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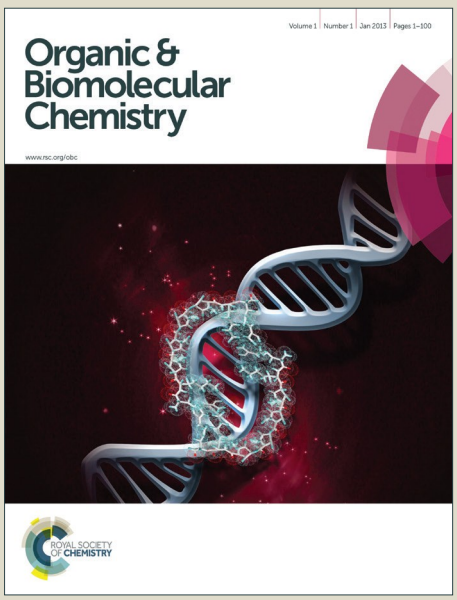

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Synthesis of Highly Enantio-enriched Stereoisomers of Hydroxy-GR24

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In contrast to a biomimetic *electrophilic* cyclisation cascade, we employ a contra-biomimetic *nucleophilic* cyclisation cascade to give the tricyclic core of 4-hydroxy-GR24 in a single step. Kinetic resolution using a stereoselective Noyori transfer hydrogenation enables the concise synthesis of any enantiomerically enriched 4-hydroxy-GR24 stereoisomer.

Strigolactones are naturally occurring signalling molecules that play key roles in plant–plant and plant–fungi communication, in addition to being phytohormones that affect plant growth and development (Fig.1).[1-7] Given the extraordinarily low natural abundance of strigolactones, functional mimics have been attractive synthetic targets that have enabled plant scientists to make initial investigations into biological modes of action and potential agrichemical applications.[8-15] For the past 30 years, the gold standard among the strigolactone mimics has been GR24 (**3**),[16] which is routinely used as a positive control in plant-based assays. For seed germination, recent assays have revealed that (−)-4-OH-*epi*-GR24 (−)-(**4**) is more potent than the parent compound,[17] and so ready access to single stereoisomers of this compound is highly desirable. There have been four previous synthetic approaches to this compound (Scheme 1). Zwanenburg accessed the racemic mixture using a metal-based oxidation of the GR24 core (±)-**5**, followed by a reduction with $NaBH_4$.[9, 18] Although highly chemoselective, the C4 alcohol of (±)-**7** was installed with the non-natural stereochemistry. De Mesmaeker and co-workers recently utilised a similar protocol and showed that the undesired stereoisomer of the GR24 core cannot undergo the formylation and condensation reaction required to build the GR24 architecture unless protected. Moreover, assays demonstrate that this diastereomer is markedly less active in seed germination. The approach by Boyer, Beau, and co-workers displaced a C4 Cl of compound (+)-(**10**) that had been installed by an atom transfer radical reaction, but also resulted in racemisation and generated the non-desired stereoisomer (±)-**7**.[19] Therefore in all cases a Mitsunobu inversion was required to install the desired stereoisomer (±)-**8**, which

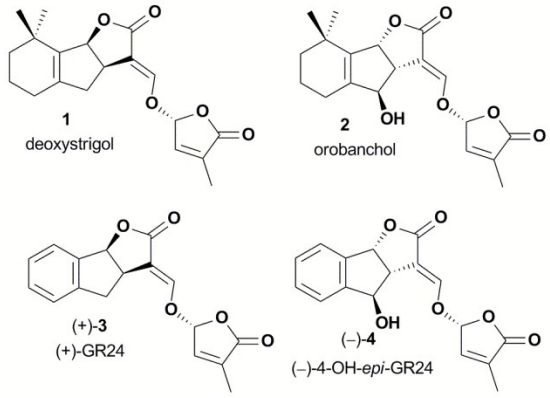
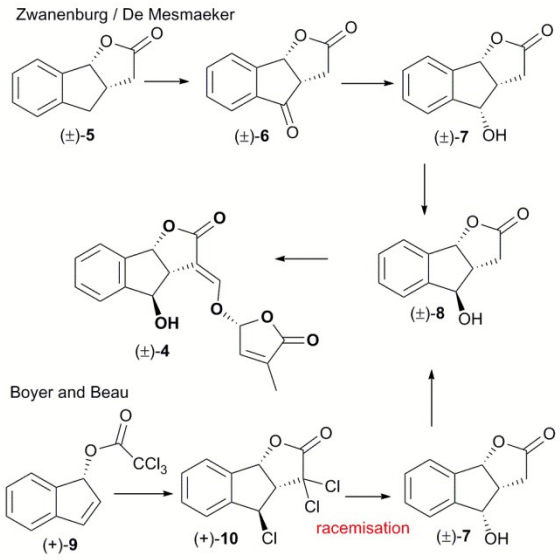


Figure 1. Representative natural (**1** and **2**) and synthetic (**3** and **4**) strigolactones.



Scheme 1. Previous syntheses of (±)-4-hydroxy-GR24 (±)-**4**.

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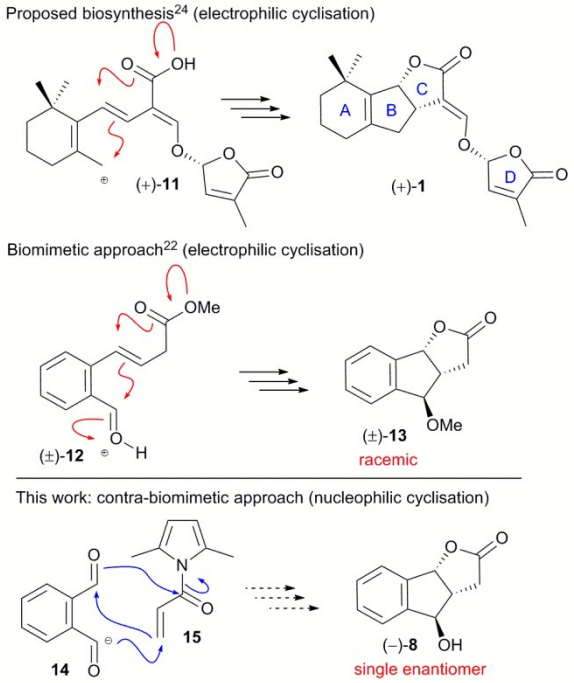


Scheme 2. Biomimetic and contra-biomimetic approaches to 4-hydroxy-GR24

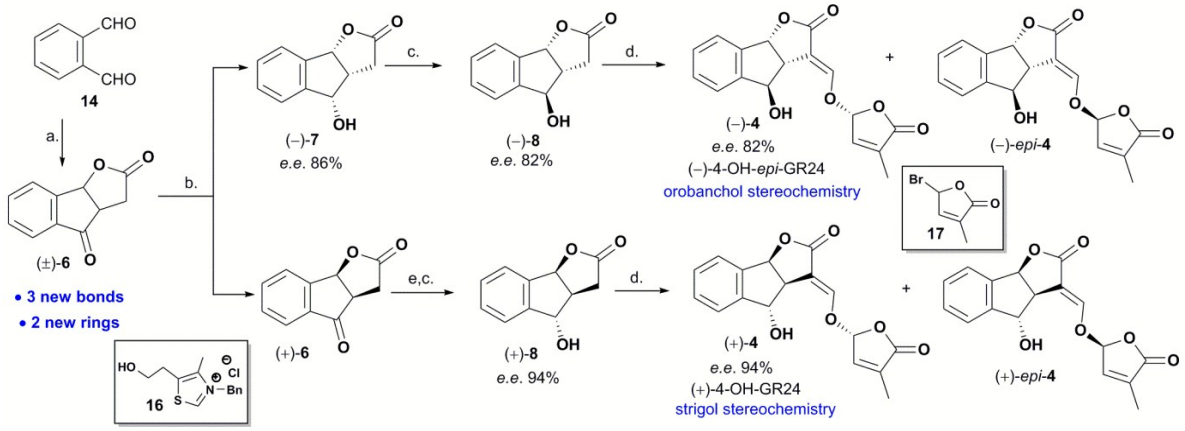
smoothly underwent extension to (±)-4-OH-GR24 (±)-(**4**). Interestingly, Takikawa reported that displacement of corresponding bromide proceeded directly to (±)-**8**.[20] Enantioselective routes to (−)-(**4**) have not yet been reported. Although we have recently described an efficient and enantioselective route to (+)-GR24 (**3**),[21] we wished to avoid the redox manipulations required to convert it into the target compound.

The only other synthetic route to C4 oxygen-containing GR24-like compound was reported by Aponick and co-workers (Scheme 2).[22] Inspired by a biosynthetic proposal regarding the strigolactones,[23, 24] Aponick utilised an electrophilic cascade that installed both the B and C rings, as well as the desired oxygen atom in one fell swoop. Although not yet reported, demethylation of that biomimetic cascade product (±)-(**13**) would give (±)-**7** and intercept the previous syntheses.

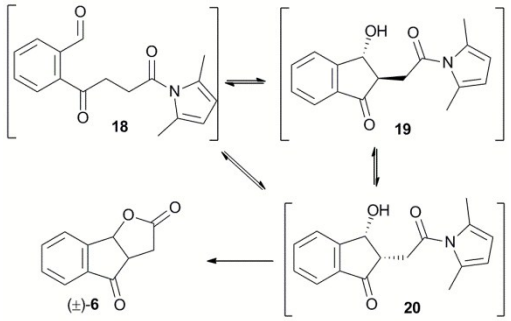
Our synthetic efforts were also informed by the proposed biosynthesis.[24] While the natural system is evolutionarily confined to particular directionality for the construction of strigolactones (i.e. the electrophilic C4 position drawing electron density toward the forming B ring), the synthetic chemist is not. We wondered if it would be more efficient to create a nucleophilic C4 position. By doing so, the B and C rings could be installed using a single intermolecular process. This would greatly increase the ease of access to such important compounds, and enable the rapid generation of analogues. The realisation of this 'contra-biomimetic' approach is reported in this communication.

As shown in Scheme 3, our contra-biomimetic synthesis involved the union of phthalaldehyde (**14**) and 2,5-dimethyl-*N*-acryloylpyrrole (**15**).[25, 26] Although the yield was modest, this process generated 3 new bonds and installed the two required rings in a single operation. Compound (±)-**6** was then subjected to the action of Noyori's (*S*,*S*)-RuTsDPEN catalyst under transfer hydrogenation conditions,[27] which effected the desired kinetic resolution to give alcohol (−)-**7** in 49% yield and 86% *e.e.*, and returned the unreacted (mismatched) ketone (+)-**6** in 49% and 94% *e.e.* Compound (−)-**7** featured the all *syn* stereochemical arrangement, so Mitsunobu inversion with benzoic acid and hydrolysis was carried out, to give the desired *anti* configured alcohol (−)-**8**, in 83% yield over the 2 steps and 82% *e.e.* Formylation and attachment of the butenolide ring occurred under standard conditions to give (−)-4-OH-*epi*-GR24 (−)-(**4**) with absolute and relative stereochemistry corresponding with naturally occurring (−)-orobanchol (**2**).

The recovered ketone (+)-**6** was highly enantiomerically enriched by the Noyori asymmetric transfer hydrogenation reaction. Luche reduction to the *syn* alcohol (+)-**7** and



Scheme 3. Enantioselective synthesis of 4-hydroxy-GR24 isomers. *Reagents and Conditions*: (a) **16** (20 mol%), **15**, Cs_2CO_3, THF, RT, 38%. (b) (*S*,*S*)-RuTsDPEN (4 mol%), HCO_2H, DIPEA, DMF RT, (−)-**7** 49%, (+)-**6** 49%. (c) PPh_3, DIAD, BzOH, THF, RT, then K_2CO_3, MeOH, (−)-**8** 83%, (+)-**8** 83% (d) HCO_2Me, *t*-BuOK, then K_2CO_3, **17**, DMF, RT, (−)-**4** 21%, (−)-*epi*-**4** 19%, (+)-**4**, 26%, (+)-*epi*-**4** 27%. (e) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, EtOH, RT, 68%.



Scheme 4. Plausible mechanism for the synthesis of (±)-**6**.

Mitsunobu inversion in the manner previous described, gave alcohol (+)-**8** in good yield (Scheme 3). This compound was the enantiomer of the previously synthesised alcohol (−)-**8**. The same synthetic sequence was then employed to deliver (+)-4-OH-GR24 (+)-(**4**) with absolute stereochemistry corresponding to (+)-deoxystrigol (**1**).

We anticipate that the contra-biomimetic cyclisation cascade proceeds *via* intermolecular Stetter reaction, intramolecular aldol reaction, and lactonisation (Scheme 4). Indeed, if catalytic amounts of base and short reaction times were employed, then compound **18** could be isolated in 71% yield. The *syn* and *anti* configured alcohols **19** and **20** can interconvert by a retro-aldol, aldol process, or by base catalysed epimerisation. The reactivity of the *N*-acylpyrrole functional group as an activated acid derivative facilitates lactonisation of the *syn* configured alcohol to give the desired tricyclic molecule (±)-**6**.

In summary, we report a rapid, stereoselective synthesis of 4-OH-GR24 isomers using a contra-biomimetic cyclisation. We anticipate that this general strategy will be widely applicable in synthesis, and in particular, it will enable the generation of a large number of naturally occurring strigolactones and their synthetic mimics. Efforts toward this goal are already underway in our laboratory and will be described elsewhere.

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