

## Transannular Claisen rearrangement reactions for the synthesis of vinylcyclobutanes: formal synthesis of ( $\pm$ )-grandisol†

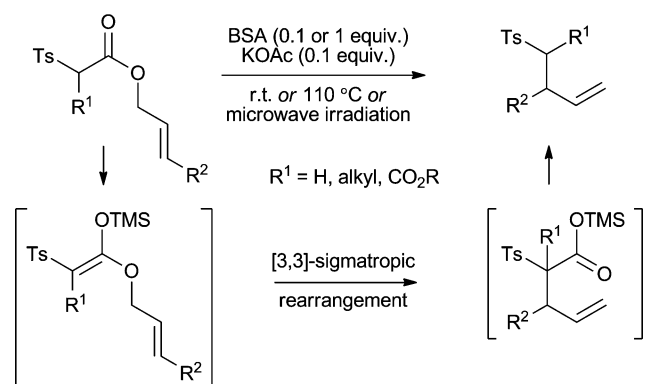
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Unsaturated eight-membered lactones undergo decarboxylative and non-decarboxylative transannular Ireland–Claisen rearrangement reactions, to give substituted vinylcyclobutanes. A formal synthesis of ( $\pm$ )-grandisol is described.

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



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

Recently we reported transannular dCr ring contraction reactions of  $\alpha$ -sulfonyl and  $\alpha$ -sulfoximinyl  $\epsilon$ -lactones as an efficient route to 2-vinylcyclopropylsulfones and -sulfoximines,

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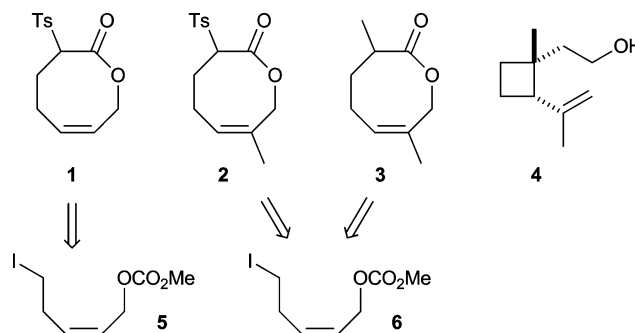
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† Electronic supplementary information (ESI) available: Experimental details and full spectroscopic data for all novel compounds, and <sup>1</sup>H and <sup>13</sup>C nmr spectra for lactones **1**, **2**, **3** and cyclobutanes **9**, **10**, **11**,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

respectively.<sup>9</sup> Previously, Funk *et al.*<sup>10</sup> and Cameron and Knight<sup>11</sup> had reported Claisen rearrangements of  $\alpha$ -unsubstituted macro-lactones 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<sup>12</sup> limits the subsequent rearrangement to a single accessible boat-like transition state.

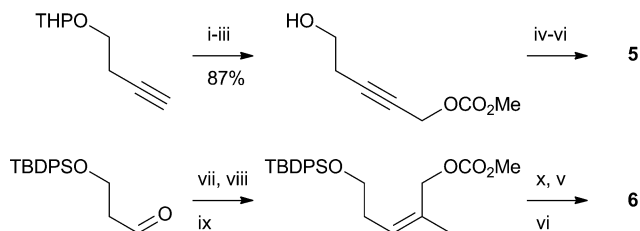
Recently, Boeckman and co-workers reported<sup>13</sup> the first example of reversible cyclobutane formation *via* transannular Claisen rearrangement. In this work the starting materials were alkenyl-substituted cyclobutanecarboxaldehydes, made by intramolecular allylation *via* an S<sub>N</sub>2'-type reaction;<sup>14</sup> the dihydrooxocene substrates for the Claisen rearrangement were accessed by retro-Claisen rearrangement of the cyclobutane. Starting from  $\zeta$ -lactones **1–3** synthesised from  $\omega$ -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 ( $\pm$ )-grandisol **4**.

The synthesis of the  $\zeta$ -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<sup>15</sup> and formation of the corresponding methyl carbonate. Deprotection of the THP group and hydrogenation of the resultant allylic alcohol, which was mesylated and then converted into **5** by reaction with sodium iodide under standard S<sub>N</sub>2 conditions. Precursor **6** was required for the synthesis of lactones **2** and **3**, and was made starting from 3-(*tert*-butyldiphenylsilyloxy)propanal.<sup>16</sup> Olefination using the Ando modification<sup>17</sup> of the



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

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.

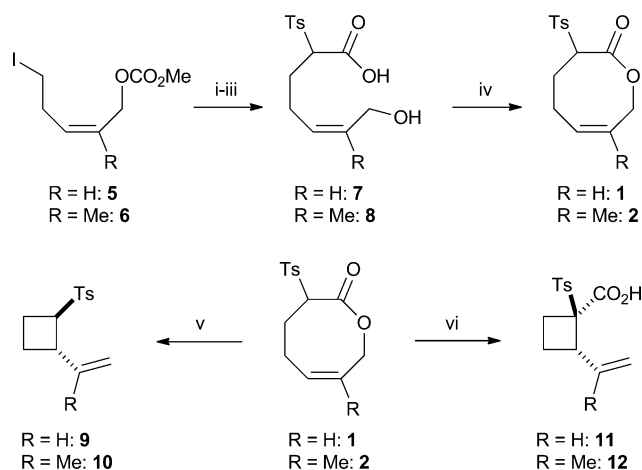


**Scheme 3** Synthesis of iodide precursors **5** and **6**. *Reagents and conditions:* (i) *n*BuLi, (CH<sub>2</sub>)<sub>n</sub>, THF, rt, 3 h, 97%; (ii) MeOCOCl, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1 h, 96%; (iii) PPTS, EtOH, 55 °C, 2 h, 93%; (iv) H<sub>2</sub>, Lindlar's catalyst, THF, rt, 1 h, 89%; (v) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 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<sub>2</sub>CCHMePO(OPh)<sub>2</sub>, DBU, NaI, THF, 0 °C, 2 h, 90%; (viii) DIBAL–H, PhMe, –78 °C → rt, 2 h, 96%; (ix) MeOCOCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1 h, 82%; (x) MeOH, conc. HCl (aq), rt, 16 h, 92%.

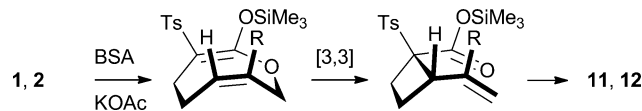
The sulfone-containing substrates **1** and **2** were investigated initially. Reaction of the sodium enolate of methyl 2-tosylacetate with crude iodides **5** and **6** prepared as described in Scheme 3 gave good yields of the alkylated products. Removal of the carbonate groups and saponification of the methyl esters gave homologous hydroxyacids **7** and **8**. For both homologues, extensive experimentation revealed the best conditions for lactonisation to be HATU<sup>18</sup>–Hünig's base in DMF, under syringe-pump-controlled, high-dilution conditions.<sup>19</sup> 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<sub>2</sub>Cl<sub>2</sub> 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  $\epsilon$ -lactones,<sup>9</sup> 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.<sup>20</sup> Initial trials sought unsuccessfully to elaborate Claisen rearrange-



**Scheme 4** Synthesis and Claisen rearrangement of lactones **1** and **2**. *Reagents and conditions:* (i) NaH, DMF, TsCH<sub>2</sub>CO<sub>2</sub>Me, 0 °C → rt, 16 h; (ii) K<sub>2</sub>CO<sub>3</sub>, 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<sub>2</sub>Cl<sub>2</sub>, rt, 16 h; **11**: 100%; **12**: 94%.

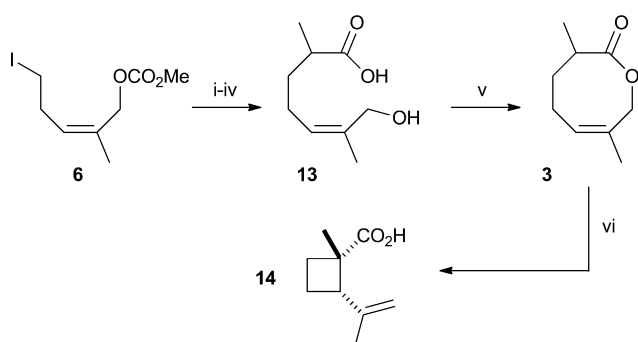


**Scheme 5** Proposed reactive conformation of ketene acetal intermediates.

ment product **12**, by methyl esterification (TMSCHN<sub>2</sub>) 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**.<sup>21</sup> Carbonate hydrolysis, decarboxylation<sup>22</sup> and saponification gave hydroxyacid **13**, which was subjected to high-yielding lactonisation in the presence of trichlorobenzoyl chloride under Mukaiyama conditions,<sup>23</sup> 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<sub>3</sub>N<sup>24</sup> in CH<sub>2</sub>Cl<sub>2</sub> at room temperature, giving acid **14** as a single diastereoisomer in excellent yield (Scheme 6).

The identity of **14** followed from comparison of its spectroscopic data with those reported in the literature.<sup>25</sup> Since sequences for the homologation of **14** and reduction of the resultant acid to (±)-grandisol have been described,<sup>26</sup> this constitutes a formal synthesis of **4**.

In summary, we have demonstrated that vinylcyclobutanes may be assembled using transannular Ireland–Claisen and decarboxylative Claisen rearrangement reactions of  $\zeta$ -lactones made by cyclisation of  $\omega$ -hydroxyacids. The ready availability of homoallylic iodides and the ease and efficiency of medium-ring cyclisation to give the  $\zeta$ -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<sub>2</sub>CO<sub>3</sub>, MeOH, 0 °C, 3 h, 100%; (iii) LiCl, H<sub>2</sub>O–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<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, 168 h, syringe pump addition of 13, 79%; (vi) TMSOTf, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h, 92%.

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