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An Ireland–Claisen Rearrangement/Lactonisation Cascade as a Key Step in Studies Towards the Synthesis of (–)-Euonyminol:

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Abstract: Progress towards the asymmetric total synthesis of (–)-euonyminol is described with the focus on the installation of the oxygenation pattern on the lower rim of the molecule. An Ireland–Claisen rearrangement/lactonisation cascade has been developed and studies towards further elaboration have uncovered an intriguing tunable diastereoselective α-bromination of the resulting γ-lactone.

Key words: Ireland–Claisen, Celastraceae, bromination, euonyminol, sesquiterpene

The natural products of the *Celastraceae* family of medicinal plants have provided inspiration for a wealth of research in both the biological sciences and synthetic organic chemistry.[1] In particular, the β-dihydroagarofuran-based sesquiterpene derivatives have been the subject of a number of synthetic studies in recent years.[2] The vast number of structures of this type isolated to date (>200) renders the selection of a single target molecule challenging. We have noted previously however, that compounds of this class having a symmetrical oxygenation pattern across the upper rim invariably display notable biological activity.[3] One structure in particular with such a pattern, (–)-euonyminol (**1**)[4] forms the basic scaffold of some of the most biologically relevant natural products isolated from the family thus far, including triptonine B[5] and hypoglaunine B,[6] both of which show promise as anti-HIV agents.[7] Consequently, the heavily oxygenated euonyminol core can be considered the archetypal high value synthesis target in this field and racemic euonyminol (**1**) has been the subject of just one previous synthesis by White and colleagues[8] (Figure 1).

This communication reports progress towards the enantioselective synthesis of (–)-euonyminol (**1**) and related derivatives of the *Celastraceae*. We have reported previously the enantioselective desymmetrisation of a *meso*-diallylic alcohol to give an advanced intermediate **2** containing the upper rim hydroxyl functionality of euonyminol (**1**).[3] The focus of the later stages of the synthesis is functionalisation of the lower rim of this molecule. To this end, initial steps towards the introduction of this functionality have been developed on a model system **4**[8] (Scheme 1).

It was envisaged that following esterification of tertiary alcohol **4**, an Ireland–Claisen [3,3]-sigmatropic rearrangement[9] of the resulting allylic ester **5** would allow for the installation of the C-7/C-11 C–C bond required in the target. The anticipated product of the rearrangement was silyl ester **6** having the desired axial stereochemistry at C-7 (Scheme 2).

However, following optimisation of reaction conditions, the silyl ester epoxide **6** was not isolated. Instead, lactone **7** was formed exclusively in 76% yield, presumably as the result of in situ 5-*exo*-*trig* lactonisation, C-5/C-6 double

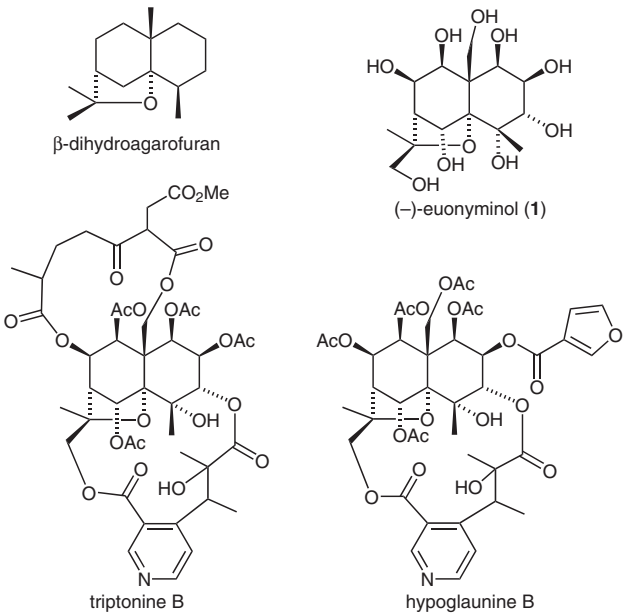

Figure 1 β-Dihydroagarofuran, (–)-euonyminol (**1**) and derived bioactive natural products of the *Celastraceae*

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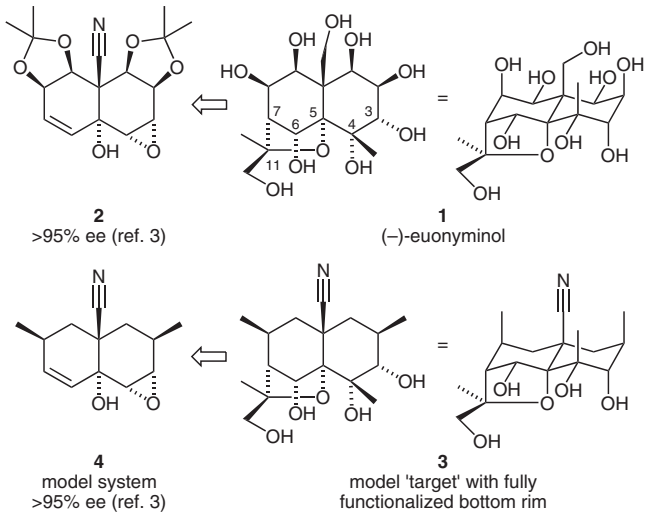
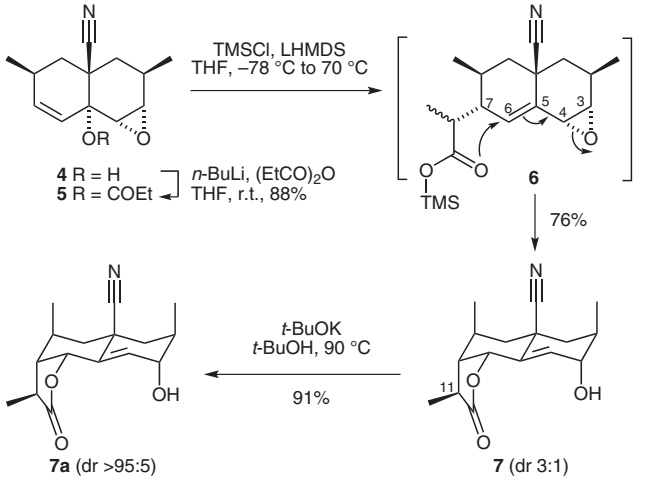


Scheme 1 Chiral intermediates **2** and **4** for the synthesis of (–)-euonyminol (**1**) and the model system **3**, respectively

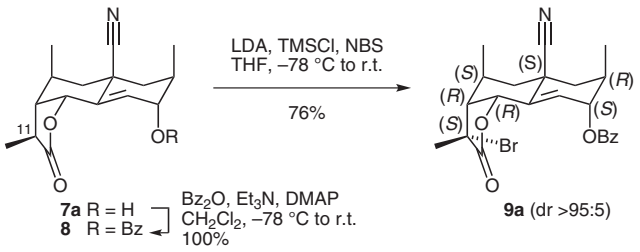


Scheme 2 Ireland–Claisen [3,3]-sigmatropic rearrangement/lactonisation cascade of propionate ester **5**

bond migration and epoxide ring opening. This expeditious cascade sets up not only the anticipated contra-thermodynamic axial C-7/C-11 C–C bond but also the requisite equatorial C-6 C–O bond and axial C-3 C–O bond stereochemistries. Two related cascade sequences have been reported previously, albeit with the lactonisation step being initiated as a separate step.[10,11] Taking these results and our own into account, one can envisage this desymmetrising epoxidation/rearrangement cascade as being a powerful general method for the enantioselective preparation of such heavily substituted 5-vinyl-γ-lactones.

Although the γ-lactone **7** was formed as a 3:1 mixture of C-11 epimers, treatment with *t*-BuOK in *t*-BuOH gave the thermodynamically favoured epimer **7a** exclusively (X-ray structure, see Supporting Information).

Further synthetic work towards installing the bottom rim functionality was performed on the single epimer model lactone **7a**. The initial objective was to establish the C-11 quaternary stereocenter via protection of the allylic alcohol as the benzoyl ester **8** then lactone α-bromination to give bromolactone **9a** (Scheme 3).



Scheme 3 α-Bromination of benzoate ester γ-lactone **7a**

Enantiomerically pure bromolactone **9a** provided crystals suitable for single crystal X-ray structure determination (Figure 2 and Supporting Information). Furthermore, analysis of the anomalous dispersion Flack parameters[12] for this diffraction experiment allowed unambiguous assignment of the absolute stereochemistry for this product, for which L-(+)-DIPT had been used as the chiral ligand in the asymmetric epoxidation leading to epoxide **4**.[3] The absolute stereochemistry was confirmed to be (2*R*,3*S*,6*R*,7*R*,8*S*,10*S*,11*S*)-**9a** (i.e. as drawn in Scheme 3) and as required for natural (–)-euonyminol (**1**).

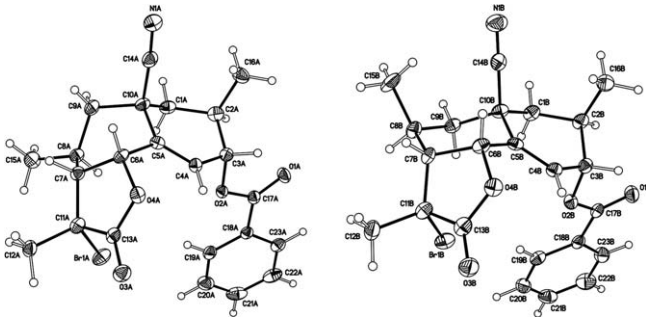
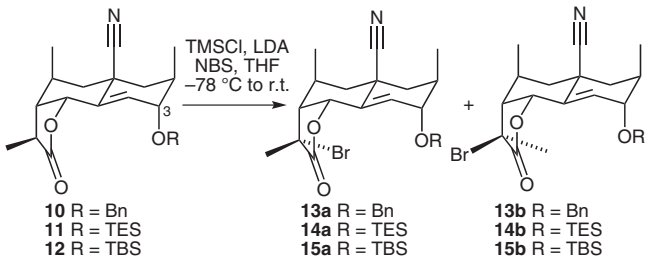


Figure 2 Molecular structure of bromolactone **9a** showing two distinct conformational isomers in the unit cell

The striking aspect of the molecular structure of α-bromolactone **9a** is the unexpected stereochemistry at C-11. Bromine has been introduced from what appears to be the more hindered concave face of the molecule.[13] Intrigued by this observation and speculating as to a possible non-steric role for the C-3 benzoate ester in influencing this selectivity, three similar substrates (**10**–**12**) were synthesised with ether protecting groups on the C-3 alcohol. These alkyl and silyl ethers were brominated under the optimised conditions with NBS (Table 1).

The choice of C-3 alcohol protecting group clearly has a dramatic influence on the stereoselectivity of the α-bromination.[14] For benzyl ether **10** (entry 1), the reaction was seen to be unselective; both C-11 epimers formed equally. However, the use of the more bulky TES and TBS ethers strongly favoured α-bromination on the convex face of the molecule; i.e. on the opposite face to that obtained when using the benzoate ester **8** (entries 2 and 3 in Table 1,

Table 1 α-Bromination of γ-Lactones **10**–**12** Bearing the C-3 Alcohol Protected as Three Different Ethers

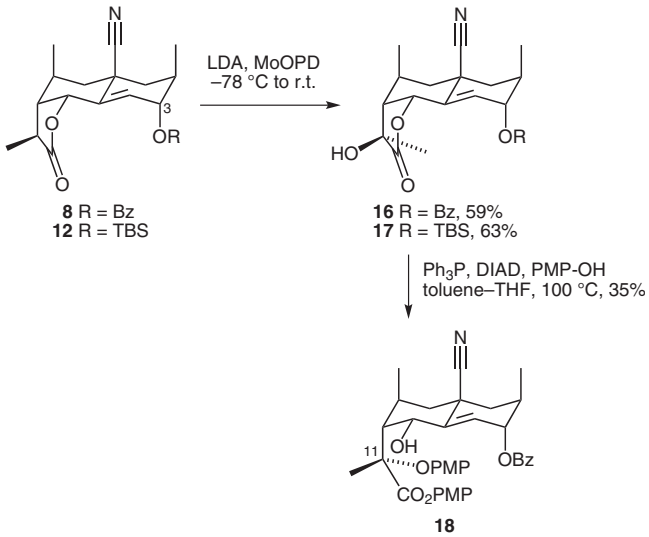


Entry	R	Starting material	Yield (%)	Ratio **a**/**b**[a]
1	Bn	**10**	ca. 66[a]	ca. 50:50[b]
2	TES	**11**	90	18:82
3	TBS	**12**	68	<5:95

[a] Determined by ^{1}H NMR spectroscopy (see ref. 16).
[b] Products not isolated.

cf. Scheme 3). The TBS-protected bromolactone **15b** was formed as a single diastereoisomer and its stereochemistry was confirmed by an X-ray structure determination (see Supporting Information).

The dramatic dependence of the stereoselectivity of lactone α-bromination on the nature of the remote C-3 alcohol protecting group clearly offers valuable flexibility in synthetic route planning towards the target. However, we were keen to see if oxygen-based electrophiles would behave similarly, as control of this C-11 stereocentre bearing an oxygen-based substituent would be particularly powerful (Scheme 4).



Scheme 4 Diastereoselective α-hydroxylation of γ-lactones **8** and **12** using MoOPD

The silylketene acetal of TBS ether lactone **12** was found to be unreactive to the peroxomolybdenum species MoOPD,[15] a variant of the MoOPH reagent initially introduced by Vedejs.[16] However, reaction with the lithium enolate of γ-lactone **12** did furnish the α-hydroxylactone **17** as a single C-11 epimer with the electrophile having being introduced on the expected convex face.[14] With the hope of inducing a stereochemical switch in the outcome of the oxidation, the benzoate ester lactone **8** was employed next as a substrate. Interestingly, no switch in facial selectivity was observed and α-hydroxylactone **17**, also resulting from electrophile introduction from the convex face, was isolated as a single epimer. It is possible that the large size of the MoOPD reagent dominates any inherent preference of the system for concave face attack of an electrophile. However, MoOPD has been previously suggested to behave like a 'small' electrophile[17] and it is plausible that the more polarisable bromonium ion is susceptible to a directing influence resulting from coordination to the Lewis basic benzoate ester carbonyl group or even a transient bromonium ion type interaction with the C-3/C-4 alkene.

Access to an alcohol derivative with presumed inverted stereochemistry at C-11 was eventually found to be possible by subjecting benzoate ester lactone **8** to a Mitsunobu-type reaction using *p*-methoxyphenol (PMP-OH).[18] This gave a product that was tentatively assigned as the ring-opened, inverted product **18**, based on mechanistic analysis, in an unoptimised 35% yield.[19]

In conclusion, we have described an Ireland–Claisen/lactonisation cascade and subsequent diastereoselective C-11 functionalisation protocols that constitute expeditious approaches to much of the functionality present on the bottom rim of the natural product core (–)-euonyminol (**1**). The ability to tune the stereochemistry at C-11 as a function of the nature of the remote protecting group on the C-3 alcohol is likely to prove instructive to the design of approaches to many *Celastraceae* sesquiterpenoids and related highly oxygenated *trans*-decalin-based natural products. Investigations are ongoing into the utility of the densely functionalised γ-lactones described herein for the synthesis of (–)-euonyminol (**1**) and related natural products. Results relating to this will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental procedures, characterisation and NMR spectra for all compounds.

Acknowledgment

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(19) Product **18** was not fully characterised due to lack of material and this line of investigation has not been pursued further to allow verification of the stereochemistry at C-11.