Silenes in organic synthesis: a short synthesis of prelactone B†

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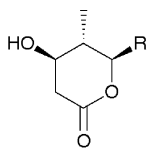
A sequence involving dihydroxylation and acid induced fragmentation of silene generated silacyclohexenes represents the key step in a concise synthetic route to β-hydroxy-δ-lactones.

δ-Lactones, specifically β-hydroxy-δ-lactones, are found as components of many bioactive natural products. In addition they also represent useful building blocks for the synthesis of more complex structures. The prelactones, **1**–**4** are a sub-group of this class of compounds isolated from various polyketide macrolide-producing microorganisms. First isolated from the bafilomycin-producing *Streptomyces griseus*, by Bindseil and Zeeck in 1993,[1] prelactone B (**1**) represents an early metabolite in the biosynthesis of polyketide antibiotics. Although a direct product of the polyketide synthase (PKS) enzyme responsible for the synthesis of the macrolide, prelactone B is not incorporated into the natural macrolide and it is believed that it is a shunt product of the biosynthetic pathway. Reflecting the general interest in this biosynthetic pathway and the potential of these compounds in other synthetic strategies a number of synthetic routes have been reported.[2]



1 prelactone B, R = $CH(CH_3)_2$
2 prelactone C, R = $CH{=}CHCH_3$
3 prelactone V, R = CH_3
4 prelactone E, R = C_2H_5

We have recently described the development of a new synthetic methodology for the generation of silacyclohexenes through the [4 bū 2] cycloaddition of silenes (compounds containing a Si=C double bond) with dienes and their subsequent elaboration to δ-lactones.[3] In this communication we describe how the allyl silane component of the silacyclohexene can be used to provide a stereocontrolled synthetic route to β-hydroxy-δ-lactones exemplified by a short synthesis of prelactone B.

The synthesis begins with the silene–diene Diels–Alder reaction which produces the silacyclohexenes **7**–**9** in good overall yield, favouring the product **7** arising from a Z(Si) silene **6** reacting in an endo Si–Ph orientation (**7a** : **8a** : **9a**, 70 : 20 : 10; **7b** : **8b** : **9b**, 80 : 20 : 0), Scheme 1. These are obtained as an inseparable mixture of isomers with the minor components reflecting the presence of small amounts of *exo* addition and trace amounts of the adducts of the alternative *E*(Si) silene. Our initial synthetic plan suggested that the desired hydroxylactones could be accessed through hydroboration of the silacyclochexene with the regiochemistry directed by the allyl silane unit followed by alcohol protection, Fleming–Tamao oxidation and oxidative cyclisation of the resulting diol. Although hydroboration afforded the desired δ-hydroxy silane we were unable to enhance the yield beyond *ca.* 45% and more importantly the subsequent steps proved inefficient. Consequently we turned to explore alternative alkene oxidation protocols. Ultimately dihydroxylation of the olefinic bond under standard catalytic conditions[4] afforded the silacyclic diols **10**–**12** in excellent yield. At this stage, simple flash column chromatography allowed separation of the minor silacycle stereoisomers providing the desired diols **10a** and **10b** as single isomers.‡ Stereochemical assignment of the required C-3 hydroxy unit was confirmed by ^{1}H NMR NOESY experiment, Fig. 1.

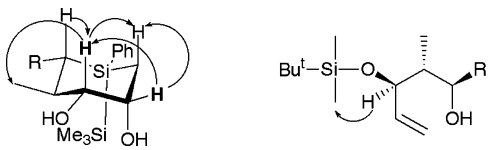


Fig. 1 Selected NOESY correlations for **10** and **14**.

With the correct C-3 stereochemistry established, treatment with $BF_3{\cdot}2AcOH$ complex exploited the directing effect of the silicon atom to afford, following oxidation under Fleming–Tamao conditions, the corresponding allylic alcohol **13** without loss of stereochemical integrity.[5] Preliminary attempts to hydroborate the terminal alkene at this stage were complicated by difficulties in isolation of the resultant triols. Consequently, selective monoprotection of the diol at the allylic position was achieved on treatment with TBDMSCl as confirmed by ^{1}H NMR NOESY studies, Fig. 1.

Initial attempts at hydroboration of the protected diols **14** with borane–dimethylsulfide complex yielded, after oxidation, a 1 : 1 mixture of regioisomeric alcohols. However, the use of dicyclohexylborane directed the hydroboration to the terminal end of the alkene with only trace amounts of the regioisomeric product.[6] Subsequent TPAP–NMO oxidation generated the lactones. Without purification, silicon deprotection using $Et_3N{\cdot}3HF$ then afforded prelactone B **1** and the C-5 phenyl analogue **16** in excellent overall yield. The ^{1}H NMR, ^{13}C NMR, IR and mass spectra of these products were all in excellent agreement with previously published data.[2]

In conclusion silene–cycloaddition chemistry enables a concise, novel and flexible approach to the total synthesis of β-hydroxy-δ-lactones, typified by prelactone B. Current work is focused on introducing enantioselectivity into this sequence and extending the methodology to more highly substituted δ-lactone natural products.

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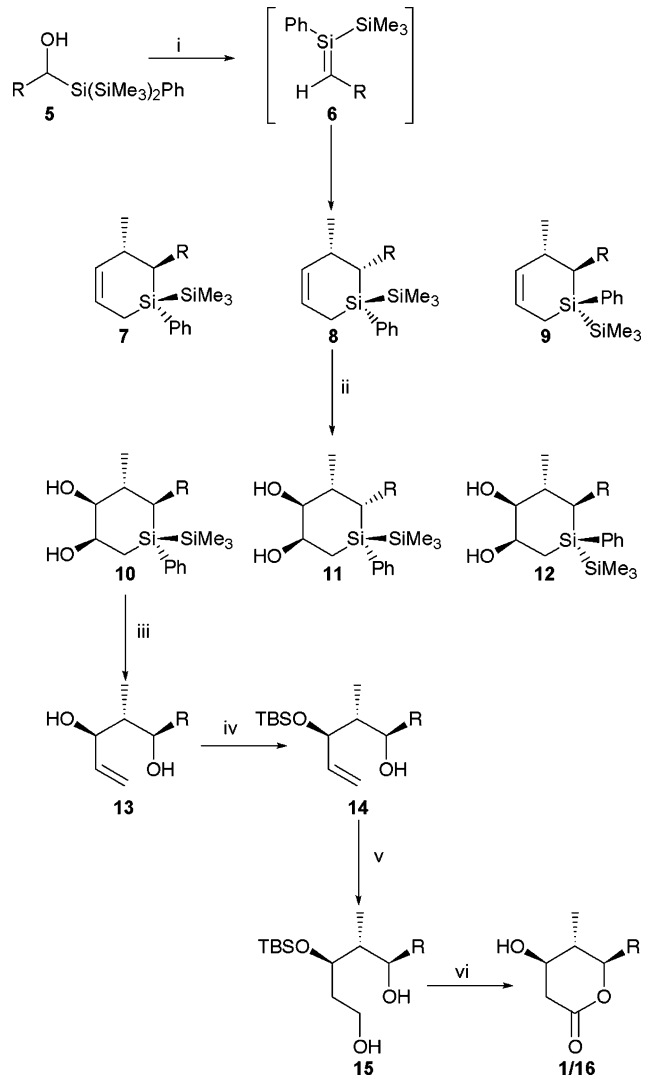
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/b608989e



Scheme 1 Reagents and conditions (R = ^{i}Pr, b R=Ph): (i) BuLi, 10 mol% LiBr, 1,3-pentadiene, THF, −20 °C (**7a** : **8a** : **9a** [70 : 20 : 10] 40%, **7b** : **8b** : **9b** [80 : 20 : 0] 45%); (ii) OsO_4 (cat.), NMO, acetone–H_2O (20 : 1), 0 °C to r.t., 30 min (**10a** 32%, **11**/**12a** 12%; **10b** 56%, **11**/**12b** 26%); (iii) BF_3·2AcOH, DCM, r.t., 5 min then $KHCO_3$, KF, H_2O_2, THF, reflux, 1 h (**13a** 64%, **13b** 72%); (iv) TBSCl, imidazole, DCM, r.t., 1 h (**14a** 52%, **14b** 70%); (v) $(C_6H_{11})_2BH$, THF, 0 °C to r.t., 1 h then H_2O_2, aq. NaOH (3 M), reflux, 1 h (**15a** 60%, **15b** 70%); (vi) TPAP, NMO, 4A MS, DCM, r.t., 1 h, then Et_3N·3HF, THF, 24 h (**1** 90%, **16** (R = Ph) 100%).

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Notes and references

‡ **(1*SR*,2*RS*,3*SR*,4*SR*,5*SR*)-4,5-Dihydroxy-3-methyl-1-phenyl-2-prop-2′-yl-1-trimethylsilylsilacyclohexane** (**10a**). A solution of silacycles **7**–**9a** (0.05 g, 0.15 mmol) in acetone–water (2.1 ml, 20 : 1) was treated with NMO (0.04 g, 0.3 mmol) and cooled to 0 °C. The solution was then treated with a catalytic amount of osmium tetroxide (0.002 g, 0.007 mmol) and reacted for 45 min. The reaction mixture was then treated with aq. $Na_2S_2O_3$ and extracted with EtOAc (3 × 5 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo.* Flash chromatography (pet. ether–ether [1 : 1], [1 : 2]) afforded the title compound **10a** as a yellow oil (0.06 g, 32%); R_f (pet. ether–ether 1 : 1) 0.3 as a single diastereoisomer; υ_{max} (thin film) 3498–3211, 2950, 2932, 2898, 2864, 1426, 1096, 1022, 992, 832, 731, 697 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 7.53–7.51 (2H, m, Ar–H), 7.31–7.30 (3H, m, Ar–H), 4.22–4.19 (1H, m, 5-*H*), 3.51–3.46 (1H, m, 4-*H*), 2.29–2.22 (1H, m, 3-*H*), 2.17–2.10 (1H, m, 2′-*H*), 1.39–1.34 (1H, dd, J 14, 9, 6-*H*H), 1.21–1.15 (1H, m, 6-H*H*), 1.09–1.07 (1H, dd, J 9, 6, 2-*H*), 1.05–1.04 (3H, d, J 7, CHCH_3), 0.98–0.96 (3H, d, J 7, 3-CH_3), 0.92–0.90 (3H, d, J 7, CHCH_3), 0.21 (9H, s, Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 140.2 (ipso-Ar–C), 134.4 (Ar–C), 128.5 (Ar–C), 128.0 (Ar–C), 78.8 (4-C), 70.2 (5-C), 36.8 (2-C), 35.8 (3-C), 29.1 (2′-C), 23.8 (CH*C*H$_3$), 19.4 (3-*C*H$_3$), 16.5 (6-C), −0.4 (Si(*C*H$_3$)$_3$); δ_{Si} (100 MHz, $CDCl_3$) −17.90, −23.36; *m*/*z* (ES^{bū}) 359 (M bū Na^{bū}); HRMS (ES^{bū}) found 359.18339 ($C_{18}H_{32}Si_2O_2Na$ requires 359.18330). **(3*RS*,4*RS*,5*RS*)-3,5-Dihydroxy-4,6-dimethylheptene** (**13a**). To a solution of silacyclic diol **10a** (0.12 g, 0.3 mmol) in dry dichloromethane (4 ml) was added trifluoroborane–acetic acid complex (0.09 ml, 0.6 mmol). The solution was stirred for 15 min at room temperature then mixed with saturated $NaHCO_3$ solution (5 ml) and extracted with DCM (3 × 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo* to give a colourless oil which was used immediately in the following step. To the colourless oil was added $KHCO_3$ (0.1 g, 1.0 mmol) and KF (0.04 g, 0.7 mmol). The mixture was dissolved in methanol–THF solution (1 : 1, 4 ml) and a 35% *w*/*w* solution of H_2O_2 in water (0.4 ml, 3.9 mmol) was added. The mixture was heated to reflux and stirred for 1 h. The mixture was then allowed to cool to room temperature and saturated $Na_2S_2O_3$ solution (5 ml) was added together with EtOAc (10 ml). The aqueous layer was separated and extracted with EtOAc (3 × 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo.* Flash chromatography (pet. ether–ether [9 : 1], [4 : 1], [3 : 2], [1 : 1], [1 : 2]) gave the title compound **13a** as a colourless oil (0.02 g, 64%); R_f ((pet. ether–ether 1 : 1) 0.3 as a single diastereoisomer; υ_{max} (thin film) 3525–3134, 2962, 2870, 1459, 1427, 1118, 1081, 974, 919, 844, 697, 639 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 5.97–5.90 (1H, ddd, J 16, 10, 5, 2-H), 5.31–5.27 (1H, d, J 18, 1-H_a), 5.20–5.18 (1H, d, J 10, 1-H_b), 4.41 (1H, s, 3-*H*), 3.40–3.39 (1H, m, 5-*H*), 3.11 (1H, –OH), 2.53 (1H, –OH) 1.92–1.86 (1H, qd, J 7, 3, 4-*H*), 1.85–1.79 (1H, m, 6-*H*), 0.95–0.93 (3H, d, J 8, 6-CH_3), 0.93–0.92 (3H, d, J 8, 7-H_3), 0.88–0.87 (3H, d, J 7, 4-CH_3); δ_C (126 MHz, $CDCl_3$) 138.9 (2-*C*), 115.4 (1-*C*), 79.8 (5-*C*), 75.1 (3-*C*), 39.6 (4-*C*), 30.6 (6-*C*), 20.0 (6-*C*H$_3$), 16.0 (7-*C*), 12.2 (4-*C*H$_3$); *m*/*z* (ES^{bū}) 181.2 (M bū Na^{bū}); HRMS (ES^{bū}) Found 181.11991 ($C_9H_{18}O_2Na$ requires 181.11990).

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