Organic Process Research & Development **2004**, *8,* 952−954

# A Novel and Efficient Route to Zafirlukast

Keesari Srinivas, Neti Srinivasan, Muddasani Rama Krishna, Chinta Raveendra Reddy, Muthulingam Arunagiri, Routhu Lalitha, Kikkuru Sri Rami Reddy, Bijjula Sreenivasa Reddy, Ghanta Mahesh Reddy, Padi Pratap Reddy, Muppa Kishore Kumar, and Manne Satyanaraya Reddy*

*Department of Research and Development, MSN Laboratories Ltd., Survey No. 317 and 323, Rudraram, Patancheru, Medak District - 502 329, A.P, India*

**Abstract:**

**Zafirlukast, an important drug for allergic pulmonary disorders such as asthma, is synthesized by a five-step, high-yielding, and inexpensive process.**

## Introduction

Zafirlukast is a potential drug used in the treatment of pulmonary disorders such as asthma.[1] Zafirlukast acts by antagonizing the pharmacological actions of one or more of the arachidonic acid metabolites known as leukotrienes.[2] The reported synthetic method for this anti-asthma drug involved eight stages (Scheme 1), esterification of **1** using acetyl chloride in methanol to give **2**, which upon bromination using free bromine in carbon tetrachloride yielded bromo compound **3**. Condensation of **3** with 5-nitro indole (**4**) in the presence of silver oxide and dioxane yielded the corresponding product **5** which on methylation with methyl iodide afforded *N*-methylated compound **6**, whose nitro group reduction gave amino compound **7**. Reaction of **7** with cyclopentyl chloroformate afforded the corresponding amide ester **8**. Methyl ester hydrolysis in **8** with lithium hydroxide in THF/MeOH mixture to give the corresponding acid **9**, and its subsequent condensation with *o*-toluenesulfonamide afforded zafirlukast (**10**). This process suffers with the disadvantage of producing some unwanted byproducts such as polysubstituted indoles.[3] Further, this process involves column chromatography purification, which is not very practical for industrial scale-up. In addition to this, usage of hazardous chemicals such as acetyl chloride, bromine, and sodium hydride make this method less attractive for industrial scale-up. A recent patent described a multistep method for the preparation of zafirlukast, which involves an expensive reagent, 1-[3-(dimethyl-amino) propyl]-3-ethylcarbodiimide hydrochloride.[4] Herein we report a five-step, high-yielding, and inexpensive process for Zafirlukast.

## Results and Discussion

In our approach we have identified 3-methoxy-4-methylbenzoic acid (**1**), a readily accessible and commercially available compound, as an apt starting material. Bromination of **1** with different brominating agents such as bromine or *N*-bromosuccinamide with different solvents such as dichloromethane, choroform, ethylenedichloride, carbon tetrachloride and dioxane combined with dibenzylperoxide at different reaction conditions yielded low-quality and poor yields, and the reaction did not proceed to completion. When we employed 1,3-dibromo-5,5-dimethylhydantoin and 2,2′-azo-bis-isobutyronitrile in chloroform, the reaction afforded bromomethylbenzoic acid derivative (**11**) in 81% yield. This brominating agent is relatively cheaper and easier to handle. As it supplies two bromine atoms, its half equivalent is sufficient to promote the reaction. Condensation of **11** with *N*-methyl-5-nitro indole (**12**) in dioxane in the presence of $Ag_2O$ as per reported conditions resulted in several impurities along with the indole derivative **13**. However, when the reaction was conducted in the presence of zinc bromide at 60−65 °C, it furnished indole derivative (**13**) in 62% yield. The required *N*-methyl-5-nitro indole **12** is readily obtained from the methylation of commercially available 5-nitro-indole.[4] The presence of any alkyl group as the indole nitrogen effectively arrested the formation of *N*-arylkyl byproducts. Further, the selectively of the reaction at the third position of the indole moiety may also be attributed to the presence of an *N*-methyl group which sterically hinders the attack at the second position in the indole moiety. The inexpensive and commercially available dicyclohexylcarbodiimide facilitated a facile condensation of indole-substituted benzoic acid derivative **13** with *o*-toluenesulfonamide in the presence of 4-(dimethylamino)pyridine as catalyst to give required intermediate **14** in 63% yield. Catalytic hydrogenation of **14** using Raney-nickel in methanol smoothly afforded amino compound **15** which, on reaction with cyclopentyl-chloroformate, yielded the desired product **10** in 89% yield (Scheme 2).

* To whom correspondence should be addressed. E-mail: drmsnl@yahoo.co.in. Fax: + 91 8455 220415.

(1) Hogaboom, G. K.; Mong, S.; Wu, H.-L.; Crooke, S. T. *Biochem. Biophys. Res. Commun.* **1983**, *116*, 1136.

(2) (a) Buckner, C. K.; Saban, R.; Castleman, W. L.; Will, J. A. *Ann. N.Y. Acad. Sci.* **1988**, *524*, 181. (b) Buckner, C.; Fedyna, J.; Krell, R.; Robertson, J.; Keith, R.; Matassa, V.; Brown, F.; Bernstein, P.; Yee, Y.; Will, J.; Fishleder, R.; Saban, R.; Hesp, B.; Giles, R. *FASEB J.* **1988**, *2*, A1264 (Abstr.). (c) Jones, T. R.; Charette, L.; Denia, D. *Can. J. Physiol. Pharmacol.* **1988**, *66*, 762. (d) Hay, D. W. P.; Muccitelli, R. M.; Tucker, S. S.; Vickery-Clark, L. M.; Wilson, K. A.; Gleason, J. G.; Hall, R. F.; Wasserman, M. A.; Torphy, T. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 474.

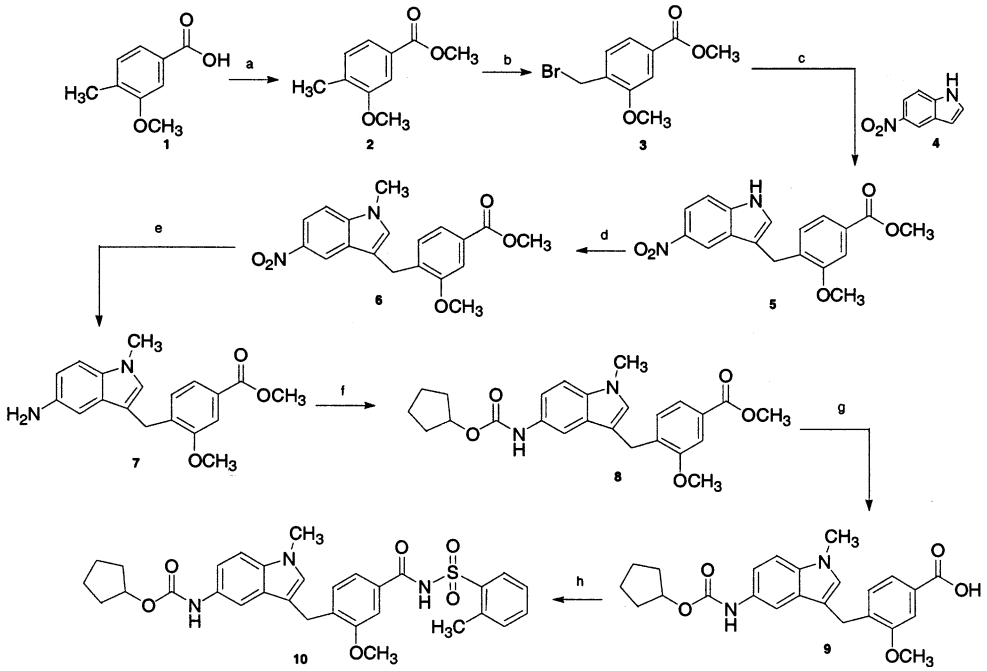
(3) (a) Matassa, V. G.; Maduskuie, T. P., Jr.; Shapiro, H. S.; Hesp, B.; Snyder, D. W.; Aharony, D.; Krell, R. D.; Keith, R. A. *J. Med. Chem.* **1990**, *33*, 1781. (b) Yee, Y. K.; Bernstein, P. R.; Adams, E, J.; Brown, F. J.; Cronk, L. A.; Hebbel, K. C.; Vacek, E. P.; Krell, R. D.; Snyder, D. W. *J. Med. Chem.* **1990**, *33*, 2437. (c) Bernstein, P. R.; Brown, F. J.; Matassa, V. G.; Yee, Y. K. U.S. Patent 4,859,692, 1989.

(4) Arie. G.; Genndy, N.; Igor, Z.; Victor, P.; Maxim, S. WO 02/46153 A2.


Published on Web 10/19/2004

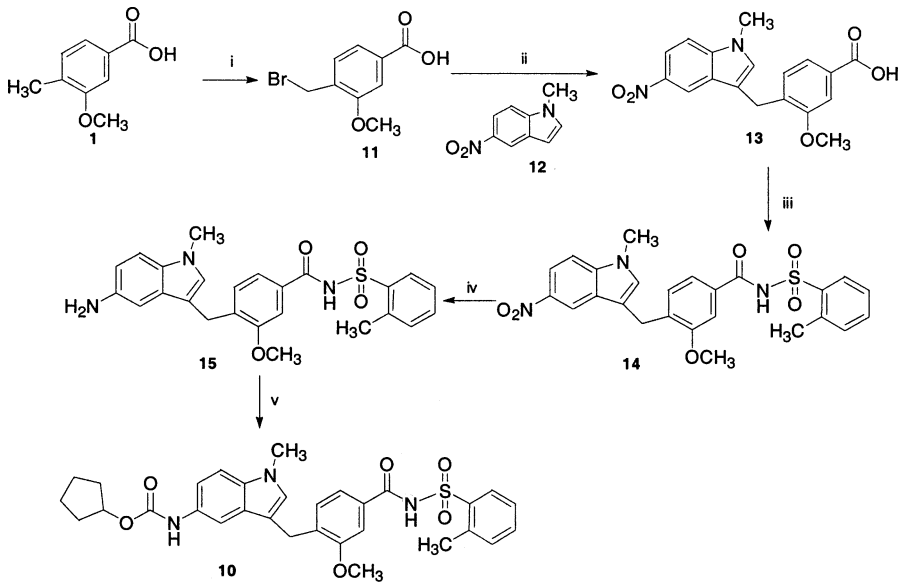
10.1021/op049869i CCC: $27.50 

**Scheme 1**[a]



[a] Reagents and conditions: a) AcCl, MeOH; b) $Br_2/CCl_4$; c) $Ag_2O$/dioxane; d) $CH_3I$/THF; e) Pd/C, MeOH, $H_2$; f) cyclopentyl chloroformate/*N*-methylmorpholine; g) LiOH·$H_2O$/THF:MeOH; h) 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, DMAP, *o*-toluenesulfonamide, $CH_2Cl_2$.

**Scheme 2**[a]



[a] Reagents and conditions: i) DBDMH/AIBN/$CHCl_3$, reflux, 81%; ii) zinc bromide/dioxane/60−65 °C, 62%; iii) dicyclohexyl carbodiimide, DMAP, *o*-toluenesulfonamide, $CH_2Cl_2$, 63%; iv) Ra-Ni,THF, $H_2$, 88%; v) cyclopentylchloroformate/*N*-methylmorpholine, $CH_2Cl_2$.

## Conclusions

In conclusion, we have provided a novel, cost-effective, and industrially scaleable approach to the anti-asthama drug, zafirlukast.

## Experimental Section

The $^1H$ and $^{13}C$NMR spectra were measured in $CDCl_3$ and DMSO, using 200 and 50 MHz, respectively, on a Varian Gemini 200 MHz FT NMR spectrometer; the chemical shifts are reported in $\delta$ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBR dispersion using Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on HP-5989A LC−MS spectrometer. The CHN analysis was carried out on a Perkin-Elmer model 2400S analyzer. The melting points were determined by using the capillary method on POLMON (model MP-96) melting point apparatus. The solvents and reagents were used without further purification.

**4-Bromomethyl-3-methoxybenzoic Acid (11).** A mixture of 3-methoxy-4-methyl benzoic acid (**1**, 50.0 g, 0.30 mol), 1,3-dibromo-5,5-dimethylhydantoin (55.0 g, 0.192 mol), and 2,2′-azobisisobutyronitrile (5.0 g, 0.030 mol) in chloroform (250 mL) was heated under reflux for 4 h. The reaction mixture was cooled to 25−35 °C, the formed byproduct was

filtered, and the filtrate was washed with water (150 mL). The organic layer was separated and concentrated under vacuum. The obtained residue was triturated with petroleum ether (150 mL), and the obtained solid was filtered and dried under vacuum: yield 60.0 g, 81%; mp 184−190 °C.

$^1$H NMR ($CDCl_3$): $\delta$ 8.9 (br s, 1H), 7.7−7.3 (m, 3H), 4.59 (s, 2H), 3.9 (s, 3H); $^{13}$C NMR: $\delta$ 179.2, 166.9,157.1, 132.6, 131.0, 130.5, 121.7, 55.8, 28.61. MS: $m/e$ = 245 $M^+$. Anal. Calcd for $C_9H_9BrO_3$: C, 44.11; H, 3.70. Found: C, 44.08; H, 3.67.

**3-Methoxy-4-(*N*-methyl-5-nitroindole-3-yl)benzoic Acid (13).** A mixture of *N*-methyl-5-nitroindole (**12**, 50.0 g, 0.284mol), 4-bromomethyl-3-methoxybenzoic acid (125.0 g, 0.510 mol), zinc bromide (37.5 g, 0.161 mol), and dioxane (250 mL) was stirred at 60−65 °C for 14 h. Reaction mass was filtered through hyflow and washed with dioxane (100 mL). The filtrate was evaporated and dissolved in dichloromethane (150 mL), basified with sodium hydroxide (10.0 g, 0.25 mol) solution. The basic aqueous layer was acidified with hydrochloric acid (12.5 mL) and was extracted with dichloromethane (250 mL). The organic layer was washed with water (250 mL) and concentrated, and a fine solid was isolated in methanol (150 mL): yield 60.0 g, 62%; mp 234−240 °C.

$^1$H NMR ($CDCl_3$): $\delta$ 8.5 (s, 1H), 8.05 (d, 1H), 7.6−7.2 (m, 4H), 6.9 (s, 1H), 4.2 (s, 2H), 3.9 (s, 3H), 3.85 (s, 3H); $^{13}$C NMR: $\delta$ 171.0, 156.6, 140.2, 139.4, 134.0, 130.2, 129.7, 125.9, 121.7, 118.7, 115.3, 110.8, 55.4, 32.7, 24.4. MS: $m/e$ = 341 $M^+$. Anal. Calcd for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23. Found: C, 63.40; H, 4.68; N, 8.19.

***N*1-{3-Methyl-4-[(*N*-methyl-5-nitro-1*H*-3-indolyl)methylbenzoyl}-2-methyl-1-benzenesulfonamide (14).** A mixture of 3-methoxy-4-(*N*-methyl-5-nitroindole-3-yl)benzoic acid (**13**, 50.0 g, 0.147 mol), 4-(dimethylamino)pyridine (5.0 g, 0.040 mol), 1,3-dicyclohexylcarbodiimide (30.0 g, 0.145 mol), and *o*-toluenesulfonamide (25.0 g, 0.146 mol) in dichloromethane (250 mL) was stirred under reflux for 5 h. After the reaction was cooled to 25−35 °C, the solid was filtered, the filtrate was washed with a solution of hydrochloric acid (25 mL) and water (225 mL) followed by rinsing with water, and the organic layer was concentrated under vacuum. The resulting crude material was dissolved in methanol (150 mL), cooled to 0 °C for 30 min; the byproduct (dicyclohexylurea) was filtered, and the solid was washed with cool methanol (25 mL), and the filtrate was concentrated under vacuum: yield 45.5 g, 63%.

$^1$H NMR ($CDCl_3$): $\delta$ 9.05 (br s, 1H), 8.51 (d, 1H), 8.25 (d, 1H), 8.11 (d, 1H), 7.5−7.1 (m, 7H), 6.92 (s, 1H), 4.10 (s, 2H), 3.88 (s, 3H), 3.78 (s, 3H), 2.68 (s, 3H). $^{13}$C NMR: $\delta$ 164.6, 156.3, 140.2, 139.1, 136.8, 134.1, 131.7, 130.3, 129.1, 126.3, 125.4, 120.5, 115.7, 115.0, 109.0, 55.1, 32.5, 24.3, 19.5. MS: $m/e$ = 493 $M^+$. Anal. Calcd for $C_{25}H_{23}N_3O_6S$: C, 60.84; H, 4.70; N, 8.51. Found: C, 60.72; H, 4.65; N, 8.46.

***N*1-{4-[(5-Amino-*N*-methyl-1H-3-indolyl)methyl]-3-methylbenzoyl}-2-methyl-1-benzenesulfonamide (15).** A solution of *N*-{3-methyl-4-[(*N*-methyl-5-nitro-1*H*-3-indolyl)-methylbenzoyl}-2-methyl-1-benzenesulfonamide (**14**, 40.0 g, 0.081 mol) tetrahydrofuran (120 mL), and Raney-nickel (8 mL) was placed under par hydrogenation apparatus under hydrogen (3.0 kg) pressure at 25−35 °C for 2 h. The reaction mass was filtered through a hyflow bed, and the catalyst was washed with tetrahydrofuran (40 mL). The combined filtrates were concentrated, and the obtained residue was triturated with petroleum ether (150 mL) resulting in 33.2 g, 88% yield of compound **15** as a fine solid.

$^1$H NMR: $\delta$ 7.93 (d, 1H), 7.57−6.67 (m, 10H), 3.88 (s, 2H), 3.85 (s, 3H), 3.69 (s, 3H), 2.49 (s, 3H); $^{13}$C NMR: $\delta$ 164.6, 157.2, 144.7, 138.3, 138.0, 136.3, 135.2, 134.8, 134.6, 132.1, 129.5, 125.6, 125.0, 121.3, 114.7, 110.8, 108.0, 55.6, 32.5, 22.9, 20.3. MS: $m/e$ = 463 $M^+$. Anal. Calcd for $C_{25}H_{25}N_3O_4S$: C, 64.78; H, 5.44; N, 9.06. Found: C, 64.70; H, 5.38; N, 8.99.

**[3[[2-Methoxy-4-[[[(2-methyl phenyl)sulfonyl]amino]-carbonyl]phenyl]methyl]-*N*-methyl-1*H*-indole-5-yl]carbamicacid Cyclopentylester (10).** To a solution of *N*1-{4-[(5-amino-*N*-methyl-1*H*-3-indolyl)methyl]-3-methylbenzoyl}-2-methyl-1-benzenesulfonamide (**15**, 25.0 g, 0.053 mol) was added dichloromethane (125 mL), *N*-methylmorpholine (25 mL, 0.227 mol), and cyclopentylchloroformate (11.25 mL, 0.087 mol) at 25−35 °C under nitrogen atmosphere, and the solution was stirred for 30 min. The reaction mixture was quenched slowly with a solution of hydrochloric acid (12.5 mL) and water (112.5 mL). The separated organic layer was washed with water (125 mL), and the solvent was completely removed under vacuum: yield as a solid 27.5 g, 89%.

$^1$H NMR ($CDCl_3$): $\delta$ 9.67 (s, 1H), 8.23 (d, 1H), 7.01−7.51 (m, 9H), 6.73 (s, 1H), 6.58 (s, 1H), 5.08−5.23 (m, 1H), 3.98 (s, 2H), 3.79 (s, 3H), 3.73 (q, 4H), 3.67 (s, 3H), 2.66 (s, 3H), 1.45−1.87 (m, 8H), 1.22 (t, 3H). $^{13}$C NMR: $\delta$ 164.6, 156.3, 135, 127, 109, 77, 55, 32.4, 23.3. MS: $m/e$ = 575 $M^+$. Anal. Calcd for $C_{31}H_{33}N_3O_6S$: C, 64.68; H, 5.78; N, 7.30. Found: C, 64.61; H, 5.68; N, 7.28.

Received for review July 2, 2004.

OP049869I