

## A New Synthesis of Substituted Dienes and its Application to an Alkylated Taxane Model System

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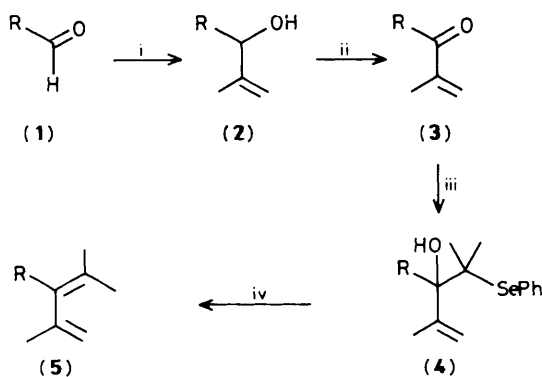
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A new synthesis of highly substituted dienes using  $\text{LiCMe}_2\text{SePh}$  is reported, along with its application to the synthesis of the taxane model compound 8,12,15,15-tetramethyltricyclo[9.3.1.0<sup>3,8</sup>]pentadecane.

Our synthetic programme on the taxane natural products has resulted in a successful stereocontrolled synthesis of the ring system containing three chiral centres in the required orientation.<sup>1</sup> In order to extend this work we required a reliable synthesis of alkyl-substituted butadienes, and we have produced an answer to this problem based on silicon chemistry.<sup>2</sup> The reagent used in this work is  $\text{LiCMe}_2\text{SiMe}_3$ , and while it works well with simple aldehydes, attempts to apply it to our taxane model were unsuccessful. It appeared that the reagent was acting as a base instead of a nucleophile on the aldehyde used. We now report an alternative synthesis of substituted dienes using the selenium reagent  $\text{LiCMe}_2\text{SePh}$ ,<sup>3</sup> which has

enabled us to synthesise an alkylated taxane ring system. Scheme 1† summarises the method of diene synthesis. Addition of the propenyl Grignard reagent to the aldehydes (**1a—d**) gave the allylic alcohols (**2a—d**) which on Collins oxidation afforded the enones (**3a—d**). The reagent  $\text{LiCMe}_2\text{SePh}$ , prepared from  $\text{Me}_2\text{C}(\text{SePh})_2$  and BuLi according to a literature procedure<sup>3</sup> added readily to the series of

† All new compounds gave satisfactory spectroscopic data; correct microanalytical data were obtained for crystalline derivatives of (**5a—c**) along with high resolution mass spectral data for (**3d**), (**5d**), and (**7**).



a; R = Ph

b; R = CH<sub>2</sub>CH<sub>2</sub>Phc; R = [CH<sub>2</sub>]<sub>5</sub>CH<sub>3</sub>

d; R =

	% Yields			
	a	b	c	d
(3)	70	60	72	51
(4)	29 <sup>§</sup>	73	86	85
(5)	66	62	65	54

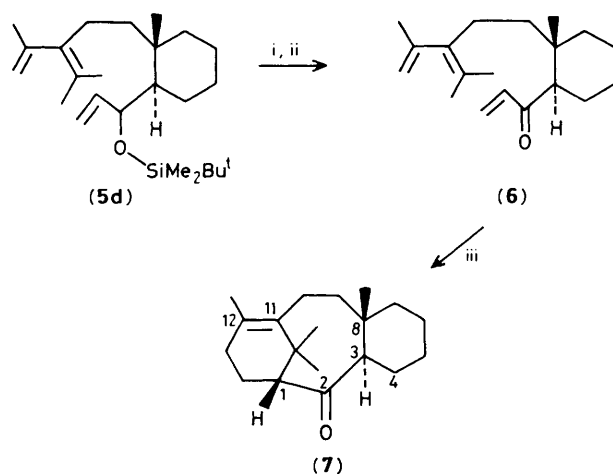
**Scheme 1.** Reagents: i, CH<sub>2</sub>=CMeMgBr (1.1 equiv.), THF, 0 °C; ii, CrO<sub>3</sub> (6 equiv.), pyridine (12 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, room temp.; iii, Me<sub>2</sub>C(SePh)<sub>2</sub>, BuLi, THF, -78 °C; iv, SOCl<sub>2</sub> (2 equiv.), Et<sub>3</sub>N (7 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, room temp.

enones (3a–d) to produce the hydroxy selenides (4a–d). Although the conversion of a 2-methylselenobut-3-enol unit into a diene has been mentioned as unpublished results by Krief,<sup>4</sup> full details and specific applications to highly substituted dienes have not been reported. We now report that the hydroxy selenides (4a–d) readily undergo elimination with thionyl chloride to give the dienes (5a–d) in good yield.

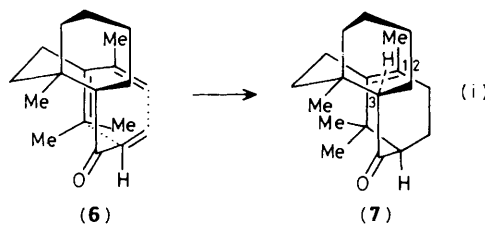
The diene (5d) produced was subjected to deprotection and oxidation to give the enone (6). Treatment of (6) with BF<sub>3</sub>·OEt<sub>2</sub> at -40 °C caused an intramolecular Diels-Alder reaction and the alkylated taxane model system (7) was isolated as an oil [55% from (5d)] (Scheme 2).

‡ Spectroscopic data for (7): ν<sub>max</sub>, 1678 cm<sup>-1</sup>; <sup>1</sup>H n.m.r. (400 MHz) δ 0.94 (3H, s), 0.98–1.21 (4H, m), 1.08 (3H, s), 1.24 (3H, s), 1.47–1.74 (6H, m), 1.82 (1H, ddd, *J* 15.5, 12.68, and 5.51 Hz, 9β-H) overlapping 1.83 (3H), 1.97 (1H, dddd, *J* 15.37, 11.25, 8.69, and 2.64 Hz, 14β-H), overlapping 2.02 (1H, ddd, *J* 18.29, 10.05, and 2.3 Hz, 13α-H), 2.09–2.17 (1H, m, 10β-H), 2.40 (1H, d, *J* 8.63 Hz, 1-H), 2.44–2.59 (1H, m, 13β-H), 2.81 (1H, ddd, *J* 14.19, 12.65, and 5.60 Hz, 10α-H), and 2.96 (1H, dd, *J* 12.22 and 2.96 Hz, 3-H); 3% nuclear Overhauser enhancement between δ 1.83 and 2.96 and 1% in the reverse direction. Extensive n.o.e. and COSY experiments were carried out to assist in assigning the proton spectrum.

§ In the case of (3a → 4a) a product resulting from Michael addition of LiCMe<sub>2</sub>SePh to the enones was also isolated in 38% yield.



**Scheme 2.** Reagents: i, HF, H<sub>2</sub>O, MeCN, room temp., 6 h; ii, CrO<sub>3</sub> (6 equiv.), pyridine (12 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, room temp.; iii, BF<sub>3</sub>·OEt<sub>2</sub> (1 equiv.), toluene, -40 °C, 24 h.



The stereochemistry of the Diels-Alder reaction (6)→(7) is consistent with that found in our previous unalkylated model<sup>1</sup> and may be summarised by the representation (i), where cyclisation occurs to give the chair-boat conformation for the eight-membered ring in the product (7). The importance of the nuclear Overhauser effect between the proton at C-3 and the methyl group at C-12 (see footnote ‡) can be clearly seen in (i); this is the clearest evidence for the stereochemical assignment of (7).

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## References

- P. A. Brown and P. R. Jenkins, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1303.
- P. A. Brown, R. V. Bonnert, P. R. Jenkins, and M. R. Selim, *Tetrahedron Lett.*, 1987, **28**, 693.
- D. Van Ende, W. Dumont, and A. Krief, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 700; A. Krief, *Tetrahedron*, 1980, **36**, 2632.
- J. Rémyon and A. Krief, *Tetrahedron Lett.*, 1976, 3743.