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Iododesilylation of TIPS-, TBDPS-, and TBS-Substituted Alkenes in Connection with the Synthesis of Amphidinolides B/D

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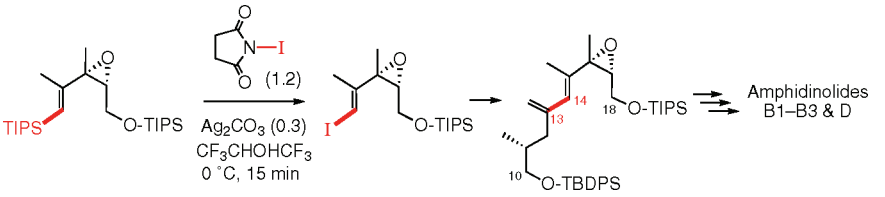
ABSTRACT

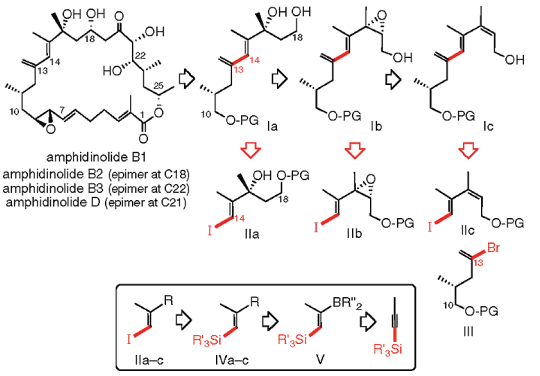


The C−Si bonds of triisopropylsilyl-substituted alkenes, 1,3-dienes, and related multifunctional substrates, as well as analogous C−TBDPS and C−TBS bonds, are readily and chemoselectively cleaved with NIS (or other sources of I^+, such as *N*-iodosaccharin, 1,3-diodohydantoin, and Ipy_2BF_4). The desired iodoalkenes are obtained stereospecifically without byproducts, provided that the reactions are carried out in $CF_3CHOHCF_3$ and, in general, with 30 mol % of Ag_2CO_3 (or AgOAc/2,6-lutidine) as an additive. Fragment C10−C18 of cytotoxic amphidinolides B1−B3 and D has been synthesized using this improved procedure.

In a total synthesis[1] of amphidinolides B1−B3 and D, 26-membered macrolides with impressive cytotoxic activities (in the nanomolar range),[2] we faced the problem of the formation of the key C13−C14 bond of the West Fragment (see Ia−c, Scheme 1) by means of Negishi couplings between IIa−c and bromoalkenes of type III. The total syntheses reported to date of amphidinolides B/D/G/H achieved similar fragments by other approaches.[3]

Fragments IIa−c could arise from the iododesilylation of IVa−c (Scheme 1, bottom), which could come from precursor V via a Suzuki C15−C16 coupling. However,

Scheme 1. Retrosynthetic Analysis of Amphidinolides B1−B3/D



after the remarkable work of Soderquist et al.,[4] it is known that the hydroboration of $R'_3Si-C\equiv C-R$ with 9-BBN gives regioisomers of type V, only with the largest silyl group examined (triisopropylsilyl, TIPS), whereas TMS, TES, and TBS afforded the undesired regioisomers and

(1) Sidera M. PhD Thesis, Universitat de Barcelona (2007−2011).
(2) (a) Kobayashi, J. *J. Antibiot.* **2008**, *61*, 271. (b) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451.
(3) (a) Lu, L.; Zhang, W.; Carter, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 7253 (B1 and B2, allyl silane addition to a methyl ketone, C14−C15), and references therein. (b) Fürstner, A.; Bouchez, L. C.; Morency, L.; Funel, J.-A.; Liepins, V.; Poree, F.-H.; Gilmour, R.; Laurich, D.; Beaufils, F.; Tamiya, M. *Chem.−Eur. J.* 2009, *15*, 3983 (B1, B4, G1, H1, and H2, Stille coupling). C16−OH lacking amphidinolides H and G: (c) Fürstner, A.; Bouchez, L. C.; Funel, J.-A.; Liepins, V.; Poree, F.-H.; Gilmour, R.; Beaufils, F.; Laurich, D.; Tamiya, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9265. Most recent reports of fragments: (d) Petri, A. F.; Schneekloth, J. S.; Mandal, A. K.; Crews, C. M. *Org. Lett.* **2007**, *9*, 3001. (e) Formentin, P.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron: Asymmetry* **2006**, *17*, 2938. (f) Gopalarathnam, A.; Nelson, S. G. *Org. Lett.* **2006**, *8*, 7. For a very recent review on the synthesis of amphidinolides, see: (g) Fürstner, A. *Isr. J. Chem.* **2011**, *51*, 329.

(4) Soderquist, J. A.; Colberg, J. C.; Valle, L. D. *J. Am. Chem. Soc.* **1989**, *111*, 4873.

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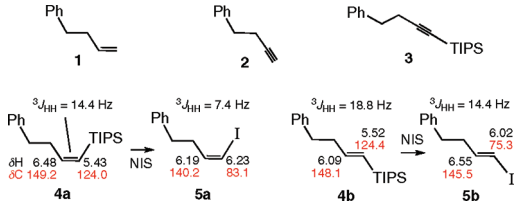
overaddition.[4] The challenge was that, whereas there are >360 reports on the substitution of I for TMS, there is none, according to an exhaustive SciFinder search, on the iododesilylation of TIPS alkenes,[5] of *tert*-butyldiphenylsilyl alkenes (C−TBDPS cleavage), or even of the less sterically crowded TBS alkenes.[6] In this connection, it is worth noting a very recent report by Zakarian et al.[7] on the use of polar, non-nucleophilic $(CF_3)_2CHOH$ (1,1,1,3,3,3-hexafluoro-2-propanol, "hexafluoroisopropanol", HFIP) as the solvent of choice to iodinate TMS alkenes and $PhMe_2Si$ alkenes with *N*-iodosuccinimide (NIS).[8] Would these iododesilylation conditions, the best reported to date,[7] allow the conversion of IVa−c into IIa−c without affecting other C−SiR_3 bonds as well as standard functional groups?

We first examined the reactions of 4-phenyl-1-butene and 4-phenyl-1-butyne derivatives shown in Scheme 2 with NIS in HFIP/$CDCl_3$, by NMR spectroscopy. For example, when an equimolar mixture of **1**, **2**, and **3** in 1:1 HFIP/$CDCl_3$ was treated with NIS at 0 °C and its NMR spectrum was registered at 20 °C, only the olefinic signals of **1** decreased. A mixture of **1** and **4a**, treated with a substoichiometric amount of NIS, gave rise to the disappearance of **4a** to form vinyl iodide **5a**, with retention of the double-bond configuration; only when more NIS was added, did **1** disappear. In another competition experiment between **4a** and **4b**, no difference in the reaction rate of **4a** (to give **5a**) and **4b** (to give **5b**) was detected, even at −20 °C. Thus, TIPS-substituted alkenes (*Z* and *E*) could be transformed into vinyl iodides under these conditions, with retention of the configuration, in the presence of alkenes, alkynes, and silylated alkynes.

Scheme 2. Competition Experiments among **1**−**4**, with NIS[a]



[a] NMR chemical shifts are given in $CDCl_3$ (the spectra were registered in $CDCl_3$ and in 1:1 HFIP/$CDCl_3$). The competition experiments were carried out in 1:1 HFIP/$CDCl_3$.

However, with samples containing oxygen functional groups and/or other double bonds conjugated with the vinyl-TIPS group, the treatment with NIS gave moderate yields and several byproducts, even in HFIP.[9]

Addition of 1 equiv of 2,6-lutidine[7] did not prevent the appearance of several spots on TLC. Even at 0 °C under Ar, with pure NIS (white),[10] protecting the vial from the light, the solution turned pink after few minutes and several byproducts began to appear while some starting material still remained (long reaction times being contraindicated). We hypothesized that radical reactions affording HI by hydrogen abstraction and I_2 (from the dimerization of iodine atoms or from the reaction of HI with remaining NIS) may promote the cleavage of some O−PG bonds and the opening of the epoxide rings; besides, I_2 and HI may add to reactive double bonds. After a series of experiments with different amounts of silver salts and/or bases to trap these impurities, we found that in the presence of 30 mol % of Ag_2CO_3 no pink color appeared during the reactions in which we used 1.2 equiv of NIS. A mixture of AgOAc (0.3−0.4 equiv) and 2,6-lutidine (0.3−0.4 equiv)[11] was similarly efficient. With either of these two procedures, no byproducts were formed; the conversions were 100%, with isolated yields around 90% (see Table 1).

Table 1 shows that enyne **4c** (entry 3 of Table 1), dienes **4d** and **4e** (entries 4 and 5), and compounds with O−Si bonds (entries 4, 5, 7, and 8) only undergo the desired C(sp^2)−TIPS bond cleavage. C−TBDPS and C−TBS bonds can also be cleaved (entries 9−12).

Other iodinating reagents such as *N*-iodosaccharin (NISac),[12] 1,3-diodo-5,5-dimethylhydantoin (DIH),[13] and bis(pyridine)iodonium tetrafluoroborate (Ipy_2BF_4), a reagent developed by Barluenga's group,[14] were examined (Table 1, last three columns). These reagents were similarly efficient. As reactions with Ipy_2BF_4 were slower but did not give rise to secondary reactions, they were allowed to warm to rt;[15] the advantage of this reagent is that the addition of Ag_2CO_3 or AgOAc/2,6-lutidine is unnecessary.

(5) There is only one related example, the desilylation of 2-TIPS-2-cyclopentenone with ICl. See: Davie, C. P.; Danheiser, R. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 5867.

(6) The desilylation of $ArSiR_3$ (*ipso*-S_EAr) is well-known, however.

(7) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727. For previous procedures, see references cited therein.

(8) (a) In our group, this procedure had been applied to the cleavage of a C−TMS bond arising from a Si-tethered RCM: Rodríguez-Escrich, C.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2008**, *10*, 5191. For similar applications: (b) Xie, Q.; Denton, R. W.; Parker, K. A. *Org. Lett.* **2008**, *10*, 5345. (c) Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472. For very recent I/TMS exchanges, see: (d) Herrmann, A. T.; Martinez, S. R.; Zakarian, A. *Org. Lett.* **2011**, *13*, 3636. (e) Parker, K. A.; Denton, R. W. *Tetrahedron Lett.* **2011**, *52*, 2115. Also see: (f) Pawluc, P.; Franczyk, A.; Walkowiak, J.; Hreczycho, G.; Kubicki, M.; Marciniec, B. *Org. Lett.* **2011**, *13*, 1976. (g) Denmark, S. E.; Muhuhi, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 11768. (h) Pawluc, P.; Madalska, M.; Hreczycho, G.; Marciniec, B. *Synthesis* **2008**, 3687.

(9) In standard solvents such as CH_3CN or in CH_2Cl_2, the outcomes were worse.

(10) Commercial samples that were yellow or red were purified by recrystallization from 1,4-dioxane/CCl_4. See: Djerassi, C.; Lenk, C. T. *J. Am. Chem. Soc.* **1953**, *75*, 3493.

(11) For the most simple cases, the addition of Ag^+ was not crucial, as mentioned (the reaction solutions turned pink, but very small amounts of byproducts were formed).

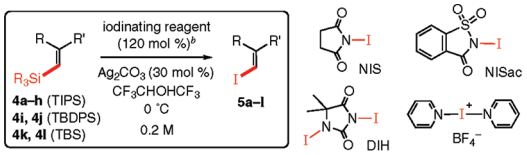
(12) (a) Dolenc, D. *Synlett* **2000**, 544. (b) Rai, A. *Synlett* **2008**, 784 and references cited therein. NISac has not been used in iododesilylations.

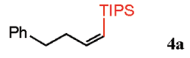
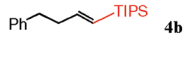
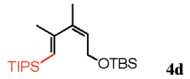
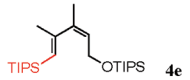
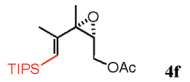
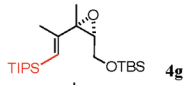
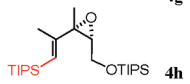
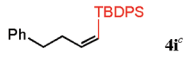
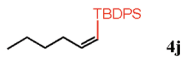
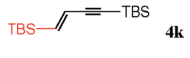
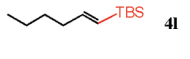
(13) Orazi, O. O.; Corral, R. A.; Bertorello, H. E. *J. Org. Chem.* **1965**, *30*, 1101. An exhaustive SciFinder search indicates that DIH has not been used as a iododesilylating reagent (*N*-iodophthalimide either).

(14) (a) Creighton, J. A.; Haque, I.; Wood, J. L. *Chem. Commun.* **1966**, 229. (b) Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem.* **1985**, *97*, 341. (c) Barluenga, J.; Alvarez-García, L. J.; González, J. M. *Tetrahedron Lett.* **1995**, *36*, 2153. (d) Barluenga, J.; Llorente, I.; Alvarez-García, L. J.; González, J. M.; Campos, P. J.; Díaz, M. R.; García-Granda, S. *J. Am. Chem. Soc.* **1997**, *119*, 6933. (e) Also see ref 8h and references cited therein.

(15) Also with Ipy_2BF_4, the use of HFIP was crucial to achieve high yields of the desired iodo derivative in relatively short reaction times.

Table 1. Iododesilylation of Molecules Containing C(sp^2)–TIPS, C(sp^2)–TBDPS, or C(sp^2)–TBS Bonds[a]



entry	silyl derivatives		NIS	NISac	DIH[b]	Ipy_2^+
			yield of iodo deriv. **5a–l** (%)			
1		**4a**	90			90
2		**4b**	87	87	89	95
3		**4c**	92	90	91	90
4		**4d**	90			
5		**4e**	95			88
6		**4f**	90			90
7		**4g**	90	86	88	91
8		**4h**	90	90	90	88
9		**4i**[c]	93	96	92	86
10		**4j**	92			
11		**4k**	91			
12		**4l**	96		95	

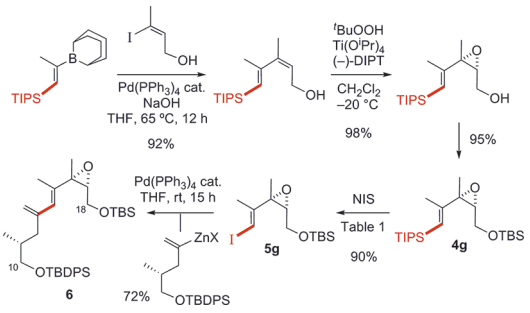
[a] With NIS, NISac, or DIH, substrates and reagents were stirred for 5–25 min at 0 °C, under Ar in the dark. With Ipy_2BF_4, the reactions were slower (at 0 °C, > 1 h was required for completion of several reactions); substrates and reagents (without Ag^+, which was not crucial with this reagent) were mixed at 0 °C, and stirring was then maintained at rt for 15–45 min. Conversions were quantitative in all cases; isolated yields after the workup are given (the yield differences are mainly due to different operation scales and isolation procedures). [b] 60 mol % of DIH was sufficient (both iodine atoms are reactive). [c] A drop of CH_2Cl_2 was added to solubilize **4i**.

The reaction rates of TIPS-substituted alkene **4c** and TBS-substituted alkene **4k** were practically identical. On the other hand, we observed by NMR that, when NIS was added in small portions (up to 90 mol %) to an equimolar mixture of **4a** and **4i** in HFIP/$CDCl_3$, the C–TIPS bond of **4a** was cleaved selectively with regard to the C–TBDPS bond of **4i**.

The fate of the silyl groups in these desilylation reactions was also examined. When the reaction of **4i** with NIS in HFIP was followed by ^1H NMR, a new signal appeared at δ 1.33 corresponding to the methyl groups (of a ^{t}Bu) of a TBDPS. We attributed this signal to $(CF_3)_2CHOTBDPS$, as it was coincident with the new signal that appeared when we heated TBDPSCl and Ag_2CO_3 in neat HFIP. These results suggest that the solvent, HFIP, acts as the main silicon trap (at least at the beginning).

With this information, the synthesis of fragment C10–C18 of amphidinolides B1–B3/D was carried out as summarized in Scheme 3.

Scheme 3. Synthesis of Fragment C10–C18



Addition of 9-BBN to 1-(triisopropylsilyl)-1-propyne, as reported by Soderquist et al.[4] followed by a standard Suzuki–Miyaura coupling,[16] Sharpless' asymmetric epoxidation,[17] and protection of the primary alcohol, gave **4g** in excellent overall yield. We subjected **4g** to the reaction conditions of Table 1 to afford **5g**. A Negishi coupling, after previous conversion of a bromoalkene (see III in Scheme 1)[18] into the corresponding organozinc reagents (with ^{t}BuLi, $ZnCl_2$),[19] gave the desired C10–C18 moiety (**6**) in 72% yield (with 15% recovery of **5g**).

In summary, it is reported here for the first time that TIPS groups (as well as TBDPS and TBS) linked to acyclic double bonds can be quickly, fully, and selectively removed by iodination with full retention of the double-bond configuration, in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). This is consistent with the very recent report by the group of Zakarian[7] of the cleavage of alkene–TMS bonds, but it can also be applied to complex multifunctional substrates in the presence of a small amount of Ag_2CO_3 (or, alternatively, of AgOAc/lutidine). Under these conditions, *N*-iodosaccharin and 1,3-diiodo-5,5-dimethylhydantoin, evaluated as iododesilylation reagents for the first time, are also efficient and do not affect either O–Si bonds, C(sp)–Si bonds, epoxides, etc. Although Ipy_2BF_4 reacts slowly, it does not require the addition of silver salts. Thus, any of the four reagents examined in Table 1 can be used in iododesilylation protocols of complex substrates; other *N*-

(16) (a) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., de Meijere, A., Eds.; Wiley-VCH: New York, 2004; Chapter 2. (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(17) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I.; Ed.; Wiley-VCH: New York, 2000; Chapter 6A.

(18) Prepared from Aux*–COEt and $BrCH_2C(=CH_2)Br$. See: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *8*, 2506.

(19) (a) Negishi, E..; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406. (b) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404.

iodoimides and iodonium ion sources, also commercially available or of easy preparation, may work similarly. The procedure has paved the way to our syntheses of 26-membered ring amphidinolides, as their West Fragment, synthetically the most complex and challenging, is now readily achievable.

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Supporting Information Available. Experimental details and spectral data, including copies of the ^{1}H and ^{13}C NMR spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.