Stereochemistry of Nucleophilic Addition Reactions. 5. Formation of Stabilized Ylides from Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside with Some *S*-Ylides; An Important Role of the Nitro Group for Stabilization of the Ylides[1]

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Treatment of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside (**1**) with dimethyloxosulfonium methylide and dimethylsulfonium α-methylphenacylide afforded cyclopropane derivatives, whereas similar reactions with dimethylsulfonium phenacylide and dimethylsulfonium ethoxycarbonylmethylide gave stabilized ylides. In all cases the *S*-ylides enter the C-2 position of **1** from the side trans to the anomeric methoxyl group. The ylide structures were determined from IR and NMR data and confirmed by transformation into the desulfurized products. Anomalous stability of these ylides are attributed to the delocalization of the negative as well as positive charge over the carbonyl and the nitro group, respectively.

Only one example[2] is known of the reactions of nitro olefin with *S*-ylides (dimethyloxosulfonium methylide), in which cyclopropane derivatives are exclusively formed. Our studies[3] on the nucleophilic addition reaction to methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside (**1**) and its α-anomer and related subjects[4] strongly suggest that under kinetically controlled conditions nucleophiles approach from the equatorial side in the β-series,[5] but predominantly from the axial side in the α-series. In order to confirm the surmise we have carried out the reactions of **1** and its α-anomer with some *S*-ylides; these seem to be controlled kinetically.[6] We wish to report the reactions of **1** with *S*-ylides in this paper.

Results and Discussion

Treatment of **1** with dimethyloxosulfonium methylide in DMSO at room temperature for 1 h gave methyl (2*R*,3*R*)-4,6-*O*-benzylidine-2,3-dideoxy-2,3-*C*-methylene-3-nitro-β-D-*erythro*-hexopyranoside (**2**) in 75% yield. The configuration of **2** was assigned from the values of $J_{1,2}=0$ Hz, indicating that the conformation of **2** is similar to that of methyl 2,3-anhydro-4,6-*O*-benzylidene-3-nitro-β-D-allopyranoside.[7,4a]

On the other hand, when **1** was treated with dimethylsulfonium phenacylide in THF at room temperature for 18 h, methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-[α-(dimethylsulfuranylidene)phenacyl]-3-nitro-β-D-glucopyranoside (**3**) was obtained in 78% yield instead of a cyclopropane derivative. The structure of **3** was determined by the following data: i) molecular ion peak *m/e* 473 was observed, ii) its IR spectrum (KBr) showed absorption bands due to a characteristic carbonyl group of ylide species[8] at 1505 cm^{-1} and due to a nitro group at 1555 cm^{-1}, iii) the NMR spectrum revealed the presence of a α-(dimethylsulfuranylidene)-phenacyl group (5-H of phenyl and 6-H of SMe_2) and *gluco* configuration for **3** ($J_{1,2}=7.5$ and $J_{2,3}=J_{3,4}=10$ Hz), iv) catalytic desulfurization over Pd/C afforded quantitatively methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-2-*C*-phenacyl-β-D-glucopyranoside (**5**), accompanied by the odor of dimethyl sulfide, whose *gluco* configuration was deduced from the values of $J_{1,2}=7.5$ and $J_{2,3}=J_{3,4}=10$ Hz.

A similar stabilized ylide **4** was prepared in 75% yield by treating **1** with dimethylsulfonium ethoxycarbonylmethylide in THF at room temperature for 18 h. The results of elemental analysis fit the formula $C_{20}H_{27}NO_8S$, which is confirmed by the molecular ion peak *m/e* 441.

TABLE 1. CHEMICAL SHIFTS (δ) AT 100 MHz IN CHLOROFORM-*d* (Me_4Si as internal standard)

Compd.	H-1	H-2	H-3	H-4	H-5	H-6a	H-6e	H–C[a]	H–C′[a]
2	4.52(s)	2.28(t)		4.96(d)	2.99(six)	3.75(t)	4.23(q)	2.28(t)[b]	1.64(t)[c]
3	5.37(d)	2.60(q)	6.20(t)	←	4.4—3.7	→		—	—
4	4.96(d) 4.71(d)	3.6—3.5 (m)	5.81(t) 5.40(t)	4.09(t)	4.06(six)	3.74(t)	4.40(q)	—	—
5	4.82(d)	2.68(m)	5.23(q)	4.18(t)	3.62(six)	3.83(t)	4.36(q)	3.24(d)	3.07(d)
6	4.65(d)	2.7—2.3 (m)	5.02(t)	4.15(t)	3.52(six)	3.82(t)	4.37(q)	← 2.3—2.7 →	
7	5.77(d)	2.57(d)	—	4.64(d)	3.15(six)	3.68(t)	4.24(q)	—	—
9	5.13(s)	—	2.64(q)	3.52(q)	3.41(six)	3.68(t)	4.24(q)	2.34(d)	—

a) The methine or methylene proton(s) of a chain or cyclopropane moiety. b) Exo proton of the cyclopropane ring, assigned by the presence of long range coupling ($J_{exo,4}=1.2$ Hz) due to "W-orientation." c) Endo proton of the cyclopropane ring.

TABLE 2. FIRST-ODER COUPLING CONSTANTS (Hz) MEASURED AT 100 MHz IN CHLOROFORM-*d*

Compd	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6e}$	$J_{6a,6e}$	
2	0	—	—	10	10	5.0	10	$J_{2,c}=J_{2,c'}=J_{c,c'}=6.0$
3	7.5	10	10					
4	7.5	10	10	10	10	5.0	10	
5	8.4	11.6	10	8.8	10	4.4	10	$J_{2,c}=J_{2,c'}=4.4$
6	7.5	10	10	10	10	5.0	10	
7	1.3	—	—	10	10	5.0	10	
9	0	—	1.5	9.4	9.4	4.4	9.4	$J_{3,c}=6.9$

The IR spectrum (KBr) showed the presence of an ester carbonyl group of ylide species[8] (1615 cm^{-1}) and a nitro group (1560 cm^{-1}). Catalytic desulfurization of **4** to **6** also supports the structure of **4**. The NMR spectrum of **4** shows a pattern quite different from that of **3**, indicating that compound **4** consists of two geometrical isomers (Fig. 1), formed by the restricted rotation about the C(ylide)–C(carbonyl) bond, in an approximately 1 : 1 ratio; the appearance of two doublets (at δ 4.96 and 4.71) and two triplets (at δ 5.81 and 5.40) due to H-1 and H-3, respectively, at 20 °C in $CDCl_3$. With respect to the sugar moiety, they have the same *gluco* configuration with the same $^4C_1$ conformation because of the same values for their coupling constants, $J_{1,2}=7.5$ and $J_{2,3}=J_{3,4}=10$ Hz, as well as the exclusive formation of **6** from **4**. The equilibrium of the isomers was studied by examining the temperature dependence of the NMR spectrum: At 90 °C the two doublets (H-1) and two triplets (H-3) collapse into broad singlets centered at δ 4.75 and 5.60, respectively. At 115 °C the former appears at δ 4.77 as a doublet and the latter at δ 5.48 as a triplet. A similar phenomenon was reported by Casanova, Jr. and Rutolo, Jr. concerning dimethylsulfonium methoxycarbonylmetflylide;[9] in NMR spectra, the methine proton signal, a sharp singlet at 45 °C, becomes a broad singlet at 0 °C and two singlets at −45 °C.

The formation of the different products according to the ylides used might be explained as follows. An intermediate zwitterion arising from the nucleophilic addition of the anionic center of the ylide to the C-2 position of the nitro olefin **1** should collapse to cyclopropane. However, if an acidic hydrogen atom was present on the ylide carbon atom, the proton shift predominates over the cyclopropanation giving the stabilized ylides. In fact the reaction of **1** with dimethylsulfonium α-methylphenacylide, bearing no available hydrogen atom, afforded the cyclopropane **7** in 71% yield. The cyclopropane structure for **7** was determined by comparison of its IR and NMR spectra with those of **2**. From the steric ground the benzoyl group on the cyclopropane ring seems to occupy the exo position and the methyl the endo position. However, no definite assignment has been established.

Ylides **3** and **4** are extremely stable as compared with the usual ylides having one anion stabilizing group such

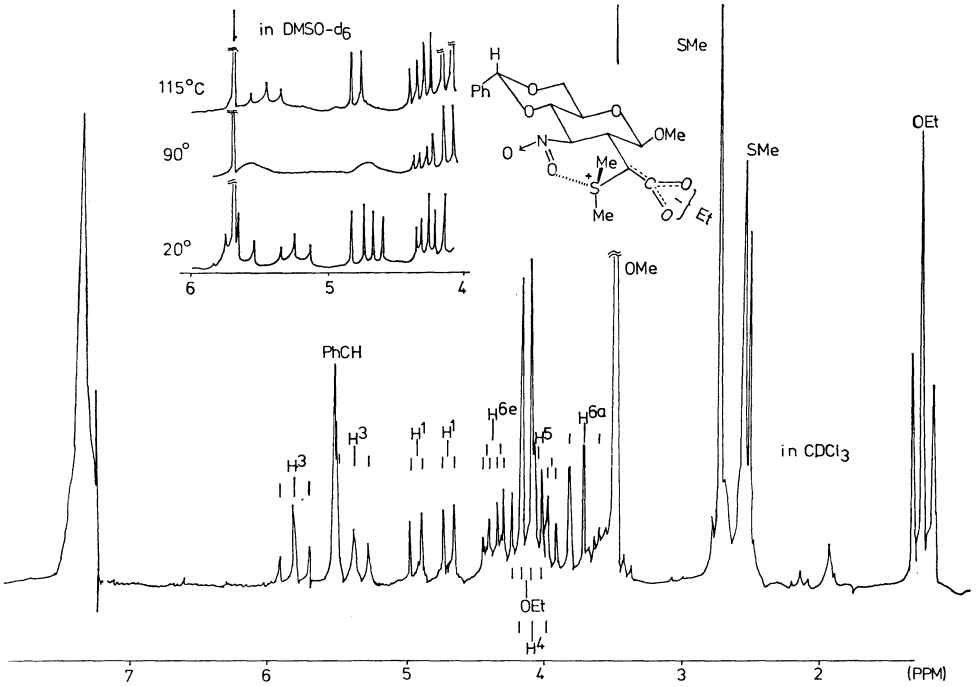
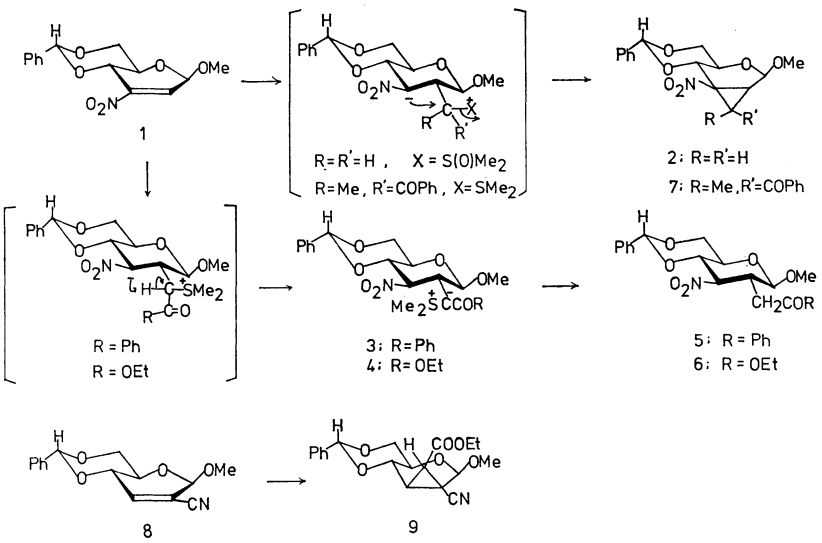


Fig. 1. The NMR spectrum of the stabilized ylide **4** (in $CDCl_3$, 100 MHz), the partial NMR spectra of **4** under the elevated temperature (in DMSO-d_6, 100 MHz), and the most plausible structure of **4**.



as carbonyl; *e.g.* the molecular ion peaks appear in EI-mass spectra, no change being observed on keeping the samples in open vessels at room temperature for 2 years or on treatment with silica gel column chromatograph. The anomalous stability of ylides **3** and **4** cannot be explained only in terms of the delocalization of negative charge over a ethoxycarbonyl or a carbonyl group. The most satisfactory explanation is based on the delocalization of the positive charge on the sulfur atom over the nitro group orientated in a suitable position to form the π_d–π_p bond with the sulfur atom through a stable six-membered ring system (Fig. 1).

This surmise was chemically supported. The reaction of methyl 5-*O*-benzoyl-2,3-dideoxy-3-nitro-β-D-*glycero*-pent-2-enofuranoside[10] with dimethylsulfonium ethoxycarbonylmethylide afforded complicated results, the isolation of products being unsuccessful. However, the NMR spectrum of the crude reaction mixture showed the absence of dimethylsulfonium moiety, indicating no formation of a stabilized ylide corresponding to **4**. This is reasonable if the formation of a stabilized ylide requires the delocalization of both the negative and positive charges, the latter being sterically impossible in the 2,3-*trans* furanose system. The reaction of methyl 4,6-*O*-benzylidene-2-cyano-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranoside (**8**)[3,4c] with dimethylsulfonium ethoxycarbonylmethylide afforded a mixture of three compounds,at least, from which the cyclopropane derivative **9** and the starting material **8** were isolated in 23 and 10% yield, respectively. During column chromatography on silica gel, generation of dimethyl sulfide was detected by its smell, suggesting the formation of a ylide corresponding to **4** and its much less stability as compared with that of **4**. Such an interaction of the linear cyano group with the sulfur atom of the ylide is stericall difficult. The cyclopropane structure for **8** was determined from the results of elemental analsysis, IR (CN at 2250 and CO at 1725 cm^{-1}) and NMR spectra (presence of cyclopropane ring protons at δ 2.34 and 2.64; $J_{3,4}$= 1.6 Hz).

Experimental

Melting points were determined in capillaries and are uncorrected. IR spectra were recorded on KBr discs for crystals and on NaCl plates for syrup. NMR spectra were determined for solutions in chloroform-*d* (tetramethylsilane as internal standard) with a JNM-4H-100 (JEOL) spectrometer. Solutions were evaporated under reduced pressure.

*Methyl (2*R*,3*R*)-4,6-O-Benzylidene-2,3-dideoxy-2,3-*C*-methylene-3-nitro-β-*D*-*erythro*-hexopyranoside (2).* A solution of the ylide was prepared from 440 mg of sodium hydride (over 55% purity), 2.64 g (12 mmol) of trimethyloxosulfonium iodide and 6 ml of DMSO.[11] A solution of 2.93 g (10 mmol) of **1**[12] in 10 ml of DMSO was added with stirring. The mixture was stirred at room temperature for 1 h and poured into 50 ml of cold water. The precipitate was separated and washed with water and recrystallized from ethanol to give 2.3 g (72%) of **2**: Mp 147.5—148.0 °C; $[\alpha]_D^{20}$ −44.2° (*c* 1, $CHCl_3$); IR 1550 (NO_2) cm^{-1}.

Found: C, 58.63; H, 5.74; N, 4.72%. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56%.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-2-C-[α-(dimethylsulfuranylidene)phenacyl]-3-nitro-β-D-glucopyranoside (3). To a solution of **1** (293 mg, 1 mmol) in distd THF (15 ml) was added dimethylsulfonium phenacylide[13] (270 mg, 1.5 mmol) at 0 °C. The mixture was kept for 18 h, the organic solvent being evaporated. The remaining solid was washed with water and recrystallized from ethanol–acetone to give 383 mg (78%) of yellow-green crystals of **3**: Mp 157—158 °C; $[\alpha]_D^{20}$+28.8° (*c* 1, $CHCl_3$); IR 1555 (NO_2) and 1505 (CO) cm^{-1}.

Found: C, 59.03; H, 5.88; N, 2.82; S, 6.79%. Calcd for $C_{24}H_{27}NO_7S \cdot H_2O$: C, 58.64; H, 5.95; N, 2.85; S, 6.52%.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-2-C-[dimethylsulfuranylidene)ethoxycarbonylmethyl]-3-nitro-β-D-glucopyranoside (4). To a solution of **1** (586 mg, 2 mmol) in distd THF (15 ml) was added dimethylsulfonium ethoxycarbonylmethylide[14] (592mg, 4 mmol) at 0 °C. The mixture was stirred at the same temperature for 4 h, the organic solvent being evaporated. The remaining solid was washed with water and recrystallized from ethanol to give 661.5 mg (75%) of yellow-green crystals of **4**: Mp 165.5—166.0 °C; $[\alpha]_D^{20}$ +39.0° (*c* 1, $CHCl_3$); IR 1615 (COOEt) and 1560 (NO_2) cm^{-1}.

Found: C, 54.34; H, 6.12; N, 3.01; S, 7.24%. Calcd for $C_{20}H_{27}NO_8S$: C, 54.41; H, 6.16; N, 3.17; S, 7.26%.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-3-nitro-2-C-phenacyl-β-D-glucopyranoside (5). A solution of **4** (316 mg, 0.64 mmol) in methanol (20 ml) was hydrogenated in the presence of 10% Pd/C (200 mg). After 17 h, the catalyst was filtered off and the filtrate was evaporated and the residue was recrystallized from ethanol to give 250 mg (94%) of cotton-like, colorless crystals of **5**: Mp 173—174 °C; $[\alpha]_D^{20}$ −27.5° (*c* 1, $CHCl_3$); IR 1685 (CO) and 1550 (NO_2) cm^{-1}.

Found: C, 63.74; H, 5.75; N, 3.65%. Calcd for $C_{22}H_{23}NO_7$: C, 63.91%; H, 5.61; N, 3.39%.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-2-C-ethoxycarbonylmethyl-3-nitro-β-D-glucopyranoside (6). A solution of **4** (441 mg, 1 mmol) in methanol (20 ml) was hydrogenated in the presence of 10% Pd/C (250 mg). After 2 days, the catalyst was filtered off and the filtrate was evaporated. The residue was recrystallized from ethanol to afford 343 mg (90%) of colorless crystals of **6**: Mp 146—146.5 °C; $[\alpha]_D^{20}$ −46.6° (*c* 1, $CHCl_3$); IR 1730 (COOEt) and 1555 (NO_2) cm^{-1}.

Found: C, 56.65; H, 5.84; N, 3.94%. Calcd for $C_{18}H_{23}NO_8$: C, 56.68; H, 6.08; N, 3.67%.

*Methyl (2R,3S)-2,3-C-(1-Benzoylethylidene)-4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hexopyranoside (7).* Dimethylsulfonium α-methylphenacylide (640 mg, 3.3 mmol), prepared according to a similar method to that for the preparation of dimethylsulfonium ethoxycarbonylmethylide, was added to a solution of **1** (879 mg, 3 mmol) in distd THF (20 ml) at room temperature. The mixture was kept for 9 h and the solvent was evaporated, affording crystalline residue, which was recrystallized from ethanol–acetone to give 906 mg (71%) of colorless crystals of **7**: Mp 143—144 °C; $[\alpha]_D^{20}$ −68.0° (*c* 1, $CHCl_3$); IR 1690 and 1675 (CO) and 1550 (NO_2) cm^{-1}.

Found: C, 65.04; H, 5.47; N, 3.12%. Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29%.

*Methyl (2R,3R)-4,6-O-Benzylidene-2-cyano-2,3-C-(ethoxycarbonylmethylene)-2,3-dideoxy-β-D-*erythro*-hexopyranoside (9).* To a solution of **8**[3,4c] (400 mg, 1.47 mmol) in THF (10 ml) was added dimethylsulfonium ethoxycarbonylmethylide (245 mg, 1.66 mmol) at room temperature with stirring. The mixture was stirred for 4 h and the solvent was evaporated to give a syrup, which was washed with water. The NMR spectrum of the crude product revealed the presence of two products at least in an approximately 1.5: 1 ratio. After separation of starting material **8** (40 mg, 10% recovery), the syrup was chromatographed on silica gel (C-300, Wakogel) with benzene to afford 121.5 mg (23%) of **9**, whose NMR spectrum agreed with that of the major product: Mp 129—129.5 °C; $[\alpha]_D^{20}$ −72.3° (*c* 1, $CHCl_3$) IR 2250 (CN) and 1725 (COOEt) cm^{-1}.

Found: C, 63.58; H, 5.98; N, 4.10%. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90%.

Smell of dimethyl sulfide was detected during the course of column chromatography on silica gel. This suggests that the ylide formed corresponding to **4** was not stable in chromatographic separation.

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