SYNTHESES OF CARPROFEN, A CARBAZOLE-BASED NON-STEROIDAL ANTI-INFLAMMATORY AGENT [a]

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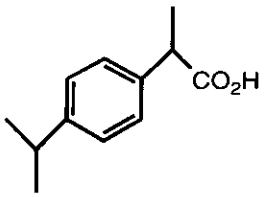
Abstract - Syntheses of carprofen (**6**) have been achieved by two approaches from carbazole (**11**). In one, 2,9-diacetylcarbazole (**12**) and 2-acetylcarbazole (**13**) were chlorinated with trichloroisocyanuric acid (**15**) to give the 6-chloro derivatives (**16**) and (**17**), respectively. Reduction of **16** with $NaBH_4$, followed by acetylation, cyanide displacement, and hydrolysis afforded **6** in 73% yield from **16**. Alternatively, **17** was converted into its trimethylsilyloxy cyanohydrin derivative (**27**), which was reduced with $SnCl_2$ and hydrolysed to give **6** in 75% yield from **17**. In the other approach, the ketone (**18**), derived by a Friedel-Crafts acylation of 9-acetylcarbazole with 2-chloropropanoyl chloride followed by chlorination with **15**, was converted into the hydroxyketal (**28**) with methanolic NaOMe. Mesylation of **28**, followed by a modified Favorskii rearrangement and hydrolysis gave **6** in 73% yield from **18**.

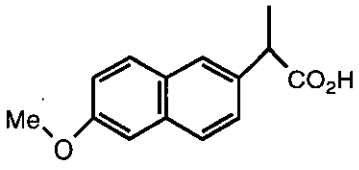
Non-steroidal anti-inflammatory drugs (NSAIDs) are used extensively to ameliorate the symptoms of inflammation and pain, particularly those associated with rheumatoid arthritis.[1] The primary mode of action of carboxylic acid NSAIDs, of which aspirin is the prototype, is the inhibition of prostaglandin biosynthesis by obstructing the action of cyclooxygenase in the arachidonic acid cascade.[2] However, associated with the chronic use of NSAIDs are several side effects that are related to the inhibition of prostaglandin synthesis, such as gastrointestinal ulceration, bleeding, and renal toxicity.[1] It should be noted that another group of arachidonic acid metabolites, the leukotrienes, are also known to contribute to inflammation and NSAID-induced side effects.[3] Among the NSAIDs, those of the 2-arylpropanoic acid class[4] are probably the most prominent, and are represented by ibuprofen (**1**), naproxen (**2**), flurbiprofen (**3**), phenoprofen (**4**), and ketoprofen (**5**). In these and other 2-arylpropanoic acid NSAIDs studied, the (*S*)-enantiomer is the biologically active isomer, but there is good evidence for the *in vivo* conversion of the (*R*)-enantiomer into the (*S*)-

[a] Dedicated to Professor Arnold Brossi on the occasion of his 70th birthday.

enantiomer, apparently *via* stereoselective formation of a CoA thioester intermediate.[2b] In an effort to find an NSAID without the aformentioned side effects, Berger and Corraz prepared a series of carbazoleacetic acid derivatives from which (*R,S*)-6-chloro-α-methylcarbazole-2-acetic acid, carprofen (**6**),[5] was developed for the treatment of rheumatoid arthritis, osteoarthritis, and gout, in addition to being an effective antipyretic. Carprofen is a weak prostaglandin inhibitor with fewer serious gastrointestinal and renal side effects compared to aspirin or ibuprofen, however, clinical studies revealed a much higher incidence of photosensitivity.[6] From metabolic studies in animals, it has been demonstrated that the biologically inactive (*R*)-(-)-enantiomer of **6** is converted into the biologically active (*S*)-(+)-enantiomer.[7]



Ibuprofen (1)



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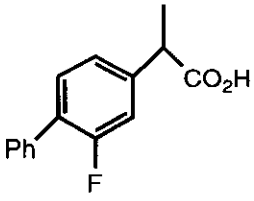
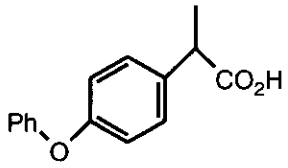
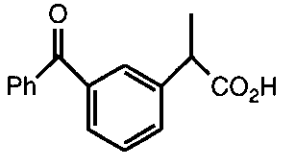


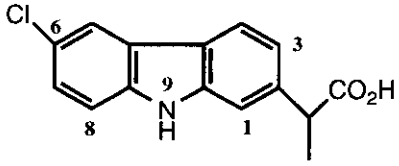
Flurbiprofen (3)



Phenoprofen (4)



Ketoprofen (5)

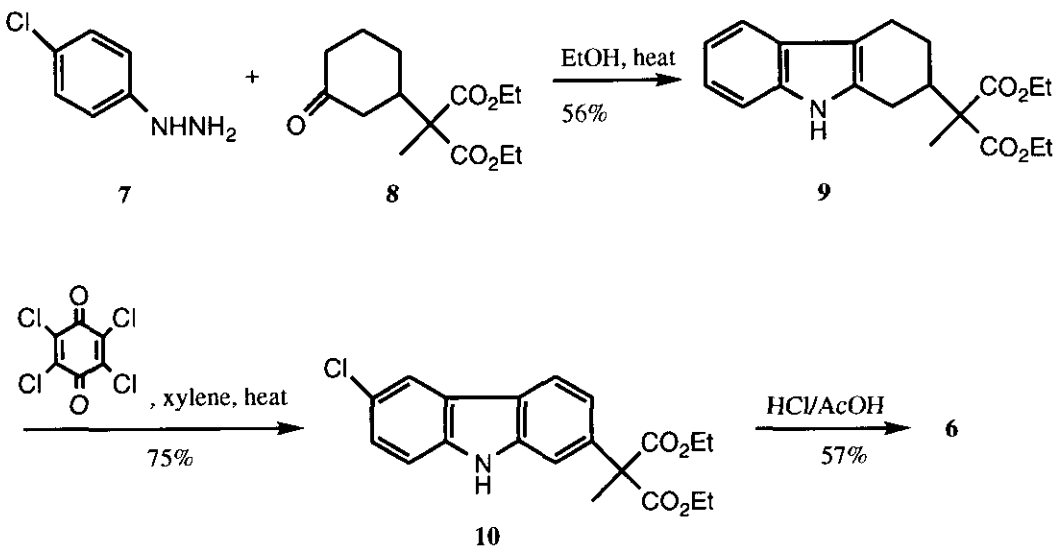


Carprofen (6)

Carprofen has been synthesized by a three-step sequence that involves a Fischer-indole condensation between *p*-chlorophenylhydrazine and the diethyl ester of α-methyl-3-oxocyclohexanemalonic acid followed by aromatization with chloranil and decarboxylation (**Scheme 1**).[8] Because of the relatively low overall yield (24% based on expensive **8**) and problems encountered during scale-up studies, a more efficient synthesis of **6** became desirable for the production of the bulk drug substance on an industrial scale. Carbazole (**11**) is an obvious starting material for the synthesis of **6** requiring two regioselective reactions: introduction of an appropriate carbon fragment at C-2 and chlorination at C-6. In the present paper we describe syntheses of **6** from carbazole, in which the C-2 propanoic acid fragment is introduced either in a step-wise manner by Friedel-Crafts acetylation, followed by cyanide addition (**Schemes 2, 3, and 4**) or directly by acylation with 2-

chloropropanoyl chloride followed by a modified Favorskii rearrangement (**Schemes 2 and 5**). The chlorination at C-6 was accomplished with trichloroisocyanuric acid (**15**).

Scheme 1

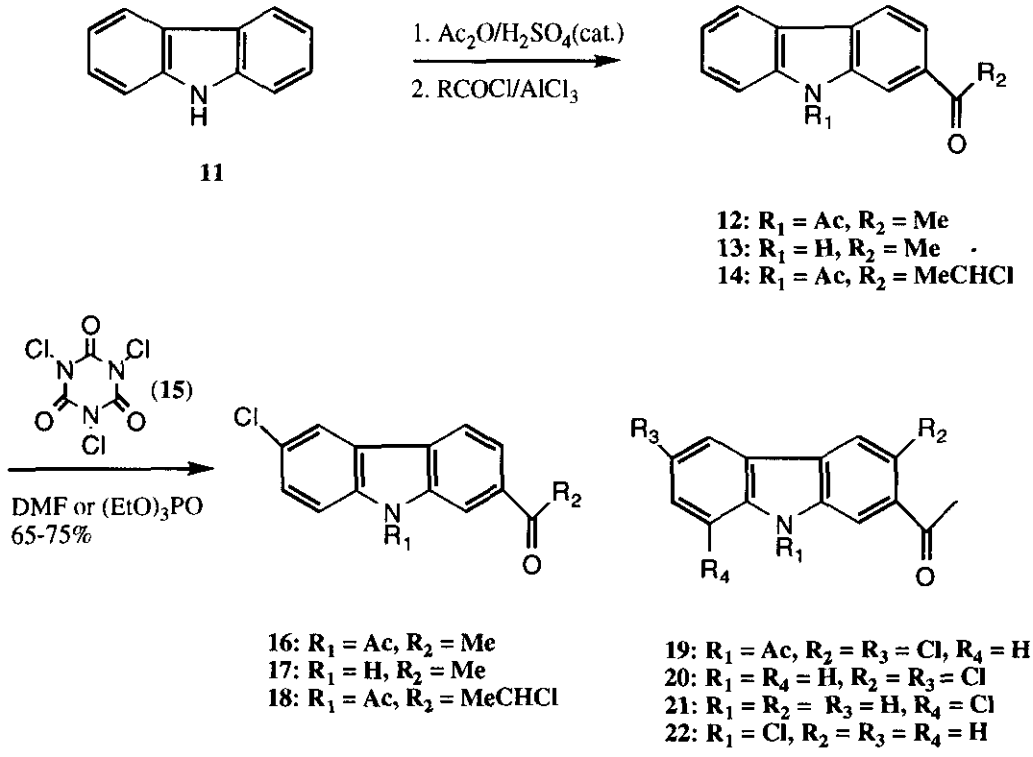


It is known that electrophilic substitution on carbazole occurs normally at C-3 but prior acylation on nitrogen directs subsequent substitution primarily at C-2.[9] This fact made it possible for us to prepare the 2-substituted ketones (**12**) and (**14**) in excellent yields by the Friedel-Crafts reaction of *N*-acetylcarbazole[9] with acetyl chloride and 2-chloropropanoyl chloride, respectively (**Scheme 2**). The *N*-acetylation (Ac_2O/H_2SO_4) of carbazole and subsequent Friedel-Crafts acylation reactions were conveniently carried out in a single-vessel procedure with tetrachloroethylene as solvent.

An extensive study of the chlorination of ketones (**12**)-(**14**) was undertaken in an effort to introduce chlorine regioselectively at C-6. The following chlorinating agents were studied for this reaction: trichloroisocyanuric acid (**15**), 1-chlorobenzotriazole, sulfuryl chloride, sodium hypochlorite, *t*-butyl hypochlorite, *N*-chlorosuccinimide, *N*-chlorophthalimide, dichlorodimethylhydantoin, hexachloroacetone, sulfur monochloride, cupric chloride, and chlorine in the presence of a variety of Lewis acids. Of these reagents, trichloroisocyanuric acid and 1-chlorobenzotriazole gave the most encouraging results in terms of isolated yield and regioselectivity, and since the former reagent showed the best regioselectivity, it was selected for development. The best yield (*ca.* 75%) of the C-6 monochlorinated product was obtained when the reaction was carried out in DMF or triethyl phosphate at 10-40 °C. The addition of acids, particularly HBF_4, $BF_3.Et_2O$, or anhydrous HCl also appeared to suppress over-chlorination. The chlorination of 2,9-diacetylcarbazole (**12**)[9] with **15** in DMF was especially useful as the desired 6-chloro derivative (**16**)

crystallized directly from the reaction mixture in *ca.* 70% yield with a purity of 98-99% based on hplc analyses. The major by-products produced in the chlorination with trichloroisocyanuric acid were the 3,6-dichloro derivatives (e.g., **19** and **20**), which were formed in 5-9% as estimated by hplc, and minor amounts (*ca.* 1%) of products derived from chlorination at C-4 (e.g., **21**). A careful tlc analysis of the chlorination of **13** revealed the formation of an intermediate, which is then converted into **17**. Isolation and spectral analysis identified the intermediate as the *N*-chloro derivative (**22**), an authentic sample of which was readily prepared by the chlorination of **13** with sodium dichloroisocyanurate in DMF. Heating **22** in MeCN produced a 2:1 mixture of **17** and **20**.

Scheme 2



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12: R_1 = Ac, R_2 = Me
13: R_1 = H, R_2 = Me
14: R_1 = Ac, R_2 = MeCHCl

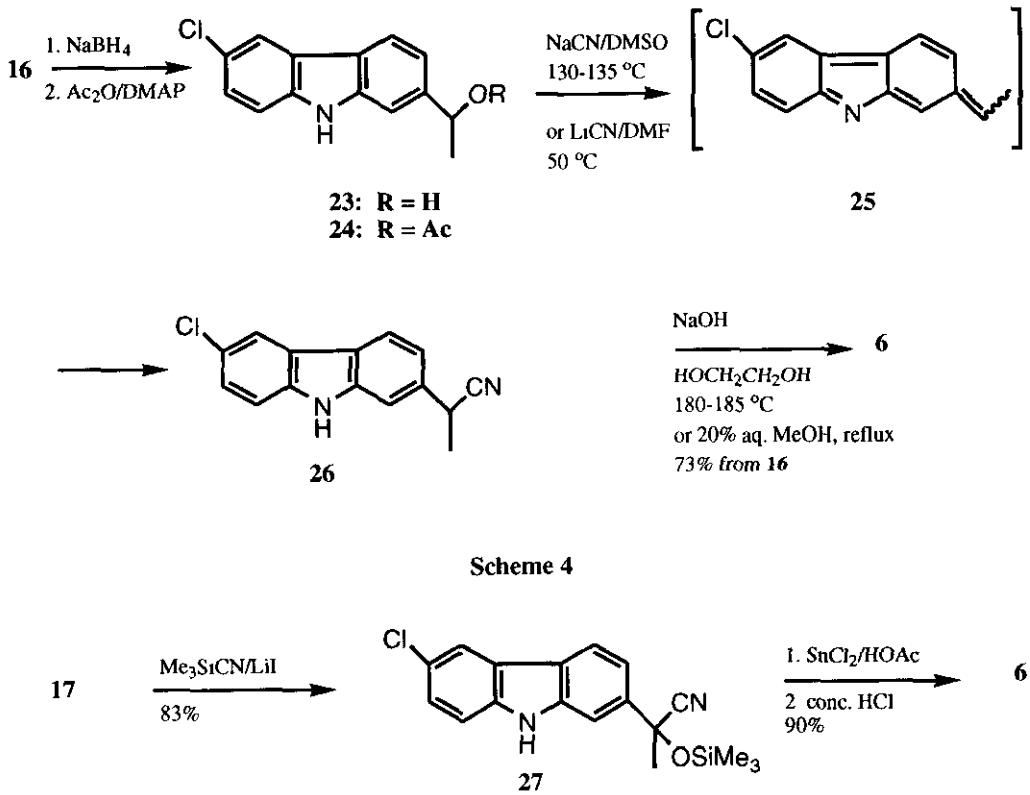
16: R_1 = Ac, R_2 = Me
17: R_1 = H, R_2 = Me
18: R_1 = Ac, R_2 = MeCHCl

19: R_1 = Ac, R_2 = R_3 = Cl, R_4 = H
20: R_1 = R_4 = H, R_2 = R_3 = Cl
21: R_1 = R_2 = R_3 = H, R_4 = Cl
22: R_1 = Cl, R_2 = R_3 = R_4 = H

With the ready availability of ketones (**16**)-(**18**), three series of transformations were employed for their conversion into carprofen. In a first approach (**Scheme 3**), **16** was converted into the acetate (**24**) by sequential reduction with sodium borohydride followed by acetylation of the derived alcohol (**23**) with acetic anhydride. The seemingly straightforward displacement of the acetate group in **24** by cyanide was

surprisingly troublesome, and, of a variety of conditions investigated, was eventually accomplished with NaCN in anhydrous DMSO at 130-135 °C or LiCN in DMF at 50 °C to give the desired nitrile (**26**). The displacement of the acetate by cyanide probably proceeds by an elimination-addition pathway *via* **25**, in agreement with the observation that a sample of optically active **24** ($[\alpha]_D$ + 85°) when treated with NaCN/DMSO gave **26** devoid of optical activity. Hydrolysis of **26** with NaOH in ethylene glycol at 180-185 °C for 2.5 h or in aqueous methanol at reflux for 24 h gave **6**, which was purified *via* its triethylamine salt. In a through-process it was possible to obtain analytically pure **6** in 73% overall yield from **16**. In a second approach (**Scheme 4**), the ketone (**17**) was converted into its trimethylsilyloxy cyanohydrin (**27**) with trimethylsilyl cyanide in the presence of ZnI_2. A smooth reduction of **27** with stannous chloride in acetic acid followed by *in situ* hydrolysis with concentrated hydrochloric acid afforded **6** in 90% yield. It should be noted that various attempts to convert **17** into a normal cyanohydrin with NaCN were unsuccessful, presumably due to the tendency of the keto group in **17** to behave as a vinylogous amide.

Scheme 3

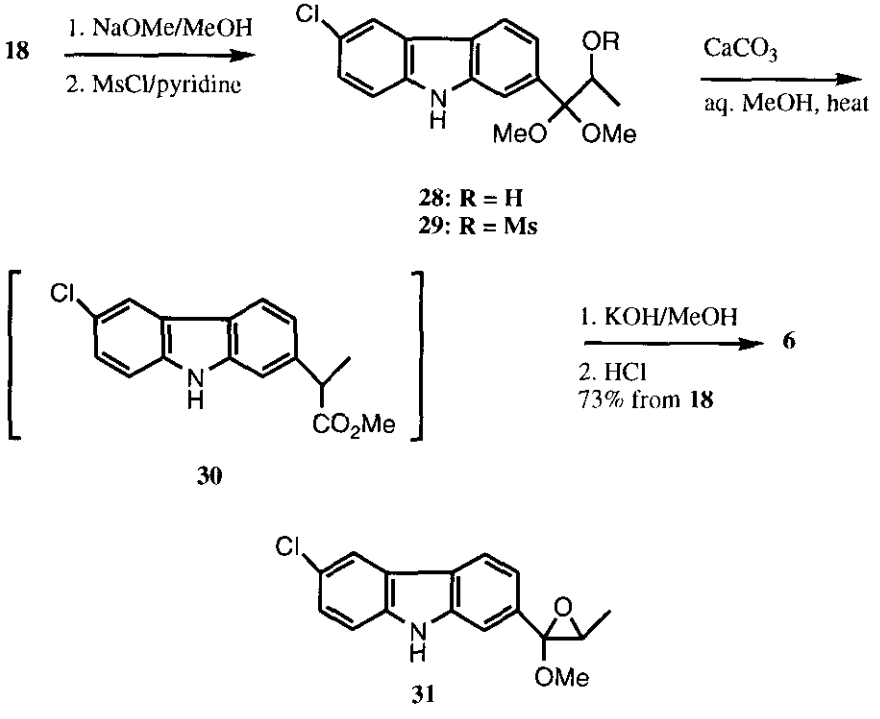


Scheme 4

Despite the high yields, the syntheses of **6** proceeding through **26** and **27** were somewhat compromised by the stringent conditions required for the cyanide displacement and the relatively high cost of trimethylsilyl cyanide. A third synthesis of **6** was therefore developed, employing as a key step a modified Favorskii rearrangement (**Scheme 5**).

We were unable to effect the classical Favorskii rearrangement[10] of the chloro ketone (**18**), but the modification of this rearrangement disclosed by Tsuchihashi *et al.*[11] was successfully adapted to a more efficient synthesis of **6**. Treatment of **18** with an excess of sodium methoxide led to the hydroxy ketal (**28**), presumably *via* **31**, which was converted into the mesylate (**29**) under standard conditions (MsCl/pyridine). Heating **29** with $CaCO_3$ in 20% aqueous methanol led to its smooth conversion into the methyl ester (**30**), which, without isolation, was hydrolyzed to give **6** in 73% overall yield from **18** after purification *via* the triethylamine salt.

Scheme 5



EXPERIMENTAL

General. Unless otherwise indicated, ir and nmr spectra were determined in $CHCl_3$ and DMSO-d_6, respectively. Chemical shifts are expressed in δ units (ppm) and coupling constants in Hz. Thin layer chromatoplates were purchased from Merck (Darmstadt) and spots were visible under short wave-length uv light or made visible by spraying with 10% phosphomolybdic acid in ethanol followed by heating the plates. High pressure liquid chromatographic analyses (hplc) were carried out on a 25 cm x 4.5 mm ID column packed with 10 mμ SI-60 silica gel using a mobile phase of 0.3:1.0:1.0 (v.v.) AcOH:MeOH:CH_2Cl_2 at a flow rate of 1.0 ml/min. Peak areas were internally normalized with corrections made for response factors.

2,9-Diacetylcarbazole (12). To a stirred solution of 167.2 g (1.0 mol) of carbazole in 2.80 l of tetrachloroethylene was added a solution of 2.0 g of conc. H_2SO_4 in 112.5 g (1.10 mol) of acetic anhydride. The mixture was stirred at reflux for 4 h and 800 ml of solvent was removed by distillation during 1.0 h. The dark mixture was left at room temperature overnight and filtered over Celite into a 3-necked, 5-l, round-bottomed flask. The first reaction flask was rinsed out with some tetrachloroethylene and the dark solid removed by filtration was washed with tetrachloroethylene (2 x 75 ml). The combined rinse and washings were added to the second reaction vessel, followed by 400 g (3 mol) of powdered anhydrous $AlCl_3$ and 111 g (1.414 mole) of acetyl chloride. The mixture was stirred at 95-100 °C for 30 min and at room temperature for 2 h. It was cooled (ice/water), treated with *ca* 2.5 kg of crushed ice (exothermic), and the organic phase separated and evaporated to give 263 g (105%) of crude **12** as a yellow-tan solid. Crystallization of a small sample that had been treated with charcoal from Et_2O/hexane gave **12**, mp 108 -110 °C (lit.,[9] mp 107-109 °C).

6-Chloro-2,9-diacetylcarbazole (16). A solution of 10.04 g (0.04 mol) of **12** in 50 ml of DMF was stirred at 30 °C until a solution was obtained. Trichloroisocyanuric acid (4.0 g, 0.0172 mol) in 15 ml of DMF was added and the mixture was stirred at room temperature for 5.5 h (after *ca.* 2.5 h precipitation of the product commenced) and then at -10 °C for 1.0 h. The product was collected by filtration, washed with water (2 x 100 ml), and dried *in vacuo* at 70 °C to give 8.95 g of crude **16**, mp 147-152 °C. Crystallization from 25 ml of hot DMF afforded 8.1 g (71%) of **16** as pale yellow crystals, mp 155-157 °C; uv (EtOH) 232 (ε = 38,000), 305 (ε = 25,800) nm; ir (KBr) 1693, 1675 cm^{-1}; ^1H nmr 2.65 (3 H, s), 2.87 (3 H, s), 7.46 (1 H, dd, J = 7, 2, H-7), 7.93 (1 H, d, J = 7, H-4), 8.16 (1 H, dd, J = 7, 2, H-3), 8. 05 (1 H, d, J = 7, H-8), 8.18 (1 H, dd, J = 7, 2, H-5), 8.69 (1 H, d, J = 2,H-1); ms *m/z* 285 (M^+, 45). Anal. Calcd for $C_{16}H_{12}NO_2Cl$: C, 67.20; H, 4.23; N, 4.90; Cl, 12.41. Found: C, 67.17; H, 4.18; N, 5.08; Cl, 12.54.

In a one-mole experiment, gaseous HCl was used as a catalyst in the chlorination and the product was crystallized from acetic acid (see also the preparation of **18**).

2-Acetyl-6-chlorocarbazole (17). (A) From the Chlorination of 2-Acetylcarbazole (13). A mixture of 52.25 g (0.25 mol) of 2-acetylcarbazole in 1.0 l of anhydrous triethyl phosphate was stirred at 30 °C until a solution was obtained, cooled to 5 °C and treated with 5.0 ml of redistilled $BF_3.Et_2O$. Stirring was continued for 15 min and the mixture was treated slowly with a solution of 22.0 g (0.094 mol) of trichloroisocyanuric acid in 250 ml of anhydrous triethylphosphate at a rate such that the temperature was kept below 10 °C. The

mixture was stirred at 0-5 °C for 1.0 h and at room temperature for 4.0 h, and then evaporated *in vacuo* at 0.5 mm (steam bath) to remove *ca.* 900 ml of solvent. Warm (60 °C) water was added to the resulting slurry with stirring and the product was collected by filtration. It was washed successively with water (2 x 250 ml), 1*N* NaOH (2 x 300 ml), and water (4 x 500 ml), and dried *in vacuo* overnight at 90 °C to give 55.6 g of crude **17**, hplc analysis of which gave 81% of **17** (retention time = 24.87 min), 8.99% of **20** (retention time = 22.82 min), 0.9% of **13** (retention time = 16.55 min), and 5.46% of **21** (retention time = 7.53 min). The crude material was crystallized by dissolving it in 110 ml of hot DMF followed by the addition of 220 ml of hot acetonitrile. After cooling to 10 °C, the product was collected by filtration and dried *in vacuo* at 60 °C (24 h) to give 42.1 g (69%) of **17**, mp 249-251 °C; uv (EtOH) 255 (ε = 40,500), 318 (ε = 25,000), 370 (ε = 3500) nm; ir 3255, 1616, 1600 cm^{-1}; ^1H nmr 2.65 (3 H, s), 7.41 (1 H, dd, J = 7, 2, H-7), 7.54 (1 H, d, J = 7, H-8), 7.74 (1 H, d, J = 7, H-3), 8.09 (1 H, s, H-1), 8.17 (1 H, d, J = 2, H-5), 11.44 (1 H, NH); ms *m/z* 245/243 (70, M^+). Anal. Calcd for $C_{14}H_{10}NOCl$: C, 69.00; H, 4.14; N, 5.75. Found: C, 68.78; H, 4.09; N, 5.61.

(B). By the Hydrolysis of 16. A solution of 25 g (0.087 mol) of **16** in 250 ml of 90% ethanol was treated with 10.6 g (0.265 mol) of NaOH and the mixture was stirred at reflux for 1.25 h followed by evaporation *in vacuo*. The residue was stirred with 250 ml of water and the product was collected by filtration. It was washed with water (4 x 125 ml), dried *in vacuo* at 80 °C for 4 h, and crystallized as before to give 20.1 g (92%) of **17**, mp 248-250 °C.

2-Acetyl-3,6-dichlorocarbazole (20) and 2-Acetyl-8-chlorocarbazole (21). A portion (320 mg) of the mother liquor obtained from the crystallization of **17** that was prepared by the chlorination of 2-acetylcarbazole (**13**) was subjected to preparative-scale tlc (silica gel, 40% ethyl acetate in hexane) and the bands at R_f 0.61 (**20**) and 0.84 (**21**) were collected and extracted into CH_2Cl_2. Filtration and evaporation gave: **20** (58 mg), mp 226-228 °C; uv (EtOH) 211 (ε = 18,032), 225 (ε = 18,605) 257 (ε = 35,456), 313 (ε = 15,512), 358 (ε = 3047) nm; ir (KBr) 3345, 1675 cm^{-1}; ^1H nmr 2.67 (3 H, s), 7.41 (1 H, dd, J = 7, 2, H-7), 7.54 (1 H, d, J = 7, H-8), 7.75 (1 H, s, H-4), 8.22 (1 H, d, J = 2, H-5), 8.24 (1 H, s, H-1); ms *m/z* 277 (M^+, 64). Anal. Calcd for $C_{14}H_9NOCl_2$: C, 60.46; H, 3.26; N, 5.04; Cl, 25.49. Found: C, 60.08; H, 3.22; N, 5.17; Cl, 25.22. Compound (**21**, 24 mg), mp 170-172 °C (from ethyl acetate/hexane); uv (EtOH) 253 (ε = 40,000), 312 (ε = 22,300), 356 (ε = 4000) nm; ^1H nmr 2.65 (3 H, s), 7.17 (1 H, d, J = 7, H-4), 7.48 (1 H, dd, J = 7, 2, H-5), 7.79 (1 H, dd, J =7, 2, H-7), 8.10 (1 H, d, J = 7, H-6), 8.12 (1 H, s, H-1), 8.18 (1 H, d, J = 7, H-3); ms *m/z* 243 (M^+, 60).

2-Acetyl-9-chlorocarbazole (22). To a stirred solution of 10.45 g (0.05 mol) of **13** in 160 ml of DMF was added, under argon, 10.0 g (0.045 mol) of sodium dichloroisocyanurate. The mixture was stirred at room temperature for 16 h, poured into 1.0 l of water, and the product was collected by filtration. It was washed with water (2 x 100 ml), dried by suction, and crystallized from 200 ml of ethyl acetate at 10 °C to give 4.2 g of **22**, mp 110 °C. An additional 8.5 g of **22** was obtained by concentration of the mother liquor. Uv (EtOH) 205 (ε = 24,400), 249 (ε = 35,600), 275-279 (shoulder, ε = 7100), 308 (ε = 24,400) nm; ir ($CHCl_3$) 1678 cm^{-1};

^{1}H nmr ($CDCl_3$) 2.64 (3 H, s), 7.33 (3 H, m), 7.90 (4 H, m); ms *m/z* 243 (M^+). Anal. Calcd for $C_{14}H_{10}NOCl$: C, 69.00; H, 4.14; N, 5.75; Cl, 14.55. Found: C, 68.85; H, 4.10; N, 5.81; Cl, 14.52.

2-(1-Hydroxethyl)-6-chlorocarbazole (23). A stirred mixture of 159.38 g (0.558 mol) of **16**, 1.0 l of ethanol, and 100 ml of a 4.4 *M* solution of $NaBH_4$ in 14 *N* NaOH was heated at reflux for 2 h and then evaporated. Water (2.5 l) was gradually added to the warm slurry, and, after stirring for 10 min, the mixture was cooled and the product was collected by filtration. It was washed with water until neutral and dried to give 134.3 g (98%) of **23**, mp 194-198 °C. An analytical sample was obtained by crystallization from 90% EtOH, mp 198-200 °C; ir 3405 (NH), 3320 (OH) cm $^{-1}$; ^{1}H nmr 1.46 (3 H, d, J = 7), 4.97 (1 H, dq, J = 7, 7), 5.01 (1 H, d, J = 7, OH), 7.11 (1 H, d, J = 7, H-3), 7.22 (1 H, d, J = 7, H-7), 7.36 (1 H, d, J = 7, H-8), 7.46 (1 H, s, H-1), 7.89 (1 H, d, J = 7, H-4), 7.94 (1 H, s, H-5), 10.76 (s, NH); ms *m/z* 245. Anal. Calcd for $C_{14}H_{12}NOCl$: C, 68.44; H, 4.92; N, 5.70; Cl, 14.43. Found: C, 68.37; H, 4.95; N, 5.53; Cl, 14.23.

2-(1-Acetoxyethyl)-6-chlorocarbazole (24). A stirred mixture of 134.3 g of crude **23** from the preceding experiment in 1.3 l of ethyl acetate was heated on a steam bath with 135 ml of acetic anhydride and 0.5 g of 4-dimethylaminopyridine until a solution was obtained. Stirring was continued at room temperature for 3.0 h and the solvent was evaporated. The residue was triturated with 1.5 l of cold water, and the product was collected by filtration, washed with cold water (3 x 250 ml), and air-dried overnight to give 157.0 g (99.8%) of crude **24**, mp 139-144 °C, hplc analysis of which indicated a purity of 97.15% An analytical sample was obtained from Et_2O/hexane, mp 142-144 °C; uv (EtOH) 238 (ε = 50, 200), 262 (ε = 23,250), 300 (ε = 21,750), 331 (ε = 3000), 345(ε = 3040) nm; ir (KBr) 3393, 1716 cm^{-1}; ^{1}H nmr 1.58 (3 H, d, J = 7), 2.10 (3 H, s, Ac), 5.93 (1 H, q, J = 7), 7.11 (1 H, d, J = 7, H-3), 7.26 (1 H, d, J = 7, H-7), 7.35 (1 H, d, J = 7, H-8), 7.40 (1 H, s, H-1), 7.90 (1 H, d, J = 7, H-4), 7.93 (1 H, s, H-5), 10.62 (1 H, s, NH); ms *m/z* 287 (M^+, 85). Anal. Calcd for $C_{16}H_{14}NO_2Cl$: C, 66.79; H, 4.90; N, 4.90; Cl, 13.32. Found: C, 66.52; H, 5.11; N, 4.55; Cl, 13.13.

2-(1-Cyanoethyl)-6-chlorocarbazole (26). (A). Using NaCN/DMSO. A 2-l, 3-necked, round-bottomed flask fitted with a mechanical stirrer, condenser and an adapter for vacuum distillation and a stopcock-argon inlet was charged with 116.35 g of the preceding acetate (**24**), 116.35 g of NaCN (vacuum oven-dried at 110 °C), and 750 ml of dry DMSO (dried over 4A molecular sieves). Vacuum was applied and the mixture was heated to 97 °C under a pressure of 2.5 mm/Hg with the collection of 75 ml of DMSO. The vacuum line was clamped off and argon was introduced into the system. The mixture was stirred at 130-132 °C for 9.5 h, the argon line was closed, the vacuum line was opened, and an additional 635 ml of DMSO distilled off. The vacuum line was closed and argon reintroduced into the system. The mixture was cooled and treated with 500 g of ice followed by 500 ml of water. After stirring overnight, the product was collected by filtration, washed with water (3 x 250 ml), and dried to give 121 g of crude **26**, mp 117-130 °C, with a purity of 86.3% (hplc). This material was used without further purification.

(B). Using LiCN-DMF. A 2-l, 3-necked, round-bottomed flask equipped with a mechanical stirrer, condenser with a Dean-Stark trap, addition funnel, and an argon inlet tube was charged with 740 ml of anhydrous DMF and 3.36 g (0.8 mol) of LiH. Acetone cyanohydrin (68 g, 0.8 mol) was added to the

suspension during 20 min and the mixture was stirred at 50 °C for 2.5 h, treated with 115.08 g (0.4 mol) of acetate (**24**) and then boiled under reflux with the collection of 50 ml of liquid. The Dean-Stark trap was removed, the mixture was heated at reflux for 5 h, and then the solvent was distilled *in vacuo* (water aspirator) at 90 °C. To the residue was slowly added 1.0 l of warm (60 °C) water, the mixture was stirred for 2.0 h, and the product was collected by filtration. It was washed with water (2 x 1.0 l) and dried to give 111.8 g of crude **26**. Hplc analysis indicated a purity of 87.85%. This material was used without further purification. Crystallization of a small sample from benzene gave off-white crystals, mp 132-135 °C. ^{1}H Nmr 1.58 (3 H, d, J = 7, *CH$_3$*), 4.30 (1 H, q, J = 7, Me*CH*), 7.20 (1 H, d, J = 7, H-7), 7.35 (3 H, m, H-1 + H-3, + H-8), 8.01 (1 H, d, J = 7, H-4), 8.10 (1 H, br s, H-5), 11.08 (1 H, s, NH). Anal. Calcd for $C_{15}H_{11}N_2Cl$: C, 70.73; H, 4.35; N, 11.00. Found: C, 70.81; H, 4.32; N, 11.01.

Trimethylsilyloxy Cyanohydrin of 17: Compound (27). To a stirred solution of **17** in 35 ml of $CHCl_3$ was added under argon 5.08 g (0.058 mol) of trimethylsilyl cyanide and 150 mg (0.42 mmol) of ZnI_2. The mixture was stirred at reflux for 4 h, treated with a further 2.5 g (0.025 mol) of trimethylsilyl cyanide and 150 mg (0.42 mmol) of ZnI_2. Boiling was continued for 18 h, then the mixture was cooled to room temperature and filtered through a plug of silica gel to give, after evaporation, 6.1 g (83%) of **27**. An analytical sample was obtained by chromatography (silica gel, 4% CH_2Cl_2 in acetone) to give, after crystallization from CH_2Cl_2/hexane, **27**, mp 151-154 °C; uv (EtOH) 217 (shoulder, ε = 25,600), 234 (shoulder, ε = 43,200), 239 (ε = 51,700), 249 (ε = 30,400) 263 (ε = 23,700), 290 (shoulder, ε = 12,500), 295 (shoulder, ε = 15,400), 301 (ε = 22,60 0), 323 (shoulder, ε = 3,000), 334 (ε = 3600), 348 (ε = 2900) nm; ir ($CHCl_3$) 3350, 2250, 1110 cm^{-1}; ^{1}H nmr 0.18 (9 H, s), 1.96 (3 H, s), 7.35 (1 H, dd, J = 7, 2, H-3), 7.41 (1 H, dd, J = 7, 2, H-7), 7.55 (1 H, d, J = 7, H-8) 7.70 (1 H, d, J = 2, H-1), 8.21 (1 H, d, J = 7, H-4), 8.23 (1 H, d, J = 2, H-5); ms *m/z* 342 (M^+, 45). Anal. Calcd for $C_{18}H_{19}N_2OClSi$: C, 63.05; H, 5.58; N, 8.17; Cl, 10.34. Found: C, 62.95; H, 5.49; N, 8.24; Cl, 10.16.

2-(α-Chloropropionyl)-9-acetylcarbazole (14). A 3-l, 3-necked, round-bottomed flask fitted with a mechanical stirrer and a condenser was charged with 83.6 g (0.5 mol) of carbazole, 1.4 l of tetrachloroethylene, and 56.25 g (0.55 mol) of acetic anhydride in which was dissolved 1.0 g of conc. H_2SO_4. The mixture was stirred at reflux for 4 h, then at room temperature overnight, and 400 ml of solvent was removed by distillation. The mixture was cooled to room temperature and, with stirring, treated with 200 g (1.5 mol) of powdered, anhydrous $AlCl_3$ followed by 90 g (0.71 mol) of 2-chloropropanoyl chloride, resulting in an exotherm. The mixture was heated to 90 °C producing hydrogen chloride as the reaction progressed. The mixture was allowed to cool to 50 °C and then treated rapidly with 1 kg of crushed ice. Stirring was continued for 2.5 h, the lower phase was separated, and the aqueous phase was re-extracted with 400 ml of tetrachloroethylene. The combined organic layers were dried (Na_2SO_4) and evaporated to give 200 g (overweight) of crude **14**. A 200-mg sample was crystallized from CH_2Cl_2/Et_2O to give pure **14**, mp 103-106 °C; ms *m/z* 299. Anal. Calcd for $C_{17}H_{14}NO_2Cl$. C, 68.12; H, 4.71; N, 4.67; Cl, 11.83. Found: C, 68.46; H, 4.67; N, 4.61; Cl, 12.09.

2-(α-Chloropropionyl)-6-chloro-9-acetylcarbazole (18). A stirred mixture of *ca.* 200 g of crude **14** (from the preceding experiment) in 350 ml of DMF was treated with 50 g of trichloroisocyanuric acid, producing an exotherm (to 40 °C). Stirring was continued for 2 h at 40 °C. At the end of 2 h, the temperature had dropped to room temperature. Gaseous HCl was introduced above the solution for a few seconds resulting in a second exotherm. The temperature was kept below 40 °C by cooling. The reaction mixture was left at room temperature overnight and the product was collected by filtration to give 124 g of crude **18**. The filtrate was evaporated *in vacuo* at 40 °C and the residue was triturated with 500 ml of water to give 125 g of a solid, which was crystallized from 450 ml of hot acetic acid to give 29 g of **18**. This was combined with the first batch and crystallized from 350 ml of hot acetic acid to afford 111.4 g (66.7%) of **18**. Recrystallization of a small portion from CH_2Cl_2 gave an analytical sample, mp 153-157 °C; ^{1}H nmr 1.73 (1 H, d, J = 7), 2.82 (3 H, s, MeCO), 5.63 (1 H, q, J = 7), 7.44 (1 H, dd, J = 7, 2, H-7), 7.98 (1 H, d, J = 7, H-4), 8.01 (1 H, d, J = 2, H-5), 8.02 (1 H, d, J = 7, H-3), 8.07 (1 H, d, J = 7, H-8), 8.73 (1 H, s, H-1); ms *m/z* 334. Anal. Calcd for $C_{17}H_{13}NO_2Cl_2$: C, 61.10; H, 3.92; N, 4.19; Cl, 21.22. Found: C, 60.95; H, 3.85; N, 4.18; Cl, 21.43.

2-(α,α-Dimethoxy-β-hydroxypropyl)-6-chlorocarbazole (28). A stirred solution of sodium methoxide (from 33.4 g of Na and 900 ml of methanol) under argon was treated with 111.15 g of **18**, a mild exotherm ensued (to 42 °C). The mixture was stirred for 2 h, 3.0 l of water was added, and stirring continued for an additional 2 h. The product, initially gummy, solidified and was isolated by filtration. It was washed with water and dried to give 103.75 g (97.4%) of crude **28** as a tan powder. An analytical sample was obtained by crystallization from ether/hexane, mp 115-120 °C (decomp.); ^{1}H nmr 1. 00 (3 H, d, J = 7, *CH*$_3$CH), 3.26 (3 H, s, O*CH*$_3$), 3.41 (3 H, s, O*CH*$_3$), 4.22 (1 H, dq, J = 7, 2, *CH*), 5.70 (1 H, br s, OH), 7.22 (1 H, d, J = 7, H-7), 7.28 (1 H, d, J = 7, H-8), 7.32 (1 H, d, J = 7, H-3), 7.56 (1 H, s, H-1), 7.94 (1 H, d, J = 7, H-4), 7.98 (1 H, d, J = 2, H-5), 8.34 (1 H, NH); ms *m/z* 319. Anal. Calcd for $C_{17}H_{19}NO_3Cl$: C, 63.85; H, 5.67; N, 4.38; Cl, 11.09. Found: C, 63.72; H, 5.42; N, 4.39; Cl, 10.88.

2-(α,α-Dimethoxy-β-methanesulfonyloxypropyl)-6-chlorocarbazole (29). Methanesulfonyl chloride (50 g, 0.436 mol) was added to a stirred mixture of 103.7 g of crude **28** (from the preceding experiment) in 1.0 l of CH_2Cl_2 and 100 ml of pyridine. The solution was stirred at room temperature for 2 h, treated with an additional 25 g of methanesulfonyl chloride, stirred for 3 h, and again treated with 25 g of methanesulfonyl chloride followed by 50 ml of pyridine. The mixture was stirred overnight at room temperature, poured into a separatory funnel, washed with water (4 x 500 ml), and the organic phase collected and evaporated at 35 °C (water aspirator followed by high vacuum) to give 147.25 g (overweight) of crude **29**, which was used in the next step without purification.

Carprofen (6). (A) From Mesylate (29). To a stirred solution of 147.25 g of crude **29** from the preceding experiment in 1.5 l of methanol were added 300 ml of water and 150 g of $CaCO_3$, and the mixture stirred at reflux for 17 h. It was treated with 56.1 g (1 mol) of KOH in 200 ml of water, stirred at reflux for a further 1.5 h, and evaporated. Water (1.0 l) was added to the residue and the precipitated solids were removed by filtration. The filter cake was washed with hot water (2 x 500 ml) and the combined filtrate and washings

were extracted with 500 ml of Et_2O. The aqueous extracts were acidified with 100 ml of conc. HCl and extracted with Et_2O. Concentration of the Et_2O followed by filtration gave 60.75 g of crude **6**. An additional 9 g of crude **6** was obtained from the original filter cake by acidification and extraction into Et_2O. The combined crude carprofen was dissolved in 300 ml of dry acetone, treated with 50 ml of Et_3N, and cooled. The crystalline salt was collected by filtration, washed with cold acetone and dried to give 84.0 g of colorless crystals. The salt was added to a mixture of 225 ml of 10% HCl and 200 ml of ethyl acetate. The mixture was shaken until the solid dissolved and the aqueous phase was discarded. The organic layer was washed with water (2 x 200 ml), treated with 10 g of charcoal (Norit A), and filtered through Celite. The filtrate was diluted with toluene and the solution was concentrated until crystallization commenced. After cooling, the product was collected by filtration, washed with cold toluene, and dried *in vacuo* at 75 °C to give 52.28 g (38.2% from **11**) of **6** as colorless crystals, mp 197-204 °C. Hplc analysis indicated a purity of 99.2%. A second crop (7.2 g) of **6**, mp 190-195 °C, was obtained from the mother liquor.

(B). From the Hydrolysis of Nitrile (26). A mixture of 121 g of crude **26** (hplc purity of 86.3%), 100 g of NaOH and 1.0 l of ethylene glycol under argon was stirred at 180-185 °C for 2.5 h, and 530 ml of the solvent was removed by distillation in vacuum. Ice (500 g) was added followed by 500 ml of water. The mixture was acidified with 300 ml of conc. HCl and the product was collected by filtration and washed with 500 ml of water. After drying, the crude product was purified *via* its Et_3N salt as described previously to give 75.9 g of **6**. The hydrolysis was also carried out with NaOH in 20% methanol at reflux for 24 h.

(C). From 27. A mixture of 1.71 g (0.005 mol) of **27** and 2.25 g (0.01 mol) of $SnCl_2.2H_2O$ in 10 ml of acetic acid was stirred under argon for 10 min and treated with 20 ml of conc. HCl. The mixture was stirred at room temperature for 18 h, then at 100 °C for 2.5 h, and concentrated *in vacuo*. To the residue was added 40 ml of water and the mixture was extracted with 100 ml of ethyl acetate. The extract was evaporated, and the residue was made basic with 40 ml of 3*N* NaOH. After extracting with 40 ml of CH_2Cl_2 (discarded), the aqueous phase was acidified with conc. HCl and extracted with 100 ml of ethyl acetate. The extract was washed with 50 ml of satd. brine, stirred with anhyd. $MgSO_4$ and 1 g of decolorizing charcoal, and filtered. Evaporation gave 1.35 g of **6**, a portion of which was crystallized from ethyl acetate/hexane (92% return), mp 196-200 °C; uv (EtOH) 220 (shoulder, ε = 800), 233 (shoulder, ε = 37,800), 239 (ε = 47,900), 249 (shoulder, ε = 32,100), 262 (ε = 23,760), 2981 (shoulder, ε = 13,000), 296 (shoulder, ε = 15,900), 302 (ε = 21,200), 318 (shoulder, ε = 3800), 330 (ε = 4100), 344 (ε = 2800) nm; ir (KBr) 3420, 2700-2500, 1701 cm^{-1}; ^1H nmr 1.47 (3 H, d, J = 7), 3.81 (1 H, d, J = 7), 7.06 (1 H, dd, J = 7, 2, H-3), 7.26 (1 H, dd, J = 7, 2, H-4), 7.36 (1 H, d, J = 2, H-1), 7.97 (1 H, d, J = 7, H-8), 8.05 (1 H, dd, J = 7,2, H-7), 8.08 (1 H, d, J = 2, H-5), 11.11 (1 H, s, NH), 12.00 (1 H, br s, OH); ms *m/z* 273 (M^+, 55). Anal. Calcd for $C_{15}H_{12}NO_2Cl$: C, 65.82; H, 4.42; N, 5.12; Cl, 12.95. Found: C, 66.08; H, 4.47; N, 5.19; Cl, 12.81.

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REFERENCES

1. (a) P. A. Insel in Goodman and Gilman 'The Pharmacological Basis of Therapeutics,' 8th ed., Pergamon Press, New York, 1991, pp. 638-681; (b) P. M. Brooks and R. O. Day, *New Engl. J. Med.*, 1991, 1716.
2. (a) G. A. Higgs, E. A. Higgs, and S. Moncada, 'Comp. Med. Chem.,' Vol. 2, ed. C. Hansch, Pergamon Press, New York, 1990, pp.147-173; (b) K. M. Williams, R. O. Day, and S. N. Breit, *Adv. Drug Res.*, 1993, **24**, 121.
3. (a) S. D. Brain and T. J. Williams, *Pharm. Ther.*, 1990, **46**, 57; (b) P. M. Vaananen, C. M. Keenan, M. B. Grisham, and J. L. Wallace, *Inflammation*, 1992, **16**, 227.
4. J.-P. Rieu, A. Boucherle, H. Cousse, and G. Mouzin, *Tetrahedron*, 1986, **42**, 4095.
5. L. Berger and A. L. Corraz, US Patent 3896145 (July 22, 1975, not available in *Chem. Abstr.*).
6. W. M. O'Brien and G. F. Bagby, *Pharmacotherapy*, 1987, **7**, 16.
7. J. K. Stoltenborg, C. V. Puglisi, F. Rubio, and F. M .Vane, *J. Pharm. Sci.*, 1981, **70**, 1207.
8. H. Gurien and S. Tietel, US Patent 4158007 (January 12, 1979; *Chem. Abstr.*, 1979, **91**, 107889c); see also ref. 5.
9. J. B. Kyziol and A. Lyzniak, *Tetrahedron*, 1980, **36**, 3017, and references cited therein.
10. A. S. Kende, *Org. React.*, 1960, **11**, 261.
11. G. Tsuchihashi, K. Kitajima, and S. Mitamura, *Tetrahedron Lett.*, 1981, **22**, 4305.

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