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Stereospecificity in the Au-catalysed cyclisation of monoallylic diols. Synthesis of (+)-isoaltholactone†

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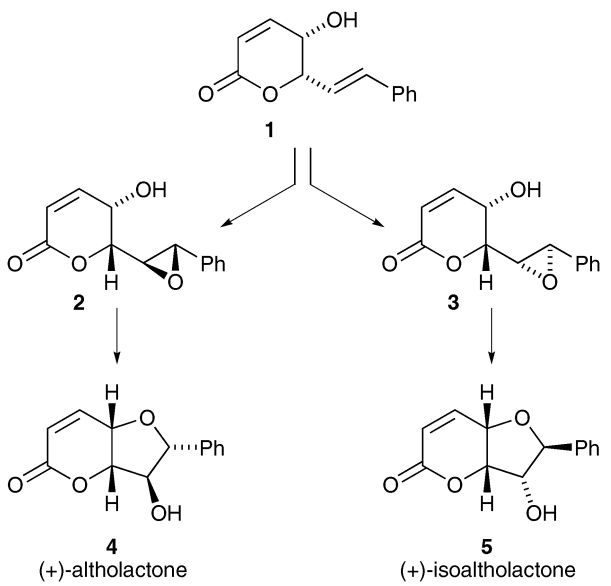
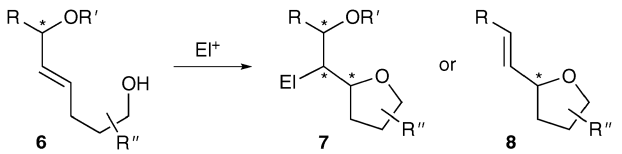
We describe a concise synthesis of (+)-isoaltholactone *via* a Au-catalysed cyclisation of a monoallylic diol to form the tetrahydrofuranyl ring. Analogous cyclisations show that the stereochemical outcome is dictated by the stereochemistry of the diol substrate.

(+)-Altholactone[1] (a.k.a. goniothalenol)[2] **4**, Scheme 1, was originally isolated from a specimen of an unnamed *Polyalthia* species, its gross structure established by chemical degradation, and its stereochemistry proposed on the basis of NMR and CD spectroscopy, later confirmed by total synthesis of the enantiomers.[3] Subsequently, interesting biological activity was found, including an antiproliferative effect on breast cancer cells,[4] induction of apoptosis in HL-60 cells,[5] and toxicity towards P388 cells.[2] Thirteen years after the first report of (+)-altholactone, the diastereomer (+)-isoaltholactone **5** was described as an isolate from combined extracts of *Goniothalamus malayanus*, *G. montanus*, and *G. tapis*.[6] Both compounds may be considered[6] to be biosynthesised by 5-*endo* cyclisation[7] of the epoxides **2** and **3** which, in turn, could arise from oxidation of either face of 5-hydroxygoniothalamin (**1**). With one exception[8i] the syntheses[8] of (+)-isoaltholactone rely on exactly this strategy in order to construct the THF ring although there are variations in the relative timing of the ring-forming steps.



Scheme 1 Key steps in the proposed biogenesis of styryl lactones altholactone and isoaltholactone.

Our interest in this area arose out of a research programme based on the cyclisation of alcohols of the form **6** (Scheme 2) onto alkenes, following electrophilic activation, to provide functionalised tetrahydrofuran cores **7** and **8** stereoselectively.[9] In this context, we assessed Aponick's Au-catalysed cyclisation of monoallylic diols that appeared in the literature whilst our study was underway.[10,11] At the time we had in hand ketone **10** (Scheme 3), available from D-ribonolactone acetonide (**9**) in four steps,[12] and conceived a short synthesis of (+)-isoaltholactone from this compound based on cyclisation under Aponick's conditions. The synthesis initiated with cross metathesis of racemic alkene **11**[13] and, following diastereoselective reduction with L-Selectride,[12] monoallylic diol **13** was obtained as an epimeric mixture at the allylic alcohol centre. Application of Aponick's conditions afforded three diastereomers of the cyclisation products (**14–16**). Such compounds have been shown to cyclise to (iso)altholactone[8g–i,14] and, initially, separated diastereomer **14** was elaborated to (+)-isoaltholactone by sequential acetonide and ester hydrolysis then lactonisation[15] of the *Z*-enoic acid formed *in situ*. In parallel, the inseparable diastereomers **15** and **16** were taken through an efficient one-pot process consisting of acetonide deprotection then lactonisation following a solvent swap from methanol to benzene; the diol derived from acetonide **15** was converted back into the acetonide *in situ* in order to allow isolation of (+)-isoaltholactone.



Scheme 2 Allylic stereoinduction accompanying electrophilic cyclo-etherification.

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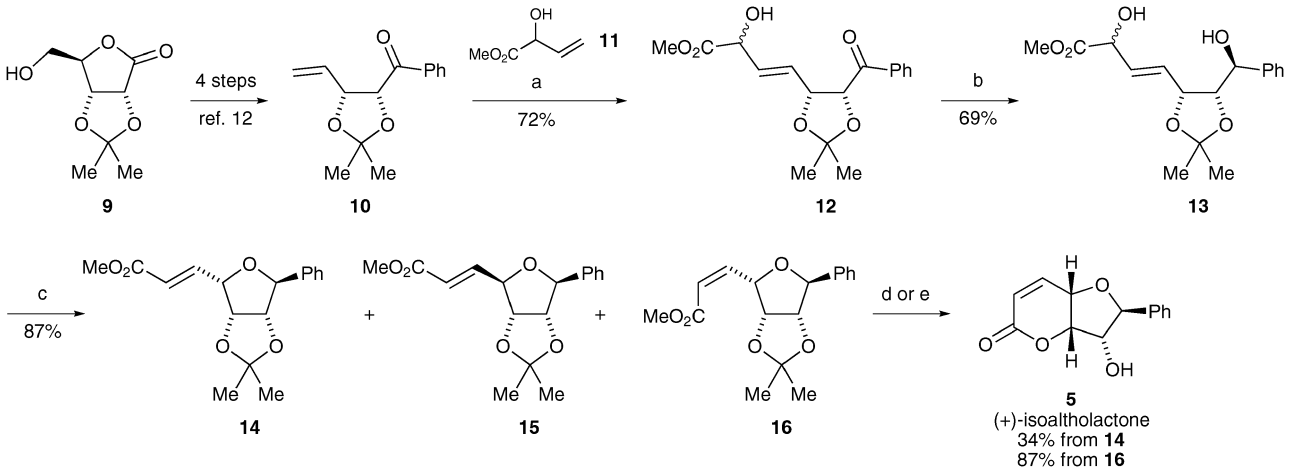
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, and support for the stereochemistry of cyclisation products. See DOI: 10.1039/c1cc11805f



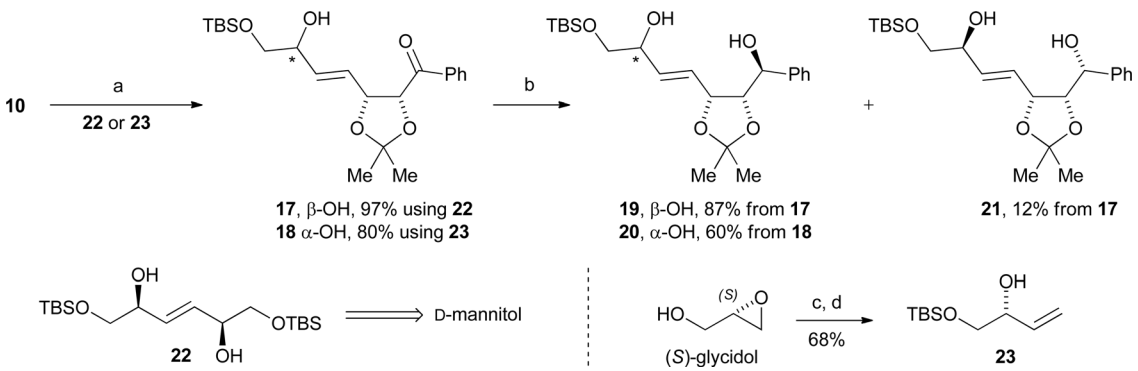
Scheme 3 *Reagents and conditions*. (a) (±)-**11**, cat. Grubbs II, CH_2Cl_2, reflux, 2 h; (b) L-Selectride, THF, −78 °C, 0.5 h; (c) cat. Ph_3PAuCl, cat. AgOTf, 4 Å MS, CH_2Cl_2, 20 °C, 2 h (*dr* ≈ 1 : 1 : 1); (d) from **14**: 1. cat. TsOH, MeOH, reflux, 18 h; 2. aq. NaOH, *i*-PrOH, 20 °C, 15 min (85% from **14**); 3. 2,4,6-trichlorobenzoyl chloride, pyridine, 20 °C, 18 h (40%); (e) from **15** & **16**: cat. TsOH, MeOH, 50 °C, 18 h; replace solvent with C_6H_6,))), 20 °C, 2 h; replace solvent with $(MeO)_2CH_2$, acetone, MeOH, 20 °C, 10 min [one-pot].

Our synthesis, at nine steps overall from D-ribonolactone, compares favourably with the shortest of those so far published. Interestingly, during the key step of this synthesis, the 2 : 1 diastereomeric ratio of alcohols **13** was carried through into the products; that is, the ratio of *E*-:*Z*- α,β-unsaturated esters (**14**/**15** : **16**) was *ca.* 2 : 1, as was the ratio of products in which the enoate side chain is located *endo*- or *exo*- on the trioxabicyclo[3.3.0]octane ring (**14**/**16** : **15** respectively).

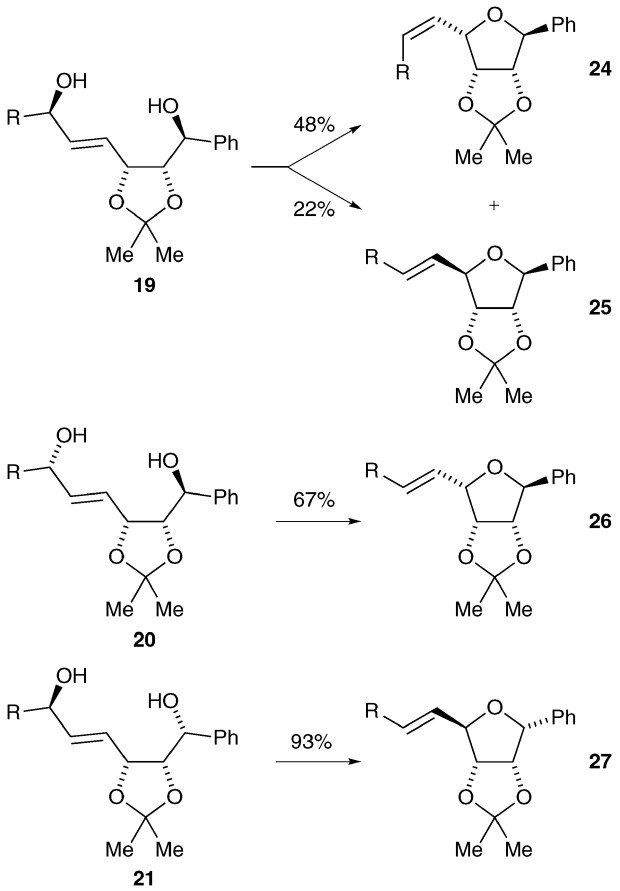
On this basis we wondered if these cyclisations are stereospecific to the extent that correct choice of monoallylic diol configuration would yield a single product diastereomer. This point had not arisen in Aponick's original publications nor in reported applications of the methodology.[16] Very recently, Aponick showed that in the synthesis of tetrahydropyrans the configuration at the newly-formed allylic centre is determined by both the alkene and the allylic alcohol configurations; however, no results were reported concerning the formation of tetrahydrofurans.[17] This information was not available to us at the time,[9] and the allylic alcohol stereochemistry in isomers **13** was not assigned; therefore, we could not draw any conclusions on the stereospecificity based on the results presented in Scheme 3. Alkene **11** had not been reported as a single enantiomer so, in order to probe this further, we prepared the stereodefined epimeric ketones **17** and **18** (Scheme 4) by cross metathesis.[18,19] The L-Selectride reduction of ketone **17** gave a 7.2 : 1 mixture of diols **19** and **21**, epimeric at the benzylic alcohol; the corresponding reduction of ketone **18** gave a single diastereomer (**20**) but in lower yield.

The results from the cyclisation reactions are summarised in Scheme 5. Comparing first the benzylic (*S*)-alcohols **19** and **20**: the allylic (*S*)-alcohol (**19**) led to the *endo*-*Z*- product (**24**) and the *exo*-*E*- product (**25**) in *ca.* 2 : 1 ratio respectively whereas the allylic (*R*)-alcohol (**20**) gave the *endo*-*E*- product (**26**) exclusively. Diastereomer **27** was the only product that could be traced back to the minor benzylic (*R*)-alcohol **21**. With these results we can infer that in the (+)-isoaltholactone synthesis, tetrahydrofuran derivative **14** arose from the diol with the (*R*)-configured allylic alcohol ('**13*R***') and diastereomers **15** and **16** arose from cyclisation of diol **13*S*** (which is therefore the major component in **13**).

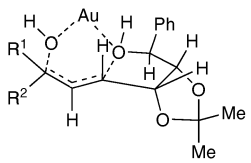
In general, these results fit Aponick's recent stereochemical model[17] but some key differences are evident that augment the emerging stereochemical picture. Specifically, (i) our results include the first examples of the formation of *Z*-olefins in this system; (ii) the stereochemical outcome does not depend exclusively on the alkene + allylic alcohol configuration; and (iii) the configuration at the incoming hydroxyl centre is important.



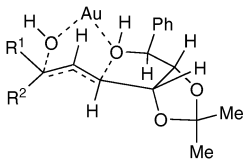
Scheme 4 *Reagents and conditions*. (a) cat. Hoveyda–Grubbs II, CH_2Cl_2, 50 °C, 1.5–3 h; (b) L-Selectride, THF, −78 °C → 0 °C, 1 h; (c) TBSCl, imidazole, DMF, 0 °C → 20 °C, 2 h; (d) $Me_3S^+I^-$, BuLi, THF, −10 °C → 20 °C, 2.5 h.



Scheme 5 Results for the Au-catalysed cyclisation of diols **19–21** (cat. Ph_3PAuCl, cat. AgOTf, 4 Å MS, CH_2Cl_2, 20 °C, 2 h). [R = CH_2OTBS].



→ *endo-Z-*
16 from **13*S***: $R^1 = CO_2Me$, $R^2 = H$
24 from **19**: $R^1 = CH_2OTBS$, $R^2 = H$



→ *exo-E-*
15 from **13*S***: $R^1 = CO_2Me$, $R^2 = H$
25 from **19**: $R^1 = CH_2OTBS$, $R^2 = H$

→ *endo-E-*
14 from **13*R***: $R^1 = H$, $R^2 = CO_2Me$
26 from **20**: $R^1 = H$, $R^2 = CH_2OTBS$

→ *exo-Z-* (not seen)
from **13*R***: $R^1 = H$, $R^2 = CO_2Me$
from **20**: $R^1 = H$, $R^2 = CH_2OTBS$

Fig. 1 A *syn*-S_N2' hydroxyl displacement model to relate substrate and product diastereomers.

Our model (Fig. 1) places the Au(I)-centre loosely co-ordinated to both hydroxyls, mediating an overall *syn*-S_N2' displacement. We stress that this is merely a rule-of-thumb mnemonic and a stereochemically equivalent *anti*-alkoxyauration/*anti*-elimination process has been advocated.[17,20]

In conclusion, application of the Au(I)-mediated cyclo-etherification of monoallylic diols to the synthesis of (+)-isoaltholactone, and a follow-up study, have revealed further elements of stereocontrol in this reaction. In particular, secondary structural elements temper predictions based upon strict control by the allylic alcohol configuration.

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