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# The Synthesis and the Stereochemistry of 4-Chromanones and 4-Chromanols with Bulky Substituents

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The synthesis and the stereochemistry of 4-chromanones and 4-chromanols with bulky substituents have been investigated. In 3-substituted chromanones, the *t*-butyl group exists mainly in the *quasi*-axial position, while the phenyl group is still in the *quasi*-equatorial environment. The preferred conformations of the isopropyl, and of the *t*-butyl group in *cis*- and *trans*-2-substituted chromanols, are equatorial, whereas *trans*-3-*t*-butylchromanol and its benzoate exist mainly as the conformations in which the *t*-butyl group is in the axial position. The conformational preference of these compounds can reasonably be explained by considering the steric interactions ($A^{(1,3)}$ strain, *gauche*, and diaxial repulsion) of these groups. The magnitude of the $A^{(1,3)}$ strain due to the hydroxyl group was estimated to be 1.3 kcal/mol.

In a previous paper,[1] we have reported that the conformational equilibria of 3-methyl- and 3-phenylchroman-4-ols can be well interpreted on the basis of the $A^{(1,3)}$ strain together with the 1,3-diaxial repulsion.

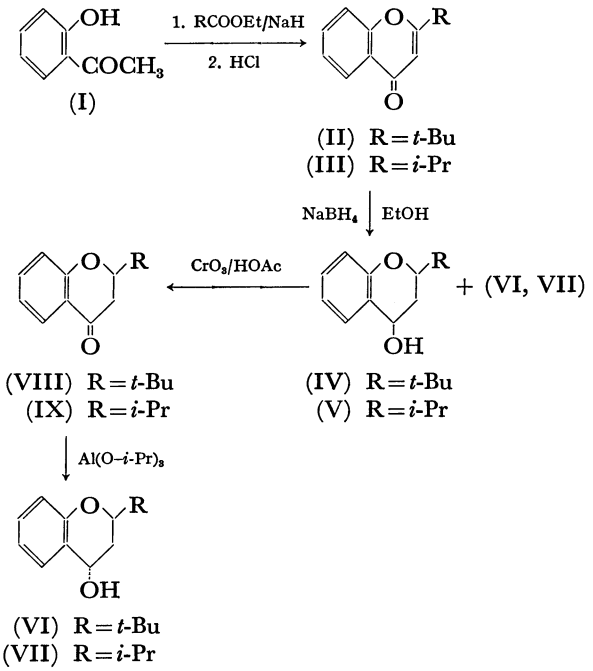
It is still not obvious, however, how the above interaction may affect the conformational equilibrium when the bulky groups are substituted on the 2- or 3-position of 4-chromanone and 4-chromanol.

In this paper, we wish to report on the synthesis and

1) S. Yamaguchi, K. Kabuto, Y. Ninomiya, and N. Inoue, This Bulletin, **43**, 3952 (1970).

the stereochemistry of 4-chromanones and 4-chromanols with bulky groups on the heterocyclic ring.

2-*t*-Butyl-(VIII), 2-isopropylchromanone (IX) and the corresponding chromanols (IV, VI; V, VII) were synthesized according to Scheme 1. *o*-Hydroxyacetophenone was allowed to react with ethyl pivalate in the presence of sodium hydride to give the diketone, which was in turn converted to the corresponding chromone (II) with concentrated hydrochloric acid.

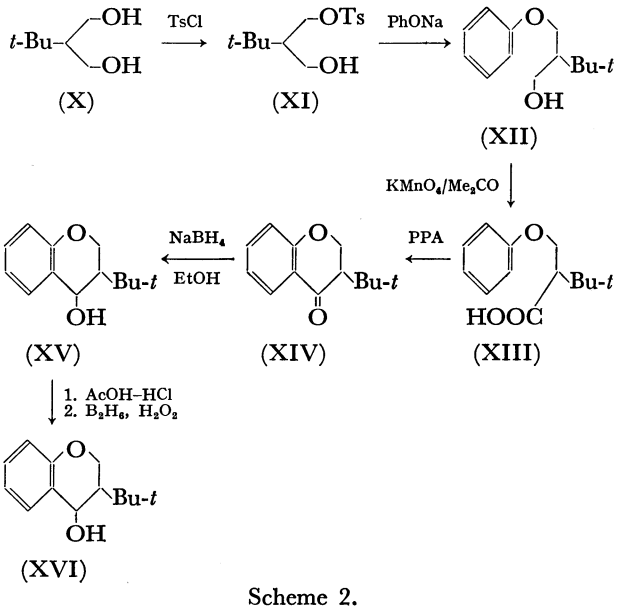



Scheme I.

When II was treated with excess sodium borohydride in boiling ethanol,[2] *cis*-2-*t*-butyl-4-chromanol (IV) was obtained as the main product. Compounds (IV) was easily oxidized by chromic acid in an acetic acid solution below 30 °C, yielding the chromanone (VIII), which subsequently afforded a mixture of *trans*- (VI, 58%) and *cis*-chromanols (IV, 22%) by Meerwein-Pondorf reduction. The NMR spectra (Table 2) of IV and VI indicate that the configurations of these compounds are *cis* and *trans* respectively. The purification of these chromanols by column or thin-layer chromatography was unsuccessful; hence, they were purified by preparative gas chromatography, using PEG 20M as the stationary phase.

The application of the synthetic route to isoflavanone[3] *via* phenoxyacetophenone cyanohydrin did not afford satisfactory results in preparing 3-*t*-butylchromanone (XIV). The chromanone (XIV) was successfully synthesized following Scheme 2, which is considered to be a suitable way for preparing chromanones with a bulky group such as the *t*-butyl group because the reaction is not so subject to steric hindrance by a bulky group.

2-*t*-Butyl-1,3-propanediol (X) was partially tosylated with tosyl chloride to give monotosylate (XI), which




Scheme 2.

was then transformed to phenoxyalcohol (XII) with sodium phenoxide in a dimethyl sulfoxide solution. 3-*t*-Butylchromanone (XIV) was prepared by the oxidation of XII with potassium permanganate, followed by the ring closure of carboxylic acid (XIII) in PPA.

The reduction of XIV with sodium borohydride resulted almost exclusively in the formation of *cis*-3-*t*-butylchromanol (XV). Compound (XV) was easily dehydrated with boiling acetic acid-hydrochloric acid to 3-*t*-butylchromene, which was then converted to the other isomer (XVI) by hydroboration, indicating that the configurations of XV and XVI are *cis* and *trans* respectively. These results are in accordance with the findings[4] that the formation of the *cis* isomer in the hydride reduction of 3-substituted chromanones increases with an increase in the size of the substituents.

The NMR spectra of substituted 4-chromanones are summarised in Table 1.

TABLE 1. NMR SPECTRA OF SUBSTITUTED 4-CHROMANONES

| Chromanone | | Preferred conformation of alkyl group |
|---|---|---|
| 2-*t*-Bu (VIII) | $J_{2,3}$:~13.0;[a] $\lvert J_{2,3}+J_{2,3'}\rvert=16.0$ | e |
| 2-*i*-Pr (IX) | $\lvert J_{2,3}+J_{2,3'}\rvert=16.0$ | e |
| 3-*t*-Bu (XIV) | $J_{2,3}$: 4.6, 4.2; $\lvert J_{2,3}+J_{2',3}\rvert=8.8$ | a' |
| 3-Ph | $\lvert J_{2,3}+J_{2',3}\rvert=14.0$ | e' |
| 3-Me | $J_{2,3}$: 10.8, 5.4; $\lvert J_{2,3}+J_{2',3}\rvert=16.2$[8] | e' |

a) Spectrum was taken in the presence of 0.30 molar ratio of $Pr(fod)_3$ in $CCl_4$.

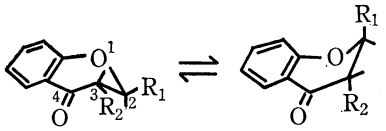
The signals of 2-H and 3-H portion of 2-*t*-butylchromanone (VIII) did not appear as the typical ABX pattern; hence the spectrum was analysed as the first-order spectrum in the presence of $Pr(fod)_3$.[5] The

2) S. Yamaguchi, S. Ito, A. Nakamura, and N. Inoue, This Bulletin, **38**, 2187 (1965).

3) N. Inoue, *Nippon Kagaku Zasshi*, **79**, 218 (1958).

4) N. Inoue, This Bulletin, **37**, 601 (1964); K. Hanaya, *ibid.*, **43**, 442 (1970).

5) Since the separation between the two strong outer lines of X part of ABX pattern is almost same to that in the absence of $Pr(fod)_3$, the geometry of chromanone ring seems not to be altered by the shift reagent.



VIIIe ($R_1$=*t*-Bu, $R_2$=H) VIIIa
IXe ($R_1$=*i*-Pr, $R_2$=H) IXa
XIVe ($R_1$=H, $R_2$=*t*-Bu) XIVa

Fig. 1.

large $J_{2,3}$ value (13 Hz) and the distance between the two outside peaks of the X part of the ABX pattern[6] indicate that VIII exists exclusively in the VIIIe conformation, though there seems to be no remarkable interaction which forces VIIIa to be unfavorable.

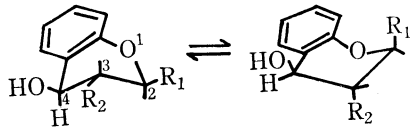
The line separation of the X part in 2-isopropylchromanone (IX) is almost the same as that of VIII; therefore, the isopropyl group in IX also favors the equatorial orientation.

The NMR spectrum of 3-*t*-butylchromanone (XIV) was analysed as being the ABX pattern[7] ($J_{2,3}$: 4.6 and 4.2 Hz), indicating that XIV exists mainly as the XIVa conformation with the *quasi*-axial *t*-butyl group, contrary to the case of 3-methylchromanone,[8] in which the methyl group is *quasi*-equatorial.

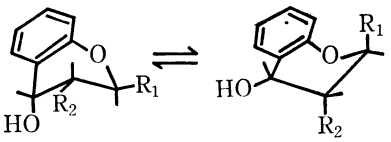
The dihedral angle (32°) between the carbonyl group and the benzene ring, calculated from the absorbance in the ultraviolet region[9] in XIV, is almost the same as those of chromanone and 2-methylchromanone,[10] suggesting that the geometry of the chromanone ring is unchanged by the *t*-butyl group.

Although the magnitude of the 2-alkylketone effect due to the *t*-butyl group (the repulsion between the *quasi*-equatorial 3-*t*-butyl and the carbonyl group) has not yet been determined, it may be presumed to be considerably larger than that of the isopropyl group (1.7 kcal/mol).[11a] Since the 2-alkylketone effect anticipated for XIVe is considered to be considerably larger than the interaction between the *quasi*-axial *t*-butyl group and the ring oxygen in XIVa, XIVa seems more likely than XIVe.

The above considerations seem to be reasonable in the following points: (1) The interaction of an axial group with a ring oxygen is smaller than its interaction with an axial hydrogen,[12] and the repulsion between the axial *t*-butyl group and the ring oxygen in 5-*t*-butyl-2-alkyl-1,3-dioxane is estimated to be 1.4 kcal/



IVe ($R_1$=*t*-Bu, $R_2$=H) IVa
Ve ($R_1$=*i*-Pr, $R_2$=H) Va
XVIe ($R_1$=H, $R_2$=*t*-Bu) XVIa
XVI'e (Benzoate of XVI) XVI'a



VIa ($R_1$=*t*-Bu, $R_2$=H) VIe
VIIa ($R_1$=*i*-Pr, $R_2$=H) VIIe
XVa ($R_1$=H, $R_2$=*t*-Bu) XVe

Fig. 2.

mol,[13] which is quite small compared to the interaction with the axial hydrogen on the cyclohexane ring (4.4 kcal/mol).[13] (2) Since the interaction of an axial group with one axial hydrogen atom is reduced to one-half its normal conformational free energy,[11a,b] it may be considered that the interaction of the *quasi*-axial 3-*t*-butyl group with the ring oxygen in XIVa would be around 0.7 kcal/mol, which is considerably smaller than the 2-alkylketone effect because there is only one oxygen in the chromanone ring.

An attempt to determine the conformational equilibrium of 3-*t*-butylchromanone by studying the IR spectra using 3-$d_2$-chromanone and 3-*d*-3-*t*-butylchromanone was unsuccessful because of the anbiguity of the C–D stretching vibrations of these compounds.

The methylene signal in 3-phenylchromanone did not separate even in the presence of Pr(fod)$_3$. The line separation of the two strong outside peaks of the X part, however, is very close to that of 3-methylchromanone;[10] therefore, the 2-alkylketone effect in 3-phenylchromanone seems not to be sufficiently large to cause the phenyl group to occupy the axial position.

The preferred conformations of *cis*-2-isopropyl- and *cis*-2-*t*-butylchromanol are expected to be almost fixed at Ve and IVe respectively, because severe diaxial repulsion due to the bulky substituents would be considerably larger than the $A^{(1,3)}$ strain (the repulsion of *quasi*-equatorial 4-hydroxyl group with 5-H).

The magnitude of the $A^{(1,3)}$ strain for the hydroxyl group was calculated to be 1.3 kcal/mol by the procedure described in the previous paper;[1] this value was almost the same as that for the acetoxyl group.

On the other hand, *trans* isomers should be VIa and VIIa, for the sum of the diaxial repulsion (*e.g.*, 2-*t*-Bu~4-H; 2.2 kcal/mol) and the $A^{(1,3)}$ strain is much larger than the interaction due to the *quasi*-axial hydroxyl group (0.4 kcal/mol). The above considerations are supported by the NMR spectra (Table 2) of these compounds.

It is difficult to determine the preferred conformation

6) It is well known that the distance between the outermost lines of X part of ABX pattern may be used as convenient method for determining the stereochemistry: L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, (1969), p. 133; B. J. Bolger, A. Hirwe, K. G. Marathe, E. M. Philbin, M. A. Vickers, and C. P. Lillya, *Tetrahedron*, **22**, 621 (1966).

7) H. J. Bernstein, J. A. Pople, and W. G. Schneider, *Can. J. Chem.*, **35**, 65 (1957).

8) A. R. Katritzky and B. Ternai, *J. Heterocyclic Chem.*, **5**, 745 (1968).

9) E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, **1955**, 3754.

10) K. Hanaya, *Bull. Yamagata Univ., Nat. Science*, **7**, 421 (1971).

11) a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N.Y. (1965), p. 114. b) *ibid.*, p. 356.

12) *ibid.*, p. 374.

13) E. L. Eliel and Sr. M. C. Knoeber, *J. Amer. Chem. Soc.*, **90**, 3444 (1968).

TABLE 2. NMR SPECTRA OF SUBSTITUTED 4-CHROMANOLS AND ITS DERIVATIVES

| Chromanol | $\lvert J_{2,3}+J_{2,3'}\rvert$ | $\lvert J_{3,4}+J_{3',4}\rvert$ | Preferred conformation of alkyl group |
|---|---|---|---|
| *cis*-2-*t*-Bu (IV) | 14.1 | 17.4 | e |
| *cis*-2-*i*-Pr (V) | 13.6 | 17.2 | e |
| *trans*-2-*t*-Bu (VI) | 13.8 | 6.0 | e |
| *trans*-2-*i*-Pr (VII) | 13.8 | 6.0 | e |
| *cis*-3-*t*-Bu (XV) | $J_{3,4}$: 3.0; $\lvert J_{2,3}+J_{2',3}\rvert$=15.0 | | e |
| Benzoate of XV | $J_{3,4}$: 2.6; $\lvert J_{2,3}+J_{2',3}\rvert$=16.0 | | e |
| *trans*-3-*t*-Bu (XVI) | $J_{3,4}$: 4.3; $\lvert J_{2,3}+J_{2',3}\rvert$=8.6 | | a |
| Benzoate of XVI | $J_{3,4}$: 3.0; $\lvert J_{2,3}+J_{2',3}\rvert$=6.0 | | a |

of *cis*-3-*t*-butylchromanol (XV) by the $J_{3,4}$ value (3.0 Hz) alone; however, the separations between the two strong outerlines ($|J_{2,3}+J_{2',3}|$) of XV and of its benzoate are 15.0 and 16.0 Hz respectively. In XV and its benzoate, the $A^{(1,3)}$ strain and the interaction of the axial *t*-butyl group with the ring oxygen would tend not to favor the XVe conformation, and the *t*-butyl group should be fixed in the equatorial environment

It is particularly interesting that the $J_{3,4}$ values in *trans*-3-*t*-butylchromanol (XVI) and its benzoate (XVI') were 4.3 and 3.0 Hz respectively, and the diaxial coupling constant expected for the XVIe conformation was not observed. Taking into account the facts that $J_{3a,4e'}$ in chromanols is as same as that of $J_{3e,4e'}$[1] and that the conformations of XV and its benzoate are homogeneous with $J_{3a,4e'}$: 3.0 and 2.6 Hz respectively, XVI and its benzoate ($J_{3,4}$: 4.3 and 3.0 Hz) can be considered to exist predominantly in the diaxial conformations (XVIa and XVI'a).

There are $A^{(1,3)}$, *gauche* (4-OR~3-*t*-Bu), and two methylhydrogen interactions due to the *t*-butyl group and $C_2$-methylene in XVIe and XVI'e. On the other hand, the above interactions are replaced by smaller steric interactions (4-OR~2-H, 3-*t*-Bu~ring oxygen, and one methyl-hydrogen interaction) in XVIa and XVI'a.

It is still obscure whether the chromanol ring in *trans*-3-*t*-butylchromanol has a half-chair or a half-boat conformation. If one may assume, however, that the energy difference between the half-chair and the half-boat conformation in the chroman ring is almost the same as that in the cyclohexene ring (2.7 kcal/mol),[14] the contribution of the half-boat conformation would be ruled out, because the unfavored interaction in XVIa is considered to be approximately 1.1 kcal/mol (0.4 kcal/mol: 1,3-diaxial repulsion due to 4-OH, 0.7 kcal/mol: *t*-Bu~ring oxygen).

## Experimental

All the melting points are uncorrected. The NMR spectra were recorded on Varian A-60D (60 MHz) and HA-100 (100 MHz) spectrometers, using TMS as the internal standard.

*2-t-Butylchromone (II).* To a stirred solution of *o*-hydroxyacetophenone (I, 11 g) in ethyl pivalate (80 ml) was added, portion by portion, sodium hydride (50% in mineral oil, 15 g) at room temperature. The mixture was then stirred at 75—85 °C on a water bath for 4 hr and allowed to stand overnight at room temperature. After the excess hydride has been decomposed with a small amount of water, the reaction mixture was poured into ice water (400 ml); the separated sodium salt was then collected, decomposed with 6 M hydrochloric acid, and extracted with ether. The organic layer was washed with saturated sodium bicarbonate and water successively, and dried over sodium sulfate.

The removal of the solvent afforded pivalyl *o*-hydroxyacetophenone as a pale yellow crystals (13 g, 72%). Needles from hexane, mp 57.5—58 °C. Found: C, 70.92; H, 7.11%. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%.

The diketone (13 g) was dissolved in concentrated hydrochloric acid (60 ml) and warmed at 40 °C for 1 hr. The solution was diluted with water (220 ml) and then extracted with ether. The organic layer was then worked up according to the usual procedure. The removal of the solvent afforded crude II, which subsequently purified by recrystallization from petroleum ether (bp 40—60 °C), mp 72—73 °C.

Found: C, 76.90; H, 6.79%. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98%. IR (KBr): 1660 $cm^{-1}$. NMR ($CCl_4$): $\delta$ 1.35 (s, 9H, *t*-Bu), 6.08 (s, 1H, $C_3$-H) ppm.

*cis-2-t-Butyl-4-chromanol (IV).* A solution of II (5 g) and sodium borohydride (5 g) in ethanol (100 ml) was refluxed for 5 hr. After the reaction mixture had then stood overnight at room temperature, the solvent was removed under reduced pressure; the residue was dissolved in 50% acetic acid (50 ml) and water (150 ml). The solution was extracted with ether, and the extract was treated as usual to give colorless crystals (4.6 g, 88%), whose vpc (20% PEG 20 M at 180 °C) showed that it was a mixture of *cis*- (94.7%) and *trans*-2-*t*-butyl-4-chromanol (5.3%). Recrystallization from pentane gave *cis*-2-*t*-butyl-4-chromanol as colorless needles; mp 58.5—60 °C.

Found: C, 75.82; H, 8.74%. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%. IR (KBr): 3270 $cm^{-1}$. NMR ($CDCl_3$+$D_2O$): $\delta$ 1.00 (s, 9H, *t*-Bu), 3.64 (dd, 1H, $C_2$-H), 4.77 (dd, 1H, $C_4$-H) ppm.

The acetate of IV was prepared according to the usual manner with acetyl chloride and pyridine: Colorless oil. IR (neat): 1738 $cm^{-1}$. NMR ($CDCl_3$): $\delta$ 1.4—2.6 (m, 5H, $C_3$-H and -OAc), 3.76 (dd, 1H, $C_2$-H), 6.10 (dd, 1H, $C_4$-H) ppm. $|J_{2,3}+J_{2,3'}|$=13.6, $|J_{3,4}+J_{3',4}|$=16.7 Hz.

*2-t-Butyl-4-chromanone (VIII).* To a stirred solution of IV (3.0 g) in 80% acetic acid (20 ml) was added chromic acid (1.68 g) in the same solvent (18 ml) below 30 °C. After the stirring has been continued for an additional hour, the reaction mixture was poured into ice water (300 ml) and extracted with ether. The extract was washed according to the usual manner. The solvent was then removed to give pale yellow crystals (2.5 g, 83%); subsequent recrystallization from hexane gave colorless crystals; mp 64.5—66 °C.

Found: C, 76.59; H, 7.80%. Calcd for $C_{13}H_{16}O_2$: C,

14) C. W. Beckett, N. K. Freeman, and K. S. Pitzer, *J. Amer. Chem. Soc.*, **70**, 4227 (1948).

76.44; H, 7.90%. IR ($CCl_4$): 1694 $cm^{-1}$. NMR ($CCl_4$): $\delta$ 1.08 (s, 9H, *t*-Bu), 2.58 (AB part of ABX, $C_3$–H), 4.06 (dd, 1H, $C_2$–H) ppm.

trans-*2-t-Butyl-4-chromanol (VI).* A solution of VIII (2.0 g) and aluminum isopropoxide (4.0 g) in isopropyl alcohol (8.0 ml) was refluxed for 3 hr. The solution was then poured into ice water (200 ml) containing concentrated hydrochloric acid (10 ml) and extracted with ether. The ethereal layer was washed as usual. The vpc of the extract showed that it was a mixture of *trans-* (58%), *cis*-2-*t*-butyl-4-chromanol (22%), and VIII (20%). The removal of the solvent gave a pale yellow oil (1.9 g), which was then purified by preparative vpc (20% PEG 20M 3/8″ 1.2 m, at 180 °C) to yield VI. Recrystallization from pentane gave VI as colorless prisms; mp 81—82 °C.

Found: C, 75.64; H, 8.82%. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%. IR (KBr): 3280 $cm^{-1}$, NMR ($CDCl_3$+$D_2O$): $\delta$ 1.00 (s, 9H, *t*-Bu), 3.78 (dd, 1H, $C_2$–H), 4.70 (t, 1H, $C_4$–H) ppm.

*Acetate of VI*: Colorless oil. IR (neat): 1736 $cm^{-1}$. NMR ($CDCl_3$): $\delta$ 1.5—2.1 (m, 5H, $C_3$–H and –OAc), 3.85 (dd, 1H, $C_2$–H), 6.00 (t, 1H, $C_4$–H) ppm. $|J_{2,3}+J_{2,3'}|=14.0$, $|J_{3,4}+J_{3',4}|=6.0$ Hz. By a procedure similar to that described above, 2-*i*-propylchromone (III, 44%), 2-*i*-propyl-4-chromanone (IX, 83%), *cis*-2-*i*-propyl-4-chromanol (V, 88%), and *trans*-2-*i*-propyl-4-chromanol (VII, 61%) were prepared.

*III*: Mp 42—43 °C; recrystallized from hexane. Found: C, 76.40; H, 6.39%. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43%. IR (KBr): 1660 $cm^{-1}$. NMR ($CCl_4$): $\delta$ 1.32 (Me of *i*-Pr), 6.00 (s, 1H, $C_3$–H) ppm.

*IX*: Colorless oil. Found: C, 75.79; H, 7.45%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%. IR ($CCl_4$): 1690 $cm^{-1}$. NMR ($CDCl_3$): $\delta$ 1.05 (Me of *i*-Pr), 2.5—2.8 (AB part of ABX, $C_3$–H), 4.17 (ddd, 1H, $C_2$–H) ppm.

*V*: Mp 88.5—89 °C, recrystallized from hexane. Found: C, 74.67; H, 8.27%. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%. IR (KBr): 3250 $cm^{-1}$. NMR ($CDCl_3$+$D_2O$): $\delta$ 1.00 (Me of *i*-Pr), 3.82 (ddd, 1H, $C_2$–H), 4.83 (dd, 1H, $C_4$–H) ppm.

*Acetate of V*: Colorless oil. IR (neat): 1739 $cm^{-1}$. NMR ($CDCl_3$): $\delta$ 1.7—2.6 (m, 6H, methine of *i*-Pr, $C_3$–H, and –OAc), 3.90 (ddd, 1H, $C_2$–H), 6.07 (dd, 1H, $C_4$–H) ppm. $|J_{2,3}+J_{2,3'}|=13.2$, $|J_{3,4}+J_{3',4}|=16.5$ Hz.

*VII*: Colorless oil. Found: C, 74.70; H, 8.54%. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%. IR (neat): 3350 $cm^{-1}$. NMR ($CDCl_3$+$D_2O$): $\delta$ 1.02 (Me of *i*-Pr), 3.91 (ddd, 1H, $C_2$–H), 4.67 (t, 1H, $C_4$–H) ppm.

*Acetate of VII*: Colorless oil. IR (neat): 1740 $cm^{-1}$. NMR ($CDCl_3$): $\delta$ 1.8—2.2 (m, 6H, methine of *i*-Pr, $C_3$–H, and –OAc), 3.96 (ddd, 1H, $C_2$–H), 5.98 (t, 1H, $C_4$–H) ppm. $|J_{2,3}+J_{2,3'}|=13.2$, $|J_{3,4}+J_{3',4}|=6.0$ Hz.

*2-t-Butyl-1,3-propanediol Monotosylate (XI).* To a stirred solution of 2-*t*-butyl-1,3-propanediol (X, 14 g) in dry pyridine (80 ml) was added, drop by drop, *p*-toluenesulfonyl chloride (20.2 g) in dry chloroform (100 ml) under ice cooling over a period of 5 hr. After the reaction mixture had then been left to stand for 2 days in a refrigerator, it was poured into ice water (500 ml) containing concentrated hydrochloric acid. The organic layer was treated in the usual way to afford a pale yellow oil (28.3 g), which was subsequently chromatographed on silica gel (400 g). Elution with benzene–ether (4: 1) afforded 2-*t*-butyl-1,3-propanediol ditosylate (8.2 g, 17.5%); mp 69.0—69.5 °C.

Found: C, 57.19; H, 6.68%. Calcd for $C_{21}H_{28}O_6S_2$: C, 57.25; H, 6.41%.

Subsequent elution gave monotosylate (XI) (16.3 g, 57.5%) as a colorless oil.

Found: C, 58.56; H, 7.93%. Calcd for $C_{14}H_{22}O_4S$: C, 58.72; H, 7.74%. IR (neat): 3450 $cm^{-1}$. NMR ($CDCl_3$): $\delta$ 0.90 (s, 9H, *t*-Bu) ppm.

*2-t-Butyl-1,3-propanediol Monophenyl Ether (XII).* To a solution of sodium ethoxide in ethanol prepared from absolute ethanol (70 ml) and sodium (1.56 g) was added phenol (6.42 g); then the solvent was removed. To the stirred suspension of sodium phenoxide in dimethyl sulfoxide (40 ml), heated at 50—60 °C, was added, drop by drop, XI (16.3 g) in dimethyl sulfoxide (30 ml) over a period of 45 min. Stirring was continued for 2 hr at 50—60 °C, and then the mixture was allowed to stand overnight at room temperature. The reaction mixture was poured into ice water (350 ml), saturated with sodium chloride, and extracted five times with ether. The combined extract was then treated as usual to give a pale yellow oil (10.6 g), which was subsequently purified by distillation, 9.7 g (83%), bp 145—147 °C/4 mmHg.

Found: C, 74.65; H, 10.05%. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68%. IR (neat): 3350 $cm^{-1}$. NMR ($CDCl_3$): $\delta$ 1.00 (s, 9H, *t*-Bu), 6.8—7.4 (m, 5H, aromatic-H) ppm.

p-*Nitrobenzoate of XII*: Colorless needles from ethanol–water, mp 63—63.5 °C. Found: N, 4.02%. Calcd for $C_{20}H_{23}NO_5$: N, 3.92%.

*α-t-Butyl-β-phenoxypropionic Acid (XIII).* To a stirred solution of XII (6.80 g) in acetone (360 ml) warmed to 30 °C was added, portion by portion, finely-powdered potassium permanganate (14 g). After the addition was complete, the stirring was continued for 24 hr. The manganese dioxide was filtered off and washed well with hot water (total volume, 300 ml). The filtrate and the washings were then combined and concentrated under reduced pressure. After 2 M sodium hydroxide (30 ml) had been added, the mixture was extracted with ether to remove the unreacted XII; the water layer was acidified with concentrated hydrochloric acid to give XIII, which was filtered, washed with water, and dried (2.67 g, 37%). Recrystallization from aqueous ethanol gave fine needles; mp 88.5—89.5 °C.

Found: C, 70.07; H, 8.12%. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%. IR (KBr); 3300—3000 $cm^{-1}$. NMR ($CDCl_3$): $\delta$ 1.10 (s, 9H, *t*-Bu) ppm.

From the ether extract XII was recovered (2.85 g, 42%).

*3-t-Butyl-4-chromanone (XIV).* A mixture of XIII (2.85 g) and polyphosphoric acid (50 g) was kept at 90 °C for 5 hr and then poured into ice water (250 ml). Colorless crystals were collected and dissolved in ether; they were then washed with 1 M sodium hydroxide and water, and dried over sodium sulfate. The solvent was removed to give crude XIV (2.2 g, 88%) as colorless crystals, which were then distilled under reduced pressure (bath 120 °C/1 mm Hg) to yield colorless crystals; mp 37—39 °C. Recrystallization from pentane gave pure XIV; mp 41.5—42 °C.

Found: C, 76.40; H, 8.11%. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90%. IR ($CCl_4$): 1684 $cm^{-1}$. NMR ($CDCl_3$): $\delta$ 1.09 (s, 9H, *t*-Bu), 2.29 (t, 1H, $C_3$–H), 4.40—4.75 (AB part of ABX, $C_2$–H) ppm. UV (95% EtOH nm $\varepsilon$): 254 (8950), 324 (3360).

The alkaline extract was acidified with dilute hydrochloric acid to give unreacted XIII (145 mg, 5%).

cis-*3-t-Butyl-4-chromanol (XV).* A solution of XIV (510 mg) and sodium borohydride (70 mg) in ethanol (5 ml) was refluxed for 3 hr. The removal of the solvent afforded an oily residue, which was then dissolved in dilute acetic acid. The mixture was extracted with ether, and the organic layer was worked up according to the usual procedure to yield crude product as colorless crystals (462 mg, 90%); whose vpc indicated that it was a mixture of XV (94.4%) and

*trans*-3-*t*-butyl-4-chromanol (XVI, 5.6%). Recrystallization from pentane gave pure XV; mp 60.5—61.0 °C.

Found: C, 75.56; H, 8.80%. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%. IR (KBr): 3450 $cm^{-1}$. NMR ($CDCl_3$+$D_2O$): $\delta$ 1.11 (s, 9H, *t*-Bu), 1.4—1.8 (ddd, 1H, $C_3$–H), 4.1—4.3 (AB part of ABX, $C_2$–H), 4.83 (d, 1H, $C_4$–H) ppm.

*Benzoate of XV*: Colorless crystals from pentane–benzene; mp 155 °C.

Found: C, 77.52; H, 7.15%. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14%. IR (KBr): 1710 $cm^{-1}$. NMR ($CDCl_3$): $\delta$ 1.06 (s, 9H, *t*-Bu), 1.8—2.2 (ddd, 1H, $C_3$–H), 4.4—4.6 (AB part of ABX, $C_2$–H), 6.50 (d, 1H, $C_4$–H) ppm.

trans-*3*-t-*Butyl-4-chromanol (XVI)*. A solution of XV (675 mg) in acetic acid (8 ml)-concentrated hydrochloric acid (2 ml) was kept at 120—130 °C for 20 min. The reaction mixture was then poured into ice water and extracted with ether, and the extract was washed as usual. The removal of the solvent afforded 3-*t*-butylchromene as a yellow oil (582 mg, 95%), which was then distilled under reduced pressure (bath 80—110 °C/1 mmHg). NMR ($CDCl_3$): $\delta$ 1.14 (s, 9H, *t*-Bu), 4.75 (d, 2H, $C_2$–H), 6.24 (bs, 1H, $C_4$–H) ppm.

To a stirred solution of 3-*t*-butylchromene (470 mg) and sodium borohydride (85 mg) in diglyme (3 ml) was added, drop by drop, boron trifluoride etherate (0.38 ml) in diglyme (0.4 ml) under a nitrogen atmosphere over a period of 15 min. After the reaction mixture had been stirred for 1 hr, water (1 ml) was added to decompose the excess diborane. To the above stirred solution, there were added 3 M sodium hydroxide (0.8 ml) and then, drop by drop, 30% hydrogen peroxide (0.8 ml) at 40—50 °C. After the stirring had been continued for an additional hour, the solution was poured into water and extracted with ether. The extract was treated in usual manner to give a colorless oil (450 mg, 87%) which crystallized on standing. Recrystallization from pentane afforded colorless prisms; mp 64.0—64.5 °C.

Found: C, 75.46; H, 8.88%. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%. IR (KBr): 3260 $cm^{-1}$. NMR ($CDCl_3$+$D_2O$): $\delta$ 0.98 (s, 9H, *t*-Bu), 1.66 (q, 1H, $C_3$–H), 4.25 (d, 2H, $C_2$–H), 4.74 (d, 1H, $C_4$–H) ppm.

*Benzoate of XVI*: Colorless oil.

Found: C, 77.64; H, 7.34%. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14%. IR (neat): 1710 $cm^{-1}$. NMR ($CDCl_3$): $\delta$ 1.01 (s, 9H, *t*-Bu), 1.87 (q, 1H, $C_3$–H), 4.42 (AB part of ABX, $C_2$–H), 6.31 (bd, 1H, $C_4$–H) ppm.