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Formation of silyloxy-substituted pyrrolizidinones, indolizidinones and quinolizidinones *via* intramolecular cyclizations of α-acylamino radicals with acylsilanes

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α-Acylamino radicals generated from acylsilanes 15, 16, 17 and 21 cyclize to give good yields of silyloxy substituted pyrrolizidinones, indolizidinones and quinolizidinones.

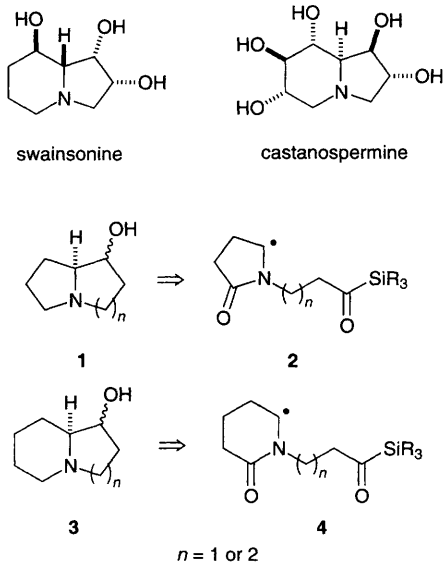
Polyhydroxylated alkaloids such as swainsonine and castanospermine are interesting compounds that exhibit a wide variety of biological activities.[1] Therefore, the synthesis of these natural products and their analogues is required for obvious pharmacological reasons. Recently, we developed a method using radical cyclizations of acylsilanes to give cycloalkyl silyl ethers.[2] Now, we have employed this methodology in the construction of several polyhydroxy alkaloid skeletons.

As shown in Scheme 1, pyrrolizidinol **1** (n = 1), indolizidinols **1** (n = 2) or **3** (n = 1) and quinolizidinol **3** (n = 2) could theoretically be synthesized *via* cyclizations of the corresponding α-acylamino radicals[3,4] **2** and **4**. The required synthetic equivalents of **2** and **4** were synthesized as shown in Scheme 2. 2-(Methyldiphenylsilyl)-1,3-dithiane **5**[5] was alkylated with 2-bromoethyl or 3-bromopropyl tetrahydropyranyl ethers followed by deprotection to afford alcohols **6** and **7**. Mitsunobu coupling[6] of succinimide with these alcohols using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine gave imides **8** and **9** in good yields. However, a similar coupling reaction carried out with glutarimide was not successful. Tsunoda *et al.*[7] recently reported a new reagent system for the Mitsunobu reaction applicable to nucleophiles with higher pK_a. Since glutarimide (pK_a = 11.43)[8] is less acidic than succinimide (pK_a = 9.62),[9] we therefore applied Tsunoda's method using 1,1′-(azodicarbonyl)dipiperidine (ADDP) and tributylphosphine as the reagents for Mitsunobu coupling and gained successfully imide **10** in 70% yield from glutarimide. In contrast, imide **11** was still unattainable *via* this route.

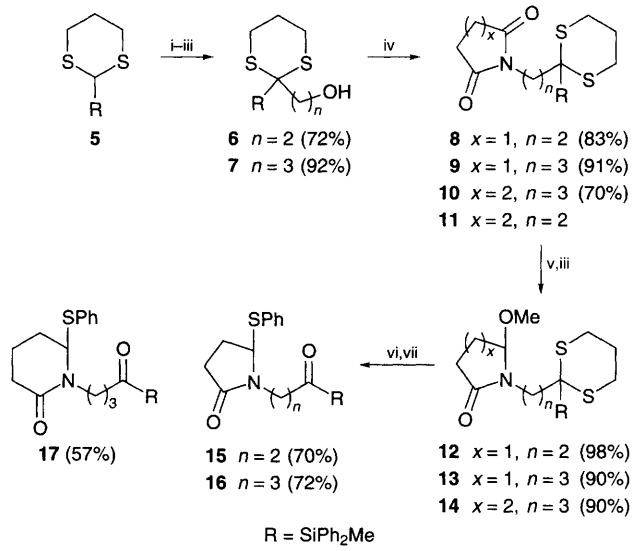
Imides **8–10** were reduced with sodium borohydride according to Hubert *et al.*,[10] and the resulting crude alcohols were converted to the corresponding methyl ethers **12–14** by stirring with a catalytic amount of acid in methanol. Hydrolysis of the dithiane moiety was conducted using (CF_3CO_2)IPh.[11] The resulting crude acylsilanes[12] were mixed with neat thiophenol in the presence of a catalytic amount of camphorsulfonic acid (CSA) to give the thioethers **15–17**.[4]

In order to synthesize **11**, we adopted a different approach. Mitsunobu coupling[6] of **6** with phthalimide gave imide **18** in high yield (Scheme 3). Imide **18** reacted with hydrazine and released the crude amine **19** which was subsequently treated with glutaric anhydride to give an amide acid. The resulting amide acid was cyclized in acetic anhydride to afford **11** (84% from **18**). In principle, this approach should be applicable to the synthesis of imides **8–10**. Preparation of **21** was accomplished from **11** in 71% yield using the methods described previously.

The cyclizations of acylsilanes **15**, **16**, **17** and **21** were carried out with tributyltin hydride in refluxing benzene, and the results were shown in Table 1. In the case of **15** (entry 1), the cyclization was the least efficient. Reduction product **26**, in which the acylsilane moiety was also reduced by tributyltin hydride, was present in 18% yield. In our model studies,[13] 1,5-cyclizations were more efficient than 1,6-cyclizations. We believe that the cyclization of **15** was hampered by the strain imposed by the pre-existing five-membered ring. In compari-



Scheme 1



Scheme 2 *Reagents and conditions*: i, BuLi; ii, Br$(CH_2)_n$OTHP; iii, TsOH (cat), MeOH; iv, DIAD, Ph_3P, succinimide, or ADDP, Bu_3P, glutarimide; v, $NaBH_4$, HCl–EtOH; vi, $(CF_3CO_2)_2$IPh, $NaHCO_3$, MeCN, H_2O; vii, CSA (cat), PhSH (1 equiv.)

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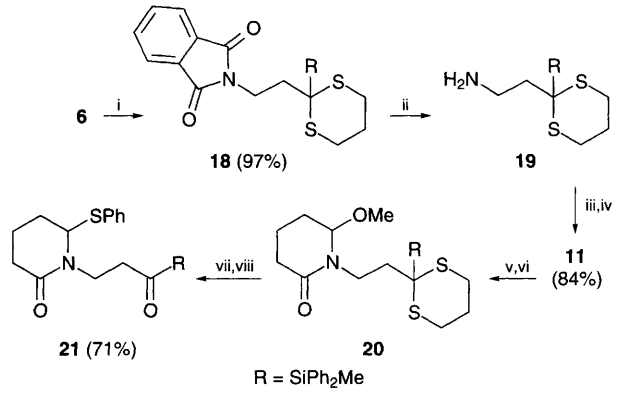
son, acylsilane **21** (entry 3) cyclized very efficiently to give silyloxyindolizidinones **28** and **30** in a total of 82% yield. Silyloxyindolizidinones **23** (63%) and **25** (16%) were also obtained from **16** (entry 2), as was a small amount of reduction product **27**. Silyloxyquinolizidinones **29** (57%) and **31** (15%) were isolated from the cyclization of **17** (entry 4). Only a trace amount of reduction product was observed, which was not fully characterized.

To determine the stereochemistry of the cyclization products, we performed NOE experiments on **24** and **30**. In the case of **24**, irradiation of H^1 at δ 4.15 (q, *J* 3.0 Hz, 1 H) resulted in a 7.7% enhancement of the bridgehead hydrogen (H^{7a}) signal at δ 3.79 (ddd, *J* 8.0, 6.0, 3.0 Hz, 1 H). For **30**, irradiation at δ 4.30 (td, *J* 3.0, 1.6 Hz, 1 H, H^1) resulted in a 14% enhancement at δ 3.31–3.41 (m, 1 H, H^{8a}). These experiments indicated the *cis*-relationship between the two hydrogens. The desilylated alcohol analogue of **23** was identical to data reported by Martín-López and Bermejo-González.[14] In **29**, the H^1 absorption showed as a td (*J* 9.4, 4.4 Hz) at δ 3.41. The coupling pattern indicated that H^1 of **29** was in the axial position, in support of its *trans*-relationship with H^{9a}. In contrast, H^1 of **31** appeared as a narrow broad signlet at δ 3.79, an indication that it was situated in the equatorial position.

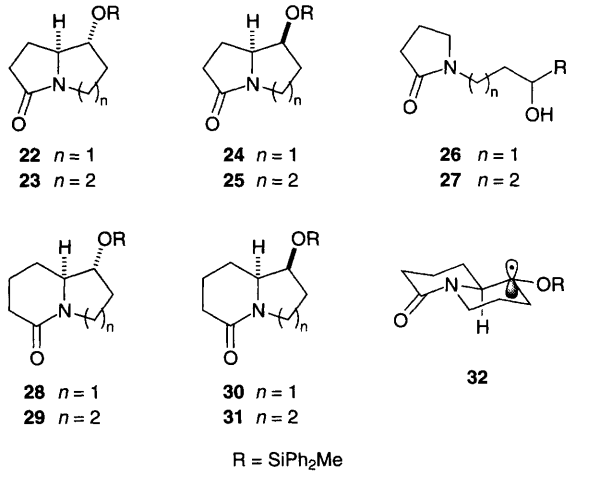


Scheme 3 *Reagents and conditions*: i, DIAD, Ph_3P, phthalimide; ii, hydrazine, MeOH, THF, 50–60 °C; iii, glutaric anhydride; iv, Ac_2O, NaOAc, 100–120 °C; v, $NaBH_4$, HCl–EtOH; vi, CSA (cat), MeOH; vii, $(CF_3CO_2)_2IPh$, $NaHCO_3$, MeCN, H_2O; viii, CSA (cat), PhSH (1 equiv.)

Table 1 Radical cyclizations of acylsilanes **15**, **16**, **17** and **21**[a]

Entry	Starting material	Product (yield, %)	*exo* : *endo*
1[b]	**15**	**22** (34), **24** (18), **26** (18)	1.9
2[c]	**16**	**23** (63), **25** (16), **27** (6)	3.9
3[c]	**21**	**28** (58), **30** (23)	2.5
4[c,d]	**17**	**29** (57), **31** (15)	3.8

[a] To a refluxing solution of the acylsilane (0.1 M in benzene) was added a solution of tributyltin hydride (1.5 equiv.; 0.1 M in benzene) and AIBN (0.1 equiv.) over a period of 1.5 h. [b] Calculated *via* high-performance liquid chromatography. [c] Isolation yields. [d] Trace amount of reduction product was observed.



In the cyclization process, α-acylamino radicals are generated and add to the acylsilane. The resulting β-silyl alkoxy radicals undergo radical-Brook rearrangement[15] to give α-silyloxy radicals, such as **32**. It is well known that cyclohexyl radicals preferentially abstract hydrogen atom from the axial position.[16] This led to the 4 : 1 *exo–endo* product ratio observed in entries 2 and 4 (Table 1). In the case of cyclopentyl radicals, the selectivity dropped due to the flexibility of the cyclopentane ring, as in entries 1 and 3.

In summary, we developed a general strategy based on radical cyclizations of acylsilanes to prepare silyl ethers of hydoxypyrrolizidinone, hydroxyquinolizidinone and two types of hydroxyindolizidinones. These cyclization products should prove useful for the synthesis of more complicated alkaloids.[13,17]

We thank the National Science Council of the Republic of China for financial support.

References

1 M. Naruse, S. Aoyagi and C. Kibayashi, *J. Org. Chem.*, 1994, **59**, 1358; K. Burgess and I. Henderson, *Tetrahedron*, 1992, **48**, 4045; A. Brandi, S. Cicchi, F. M. Cordero, R. Frignoli, A. Goti, S. Picasso and P. Vogel, *J. Org. Chem.*, 1995, **60**, 6806 and references cited therein.
2 Y.-M. Tsai and C.-D. Chern, *Tetrahedron Lett.*, 1991, **32**, 3515; Y.-M. Tsai and S.-Y. Chang, *J. Chem. Soc., Chem. Commun.*, 1995, 981.
3 M. D. Bachi, F. Frolow and C. Hoornaert, *J. Org. Chem.*, 1983, **48**, 1841.
4 J. M. Dener, D. J. Hart and S. Ramesh, *J. Org. Chem.*, 1988, **53**, 6022; D. A. Burnett, J.-K. Choi, D. J. Hart and Y.-M. Tsai, *J. Am. Chem. Soc.*, 1984, **106**, 8201; D. J. Hart and Y.-M. Tsai, *J. Am. Chem. Soc.*, 1984, **106**, 8209.
5 A. G. Brook, J. M. Duff, P. F. Jones and N. R. Davis, *J. Am. Chem. Soc.*, 1967, **89**, 431; E. J. Corey, D. Seebach and R. Freedman, *J. Am. Chem. Soc.*, 1967, **89**, 434.
6 O. Mitsunobu, *Synthesis*, 1981, 1.
7 T. Tsunoda, Y. Yamamiya and S. Itô, *Tetrahedron Lett.*, 1993, **34**, 1639.
8 G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162.
9 H. F. Walton and A. A. Schilt, *J. Am. Chem. Soc.*, 1952, **74**, 4995.
10 J. C. Hubert, J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron*, 1975, **31**, 1437.
11 G. Stork and K. Zhao, *Tetrahedron Lett.*, 1989, **30**, 287.
12 Y.-M. Tsai, H.-C. Nieh and C.-D. Chern, *J. Org. Chem.*, 1992, **57**, 7010.
13 Y.-M. Tsai, K.-H. Tang and W.-T. Jiaang, *Tetrahedron Lett.*, 1993, **34**, 1303.
14 M. J. Martín-López and F. Bermejo-González, *Tetrahedron Lett.*, 1994, **35**, 8843.
15 J. C. Dalton and R. A. Borque, *J. Am. Chem. Soc.*, 1981, **103**, 699; J. M. Harris, I. MacInnes, J. C. Walton and B. Maillard, *J. Organomet. Chem.*, 1991, **403**, C25.
16 B. Giese, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 969.
17 H. Takahata, Y. Banba and T. Momose, *Tetrahedron*, 1991, **47**, 7635; T. Oishi, T. Iwakuma, M. Hirama and S. Itô, *Synlett*, 1995, 404.

Received, 13th August 1996; Com. 6/05686E