55, 99, 149.

[14] G. M. Sheldrick, SHELXTL. User Manual, Nicolet Instrument Co., 1981.