Chem. Pharm. Bull. 39(8) 1972—1982 (1991) Vol. 39, No. 8

Selective Monoalkylation of Acyclic Diols by Means of Dibutyltin Oxide and Fluoride Salts[1,2]

Nobuo NAGASHIMA and Masaji OHNO[*,3]

Faculty of Pharmaceutical Sciences, University of Tokyo, 7–3–1, Hongo, Bunkyo-ku, Tokyo 113, Japan.

Received February 12, 1991

Fluoride anion was found to promote monoalkylation reaction of diols by the stannylene acetal method, and selective monoalkylation of various acyclic diols was accomplished in good yields under mild conditions by employing this new method. Functional groups such as carboxylic acid ester, carboxamide, carbamate, nitrile, alkyl chloride, and ether were not affected under the reaction conditions.

Keywords monoalkylation; stannylene acetal; cesium fluoride; 1,2-diol; 1,3-diol

It is highly desirable to develop an efficient method for selective protection of symmetric and unsymmetric diols, because the monoprotected diols are often useful as synthetic intermediates of bifuntional compounds in organic synthesis. Therefore, various methods have been developed[4] especially for selective protection of unsymmetric diols, though the monoprotection of symmetric diols[5] still remains to be explored. In general, the use of one stoichiometric equivalent of a protecting reagent to a diol results in a statistical mixture of diprotected, monoprotected, and unprotected products. To overcome this difficulty, a large excess of diol is commonly used.[6] However, the method cannot be applied in the case of diols obtained by multi-step synthesis. Therefore, monoprotection[7] of diols with 1 eq amount of protective groups is indeed required. From this point of view, monoprotection of diols through reductive opening of alkylidene acetals[8] or stannylene acetals[9] has been developed successfully, and the latter was found to be particularly efficient for various monofunctionalizations of diols.[10] However, monoalkylation of diols by the stannylene acetal method requires rather strong reaction conditions (*i.e.*, elevated temperature and prolonged reaction time [9,11]) even with the assistance of a stannophilic catalyst, such as a tetraalkylammonium halide.[12] If this reaction could be carried out under milder conditions, its synthetic utility would be considerably increased. In a previous communication,[1] we reported an efficient method for the monoalkylation of dimethyl L-tartrate by use of dibutyltin oxide and cesium fluoride under mild reaction conditions. In this paper, we wish to report the details of the methodology with examples of selective benzylation of unsymmetric diols.

Results and Discussion

Monoalkylation of Dialkyl Tartrates We first used dialkyl tartrates as substrates for monoalkylation, because dialkyl tartrates have been widely used as chiral synthons for the synthesis of various biologically active compounds or enantiomerically pure compounds[13] and also because only a few reports about the monoalkylation of dialkyl tartrates are available.[14] We first examined monobenzylation of dimethyl L-tartrate using the method developed by Moffatt

TABLE I. Monoalkylation of Dialkyl Tartrates

Entry	Tartrate	R′X (eq)	Fluoride salt (eq)	Solvent	Temperature	Time	Product	Yield[a)] (%)
1	**1**	$PhCH_2Br$ (2.04)	No salt	DMF	100 °C	3 h	**4**	41
2	**1**	$PhCH_2Br$ (3.00)	*n*-Bu_4NBr (0.5)	PhMe	100 °C	1 h	**4**	13
3	**1**	$PhCH_2Br$ (2.19)	CsF (1.22)	DMF	rt	2 h	**4**	85
4	**1**	$PhCH_2I$ (1.11)	No salt	DMF	100 °C	2 h	**4**	13
5	**1**	$PhCH_2I$ (2.84)	CsF (1.93)	DMF	rt	1 h	**4**	99
6	**1**	$PhCH_2I$ (1.71)	KF (1.53)	DMF	50 °C→rt	2 h→11.0 h	**4**	55
7	**1**	$PhCH_2I$ (2.11)	*n*-Bu_4NF (1.60)	DMF	rt	24 h	**4**	67
8	**1**	$PhCH_2I$ (2.41)	CsF (2.03)	PhMe[b)]	rt	25 h	**4**	48
9	**1**	$PhCH_2I$ (2.33)	CsF (1.70)	PhMe[c)]	rt	45 h	**4**	75
10	**1**	$PhCH_2I$ (1.91)	CsF (1.30)	PhMe[d)]	rt	45 h	**4**	3.8
11	**1**	$PhCH_2I$ (1.52)	CsF (1.64)	THF	rt	25 h	**4**	69
12	**1**	*p*-$NO_2C_6H_4CH_2I$ (2.00)	CsF (1.29)	DMF	rt	3.5 h	**5**	84
13	**1**	*p*-$NO_2C_6H_4CH_2Br$ (1.50)	CsF (1.90)	DMF	rt	46 h	**5**	93
14	**1**	*p*-$MeOC_6H_4CH_2Cl$ (1.12)[e)]	*n*-Bu_4NF (1.00)	THF	rt	72 h	**6**	45
15	**1**	*p*-$MeOC_6H_4CH_2Cl$ (1.44)[e)]	KF (1.23)	DMF	rt	14 h	**6**	52
16	**1**	*p*-$MeOC_6H_4CH_2Cl$ (1.54)[f)]	KF (1.27)	DMF	rt	72 h	**6**	68
17	**1**	*p*-$MeOC_6H_4CH_2Cl$ (1.35)[f)]	CsF (1.19)	DMF	0 °C→rt	20 min→1 h	**6**	67
18	**1**	*p*-$MeOC_6H_4CH_2I$ (2.10)	CsF (2.05)	DMF	0 °C→rt	20 min→20 min	**6**	72
19	**1**	$CH_2=CHCH_2Br$ (1.26)	CsF (1.39)	DMF	rt	20 h	**7**	83
20	**1**	$CH_2=CHCH_2I$ (1.53)	CsF (1.62)	DMF	rt	6 h	**7**	98
21	**2**	MeI (4.29)	CsF (1.26)	DMF	rt	21 h	**8**	72
22	**2**	$PhCH_2I$ (1.55)	CsF (1.37)	DMF	rt	3 h	**9**	92
23	**3**	$PhCH_2I$ (2.22)	KF (2.03)	MeCN	rt	50 h	**9**	90
24	**3**	$PhCH_2I$ (2.13)	CsF (1.52)	DMF	rt	5 h	**10**	94

a) Isolated yields after chromatography on silica gel. *b*) The reaction was carried out in the presence of 10 mol% of dibenzo-24-crown-8. *c*) The reaction was carried out in the presence of 10 mol% of dicyclohexano-18-crown-6. *d*) No crown ether was used. *e*) Tetra-*n*-butylammonium iodide (10 mol% in entry 14 and 1 eq in entry 15) was also used as an additive. *f*) Potassium iodide (1.54 eq in entry 16 and 1.33 eq in entry 17) was also used as an additive. rt = room temperature.

et al.,[9] but the yield of the desired product was only 41% (entry 1 in Table I). The same reaction using benzyl iodide gave a much lower yield (entry 4 in Table I) than in the case of benzyl bromide. The results clearly showed that the procedure cannot be applied to monobenzylation of dimethyl L-tartrate. Furthermore, monobenzylation of dimethyl L-tartrate by David's procedure[12a] also gave a low yield of the monoalkylation product (entry 2 in Table I). Therefore, we attempted to improve Moffatt's procedure by the use of additives. By analogy with the fluorodesilylation process, we first examined the effect of fluoride salts in the monoalkylation reaction of dialkyl tartrates (Eq. 1).

The results are listed in Table I. It is apparent from Table I that fluoride anion promoted the reactions, allowing them to proceed even at room temperature with good to excellent yields of the monoalkylated products (entries 3, 5 to 7 *vs.* entries 1 and 4 in Table I). Among the fluoride salts tested, cesium fluoride showed a most remarkable effect. Thus, monobenzylation of tartrate 1 using benzyl iodide and cesium fluoride in *N*,*N*-dimethylformamide (DMF) took place within 1 h at room temperature and gave a quantitative yield of monobenzylated tartrate, **4** (entry 5 in Table I). Other alkyl groups such as *p*-nitrobenzyl, *p*-methoxybenzyl, allyl, and methyl were also introduced in good to excellent yields (entries 13, 18, 20 and 21 in Table I).

As the reaction solvents, polar aprotic solvents such as DMF, tetrahydrofuran (THF) and acetonitrile were successfully employed (entries 5, 11 and 23 in Table I); DMF usually gave the best results. The reactions in nonpolar solvents such as toluene were also possible with the aid of phase transfer catalysts (entries 8 to 10 in Table I). However, the reactions were slower and the yields of products were not so high.

As for the alkylating reagents, the reactions with alkyl iodides usually gave better yields than those with the corresponding bromides (entries 5 *vs.* 3 and 20 *vs.* 19 in Table I), and in the case of an unstable alkyl iodide (entry 18 in Table I), it can be formed *in situ* from the corresponding chloride and the appropriate iodides (entries 14 to 17 in Table I). When dimethyl L-tartrate was treated with 1 eq of benzyl bromide and 1 eq of cesium fluoride in DMF at room temperature, the reaction gave only a 5% yield of the monobenzylated tartrate, **4** (Eq. 2). Therefore, it is evident that the combined use of stannylene acetal of tartrates and cesium fluoride is essential for the selective preparation of the monoalkylated tartrates.

As an efficient method for monoalkylation of symmetric diols had thus been realized, we next examined regioselectivity in monobenzylation of unsymmetrical diols.

Regioselective Benzylation of Unsymmetrical Diols 1-Phenylethanediol was selected as a simple unsymmetrical diol and subjected to monobenzylation under various conditions (Eq. 3). The results are shown in Table II.

The influence of various factors such as benzyl halides, metal fluorides, solvents and temperatures was investigated.

Table II. Regioselective Benzylation of 1-Phenylethanediol

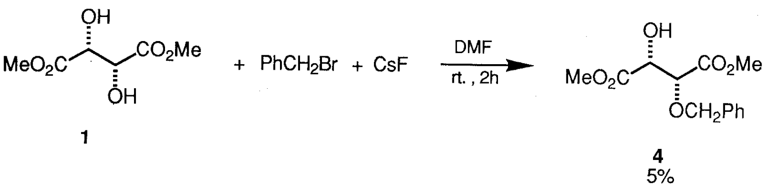
Entry	X in $PhCH_2X$ (eq)	MF (eq)	Solvent	Temperature (°C)	Time (h)	Yield[a)] (%) of **29a** and **29b**	Ratio (**29a**: **29b**)
1	I (1.71)	CsF (1.90)	DMF	0—3	1.5	Quant.	90:10
2	I (2.18)	No salt	DMF	0—3	2	0	—
3	I (1.75)	CsF (1.93)	DMF	20—21	1.5	94	91: 9
4	F (1.70)	CsF (1.90)	DMF	0—3	2	0	—
5	Cl (1.71)	CsF (1.92)	DMF	21—22	24	83	87:13
6	Br (1.72)	CsF (1.94)	DMF	21—22	6	95	90:10
7	I (1.72)	CsF (1.96)	THF	20—22	17	96	90:10
8	I (1.82)	CsF (1.93)	MeCN	21—22	5	96	88:12
9	I (1.74)	CsF (1.90)	Me_2CO	21—22	6	99	85:15
10	I (1.71)	CsF (1.97)	$MeNO_2$	21—22	20	N.D.[b)]	—
11	I (1.74)	KF (2.01)	DMF	21—22	45	20	88:12
12	I (1.74)	KF (2.26)	MeCN	21—22	50	40	88:12
13	I (1.79)	KF (2.16)	PhMe[c)]	21—22	100	64	88:12
14	I (1.81)	KF (2.09)	PhMe[d)]	21—22	100	0.6>	—

a) Isolated yields after chromatography on silica gel. *b)* N.D. means not determined. The yield could not be determined because of the formation of an inseparable unknown product together with the monobenzylated products, **29a** and **29b**. *c)* The reaction was carried out in the presence of 5 mol% of dicyclohexano-18-crown-6. *d)* No crown ether was used.

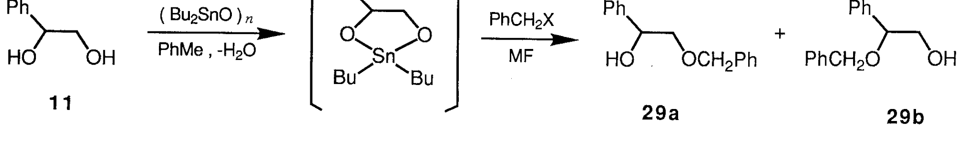
$$RO_2CCH(OH)CH(OH)CO_2R \xrightarrow[\text{2) R'X, fluoride salt}]{\text{1) }(Bu_2SnO)_n\text{ / PhMe, -}H_2O} RO_2CCH(OH)CH(OR')CO_2R \qquad (1)$$

	R	
1	Me	(*R*, *R*)
2	Me	*meso*
3	$PhCH_2$	(*R*, *R*)

	R	R′	
4	Me	$PhCH_2$	(*R*, *R*)
5	Me	*p*-$NO_2C_6H_4CH_2$	(*R*, *R*)
6	Me	*p*-$MeOC_6H_4CH_2$	(*R*, *R*)
7	Me	$CH_2{=}CHCH_2$	(*R*, *R*)
8	Me	Me	(*R*, *R*)
9	Me	$PhCH_2$	(*R*, *S*) and (*S*, *R*)
10	$PhCH_2$	$PhCH_2$	(*R*, *R*)



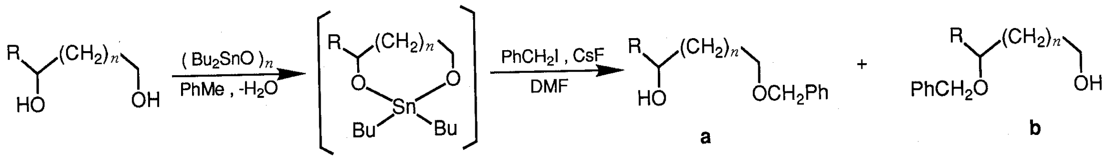
1 **4** 5% (2)



11 **29a** **29b** (3)

It was shown that the reaction rate increased in the following order (entries 3 to 6 in Table II); benzyl fluoride (no reaction) < benzyl chloride < benzyl bromide < benzyl iodide, while the regioselectivity in the reactions was found to be almost the same. Therefore, among the benzyl halides, benzyl iodide was found to be the best one. Next, the effect of the metal fluorides was investigated. No significant difference in the regioselectivity was observed between cesium fluoride and potassium fluoride, while the reaction rates and yields were markedly reduced in the latter case (entries 3 *vs.* 11; 8 *vs.* 12 in Table II). It is very clear that the reaction requires fluoride salts (entries 2 *vs.* 1 in Table II). Then, the solvent effect on the regioselectivity and the reaction rates was examined. While the reaction rates varied depending upon the solvents used, again no significant solvent effect on the regioselectivity was observed (entries 3, 7 to 9 and 12 to 14 in Table II). Among the solvents used, DMF gave the best result (entry 3 in Table II). No temperature-dependency was observed (entries 1 *vs.* 3 in Table II). Thus, the reaction using benzyl iodide and cesium fluoride in DMF at 0 °C to room temperature was found to proceed most smoothly.

Next, the regioselective benzylation of various acyclic diols (Eqs. 4 and 5) was examined. The results are listed in Tables III and IV. In Table III, the examples of diols containing primary and secondary hydroxyl groups are shown, and the examples of diols containing secondary–secondary or secondary–tertiary hydroxyl groups are shown in Table IV. Some functional groups were introduced into the diols in order to clarify the substituent effects on the regioselection and to examine the compatibility of various functional groups under the reaction conditions. Generally, the monobenzylation reaction of the diols listed in Tables III and IV proceeds in good to excellent yields, although there are some examples of moderate yields (entries 5, 6 and 16 in Table III and entry 5 in Table IV). The reaction of 1,2-diols is faster than that of corresponding 1,3-diols (entries 1 *vs.* 2 and 3 *vs.* 4 in Table III). In addition,

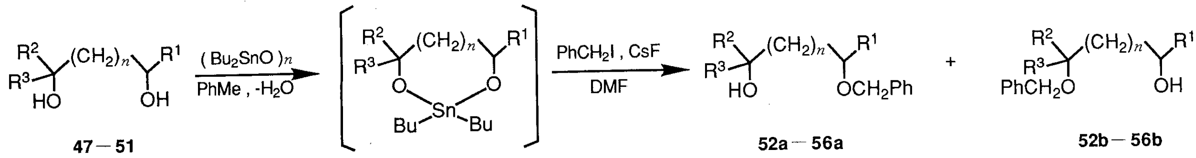


(4)

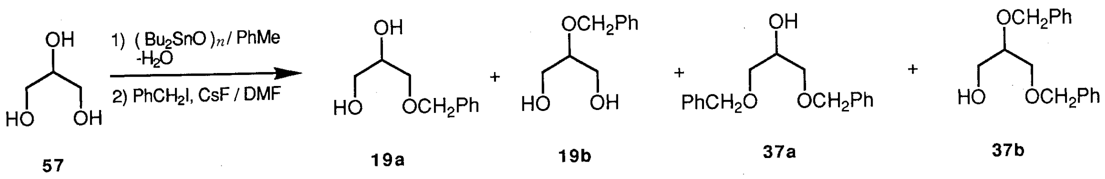
	R	*n*
11	Ph	0
12	Ph	1
13	Me	0
14	Me	1
15	ClCH$_2$	0
16	NCCH$_2$	0
17	MeOCH$_2$	0
18	*tert*-BuOCH$_2$	0
19	PhCH$_2$OCH$_2$	0
20	PhCOOCH$_2$	0
21	BocNHCH$_2$	0
22	CbzNHCH$_2$	0
23	TsOCH$_2$	0
24	CO$_2$Me	0
25	CONH$_2$	0
26	CONHMe	0
27	CONMe$_2$	0
28	COPh	0

	R	*n*
29a,b	Ph	0
30a,b	Ph	1
31a,b	Me	0
32a,b	Me	1
33a,b	ClCH$_2$	0
34a,b	NCCH$_2$	0
35a,b	MeOCH$_2$	0
36a,b	*tert*-BuOCH$_2$	0
37a,b	PhCH$_2$OCH$_2$	0
38a,b	PhCOOCH$_2$	0
39a,b	BocNHCH$_2$	0
40a,b	CbzNHCH$_2$	0
41a,b[a]	TsOCH$_2$	0
42a,b	CO$_2$Me	0
43a,b	CONH$_2$	0
44a,b	CONHMe	0
45a,b	CONMe$_2$	0
46a,b[a]	COPh	0

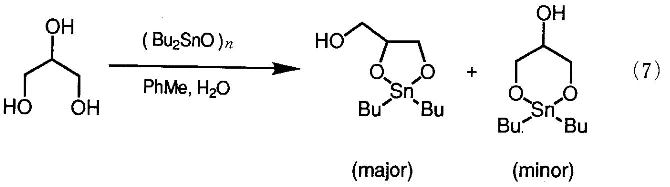
[a] in the case of the diols **23** and **28**, the expected products were not obtained



(5)



(6)



(7)

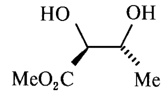
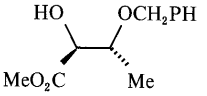
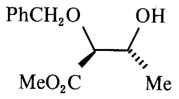
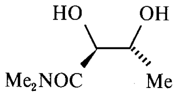
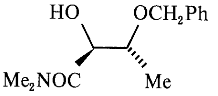
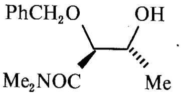
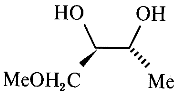
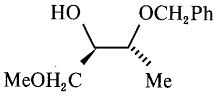
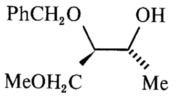
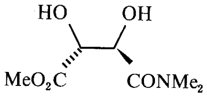
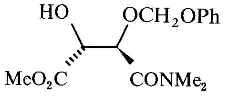
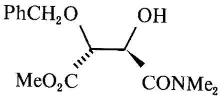
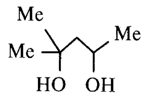
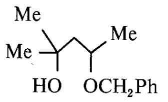
the reaction can be successfully carried out with diols containing functional groups such as carboxylic acid esters, carboxamides, carbamates, nitriles, alkyl chlorides, and others. However, *O*-tosylate and phenyl ketone groups are not compatible with the reaction conditions (entries 14 and 19 in Table III). For the diols in Table III, selective benzylation occurred at the primary hydroxyl groups[15]

TABLE III. Regioselective Benzylation of Acyclic 1,2- and 1,3-Diols Containing Primary and Secondary Hydroxyl Groups

Entry	Diol	Equiv. of $PhCH_2I$	Equiv. of CsF	Temperature (°C)	Time (h)	Product	Yield[a] (%)	**a**:**b** ratio
1	**11**	1.74	2.01	0—3	1.5	**29a, b**	Quant.	90:10
2	**12**	2.06	2.09	−5—3	21	**30a, b**	80	85:15
3	**13**	1.57	2.07	0—3	24	**31a, b**	Quant.	91: 9
4	**14**	1.65	2.58	0—3	50	**32a, b**	86	97: 3
5	**15**	1.98	1.51	rt	22	**33a, b**	64	81:19
6	**16**	2.10	1.31	rt	24	**34a, b**	51	93: 7
7	**17**	1.66	1.33	rt	44	**35a, b**	77	87:13
8	**18**	1.93	1.72	rt	50	**36a, b**	81	82:18
9	**19a**	2.17	1.91	rt	10	**37a, b**	81	89:11
10	**20**	1.97	1.64	rt	2	**38a, b**	81	87:13[b]
11	**21**	2.00	1.05	rt	120	**39a, b**	71[c]	94: 6
12	**22**	1.85	1.12	rt	140	**40a, b**	74[d]	94: 6
13	**22**	$PhCH_2Br$; 2.00	No salt	100	2	**40a, b**	17	87:13
14	**23**	1.63	1.45	rt	6	[e]	0	—
15	**24**	1.44	1.57	0—3	24	**42a, b**	76	82:18
16	**25**	1.88	1.15	0—3	2	**43a, b**	67[f]	82:18
17	**26**	1.88	1.01	0—3	22	**44a, b**	77[g]	91: 9
18	**27**	1.89	1.11	0—3	20	**45a, b**	98	89:11
19	**28**	1.62	1.21	rt	1	[e]	0	—

a) Isolated yields after chromatography on silica gel. *b*) The ratio was determined after the removal of the benzoyl group. See the experimental section. *c*) *O,O*-Dibenzylated product was also formed in 1.5% yield. *d*) *O,O*-Dibenzylated product was also formed in 3% yield. *e*) The reaction was not clean and no desired product was obtained. *f*) *O,O*-Dibenzylated product was also formed in 17.5% yield. *g*) *O,O*-Dibenzylated product was also formed in 9.7% yield.

TABLE IV. Regioselective Benzylation of Acyclic 1,2- and 1,3-Diols Containing Secondary–Secondary or Secondary–Tertiary Hydroxyl Groups

Entry	Diol	Equiv. of $PhCH_2I$	Equiv. of CsF	Temperature (°C)	Time (h)	Yield[a] (%)	Product ratio	
1	 **47**	1.43	1.15	0—3	16	85	 **52a** (65 :	 **52b** 35)
2	 **48**	2.07	1.62	0—3	45	92	 **53a** (81 :	 **53b** 19)
3	 **49**	2.13	1.56	rt	20	76	 **54a** (50 :	 **54b** 50)
4	 **50**	2.11	1.16	0—3	40	95	 **55a** (75 :	 **55b** 25)
5	 **51**	1.83	1.40	50—53	42	50	Only	 **56a**

a) Isolated yields after chromatography on silica gel.

and the regioselectivity (the ratio of the major isomer to the minor isomer) was in the range of 81 : 19 to 97 : 3. Furthermore, the regioselectivity was not necessarily improved when the bulkiness of the substituent R in diols was increased (entries 3 *vs.* 1, 5 to 12 in Table III and entries 4 *vs.* 2 in Table III). This fact seems to show that steric hindrance is not the major factor controlling the regioselectivity in these reactions. It should be emphasized that the present methodology afforded the expected product even in the case of unsuccessful Moffatt's procedure (entries 13 *vs.* 12 in Table III). In some cases (entries 11, 12, 16 and 17 in Table III), dibenzylation of the diols was also observed. This phenomenon was observed only for the diols containing NH groups of carboxamides or carbamates. The NH groups of carboxamides or carbamates form strong hydrogen bonding with fluoride anion.[16] Therefore, activation through the NH group is considered to occur in diols **21**, **22**, **25** and **26**. A similar effect of an OH group was also observed in the benzylation of glycerol (*vide post*). For the diols containing two secondary hydroxyl groups, modest regioselectivity was observed (entries 1, 2 and 4 in Table IV). Thus, preferential benzylation took place at the hydroxyl groups bonding to the carbon atoms which bear more electron-donating substituents (Me *vs.* CO_2Me or $CONMe_2$; $CONMe_2$ *vs.* CO_2Me). The 1,3-glycol **51**, which bears secondary and tertiary hydroxyl groups, was benzylated only at the secondary hydroxyl group (entry 5 in Table IV).

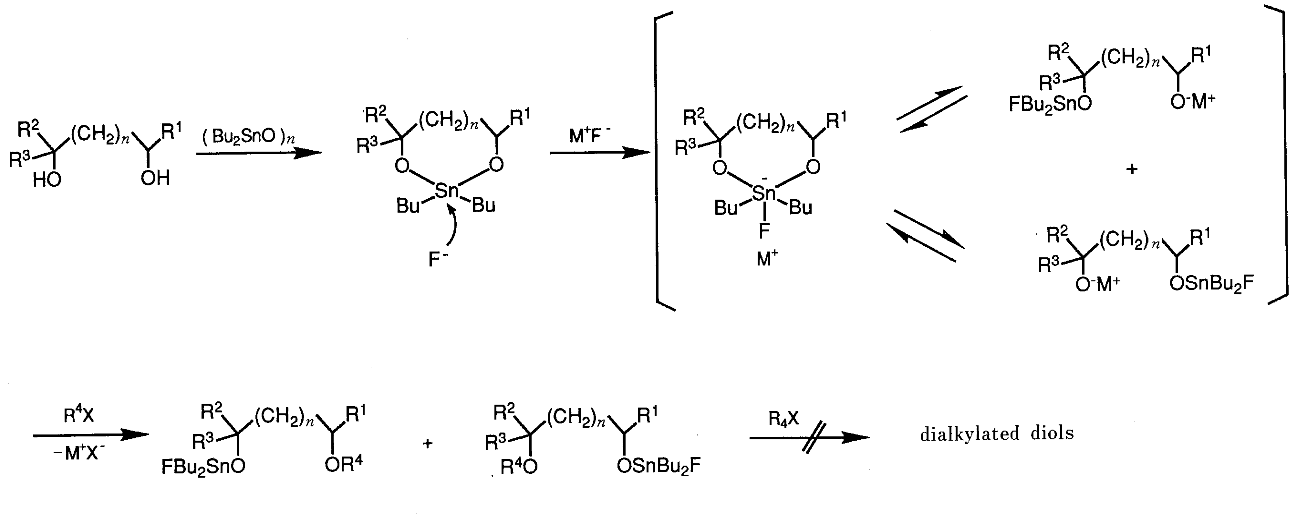
Benzylation of Glycerol Finally, the benzylation reaction of glycerol was examined (Eq. 6). The results are shown in Table V. If the five-membered stannylene acetal of glycerol is formed predominantly over the six-membered one (Eq. 7),[17] the expected benzylation products will be monobenzylated glycerol derivatives, **19a** and **19b**. However, Table V clearly shows that considerable amounts of dibenzylated glycerol derivatives, **37a** and **37b**, are also formed (entries 1 and 2 in Table V). Furthermore, the dibenzylated products, **37a** and **37b**, are also formed even in a reaction using Moffatt's procedure (entry 4 in Table V). These facts imply that the activation of the free OH group toward further benzylation probably occurs through the interactions of the OH group with tin atom and/or fluoride anion (hydrogen bond formation). When more than 2 eq of benzyl iodide and cesium fluoride were used, the reaction gave a good yield (71%) of dibenzylated derivatives, **37a** and **37b**, with the ratio of 9 to 1 (entry 3 in Table V). Thus, a direct and selective dibenzylation for glycerol has been achieved for the first time.

Mechanistic Aspect of the Reaction At present, the precise mechanism of the reaction is not known and mechanistic studies using ^{19}F- and/or ^{119}Sn-NMR remain to be done. However, it seems to be worthwhile to consider the mechanism of the present reaction. It is known that fluoride anion attacks tin atoms of *C*-trialkylstannylated compounds to form carbanion equivalents,[18] and transient formation of pentacoordinated tin complexes[19] is postu-

Table V. Benzylation of Glycerol

Entry	Equiv. of $PhCH_2I$	Equiv. of CsF	Temperature (°C)	Time (h)	Yield (%)[a]		Ratio	
					19a, b	**37a, b**	**19a : 58b**	**37a : 37b**
1	1.45	1.90	0—3	24	21	50	86 : 14	81 : 19
2	1.06	1.00	0—3	24	33	24.5	91 : 9	86 : 14
3	2.48	2.12	0—3	41	Trace[b]	71	—	90 : 10
4	$PhCH_2Br$; 2.01	No salt	100	2	27	14	91 : 9	79 : 21

a) Isolated yields after chromatography on silica gel. *b*) Detected on TLC.



$n = 0, 1$; $M^+ = Cs^+, K^+, n\text{-}Bu_4N^+$; $X = I, Br$

Chart 1

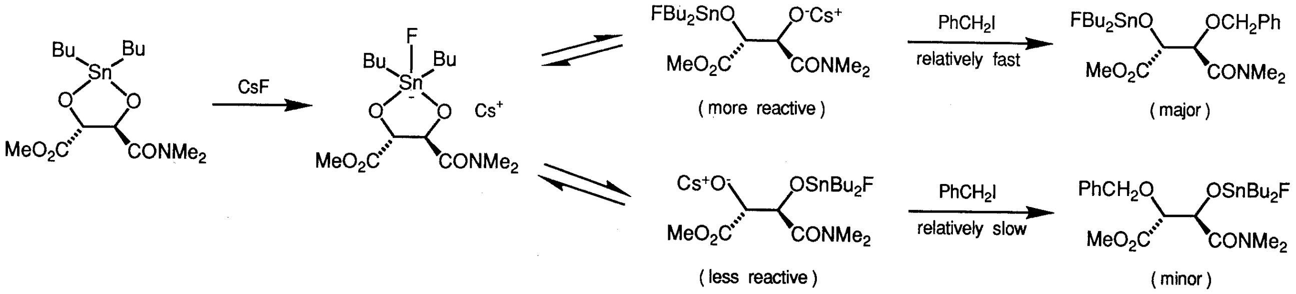
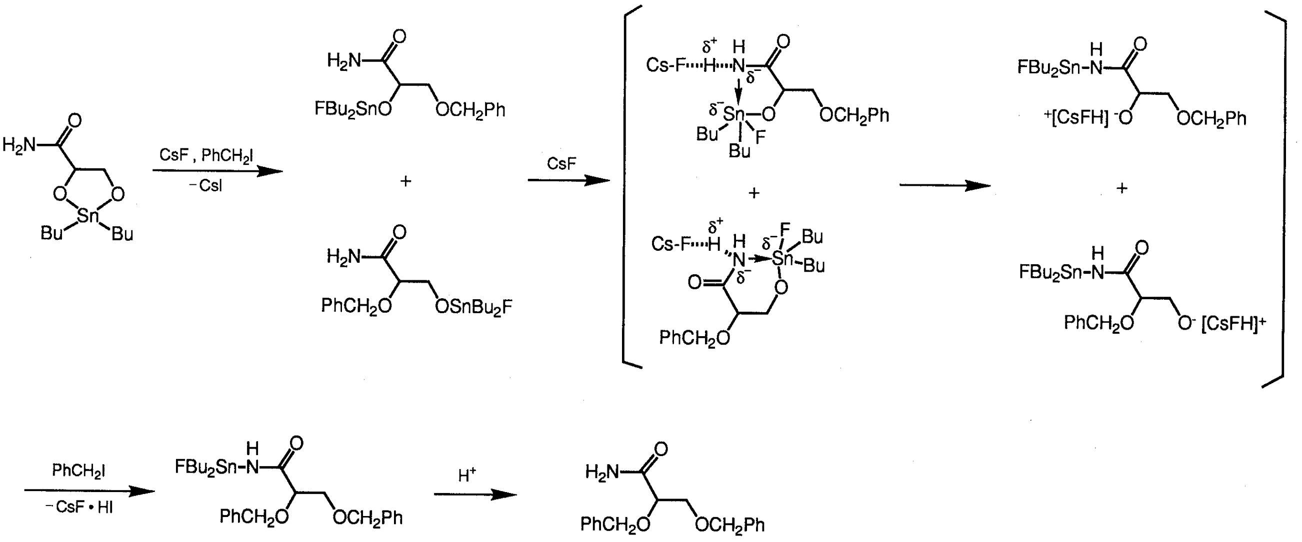


Chart 2



The case of the diol **25** is shown

Chart 3

lated. Recently, Harpp *et al.* reported that fluoride anion attacks tin atoms of organotin sulfides to generate pentacoordinated intermediates.[20] Therefore, it is reasonable to assume that fluoride anion attacks tin atom of the stannylene acetal of a diol to form the pentacoordinated complex, which can reversibly dissociate into a highly reactive alkoxide anion.[21] The resulting alkoxide anion has greater nucleophilicity than the original stannylene acetal and reacts smoothly with alkyl halides to give the monoalkylated derivatives. These monoalkylated derivatives are thought to be inactive to further alkylation under the reaction conditions employed, because dialkylation is not usually observed. The above process is illustrated in Chart 1. On the other hand, the observed regioselectivity can be explained in terms of the reactivity of the alkoxide anions formed. For example, monobenzylation of the diol **50** is thought to proceed through the preferential reaction of the more reactive alkoxide anion with benzyl iodide (Chart 2).

In the case where the diols have NH or OH groups and can form a hydrogen bond with fluoride anion, dibenzylation of the diol occurs (*vide ante*). This phenomenon may be explained as shown in Chart 3. For example, stannylene acetal of the diol **25** is thought to react with cesium fluoride and benzyl iodide to give *O*-fluorostannyl derivatives, whose NH groups may be activated through the hydrogen bonding with cesium fluoride in the reaction mixture. The activated NH groups may interact with Lewis acidic tin atoms to generate reactive anionic oxygen species by the migration of fluorostannyl groups from oxygen to nitrogen. Then the anionic oxygen species may react with benzyl iodide to form the dibenzylated product.

Conclusion

The original Moffatt's procedure for the monoalkylation of diols has been improved by the concomitant use of cesium fluoride. Thus, the alkylation reaction was found to proceed smoothly under very mild reaction conditions and higher yields were obtained. In addition, this new procedure could be successfully applied to the selective alkylation of symmetrical and unsymmetrical diols containing some other functional groups. Therefore, this procedure is expected to be useful synthetically.[21]

Experimental

General Reactions were performed under an inert atmosphere of argon unless otherwise specified, using a standard syringe technique for the transfer of materials. The solvents were generally redistilled before use. Thin-layer chromatography (TLC) was performed on Kieselgel 60 F_{254} precoated plates (0.25 mm), and spots were visualized with molybdophosphoric acid in sulfuric acid. Preparative TLC was accomplished on Kieselgel 60 PF_{254} precoated plates (0.75 mm; 20 x 20 cm^2). Wako-gel C200 and Silicagel BW-200 were used for column chromatography. The melting points were determined on a Yanagimoto micro hot stage melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded with a JASCO A-102 spectrometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured on a Varian EM390 spectrometer. The chemical shift values (δ) are reported in ppm downfield from tetramethylsilane as the internal standard. The optical rotations were measured on a JASCO DIP-140 polarimeter. The mass spectra (MS) were recorded with a JEOL JMS-DX 300 apparatus.

Materials Commercially available reagents were used without further purification. Tetrabutylammonium fluoride (n-Bu_4NF) was dried according to the reported procedure[23] and was used as a DMF solution (entry 7 in Table I), while commercial n-Bu_4NF solution in THF ($1\ mol \cdot dm^{-3}$) was used without drying (entry 14 in Table I). The following compounds were prepared according to the reported methods: dibenzyl (*R*,*R*)-(+)-tartrate (**3**)[24]; 3,4-dihydroxybutyronitrile (**16**)[25]; 1-*O*-methylglycerol (**17**)[26]; 1-*O*-*tert*-butylglycerol (**18**)[27]; 1-*O*-benzylglycerol (**19a**)[27]; 1-*O*-benzylglycerol (**20**)[27]; 1-*O*-*p*-toluenesulfonylglycerol (**23**)[28]; α,β-dihydroxypropiophenone (**28**)[29] and methyl (2*S*,3*R*)-2,3-dihydroxybutyrate (**47**).[30] 1-Phenyl-1,3-propanediol (**12**) was prepared by the lithium aluminum hydride reduction of ethyl benzoylacetate in THF. 3-((*tert*-Butoxycarbonyl)amino)-1,2-propanediol (**21**) was obtained by the reaction of 3-amino-1,2-propanediol with di-*tert*-butyl pyrocarbonate. 3-((Benzyloxycarbonyl)amino)-1,2-propanediol (**22**) was also prepared from 3-amino-1,2-propanediol and benzyl chloroformate. 2,3-Dihydroxypropionamide (**25**) was synthesized by the aminolysis reaction of methyl glycerate using concentrated ammonia-water in methanol (MeOH). 2,3-Dihydroxy-*N*-methylpropionamide (**26**) and 2,3-dihydroxy-*N*,*N*-dimethylpropionamide (**27**) were also synthesized in a similar manner, using methyl glycerate and 40% methylamine solution in MeOH or 50% aqueous solution of dimethylamine.

(2*S*,3*R*)-2,3-Dihydroxy-*N*,*N*-dimethylbutyramide (48) A 50% aqueous solution of dimethylamine (10 ml) was added dropwise to solid potassium hydroxide and the evolved gaseous dimethylamine was collected at −78 °C. To the liquid dimethylamine thus obtained, a solution of ester **47** (206 mg, 1.54 mmol) in dry MeOH (20 ml) was added, and the mixture was stirred at room temperature for 6 d. The solvent was evaporated off and the resulting residue was chromatographed on silica gel (ethyl acetate (EtOAc) : ethanol : water = 7 : 1 : 1) to give 188 mg (83%) of **48** as an oil, $[\alpha]_D^{23} +23.6°$ ($c=1.17$, MeOH). IR (neat): 3380, 1630 cm^{-1}. NMR (CD_3OD): 1.21 (d, $J=6.4$ Hz, 3H, $CHC\underline{H}_3$), 2.99 (s, 3H, N-CH_3), 3.14 (s, 3H, N-CH_3), 3.97 (qd, $J=6.4$, 4.2 Hz, 1H, $C\underline{H}CH_3$), 4.31 (d, $J=4.2$ Hz, 1H, $C\underline{H}CON\ (CH_3)_2$), 4.70 (s, 2H, OH × 2). MS *m*/*z*: 148 ($M^+ + 1$), 103 ($M^+ - 44$ (Me_2N)).

(4*R*,5*R*)-5-Hydroxymethyl-2,2,4-trimethyl-1,3-dioxolane (58) from 47 A mixture of the diol **47** (0.764 g, 5.7 mmol), 2,2-dimethoxypropane (2.5 ml) and *p*-toluenesulfonic acid monohydrate (110 mg, 0.58 mmol) in acetone (25 ml) was stirred at room temperature for 41 h. After the addition of triethylamine (0.5 ml) to the reaction mixture, the acetone and excess 2,2-dimethoxypropane were removed and an aqueous solution of sodium bicarbonate was added to the resulting oily residue. The mixture was extracted three times with methylene chloride and the combined extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent gave 1.15 g of a yellow oil, which was used for the following step without further purification. Lithium aluminum hydride (309 mg, 8.1 mmol) was added in one portion to a solution of this oil (1.15 g) in dry THF (25 ml) under ice-water cooling and the mixture was stirred at room temperature for 61 h. The reaction mixture was cooled to 0 °C, diluted with EtOAc, and quenched by the addition of saturated aqueous sodium bicarbonate. The precipitate formed was filtered through a pad of Celite and washed thoroughly with EtOAc. The filtrate and washings were combined, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane–EtOAc (20—30%)) to afford 598 mg (72%) of **58** as a colorless oil, $[\alpha]_D^{24} -1.37°$ ($c=6.02$, $CHCl_3$). IR (neat): 3450, 1380, 1370 cm^{-1}. NMR ($CDCl_3$); 1.31 (d, $J=5.8$ Hz, 3H, $CHC\underline{H}_3$), 1.42 (s, 3H, $C\ (CH_3)_2$), 1.43 (s, 3H, $C(CH_3)_2$), 2.83 (br t, $J=5.7$ Hz, 1H, OH), 3.51—4.17 (m, 4H, $C\underline{H}CH_3$, $C\underline{H}C\underline{H}_2OH$). MS was measured after *O*-trimethylsilylation. *m*/*z*: 203 ($M^+ - 15$(Me)), 204 (($M^+ + 1$) − 15(Me)), 205 (($M^+ + 2$) − 15 (Me)), 145 ($M^+ - 73$ (TMS)).

(2*R*,3*R*)-1-Methoxy-2,3-butanediol (49) A 25% potassium hydride oil dispersion (1 ml, 6.2 mmol) was slowly added to a solution of **58** (552 mg, 3.8 mmol) in dry THF (15 ml) under ice-water cooling. The reaction mixture was stirred at 0 °C for an additional 10 min, and then methyl iodide (1.2 ml, 19.3 mmol) was added. The reaction mixture was stirred at 0 °C for 20 min and then at room temperature for 2.5 h, cooled to 0 °C, and quenched by the addition of water (1.5 ml). Then 6 N hydrochloric acid (3 ml) was added to the resulting mixture, and stirring was continued at room temperature for 17 h. The reaction mixture was neutralized by the addition of solid sodium bicarbonate and then concentrated to give an oil-solid residue. Chloroform ($CHCl_3$) was added to this residue and the resulting insoluble materials were filtered off. The filtrate was concentrated to give an orange oil, which was purified by silica gel column chromatography (hexane : EtOAc = 2 : 1; finally EtOAc) to afford 283 mg (62%) of **49** as a pale yellow oil. $[\alpha]_D^{22} +3.83°$ ($c=2.09$, $CHCl_3$). IR (neat): 3400 cm^{-1}. NMR ($CDCl_3$): 1.22 (d, $J=6.4$ Hz, 3H, $CHC\underline{H}_3$), 3.00 (br s, 2H, OH × 2), 3.41 (s, 3H, OCH_3), 3.51 (s, 2H, $C\underline{H}_2OCH_3$), 3.40—3.67 (m, 1H) and 3.67—3.98 (m, 1H) ($CH_3C\underline{H}C\underline{H}CH_2OCH_3$). MS *m*/*z*: 75 ($M^+ - 45$ ($MeOCH_2$)).

Methyl (2*R*,3*R*)-2,3-Dihydroxy-3-(*N*,*N*-dimethylcarbamoyl)propionate (50) A mixture of methyl hydrogen (2*R*,3*R*)-2,3-*O*-isopropylidenetartrate[30] (1 g, 4.9 mmol) and dimethylamine (30 ml) in dry MeOH (20 ml) was stirred at room temperature for 9 d. After the evaporation of the solvent and excess dimethylamine, *p*-toluenesulfonic acid monohydrate (1.13 g, 5.96 mmol) and MeOH (50 ml) were added to the oily residue and the mixture was stirred at room temperature for 23 h. The solvent was evaporated off and the resulting residue was dissolved in acetic acid (40 ml) and water (10 ml). This mixture was stirred at 50 °C for 3 h and then the solvent was removed under reduced pressure. The resulting residue was again dissolved in MeOH (50 ml) and the mixture was stirred at room temperature for 21 h. Removal of the solvent gave an oily residue, which was purified twice by silica gel column chromatography (EtOAc then EtOAc : ethanol : water = 7 : 1 : 1) to afford 746 mg (80%) of **50** as a pale yellow oil. This oil solidified upon standing at room temperature, but all attempts to crystallize this solid from various mixed solvents failed. $[\alpha]_D^{21} -17.0°$ ($c=1.89$, MeOH). IR (KBr): 3425, 1747, 1644 cm^{-1}. NMR (CD_3OD): 3.00 (s, 3H, $N(CH_3)_2$), 3.16 (s, 3H, $N(CH)_3)_2$), 3.81 (s, 3H, CO_2CH_3), 4.44 (d, $J=3$ Hz, 1H, $C\underline{H}CON\ (CH_3)_2$), 4.71 (s, 2H, OH × 2), 4.81 (d, $J=3$ Hz, 1H, $C\underline{H}CO_2CH_3$). MS *m*/*z*: 192 ($M^+ + 1$), 132 ($M^+ - 59$ (CO_2Me)), 119 ($M^+ - 72$ ($CONMe_2$)).

General Procedure for Monoalkylation of Dialkyl Tartrates An equimolar mixture of dialkyl tartrate (0.5—1 mmol) and dibutyltin oxide (0.5—1 mmol) in toluene (3—5 ml) was heated under reflux for 1—2 h, removing water formed as the azeotropic mixture. The solution was evaporated to complete dryness *in vacuo* to give the stannylene acetal of dialkyl tartrate, which was used for the following step without purification. To the stannylene acetal thus obtained, a fluoride salt (CsF, KF) and an additive (crown ether, n-Bu_4NI, KI) were added when they were used; the amounts of these ragents are shown in Table I. The resulting mixture was dried at room temperature *in vacuo* for 1—2 h, and a suitable amount of alkyl halide dissolved in dry solvent (3—5 ml) was added at room temperature or 0 °C. The reaction mixture was stirred vigorously under the conditions given in Table I. When n-Bu_4NF was used (entry 7 in Table I), n-Bu_4NF in dry DMF and benzyl iodide in dry DMF were successively added to the stannylene acetal at room temperature, and the resulting mixture was stirred under the condition given in Table I. After stirring, the solvent was removed under vacuum and the residue obtained was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated, and purified by silica gel column chromatography using hexane–EtOAc as an eluent. If necessary, further purification by preparative TLC on silica gel was also carried out. The following compounds were obtained in the yields shown in Table I.

Dimethyl (2*R*,3*R*)-2-*O*-Benzyltartrate (4) Colorless needles from ether–hexane, mp 69—70 °C, $[\alpha]_D^{22} +87.5°$ ($c=1.17$, $CHCl_3$). IR (KBr): 3500, 1730, 748, 705 cm^{-1}. NMR ($CDCl_3$): 3.23 (d, $J=9.2$ Hz, 1H, OH), 3.69 (s, 3H, CO_2CH_3), 3.85 (s, 3H, CO_2CH_3), 4.35 (d, $J=2.4$ Hz, 1H, $C\underline{H}OCH_2C_6H_5$), 4.62 (dd, $J=9.2$, 2.4 Hz, 1H, $C\underline{H}OH$), 4.45 and 4.88 (ABq, $J=12.3$ Hz, 2H, $C\underline{H}_2C_6H_5$), 7.37 (s, 5H, C_6H_5). *Anal.* Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.02; H, 5.95.

Dimethyl (2*R*,3*R*)-2-*O*-(*p*-Nitrobenzyl)tartrate (5) Pale yellow prisms from ether–hexane, mp 74.5—75.5 °C, $[\alpha]_D^{24} +68.1°$ ($c=1.03$, $CHCl_3$). IR (KBr): 3520, 1740, 1605, 1520 cm^{-1}. NMR ($CDCl_3$): 3.29 (br s, 1H, OH), 3.79 (s, 3H, CO_2CH_3), 3.86 (s, 3H, CO_2CH_3), 4.46 (d, $J=2.4$ Hz, 1H, $C\underline{H}OCH_2C_6H_4NO_2$), 4.70 (d, $J=2.4$ Hz, 1H, $C\underline{H}OH$), 4.59 and 4.99 (ABq, $J=13.2$ Hz, 2H, $C\underline{H}_2C_6H_4NO_2$), 7.54 and 8.24 ($A_2B_2$q, $J=9$ Hz, 4H, C_6H_4). *Anal.* Calcd for $C_{13}H_{15}NO_8$: C, 49.84; H, 4.83; N, 4.47. Found: C, 49.73; H, 4.82; N, 4.55.

Dimethyl (2*R*,3*R*)-2-*O*-(*p*-Methoxybenzyl)tartrate (6) Colorless oil. $[\alpha]_D^{23} +84.0°$ ($c=1.72$, $CHCl_3$). IR (neat): 3500, 1748, 1612, 1515 cm^{-1}. NMR ($CDCl_3$): 3.12 (d, $J=9$ Hz, 1H, OH), 3.68 (s, 3H, OCH_3), 3.80 (s, 3H, CO_2CH_3), 3.83 (s, 3H, CO_2CH_3), 4.31 (d, $J=2.4$ Hz, 1H, $C\underline{H}OCH_2C_6H_4OCH_3$), 4.57 (dd, $J=9$, 2.4 Hz, 1H, $C\underline{H}OH$), 4.41 and 4.75 (ABq, $J=12$ Hz, 2H, $C\underline{H}_2C_6H_4OCH_3$), 6.88 and 7.22 ($A_2B_2$q, $J=9$ Hz, 4H, C_6H_4). MS *m*/*z*: 298 (M^+).

Dimethyl (2*R*,3*R*)-2-*O*-Allyltartrate (7) Colorless oil. $[\alpha]_D^{22.5} +34.1°$ ($c=1.28$, $CHCl_3$). IR (neat): 3500, 1748, 1645 cm^{-1}. NMR ($CDCl_3$): 3.29 (d, $J=8.6$ Hz, 1H, OH), 3.83 (s, 6H, CO_2CH_3 × 2), 3.77—4.10 (m, 1H, $C\underline{H}_2CH=CH_2$), 4.20—4.50 (m, 1H, $C\underline{H}_2CH=CH_2$), 4.35 (d, $J=2.4$ Hz, 1H, $C\underline{H}OCH_2CH{=}CH_2$), 4.63 (dd, J=8.6, 2.4 Hz, 1H, CHOH), 5.10—5.40 (m, 2H, $CH{=}C\underline{H}_2$), 5.63—6.10 (m, 1H, $C\underline{H}{=}CH_2$). MS m/z: 219 ($M^+ + 1$), 160 ($M^+ - 58$ ($CH_2{=}CHCH_2OH$)).

Dimethyl (2*R*,3*R*)-2-*O*-Methyltartrate (8) Colorless oil. $[\alpha]_D^{21}$ +39.0° (c=1.07, $CHCl_3$). IR (neat): 3500, 1745 cm^{-1}. NMR ($CDCl_3$): 3.33 (d, J=8.7 Hz, 1H, OH), 3.49 (s, 3H, OCH_3), 3.86 (s, 3H, CO_2CH_3), 3.88 (s, 3H, CO_2CH_3), 4.22 (d, J=2.7 Hz, 1H, $C\underline{H}OCH_3$), 4.63 (dd, J=8.7, 2.7 Hz, 1H, CHOH). MS m/z: 193 ($M^+ + 1$), 133 ($M^+ - 59$ (CO_2Me)).

Dimethyl (2*R*,3*S*) and (2*S*,3*R*)-2-*O*-Benzyltartrate (9) Colorless oil. IR (neat): 3475, 1740, 1603, 1499, 745, 702 cm^{-1}. NMR ($CDCl_3$): 3.37 (d, J=7.2 Hz, 1H, OH), 3.78 (s, 6H, $CO_2CH_3 \times 2$), 4.36 (d, J=3 Hz, 1H, $C\underline{H}OCH_2C_6H_5$), 4.63 (dd, J=7.2, 3 Hz, 1H, $C\underline{H}OH$), 4.54 and 4.88 (ABq, J=12.2 Hz, 2H, $C\underline{H}_2C_6H_5$), 7.40 (s, 5H, C_6H_5). MS m/z: 268 (M^+).

Dibenzyl (2*R*,3*R*)-2-*O*-Benzyltartrate (10) Colorless needles from ether–hexane, mp 57—58 °C, $[\alpha]_D^{23}$ +60.2° (c=1.42, $CHCl_3$), $[\alpha]_D^{20.5}$ +72.6° (c=1.01, EtOAc) (lit.[6c] mp 50—52 °C, $[\alpha]_D^{20}$ +64.0° (c=1, EtOAc)). IR (KBr): 3520, 1750, 1605, 1499, 738, 730, 700 cm^{-1}. NMR ($CDCl_3$); 3.18 (d, J=9 Hz, 1H, OH), 4.37 (d, J=2.3 Hz, 1H, $C\underline{H}OCH_2C_6H_5$), 4.65 (dd, J=9, 2.3 Hz, 1H, $C\underline{H}OH$), 4.32 and 4.76 (ABq, J=11.6 Hz, 2H, $OC\underline{H}_2C_6H_5$), 5.03 and 5.15 (ABq, J=12 Hz, 2H, $CO_2C\underline{H}_2C_6H_5$), 5.23 (s, 2H, $CO_2C\underline{H}_2C_6H_5$), 7.10—7.33 (m, 10H, $C_6H_5 \times 2$), 7.36 (s, 5H, C_6H_5). *Anal.* Calcd for $C_{25}H_{24}O_6$: C, 71.4; H, 5.75. Found: C, 71.17; H, 5.76. This compound was prepared on a 20 mmol scale by the following procedure. A mixture of **3** (6.61 g, 20 mmol) and dibutyltin oxide (5.16 g, 20.7 mmol) in toluene (65 ml) was refluxed for 1 h, while water formed was removed as the azeotropic mixture. After the complete removal of the solvent under vacuum, a white solid was obtained, CsF (assay min. 90%, 5.12 g, 30.4 mmol) was added to this solid and the mixture was dried at room temperature *in vacuo* for 1 h. Benzyl iodide (9.27 g, 42.5 mmol) in dry DMF (65 ml) was added at room temperature and the resulting suspension was vigorously stirred at room temperature for 5 h. The solvent was removed under vacuum and the resulting residue was extracted with ether. The organic layer was dried over anhydrous sodium sulfate, concentrated, and purified by silica gel column chromatography (hexane : EtOAc = 4 : 1) to afford 7.87 g (94%) of **10** as a colorless solid.

Monobenzylation of 1-Phenylethanediol (11). General Procedure A mixture of **11** (91.2 mg, 0.66 mmol) and dibutyltin oxide (164.3 mg, 0.66 mmol) in toluene (3 ml) was refluxed for 1 h, while water formed was removed as the azeotropic mixture. After the complete removal of the solvent under vacuum, a white solid was obtained. To this solid, a suitable amount of fluoride salt was added, and the resulting mixture was further dried at room temperature *in vacuo* for 1—2 h. In the case of entry 13 in Table II, 5 mol% of dicyclohexano-18-crown-6 was also added with the fluoride salt at this stage and the mixture was dried as above. Then, a suitable amount of benzyl halide in dry solvent (3 ml) was added at the temperature shown in Table II and the reaction mixture was stirred vigorously under the conditions given in Table II. After the removal of the solvent under reduced pressure, benzene was added to the residue and the resulting solution was subjected to silica gel column chromatography using hexane–EtOAc as an eluent. The monobenzylated products, **29a** and **29b**, were obtained as a mixture in the yields shown in Table II. The ratios of regioisomers were determined from the peak intensities of benzylic protons of each isomer in the ^1H-NMR spectra. The peak corresponding to the benzylic protons of the major isomer **29a** appears at δ 4.57 as a singlet, while that of the minor isomer **29b** appears at δ 4.34 and 4.52 as an ABq signal (J=11.7 Hz).

Mixture of 2-Benzyloxy-1-phenylethanol (29a) and 2-Benzyloxy-2-phenylethanol (29b) IR (neat): 3425, 1604, 1497, 740, 700 cm^{-1}. NMR ($CDCl_3$): 2.94 (br s, 1H, OH), 3.34—3.90 (m, 2H, $CHC\underline{H}_2O$), 4.34 and 4.52 (ABq, J=11.7 Hz), 4.57 (s) (total 2H, $C\underline{H}_2C_6H_5$), 4.51 (dd, J=7.3, 4.8 Hz), 4.87 (dd, J=8.3, 4.2 Hz) (total 1H, $C_6H_5C\underline{H}CH_2O$), 7.35 (s, 10H, $C_6H_5 \times 2$). MS m/z: 228 (M^+).

General Procedure for Regioselective Benzylation of Unsymmetric Diols An equimolar mixture of a diol (0.5—2.1 mmol) and dibutyltin oxide (0.5—2.1 mmol) in toluene (3—5 ml) was refluxed for 1 h, while water formed was removed as the azeotropic mixture. In the case of the diol **15**, the refluxing time was 15 min, while it was 30 min for the diol **20**. After the complete removal of the solvent under vacuum, the stannylene acetal of the diol was obtained as a solid or a syrup. To this stannylene acetal, a suitable amount of cesium fluoride was added, and the resulting mixture was further dried at room temperature *in vacuo* for 1—2 h. Benzyl iodide, in the amount given in Table III or IV, in dry DMF (3—6 ml) was then added at the temperature shown in Table III or IV and the mixture was vigorously stirred at the same temperature for a suitable period of time. The solvent was removed under vacuum, and the residue was extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate, concentrated, and purified by silica gel column chromatography; elution was carried out with hexane containing increasing amounts of EtOAc and in some cases finally with EtOAc. If necessary, repeated purifications by column chromatography and/or preparative TLC on silica gel were also employed. The products were obtained in the yields shown in Tables III and IV. The ratios of the products were determined from the peak intensities of benzylic protons of each isomer in the ^1H-NMR spectra or from the weights of each isomer separated.

3-Benzyloxy-1-phenylpropanol (30a) and 3-Benzyloxy-3-phenylpropanol (30b) These compounds were completely separated and the ratio of **30a** to **30b** was determined from their weights.

30a: IR (neat): 3420, 1603, 1497, 739, 700 cm^{-1}. NMR ($CDCl_3$): 1.88—2.16 (m, 2H, $CHC\underline{H}_2CH_2O$), 3.33 (br s, 1H, OH), 3.45—3.83 (m (t like), 2H, $CHCH_2C\underline{H}_2O$), 4.51 (s, 2H, $C\underline{H}_2C_6H_5$), 4.90 (br t, J=6 Hz, 1H, $C_6H_5C\underline{H}$–OH), 7.36 (s, 5H, C_6H_5), 7.37 (s, 5H, C_6H_5). MS m/z: 242 (M^+).

30b: IR (neat): 3415, 1602, 1496, 740, 703 cm^{-1}. NMR ($CDCl_3$): 1.64—2.32 (m, 2H, $CHC\underline{H}_2CH_2O$), 2.81 (br s, 1H, OH), 3.51—3.94 (m (t like), 2H, $CHCH_2C\underline{H}_2O$), 4.29 and 4.47 (ABq, J=11.9 Hz, 2H, $C\underline{H}_2C_6H_5$), 4.59 (dd, J=8.5, 4.2 Hz, 1H, $C_6H_5C\underline{H}OH$), 7.34 (s, 5H, C_6H_5), 7.41 (s, 5H, C_6H_5). MS m/z: 242 (M^+).

Mixture of 1-Benzyloxy-2-propanol (31a) and 2-Benzyloxypropanol (31b) These compounds could not be separated and the ratio of **31a** to **31b** was determined by ^1H-NMR. IR (neat): 3425, 1604, 1498, 740, 700 cm^{-1}. NMR ($CDCl_3$): 1.12 (d, J=6.5 Hz), 1.17 (d, J=6.5 Hz) (total 3H, CH_3), 2.69 (br s, 1H, OH), 3.14—3.87 (m), 3.72—4.25 (m) (total 3H, $CHCH_2$), 4.52 and 4.63 (ABq, J=11.7 Hz), 4.55 (s) (total 2H, $C\underline{H}_2C_6H_5$), 7.37 (s, 5H, C_6H_5). MS m/z: 166 (M^+).

Mixture of 4-Benzyloxy-2-butanol (32a) and 3-Benzyloxybutanol (32b) These compounds could not be separated and the ratio of **32a** to **32b** was determined by ^1H-NMR. IR (neat): 3400, 1602, 1498, 738, 700 cm^{-1}. NMR ($CDCl_3$): 1.19 (d, J=6.4 Hz), 1.25 (d, J=6.2 Hz) (total 3H, CH_3), 1.58—1.89 (m, 2H, $CHC\underline{H}_2CH_2O$), 3.02 (br s, 1H, OH), 3.46—3.86 (m (t like)), 3.55—4.02 (m), 3.83—4.23 (m) (total 3H, $CH_3C\underline{H}CH_2C\underline{H}_2O$), 4.52 (s), 4.46 and 4.62 (ABq, J=12Hz) (total 2H, $C\underline{H}_2C_6H_5$), 7.36 (s, 5H, C_6H_5). MS m/z: 180 (M^+).

1-Benzyloxy-3-chloro-2-propanol (33a) and 2-Benzyloxy-3-chloropropanol (33b) These compounds were completely separated and the ratio of **33a** to **33b** was determined from their weights.

33a: IR (neat): 3410, 1603, 1497, 740, 700 cm^{-1}. NMR ($CDCl_3$): 2.94 (br s, 1H, OH), 3.40—3.77 (m, 4H, $C\underline{H}_2CHC\underline{H}_2$), 3.83—4.12 (m, 1H, $CH_2C\underline{H}CH_2$), 4.54 (s, 2H, $C\underline{H}_2C_6H_5$), 7.35 (s, 5H, C_6H_5). MS m/z: 202 ($M^+ + 2$), 200 (M^+).

33b: IR (neat): 3400, 1604, 1499, 742, 702 cm^{-1}. NMR ($CDCl_3$): 2.02 (br t, J=5.7 Hz, 1H, OH), 3.43—3.87 (m, 5H, $C\underline{H}_2C\underline{H}C\underline{H}_2$), 4.64 and 4.71 (ABq, J=11.7 Hz, 2H, $C\underline{H}_2C_6H_5$), 7.40 (s, 5H, C_6H_5). MS m/z: 202 ($M^+ + 2$), 200 (M^+).

1-Benzyloxy-3-cyano-2-propanol (34a) and 2-Benzyloxy-3-cyano propanol (34b) These compounds were completely separated and the ratio of **34a** to **34b** was determined from their weights.

34a: IR (neat): 3440, 2255, 1604, 1498, 743, 702 cm^{-1}. NMR ($CDCl_3$): 2.52 (d, J=6 Hz, 2H, CH_2CN), 3.35 (br s, 1H, OH), 3.48 (d, J=5.7 Hz, 2H, CH_2O), 3.76—4.19 (m, 1H, $C\underline{H}OH$), 4.52 (s, 2H, $C\underline{H}_2C_6H_5$), 7.32 (s, 5H, C_6H_5). MS m/z: 191 (M^+).

34b: IR (neat): 3440, 2250, 1498, 740, 699 cm^{-1}. NMR ($CDCl_3$): 2.07 (br s, 1H, OH), 2.63 (d, J=5.7 Hz, 2H, CH_2CN), 3.47—3.93 (m, 3H, $C\underline{H}C\underline{H}_2OH$), 4.64 and 4.68 (ABq, J=11.4 Hz, 2H, $C\underline{H}_2C_6H_5$), 7.40 (s, 5H, C_6H_5). MS m/z: 191 (M^+).

1-*O*-Benzyl-3-*O*-methylglycerol (35a) and 2-*O*-Benzyl-1-*O*-methylglycerol (35b) These compounds were partially separated by repeated chromatography and the ratio of **35a** to **35b** was determined by ^1H-NMR.

35a: IR (neat): 3450, 1605, 1499, 740, 700 cm^{-1}. NMR ($CDCl_3$): 2.79 (d, J=4.4 Hz, 1H, OH), 3.37 (s, 3H, OCH_3), 3.39—3.63 (m, 4H, $C\underline{H}_2CHC\underline{H}_2$), 3.83—4.18 (m, 1H, $CH_2C\underline{H}CH_2$), 4.56 (s, 2H, $C\underline{H}_2C_6H_5$), 7.38 (s, 5H, C_6H_5). MS m/z: 196 (M^+).

35b: IR (neat): 3425, 1604, 1497, 740, 700 cm^{-1}. NMR ($CDCl_3$): 2.32 (br s, 1H, OH); 3.37 (s, 3H, OCH_3), 3.44—3.80 (m, 5H, $C\underline{H}_2C\underline{H}C\underline{H}_2$), 4.65 and 4.69 (ABq, J=12 Hz, 2H, $C\underline{H}_2C_6H_5$), 7.38 (s, 5H, C_6H_5). MS m/z: 196 (M^+).

1-*O*-Benzyl-3-*O*-*tert*-butylglycerol (36a) and 2-*O*-Benzyl-1-*O*-*tert*-butylglycerol (36b) These compounds were partially separated by repeated chromatography and the ratio of **36a** to **36b** was determined by ^1H-NMR.

36a: IR (neat); 3450, 1604, 1498, 1390, 1368, 738, 700 cm^{-1}. NMR ($CDCl_3$): 1.19 (s, 9H, $(CH_3)_3C$), 2.71 (d, 1H, J=4.2 Hz, OH), 3.27—3.70

(m, 4H, $C\underline{H}_2CHCH_2$), 3.75—4.12 (m, 1H, $CH_2C\underline{H}CH_2$), 4.57 (s, 2H, $C\underline{H}_2C_6H_5$), 7.38 (s, 5H, C_6H_5). MS *m*/*z*: 238 (M^+).

36b: IR (neat): 3430, 1603, 1496, 1389, 1366, 737, 698 cm^{-1}. NMR ($CDCl_3$): 1.20 (s, 9H, $(CH_3)_3C$), 2.59 (br s, 1H, OH), 3.37—3.82 (m, 5H, $C\underline{H}_2C\underline{H}C\underline{H}_2$), 4.65 and 4.68 (ABq, *J* = 12 Hz, 2H, $C\underline{H}_2C_6H_5$), 7.37 (s, 5H, C_6H_5). MS *m*/*z*: 223 ($M^+ - 15$ (Me)), 181 ($M^+ - 57$ (*tert*-Bu)), 165 ($M^+ - 73$ (*tert*-BuO)), 147 ($M^+ - 91$ ($PhCH_2$)).

1,3-Di-*O*-benzylglycerol (37a) and 1,2-Di-*O*-benzylglycerol (37b) These compounds were partially separated by repeated chromatography and the ratio of **37a** to **37b** was determined by ^{1}H-NMR.

37a: IR (neat): 3440, 1604, 1498, 739, 700 cm^{-1}. NMR ($CDCl_3$): 2.78 (br s, 1H, OH), 3.38—3.76 (m (d like), 4H, $C\underline{H}_2CHC\underline{H}_2$), 3.87—4.16 (m, 1H, $CH_2C\underline{H}CH_2$), 4.53 (s, 4H, $C\underline{H}_2C_6H_5 \times 2$), 7.35 (s, 10H, $C_6H_5 \times 2$). MS *m*/*z*: 272 (M^+).

37b: IR (neat): 3440, 1604, 1498, 740, 701 cm^{-1}. NMR ($CDCl_3$): 2.32 (br s, 1H, OH), 3.47—3.89 (m, 5H, $C\underline{H}_2C\underline{H}C\underline{H}_2$), 4.53 (s, 2H, $C\underline{H}_2C_6H_5$), 4.62 and 4.67 (ABq, *J* = 12 Hz, 2H, $C\underline{H}_2C_6H_5$), 7.35 (s, 10H, $C_6H_5 \times 2$). MS *m*/*z*: 272 (M^+).

Mixture of 1-*O*-Benzoyl-3-*O*-benzylglycerol (38a) and 1-*O*-Benzoyl-2-*O*-benzylglycerol (38b) These compounds could not be separated and the ratio of **38a** to **38b** was determined by ^{1}H-NMR after the removal of the benzoyl group. NMR ($CDCl_3$): 2.45 (br s), 2.87 (d, *J* = 5.1 Hz) (total 1H, OH), 3.47—4.07 (m), 4.07—4.33 (m), 4.33—4.57 (m) (total 5H, $C\underline{H}_2C\underline{H}C\underline{H}_2$), 4.58 (s), 4.69 and 4.74 (ABq, *J* = 12 Hz) (total 2H, $C\underline{H}_2C_6H_5$), 7.20—7.72 (m, 3H, C_6H_5CO), 7.33 (s, 5H, $CH_2C_6H_5$), 7.97—8.20 (m, 2H, C_6H_5CO).

1-Benzyloxy-3-((*tert*-butoxycarbonyl)amino)propan-2-ol (39a) and 2-Benzyloxy-3-((*tert*-butoxycarbonyl)amino)propanol (39b) A mixture of the diol **21** (340 mg, 1.78 mmol) and dibutyltin oxide (443 mg, 1.78 mmol) in toluene (6 ml) was refluxed for 1 h, while water formed was removed as the azeotropic mixture. The solution was evaporated to complete dryness under vacuum and CsF (314 mg, 1.86 mmol) was added to the residue. The mixture was further dried at room temperature *in vacuo* for 1 h and then dry DMF (5 ml) was added. The resulting solution was stirred at room temperature for 3 h, then benzyl iodide (776 mg, 3.56 mmol) in dry DMF (2 ml) was added. The reaction mixture was further stirred at room temperature for 120 h. The solvent was removed under vacuum and the residue was extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate, concentrated, and purified repeatedly by silica gel column chromatography (hexane– EtOAc) to afford 356 mg (71%) of **39a** and **39b** as an oil. This mixture was subjected to ^{1}H-NMR measurement to determine the ratio of **39a** to **39b**. Partial separation of **39a** and **39b** was accomplished through the above purification.

39a: IR (neat): 3390, 1700, 1392, 1368, 739, 700 cm^{-1}. NMR ($CDCl_3$): 1.44 (s, 9H, $(CH_3)_3C$), 2.95—3.65 (m, 5H, $C\underline{H}_2CHC\underline{H}_2$ and OH), 3.72—4.07 (m, 1H, $CH_2C\underline{H}CH_2$), 4.54 (s, 2H, $C\underline{H}_2C_6H_5$), 5.17 (br t, *J* = 5.7 Hz, 1H, NH), 7.37 (s, 5H, C_6H_5). MS *m*/*z*: 208 ($M^+ - 73$ (*tert*-BuO)), 180 ($M^+ - 101$ (*tert*-BuOCO)).

39b: IR (neat): 3370, 1700, 1392, 1368, 739, 700 cm^{-1}. NMR ($CDCl_3$): 1.45 (s, 9H, $(CH_3)_3C$), 3.10 (br s, 1H, OH), 3.22—3.80 (m, 5H, $C\underline{H}_2C\underline{H}C\underline{H}_2$), 4.61 (s, 2H, $C\underline{H}_2C_6H_5$), 4.97 (br s, 1H, NH), 7.40 (s, 5H, C_6H_5). MS *m*/*z*: 208 ($M^+ - 73$ (*tert*-BuO)), 180 ($M^+ - 101$ (*tert*-BuOCO)).

1,2-Di(benzyloxy)-3-((*tert*-butoxycarbonyl)amino)propane (9.7 mg, 1.5%) was also isolated. IR (neat): 3430, 3370, 1700, 1392, 1368, 737, 700 cm^{-1}: NMR ($CDCl_3$): 1.44 (s, 9H, $(CH_3)_3C$), 3.19—3.83 (m, 5H, $C\underline{H}_2C\underline{H}C\underline{H}_2$), 4.56 (S, 2H, $C\underline{H}_2C_6H_5$), 4.63 and 4.68 (ABq, *J* = 12 Hz, 2H, $CH_2C_6H_5$), 4.81 (br s, 1H, NH), 7.39 (s, 10H, $C_6H_5 \times 2$). MS *m*/*z*: 314 ($M^+ - 57$ (*tert*-Bu)), 298 ($M^+ - 73$ (*tert*-BuO)), 270 ($M^+ - 101$ (*tert*-BuOCO)).

1-Benzyloxy-3-((benzyloxycarbonyl)amino)propan-2-ol (40a) and 2-Benzyloxy-3-((benzyloxycarbonyl)amino)propanol (40b) These compounds were prepared from the diol **22** in 74% yield in a manner similar to that described for the preparation of compounds **39a** and **39b** from the diol **21**; the ratio of **40a** to **40b** was determined by ^{1}H-NMR. Partial separation of **40a** and **40b** was possible by repeated chromatography.

40a: IR (neat): 3400, 1700, 740, 700 cm^{-1}. NMR ($CDCl_3$): 2.98 (d, *J* = 4.2 Hz, 1H, OH), 3.07—3.63 (m, 4H, $C\underline{H}_2CHC\underline{H}_2$), 3.70—4.05 (m, 1H, $CH_2C\underline{H}CH_2$), 4.51 (s, 2H, $C\underline{H}_2C_6H_5$), 5.10 (s, 2H, $C_6H_5C\underline{H}_2OCO$), 5.31 (br s, 1H, NH), 7.35 and 7.37 (S × 2, 5H × 2, $C_6H_5 \times 2$). MS *m*/*z*: 224 ($M^+ - 91$ ($PhCH_2$)), 180 ($M^+ - 135$ ($PhCH_2OCO$)).

40b: IR (neat): 3420, 3330, 1700, 740, 700 cm^{-1}. NMR ($CDCl_3$): 2.70 (br s, 1H, OH), 3.20—3.80 (m, 5H, $C\underline{H}_2C\underline{H}C\underline{H}_2$), 4.58 (s, 2H, $C\underline{H}_2C_6H_5$), 5.11 (s, 2H, $C_6H_5C\underline{H}_2OCO$), 5.17 (br s, 1H, NH), 7.36 and 7.38 (S × 2, 5H × 2, $C_6H_5 \times 2$). MS *m*/*z*: 224 ($M^+ - 91$ ($PhCH_2$)), 180 ($M^+ - 135$ ($PhCH_2OCO$)).

1,2-Di(benzyloxy)-3-((benzyloxycarbonyl)amino)propane was also obtained in 3% yield. IR (neat): 3425, 3330, 1712, 737, 700 cm^{-1}. NMR ($CDCl_3$): 3.14—3.86 (m, 5H, $C\underline{H}_2C\underline{H}C\underline{H}_2$), 4.53 (s, 2H, $C\underline{H}_2C_6H_5$), 4.60 and 4.65 (ABq, *J* = 12 Hz, 2H, $C\underline{H}_2C_6H_5$), 5.08 (br s, 1H, NH), 5.11 (s, 2H, $C_6H_5C\underline{H}_2OCO$), 7.37 (s), 7.39 (s) (total 15H, $C_6H_5 \times 3$). MS *m*/*z*: 314 ($M^+ - 91$ ($PhCH_2$)), 270 ($M^+ - 135$ ($PhCH_2OCO$)).

Methyl 2-Hydroxy-3-(benzyloxy)propionate (42a) and Methyl 2-Benzyloxy-3-hydroxypropionate (42b) These compounds were partially separated by repeated chromatography and the ratio of **42a** to **42b** was determined by ^{1}H-NMR.

42a: IR (neat): 3475, 1740, 1604, 1498, 742, 700 cm^{-1}. NMR ($CDCl_3$): 3.32 (d, *J* = 6.9 Hz, 1H, OH), 3.75 (d, *J* = 3.1 Hz, 2H, $CHC\underline{H}_2$), 3.77 (s, 3H, CO_2CH_3), 4.20—4.44 (m, 1H, $C\underline{H}CH_2$), 4.57 (s, 2H, $C\underline{H}_2C_6H_5$), 7.33 (s, 5H, C_6H_5). MS *m*/*z*: *210* (M^+).

42b: IR (neat): 3450, 1737, 1604, 1498, 743, 701 cm^{-1}. NMR ($CDCl_3$): 2.58 (br s, 1H, OH), 3.77 (s, 3H, CO_2CH_3), 3.85 (m, 2H, $C\underline{H}_2OH$), 4.08 (dd, *J* = 5.6, 3.9 Hz, 1H, $C\underline{H}CH_2$), 4.52 and 4.80 (ABq, *J* = 11.5 Hz, 2H, $C\underline{H}_2C_6H_5$), 7.39 (s, 5H, C_6H_5). MS *m*/*z*: 210 (M^+).

2-Hydroxy-3-(benzyloxy)propionamide (43a) and 2-Benzyloxy-3-hydroxypropionamide (43b) These compounds were partially separated by repeated chromatography and the ratio of **43a** to **43b** was determined by ^{1}H-NMR.

43a: Colorless leaflets from hexant–ether–EtOAc. mp 98—98.5 °C. IR (KBr): 3450, 3330, 3200, 1650, 748, 700 cm^{-1}. NMR (CD_3OD): 3.56—3.86 (m, 2H, $CHC\underline{H}_2$), 4.25 (dd, *J* = 5.1, 4.0 Hz, 1H, $C\underline{H}CH_2$), 4.57 (s, 2H, $C\underline{H}_2C_6H_5$), 4.76 (s, 3H, OH and $CONH_2$), 7.38 (s, 5H, C_6H_5). *Anal.* Calcd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.48; H, 6.72; N, 6.99.

43b: Colorless needles from hexane–ether–EtOAc, mp 112.5—113.5 °C. IR (KBr): 3370, 3220, 1658, 740, 700 cm^{-1}. NMR (CD_3OD): 3.52—4.02 (m, 3H, $C\underline{H}C\underline{H}_2$), 4.67 (s, 2H, $C\underline{H}_2C_6H_5$), 4.77 (s, 3H, OH and $CONH_2$), 7.41 (s, 5H, C_6H_5). *Anal.* Calcd for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.22; H, 6.58; N, 6.88.

2,3-Di(benzyloxy)propionamide was also formed in 17.5% yield in this reaction. Colorless needles from hexane–ether, mp 74.5—76 °C. IR (KBr): 3377, 3200, 1657, 1498, 742, 700 cm^{-1}. NMR ($CDCl_3$): 3.64—3.99 (m, 2H, $CHC\underline{H}_2$), 4.08 (dd, *J* = 5.0, 3.1 Hz, 1H, $C\underline{H}CH_2$), 4.57 (s, 2H, $C\underline{H}_2C_6H_5$), 4.67 (s, 2H, $C\underline{H}_2C_6H_5$), 6.56 (br s, 1H, $CONH_2$), 6.76 (br s, 1H, $CONH_2$), 7.36 (s, 5H, C_6H_5), 7.38 (s, 5H, C_6H_5). *Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.30; H, 6.72; N, 5.16.

***N*-Methyl-2-hydroxy-3-(benzyloxy)propionamide (44a) and *N*-Methyl-2-benzyloxy-3-hydroxypropionamide (44b)** These compounds were completely separated and the ratio of **44a** to **44b** was determined from their weights.

44a: IR (neat): 3350, 1650, 1498, 741, 701 cm^{-1}. NMR ($CDCl_3$): 2.79 and 2.85 (S × 2, 3H, $CONHC\underline{H}_3$), 3.46—3.90 (m, 3H, $C\underline{H}_2OCH_2C_6H_5$ and OH), 4.10—4.36 (m, 1H, $C\underline{H}CONHCH_3$), 4.56 (s, 2H, $C\underline{H}_2C_6H_5$), 6.83 (br s, 1H, $CON\underline{H}CH_3$), 7.38 (s, 5H, C_6H_5). MS *m*/*z*: 210 ($M^+ + 1$), 179 ($M^+ - 30$(MeNH)), 118 ($M^+ - 91$ ($PhCH_2$)).

44b: IR (neat); 3360, 1650, 1498, 738, 700 cm^{-1}. NMR ($CDCl_3$): 2.79 and 2.85 (S × 2, 3H, $CONHC\underline{H}_3$), 2.92 (br s, 1H, OH), 3.70—4.08 (m, 3H, $C\underline{H}C\underline{H}_2$), 4.64 and 4.66 (ABq, *J* = 11.7 Hz, 2H, $C\underline{H}_2C_6H_5$), 6.78 (br s, 1H, $CON\underline{H}CH_3$), 7.39 (s, 5H, C_6H_5). MS *m*/*z*: 210 ($M^+ + 1$), 179 ($M^+ - 30$ (MeNH)).

N-Methyl-2,3-di(benzyloxy)propionamide was also formed in 9.7% yield in this reaction. IR (neat): 3425, 3330, 1660, 1498, 734, 698 cm^{-1}. NMR ($CDCl_3$): 2.79 and 2.85 (S × 2, 3H, $CONHC\underline{H}_3$), 3.62—4.0 (m, 2H, $CHC\underline{H}_2$), 4.10 (dd, *J* = 4.8, 2.7 Hz, 1H, $C\underline{H}CH_2$), 4.56 (s, 2H, $CH_2C_6H_5$), 4.63 and 4.69 (ABq, *J* = 11.7 Hz, 2H, $C\underline{H}_2C_6H_5$), 6.77 (br s, 1H, $CON\underline{H}CH_3$), 7.35 (s, 5H, C_6H_5); 7.38 (s, 5H, C_6H_5). MS *m*/*z*: 300 ($M^+ + 1$), 208 ($M^+ - 91$ ($PhCH_2$)), 192 ($M^+ - 107$ ($PhCH_2O$)).

***N*,*N*-Dimethyl-2-hydroxy-3-(benzyloxy)propionamide (45a) and *N*,*N*-Dimethyl-2-benzyloxy-3-hydroxypropionamide (45b)** These compounds were completely separated and the ratio of **45a** to **45b** was determined from their weights.

45a: IR (neat): 3400, 1638, 1498, 740, 700 cm^{-1}: MMR ($CDCl_3$): 2.96 (s, 3H, $N(CH_3)_2$), 3.01 (s, 3H, $N(CH_3)_2$), 3.62 (d, *J* = 5.1 Hz, 2H, $CHC\underline{H}_2$), 3.77 (br s, 1H, OH), 4.58 (s, 2H, $C\underline{H}_2C_6H_5$), 4.63 (br t, *J* = 5.1 Hz, 1H, $C\underline{H}OH$), 7.38 (s, 5H, C_6H_5). MS *m*/*z*: 223 (M^+).

45b: IR (neat): 3400, 1637, 1500, 739, 702 cm^{-1}. NMR ($CDCl_3$): 2.79 (br s, 1H, OH), 2.97 (s, 3H, $N(CH_3)_2$), 3.02 (s, 3H, $N(CH_3)_2$), 3.91 (d, *J* = 5.1 Hz, 2H, $CHC\underline{H}_2$), 4.35 (t, *J* = 5.1 Hz, 1H, $C\underline{H}CH_2$), 4.57 and 4.63 (ABq, *J* = 11.7 Hz, 2H, $C\underline{H}_2C_6H_5$), 7.39 (s, 5H, C_6H_5). MS *m*/*z*: 224 ($M^+ + 1$), 151 ($M^+ - 72$ ($CONMe_2$)), 132 ($M^+ - 91$ ($PhCH_2$)).

Methyl (2*S*,3*R*)-2-Hydroxy-3-(benzyloxy)butyrate (52a) and Methyl

(2*S*,3*R*)-2-Benzyloxy-3-hydroxybutyrate (52b) These compounds were completely separated and the ratio of **52a** to **52b** was determined from their weights.

52a: $[\alpha]_D^{23}$ −27.2° ($c=1.59$, $CHCl_3$). IR (neat): 3475, 1740, 1604, 1498, 739, 699 cm^{-1}. NMR ($CDCl_3$): 1.30 (d, $J=6.4$ Hz, 3H, $CHC\underline{H}_3$), 3.18 (d, $J=7.8$ Hz, 1H, OH), 3.69 (s, 3H, CO_2CH_3), 3.90 (qd, $J=6.4$, 2.5 Hz, 1H, $C\underline{H}CH_3$), 4.06 (dd, $J=7.8$, 2.5 Hz, 1H, $C\underline{H}CO_2CH_3$), 4.40 and 4.57 (ABq, $J=11.7$ Hz, 2H, $C\underline{H}_2C_6H_5$), 7.31 (s, 5H, C_6H_5). MS *m/z*: 224 (M^+).

52b: $[\alpha]_D^{23}$ −89.6° ($c=1.57$, $CHCl_3$). IR (neat) 3475, 1740, 1604, 1499, 748, 702 cm^{-1}. NMR ($CDCl_3$): 1.21 (d, $J=6.3$ Hz, 3H, $CHCH_3$), 2.52 (d, $J=4.8$ Hz, 1H, OH), 3.76 (s, 3H, CO_2CH_3), 3.81 (d, $J=4.8$ Hz, 1H, $C\underline{H}CO_2CH_3$), 3.89—4.22 (m, 1H, $C\underline{H}CH_3$), 4.43 and 4.74 (ABq, $J=11.4$ Hz, 2H, $C\underline{H}_2C_6H_5$), 7.37 (s, 5H, C_6H_5). MS *m/z*: 165 (M^+-59 (CO_2Me)), 91 ($PhCH_2$).

(2*S*,3*R*)-*N*,*N*-Dimethyl-2-hydroxy-3-(benzyloxy)butyramide (53a) and (2*S*,3*R*)-*N*,*N*-Dimethyl-2-benzyloxy-3-hydroxybutyramide (53b) These compounds were completely separated and the ratio of **53a** to **53b** was determined from their weights.

53a: $[\alpha]_D^{23}$ +7.68° ($c=2.87$, $CHCl_3$). IR (neat): 3425, 1635, 740, 700 cm^{-1}. NMR ($CDCl_3$): 1.22 (d, $J=6.3$ Hz, 3H, $CHC\underline{H}_3$), 2.89 (s, 3H, $N(CH_3)_2$), 2.97 (s, 3H, $N(CH_3)_2$), 3.76 (qd, $J=6.3$, 3.6 Hz, 1H, $C\underline{H}CH_3$), 3.89 (d, $J=7.3$ Hz, 1H, OH), 4.42 (dd, $J=7.3$, 3.6 Hz, 1H, $C\underline{H}CON(CH_3)_2$), 4.49 and 4.62 (ABq, $J=12.3$ Hz, 2H, $C\underline{H}_2C_6H_5$), 7.35 (s, 5H, C_6H_5). MS *m/z*: 238 (M^++1), 193 (M^+-44 (NMe_2)), 146 (M^+-91 ($PhCH_2$)).

53b: $[\alpha]_D^{23}$ −57.3° ($c=1.00$, $CHCl_3$). IR (neat): 3410, 1632, 738, 700 cm^{-1}. NMR ($CDCl_3$): 1.21 (d, $J=6.2$ Hz, 3H, $CHC\underline{H}_3$), 2.96 (s, 3H, $N(CH_3)_2$), 3.02 (s, 3H, $N(CH_3)_2$), 3.28 (br s, 1H, OH), 3.81—4.24 (m, 1H, $C\underline{H}CH_3$), 4.09 (d, $J=2.6$ Hz, 1H, $C\underline{H}CON(CH_3)_2$), 4.48 and 4.70 (ABq, $J=11.7$ Hz, 2H, $C\underline{H}_2C_6H_5$), 7.37 (s, 5H, C_6H_5). MS *m/z*: 193 (M^+-44 (NMe_2)), 146 (M^+-91 ($PhCH_2$)).

Mixture of (2*R*,3*R*)-1-Methoxy-3-(benzyloxy)butan-2-ol (54a) and (2*R*,3*R*)-1-Methoxy-2-(benzyloxy)butan-3-ol (54b) These compounds could not be separated and the ratio of **54a** to **54b** was determined by ^{1}H-NMR.

This mixture showed the optical rotation; $[\alpha]_D^{22}$ −39.0° ($c=5.53$, $CHCl_3$). IR (neat): 3440, 1604, 1498; 740, 700 cm^{-1}. NMR ($CDCl_3$): 1.18 (d, $J=6.4$ Hz) and 1.21 (d, $J=6.2$ Hz) (total 3H, $CHC\underline{H}_3$), 2.70 (d, $J=5.2$ Hz) and 2.82 (d, $J=4.2$ Hz) (total 1H, OH), 3.36 (s, 3H, OCH_3), 3.36—4.09 (m, 4H, $CH_3C\underline{H}C\underline{H}C\underline{H}_2OCH_3$), 4.49 and 4.63 (ABq, $J=11.4$ Hz), 4.59 and 4.76 (ABq, $J=11.7$ Hz) (total 2H, $C\underline{H}_2C_6H_5$), 7.37 (s) and 7.38 (s) (total 5H, C_6H_5). MS *m/z*: 210 (M^+).

Methyl (2*R*,3*R*)-2-Hydroxy-3-(*N*,*N*-dimethylcarbamoyl)-3-(benzyloxy)propionate (55a) and Methyl (2*R*,3*R*)-2-Benzyloxy-3-(*N*,*N*-dimethylcarbamoyl)-3-hydroxypropionate (55b) These compounds were completely separated and the ratio of **55a** to **55b** was determined from their weights.

55a: Pale yellow prisms from hexane–ether–EtOAc. mp 63.5—64.5 °C, $[\alpha]_D^{23}$ +103.7° ($c=1.02$, $CHCl_3$). IR (KBr): 3410, 1750, 1643, 1500, 750, 703 cm^{-1}. NMR ($CDCl_3$): 2.68 (s, 3H, N $(CH_3)_2$) and 2.93 (s, 3H, $N(CH_3)_2$), 3.86 (s, 3H, CO_2CH_3), 4.14 (d, $J=2.7$ Hz, 1H, $C\underline{H}CON$ $(CH_3)_2$), 4.17 (d, $J=8.1$ Hz, 1H, OH), 4.77 (dd, $J=8.1$ Hz, 2.7 Hz, 1H, $C\underline{H}CO_2CH_3$), 4.43 and 4.87 (ABq, $J=12.8$ Hz, 2H, $C\underline{H}_2C_6H_5$), 7.37 (s, 5H, C_6H_5). *Anal.* Calcd for $C_{14}H_{19}NO_5$: C, 59.77; H, 6.81; N, 4.98. Found: C, 59.84; H, 6.82; N, 4.88.

55b: $[\alpha]_D^{24}$ +36.6° ($c=1.64$, $CHCl_3$). IR (neat): 3370, 1744, 1640, 1500, 750, 703 cm.$^{-1}$ NMR ($CDCl_3$): 3.01 (s, 3H, $N(CH_3)_2$) and 3.10 (s, 3H, $N(CH_3)_2$), 3.76 (br s, 1H, OH), 3.73 (s, 3H, CO_2CH_3), 4.55 (d, $J=3$ Hz, 1H, $C\underline{H}CON$ $(CH_3)_2$), 4.60 (d, $J=3$ Hz, 1H, $C\underline{H}CO_2CH_3$), 4.43 and 4.74 (ABq, $J=12$ Hz, 2H, $C\underline{H}_2C_6H_5$), 7.36 (s, 5H, C_6H_5). MS *m/z*: 282 (M^++1), 222 (M^+-59 (CO_2Me)), 190 (M^+-91 ($PhCH_2$)), 91 ($PhCH_2$), 72 ($CONMe_2$).

2-Methyl-4-(benzyloxy)pentan-2-ol (56a) A mixture of the diol 51 (146 mg, 1.23 mmol) and dibutyltin oxide (307 mg, 1.23 mmol) in toluene (4 ml) was refluxed for 2 h, while water formed was removed as the azeotropic mixture. The solution was evaporated to complete dryness under vacuum and CsF (assay min. 90%, 290 mg, 1.72 mmol) was added to the residue. The mixture was further dried at room temperature *in vacuo* for 1 h and then dry DMF (2 ml) was added. The resulting solution was stirred at 50 to 53 °C for 1 h, then benzyl iodide (490 mg, 2.25 mmol) in dry DMF (4 ml) was added. The reaction mixture was further stirred at the same temperature for 42 h. The solvent was removed under vacuum and the residue was extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate, concentrated, and purified by silica gel column chromatography (hexane–EtOAc) to give an oil. This oil was further purified by preparative TLC on silica gel (benzene: EtOAc = 2 : 1) to afford 128 mg (50%) of **56a** as a colorless oil. IR (neat): 3475, 1602, 1500, 740, 700 cm^{-1}. NMR ($CDCl_3$): 1.21 (s, 6H, $CH_3\times2$), 1.24 (d, $J=7.2$ Hz, 3H, $CHC\underline{H}_3$), 1.37—2.03 (m, 2H, $C\underline{H}_2CHCH_3$), 3.77—4.17 (m, 1H, $CH_2C\underline{H}CH_3$), 3.98 (s, 1H, OH), 4.42 and 4.64 (ABq, $J=11.4$ Hz, 2H, $CH_2C_6H_5$), 7.37 (s, 5H, C_6H_5). MS *m/z*: 208 (M^+).

General Procedure for Benzylation of Glycerol A mixture of glycerol (89 mg, 0.97 mmol) and dibutyltin oxide (241 mg, 0.97 mmol) in toluene (3 ml) was refluxed for 1 h, while water formed was removed as the azeotropic mixture. The solution was evaporated to complete dryness under vacuum and a suitable amount of CsF was added to the resulting white solid. The mixture was further dried at room temperature *in vacuo* for 1 h. Then benzyl iodide, in the amount shown in Table V, in dry DMF (3 ml) was added at 0 °C. The reaction mixture was stirred vigorously at 0 to 3 °C for the period of time shown in Table V. EtOAc was then added to the reaction mixture and the resulting insoluble materials were filtered through a pad of Celite and washed with EtOAc. The filtrate and washings were combined, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using hexane–EtOAc as an eluent. The monobenzylated products and the dibenzylated products were easily separated, and both of them were isolated as mixtures of regioisomers. The isolated yields are listed in Table V. The ratios of regioisomers were determined from the peak intensities of benzylic protons of each isomer in the ^{1}H-NMR spectra. ^{1}H-NMR data for the mixture are given below.

19a and **19b**: NMR ($CDCl_3$): 3.30—4.03 (m, 7H, $C\underline{H}_2C\underline{H}C\underline{H}_2$ and $OH\times2$), 4.52 (s) and 4.61 (s) (total 2H, $C\underline{H}_2C_6H_5$), 7.36 (s, 5H, C_6H_5).

37a and **37b**: NMR ($CDCl_3$): 2.49 (br s) and 2.84 (d, $J=3.9$ Hz) (total 1H, OH), 3.37—3.79 (m) and 3.84—4.16 (m) (total 5H, $C\underline{H}_2C\underline{H}C\underline{H}_2$), 4.52 (s), 4.62 and 4.67 (ABq, $J=12$ Hz) (total 4H, $C\underline{H}_2C_6H_5\times2$), 7.33 (s, 10H, $C_6H_5\times2$).

References and Notes

1) A part of this work was presented at the 106th Annual Meeting of the Pharmaceutical Society of Japan, Chiba, April 1986, Abstract of Papers, p. 399; and also at the 107th Annual Meeting of the Pharmaceutical Society of Japan, Kyoto, April 1987, Abstract of Papers, p. 234. See also; N. Nagashima and M. Ohno, *Chem. Lett.*, **1987**, 141.

2) An excellent ring closure reaction using stannylene acetal of a diol and CsF was independently reported by Danishefsky *et al.* See; S. Danishefsky and R. Ungate, *J. Am. Chem. Soc.*, **108**, 2486 (1986).

3) Present address: *Eisai Co., Ltd., 1–3, Tokodai 5-chome, Tsukuba-shi, Ibaraki 300–26, Japan.*

4) T. W. Green, "Protective Groups in Organic Synthesis," John Wiley & Sons Inc., New York, 1981, pp. 10—86.

5) For a discussion of this problem, see; C. C. Leznoff, *Acc. Chem. Res.*, **11**, 327 (1978).

6) For example, see; *a*) Y. Ikeda, J. Ukai, N. Ikeda, and H. Yamamoto, *Tetrahedron Lett.*, **25**, 5177 (1984); *b*) B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **102**, 4743 (1980).

7) *a*) P. B. McDougal, J. G. Rico, Young-Im Oh, and B. D. Condon, *J. Org. Chem.*, **51**, 3388 (1986); *b*) A. Gateau-Oleskear, J. Cléphax, and S. D. Géro, *Tetrahedron Lett.*, **27**, 41 (1986); *c*) T. G. Hansson and J. O. Kihlberg, *J. Org. Chem.*, **51**, 4490 (1986); *d*) E. Hungerbühler and D. Seebach, *Helv. Chim. Acta.*, **64**, 687 (1981); *e*) H. Iida, N. Yamazaki and C. Kibayashi, *J. Org. Chem.*, **51**, 1069 (1986); *f*) P. J. Garegg, T. Iversen, and S. Oscarson, *Carbohydr. Res.*, **50**, C12 (1976); *g*) R. D. Walkup and R. T. Cunningham, *Tetrahedron Lett.*, **28**, 4019 (1987).

8) *a*) E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Am. Chem. Soc.*, **84**, 2371 (1962); *b*) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **42**, 990 (1964); *c*) B. Fleming and H. I. Balker, *ibid.*, **52**, 888 (1974); *d*) D. Seeback and E. Hungerbüler, "Modern Synthetic Methods," ed. by R. Scheffold, Salle and Sauerländer, Berlin, 1980, p. 152; *e*) K. Fujita, H. Nakai, S. Kobayashi, K. Inoue, S. Nojima, and M. Ohno, *Tetrahedron Lett.*, **24**, 3507 (1982); *f*) S. Takano, A. Kurotaki, Y. Sekiguchi, S. Satoh, M. Hirama, and K. Ogasawara, *Synthesis*, **1986**, 811; *g*) T. Wakamiya, K. Yamanoi, K. Kanou, and T. Shiba, *Tetrahedron Lett.*, **28**, 5887 (1987); *h*) P. J. Garegg, *Pure Appl. Chem.*, **56**, 845 (1984); *i*) R. Johansson and B. Samuelsson, *J. Chem. Soc., Chem. Commun.*, **1984**, 201; *j*) H. Kotsuki, Y. Ushio, N. Yoshimura, and M. Ochi, *J. Org. Chem.*, **52**, 2594 (1987).

9) For a review, see; S. David and S. Hanessian, *Tetrahedron*, **41**, 643 (1985) and references cited therein. See, particularly; D. Wagner, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, **39**, 24 (1974).

10) *a*) For monoacylation, see: A. Shanzer, *Tetrahedron Lett.*, **21**, 221

(1980); Y. Tsuda, Md. E. Haque, and K. Yoshimoto, *Chem. Pharm. Bull.*, **31**, 1612 (1983); *b*) For monotosylation, see: J. Thiem and Hans-Peter Wessel, *Tetrahedron Lett.*, **21**, 3571 (1980); M. Muraoka, *Chem. Pharm. Bull.*, **29**, 3449 (1981); *c*) For monoacetalization, see: M. A. Nashed, M. S. Chowdhary, and L. Anderson, *Carbohydr. Res.*, **102**, 99 (1982); *d*) For monosilylation, see: A. Ricci, S. Roelens, and A. Vannucchi, *J. Chem. Soc., Chem. Commun.*, **1985**, 1457; U. Berlage, J. Schmidt, U. Peters, and P. Welzel, *Tetrahedron Lett.*, **28**, 3091 (1987); *e*) For monoalkylation, see: C. Augé, S. David, and A. Veyrières, *J. Chem. Soc., Chem. Commun.*, **1976**, 375; M. A. Nashed and L. Anderson, *Carbohydr. Res.*, **56**, 419 (1977); H. Takaku, K. Kamaike, and H. Tsuchiya, *J. Org. Chem.*, **49**, 51 (1984).

11) M. A. Nashed and L. Anderson, *Tetrahedron Lett.*, **1976**, 3503.

12) *a*) S. David, A. Thieffry, and A. Veyrières, *J. Chem. Soc., Perkin Trans., 1*, **1981**, 1796; *b*) J. Alais, A. Maranduba, and A. Veyrières, *Tetrahedron Lett.*, **24**, 2383 (1983).

13) See ref. 8*d*, p. 91 and references cited therein.

14) During the course of our study, two reports on the monoalkylation of dialkyl tartrates were published. See refs. 7*b* and 7*c*.

15) For other examples of selective alkylation of unsymmetric diols, see: *a*) T. Ogawa and T. Horisaki, *Carbohydr. Res.*, **123**, Cl (1983); *b*) O. Sakanaka, T. Ohmori, S. Kozaki, and T. Suami, *Bull. Chem. Soc. Jpn.*, **59**, 3523 (1986); *c*) *Idem*, *ibid.*, **60**, 1057 (1987); *d*) S. Kozaki, O. Sakanaka, T. Yasuda, T. Shimizu, S. Ogawa, and T. Suami, *J. Org. Chem.*, **53**, 281 (1988); *e*) See also ref. 7*g*.

16) *a*) J. Emsley, D. J. Jones, J. M. Miller, R. E. Overill, and R. A. Waddilove, *J. Am. Chem. Soc.*, **103**, 24 (1981); *b*) J. H. Clark and J. M. Miller, *J. Chem. Soc., Perkin Trans., 1*, **1977**, 2063.

17) T. Mukaiyama, Y. Tanabe, and M. Shimizu, *Chem. Lett.*, **1984**, 401.

18) *a*) N. H. Andersen, D. A. McCrae, D. B. Grotjahn, S. Y. Gabhe, L. J. Theodore, R.M. Ippolito, and T. K. Sarkar, *Tetrahedron*, **37**, 4069 (1981); *b*) M. Gielen and R. Fosty, *J. Chem. Res.* (*s*), **1977**, 214; *c*) A. Degl'Innocenti, S. Pike, and D. R. M. Walton, *J. Chem. Soc., Chem. Commun.*, **1980**, 1201; *d*) B. A. Pearlman, S. R. Putt, and J. A. Fleming, *J. Org. Chem.*, **50**, 3622 (1985).

19) A formation of pentacoordinate tin complex has also been postulated for trialkyltin alkoxide. See: J. Alais and A. Veyrières, *J. Chem. Soc., Perkin Trans., 1*, **1981**, 377.

20) M. Gingras, T. H. Chan, and D. N. Harpp, *J. Org. Chem.*, **55**, 2078 (1990).

21) Danishefsky makes a similar assumption in ref. 2.

22) For synthetic applications of our procedure, see; *a*) H. Niwa *et al.*, 30th Symposium on the Chemistry of Natural Products, 1988, Abstract, 418; *b*) K.-L. Yu and B. Fraser-Reid, *Tetrahedron Lett.*, **29**, 979 (1988); *c*) Y.-C. Liu and C.-S. Chen, *ibid.*, **30**, 1617 (1989); *d*) C. J. J. Elie, C. E. Dreef, R. Verduyn, G. A. Van Der Marel, and J. H. Van Boom, *Tetrahedron*, **45**, 3477 (1989); *e*) C. Murakata and T. Ogawa, *Tetrahedron Lett.*, **31**, 2439 (1990); *f*) T. Sato, T. Tada, J. Otera, and H. Nozaki, *ibid.*, **30**, 1665 (1989); *g*) T. Sato, J. Otera, and H. Nozaki, *ibid.*, **30**, 2959 (1989).

23) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).

24) H. L. Smith, E. S. Brown, J. D. Smith, and J. Andrako, *J. Pharm. Sci.*, **54**, 1269 (1965).

25) M. E. Jung and T. J. Shaw, *J. Am. Chem. Soc.*, **102**, 6304 (1980).

26) H. Hibbert and N. M. Carter, *J. Am. Chem. Soc.*, **50**, 3120 (1928).

27) J. P. Amma and J. K. Stille, *J. Org. Chem.*, **47**, 468 (1982).

28) J. J. Baldwin, A. W. Raab, K. Mensler, B. H. Arison, and D. E. McClure, *J. Org. Chem.*, **43**, 4876 (1978).

29) M. Cahnmann, *Bull. Soc. Chim. Fr.* **4**, 226 (1937).

30) C. Fuganti, P. Grasselli, and G. Pedrocchi-Fantoni, *Tetrahedron Lett.*, **22**, 4017 (1981).

31) Ref. 8*d*, p. 151.