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Asymmetric synthesis of the four stereoisomers of 5-deoxystrigol

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ABSTRACT

Two approaches to the strigolactone tricyclic lactone skeleton **2** were investigated using ketene/ketene-iminium cycloaddition to olefins. Finally, the first enantioselective access to the four stereoisomers of 5-deoxystrigol **1** is reported using an intramolecular [2+2] cycloaddition of homochiral ketene-iminium salts **5**. Very high asymmetric control was achieved with C-2 symmetric pyrrolidines as chiral auxiliary.

Strigolactones are a family of plant hormones, whose first member, strigol, was isolated in the sixties for its effect on the germination of *Striga* seeds, a parasitic weed.[1] Recently, their role as signaling molecules in the rhizosphere and as plant hormone was unveiled and strigolactones were found to be involved in controlling plant architecture (shoot and root branching), root growth, secondary growth as well as germination.[2]

Strigolactones are derived from the carotenoid pathway, with carlactone identified in 2012 as a key intermediate in the biosynthesis, which is later converted to 5-deoxystrigol, the alleged parent of the different members of the strigolactone family.[3] Although first isolated only in 2005 from *Lotus japonicus*,[4] 5-deoxystrigol **1** was prepared for the first time as an intermediate in the synthesis of strigol in 1991, wherein the tricyclic lactone skeleton was accessed by a Nazarov type cyclization.[5] Since then, two other approaches were reported involving also a Nazarov cyclization[6] or a reductive carbon–carbon bond formation.[7] However, to the best of our knowledge, the enantioselective synthesis of 5-deoxystrigol has never been described.

We have previously reported the use of asymmetric [2+2] cycloaddition to access (+)-GR-24[8] and we report here the extension of this methodology to the asymmetric synthesis of the four stereoisomers of 5-deoxystrigol.

Our retrosynthetic analysis of (+)-5-deoxystrigol **1** and related stereoisomers is depicted in Scheme 1. Lactone **2** could be accessed via a regioselective Baeyer–Villiger oxidation of cyclobutanone **3**, which would result from the cycloaddition of a ketene **4** or ketene-iminium salt **5** derived from the acid **6** or the amide **7**.

Thus, commercially available 2,2-dimethylcyclohexanone **8** was alkylated with allyl bromide. Then, the olefination of the ketone **9** is required to get the α,β-unsaturated ester. The standard Horner–Wadsworth–Emmons reaction with phosphonate ester gave only recovery of the starting material. Similar results were obtained when attempting a Peterson olefination, due to the high hindrance of the ketone **9**. Recently, Dudley et al. have reported a two-step procedure for the olefination of bulky ketones, based on a Meyer–Schuster rearrangement.[9] The acetylenic organolithium obtained by deprotonation of ethoxyacetylene was added to the ketone **9**, providing alcohol **10** in high yield. Then, the Lewis acid-catalyzed Meyer–Schuster rearrangement afforded the desired α,β-unsaturated ester **11** as a 1:1 mixture of *E* and *Z* isomers, which were easily separated by chromatography on silica gel. Both $AuCl_3$ and $Sc(OTf)_3$ were very efficient as Lewis acids in promoting this reaction. Esters-**11** were hydrolyzed separately without isomerization to acids (*E*)-**6** and (*Z*)-**6**, which were coupled with pyrrolidine to afford the corresponding amides (*E*)-**7a** and (*Z*)-**7a** (see Scheme 2).

The [2+2] intramolecular cycloaddition of ketene-iminium salts derived from amides **7a** was attempted at first, because ketene-iminium salts are more reactive than the corresponding ketenes.[10] Unfortunately, starting material was recovered for both diastereoisomers (Scheme 3).

The formation of ketene-iminium salts involving γ-deprotonation of α,β-unsaturated amides has never been reported in the literature. On the contrary, reactions involving α,β-unsaturated ketenes are well studied, in particular in the case of cyclopentene[11]

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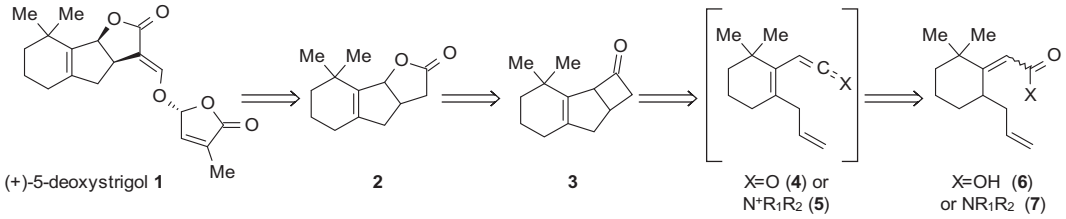
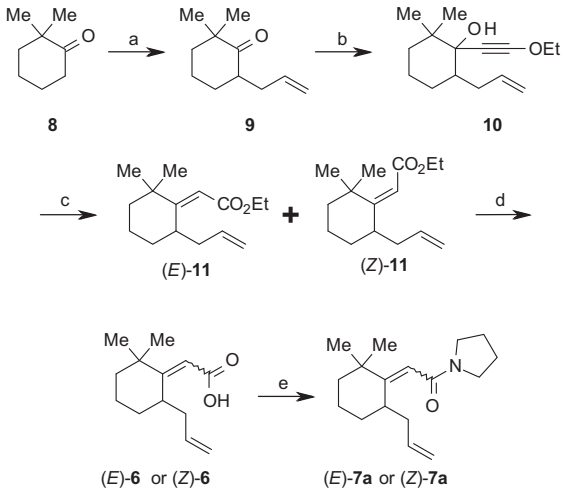
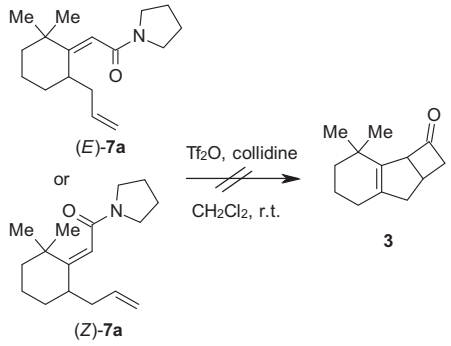


Scheme 1. Retrosynthetic analysis of (+)-5-deoxystrigol **1**.



Scheme 2. Preparation of the precursors for the intramolecular cycloaddition. Reagents and conditions: (a) LiHMDS, allyl bromide, THF, −78 °C, 65%; (b) ethoxyacetylene, *n*-BuLi, THF, −78 °C, then **9**; 77%; (c) $Sc(OTf)_3$ (5%), CH_2Cl_2, EtOH, 82%, *E*/*Z* = 1/1, separation of isomers; or $AuCl_3$ (5%), CH_2Cl_2, EtOH, 90%; (d) NaOH, THF/H_2O, 95% (*E*)-**11**; quant. (*Z*)-**11**; (e) PyBop (1.1 equiv), pyrrolidine (1.1 equiv), Hunig's base (3.0 equiv), DMF, 87% (*E*)-**7a** or (*Z*)-**7a**.

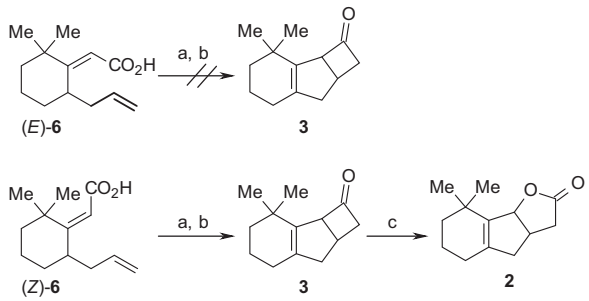


Scheme 3. Attempted [2+2] cycloaddition of the ketene-iminium salts from amide (*E*)-**7a** or (*Z*)-**7a**.

or cyclohexene ring.[12] Thus, the cycloaddition of the ketene was attempted on both (*E*)-**6** and (*Z*)-**6** separately (Scheme 4). After formation of the acid chloride with Ghosez reagent, the ketene was formed by deprotonation with triethylamine. To our surprise, the *E* isomer did not react under these conditions and the starting acid (*E*)-**6** was recovered. Under the same conditions b the *Z* isomer afforded cyclobutanone **3** in low yield, which could be further improved up to 28% adding DMAP (Scheme 4).

The Baeyer–Villiger oxidation was nevertheless carried out and the tricyclic lactone core structure **2** was obtained. At this stage, our data fully matched the one reported in the literature.[5]

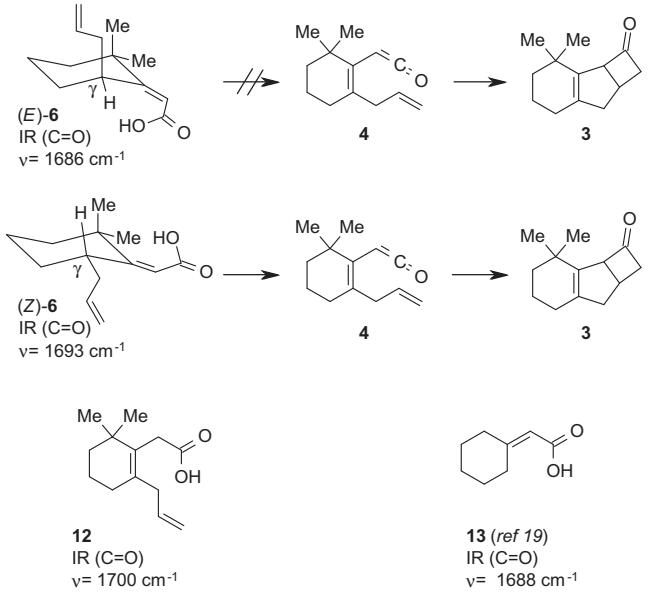
Although successful, this route was limited by the low yield of the intramolecular ketene cycloaddition. In the case of the *Z* isomer, we suspect that repulsion between the gem-dimethyl group



Scheme 4. Intramolecular [2+2] cycloaddition of the ketene and synthesis of the racemic lactone **2**. Reagents and conditions: (a) $Me_2C{=}CClNMe_2$ (Ghosez reagent), CH_2Cl_2; (b) Et_3N (2.0 equiv), DMAP (1.0 equiv), CH_2Cl_2, reflux, 46%; (c) H_2O_2, AcOH, 92%.

and the acid chloride induces the rotation of the carbonyl group out of the plane of the C=C bond, which results in their partial deconjugation. This hypothesis is supported by the observed difference in stretching frequencies of the C=O in the IR spectra (Scheme 5, compound (*Z*)-**6** versus **12** and (*E*)-**6** versus **13**)[19]. Consequently, the lower acidity of the γ proton disfavors the formation of the ketene. In the case of the *E* isomer, we postulate that, due to steric repulsion between the carbonyl and the allyl group, the latter adopts an axial orientation, reducing considerably the acidity of the γ proton, preventing the formation of the corresponding ketene.

A solution to facilitate the formation of the ketene/ketene-iminium salt would be to start from the deconjugated acid **12** or amides



Scheme 5. Plausible conformational restrictions for ketene formation.