

THE CHEMISTRY OF *o*-SILYLATED KETENE ACETALS; DIASTEREOSELECTIVE ALDOL
REACTION OF 2,3-O-ISOPROPYLIDENE-D (AND L)-GLYCERALDEHYDES
LEADING TO 2-DEOXY-D (AND L)-RIBOSES

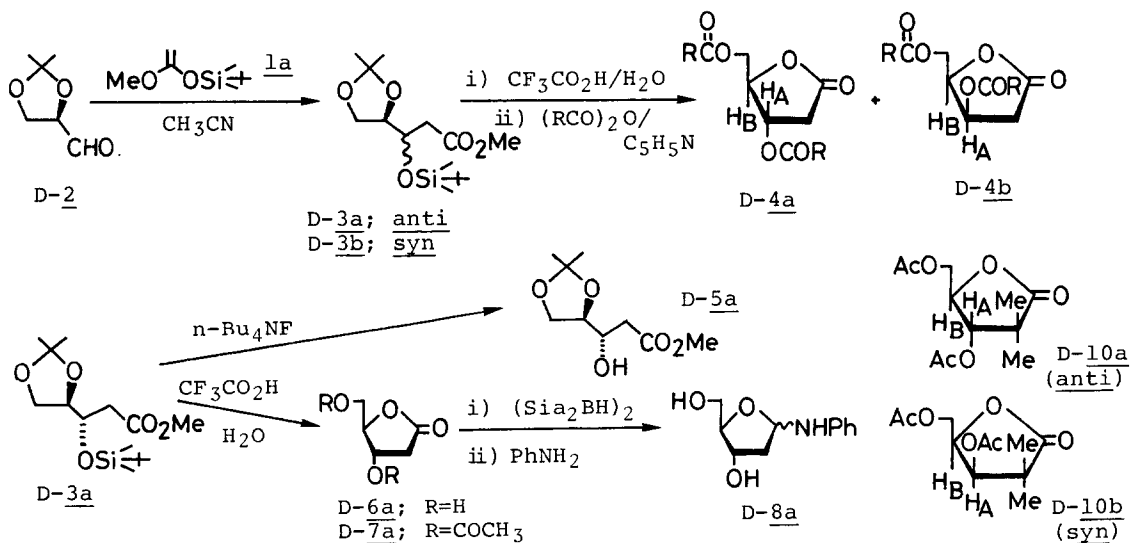
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Summary: Diastereoselective carbon-carbon bond forming reaction of 2,3-O-isopropylidene-D (and L)-glyceraldehydes (D and L-2) with ketene silyl acetals (1a,b) occurred in acetonitrile under mild conditions to give the corresponding anti- β -siloxyesters (D and L-3a) as major products, which could be converted through a few additional steps to 2-deoxy-D (and L)-riboses.

Considerable attention has been focused on the development of methodology for the aldol and the conjugate addition reactions of ketene silyl acetals under neutral or nearly neutral conditions¹ since we published² the regiospecific silyl enol ether formation by conjugate addition of ketene silyl acetals to α,β -unsaturated carbonyl compounds accompanied by a silyl group transfer in CH₃CN in the absence of catalyst.³ We report here the application of the silyl group transfer-addition reaction of ketene silyl acetals (1) in CH₃CN with the optically active carbonyl compounds, 2,3-O-isopropylidene-D (and L)-glyceraldehydes (2)⁴ which causes a highly asymmetric induction for the bond construction process to give the anti- β -siloxyesters (D and L-3a) as major products. These reactions were successfully applied to the stereoselective synthesis of 2-deoxy-D (and L)-riboses.

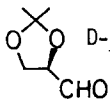
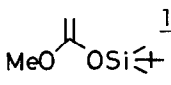
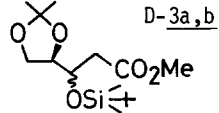
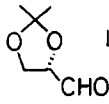
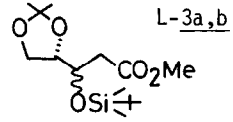
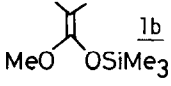
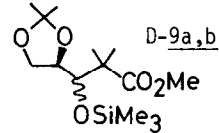
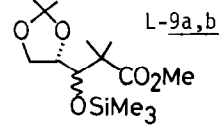
The starting material, 2,3-O-isopropylidene-D-glyceraldehyde (D-2), readily available from D-mannitol,⁵ was reacted with *o*-methyl-*o*-*t*-butyldimethylsilyl ketene acetal (1a) in CH₃CN at 70°C for 48h to give an 83:17 diastereomixture of the β -*t*-butyldimethylsiloxyesters (D-3a,b) in 73% yield as shown by gas chromatography (FID, butanediol succinate polyester) (run 1). The stereochemistry of the aldol addition of 1 to D-2 was extensively studied under various conditions (see Table 1), and the best result was obtained when the reaction was carried out at 0°C to room temperature (r.t.) for 48h in the presence of catalytic amounts of zinc iodide in CH₃CN (run 2). The diastereomixture was converted to the corresponding *O,O'*-diphenoxyacetyl-2-deoxy-D-ribo-1,4-lactones (D-4a,b) by deblocking with CF₃CO₂H-H₂O followed by phenoxyacetylation with phenoxyacetic anhydride in pyridine. The small *J*-value (D-4a, R=PhOCH₂, *J*=2 Hz) of the ¹H-NMR coupling constant between H_A and H_B obtained by its 2D COSY method and decoupling technique seems to indicate an anti (or erythro) stereostructure

for the major product (D-3a) compared with the reported J-values of the *anti*-0,0'-diacyl analogues (D-4a, R=Ph; J=2 Hz, D-4a, R=Me; J=1.75 Hz).⁶ The assignment of the structure was finally established by a direct way: The mixture of diastereomers (D-3a,b, *anti*/*syn*=93/7) was separated by column chromatography on silica gel with n-hexane:ether (10:1) as an eluting solvent to give the pure D-3a and D-3b {D-3a; $[\alpha]_D^{22} = -3.3^\circ$ (c 1.21, CH₂Cl₂), D-3b; $[\alpha]_D^{22} = +35^\circ$ (c 0.736, CH₂Cl₂)}. Desilylation of D-3a with n-Bu₄NF in THF at r.t. for 0.5h gave a 92% yield of the β-hydroxyester (D-5a) { $[\alpha]_D^{24} = -11.5^\circ$ (c 0.755, CH₂Cl₂), lit.⁷ $[\alpha]_D^{24} = -11.2^\circ$ (c 0.602, CH₂Cl₂)}. Furthermore, the ester (D-3a) was deblocked with CF₃CO₂H-H₂O at r.t. for 3h to give a quantitative yield of 2-deoxy-D-ribo-1,4-lactone (D-6a), which was acetylated with Ac₂O-DMAP (0.46 equiv) in pyridine at r.t. overnight to give the diacetate (D-7a) { $[\alpha]_D^{25} = -5.2^\circ$ (c 0.929, EtOH), lit.⁶ $[\alpha]_D^{25} = -5.2^\circ$ (c 0.93, EtOH)}. All these spectral and physical data are in good accordance with those of the corresponding *anti*-derivatives. Reduction of D-6a by disiamylborane [(Sia)₂BH₂] in THF at r.t. for 22h followed by treatment with aniline in EtOH-H₂O at 5°C overnight gave a 66% yield of the known 2-deoxy-D-ribose anilide (D-8a) {mp 167-167.5°; $[\alpha]_D^{20} = +57^\circ$ (after 30h, c 0.873, pyridine), lit.⁸ mp 167-169°; $[\alpha]_D^{20} = +56^\circ$ (after 30h, c 0.99, pyridine)}. Similarly, reaction of 2,3-O-isopropylidene-L-glyceraldehyde (L-2), obtained from readily available L-arabinose,⁹ with 1a gave a diastereomixture of the β-t-butylidimethylsilyloxyesters (L-3a,b) in a similar high diastereoselectivity (runs 7 and 8). The separated siloxyester {L-3a; $[\alpha]_D^{22} = +3.4^\circ$ (c 0.990, CH₂Cl₂)} was readily converted to 2-deoxy-L-ribose anilide (L-8a) {mp 167-168°, $[\alpha]_D^{20} = -56^\circ$ (after 38h, c 0.686, pyridine)} in 64% overall yield from L-3a by a series of reactions mentioned in D-series. The present synthetic method for 2-deoxy-D (and L)-riboses is advantageous over the reported methods^{7,8,10,11} in terms of high asymmetric induction, ease of performance and work-up, short reaction step, and high overall yield of the product.



We also investigated the reaction of D and L-2 with the O-methyl-O-trimethylsilyl ketene acetal (1b) under similar conditions, which proceeded erythro-selectively to give a diastereomixture of the corresponding β -trimethylsilyloxyesters (D-9a,b and L-9a,b). These results are listed in Table I.

Table I Aldol Reaction of 2,3-O-Isopropylidene-D (and L)-glyceraldehydes

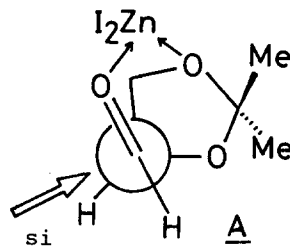
Run	Aldehydes	Ketene Silyl Acetals	Reaction Conditions ^a	Yield ^b (%)	Products	Diastereo-Selectivity <u>anti:syn</u>
1	 D- <u>2</u>	 <u>1a</u>	no catalyst, 70°C, 48h	73	 D- <u>3a,b</u>	83:17
2	"	"	0.05eq ZnI ₂ , 0°C→r.t., 48h	69	"	93:7
3	"	"	1eq ZnI ₂ , r.t.→50°C, 48h	36	"	93:7
4	"	"	0.05eq ZnBr ₂ , 0°C→r.t., 48h	39	"	85:15
5	"	"	0.05eq ZnCl ₂ , 0°C→r.t., 48h	44	"	88:12
6	"	"	0.05eq ZrCl ₄ (CH ₃ CN:CH ₂ Cl ₂ =1:1), 0°C→r.t., 48h	13	"	95:5
7	 L- <u>2</u>	"	no catalyst, 70°C, 48h	69	 L- <u>3a,b</u>	85:15
8	"	"	0.05eq ZnI ₂ , 0°C→r.t., 48h	67	"	96:4
9	D- <u>2</u>	 <u>1b</u>	no catalyst, 70°C, 48h	65	 D- <u>9a,b</u>	75:25 ^c
10	"	"	0.05eq ZnI ₂ , 0°C→r.t., 48h	79	"	90:10 ^c
11	L- <u>2</u>	"	no catalyst, 70°C, 48h	62	 L- <u>9a,b</u>	77:23 ^c
12	"	"	0.05eq ZnI ₂ , 0°C→r.t., 48h	70	"	91:9 ^c

a) The use of catalytic amounts of other Lewis acids such as SnCl₄, AlCl₃, TiCl₄, BF₃·Et₂O, MgBr₂, and FeCl₃ in CH₃CN gave no satisfactory result. b) Distilled yields are given. c) The stereochemistry is tentatively assigned by the comparison of the chemical shift and the coupling constant of H_A of 0,0'-diacetyl-2-deoxy-D (and L)-ribo-1,4-lactones (D and L-10) with those of the related anti and syn diastereomers.¹⁰

The possibility of epimerization under the reaction conditions was examined by careful ¹H NMR study of the 0,0'-diacetyl- γ -lactones (D and L-10a) readily obtained from the aldol adducts (D and L-9a), by using Eu(tfc)₃ as the chiral shift reagent: The methine doublet

(H_A) at δ 5.33 ppm ($J=3.8$ Hz) of racemic 10a (1:1 mixture of D and L-10a) shifted to two doublets at δ 5.98 and δ 6.03 ppm in contrast to the fact that the optically active D-10a shifted the resonance only to δ 5.98 ppm (no detectable peak at δ 6.03 ppm) and L-10a only to δ 6.03 ppm (no detectable peak at δ 5.98 ppm). These results clearly show that epimerization was not observed in the present reaction of 1 with 2.

The observed diastereoselection may arise from the si face addition via a Felkin-Anh type transition state.¹² The enhancement of the anti-selectivity in the presence of zinc iodide can be explained by a chelate with β -oxygen as in the transition state (A): The re face of the aldehyde becomes much more crowded than the si face.



References and Notes

- 1) R. A. Bunce, M. F. Schlecht, W. G. Dauben, and C. H. Heathcock, *Tetrahedron Lett.*, **24**, 4943 (1983); Y. Yamamoto, K. Maruyama, and K. Matsumoto, *J. Chem. Soc. Chem. Commun.*, **1983**, 489; Idem, *Tetrahedron Lett.*, **25**, 1075 (1984); O. W. Webster, W. R. Hertler, D. Y. Sogah, W. B. Farnham, and T. V. RajanBabu, *J. Am. Chem. Soc.*, **105**, 5706 (1983); T. V. RajanBabu, *J. Org. Chem.*, **49**, 2083 (1984); J. Jurczak and S. Pikuł, *Tetrahedron Lett.*, **25**, 3107 (1984).
- 2) Y. Kita, J. Segawa, J. Haruta, T. Fujii, and Y. Tamura, *ibid.*, **21**, 3779 (1980); Y. Kita, J. Segawa, J. Haruta, H. Yasuda, and Y. Tamura, *J. Chem. Soc. Perkin I*, **1982**, 1099. Very recently, we reported the Pummerer rearrangement of sulfoxides into α -siloxy sulfides by utilizing ketene silyl acetals under similar conditions: Y. Kita, H. Yasuda, O. Tamura, F. Itoh, and Y. Tamura, *Tetrahedron Lett.*, **25**, 4681 (1984); Idem, *Chem. Pharm. Bull.*, in press.
- 3) Lewis acid-mediated conjugated addition of silyl enol ethers or ketene silyl acetals to α,β -unsaturated compounds has been reported by Mukaiyama and co-workers: K. Narasaka, K. Soai, Y. Aikawa, and T. Mukaiyama, *Bull. Chem. Soc. Jap.*, **49**, 779 (1976); K. Saigo, M. Osaki, and T. Mukaiyama, *Chem. Lett.*, **1976**, 163. Recent studies on the Lewis acid mediated aldol addition of ketene silyl acetals, see: T. H. Chan, T. Aida, P. W. K. Lau, V. Gorys, and D. N. Harpp, *Tetrahedron Lett.*, **1979**, 4029; G. Wenke, E. N. Jacobsen, G. E. Totten, A. C. Karydas, and Y. E. Rhodes, *Synth. Commun.*, **13**, 449 (1983); M. T. Reetz, K. Kesseler, and A. Jung, *Tetrahedron Lett.*, **25**, 729 (1984); C. H. Heathcock, K. T. Hug, and L. A. Flippin, *ibid.*, **25**, 5973 (1984); B. D. Gray and J. D. White, *J. Chem. Soc. Chem. Commun.*, **1985**, 20; C. H. Heathcock and S. H. Montgomery, *Tetrahedron Lett.*, **26**, 1001 (1985); Y. Tomo and K. Yamamoto, *ibid.*, **26**, 1061 (1985).
- 4) 2,3-O-Isopropylidene-D (or L)-glyceraldehyde has become an extremely valuable chiral building block for carbohydrate synthesis. For a review, see: G. J. McGarvey, M. Kimura, T. Oh, and J. M. Williams, *J. Carbohyd. Chem.*, **3**, 125 (1984). Recent studies, see: C. Papageorgiou and C. Benezra, *J. Org. Chem.*, **50**, 157 (1985); J. T. Welch and S. Eswarakrishnan, *J. Chem. Soc. Chem. Commun.*, **1985**, 186; K. Mead and T. L. Macdonald, *J. Org. Chem.*, **50**, 422 (1985).
- 5) E. Baer and H. O. L. Fischer, *J. Am. Chem. Soc.*, **61**, 761 (1939); J.-L. Debost, J. Gelas, and D. Horton, *J. Org. Chem.*, **48**, 1381 (1983).
- 6) It has been reported that the erythro-isomer of O-benzoyl and O-acetyl-2-deoxy-D-ribo-1,4-lactones have the smaller coupling constants ($J=2$ and 1.75 Hz) than those ($J=4.6$ and 4.75 Hz) of threo-isomers: K. Bock, I. Lundt, and C. Pedersen, *Carbohyd. Res.*, **90**, 17 (1981); B. Rague, Y. Chaleur, and B. Castro, *J. Chem. Soc. Perkin I*, **1982**, 2063.
- 7) A. P. Kozikowski and A. K. Ghosh, *J. Org. Chem.*, **49**, 2762 (1984).
- 8) M. Murakami and T. Mukaiyama, *Chem. Lett.*, **1982**, 241; G. Nakaminami, S. Shioi, Y. Sugiyama, S. Isemura, M. Shibuya, and M. Nakagawa, *Bull. Chem. Soc. Jap.*, **45**, 2624 (1972).
- 9) S. B. Baker, *J. Am. Chem. Soc.*, **74**, 827 (1952).
- 10) T. Shono, N. Kise, and T. Suzumoto, *ibid.*, **106**, 259 (1984).
- 11) C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, and D. VanDerveer, *J. Org. Chem.*, **45**, 3846 (1980); T. Harada and T. Mukaiyama, *Chem. Lett.*, **1981**, 1109; J. Mulzer, M. Kappert, G. Huttner, and I. Jibril, *Ang. Chem. Int. Ed. Engl.*, **23**, 704 (1984).
- 12) M. Chérest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, **1968**, 2199; N. T. Anh and O. Eistenin, *Nov. J. Chim.*, **1**, 61 (1977).

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