Triply Convergent, Stereospecific Alkene Formation via Peterson Olefination

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α-Iodo silanes 8 were prepared from α-hydroxy silanes and after halogen/metal exchange and treatment with copper(I) bromide–dimethyl sulfide were coupled with acid chlorides to yield α-silyl ketones 2. Cram controlled addition with a variety of nucleophiles followed by treatment with acid or base led to either the (*E*)- or (*Z*)-alkene in good overall yields from the iodide (47–67%) and with excellent stereoselectivities (>95/<5 for disubstituted cases and 67/33 to 95/5 for trisubstituted). The procedure was used iteratively in the total synthesis of 4(*E*),8(*Z*)-tetradecadien-1-yl acetate (15) in >95/<5 isomeric purity.

Introduction

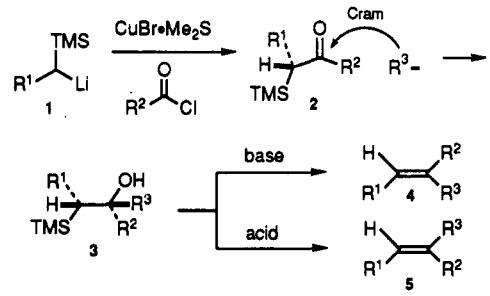
The Peterson olefination is the cumulative reaction of an α-silyl carbanion with a carbonyl compound to form a β-hydroxy silane, followed by elimination to yield the corresponding alkene.[1] The convergent formation of carbon-carbon double bonds is a reaction of fundamental importance in synthetic organic chemistry. Many related procedures, including the Wittig reaction, have been developed and used extensively for this purpose. Peterson olefination is a potentially useful alternative to this and other procedures because diastereoisomerically pure β-hydroxy silanes can be stereospecifically eliminated in either a syn or anti manner.[2] Therefore either the (*E*)- or (*Z*)-alkene is available from a single precursor. Its failure to find widespread use is a result of the few available methods for the production of α-lithio silanes[3] and because there is no general, experimentally concise, and convergent method of preparing diastereoisomerically pure β-hydroxy silanes.[4]

Unlike the Wittig olefination or the Julia coupling,[5] in which alkyl phosphonium salts or sulfones are readily metalated, direct deprotonation of alkylsilanes to produce the derived α-silyl carbanion is generally not feasible. If, however, an anion stabilizing group is present on the carbon atom, direct deprotonation is possible and the resultant α-silyl carbanions have been used to prepare functionalized alkenes such as α,β-unsaturated esters or 1,3-dienes.[6] Indirect methods have been developed to produce α-silyl carbanions to overcome this preparative deficiency. Perhaps the most versatile of these methods is the reductive cleavage of α-silyl sulfides with lithium naphthalenide[3e] or, more conveniently, lithium (dimethylamino)naphthalenide.[3d] α-Halo silanes should also be convenient precursors for olefinations but, unfortunately, have found little use synthetically. The commercial availability of (chloromethyl)trimethylsilane has led to the use of the corresponding Grignard or lithium derivative for the methylenation of carbonyl compounds.[4f] However, the lack of methods for the formation of other α-halo silanes has curtailed the generalization of this procedure.

There are a number of methods for the synthesis of diastereoisomerically pure β-hydroxy silanes.[4] The majority of these procedures, however, do not involve a carbon–carbon bond-forming step between the two atoms that will eventually comprise the double bond, and the methods therefore lack the convergence of a Wittig or other olefination procedure. A particularly general and consistent method of preparing diastereoisomerically pure β-hydroxy silanes is via the Cram controlled addition of a nucleophile to an α-silyl ketone.[4a,b] Either tri- or disubstituted alkenes can be accessed with this procedure. In spite of these results, α-silyl ketones are rarely used for the stereospecific formation of alkenes, since there are few general, concise, and high yielding methods for their production.

Herein we report that readily available α-iodo silanes undergo halogen/metal exchange[7] to yield α-silyl carbanions. Additionally, conversion to the corresponding or-

Scheme I



(1) (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780. For reviews, see: (b) Ager, D. J. *Org. React.* In press. (c) Ager, D. J. *Synthesis* **1984**, 384. (d) Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press: New York, 1988. (e) Chan, T. H. *Acc. Chem. Res.* **1977**, *10*, 442.

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(5) Wittig olefination: Smith, D. J. H. "Phosphazenes and Phosphorus Ylides" in *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 2, pp 1316–1325. Julia Lythgoe olefination: (a) Julia, M.; Paris, M.-J. *Tetrahedron Lett.* **1973**, 4833. (b) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045.

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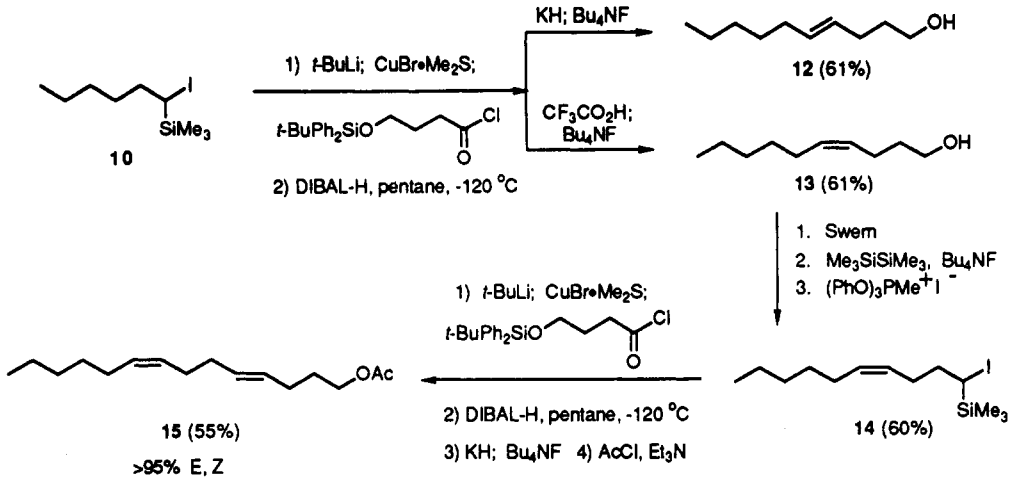
(7) Ashby, E. C.; Phan, T. M. *J. Org. Chem.* **1987**, *52*, 1291 and references cited therein.

0022-3263/91/1956-0638$02.50/0

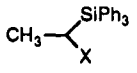
Scheme II



ganocopper reagent[8] and coupling with an acid chloride leads to the α-silyl ketone 2 (Scheme I). Cram controlled addition with various nucleophiles provides a triply convergent method for the production of predominantly one β-hydroxy silane. Subsequent treatment with either acid or base leads to either the (*E*)- or (*Z*)-alkene.

Results and Discussion

Relatively poor results have been obtained for the synthesis and halogen/metal exchange of α-bromo silanes. For example, Brook reported that alcohol **6a** was converted, via bromide **6b**, into acid **6c** (6%) by sequential reaction with PBr_3, BuLi, and CO_2.[3a] In light of these results with α-bromo silanes, we have investigated the use of α-iodo silanes as precursors to α-silyl carbanions.



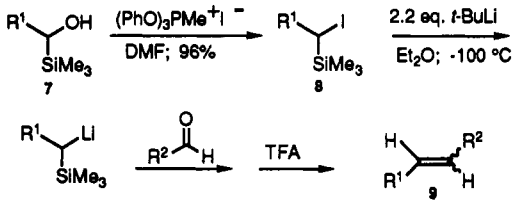
6

a X = OH
b X = Br
c X = CO_2H

α-Iodo silanes 8 were readily prepared from α-hydroxy silanes 7[9] (96%) by treatment with methyltriphenoxyphosphonium iodide[10] (1.5 equiv) in DMF (Table I). Subsequent halogen/metal exchange was accomplished by addition of the α-iodo silane to *t*-BuLi (2.2 equiv in 2:1 Et_2O/pentane) at −100 °C, and the α-silyl carbanions were used directly in Peterson olefinations. The addition of an aldehyde, followed by trifluoroacetic acid, resulted in the one-pot generation of a variety of alkenes (**9a–d**), which are summarized in Table I. The results demonstrate that α-iodo silanes are readily accessible precursors to a variety of substituted α-silyl carbanions. The versatility and yields in the procedure offer distinct advantages over the existing methods for α-silyl carbanion preparation.

We have additionally investigated utilizing the Peterson olefination for the triply convergent, stereospecific generation of tri- and disubstituted double bonds (Table II). To this end, α-iodo silane 10 was converted to the corresponding organocopper reagent (2.2 equiv of *t*-BuLi; CuBr–Me_2S) and treated with an acid chloride. The resultant α-silyl ketone underwent smooth reduction with diisobutylaluminum hydride (pentane, −120 °C) to yield, after elimination, disubstituted alkenes that were formed with excellent stereoselectivity (<5/>95).[11] Trisubstituted alkenes were prepared by the addition of an organolithium or Grignard reagent to the α-silyl ketone and subsequent

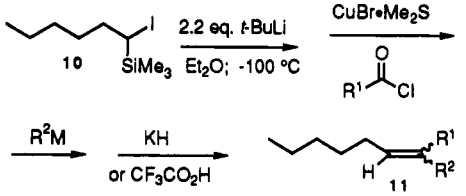
Table I. Peterson Olefination Reactions Utilizing α-Iodo Silanes



entry	R^1	R^2	*E*/*Z*	alkene (%)
1	$CH_3(CH_2)_4$	Ph	73/27	**9a** (83)
2	$Ph(CH_2)_2$	Ph	79/21	**9b** (84)
3	$CH_3(CH_2)_4$	$Ph(CH_2)_2$	*a*	**9c** (71)
4	$CH_3(CH_2)_4$	*t*-$BuPh_2SiO(CH_2)_4$	*a*	**9d** (67)

[a] *E*/*Z* ratio was not determined.

Table II. Preparation of Di- and Trisubstituted Alkenes



entry	R^1	R^2M	elim.	*E*/*Z*	alkene (%)[a]
1	Me	*n*-BuLi	TFA	94/6	**11a** (59)
2	Me	*n*-BuLi	KH	5/95	**11b** (57)
3	Me	*n*-BuMgBr	TFA	93/7	**11a** (56)
4	Me	DIBAL-H	TFA	<5/>95	**11c** (64)
5	Me	DIBAL-H	KH	>95/<5	**11d** (63)
6	Me	PhLi	TFA	67/33	**11e** (47)
7	$Ph(CH_2)_2$	MeLi	TFA	9/91	**11f** (57)
8	Me	*t*-$BuPh_2SiO$-$(CH_2)_5Li$	TFA	93/7	**11g** (53)

[a] Overall yield from iodide 10.

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(11) Hudrlik, P. F.; Peterson, D. *Tetrahedron Lett.* **1974**, 1133.

acid- or base-mediated elimination. The high stereoselectivity remained consistent except for conjugated cases such as in the addition of phenyllithium (entry 6, Table II). As shown in entries 7 and 8 (Table II), the methyl group can by introduced at different stages in the process. Either of the two possible diastereoisomers of the β-hydroxy silane can be formed by alternating this sequence. Therefore, should an alkene be desired that contains acid-sensitive functionality, the correct β-hydroxy silane can be tailor-made such that the elimination could be carried out using KH.

The procedure was used iteratively in the total synthesis of the dienyl acetate **15**[12] (Scheme II). Thus, conversion of the α-silyl iodide **10** to the corresponding organocopper reagent and reaction with 4-[(*tert*-butyldiphenylsilyl)oxy]butanoyl chloride[13] followed by reduction with diisobutylaluminum hydride yielded predominantly one β-hydroxy silane. Both the α-silyl ketone and β-hydroxy silane proved unstable to silica and were not isolated. Direct treatment of the β-hydroxy silane with KH or trifluoroacetic acid yielded, after deprotection, the (*E*)- or (*Z*)-hydroxyalkene (**12** and **13**), respectively (61%). (*Z*)-Hydroxyalkene **13** was oxidized to the aldehyde and transformed into the corresponding α-iodo silane **14** (60%). Repetition of the Peterson sequence and acetylation yielded 4(*E*),8(*Z*)-tetradecadien-1-yl acetate (**15**) (55%) in >95/<5 isomeric purity. The synthesis highlights several important features of the methodology. First, the hydroxyalkenes **12**(*E*) and **13**(*Z*) were both formed with excellent stereocontrol, *from the same precursor*. Also, a Wittig reaction or other convergent olefination procedure could not have been used to form the alkenes with such a high degree of selectivity.

In summary, many aliphatic tri- and disubstituted alkene chains can be assembled convergently and with excellent stereocontrol utilizing the procedure described herein. This modification of the Peterson olefination should make it a preferable alternative to other methods of alkene synthesis. Work in this laboratory is focusing on further applications of this methodology.

Experimental Section

Hexane, diethyl ether, and ethyl acetate were purified by distillation. THF was dried by distillation under nitrogen from sodium benzophenone ketyl. DMF and CH_2Cl_2 were freshly distilled from CaH_2. All reactions were carried out under dry nitrogen. Silica gel for chromatography refers to the Merck product Kieselgel 60 (art. no. 9385). Thin layer chromatography was performed on Merck Kieselgel 60 F254 (art. no. 5715).

General Procedure for the Preparation of α-Silyl Iodides. Anhydrous TBAF (0.5 mL, 0.1 equiv) was added to a solution of hexamethyldisilane (1.55 mL, 1.5 equiv) and HMPA (10 mL). The resultant yellow solution was stirred for 5 min followed by the dropwise addition of the aldehyde (5 mmol). After 5 h the reaction mixture was treated with concentrated HCl/MeOH (1/10) (ca. 5 mL), diluted with H_2O (20 mL), and extracted with ether (3 × 30 mL). The combined ether extracts were washed with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$), and evaporated. DMF (20 mL) was added to the reaction mixture followed by $(PhO)_3PMeI$ (3.39 g, 1.5 equiv), and the solution was stirred in the dark for 12 h. MeOH (ca. 2 mL) was added followed by saturated aqueous $Na_2S_2O_3$ (ca. 10 mL), and the reaction mixture was extracted with Et_2O (3 × 30 mL). The combined Et_2O extracts were washed with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$), and evaporated. Purification of the residue by flash chromatography (hexane) on silica followed by Kugelrohr distillation at 110 °C and 0.7 mmHg yielded the stable α-silyl iodides.

1-Iodo-1-(trimethylsilyl)hexane (10): oil; IR (film) 2940, 1465, 1260, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.13 (dd, 1 H, *J* = 11.6, 3.2 Hz), 1.18–1.72 (m, 8 H), 0.90 (t, 3 H, *J* = 6 Hz), 0.15 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 33.6, 31.4, 30.8, 24.5, 22.5, 14.1, −2.0; mass spectrum (CI), *m/z* 284 ($M^{+\bullet}$), 185, 157, 73, 59. Anal. Calcd for $C_9H_{21}ISi$: C, 38.03; H, 7.70. Found: C, 38.26; H, 7.51.

1-Iodo-1-(trimethylsilyl)-2-phenylpropane (8, R¹ = Ph-$(CH_2)_2$): oil; IR (film) 3990, 1620, 1460, 1265, 850, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18–7.32 (m, 5 H), 2.98–3.08 (m, 2 H), 2.61, 2.72 (m, 1 H), 1.80–2.02 (m, 2 H), 0.13 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 128.6, 128.4, 126.0, 37.6, 35.5, 23.1, −2.1; mass spectrum (CI), *m/z* 318 ($M^{+\bullet}$), 185, 118, 91, 73, 59. Anal. Calcd for $C_{12}H_{19}ISi$: C, 45.28; H, 6.02. Found: C, 45.53; H, 6.06.

1-Iodo-1-(trimethylsilyl)-4(*Z*)-decene (14): oil; IR (film) 2940, 1235, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.25–5.50 (m, 2 H), 3.13 (dd, 1 H, *J* = 11.6, 3.2 Hz), 1.52–2.40 (m, 6 H), 1.25–1.41 (m, 6 H), 0.85–0.95 (m, 3 H), 0.05 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.8, 127.7, 33.8, 31.5, 29.5, 29.3, 27.5, 23.5, 22.6, 14.1, −2.1; mass spectrum (CI), *m/z* 338 ($M^{+\bullet}$), 185, 73. Anal. Calcd for $C_{13}H_{27}ISi$: C, 46.15; H, 8.05. Found: C, 46.34; H, 8.18.

Reaction of α-Iodo Silanes with Carbonyl Compounds. *t*-BuLi (3.88 mL of a 1.7 M solution in pentane, 2.2 equiv) was added to Et_2O (10 mL) at −100 °C. The α-silyl iodide (3 mmol) in Et_2O (2 mL) at −100 °C was added dropwise, maintaining the temperature at −100 °C. The aldehyde and Et_2O (1 mL) at −78 °C were added, and the reaction mixture was stirred at −78 °C for 30 min. Trifluoroacetic acid (2 equiv) was added, and the solution was slowly warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with Et_2O (75 mL) and washed with saturated aqueous NH_4Cl (3 × 15 mL) and saturated aqueous $NaHCO_3$ (3 × 20 mL), dried ($MgSO_4$), and evaporated. Purification of the residue by flash chromatography (hexane) on silica yielded the alkenes **9a–d**. 1-Phenyl-1-heptene (**9a**) was obtained as a 73/27 mixture of *E*/*Z* isomers, with spectra identical with that of the known compounds.[14]

1,4-Diphenyl-1(*E*)-butene (9b). The crude reaction mixture showed a 79/21 ratio of *E*/*Z* isomers by 400-MHz ^1H NMR.[15] This was recrystallized (hexanes) to yield the pure *E* isomer: mp = 36–38 °C; IR (film) 3040, 1620, 1455, 980, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16–7.34 (m, 10 H), 6.41 (d, 1 H, *J* = 16 Hz), 6.25 (dt, 1 H, *J* = 16, 6.8 Hz), 2.79 (t, 2 H, *J* = 8 Hz), 2.52 (q, 2 H, *J* = 8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7, 137.7, 130.3, 129.9, 128.5, 128.3, 126.9, 125.96, 125.86, 35.86, 34.87; mass spectrum (CI), *m/z* 192 ($M^{+\bullet}$), 117, 91, 65. Anal. Calcd for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 92.29; H, 7.77.

1-Phenyl-3-nonene (9c) was prepared as a mixture of isomers: IR (film) 3040, 1620, 970, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13–7.30 (m, 5 H), 5.33–5.44 (m, 2 H), 2.62–2.69 (m, 2 H), 2.26–2.39 (m, 2 H), 1.92–2.01 (m, 2 H), 1.20–1.37 (m, 6 H), 0.89 (t, 3 H, *J* = 6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 130.7, 128.6, 128.4, 128.2, 125.7, 36.1, 36.0, 34.2, 32.6, 31.5, 31.2, 29.3, 29.2, 27.2, 22.6, 14.1; mass spectrum (CI), *m/z* 202 ($M^{+\bullet}$), 104, 91, 69, 55. Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.29; H, 11.20.

1-[(*tert*-Butyldiphenylsilyl)oxy]-5-undecene (9d) was prepared as a mixture of *E*/*Z* isomers: IR (film) 1440, 1120, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.75 (m, 4 H), 7.32–7.46 (m, 6 H), 5.28–5.42 (m, 2 H), 3.66 (t, 2 H, *J* = 8.4 Hz), 1.92–2.08 (m, 4 H), 1.21–1.62 (m, 2 H), 1.06 (s, 9 H), 0.89 (t, 3 H, *J* = 6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6, 134.4, 130.2, 129.7, 129.5, 127.6, 64.0, 32.6, 32.3, 32.1, 31.6, 31.4, 29.4, 29.3, 27.2, 27.0, 26.0, 25.9, 22.6, 22.5, 19.3, 14.0; mass spectrum (CI), *m/z* 408 ($M^{+\bullet}$), 351, 273, 199, 135, 95, 55. Anal. Calcd for $C_{27}H_{40}OSi$: C, 79.35; H, 9.87. Found: C, 79.14; H, 9.95.

1-[(*tert*-Butyldiphenylsilyl)oxy]butyric Acid. 4-[(*tert*-Butyldiphenylsilyl)oxy]butanol (14 mmol), pyridinium dichromate (2.5 equiv), and DMF (100 mL) were stirred at 25 °C for 14 h.

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(13) Barrett, A. G. M.; Bezuidenhoudt, B.; Gasiecki, A. F.; Howell, A. R.; Russell, M. R. *J. Am. Chem. Soc.* **1989**, *111*, 1392.
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The reaction mixture was diluted with Et_2O (75 mL), filtered through a 2-cm pad of silica, washed with saturated aqueous NH_4Cl (3 × 15 mL), saturated aqueous $NaHCO_3$ (3 × 20 mL), and brine (15 mL), dried ($MgSO_4$), and evaporated. Purification of the residue by flash chromatography (hexane/Et_2O 1/1) on silica yielded the title compound (1.63 g, 34%) as a white solid: mp 64 °C; IR (film) 3540–2400, 1710, 1460, 1110, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.50 (br s, 1 H), 7.64–7.69 (m, 2 H), 7.34–7.43 (m, 3 H), 3.70 (t, 2 H, J = 5.6 Hz), 2.52 (t, 2 H, J = 7.6 Hz), 1.87–1.93 (m, 2 H), 1.05 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1, 135.5, 133.6, 129.6, 127.7, 62.7, 30.8, 27.4, 26.8, 19.2; mass spectrum (EI), m/z 285 (M – t-Bu), 207,199. Anal. Calcd for $C_{20}H_{26}O_3Si$: C, 70.13; H, 7.65. Found: C, 70.18; H, 7.74.

1-[(*tert*-Butyldiphenylsilyl)oxy]pentanal. 5-[(*tert*-Butyldiphenylsilyl)oxy]pentanol (14 mmol), pyridinium dichromate (1.5 equiv), and CH_2Cl_2 (100 mL) were stirred at room temperature for 14 h. The reaction mixture was diluted with Et_2O (75 mL), filtered through a 10-cm pad of silica, washed with saturated aqueous NH_4Cl (3 × 15 mL), saturated aqueous $NaHCO_3$ (3 × 20 mL), and brine (15 mL), dried ($MgSO_4$), and evaporated. Purification of the residue by flash chromatography (hexane/Et_2O 80/20) yielded the title compound (3.04 g, 64%) as a colorless oil: IR (film) 2940, 1730, 1440, 1100, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1 H), 7.64–7.69 (m, 4 H), 7.34–7.43 (m, 6 H), 3.67 (t, 2 H, J = 6 Hz), 2.39 (t, 2 H, J = 7.2 Hz), 1.69–1.78 (m, 2 H), 1.52–1.62 (m, 4 H), 1.05 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.5, 135.5, 133.8, 129.5, 127.6, 63.2, 43.4, 31.8, 26.8, 19.2, 18.5; mass spectrum (EI), m/z 283 (M – t-Bu), 199, 139, 77; exact mass calcd for (M – t-Bu) 283.1155, found 283.1149.

1-Bromo-5-[(*tert*-butyldiphenylsilyl)oxy]pentane. 5-[(*tert*-Butyldiphenylsilyl)oxy]pentanol (5.8 mmol), CBr_4 (5.8 mmol), Ph_3P (5.8 mmol), and THF (75 mL) were stirred at room temperature for 6 h. The reaction mixture was diluted with Et_2O (75 mL), washed with saturated aqueous NH_4Cl (3 × 15 mL), saturated aqueous $NaHCO_3$ (3 × 20 mL), and brine (15 mL), dried ($MgSO_4$), and evaporated. Purification of the residue by flash chromatography (hexane) on silica yielded the title compound (4.18 g, 72%) as a colorless oil: IR (film) 2980, 2920, 1460, 1100, 830, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.69 (m, 4 H), 7.33–7.43 (m, 6 H), 3.66 (t, 2 H, J = 6.4 Hz), 3.38 (t, 2 H, J = 6.8 Hz), 1.80–1.89 (m, 2 H), 1.47–1.61 (m, 4 H), 1.05 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6, 134.0, 129.5, 127.6, 63.5, 33.8, 32.5, 31.6, 26.9, 24.5, 19.2; mass spectrum (EI), m/z 349, 293, 263, 199, 91, 69. Anal. Calcd for $C_{21}H_{29}BrOSi$: C, 62.21; H, 7.21. Found: C, 62.54; H, 7.29.

Preparation of α-Silyl Ketones. t-BuLi (3.88 mL of a 1.7 M solution in pentane, 2.2 equiv) was added to Et_2O (10 mL) at −100 °C. The α-silyl iodide (3 mmol) in Et_2O (3 mL) at −100 °C was added dropwise, maintaining the temperature at −100 °C. This solution was transferred via cannula to a separate flask containing $CuBr{\cdot}SMe_2$ (1 equiv) in Et_2O (5 mL) at −78 °C. The reaction mixture was warmed over 15 min to −35 °C, maintained at −35 °C for 5 min, and cooled to −78 °C. The acid chloride (1 equiv) in Et_2O (2 mL) was cooled to −78 °C and added to the reaction mixture. The solution was kept at −78 °C for 0.5 h, warmed over 1 h to 0 °C, and maintained at 0 °C for 1 h. The reaction mixture was poured onto saturated aqueous NH_4Cl (20 mL) overlaid with Et_2O (100 mL), washed with saturated aqueous NH_4Cl (3 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and evaporated. The α-silyl ketones were used in subsequent reactions without further purification.

Preparation of Disubstituted Alkenes. The crude α-silyl ketone (3 mmol) and pentane (10 mL) were cooled to −120 °C. Diisobutylaluminum hydride (9 mmol) and pentane (15 mL) at −120 °C were added via cannula, and the resultant solution was stirred at −120 °C for 3 h. The reaction mixture was warmed slowly to 20 °C over 12 h and then poured onto 2 N HCl (20 mL) overlaid with Et_2O (100 mL), washed with saturated aqueous $NaHCO_3$ (3 × 20 mL) and brine (15 mL), dried ($MgSO_4$), and evaporated. The β-hydroxy silane was used in subsequent reactions without further purification. The products (*Z*)-2-octene (**11c**) and (*E*)-2-octene (**11d**) showed spectroscopic data identical with reported values.[14]

1-Hydroxy-4(*E*)-decene (12) was prepared as a >95/<5 mixture of *E*/*Z* isomers: IR (film) 3300, 2950, 1465, 1060, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.38–5.51 (m, 2 H), 3.7 (t, 2 H, J = 6.4 Hz), 2.22 (br s, 1 H), 2.02–2.13 (m, 2 H), 1.97–2.02 (m, 2 H), 1.60–1.70 (m, 2 H), 1.23–1.40 (m, 6 H), 0.89–0.97 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.1, 129.3, 62.3, 32.5, 32.4, 31.3, 29.2, 28.8, 22.5, 14.0; mass spectrum (EI), m/z 156 ($M^{+\cdot}$), 138, 110, 95, 81, 67, 55. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.57; H, 13.07.

1-Hydroxy-4(*Z*)-decene (13) was prepared as a <5/>95 mixture of *E*/*Z* isomers: IR (film) 3300, 2950, 1465, 1060, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.33–5.44 (m, 2 H), 3.61–3.68 (m, 2 H), 2.09–2.17 (m, 2 H), 2.00–2.09 (m, 2 H), 1.89 (br s, 1 H), 1.58–1.67 (m, 2 H), 1.22–1.40 (m, 6 H), 0.89 (t, 3 H, J = 7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.7, 128.8, 62.5, 32.6, 31.5, 29.3, 27.1, 23.5, 22.5, 14.0; mass spectrum (EI), m/z 156 ($M^{+\cdot}$), 138, 110, 95, 81, 68, 55. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.74; H, 13.18.

1-Hydroxy-4(*E*),8(*Z*)-tetradecadiene and 4(*E*),8(*Z*)-Tetradecadien-1-yl Acetate (15). The alcohol was isolated as a >95:<5 mixture of isomers: IR (film) 3300–3100, 2920, 1434, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.31–5.47 (m, 4 H), 3.62 (t, 2 H, J = 6.4 Hz), 2.41 (br s, 1 H), 1.93–2.17 (m, 8 H), 1.58–1.67 (m, 2 H), 1.23–1.43 (m, 6 H), 0.85–0.93 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.4, 129.8, 129.2, 128.9, 62.2, 32.5, 31.4, 29.3, 27.25, 27.17, 27.1, 23.5, 22.5, 14.0; mass spectrum (EI), m/z 210, 121, 110, 95, 81, 69, 55, 41; exact mass calcd for $C_{14}H_{26}O$ 210.1984, found 210.1987. Acetylation of the alcohol using AcCl and Et_3N in Et_2O gave **15**[12] as a >95/<5 mixture of isomers.

Formation of Trisubstituted Alkenes. Acidic Eliminations. The appropriate nucleophile (1.1 equiv) was added to the α-silyl ketone (3 mmol) in Et_2O (10 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, warmed over 1 h to room temperature, and stirred an additional 6 h. The reaction mixture was cooled to −78 °C, trifluoroacetic acid (2 equiv) was added, and the solution was warmed over 1 h to room temperature and stirred for 1 h. The reaction mixture was diluted with Et_2O (75 mL), washed with saturated aqueous NH_4Cl (1 × 15 mL), saturated aqueous $NaHCO_3$ (3 × 20 mL), and brine (15 mL), dried ($MgSO_4$), and evaporated. Purification of the residue by flash chromatography yielded the alkene.

Basic Eliminations. The appropriate nucleophile (1.1 equiv) was added to the α-silyl ketone (3 mmol) in THF (10 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, warmed over 1 h to room temperature, and stirred an additional 6 h. The reaction mixture was cooled to −78 °C, KH (2 equiv) was added, and the solution was warmed over 1 h to room temperature and stirred for 1 h. *i*-PrOH (ca. 0.5 mL) was added to quench the excess KH. The reaction mixture was diluted with Et_2O (75 mL), washed with saturated aqueous NH_4Cl (1 × 15 mL), saturated aqueous $NaHCO_3$ (3 × 20 mL), brine (15 mL), dried ($MgSO_4$), and evaporated. Purification of the residue by flash chromatography yielded the alkene.

5-Methyl-5(*E*)-undecene (11a) was prepared as a 94/6 mixture of *E*/*Z* isomers: IR (film) 2940, 1465, 1250, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.13 (t, 1 H, J = 6.8 Hz), 1.95–2.07 (m, 4 H), 1.69 (s, 21 H), 1.60 (s, 2.79 H), 1.23–1.43 (m, 10 H), 0.88–0.96 (m, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1, 124.6, 39.5, 31.6, 30.3, 29.6, 27.9, 22.7, 22.4, 15.8, 14.1, 14.0; mass spectrum (EI), m/z 168 ($M^{+\cdot}$), 111, 97, 83, 70, 55. Anal. Calcd for $C_{12}H_{24}$: C, 85.63; H, 14.37. Found: C, 85.90; H, 14.69.

5-Methyl-5(*Z*)-undecene (11b) was prepared as a 95/5 mixture of *Z*/*E* isomers: IR (film 2940, 1465, 1250, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.11 (t, 1 H, J = 6.4 Hz), 1.93–2.03 (m, 4 H), 1.69 (s, 2.85 H), 1.60 (s, 0.15 H), 1.21–1.39 (m, 10 H), 0.83–0.93 (m, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.4, 125.3, 31.6, 31.5, 30.3, 29.8, 27.8, 23.4, 22.7, 22.6, 14.13, 14.09; mass spectrum (EI), m/z 168 ($M^{+\cdot}$), 111, 97, 83, 70; exact mass calcd for $C_{12}H_{24}$ 168.1878, found 168.1876.

2-Phenyl-2(*E*/*Z*)-octene (11e) was prepared as a 67/33 mixture of *E*/*Z* isomers: IR (film) 2940, 1610, 1500, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.51 (m, 5 H), 5.90 (t, 0.67 H, J = 7 Hz), 5.57 (t, 0.33 H, J = 7 Hz), 2.26–2.33 (m, 1.34 H), 2.12 (s, 3 H), 2.02–2.11 (m, 0.66 H), 1.30–1.61 (m, 6 H), 0.96–1.09 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1, 142.3, 135.9, 134.4, 128.8, 128.1, 127.9, 126.4, 126.3, 125.6, 31.6, 31.5, 29.8, 29.3, 29.0, 28.8, 25.6, 22.6, 22.5, 15.7, 14.1, 14.0; mass spectrum (EI), m/z 188 ($M^{+\cdot}$), 131, 118, 91. Anal. Calcd for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 89.04; H, 10.78.

3-Methyl-1-phenyl-3(*Z*)-nonene (11f) was prepared as a 9/91 mixture of *E*/*Z* isomers: IR (film) 2930, 1450, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18–7.33 (m, 5 H), 5.18 (t, 1 H, J = 6.8 Hz), 2.67–2.74 (m, 2 H), 2.28–2.37 (m, 2 H), 1.98–2.03 (m, 2 H), 1.89–1.98 (m, 1.8 H), 1.76 (s, 2.7 H), 1.66 (s, 0.3 H), 1.23–1.40 (m, 6 H), 0.88–0.96 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 134.1, 128.4, 128.3, 128.2, 126.3, 125.7, 34.5, 34.0, 31.6, 29.6, 27.8, 23.5, 22.6, 14.1; mass spectrum (EI), m/z 216 ($M^{+\cdot}$), 104, 91, 69, 55; exact mass calcd for $C_{16}H_{24}$ 216.1879, found 216.1880.

1-[(*tert*-Butyldiphenylsilyl)oxy]-6-methyl-6(*E*)-dodecene (11g) was prepared as a 93/7 mixture of *E*/*Z* isomers: IR (film) 2940, 1430, 1110, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.71 (m, 4 H), 7.33–7.43 (m, 6 H), 5.10 (t, 1 H, J = 6.4 Hz), 3.65 (t, 2 H, J = 6.4 Hz), 1.90–1.99 (m, 2 H), 1.65 (s, 0.21 H), 1.55 (s, 2.79 H), 1.19–1.40 (m, 14 H), 1.05 (s, 9 H), 0.88 (t, 3 H, J = 7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6, 134.9, 134.2, 129.5, 127.5, 124.7, 64.0, 39.7, 32.5, 32.3, 31.6, 29.6, 28.0, 27.9, 27.7, 26.9, 25.4, 22.6, 19.2, 15.9, 14.12, 14.10; mass spectrum (EI), m/z 436 ($M^{+\cdot}$), 379, 335, 269, 199. Anal. Calcd for $C_{29}H_{44}OSi$: C, 79.75; H, 10.16. Found: C, 79.98; H, 10.32.

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Applications of Intramolecular Diels–Alder Reactions to Alkaloid Synthesis. A Formal Total Synthesis of (±)-Dendrobine

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A facile synthesis of the tricyclic enone **3** was completed; since **3** was an intermediate in a previous synthesis of (±)-dendrobine (**1**), this achievement constitutes a formal total synthesis of the racemic title alkaloid. The key strategic element of the approach involved the intramolecular Diels–Alder reaction of the olefinic dienamide **10g**, which was prepared by N-acylation of imine **9g** with acid chloride **8**, to furnish the tricyclic cycloadduct **11g** as the major product. Subsequent elaboration of **11g** into **3** was then consummated by epoxidation, followed by epoxide rearrangement and oxidation of the intermediate allylic alcohol **23**. The synthetic investigations were preceded by a series of model studies that were executed in order to assess the viability and to probe the scope and limitations of the crucial intramolecular [4 + 2] cycloaddition. In these preliminary investigations, we discovered that thermolyses of dienamido olefins **10a–f** afforded mixtures (3.5–14:1) of epimeric cycloadducts **11a–f** and **12a–f**. The steric bulk of the *N*-alkyl substituent on **10a–d** exerted considerable influence upon the energy of activation and the stereochemical course of the respective cycloaddition reactions. A cyclopropyl or isopropyl group positioned at C(8) on the diene moiety of the unsaturated dienamides **10e–g** also facilitated the cyclization and enhanced the endo selectivity of the process.

Introduction

The ornamental orchid "Jinchai Shihu" (*Dendrobium nobile* Lindl.) has been employed in traditional herbal medicine in China as a tonic for the promotion of general health.[2] Although a number of structurally related sesquiterpene alkaloids have been isolated from this plant,[3] the archtypical member of this class and the major alkaloidal constituent is dendrobine (**1**),[4] which itself exhibits antipyretic, hypotensive, and convulsant activity.[5,6] Dendrobine is structurally related to the novel sesquiterpene bislactone picrotoxinin (**2**),[6,7] a potent convulsant and GABA antagonist.[8] Inasmuch as **1** incorporates a total of seven stereogenic centers distributed among a mere 17 skeletal atoms compactly arranged in four rings, it may be argued that dendrobine ranks as one of the most complex molecules of its size. Given its intricate architecture coupled with its biological activity, it is not surprising that dendrobine and its analogues have been subject to a number of biosynthetic[9] and synthetic[10–18] investigations.

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