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Factors controlling the biomimetic triple cyclisation of xylulose β-keto-esters to syringolides. Part 1: Synthesis of 4′-deoxysyringolide 2

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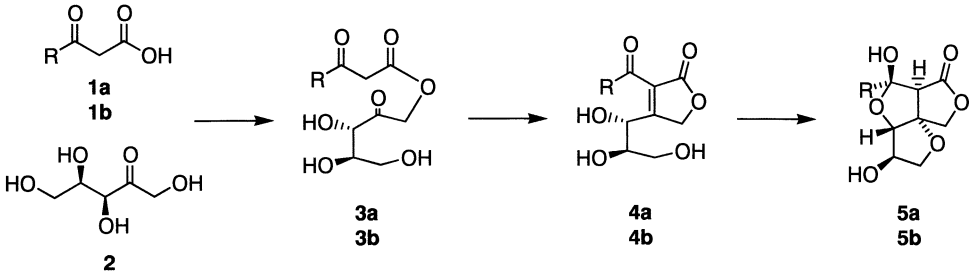
Abstract—Treatment of the 4-deoxy-D-xylulose β-ketodecanoate **13c** with basic alumina affords 4′-deoxysyringolide 2 **14** as a single stereoisomer, indicating that the course of the biomimetic triple cyclisation of the corresponding D-xylulose ester **3b** to syringolide 2 **5b** is not dependent upon the presence of the 4*R*-hydroxyl group. The diacyl butanolide **15** is formed simultaneously by a side reaction of the initial Knoevenagel condensation product of the ester **13c**.

Syringolides 1 **5a** and 2 **5b** are microbial elicitors, specific signal molecules produced by the bacterial plant pathogen *Pseudomonas syringae* pv. *tomato*, which trigger a hypersensitive defence response in resistant soybean cultivars.[1,2] They are the only known non-proteinaceous elicitors,[3] and have attracted considerable synthetic interest.[4–6]

Smith and Midland et al.[1,2] proposed that the syringolides **5a** and **5b** are formed biosynthetically from the appropriate β-keto-acids **1a** and **1b** and D-xylulose **2**. The most plausible way that these two units could be linked is by an initial esterification to form the β-keto-esters **3a** and **3b**, followed by an intramolecular Knoevenagel condensation to form the butenolides **4a** and **4b** (Scheme 1). Stereospecific Michael addition and hemiketalisation reactions would then complete the syringolide structures **5a** and **5b**.

This hypothesis formed the basis of a concise four-step biomimetic synthesis of syringolide 2 **5b**, reported by Henschke and Rickards in 1996 (Scheme 2).[5] D-Xylulose **2** was converted into its anisylidene ketal **6** which was regioselectively esterified to give the primary β-ketodecanoate **7a**. Hydrogenolysis gave the putative biosynthetic precursor, the xylulose β-keto-ester **3b** (acyclic form only shown). This was cyclised on basic alumina in THF, undergoing concomitant Knoevenagel, Michael and hemiketalisation reactions, to give syringolide 2 **5b** in low yield. Zeng et al. in 1997 described variants of this biomimetic route using acetonide rather than anisylidene ketal protection.[6]



Scheme 1. Proposed biosynthesis of syringolides 1 **5a** and 2 **5b**. **a**, R = *n*-C_5H_{11}; **b**, R = *n*-C_7H_{15}.

Keywords: biomimetic; cyclisation; 4′-deoxysyringolide 2; elicitor; syringolide 2; syringolide analogues; 4,5,6,7-tetranorsyringolide 1; xylulose β-keto-esters.

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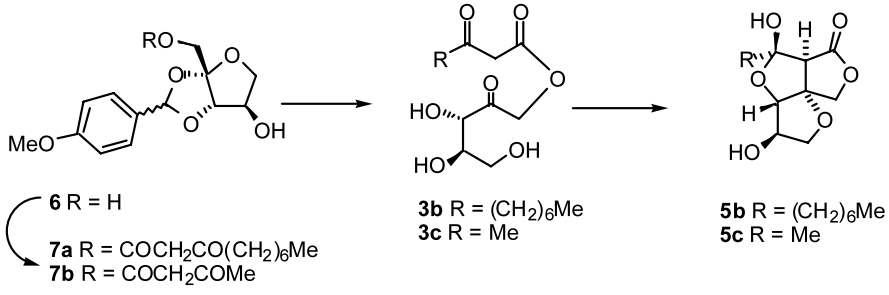
The utility of the biomimetic route is emphasised by synthesis of the short chain analogue 4,5,6,7-tetranorsyringolide 1 **5c** in three steps from the D-xylulose anisylidene ketal **6** via the acetoacetates **7b** (45%) and **3c** (47%) (Scheme 2). The triple cyclisation process again proceeded with the formation of only a single stereoisomer (10% yield). Comparison of the spectra of this product[7] with those of the syringolides[1,2] confirmed its structure **5c**.

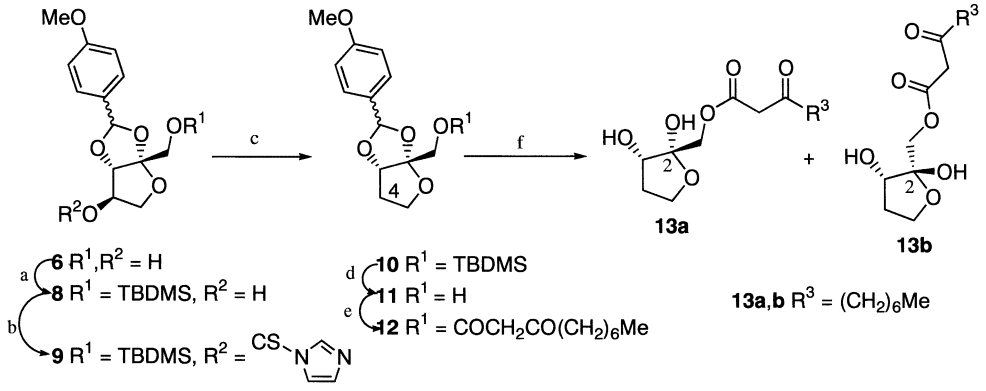
The one-pot conversion of the acyclic β-keto-esters **3b** and **3c** into syringolide 2 **5b** and its homologue **5c** establishes three rings and three new stereogenic centres with total stereocontrol. Considerable decomposition occurs, probably of both the starting materials and the sensitive products, but no intermediates or diastereomeric products are detectable. In order to explore the structural and stereochemical factors controlling this remarkable biomimetic triple cyclisation, we have synthesised the 4-deoxy analogue **13c** of the putative biosynthetic precursor **3b** of syringolide 2, and studied its behaviour under similar cyclisation conditions. As the 4*R*-hydroxyl group of the precursor **3b** is not directly involved in the ensuing reactions, its influence on the course of the cyclisation would be expected to be limited to hydrogen bonding effects, including the possible promotion of favourable reactant conformations. In contrast, the 3*S*-hydroxyl group of the xylulose β-keto-ester **3b** is actively involved at least in the hemiketalisation stage, and its *S*-configuration is crucial for successful cyclisation beyond the initial butenolide stage to the tricyclic syringolide system.[6]

The syringolide precursor analogue **13c** was prepared by incorporating a deoxygenation step, at C-4 of the D-xylulose component, into the original biomimetic synthesis[5] (Scheme 3). This necessitated temporary selective protection of the primary hydroxyl group of the xylulose anisylidene ketal **6** by treatment with TBDMSCl in pyridine to form the monosilyl ether **8**. The free C4-hydroxyl group was then removed in 66% yield by radical reduction with tri-*n*-butylstannane of its imidazolylthiocarbonyl derivative **9**, formed by treating the silyl ether **8** with *N*,*N*′-thiocarbonyldiimidazole and DMAP.[8] The silyl group of the 4-deoxyxylulose derivative **10** was then cleaved with TBAF, and the resulting primary hydroxyl group esterified with an excess of C-octanoyl Meldrum's acid[9] to produce the protected β-ketodecanoate **12**.

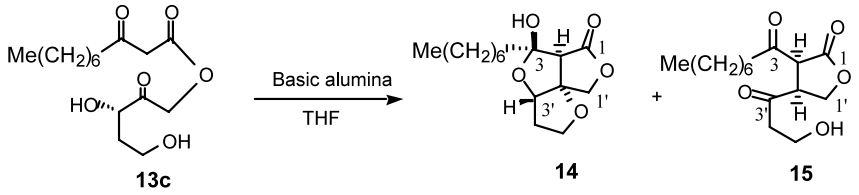
Hydrogenolysis with Pearlman's catalyst[10] selectively removed the anisylidene group to furnish the requisite 4-deoxyxylulose β-keto-ester. ^{1}H and ^{13}C NMR spectra (in $CDCl_3$) of this compound showed that it existed as a 2.4:1 mixture of furanosides, assigned on steric grounds as the α- and β-forms **13a** and **13b** respectively (C2 δ 100.4, 105.0), with no detectable quantity of the acyclic keto-form **13c** present. Nevertheless, the three species must be in equilibrium because treatment with basic alumina in THF under the conditions[5] used to form syringolide 2 **5b** produced two isomeric products with molecular formulae $C_{15}H_{24}O_5$, both of which were



Scheme 2. Biomimetic synthesis of syringolide 2 **5b** and the analogue **5c**.



Scheme 3. Synthesis of the 4-deoxy-D-xylulose-β-ketodecanoate **13**. *Reagents and conditions*: (a) TBDMSCl, pyridine, 72%; (b) TCDI, DMAP, THF, 92%; (c) Bu_3SnH, toluene, Δ, 72%; (d) TBAF, THF, 9(octanoyl-Meldrum's acid, THF, 84%; (f) $Pd(OH)_2/C$, AcOH, 62%.



Scheme 4. Cyclisation of the 4-deoxy-D-xylulose-β-ketodecanoate **13c**.

derived by Knoevenagel condensation from the keto-form **13c** (Scheme 4).

The least polar product,[11] isolated in 16% yield, was not UV active. Comparison of NMR spectra of this compound with those of syringolide 2 **5b**[1,2] confirmed that it was 4′-deoxysyringolide 2 **14**. Signals characteristic of the tricyclic syringolide system were observed (in Me_2CO-d_6) at δ_H 3.11 (s, H2) and at δ_C 59.9 (C2), 86.6 (C3′), 99.4 (C2′), and 108.5 (C3). The ^1H spectrum of the deoxy analogue differed significantly from that of syringolide 2 only in that the H4′ methylene protons appeared as a multiplet between δ 1.92–1.97, shifted upfield from the H4′ methine doublet of doublets at δ 4.13 in the natural compound. A corresponding upfield shift of C4′ itself from δ 75.4 to δ 39.5 was also observed.

The more polar isomer,[12] isolated from the cyclisation reaction in 8% yield, was UV active. Its NMR spectra were unlike those of 4′-deoxysyringolide, and defined the structure as that of the diacyl butanolide **15**. The ^{13}C spectrum displayed the lactone carbonyl at δ 170.4 (C1), ketonic resonances at δ 201.3 (C3) and 206.3 (C3′), and methine resonances at δ 48.2 (C2′) and 54.0 (C2). In the ^1H spectrum a four spin system linked the geminal H1′ protons at δ 4.54 (t, J 8.9 Hz) and 4.33 (dd, J 8.9 and 7.7 Hz) to the H2′ proton at δ 4.20 (ddd, J 8.9, 8.1 and 7.7 Hz) which in turn was coupled to the H2 resonance at δ 4.06 (d, J 8.1 Hz). The assignments together with structure **15** were confirmed by HMQC and HMBC data. A NOESY correlation between H2 and H2′ indicates their *cis*-relationship, in agreement with their mutual coupling constant of 8.1 Hz.[13]

This diacyl butanolide **15** clearly arises under the basic conditions by enolisation and subsequent ketonisation of the initial Knoevenagel condensation product, the deoxy analogue of the acyl butenolide **4b**. Its formation shows that, at least in the case of the 4-deoxyxylulose β-ketoester **13c**, there is a discrete alternative process competing with the later stages of the triple cyclisation. This process may help to explain the low yields observed in the original biomimetic synthesis of syringolide 2 **5b**.

The facile formation of 4′-deoxysyringolide 2 **14** by cyclisation of the 4-deoxyxylulose β-ketodecanoate **13c** indicates that the occurrence and stereospecificity of the biomimetic triple cyclisation of the corresponding D-xylulose ester **3b** to syringolide 2 **5b** are not dependent upon the presence of the 4*R*-hydroxyl group. Furthermore, it reinforces the utility of the biomimetically-based approach for providing analogues of the natural elicitor that could be useful in elucidating its mechanism of action.

Acknowledgements

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7. **5c**; ^1H NMR (300 MHz, CD_3OD) δ 1.64 (3H, s, H4), 3.09 (1H, s, H2), 3.87 (1H, dd, J 10.1 and 2.7 Hz, H5′a), 3.99 (1H, d, J 10.1 Hz, H5′b), 4.15 (1H, d, J 2.7 Hz, H4′), 4.46 (1H, d, J 10.5 Hz, H1′a), 4.47 (1H, s, H3′), 4.76 (1H, d, J 10.5 Hz, H1′b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8 (C4), 62.7 (C2), 75.4 (C1′ or C5′), 76.2 (C4′), 77.3 (C1′ or

C5′), 93.1 (C3′), 100.2 (C2′), 107.8 (C3), 175 (C1); EIMS m/z 216 (M^+, 19%). Found 216.0634, calc. for $C_9H_{12}O_6$ 216.0631.

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11. **14**; Mp 103°C; Found C 63.5, H 8.1. Calc. for $C_{15}H_{24}O_5$ C 63.4, H 8.5; ^{1}H NMR (300 MHz, Me_2CO-d_6) δ 0.88 (3H, t, J 7.0 Hz, H10), 1.33–1.39 (8H, m, H6, H7, H8 and H9), 1.48–1.52 (2H, m, H5), 1.91–1.97 (4H, m, H4 and H4′), 3.11 (1H, s, H2), 3.71–3.80 (1H, m, H5′a), 4.03–4.09 (1H, m, H5′b), 4.28 (1H, d, J 10.1 Hz, H1′a), 4.69 (1H, d, J 10.1 Hz, H1′b), 4.81 (1H, dd, J 2.3 and 2.4 Hz, H3′), 5.32 (1H, d, J 1.9 Hz, OH); ^{13}C NMR (75 MHz, Me_2CO-d_6) δ 14.3 (C10), 23.3 (C9), 24.4 (C5), 29.9 and 30.4 (C6 and C7), 32.5 and 33.6 (C4 and C8), 39.5 (C4′), 59.9 (C2), 67.9 (C5′), 75.7 (C1′), 86.6 (C3′), 99.4 (C2′), 108.5 (C3), 172.9 (C1); EIMS m/z 284 (M^+, 4%). Found 284.1629, calc. for $C_{15}H_{24}O_5$ 284.1623.
12. **15**; Found C 63.5, H 8.5. Calc. for $C_{15}H_{24}O_5$ C 63.4, H, 8.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, J 6.6 Hz, H10), 1.26–1.31 (8H, m, H6, H7, H8 and H9), 1.58–1.63 (2H, m, H5), 2.68 (1H, ddd, J 18.1, 7.3 and 7.1 Hz, H4a), 2.74 (2H, t, J 5.4 Hz, H4′), 3.07 (1H, ddd, J 18.1, 7.5 and 7.4 Hz, H4b), 3.90–3.94 (2H, m, H5′), 4.06 (1H, d, J 8.1 Hz, H2), 4.20 (1H, ddd, J 8.9, 8.1 and 7.7 Hz, H2′), 4.33 (1H, dd, J 8.9 and 7.7 Hz, H1′a), 4.54 (1H, t, J 8.9 Hz, H1′b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (C10), 22.5 (C9), 23.2 (C5), 28.9 and 29.6 (C6 and C7), 31.5 (C8), 42.0 (C4), 44.1 (C4′), 48.2 (C2′), 54.0 (C2), 57.4 (C5′), 66.6 (C1′), 170.4 (C1), 201.3 (C3), 206.3 (C3′); EIMS m/z 284 (M^+, 7%). Found 284.1622, calc. for $C_{15}H_{24}O_5$ 284.1624.
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