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Synthesis of isomeric polyacetylenes based on natural hydroxy matricaria esters

Solange Garrais, Jennifer Turkington, William P.D. Goldring *

School of Chemistry and Chemical Engineering, Queen's University Belfast, David Keir Building, Stranmillis Road, Belfast, Northern Ireland BT9 5AG, United Kingdom

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ABSTRACT

The construction of a library of natural and related polyacetylenes using a convergent synthetic strategy based on a palladium mediated cross-coupling reaction is described. The systematic synthetic study led to all possible alkene isomers of the hydroxy matricaria esters **29**–**32**, and the corresponding tiglates **1**–**4**. The synthesis of many of these compounds is described for the first time.

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1. Introduction

A wide variety of polyacetylenes have been isolated from natural sources for decades,[1] and have been pursued in target synthesis for over 50 years.[2] Among this class of natural products are the matricaria esters, which are structurally characterised by a conjugated ene–diyne–ene system. This core structure is commonly substituted with alkyl groups, allylic alcohols and esters, in all possible alkene isomer combinations.

Natural matricaria-type esters, such as the tiglate **4** and the hydroxy ester **29**, possess insecticidal activity,[3] together with activity against *Mycobacterium tuberculosis*, the cause of the bacterial disease tuberculosis (TB), and *Mycobacterium avium*, a bacteria which targets patients with immune deficiency, such as AIDS.[4] Furthermore, other structurally related matricaria esters isolated in Nature possess antibacterial and antitumour activity.[5]

The polyacetylenes continue to be pursued as targets for synthesis, and a number of recent examples highlight the importance of, and interest in these natural compounds.[6] In this article we describe the syntheses of all possible alkene isomers of the hydroxy matricaria esters **29**–**32**, and the corresponding tiglates **1**–**4**, using a convergent strategy based on palladium mediated cross-coupling methodology. We also describe the construction of related metabolites, such as the isomeric dimethyl esters **21**–**23**, and the diols **24**–**26**.

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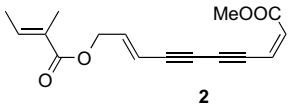

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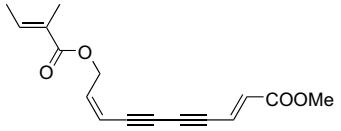

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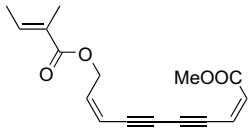

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2. Results and discussion

Our plan for the construction of a library of matricaria-type esters relied on the Sonogashira coupling reaction as the key step in the assembly of the core diene–diyne structure. Therefore, a number of enyne subunits, readily accessible in both alkene isomers and with the appropriate substitution, were required for this alkyne–alkyne cross-coupling strategy. This includes, for example,

* Corresponding author. Tel.: +44 (0)28 9097 4414; fax: +44 (0)28 9097 6524.
E-mail address: w.goldring@qub.ac.uk (W.P.D. Goldring).

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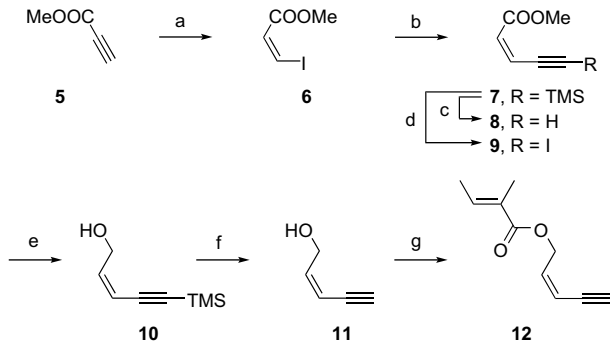
a number of isomeric enyne alcohol (cf. **11**) and iodoalkyne ester (cf. **9**) subunits, which in turn could be derived from the corresponding vinyl iodide and acetylene.

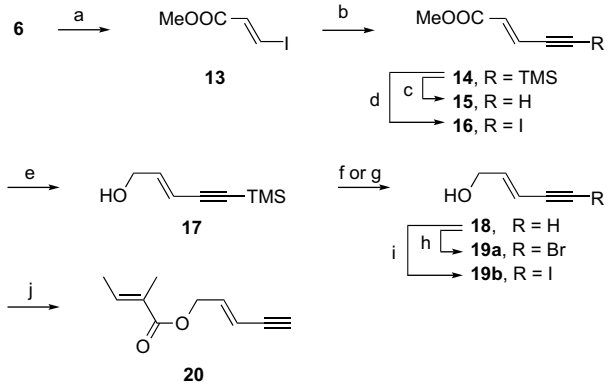
Construction of the (*Z*)-enyne subunits started from commercially available methyl propiolate (**5**). Treatment of the alkyne **5** with sodium iodide in acetic acid led exclusively to the (*Z*)-vinyl iodide **6** in quantitative yield (Scheme 1).[7] Under Sonogashira coupling conditions the vinyl iodide **6** was coupled with ethynyltrimethylsilane to give the enyne ester (*Z*)-**7** in quantitative yield.[8] The enyne **7** was used to access a number of important coupling partners required for our synthesis. For example, deprotection of the TMS-protected alkyne **7**, using TBAF, gave the enyne (*Z*)-**8** in 73% yield.[8] Alternatively, deprotection of **7** with silver nitrate in a mixture of ethanol and water, followed by treatment of the resulting alkynyl silver salt with iodine gave the iodoalkyne (*Z*)-**9** in 68% yield.[9]



Scheme 1. Reagents and conditions: (a) NaI, AcOH, 70 °C, 99%; (b) TMSC≡CH, $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, 99% (**7**); (c) TBAF, THF, 0 °C to rt, 73%; (d) $AgNO_3$, EtOH/H_2O (1:1); then I_2, CH_2Cl_2, 68%; (e) DIBALH, CH_2Cl_2, −78 °C, 96%; (f) TBAF, THF, 0 °C to rt, 95%; (g) tiglic acid, DCC, DMAP, CH_2Cl_2, 90%.

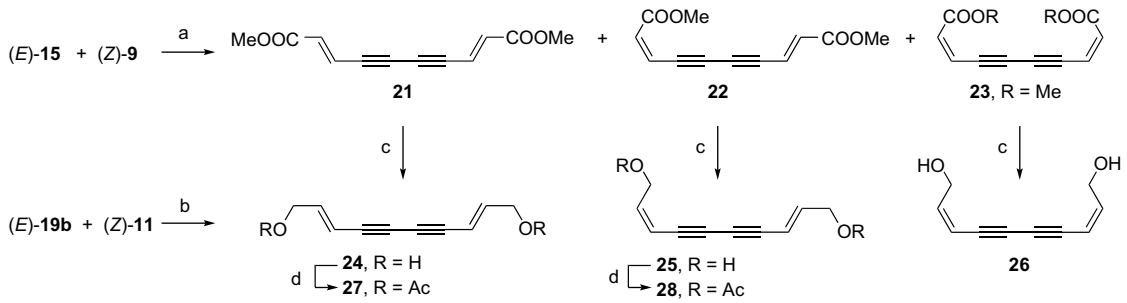
The corresponding (*Z*)-enyne alcohol coupling partners were elaborated from the enyne ester (*Z*)-**7**. During our synthetic studies towards these subunits we examined the order of steps for the conversion of **6** into **10**. For example, we were disappointed to discover the reduction of the ester **6**, using DIBALH, followed by Sonogashira coupling of the resulting vinyl iodide with ethynyltrimethylsilane gave the enyne **10** in 10% yield over two steps. The overall yield of this two-step process was significantly improved when the vinyl iodide **6** was coupled with TMS–acetylene, as described earlier, followed by reduction of the resulting ester **7** with DIBALH to give the allylic alcohol **10** in 96% yield over two steps. Deprotection of the TMS-protected alkyne **10**, using TBAF, gave the enyne (*Z*)-**11** in 95% yield.[10] Finally, esterification of the alcohol **11** with tiglic acid under standard DCC coupling conditions gave an inseparable 13:1 mixture of the isomeric tiglates (*Z*)-**12** and (*E*)-**20** in 90% combined yield.

The isomeric (*E*)-series of coupling partners were synthesised in a similar manner from the vinyl iodide (*E*)-**13**, which was previously prepared from (*Z*)-iodoacrylic acid via an isomerisation–methylation sequence.[11] We, however, employed a direct approach and were pleased to observe the smooth isomerisation of (*Z*)-**6**, in the presence of HI, into the vinyl iodide (*E*)-**13** (Scheme 2).[12] The vinyl iodide (*E*)-**13** was then coupled with ethynyltrimethylsilane to give the enyne ester (*E*)-**14** in quantitative yield over two steps. Deprotection of the TMS-protected alkyne **14**, using TBAF, gave the enyne (*E*)-**15** in 74% yield. Treatment of the alkyne **14** with silver nitrate, and then iodine, led directly to the iodoalkyne (*E*)-**16** in 86% yield. Using a reduction–deprotection sequence the enyne alcohol (*E*)-**18** was elaborated from the ester **14**, via the TMS-protected alkyne **17**, in 82% yield over two steps. The enyne **18** was converted into either the bromoalkyne **19a**, using silver nitrate and *N*-bromosuccinimide,[6a,c,13] or the iodoalkyne **19b**, using iodine and potassium hydroxide. The TMS-protected acetylene **17** could be converted directly into the bromoalkyne **19a** under the conditions described above (viz. **18**→**19a**). Finally, esterification of the alcohol **18** with tiglic acid under standard DCC coupling conditions gave an inseparable 32:1 mixture of the isomeric tiglates (*E*)-**20** and (*Z*)-**12** in 93% combined yield.



Scheme 2. Reagents and conditions: (a) HI, benzene, 80 °C, 99%; (b) TMSC≡CH, $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, 99% (**14**); (c) TBAF, THF, 0 °C to rt, 74%; (d) $AgNO_3$, EtOH/H_2O (1:1); then I_2, CH_2Cl_2, 86%; (e) DIBALH, CH_2Cl_2, −78 °C, 85%; (f) NaOH, MeOH, −10 °C, 97% (**18**); (g) NBS, $AgNO_3$, acetone, 0 °C, 84% (**19a**); (h) NBS, $AgNO_3$, acetone, 0 °C, 84%; (i) KOH, I_2, MeOH, H_2O, 64%; (j) tiglic acid, DCC, DMAP, CH_2Cl_2, 93%.

Construction of the enyne structures set the stage for a synthesis of all possible hydroxy matricaria ester isomers, and the corresponding tiglates, via cross-coupling of the appropriate terminal alkyne and iodoalkyne subunits. We first set out to construct all possible diene–diyne dimethyl ester isomers from the enyne ester (*E*)-**15** and the iodoalkyne ester (*Z*)-**9**. The coupling of **15** and **9**, under Sonogashira conditions ($PdCl_2(PPh_3)_2$, CuI and diisopropylamine), gave a mixture of the dimethyl esters (*E*,*E*)-**21**, (*E*,*Z*)-**22** and (*Z*,*Z*)-**23** in 45%, 25% and 19% yield, respectively (Scheme 3). In comparison, treatment of the enyne ester (*Z*)-**8**, under the same conditions, gave the dimethyl ester (*Z*,*Z*)-**23** in 80% yield. We did not



Scheme 3. Reagents and conditions: (a) $PdCl_2(PPh_3)_2$, CuI, *i*-Pr_2NH, THF, 45% (**21**), 25% (**22**) and 19% (**23**); (b) $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, 27% (**24**), 12% (**25**) and 23% (**26**); (c) DIBALH, CH_2Cl_2, 80% (**24**), or 99% (**25**), or 58% (**26**); (d) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 66% (**27**), or 80% (1:2, **27**/**28**).

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