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New Methods and Reagents in Organic Synthesis. 35.[1] A New Synthesis of Some Non-Steroidal Anti-Inflammatory Agents with the 2-Arylpropionic Acid Skeleton by the Use of Diphenyl Phosphorazidate (DPPA) as a 1,3-Dipole[2]

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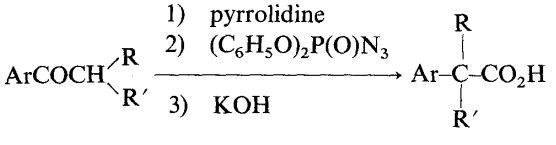
Reaction of diphenylphosphinic azide (**8**) with the pyrrolidine enamine **13** of 4-isobutylpropiophenone afforded two amidines **15a** and **16a**, which were derived from the 1,3-dipolar cycloadduct **14a** by the expulsion of nitrogen followed by 1,2-aryl migration (path a) and by 1,3-dipolar elimination (path b), respectively. Although diphenylthiophosphinic azide (**9**) and ethyl phenylthiophosphonoazidate (**10**) also gave similar results, diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$) furnished the amidine **15d** formed *via* path a as the sole isolable product. Hydrolysis of **15d** with potassium hydroxide afforded ibuprofen (**3**) in good yield. Other non-steroidal antiinflammatory agents, naproxen (**4**), ketoprofen (**5**), and flurbiprofen (**6**), were analogously and conveniently prepared from the ketones **17**, **22**, and **25**, respectively, by a similar three-step operation using pyrrolidine, DPPA, and potassium hydroxide. 2-(2-Dibenzofuranyl)-propionic acid (**7**) was also prepared from the ketone **28** by the three-step procedure.

Keywords——enamine; phosphorus azide; diphenyl phosphorazidate; 1,3-dipolar cycloaddition; 1,2-migration; 1,3-dipolar elimination; *N*-phosphorylated amidine; alkaline hydrolysis; 2-arylpropionic acid; anti-inflammatory agent

Our preceding paper[1] reported that alkyl phenyl ketones **1** can be conveniently converted to 2-phenylalkanoic acids **2** by a three-step operation using pyrrolidine, diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$), then potassium hydroxide, as shown in Chart 1.



1 **2**

Ar = phenyl

Chart 1

We now wish to report that the same reaction sequence can be successfully applied to the preparation of non-steroidal anti-inflammatory agents[4] having the 2-arylpropionic acid skeleton.[5] Ibuprofen[2-(4-isobutylphenyl)propionic acid] (**3**),[6] rac-naproxen [2-(6-methoxy-2-naphthyl)propionic acid] (**4**),[7] ketoprofen [2-(3-benzoylphenyl)propionic acid] (**5**),[8] and flurbiprofen [2-(3-fluoro-4-biphenyl)propionic acid] (**6**)[9] were chosen as representative target agents (Chart 2). 2-(2-Dibenzofuranyl)propionic acid (**7**)[10] was also prepared as an example of a 2-(heteroaromatic)propionic acid.

First, several phosphorus azides **8**—**10** were prepared by the reaction of the correspond-

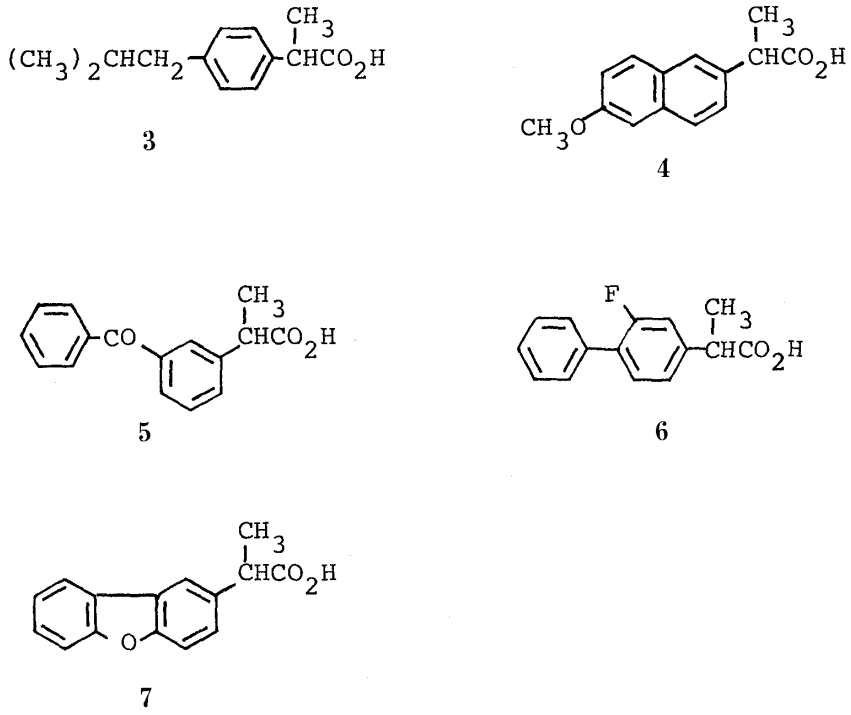


Chart 2

ing chlorides with sodium azide, and we investigated the reaction of these azides as well as DPPA with the pyrrolidine enamine **13** prepared from 4-isobutylbenzene (**11**) *via* 4-isobutylpropiophenone (**12**), as shown in Chart 3. The reaction of diphenylphosphinic azide (**8**) with the enamine **13** in ethyl acetate afforded the desired amidine **15a** as the major product, which was formed from the 1,3-dipolar cycloadduct **14a** by the expulsion of nitrogen followed by 1,2-aryl migration (path a in Chart 3). Another amidine **16a**, formed by 1,3-dipolar elimination from **14a** (path b),[1,11] was also obtained in a lesser amount. Changing the reaction solvent from ethyl acetate to higher boiling toluene increased the formation of the 1,3-dipolar elimination product **16a**. Similar results were obtained by the use of diphenylthiophosphinic azide (**9**) and ethyl phenylthiophosphonoazidate (**10**), as shown in Table I. However, the reaction of DPPA with the pyrrolidine enamine **13** in tetrahydrofuran afforded the desired amidine **15d** in good yield, but the other amidine **16d** could not be isolated.[12] As described in our preceding paper,[1] the one-flask procedure in which the purification of the enamine **13** by distillation was omitted gave a better overall yield based on 4-isobutylpropiophenone (**12**). Since this preliminary survey suggested that DPPA in tetrahydrofuran would afford the best result in the formation of the desired amidine, we chose the same reaction species for subsequent experiments. Hydrolysis of the *N*-phosphorylated amidine **15d** with potassium hydroxide in refluxing ethylene glycol[1] afforded ibuprofen (**3**) in 79% yield.

Preparation of naproxen (**4**), in its racemic form, started with 6-methoxy-2-propionylnaphthalene (**17**),[13] which was converted to the corresponding pyrrolidine enamine **18**. Reaction of **18** with DPPA afforded the desired amidine **19**. The one-flask procedure again gave the better result. Alkaline hydrolysis of **19** afforded rac-naproxen (**4**) in 68% overall yield from **17** (Chart 4).

The key intermediate for the preparation of ketoprofen (**5**) was 3-propionylbenzophenone (**22**), which was prepared from 3-bromopropiophenone ethylene acetal (**21**) by successive treatments with butyllithium, benzonitrile, and hydrochloric acid, as shown in Chart 5. The acetal **21** was obtained by the acetalization of 3-bromopropiophenone (**20**), which was prepared from propiophenone according to the literature.[14] The key ketone **22** was

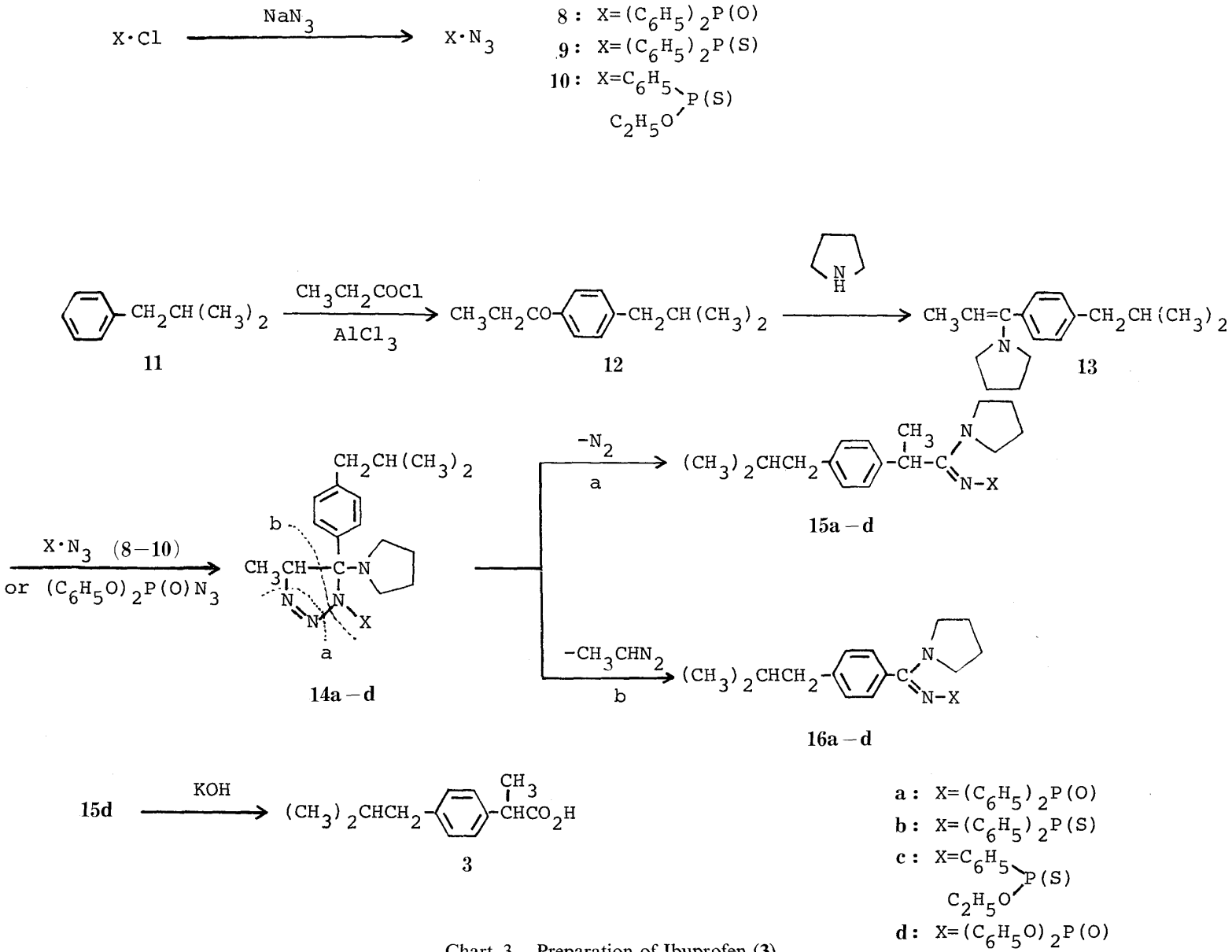


Chart 3. Preparation of Ibuprofen (3)

Table I. Reaction of the Enamine **13** with Phosphorus Azides **8**—**10** and DPPA

Run	$X \cdot N_3$	Reaction			Yield (%) of	
		Solvent	Temp.	Time (h)	**15**	**16**
1	$(C_6H_5)_2P(O)N_3$	Ethyl acetate[a]	Room temp.	0.5	37[b]	8[b]
			Reflux	30		
2	$(C_6H_5)_2P(O)N_3$	Toluene	Room temp.	1	26	39
			Reflux	5		
3	$(C_6H_5)_2P(S)N_3$	Ethyl acetate	Room temp.	2	40	20
			Reflux	22		
4	$(C_6H_5)_2P(S)N_3$	Toluene	Room temp.	1	36	41
			Reflux	5		
5	$C_6H_5(C_2H_5O)P(S)N_3$	Ethyl acetate	Room temp.	1	57	13
			Reflux	18		
6	$C_6H_5(C_2H_5O)P(S)N_3$	Toluene	Room temp.	1	31	21
			Reflux	5		
7	$(C_6H_5O)_2P(O)N_3$	Tetrahydrofuran	Room temp.	1	76	—
			40 °C	1		
			Refulx	2		
8	$(C_6H_5O)_2P(O)N_3$	Tetrahydrofuran[a]	Room temp.	1	78[b]	—
			40 °C	1		
			Reflux	2		

a) By the one-flask procedure.
b) Based on the ketone **12**.

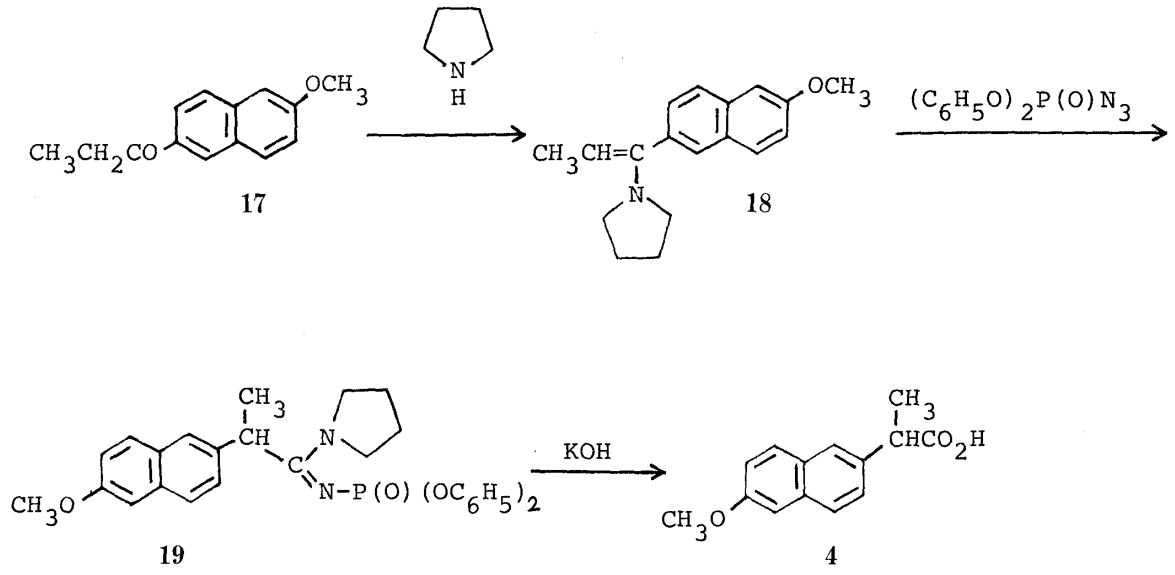


Chart 4. Preparation of Naproxen (**4**)

converted to its pyrrolidine enamine **23**, which reacted with DPPA to give the *N*-phosphorylated amidine **24**. Hydrolysis of **24** with potassium hydroxide in ethylene glycol afforded a carboxylic acid which had no carbonyl function but had a hydroxyl function. Apparently the carbonyl group between the two phenyl groups was reduced under hydrolytic conditions. An analogous reduction of the carbonyl group of benzophenone was attained with potassium hydroxide in ethylene glycol by Kleinfelter.[15] Jones' oxidation of the crude carboxylic acid gave ketoprofen (**5**) in 72% yield from the amidine **24**.

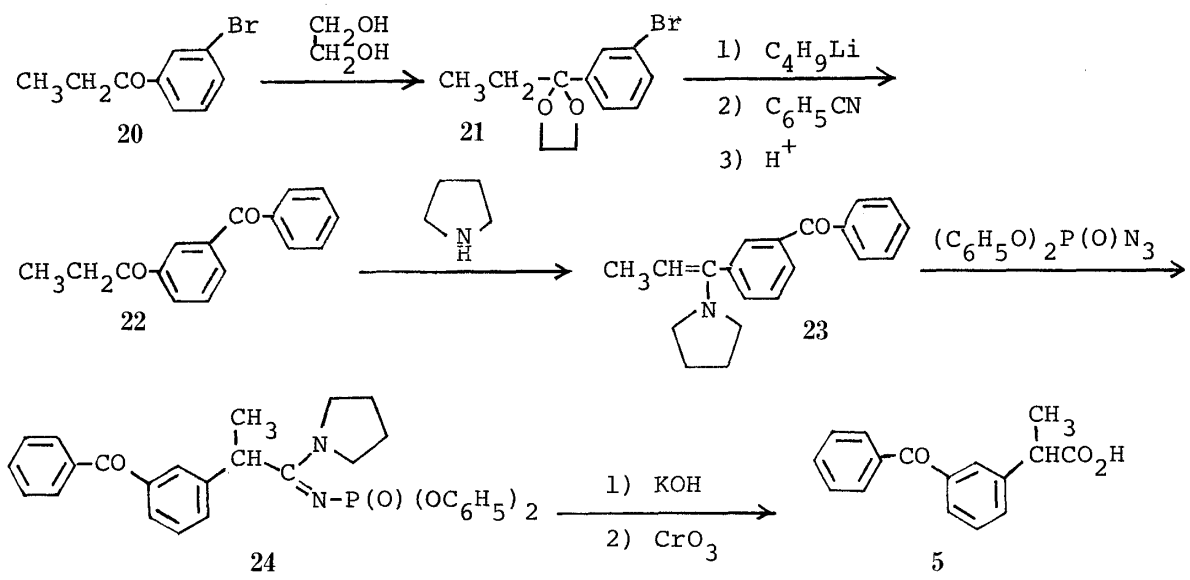


Chart 5. Preparation of Ketoprofen (**5**)

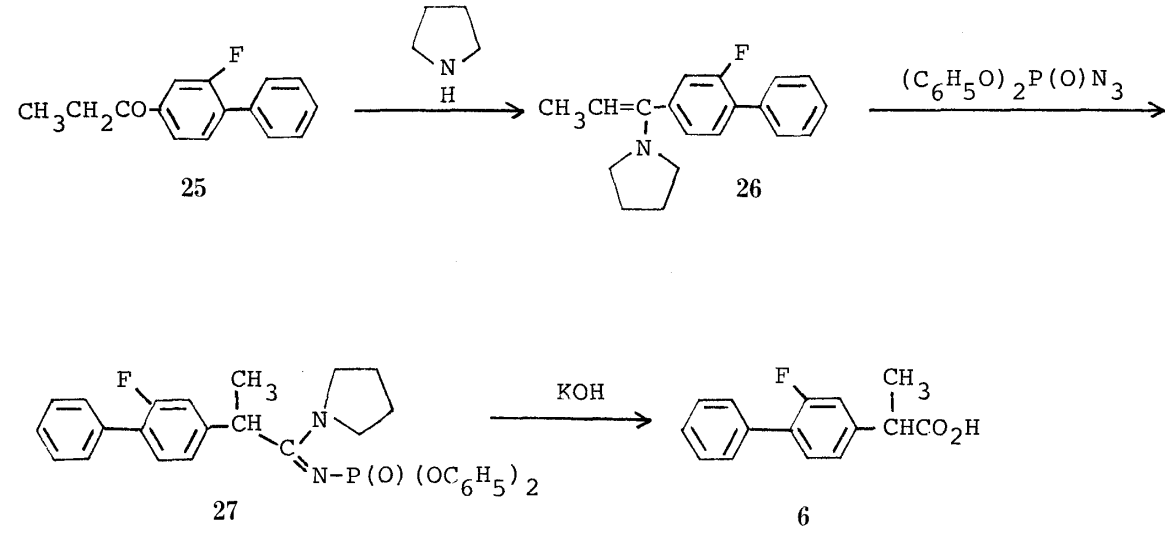


Chart 6. Preparation of Flurbiprofen (**6**)

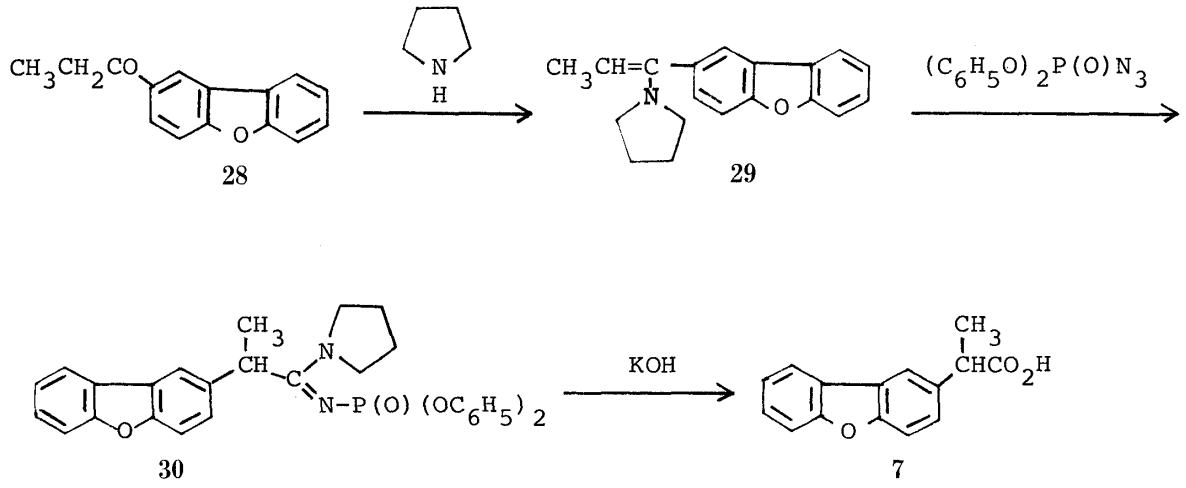


Chart 7. Preparation of 2-(2-Dibenzofuranyl)propionic Acid (**7**)

Flurbiprofen (**6**) was analogously prepared from 3-fluoro-4-phenylpropiophenone (**25**).[16] Thus, the ketone **25** was allowed to react with pyrrolidine to give the pyrrolidine enamine **26**, which on treatment with DPPA furnished the *N*-phosphorylated amidine **27**. Hydrolysis of **27** with potassium hydroxide afforded flurbiprofen (**6**).

Finally, 2-(2-dibenzofuranyl)propionic acid (**7**) was prepared as an example of a 2-(heteroaromatic)propionic acid. Preparation of the starting ketone **28**, 2-propionyldibenzofuran, was carried out from dibenzofuran according to the literature.[17] Successive treatments of the ketone **28** with pyrrolidine, DPPA, and potassium hydroxide afforded **7** in 65% overall yield *via* the enamine **29** and the amidine **30**.

The present study has confirmed the 1,3-dipolar behavior of DPPA toward enamines. Furthermore, the convenient three-step conversion of aryl ethyl ketones to 2-arylpropionic acids[18] may have wide applicability, especially to the preparation of many important medicinal agents having 2-arylalkanoic acid structures.

Experimental

General experimental procedures employed were essentially the same as described in our preceding paper.[1]

General Procedure for the Preparation of Phosphorus Azides 8—10——A mixture of phosphorus chloride (5 mmol) and sodium azide (0.65 g, 10 mmol) in acetone (3.5 ml) was stirred at room temperature for 18 h under nitrogen, then filtered. The filtrate was concentrated *in vacuo* and the residue was distilled in a Kugelrohr apparatus.

Diphenylphosphinic azide (**8**) was obtained in 66% yield, bp 140 °C (0.025—0.030 mmHg) [lit.[19] bp 137—140 °C (0.05 mmHg)]. Infrared (IR) ν_{max} cm^{-1}: 2150, 1260.

Diphenylthiophosphinic azide (**9**)[19] was obtained in 76% yield, bp 125 °C (0.01—0.02 mmHg). IR ν_{max} cm^{-1}: 2140, 1253.

Ethyl phenylthiophosphonoazidate (**10**) was obtained in 89% yield, bp 80 °C (0.003 mmHg). IR ν_{max} cm^{-1}: 2140, 1260. Nuclear magnetic resonance (NMR) δ ppm: 1.43 (3H, t, J=7 Hz), 4.41 (2H, m), 7.54 (3H, m), 8.06 (2H, m).

Preparation of Ibuprofen (3)

4-Isobutylpropiophenone (12)——Propionyl chloride (7.77 g, 60 × 1.4 mmol) was added to aluminum chloride (10.56 g, 60 × 1.3 mmol) suspended in methylene chloride (36 ml) with ice-cooling and stirring during 20 min. Isobutylbenzene (8.04 g, 60 mmol) was added to the above mixture during 1 h, and the whole was stirred at room temperature for 2 h, then left to stand overnight. The reaction mixture was poured into a mixture of ice (120 g) and concentrated hydrochloric acid (17 ml) to obtain the methylene chloride layer, and the water layer was extracted with chloroform. The combined organic layer was washed successively with water, 2% aqueous sodium hydroxide, and water, then dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was distilled at 86—87 °C (0.3 mmHg) to give **12** (9.86 g, 87%) as a colorless oil. IR ν_{max} cm^{-1}: 1695. NMR δ ppm: 0.95 (6H, d), 1.20 (3H, t, J=8 Hz), 1.9 (1H, m), 2.50 (2H, d, J=8 Hz), 2.92 (2H, q, J=8 Hz), 7.15 and 7.82 (4H, AB q).

The ketone **12** was converted to its 2,4-dinitrophenylhydrazone, mp 170—171.5 °C (recrystallized from ethyl acetate). *Anal.* Calcd for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.72; H, 6.03; N, 14.85.

1-[1-(4-Isobutylphenyl)-1-propenyl]pyrrolidine (13)——A mixture of 4-isobutylpropiophenone (**12**) (3.80 g, 20 mmol), pyrrolidine (4.27 g, 20 × 3 mmol), and boron trifluoride etherate (0.28 g, 20 × 0.1 mmol) in benzene (40 ml) was refluxed for 50 h using a Cope water separator with molecular sieve 4A as the dehydrating agent. The mixture was concentrated *in vacuo*, and the residue was distilled at 112—114 °C (0.4 mmHg) to give **13** (3.84 g, 79%) as a pale yellow viscous oil. IR ν_{max} cm^{-1}: 1640. NMR δ ppm: 0.90 (6H, d, J=6 Hz), 1.43 (3H, d, J=7 Hz), 1.7 (5H, m), 2.43 (2H, d, J=7 Hz), 2.8 (4H, m), 4.26 (1H, q, J=7 Hz), 7.05 (4H, s).

Reaction of the Enamine 13 with Diphenylphosphinic Azide (8)——(i) In Ethyl Acetate: A mixture of 4-isobutylpropiophenone (**12**) (0.95 g, 5 mmol), pyrrolidine (2.84 g, 5 × 8 mmol), and boron trifluoride etherate (0.21 g, 1.5 mmol) in toluene (20 ml)–hexane (5 ml) was refluxed for 20 h using a Cope water separator with molecular sieve 4A, then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (10 ml), and diphenylphosphinic azide (**8**) (1.46 g, 6 mmol) in ethyl acetate (5 ml) was added. The mixture was stirred under nitrogen at room temperature for 0.5 h, refluxed for 30 h, then concentrated *in vacuo*. The residue was dissolved in ethyl acetate–benzene (1 : 1, 100 ml) and the mixture was washed with 100 ml each of 5% aqueous citric acid, water, saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride, then dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was subjected to a silica gel column chromatography with acetone–ethyl acetate–hexane (4 : 4 : 1).

The first eluate fraction afforded the amidine **15a** (0.36 g, 37%) as colorless prisms, mp 116—116.5 °C (petroleum benzin). IR ν_{max} cm^{-1}: 1555, 1320, 1203, 1110. NMR δ ppm: 0.84 (6H, d, J=7 Hz), 1.36—2.04 (br m) and 1.52 (d, J=

8 Hz) (8H), 2.42 (2H, d, J=7 Hz), 2.58—2.96 (1H, m), 3.04—3.40 (1H, m), 3.64—3.96 (2H, m), 5.12 (1H, q, J=8 Hz), 5.92—7.24 (4H, m), 7.24—7.60 (6H, m), 7.8—8.2 (4H, m). *Anal.* Calcd for $C_{29}H_{35}N_2OP$: C, 75.95; H, 7.69; N, 6.11. Found: C, 76.26; H, 7.83; N, 6.20.

The second eluate fraction afforded the amidine **16a** as pale yellow prisms, mp 130—131 °C (petroleum benzin). IR ν_{max} cm^{-1}: 1558, 1230, 1202, 1110. NMR δ ppm: 0.91 (6H, d, J=7 Hz), 1.64—2.24 (5H, br m), 2.40 (2H, d, J=7 Hz), 3.12 (2H, m), 3.90 (2H, m), 7.00 (4H, d), 7.14—7.42 (6H, m), 7.50—7.88 (4H, m). *Anal.* Calcd for $C_{27}H_{31}N_2OP$: C, 75.33; H, 7.26; N, 6.51. Found: C, 75.35; H, 7.59; N, 6.39.

(ii) In Toluene: A mixture of the enamine **13** (1.22 g, 5 mmol) and diphenylphosphinic azide (**8**) (1.46 g, 5 × 1.2 mmol) in toluene (15 ml) was stirred at room temperature for 1 h, then refluxed for 5 h. Work-up as described in (i) afforded the crude product (2.25 g), a part (200 mg) of which was fractionated by silica gel preparative layer chromatography with acetone–ethyl acetate–hexane (1 : 2 : 1) to give the amidines **15a** (53 mg, 26%) and **16a** (74 mg, 39%).

Reaction of the Enamine 13 with Diphenylthiophosphinic Azide (9)——(i) In Ethyl Acetate: Diphenylthiophosphinic azide (**9**) (0.81 g, 3 mmol) in ethyl acetate (4 ml) was added to the enamine **13** (0.63 g, 2.6 mmol) in ethyl acetate (6 ml) under nitrogen. The mixture was stirred at room temperature for 2 h and refluxed for 22 h. After work-up as described in the case of the reaction of the enamine **13** with **8**, the crude product was separated by silica gel column chromatography with ethyl acetate–hexane (1 : 12).

The first eluate fraction afforded the amidine **15b** (0.49 g, 40%) as colorless needles, mp 179—180 °C (ethyl acetate–petroleum benzin). IR ν_{max} cm^{-1}: 1532, 1309, 1110. NMR δ ppm: 0.82 (6H, d, J=7 Hz), 1.13 (3H, d, J=7 Hz), 1.44—2.04 (5H, br m), 2.24—2.72 (br m) and 2.38 (d, J=8 Hz) (3H), 2.96—3.30 (1H, m), 3.60—3.94 (2H, m), 5.52 (1H, q, J=7 Hz), 6.98 (4H, s), 7.10—7.64 (6H, m), 7.06—8.30 (4H, m). *Anal.* Calcd for $C_{29}H_{35}N_2PS$: C, 73.38; H, 7.43; N, 5.90. Found: C, 73.53; H, 7.53; N, 5.85.

The second eluate fraction afforded the amidine **16b** (0.23 g, 20%) as colorless needles, mp 118—118.5 °C (petroleum benzin). IR ν_{max} cm^{-1}: 1550, 1102. NMR δ ppm: 0.88 (6H, d, J=7 Hz), 1.56—2.16 (5H, br m), 2.38 (2H, d, J=7 Hz), 3.07 (2H, m), 3.90 (2H, m), 6.90 (4H, s), 7.04—7.40 (6H, m), 7.58—7.96 (4H, m). *Anal.* Calcd for $C_{27}H_{31}N_2PS$: C, 72.61; H, 6.70; N, 6.27. Found: C, 72.38; H, 6.93; N, 6.33.

(ii) In Toluene: A mixture of the enamine **13** (1.22 g, 5 mmol) and diphenylthiophosphinic azide (**9**) (1.56 g, 5 × 1.2 mmol) in toluene (15 ml) was treated as described in (ii) for the reaction of **13** with **8**. A part (200 mg) of the crude product (2.33 g) was separated on a silica gel preparative layer plate with ethyl acetate–hexane (1 : 9) to give the amidines **15b** (74 mg, 36%) and **16b** (78 mg, 41%).

Reaction of the Enamine 13 with Ethyl Phenylthiophosphonoazidate (10)——(i) In Ethyl Acetate: Ethyl phenylthiophosphonoazidate (**10**) (0.74 g, 3.2 mmol) in ethyl acetate (3 ml) was added to the enamine **13** (1.20 g, 4.9 mmol) in ethyl acetate (6 ml), and the mixture was stirred at room temperature for 1 h, then refluxed for 18 h under nitrogen. After work-up as described for the reaction of the enamine **13** with **8**, the crude product was separated by silica gel column chromatography with ethyl acetate–hexane (1 : 10).

The first eluate fraction afforded the amidine **15c** (0.82 g, 57%) as colorless needles, mp 99—100.5 °C (petroleum benzin). IR ν_{max} cm^{-1}: 1553, 1315, 1110. NMR δ ppm: 0.88 (6H, d-d, J=7 Hz and 3 Hz), 1.12—1.48 (3H, m), 1.54—1.92 (4H, m), 2.32—2.80 (3H, br m), 2.96—3.32 (1H, m), 3.55—3.80 (2H, m), 3.80—4.32 (2H, m), 5.16—5.60 (1H, m), 7.03 (4H, s), 7.12—7.56 (3H, m), 7.96—8.28 (2H, m). *Anal.* Calcd for $C_{25}H_{35}N_2OPS$: C, 67.84; H, 7.97; N, 6.33. Found: C, 67.80; H, 7.87; N, 6.41.

The second eluate fraction afforded the amidine **16c** (0.18 g, 13%) as a colorless oil, bp 210—220 °C (0.032 mmHg) on Kugelrohr distillation. IR ν_{max} cm^{-1}: 1550, 1333, 1112. NMR δ ppm: 0.90 (6H, d, J=7 Hz), 1.11 (3H, m), 1.60—2.08 (5H, br m), 2.43 (2H, d, J=8 Hz), 3.08 (2H, m), 3.64—4.00 (4H, m), 7.06 (4H, s), 7.16—7.44 (3H, m), 7.64—7.92 (2H, m). *Anal.* Calcd for $C_{23}H_{31}N_2OPS$: C, 66.64; H, 7.54; N, 6.76. Found: C, 66.75; H, 7.85; N, 6.84.

(ii) In Toluene: A mixture of the enamine **13** (1.22 g, 5 mmol) and ethyl phenylthiophosphonoazidate (**10**) (1.36 g, 5 × 1.2 mmol) in toluene (15 ml) was treated as described in (ii) for the reaction of **13** with **8**. A part (210 mg) of the crude product (2.19 g) was separated on a silica gel preparative layer plate with ethyl acetate–hexane (1 : 4) to give the amidines **15c** (47 mg, 31%) and **16c** (30 mg, 21%).

Diphenyl *N*-[2-(4-Isobutylphenyl)-1-pyrrolidinopropylidene]phosphoramidate (15d)——(i) From the Isolated Enamine 13: A mixture of the enamine **13** (1.22 g, 5 mmol) and DPPA (1.65 g, 5 × 1.2 mmol) in tetrahydrofuran (15 ml) was stirred at room temperature for 1 h, and at 40 °C for 1 h, then refluxed for 2 h. Ethyl acetate–benzene (1 : 1, 100 ml) was added, and the mixture was successively washed with 30 ml each of 5% aqueous citric acid, water, saturated aqueous sodium chloride, saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride, then dried over magnesium sulfate. The solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography with ethyl acetate–hexane (1 : 1) to give the amidine **15d** (1.86 g, 76%) as a colorless viscous oil. IR ν_{max} cm^{-1}: 1565, 1246, 1222, 1203. NMR δ ppm: 0.89 (6H, d, J=7 Hz), 1.47 (d, J=7 Hz) and 1.54 (m) (8H), 2.40 (2H, d, J=8 Hz), 2.58—3.72 (4H, m), 4.77 (1H, q, J=7 Hz), 6.93, 7.11, 7.18 (14H, m). *Anal.* Calcd for $C_{29}H_{35}N_2O_3P$: C, 71.00; H, 7.19; N, 5.71. Found: C, 71.01; H, 7.20; N, 5.76.

(ii) By the One-flask Procedure: A mixture of 4-isobutylpropiophenone **12** (0.95 g, 5 mmol), pyrrolidine (1.07 g, 5 × 3 mmol), and boron trifluoride etherate (0.07 g, 5 × 0.1 mmol) in benzene (60 ml) was refluxed for 50 h using a

Cope water separator with molecular sieve 4A as the dehydrating agent. The mixture was concentrated *in vacuo*, then DPPA (1.65 g, 5 × 1.2 mmol) in tetrahydrofuran (15 ml) was added to the residue under argon, and the mixture was treated as described in (i) to give the amidine **15d** (1.91 g, 78%, based on **12**).

Ibuprofen[2-(4-Isobutylphenyl)propionic Acid] (3)——A mixture of the amidine **15d** (1.473 g, 3 mmol) and potassium hydroxide (2.95 g, 3 × 15 mmol) in ethylene glycol (35 ml) was refluxed for 12 h. Water (300 ml) was added and the pH of the solution was adjusted to 9 by introduction of carbon dioxide gas. After being washed with diethyl ether (50 ml × 6), the mixture was acidified with hydrochloric acid and extracted with diethyl ether (50 ml × 6) and ethyl acetate (50 ml × 2). The organic extracts were washed with water and saturated aqueous sodium chloride, then dried over magnesium sulfate. The mixture was concentrated *in vacuo* to give ibuprofen (**3**) (489 mg, 79%) as a brown solid. Recrystallization from petroleum benzin afforded colorless needles, mp 74—75 °C (lit.[6] mp 75—77 °C). IR ν_{max} cm^{-1}: 2800, 1730. NMR δ ppm: 0.91 (6H, d, J=7 Hz), 1.47 (J=7 Hz) and 1.8 (m) (4H), 2.43 (2H, d, J=7 Hz), 3.68 (1H, q, J=7 Hz), 7.13 (4H, m), 9.44 (1H, br s).

Preparation of Naproxen (4)

6-Methoxy-2-propionylnaphthalene (17)——Prepared from 2-methoxynaphthalene (31.64 g, 0.2 mol), aluminum chloride (34.7 g, 0.2 × 1.3 mol), and propionyl chloride (24.06 g, 0.2 × 1.3 mol) in nitrobenzene (160 ml) according to the method in the literature,[13,20] bp 171—174 °C (0.3 mmHg) and mp 109—110 °C (methanol) (lit.[13] bp 180—185 °C (0.3 mmHg) and mp 109 °C). IR ν_{max} cm^{-1}: 1685. NMR δ ppm: 1.23 (3H, t, J=7 Hz), 3.02 (2H, q, J=7 Hz), 3.84 (3H, s), 7.02—8.23 (6H, m).

1-[1-(6-Methoxy-2-naphthyl)-1-propenyl]pyrrolidine (18)——A mixture of the ketone **17** (6.43 g, 30 mmol), pyrrolidine (6.40 g, 30 × 3 mmol), and boron trifluoride etherate (0.43 g, 30 × 0.1 mmol) in benzene (50 ml) was refluxed for 68 h using a Cope water separator with molecular sieve 4A as the dehydrating agent. The mixture was concentrated *in vacuo*, and the residue was distilled at 148—154 °C (0.2 mmHg) to give the enamine **18** (5.25 g, 65%) as a yellow viscous oil, which contained a small amount of impurities but solidified later, mp 55—62 °C. IR ν_{max} cm^{-1}: 1640. NMR δ ppm: 1.52 (d, J=7 Hz) and 1.79 (m) (7H), 2.79 (4H, m), 3.84 (3H, s), 4.35 (1H, q, J=7 Hz), 6.96—7.63 (6H, m).

Diphenyl *N*-[2-(6-Methoxy-2-naphthyl)-1-pyrrolidinopropylidene]phosphoramidate (19)——(i) From the Isolated Enamine 18: A mixture of the enamine **18** (1.07 g, 4 mmol) and DPPA (1.32 g, 4 × 1.2 mmol) in tetrahydrofuran (12 ml) was stirred under argon at room temperature for 1 h, then at 40 °C for 2 h, and at 50 °C for 1 h. The mixture was worked up as described for the preparation of **15d**, and the crude product was purified by silica gel column chromatography with ethyl acetate–hexane (2 : 1) to give the amidine **19** (1.33 g, 65%) as a pale yellow viscous oil, which solidified with diethyl ether–hexane. Recrystallization from ethyl acetate–hexane afforded colorless needles, mp 102.5—105 °C. IR ν_{max} cm^{-1}: 1561, 1244, 1219, 1204. NMR δ ppm: 1.57—1.68 (7H, d, J=6.6 Hz, and m), 2.5—3.7 (4H, m), 3.86 (3H, s), 4.92 (1H, q, J=7 Hz), 7.02—7.62 (16H, m). *Anal.* Calcd for $C_{30}H_{31}N_2O_3P$: C, 70.02; H, 6.07; N, 5.45. Found: C, 70.18; H, 6.28; N, 5.52.

(ii) By the One-Flask Procedure: Using the ketone **17** (1.07 g, 5 mmol), the reaction was carried out as described in (ii) for the preparation of **15d**. The crude product was purified by silica gel column chromatography with ethyl acetate–hexane (2 : 1) to give the amidine **19** (2.10 g, 82%, based on the ketone **17**).

***rac*-Naproxen[2-(6-Methoxy-2-naphthyl)propionic Acid] (4)**——A mixture of the amidine **19** (515 mg, 1 mmol) and potassium hydroxide (0.35 g, 1 × 5 mmol) in ethylene glycol (10 ml) was refluxed for 8 h. Work-up as described for the preparation of **3** afforded **4** (184 mg, 83%), which was further purified by silica gel column chromatography with chloroform–methanol–acetic acid (200 : 10 : 1) to give colorless needles (157 mg, 71%), mp 151.5—152.5 °C (lit.[7] mp 150—151.5 °C). IR ν_{max} cm^{-1}: 1705. NMR δ ppm: 1.58 (3H, d, J=7 Hz), 3.85 (1H, q), 3.88 (3H, s), 7.05—7.73 (6H, m).

Preparation of Ketoprofen (5)

3-Bromopropiophenone Ethylene Acetal (21)——A mixture of 3-bromopropiophenone[14] (**20**) (10.65 g, 50 mmol), ethylene glycol (8.3 ml), and *p*-toluenesulfonic acid (0.48 g) in benzene (100 ml) was refluxed for 7 h using a Cope water separator. Benzene (100 ml) was added, and the mixture was washed with saturated aqueous sodium bicarbonate then dried over magnesium sulfate. The solvent was removed *in vacuo*, and the residue was distilled at 94—96 °C (3 mmHg) to give the acetal **21** (11.32 g, 88%) as a colorless oil, whose IR showed no carbonyl group. NMR δ ppm: 0.88 (3H, t, J=7 Hz), 1.80 (2H, q, J=7 Hz), 3.8 (4H, m), 6.9—7.5 (4H, m). *Anal.* Calcd for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.10. Found: C, 51.28; H, 5.08.

3-Propionylbenzophenone (22)——Butyllithium in hexane (20 ml, 25 × 1.1 mmol) was added to the acetal **21** (6.43 g, 25 mmol) in tetrahydrofuran (40 ml) during 15 min under argon. After the mixture had been stirred at room temperature for 2 h, benzonitrile (2.83 g, 25 × 1.1 mmol) was added and the whole was stirred at room temperature for 0.5 h. After the addition of 10% hydrochloric acid (20 ml), the reaction mixture was refluxed for 2 h and stirred at room temperature overnight. Ethyl acetate–benzene (1 : 1, 200 ml) was added and the organic layer was washed with saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride, then dried over magnesium sulfate. The solvent was removed *in vacuo*, and the residue was ditilled at 160—164 °C (3 mmHg) to give the ketone **22** (3.49 g, 59%). Pentane was added to oily **22**, and the mixture was kept in a freezer until it crystallized. Recrystallization from diethyl ether–pentane afforded colorless scales, mp 38.5—39 °C. IR ν_{max} cm^{-1}: 1690, 1665.

NMR δ ppm: 1.14 (3H, t, J=7 Hz), 2.89 (2H, q, J=7 Hz), 7.5—8.25 (9H, m). *Anal.* Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.94; H, 5.92.

1-[1-(3-Benzoylphenyl)-1-propenyl]pyrrolidine (23)——A mixture of the ketone **22** (1.67 g, 7 mmol), pyrrolidine (1.49 g, 7 × 3 mmol), and boron trifluoride etherate (0.10 g, 7 × 0.1 mmol) in toluene (60 ml) was refluxed for 25 h using a Cope water separator with molecular sieve 4A as the dehydrating agent. After concentration *in vacuo*, the residue was distilled at 160—162 °C (0.11 mmHg) to give the enamine **23** (0.83 g, 41%) as an orange viscous oil. IR ν_{max} cm^{-1}: 1665, 1635. NMR δ ppm: 1.55 (d, J=7 Hz) and 1.78 (m) (7H), 2.84 (4H, m), 4.47 (1H, q, J=7 Hz), 7.42—7.84 (9H, m).

Diphenyl *N*-[2-(3-Benzoylphenyl)-1-pyrrolidinopropylidene]phosphoramidate (24)——A mixture of the enamine **24** (0.71 g, 2.4 mmol) and DPPA (0.81 g, 2.4 × 1.2 mmol) in tetrahydrofuran (7.5 ml) was stirred under argon at room temperature for 1 h, and at 40 °C for 1 h, then refluxed for 2 h. Work-up as described for the preparation of **15d**, followed by silica gel column chromatography of the crude product with ethyl acetate–hexane (3 : 1) afforded the amidine **24** (0.93 g, 72%) as a pale yellow amorphous solid. IR ν_{max} cm^{-1}: 1656, 1559, 1241, 1218, 1196. NMR δ ppm: 1.54 (d, J=7 Hz) and 1.63 (m) (7H), 3.0 and 3.4 (4H, m), 4.82 (1H, q, J=7 Hz), 7.15—7.77 (19H, m). *Anal.* Calcd for $C_{32}H_{31}N_2O_4P$: C, 71.36; H, 5.80; N, 5.20. Found: C, 71.66; H, 6.10; N, 5.07.

Ketoprofen[2-(3-Benzoylphenyl)propionic Acid] (5)——A mixture of the amidine **24** (423 mg, 0.78 mmol) and potassium hydroxide (0.77 g, 0.78 × 15 mmol) in ethylene glycol (15 ml) was refluxed for 6 h. Work-up as described for the preparation of **3** afforded the crude product (199 mg). A part (179 mg) of the crude product was dissolved in ethyl acetate (60 ml) and extracted with saturated aqueous sodium bicarbonate (20 ml × 2). The alkaline extracts were acidified with hydrochloric acid, and extracted with ethyl acetate (20 ml × 3). The organic extracts were washed with water and saturated aqueous sodium chloride, then dried over magnesium sulfate. The solvent was removed *in vacuo* to give a brown solid (161 mg), 154 mg of which was purified by silica gel column chromatography with chloroform–methanol–acetic acid (200 : 10 : 1) to give a pale yellow solid (139 mg). IR ν_{max} cm^{-1}: 3400. NMR δ ppm: 5.8 (1H, s). A part (52 mg) of the solid was dissolved in acetone (2 ml), and Jones' reagent[21] was added at room temperature till the color of the solution turned reddish-yellow. After the addition of isopropanol to decompose chromic acid, chloroform (70 ml) was added and the precipitates were filtered off. The filtrate was washed with water and dried over magnesium sulfate. Concentration *in vacuo* afforded ketoprofen (**5**) (46 mg, 72%) as a colorless viscous oil (lit.[8] mp 94 °C). IR ν_{max} cm^{-1}: 1730, 1705, 1655. NMR δ ppm: 1.50 (3H, d, J=7 Hz), 3.76 (1H, q, J=7 Hz), 7.2—7.75 (9H, m), 11.29 (1H, br s).

Preparation of Flurbiprofen (6)

1-[1-(2-Fluoro-4-biphenylyl)-1-propenyl]pyrrolidine (26)——A mixture of 3-fluoro-4-phenylpropiophenone (**25**)[16] (1.14 g, 5 mmol), pyrrolidine (1.07 g, 5 × 3 mmol), and boron trifluoride etherate (0.07 g, 5 × 0.1 mmol) in toluene (50 ml) was refluxed for 38 h and worked up as described for the preparation of **13** to give the enamine **26** (579 mg, 33%) as a yellow viscous oil, bp 136—138 °C (0.11 mmHg). IR ν_{max} cm^{-1}: 1650, 1635. NMR δ ppm: 1.54 (d, J=7 Hz) and 1.77 (m) (7H), 2.83 (4H, m), 4.44 (1H, q, J=7 Hz), 6.97—7.41 (8H, m).

Diphenyl *N*-[2-(2-Fluoro-4-biphenylyl)-1-pyrrolidinopropylidene]phosphoramidate (27)——A mixture of the enamine **26** (531 mg, 1.89 mmol) and DPPA (0.62 g, 1.89 × 1.2 mmol) in tetrahydrofuran (6 ml) was treated as described in (i) for the preparation of **15d** to give the crude amidine **27**, which was purified by silica gel column chromatography with ethyl acetate–benzene (3 : 1) to furnish the pure amidine **27** (674 mg, 68%). Recrystallization from ethyl acetate–hexane afforded colorless crystals, mp 70—73 °C. NMR δ ppm: 1.54 (d, J=7 Hz) and 1.72 (m) (7H), 3.1 and 3.5 (4H, m), 4.81 (1H, q, 7 Hz), 7.2 (18H, m). *Anal.* Calcd for $C_{31}H_{30}FN_2O_3P$: C, 70.44; H, 5.72; N, 5.30. Found: C, 70.34; H, 5.95; N, 5.08.

Flurbiprofen[2-(2-Fluoro-4-biphenylyl)propionic Acid] (6)——A mixture of the amidine **27** (528 mg, 1 mmol) and potassium hydroxide (0.3 g, 1 × 4.5 mmol) in ethylene glycol (10 ml) was refluxed for 8 h, and worked up as described for the preparation of **3** to give **6** (73 mg, 30%). Recrystallization from ethyl acetate–hexane afforded colorless crystals, mp 113—114 °C (lit.[9] mp 110—111 °C).

Preparation of 2-(2-Dibenzofuranyl)propionic Acid (7)

1-[1-(2-Dibenzofuranyl)-1-propenyl]pyrrolidine (29)——A mixture of 2-propionyldibenzofuran (**28**)[17] (2.00 g, 10 mmol), pyrrolidine (2.13 g, 10 × 3 mmol), and boron trifluoride etherate (0.14 g, 10 × 0.1 mmol) in toluene (50 ml) was treated as described for the preparation of **13** to give the enamine **29** (0.95 g, 34%) as a yellow viscous oil, bp 168—170 °C (0.45 mmHg). IR ν_{max} cm^{-1}: 1610. NMR δ ppm: 1.51 (d, J=7 Hz) and 1.75 (m) (7H), 2.83 (4H, m), 4.37 (1H, q, J=7 Hz), 7.16—7.93 (7H, m).

Diphenyl *N*-[2-(2-Dibenzofuranyl)-1-pyrrolidinopropylidene]phosphoramidate (30)——The enamine **29** was prepared as above, from the ketone **28** (601 mg, 3 mmol), pyrrolidine (640 mg, 3 × 3 mmol), and boron trifluoride etherate (40 mg) in toluene (30 ml). The crude enamine **29** was dissolved in tetrahydrofuran (9 ml), and allowed to react with DPPA (990 mg, 3 × 1.2 mmol) under argon. The reaction mixture was treated as described in (ii) for the preparation of **15d** to give the amidine **30** (1.11 g, 71%, based on **28**) as a yellow viscous oil. IR ν_{max} cm^{-1}: 1560, 1241, 1218, 1195. NMR δ ppm: 1.6 (7H, d and br m), 2.5—3.5 (4H, m), 4.88 (1H, q, J=7 Hz), 7.19 and 7.76 (17H, m). *Anal.* Calcd for $C_{31}H_{29}O_4N_2P$: C, 70.98; H, 5.57; N, 5.34. Found: C, 71.19; H, 5.87; N, 5.64.

2-(2-Dibenzofuranyl)propionic Acid (7)——A mixture of the amidine **30** (825 mg, 1.57 mmol) and potassium

hydroxide (1.57 g, 1.57 × 15 mmol) in ethylene glycol (30 ml) was refluxed for 7 h, and worked up as described for the preparation of **3** to give **7** (345 mg, 92%) as a pale brown solid. Recrystallization from ethyl acetate–hexane afforded colorless neeles, mp 141—142.5 °C (lit.[10] mp 139—140 °C). IR ν_{max} cm^{-1}: 1697, 1197. NMR δ ppm: 1.59 (3H, d, J= 6 Hz), 3.86 (1H, q, J=6 Hz), 7.2—7.4 and 7.8 (7H, m), 9 (1H, br s).

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