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Efficient Protiodesilylation of Unactivated C(sp³)–$SiMe_2Ph$ Bonds Using Tetrabutylammonium Fluoride

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Abstract

The protiodesilylation of unactivated C(sp^3)–$SiMe_2Ph$ bonds proceeds efficiently by treatment with tetrabutylammonium fluoride in wet DMF or THF via isolable dimethylsilanol intermediates

An important strategy for the stereoselective synthesis of highly substituted tetrahydrofurans involves the [3+2]-annulation of chiral crotyl- and allylsilanes with aldehydes.[1] Our laboratory has contributed to this area by demonstrating the predictable stereochemical outcome of [3+2]-annulation reactions of chiral allylsilanes via a formal three-component coupling of two aldehydes and the chiral γ-silyl substituted allylborane **1** (Figure 1).[2,3] Initial coupling of chiral allylborane **1** with an aldehyde (R_1CHO) followed by exposure of the protected α-hydroxy allylsilane **2** to a Lewis acid and a second aldehyde (R_2CHO), selectively affords either *c i s* - or *trans*-substituted tetrahydrofurans **3** or **4** in good yields. Importantly, the stereochemistry of the [3+2]-annulation reaction is determined by the nature of the Lewis acid employed (Figure 1).[2a] The 2,5-*cis* tetrahydrofuran **3** is obtained typically with ≥20 : 1 selectivity when BF_3•OEt_2 is employed, while the diastereomeric 2,5-*trans* disubstituted tetrahydrofuran **4** is obtained, also typically with ≥20 : 1 d.s., by using $SnCl_4$ (via a chelate controlled transition state, requiring that R_2CHO be capable of chelate formation). In principle, manipulation of the –$SiMe_2Ph$ substituent in **3** or **4** via Tamao-Fleming oxidation[4] or protiodesilylation[5] should allow for general access to tetrahydrofurans **5** and **6**, respectively.

The established literature procedure for protiodesilylation of unactivated C(sp3)–$SiMe_2R$ bonds (i.e. RCH_2SiMe_3 or $RCH_2SiMe_2Ph \rightarrow RCH_3$) involves extended basic hydrolysis (DMSO/H_2O, 5–10% KO*t*Bu, 18-crown-6, 95 °C, 2–7 days).[2,5] Although tetrahydrofurans **6** can be obtained from **3** or **4** using this procedure,[2] the extended reaction times and extremely harsh conditions severely limit the potential applications of this method, with protiodesilylation generally failing for substrates with any reasonably complex R_1 or R_2 (vida infra).[2c]

During the course of several ongoing studies in natural product synthesis, it became paramount that a mild method for accomplishing this protiodesilylation (e.g., **3** or **4** → **6**) reaction be developed. In particular, in connection with studies on the synthesis of amphidinolide F,[6] we demonstrated that protiodesilylation of highly functionalized tetrahydrofurans of general structure **4** could be effected by treatment with TBAF in DMF (Scheme 1).[2c] We report herein a much wider range of examples of this process, which serve to define the scope of this mild and efficient protiodesilylation reaction.

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We began with a careful exploration of the original Hudrlik-type conditions[5a–c] by using tetrahydrofurans **1 1** and **14α/β** (Scheme 2).[7] Initially, we anticipated that a neighboring hydroxyl group was required to activate the–$SiMe_2Ph$ group toward protiodesilylation by analogy to the trimethylsilane substrates investigated by Hudrlik,[5a–c] the diphenylsilyl analogs explored by Landais,[5d] and the isolated siloxanes investigated by Hoveyda and Stork.[5e,8] Accordingly, tetrabutylammonium fluoride (TBAF) was added to the standard Hudrlik reaction conditions (DMSO/H_2O, 5–10% KO*t*Bu, 18-crown-6, 95 °C) to effect *in situ* desilylation of the TBS ethers present in both substrates. Unfortunately, these reactions were highly irreproducible, requiring reaction times from 1 day to 1 week for complete conversion. The long reaction times necessitated that these experiments be performed in sealed pressure tubes (to prevent evaporation of solvent), which proved highly inconvenient for reaction monitoring. In addition, significant decomposition of even the relatively simple tetrahydrofuran **11** was observed.

Interestingly, brief treatment of both **11** and **1 4 α** or **14β** under the TBAF-modified Hudrlik conditions led to the generation of the sensitive but isolable silanols **15**, **17α**, and **17β** after aqueous work-up (Scheme 2).[9] Both **15** and **17α/β** were competent in the further conversion to **16** and **18α/β** upon exposure to the reaction conditions. These silanol intermediates are likely not accessible from the corresponding trimethylsilyl derivatives explored by Hudrlik.[5] This suggested to us that the protiodesilylation of –$SiMe_2Ph$ groups might occur via a different mechanistic pathway compared to the –$SiMe_3$ derivatives, and that a cyclic silicate or siloxane may not be a required intermediate.

Significant differences in substrate scope for the present process compared to the –$SiMe_3$ substrates studied by Hudrlik quickly became evident. Tetrahydrofurans **19–21**[10] undergo smooth carbon-silicon bond cleavage to afford protiodesilylated adducts **22**–**24** in good yields (entries 1–3, conditions A, Table 1). Interestingly, the protiodesilylation of **20** and **21** proceeds smoothly even though they lack a proximal hydroxyl group—clearly indicating that a neighboring hydroxyl group is not required for the protiodesilylation of –SiMe2Ph groups [11]

A systematic study of the reagents employed for the conversion of **21** to **24** indicated that TBAF played a role beyond simple in situ desilylation of the silicon protecting groups. In fact, commercial (wet) TBAF alone[12] (added as a solution in tetrahydrofuran) to **19**–**21** in either wet DMF or THF led to rapid and clean conversion to the corresponding protiodesilylated products **22**–**24**, again via the intermediacy of the corresponding silanols (entries 1–3, conditions B, Table 1).[13] Importantly, a substantial improvement in the isolated yield of **1 6** from the protiodesilylation of **11** was realized under these new conditions (entry 4, Table 1).

The reproducible isolation of silanol intermediates in all the systems studied, and the competence of these silanols toward further protiodesilylation, suggests that the Ph–$SiMe_2R$ bond undergoes rapid protiodesilylation as an initial step.[12a–c] The deuterium labeling study illustrated in Scheme 3 indicates that the Si–substrate bond in a subsequently formed silicate intermediate (e.g., **25**)[14] is sufficiently nucleophilic to undergo efficient and stereoselective protonolysis with complete retention of stereochemistry in the one case studied (i.e. **2 5** → **26**, Scheme 3). The significant enhancement of reaction rate (5 d → 4 h) of the TBAF-mediated protiodesilylation reaction (new conditions) compared to the original hydroxide-mediated reaction conditions[5] indicates that a fluorosilicate intermediate analogous to **25** with –F replacing one or more –OD groups in **25** may be a key intermediate in the TBAF-mediated process.

This TBAF-mediated procedure for protiodesilylation of unactivated C(sp3)–$SiMe_2Ph$ bonds has proven to be crucial in our efforts to apply the [3+2]-annulation reaction strategy in a variety of ongoing total synthetic endeavors. Specifically, amphidinolide E precursors **27** and **28**,

which could only be coaxed into slow decomposition using the original Hudrlik-type protocol,[5] now undergo efficient protiodesilylation in >90% yield (entries 1–2, Table 2). Furthermore, global desilylation of **7** and **2 9** afford versatile C(15)–C(26)[2c] and C(1)–C(9) fragments of amphidinolide F (entries 3–4, Table 2). Bistetrahydrofurans **30**–**32**, assembled using sequential [3+2] annulations,[15] can be efficiently protiodesilylated using this modified protocol (entries 5–7, Table 2), and represent important steps in our ongoing efforts toward asimicin and a variety of other Annonaceous acetogenins. The protiodesilylation of the benzhydryldimethylsilane **3 3** (entry 8, Table 2) is noteworthy in that the reaction proceeded with comparable efficiency using either method A or B. Interestingly, the conversion of **33** to **40** was found to proceed through a stable cyclic siloxane intermediate, the only such example uncovered during the course of these studies.[16]

In conclusion, a systematic investigation of the protiodesilylation reactions of Me_2PhSi–substituted tetrahydrofurans has revealed that (*i*) free hydroxyl groups adjacent to the silicon substituent are not required for activation of the C(sp3)–$SiMe_2Ph$ bond (**20**→**23**, **21**→ **24**, **28**→**35** and **29**→**36**) (*ii*) silanols (i.e. $RSiMe_2OH$) are isolable intermediates and are competent for conversion to protiodesilylated products when resubjected to the reaction conditions, and (*iii*) use of TBAF (wet) rather than KO*t*Bu and 18-crown-6 leads to a substantial increase in reaction rate, functional group tolerance, and overall efficiency in the protiodesilylation of –$SiMe_2Ph$ groups Applications of this method in the total synthesis of natural products will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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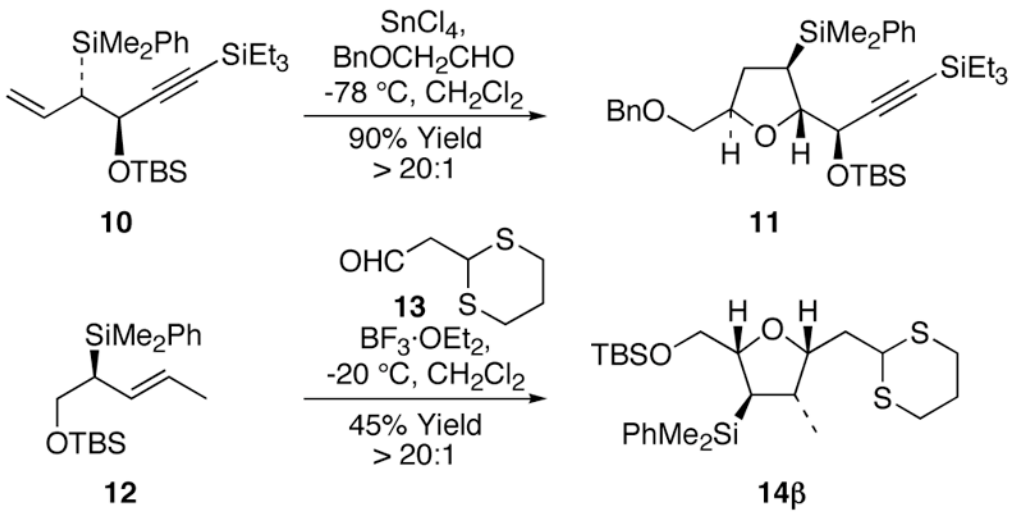
References

1. (a) Panek J, Yang M. J Am Chem Soc 1991;113:9868. (b) Panek J, Beresis R. J Org Chem 1993;58:809. (c) Masse CE, Panek JS. Chem Rev 1995;95:1293. (d) Peng ZH, Woerpel KA. Org Lett 2002;4:2945. [PubMed: 12182595] (e) Peng ZH, Woerpel KA. J Am Chem Soc 2003;125:6018. [PubMed: 12785807]
2. (a) Micalizio GC, Roush WR. Org Lett 2000;2:461. [PubMed: 10814351] (b) Micalizio GC, Roush WR. Org Lett 2001;3:1949. [PubMed: 11405752] (c) Shotwell JB, Roush WR. Org Lett 2004;6:3865. [PubMed: 15469369]
3. Roush W, Pinchuk A, Micalizio G. Tetrahedron Lett 2000;41:9413.
4. Jones GR, Landais Y. Tetrahedron 1996;52:7599.
5. (a) Hudrlik P, Hudrlik A, Kulkarni A. J Am Chem Soc 1982;104:6809. (b) Hudrlik P, Holmes P, Hudrlik A. Tetrahedron Lett 1988;29:6395. (c) Hudrlik P, Gebreselassie P, Tafesse L, Hudrlik A. Tetrahedron Lett 2003;44:3409. (d) Landais Y, Mahieux C. Tetrahedron Lett 2005;46:675. (e) Stork G, Sofia MJ. J Am Chem Soc 1986;108:6826.
6. Kobayashi J, Ishibashi M, Wälchli M, Nakamura H, Hirata Y, Sasaki T, Ohizumi Y. J Am Chem Soc 1988;110:490.
7. Tetrahydrofurans **11** and **14β** were prepared as summarized below.



8. Hale M, Hoveyda A. J Org Chem 1992;57:1643.

9. See: Murakami M, Suginome M, Fujimoto K, Nakamura H, Andersson P, Ito Y. J Am Chem Soc 1995;115:6487. In our hands silanols 17α/β show a marked propensity toward oligomerization upon attempted isolation (see Supporting Information). These oligomeric mixtures are competent intermediates toward further protiodesilylation.

10. Available from the [3+2]-annulation of **1 2** with α-benzyloxyacetaldehyde under non-chelate conditions and subsequent standard transformations (see Supporting Information).

11. Silanols corresponding to **20** and **21** (R = $SiMe_2OH$) have been isolated and fully characterized. These silanols are easily handled, suggesting that the oligomerization of **17α/β** proceeds via condensation of the C(7) hydroxyl and silanol (see Supporting Information).

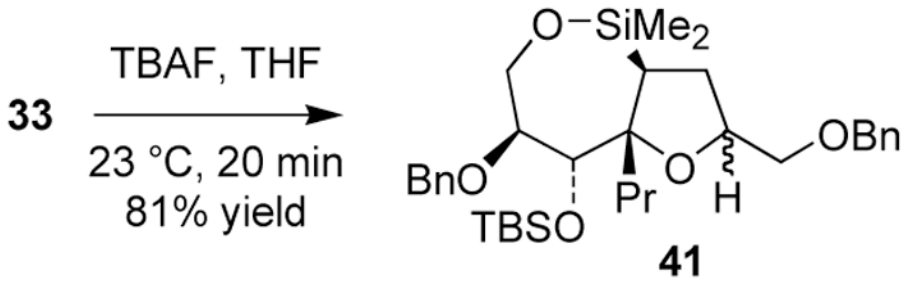
12. For protiodesilylations of stabilized or C(sp^2) systems via silanol intermediates see: (a) Anderson J, Flaherty A. J Chem Soc, Perkin Trans 1 2000:3025. (b) Anderson JC, Munday RH. J Org Chem 2004;69:8971. [PubMed: 15575787] (c) Anderson JC, Anguille S, Bailey R. Chem Commun 2002:2018.Where silanols have not been implicated: (d) Hulme AN, Henry SS, Meyers AI. J Org Chem 1995;60:1265. (e) Ni Y, Montgomery J. J Am Chem Soc 2004;126:11162. [PubMed: 15355092]

13. TBAF is apparently unique in promoting this reaction, as screening of several other fluoride sources for protiodesilylation of **21** (CsF, KF, TAS-F) in various solvent/temperature combinations (MeCN, DMF, DMSO, 23 °C→90 °C, pressure tube) led only to recovered starting materials. Additionally, tetrabutylammonium hydroxide does not promote this transformation (see ref. 2c).

14. Chuit C, Corriu RJP, Reye C, Young JC. Chem Rev 1993;93:1371.

15. Tinsley JM, Roush WR. J Am Chem Soc. submitted

16. Siloxane **41** was formed cleanly upon brief exposure of **33** to excess TBAF at room temperature:



Siloxane **41** was efficiently protiodesilylated to give **40** upon exposure to the reagent combination of method B (89% yield).

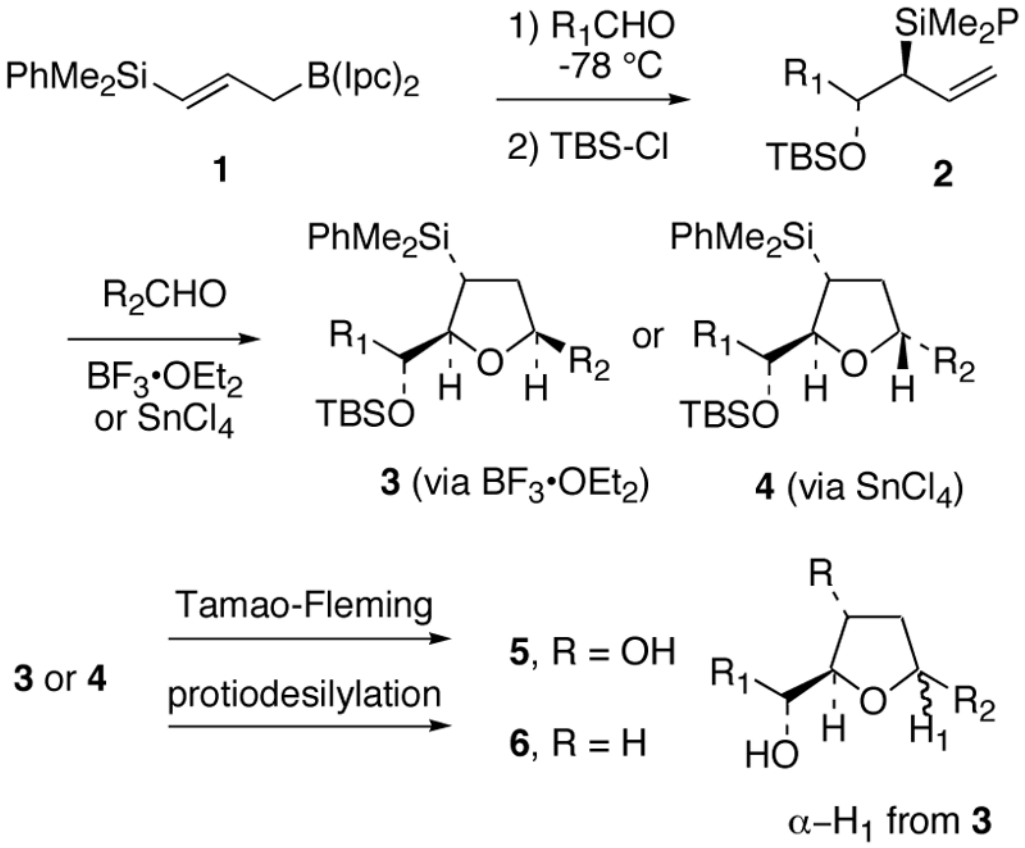
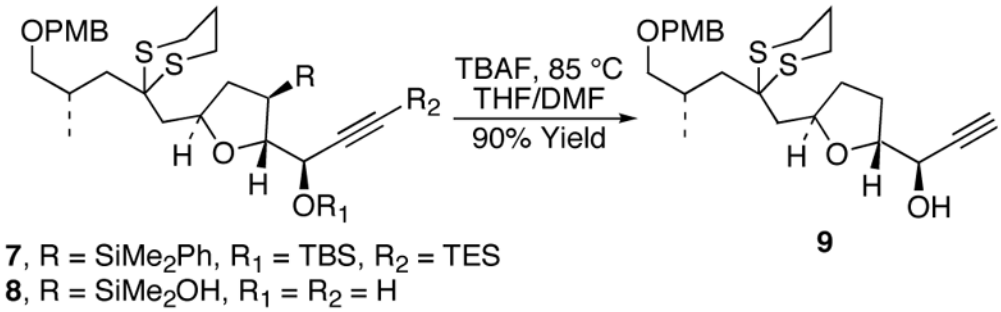


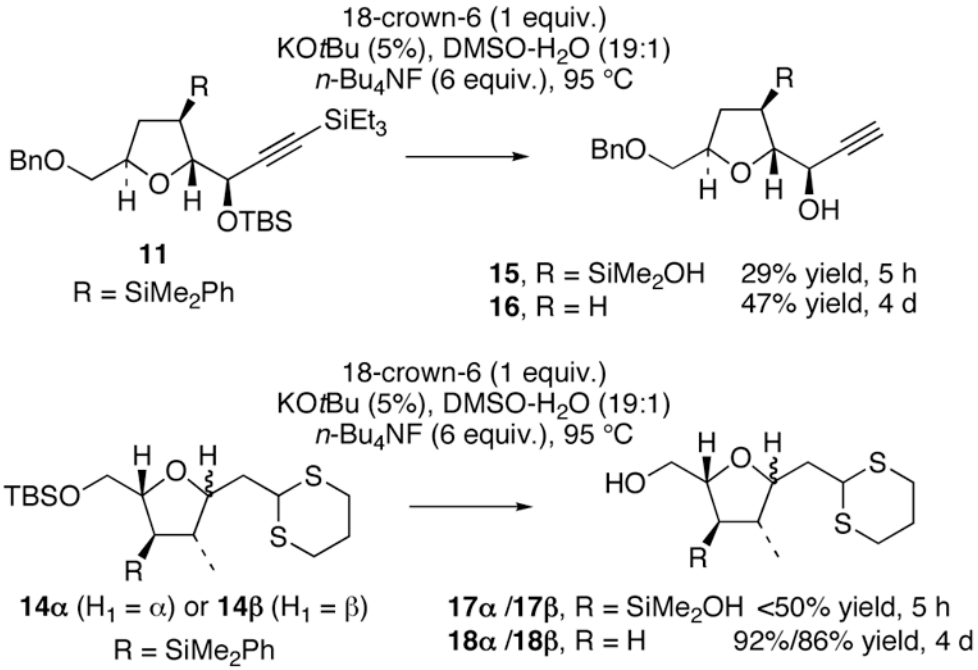
Figure 1.
Three-Components Coupling Strategy for the Stereocontrolled Synthesis of Tetrahydrofurans



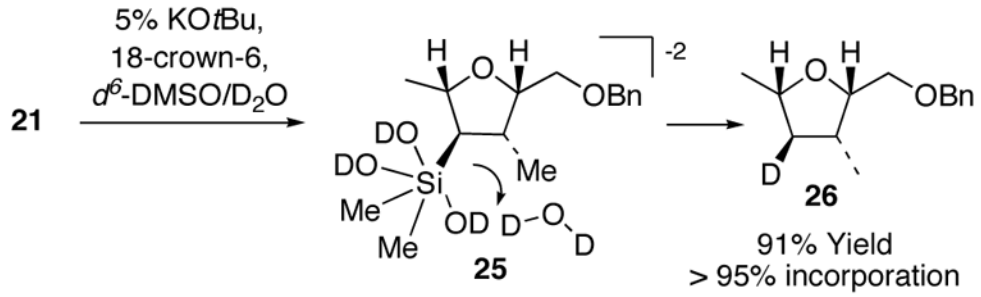
7, R = $SiMe_2Ph$, R_1 = TBS, R_2 = TES
8, R = $SiMe_2OH$, $R_1 = R_2 = H$

9

Scheme 1.
Key TBAF-mediated Protiodesilylation of an Amphidinolide F Precursor (**7**)[3c]



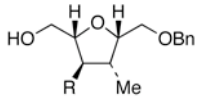
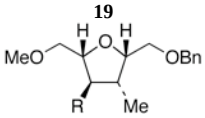
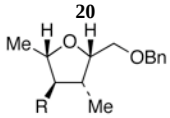
Scheme 2.
Protiodesilylations of Tetrahydrofurans **11** and **14α/β** by using TBAF-modified Literature Conditions



Scheme 3.
Protonation of Intermediate Silanols Proceeds with Retention of Stereochemistry

Table 1

Probing the Role of Neighboring Hydroxyl Assistance in the Protiodesilylation of **19**–**21**

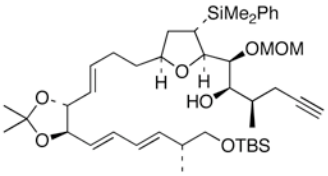
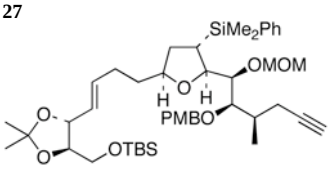
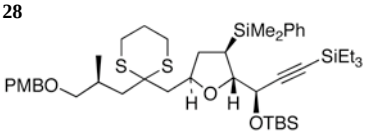
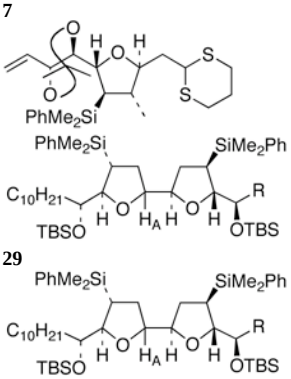
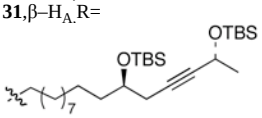
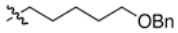
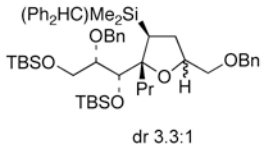
entry	substrate R = $SiMe_2Ph$	Product R = H	Cond. A	cond. B
1	 **19**	**22**	85%	83%
2	 **20**	**23**	92%	82%
3	 **21**	**24**	91%	83%
4	**11**	**16**	47%	86%
5	**14*α***	**18*α***	92%	99%

A: 18-crown-6 (1 equiv.), KO*t*Bu (5%), DMSO/H_2O (19:1), 95 °C, TBAF (6 equiv.), 1–7 d

B: TBAF (3 equiv.), DMF/THF, 75 °C, 4–16 hr

Table 2

Key Protiodesilylation Reactions Directed Toward Natural Product Syntheses

Entry	Substrate	product (all Si→ H)	cond.A	cond.B
1	 **27**	**34**	<10%	91%
2	 **28**	**35**	<10%	97%
3	 **7**	**9**	0–48%	90%
4	 **29**	**36**	41%	87%
5	**30**,β–H_A,R=$C_{10}H_{21}$	**37**	< 20%	60%
6	**31**,β–H_A,R= 	**38**	0–40%	55%
7	**32**,α–H_A,R= 	**39**	0–50%	72%
8	 dr 3.3:1 **33**	**40**	76%	77%

A: 18-crown-6 (1 equiv.), KO*t*Bu (5%), DMSO/H_2O (19:1), 95 °C, *n*Bu_4NF (6 equiv.), 1–4 d

B: TBAF (6 equiv.), DMF/THF, 75 °C, 4–16 hr