J. Org. Chem. **1994,** *59,* 5527–5529

Synthesis of (*E*)- and (*Z*)-1-(Trimethylsilyl)-2-(siloxymethyl)-1,3-butadienes: Versatile Building Blocks for Diels–Alder Cycloadditions Including an Approach toward Taxoids

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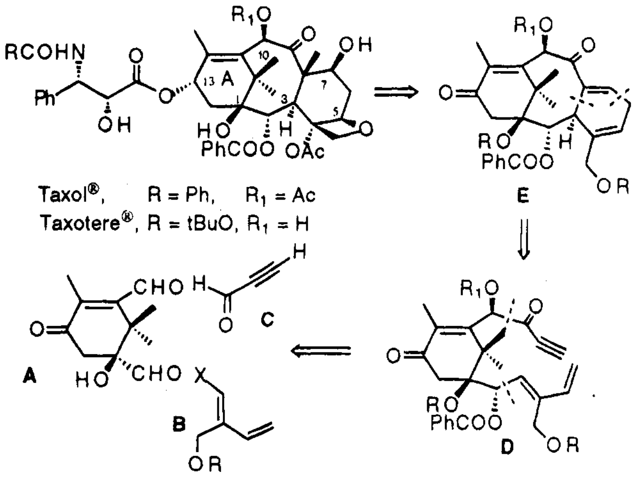
Received June 13, 1994[®]

Summary: The synthesis of the *E*- and *Z*-substituted 1,3-butadienes **5** and **12** and their halodesilylation products **13–16**, via Pd(0) mediated coupling of functionalized alkenes of defined stereochemistry, is described.

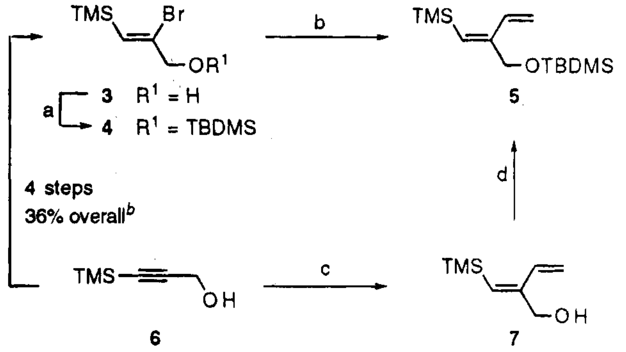
Recently the potent antitumor agent paclitaxel (Taxol) and the related semisynthetic analog docetaxel (Taxotere) have elicited considerable attention due to the synthetic challenge presented by their rare ring system, their therapeutic promise, and their novel mode of action.[1] Two total syntheses of taxol have been completed,[2] and many more are under investigation.[3] Motivated in part by our desire to develop a general strategy that will suffice both for the natural product and the preparation of various analogs with medicinal potential, we required the diene unit **B**. This requirement is based on our successful synthesis of the taxane ABC ring system using an intramolecular Diels–Alder reaction.[4] Thus, we currently envisage the convergent approach illustrated retrosynthetically in Scheme 1, in which this diene **B** is condensed with a suitably functionalized tricarbonyl ring A synthon (**A**) and in a related fashion a second condensation will attach the acetylenic dienophile component **C** to generate the Diels–Alder precursor **D**. Cycloaddition will thus lead to a highly functionalized adduct **E** for subsequent manipulation.

In order to develop suitable diene–dienophile precursors and investigate the subtle aspects of diene geometry and π-facial selectivity involved in this strategy we required functionalized 1,3-butadienes of defined stereochemistry. These dienes must contain suitable structural elements for the eventual introduction of the ring D oxetane and help control the stereochemistry of the C_3 center. In spite of the relatively simple appearance of a diene such as **B** the literature routes were either nonexistent or inappropriate.[5] Thus, we wish to report a general preparation of the novel, configurationally-defined, silyl-substituted dienes **5** [(*E*)-1-(trimethylsilyl)-2-(siloxymethyl)-1,3-butadiene, Scheme 2] and **12** [(*Z*)-1-(trimethylsilyl)-2-(siloxymethyl)-1,3-butadiene, Scheme 3] and their halodesilylated[6] derivatives **13–16** (Figure 1). These diene building blocks can thus serve for the construction of complex ring systems by either intra- or intermolecular cycloadditions and/or be further transformed to more highly oxidized and differentially functionalized systems by metallo–halogen exchange.

Scheme 1



Scheme 2[a]



[a] Key: (a) TBDMSCl, imidazole, CH_2Cl_2, 21 °C, 15 min (96%); (b) $CH_2{=}CHMgBr$, $(Ph_3P)_4Pd$, THF, reflux, 4 h (85%); (c) $CH_2{=}CHMgCl$ (3.2 equiv), THF, reflux, 18.5 h; NH_4Cl (aq) (75%); (d) TBDMSCl, imidazole, CH_2Cl_2, rt, 20 min (86%). [b] Reference 5.

The synthesis of the diene **5** commenced with the known vinyl bromide **3**,[7] itself prepared by the sequence

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[®] Abstract published in *Advance ACS Abstracts,* September 1, 1994.

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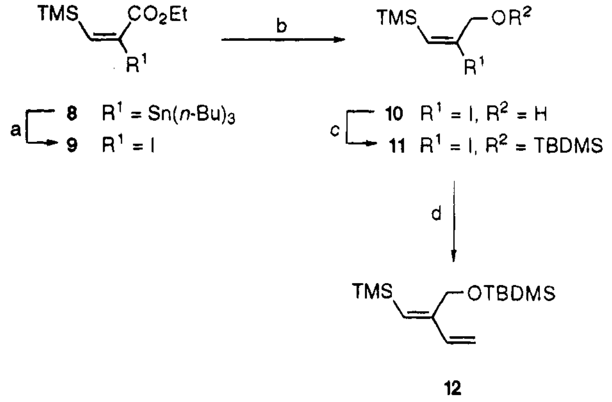
Scheme 3[a]



[a] Key: (a) I_2, CH_2Cl_2, rt, 15 min (94–99%); (b) DIBALH (2.3 equiv in toluene), CH_2Cl_2, −78 °C, 0.5 h; then 0 °C, 0.75 h (82%); (c) TBDMSCl, imidazole, CH_2Cl_2, 21 °C, 25 min (96%); (d) $CH_2{=}CHMgBr$, $(Ph_3P)_4Pd$, THF, reflux, 4 h (75%).

13 X = Br (5% NOE)
14 X = I (7% NOE)

15 X = Br
16 X = I

Figure 1. Vinyl halides obtained from dienes **5** and **12**.

of Borrelly and Paquette (Scheme 2). Protection of **3** as its *tert*-butyldimethylsilyl (TBDMS) ether **4**, followed by Pd(0)-catalyzed coupling with vinylmagnesium bromide[8] in refluxing THF, afforded diene **5** in 85% yield. A shorter, more direct route to **5** utilized the propargyl alcohol **6**. Modification of the procedure reported by Richey and von Rein[9] gave the alcohol **7** as a single geometric isomer in 59% yield, when **6** was treated with excess (7 equiv) vinylmagnesium bromide in refluxing THF (48 h). The yield was improved significantly (75%) by using vinylmagnesium chloride (3.2 equiv) in refluxing THF (18.5 h). Subsequent protection of **7** as its *tert*-butyldimethylsilyl ether **5** completed this alternative route.

Table 1. Preparation of Vinyl Halides 13–16 from Vinylsilanes 5 and 12

entry	substrate	condns[a]	products (ratio)	major isomer[b] (%)
1	**5**	NBS (1.2 equiv), DMF, 35 min	**13**/**15** (33:1)[c]	84
2	5	Br_2 (1.1 equiv), CH_2Cl_2, −10 °C, 1 h	**13**/**15** (16:1)[c]	67[d]
3	**5**	NIS (1.3 equiv), DMF, 20 h	**14**/**16** (15:1)[e]	70
4	**5**	I_2 (1.1 equiv), CH_2Cl_2, 30 min	**14**/**16** (>95:5)[e]	63[d]
5	**12**	NBS (1.1 equiv), DMF, 1.5 h	**13**/**15** (1:10)[c]	82
6	**12**	NIS (3.6 equiv), DMF, 4.5 h	**14**/**16** (1:4)[e]	53
7	**12**	I_2 (1.1 equiv), CH_2Cl_2, 1.25 h	**14**/**16** (>95:5)[e]	52

[a] All reactions were carried out at room temperature (21 °C) unless otherwise stated. [b] Yields refer to isolated material after column chromatography. [c] The product ratio was determined by GC–MS analysis. [d] Combined yield of isomers after column chromatography. [e] The ratio of the products was determined by integration of ^{1}H NMR signals.

The corresponding (*Z*)-diene **12** was prepared from the known vinylstannylsilane **8**[10] (Scheme 3). Thus, iododestannylation of **8** with iodine in CH_2Cl_2 at room temperature (21 °C) produced the vinyl iodide **9** in high yield.[11] Reduction of **9** with excess diisobutylaluminum hydride (DIBALH) in dichloromethane afforded the allylic alcohol **10** (82%). Protection of **10** as its *tert*-butyldimethylsilyl ether, as above, followed by Pd(0)-catalyzed coupling with vinylmagnesium bromide in refluxing THF gave the desired diene **12** in 72% overall yield from **10**. Both the Pd(0)-catalyzed reactions to dienes **12** and **5** proceeded with no apparent loss of stereochemical integrity and with net retention of the starting alkene configuration.[8]

The silyl functionality in the dienes **5** and **12** was replaced by halogen upon treatment with either *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) in dimethylformamide (DMF).[6g] The corresponding halo dienes **13–16** were formed with high stereoselectivity (Table 1). In all cases, the reactions with NBS or NIS occurred with retention of the double bond configuration in yields of 50–85%.

Treatment of diene **12** with bromine (1.1 equiv) in CH_2Cl_2 (21 °C) for 10 min gave a complex mixture in which the bromide **15** was detected by gas chromatography–mass spectrometry (GC–MS) and ^{1}H NMR spectroscopy of the crude mixture after workup. In contrast, similar treatment of **5** afforded the bromides **13** and **15** in 67% combined yield (16:1 ratio; entry 2, Table 1). Of the cases examined, only the reaction of **12** with iodine in CH_2Cl_2 (entry 7, Table 1) proceeded with inversion of configuration to give the (*E*)-vinyl iodide **14** in 52% yield. The iododesilylation of **5** under similar conditions produced **14** in 63% yield. The assignment of the diene stereochemistry for the products derived from vinylsilanes **5** and **12** was established by NOE experiments on bromide **13** and iodide **14** as summarized in Figure 1.

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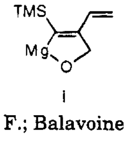
[7] Compound **3** was prepared in four steps starting from propargyl alcohol **6** in 36% overall yield; see: Borrelly, S.; Paquette, L. A. *J. Org. Chem.* **1993**, *58*, 2714.

[8] The stereospecific outcome of the Pd(0)-catalyzed reactions of vinyl iodides with vinyl Grignard reagents was shown by Dang and Linstrumelle to proceed with retention of double bond configuration in all the cases examined. Dang, H. P.; Linstrumelle, G. *Tetrahedron Lett.* **1978**, 191.

[9] Compound **7** is derived from the chelate intermediate **i** and was structurally correlated with the vinylsilane **5** obtained from **4**. (Richey, H. G., Jr.; Von Rein, F. W. *J. Organomet. Chem.* **1969**, *20*, 32 and references cited therein.) In principle, direct condensation of **i** with aldehydes is attractive for many applications; however, in practice this is not yet experimentally viable due to the excess Grignard reagent required for the initial reaction.



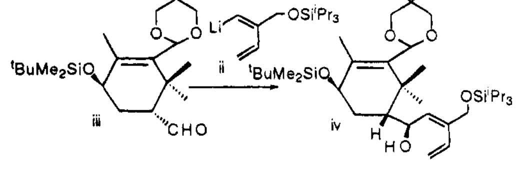
i

[10] Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

[11] Rossi, R.; Carpita, A.; Cossi, P. *Tetrahedron* **1992**, *48*, 8801.

[12] All new compounds were fully characterized by IR, ^{1}H NMR, and ^{13}C NMR; elemental composition was established by elemental analysis and/or high-resolution mass spectrometry.

[13] Preliminary experiments revealed that the addition of **ii** (related to bromide **13**) to the aldehyde **iii** (1.4 equiv of **ii**, −78 °C, 10 min, 21 °C, 10 min) gave the secondary alcohol **iv** (81%).



We are currently developing further applications of these new dienes[9,12] using electrophilic substitution[6f] and halogen–metal exchange reactions.[6e] For example, lithium exchange occurs smoothly (*s*-BuLi) and the resulting vinyl anion can be added to various aldehydes with high stereoselectivity.[13] These results and their application to natural product synthesis will be reported in due course.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada and Rhône-Poulenc Rorer for financial support of this research.

Supplementary Material Available: Experimental procedures for the preparation of compounds **4**, **5**, **7**, and **9–16** and ^{1}H and ^{13}C NMR spectral data for all new compounds (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.