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Synthesis of (2*S*,7*S*)-dibutyroxynonane, the sex pheromone of the orange wheat blossom midge, *Sitodiplosis mosellana* (Géhin) (Diptera: Cecidomyiidae), by diastereoselective silicon-tethered ring-closing metathesis

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Abstract—The sex pheromone of *Sitodiplosis mosellana*, (2*S*,7*S*)-dibutyroxynonane, has been synthesised using a mixed di-*t*-butylsilaketal prepared from (*S*)-5-hexen-2-ol and prochiral 1,4-pentadiene-3-ol. Ring-closing metathesis occurs diastereoselectively and after the removal of the silyl group and the reduction of the double bonds, generates (2*S*,7*S*)-nonanediol with a diastereoisomeric excess of 94% as measured by gas chromatographic analysis of the diacetylated product.

The orange wheat blossom midge, *Sitodiplosis mosellana* (Géhin) (Diptera: Cecidomyiidae), is a serious pest in all parts of the world where wheat is grown. Adult insects emerge from the soil during a short period in spring and, after mating, females lay eggs producing larvae that feed on the developing kernels causing damage, a decrease in grain quality and facilitating secondary fungal attack.[1,2] *S. mosellana* within a region has a patchy distribution, is difficult to detect and infestations can vary enormously from year to year depending on climatic conditions around the time of adult emergence in the spring.[3] Measures to protect crops from the orange wheat blossom midge therefore employ prophylactic spraying of insecticides throughout the time of possible emergence and so are wasteful economically and detrimental to the environment. The sex pheromone of *S. mosellana* has been identified as (2*S*,7*S*)-dibutyroxynonane[4] ((2*S*,7*S*)-**1**) and a mixture of (2,7)-dibutyroxynonane isomers is now used in trap monitoring of emerging adults to allow the timing of insecticide spraying to coincide with the presence of emerging adult *S. mosellana*, so optimising pesticide treatment.[5] Although the pheromone traps only catch males, the data provide the time of peak emergence, midge abundance through the season and predict the level of larval damaged grain through the laying of eggs by females. Traps with lures containing a mixture of stereoisomers of 2,7-dibutyroxynonane in our study,[5] and in other published work,[4] were effective at catching male insects. However, the greatest biological activity shown in both studies was found with the (2*S*,7*S*)-**1** isomer, the same isomer as the natural pheromone. We previously reported the preparation of (2*S*,7*S*)-**1** by a biotechnological approach, resolving racemic 2,7-nonanediol with a lipase from *Pseudomonas cepacia*. This approach utilised the racemic diol and a minimum loss of 75% in the resolution step to remove undesired stereoisomers makes this route very inefficient.[5] Other workers have described the synthesis of (2*S*,7*S*)-**1** using chiral pool (*S*)-propylene oxide to produce the 2*S* stereocentre and enantioselective hydrolytic kinetic resolution of a racemic terminal epoxide with Jacobsen's catalyst to generate (7*S*)-configuration of the stereocentre at C7, but only achieved a moderate de of 77%.[4] The distance of five carbon atoms between the two stereocentres makes it difficult for one stereocentre to direct the creation of the second with high stereoselectivity. However, the

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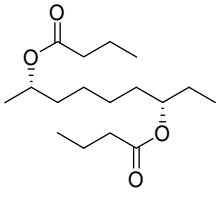
recent popularity of metathesis reactions,[6] in particular ring-closing metathesis (RCM)[7,8] and silicon-tethered ring-closing metathesis,[9–12] has revealed that long-range asymmetric induction of 1,4-, 1,5- and 1,6-stereocentres is possible. We hypothesised that this methodology could be applied to our particular challenge, the synthesis of (2*S*,7*S*)-**1**, by 1–6 induction to generate the (7*S*)-configuration.



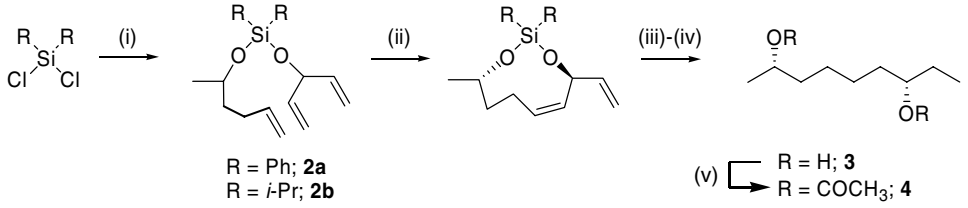
(2*S*,7*S*)-1

The substrates for RCM examination, silaketals **2a** and **2b**, were prepared from their respective dichlorosilane, racemic 5-hexen-2-ol and prochiral 1,4-pentadien-3-ol (Scheme 1) and purified only by filtration through a neutral alumina plug in petroleum ether. After RCM, the crude product was analysed by ^{1}H NMR, which revealed a dioxasilacycle with the internal double bond being exclusively cis ($J = 11.4$ Hz). This crude product was reduced with H_2 and subsequently desilylated with TBAF to yield diol **3**. Finally, the respective nonanediols were diacetylated for analysis by enantioselective gas chromatography. Diacetates **4** were prepared for analysis, as the dibutyrates were not separable using the β-cyclodextrin column available,[13] and the stereochemistry was defined by GC co-elution with samples prepared by resolution using a *P. cepacia* lipase.[5,14] The desired stereoisomer, (2*SR*,7*SR*)-**4**, was generated in 89% de from **2a** and 91% de from **2b** (Table 1). However,

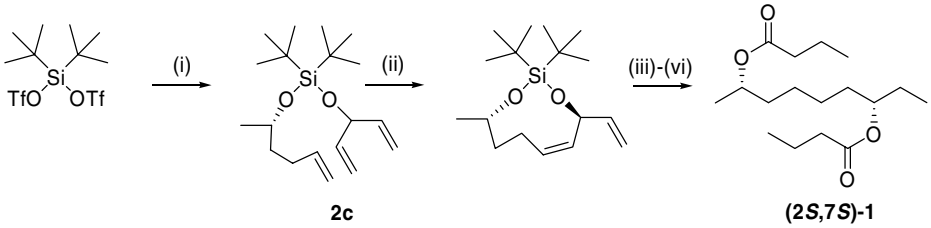
Table 1. Diastereoselectivity of RCM on silaketals

Diacetylated product	RCM substrate (Si group)	Diastereomeric excess (%)
(2*SR*,7*SR*)-**4**	**2a** (phenyl)	89
(2*SR*,7*SR*)-**4**	**2b** (*i*-propyl)	91
(2*SR*,7*SR*)-**4**	**2c** (*t*-butyl)	95
(2*S*,7*S*)-**4**	(*S*)-**2c** (*t*-butyl)	94

NMR and GC analysis revealed that **2a** and **2b** were contaminated with the symmetric silaketals which were difficult to remove chromatographically. Also, in the case of **2b**, a fivefold excess of reagent was required to reduce the amount of symmetric product making the synthesis inefficient. We anticipated that using a pendant silyl group with greater steric bulk than the isopropyl or phenyl group would increase the diastereoselectivity and might also allow preparation of the desired mixed silaketal without using excess silylating reagent. Indeed, a chemoselective synthesis of the desired silaketal could be achieved by treating di-*t*-butyl bis(trifluoromethanesulfonate) with pyridine and adding 5-hexen-2-ol dropwise at −78 °C, then adding 1,4-pentadien-3-ol after warming the mixture to room temperature. When **2c** was subjected to RCM, the crude mixture contained only 4% of the symmetric silaketal by GC analysis. Deprotection of **2c** was problematic as there was no reaction with TBAF, HF, HF/pyridine or $BF_3{\cdot}Et_2O$, but was solved by adding 4 Å molecular sieves to an excess of TBAF and refluxing overnight. Reduction with H_2/PtO_2 and diacetylation yielded (2*SR*,7*SR*)-**4** with 95% de by GC. With the diastereoselectivity of RCM on **2c** giving excellent results, commercially available[15] (*S*)-5-hexen-2-ol was used to synthesise a single enantiomer of di-*t*-butylsilaketal (*S*)-**2c** (Scheme 2) which was converted to the sex pheromone (2*S*,7*S*)-**1**[16] in an overall



Scheme 1. Synthesis of (2*SR*,7*SR*)-**4**. Reagents and conditions (**2a**): (i) lithium 5-hexen-2-oxide, −78 °C, THF, dichlorodiphenylsilane (1 equiv), warm to rt, imidazole, 1,4-pentadien-3-ol, 71%; (**2b**): (i) lithium 5-hexen-2-oxide, −78 °C, THF, diisopropyldichlorosilane (5 equiv), warm to rt, high vacuum, imidazole, 1,4-pentadien-3-ol, 86%; (ii) Grubbs' 1st generation catalyst (bis(tricyclohexylphosphine)benzylidene ruthenium(IV) chloride), CH_2Cl_2, 40 °C; R = Ph, 57%; R = *i*-Pr, 94%; (iii) H_2, 10% Pd/C, MeOH; (iv) 3 equiv TBAF, **3**: R = Ph, 57% over two steps; R = *i*-Pr, 80% over two steps; (v) CH_3COCl, pyridine, DMAP, quant.



Scheme 2. Synthesis of (2*S*,7*S*)-**1**. Reagents and conditions: (i) 0 °C, THF, pyridine, DMAP, cool to −78°C, (*S*)-5-hexen-2-ol, warm to rt, 1,4-pentadien-3-ol; (ii) Grubbs' catalyst (bis(tricyclohexylphosphine)benzylidene ruthenium(IV) chloride), CH_2Cl_2, 40 °C, 70% over two steps; (iii) 10 equiv TBAF, 4 Å mol sieves, reflux 18 h, 78%; (iv) H_2, PtO_2, MeOH, 83%, (v) butyric anhydride, pyridine, DMAP, 85%.

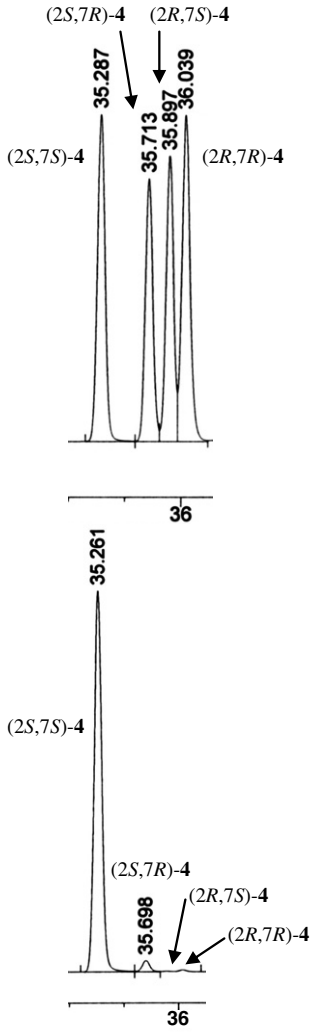


Figure 1. Enantioselective gas chromatograms of a mixture of the four isomers of 2,7-diacetoxynonane (**4**) (above) and (below) the diacetoxynonane mixture produced after silicon-tethered RCM of silaketal (*S*)-**2c**.

yield of 22% in 99% ee and 94% de (Fig. 1). Thus, this cheaper and more direct route to the natural pheromone isomer, with high chemical and isomeric purity conferring a high biological activity, provides the potential basis for a commercial pheromone lure production.

Acknowledgement

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16. *Methodology for the synthesis of* (2*S*,7*S*)-**1**.
Pyridine (0.34 ml, 4.2 mmol) and a small spatula of DMAP were added to a solution of di-*t*-butylsilyl bis(trifluoromethanesulfonate) (0.65 ml, 2.0 mmol) in dry THF (10 ml) in a flame-dried flask at room temperature. The solution was cooled to −78 °C and a solution of (*S*)-5-hexen-2-ol (0.24 ml, 2 mmol) in dry THF (5 ml) at −78 °C was added dropwise via a cannula. The reaction was warmed to room temperature over 5 h and a solution of 1,4-pentadien-3-ol (0.19 ml, 2 mmol) in dry THF (1 ml) was added dropwise. The mixture was stirred overnight, concentrated in vacuo and filtered through a pad of neutral alumina to yield 540 mg of crude (*S*)-**2c**. To a solution of the crude product (300 mg, 0.93 mmol) in dry CH_2Cl_2 (40 ml) was added a solution of Grubbs' catalyst (bis(tricyclohexylphosphine)benzylidene ruthenium(IV) chloride) (40 mg, 5 mol%) in CH_2Cl_2 (10 ml) via a cannula. All apparatus was flame-dried under N_2. The mixture was heated to reflux for 1 h, cooled, concentrated in vacuo and filtered through a pad of neutral alumina to yield the product (230 mg, 70% over two steps). Without further purification, the product (220 mg, 0.75 mmol) was dissolved in dry THF (20 ml), treated with TBAF (7.5 mmol, 1 M, 7.5 ml), microwave-dried 4 Å molecular sieves (8 g) and refluxed overnight. The mixture was filtered through Celite and purified by flash column chromatography (Et_2O) to yield (2*S*,7*S*)-1,4-nonadien-2,7-diol (90 mg, 78%). Dienediol (45 mg, 0.29 mmol) was dissolved in anhydrous MeOH (5 ml) and treated with a

spatula tip of PtO_2 and stirred under H_2 for 10 min. The product was filtered to yield the nonanediol (22 mg, 48%). Acylations were performed with acyl anhydride/pyridine/DMAP as previously described[2] to yield either diacetate for enantioselective GC analysis or dibutyrate (2*S*,7*S*)-**1** (85%), 99% ee, 94% de. Analytical data of (2*S*,7*S*)-dibutyroxynonane. $[\alpha]_D^{20}$ −6.7 (*c* 0.6, $CHCl_3$). δ_H ($CDCl_3$, 500 MHz) 4.84 (1H, sex, $J = 6.5$ Hz, 2-H), 4.76 (1H, qn, $J = 6.5$ Hz, 7-H), 2.22 (2H, t, $J = 7.4$ Hz, CH_2CO), 2.20 (2H, t, $J = 7.4$ Hz, CH_2CO), 1.61 (2H, sep, $J = 7.4$ Hz, CH_2CH$_2$CO), 1.60 (2H, sep, $J = 7.4$ Hz, CH_2CH$_2$CO), 1.54–1.38 (6H, m, 3-, 6-,8-H_2), 1.25 (4H, m, 4-,5-H_2), 1.14 (3H, d, $J = 6.3$ Hz, 1-H_3), 0.90 (3H, t, $J = 7.4$ Hz, Butyl-CH_3), 0.89 (3H, t, $J = 7.4$ Hz, Butyl-CH_3), 0.82 (3H, t, $J = 7.4$ Hz, 9-H_3); δ_C ($CDCl_3$, 125 MHz) 173.4, 173.2, 74.9, 70.4, 36.5, 36.5, 35.8, 33.4, 26.9, 25.2, 25.1, 19.9, 18.5, 18.4, 13.6, 13.5, 9.5. EIMS at 70 eV; *m*/*z* 213 (1, $M^+-C_4H_7O_2$), 212 (1, $M^+-C_4H_8O_2$), 183 (3), 168 (4), 154 (6), 141 (5), 125 (9, $M^+-2(C_4H_7O_2)$-H), 124 (10, $M^+-2(C_4H_8O_2)$), 113 (14), 95 (14), 89 (13), 83 (10), 82 (19), 71 (100), 69 (18), 55 (10), 43 (32). HRMS calcd for $C_{17}H_{32}O_4$ (M^+): 300.2301, found: 300.2319.