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Asymmetric synthesis of avenaciolide *via* cascade palladium catalysed cyclisation–carbonylation of bromodienes†

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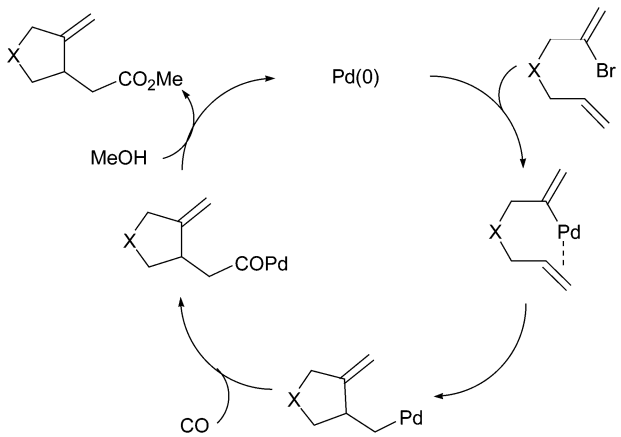
An asymmetric synthesis of the secondary metabolite avenaciolide has been achieved utilising a diastereoselective palladium catalysed cyclisation–carbonylation of bromodienes.

Palladium catalysed cascade reactions provide versatile methods to rapidly build up complexity from relatively simple substrates.[1] Recently we showed that 2-bromo-1,6-dienes can be converted into cyclic γ,δ-unsaturated carboxylic esters through a palladium catalysed cyclisation–carbonylation cascade process in the presence of carbon monoxide (Scheme 1).[2] We also developed a similar process for the conversion of enynes to cyclic γ,δ-unsaturated carboxylic acids, using an excess of acetic acid.[3]

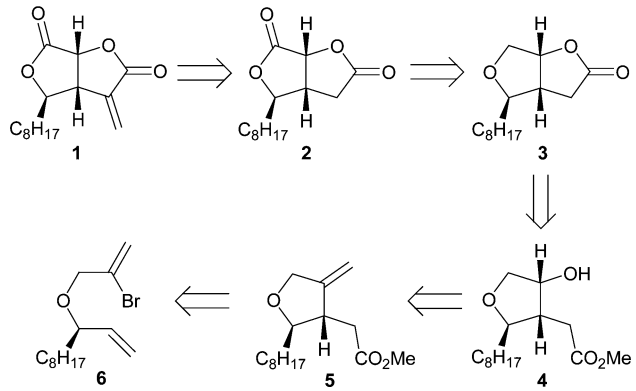


Scheme 1 Cyclisation–carbonylation of 2-bromo-1,6-dienes.

These functionalised carbocycles and heterocycles are potentially useful intermediates in natural product synthesis.[4] We now report a new asymmetric synthesis of avenaciolide **1** utilising our palladium catalysed cyclisation–carbonylation of bromodienes as the key step.

Avenaciolide is a secondary metabolite, isolated from *Aspergillus* fermentation broths.[5] It was found to exhibit antifungal and weak antibacterial properties. Furthermore it was found to inhibit glutamate transport in rat liver mitochondria.[6] The biological activity coupled with its interesting structure (bis-fused γ-lactone core with three contiguous chiral centres) has stimulated considerable synthetic activity in avenaciolide resulting in numerous syntheses.[7] One particularly elegant total synthesis utilised an intramolecular alkoxycarbonylation of tungsten–π-allyl complexes in the key step.[8]

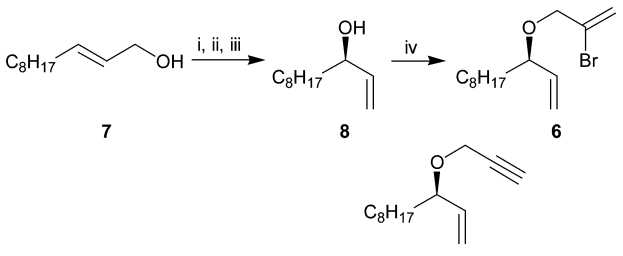
Our retrosynthetic analysis of avenaciolide **1** is outlined in Scheme 2. As in previous syntheses,[9] the first disconnection is removal of the methylene group to afford the known bislactone **2**. Change in oxidation state of one of the lactones provides the cyclic ether **3**, which can be disconnected to the alcohol **4**, and thus alkene **5**. The γ,δ-unsaturated carboxylic ester **5** can be formed from the chiral bisallyl ether **6** using our methodology. This would represent the first application of our methodology to a chiral system, and in addition it would allow us to explore the diastereoselectivity of the key cyclisation–carbonylation step.



Scheme 2 Retrosynthetic analysis of avenaciolide **1**.

Our synthesis began with Sharpless epoxidation[10] of allylic alcohol **7** followed by conversion to allylic alcohol **8** using the protocol developed by Ibuka *et al.*[11] The alcohol **8** was formed in high enantioselectivity (90% *ee*). Alternative approaches starting from nonanal and using asymmetric addition of divinyl zinc[12] or zinc catalysed addition of 2-methyl-3-butyn-2-ol[13] with *N*-methylephedrine as chiral ligand gave both lower enantioselectivities and lower yields.

Etherification of **8** with 2,3-dibromopropene under a variety of permutations of the standard conditions (addition of the dibromide to a suspension of NaH in the presence of the alcohol) resulted in a mixture of starting material, product **6** and enyne **9**. However, by premixing the dibromide and sodium hydride in the absence of any solvent and adding the alcohol to this mixture, good yields of **6** were obtained. After 6 d the desired ether **6** was obtained in 93% yield (Scheme 3).



Scheme 3 *Reagents and conditions*: i, TBHP, (−)-DET, $Ti(O^iPr)_4$, DCM, −10 °C, 86%; ii, TsCl, DMAP, NEt_3, 92%; iii, KI, then PPh_3, I_2 (cat.), 55%; iv, 2,3-dibromopropene, NaH, then **8**, 6 d, rt, 93%.

For the cyclisation–carbonylation reaction, we first used the conditions developed in the previous investigations.[2] Although the cyclised product **5** was the major product, significant quantities of the linear ester **10** were also formed (Table 1, entry 1). Using triphenylphosphine instead of trifurylphosphine gave a higher yield of the cyclic ester **5**, which increased further with increased loading of the palladium catalyst (entries 2 and 3). At the same time the diastereoselectivity of the cyclisation increased up to a 10 : 1 ratio for the desired diastereomer.

† Electronic supplementary information (ESI) available: experimental. See http://www.rsc.org/suppdata/cc/b4/b403183k/

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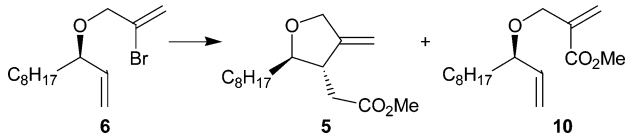
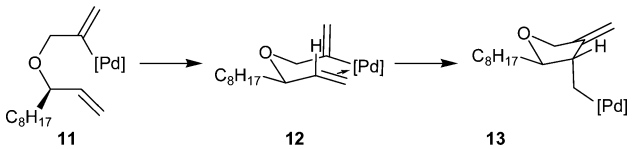
Table 1 Palladium catalysed cyclisation–carbonylation of **6**



			Yields (%)[a]		
Entry	Conc. [Pd]	Phosphine	**5**	**10**	dr[b]
1	5 mol%	$P(2\text{-furyl})_3$	51	19	4 : 1
2	2 mol%	PPh_3	56	18	8 : 1
3	5 mol%	PPh_3	61	7	10 : 1

Reagents and conditions: $PdCl_2(PPh_3)_2$, ratio phosphine : [Pd] = 4 : 1, MeOH/MeCN/H_2O (1/2/0.1), 2 atm. CO, 24 h, 85 °C. [a] Isolated yields of esters purified by column chromatography. [b] Determined by ^1H NMR.

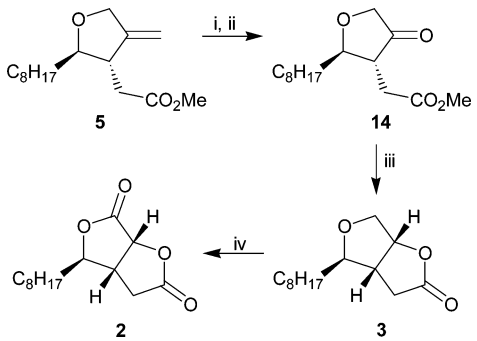
The high diastereoselectivity can be explained by the preferred conformation of the transition state **12**, assuming that both the octyl group and the ligated palladium prefer a pseudo equatorial position (Scheme 4). A similar model was proposed by Negishi for the cyclisation of iododienes.[14]



Scheme 4 Model for the diastereoselectivity of the cyclisation.

Attempts to utilise enyne **9** in the related cyclisation suffered from low yields due to the sensitivity of the allylic ether towards acid.

Ozonolysis of **5** afforded the ketone **14**.[4] This ketone was treated with DBU in refluxing THF giving exclusively the thermodynamically favoured *trans*-diastereomer. During this process some ester hydrolysis occurred, but both the ketone **14** and its corresponding free carboxylic acid underwent a diastereoselective reduction with L-selectride in good yield giving the cyclic lactone **3** after acidic work-up (Scheme 5). Studies by Loza *et al.* on the stereochemical aspects of the reductions of 2,3-disubstituted cyclopentenones have already shown that the attack of L-selectride at low temperatures occurs *trans* to the substituent in the 2-position.[15]



Scheme 5 *Reagents and conditions*: i, O_3, DCM, −78 °C, then Me_2S, −78 °C to rt; ii, DBU (1 equiv.), THF, 3 h, reflux, 69% (over two steps); iii, L-selectride (1.2 equiv.), THF, −78 °C, 70%; iv, $RuCl_3$ (5 mol%), $NaIO_4$ (4.1 equiv.), CCl_4/MeCN/H_2O (2 : 2 : 3), 29% (40% based on recovery).

The formal synthesis of avenaciolide was then completed by oxidising **3** under Sharpless' conditions[16] to afford the bislactone **2**. Although the lactone **2** was obtained in only 29% yield, 28% of the starting material was recovered. Addition of further quantities of the ruthenium catalyst did not improve the yield and other oxidants (pyridinium dichromate,[17] manganese salen complexes[18] and cobalt(III) complexes[19]) were not effective.

In conclusion we have developed a new asymmetric formal synthesis of avenaciolide starting from simple, inexpensive materials utilising our cyclisation–carbonylation methodology. We were able to show that this palladium catalysed reaction is not only highly efficient for the construction of rings which do not have a high propensity for cyclisation, but also that the process is highly diastereoselective. The heterocyclic γ,δ-unsaturated carboxylic esters can easily be converted to lactones and bislactones.[20]

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Notes and references

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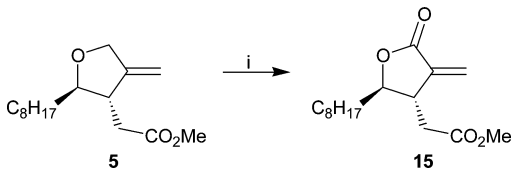
20 The heterocyclic ester **5** can representatively be easily oxidised to the highly substituted lactone **15**, further demonstrating the use of such methodology to form biologically relevant molecules in a rapid and efficient manner (Scheme 6).



Scheme 6 *Reagents and conditions*: i, py·CrO_3, DCM, 1 h, reflux, 64%.