Tetrahedron Letters, Vol. 34, No. 52, pp. 8391-8394, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Stereoselective Synthesis of Enediynes and Enynes by Condensation of Aldehydes with γ-(Trialkylsilyl)allenylboranes

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Abstract: Enediynes and enynes with high geometric purity were synthesized by treating acetylenic and simple aldehydes with γ-(*tert*-butyldimethylsilyl)allenylborane **2a** followed by the elimination step of the Peterson olefination reaction.

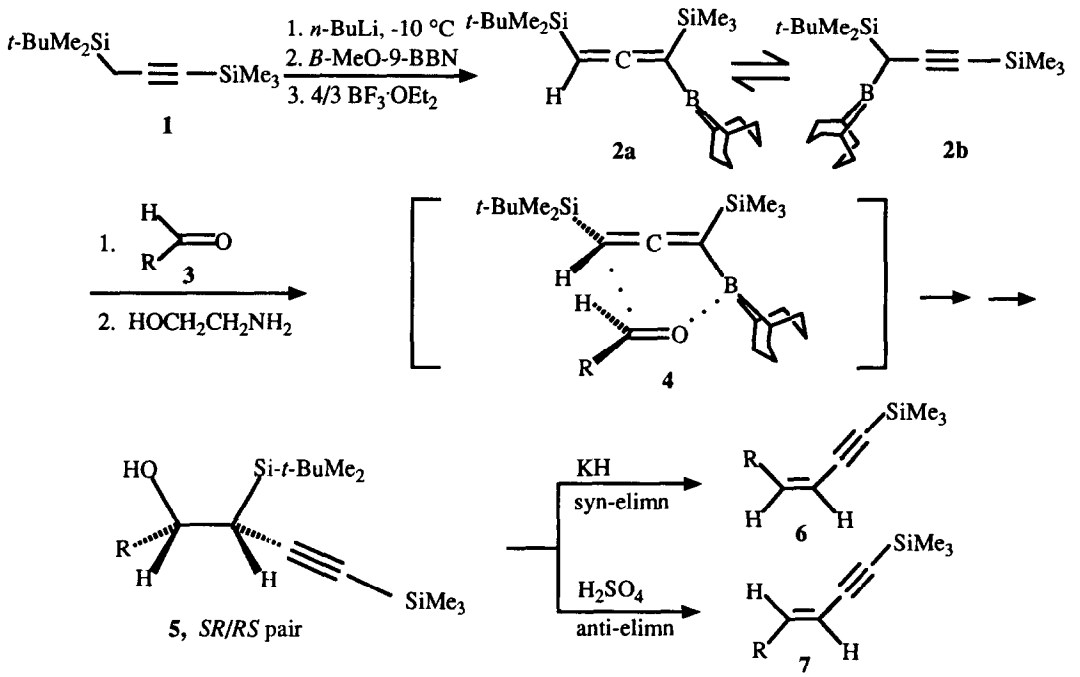
The Bergman cyclization reaction of (*Z*)-3-hexen-1,5-diynes (enediynes) provides an easy entry to 1,4-dehydrobenzene biradicals.[1] Recent renewed interest in this thermally-induced reaction is due mainly to the discovery of several very potent antitumor antibiotics having the cyclic enediyne structure.[2] A number of synthetic methods for enediynes have been reported.[2,3] We recently developed a facile synthesis of (*Z*)-1,2,4-heptatrien-6-ynes (enyne-allenes) by the condensation reaction of conjugated allenic aldehydes with γ-(trimethylsilyl)allenylboranes followed by the elimination step of the Peterson olefination reaction.[4] We now have successfully extended this synthetic strategy to enediynes by condensation with conjugated acetylenic aldehydes. Similarly, enynes were prepared by condensation with simple aldehydes.

Treatment of the readily available 3-(*tert*-butyldimethylsilyl)-1-(trimethylsilyl)-1-propyne (**1**)[5] with *n*-butyllithium followed by *B*-methoxy-9-borabicyclo[3.3.1]nonane (*B*-MeO-9-BBN) and 4/3 $BF_3{\cdot}OEt_2$[6] produced **2**, which exhibited a strong IR signal at 1872 cm^{-1} attributable to **2a** having an allenic structure and a less intense signal at 2151 cm^{-1} attributable to **2b** having an acetylenic structure (Scheme 1). Subsequent condensation with conjugated acetylenic aldehydes **3a** (R = *n*-Bu-C≡C) and **3b** (R = Ph-C≡C)[7] furnished, after workup with 2-aminoethanol, the condensation adducts **5a** and **5b** with high diastereoselectivity (de > 96%). Enediynes **6a** and **6b** having the *Z* geometry (>99% *Z*) were produced by treating **5a** and **5b** with KH, whereas enediynes **7a** and **7b** having the *E* geometry (≥98% *E*) were obtained by treating the condensation adducts with concentrated H_2SO_4.[8] The conjugated enynes **6c,d** and **7d**[5] were synthesized by treating **2a** with hexanal and benzaldehyde followed by the elimination step of the Peterson olefination reaction (Table 1).

The essentially exclusive formation of **5** suggests that the condensation reaction proceeded through the pericyclic transition state **4** with **2a** as the actual reacting species. The lack of direct reaction of **2b** with aldehydes to produce the corresponding α-allenic alcohols[9] is probably due to the presence of the sterically demanding *tert*-butyldimethylsilyl group in close proximity to the boron atom, preventing an efficient coordination of the carbonyl group with the boron atom. Rearrangement of **2b** to **2a** prior to condensation becomes the preferred reaction pathway. Such an indirect reaction route for **2b** has been observed previously in other similar systems.[9,10] The high diastereoselectivity in forming **5** could be attributed to the preferential adoption of the *tert*-butyldimethylsilyl group and the alkyl group of the aldehydes on the opposite sides of the six-membered transition state in order to minimize nonbonded steric interactions.

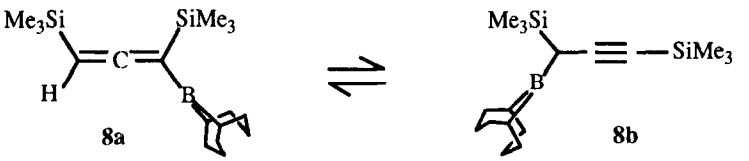
The use of allenylborane **2a**, instead of the corresponding lithium or titanium derivatives,[5] is essential for achieving high diastereoselectivity during condensation with acetylenic aldehydes. Direct treatment of the allenic lithium reagent with acetylenic aldehydes **3a** and **3b** gave only low geometric purity of the resulting enediynes (**6a**:**7a** = 3:2, 75% isolated yield; **6b**:**7b** = 3:2, 70% isolated yield). Similarly, low

Scheme 1



geometric selectivity (**6a**:**7a** = 2:1, 90% isolated yield; **6b**:**7b** = 2:1, 93% isolated yield) was also observed when the allenic titanium reagent, derived from treatment of the lithium reagent with $Ti(O\text{-}i\text{-}Pr)_4$, was utilized. It is worth noting that condensation of **2a** with benzaldehyde still produces the *SR/RS* pair **5d** exclusively. This is in sharp contrast to the exhibition of low or reversed diastereoselectivity when lithium, magnesium, or titanium reagent was utilized.[5,11]

The IR spectrum of **8a** and **8b**, prepared from 1,3-bis(trimethylsilyl)propyne[5] in THF, also exhibited strong allenic and acetylenic absorptions at 1873 cm^{-1} and 2149 cm^{-1}, respectively (eq 1). Interestingly, treatment of **8** with **3a** produced, in addition to the β-acetylenic alcohol similar to **5a**, the corresponding α-allenic alcohol derived from direct condensation with **8b** in a 2 to 1 ratio (combined yield = 72%). Presumably, replacing the *tert*-butyldimethylsilyl group with the sterically less demanding trimethylsilyl group in **8b** allows it to compete more effectively with **8a** for direct condensation with **3a**. Formation of α-allenic alcohols from condensation with propargylic boranes has also been observed previously.[9]



(1)

Condensation of acetylenic aldehydes and simple aldehydes with γ-(trimethylsilyl)allenylborane **9**[4a] were also studied (Scheme 2). Poor diastereoselectivities were observed with acetylenic aldehydes **3a**,**b**, giving rise to low geometric purity in the resulting enediynes (Table 1). With hexanal and benzaldehyde, the condensation reactions exhibited higher diastereoselectivity, leading to enynes with improved geometric purity. As observed previously for condensation of allenic aldehydes with **9**,[4a] a surprising reversal of diastereoselectivity in producing predominantly the *RR/SS* pair was also observed in the present cases.

Scheme 2

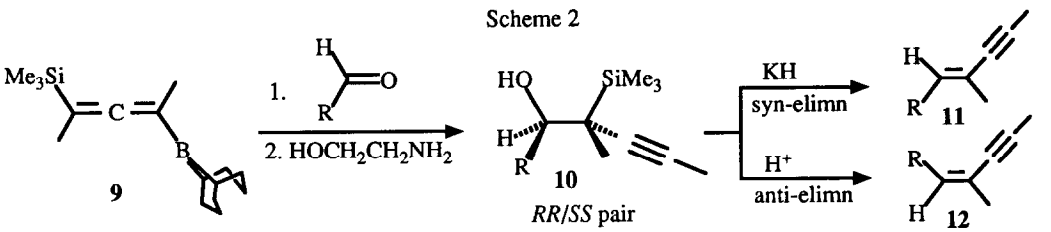
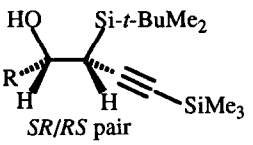
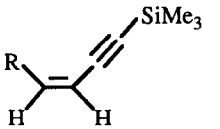
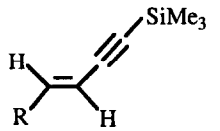
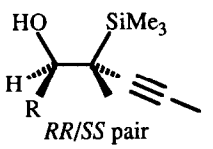
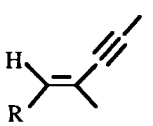
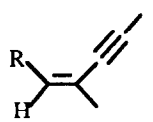


Table 1. Stereoselective Synthesis of Enediynes and Enynes

		elimination condition,[a] base or acid	isolated yield,[b] %	isomer ratio[c]
 *SR/RS* pair				*SR/RS*:*RR/SS*
	5a: R = *n*-Bu-C ≡ C-		73	> 98:2
	5b: R = Ph-C ≡ C-		64	> 98:2
	5c: R = *n*-C_5H_{11}		98	> 98:2
	5d: R = Ph		63	> 98:2
				*Z*:*E*
	6a: R = *n*-Bu-C ≡ C-	KH (Et_2O, rt, 30 min)	94	> 99:1
	6b: R = Ph-C ≡ C-	KH (Et_2O, rt, 30 min)	81	> 99:1
	6c: R = *n*-C_5H_{11}	KH (Et_2O, rt, 1 h)	87	> 99:1
	6d: R = Ph	KH (Et_2O, rt, 30 min)	94	> 99:1
				*E*:*Z*
	7a: R = *n*-Bu-C ≡ C-	H_2SO_4 (rt, 5 h)	85	98:2
	7b: R = Ph-C ≡ C-	H_2SO_4 (rt, 2 h)	79	> 98:2
	7d: R = Ph	H_2SO_4 (rt, 2 h)	88	98:2
 *RR/SS* pair				*RR/SS*:*SR/RS*
	10a: R = *n*-Bu-C ≡ C-		92	7:3
	10b: R = Ph-C ≡ C-		93	7:3
	10c: R = *n*-C_5H_{11}		98	85:15
	10d: R = Ph		91	95:5
				*E*:*Z*
	11a: R = *n*-Bu-C ≡ C-	KH (THF, rt, 20 min)	91	7:3
	11b: R = Ph-C ≡ C-	KH (THF, rt, 20 min)	90	2:1
	11c: R = *n*-C_5H_{11}	KH (THF, rt, 20 min)	97	83:17
	11d: R = Ph	KH (THF, rt, 10 min)	97	93:7
				*Z*:*E*
	12c: R = *n*-C_5H_{11}	H_2SO_4 (THF, rt, 20 min)	92	86:14
	12d: R = Ph	AcOH/NaOAc (50 °C, 50 h)	98	95:5

[a]The elimination step was conducted in a 1:1 mixture of pentane/diethyl ether as described previously[4] unless otherwise indicated.
[b]The isolated products were characterized by IR, ^1H (270 MHz) and/or ^{13}C (67.9 MHz) NMR,[12] and/or MS.
[c]Determined by integration of the ^1H NMR spectrum.

The following procedure for the synthesis of **5a** is representative for condensation with **2**. To 0.68 g of **1** (3.0 mmol) in 15 mL of THF was added 1.20 mL of a 2.5 M solution of *n*-butyllithium (3.0 mmol) in hexanes at -10 °C. After 0.5 h at -10 °C, 0.50 mL of *B*-MeO-9-BBN (0.46 g, 3.0 mmol) was introduced by a syringe. After an additional 45 min at 0 °C, 0.50 mL of $BF_3{\cdot}OEt_2$ (0.57 g, 4.0 mmol) was added and the

reaction mixture was stirred at 0 °C for 20 min before 0.33 g of 2-heptynal (3.0 mmol)[7] was introduced. The reaction mixture was allowed to warm to room temperature and was stirred for 2 h. THF and hexanes were then removed at a reduced pressure under a slow stream of N_2, and the pressure was then restored with N_2. Hexane (20 mL) was added followed by 0.5 mL of 2-aminoethanol, and a white precipitate was formed almost immediately. After 15 min, the precipitate was removed by filtration, and the filtrate was washed with water, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, 5% diethyl ether in hexane) to afford 0.74 g (2.2 mmol, 73%) of **5a** as a colorless liquid: IR (neat) 3496 (OH, br), 2160 (s), 1468(m), 1246 (s), 1008 (m), 843 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.41 (1 H, ddt, J = 8.4, 4.4, and 2 Hz), 2.34 (1 H, d, J = 8.4 Hz), 2.26 (1 H, d, J = 4.4 Hz), 2.21 (2 H, td, J = 6.9 and 1.8 Hz), 1.55-1.35 (4 H, m), 0.94 (9 H, s), 0.90 (3 H, t, J = 7.2 Hz), 0.14 (12 H, s), 0.10 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 105.01, 89.86, 85.44, 80.89, 61.92, 30.61, 29.36, 26.91, 21.90, 18.39, 17.49, 13.62, 0.10, -6.41.

Acknowledgment. The financial support of the National Science Foundation for the purchase of a JEOL GX-270 NMR spectrometer (RII-8011453) and an HP 5970B GC/MSD system (CHE-8913626) is gratefully acknowledged.

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12. The ^1H and ^{13}C NMR spectra ($CDCl_3$) and MS of **5b**, **6a,b**, and **7a,b**. **5b**: ^1H δ 7.47-7.42 (2 H, m), 7.29-7.32 (3 H, m), 4.66 (1 H, dd, J = 8.6 and 4.4 Hz), 2.51 (1 H, d, J = 8.6 Hz), 2.41 (1 H, d, J = 4.4 Hz), 0.98 (9 H, s), 0.20 (3 H, s), 0.17 (12 H, s); ^{13}C δ 131.78, 128.37, 128.24, 122.69, 104.70, 90.21, 89.88, 84.73, 62.32, 29.20, 26.92, 17.53, 0.13, -6.34.; **6a**: ^1H δ 5.82 (1 H, dt, J = 10.8 and 2.0 Hz), 5.74 (1 H, J = 10.8 Hz), 2.41 (2 H, td, J = 6.8 and 2.0 Hz), 1.6-1.4 (4 H, m), 0.92 (3 H, t, J = 7.2 Hz), 0.21 (9 H, s); ^{13}C δ 121.51, 118.13, 102.25, 101.70, 99.51, 78.17, 30.67, 21.90, 19.44, 13.62, -0.14; MS m/e 204 (M^+),189, 147, 73.; **6b**: ^1H δ 7.53-7.47 (2 H, m), 7.37-7.32 (3 H, m), 6.08 (1 H, d, J = 10.8 Hz), 5.91 (1 H, d, J = 11.0 Hz), 0.27 (9 H, s); ^{13}C δ 131.76, 128.63, 128.32, 123.03, 120.69, 119.35, 103.33, 102.20, 97.58, 87.09, -0.11; MS m/e 224 (M^+), 209, 193, 165.; **7a**: ^1H δ 6.00 (1 H, dt, J = 15.9 and 2.2 Hz), 5.87 (1 H, d, J = 15.9 Hz), 2.32 (2 H, td, J = 6.9 and 2.0 Hz), 1.6-1.3 (4 H, m), 0.90 (3 H, t, J = 7.2 Hz), 0.17 (9 H, s); ^{13}C δ 122.80, 119.28, 103.37, 98.76, 96.68, 78.97, 30.59, 21.95, 19.33, 13.56, -0.21; MS m/e 204 (M^+), 189, 147, 73.; **7b**: ^1H δ 7.47-7.42 (2 H, m), 7.35-7.30 (3 H, m), 6.25 (1 H, d, J = 15.9 Hz), 6.07 (1 H, d, J = 15.9 Hz), 0.22 (9 H, s); ^{13}C δ 131.63, 128.66, 128.37, 122.76, 121.92, 120.53, 103.23, 100.51, 94.98, 87.76, -0.19; MS m/e 224 (M^+) 209, 193, 165.

(Received in USA 9 August 1993; accepted 18 October 1993)