Pergamon

Tetrahedron Letters, Vol. 36, No. 4, pp. 567-570, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02254-2

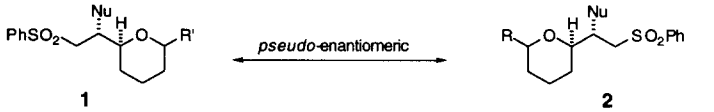
Heteroconjugate Addition at C-1 Position of Pyranose Derivative, Pseudoenantiomeric Methodology for Asymmetric Introduction

Minoru Isobe* and Yimin Jiang

Laboratory of Organic Chemistry, School of Agricultural Sciences, Nagoya University, Chikusa, Nagoya 464-01, Japan

Abstract : A new synthetic method providing both enantiomers by heteroconjugate addition strategy is described for stereocontrolled synthesis of optically active compounds from sugar chirons. Preparation includes introduction of phenylthioacetylene, acidic epimerization via dicobalthexacarbonyl complex, hydrosilylation and oxidation. Addition of carbon nucleophiles to the heteroolefins extended at the C-1 position yielded the product with high stereoselectivity. Mode of addition was switchable via α- or β-chelation control.

In the asymmetric organic synthesis directed toward optically active molecules, sugar chirons have long time been used as the starting materials. We have already established a method extending a carbon-carbon bond away from the pyranose ring with high stereoselectivity, and reported several examples along this line in the total syntheses of natural products.[1] Since most of the sugar chirons are available in D-form, a method that can converted those chirons to both enantiomers, is necessary. We became interested in developing a new method expanding utility of sugar chirons along this line.



1 2 eq. 1

The heteroconjugate addition strategy[2] based on glucose derivative has been designed to place the electron-deficient olefin conjugated to hetero-atom groups at the C-5 position of carbohydrate (Fig 1, upper column). A new method, which could develop above concept, may be realized in the similar system by placing the olefin at the C-1 position (Fig. 1 lower column). The enantiomeric relationship around nucleophile and the neighboring is shown in eq. 1, although some portion in the carbohydrate skeleton is not identical (R ≠ R'). The authors propose it to be *pseudoenantiomeric*.[3]

Fig 1

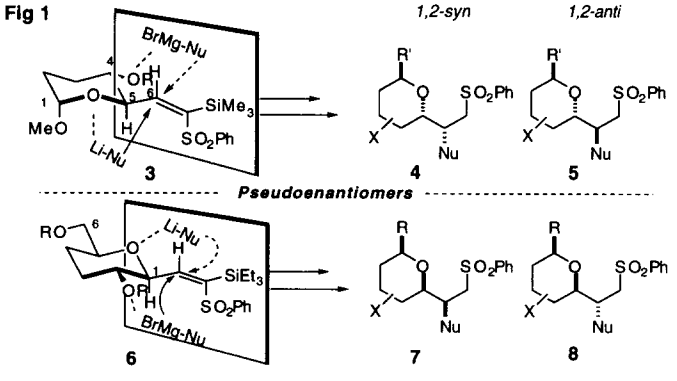
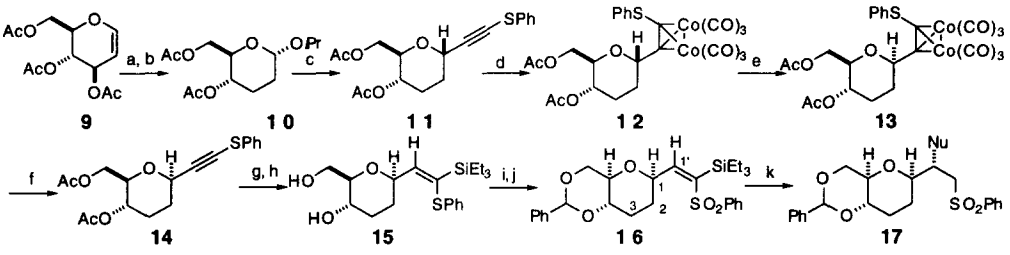


Fig. 1 illustrates the mode of the conjugate addition to the heteroolefin at the C-5 (**3**) and at the C-1 (**6**) position. Original addition to **3** was controlled by the α-oxygen atom through the chelation with lithium alkyls or by the β-alkoxide with Grignard reagents. The former (α-chelation control) gave, in fact, 1,2-*syn*-adduct **4**, while the latter (β-chelation) gave the 1,2-*anti*-adduct **5**. When the corresponding electrophile **6** (having the electron-deficient olefin at the C-1 position) could be prepared, a very similar situation would be realized as expected in Fig. 1 (lower column). Thus, the α-chelation control will happen from the rear face (dotted line) and the β-chelation will occur on the front face with the C-2 equatorial hydroxy group to afford **7** and **8**, (*pseudoenantiomeric* to **4** and **5**), respectively.[4]

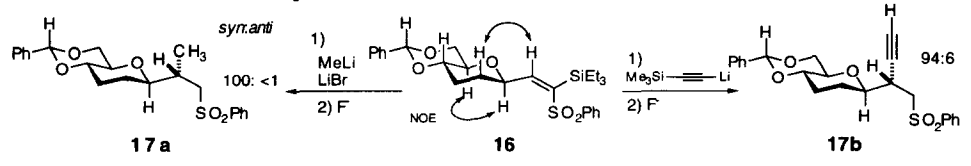
Synthesis of this electrophile at the C-1 position was initiated by C-glycosidation with phenylthio(trimethylsilyl)acetylene to a sugar derivative **10**, which was derived from tri-*O*-acetyl-D-glucal **9**.[5] The stereochemistry of phenylthioacetylenic group in **11** was exclusively introduced in pure alpha, and the acetylenic group was epimerized through cobalthexacarbonyl complexes (**12**, **13**) into β isomer **14** under an equilibrium condition using TfOH in dichloromethane as solvent, the α:β ratio being 1:14.[6] The acetylenic moiety was regioselectively hydrosilylated to the olefin **15** with triethylsilane in the presence of 0.5 mol % of platinum catalyst.[7] Other functional groups were manipulated to give the heteroolefin **16** ($J_{1,2\alpha\beta}$ = 11, 2.5 Hz, $J_{1,1'}$ = 8 Hz) as summarized in Scheme 1.

Scheme 1



a) *i*-PrOH, BF_3•OEt_2; b) H, Pd-C (97%); c) Me_3Si-C≡C-SPh, BF_3•OEt_2; d) $Co_2(CO)_8$ (91%); e) CF_3SO_3H (83%); f) I_2 (94%); g) Et_3SiH, Na_2PtCl_6•$6H_2O$, 90 °C (74%); h) CH_3ONa (99%); i) MCPBA (95%); j) $PhCH(OMe)_2$/CSA (92%); k) Nu-Li (MeLi 86%; Li-C≡C-$SiMe_3$ 90%) then KF.

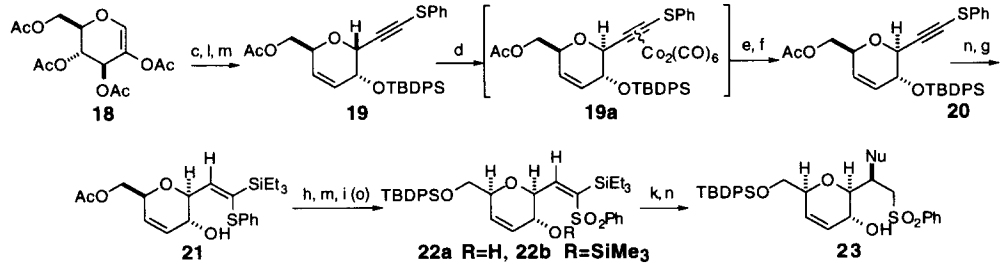
Two kinds of nucleophiles (MeLi•LiBr and Li-C≡C-$SiMe_3$) were added to **16** as example to give products **17a** and **17b** with high stereoselectivity, respectively. *Syn*-stereochemistry of the methyl adduct **17a** was assigned on basis of the chemical shift of ^{13}C nmr (δ 14.6) of the methyl group, which in fact added through the α-chelation.[8] The stereochemistry of the acetylene adduct **17b** was assumed to be *syn* dominant (94:6) from this mechanistic view point.



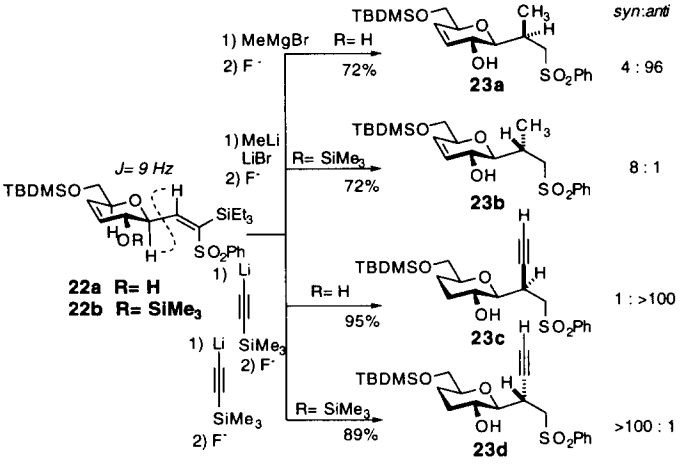
Another electrophile **22** was similarly prepared from 2-acetoxy glucal derivative (**18**) through steps involving C-glycosidation, hydride reduction and protection of the resulting hydroxy group (**19**), acid epimerization (**20**) *via* dicobalthexacarbonyl complex (**19a**, α:β = 1:7; separated), hydrosilylation etc. to give

22a ($[\alpha]_D$ -18.9°) with free hydroxy group and **22b** ($[\alpha]_D$ -122.4°) with trimethylsilyl-protection at the C-2 position. Orientation of these electrophilic moieties was equatorial and the coupling constants were $J_{1,1'} = 9$ Hz with **22a,b** as shown. Conjugate addition of MeMgBr to **22a** in THF at room temp followed by treatment

Scheme 2



l) $NaBH_4$, $CeCl_3$; m) TBDPSCl, imidazole, DMF; n) *n*-BuN_4F; o) TMSCl, Et_3N, THF.



with KF gave **23a** (R= H; $[\alpha]_D$ -51.3°) as *anti* isomer {CH_3, δ 1.16 (d, J= 7 Hz); δ 18.7 of the methyl signal}. On the other hand, MeLi•LiBr was added to **22b** (R= $SiMe_3$) in a mixture of hexane and ether at -20°C afforded *syn* isomer **23b** ($[\alpha]_D$ -69.4°) as dominant product {CH_3, δ 1.05 (d, J= 7 Hz); 13.6 ppm}. Simple switching of *syn-anti* selectivity was noteworthy by protection or non-protection of the 2-hydroxy group of **22**.

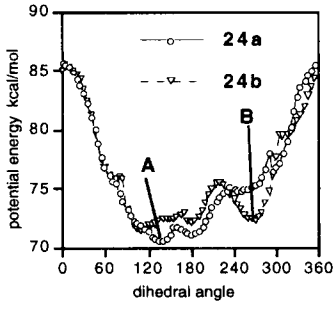


Fig. 2

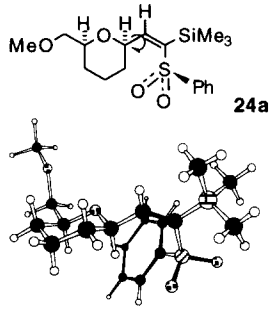


Fig. 3 **A** 135° 70.5 kcal

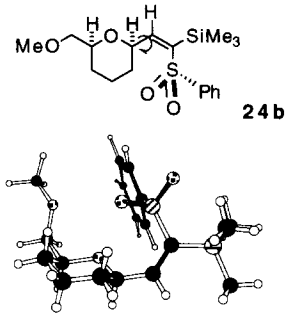


Fig. 4 **B** 270° 72.3 kcal

Addition of lithium trimethylsilylacetylide to **22a** at 0 °C in a mixture of hexane and ether provided *syn* adduct **23c** (≡-H, δ 2.09, d, J = 2.5 Hz, $[\alpha]_D$ -45.7°), while **22b** (R= $SiMe_3$) afforded *anti* isomer **23d** (≡-H, δ 1.99, d, J = 2.5 Hz, $[\alpha]_D$ -31.6°). Assignment of the stereochemistry of the products was based on the previous studies on *pseudoenantiomeric* cases.[4]

Mode of above heteroconjugate addition depended on two factors of the preferential conformation and of the strong metal chelation as postulated earlier.[2] The conformation of the transition state would be similar to that of the grand state. Potential energy was calculated with two rotamers of the sulfone of **24a,b** by minimizing each conformer generated in every 5° around the dihedral angle of the C_2-C_1-$C_{1'}$=$C_{2'}$ and plotted in clockwise (Fig. 2). Global minimum conformation in Fig. 2 is drawn as **A** in Fig. 3, which has the angle of 135° and fits with the observed nmr data ($J_{1,1'}$= 8~9 Hz). Fig. 4 is the local minimum of another rotamer **B** (Fig. 2), which would not reduce the selectivity because of very little contribution due to higher energy difference (1.8 kcal/mol) from **A**. These calculations[9] ascertained the selectivity of heteroconjugate addition depending on the population of the ground state conformation of the electrophile.

The current methodology provided switching the *syn-anti* selectivity in the new preparation involving C-glycosidation and epimerization. Application of this method for synthesis of natural products is now in progress.

Acknowledgments The authors are indebted to Dr. Yoshiyasu Ichikawa, Mr. Toshio Nishikawa and Mr. Shigeyoshi Tanaka for helpful discussions to persuade these experiments. The research was financially supported by a Grant-in-Aid for Scientific Research from Ministry of Education, Science and Culture of Japan. Y. J. express his gratitude to Scholarship from Iyakushigen Zaidan and the Ministry E.S.C.J.

References and Notes

1. (a) Isobe, M.; Ichikawa, Y.; Goto, T. *Tetrahedron Lett.*, **1981**, *22*, 4287-4290. (b) Isobe, M.; Kitamura, M.; Goto, T. *J. Am. Chem. Soc.*, **1982**, *104*, 4997-4999. (c) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.*, **1984**, *106*, 3252-3257. (d) Isobe, M.; Ichikawa, Y.; Goto, T. *Tetrahedron Lett.*, **1986**, *27*, 963-966. (e) Isobe, M.; Ichikawa, Y.; Bai, D-L.; Masaki, H.; Goto, T. *Tetrahedron*, **1987**, *43*, 4767-4776.
2. Perspectives in the Organic Chemistry of Sulfur, Ed. by Zwanenburg, B.; Klunder, A. J. H. "New Synthetic Methods Using Vinyl Sulfones--- Developments in Heteroconjugate Addition" Isobe, M. *Studies in Organic Chemistry*, **1987**, *28*, 209-229 Elsevier Science Publishers.
3. Compounds **1** and **2**; **4** and **7**; **5** and **8** are all *pseudoenantiomeric* to each other, respectively. When R = R', compounds **1**, **4** and **5** are enantiomeric to **2**, **7** and **8**, respectively.
4. (a) Isobe, M.; Funabashi, Y.; Ichikawa, Y.; Mio, S.; Goto, T. *Tetrahedron Lett.*, **1984**, *25*, 2021-2024. (b) Isobe, M.; Ichikawa, Y.; Funabashi, Y.; Mio, S.; Goto, T. *Tetrahedron*, **1986**, *42*, 2863-2872.
5. (a) Ichikawa, Y.; Isobe, M.; Konobe, M.; Goto, T. *Carbohydrate Research*, **1987**, *171*, 193-199. (b) Tsukiyama, T.; Isobe, M. *Tetrahedron Lett.*, **1992**, *33*, 7911-7914. (c) Tsukiyama, T.; Peters, S.; Isobe, M. *Synlett.*, **1993**, 413-415.
6. (a) Tanaka, S.; Tsukiyama, T.; Isobe, M. *Tetrahedron Lett.*, **1993**, *34*, 5757-5760. (b) Tanaka, S.; Isobe, M. *Tetrahedron in press.* (c) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207-214, and references cited therein.
7. (a) Isobe, M.; Obeyama, J.; Funabashi, Y.; Goto, T. *Tetrahedron Lett.*, **1988**, *29*, 4773-4776. (b) for review, see Hiyama, T.; Kusumoto, T. *Comprehensive Org. Syn.; Pergamon Press, Ed. by Trost, B. M.;* **1991**, *8*, 763-792.
8. Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.*, **1980**, *21*, 4727-4730.
9. Calculated on a Biograf (supplied from Molecular Simulation Co. Ltd.) using Dreiding as force field on a SiliconGraphics Power Iris 220GTXB; for details see, Mayo, S. L.; Olafson, B. D.; Godard III, W. A. *J. Phys. Chem.* **1990**, *94*, 8897-8909.

(*Received in Japan* 8 *September* 1994; *revised* 28 *October* 1994; *accepted* 11 *November* 1994)