Diastereoselective Synthesis of (2S*,3R*)- and (2R*,3R*)-2,6-Dimethyl-2-homoprenyl-chroman-3-ol

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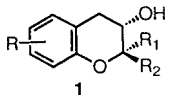
Received 29 March 1998

Abstract: Diastereoselective synthesis of (2*S**,3*R**)- and (2*R**,3*R**)-2,2-dialkylchroman-3-ols was achieved by stereoselective epoxide-opening cyclization of *ortho*-(2,3-epoxyalkyl)phenols which were prepared by the coupling of *p*-cresol and (2*R**,3*R**)- and (2*R**,3*S**)-2,3-diacetoxyalkyl isopropyl sulfides, which were in turn derived from geraniol and nerol, respectively.

2,2-Dialkylchroman-3-ol skeleton (**1**) is found in naturally occurring bioactive compounds, such as NG-121,[1] stachybotrins A and B,[2] and stachybotrin C.[3] Effective methods for their stereoselective construction are highly needed to develop an effective path for the total synthesis of such bioactive natural products.



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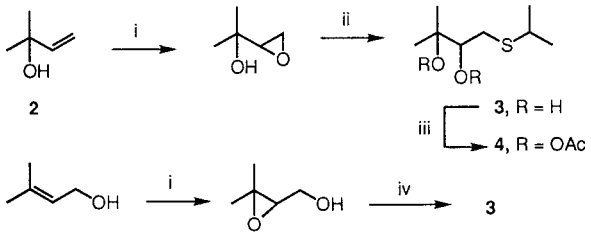
We have extensively studied on the *ortho*-alkylation of phenols via [2,3]sigmatropic rearrangement reaction under mild conditions[4] and previously reported their application to the stereoselective synthesis of 2,2-dialkylchroman[4a,4b] and others.[4c,5] As a part of our continuing study on the stereoselective synthesis of polysubstituted chromans, we here report an effective diastereoselective synthesis of (2*S**,3*R**)- and (2*R**,3*R**)-2,6-dimethyl-2-homoprenylchroman-3-ol.

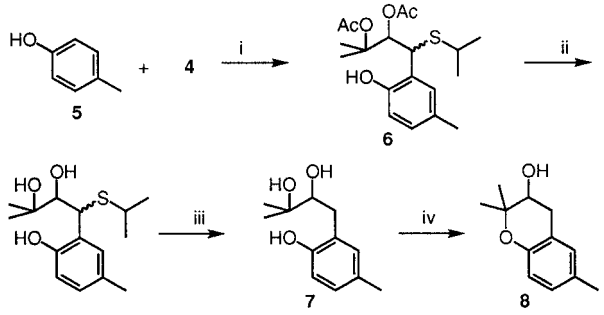
For a preliminary study, synthesis of 2,2,5-trimethylchroman-3-ol (**8**) was investigated. 2-Methyl-3-buten-2-ol (**2**) was subjected to Sharpless epoxidation[6] to give epoxy alcohol, which was treated with isopropyl mercaptan in the presence of sodium hydride to give 1-(1-methylethylthio)-3-methylbutan-2,3-diol (**3**). The same diol **3** was also obtained from 2,3-epoxy-3-methyl-1-butanol by the reaction with sodium isopropyl mercaptide under Payne rearrangement conditions.[7] Diol **3** was converted to diacetate **4** in good yield.



Reagent and conditions: (i) ^{t}BuOOH, VO(acac)$_2$, CH_2Cl_2, rt, 5 h; (ii) ^{i}PrSH, NaH, CH_2Cl_2, rt, 1 d, Y. 84% from **2**; (iii) Ac_2O, Py, CH_2Cl_2, rt, 12 h, Y. 79%; (iv) 1N NaOH, ^{t}BuOH, ^{i}PrSNa, EtOH, rt, 12 h

Scheme 1

The *ortho*-alkylation of *p*-cresol (**5**) with sulfide **4** was effected by [2,3]sigmatropic rearrangement of phenoxysulfonium ylide intermediate. Thus, a mixture of **4** and **5** in dichloromethane was treated with sulfuryl chloride at –50 °C, followed by addition 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 desired product **6** in 80% yield. Acetyl groups in **6** were deprotected by the action of $LiAlH_4$, and the isopropylthio group was removed by hydrogenolysis with freshly prepared Raney Ni (W4) in ethanol at room temperature to give triol **7**. The cyclization of **7** was effected in the presence of *p*-toluenesulfonic acid in benzene at reflux to furnish 2,2,5-trimethylchroman-3-ol (**8**) (Scheme 2).



Reagent and conditions: (i) SO_2Cl_2, *s*-Collidine, Et_3N, CH_2Cl_2, –50 °C, Y. 80%; (ii) $LiAlH_4$, ether, rt, 12 h, Y. 62%; (iii) Raney Ni (W4), EtOH, rt, 45 min, Y. 82%; (iv) C_6H_6, *p*-TsOH, reflux, 5 h, Y.46%

Scheme 2

According to ^{1}H-NMR data,[8] coupling constants between the proton at C-3 and two protons at C-4 position are 5.0 and 5.3 Hz. These indicate that the hydroxyl group is probably axially oriented. This was confirmed by X-ray crystallographic analysis[9] and it was found that two molecules, (3*R*)-**8** and (3*S*)-**8** are united by a hydrogen bond (Figure 1) and four molecules are in a unit-cell. The conformations of the two molecules are slightly different to one another. The notable difference between the two conformers is in bond angle of C(4)-C(3)-O by 3°.

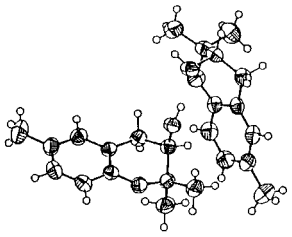
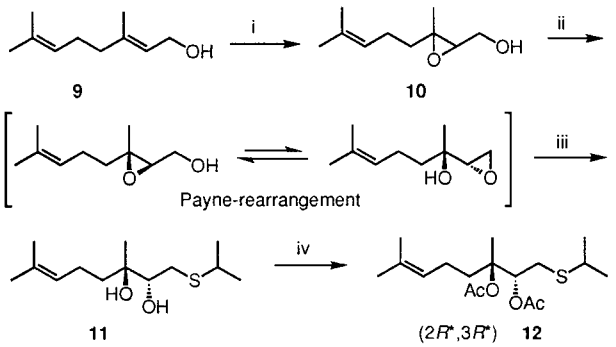


Figure 1. ORTEP Drawing of racemic **8**

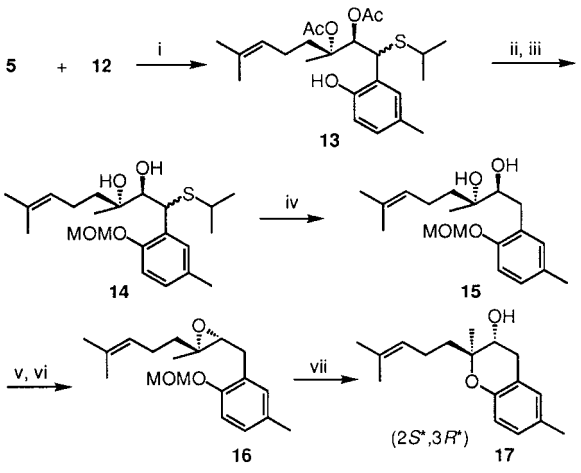
Next we examined the diastereoselective synthesis of 2,6-dimethyl-2-homoprenylchroman-3-ol. For this propose, first we prepared diol sulfide **11** of the defined relative stereochemistry from *trans*-allylic alcohol, geraniol (**9**), by selective Sharpless epoxidation[6] followed by the action of sodium isopropyl sulfide under Payne rearrangement conditions.[7] Then it was converted to (2*R**,3*R**)-2,3-diacetoxy-1-(1-methylethylthio)-3,7-dimethyl-6-octene (**12**) for *ortho*-alkylation reaction (Scheme 3).

p-Cresol (**5**) and sulfide **12** were reacted as before to give *ortho*-alkylated product **13** in good yield. It is noteworthy that relatively bulky group was transferred to the *ortho* position of phenol *via* [2,3]sigmatropic rearrangement of phenoxysulfonium ylide. The



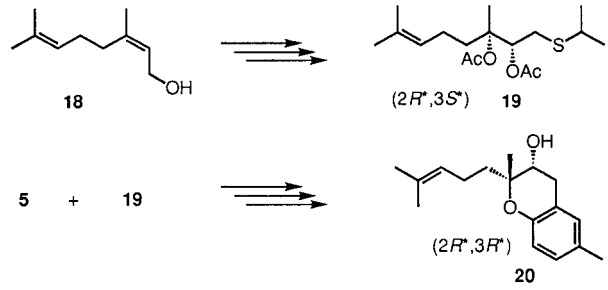
Reagent and conditions: (i) ^{t}BuOOH, VO(acac)$_2$, CH_2Cl_2, –20 °C, 4 h, Y. 96%; (ii) 1N NaOH, ^{t}BuOH; (iii) ^{i}PrSNa, EtOH, rt, 12 h, Y. 70%; (iv) Ac_2O, Py, CH_2Cl_2, rt, 12 h, Y. 60%

Scheme 3



Reagent and conditions: (i) SO_2Cl_2, *s*-Collidine, Et_3N, CH_2Cl_2, –60 ~–70 °C, Y. 78%; (ii) MOMCl, NaH, DMF, 4 h; (iii) $LiAlH_4$, THF, rt, 1 d, Y. 79%; (iv) Raney Ni (W4), EtOH, rt, 1 h, Y. 57%; (v) MsCl, Py, rt, 4 h; (vi) K_2CO_3, rt~80 °C, 1 h, Y. 71%; (vii) 10N HCOOH, AcOEt, rt, 5 min, Y. 30%

Scheme 4



Scheme 5

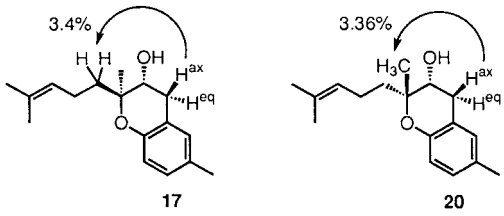


Figure 2. Stereochemical structure of **17** and **20**

phenolic hydroxyl group of **13** was protected by methoxymethyl group, then acetyl groups were deprotected to give **14**. The isopropylthio group was cleaved by the action of Raney Ni (W4) to give the compound **15**. Similar to the model compound **7**, cyclization of 15 was attempted by refluxing the benzene solution of the demethoxymethylated **15** in the presence of *p*-toluenesulfonic acid, resulting in the recovery of the starting material. Then, in order to activate the diol moiety for cyclization and to carry out the cyclization stereospecifically, **15** was converted into an epoxide. The secondary hydroxyl group in **15** was selectively mesylated, then the resulting mesylate was converted to epoxide **16** by treating with saturated potassium carbonate. After several efforts were devoted to effect cyclization of **16** to chroman-3-ol by nucleophilic epoxide-opening reaction, (2*S**,3*R**)-2,6-dimethyl-2-homoprenylchroman-3-ol (**17**) was obtained stereoselectively as a single isomer when **16** was treated with 10N formic acid in ethyl acetate at room temperature.

Structure and stereochemistry of **17** was determined by ^{1}H-NMR spectra[10] and NOE experiments and it was found that 3-hydroxyl group and homoprenyl carbon chain were oriented at the axial position. The chemical shift of a three-proton singlet of the methyl protons at C-2 (δ 1.32) was very close to that of the equatorial methyl protons in **8** (δ 1.35), and irradiation of the axial proton at C-4 (δ 3.01) gave a 3.4% enhancement of the α-protons of the homoprenyl group at C-2 (Figure 2).

The formation of the sole cyclization product of (2*S**,3*R**) configuration indicates that intramolecular cyclization proceeded by nucleophilic attack of phenolic oxygen to tertiary carbon of the epoxide ring in spite of less favorable 5-*endo*-mode according to Baldwin's rule.[11]

On the other hand, diastereomer of **17**, (2*R**,3*R**)-2,6-dimethyl-2-homoprenylchroman-3-ol (**20**), was successfully synthesized stereoselectively using diastereomeric (2*R**,3*S**) sulfide **19**, which was prepared from *cis*-allylic alcohol, nerol (**18**), by a similar method (Scheme 5). Structure of **20** was similarly determined by ^{1}H-NMR spectra[10] and NOE, which showed that 3-hydroxyl group was oriented at the axial position and 2-homoprenyl carbon chain was at equatorial position. Irradiation of the axial proton at C-4 (δ 3.01) gave a 3.36% enhancement of axial oriented methyl protons at C-2 (δ 1.25) (Figure 2).

To our knowledge, this is the first effective method for the diastereoselective synthesis of chroman-3-ol derivatives with a terpene chain at C-2. This method has several advantages: (1) desired diastereomer can be synthesized merely starting from *trans* or *cis* allylic alcohol, (2) desired side chain at C-2 can be introduced at the initial stage of the synthesis by a proper choice of the starting alcohol, (3) optically active compounds would be prepared by using Katsuki-Sharpless asymmetric epoxidation[12] at an earlier stage.

In conclusion, the present study provides the first example of efficient diastereoselective synthesis of (2*S**,3*R**)- and (2*R**,3*R**)-2,6-dimethyl-2-homoprenylchroman-3-ols. Further synthetic applications of this methodology is currently under progress.

Acknowledgement

This work was supported by a Grant-in-Aid for Scientific Research (No. 09450339) from the Ministry of Education, Science, Sport, and Culture of Japan. We thank Dr. Tomomi Ota and Mr. Keita Matsumoto of Taisho Pharmaceutical Co. Ltd., Japan for X-ray crystallographic analysis of **8**.

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(8) Spectral data for **8**: mp 85 °C; IR (KBr) 3292, 2981, 2939, 1616, 1587, 1497, 1450, 1389, 1300, 1262, 1223, 1183, 1144, 1065, 960, 849, 817, 570 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.29 (s, 3H, CH_3-2^{ax}), 1.35 (s, 3H, CH_3-2^{eq}), 2.26 (s, 3H, CH_3-6), 2.75 (dd, *J*=16.5, 5.3 Hz, 1H, H-4^{eq}), 3.07 (dd, *J*=16.5, 5.0 Hz,1H, H-4^{ax}), 3.79 (dd, *J*=5.3, 5.0 Hz, 1H, H-3^{eq}), 6.90–6.91 (m, 3H, Ar-H).

(9) Crystal data for **8**: $C_{12}H_{16}O_2$, *M* = 192.30, triclinic, space group P_1 (no. 2), *a* = 12,066(2), *b* = 12.412(2), *c* = 7.541(1) Å, α = 90.12(2)°, β = 91.63(1)°, γ = 76.31(1)°, *V* = 1092.9(3) $Å^3$, *Z* = 4, *D*c = 1.17 g cm^{-3}.

(10) Spectral data for **17**: IR (neat) 3360, 2940, 1595, 1500, 1450, 1390, 1300, 1270, 1240, 1140, 1065, 1030, 970, 900, 820 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.32 (s, 3H, CH_3-2^{eq}), 1.58 (s, 3H, CH_3-5'), 1.66 (s, 3H, CH_3-5"), 1.78 (m, 2H, CH_2-1'), 2.12 (m, 2H, CH_2-2'), 2.25 (s, 3H, CH_3-6), 2.75 (dd, *J*=17.17, 5,45 Hz, 1H, H-4^{eq}), 3.01 (dd, *J*=17.17, 4.95 Hz, 1H, H-4^{ax}), 3.84 (dd, *J*=5.45, 4.95 Hz, 1H, H-3^{eq}), 5.06 (tt, 1H, olefinic H), 6.73 (d, 1H, Ar-H), 6.88 (d, 1H, Ar-H), 6.95 (d, 1H, Ar-H). **20**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.25 (s, 3H, CH_3-2^{ax}), 1.61 (s, 3H, CH_3-5'), 1.68 (s, 3H, CH_3-5"), 1.73 (m, 2H, CH_2-1'), 2.11 (m, 2H, CH_2-2'), 2.25 (s, 3H, CH_3-6), 2.75 (dd, *J*=17.16, 4.62 Hz, 1H, H-4^{eq}), 3.01 (dd, *J*=17.16, 4.95 Hz, 1H, H-4^{ax}), 3.82 (dd, *J*=4.62, 4.95 Hz, 1H, H-3^{eq}), 5.13 (tt, 1H, olefinic H), 6.73 (d, 1H, Ar-H), 6.86 (d, 1H, Ar-H), 6.92 (d, 1H, Ar-H).

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