Regioselective Synthesis of Furan-Fused 3-Hydroxy-2,2-dimethylchroman, NG-121 Model Compound

Seiichi Inoue,*[a] Chihiro Nakagawa,[a] Hidetaka Hayakawa,[b] Fumiyoshi Iwasaki,[b] Yujiro Hoshino,[a] Kiyoshi Honda[b]

[a] Graduate School of Environment and Information Sciences, Yokohama National University, Tokiwadai, Hodogaya-ku, Yokohama 240-8501, Japan
Fax +81(45)3351536; E-mail: s-inoue@ynu.ac.jp

[b] Graduate School of Engineering, Yokohama National University, Tokiwadai, Hodogaya-ku, Yokohama 240-8501, Japan

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Abstract: Regioselective synthesis of the model compound of NG-121 was achieved. The key steps are *ortho*-alkylation of the phenol via [2,3]sigmatropic rearrangement of a sulfur ylide and the regioselective construction of the attached lactone ring.

Key words: phenols, ylides, sigmatropic rearrangement, regioselective formylation, lactones

Recently, a new type of biologically active compound, NG-121 (**1**),[1] was isolated from the culture broth of *Stachybotrys parvispora* F-4708 (Figure 1). It shows the nerve growth stimulating activity of nerve growth factor (NGF), which is suggested to be effective against Alzheimer's disease.[1] Since only small amounts of this compound can be isolated from natural sources, an effective method for the enantiocontrolled synthesis of NG-121 is highly desired.

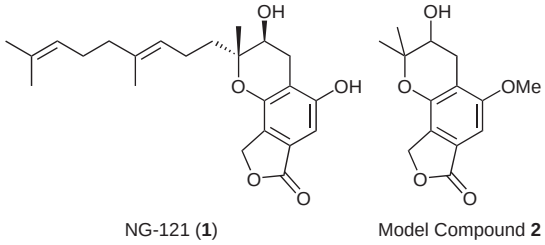

Figure 1

We have extensively studied the *ortho*-alkylation of phenols via the [2,3]sigmatropic rearrangement of a sulfur ylide under very mild conditions[2] and previously reported its application to the stereoselective synthesis of 2,2-dialkylchroman compounds[2a,3b] and others.[2,3] We further expanded the application of the [2,3]sigmatropic rearrangement of a sulfur ylide when we reported the stereoselective synthesis of 3-hydroxy-2,2-dialkylchromans.[4] Therefore, the [2,3]sigmatropic rearrangement of a sulfur ylide was expected to be the most suitable reaction for the enantiocontrolled construction of the 3-hydroxy-2,2-dialkylchroman moiety in NG-121 (Figure 1).

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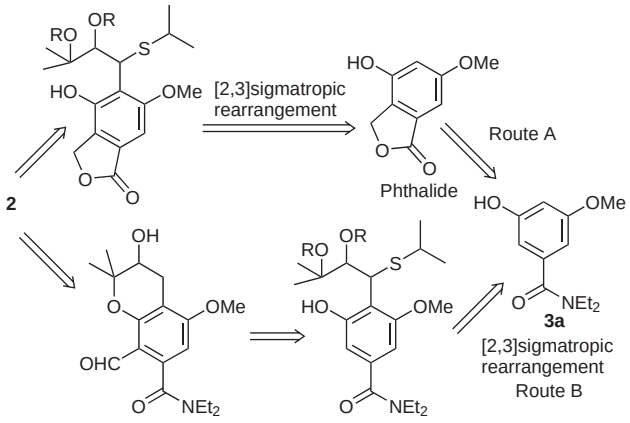
Herein, we would like to report the first regioselective synthetic method of the model compound, furan-fused 3-hydroxy-2,2-dimethylchroman **2**, using a [2,3]sigmatropic rearrangement and the regioselective construction of the lactone onto the aromatic nucleus as the key steps.



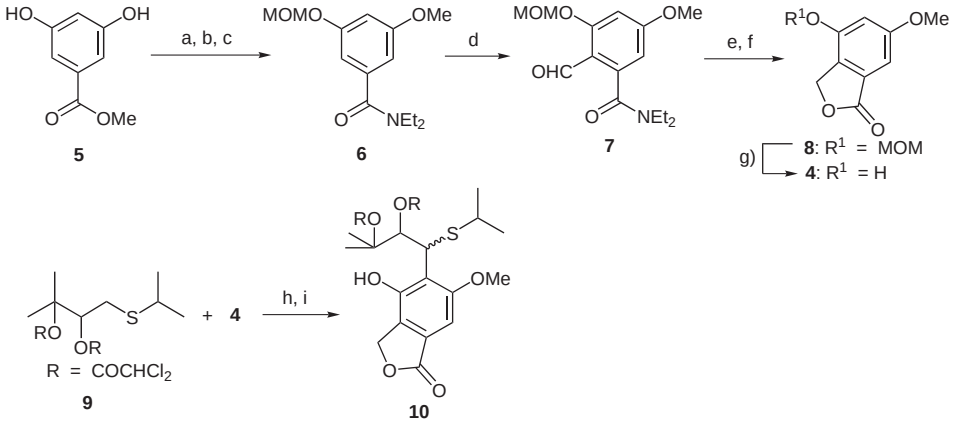
Scheme 1

Two possible retrosynthetic routes are shown in Scheme 1, which differ in the order of the construction of two fused rings (i.e. pyran and furan ring).

In route A, the functionalized alkyl group can be introduced into the *ortho* position of the phenol via [2,3]sigmatropic rearrangement to give the desired compound exclusively. In route B, the functionalized alkyl group may be introduced into the C-2 or C-4 position of the benzamide **3a** to give a mixture of the desired compound and a regioisomer, thus, it will be necessary to separate the two products. Another important point to consider is the regioselective construction of the lactone, which is required no matter which route is chosen. Patterson reported the conversion of *N*,*N*-diethylbenzamide to phthalide,[5] which we thought would be applicable to the construction of the lactone in NG-121 and the model compound **2**.

Taking into account the regioselectivity of the [2,3]sigmatropic rearrangement and the construction of the lactone, we first studied the synthesis of **2** according to route A. Initially, we investigated the synthesis of 4-hydroxyphthalide **4** (Scheme 2).

We started the synthesis of **4** from commercially available ester **5**; one of the two hydroxyl groups present was pro-

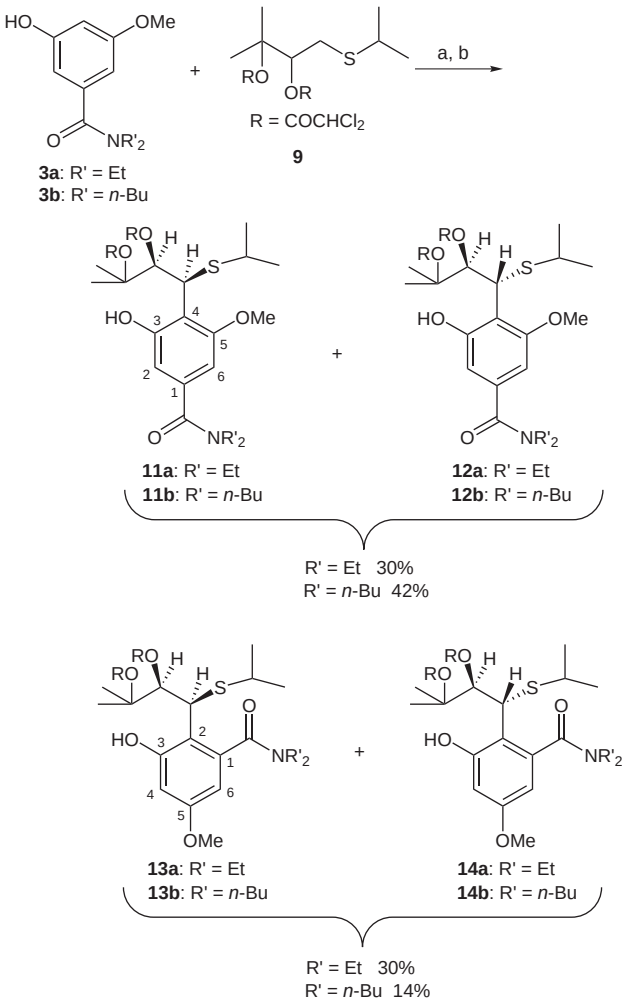


Scheme 2 *Reagents and conditions*: a) MeI, K_2CO_3, acetone, 0 °C → r.t., 15 h (38%); b) MOMCl, NaH, DMF, r.t., 3 h (95%); c) Et_2NH, $AlMe_3$, toluene, 75 °C, 18 h (95%); d) *t*-BuLi, DMF, TMEDA, THF, –78 °C, 3 h, (62%); e) $NaBH_4$, EtOH, 50 °C, 24 h; f) AcOH, EtOAc, r.t., 1 h (79%); g) 1 N HCl, CH_3CN–H_2O (10:1), reflux, 5 h (97%); h) SO_2Cl_2, s-collidine, CH_2Cl_2–DMF (10:1), –78 °C, 12 min; i) Et_3N, CH_2Cl_2, –78 → 0 °C, 5 h (10%).

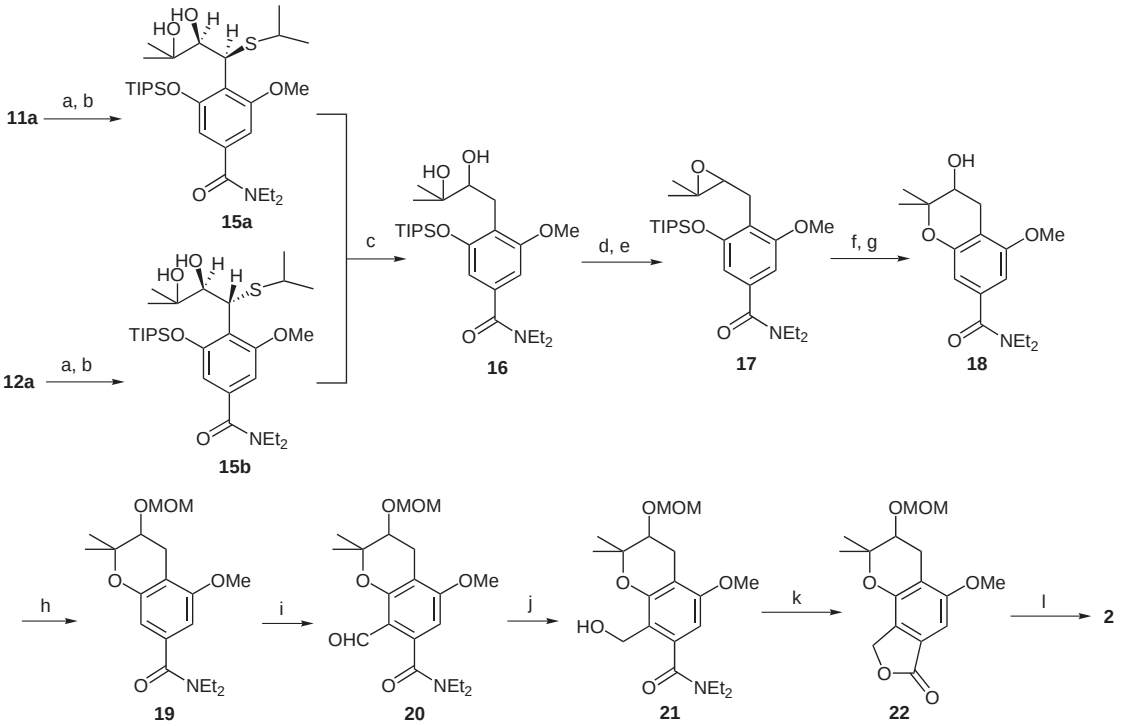
tected as the methyl ether, the remaining hydroxyl group was protected as a methoxymethyl group. Then, the ester was converted into diethylamide **6** by reaction with aluminum amide prepared from diethylamine and trimethylaluminum.[6] The amide **6** was lithiated by reaction with *t*-BuLi and the resulting *o*-lithioamide quenched with DMF to give aldehyde **7**. The other *ortho* position of the carbamoyl group of **6** was partly formylated to give a regioisomer as the minor product in 31% yield. Reduction of **7** with sodium borohydride gave the corresponding alcohol, which was cyclized to phthalide **8** in the presence of acetic acid. Finally, the methoxymethyl group was removed to give the desired compound **4**.

The *ortho*-alkylation of phthalide **4** with sulfide **9**[7] was effected by the [2,3]sigmatropic rearrangement of the phenoxysulfonium ylide intermediate. Thus, a mixture of **4** and **9** in dichloromethane–DMF (10:1) was treated with sulfuryl chloride at –78 °C, followed by addition of a solution of triethylamine in dichloromethane. The reaction mixture was allowed to warm to room temperature and usual work-up followed by column chromatography on silica gel afforded the desired product **10** in 10% yield along with unreacted starting materials. We looked at the reaction conditions in detail; however, we failed to improve the yield of **10**. Therefore, we decided to shift our attention from route A to route B.

N,*N*-Diethylbenzamide **3a** was reacted with sulfide **9** to give the desired *ortho*-alkylphenols, **11a** and **12a**, along with the regioisomers, **13a** and **14a**, in moderate yields in a 1:1 ratio (Scheme 3). Fortunately, the desired benzamides **11a** and **12a** and the regioisomers **13a** and **14a**[8,9] were separable by column chromatography on silica gel. In order to improve the regioselectivity of **11** and **12** over **13** and **14**, we decided to increase the bulkiness of the amide group. When *N*,*N*-dibutylbenzamide **3b** was reacted with sulfide **9**, we obtained the desired *ortho*-alkylphenols and their regioisomers in a 3:1 ratio.[10,11]



Scheme 3 *Reagents and conditions*: a) SO_2Cl_2, s-collidine, CH_2Cl_2, –78 °C, 12 min; b) Et_3N, CH_2Cl_2, –78 → 0 °C, 5 h.



Scheme 4 *Reagents and conditions*: a) TIPSOTf, Et_3N, CH_2Cl_2, r.t., 1 h (98%); b) $NaBH_4$, CH_2Cl_2, reflux, 2 h (90%); c) Raney Ni T-4, r.t., 30 min (90%); d) MsCl, py, r.t., 3 h; e) K_2CO_3, r.t., 1 h (50%); f) $Sc(OTf)_3$, CH_2Cl_2, r.t., 1 h (90%); g) 1 N HCl–EtOH (1:1), r.t., 9 h (90%); h) MOMCl, Et_3N, CH_2Cl_2, r.t., 2 h (98%); i) *t*-BuLi, DMF, THF, –78 → 0 °C, 4 h (60%); j) $NaBH_4$, EtOH, r.t., 2 h (90%); k) AcOH, EtOAc, r.t., 3 h (90%); l) 1 N HCl, r.t., 3 h (90%).

Subsequently, the phenolic hydroxyl groups of **11a** and **12a** were protected with a TIPS group. Then, the dichloroacetyl groups were deprotected to give **15a** and **15b**, respectively (Scheme 4). The isopropylsulfanyl groups of **15a** and **15b** were removed by hydrogenolysis with freshly prepared Raney Ni (T-4) in ethanol at room temperature to give the same alcohol **16**. Based on this experimental result we can safely conclude that **11a** and **12a** were the required diastereomers.

The secondary hydroxyl group in **16** was selectively mesylated, followed by conversion of the mesylate into epoxide **17** by treatment with potassium carbonate. Although the TIPS group is usually removed by TBAF, the reaction did not occur in the case of **17**. After several efforts, the TIPS group was cleanly cleaved by the action of $Sc(OTf)_3$ followed by treatment with 1 N HCl at room temperature to furnish 2,2-dimethylchroman-3-ol **18**.

We then explored the construction of the third ring. After the hydroxyl group of **18** was protected as the MOM ether, chroman **19** was lithiated with *t*-BuLi and the resulting *o*-lithioamide quenched with DMF to afford aldehyde **20** as the sole product.[12] To our surprise, no regioisomer was obtained, which can probably be attributed to the vicinal repulsion of the two hydrogen atoms on the pyran ring, which results in the methoxy group of the chroman **19** taking up the orientation shown in Figure 2. Thus, approach of *t*-BuLi from this side will be hindered providing **20** selectively. Reduction of **20** with $NaBH_4$ gave the alcohol **21** which cyclized to the tricyclic compound **22** in excellent yields. The structure of **22** was determined by ^1H NMR spectroscopy and NOE studies. Irradiation of the protons of the methoxy group resulted in a 9% enhancement to the aromatic proton. Finally, the MOM group was removed to obtain the tricyclic chroman model compound **2**.[13]

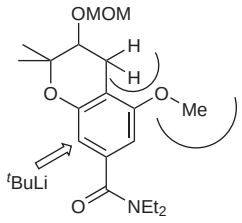


Figure 2

To the best of our knowledge, this is the first method for the synthesis of furan-fused 3-hydroxy-2,2-dialkylchroman. The key steps were the *ortho*-alkylation of the phenol via the [2,3]sigmatropic rearrangement of a sulfur ylide and the regioselective construction of the lactone. As the [2,3]sigmatropic rearrangement proceeds under mild conditions, this method has an important advantage that an optically active side chain can be introduced into the aromatic ring. Currently, the synthetic application of this methodology to the total synthesis of NG-121 is in progress.

Acknowledgment

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(7) The sulfide **9** was synthesized from commercially available 2-methyl-3-buten-2-ol according to the previously reported procedure, see ref. 4.

(8) The structures of **11a**, **12a**, **13a**, and **14a** were determined by ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H COSY, ^{1}H- ^{13}C COSY, and DEPT spectroscopy. It was impossible to determine the relative configuration of **11a**, **12a**, **13a**, and **14a**.

(9) In support of the assigned regiochemistry for **11a** and **12a**, a strong NOESY correlation was observed between the signals for the methoxy group and the C-6 proton of the aromatic ring. On the other hand, for **13a** and **14a**, a strong NOESY correlation was observed between the signals for the methoxy group and the C-4 and C-6 protons of the aromatic ring.

(10) Amides **11b**, **12b**, **13b**, and **14b** were also isolated by column chromatography on silica gel.

(11) The [2,3]sigmatropic rearrangement of 3-hydroxy-5-methoxy-*N*,*N*-diisopropylbenzamide and a higher terpenyl sulfide, prepared from geraniol according to a method similar to the synthesis of **9**, afforded the *para*-alkylated benzamide and the *ortho*-alkylated isomer in a 2:1 ratio. Similar alkylation of 3-hydroxy-5-methoxy-*N*,*N*-dibutylbenzamide **3b** afforded the *para*-alkylated benzamide and the *ortho*-alkylated isomer in a 3:1 ratio and alkylation of 3-hydroxy-5-methoxy-*N*,*N*-dihexylbenzamide also afforded the *para*-alkylated benzamide and the *ortho*-alkylated isomer in a 3:1 ratio.

(12) After a terpenyl sulfide was synthesized from (*E*,*E*)-farnesol according to the previously reported procedure,[4] the terpenyl sulfide was reacted with **3b** to give the *para*-alkylated benzamide and the *ortho*-alkylated isomer in a 3:1 ratio. The *para*-alkylated benzamide was converted to the corresponding 3-hydroxy-2,2-dialkylchroman according to a similar synthetic route to that shown in Scheme 4. The chroman compound was regioselectively formylated in 58% yield.

(13) Spectral data for **2**: IR (neat): 3454, 2926, 1730, 1623, 1468, 1349, 1138, 1110 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.90 (s, 1 H, ArH), 5.20 (s, 2 H, $ArCH_2$), 3.89 (s, 4 H, OCH_3, H-3), 2.97 (dd, *J* = 4.95, 18.47 Hz, 1 H, H-4), 2.77 (dd, *J* = 5.28, 18.47 Hz, 1 H, H-4), 1.39 (s, 3 H, CH_3-2), 1.33 (s, 3 H, CH_3-2); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 171.8, 159.5, 147.9, 127.6, 125.2, 114.5, 97.14, 77.59, 68.64, 68.09, 55.90, 26.97, 24.58, 22.03.