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A Practical and Efficient Process for the Preparation of Tazarotene

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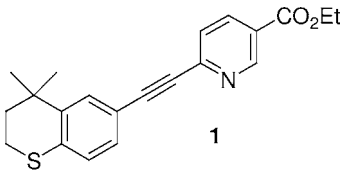
Abstract:

We describe an efficient process for the preparation of tazarotene starting from 4,4-dimethyl-6-bromothiochromane *S*-oxide (9), 2-methyl-3-butyn-2-ol (10), and 6-chloronicotinic acid ethyl ester (8). Our synthetic pathway compares favorably over the previously reported procedures since tazarotene was prepared straightforwardly using cheap reagents and without the employment of hazardous organometallic compounds. The process is based on the use of sulfoxide 9 as key starting material. The C-15 framework of the target was built up by means of two different approaches based on a palladium-mediated coupling reaction. The molecular structure of compound has been confirmed by X-ray crystallography.

Introduction

Retinoids are biologically active molecules that exert strong effects on cell growth, apoptosis, and differentiation. The anti-inflammatory and chemopreventive activities of the first generation retinoids tretinoin (all *trans*-retinoic acid) and isotretinoin (13-*cis*-retinoic acid) have been successfully employed in dermatology and oncology. Conversely, certain toxic side effects have limited the application of the latter compounds prompting the studies on the synthesis of more specific drugs.[1,2] Tazarotene **1** (Figure 1) is a member of this new generation of receptor-selective, synthetic retinoids, and it is topically effective in the treatment of acne, psoriasis, and photoaging. This acetylenic compound has been developed by Allergan Inc. that patented[3] its preparation and use as a topical drug (Tazorac/Zorac) and more recently as an oral drug (Tazoral). Structurally, tazarotene is composed of two units that are a thiochromane moiety and a nicotinic acid ester, linked with an acetylenic bond. From a synthetic point of view the stereospecific preparation of this compounds shows some difficulties. Although 4,4-dimethyl thiochromane and substituted nicotinic acids derivatives are easily available, the construction of the triple bond directly linked to the two aromatic rings is not readily achievable on an industrial scale.

The reported synthetic approach[3] is based on the Sonogashira coupling[4] of 4,4-dimethyl-6-ethynylthiochromane **4**



Tazarotene (Tazorac/Zorac)

Figure 1. **Chemical structure of tazarotene.**

(Scheme 1) with 6-chloronicotinic acid ethyl ester **8**. The compound **4** has been prepared by two different C-2 homologation pathways. The first is based on the use of 4,4-dimethylthiochromane **2** that was submitted to Friedel–Crafts acylation with acetyl chloride to give 4,4-dimethyl-6-acetylthiochromane **3**. The methyl-ketone functionality was converted into the acetylenic moiety by lithium diisopropylamide-mediated elimination of the corresponding enol-phosphate ester. Otherwise, palladium-mediated coupling of 4,4-dimethyl-6-bromothiochromane **5** with trimethylsilylacetylene **6** followed by basic hydrolysis of the trimethylsilyl protecting group could give again **4**. Both methods suffer different drawbacks. The transformation of the ketone **3** to acetylene **4** needed the handling and the extensive employment of hazardous reagents as LDA (3 equiv) and of the intermediate phosphate ester. Moreover, trimethylsilylacetylene is rather expensive, and the Sonogashira coupling with the bromo derivative **5** is not effective and requires forcing conditions to reach acceptable conversions. Therefore a practical synthesis was needed for **1** using a suitable procedure.

To overcome the use of LDA, a recent patent from Glenmark Pharmaceuticals Ltd[5] describes an improvement of initial work of Allergan. Acetylene **4** was prepared from **3** by a two steps procedure involving Wilsmeier–Haack reaction on **3** followed by sodium hydroxide treatment.

Otherwise, we have reinvestigated the palladium-mediated coupling of a protected acetylene with the thiochromane moiety as a method for C-2 homologation. Our studies were based on envisaging that two different improvements could be achieved. First of all the modification of the oxidation state of the sulfur atom of **5** could activate the above-mentioned coupling. Moreover, several propyn-ol derivatives, e.g., 2-methyl-3-butyn-2-ol **10**, are cheap and an efficient synthetic equivalent of acetylene. On the basis of this thinking, we now report a practical synthesis of tazarotene starting from inexpensive starting materials avoiding the use

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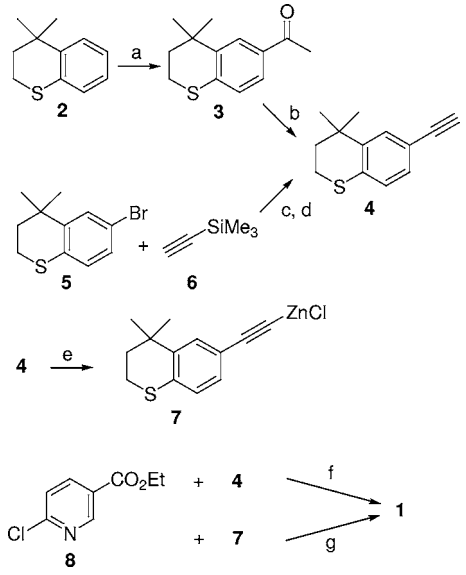
Scheme 1[a]



[a] Reagents: (a) AcCl, benzene, $SnCl_4$ cat.; (b) LDA 1 equiv, THF, −78 °C, $(EtO)_2POCl$ 1 equiv, then LDA 2 equiv, rt, 15 h; (c) CuI cat., $(Ph_3P)_2PdCl_2$ cat., Et_3N sealed tube 100 °C, 64 h; (d) KOH aq. 1 N, ^{i}PrOH, rt 16 h; (e) BuLi 1 equiv THF, $ZnCl_2$; (f) CuI cat., $(Ph_3P)_2PdCl_2$ cat., Et_3N, 55 °C, 18 h; (g) $(Ph_3P)_4Pd$ cat., THF, rt 20 h.

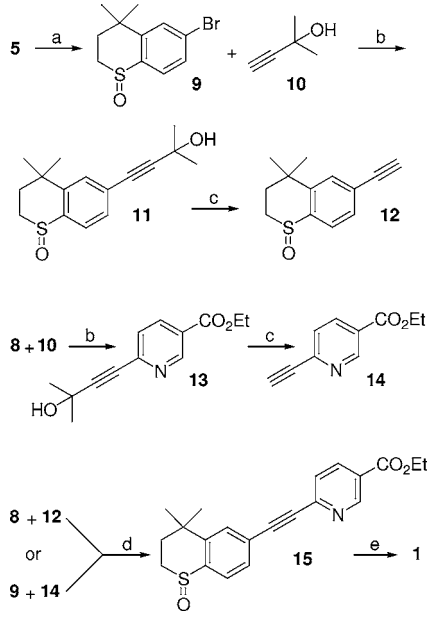
of special equipment for handling of dangerous reagents and intermediates.

Results and Discussion

As mentioned above, we first examined the oxidation of 4,4-dimethyl-6-bromothiochromane **5**. In considering that the sulfur atom should be reduced again to prepare tazarotene and that sulfones are only with some difficulty[6] reduced to sulfides, we settled on the sulfoxide derivative to be employed in our synthetic route. We found out that 4,4-dimethyl-6-bromothiochromane S-oxide **9** was readily obtainable from **5** by *m*-CPBA or peracetic acid treatment in CH_2Cl_2 solution at 0 °C (Scheme 2). In addition, **9** was isolated by simple crystallization avoiding the use of chromatographic separations. Therefore, we tested **9** in the coupling reaction with the acetylenic derivative **10**. Indeed, 2-methyl-3-butyn-2-ol **10** is an inexpensive synthetic equivalent of acetylene[7] since it can be transformed in acetylene and acetone by treatment with a catalytic amount of base. The homologation process was then performed using Cosford protocol[8] that is based on a catalytic system consisting of Pd/C in combination with PPh_3 and CuI. Accordingly, coupling of **9** and **10** was achieved by heating the latter compounds in DME/water solution in the presence of K_2CO_3 as base and of the Pd/C (2% mol), CuI (4% mol), PPh_3 (8% mol) catalysts. Compound **11** was therefore obtained in very good yields (83%) as a crystalline solid and through a simple procedure of workup and purification. Since comparative coupling experiments between **5** and **10** were unsuccessful, these results confirm the assumption that oxidation of the sulfur atom of **5** activate the reaction.

The following deprotection was accomplished by treatment of a toluene solution of **11** with a catalytic amount

Scheme 2[a]



[a] Reagents: (a) MCPBA, CH_2Cl_2, 0 °C, 1 h; (b) K_2CO_3, CuI cat., 10% Pd/C cat., Ph_3P cat., H_2O/DME 80 °C, 5 h; (c) NaH cat., toluene, reflux; (d) CuI cat., $(Ph_3P)_2PdCl_2$ cat., Et_3N, DMF, 50 °C, 3 h; (e) PCl_3, DMF, −20 °C, 1 h.

(10−15% mol.) of sodium hydride and distilling off the toluene/acetone mixture hence formed. After workup, crystalline 4,4-dimethyl-6-ethynylthiochromane *S*-oxide **12** was obtained in good yields (84%) and purity (95%) by simple concentration of organic solution and without any further purification. Moreover, the latter approach proved to be very flexible. In effect, the C-2 homologation step could be directed also to a nicotinic ester moiety. Coupling of 6-chloronicotinic acid ester **8** with **10** afforded **13** in satisfactory yields (69%). The following deprotection was conducted in the same condition described above for preparation of **12** and gave acetylenic derivative **14** (72%). Therefore, two approaches to the tazarotene framework become possible: coupling of acetylenic sulfoxide **12** with 6-chloronicotinate **8** and coupling of bromothiochromane derivative **9** with 6-ethynylnicotinate **14**. We tested the latter pathway by the Sonogashira reaction and found that both were effective with minor differences. In both cases the synthesis was performed at 50 °C in DMF solution using $(Ph_3P)_2PdCl_2$ (5% mol) and CuI (10% mol) as catalyst and triethylamine as base. Coupling of **8** with **12** gave tazarotene *S*-oxide **15** in 79% yield whilst reaction of **9** with **14** afforded **15** in 57% yield. Initially, **15** was purified by chromatography, but further experiments on a larger scale demonstrated that crystallization gave a product of purity adequate to be employed in the next step. The most appropriate conditions for reduction of the sulfoxide functionality[9] were identified after several experiments. We found that the reaction of **15** in DMF solution with PCl_3 at −20 °C smoothly afforded tazarotene **1** in 79% yield. Purification by chromatography and crystallization from hexane allowed us to obtained **1** as

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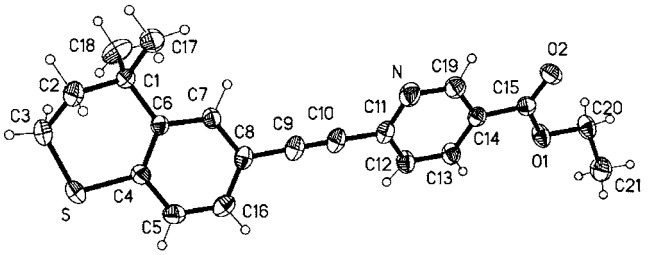

Figure 2. **ORTEP diagram of molecular structure of 1, with atom-labeling scheme. The non-H atoms are shown at 30% probability displacement ellipsoids.**

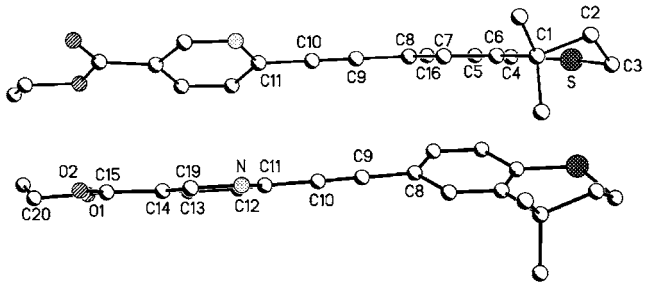

Figure 3. **Two selected views of the molecule showing the two moieties of nearly coplanar atoms.**

a crystalline product of acceptable quality for single-crystal X-ray investigation. The structure of **1** is reported in Figure 2. The molecular conformation has been found to be chatacterized by two sets of nearly coplanar atoms as shown in Figure 3. The two moieties form an interplanar angle of 30.9(1)° with one another. The fused six-membered heteronuclear ring adopts an envelop (half-boat) conformation.

Conclusions

In summary, we have successfully developed a practical and efficient process for the synthesis of the acetylenic retinoid tazarotene **1**. Our pathway is superior over the previously reported approaches for several reasons. The employment of expensive starting materials and reagents has been reduced, and the use of special equipment for handling of dangerous reagents and intermediates has been avoided. In addition the introduction of sulfoxide functionality was beneficial. The coupling reactions were more effective increasing yields, experimental conditions become milder, and the products were often crystalline. Moreover, the reaction procedures were operationally simple, robust, and susceptible for industrial application.

Experimental Section

General. All solvents and reagents were purchased from the suppliers and used without further purification. ^{1}H NMR spectra were recorded in $CDCl_3$ solution at room temperature unless otherwise stated, on a Bruker AC-400 spectrometer (400 MHz ^{1}H). The chemical-shift scale is based on internal tetramethylsilane. IR spectra were recorded on a Perkin-Elmer 2000 FTIR spectrometer. Mass spectra were measured on a Finnigan-MAT TSQ 70 spectrometer. Melting points were measured on a Reichert melting-point apparatus, equipped with a Reichert microscope, and are uncorrected. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. Microanalyses were determined on an analyser *1106* from *Carlo Erba*. All the chromatographic separations were carried out on silica gel columns. GC analyses: *HP-6890* gas chromatograph; determined on an *HP-5* column (30 m × 0.32 mm; *Hewlett-Packard*).

4,4-Dimethyl-6-bromothiochromane *S*-Oxide (9). 4,4-Dimethyl-6-bromothiochromane (30.2 g, 117 mmol) was dissolved in CH_2Cl_2 (400 mL), and the resulting solution was cooled at 0 °C. MCPBA 75% (28.1 g, 118 mmol) was added portionwise under stirring and keeping the reaction temperature below 5 °C. After addition the mixture was stirred for 1 h at 0 °C and 2 h at rt. The MCBA formed was removed by filtration, and the organic phase was washed with a saturated solution of $Na_2S_2O_5$ (100 mL) and with a saturated solution of $NaHCO_3$ (200 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The solid residue was taken up in a mixture of hexane (120 mL) and ethyl acetate (80 mL) and heated to reflux. The obtained homogeneous solution was then cooled to 0 °C and the crystalline material that separated was collected by filtration and washed with cold hexane (50 mL) to give pure (98% GC) **9** (25 g, 78% yield); mp 120−122 °C; ^{1}H NMR δ 1.31(3H, s), 1.45 (3H, s), 1.87 (1H, ddd, J = 2.6, 8.4, 15.0 Hz), 2.45 (1H, ddd, J = 2.6, 10.5, 15.0 Hz), 3.12 (2H, m), 7.49 (1H, dd, J = 1.9, 8.3 Hz), 7.58 (1H, d, J = 1.9 Hz), 7.61 (1H, d, J = 8.3 Hz); IR (Nujol) cm^{-1} 1578, 1549, 1412, 1088, 1030, 924, 810, 760; EI-MS (*m*/*z*) 274 (5), 272 (5), 257 (100), 255 (98), 243 (23), 241 (28), 229 (48), 227 (32), 215 (12), 176 (37), 162 (58), 148 (99), 129 (39), 115 (32), 102 (11), 89 (10), 77 (9), 63 (11). Anal. Calcd for $C_{11}H_{13}BrOS$: C, 48.36; H, 4.80; Br, 29.25; S, 11.74. Found: C, 48.50; H, 4.75; Br, 29.25; S, 11.80.

4-(4,4-Dimethylthiochroman-6yl)-2-methyl-3-butyn-2-ol *S*-Oxide (11). To a solution of **9** (7.94 g, 29,0 mmol) in DME (120 mL) was added water (55 mL), K_2CO_3 (10.01 g, 72.4 mmol), CuI (0.22 g, 1.16 mmol), Ph_3P (0.60 g, 2.3 mmol), and 10% Pd/C (0.62 g, 0.58 mmol). The resulting mixture was stirred at rt for 30 min, and then 2-methyl-3-butyn-2-ol (7.1 mL, 72.4 mmol) was added and the reaction warmed at 80 °C for 5 h. The mixture was cooled to rt and filtered on a Celite pad washing with ethyl acetate. The solution was diluted with water (400 mL) and extracted with ethyl acetate (2 × 300 mL). The organic phase was washed with brine (150 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography (eluent hexanes−ethyl acetate 2:1) and crystallization (hexane−acetate 1:3, 60 mL) to give 6.61 g of pure (97% GC) **11** (83% yield); mp 109−110 °C; ^{1}H NMR δ 1.31(3H, s), 1.45 (3H, s), 1.63 (6H, s), 1.87 (1H, ddd, J = 2.3, 8.6, 14.7 Hz), 2.45 (1H, ddd, J = 2.3, 10.5, 14.7 Hz), 3.12 (2H, m), 7.37 (1H, dd, J = 1.6, 8.1 Hz), 7.47 (1H, d, J = 1.6 Hz), 7.68 (1H, d, J = 8.1 Hz); IR (Nujol) cm^{-1} 3292, 1593, 1256, 1177, 1055, 1032, 945, 896, 825; EI-MS (*m*/*z*) 276 (10), 259 (100), 245 (38), 233 (17), 213 (28), 201 (40), 187 (16), 173 (20), 171 (19), 165 (5), 153 (11), 139 (9), 128 (10), 115 (20), 101 (5), 89 (5). Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.53; H, 7.29; S, 11.58. Found: C, 69.60; H, 7.35; S, 11.50.

In a further experiment the crude reaction mixture obtained by coupling of **9** (16 g) and **10** (14 mL) was purified without chromatography by two crystallizations (hexane−acetate 1:3, 2 × 80 mL) to give 11.6 g of **11** (94% GC, 72% yield).

4,4-Dimethyl-6-ethynylthiochromane *S*-Oxide (12). NaH (400 mg of a 60% dispersion in mineral oil, 10 mmol) was added to a stirred solution of **11** (32.86 g, 119 mmol) in dry toluene (400 mL). The suspension was slowly distilled until about 200 mL of the toluene/acetone mixture were collected. The residue was cooled and concentrated under reduced pressure. The obtained solid was dissolved in diethyl ether (400 mL), and the mixture was washed with 1 M Na_2CO_3 solution (100 mL), water (60 mL), and brine (100 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give **12** (95% GC, 21.7 g, 84% yield); mp 105−107 °C; ^{1}H NMR δ 1.32 (3H, s), 1.45 (3H, s), 1.88 (1H, ddd, J = 2.5, 8.8, 15.1 Hz), 2.44 (1H, ddd, J = 2.5, 10.3, 15.1 Hz), 3.08 (1H, ddd, J = 2.5, 8.8, 13.1 Hz), 3.17 (1H, s), 3.19 (1H, m), 7.46 (1H, dd, J = 1.5, 8.1 Hz), 7.56 (1H, d, J = 1.5 Hz), 7.71 (1H, d, J = 8.1 Hz); IR (Nujol) cm^{-1} 3206, 2102, 1593, 1544, 1409, 1110, 1030, 827; EI-MS (*m*/*z*) 218 (8), 201 (100), 187 (11), 175 (23), 173 (49), 159 (17), 147 (5), 139 (9), 129 (11), 115 (18), 102 (3), 89 (5). Anal. Calcd for $C_{13}H_{14}OS$: C, 71.52; H, 6.46; S, 14.69. Found: C, 71.45; H, 6.50; S, 14.75.

6-[2-(4,4-Dimethylthiochroman-6yl)ethynyl]nicotinic Acid Ethyl Ester *S*-Oxide (15) via Coupling of 8 and 12. $(Ph_3P)_2PdCl_2$ (5.93 g, 8.5 mmol) and CuI (2.37 g, 12.4 mmol) were added under nitrogen to a solution of **8** (21.24 g, 114.5 mmol), triethylamine (60 mL), and **12** (21,7 g, 99.5 mmol) in *N*,*N*-dimethylformamide (400 mL). The mixture was warmed to 50 °C and stirred until no more starting **12** was detected by TLC analysis (3 h). After cooling to rt the reaction was diluted with ethyl acetate (600 mL) and washed with water (3 × 300 mL). The aqueous phases were extracted again with ethyl acetate (2 × 200 mL), and the combined organic phases were washed with brine (200 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography (hexane/acetate 5:2) and crystallization from a mixture of hexane (90 mL) and ethyl acetate (10 mL) to afford pure (98% GC) **15** (29.0 g, 79% yield); mp 144−146 °C; ^{1}H NMR δ 1.34 (3H, s), 1.43 (3H, t, J = 7.1 Hz), 1.48 (3H, s), 1.91 (1H, ddd, J = 2.4, 8.9, 15.1 Hz), 2.45 (1H, ddd, J = 2.4, 10.1, 15.1 Hz), 3.16 (2H, m), 4.45 (2H, q, J = 7.1 Hz), 7.58 (1H, dd, J = 1.6, 8.1 Hz), 7.62 (1H, m), 7.71 (1H, d, J = 1.6 Hz), 7.78 (1H, d, J = 8.1 Hz), 8.31 (1H, dd, J = 2.1, 8.1 Hz), 9.23 (1H, m); IR (Nujol) cm^{-1} 2210, 1723, 1589, 1376, 1292, 1134, 1114, 1034, 827, 779. Anal. Calcd for $C_{21}H_{21}NO_3S$: C, 68.64; H, 5.76; N, 3.81; S, 8.73. Found: C, 68.60; H, 5.75; N, 3.75; S, 8.75.

In a further experiment the crude reaction mixture obtained by coupling of **8** (40 g) and **12** (40 g) was purified without chromatography by two crystallizations (hexane−acetate 9:1, 2 × 160 mL) to give 41.2 g of **15** (94% GC, 61% yield).

Coupling Experiments between 5 and 10: 4,4-Dimethyl-6-bromothiochromane **5** (3 g) and 2-methyl-3-butyn-2-ol **10** (10 mL) were coupled using the experimental conditions described for **9**/**10** coupling and **8**/**12** coupling. The GC−MS analyses of the crude reaction mixtures do not evidence the presence of the expected coupling product.

6-[2-(4,4-Dimethylthiochroman-6-yl)ethynyl]nicotinic Acid Ethyl Ester (1). PCl_3 (6.9 mL, 79.0 mmol) was added dropwise to a stirred solution of **15** (29.0 g, 79.0 mmol) in *N*,*N*-dimethylformamide (300 mL) at −20 °C. After 1 h, the mixture was warmed to rt, diluted with ethyl acetate (400 mL), and washed with 5% $NaHCO_3$ solution (200 mL), water (200 mL), and brine (200 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography (hexane/acetate 9:1) and crystallization from hexane (100 mL) to afford pure (99% GC) **1** (16.4 g, 59% yield); mp 97−98 °C); ^{1}H NMR δ 1.34 (6H, s), 1.42 (3H, t, J = 7.1 Hz), 1.96 (2H, m), 3.05 (2H, m), 4.42 (2H, q, J = 7.1 Hz), 7.08 (1H, d, J = 8.0 Hz), 7.25 (1H, dd, J = 1.8, 8.0 Hz), 7.55 (1H, d, J = 8.0 Hz), 7.62 (1H, d, J = 1.8 Hz), 8.26 (1H, dd, J = 2.1, 8.0 Hz), 9.23 (1H, d, J = 2.1 Hz); ^{13}C NMR δ 13.9, 22.9, 29.5, 29.5, 32.6, 36.7, 61.1, 87.7, 92.7, 116.5, 124.2, 125.9, 126.3, 129.0, 130.0, 134.7, 136.6, 141.8, 146.8, 150.7, 164.4; IR (Nujol) cm^{-1} 2202, 1720, 1586, 1377, 1287, 1269, 1155, 1134, 1107, 1056, 1025, 851, 824, 778; EI-MS (*m*/*z*) 353 (5), 352 (22), 351 (100), 336 (17), 309 (5), 308 (29), 293 (6), 262 (5), 185 (3), 84 (7). Anal. Calcd for $C_{21}H_{21}NO_2S$: C, 71.76; H, 6.02; N, 3.99; S, 9.12. Found: C, 71.80; H, 6.00; N, 4.00; S, 9.10.

6-[(3-Methyl-3-hydroxy)but-1-yn]nicotinic Acid Ethyl Ester (13). To a solution of **8** (7.0 g, 37.8 mmol) in DME (200 mL) was added water (90 mL), K_2CO_3 (20.85 g, 150.9 mmol), CuI (0.29 g, 1.5 mmol), Ph_3P (0.79 g, 3 mmol), and 10% Pd/C (0.80 g, 0.75 mmol). The resulting mixture was stirred at rt for 30 min, and then 2-methyl-3-butyn-2-ol **10** (14.7 mL, 151 mmol) was added and the reaction warmed at 80 °C for 3 h. The mixture was cooled to rt and filtered on a Celite pad washing with ethyl acetate. The solution was diluted with water (400 mL) and extracted with ethyl acetate (2 × 300 mL). The organic phase was washed with brine (150 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexanes−ethyl acetate 9:1 to afford pure (96% GC) **13** as a pale yellow oil (6.1 g, 69% yield); ^{1}H NMR δ 1.40 (3H, t, J = 7.1 Hz), 1.65 (6H, s), 4.40 (2H, q, J = 7.1 Hz), 7.50 (1H, dd, J = 0.7, 8.0 Hz), 8.20 (1H, dd, J = 2.1, 8.0 Hz), 9.10 (1H, dd, J = 0.7, 2.1 Hz); IR (neat) cm^{-1} 3375, 2235, 1724, 1593, 1557, 1471, 1373, 1285, 1269, 1172, 1114, 1025, 968, 913, 856, 780, 730; EI-MS (*m*/*z*) 233 (3), 218 (75), 204 (2), 190 (100), 174 (5), 162 (38), 148 (81), 130 (14), 117 (23), 102 (27), 89 (12), 75 (22). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.05; H, 6.45; N, 6.05.

6-Ethynylnicotinic Acid Ethyl Ester (14). NaH (100 mg of a 60% dispersion in mineral oil, 2.5 mmol) was added to a stirred solution of **13** (6.86 g, 29.4 mmol) in dry toluene (200 mL). The suspension was slowly distilled until about 100 mL of the toluene/acetone mixture were collected. The

residue was cooled and concentrated under reduced pressure. The obtained solid was dissolved in diethyl ether (200 mL), and the mixture was washed with 0.5 M Na_2CO_3 solution (100 mL) and brine (100 mL). The aqueous phases were extracted again with ether (2 × 70 mL), and the combined organic phases were washed with brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexanes−ethyl acetate 95:5 to afford pure (97% GC) **14** (3.73 g, 72% yield); mp 49−51 °C; ^{1}H NMR δ 1.41 (3H, t, J = 7.1 Hz), 3.30 (1H, s), 4.42 (2H, q, J = 7.1 Hz), 7.54 (1H, d, J = 8.1 Hz), 8.26 (1H, dd, J = 2.1, 8.1 Hz), 9.17 (1H, d, J = 2.1 Hz); IR (Nujol) cm^{-1} 2110, 1717, 1592, 1558, 1377, 1286, 1278, 1216, 1179, 1131, 1108, 1024, 862, 780, 724; EI-MS (*m*/*z*) 175 (40), 147 (72), 130 (100), 102 (44), 75 (35), 50 (9). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.65; H, 5.20; N, 7.95.

6-[2-(4,4-Dimethylthiochroman-6yl)ethynyl]nicotinic Acid Ethyl Ester *S*-Oxide (15) via Coupling of 9 and 14. $(Ph_3P)_2PdCl_2$ (0.90 g, 1.3 mmol) and CuI (0.41 g, 2.1 mmol) were added under nitrogen to a solution of **14** (3.0 g, 17.1 mmol), triethylamine (60 mL), and **9** (5.4 g, 19.7 mmol) in *N*,*N*-dimethylformamide (45 mL). The mixture was warmed to 50 °C and stirred until no more starting **11** was detected by TLC analysis (3 h). After cooling to rt the reaction was diluted with ethyl acetate (200 mL) and washed with water (3 × 100 mL). The acquous phases were extracted again with ethyl acetate (2 × 100 mL), and the combined organic phases were washed with brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography (hexane/acetate 9:1) and crystallization from a mixture of hexane (30 mL) and ethyl acetate (3 mL) to afford pure (98% GC) **15** (3.6 g, 57% yield); mp 144−146 °C; ^{1}H NMR; IR; EI-MS in accordance with that of **15** obtained via coupling of **8** and **12**. Anal. Calcd for $C_{21}H_{21}NO_3S$: C, 68.64; H, 5.76; N, 3.81; S, 8.73. Found: C, 68.70; H, 5.75; N, 3.80; S, 8.75.

In a further experiment the crude reaction mixture obtained by coupling of **9** (7 g) and **14** (4.3 g) was purified without chromatography by two crystallizations (hexane−acetate 9:1, 2 × 40 mL) to give 3.9 g of **15** (93% GC, 43% yield).

Crystal-Structure Analysis of 1. A large orange crystal (from hexane crystallization) was cut to give a fragment of approximate dimensions 0.2 × 0.4 × 0.6 mm^3. Intensities data were measured, at room temperature, using a Siemens P4 diffractometer with graphite monochromated Cu Kα radiation (λ = 1.541 79 Å), using a $\theta/2\theta$ scan technique. A total of 5454 reflections were collected up to 136° in 2θ. No absorption correction was deemed necessary, and no significant intensity decay was observed during data collection. The structure was solved by direct methods using SIR97 program[10] which revealed the position of all non H-atoms; the methyl H atoms were geometrically positioned after each cycle of refinement, while the other H atoms were located by difference electron density map and freely refined. The refinement was carried out on F^2 by a full-matrix least-squares procedure with SHELXL97[11] for 277 parameters, with anisotropic temperature factors for non-H atoms. The final stage converged to R = 0.0592 (R_w = 0.126) for 2765 observed reflections, and 0.0644 for all unique reflections after merging. The full CIF file is provided as Supporting Information.

Supporting Information Available

The full CIF file of crystal-structure analysis of **1** is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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