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Preparation and Double Michael Addition Reactions of a Synthetic Equivalent of the Nazarov Reagent

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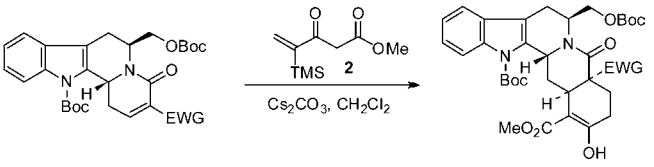
ABSTRACT



A synthetic equivalent of the Nazarov reagent, the silyl derivative 2, able to undergo base-catalyzed double Michael addition reactions with α,β-unsaturated carbonyl compounds has been developed. The new reagent satisfactorily reacts with unsaturated indolo[2,3-*a*]quinolizidine lactams to give pentacyclic yohimbinone-type derivatives.

The Nazarov reagent (methyl or ethyl 3-oxo-4-pentenoate)[1] is a well-known annelating agent that has been extensively used in terpene and alkaloid syntheses.[2] Its usefulness and synthetic versatility stem from its dense functionalization, with a nucleophilic acidic carbon in the β-keto ester moiety and an electrophilic carbon included in an α,β-unsaturated ketone fragment (Scheme 1). The Nazarov reagent (**1**) has successfully been used in a variety of Robinson-type annulations with enolizable ketones,[3] β-dicarbonyl compounds,[4] enamino esters,[5] imines,[6] enamines,[7] dienamines,[8] and (thio)imidates,[9] in which the reagent undergoes an initial Michael addition and the resulting β-keto ester enolate acts as a nucleophile.

Scheme 1. A Synthetic Equivalent of the Nazarov Reagent

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(1) (a) First reported by: Nazarov, I. N.; Zavyalov, S. I. *Zh. Obshch. Khim.* **1953**, *23*, 1703. *Engl. Transl.* **1953**, *23*, 1793. *Chem. Abstr.* **1954**, *48*, 13667h. For improved preparations, see: (b) Zibuck, R.; Streiber, J. M. *J. Org. Chem.* **1989**, *54*, 4717–4719. (c) Zibuck, R.; Streiber, J. M. *Org. Synth.* **1993**, *71*, 236–241 and references cited therein.

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(3) (a) Wenkert, E.; Afonso, A.; Bredenberg, J. B-S.; Kaneko, C.; Tahara, A. *J. Am. Chem. Soc.* **1964**, *86*, 2038–2043. (b) Schkeryantz, J. M.; Luly, J. R.; Coghlan, M. J. *Synlett* **1998**, 723–724. (c) Beauhaire, J.; Ducrot, P.-H. *Tetrahedron Lett.* **2002**, *43*, 4637–4639.

(4) (a) Pelletier, S. W.; Chappel, R. L.; Prabhakar, S. *J. Am. Chem. Soc.* **1968**, *90*, 2889–2895. (b) Brutcher, F. V.; Vanderwerff, W. D.; Dreikorn, B. *J. Org. Chem.* **1972**, *37*, 297–302. (c) Caselli, A. S.; Collins, D. J.; Stone, G. M. *Aust. J. Chem.* **1982**, *35*, 799–808. (d) Watson, A. T.; Park, W. Y.; Wiemer, D. F.; Scott, W. J. *J. Org. Chem.* **1995**, *60*, 5102–5106. (e) Ling, T.; Chowdhury, C.; Kramer, B. A.; Vong, B. G.; Palladino, M. A.; Theodorakis, E. A. *J. Org. Chem.* **2001**, *66*, 8843–8853. (f) Ghosh, S.; Rivas, F.; Fischer, D.; Gonzalez, M. A.; Theodorakis, E. A. *Org. Lett.* **2004**, *6*, 941–944.

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(6) (a) Dodd, D. S.; Oehlschlager, A. C.; Georgopapadakou, N. H.; Polak, A.-M.; Hartman, P. G. *J. Org. Chem.* **1992**, *57*, 7226–7234. (b) Nagata, K.; Sekishiro, Y.; Itoh, T. *Heterocycles* **2007**, *72*, 175–179.

(7) (a) Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.* **1972**, *94*, 5109–5110. (b) Kametani, T.; Hirai, Y.; Kajiwara, M.; Takahashi, T.; Fukumoto, T. *Chem. Pharm. Bull.* **1975**, *23*, 2634–2642. (c) Shono, T.; Hamaguchi, H.; Sasaki, M.; Fujita, S.; Nagami, K. *J. Org. Chem.* **1983**, *48*, 1621–1628. (d) Barrero, A. F.; Arseniyadis, S.; Quílez del Moral, J. F.; Herrador, M. M.; Rosellón, A. *Synlett* **2005**, 789–792.

(8) Kuehne, M. E.; Muth, R. S. *J. Org. Chem.* **1991**, *56*, 2701–2712.

(9) (a) Trost, B. M.; Kunz, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 7152–7157. (b) Celerier, J. P.; Eskenazi, C.; Lhommet, G.; Maitte, P. *J. Heterocycl. Chem.* **1979**, *16*, 953–955. (c) Takahata, H.; Yamabe, K.; Suzuki, T.; Yamazaki, T. *Chem. Pharm. Bull.* **1986**, *34*, 4523–4526. (d) Ortuno, J. C.; Langlois, Y. *Tetrahedron Lett.* **1991**, *32*, 4491–4494.

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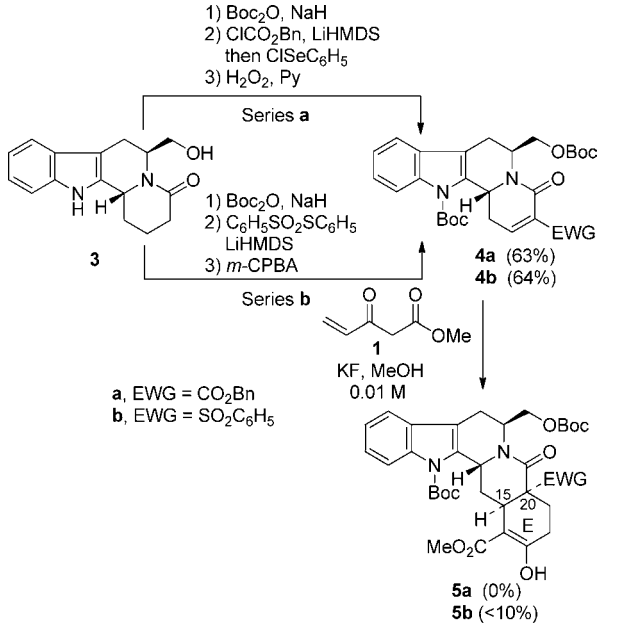
However, the instability of **1** under basic conditions[10] has restricted its use in annulations with α,β-unsaturated carbonyl derivatives, in which the reagent successively acts as a Michael donor and a Michael acceptor.[11,12] To overcome this limitation, as well as the difficulties associated with the preparation and purification of the Nazarov reagent, more stable modified reagents substituted at the olefinic carbons[13] and suitable precursors allowing its *in situ* generation[14] have been developed. In contrast with the original Nazarov reagent, the substituted reagents, extensively used by Deslongchamps, react in their enolate form, smoothly undergoing base-catalyzed double Michael addition reactions to give *cis*-decalin derivatives.[13]

In this letter we present a stable and practical synthetic equivalent of the Nazarov reagent, the silyl derivative **2**, that we have developed in the context of our studies on the use of tryptophanol-derived lactams in the enantioselective synthesis of indole alkaloids.[15] We envisaged a straightforward approach to pentacyclic yohimbine-type derivatives, in which the carbocyclic E ring would be assembled by a double Michael addition of the Nazarov reagent (**1**) to unsaturated indoloquinolizidine lactams **4**. These lactams, which incorporate an additional activating electron-withdrawing substituent, were prepared in good overall yields by conventional methods from the known lactam **3**,[16] as outlined in Scheme 2.

Initial attempts to perform the annulation of the Nazarov reagent **1** with unsaturated lactam **4a** (Cs_2CO_3/ CH_2Cl_2 or KF/MeOH) were unsuccessful, resulting in complete degradation of **1**. When using lactam **4b**, which bears a benzenesulfonyl activating substituent, annulation occurred to some extent, pentacycle **5b** being isolated in very low yield from the resulting complex mixture.

Despite these unsatisfactory results, the viability of our double Michael addition strategy was confirmed by the successful Cs_2CO_3-mediated reaction of the more stable

Scheme 2. Attempted Double Michael Addition with the Nazarov Reagent, **1**



methyl substituted Nazarov reagent **6**[17] with the above lactams **4a** and **4b** to give the respective pentacyclic derivatives **8a** and **8b** as single stereoisomers in excellent yields[18] (Scheme 3). Although it was possible to stereoselectively remove the benzenesulfonyl group of **8b** with retention of the configuration,[19] the presence of the methyl substituent in the carbocyclic E ring makes pentacyclic derivative **9** unsuitable for the synthesis of yohimbine-type natural products.

At this point, we decided to design a synthetic equivalent of the Nazarov reagent that would overcome the inconveniences and limitations of the original reagent **1**. Bearing in mind that α-silylated vinyl ketones have been extensively used as surrogate vinyl ketones in annulation reactions,[20] we planned to prepare a Nazarov-type reagent, such as **2**, silylated at the α-position of the enone (Scheme 4). The α-trimethylsilyl group would increase the electrophilicity of the β-carbon, stabilize the α-anion formed upon Michael addition, and slow down the polymerization due to its steric bulk. Additionally, being α-ketonic in the final compound, the silyl substituent could readily be removed by nucleophiles.

The silyl derivative **2** was prepared from (1-bromovinyl)-trimethylsilane (**10**) via the known[21] allylic alcohol **11**, by a route inspired in the preparation of the Nazarov reagent **1**.[1b,c] Dess-Martin oxidation of **11**, followed by acylation of the unstable acrolein derivative **12** with the enolate

(10) Benetti, S.; Carlo, S.; De Risi, C.; Pollini, G. P.; Veronese, A. C.; Zanirato, V. *Synlett* **2008**, 2609–2612.

(11) (a) For the double Michael addition of the Nazarov reagent to a nitroalkene, see: Albertini, E.; Barco, A.; Benetti, S.; Risi, C. D.; Pollini, G. P.; Romagnoli, R.; Zanirato, V. *Tetrahedron Lett.* **1994**, *35*, 9297–9300. (b) However, see: Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron* **2006**, *62*, 365–374.

(12) For the use of the Nazarov reagent in organocatalytic asymmetric tandem Michael/Morita–Baylis–Hillman reactions, see: Cabrera, S.; Alemán, J.; Bolze, P.; Bertelsen, S.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 121–125.

(13) (a) Lavallée, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 5117–5118. (b) Lavallée, J.-F.; Spino, C.; Ruel, R.; Hogan, K. T.; Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 1406–1426.

(14) (a) Ellis, J. E.; Dutcher, J. S.; Heathcock, C. H. *Synth. Commun.* **1974**, *4*, 71–77. (b) Wakselman, C.; Molines, H. *Synthesis* **1979**, 622–623. (c) Michael, J. P.; Zwane, M. I. *Tetrahedron Lett.* **1992**, *33*, 4755–4758. See also ref 10.

(15) (a) Amat, M.; Santos, M. M. M.; Bassas, O.; Llor, N.; Escolano, C.; Gómez-Esqué, A.; Molins, E.; Allin, S. M.; McKee, V.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 5193–5201. (b) Amat, M.; Gómez-Esqué, A.; Escolano, C.; Santos, M. M. M.; Molins, E.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1205–1211. (c) Pérez, M.; Arioli, F.; Rigacci, G.; Santos, M. M. M.; Gómez-Esqué, A.; Escolano, C.; Florindo, P.; Ramos, C.; Bosch, J.; Amat, M. *Eur. J. Org. Chem.* **2011**, 3858–3863. (d) Amat, M.; Ramos, C.; Pérez, M.; Molins, E.; Florindo, P.; Santos, M. M. M.; Bosch, J. *Chem. Commun.* **2013**, *49*, 1954–1956.

(16) Allin, S. M.; Thomas, C. I.; Doyle, K.; Elsegood, M. R. J. *J. Org. Chem.* **2005**, *70*, 357–359.

(17) Pollet, P.; Gelin, S. *Synthesis* **1978**, 142–143.

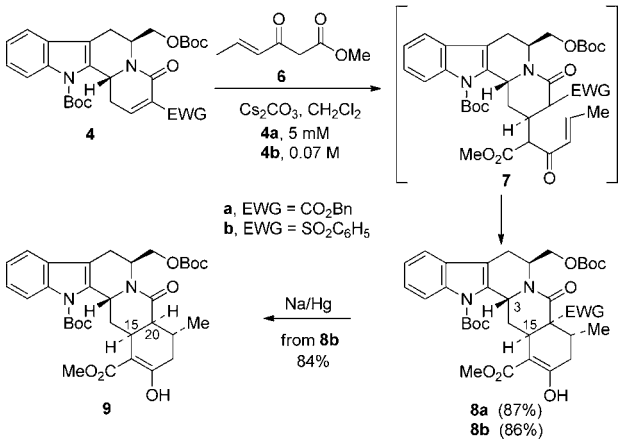
(18) When the reaction from **4b** was conducted for shorter times, mixtures of **8b** and the intermediate Michael adduct **7b** were formed.

(19) The *cis* D/E ring junction in **9** and **16** was evident from the positive NOE effect between 15-H and 20-H.

(20) Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152–6153.

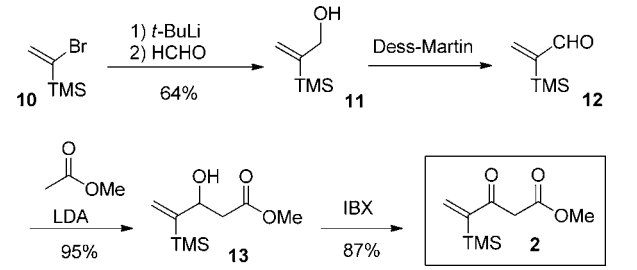
(21) Lipshutz, B. H.; Mollard, P.; Lindsley, C.; Chang, V. *Tetrahedron Lett.* **1997**, *38*, 1873–1876.

Scheme 3. Double Michael Addition of Methyl 3-Oxo-4-hexenoate (**6**)



of methyl acetate, and IBX oxidation of the resulting β-hydroxy ester **13** gave **2** in 53% overall yield in four steps. This silylated Nazarov reagent was stable in storage at −20 °C under nitrogen for several months.[22]

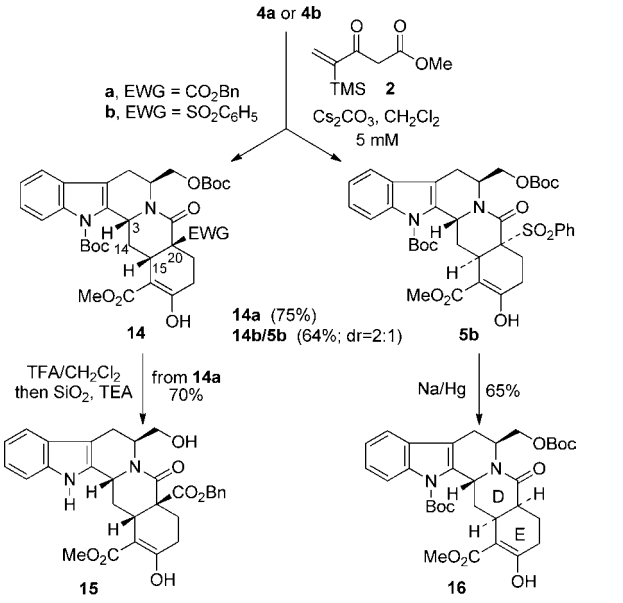
Scheme 4. Preparation of the New Nazarov Reagent **2**



To our delight, reagent **2** satisfactorily reacted with unsaturated lactams **4a** and **4b** to give double Michael addition products, in which the trimethylsilyl group had undergone *in situ* protodesilylation.[23] Thus, treatment of **4a** with **2** under the reaction conditions outlined in Scheme 5 stereoselectively led to a single pentacycle **14a** in excellent yield. A subsequent removal of the Boc protecting group provided **15**. A similar reaction from **4b** afforded a diastereoisomeric mixture of pentacycles **14b** and **5b** (2:1 ratio; 64%),[24] the latter being stereoselectively converted to the epi-*allo*-yohimbinone derivative **16** by reductive removal of the activating benzenesulfonyl group.[19]

The absolute configuration of **5b** was unambiguously established by X-ray crystallography. In turn, the 3-H/15-H *cis* relationship in the isomers **14a** and **14b** (as well as in **19**; see Scheme 6) was deduced from the positive NOE effect between these protons. With these assignments taken into account, the NMR chemical shifts of the protons and carbons at the 3- and 14-positions were of diagnostic value to assign the C-3, C-15, and C-20 relative stereochemistry of the pentacyclic derivatives reported in this work (see tables in the Supporting Information).

Scheme 5. Double Michael Addition of the Nazarov Reagent Equivalent **2** to Unsaturated Lactams **4**



Similar satisfactory results were obtained in the reaction of the silylated Nazarov reagent **2** with unsaturated lactams **18** (Scheme 6), which lacks the *O*-Boc hydroxymethyl substituent, and **20** (Scheme 7), unprotected at the hydroxy function and indole nitrogen. The former was prepared from the known saturated lactam **17**[25] as outlined in Scheme 6, whereas the latter by was prepared by TFA treatment of the above lactam **4a**.

Somewhat surprisingly, whereas lactam **18** behaved like lactams **4**, stereoselectively leading to an all-*cis* pentacycle, **19**, the annulation from **20** took place with opposite facial selectivity, giving pentacycle **21** as the major product.[26]

The stereochemical outcome of the double Michael additions deserves comment. The configuration of the C-15 stereocenter is generated in the initial attack of the Nazarov enolate, and it is known that conjugate addition to unsaturated indolo[2,3-*a*]quinolizidine lactams usually

(22) Reagent **2** was stable enough to be purified by flash chromatography. Although TLC showed that no significant decomposition occurred on stirring a CH_2Cl_2 solution of **2** at 0 °C for 2 h in the presence of Cs_2CO_3, extensive polymerization was observed when the experiment was performed at rt.

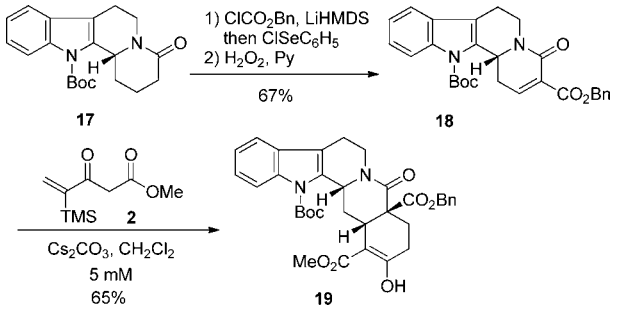
(23) In some runs from **4b**, a trimethylsilyl derivative was detected (NMR) during chromatografic purification of the crude reaction mixture.

(24) When the reaction was carried out at a higher concentration (0.1 M), an inversion of the stereochemistry was observed (**5b**/**14b** ratio 2:1; 62% yield). There are few cases in which concentration has a dramatic effect on the stereoselectivity of a reaction: Yang, F.; Zhu, Y.; Yu, B. *Chem. Commun.* **2012**, *48*, 7097–7099 and ref cited therein.

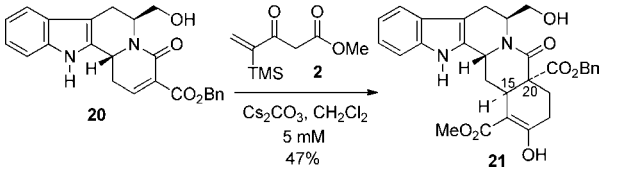
(25) Allin, S. M.; Khera, J. S.; Thomas, C. I.; Witherington, J.; Doyle, K.; Elsegood, M. R. J.; Edgar, M. *Tetrahedron Lett.* **2006**, *47*, 1961–1964.

(26) Trace amounts of the 15,20-epimer were also formed.

Scheme 6. Double Michael Addition of the Nazarov Reagent Equivalent **2** to Unsaturated Lactam **18**



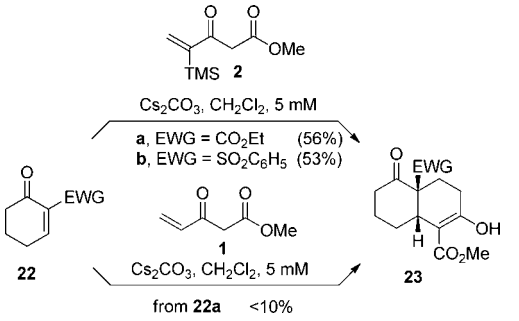
Scheme 7. Double Michael Addition of the Nazarov Reagent Equivalent **2** to Unsaturated Lactam **20**



leads to *trans* 3-H/15-H derivatives, although, for steric reasons, a reversal of the facial selectivity is observed when the indole nitrogen is Boc-protected.[27] On the other hand, the *cis* D/E ring junction[28] results from stereoelectronic control during the second Michael addition.[29]

To further illustrate the synthetic usefulness of the silylated Nazarov reagent **2** as a synthetic equivalent of the original reagent **1**, we also studied Cs_2CO_3-promoted double Michael annulations from cyclohexenones **22a** and **22b** (Scheme 8). Earlier attempts to perform the annulation of **22a** with **1** had only resulted in a very poor yield of **23a**. In contrast, the silylated derivative **2** satisfactorily gave the respective highly functionalized *cis*-decalins **23a**[30] and **23b** in acceptable yields.

Scheme 8. Double Michael Addition of the Nazarov Reagent Equivalent **2** to Enones **22**



In summary, we have developed a synthetic equivalent of the Nazarov reagent, the silyl derivative **2**, which is able to participate in Cs_2CO_3-promoted double Michael annulations with α,β-unsaturated carbonyl compounds, avoiding the polymerization problem associated with the original Nazarov reagent. Starting from unsaturated indolo[2,3-*a*]-quinolizidine lactams, this silylated Nazarov reagent allows the straightforward construction of pentacyclic yohimbinone-type systems.

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Supporting Information Available. Detailed experimental procedures for all new compounds, tables with ^1H and ^{13}C NMR chemical shifts of the pentacyclic derivatives, copies of ^1H and ^{13}C NMR spectra for selected compounds, and X-ray crystallographic information file (CIF) for **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

(27) (a) Naito, T.; Miyata, O.; Ninomiya, I. *Heterocycles* **1987**, *26*, 1739–1742. (b) Overman, L. E.; Robichaud, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 300–308. (c) Gomez-Pardo, D.; Desmaële, D.; d'Angelo, J. *Tetrahedron Lett.* **1992**, *33*, 6633–6636. (d) Deiters, A.; Petterson, M.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 6547–6561. See also ref 25. The *trans* 3-H/15-H stereochemistry in **8** can be rationalized by considering that the substituent at the terminal carbon of the Nazarov reagent **6** slows down cyclization, thus allowing equilibration at C-15.

(28) All pentacyclic derivatives prepared in this work were predominantly (or completely) enolic in solution, as expected for a *cis*-D/E ring junction in yohimbinone-type systems: (a) Albright, J. D.; Goldman, L. *J. Org. Chem.* **1965**, *30*, 1107–1110. (b) Brutcher, F. V., Jr.; Vanderwerff, W. D.; Dreikorn, B. *J. Org. Chem.* **1972**, *37*, 297–302.

(29) Berthiaume, G.; Lavallée, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1986**, *45*, 5451–5454.

(30) TLC of the crude reaction mixture showed the presence of a major compound and only minor amounts of the final product **23a**. After flash chromatography, *cis*-decalin **23a** was the only isolated compound, thus suggesting that protodesilylation mainly occurs during evaporation and purification.

The authors declare no competing financial interest.