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COMMUNICATION

Transannular Claisen rearrangement reactions for the synthesis of vinylcyclobutanes: formal synthesis of (±)-grandisol†

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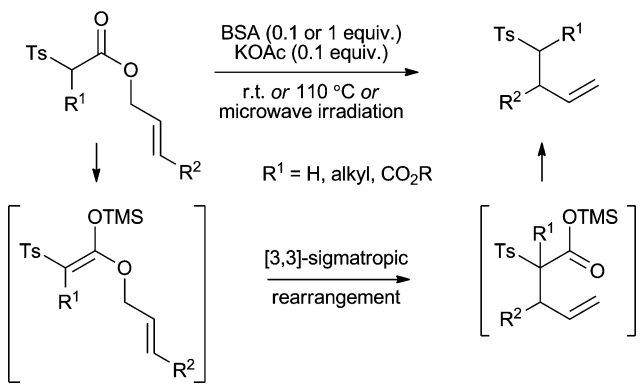
Unsaturated eight-membered lactones undergo decarboxylative and non-decarboxylative transannular Ireland–Claisen rearrangement reactions, to give substituted vinylcyclobutanes. A formal synthesis of (±)-grandisol is described.

Since its discovery in 1972, the Ireland–Claisen rearrangement[1] has become a mainstay of organic synthesis, because it enables regiospecific and stereoselective C–C bond formation from readily obtained allylic esters.[2] The decarboxylative Claisen rearrangement (dCr) reaction (Scheme 1) is a catalysed variant[3] of the transformation[4] whose utility has been demonstrated in the dearomatisation of heteroaromatic substrates,[5] the *de novo* synthesis of pyridines[6] and in natural product total synthesis.[7] In addition, we have studied quantitatively the relationship between substrate structure and reactivity in the dCr reactions of allylic tosylmalonates.[8]

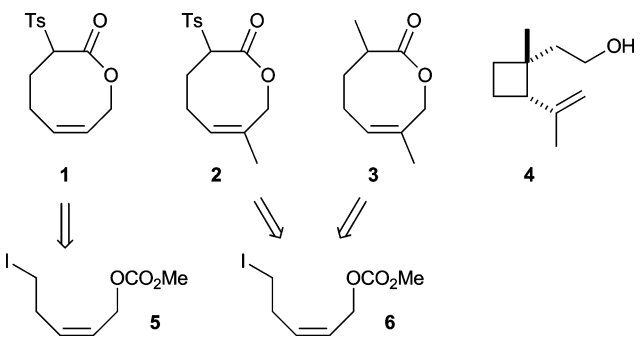


Scheme 1 Decarboxylative Claisen rearrangement reaction (BSA = *N*,*O*-bis(trimethylsilyl)acetamide).

Recently we reported transannular dCr ring contraction reactions of α-sulfonyl and α-sulfoximinyl ε-lactones as an efficient route to 2-vinylcyclopropylsulfones and -sulfoximines, respectively.[9] Previously, Funk *et al.*[10] and Cameron and Knight[11] had reported Claisen rearrangements of α-unsubstituted macrolactones which gave ring-contracted cyclic products bearing *cis*-disposed carboxylic acid and alkenyl groups. This arises because the silyl ketene acetal (*E*)-geometry imposed by the ring[12] limits the subsequent rearrangement to a single accessible boat-like transition state.

Recently, Boeckman and co-workers reported[13] the first example of reversible cyclobutane formation *via* transannular Claisen rearrangement. In this work the starting materials were alkenyl-substituted cyclobutanecarboxaldehydes, made by intramolecular allylation *via* an S_N2'-type reaction;[14] the dihydrooxocene substrates for the Claisen rearrangement were accessed by retro-Claisen rearrangement of the cyclobutane. Starting from ζ-lactones **1–3** synthesised from ω-hydroxyacids, this communication describes the first synthesis of substituted vinylcyclobutanes *via* irreversible transannular Claisen rearrangement reactions, and application of the chemistry in a formal synthesis of the boll weevil pheromone (±)-grandisol **4**.

The synthesis of the ζ-lactones required for this study necessitated the preparation of allylic carbonates **5** and **6** depicted in Scheme 2. For lactone **1**, the synthesis of precursor **5** was carried out by hydroxymethylation of the THP ether of but-3-yn-1-ol[15] and formation of the corresponding methyl carbonate. Deprotection of the THP group and hydrogenation of the resultant alkynol gave a *Z* homoallylic alcohol, which was mesylated and then converted into **5** by reaction with sodium iodide under standard S_N2 conditions. Precursor **6** was required for the synthesis of lactones **2** and **3**, and was made starting from 3-(*tert*-butyldiphenylsilyloxy)propanal.[16] Olefination using the Ando modification[17] of the



Scheme 2 Retrosynthesis of lactones **1–3**.

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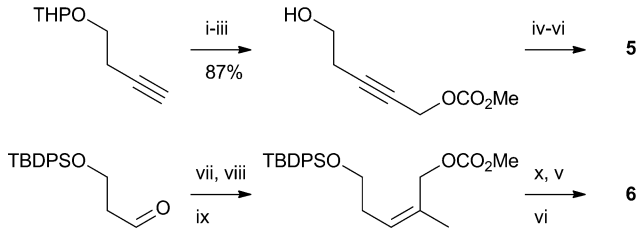
† Electronic supplementary information (ESI) available: Experimental details and full spectroscopic data for all novel compounds, and ^{1}H and ^{13}C nmr spectra for lactones **1**, **2**, **3** and cyclobutanes **9**, **10**, **11**, **12** and **14**. See DOI: 10.1039/c1ob06619f

Horner–Wadsworth–Emmons reaction gave the unsaturated, homologated ester as a 6.7 : 1 mixture of *Z* and *E* isomers. Reduction using DIBAL–H and conversion into the methyl carbonate was followed by desilylation and iodide formation using the two-step method described above. The syntheses of **5** and **6** are depicted in Scheme 3.

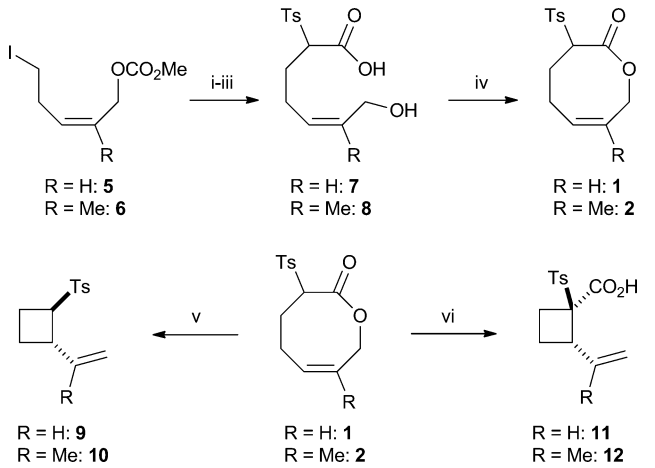


Scheme 3 Synthesis of iodide precursors **5** and **6**. *Reagents and conditions*: (i) *n*BuLi, $(CH_2O)_n$, THF, rt, 3 h, 97%; (ii) MeOCOCl, pyridine, CH_2Cl_2, 0 °C, 1 h, 96%; (iii) PPTS, EtOH, 55 °C, 2 h, 93%; (iv) H_2, Lindlar's catalyst, THF, rt, 1 h, 89%; (v) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, used crude in next step; (vi) NaI, MeCN, 70 °C, 16 h, used crude in step (i), Scheme 4; (vii) $EtO_2CCHMePO(OPh)_2$, DBU, NaI, THF, 0 °C, 2 h, 90%; (viii) DIBAL-H, PhMe, −78 °C → rt, 2 h, 96%; (ix) MeOCOCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 82%; (x) MeOH, conc. HCl (aq), rt, 16 h, 92%.

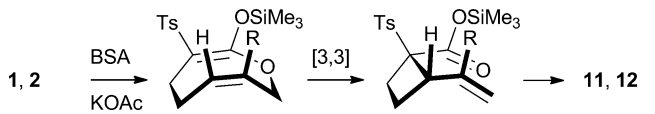
The sulfone-containing substrates **1** and **2** were investigated initially. Reaction of the sodium enolate of methyl 2-tosylacetate with crude iodides **5** and **6** prepared as described in Scheme 3 gave good yields of the alkylated products. Removal of the carbonate groups and saponification of the methyl esters gave homologous hydroxyacids **7** and **8**. For both homologues, extensive experimentation revealed the best conditions for lactonisation to be HATU[18]–Hünig's base in DMF, under syringe-pump-controlled, high-dilution conditions.[19] Lactones **1** and **2** were subjected to both dCr and Ireland–Claisen reactions. Microwave irradiation of a 0.2 M DMF solution of **1** containing 1 equiv. BSA and 10 mol % KOAc gave the *trans* disubstituted cyclobutane **9** in high yield. Similar treatment of lactone **2** gave the homologous cyclobutane **10**. Carrying out the reactions at ambient temperature in CH_2Cl_2 gave the carboxylic acids **11** and **12**, the products of Ireland–Claisen rearrangement (Scheme 4).

All the cyclobutane products were formed as single diastereoisomers. The assignment of the *cis* relationship of the alkenyl and carboxyl substituents in acids **11** and **12** followed from consideration of the constrained boat/boat-like reactive conformation of the ketene acetal intermediates (Scheme 5). For the decarboxylated products **9** and **10**, the *trans* relationship of the alkenyl and arylsulfonyl substituents was assigned based on the precedent established in our studies of cyclopropane formation *via* dCr reactions of ε-lactones,[9] where decarboxylation gave the sterically less crowded and thermodynamically more stable *trans* 1,2-disubstituted products.

With the viability of cyclobutane formation by transannular Claisen rearrangement established, the final part of this investigation was directed towards the formal synthesis of a natural product. (+)-Grandisol **4** is the primary active component of the male boll weevil pheromone; the strained cyclobutane ring system possessing a quaternary carbon centre has attracted significant interest from synthesis chemists, in the contexts both of synthesis method development and asymmetric catalysis.[20] Initial trials sought unsuccessfully to elaborate Claisen rearrangement product **12**, by methyl esterification ($TMSCHN_2$) followed by desulfonylation (Li naphthalenide) and methylation of the product enolate *in situ*; these unsuccessful experiments were hampered significantly by product volatility. In view of these failures, a more direct approach was developed. Alkylation of dimethyl 2-methylmalonate was carried out by treatment of the sodium enolate with purified iodide **6**.[21] Carbonate hydrolysis, decarboxylation[22] and saponification gave hydroxyacid **13**, which was subjected to high-yielding lactonisation in the presence of trichlorobenzoyl chloride under Mukaiyama conditions,[23] again using a syringe pump so as to maintain low substrate concentrations. Ireland–Claisen rearrangement of lactone **3** was effected by treatment with TMSOTf–Et_3N[24] in CH_2Cl_2 at room temperature, giving acid **14** as a single diastereoisomer in excellent yield (Scheme 6).

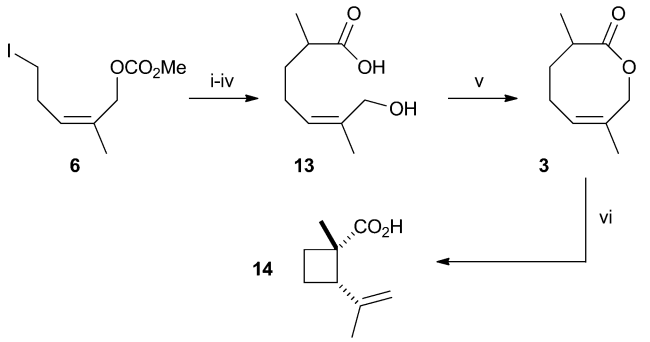


Scheme 4 Synthesis and Claisen rearrangement of lactones **1** and **2**. *Reagents and conditions*: (i) NaH, DMF, $TsCH_2CO_2Me$, 0 °C → rt, 16 h; (ii) K_2CO_3, MeOH, 0 °C, 1 h; (iii) 2 M LiOH (aq), THF, rt, 16 h, **7**: 39% over five steps from *Z*-5-hydroxypent-2-enyl methyl carbonate; **8**: 39% over five steps from *Z*-5-hydroxy-2-methylpent-2-enyl methyl carbonate; (iv) HATU (5 equiv.), DIPEA (10 equiv.), DMF, rt, 20 h, syringe pump addition of **7**/**8**; **1**: 66%; **2**: 85%; (v) BSA (1 equiv.), KOAc (0.1 equiv.), DMF, microwave, 160 °C, 10 min; **9**: 85%; **10**: 90%; (vi) BSA (1 equiv.), KOAc (0.1 equiv.), CH_2Cl_2, rt, 16 h; **11**: 100%; **12**: 94%.



Scheme 5 Proposed reactive conformation of ketene acetal intermediates.

In summary, we have demonstrated that vinylcyclobutanes may be assembled using transannular Ireland–Claisen and decarboxylative Claisen rearrangement reactions of ζ-lactones made by cyclisation of ω-hydroxyacids. The ready availability of homoallylic iodides and the ease and efficiency of medium-ring cyclisation to give the ζ-lactone substrates are such that this method should be amenable to the synthesis of a diverse range of cyclobutane-containing compounds.



Scheme 6 Synthesis and Ireland-Claisen rearrangement of lactone **3**. *Reagents and conditions*: (i) dimethyl 2-methylmalonate, NaH, DMF, 0 °C → rt, then add **6**, 0 °C, then rt, 2 h, 63%; (ii) K_2CO_3, MeOH, 0 °C, 3 h, 100%; (iii) LiCl, H_2O–DMSO, microwave, 180 °C, 15 min, 67%; (iv) aq. LiOH (2 M) THF, 0 °C, 16 h, 95%; (v) 2,4,6-trichlorobenzoyl chloride, Et_3N, CH_2Cl_2, 40 °C, 168 h, syringe pump addition of **13**, 79%; (vi) TMSOTf, Et_3N, CH_2Cl_2, rt, 16 h, 92%.

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