

Fluoroallylboration—Olefination for the Synthesis of (*Z*)-4,4-Difluoropent-2-enoates and 5,5-Difluoro-5,6-dihydropyran-2-ones

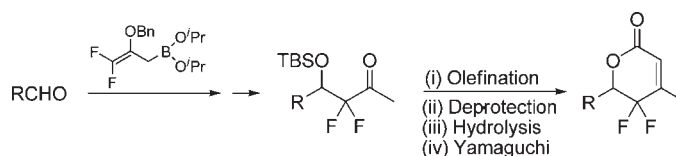
P. Veeraraghavan Ramachandran,* Agnieszka Tafelska-Kaczmarek, Kaumba Sakavuyi, and Anamitra Chatterjee

Herbert C. Brown Center for Borane Research, Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907-2084, United States

chandran@purdue.edu

Received December 21, 2010

ABSTRACT



Horner—Wadsworth—Emmons (HWE) or Still—Gennari olefination of TBS-protected 3,3-difluoro-4-hydroxy-2-ones, derived from the difluoroallylboration of aldehydes, provides the *Z*-isomer of 4,4,-difluoropent-2-enoates. These, upon hydrolysis, followed by Yamaguchi cyclization, afford 5,5-difluoro-4-methyl-5,6-dihydro- α -pyrones in high yields.

The success of partially fluorinated analogues of natural and unnatural molecules in medicinal chemistry gave an impetus to synthetic fluoro-organic chemistry.¹ Often this chemistry blazes a path different from that of the nonfluorinated counterparts, making the synthesis of appropriately substituted fluorine-containing molecules a fascinating and challenging exercise.² As part of our projects on fluoroorganic synthesis via boranes,³ we had recently reported the preparation of 3-(benzyloxy)-2,2-difluoro-but-3-en-1-ols (**1**), α,α -difluoro- β -hydroxy ketones (**2**), and the corresponding *cis*- and *trans*-1,3-diols via fluoroallylboration of aldehydes.⁴ In continuation, we envisaged further applications of **1** for the preparation of *E*- and *Z*-4,4-difluoropent-2-enoates and 4-hydroxy- and 4-methyl-5,5-difluoro-5,6-dihydro-2-pyranones (Figure 1).

Sequential allylboration-ring-closing metathesis (RCM) is a demonstrated strategy for the preparation of α -pyrones,⁵ including 6-fluoroalkyl analogues.⁶ α -Pyrones are important constituents of natural products that have been exploited as end products⁷ or intermediates⁸ in synthetic and medicinal applications. The preparation of *gem*-difluorinated pyranone derivatives was envisaged as depicted in Scheme 1, via fluoroallylboration.⁴

(5) (a) Reddy, M. V.; Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem.* **2001**, *624*, 239. (b) Ramachandran, P. V.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron Lett.* **2000**, *41*, 583.

(6) Ramachandran, P. V.; Padiya, K. J.; Rauniyar, V.; Reddy, M. V.; Brown, H. C. *J. Fluorine Chem.* **2004**, *125*, 615.

(7) Examples of these include β -hydroxy- δ -lactones that are pharmacophores of LDL cholesterol-lowering statin drugs (e.g., Lovastatin, Merck: Mevacor),^{7a} and oncorhyncholide.^{7b} (a) Clive, D. L. J.; Murthy, K. S. K.; Wee, A. G. H.; Prasad, J. S.; Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D.; Heerze, L. D.; Barrie, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 3018. (b) Needham, J.; Andersen, R. J.; Kelly, M. T. *Tetrahedron Lett.* **1991**, *32*, 315.

(8) β -Methylpyranones are intermediates for the synthesis of 13-*cis*-retinoic acid,^{8a} longifolene,^{8b} Vitamin E,^{8c} and Fumonisin B₂^{8d} kavalactone derivatives: (a) Cahard, D.; Mammeri, M.; Poirier, J.-M.; Duhamel, L. *Tetrahedron Lett.* **2000**, *41*, 3619. (b) Lei, B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 4609. (c) Takano, S.; Shimazaki, Y.; Iwabuchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1990**, *31*, 3619. (d) Shi, Y.; Peng, L. F.; Kishi, Y. *J. Org. Chem.* **1997**, *62*, 5666.

(1) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.

(2) (a) Ramachandran, P. V.; Jennings, M. P. *Chem. Commun.* **2002**, 386. (b) Itoh, Y.; Yamanaka, M.; Mikami, K. *Org. Lett.* **2003**, *5*, 4803.

(3) (a) Ramachandran, P. V.; Jennings, M. P.; Brown, H. C. *Org. Lett.* **1999**, *1*, 1399. (b) Ramachandran, P. V.; Jennings, M. P. *Org. Lett.* **2001**, *3*, 3789. (c) Ramachandran, P. V.; Parthasarathy, G.; Gagare, P. D. *Org. Lett.* **2010**, *12*, 4474.

(4) Ramachandran, P. V.; Chatterjee, A. *Org. Lett.* **2008**, *10*, 1195.

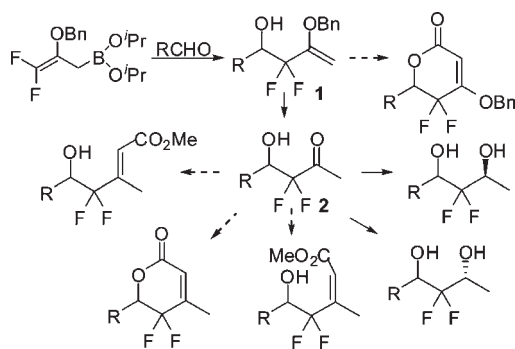
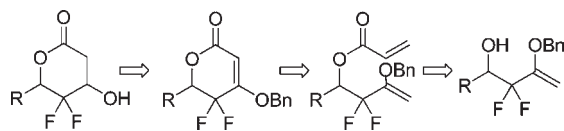


Figure 1. Fluoro-organic targets via difluoroallylboration.

Scheme 1. Retrosynthetic Analysis for the Preparation of Difluoro- α -pyrones via Ring-Closing Metathesis



3-(Benzyloxy)-2,2-difluoro-1-phenylbut-3-en-1-ol (**1a**), obtained via the allylboration of benzaldehyde with diisopropyl 2-(benzyloxy)-3,3-difluoroallylboronate,⁴ was converted to the corresponding acrylic ester. Attempted ring-closure of this ester via metathesis, under a variety of conditions using Grubb's first and second generation catalyst, was to no avail. A similar difficulty was reported by Qing⁹ and Percy¹⁰ and their co-workers during the preparation of 5,5-difluoro-5,6-dihydropyran-2-ones (α -pyrones), although Qing succeeded in achieving the RCM in the presence of $\text{Ti}(\text{O}-i\text{-Pr})_4$.¹¹

An alternative route to fluorinated α -pyrones was designed via an olefination–cyclization protocol (Scheme 2).¹² Wittig reactions¹³ of fluorocarboxyls are reported to be faster^{14,15} and there have been reports of reversal of selectivity in the olefination of α -fluorinated alkyl aryl ketones compared to the nonfluorinated ketones.¹⁶ We examined

(9) You, Z.-W.; Jiang, Z.-X.; Wang, B.-L.; Qing, F.-L. *J. Org. Chem.* **2006**, *71*, 7261.

(10) Audouard, C.; Fewcett, J.; Griffiths, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A. *Org. Biomol. Chem.* **2004**, *2*, 528.

(11) You, Z.-W.; Wu, Y.-Y.; Qing, F.-L. *Tetrahedron Lett.* **2004**, *45*, 9479.

(12) For a similar reaction with non-fluorinated β -hydroxy carbonyls, see: Sabitha, G.; Sudhakar, K.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 8599.

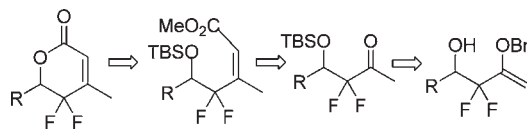
(13) For a review, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Vedejs, E.; Peterson, M. J. *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons, Inc.: New York, 1994; Vol. 21, pp 1–158.

(14) Dull, D. L.; Baxter, I.; Mosher, H. S. *J. Org. Chem.* **1967**, *32*, 1622.

(15) Shimada, Y.; Taniguchi, N.; Matsuhisa, A.; Sakamoto, K.; Yatsu, T.; Tanaka, A. *Chem. Pharm. Bull.* **2000**, *48*, 1644.

(16) Eguchi, T.; Aoyama, T.; Kakinuma, K. *Tetrahedron Lett.* **1992**, *33*, 5545.

Scheme 2. Retrosynthetic Analysis for the Preparation of Difluoro- α -pyrones via Olefination–Cyclization



the Wittig, Still–Gennari, and Horner–Wadsworth–Emmons (HWE) olefinations of 4-(*tert*-butyldimethylsilyloxy)-3,3-difluoro-4-phenylbutan-2-one (**3a**) derived from **1a**. The difficulties and anomalies due to the presence of the difluoromethylene group and the successful preparation of a series of 6-substituted 5,5-difluoro-4-methyl-5,6-dihydropyran-2-ones are described herein.

The Wittig reaction of α,α -difluoro- β -hydroxy ketone **2a**, prepared by the debenzylation of the β -hydroxy enol benzyl ether **1a** with sodium in liquid ammonia⁴ and (carbethoxymethylene)triphenylphosphorane in refluxing toluene, yielded 29% of the olefinic ester (**5a'**) in a 10:1 isomeric ratio in favor of the *Z*-isomer (vide infra). This is contrary to the formation of the *E*-isomer for the Wittig reaction of α -difluorocarbonyls reported by Kakinuma and co-workers,^{16,17} whereas Tanaka and co-workers reported a 1:1 mixture of *E*- and *Z*-olefinic esters for the Wittig, Still–Gennari, and HWE reaction of α -difluoro cyclic ketones.¹⁵ With the hope that the TBS-protected ketone might provide improved yields for the reaction, **2a** was converted to the corresponding silyl ether **3a**, followed by the Wittig reaction in refluxing toluene. A single isomer of the olefin (¹⁹F NMR) was isolated in 35% yield,¹⁸ identified as the *Z*-isomer (vide infra) of ethyl 5-(*tert*-butyldimethylsilyloxy)-4,4-difluoro-3-methyl-5-phenylpent-2-enoate (**4a'**).

To establish the stereochemistry of the above olefin and to prepare the corresponding α -pyrones, *Z*-stereospecific Still–Gennari olefination of **3a** was examined.¹⁹ Thus, **3a** was treated with bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate and potassium bis(trimethylsilyl)amide in the presence of 18-crown-6 in THF at -40 °C. The reaction was complete within 18 h (TLC) and the usual workup provided a much improved, 86% yield of the desired protected δ -hydroxy olefinic ester **4a** (Scheme 3). The ¹⁹F NMR spectrum revealed the clean formation of a single stereoisomer. The *Z*-stereochemistry, similar to the results that have been reported for α -difluoro ketones,¹⁶ was confirmed by the cyclization of this product to the α -pyrone **6a** (vide infra).

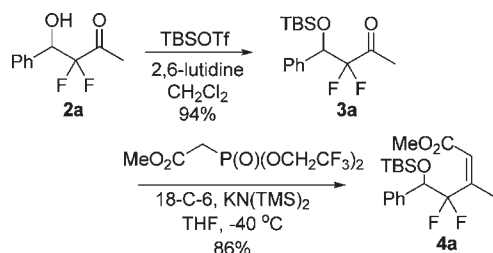
Having achieved the targeted TBS-protected olefinic ester, we turned our attention to the deprotection–cyclization to

(17) Aoyama, T.; Eguchi, T.; Oshima, T.; Kakinuma, K. *J. Chem. Soc., Perkin Trans. I* **1995**, 1905.

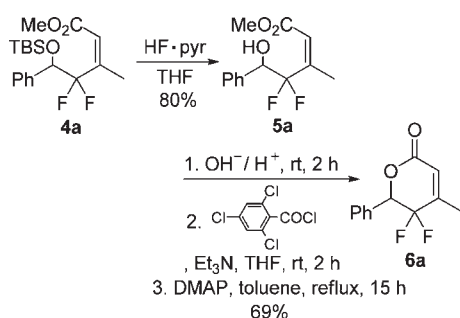
(18) Similar low yields have been reported for the methylenation of a β -acetoxy ketone during Wittig reaction: Hibino, J. I.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579.

(19) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

Scheme 3. Preparation of *Z*-4,4-Difluoropent-2-enoate



Scheme 4. Preparation of δ,δ -Difluoro- α -pyrone



prepare the difluorinated pyrone. The standard deprotection of the TBS ether with TBAF resulted in poor yields of the hydroxy ester **5a**. Hydrolysis with a catalytic amount of *p*-TSA and cyclization²⁰ in refluxing toluene did not go to completion even after 2 days.

Deprotection of the TBS ether was then examined with HF–pyridine in THF, which yielded the δ -hydroxy ester **5a** in 80% yield (Scheme 4). Sodium hydroxide-mediated hydrolysis provided the crude δ -hydroxy acid, in quantitative yield, which was subjected to cyclization under Yamaguchi conditions²¹ to achieve the targeted α -pyrone **6a** in 69% yield.

The successful synthesis of the difluoro- α -pyrone from **1a** was then extended to a series of 3-(benzyloxy)-2,2-difluorobut-3-en-1-ols (**1b–g**), after conversion to the corresponding α,α -difluoro β -hydroxy ketones (**2b–g**). Thus, the

(20) Aurell, M. J.; Ceita, L.; Mestres, R.; Parra, M.; Tortajada, A. *Tetrahedron* **1995**, *51*, 3915.

(21) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(22) Attempts to debenzylate the benzyloxy alcohols **1**, prepared via the fluoroallylboration of benzaldehyde bearing electron-withdrawing groups, such as *p*-fluoro, *p*-chloro, and *p*-trifluoromethyl groups, resulted in dehalogenation along with debenzylation forming **2a**, **2a**, and **2c**, respectively. Debonylation of the benzyloxy alcohol derived from *p*-nitrobenzaldehyde resulted in the formation of the corresponding *p*-amino compound, 3,3-difluoro-4-hydroxy-4-(4-aminophenyl)butan-2-one.

(23) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

hydroxy ketones derived from benzaldehydes possessing electron-donating groups²² at ortho-, para-, and meta-positions and aliphatic aldehydes, such as hydrocinnamaldehyde and cyclohexanecarboxaldehyde were olefinated to demonstrate the generality of the process for difluorinated α -pyrones.

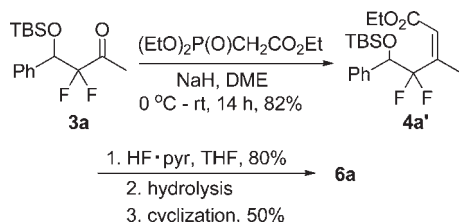
The following benzyloxy alcohols **1** derived from the corresponding aldehydes [shown in brackets] were converted to the corresponding 5,5-difluoro-5,6-dihdropyran-2-ones in 20–39% overall yields in six steps: 3-(benzyloxy)-2,2-difluoro-1-(4-methoxyphenyl)-but-3-en-1-ol (**1b**) [4-methoxybenzaldehyde], 3-(benzyloxy)-2,2-difluoro-1-*p*-tolylbut-3-en-1-ol (**1c**) [*p*-tolualdehyde], and [3-(benzyloxy)-2,2-difluoro-1-(3-methoxyphenyl)-but-3-en-1-ol (**1d**) [3-methoxybenzaldehyde], as well as 3-(benzyloxy)-1-(2,6-dimethylphenyl)-2,2-difluorobut-3-en-1-ol (**1e**) [2,6-dimethylbenzaldehyde], 5-(benzyloxy)-4,

(24) (a) Otaka, A.; Watanabe, J.; Yukimasa, A.; Watanabe, H.; Kinoshita, T.; Oishi, S.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2004**, *69*, 1634. (b) Also see: Kitazume, T.; Tsukamoto, T.; Yoshimura, K. *Chem. Commun.* **1994**, 1355.

(25) A typical experimental procedure for the preparation of **6a** is as follows. (a) **Preparation of 4-(tert-butyldimethylsilyloxy)-3,3-difluoro-4-phenylbutan-2-one (3a)**: 2,6-Lutidine (0.55 mL, 4.65 mmol) was added to a solution of 3,3-difluoro-4-hydroxy-4-phenylbutan-2-one (**2a**) (0.31 g, 1.55 mmol) in CH_2Cl_2 (6 mL) at 0 °C, followed by dropwise addition of TBDMSOTf (0.72 mL, 3.10 mmol), and the mixture was stirred at 0 °C for 3 h, and at RT for 3 h. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous NH_4Cl (8 mL). The organic layer was washed with brine, dried (anhyd. MgSO_4), filtered, and concentrated. The residue was purified by flash silica chromatography (hexane/EtOAc = 95/5) to yield **3a** as a colorless liquid (0.45 g, 94%). (b) **Preparation of *Z*-methyl 5-(tert-butyldimethylsilyloxy)-4,4-difluoro-3-methyl-5-phenylpent-2-enoate (4a)**: To a solution of 18-crown-6 (0.85 g, 3.18 mmol) in THF (11 mL), at –78 °C, was added bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (0.36 mL, 1.59 mmol) and a solution of **3a** (0.50 g, 1.59 mmol) in THF (3 mL) and further stirring for 30 min and at –40 °C for 18 h. The reaction was allowed to warm to RT and quenched with sat. aqueous NH_4Cl (10 mL). The organics were extracted with Et_2O (3 \times 20 mL) and the combined Et_2O layers were washed with sat. aq. NaHCO_3 solution, dried (anhyd. MgSO_4), filtered, and concentrated. The residue was purified by flash silica chromatography (hexane/EtOAc = 95/5) to provide **4a** as a colorless oil (0.51 g, 86%). (c) **Preparation of *Z*-methyl 4,4-difluoro-5-hydroxy-3-methyl-5-phenylpent-2-enoate (5a)**: HF–pyridine complex (70%, 3.7 mL) was added to a solution of **4a** (0.14 g, 0.39 mmol) in THF (10 mL) at 0 °C, and the solution was stirred at RT for 18 h. The reaction was cautiously quenched with sat. aq. NaHCO_3 solution (9 mL) and extracted with EtOAc (3 \times 10 mL). The combined extracts were washed with water and brine, dried (anhyd. MgSO_4), filtered, and concentrated. The residue was purified by flash silica chromatography (hexane/Et₂O = 1/1) to provide **5a** as a colorless oil (0.08 g, 80%). (d) **Preparation of 5,5-difluoro-4-methyl-6-phenyl-5,6-dihydro-2H-pyran-2-one (6a)**: A mixture of **5a** (58 mg, 0.23 mmol) and 2 M NaOH solution (0.34 mL) in THF (1.9 mL) was stirred for 2 h at RT and the mixture was concentrated to provide a light yellow solid. This was acidified with aq. 2 M HCl and extracted with Et_2O (3 \times 5 mL). The organic layer was washed with brine, dried (anhyd. MgSO_4), filtered, and concentrated to obtain the crude β -hydroxy acid as a light yellow oil (90 mg). 2,4,6-Trichlorobenzoyl chloride (0.07 mL, 0.41 mmol) was added to a mixture of the above β -hydroxy acid (90 mg, 0.37 mmol) and triethylamine (0.07 mL, 0.48 mmol) in THF (3.5 mL) and the mixture was stirred for 2 h at RT. After removal of triethylamine hydrochloride, the filtrate was diluted with toluene (25 mL) and added to a refluxing solution of 4-dimethylaminopyridine (0.18 g, 1.48 mmol) in toluene (35 mL) over a period 1.5 h. The reaction mixture was refluxed for 15 h, cooled to RT, then diluted with Et_2O , washed with 3% aq. HCl (2 \times 15 mL), water, sat. aq. NaHCO_3 solution, and water, dried (anhyd. MgSO_4), filtered and concentrated. The residue was purified by flash silica chromatography (hexane/Et₂O = 1/1) to provide δ -lactone **6a** as a white solid (35 mg, 69%), mp 112–113 °C.

Table 1. Preparation of (*Z*)-4,4,-Difluoropent-2-enoates and 5,5-Difluoro-5,6-dihydropyran-2-ones

| entry | Structure 1 | | | Structure 2 | | Structure 3 | | Structure 4 | |
|-------|-------------|-----------------------------------|--------------------|-------------|--------------------|-------------|--------------------|-------------|--------------------|
| | no. | R | yield ^a | no. | yield ^a | no. | yield ^a | no. | yield ^a |
| 1 | 3a | Ph | 94 | 4a | 86 | 5a | 80 | 6a | 69 |
| 2 | 3b | 4-MeO-Ph | 85 | 4b | 81 | 5b | 85 | 6b | 74 |
| 3 | 3c | <i>p</i> -Tol | 80 | 4c | 77 | 5c | 76 | 6c | 73 |
| 4 | 3d | 3-MeO-Ph | 81 | 4d | 83 | 5d | 95 | 6d | 64 |
| 5 | 3e | 2,6-Me ₂ -Ph | 88 | 4e | 95 | 5e | 87 | 6e | 71 |
| 6 | 3f | PhCH ₂ CH ₂ | 72 | 4f | 86 | 5f | 78 | 6f | 78 |
| 7 | 3g | Chx | 70 | 4g | 74 | 5g | 65 | 6g | 75 |

^a Isolated yield after column chromatography.**Scheme 5.** HWE Reaction of α -Difluoroketone

4-difluoro-1-phenylhex-5-en-3-ol (**1f**) [hydrocinnamaldehyde], and 3-(benzyloxy)-1-cyclohexyl-2,2-difluorobut-3-en-1-ol (**1g**) [cyclohexanecarboxaldehyde]. The results are summarized in Table 1.

To expand the scope of the fluoroallylboration reaction, the *E*-specific Horner–Wadsworth–Emmons (HWE) reaction of **3a** was carried out with triethyl phosphonoacetate.²³ To our surprise, the reaction product **4a'**, a single stereoisomer of the olefinic ester, was similar to **4a** by ¹⁹F NMR, revealing the formation of the *Z*-isomer (Scheme 5). Deprotection, hydrolysis, and cyclization afforded **6a** in 40% overall yield (three steps), confirming our observation, which was further corroborated in the case of **3f** as well.

This is contrary to the *E*-isomer reported for the HWE reaction of 3-(*tert*-butyldimethylsilyloxy)-2,2-difluoro-4-phenylbutanal by Otaka and co-workers.²⁴ Kakinuma also had reported opposite stereoisomers for Still–Gennari and HWE reactions of α -difluoroalkyl aryl ketones.¹⁶ We are further investigating this anomaly.

In summary, we have described the conversion of α , α -difluoro- β -hydroxybutan-2-ones, prepared via difluoroallylboration of aldehydes, to *Z*-4,4-difluoropent-2-enoates employing either Still–Gennari or Horner–Wadsworth–Emmons olefinations in high (74–95%) yields. The fluorinated *Z*-pentenoates were hydrolyzed to provide the corresponding δ -hydroxy acids and cyclized to 5, 5-difluoro-2-pyranones under Yamaguchi's lactonization conditions.²⁵ Explorations are underway to prepare the *E*-isomer of **4**.

Acknowledgment. Financial support from the Herbert C. Brown Center for Borane Research is gratefully acknowledged.

Supporting Information Available. Experimental details and spectral data of all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.