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Asymmetric Alkylation of β-Keto Esters with Alkylsulfonium Salts Containing a Sugar Group

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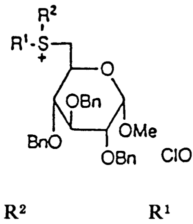
Synopsis. The asymmetric alkylation of 2-methoxycarbonyl-1-indanone (**2**) and ethyl 2-methylacetoacetate (**5**) with an alkylsulfonium salt containing a sugar group were investigated. (*S*)-Ethyl 2-allyl-2-methylacetoacetate (**6b**) was obtained with up to 25% optical purity on alkylation of the enolate ion of **5** using the allyl(*p*-tolyl)sulfonio D-glucoside derivative (**1h**).

S-Adenosylmethionine (AdoMet) is an important biological methylating agent, which is the source of the methyl groups of such compounds as DNA, RNA, proteins, and biogenic amines.1) A few stereochemical studies have been reported on the methylation reaction of phenolic oxygens with *S*-adenosylmethionine via S_N2-type process in enzymic systems.2) In recent years, a few studies have been published on the alkylation reaction of oxygen nucleophiles such as carboxylate, nitrogen nucleophiles such as amines, and carbon nucleophiles (e.g. enolate ions of β-keto esters) with racemic alkylsulfonium salts.3) More recently, we have reported the first examples of asymmetric alkylation of β-keto esters with optically active alkylsulfonium salts.4) We now describe herein the synthesis of alkylsulfonium salts containing sugar groups, since *S*-adenosylmethionine has a sugar group at the α-position of the sulfur atom. The asymmetric alkylation of cyclic and acyclic β-keto esters using the sulfonium salts is also described.5)

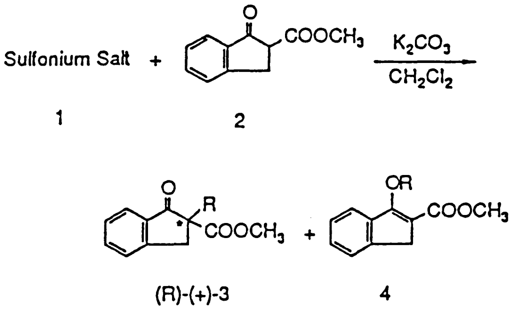
Alkylsulfonium salts containing sugar groups (**1a**—**k**) were prepared from D-glucose. The sulfonium salts (**1e** and **1i**) were shown to be diastereomeric mixtures on the sulfur atom by ^{1}H NMR analysis (see Experimental section). They could not be separated by recrystallization.



	R^1	R^2		R^1	R^2
1a:	CH_3	CH_3	**1g**:	NO_2-C_6H_4	C_2H_5
1b:	C_2H_5	C_2H_5	**1h**:	CH_3-C_6H_4	$CH_2CH{=}CH_2$
1c:	C_2H_5	CH_3	**1i**:	Cl-C_6H_4	CH_2-C_6H_5
1d:	CH_3-C_6H_4	CH_3	**1j**:	CH_3-C_6H_4	CH_2-C_6H_5
1e:	NO_2-C_6H_4	CH_3	**1k**:	Cl-C_6H_4	$CH_2CH{=}CH_2$
1f:	CH_3-C_6H_4	C_2H_5			

2-Methoxycarbonyl-1-indanone (**2**) was alkylated with a dimethylsulfonio D-glucoside derivative (**1a**) in the presence of anhydrous potassium carbonate in dichloromethane at room temperature for 3 days (Eq. 1). Purification of the reaction mixture by silica-gel chromatography gave *C*-methylated product, (*R*)-(+)-2-methyl-2-methoxycarbonyl-1-indanone (**3a**) (71% yield; o.p. 4.1%),4) and the *O*-methylated product, **4a** (9% yield). In a similar manner, alkylation of **2** with diethylsulfonio D-glucoside derivative (**1b**) gave the *C*-ethylated product (*R*)-(+)-**3b** (77% yield; o.p. 4.7%),4) and the *O*-ethylated product **4b** (12% yield).

When the methyl(*p*-tolyl)sulfonio D-glucoside derivative (**1d**) was employed for the reaction with **2**, only the methyl group was introduced to the α-carbon and oxygen atom of **2** to give **3a** and **4a**, respectively. The major product **3a** was also optically active with *R*-configuration.

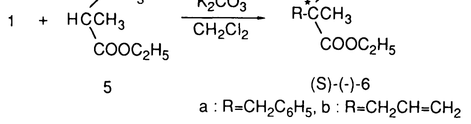


(1)

a : $R{=}CH_3$, b : $R{=}C_2H_5$, c : $R{=}CH_2CH{=}CH_2$

Similarly, the alkylation of **2** with the methyl(*p*-nitrophenyl)sulfonio D-glucoside derivative (**1e**) gave (*R*)-(+)-**3a** (78% yield; o.p. 6.6%) and product **4a** in 10% yield (Entry 4). Alkylation with arylethylsulfonium salts (**1f** and **1g**) gave (*R*)-(+)-**3b** in 71% yield (o.p. 5.3%) and (*R*)-(+)-**3b** in 74% yield (o.p. 11.9%), respectively (Entries 5 and 6). As shown in Entry 7, the exclusive *C*-allylation of **2** occurred without being accompanied by *O*-allylation. No significant effects on the optical yields were observed when the para-substituent on the aromatic ring was changed from a methyl group (**1d** and **1f**) to a nitro group (**1e** and **1g**).

The alkylation of ethyl 2-methylacetoacetate (**5**) with alkylsulfonium salts containing sugar group **1** was also investigated (Eq. 2).



(2)

a : $R{=}CH_2C_6H_5$, b : $R{=}CH_2CH{=}CH_2$

When ester **5** was alkylated with sulfonium salt (**1i**), it afforded the *C*-benzylated product (*S*)-(−)-**6a** in 49% yield (o.p. 4.7%).6) Similarly, allylation of **5** with sulfonium salt (**1h**) gave *C*-allylated products (*S*)-(−)-**6b** in 18% yield (o.p. 25.0%). The results are sum-

Table 1. Alkylation of **2** with Alkylsulfonium Salts **1**

Entry	Sulfonium salt	Product **3**			Yield[a] of **4**
		Yield[a]/%	[α]D/deg. (CHCl$_3$)	o.p./% (confn)	%
1	**1a**	**3a** 71	+0.87	4.1 (*R*)	**4a** 9
2	**1b**	**3b** 77	+3.5	4.7 (*R*)	**4b** 12
3	**1d**	**3a** 78	+2.2	10.4 (*R*)	**4a** 12
4	**1e**	**3a** 78	+1.4	6.6 (*R*)	**4a** 10
5	**1f**	**3b** 71	+3.9	5.3 (*R*)	**4b** 15
6	**1g**	**3b** 74	+8.8	11.9 (*R*)	**4b** 14
7	**1h**	**3c** 89	+8.1		— —

a) Isolated yield.

Table 2. Alkylation of **5** with Alkylsulfonium Salts **1**

Entry	Sulfonium salt	Product **6**		
		Yield[a]/%	[α]D/deg. (CHCl$_3$)	o.p./% (confn)
8	**1i**	**6a** 49	−3.0	4.7 (*S*)
9	**1j**	**6a** 54	−1.8	2.8 (*S*)
10	**1k**	**6b** 65	−2.2	7.4 (*S*)
11	**1h**	**6b** 18	−7.4	25.0 (*S*)

a) Isolated yield.

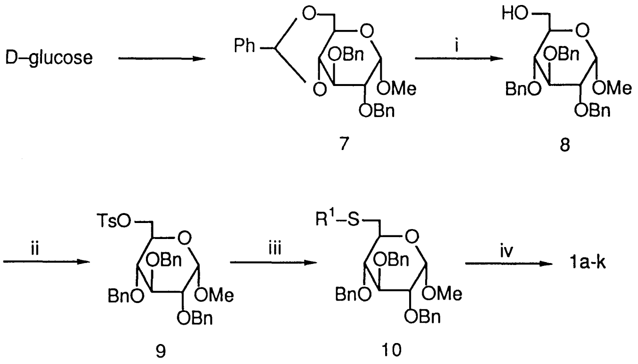
marized in Table 2.

As shown in Tables 1 and 2, we have achieved asymmetric alkylation using alkylsulfonium salts containing sugar groups, although this method has shown only a small enrichment of one enantiomer by an asymmetric induction effect. Two factors may be considered to explain this asymmetric induction: that is, the chiral transfer from the chiral sulfur atom of the sulfonium salt and the steric control by the sugar moiety. The former factor is not clear, since small asymmetric inductions were observed for the alkylation of **2** with dimethyl- and diethylsulfonium salts (**1a** and **1b**) and alkylarylsulfonium salts (**1e** and **1i**), although **1e** and **1i** were 1 : 1 diastereomeric mixtures. Accordingly, this asymmetric alkylation is mainly attributable to the steric control by the sugar portion when the enolate ion of **2** attacks at the alkyl carbon atom of the sulfonium salt via an S$_N$2 process. The S$_N$2 mechanism is supported by the fact that the ratio of *C*-methylated and *C*-ethylated product of **2** with ethylmethylsulfonium salt (**1c**) was 2.8 : 1.[7,8]

Experimental

The procedure for the preparation of sulfonium salts **1** is outlined in Scheme 1.

Preparation of Methyl 6-*O*-Tosyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (9). A mixture of methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α-D-glucopyranoside (**7**) (4.78 g), was prepared from D-glucose by the ordinary procedures, and lithium aluminum hydride (764 mg) in 55 cm^3 of dry CH$_2$Cl$_2$–Et$_2$O (7 : 4) was stirred and heated to reflux. After the addition of aluminum chloride (2.68 g) in 15 cm^3 of dry ether, the solution was refluxed again for 3 h to give methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**8**) (4.67 g, 99% yield). To a pyridine solution (10 cm^3) of **8** (2.03 g) was added *p*-toluenesulfonyl chloride (1.27 g) at 0 °C, and the mixture was stirred for 1 day at room temperature to give methyl 6-*O*-tosyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**9**) (2.59 g, 96% yield); [α]D+24.8° (*c* 2.26, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ=2.24 (3H, s), 3.17 (3H, s), 3.23—4.93 (13H, m), 6.92—7.83 (19H, m); MS, *m/z* 618 (M$^+$); HRMS, Calcd for C$_{35}$H$_{38}$O$_8$S: M, 618.2286. Found: *m/z* 618.2260.



Scheme 1. Reagents: i, LiAlH$_4$–AlCl$_3$, CH$_2$Cl$_2$–Et$_2$O; ii, TsCl, pyridine; iii, R^{1}SH, EtOH–NaOEt; iv, R^{2}X–AgClO$_4$, CH$_3$CN.

General Procedure for the Synthesis of 6-Deoxy-6-[alkylthio (or arylthio)]-α-D-glucopyranoside (10). The thiol (5 mmol) was added to an ethanol solution of sodium ethoxide with stirring. The mixture was cooled to 0 °C and **9** (4 mmol) was added to it. The reaction mixture was stirred for 1 h at 0 °C and for 24 h at room temperature to give 6-deoxy-6-[alkylthio (or arylthio)]-α-D-glucopyranoside (**10a**—**d**).

Methyl 6-Deoxy-6-(*p*-tolylthio)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (10a): 69% yield; colorless syrup; ^{1}H NMR (CDCl$_3$) δ=2.24 (3H, s), 3.32 (3H, s), 2.67—5.04 (7H, m), 4.38—5.04 (6H, m), 6.92 and 7.14 (4H, A$_2$B$_2$, J=8.4 Hz), 7.20 (15H, br-s); [α]D+22.3° (*c* 1.73, CHCl$_3$); MS, *m/z* 570 (M$^+$); Calcd for C$_{35}$H$_{38}$O$_5$S: C, 73.68, H, 6.72%. Found: C, 73.53, H, 6.79%.

Methyl 6-Deoxy-6-(*p*-nitrophenylthio)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (10b): 86% yield; colorless syrup; ^{1}H NMR (CDCl$_3$) δ=3.13—3.93 (6H, m), 3.28 (3H, s), 4.41—4.90 (6H, m), 5.06 (1H, d, J=3.6 Hz), 6.98 and 7.90 (4H, A$_2$B$_2$, J=8.4 Hz), 7.20 (15H, br-s); [α]D+24.1° (*c* 3.52, CHCl$_3$); MS, *m/z* 601 (M$^+$); HRMS, Calcd for C$_{34}$H$_{35}$O$_7$NS: M, 601.2132. Found: *m/z* 601.2238.

Methyl 6-Deoxy-6-(*p*-chlorophenylthio)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (10c): 96% yield; colorless syrup; ^{1}H NMR (CDCl$_3$) δ=2.60—3.96 (6H, m), 3.23 (3H, s), 3.32—4.73 (6H, m), 4.93 (1H, d, J=3.8 Hz), 7.00—7.10 (19H, m); [α]D+29.6° (*c* 1.95, CHCl$_3$); MS, *m/z* 590 (M$^+$); HRMS, Calcd for $C_{34}H_{35}O_5SCl$: M, 590.1892. Found: m/z 590.1938.

Methyl 6-Deoxy-6-(methylthio)-2,3,4-tri-*O*-benzyl-*α*-D-glucopyranoside (10d): 89% yield; colorless syrup; ^{1}H NMR ($CDCl_3$) δ=2.02 (3H, s), 2.32—2.83 (2H, m), 3.05—3.97 (3H, m), 3.29 (3H, s), 4.37—4.75 (7H, m), 4.92 (1H, d, J=4.0 Hz), 7.07 (10H, br-s), 7.12 (5H, br-s); $[\alpha]_D$+36.4° (c 5.77, $CHCl_3$); MS, m/z 494 (M^+); HRMS, Calcd for $C_{29}H_{34}O_5S$: M, 494.2126. Found: m/z 494.2153.

Methyl 6-Deoxy-6-(ethylthio)-2,3,4-tri-*O*-benzyl-*α*-D-glucopyranoside (10e): 92% yield; colorless syrup; ^{1}H NMR ($CDCl_3$) δ=1.33 (3H, t, J=6.4 Hz), 2.37—2.87 (2H, m), 2.56 (2H, q, J=6.4 Hz), 3.68 (3H, s), 3.20—4.12 (3H, m), 4.83—4.47 (7H, m), 5.05 (1H, d, J=4.2 Hz), 7.23 (5H, s), 7.27 (10H, s); $[\alpha]_D$+40.0° (c 1.63, $CHCl_3$); MS, m/z 507 (M^+-1); HRMS, Calcd for $C_{30}H_{35}O_5S$ (M^+-1): 507.2204. Found: m/z 507.2208.

General Synthetic Procedure for Alkylaryl- and Dialkylsulfonium Salts Containing a Sugar Group (1a—k). To a mixture of silver perchlorate (2.5 g, 12 mmol) and sulfide **10** (12 mmol) in acetonitrile (15 cm^3) was added slowly an acetonitrile solution (5 cm^3) of alkyl iodide (60 mmol) at 0 °C. The mixture was stirred for 2 days at room temperature to give perchlorate salts of alkylaryl- and dialkylsulfonium containing sugar group (**1a**—**k**).

Perchlorate Salt of Methyl 6-Deoxy-6-(dimethylsulfonio)-2,3,4-tri-*O*-benzyl-*α*-D-glucopyranoside (1a): 90% yield; colorless syrup; ^{1}H NMR ($CDCl_3$) δ=2.72 (3H, s), 2.81 (3H, s), 3.33 (3H, s), 3.17—4.07 (6H, m), 4.40—5.03 (7H, m), 7.23 (15H, br-s); $[\alpha]_D$+59.5° (c 2.55, $CHCl_3$). **1b**: 73% yield; colorless syrup; ^{1}H NMR ($CDCl_3$) δ=1.32 (3H, t, J=7.2 Hz), 1.36 (3H, t, J=7.2 Hz), 3.11—4.09 (10H, m), 3.33 (3H, m), 4.23—5.10 (7H, m), 7.23 (15H, br-s); $[\alpha]_D$+31.9° (c 8.63, $CHCl_3$). **1c**: 99% yield; Mp 131—132 °C; ^{1}H NMR ($CDCl_3$) δ=1.30 (3H, t, J=7.0 Hz), 2.73 (3H, s), 3.10—4.07 (8H, m), 3.30 (3H, s), 4.37—4.87 (6H, m), 4.93 (1H, d, J=6.6 Hz), 7.22 (15H, br-s); $[\alpha]_D$+58.9° (c 1.0, $CHCl_3$); Calcd for $C_{31}H_{39}O_9SCl$: C, 59.74, H, 6.32%. Found: C, 59.97, H, 6.71%. **1d**: 86% yield; colorless syrup; ^{1}H NMR (acetone-d_6) δ=2.40 (3H, s), 3.28 (3H, s), 3.37 (3H, s), 3.50—4.98 (13H, m), 7.20 (15H, br-s), 7.46 and 7.90 (4H, A_2B_2, J=8.4 Hz); $[\alpha]_D$+55.6° (c 1.18, acetone). **1e**: 82% yield; colorless syrup; ^{1}H NMR (acetone-d_6) δ=3.23 (1.5H, s), 3.29 (1.5H, s), 3.33 (3H, s), 3.15—4.20 (6H, m), 4.35—5.12 (7H, m), 7.15 (15H, br-s), 7.92 and 8.26 (4H, A_2B_2, J=8.0 Hz); $[\alpha]_D$+39.1° (c 1.08, acetone). **1f**: 91% yield; colorless syrup; ^{1}H NMR ($CDCl_3$) δ=1.20 (3H, t, J=7.2 Hz), 2.42 (3H, s), 3.23 (3H, s), 3.30—5.00 (15H, m), 7.22 (15H, br-s), 7.30 and 7.60 (4H, A_2B_2, J=8.2 Hz); $[\alpha]_D$+43.4° (c 2.17, acetone). **1g**: 68% yield; colorless syrup; ^{1}H NMR ($CDCl_3$) δ=1.52 (3H, t, J=8.0 Hz), 3.28 (3H, s), 3.13—4.16 (8H, m), 4.33—5.10 (7H, m), 7.13 (15H, br-s), 7.90 and 8.23 (4H, A_2B_2, J=8.0 Hz); $[\alpha]_D$+54.0° (c 1.04, acetone). **1h**: 99% yield; colorless syrup; ^{1}H NMR ($CDCl_3$) δ=2.38 (3H, s), 3.17 (3H, s), 3.13—4.00 (6H, m), 4.16—4.87 (9H, m), 5.33—5.60 (3H, m), 6.93 and 7.61 (4H, A_2B_2, J=8.0 Hz), 7.20 (15H, br-s); $[\alpha]_D$+38.3° (c 3.39, acetone). **1i**: 75% yield; colorless syrup; ^{1}H NMR ($CDCl_3$) δ=3.13 (1.5H, s), 3.21 (1.5H, s), 3.31—4.17 (6H, m), 4.27—5.03 (9H, m), 7.07—7.67 (24H, m); $[\alpha]_D$+17.3° (c 8.5, $CHCl_3$). **1j**: 85% yield; colorless syrup; ^{1}H NMR ($CDCl_3$) δ=2.38 (3H, s), 3.25 (3H, s), 3.47—4.97 (15H, m), 7.10—7.33 (20H, m), 7.45 and 7.88 (4H, A_2B_2, J=8.4 Hz); $[\alpha]_D$+38.2° (c 2.31, $CHCl_3$). **1k**: 92% yield; colorless syrup; ^{1}H NMR ($CDCl_3$) δ=3.19 (3H, s), 3.16—4.03 (7H, m), 4.17—5.10 (8H, m), 5.31—5.61 (3H, m), 6.95—7.80 (19H, m); $[\alpha]_D$+42.3° (c 1.53, $CHCl_3$).

General Procedure for Asymmetric Alkylation of *β*-Keto Ester 2 (or 5) with 1. A mixture of alkylsulfonium salts **1** (1 mmol), *β*-keto ester **6** (or **8**) (1 mmol) and anhydrous potassium carbonate (1.3 mmol) was stirred in dry dichloromethane (10 cm^3) at room temperature for 3 days. After filtration of insoluble materials, the alkylated products of the *β*-keto ester were purified by column chromatography (silica gel) and GPC. The optical purity and the absolute configuration were determined by ^{1}H NMR analysis for compound **3b** in the presence of chiral shift reagent (Eu(hfc)$_3$) and by HPLC analysis for compound **3a**, using an optically active column (DAICEL CHEMICAL CHIRALCEL CA-1; methanol as eluent): the results are listed in Table 1. The structures of **6a** and **6b** were determined on the basis of the following spectroscopic data and their optical purity and absolute configuration were determined in comparison with authentic samples.[6]

Ethyl 2-Benzyl-2-methylacetoacetate (6a); ^{1}H NMR ($CDCl_3$) δ=1.18 (3H, s), 1.18 (3H, t, J=7.0 Hz), 2.03 (3H, s), 3.03 (2H, d, J=5.0 Hz), 4.06 (2H, q, J=7.0 Hz), 6.90—7.23 (5H, m); MS, m/z 234 (M^+); HRMS, Calcd for $C_{14}H_{18}O_3$: M, 234.1255. Found: m/z 234.1248.

Ethyl 2-Allyl-2-methylacetoacetate (6b); ^{1}H NMR ($CDCl_3$) δ=1.23 (3H, s), 1.25 (3H, t, J=7.0 Hz), 2.03 (3H, s), 2.45 (2H, d, J=6.4 Hz), 4.03 (2H, q, J=7.0 Hz), 4.77—5.90 (3H, m); MS, m/z 184 (M^+); HRMS, Calcd for $C_{10}H_{16}O_3$: M, 184.1099. Found: m/z 184.1069.

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5) The direct alkylation of **2** using the AdoMet (*S*-adenosyl-5′-L-methionine sulfate, *p*-toluenesulfonate (from Yeast), purchased from Tokyo Kasei Kogyo Co., Ltd.) was examined under similar conditions (K_2CO_3, dimethyl sulfoxide). However, no alkylation product corresponding to **3** was obtained.

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7) Ethylmethylsugarsulfonium salt (**1c**) ($[\alpha]_D$+42.4° (c 2.8, $CHCl_3$)) was obtained as crystals and the salt was recrystallized from acetonitrile–ether several times to give the optically active sulfonium salt on the sulfonium sulfur atom ($[\alpha]_D$+58.9° (c 1.0, $CHCl_3$)); d.e. 86% determined by ^{1}H NMR (300 MHz, $CDCl_3$) analysis of sulfonium salt **5c**: the diastereomeric methyl groups on the sulfonium sulfur atom were observed at δ 2.78 and 2.86 and the ratio of diastereomeric methyl groups is 7:93. However, the absolute configuration was not yet determined. The alkylation of **2** with optically active sulfonium salt **5c** (d.e. 86%) under the similar conditions (K_2CO_3, CH_2Cl_2) gave the *C*-methylated product (*R*)-(+)-**3a** (56% yield; o.p. 19.8%) and the *C*-ethylated product (*R*)-(+)-**3b** (21% yield; o.p. 12.6%).

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