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Silicon-Directed Oxa-Pictet–Spengler Cyclization and an Unusual Dimerization of 2-Trimethylsilanyl Tryptophols

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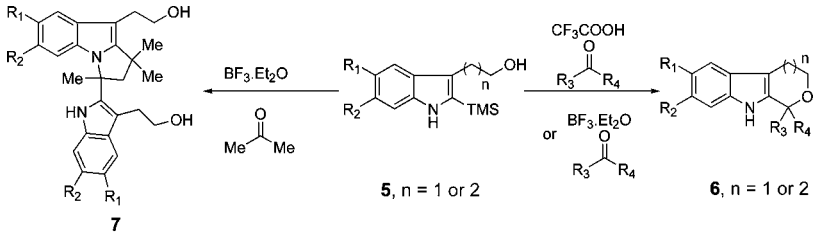
ABSTRACT



The tetrahydro-pyrano[3,4-*b*]indoles 6 were synthesized from 2-(2-trimethylsilanyl-1*H*-indol-3-yl)-ethanols 5 and various ketones or aldehydes through silicon-directed oxa-Pictet–Spengler cyclizations. An unusual reaction led to the dimeric products 7 when some of 5 was treated with acetone using BF_3 as the catalyst.

The tetrahydro-pyrano[3,4-*b*]indole scaffold **1** (Figure 1) has been widely explored in the field of pharmaceutical research. One of the more successful examples, etodolac (**2**) (brand name: Lodine), was discovered as a novel cyclooxygenase-2 (COX-2) inhibitor.[1] This clinical success, along with recent reports that COX-2 may play an important role during premalignant hyperproliferation,[2] has triggered the reinvestigation of tetrahydro-pyrano[3,4-*b*]indoles in the areas of both synthetic and medicinal chemistry.

Versatile methods for synthesizing tetrahydro-pyrano[3,4-*b*]indoles have been documented in the literature. The most efficient method is the traditional oxa-Pictet−Spengler acid-catalyzed cyclocondensation of tryptophols with either ketones or aldehydes.[3,4] However, this method appears to be limited to the assembly of electron-rich or electron-neutral

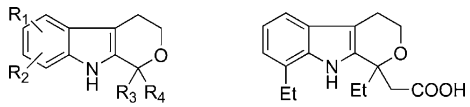


Figure 1.

tetrahydro-pyrano[3,4-*b*]indoles. Moreover, the tryptophol precursors for the oxa-Pictet−Spengler cyclization are generally prepared through classical methods such as Fisher, Madelung, and Reissert procedures,[5] which are limited both in the degree of substitution and the type of functionality that can be incorporated into the indole nucleus. During the course of structure−activity relationship studies, we needed

(1) (a) Demerson, C. A.; Humber, L. G., Dobson, T. A.; Jirkovsky, I. L. *Ger. Offen.* **1973**, 2226340. (b) Vetter, G. Placchi, M. Joubert, L. *J. Clin. Pharmacol. Ther. Toxicol.* **1982**, *20*, 240. (c) Demerson, C. A.; Humber, L. G.; Phillipp, A. H.; Martel, R. R. *J. Med. Chem.* **1976**, *19*, 391. (d) Humber, L. G. *Med. Res. Rev.* **1987**, *7*, 1.

(2) (a) Kreft, A. F.; Caufield, C. E.; Failli, A. A.; Caggiano, T. J.; Greenfield, A. A.; Kubrak, D. M. U.S. Patent 5776967, 1998. (b) Kreft, A. F.; Caufield, C. E.; Failli, A. A.; Caggiano, T. J.; Greenfield, A. A.; Kubrak, D. M. U.S. Patent 5824699, 1998. (c) Carson, D. A.; Cottam, H. B.; Adachi, S.; Leoni, L. M. WO 01/06990, 2002.

(3) (a) Demerson, C. A.; Humber, T. A. *J. Med. Chem.* **1983**, *26*, 1778. (b) Cabral, L. M.; Costa, P. R. R.; Vasconcellos, M. L. A. A.; Barreiro, E. J.; Castro, R. N. *Synth. Commun.* **1996**, *26*, 3671. (c) Soll, R. M.; Guinosso, C.; Asselin, A. *J. Org. Chem.* **1988**, *53*, 2844. (d) Danieli, B. Lesma, G.; Passarella, D.; Slvani, A. *Tetrahedron Lett.* **2000**, *41*, 3489. (e) Chou, S.-Y. *Heterocycles* **2003**, *60*, 1095.

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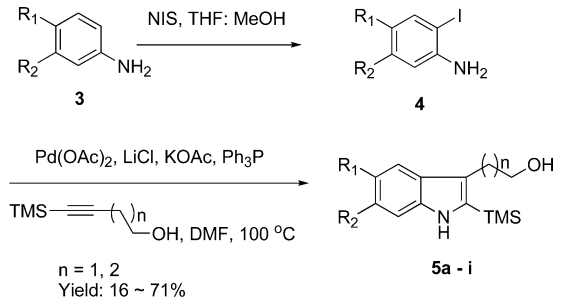
Scheme 1



to prepare a series of electron-withdrawing group-substituted tetrahydro-pyrano[3,4-*b*]indoles. Here, we describe an efficient methodology for syntheses of various electron-demanding tetrahydro-pyrano[3,4-*b*]indoles using Larock's palladium-catalyzed indole synthesis followed by silicon-directed oxa-Pictet−Spengler cyclization of resultant tryptophols with ketones or aldehydes. The scope and limitation of this methodology are also discussed.

The required tryptophol components, 2-(2-trimethylsilanyl-1*H*-indol-3-yl)-ethanols, and 2-(2-trimethylsilanyl-1*H*-indol-3-yl)-propanols **5** were easily prepared in two steps as described by Larock (Scheme 1).[6] First, selective ortho iodinations of anilines **3** afforded the 2-iodinated products **4** in modest to good yields.[7] Palladium-catalyzed heteroannulation of *ortho*-iodoanilines with 4-(trimethylsilanyl)-3-butyn-1-ol or 5-(trimethylsilanyl)-4-pentyn-1-ol gave the corresponding 2-(2-trimethylsilanyl-1*H*-indol-3-yl)-ethanols or 2-(2-trimethylsilanyl-1*H*-indol-3-yl)-propanols **5** with no regioisomeric products isolated. Generally, this reaction proceeded in reasonable yields, excellent regioselectivity, and good tolerance for substitution on the indole cores.

Our initial study on the oxa-Pictet−Spengler cyclization started with 2-(2-trimethylsilanyl-1*H*-indol-3-yl)-ethanol **5a** (entries 1 and 2). As expected on the basis of the well documented behavior of tryptophol, the tetrahydro-pyrano-[3,4-*b*]indole **6a** was obtained in reasonable yield when **5a** was condensed with acetone in trifluoroacetic acid (TFA). To our surprise, when BF_3 etherate was employed as the promoter the reaction of **5a** with acetone always produced complicated mixtures. We tried optimizing the reaction conditions by varying time, temperature, and concentration. Ultimately, a dimeric species was isolated in 45% yield, and the structure was determined to be **7a**. To reconcile the divergent results from TFA- and BF_3-promoted cyclization experiments, we prepared the substrates **5** containing various substitution patterns on the indole cores. These results are summarized in Table 1.[8] Generally, regardless of the strength of the electron-withdrawing groups on the silyl tryptophols **5**, condensation with acetone under TFA promotion to produce tetrahydro-pyrano[3,4-*b*]indoles **6** proceeded in moderate to good yields without detection of the dimers **7** (entries 1, 7, 10, 12, 14, and 18). Benzophenone under these reaction conditions failed to give any cyclization adduct probably due to the steric hindrance (entry 13). Instead, the desilylated product **8a** was obtained after workup. Similarly, the uncyclized adducts **9a** and **9b** were obtained when the electron-deficient trytophols **5g** and **5h** were employed for the condensations with cyclohexanone under identical conditions (entries 15 and 19). It is worth noting that **10** could be generated from the reaction of homotryptophol **5i** with CH_3-CHO in satisfactory yield (entry 21, 54%), though the similar reaction with acetone only gave the desilylated product **8b** without any cyclization (entry 20).

A possible mechanism for the silicon-promoted formation of the tetrahydro-pyrano[3,4-*b*]indoles **6** is shown in Scheme 2. Two pathways are likely involved in this process. Pathway A involves the acid-catalyzed formation of the oxocarbenium ion species **12**, followed by intramolecular electrophilic aromatic substitution on the activated position *ipso* to the trimethylsilyl group of **12**. Intermediate **13** is then believed to form due to the stabilizing hyperconjugation of the TMS group on the β-carbocation.[9] Desilylation of **13** then affords

(4) For references regarding other uses of the oxa-Pictet−Splengler cyclization, see: (a) Bianchi, D. A.; Cipulli, M. A.; Kaufman, T. S. *Eur. J. Org. Chem.* **2003**, *24*, 4731. (b) Bianchi, D. A.; Rua, F.; Kaufman, T. S. *Tetrahedron Lett.* **2004**, *45*, 411. (c) Guiso, M.; Bianco, A.; Marra, C.; Cavarischia, C. *Eur. J. Org. Chem.* **2003**, *17*, 3407. (d) Miles, W. H.; Heinsohn, S. K.; Brennan, M. K.; Swarr, D. T.; Eidam, P. M.; Gelato, K. A. *Synthesis* **2002**, *11*, 1541. (e) Guiso, M.; Marra, C.; Cavarischia, C. *Tetrahedron Lett.* **2001**, *42*, 6531. (f) Wuensch, B.; Zott, M.; Hoefner, G.; Bauschke, G. *Arch. Pharm.* **1995**, *328*, 487. (g) Wuensch, B.; Zott, M. *Tetrahedron: Asymmetry* **1993**, *4*, 2309. (h) Wuensch, B.; Zott, M. *Liebigs Ann. Chem.* **1992**, *1*, 39.

(5) (a) Willette, R. E. *Adv. Heterocycl. Chem.* **1968**, *9*, 27. (b) Yakhonto, L. N.; Prokopov, A. A. *Russ. Chem. Rev.* **1980**, *49*, 428. (c) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

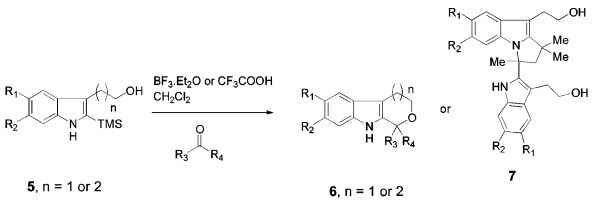
(6) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Ujjainwalla, F.; Warner, D. *Tetrahedron Lett.* **1998**, *39*, 5355. (c) Walsh, T.; Toupence, R.; Ujjainwalla, F.; Young, J.; Goulet, M. *Tetrahedron* **2001**, *57*, 5233.

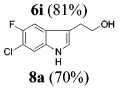
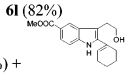
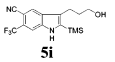
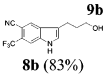
(7) Iodo-4,5-dichloroaniline and 2-iodo-4-fluoro-5-chloroaniline were obtained along with their regioisomers.

(8) (a) **Typical Procedure for TFA-Promoted Oxa-Pictet−Spengler Cyclization, Preparation of 6i.** Acetone (0.2 mL) was added into **5f** (100 mg, 0.35 mmoL) in 3 mL of 2:1 CH_2Cl_2/trifluoroacetic acid solution at 0 °C. The reaction was stirred for 2 h from 0 °C to rt. The reaction was then quenched with saturated $NaHCO_3$ solution and extracted 3x with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by column chromatography (silica gel, hexanes/ EtOAc from 2:1 as the eluent) to give **6i** as a white solid (75 mg, 81%): ^{1}H NMR ($CDCl_3$) δ 7.60 (br, s, 1H), 7.16 (d, J = 3.5 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 3.92 (t, J = 8.5 Hz, 2H), 2.62 (t, J = 8.5 Hz, 2H), 1.42 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.2, 151.8, 141.2, 131.8, 114.7, 112.3, 106.9, 104.4, 71.6, 60.2, 27.6, 22.1; MS (*m*/*z*) MH^- 284. Anal. Calcd for $C_{13}H_{13}ClFNO$: C, 61.54; H, 5.16. Found: C, 61.23; H, 5.09. (b) **Typical Procedure for BF_3-Promoted Dimerization, Preparation of 7c.** BF_3 etherate (0.23 mL, 3.70 mmoL) was added dropwise into the mixture of **5f** (480 mg, 1.68 mmoL) and acetone (0.14 mL, 1.85 mmoL) in 5 mL of dichloromethane at 0 °C. The reaction was slowly warmed to rt over 2 h, and stirring was continued for another 4 h. The mixture was then poured into saturated $NaHCO_3$ solution and extracted three times with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by column chromatography (silica gel, hexanes/EtOAc from 3:1 to 1:1 as the eluent) to give the dimer **7c** as a white solid (285 mg, 67%): ^{1}H NMR ($CDCl_3$) δ 7.66 (br, s, 1H), 7.28 (d, J = 9.0 Hz, 1H), 7.24 (d, J = 4.0 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.01 (d, J = 4.5 Hz, 1H), 3.88 (m, 2H), 3.76 (m, 1H), 3.52 (m, 1H), 3.05 (t, J = 8.5 Hz, 2H), 2.98 (abq, J = 13.5 Hz, 1H), 2.85 (m, 2H), 2.62 (abq, J = 13.5 Hz, 1H), 2.11 (s, 3H), 1.53 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.9, 150.6, 149.8, 139.4, 131.4, 129.2, 127.3, 125.8, 115.6, 114.3, 113.3, 112.3, 111.0, 109.8, 109.0, 106.0, 104.2, 103.3, 101.1, 61.6, 60.8, 56.0, 37.0, 28.4, 27.5, 26.4, 26.0; IR (film, cm^{-1}) 3362, 3290, 1470; MS (*m*/*z*) MH^+ 507, MNa^+ 529. HRMS calcd for $C_{26}H_{26}F_2N_2O_2Cl_2$ 506.1339, found 506.1342.

(9) (a) Wierschke, S. G.; Chandrasekhar, J.; Jorgensen, W. *J. Am. Chem. Soc.* **1985**, *107*, 1496. (b) Lambert, J. B.; Wang, G.; Finzel, R. B.; Teramura, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7838.

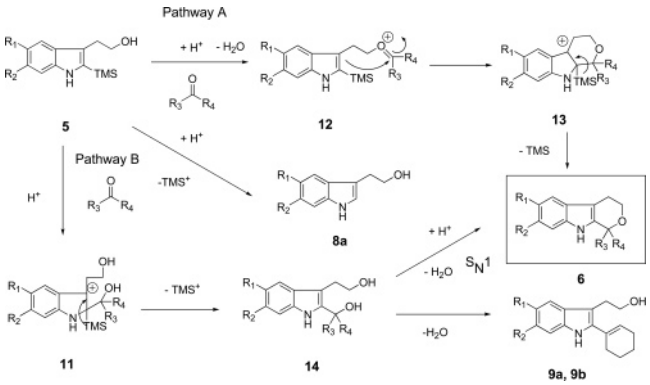
Table 1. Reaction of Silanyl Derivatives **5** with Carbonyls under CF_3COOH or BF_3 Etherate Promotion[a,b]



entry	substrate **5**	promotor	reagent (ketone or aldehyde)	product **6** or **7** and isolated yield (%)
1	R_1 = H, R_2 = H	CF_3COOH	CH_3COCH_3	**6a** (51%)
2	**5a**	BF_3	CH_3COCH_3	**7a**[c] (45%)
3	R_1 = CN, R_2 = CF_3	BF_3	CH_3COCH_3	**6b** (95%)
4	**5b**		CH_3COCH_2SMe	**6c** (68%)
5			CH_3COCH_2SEt	**6d** (65%)
6			CH_3COCH_2SBn	**6e** (62%)
7	R1 = Cl, R_2 = CF_3 **5c**	CF_3COOH	CH_3COCH_3	**6f** (75%)
8	R1 = NO_2, R_2 = CF_3 **5d**	BF_3	CH_3COCH_3	**6g** (60%)
9	R_1 = Cl, R_2 = Cl **5e**	BF_3	CH_3COCH_3	**7b** (80%)
10		CF_3COOH	CH_3COCH_3	**6h** (90%)
11	R_1 = F, R_2 = Cl	BF_3	CH_3COCH_3	**7c** (67%)
12	**5f**	CF_3COOH	CH_3COCH_3	**6i** (81%)
13			PhCOPh	 **8a** (70%)
14	R_1 = CF_3, R_2 = H	CF_3COOH	CH_3COCH_3	**6j** (50%)
15	**5g**		Cyclohexanone	 **9a** (65%)
16	R_1 =CO_2Me, R_2 = H	BF_3	CH_3COCH_3	**7d** (80%)
17	**5h**		CH_3COCH_2SEt	**6k** (20%)
18		CF_3COOH	CH_3COCH_3	**6l** (82%)
19			Cyclohexanone	 **6m** (30%) + **9b** (60%)
20	 **5i**	CF_3COOH	CH_3COCH_3	 **8b** (83%)
21			CH_3CHO	 **10** (58%)

[a] CF_3COOH procedure: **5** (1.0 equiv), ketone or aldehyde (1.5∼2.0 equiv) in CF_3COOH (c = 0.1 M) at 0 °C, then warm to rt, continue for 4∼8 h. [b] BF_3 etherate procedure: **5** (1.0 equiv), ketone (1.5∼2.0 equiv), BF_3 etherate (2.0∼3.0 equiv) in CH_2Cl_2 (c = 0.1 M) at 0 °C, then warmed to rt, continue for 4∼8 h. [c] Complex mixture was obtained, and **7a** was the only product that could be characterized. Replacing **5a** with trytophol gave a similar result.

Scheme 2

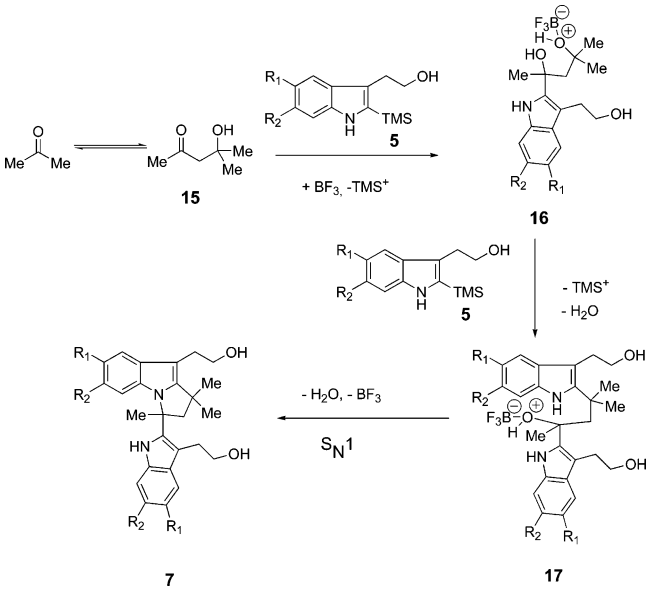


the tetrahydro-pyrano[3,4-*b*]indole **6**. In pathway B, a type of Mukaiyama adol condensation of **5** occurs also assisted by TMS group hyperconjugation. Thus, desilylation of **11** forms the diol **14**. S_N1-type of displacement of H_2O catalyzed by acid in **14** affords the tetrahydro-pyrano[3,4-*b*]indole **6**. Dehydration of **14** was observed to give the isolated products **9a** and **9b** when cyclohexanone was employed as a ketone component. For less reactive ketones such as benzophenone, a simple protodesilylation process occurs to generate **8a**. Overall, a TMS group at the α-position of indole **5**, acting as a "big" hydrogen, could facilitate either the electrophilic aromatic substitution or Mukaiyama adol process and results in substitution by either an intermolecular or intramolecular electrophile. It is of interest that the proposed mechanism here has precedent in the literature described by Kohno and Sekine.[10] This modification on the precursor, compared with that of traditional oxa-Pictet−Spengler cyclization, is extremely effective when an electron-deficient tryptophol is employed as the substrate. For example, acid-catalyzed cyclization of the nonsilylated substrate of **5d** (structure not shown) with acetone only gave a trace amount of **6g**, with most starting material being recovered, while when more harsh conditions (strong acid and heat) were applied, decomposition of the substrate occurred.

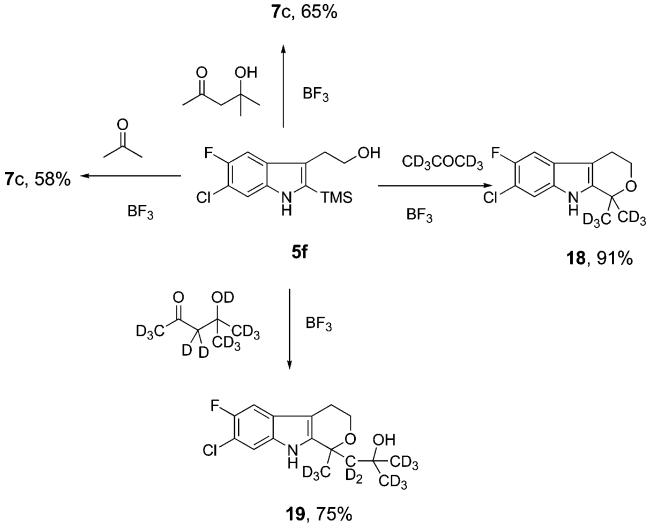
The outcome of the BF_3-promoted cyclization appears to be related to the structures of both the tryptophols **5** and the ketones. Formations of the dimers **7a**−**d** could be observed when acetone and electron-rich, electron-neutral, or weakly electron-deficient 2-(2-trimethyl-silanyl-1*H*-indol-3-yl)-ethanols such as **5a**, **5e**, **5f**, and **5h** were employed in the reactions (entries 2, 9, 11, and 16). BF_3-promoted reactions of **5** with the ketones other than acetone afforded the tetrahydro-pyrano[3,4-*b*]indoles **6** in moderate to good yields (entries 4−6, 17, and 19). Surprisingly, in the case of the BF_3-promoted reactions of some strongly electron-deficient 2-(2-trimethylsilanyl-1*H*-indol-3-yl)-ethanols such as **5b** or **5d** and acetone, the cyclization product formed was the tetrahydro-pyrano[3,4-*b*]indole **6b** or **6g**, respectively (entries 3 and 8). The structure and the relative stereochemistry of **7a** were confirmed by X-ray crystallography. Formation of the dimer **7** appears to be due to the reaction between **5** and 4-hydroxy-4-methyl-2-pentanone **15** generated from BF_3-catalyzed self-condensation of acetone. Supporting evidence for this pathway is illustrated in Scheme 4; utilizing **15** as the ketone component in the oxa-Pictet−Spengler process led to isolation of the dimer **7c**. Although mechanistically unclear, this dimerization process can be envisioned as shown in Scheme 3. Acid-catalyzed dimerization of acetone is in equilibrium with dissociation of **15**. It is more likely that the initial process is the same as pathway B shown in Scheme 2. Thus, the Mukaiyama adol condensation of **5** with **15** gave the intermediate **16**, which acts as the electrophile at the *gem*-dimethyl alcohol site for a Friedel−Craft-type process at the α-position of the second equivalent of **5** to form a dimeric species **17**. It is probably due to the steric hindrance of the allylic alcohol site next to the indole core (the other tertiary alcohol) that the intramolecular process occurs only at the less hindered *gem*-dimethyl alcohol position. Finally, an intramolecular cyclization of **17** results in the dimer **7**. In

(10) Kohno, H.; Sekine, Y. *Heterocycles* **1996**, *42*, 141.

Scheme 3



Scheme 4



the TFA-promoted reaction, the equilibrium shown in Scheme 3 favors the acetone side, leading to the normal oxa-Pictet−Spengler cyclization to form **6**. In comparison, using BF_3 as the promoter in the reaction favors the **15** side probably due to the formation of the stable complex ion between BF_3 and the carbonyl group of **15**.[11] Thus, the dimer **7** is generated through the sequential steps shown in Scheme 3. Probably due to the strong electron-deficiency in **5b** and **5d**, the poor nucleophilicity of silyl indole prohibits the Mukaiyama adol process. Instead, pathway A in Scheme 2 occurred to generate pyrano indoles **6b** and **6g** without any dimers **7**. To our surprise, applying d_6-acetone in BF_3-promoted cyclization with **5f** only gave the deuterated Pictet−Spengler product **18** in 91% yield (Scheme 4). It is reported that the primary isotope effect (k_H/k_D) of acid-catalyzed enolization of acetone, which is the rate-determining step of acetone self-condensation process, is about 7.[12] The substantial difference results in completely different reaction pathways between acetone and d_6-acetone since the dimerization process to **7c** is blocked by slow conversion of d_6-acetone to d_{12}-4-hydroxy-4-methyl-2-pentanone. Unlike **15**, its fully deuterated agent, d_{12}-4-hydroxy-4-methyl-2-pentanone, when employed in BF_3-catalyzed reaction with **5f**, afforded **19** in 75% yield without detection of any deuterated dimer **7c** (Scheme 4). The mechanism is still under investigation. It may be related to the isotope effect during the dissociation of the *tert*-OH to form the five-membered ring of the dimer **7**.

In summary, we have successfully established an efficient synthetic method for the preparation of tetrahydro-pyrano-[3,4-*b*]indoles **6** by a Larock heteroannulation and silicon-directed oxa-Pictet−Spengler cyclization process. From a synthetic point of view, this new procedure constitutes a significant improvement of the traditional oxa-Pictet−Spengler reaction by overcoming its limitation to electron-rich or electron-neutral pyranoindoles. Finally, an unusual dimeric structure, **7**, was isolated and characterized during the BF_3 etherate-promoted reaction of 2-(2-trimethylsilanyl-1*H*-indol-3-yl)-ethanols **5** with acetone.

Supporting Information Available: Experimental procedures and full characterization of new compounds **5**−**7**, **9**, **10**, **18**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Bally, I.; Ciornei, E.; Vasilescu, A.; Balaban, A. T. *Tetrahedron* **1973**, *9*, 3185. (b) Hohaus, E.; Umland, F. *Chem. Ber.* **1969**, *102*, 4025.
(12) Reitz, K. Z. *Phys. Chem. Abt. A* **1939**, *184*, 429.