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A Convergent Synthesis of Ro24-5913, a Novel Leukotriene D_4 Antagonist

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Abstract: A new and convergent synthesis of the leukotriene D_4 antagonist Ro24-5913 (**9**) has been developed that can serve both for technical production and combinatorial structure optimization. The synthesis of **6**, achieved in 90% yield, is described. The conversion of **6** to **9** has been disclosed previously.

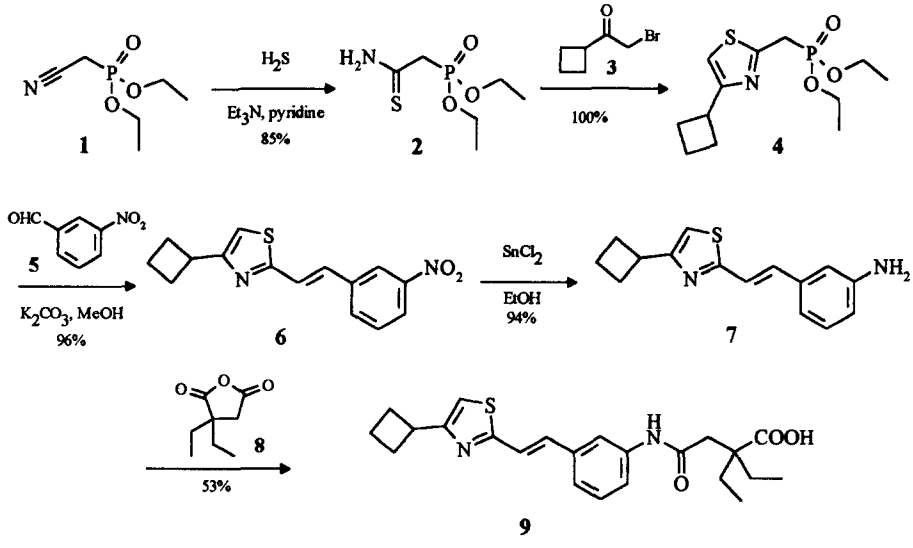
N-Succinyl-3-(2-thiazolethenyl)anilides represent a distinct class of high-affinity LTD_4 receptor antagonists of which **9** (Ro24-5913) appears to be the most active member.[1] This compound had previously been synthesized by two different routes,[2] both leading to the principal intermediate **6**. In one lengthy protocol, 3-nitrobenzaldehyde is converted to 3-nitrothiocinnamide via 3-nitrocinnamic acid, followed by a Hantsch thiazole construction using bromoacetylcyclobutane. A more convergent attempt at the assembly of **6** by a Claisen-type condensation of the 3-nitrobenzaldehyde and 4-cyclobutyl-2-methylthiazole, followed by dehydration, was met with low yields.

The development of a highly convergent synthesis of **9** was consequential to us for two reasons. We planned combinatorial synthetic variations of **9** on the one hand, and required a basis for an efficient technical synthesis of this compound, or its successor, on the other. In view of the low yield obtained in the condensation of 3-nitrobenzaldehyde and 4-cyclobutyl-2-methylthiazole, a reaction using a (2-thiazolylmethyl) phosphonium salt or respective phosphonate with the nitrobenzaldehyde would be expected to give **6** in a more efficient manner. The selection in favor of the Wittig-Horner reagent was based on synthetic simplicity and economy, and high product yield with a favorable *E*:*Z* ratio.[3]

The required intermediate **2** had previously been prepared in low yield by mercaptolysis of **1**[4] and, with the additional support of a Russian patent,[5] a process suitable for laboratory scale was developed. Spurred by the interest in the synthetic route presented here, further advances toward of a technical synthesis of **2** have recently been achieved.[6,7] Bromoacetylcyclobutane (**3**), prepared from cyclobutyl methyl ketone,[8] on reaction with **2**[9] furnished **4** in quantitative yield. A number of mild, inorganic bases were recently explored for condensations with Wittig-Horner and Wittig-type reagents. Examples include potassium carbonate,[10-13] cesium carbonate,[14,15] magnesium oxide,[16] zinc oxide,[16] potassium fluoride[17] and even potassium hydrogen carbonate.[18] We found that the condensation of 3-nitrobenzaldehyde and **4**, where the typical electron-withdrawing group of

a Wittig-Horner reagent is now replaced by the π-excessive 2-thiazolyl group, proceeded in very high yield and product purity employing potassium carbonate and methanol.[19] The resulting **6** was contaminated with 2.7% of the *Z*-isomer which could be removed by conversion to the crystalline hydrochloride salt. The subsequent reduction of **6** and the acylation of the resulting **7** by **8** have been described.[2]

The protocol presented here constitutes a suitable basis for further technical development and lends itself for combinatorial synthetic variations of **9**. Structural diversity can now be introduced at each of the three building blocks, namely at the thiazole, benzene, and carboxylic acid anhydride moieties.



Experimental

(2-Amino-2-thioxoethyl)phophonic acid diethyl ester (**2**)

Hydrogen sulfide (13.3 g, 0.39 mol) was added, via submerged tube, to a mixture of diethyl cyanomethyl phosphonate (50 g, 0.282 mol), triethylamine (79 mL, 0.567 mol) and pyridine (53 mL, 0.655 mol), contained in a round bottom flask equipped with dry-ice condenser and potassium-hydroxide-filled vent tube. The contents of the sealed flask were stirred at room temperature for 16 h, then evaporated at 55 °C under reduced pressure to afford a crystalline residue. This material was dissolved in dichloromethane (200 mL) and the solution washed with 1:1 water - saturated sodium chloride solution (200 mL). The aqueous phase was reextracted with dichloromethane (100 mL) and a 1:1 water - saturated sodium chloride solution (50 mL) was used to wash, sequentially, the first and second extract. The organic extracts were combined and evaporated, and the crystalline residue was dried at 45 °C and 10 torr to afford 50.5 g (85%) of **2** which was used directly in the next step. An analytically pure sample was obtained after flash chromatography (ethyl acetate), mp 73-75 °C, 400 MHz ^{1}NMR ($CDCl_3$): δ 1.36 (6H, t, 2×CH_3 of Et, J = 6.8 Hz), 3.41 (2H, d, CH_2-P, $J_{H,P}$ = 20.8 Hz), 4.17 (4H, m, 2× CH_2O), 7.62 and 8.38 (1H each, br s, NH_2).

[(4-Cyclobutyl-2-thiazol)methyl]phosphonic acid diethyl ester (**4**)

A solution of **3** was prepared as follows. A mixture of cyclobutyl methyl ketone (10 g, 0.102 mol) and methanol (80 mL) was cooled to 5 °C and acetic acid containing 30% hydrobromic acid (0.8 mL) was added.[20] Bromine (5 mL, 0.097 mol) was then added dropwise to this solution over a 10 min period while the temperature was maintained at 5 °C. An ice - water mixture was added (10 g) after 4 h. The mixture was then stirred for 45 min at ambient temperature, cooled again in an ice bath, and the crude, powdered thioamide **2** (20.45 g, 0.0968 mol) was added to the stirred solution without exceeding the temperature of 30 °C. A solution was gradually obtained while the yellow color faded. After stirring at room temperature overnight, **2** was no longer detectable. The solution was cooled again in an ice bath, rendered basic by the dropwise addition of concentrated ammonium hydroxide solution, and evaporated. The residue was taken up in ethyl acetate (150 mL) and the solution was washed with water (100 mL). The aqueous phase was reextracted with ethyl acetate (75 mL) and 50 mL of saturated sodium chloride solution was used to wash the first and then the second extract. The extracts were combined, dried (sodium sulfate) and evaporated. The residue was further dried at 60 °C and 10 torr to afford **4** as a dark oil (28 g, 100% yield based on **2**, 99.8% purity by RP-HPLC, Nova C_{18}, 4 μ, 15 cm × 4 mm, 1 mL/min, 5:33:62, tetrahydrofuran - acetonitrile - 0.01 M tetrabutylammonium phosphate, pH 5.7, 14.4 min, 240 nm) that was used without further purification. An analytically pure sample was obtained by flash chromatography (ethyl acetate) followed by Kugelrohr distillation at 92-95 °C and 0.2 torr, 400 MHz ^{1}NMR ($CDCl_3$): δ 1.30 (6H, t, 2×CH_3 of Et, J = 7 Hz), 1.85-2.08 (2H, m, H-3 of cyclobutyl), 2.17-2.39 (4H, m, H-2 and H-4 of cyclobutyl), 3.61 (2H, d, $J_{H,P}$ = 21.2 Hz, CH_2-P), 3.64 (1H, m, H-1 of cyclobutyl), 4.12 (4H, m, 2× CH_2O), 6.84 (1H, s, H-5 of thiazol), EI mass spectrum m/z (rel intensity): 289 (29, $[M]^+$), 261 (100, [M–C_2H_4]), 244 (6, [M–OC_2H_5]), 233 (8, [261–C_2H_4]), 216 (6, [261–OC_2H_5]), 205 (10, [233–C_2H_4]), 187 (13, [233–C_2H_5OH]), 152 (36, [M–diethylphosponyl]), 138 (52, [M–cyclobutylthiazolyl methyl]), HR mass spectrum: calcd for [M]: 289.0901, found: 289.0894.

(E)-4-Cyclopentyl-2-[2-(3-nitrophenyl)ethenyl]thiazole (**6**)

Powdered potassium carbonate (40.1 g, 0.29 mol) was added to a vigorously stirred mixture of crude **4** (28 g, 0.0968 mol), **5** (15.2 g, 0.1 mol) and methanol (400 mL). After stirring overnight at room temperature, **4** was no longer detectable (TLC 95:5, ethyl acetate - methanol). The suspension was concentrated under reduced pressure to remove ca. half of the methanol, diluted with water (200 mL) and stirred for one h. The suspension was filtered, and the solids washed with water (2×100 mL) and dried for 16 h at 30 °C and 10 torr to furnish 26.6 g of **6** as a mustard-colored powder, 96% yield based on crude **4** used, 96.8% purity by RP-HPLC (same experimental conditions as described for **4**), 67.7 min. The *Z*-isomer was present at a concentration of 2.7% (62.7 min). The crude **6** (24.5 g, 0.855 mol) was dissolved in methanol (250 mL) by heating to reflux temperature and the solution was allowed to cool to ca 40 °C, whereupon concentrated hydrochloric acid (15 mL) was added dropwise. The mixture was heated for 30 min at reflux temperature, then

allowed to cool. The resulting suspension was cooled in an ice bath for 30 min and filtered. The solids were washed with methanol (2×40 mL) and dried for 16 h at 55 °C and 20 torr to furnish 26 g of **6** hydrochloride as pale yellow crystals, 94% yield based on crude **6** used, 99.8% purity by RP-HPLC (same experimental conditions as described for **4**). The *Z*-isomer could not be detected. 400 MHz ^{1}NMR ($CDCl_3$): δ 1.83-2.07 (2H, m, H-3 of cyclobutyl), 2.20-2.35 (4H, m, H-2 and H-4 of cyclobutyl), 3.66 (1H, m, H-1 of cyclobutyl), 7.38 (1H, s, H-5 of thiazol), 7.62 and 7.73 (1H each, AB, CH=CH, J_t = 16 Hz), 7.69 (1H, t, H5 of Ph, J_o = 8 Hz), 8.16 (1H, dd, H6 of Ph, J_o = 8 Hz, J_m = 2 Hz), 8.20 (1H, d, H4 of Ph, J_o = 8 Hz), 8.55 (1H, s, H2 of Ph). Anal. calcd for $C_{15}H_{14}N_2O_2S$·HCl: C, 55.81, H, 4.68, N, 8.68, S, 9.93; found: C, 55.74, H, 4.53, N, 8.53, S, 9.90.

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