Heterocycles. XXV [1]. Sodium Borohydride Reduction of Flavanonols

Shaoshun Li and Masayuki Onda*

Shenyang College of Pharmacy, Wenhua-lu, Shenyang, China

Hitoshi Kagawa, Hiromi Kawase, Mieko Iguchi and Yoshihiro Harigaya*

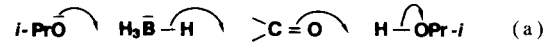
School of Pharmaceutical Sciences, Kitasato University,
Minato-ku, Tokyo 108, Japan

Received April 27, 1990

Solvent effects on the stereochemistry in the sodium borohydride reduction of (±)-flavanonols have been examined. The effects observed for the (±)-flavanonols with 5-OMe in 2-propanol, dioxane and methanol are explainable by the differences between the steric interactions inherent in the product-like transition states **A** and **B**. It has been also found that 5-OAc peculiarly affects the stereochemistry in the reduction to produce the (±)-catechin-type compounds in a one-pot process. The solvent and temperature effects are examined using a model analogous to the above.

J. Heterocyclic Chem., **27**, 2029 (1990).

In 1979, Wigfield established the reaction mechanism of the sodium borohydride reduction of cyclohexanones in 2-propanol [2]: (1) The gross transition state (TS) geometry for the transfer of hydride is an acyclic arrangement of four species (a). (2) Steric interactions inherent in the product-like TS determine the stereochemistry in the reduction. We previously reported that the interesting effects of 5-substituents (OH, OMe and OAc) observed on the stereochemistry in the sodium borohydride reduction of the (±)-flavanonols in 2-propanol are explainable by Wigfield's proposal [3]. For the completion of this series of works, we examined the sodium borohydride reduction of the (±)-flavanonols with 5-OMe and 5-OAc in three kinds of solvents.



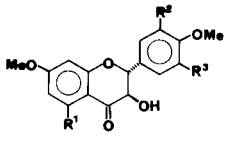
(a)

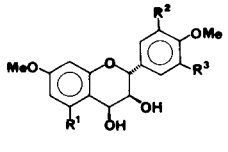
Preparation of the (±)-Flavanonols with 5-OMe.

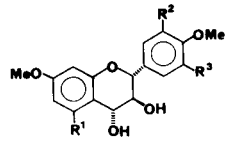
The synthesis of the following compounds were already reported: (±)-2,3-*trans*-7,4'-dimethoxyflavanonol (**1**) [4], (±)-aromadendrin trimethyl ether (**4**) [5] and (±)-taxifolin (dihydroquercetin) tetramethyl ether (**7**) [6].

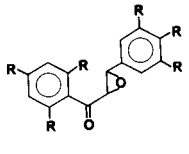
Treatment of (±)-chalcone epoxide **13** [7] with hydrogen chloride/methanol stereoselectively gave (±)-ampelopsin (dihydromyricetin) (**14**) (71%) as the sole product, which was converted to its pentamethyl ether **10** (58%) on methylation with dimethyl sulfate. The assignment of 2,3-*trans*-(2,3-diequatorial substituents)-configuration of

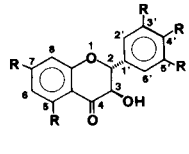
Chart 1

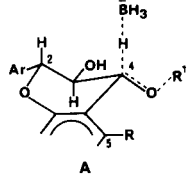

1: R^1–R^3 = H
4: R^1 = OMe, R^2 = R^3 = H
7: R^1 = R^2 = OMe, R^3 = H
10: R^1–R^3 = OMe

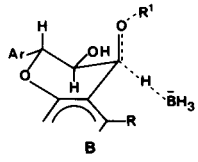

2: R^1–R^3 = H
5: R^1 = OMe, R^2 = R^3 = H
8: R^1 = R^2 = OMe, R^3 = H
11: R^1–R^3 = OMe

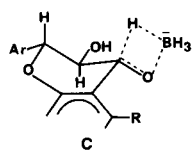

3: R^1–R^3 = H
6: R^1 = OMe, R^2 = R^3 = H
9: R^1 = R^2 = OMe, R^3 = H
12: R^1–R^3 = OMe

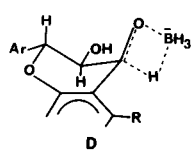

13: R = OCH_2OMe


14: R = OH


A


B


C


D

R^1 = H, δ^-

10 and **14** was based on the ^{1}H nmr spectra (each $J_{2,3}$ = 12.0 Hz).

Reduction of the (±)-Flavanonols with 5-OMe.

The solvents used included anhydrous 2-propanol, dioxane and methanol. Reduction was run at room temperature or under reflux for **10** in methanol (poor solubility). A large excess of sodium borohydride was used, and the completion of reduction was monitored by tlc. As far as possible, a uniform procedure was employed for all reactions. The relative amounts of the isomeric 3,4-diols were estimated on the basis of the direct isolation of the products by preparative tlc. The stereochemistry of the products was determined by the ^{1}H nmr spectra ($J_{3,4}$ = 3.6-4.0 Hz for 3,4-*cis*-diols, $J_{3,4}$ = 7.2-7.5 Hz for 3,4-*trans*-diols) [5,6]. In addition, tlc analysis confirmed that the isomeric 3,4-diols are not epimerized to each other under the reaction conditions employed. The results obtained are given in Table I.

First, reduction of **1** was examined as a criterion for the comparison. The 3,4-*trans*-diol **3** was only (exclusively) obtained in all solvents used, suggesting no significant solvent effect on the product formation. Reduction of **4**, **7** and **10** in either 2-propanol or dioxane respectively gave two isomeric 3,4-diols in the ratios of *trans*/*cis* > 1.3:1. On the contrary, the ratios of *cis*/*trans* > 2:1 were obtained in methanol. Thus, the reduction of the (±)-flavanonols with 5-OMe was affected by the solvents.

It has been proposed that steric interactions inherent in the product-like TS-**A** and -**B** (R^1 = H) govern the stereochemistry in the sodium borohydride reduction of the (±)-flavanonols in 2-propanol [3] (Chart 1). The TS-**A** contains a steric interaction between 4eq-OH (forming) and 5-substituent. Because 2ax-H does not reach up far

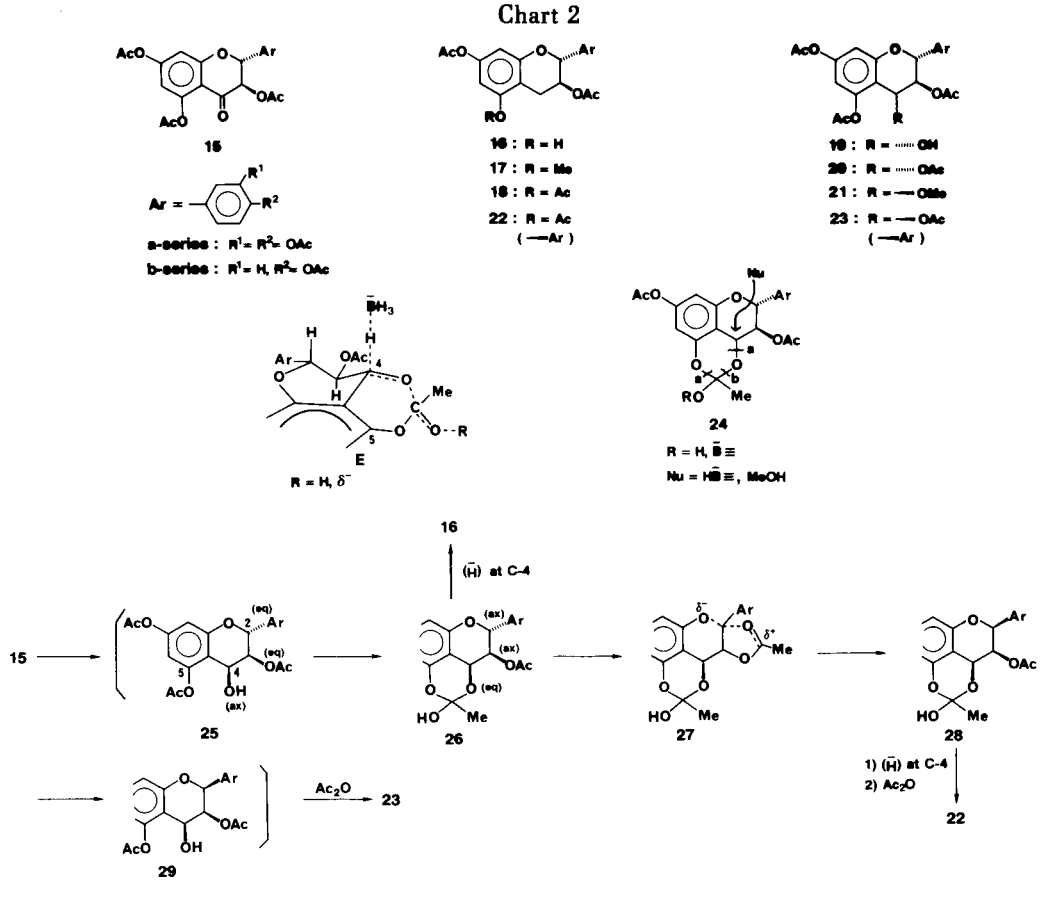
Table I

Reduction Data for the (±)-Flavanonols with 5-OMe

	Solvent	Temperature [a]	Time, hours	3,4-*cis*-Diol (%)	3,4-*trans*-Diol (%)
1	2-propanol	RT	2		94.5
	dioxane	RT	3		87
	methanol	RT	1.5	6	89.5
4	2-propanol	RT	3	40.5	53
	dioxane	RT	3	38	54.5
	methanol	RT	1	60	30.5
7	2-propanol	RT	3	37	55
	dioxane	RT	3	31	56
	methanol	RT	1.5	65.5	32
10	dioxane	RT	3	18	69.5
	methanol	reflux	1.5	59	16

[a] RT = Room temperature.

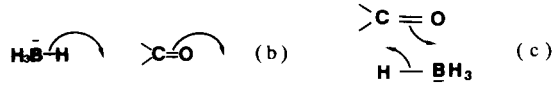
Chart 2



enough to interact, borohydride (incoming) scarcely affects the TS-**A**. The TS-**B** involves a steric interaction between 4ax-OH (forming) and 2ax-H, and a *gauche* effect between 4ax-OH (forming) and C(2)-C(3) bond. In addition, a steric interaction is operative between borohydride (incoming) and 5-substituent. However, when R = H, this interaction is hardly operative for the same reason as above.

The results obtained in 2-propanol are straightly explainable by these models. When R = H, the steric interactions arising from 4ax-OH (forming) in the TS-B are very much stronger than that between 4eq-OH (forming) and 5-H in the TS-**A**. As a result, the TS-**A** is the sole (main) path from **1** to **3**. When R = OMe, the comparative balance between the steric interactions inherent in the TS-**A** and -**B** leads to that **A** is rather preferable to **B**. This is a reason why the (±)-flavanonols with 5-OMe preferably give the 3,4-*trans*-diols.

The results obtained in dioxane were quite similar to those in 2-propanol. In aprotic solvents, an alternative acyclic (b) or a four-center arrangement of two species (c) [8] should be chosen as the gross TS geometry for the transfer of hydride. Steric interactions inherent in the four-center TS-**C** and -**D** arising from the four-center arrangement (c) will be different from those in the TS-**A** and -**B** (Chart 1). If the four-center mechanism is operative in dioxane, the different results must be obtained in 2-propanol and dioxane. Furthermore, the four-center mechanism will be prevented by a forbidden [π 2s + σ 2s] cycloaddition from occurring [9]. We now assume for the reduction in dioxane the same models ($R^1 = \delta^-$) arising from the acyclic arrangement (b) as the TS-**A** and -**B** by which the stereochemistry in the reduction is correctly explainable on the basis of the same considerations as above.



The most striking features of the results obtained in methanol were that the 3,4-*cis*-diols are the major product. Methanol reacts very rapidly with sodium borohydride to yield sodium methoxyborohydrides [10]. (The reaction of 2-propanol is almost negligible). Thus, four different reducing agents are involved in the reduction in methanol, and moreover, these species would be equally effective for ketones. For example, it is known that sodium trimethoxyborohydride in methanol gives almost the same epimer ratio and reaction yield of 3-cholestanols as sodium borohydride in methanol in the reduction of 3-cholestanone [11]. On the other hand, from the studies of the solvent effects on the sodium borohydride reduction, it was concluded that the ability of solvent to ionize must be involved in the reaction mechanism [10] and that the ionization of reagent is most favored in methanol [11]. If it is assumed that whatever is the reducing agent, a hydrogen atom attached to boron nearly reach the state of an ionic species, *i.e.* hydride (H^-), in the TS, the results obtained in methanol are explainable by the same models as above. Thus, the steric interaction between the reducing agent (incoming) and 5-OMe in the TS-**B** is negligible, so that the TS-**B** is preferable to **A**, giving the 3,4-*cis*-diols as the major product.

Reduction of the (±)-Flavanonols with 5-OAc.

Reduction of (±)-taxifolin pentaacetate (**15a**) in dioxane at room temperature gave (±)-catechin 3,7,3′,4′-tetraacetate (**46a**) (56%) which afforded the 5-OMe compound **17a** (75%) and the 5-OAc compound **18a** (93%), respectively, on methylation with dimethyl sulfate and acetylation with acetic anhydride. The confirmation of 5-OH and 5-OMe in **16a** and **17a** was achieved by nOe observed at 4-H_2 on saturation of 5-OH and 5-OMe, respectively. The identification of **18a** was made by the direct comparison with an authentic sample obtained from a commercially available (±)-catechin. Reduction of **15a** in dioxane at room temperature, followed by acetylation, gave **18a** (91%).

It has been reported that reduction of (±)-aromadendrin tetraacetate (**15b**) in methanol at -20° furnishes the 4-OH compound **19b** which is converted to the 4-OAc compound **20b** in 86% overall yield on acetylation [5]. Also, reduction of **15a** in methanol [12] at -30° afforded **19a** (87%). (Because of instability, **19a** was immediately used in the next step). Reduction of **19a** in 2-propanol at room temperature, followed by acetylation, yield **18a** (82%). Treatment of **19a** in methanol as above gave **18a** (63%) and the 4-OMe compound **21a** (30%). The ^{1}H nmr spectra of **21a** showed couplings, $J_{2,3}$ = 10.5 Hz and $J_{3,4}$ = 3.0 Hz, and nOes between 2-H and 4-OMe and between 3-H and 4-H, pointing out the 2,3-*trans*-3,4-*cis*-configuration for **21a**.

Reduction of **15a** in 2-propanol at room temperature, followed by acetylation, gave **18a** (74%) and (±)-epicatechin pentaacetate (**22a**) (8.5%). The ir and ^{1}H nmr spectra of **22a** were identical with those of (-)-epicatechin pentaacetate prepared from a commercially available (-)-epicatechin. Treatment of **15a** in methanol as above afforded **18a** (71%) and a mixture (*ca.* 11%) of **21a** and the 4-OAc compound **23a** (2.5:1 ratio). The ^{1}H nmr spectrum of the mixture showed couplings, $J_{2,3}$ = 0.9 Hz and $J_{3,4}$ = 4.2 Hz, for **23a**, suggesting the 2,3-*cis*-3,4-*cis*-configuration for **23a** [13]. (Furthermore, nOes were observed among 2-H, 3-H and 4-H for **23b**).

(±)-Aromadendrin tetraacetate (**15b**) and the 4-OH compound **19b** reacted in the similar manner to **15a** and **19a**, respectively, to give the **b**-series compounds corresponding to the **a**-series compounds.

It seems that the results obtained are due to the unique effect of 5-OAc. At first glance, the TS-**A** and -**B** (R = OAc) are destabilized by the large interactions arising from 5-OAc. However, partial binding between 4eq-OR[1] (forming) and 5-OAc in the TS-**A** releases the steric interaction between them. The TS-**E** arising from **A** overwhelmingly becomes advantageous compared to **B**, giving the dioxane **24** (Chart 2). The over-reduction or methanolysis of **24** does not occur at -30°, and **19** is successively produced by the path-b cleavage. These compounds are reversible at room temperature, and **19** is reduced *via* **24**. The reduction or methanolysis at C-4 in **24** accompanied by the path-a cleavage gives **16** or **21** (after acetylation).

The formations of **22** and **23** are speculated as follows. The reduction of **15** in protic solvents at room temperature would give the 4-OH compound **25** (isomeric to **19**) as a by-product. Binding between 4-OH and 5-OAc (compound **26**) accompanied by epimerization at C-2 *via* the intermediate **27** would afford the compound **28** which is successively reduced at C-4 in 2-propanol to yield **22**. On the other hand, **28** would not be reduced in methanol, and would give **23** *via* the compound **29** on acetylation. Of course, the formation of **16** from **26** cannot be ruled out.

The pathways *via* **24** and **26** would proceed in a concerted or a stepwise (probably ion pair) mode.

EXPERIMENTAL

Melting points (uncorrected) were determined on a micro hot-stage apparatus. Spectra were recorded on the following spectrometers: ir, Hitachi 260-30; ^{1}H nmr, Varian EM-390 (90 MHz), VXR-300 (300 MHz), XL-400 (400 MHz) (reference, TMS); ms, JEOL, JMS DX-300; elemental analysis, Perkin-Elmer 240B. The nOe spectra were recorded by means of nOe difference spectroscopy.

Preparative tlc was carried out on silica gel plates using acetone/benzene = 1:10 as solvent unless otherwise noted.

The reduction of **1** is shown as a representative procedure for the (±)-flavanonols with 5-OMe. The reduction of **4**, **7** and **10** was carried out in the same manner (Table I). Among the isomeric 3,4-diols obtained, **5**, **6**, **8** and **9** were identified by the direct comparisons with the authentic samples obtained previously under the different reaction conditions [5,6]. The properties of the new compounds **11** and **12** are described below.

The compounds **16b**-**23b** were prepared by the same procedures as those employed for the **a**-series compounds, and their properties are described under each corresponding **a**-series compound.

(±)-Ampelopsin (**14**).

A mixture of **13** (7) (200.1 mg, 0.342 mmole) and 12% hydrogen chloride/anhydrous methanol (0.8 ml) in anhydrous methanol (1 ml) was stirred at 50° for 20 minutes. Concentration of the reaction mixture *in vacuo*, followed by preparative tlc (chloroform/methanol = 10:1) of the product, afforded **14** (77.6 mg, 71%), Rf 0.15, as colorless needles of mp 195-198° dec (water); ir (potassium bromide): ν 3425, 3300 (OH), 1640 (C=O) cm^{-1}; ^{1}H nmr (90 MHz, acetone-d_6): δ 6.63 (2H, s, 2'-, 6'-Hs), 5.98, 5.96 (each 1H, d, J = 1.8 Hz, 6-, 8-Hs), 4.90 (1H, d, J = 12.0 Hz, 2-H), 4.50 (1H, d, J = 12.0 Hz, 3-H); ms: m/z M$^+$, 320.0534 (M, 320.0531 for $C_{15}H_{12}O_8$).

Anal. Calcd. for $C_{15}H_{12}O_8$: C, 56.26; H, 3.78. Found: C, 56.18; H, 3.99.

(±)-Ampelopsin Pentamethyl Ether (**10**).

A solution of **14** (151.0 mg, 0.472 mmole) in anhydrous acetone (1 ml) was added to a mixture of dimethyl sulfate (396.5 mg, 3.14 mmoles) and potassium carbonate (1.04 g, 7.5 mmoles) in anhydrous acetone (10 ml), and the whole was refluxed under nitrogen for 6 hours. The reaction mixture was filtered and concentrated *in vacuo*. The obtained residue was extracted with ethyl acetate. Work-up of the organic layer afforded a solid which was purified by preparative tlc to yield **10** (106.0 mg, 58%), Rf 0.23, as colorless needles, mp 191-193° (ethanol); ir (chloroform): ν 3475 (OH), 1670 (C=O) cm^{-1}; ^{1}H nmr (90 MHz, deuteriochloroform): δ 6.80 (2H, s, 2'-, 6'-Hs), 6.17 (2H, s, 6-, 8-Hs), 5.97 (1H, d, J = 12.0 Hz, 2-H), 4.43 (1H, dd, J = 12.0, 1.8 Hz, 3-H, changed to a doublet with J = 12.0 Hz on addition of deuterium oxide), 4.07 (1H, d, J = 1.8 Hz, 3-OH, exchangeable with deuterium oxide), 3.92 (3H, s, OMe), 3.90 (6H, s), 3.85, 3.83 (each 3H, s) (5 x OMe); ms: m/z M$^+$, 390.1314 (M, 390.1313 for $C_{20}H_{22}O_8$).

Anal. Calcd. for $C_{20}H_{22}O_8 \cdot \frac{1}{4}H_2O$: C, 60.83; H, 5.74. Found: C, 60.74; H, 5.79.

(±)-2,3-*trans*-3,4-*cis*-7,4'-Dimethoxyflavan-3,4-diol (**2**) and Its 3,4-*trans* Isomer **3**.

a) Sodium borohydride (10.3 mg, 0.272 mmole) was added to a solution of **1** [4] (12.4 mg, 0.039 mmole) in anhydrous 2-propanol (5 ml), and the whole was stirred at room temperature for 2 hours. Work-up of the reaction mixture, followed by preparative tlc (acetone/benzene = 1:5) of the product, gave **3** (11.8 mg, 95%), Rf 0.28.

b) Treatment of a mixture of **1** (20.2 mg, 0.067 mmole) and sodium borohydride (18.3 mg, 0.483 mmole) in anhydrous dioxane (5 ml) at room temperature for 3 hours afforded **3** (17.7 mg, 87%).

c) Treatment of a mixture of **1** (10.0 mg, 0.033 mmole) and sodium borohydride (9.5 mg, 0.25 mmole) in anhydrous methanol (4 ml) at room temperature for 1.5 hours furnished **2** (0.6 mg, 6%), Rf 0.33, and **3** (9.0 mg, 90%).

The properties of **2** are colorless needles, mp 132-135° (ethanol); ir (chloroform): ν 3568, 3380 (OH) cm^{-1}; ^{1}H nmr (90 MHz, deuteriochloroform): ν 7.42 (2H, d, J = 9.0 Hz, 2'-, 6'-Hs), 7.25 (1H, d, J = 9.0 Hz, 5-H), 6.96 (2H, d, J = 9.0 Hz, 3'-, 5'-Hz), 6.58 (1H, dd, J = 9.0, 2.4 Hz, 6-H), 6.45 (1H, d, J = 2.4 Hz, 8-H), 4.98 (1H, d, J = 10.2 Hz, 2-H), 4.75 (1H, d, J = 3.6 Hz, 4-H), 4.02 (1H, dd, J = 10.2, 3.6 Hz, 3-H), 3.83, 3.76 (each 3H, s, 2 x OMe), 2.20 (2H, s, 2 x OH, exchangeable with deuterium oxide); ms: m/z M$^+$, 302.1159 (M, 302.1153 for $C_{17}H_{18}O_5$).

Anal. Calcd. for $C_{17}H_{18}O_5 \cdot \frac{1}{4}H_2O$: C, 66.55; H, 6.08. Found: C, 66.81; H, 5.91.

The properties of **3** are colorless needles, mp 120-123° (ethanol); ir (chloroform): ν 3566, 3390 (OH) cm^{-1}; ^{1}H nmr (90 MHz, deuteriochloroform): δ 7.37 (1H, d, J = 9.0 Hz, 5-H), 7.35 (2H, d, J = 9.0 Hz, 2'-, 6'-Hs), 6.93 (2H, d, J = 9.0 Hz, 3'-, 5'-Hs), 6.57 (1H, dd, J = 9.0, 2.4 Hz, 6-H), 6.41 (1H, d, J = 2.4 Hz, 8-H), 4.74 (1H, d, J = 7.2 Hz, 4-H), 4.72 (1H, d, J = 10.2 Hz, 2-H), 3.83

(1H, dd, J = 10.2, 7.2 Hz, 3-H), 3.80, 3.73 (each 3H, s, 2 x OMe), 2.50 (2H, s, 2 x OH, exchangeable with deuterium oxide); ms: m/z M$^+$, 302.1146 (M, 302.1153 for $C_{17}H_{18}O_5$).

Anal. Calcd. for $C_{17}H_{18}O_5 \cdot \frac{1}{4}H_2O$: C, 66.55; H, 6.08. Found: C, 66.79; H, 5.96.

(±)-2,3-*trans*-3,4-*cis*-5,7,3',4',5'-Pentamethoxyflavan-3,4-diol (**11**) and Its 3,4-*trans* Isomer **12**.

The properties of **11** are colorless needles of mp 205-206° (ethanol), Rf 0.39; ir (chloroform): ν 3620, 3570 (OH) cm^{-1}; ^{1}H nmr (90 MHz, deuteriochloroform): δ 6.72 (2H, s, 2'-, 6'-Hs), 6.12 (2H, s, 6-, 8-Hs), 5.04 (1H, d, J = 4.0 Hz, 4-H), 4.89 (1H, d, J = 10.2 Hz, 2-H), 3.99 (1H, m, 3-H), 3.86 (6H, s), 3.84, 3.82, 3.74 (each 3H, s) (5 x OMe), 2.75, 2.63 (each 1H, s, 2 x OH, exchangeable with deuterium oxide); ms: m/z M$^+$, 392.1467 (M, 392.1470 for $C_{20}H_{24}O_8$).

Anal. Calcd. for $C_{20}H_{24}O_8 \cdot \frac{1}{4}H_2O$: C, 60.52; H, 6.22. Found: C, 60.55; H, 6.14.

The properties of **12** are colorless needles, mp 197-198° (ethanol), Rf 0.28; ir (chloroform): ν 3580 (OH) cm^{-1}; ^{1}H nmr (90 MHz, deuteriochloroform): δ 6.72 (2H, s, 2'-, 6'-Hs), 6.14, 6.11 (each 1H, d, J = 1.8 Hz, 6-, 8-Hs), 5.00 (1H, d, J = 7.5 Hz, 4-H), 4.67 (1H, d, J = 10.2 Hz, 2-H), 4.07 (1H, dd, J = 10.2, 7.5 Hz, 3-H), 3.85 (9H, s), 3.82, 3.72 (each 3H, s) (5 x OMe), 2.59, 1.79 (each 1H, s, 2 x OH, exchangeable with deuterium oxide); ms: m/z M$^+$, 392.1470 (M, 392.1470 for $C_{20}H_{24}O_8$).

Anal. Calcd. for $C_{20}H_{24}O_8 \cdot \frac{3}{4}H_2O$: C, 59.18; H, 6.33. Found: C, 59.25; H, 6.02.

(±)-Taxifolin Pentaacetate (**15a**).

A mixture of (±)-taxifolin [6] (59.3 mg, 0.195 mmole), anhydrous pyridine (2 drops) and acetic anhydride (2 ml) was stirred at room temperature for 20 hours. Work-up of the reaction mixture, followed by preparative tlc of the product, gave **15a** (82.3 mg, 82%) as colorless needles, mp 147-149° (ethanol), Rf 0.65; ir (chloroform): ν 1785 (OAc), 1725 (C=O) cm^{-1}; ^{1}H nmr (90 MHz, deuteriochloroform): δ 7.45-7.19 (3H, m, 2'-, 5'-, 6'-Hs), 6.77, 6.61 (each 1H, d, J = 2.2 Hz, 6-, 8-Hs), 5.67 (1H, d, J = 12.6 Hz, 2-H), 5.39 (1H, d, J = 12.6 Hz, 3-H), 2.36 (3H, s), 2.29 (9H, s), 2.03 (3H, s) (5 x OAc); ms: m/z M$^+$, 514.1116 (M, 514.1110 for $C_{25}H_{22}O_{12}$).

Anal. Calcd. for $C_{25}H_{22}O_{12}$: C, 58.37; H, 4.31. Found: C, 58.49; H, 4.36.

(±)-Aromadendrin Tetraacetate (**15b**) [5].

This compound was prepared from (±)-aromadendrin in 83% yield as colorless needles, mp 124-126° (ethanol), Rf 0.61; ms: m/z M$^+$, 456.1040 (M, 456.1055 for $C_{23}H_{20}O_{10}$).

Anal. Calcd. for $C_{23}H_{20}O_{10}$: C, 60.53; H, 4.42. Found: C, 60.47; H, 4.44.

(±)-Catechin 3,7,3',4'-Tetraacetate (**16a**).

A mixture of **15a** (20.5 mg, 0.040 mmole) and sodium borohydride (7.3 mg, 0.193 mmole) in anhydrous dioxane (4 ml) was stirred at room temperature for 5 hours. Work-up of the reaction mixture, followed by preparative tlc (acetone/benzene = 1:5) of the product, afforded **16a** (10.2 mg, 56%), Rf 0.69, as colorless needles, mp 165-166.5° (methanol); ir (chloroform): ν 3272 (OH), 1768, 1740 (OAc) cm^{-1}; ^{1}H nmr (400 MHz, deuteriochloroform): δ 7.24 (1H, dd, J = 8.0, 2.0 Hz, 6'-H), 7.16 (1H, d, J = 2.0 Hz, 2'-H), 7.16 (1H, d, J = 8.0 Hz 5'-H), 6.30 (1H, d, J = 2.0 Hz, 8-H), 6.17 (1H, d, J = 2.0 Hz, 6-H), 5.82 (1H, s, 5-OH, exchangeable with deuterium oxide), 5.28 (1H, dt, J = 5.4, 6.0 Hz, 3-H), 5.14 (1H, d, J = 6.0 Hz, 2-H), 2.83 (1H, dd, J = 17.0, 5.4 Hz, 4α-H), 2.70 (1H, dd, J = 17.0, 6.0 Hz, 4β-H), 2.27 (12H, s), 2.00 (3H, s) (4 x OAc); nOe (400 MHz), deuteriochloroform) (%): 5-OH → 4α-H (3.4), 4β-H (1.7), 6-H (10.5); OAc (δ 2.27) → 6-, 8-Hs (each 1.8), 2'-, 5'-Hs (each 1.7); 2-H → 4β-H (1.7), 2'-H (3.4), 6'-H (1.0); ms: m/z M$^+$, 458.1217 (M, 458.1211 for $C_{23}H_{22}O_{10}$).

Anal. Calcd. for $C_{23}H_{22}O_{10} \cdot \frac{1}{2}H_2O$: C, 59.10; H, 4.96. Found: C, 59.32; H, 4.95.

(±)-Afzelechin 3,7,4'-Triacetate (**16b**).

This compound was prepared from **15b** in 51% yield as colorless needles, mp 178-180° (ethanol), Rf 0.46; ir (chloroform): ν 3282 (OH), 1768, 1748 (OAc) cm^{-1}; ^{1}H nmr (400 MHz, deuteriochloroform): δ 7.35 (2H, d, J = 8.5 Hz, 2'-, 6'-Hs), 7.07 (2H, d, J = 8.5 Hz, 3'-, 5'-Hs), 6.33 (1H, d, J = 2.0 Hz, 8-H), 6.18 (1H, d, J = 2.0 Hz, 6-H), 5.33 (1H, s, 5-OH, exchangeable with deuterium oxide), 5.33 (1H, dt, J = 5.2, 6.0 Hz, 3-H), 5.15 (1H, d, J = 6.0 Hz, 2-H), 2.83 (1H, dd, J = 18.0, 5.2 Hz, 4α-H), 2.71 (1H, dd, J = 18.0, 6.0 Hz, 4β-H), 2.29 (3H, s), 2.28 (3H, s), 1.99 (3H, s) (3 x OAc); ms: m/z M$^+$, 400.1191 (M, 400.1157 for $C_{21}H_{20}O_8$).

Anal. Calcd. for $C_{21}H_{20}O_8 \cdot \frac{1}{2}H_2O$: C, 61.61; H, 5.17. Found: C, 61.90; H, 5.16.

(±)-Catechin 5-Methyl Ether Tetraacetate (**17a**).

A mixture of **16a** (20.0 mg, 0.044 mmole), dimethyl sulfate (97.7 mg, 0.78 mmole) and potassium carbonate (403.5 mg, 2.92 mmoles) in anhydrous acetone (5 ml) was refluxed for 4 hours. Work-up of the reaction mixture, followed by preparative tlc of the product, yielded **17a** (15.3 mg, 75%), Rf 0.64, as colorless needles, mp 160-162° (methanol); ir (chloroform): 1765, 1740 (OAc) cm^{-1}; ^{1}H nmr (400 MHz, deuteriochloroform): δ 7.25 (1H, dd, J = 8.0, 2.0 Hz, 6'-H), 7.16 (1H, d, J = 2.0 Hz, 2'-H), 7.16 (1H, d, J = 8.0 Hz, 5'-H), 6.36 (1H, d, J = 2.0 Hz, 8-H), 6.23 (1H, d, J = 2.0 Hz, 6-H), 5.28 (1H, dt, J = 5.2, 6.0 Hz, 3-H), 5.14 (1H, d, J = 6.0 Hz, 2-H), 3.77 (3H, s, 5-OMe), 2.87 (1H, dd, J = 17.0, 5.2 Hz, 4α-H), 2.70 (1H, dd, J = 17.0, 6.0 Hz, 4β-H), 2.29 (3H, s), 2.27 (6H, s), 2.00 (3H, s) (4 x OAc); nOe (400 MHz, deuteriochloroform) (%): 5-OMe → 4α-H (5.7), 4β-H (3.7), 6-H (20.4); 2-H → 4β-H (1.9), 2'-H (5.0), 6'-H (1.4); ms: m/z M$^+$, 472.1366 (M, 472.1368 for $C_{24}H_{24}O_{10}$).

Anal. Calcd. for $C_{24}H_{24}O_{10}$: C, 61.01; H, 5.12. Found: C, 60.92; H, 5.11.

(±)-Afzelechin 5-Methyl Ether Triacetate (**17b**).

This compound was prepared from **16b** in 84% yield as colorless needles, mp 173-175° (ethanol), Rf 0.56; ir (chloroform): ν 1770, 1750 (OAc), cm^{-1}; ^{1}H nmr (400 MHz, deuteriochloroform): δ 7.35 (2H, d, J = 8.5 Hz, 2'-, 6'-Hs), 7.05 (2H, d, J = 8.5 Hz, 3'-, 5'-Hs), 6.73 (1H, d, J = 2.0 Hz, 8-H), 6.22 (1H, d, J = 2.0 Hz, 6-H), 5.32 (1H, dt, J = 5.2, 6.0 Hz, 3-H), 5.14 (1H, d, J = 6.0 Hz, 2-H), 3.77 (3H, s, 5-OMe), 2.89 (1H, dd, J = 18.0, 5.2 Hz, 4α-H), 2.71 (1H, dd, J = 18.0, 6.0 Hz, 4β-H), 2.29 (3H, s), 2.28 (3H, s), 1.98 (3H, s) (3 x OAc); nOe (400 MHz, deuteriochloroform) (%): 5-OMe → 4α-H (0.9), 4β-H (0.4), 6-H (17.3); 2-H → 4β-H (3.7), 2'-, 6'-Hz (4.8); ms: m/z M$^+$, 414.1317 (M, 414.1313 for $C_{22}H_{22}O_8$).

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.57; H, 5.40.

(±)-Catechin Pentaacetate (**18a**).

A mixture of **16a** (11.4 mg, 0.025 mmole), anhydrous pyridine (2 drops) and acetic anhydride (1 ml) was stirred at room temperature for 20 hours. Work-up of the reaction mixture, followed by preparative tlc of the product, gave **18a** (11.6 mg, 94%), Rf 0.54, as colorless needles of mp 163-165° (methanol); ir (chloroform): ν 1770, 1750 (OAc) cm^{-1}; ^1H nmr (90 MHz, deuteriochloroform): δ 7.24-7.15 (3H, m, 2'-, 5'-, 6'-Hs), 6.65, 6.59 (each 1H, d, J = 2.4 Hz, 6-, 8-Hs), 5.25 (1H, dt, J = 5.4, 6.0 Hz, 3-H), 5.12 (1H, d, J = 6.0 Hz, 2-H), 2.90 (1H, dd, J = 16.8, 5.4 Hz, 4-Ha), 2.60 (1H, dd, J = 16.8, 6.0 Hz, 4-Hb), 2.26 (12H, s), 1.98 (3H, s) (5 x OAc); ms: m/z M^+, 500.1315 (M, 500.1317 for $C_{25}H_{24}O_{11}$).

Anal. Calcd. for $C_{25}H_{24}O_{11}$: C, 59.99; H, 4.83. Found: C, 59.79; H, 4.93.

(±)-Afzelechin Tetraacetate (**18b**).

This compound was prepared from **16b** in 93% yield as colorless needles, mp 157-159° (ethanol), Rf 0.62; ir (chloroform): ν 1764, 1750 (OAc) cm^{-1}; ^1H nmr (90 MHz, deuteriochloroform): δ 7.35 (2H, d, J = 8.7 Hz, 2'-, 6'-Hs), 7.07 (2H, d, J = 8.7 Hz, 3'-, 5'-Hs), 6.65, 6.57 (each 1H, d, J = 2.4 Hz, 6-, 8-Hs), 5.29 (1H, dt, J = 5.2, 6.0 Hz, 3-H), 5.14 (1H, d, J = 6.0 Hz, 2-H), 2.83 (1H, dd, J = 16.2, 5.4 Hz, 4-Ha), 2.61 (1H, dd, J = 16.2, 6.0 Hz, 4-Hb), 2.26 (9H, s), 1.96 (3H, s) (4 x OAc); ms: m/z M^+, 442.1241 (M, 442.1262 for $C_{23}H_{22}O_9$).

Anal. Calcd. for $C_{23}H_{22}O_9 \cdot 1/4\ H_2O$: C, 61.81; H, 5.07. Found: C, 61.85; H, 5.06.

(±)-2,3-*trans*-3,4-*trans*-4-Hydroxy-3,5,7,3',4'-pentaacetoxyflavan (**19a**).

A mixture of **15a** (15.2 mg, 0.030 mmole) and sodium borohydride (6.8 mg, 0.179 mmole) in anhydrous methanol (5 ml) was stirred at -30° for 1 hour. Work-up of the reaction mixture, followed by preparative tlc (acetone/benzene = 1:6) of the product, gave **19a** (13.2 mg, 87%), Rf 0.43, as a colorless oil; fab ms: m/z M^++Na, 539 (M, 516 for $C_{25}H_{24}O_{12}$). Because of instability, this compound was immediately used in the next step.

(±)-2,3-*trans*-3,4-*trans*-4-Hydroxy-3,5,7,4'-tetraacetoxyflavan (**19b**).

This compound was prepared from **15b** in 82% yield as a colorless oil, Rf 0.41; fab ms: m/z M^++Na, 481 (M, 458 for $C_{23}H_{22}O_{10}$).

Reduction of **19a** at Room Temperature and Acetylation.

a) A mixture of **19a** (25.2 mg, 0.049 mmole) and sodium borohydride (8.0 mg, 0.211 mole) in anhydrous 2-propanol (5 ml) was stirred for 2 hours. Work-up, acetylation and preparative tlc of the product yielded **18a** (20.0 mg, 82%).

b) A mixture of **19a** (10.1 mg, 0.020 mmole) and sodium borohydride (5.0 mg, 0.120 mmole) in anhydrous methanol (5 ml) was stirred for 2 hours. Treatment as above gave **18a** (6.1 mg, 63%), and **21a** (3.1 mg, 30%), Rf 0.40, as a colorless oil.

The properties of (±)-2,3-*trans*-3,4-*cis*-4-methoxy-3,5,7,3',4'-pentaacetoxylflavan (**21a**) are: ir (chloroform): ν 1770, 1755 (OAc) cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 7.36 (1H, dd, J = 8.5, 2.0 Hz, 6'-H), 7.27 (1H, d, J = 2.0 Hz, 2'-H), 7.22 (1H, d, J = 8.5 Hz, 5'-H), 6.67, 6.61 (each 1H, d, J = 2.0 Hz, 6-, 8-Hs), 5.35 (1H, d, J = 10.5 Hz, 2-H), 5.17 (1H, dd, J = 10.5, 3.0 Hz, 3-H), 4.60 (1H, d, J = 3.0 Hz, 4-H), 3.52 (3H, s, 4-OMe), 2.34, 2.29, 2.285, 2.70, 1.95 (each 3H, s, 5 x OAc); nOe (400 MHz, deuteriochloroform) (%): 2-H → 4-OMe (1.6); 3-H → 4-H (4.9), 4-OMe (1.4); 4-H → 3-H (8.2), 4-OMe (2.7); ms: m/z M^+, 530.1420 (M, 530.1424 for $C_{26}H_{26}O_{12}$).

Reduction of **19b** at Room Temperature and Acetylation.

a) (2-Propanol) **19b** gave **18b** (80%).

b) (Methanol) **18b** (62%), and **21b** (20%), Rf 0.48, a colorless oil, were obtained.

The properties of (±)-2,3-*trans*-3,4-*cis*-4-methoxy-3,5,7,4'-tetraacetoxylflavan (**21b**) are: ir (chloroform): ν 1773, 1750 (OAc) cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 7.45 (2H, d, J = 8.5 Hz, 2'-, 6'-Hs), 7.12 (2H, d, J = 8.5 Hz, 3'-, 5'-Hs), 6.67, 6.61 (each 1H, d, J = 2.3 Hz, 6-, 8-Hs), 5.37 (1H, d, J = 10.5 Hz, 2-H), 5.23 (1H, dd, J = 10.5, 3.0 Hz, 3-H), 4.60 (1H, d, J = 3.0 Hz, 4-H), 3.53 (3H, s, 4-OMe), 2.34, 2.30, 2.27, 1.91 (each 3H, s, 4 x OAc); nOe (400 MHz, deuteriochloroform) (%): 2-H → 4-OMe (0.8); 3-H → 4-H (6.9), 4-OMe (0.8); 4-H → 3-H (9.2), 4-OMe (2.3); 4-OMe → 2-H (4.2), 4-H (9.2); ms: m/z M^+, 472.1343 (M, 472.1369 for $C_{24}H_{24}O_{10}$).

Reduction of **15a** at Room Temperature and Acetylation.

a) A mixture of **15a** (40.7 mg, 0.079 mmole) and sodium borohydride (16.4 mg, 0.433 mmole) in anhydrous dioxane (5 ml) was stirred for 5 hours. Work-up, acetylation and preparative tlc of the product furnished **18a** (36.9 mg, 91%).

b) A mixture of **15a** (64.5 mg, 0.125 mmole) and sodium borohydride (21.1 mg, 0.558 mmole) in anhydrous 2-propanol (15 ml) was stirred for 5 hours. Treatment as above afforded **18a** (46.0 mg, 74%) and **22a** (5.3 mg, 8.5%), Rf 0.48, as a colorless oil.

The properties of (±)-epicatechin pentaacetate (**22a**) are: ir (chloroform): ν 1770, 1740 (OAc) cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 7.35 (1H, d, J = 2.0 Hz, 2'-H), 7.27 (1H, dd, J = 8.5, 2.0 Hz, 6'-H), 7.20 (1H, d, J = 8.5 Hz, 5'-H), 6.67, 6.57 (each 1H, d, J = 2.2 Hz, 6-, 8-Hs), 5.38 (1H, ddd, J = 4.5, 1.8, 1.5 Hz, 3-H), 5.11 (1H, d, J = 1.5 Hz, 2-H), 2.97 (1H, dd, J = 18.0, 4.5 Hz, 4α-H), 2.89 (1H, dd, J = 18.0, 1.8 Hz, 4β-H), 2.30 (9H, s), 2.28, 1.92 (each 3H, s) (5 x OAc); nOe (400 MHz, deuteriochloroform) (%): 2-H → 3-H (6.0), 4α-H (4.0), 2'-H (6.0), 6'-H (8.0); 3-H → 2-H (7.0), 4α-H (6.0), 4β-H (4.0), 2'-, 6'-Hs (each 3.0); 4α-H → 2-H (2.0), 3-H (4.0), 4β-H (2.0); 4β-H → 3-H (2.0); ms: m/z M^+, 500.1303 (M, 500.1318 for $C_{25}H_{24}O_{11}$).

c) A mixture of **15a** (40.9 mg, 0.080 mmole) and sodium borohydride (21.3 mg, 0.563 mmole) in anhydrous methanol (10 ml) was stirred for 5 hours. Treatment as above gave **18a** (28.2 mg, 71%) and a mixture (5.0 mg, *ca.* 11%) of **21a** and (±)-2,3-*cis*-3,4-*cis*-3,4,5,7,3',4'-hexaacetoxyflavan (**23a**), Rf 0.40, as a colorless oil; ^1H nmr (400 MHz, deuteriochloroform): δ for **23a**, 6.40 (1H, d, J = 5.0 Hz, 4-H), 5.58 (1H, dd, J = 5.0, 1.8 Hz, 3-H), 5.29 (1H, d, J = 1.8 Hz, 2-H); for **21a**, see above; (The intensity of corresponding each proton showed **21a**/**23a** = 2.5:1); ms: m/z M^+, 558 ($C_{27}H_{26}O_{13}$, **23a**), 530 ($C_{26}H_{26}O_{12}$, **21a**).

Reduction of **15b** at Room Temperature and Acetylation.

a) (Dioxane) **15b** gave **18b** (87%).

b) (2-Propanol) **18b** (82%) and **22b** (12%), Rf 0.53, a colorless oil, were obtained.

The properties of (±)-epiafzelechin tetraacetate (**22b**) are: ir (chloroform): ν 1764, 1750 (OAc) cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 7.45 (2H, d, J = 8.7 Hz, 2'-, 6'-Hs), 7.12

(2H, d, J = 8.7 Hz, 3'-, 5'-Hs), 6.68, 6.57 (each 1H, d, J = 2.1 Hz, 6-, 8-Hs), 5.40 (1H, dd, J = 4.5, 2.3 Hz, 3-H), 5.12 (1H, br s, 2-H), 2.99 (1H, dd, J = 17.7, 4.5 Hz, 4α-H), 2.89 (1H, dd, J = 17.7, 2.3 Hz, 4β-H), 2.304, 2.295, 2.82 (each 3H, s), 1.90 (3H, s) (4 x OAc); ms: m/z M^+, 442.1250 (M, 442.1263 for $C_{23}H_{22}O_9$).

c) (Methanol) **18b** (63%) and a mixture (*ca.* 21%) of **21b** and (±)-2,3-*cis*-3,4-*cis*-3,4,5,7,4'-pentaacetoxyflavan (**23b**), Rf 0.48, a colorless oil, were obtained; ^1H nmr (300 MHz, deuteriochloroform): δ for **23b**, 6.41 (1H, d, J = 5.0 Hz, 4-H), 5.58 (1H, dd, J = 5.0, 1.5 Hz, 3-H), 5.28 (1H, d, J = 1.5 Hz, 2-H); for **21b**, see above; (The intensity of each corresponding proton showed **21b**/**23b** = 1:1.3); nOe (300 MHz, deuteriochloroform) (%): for **23b**, 2-H → 3-H (7.8), 4-H (7.9); 3-H → 2-H (6.2), 4-H (11.0); 4-H → 2-H (5.4), 3-H (10.1); ms: m/z M^+, 500.1284 (M, 500.1318 for $C_{25}H_{24}O_{11}$, **23b**), 472.1395 (M, 472.1370 for $C_{24}H_{24}O_{10}$, **21b**).

Acknowledgements.

We thank Professor H. Ogura and Professor H. Umeyama, Kitasato University, for their valuable discussions.

REFERENCES AND NOTES

[1] Part **XXIV**: M. Onda, S. Li, X. Li, Y. Harigaya, H. Takahashi, H. Kawase, and H. Kagawa, *J. Nat. Prod.*, **52**, 1100 (1989).

[2] D. C. Wigfield, *Tetrahedron*, **35**, 449 (1979).

[3] H. Takahashi, Y. Kubota, M. Iguchi, and M. Onda, *Chem. Pharm. Bull.*, **33**, 3134 (1985).

[4] T. Oyamada and H. Baba, *Bull. Chem. Soc. Japan*, **39**, 507 (1966).

[5] H. Takahashi, Y. Kubota, M. Iguchi, L. Fang, and M. Onda, *Heterocycles*, **24**, 369 (1986).

[6] H. Takahashi, Y. Kubota, H. Miyazaki, and M. Onda, *Heterocycles*, **22**, 1147 (1984).

[7] H. Takahasi, S. Li, Y. Harigaya, and M. Onda, *Heterocycles*, **26**, 3239 (1987).

[8] E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970); B. Caro and G. Jaoqen, *Tetrahedron Letters*, 2061, 3539 (1974); R. D. Burnett and D. N. Kirk, *J. Chem. Soc., Perkin Trans. 2*, 1523 (1976).

[9] D. C. Wigfield, S. Feiner, and F. W. Gowland, *Tetrahedron Letters*, 3377 (1976).

[10] H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **83**, 4372 (1961).

[11] O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962).

[12] Dioxane (mp 11°) and 2-propanol (poor solubility) were unsuitable for the reduction at -30°.

[13] H. M. Saayman and D. G. Roux, *Biochem. J*, **96**, 36 (1965); S. E. Drewes and D. G. Roux, *ibid.*, **98**, 493 (1966).