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A Formal Total Synthesis of Colchicine via the Scott's Intermediate. Palladium(0)-Mediated *meta*-Ethynylation of a Tropolone Derivative

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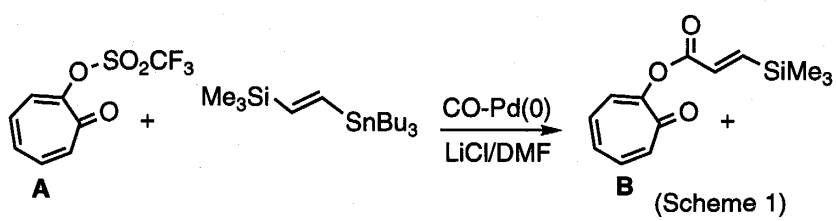
Colchicine was formally synthesized from 4-hydroxytropolone in a few-step sequence. The key step of the synthesis is palladium(0)-catalyzed ethynylation of 4-(trifluoromesyloxy)-2-methoxytropone. The present method has a potential in synthesizing various structurally modified colchicine derivatives.

Up to the present, numerous syntheses of colchicine (**1**) have been reported.[1,2] Since the unique physiological activity of **1** has been a focus of interest, development of an effective synthesis is desirable. Herein, we report a short formal synthesis of **1** based on the troponoid chemistry.

Among the recently developed transition metal-mediated C-C bond formation reactions, there might be some promising method applicable to troponoid chemistry. A notable development was reported by Stille,[3] i.e., the palladium metal-catalyzed condensation of carbon monoxide and 1-(tributylstannyl)-2-(trimethylsilyl)ethene with 2-(trifluoromethylsulfonyloxy)tropone (**A**) afforded 2-(3-trimethylsilylpropenoyl)tropone (**B**) in a good yield (Scheme 1). In addition, diphenylethyne formation by the palladium catalyzed oxidative



A **B** (Scheme 1)

coupling of iodobenzene and ethyne, developed by Sonogashira et al.,[4] has another superior feature in view of potential in troponoid chemistry, i.e., this ethyne substitution occurred smoothly with an aryl halide and a terminal acetylenic hydrocarbon. We have now applied this palladium(0)-mediated ethynylation to the troponoid chemistry.

For a sake of convenience, 2,5-di(trifluoromethylsulfonyloxy)tropone (**2**, 2,5-di(trifluoromesyloxy)tropone),[5] which could be prepared from 5-hydroxytropolone, was at first subjected for the reaction; the reaction of **2** with 1-hexyne in the presence of tetrakis(triphenylphosphine)palladium(0) complex generated from palladium(II) chloride, triphenylphosphine, copper(I) iodide, benzyltrimethylammouium chloride, and aqueous sodium hydroxide under argon atmosphere, serves itself as the reactive agent to afford 2-(trifluoromesyloxy)-5-(2-phenylethynyl)tropone (**3**) in 61% yield. However, the transformation of the 2-(trifluoromesyloxy) group was difficult.

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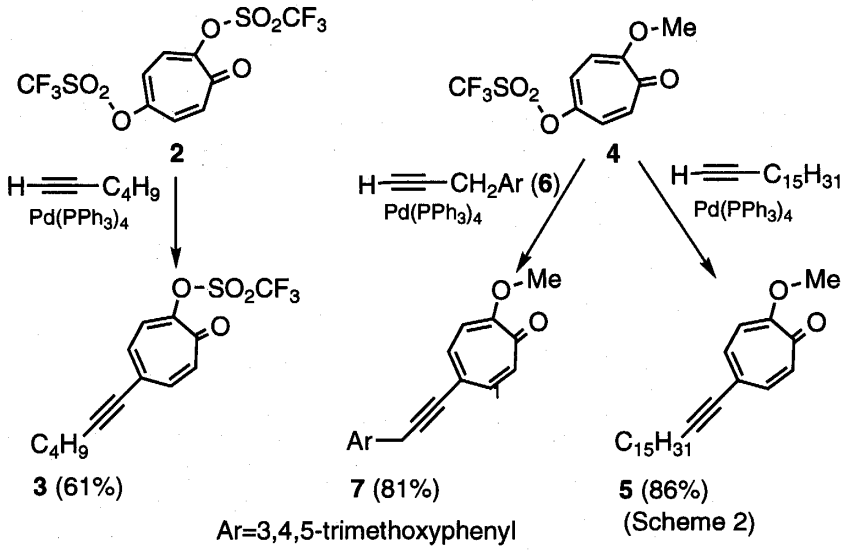
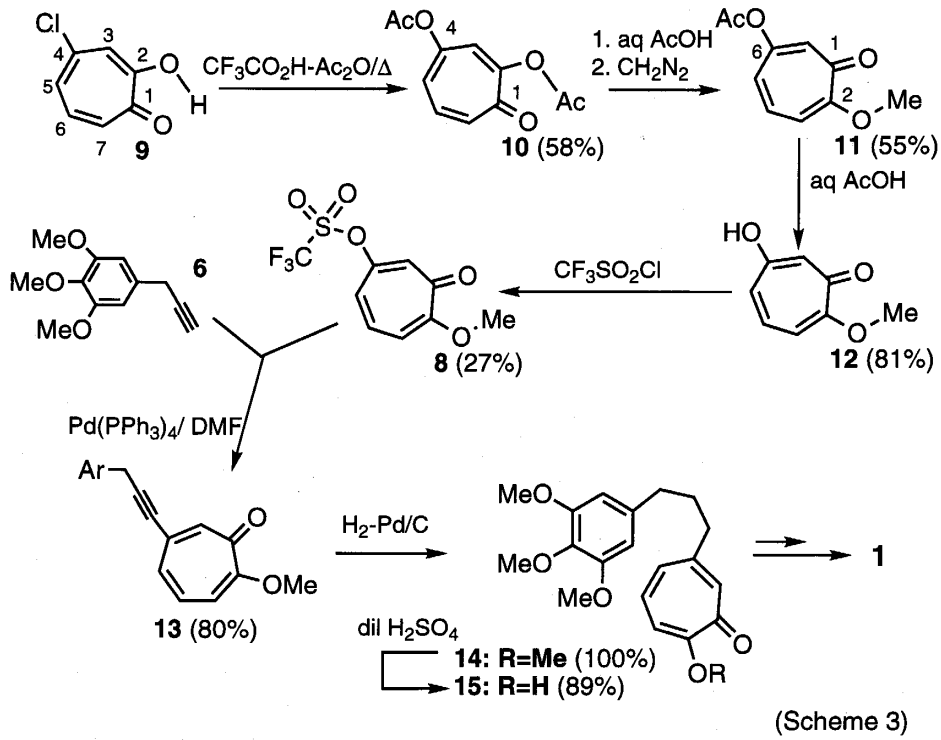
To overcome the difficulty, the trifluoromesyloxy group on the C-2 position should be changed to an electron-donating alkoxyl group, and 2-methoxy-5-(trifluoromesyloxy)-tropone (**4**) was studied; under the similar conditions, but triethylamine instead of sodium hydroxide, **4** and 1-heptadecyne gave 5-(1-heptadecynyl)-2-methoxytropone (**5**) in 86% yield. This result with the higher homologue of 1-alkyne is quite promising. Furthermore, the reaction of **4** with 3-(3,4,5-trimethoxyphenyl)-1-propyne (**6**) gave 2-methoxy-5-[3-(3,4,5-trimethoxyphenyl)-1-propynyl]tropone (**7**) (Scheme 2).



These findings on the preliminary studies led to extend the reaction with a *meta*-substituted derivative, 2-methoxy-6-(trifluoromesyloxy)tropone as the direct starting material leading to **1**. Although, in general, direct introductions of carbon substituents on the meta position of tropolones are limited,[6] the required 6-(trifluoromesyloxy)-2-methoxytropone (**8**) was prepared as follows: heating of 4-chlorotropolone (**9**) in a sealed tube with a mixture of acetic anhydride and trifluoroacetic acid[7] at 80 °C for 35 h gave 2,6-diacetoxytropone (**10**), which was then converted into 6-acetoxy-2-methoxytropone (**11**) by mild acetic acid treatment followed by methylation with diazomethane. A mild hydrolysis of **11** with aqueous acetic acid gave 6-hydroxy-2-methoxytropone (**12**). Then, **12** was treated with trifluoromesyl chloride to give 6-(trifluoromesyloxy)-2-methoxytropone (**8**). The palladium(0)-mediated coupling, as above, of **8** with 3-(3,4,5-trimethoxyphenyl)-1-propyne (**6**) in *N*, *N*-dimethylformamide with added dimethylamine afforded 2-methoxy-6-[3-(3,4,5-trimethoxyphenyl)-1-propynyl]tropone (**13**). Catalytic hydrogenation of **13** gave 2-methoxy-6-[3-(3,4,5-trimethoxyphenyl)propyl]tropone (**14**), which was further hydrolyzed to 4-[3-(3,4,5-trimethoxyphenyl)propyl]tropolone (**15**). The ^{1}H NMR spectra of **14** and **15** were identical with those of the authentic samples (Scheme 3).

This led to an efficient formal synthesis of colchicine by obtaining desacetoamido-B-seco-colchiceine (**15**), the intermediate in the former total synthesis of **1**.



(Scheme 3)

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5) The following ^{1}H and/or ^{13}C NMR data were compiled for characterization of key compounds:
2: δ(H) = 7.02 (1H, ddd, J = 10.3, 2.7, 0.7 Hz), 7.23 (1H, dd, J = 13.2, 2.7 Hz), 7.35 (1H, d, J = 10.3 Hz), and 7.41 (1H, d, J = 13.2, 0.7 Hz); δ (C) = 111.6 (q, J_{C-F} = 320.8 Hz), 117.3, 120.9, 122.1, 125.5, 125.6, 132.7, 141.6, 152.8, 155.7, and 176.6.
3: δ(H) = 0.95 (3H, t, J = 7.3 Hz), 1.39-1.78 (4H, m) , 2.45 (2H, t, J = 7.0 Hz), 7.08 (1H, d, J = 10.3 Hz), 7.23 (1H, d, J = 12.8 Hz), 7.25 (1H, dd, J = 10.3, 1 Hz), and 7.33 (1H, dd, J = 12.8, 1.5 Hz); δ(C) = 13.5, 19.4, 22.0, 30.3, 82.3, 100.2, 116.3, 121.0, 127.7, 132.1, 133.3, and 177.6.
4: δ(H) = 4.03 (3H, s), 6.62 (1H, d, J = 11 Hz), 7.06 (1H, ddd, J = 11, 2.5, 0.5 Hz), 7.16 (1H, dd, J = 13, 2.5 Hz), and 7.23 (1H, dd, J = 13, 0.5 Hz).
5: δ(C) = 14.0, 23.6, 24.7, 28.8, 29.0, 29.2, 29.4, 29.50 (3C), 29.53 (3C), 31.8, 56.2, 82.1, 93.1, 111.9, 124.4, 135.1, 135.9, 139.3, 164.5, and 179.7.

6: δ(H) = 2.21 (1H, t, J = 2.5 Hz), 3.56 (1H, d, J = 2.5 Hz), 3.83 (3H, s), 3.87 (6H, s), and 6.58 (2H, s).
7: δ(H) = 3.77 (2H, s), 3.84 (3H, s), 3.88 (6H, s), 3.96 (3H, s), 6.59 (2H, s), 6.65 (1H, dd, J = 10, 1.5 Hz), 7.14 (1H, d, J = 12 Hz), 7.26 (1H, dd, J = 10, 1.5 Hz), 7.30 (1H, d, J = 12 Hz); δ (C) = 25.9, 56.2 (2C), 56.3, 60.7, 84.0, 89.9, 104.9 (2C), 111.8, 123.7, 128.3, 131.8, 135.6, 136.0, 139.0, 153.2 (2C), 164.8, and 179.7.
8: δ(H) = 4.00 (3H, s), 6.78-6.85 (2H, m), 7.17 (1H, d, J = 2.5 Hz), 7.22 (1H, dd, J = 10.5, 1 Hz); δ(H) = 56.5, 111.3, 118.3 (q, J = 321 Hz), 122.6, 128.1, 133.4, 156.2, 166.2, and 176.7.
9: δ(H) = 7.11-7.24 (3H, m) and 7.50 (1H, d, J = 2 Hz).
10: δ(H) = 2.31 (3H, s), 2.35 (3H, s), 6.84 (1H, ddd, J = 10.5, 2.5, 1 Hz), 7.01 (1H, d, J = 2.5 Hz), 7.06 (1H, t, J = 10.5 Hz), and 7.13 (1H, dd, J = 10.5, 1 Hz).
13: δ(H) = 3.77 (2H, s), 3.84 (3H, s), 3.88 (6H, s), 3.93 (3H, s), 6.58 (2H, s), 6.63 (1H, d, J = 8.5 Hz), 6.69-6.87 (2H, m), and 7.42 (1H, s); δ(C) = 26.0, 56.1 (2C), 56.3, 60.8, 84.1, 92.5, 104.9 (2C), 111.2, 130.7, 131.2, 131.3, 133.1, 136.8, 139.5, 153.3 (2C), 165.7, and 179.0.
14: δ(H) = 1.89-2.01 (2H, m), 2.54-2.63 (2H, m), 3.83 (3H, s), 3.85 (6H,s), 3.93 (3H, s), 6.38 (2H, s), 6.64 (1H, d, J = 10 Hz), 6.74 (1H, d, J = 11 Hz), 6.98 (1H, m), and 7.18 (1H, s); δ(C) = 32.2, 35.5, 40.1, 56.0 (2C), 58.3, 60.8, 105.1 (2C), 111.5, 130.6, 131.5, 136.1, 136.4, 137.2, 151.7, 153.1 (2C), 164.9, and 179.6.
15: δ(H) = 1.93-2.04 (2H, m), 2.63 (2H, t, J = 7.5 Hz), 2.67 (2H, t, J = 7.5 Hz), 3.83 (3H, s), 3.86 (6H, s), 6.39 (2H, s), 6.92 (2H, d, J = 9 Hz), and 7.20-7.33 (3H, m); δ(C) = 32.8, 35.6, 56.0 (2C), 60.8, 105.2 (2C), 122.2, 125.2, 129.4, 136.2 (2C), 137.0, 137.1, 153.1 (2C), 153.9, and 170.9.

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