Pergamon

Tetrahedron Letters 39 (1998) 3115–3116

TETRAHEDRON LETTERS

AN UNUSUAL BORON-ASSISTED SUBSTITUTION IN THE SYNTHESIS OF α-METHOXYLATED FATTY ACIDS ISOLATED FROM CARIBBEAN SPONGES[1]

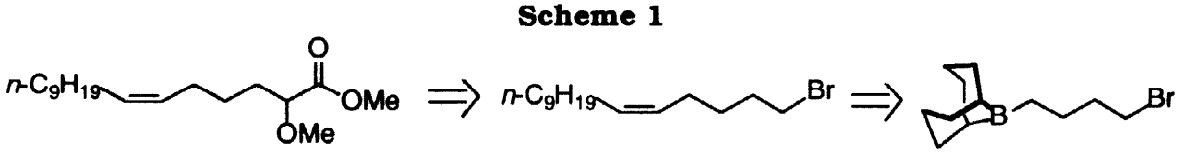
John A. Soderquist,* Izander Rosado,[2] and Yernan Marrero[3]
Department of Chemistry, University of Puerto Rico
Rio Piedras, PR 00931-3346

Received 4 February 1998; revised 23 February 1998; accepted 24 February 1998

Abstract: *The Suzuki-Miyaura cross coupling of 4-bromo-1-butyl-9-BBN produces 4-hydroxybutyl products evidently arising from a boron-assisted hydroxide substitution. This process was utilized in the synthesis of (±)-2-methoxy-5Z-hexadecenoic acid methyl ester (**1**), a derivative of the phospholipids isolated from the Caribbean sponge, Spheciospongia cuspidifera.*

The fatty acid portions of the phospholipids found in the African sponge, *Higginsia tethyoides* and in two Caribbean sponges, *Spheciospongia cuspidifera* (*cf.* **1**) and *Tethya crypta* contain α-methoxylated components, a rare phenomenon for such organisms.[4] We chose to develop a boron-based synthesis to these structurally simple compounds, selecting **1** as a representative example. Through this approach, we hoped to provide useful quantities of these compounds for biochemical studies, and also, to evaluate the compatibility of halo functionality in the organoborane partner in itsSuzuki-Miyaura coupling.[5] We envisaged the coupling of **3** to **6** as providing an efficient route to **2** which could be easily converted to **1** (Scheme 1).

Scheme 1



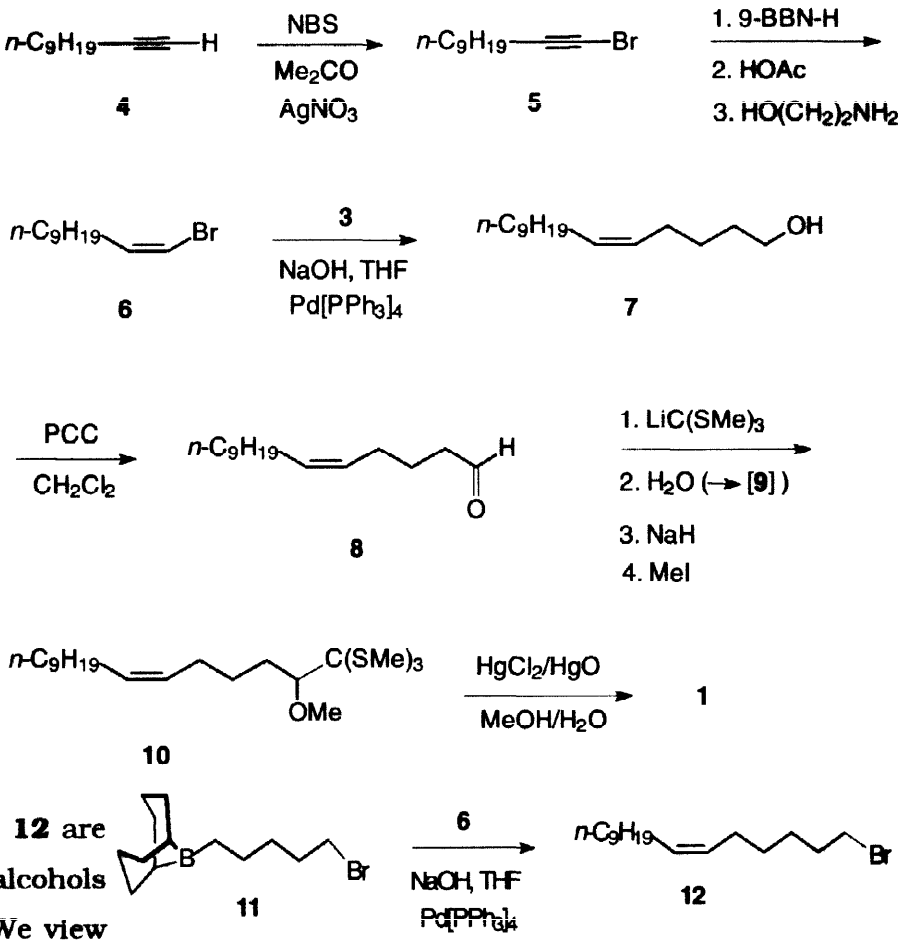
1 **2** **3**

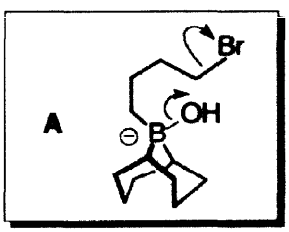
Superior to other standard methods for the conversion of **4** to its 1-bromo derivative, **5**, the $AgNO_3$-catalyzed *N*-bromosuccinimide (NBS) process produces excellent results (93%) for this long-chain substrate (Scheme 2).[6] The monohydroboration[7] of **5** with 9-borabicyclo[3.3.1]nonane (9-BBN-H) followed by protonolysis and a non-oxidative work-up, gives the pure *cis*-vinyl bromide **6** in excellent yield (88%).[6] **3** (^{11}B NMR δ 85) is formed cleanly by the hydroboration of 4-bromo-1-butene with 9-BBN-H (4 h, C_6H_{14}, 25 °C). However, its Pd-catalyzed cross coupling to **6** ($Pd[PPh_3]_4$ (1 mol %), THF, NaOH (2 equiv of 3 N), 5 h, reflux) does not lead to **2**, but rather produces the corresponding alcohol **7** (82%). This unexpected product was oxidized to the aldehyde **8** (76%, PCC (100% excess, CH_2Cl_2, 4 h, 25 °C). The addition of **8** to tris(methylthio)methyllithium[8] (60% excess, THF, -70 °C) produces the unstable α-hydroxy ortho(trithio)ester **9** which is best methylated *in situ* (NaH, DMF, THF, followed by MeI) affording the stable **10** (96% from **8**). Hydrolysis ($HgCl_2$/HgO (2.5:1), MeOH/H_2O (12:1), EE, 1 h, 25 °C) of **10** furnishes the desired ester, **1** (87%).

0040-4039/98/$19.00
PII: S0040-4039(98)00515-2

To test the generality of this efficient route (48% overall yield from **4**) to such α-methoxy esters, we chose to also examine the cross coupling of ϵ-bromopentyl-9-BBN (**11**) to **6**, which gives the expected 1-bromo-6*Z*-hexadecene (**12**, 79%). Since the alkyl chain length in **3** appeared critical to the substitution, it was treated with NaOH (2 equiv of 3 N, 4 h, 25 °C) in EtOH. By ^{13}C NMR and GCMS analysis, the oxidized (H_2O_2) consists of nearly equal amounts of 1,4-butanediol, THF and the expected 4-bromobutan-1-ol. Neither 1-bromooctane nor **12** are converted to the corresponding alcohols under any of these conditions. We view this new process as a boron-assisted substitution which can effectively deliver the nucleophile through a favorable cyclic process (*e.g.* **A**).[9] While evidently limited to special systems, the potential of this new process to orchestrate substitutions with highly basic nucleophiles is currently under study.

Scheme 2





Acknowledgment. Support from NIH-MBRS (SO6-GM08102), DOE (DE-FC02-91ER75674) and NSF (HRD-9011964) is gratefully acknowledged.

REFERENCES AND NOTES

1. This work is dedicated to the memory of the late Manuel Rosado.
2. Graduate student supported by the NIH-MBRS program (SO6-GM08102).
3. Undergraduate student supported by the NSF-RCMS program (HRD-9011964).
4. (a) Djerassi, C.; Ayanaglu, E.; Popov, S.; Kornprobst, J. M.; Aboud-Bichara, A. *Lipids* **1983**, 830. (b) Carballeira, N.; Sepúlveda, J. A. *Ibid.* **1992**, *27*. 72.
5. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
6. (a) Brown, H. C.; Midland, M. M.; Levy, A. B.; Kramer, G. W. *Organic Synthesis via Boranes*, Wiley-Interscience, New York, 1975, p 180. (b) Shulte, K. E.; Goes, M. *Arch. Pharm.* **1959**, *118*, 290. (c) Pelter, A.; Gould, K. J.; Harrison, C. R. *J. Chem. Soc. Perkkin I*, **1982**, 2428.
7. Brown, H. C.; Nelson, D.; Blue, C. D. *J. Org. Chem.* **1989**, *54*, 6064. See also: Soderquist, J. A.; Santiago, B. *Tetrahedron Lett.* **1990**, *31*, 5113.
8. Fuchs, P. L.; Dailey, O. D. *J. Org. Chem.* **1980**, *45*, 216.
9. For a discussion of related processes, see: Soderquist, J. A. in *Encyclopedia of Inorganic Chemistry*, R. B. King (ed.), J. Wiley & Sons, Ltd.: London, UK (1994) pp 401-432.