Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 1693–1697

Tetrahedron Letters

Synthesis of 1,1-diarylethylenes from an α-stannyl β-silylstyrene

Makonen Belema,* Van N. Nguyen and F. Christopher Zusi

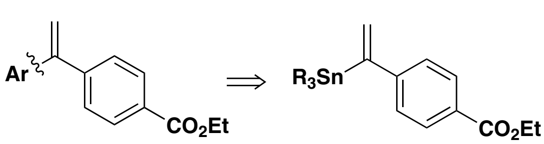
Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA

Received 23 November 2003; revised 8 December 2003; accepted 17 December 2003

Abstract—The synthesis of a family of 1,1-diarylethylenes from an α-stannyl β-silylstyrene through a combination of a Stille coupling and a protodesilylation reaction is described. This approach avoids the problematic *cine*-substitution, which is a well documented side reaction during the palladium-assisted elaboration of α-substituted vinylstannanes to 1,1-disubstituted ethylenes.

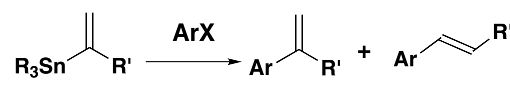
1. Introduction

In one of our programs, we were interested in preparing a family of diarylethylenes (**1**), in which the benzoate moiety was kept constant (Fig. 1). One logical disconnection is at the aryl–alkene C–C bond, putatively formed from vinylstannane **2** and an aryl halide or triflate. A review of the literature however reveals that the palladium-assisted coupling of vinylstannanes (**3**) with electrophilic halides/triflates affords a mixture of *ipso*- and *cine*-substituted products (Scheme 1).[1,2] A number of investigators have reported that for a given vinylstannane, the *ipso*/*cine* ratio and the efficiency of the reaction are influenced by the position of electron withdrawing groups on the electrophilic halides and the nature of the coupling conditions employed, among other factors.[3] It is not yet apparent how these factors influence the *ipso*/*cine* selectivity based on the currently accepted mechanism for the formation of the *cine*-substituted products.[4]



1 2

Figure 1.



3 4 5

Scheme 1. For example, R′ = CO_2Me, Ph; X = Br, I.

Although optimizing Stille coupling conditions to minimize the formation of the *cine*-products from stannane **2** was considered, we elected instead to explore the applicability of the readily accessible α-stannyl β-silylstyrenes (such as **8**) in the preparation of the target family of compounds. The seminal work of Mitchell et al.[5] and Chenard et al.[6] has demonstrated that *cis*-α-stannyl β-silylolefins can be prepared regio- and stereoselectively by the addition of $R_3SiSnR'_3$ (e.g., R = Me, R′ = *n*-Bu) to an alkyne, and that they would couple with various electrophilic halides under Stille conditions. There are reports on the further elaboration of the resultant Stille products, that is, the 2,2-disubstituted vinylsilanes,[7] but to the best of our knowledge their desilylation as an entry to 1,1-disubstituted ethylenes has not been described. In this communication, we report that 1,1-diarylethylenes can be synthesized from an α-stannyl β-silylstyrene and aryl iodides or bromides, in respectable yields, through a combination of Stille coupling and protodesilylation protocols.

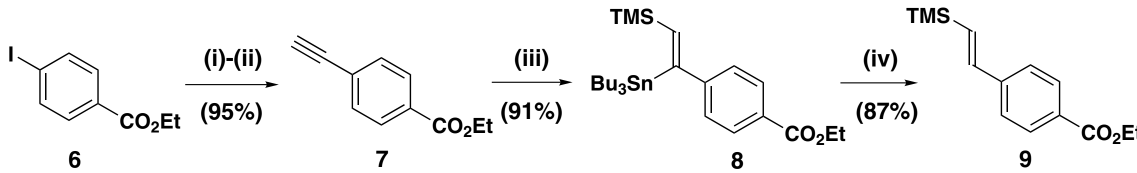
2. Results and discussion

Alkyne **7** was synthesized from iodide **6** under standard conditions (Scheme 2). Addition of the commercially

Keywords: 1,1-Diarylethylene; *cine*-Substitution; Stille coupling; Protodesilylation.

* Corresponding author. Tel.: +1-203-677-6928; fax: +1-203-677-7702; e-mail: makonen.belema@bms.com

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2003.12.106



Scheme 2. Reagents and conditions: (i) HCCTMS, $Pd(Ph_3P)_4$, CuI, Et_3N, DMF, 25 °C; (ii) catalytic K_2CO_3, EtOH, 25 °C; (iii) *n*-Bu_3SnTMS, $Pd(Ph_3P)_4$, dioxane, Δ; (iv) 1% TFA/CH_2Cl_2.

available *n*-Bu_3SnTMS across the alkyne bond of **7** afforded silylstannane **8** in a high yield. The regio- and stereochemical assignments, which were based on the works of Mitchell et al. and Chenard et al.,[5,6] have been confirmed by chemical and spectroscopic means. ^{1}H NMR revealed Sn/vinyl hydrogen *J*-couplings of 154 and 161 Hz, which are consistent with their *trans*-disposition.[8] In addition, the treatment of silylstannane **8** with 1% TFA/CH_2Cl_2 afforded *trans*-silylstyrene **9**, which confirmed the regiochemical assignment.

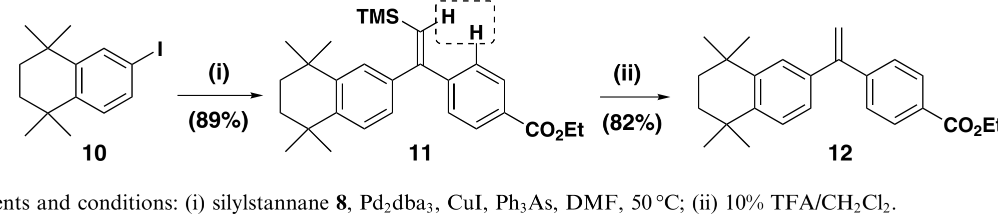
In a typical reaction, silylstannane **8** was coupled with iodide **10** under palladium catalysis to afford vinylsilane **11** (Scheme 3).[9,10] Although the stereochemical outcome of this reaction was inconsequential for the next step, NOE studies indicated that the coupling was stereospecific. However, vinylsilane **11** was susceptible to *cis*/*trans*-isomerization when exposed to traces of acid (such as the DCl present in $CDCl_3$). The protodesilylation of vinylsilane **11** with 10% TFA/CH_2Cl_2 afforded the desired product (**12**) in a 73% overall yield.

The two-step procedure described for iodide **10** was applied to a set of aryl iodides (see entries 1–8 and 10 in Table 1) and the following observations were made. For entries 1–7, LC/MS analysis of the crude reaction mixture indicated that, in general, the desilylation step proceeded cleanly. Thus, the overall yield for the two-step process reflects the efficiency of the Stille coupling step. It is apparent that the coupling step tolerated a number of functional groups, and that the yield eroded noticeably in one case (entry 3) due to the steric interference of the *ortho*-carboxylate group. The main side product from the Stille coupling was vinylsilane **9**.[11] It was isolated in about 10% yield for entry 9, and in this case we believe that the relatively acidic phenol-OH may have helped the destannylation of silylstannane **8**.

During the TFA/CH_2Cl_2 desilylation studies of the various vinylsilane intermediates (**11**, **13**–**20**, **22**), it was observed that the reaction time was inversely related to the 'electron richness' of the incoming aryl substrate. For example, the desilylation of **11** was complete in about 0.5 h, but required 22 h for **17**. This is consistent with the desilylation step involving a benzylic carbocation, vide infra. Interestingly, when the incoming aryl moiety was more electron rich, as was the case for vinylsilane **20**, the desilylation was complete in less than 10 min and the product (**20a**) began to pseudo-dimerize (Scheme 4).[12] The pseudo-dimer was assigned structure **24** based on HRMS and NMR studies, and the stereochemistry of the olefin was not determined. Pseudo-dimerization was not observed for the other aryl halides, and it is believed that the electron-donating ability of the *p*-methoxyphenyl group is responsible for such a reaction. Milder acidic conditions (AcOH/50 °C/40 h) did effect the desilylation of **20** cleanly, albeit slowly, without any noticeable pseudo-dimerization. The desilylation of **21** was also conducted under similar conditions and it was complete in about 22 h.

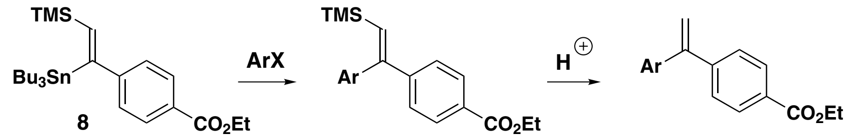
Not surprisingly, the TFA/CH_2Cl_2 desilylation failed when a pyridine moiety was present (see entry 10). Vinylsilane **22** was stable to 10% TFA/CH_2Cl_2, and only a minor amount of the desired product (**22a**) was detected after 40 h of reaction time. Increasing the TFA content from 10% to 20% made no significant difference. It is believed that the protonation of the pyridine moiety prevented the formation of the carbocation intermediate (**25**) (Scheme 5). After several attempts, the desilylation was cleanly effected under a microwave condition (170 °C, AcOH, 6 h). The absence of the ester group allows desilylation under milder and nonacidic conditions. For example, vinylsilane **28**, readily synthesized from the commercially available alkyne **26**, was desilylated cleanly with TBAF/THF (Scheme 6). Interestingly, the same yield was obtained when the microwave procedure was applied to substrate **28**. As noted above, the overall yield of ethylene **29** reflects the efficiency of the Stille coupling, and no attempt has been made to optimize this step for substrate **27**.

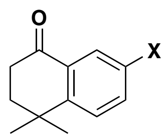
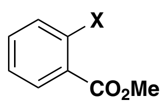
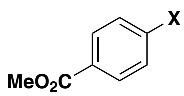
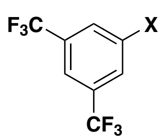
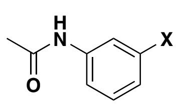
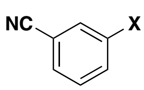
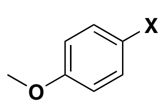
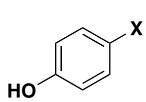
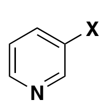
The Stille condition employed for the aryl iodides (Pd_2dba_3/CuI/Ph_3As/DMF) failed for the corresponding



Scheme 3. Reagents and conditions: (i) silylstannane **8**, Pd_2dba_3, CuI, Ph_3As, DMF, 50 °C; (ii) 10% TFA/CH_2Cl_2.

Table 1. Conditions and yields for the synthesis of 1,1-diarylethylenes

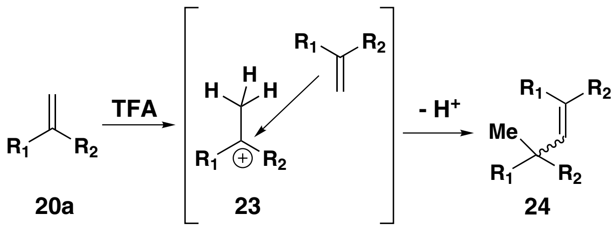


Entry	ArX	X[a]	Diarylvinylsilane	Desilylation[c] conditions	Final product	Yield[d]
1		I	**13**	(i)	**13a**	66
2	PhX	I/Br I[b]	**14**	(i)	**14a**	77/80 88
3		I	**15**	(i)	**15a**	56
4		I Br	**16**	(i)	**16a**	72 89
5		I	**17**	(i)	**17a**	77
6		I	**18**	(i)	**18a**	68
7		I Br	**19**	(i)	**19a**	71 83
8		I	**20**	(ii)	**20a**	72
9		I	**21**	(ii)	**21a**	64
10		I	**22**	(iii)	**22a**	73

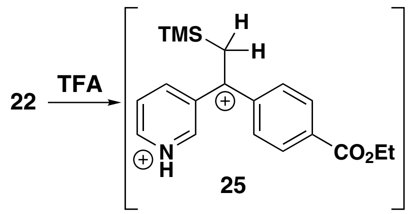
[a] For the Stille coupling of ArI and ArBr, [Pd_2dba_3, Ph_3As, CuI, DMF, 50 °C] and [$Pd(Ph_3P)_4$, CuI, LiCl, DMF, 70 °C] were employed, respectively.
[b] The Stille coupling step was carried out under [$Pd(Ph_3P)_4$, CuI, LiCl, DMF, 70 °C].
[c] Desilylating conditions: (i) 10% TFA/CH_2Cl_2; (ii) AcOH, 50 °C, 24–40 h; (iii) AcOH, microwave at 170 °C for 6 h.
[d] Combined isolated yields for the Stille coupling and desilylation steps.

aryl bromides. After a careful study of catalysts/additives/solvents on a bromobenzene/silylstannane **8** system, it was observed that the coupling could be effected readily with $Pd(Ph_3P)_4$/CuI/LiCl/DMF (see entries 2, 4, and 7). Compared to the aryl iodides, the aryl bromides reacted cleanly under the new condition, and there was a noticeable improvement in yields for entries 4 and 7. Interestingly, when the new coupling condition was applied to iodobenzene, the overall yield increased to 88% (see entry 2), suggesting a more effective catalyst system.

In conclusion, we have devised a two-step protocol that readily elaborates an α-stannyl β-silylstyrene to a family



Scheme 4. R_1 = *p*-MeOPh; R_2 = *p*-EtO_2CPh.



Scheme 5.

of 1,1-diarylethylenes. In order to expand the substrate scope, a number of complementary Stille coupling and desilylation protocols have been developed. Considering the ease of synthesis of α-stannyl β-silylstyrenes and the *ipso*/*cine*-substitution complications associated with the Stille coupling, the approach communicated in this manuscript should prove valuable in the synthesis of 1,1-diarylethylenes.

3. Representative procedures

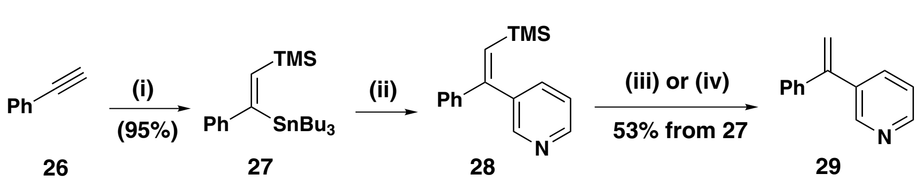
Final products were fully characterized with $^1H/^{13}C$ NMR, MS, and either elemental analysis or HRMS. The molecular ion of silylstannane **27** was not observed in MS analysis, albeit the sample gave satisfactory $^1H/^{13}C$ NMR and elemental analysis. Except for **11** and **13**, the vinylsilane intermediates were not characterized; for these intermediates, only LC/MS data was obtained.

Silylstannane **8**: $Pd(Ph_3P)_4$ (855 mg, 0.740 mmol) was added to a 1,4-dioxane (90 mL) solution of alkyne **7** (8.32 g, 47.76 mmol) and *n*-Bu_3SnTMS (19.95 g, 54.92 mmol), and the reaction mixture was refluxed for 35 min. The volatile components were removed in vacuo and the residue was submitted to flash chromatography (2.5% EtOAc/hexanes) to afford silylstannane **8** as a colorless viscous oil (23.47 g, 91%). ^1H NMR (500.1 MHz, $CDCl_3$, $\delta = 7.26$): 7.94 (d, $J = 8.3$, 2H), 7.02 (d, $J = 8.2$, 2H), 6.56 (s, 1H; two satellite peaks were observed with $J_{Sn-H} = 153.8$ and 160.8), 4.37 (q, $J = 7.1$, 2H), 1.57–1.37 (m, 9H), 1.29–1.22 (m, 6H), 0.92–0.83 (m, 15H), 0.18 (s, 9H). ^{13}C NMR (125.8 MHz, $CDCl_3$, $\delta = 77.0$): 166.8, 165.4, 156.8, 149.5, 129.4, 127.4, 125.8 ($J_{Sn-C} = 14.0$), 60.8, 29.0 ($J_{Sn-C} = 19.7$), 27.3 ($J_{Sn-C} = 60.4$), 14.4, 13.6, 12.0 ($J_{Sn-C} = 330.3$, 315.7), 0.12. MS (CI) $(M+H)^+ = 539.25$. Anal. Calcd for $C_{26}H_{46}O_2SiSn$: C, 58.11; H, 8.63. Found: C, 58.46; H, 8.64.

Vinylsilane **13**: A mixture of Pd_2dba_3 (15.9 mg, 0.017 mmol), Ph_3As (20.0 mg, 0.065 mmol), and CuI (11.0 mg, 0.058 mmol) was added to a DMF (4.0 mL) solution of silylstannane **8** (300 mg, 0.558 mmol) and 7-iodo-4,4-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (195.2 mg, 0.650 mmol). After N_2 was bubbled through the reaction mixture for 2 min, it was stirred at room temperature for 5 min and at 50 °C for 6 h. The volatile components were removed in vacuo, and the residue was submitted to flash chromatography (5% EtOAc/hexanes) to afford the desired compound (**13**) along with minor impurities. Rechromatographing (20% CH_2Cl_2/hexanes) afforded clean **13** as a viscous colorless oil (162 mg, 69%). ^1H NMR (500.1 MHz, $CDCl_3$, $\delta = 7.26$): 7.93 (d, $J = 8.5$, 2H), 7.89 (d, $J = 2.0$, 1H), 7.41 (d, $J = 8.0$, 1H), 7.32–7.30 (m, 3H), 6.39 (s, 1H), 4.36 (q, $J = 7.0$, 2H), 2.76 (t, $J = 6.8$, 2H), 2.07 (t, $J = 6.8$, 2H), 1.43 (s, 6H), 1.38 (t, $J = 7.0$, 3H), 0.12 (s, 9H). ^{13}C NMR (125.8 MHz, $CDCl_3$, $\delta = 77.0$): 198.2, 166.4, 155.1, 151.9, 147.1, 140.1, 134.8, 133.4, 130.7, 129.5, 129.4, 128.3, 127.2, 125.6, 60.9, 37.1, 35.2, 33.9, 29.8, 14.3, −0.1. MS (EI) $(M+H)^+ = 421.2$. Anal. calcd for $C_{26}H_{32}O_3Si$: C, 74.24; H, 7.67. Found: C, 73.96; H, 7.62.

Diarylethylene **13a**: 10% TFA/CH_2Cl_2 (2.0 mL) was added to vinylsilane **13** (140 mg, 0.333 mmol). The resulting reaction mixture was stirred at room temperature for 105 min and the volatile components were removed in vacuo. The residue was submitted to flash chromatography (10% EtOAc/hexanes) to afford diarylethylene **13a** as a viscous oil (110 mg, 95%). ^1H NMR (500.1 MHz, $CDCl_3$, $\delta = 7.26$): 8.02–8.00 (m, 3H), 7.44–7.36 (m, 4H), 5.58 (s, 1H), 5.55 (s, 1H), 4.39 (q, $J = 7.1$, 2H), 2.75 (app t, $J = 6.8$, 2H), 2.04 (app t, $J = 6.8$, 2H), 1.41 (s, 6H), 1.40 (t, $J = 7.1$, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$, $\delta = 77.0$): 198.3, 166.4, 152.0, 148.3, 145.6, 138.9, 133.5, 131.2, 129.9, 129.6, 128.1, 126.8, 126.0, 116.4, 61.0, 37.0, 35.2, 33.9, 29.7, 14.4. HRMS (CI) calcd for $C_{23}H_{25}O_3$ $(M+H)^+ = 349.1804$, found 349.1793.

A general Stille coupling condition for aryl bromides: LiCl (101 mg, 2.38 mmol) followed by a mixture of $Pd(Ph_3P)_4$ (57.1 mg, 0.0494 mmol) and CuI (29.8 mg,



Scheme 6. Reagents and conditions: (i) *n*-Bu_3SnTMS, $Pd(Ph_3P)_4$, dioxane, Δ; (ii) 3-iodopyridine, Pd_2dba_3, CuI, Ph_3As, DMF, 50 °C; (iii) AcOH, microwave at 170 °C, 5 h; (iv) TBAF/THF, 50 °C, <26 h.

0.156 mmol) were added to a DMF (6.0 mL) solution of silylstannane **8** (534.2 mg, 0.994 mmol) and the aryl bromide (1.23 mmol). N_2 was bubbled through the reaction mixture for 2 min, and it was heated at 70 °C until the stannane was consumed as determined by TLC and/or LC/MS. The product was isolated by employing standard chromatographic techniques. The resultant vinylsilane was submitted to the corresponding desilylation protocol described in Table 1, and the final product was purified by a standard flash chromatography.

Acknowledgements

We thank Dr. Stella Huang and Dr. Daniel Schroeder for conducting a number of NMR studies.

References and notes

1. For *cine*-substitution in the coupling of vinylstannanes with aryl halides, or arylstannanes with vinyl triflates, see: (a) Stork, G.; Isaacs, R. C. A. *J. Am. Chem. Soc.* **1990**, *112*, 7399–7400; (b) Levin, J. I. *Tetrahedron Lett.* **1993**, *34*, 6211–6214; (c) Chen, S. *Tetrahedron Lett.* **1997**, *38*, 4741–4744; (d) Quayle, P.; Wang, J.; Xu, J. *Tetrahedron Lett.* **1998**, *39*, 489–492; (e) Flohr, A. *Tetrahedron Lett.* **1998**, *39*, 5177–5180.
2. For *cine*-substitution in the coupling of vinylstannanes with diazonium salts, and a vinyl bromide with organozinc reagents, see: (a) Kikukawa, K.; Umekawa, H.; Matsuda, T. *J. Organomet. Chem.* **1986**, *311*, C44–C46; (b) Ennis, D. S.; Gilchrist, T. L. *Tetrahedron Lett.* **1989**, *30*, 3735–3736.
3. (a) See Refs. 1b,c,e. (b) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.
4. (a) Busacca, C. A.; Swestock, J.; Johnson, R. E.; Bailey, T. R.; Musza, L.; Rodger, C. A. *J. Org. Chem.* **1994**, *59*, 7553–7556; (b) Farina, V.; Hossain, M. A. *Tetrahedron Lett.* **1996**, *37*, 6997–7000; (c) Fillion, E.; Taylor, N. J. *J. Am. Chem. Soc.* **2003**, *125*, 12700–12701; (d) For an alternative mechanism, see Ref. 2a.
5. Mitchell, T. N.; Wickenkamp, R.; Amamria, A.; Dicke, R.; Schneider, U. *J. Org. Chem.* **1987**, *52*, 4868–4874.
6. (a) Chenard, B. L.; Van Zyl, C. M.; Sanderson, D. R. *Tetrahedron Lett.* **1986**, *27*, 2801–2804; (b) Chenard, B. L.; Van Zyl, C. M. *J. Org. Chem.* **1986**, *51*, 3561–3566.
7. (a) Timbart, L.; Cintrat, J.-C. *Chem. Eur. J.* **2002**, *8*, 1637–1640; (b) See also Refs. 5,6.
8. Tin has two NMR active isotopes, ^{117}Sn and ^{119}Sn, with a natural abundance of 7.7% and 8.7%, respectively, and a spin of 1/2: (a) Jackman, L. M.; Sternhell, S. In *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*. 2nd ed.; Pergamon: New York, NY, 1993; pp 354–356; (b) Leusink, A. J.; Budding, H. A.; Marsman, J. W. *J. Organomet. Chem.* **1967**, *9*, 285–294.
9. (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595; (b) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905–5911; (c) Ciattini, P. G.; Morera, E.; Ortar, G. *Synth. Commun.* **1995**, *25*, 2883–2894; (d) The Stille coupling failed when CuI was omitted, and everything else was kept the same.
10. It was convenient to prepare and use a stock sample of a 'pre-mixed' catalyst by grinding together Pd_2dba_3/CuI/Ph_3As in the ratio indicated in the experimental section. Such a mixture kept its catalytic activity for at least eight weeks, when stored at ambient temperature.
11. Although the presence of traces of acid may contribute to protodestannylation, one study indicates that the interplay of steric/electronic factors may also be important: Keay, B. A.; Bontront, J.-L. J. *Can. J. Chem.* **1991**, *69*, 1326–1330.
12. According to LC/MS monitoring of the desilylation step, the following HPLC ratios of desired product **20a** to pseudo-dimer **24** were observed: 15.1/1.0 (at 10 min) and 1.0/2.4 (at 26.5 h). The LC/MS was conducted at 220 nm wavelength.