ORGANIC LETTERS

2006
Vol. 8, No. 15
3291−3294

Radical Reactions with 2-Bromobenzylidene Group, a Protecting/Radical-Translocating Group for the 1,6-Radical Hydrogen Transfer Reaction

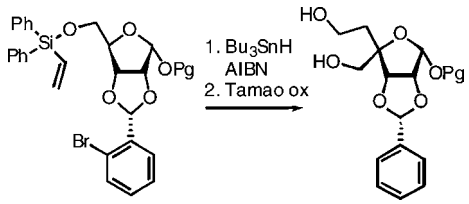
Natsumi Sakaguchi, Shinpei Hirano, Akira Matsuda, and Satoshi Shuto*

Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan

shu@pharm.hokudai.ac.jp

Received May 11, 2006

ABSTRACT

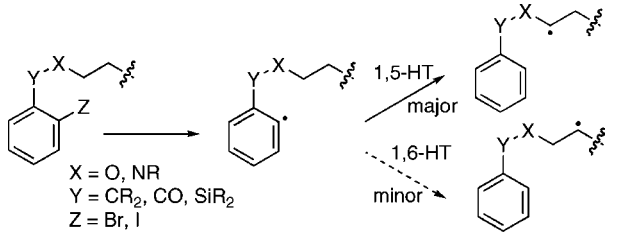


The 2-bromobenzylidene group, designed as a novel protecting/radical-translocating (PRT) group, proved to be effective for an unusual 1,6-hydrogen transfer reaction. Using this PRT group, 4-branched ribose derivatives were stereoselectively prepared.

Protecting/radical-translocating (PRT) groups[1] allow remote functionalization of alcohols, amines, and amides.[2] PRT groups should be easy to introduce and should function as normal protecting groups for alcohols and/or amines before the radical reaction, at which point they should effectively generate a radical at the desired position via hydrogen transfer (HT). After the radical reaction, they need to be easily removed. PRT groups have the distinct advantage of homolytically cleaving an inactive C−H bond.[1,2] As shown in Scheme 1, benzene derivatives are often used as PRT groups, since aromatic radicals generated from them are active enough to abstract a hydrogen on an aliphatic carbon.

PRT groups can generate a radical via homolytic cleavage of an inactive C−H bond (Scheme 1), in which the radical adjacent to the oxygen or nitrogen atom is selectively formed via a 1,5-hydrogen transfer process.[3] Although there are a few examples of radical 1,6-HT reactions,[4] no report of a PRT group selectively abstracting a hydrogen at the position β to the oxygen or nitrogen in a 1,6-HT reaction has appeared in the literature. We describe here radical reactions with a 2-bromobenzylidene group, designed as a novel PRT group for unusual 1,6-selective HT reactions.

Scheme 1



If the initially generated aromatic radical intermediate could accommodate the stereoelectronic preference for 1,6-hydrogen abstraction, where the radical orbital and the C−H

(1) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900−5902.

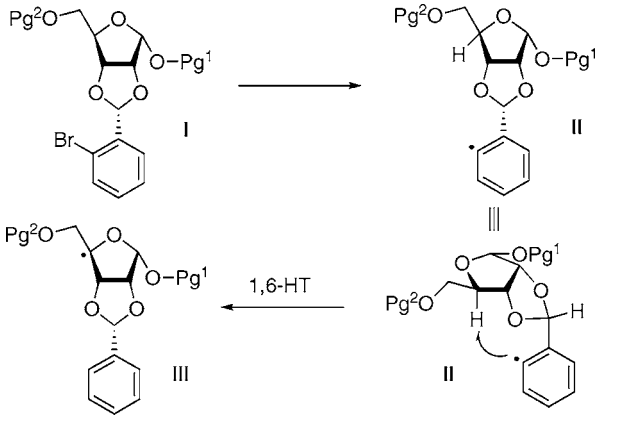
(2) For examples of PRT groups, see: Feray, L.; Kuznetsov, N.; Renaud, P. Hydrogen Atom Abstraction. In *Radicals in Organic Synthesis;* Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 246−278.

10.1021/ol061162o CCC: $33.50
Published on Web 06/28/2006

bond of the hydrogen to be abstracted are linear or nearly linear, we concluded that the 1,6-HT reaction with a PRT group would likely take place. Thus, we chose the 2-bromobenzylidene group as a novel PRT group, thinking that it would be useful in protecting 1,2- or 1,3-diols similar to other benzylidene groups and the reactive aryl radical generated from it could abstract a hydrogen on an aliphatic carbon. We anticipated that the regio- as well as stereoselective 1,6-hydrogen abstraction might occur with the 2-bromobenzylidene PRT group, because the bromophenyl moiety seemed to be conformationally constrained as a result of the rigid 1,3-dioxo ring formed from a diol and 2-bromobenzaldehyde or its equivalent.

We decided to examine the potential of 2-bromobenzylidene group as a PRT group using ribose derivatives as reaction substrates. Thus, 2,3-*O*-*endo*-benzylidene-α-D-ribose derivative **I** was designed as a model substrate (Scheme 2).

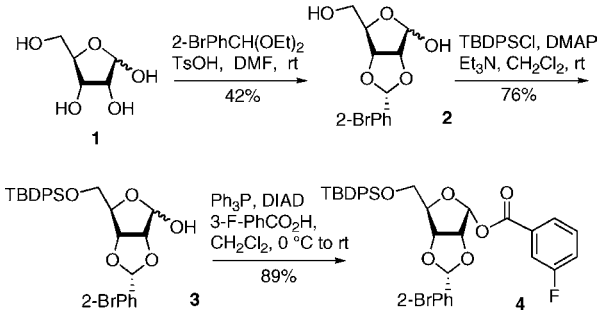
Scheme 2



Treatment of the substrate **I** under reductive radical reaction conditions, such as a Bu_3SnH/AIBN system, would generate the aryl radical **II**. The 1,5-HT, i.e., abstraction of a hydrogen at the 2- or 3-position of the ribose by the aryl radical, would be impossible as a result of the steric demand of the *endo*-benzylidene structure. Thus, we expected that, because of the rigid ring system, the desired 1,6-HT might selectively occur to generate the ribose 4-radical **III**. If, by this method, the ribose 4-radical **III** could be effectively generated, 4-branched ribose derivatives, which are useful, for example, as precursors for 4′-branched nucleosides having considerable biological importance,[5,6] would be synthesized via radical C−C bond formation at the 4-position.

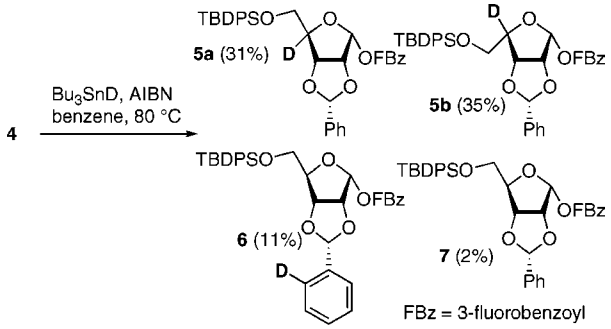
Thus, 1-*O*-(3-fluorobenzoyl)-2,3-*O*-*endo*-2-bromobenzylidene-5-*O*-*tert*-butyl-diphenylsilyl (TBDPS)-α-D-ribose (**4**) was synthesized as the substrate for examining the 1,6-HT reaction (Scheme 3). Treatment of D-ribose with 2-Br-

Scheme 3



$PhCH(OEt)_2$ and *p*-TsOH in DMF at room temperature gave the desired *endo*-benzylidene product **2**. After selective protection of the 5-hydroxyl of **2** with a TBDPS group, Mitsunobu reaction of the product **3** with a Ph_3P/diisopropyl azodicarboxylate (DIAD)/3-F-$PhCO_2H$ system in CH_2Cl_2 gave highly stereoselectively the α-riboside **4**,[7] the substrate for the radical reaction. Deuterium-labeling experiments of

Scheme 4



4 with Bu_3SnD were first investigated with the idea of clarifying whether the desired 1,6-HT reaction had indeed

(3) For examples of HT reactions, see: (a) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900−5902. (b) Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81−82. (c) Wiedenfeld, D.; Breslow, R. *J. Am. Chem. Soc.* **1991**, *113*, 8977−8978. (d) Brown, C. D. S.; Simpkins, N. S.; Clinch, K. *Tetrahedron Lett.* **1993**, *34*, 131−132. (e) Bosch, E.; Bachi, M. D. *J. Org. Chem.* **1993**, *58*, 5581−5582. (f) Robertson, J.; Peplow, M. A.; Pillai, J. *Tetrahedron Lett.* **1996**, *37*, 5825−5828. (g) Bertrand, M. P.; Crich, D.; Nouguier, R.; Samy, R.; Stien, D. *J. Org. Chem.* **1996**, *61*, 3588−3589. (h) Kittaka, A.; Asakura, T.; Kuze, T.; Tanaka, H.; Yamada, N.; Nakamura, K.; Miyasaka, T. *J. Org. Chem.* **1999**, *64*, 7081−7093. (i) Chatgilialoglu, C.; Gimisis, T.; Spada, G. P. *Chem. Eur. J.* **1999**, *5*, 2866−2876. (j) Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94−103 and references therein.

(4) (a) Bosch, E.; Bachi, M. D. *J. Org. Chem.* **1993**, *58*, 5581−5582. (b) Baldwin, J. E.; Adlington, R. M.; Robertson, J. *Tetrahedron* **1991**, *47*, 6795−6812.

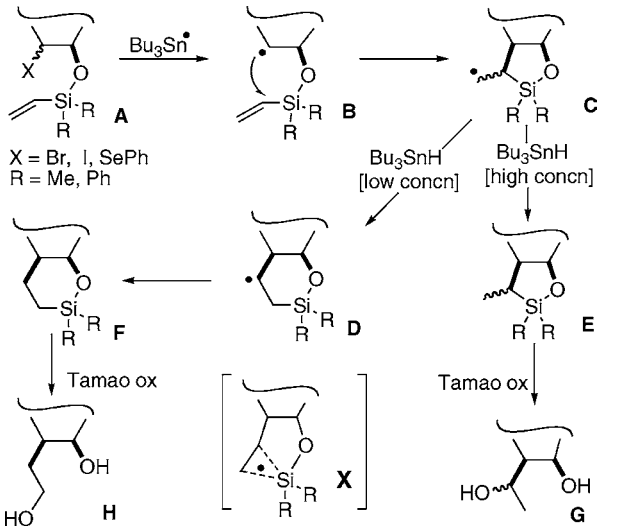
(5) (a) Giese, B.; Erdmann, P.; Schafer, T.; Schwitter, U. *Synthesis* **1994**, 1310−3112. (b) Hayakawa, H.; Kohgo, S.; Kitano, K.; Ashida, N.; Kodama, E.; Mitsuya, H.; Ohrui, H. *Antiviral Chem. Chemother.* **2004**, *15*, 169−187 and references therein.

(6) (a) Shuto, S.; Kanazaki, M.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 5676−5677. (b) Shuto, S.; Kanazaki, M.; Ichikawa, S.; Minakawa, N.; Matsuda, A. *J. Org. Chem.* **1998**, *63*, 746−754. (c) Ueno, Y.; Nagasawa, Y.; Sugimoto, I.; Kojima, N.; Kanazaki, M.; Shuto, S.; Matsuda, A. *J. Org. Chem.* **1998**, *63*, 1660−1667. (d) Sugimoto, I.; Shuto, S.; Mori, S.; Shigeta, S.; Matsuda, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 385−388. (e) Kanazaki, M.; Ueno, Y.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **2000**, *122*, 2422−2432. (f) Yamamoto, Y.; Shuto, S.; Tamura, Y.; Kodama, T.; Hoshika, S.; Ichikawa, S.; Ueno, Y.; Ohtsuka, E.; Komatsu, Y.; Matsuda, A. *Biochemistry* **2004**, *43*, 8690−8699 and references therein.

occurred. When the substrate **4** (0.01 M) was heated in the presence of Bu_3SnD (3.0 equiv) and AIBN (0.6 equiv) in benzene under reflux, the desired deuterium-labeled products at the 4-position **5a** and **5b**[7] were obtained in 66% yield in a 1:1.1 ratio, along with the compound deuterium-labeled at the phenyl moiety **6** (11%) and the unlabeled reduction product **7** (2%). Thus, the desired 1,6-HT reaction did in fact occur to generate the radical at the 4-position of the ribose derivative.

In recent years, we have developed a regio- and a stereoselective method for introducing C2-substituents at the position β to the hydroxyl group in halohydrins or in α-phenylselenoalkanols **A** using an intramolecular radical cyclization reaction with a dimethyl- or a diphenylvinylsilyl group as a temporary connecting radical-acceptor tether (Scheme 5).[6,8,9] Thus, the selective introduction of both the

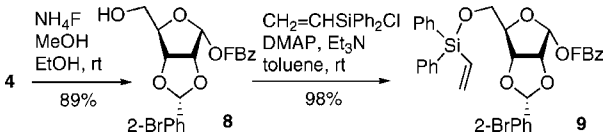
Scheme 5



1-hydroxyethyl and 2-hydroxyethyl groups can be achieved, depending on the concentration of Bu_3SnH in the reaction system, via a 5-*exo*-cyclization intermediate **E** or a 6-*endo*-cyclization intermediate **F**, respectively, after oxidative ring cleavage by treating the cyclization products under Tamao oxidation conditions,[10] as shown in Scheme 5. In this reaction, the kinetically favored 5-*exo*-cyclized radical **C**, formed from radical **B**, was trapped when the concentration of Bu_3SnH was high enough to give **E**. At lower concentrations of Bu_3SnH and higher reaction temperatures, the radical **C** rearranged into the more thermodynamically stable ring-enlarged radical **D** via a pentavalent-like silicon radical transition state **X**, which was then trapped with Bu_3SnH to give **F**.[8d]

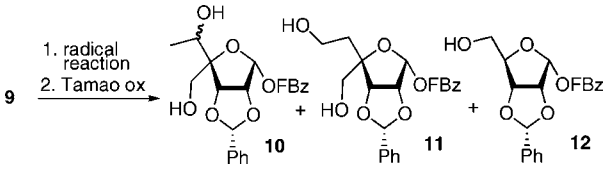
In this study, we planned to employ this temporary connecting silicon tether in the intramolecular radical C−C bond formation at the ribose 4-position via the 1,6-HT reaction with a 2-bromobenzylidene group. Consequently, the 2,3-*O*-(2-bromobenzylidene)ribose derivative **9** with a diphenylvinylsilyl group at the 5-hydroxyl was designed as the substrate, which was prepared from **4** via **8**, as shown in Scheme 6.

Scheme 6



The radical reaction of **9** was performed with Bu_3SnH (3.0 equiv)/AIBN (0.6 equiv) or Et_3B (1.0 equiv), and the products were obtained after Tamao oxidation. The results are shown in Table 1. A mixture of **9** (0.01 M), Bu_3SnH, and AIBN was first heated in benzene under reflux. The reaction gave the 4-branched products **10** and **11** in 75% yield in a 2:1 ratio, along with the reduction product **12** in 16% yield (entry 1). When a mixture of Bu_3SnH and AIBN in benzene was added slowly to a solution of **9** (0.01 M) in refluxing benzene, the 4-branched products **10** and **11** were

Table 1. Radical Reaction of the Substrate 9



			yield, %[b]	
entry	method[a]	temp, °C	**10** + **11** (ratio)[c]	**12**
1	A	80	75 (2:1)	16
2	B	80	64 (1:3.9)	trace
3	B	130	47 (only **11**)	0
4	A	rt	50 (only **10**)	34

[a] Method A: a mixture of **9** (0.01 M) and Bu_3SnH (3.0 equiv) was heated with AIBN (0.6 equiv) under reflux (entry 1) or stirred with Et_3B (1.0 equiv) at room temperature (entry 4) in benzene. Method B: to a solution of **9** (0.01 M) in benzene (entry 2) or chlorobenzene (entry 3) was added slowly a solution of Bu_3SnH (3.0 equiv) and AIBN (0.6 equiv) in the same solvent. [b] Isolated yield. [c] The ratio was based on the isolated yields.

(7) Stereochemistries of the compounds were confirmed by NOE and/or NOESY data: see Figure S1 in Supporting Information.

(8) (a) Sugimoto, I.; Shuto, S.; Matsuda, A. *J. Org. Chem.* **1999**, *64*, 7153−7157. (b) Yahiro, Y.; Ichikawa, S.; Shuto, S.; Matsuda, A. *Tetrahedron Lett*. **1999**, *40*, 5527−5531. (c) Sugimoto, I.; Shuto, S.; Matsuda, A. *Synlett* **1999**, 1766−1768. (d) Shuto, S.; Sugimoto, I.; Matsuda, A. *J. Am. Chem. Soc.* **2000**, *122*, 1343−1351. (e) Sukeda, M.; Ichikawa, S.; Matsuda, A.; Shuto, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 4748−4750. (f) Sukeda, M.; Ichikawa, S.; Matsuda, A.; Shuto, S. *J. Org. Chem*. **2003**, *68*, 3465−3475.

(9) (a) Yahiro, Y.; Ichikawa, S.; Shuto, S.; Matsuda, A. *Tetrahedron Lett*. **1999**, *40*, 5527−5531. (b) Shuto, S.; Yahiro, Y.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2000**, *65*, 5547−5557. (c) Terauchi, M.; Yahiiro, Y.; Abe, H.; Ichikawa, S.; Stephen, C.; Tovey, S. C.; Dedos, S. G.; Taylor, C. W.; Potter, B. V. L.; Matsuda, A.; Shuto, S. *Tetrahedron* **2005**, *61*, 7865−7873. (d) Terauchi, M.; Matsuda, A.; Shuto, S. *Tetrahedron Lett*. **2005**, *46*, 6555−6558.

(10) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694−1696.

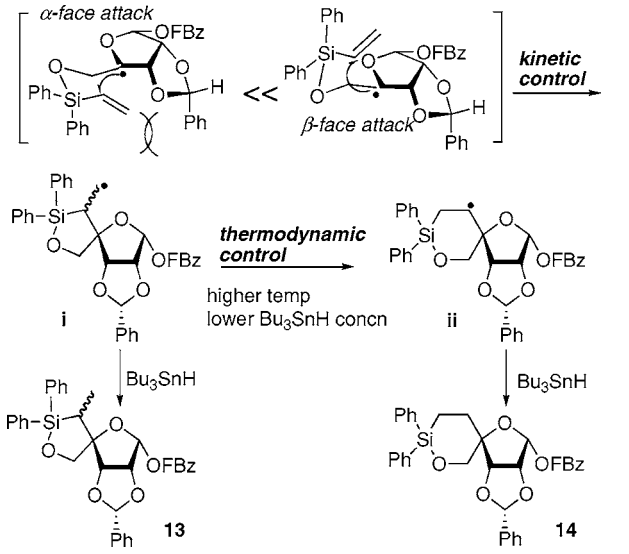
obtained in 64% yield in a ratio of 1:3.9, and the reduction product **12** was formed in trace amounts (entry 2). A similar reaction using the slow addition method at 130 °C with chlorobenzene as a solvent gave the 4-branched product **11** as the only isolated product in 47% yield. On the contrary, treatment of **9** at room temperature with Bu_3SnH using Et_3B as the initiator produced **10** in 50% yield as the only 4-branched product isolated, along with the reduction product **12** in 34% yield.

In the 4-branched products **10** and **11**, the stereochemistry at the 4-position proved to be completely inverted.[7] On the other hand, the 4-stereochemistry of the reduction product **12** was completely retained, suggesting that **12** was produced by the direct reduction of the phenyl radical before the 1,6-HT reaction occurred.

Access of the vinylsilyl moiety to the 4-radical from the α-face seems to be hampered as a result of the steric repulsion of the bulky *endo*-benzylidene group, and accordingly, addition from the *β*-face would be preferred to form the *exo*-cyclized radical **i** highly stereoselectively, as shown in Scheme 7. Under the kinetic conditions, i.e., higher Bu_3SnH concentration at a lower reaction temperature, the radical **i** was trapped with Bu_3SnH to form mainly **13**. Under the thermodynamic conditions, i.e., lower Bu_3SnH concentration at a higher reaction temperature, the radical **i** rearranged into the ring-enlarged radical **ii** to produce **14**. It is interesting to note that the stereochemistry of the 4-position was completely controlled throughout the reaction. This high stereoselectivity would be due to the steric demand of both the rigid benzylidene moiety and the intramolecular 5-*exo*-cyclization process.

In conclusion, the 2-bromobenzylidene group was designed as a new PRT group to realize a selective 1,6-HT reaction. Deuterium-labeling experiments with the 2,3-*O*-bromobenzylideneribose derivative **4** indicated that the 1,6-HT reaction did indeed occur. The intramolecular C−C-bond formation reaction with a silicon tether successfully proceeded via the 1,6-HT reaction with the 2-bromobenzylidene group. Thus, the 2-bromobenzylidene group has proved to be the first effective PRT group for the 1,6-HT reaction.

Scheme 7



Acknowledgment. We wish to acknowledge financial support from Ministry of Education, Culture, Sports, Science and Technology, Japan for Scientific Research 17659027 and 17390027.

Supporting Information Available: Experimental procedures and spectroscopic data of all new compounds, NOE and NOESY data for determination of the stereochemistries, and ^1H, ^{13}C, and ^1H-2D NMR spectra of key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061162O