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Metallated α-Alkoxypropargyl and γ-Alkoxyallenyl derivatives : Applications in Some Aldol Reactions Towards Diterpene Synthesis

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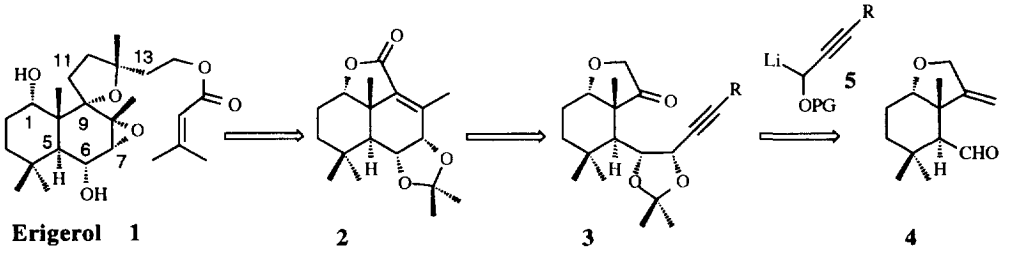
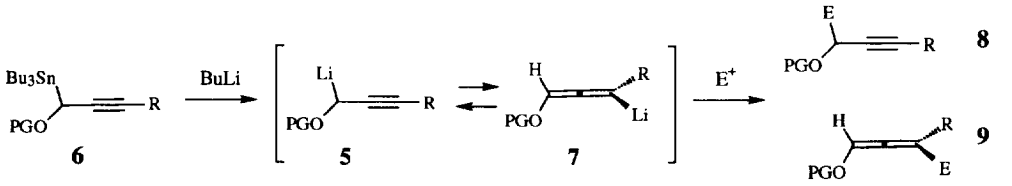
Abstract : The allenyl titanium **11a**, prepared using Yamamoto's conditions reacted with different aldehydes **12a-c** to produce the *anti* acetylenic diols **13a-c**. In a synthetic approach to erigerol **1** this reaction was applied to the aldehyde **4** and thr expected key intermediate **13d** was obtained in 40% yield after removal of the THP group. During this study the α-alkoxypropargylstannane **14** and the α-alkoxyallenylstannane **15** were prepared in good yields after transmetallation of the corresponding lithio derivatives **5b** and **7b** by $Ti(O^iPr)_4$ or Et_2ZnCl. Copyright © 1996 Elsevier Science Ltd

Erigerol **1** was isolated from *Erigeron philadelphicus* L and its structure was determined by NMR spectroscopy and X-ray analysis.[1] The great structural similitude of erigerol **1** with forskoline, which is an important adenylate cyclase activator,[2] made erigerol **1** an attractive challenge for organic chemists and at this time only one total synthesis of erigerol has been achieved by Kienzle,[3] who is under studying potential biological activites of erigerol. Our retrosynthetic scheme is based on the preparation of the unsaturated lactone **2** resulting from a key cyclisation reaction of the ynone **3**, promoted by samarium diiodide.[4] In this strategy the problem was to build the acetylenic-diol system **3** in a stereospecific way *via* an addition reaction of the α-alkoxy(prop-2-ynyl)lithium **5** (or an equivalent) to the aldehyde **4**.[4]

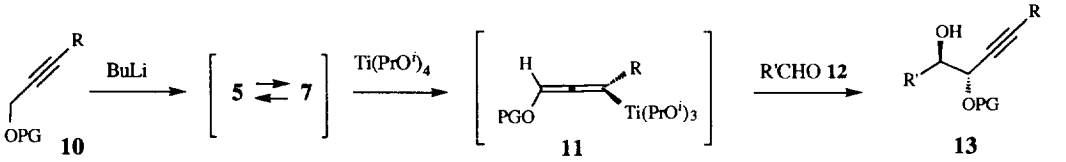


Erigerol 1 **2** **3** **4**

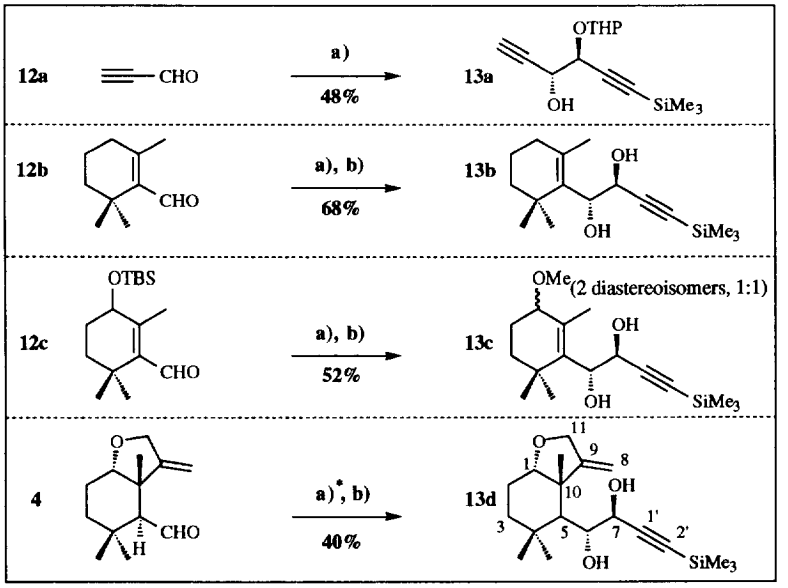
The α-alkoxy(2-alkenyl)stannanes are convenient precursors for the corresponding lithium derivatives and they can be prepared by different methodologies, [5] one being the addition of tributyl or trimethylstannyl lithium to the corresponding conjugated aldehyde, however α-alkoxy(prop-2-ynyl)stannanes **6** cannot be obtained in such a way. Methods to prepare **6** using either addition of stannylcuprate on propargyl aldehydes [6] or Bu_3SnH addition on carbene complexes have been described.[7] However transmetallation of **6** did not give the expected corresponding pure α-alkoxy(prop-2-ynyl)lithium **5** but a mixture of **5** and the isomeric allenyllithium **7**.



The isomerisation reaction of propargyl and allenyllithium derivatives **5** <–> **7** was reported earlier.[8] Metallation of propargyloxy derivatives **10** using *t*BuLi/TMEDA, followed by quenching of the lithio derivative intermediates **5** and **7**, results in the formation of either the propargyl or allenyl compound **8** or **9**, depending on the R substitutent of the starting material and the electrophile reactant. A solution to this problem was given by Yamamoto [9] who achieved a transmetallation with titanium tetraisopropoxide of the lithio intermediates **5** and **7**. The resulting allenyltitanium intermediate **11** was then condensed with aldehydes **12** to afford the pure *anti* acetylenic diols **13** *via* a cyclic transition state.[9]



Application of the reaction of the allenyltitanium **11** to generate acetylenic-diol systems **13** received few attention in total synthesis,[10] and for our approach of erigerol **1** we decided to evaluate the reactivity of **11** toward several aldehydes. This aldol reaction was performed between the propargyloxy derivative **10a** (PG = THP, R = $SiMe_3$) [10] and aldehydes **12a-c** and **4** [11] under Yamamoto's conditions.[10]



a) i- **10a**, *t*BuLi, 1.1 equiv, -78°C. ii- $Ti(O^iPr)_4$, 1.1 equiv, -78°C. iii- **12**, -78°C. **b)** MeOH, PPTS cat. 0°C->25°C. **a)*** i- **10a**, *t*BuLi, 2.2 equiv, -78°C. ii- $Ti(O^iPr)_4$, 2.2 equiv, -78°C. iii- **4**, -78°C.

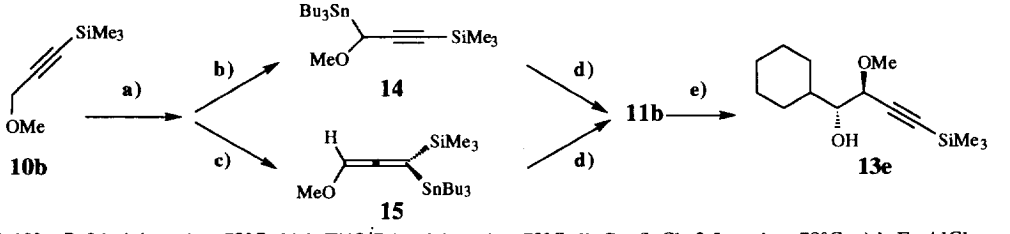
For ynal **12a** and conjugated aldehydes **12b** and **12c** reaction took place when one equivalent of the

allenyltitanium **11a** (PG = THP, R = $SiMe_3$) was used. The ynal **12a** gave the diol derivative **13a** in 48% yield; for aldehydes **12b** and **12c** a subsequent acidic treatment delivered the expected *anti* diols **13b** and **13c** in, 68 and 52% yield respectively. For **13c** (two diastereoisomers, 1:1 mixture) an allylic rearrangement, led to a substitution of the OTBS group by OMe during removal of the THP group.

In the case of aldehyde **4** two equivalents of the allenyltitanium **11a** were required for the reaction to take place, subsequent acidic hydrolysis of the THP group gave the expected *anti* diol **13d** [12] in 40% for the two steps. This diol **13d** is a key intermediate for our synthetic approach of erigerol **1**.[4]

During this work we also examined the reactivity of the propargyl and allenyllithium intermediates **5b** and **7b** (PG = Me, R = $SiMe_3$) when submitted to transmetallation and subsequent Bu_3SnCl quench. Starting from **10b** (PG = Me, R = $SiMe_3$) [13] metallation with *t*BuLi was conducted as before. In a first experiment, after transmetallation of propargyl and allenyllithium **5b** and **7b** with $Ti(O^iPr)_4$, a Bu_3SnCl addition to the mixture at -78°C gave the propargylstannane **14** in 89% yield.[7,14] When the transmetallation was achieved with Et_2AlCl quenching with Bu_3SnCl resulted in the formation of the allenylstannane **15** in 83% yield.[15]

It was checked that propargylstannane **14** or allenylstannane **15** could be in turn transmetallated with *n*BuLi to deliver the propargyl and allenyllithium **5b** and **7b**, then with $Ti(O^iPr)_4$ to regenerate the allenyltitanium **11b**. In this experiment **11b** reacted with cyclohexylcarbaldehyde to furnish compound **13e** in 60% yield.



a) **10b**, *t*BuLi, 1.1 equiv, -78°C. **b)** **i-** $Ti(O^iPr)_4$, 1.1 equiv, -78°C. **ii-** Bu_3SnCl, 2.5 equiv, -78°C. **c)** **i-** Et_2AlCl, 1.1 equiv, -78°C. **ii-** Bu_3SnCl, 2.5 equiv, -78°C. **d)** **i-** **14** or **15**, *n*BuLi, 1.1 equiv, -78°C. **ii-** $Ti(O^iPr)_4$, 1.1 equiv, -78°C. **e)** cyclohexylcarbaldehyde, -78°C.

*For an approach to erigerol **1**, preparation of allenyltitanium **11a** from **10a** allowed us to achieve a stereospecific preparation of our key intermediate anti-diol **13d**. Starting from the propargyloxy derivative **10b**, an efficient preparation of the propargyl and the allenylstannane **14** and **15**, which could be considered as stabilized precursors of **11b**, was described. Work is now focused on the reactivity of stannanes **14** and **15**, and particularly on the Lewis acid catalyzed reaction of allenylstannane **15** with aldehydes, which could be a complementary study of Yamamoto's reaction.*

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12) The *anti* diol structure of **13d** was further proved, after cyclisation of the ynone **3** with SmI_2, ref 4.
To a solution of **10a** (PG = THP, R = $SiMe_3$, 1.3 g, 7.5 mmol, 2.5 equiv) in THF (13 mL), cooled to -78°C, was added dropwise a 1.5M *t*-BuLi solution in pentane (5.0 mL, 7.5 mmol, 2.5 equiv) and the resulting solution stirred at this temperature for 40 min. $Ti(O^iPr)_4$ (3.1 mL, 7.5 mmol, 2.5 equiv) was then added to the resulting orange anion and the slightly darkened solution stirred at -78°C for 10 min. A solution of aldehyde **4** (620 mg, 3.0 mmol) in THF (6 mL) was transferred *via* cannula. The reaction mixture was stirred at -78°C for 1 h, allowed to warm to 25°C over 2 h and the reaction quenched with saturated aqueous NH_4Cl (20 mL). The heterogenous mixture was then filtered over a plug of celite and the white precipitate rinsed with 100 mL of diethyl ether. The phases were separated, the aqueous phase was extracted with 3 x 50 mL of diethyl ether and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo* to give a crude mixture (1.2 g) which was carried on to the next step without further purification.
To a solution cooled to 0°C of the preceding crude mixture (1.2 g) in methanol (5 mL) was added TsOH (57 mg, 0.3 equiv) and the reaction mixture stirred at this temperature for 30 min, allowed to warm to 25°C over 30 min and partitioned between 20 mL of a saturated aqueous $NaHCO_3$ solution and 50 mL of diethyl ether. The phases were separated, the aqueous phase was extracted with 3 x 50 mL of diethyl ether and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. Purification by flash-chromatography on silica gel gave diol **13d** (404 mg, 40% yield).
^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.20 [3s, 9H, $Si(CH_3)_3$], 1.13, 1.24 and 1.26, (3s, 9H, $3CH_3$), 1.60-1.94 (m, 6H, H_2-2, H_2-3, 2-OH), 2.10 (d, *J* = 3.7 Hz, 1H, H-5), 3.60 (t, *J* = 2.5 Hz, 1H, H-1), 3.61 (dd, *J* = 6.7, 1.9 Hz, 1H, H-7), 4.26 (dt, *J* = 14.8, 2.0 Hz, 1H, H-11a), 4.30 (dd, *J* = 6.7, 3.7 Hz, 1H, H-6), 4.52 (dt, *J* = 14.8, 2.0 Hz, 1H, H-11b), 4.86 (t, *J* = 1.9 Hz, 1H, H-8a), 4.95 (t, *J* = 1.9 Hz, 1H, H-8b). **^{13}C NMR** ($CDCl_3$, 50.3 MHz) δ -0.1 [$3CH_3$, $Si(CH_3)_3$], 17.4 (CH_3), 22.6 (C-3), 23.7 (CH_3), 33.5 (CH_3), 33.7 (C-4), 38.5 (C-2), 42.9 (C-5), 48.4 (C-10), 67.1 (C-7), 69.9 (C-11), 74.9 (C-2'), 75.2 (C-6), 84.0 (C-1), 84.0 (C-1'), 105.3 (C-8), 159.5 (C-9).

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14) **14**: **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.20 [s, 9H, $3CH_3$, $Si(CH_3)_3$], 0.90 {t, *J* = 6.0 Hz, 9H, $3CH_3$, Sn-[$(CH_2)_3$-CH_3)]3}, 0.91 {t, *J* = 6.0 Hz, 6H, 3 Sn-[CH_2-$(CH_2)_2$-CH_3]3}, 1.30-1.50 [m, 12H, Sn-$(CH_2$-CH_2-CH_2-$CH_3)_3$], 3.35 (s, 3H, CH_3, OCH_3), 4.20 (s, 1H, H-1, *J* H-^{117}Sn = *J* H-^{119}Sn = 37.5 Hz). **^{13}C NMR** ($CDCl_3$, 50.3 MHz) δ -0.3 [$3CH_3$, $Si(CH_3)_2$], 10.25 [$3CH_2$, Sn-(CH_2-)$_3$, *J* C-^{117}Sn = 345.0 Hz, *J* C-^{119}Sn = 338.0 Hz], 13.64 {$3CH_3$, Sn-[$(CH_2)_3$-CH_3]3}, 27.79 [$3CH_2$, Sn-(CH_2-CH_2-CH_2-$CH_3)_3$, *J* C-^{117}Sn = *J* C-^{119}Sn = 61.0 Hz], 29.05 [$3CH_2$, Sn-(CH_2-CH_2-CH_2-$CH_3)_3$, *J* C-^{117}Sn = *J* C-^{119}Sn = 26.0 Hz], 65.0 (C-1), 59.14 (CH_3, OCH_3), 94.30 (C-2), 107.26 (C-3).

15) **15**: **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 0.20 [s, 9H, $3CH_3$, $Si(CH_3)_3$], 0.90 {t, *J* = 6.0 Hz, 9H, $3CH_3$, Sn-[$(CH_2)_3$-CH_3)]3}, 0.91 {t, *J* = 6.0 Hz, 6H, Sn-[CH_2-$(CH_2)_2$-CH_3]3}, 1.30-1.50 [m, 12H, Sn-$(CH_2$-CH_2-CH_2-$CH_3)_3$], 3.32 (s, 3H, CH_3, OCH_3), 6.55 (s, 1H, H-1, *J* H-^{117}Sn = *J* H-^{119}Sn = 38.0 Hz). **^{13}C NMR** ($CDCl_3$, 50.3 MHz) δ -0.3 [$3CH_3$, $Si(CH_3)_2$], 11.22 [$3CH_2$, Sn-(CH_2-)$_3$, *J* C-^{117}Sn = 345.0 Hz, *J* C-^{119}Sn = 338.0 Hz], 13.64 {$3CH_3$, Sn-[$(CH_2)_3$-CH_3]3}, 26.92 [$3CH_2$, Sn-(CH_2-CH_2-CH_2-$CH_3)_3$, *J* C-^{117}Sn = *J* C-^{119}Sn = 61.0 Hz], 29.05 [$3CH_2$, Sn-(CH_2-CH_2-CH_2-$CH_3)_3$, *J* C-^{117}Sn = *J* C-^{119}Sn = 26.0 Hz], 56.35 (CH_3, OCH_3), 119.6 (C-1), 163.9 (C-3), 207.4 (C-2).

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