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COMMUNICATION

Synthetic studies on the solanacol ABC ring system by cation-initiated cascade cyclization: implications for strigolactone biosynthesis†

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We report a new method for constructing the ABC ring system of strigolactones, in a single step from a simple linear precursor by acid-catalyzed double cyclization. The reaction proceeds with a high degree of stereochemical control, which can be qualitatively rationalized using DFT calculations. Our concise synthetic approach offers a new model for thinking about the (as yet) unknown chemistry that is employed in the biosynthetic pathways leading to this class of plant hormones.

Strigol **1** (Fig. 1) was isolated in 1966 from cotton root exudates,[1] and a relatively large family of related strigolactones has subsequently been characterized.[2] These compounds were originally identified as germination stimulants for parasitic weeds and later as chemical signaling agents for root colonization by symbiotic arbuscular mycorrhizal fungi.[3] The recent discovery that strigolactones are a new class of plant hormones that function to regulate shoot branching[4] has renewed biochemical interest in this family of natural products.[2,5] Little is known about the biosynthesis of strigolactones other than that they are likely derived from carotenoid precursors.[6] In part, this is because (i) genetic studies suggest that only a small number of enzymes are involved in the pathway,[7] and (ii) technical problems have been encountered in feeding studies employing suitably labeled precursors.[5d]

Our interest in these molecules stems from this lack of biosynthetic information, coupled with the unique structural diversity found in this family of natural products. As can be seen in Fig. 1, simple strigol congeners have been identified such as orobanchol **2** with the allylic alcohol transposed from the A- to B-ring.[8] However, a much more interesting structural difference is observed in the epoxy-derivative fabacyl acetate **3**[9] and the aromatic congener solanacol **4**,[10] whose core stereochemistries are enantiomeric with the ostensible parent compound strigol **1** or orobanchol **2**.

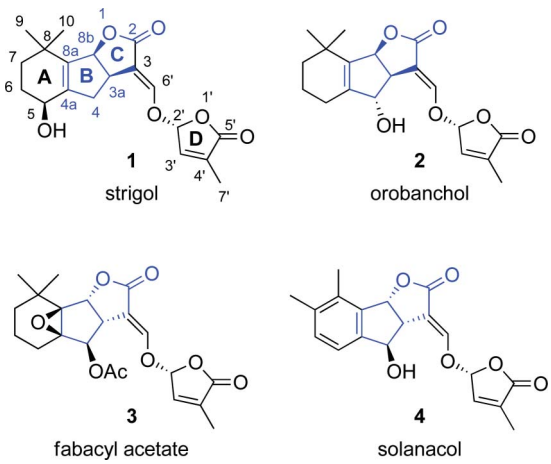
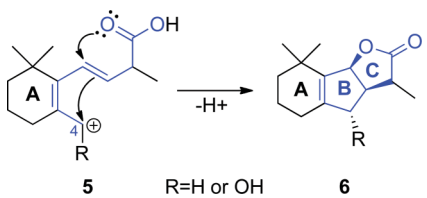


Fig. 1 Select examples of strigolactone natural products.

The structural complexity of these carotenoid-derived natural products, notably the ABC tricyclic ring system, has generated considerable synthetic interest and several strategies have been developed for their construction.[10a,11] To date, however, there seem to have been no efforts to employ a "biomimetic" strategy to build the ABC ring system, such as cation-initiated cyclization, which is widely employed by enzymes such as sesquiterpene and diterpene cyclases.[12] We have examined the feasibility of obtaining the tricyclic skeleton by formation of the B- and C-rings in a single step *via* a cascade cyclization from a linear precursor (Scheme 1), and now report conditions under which this reaction proceeds with high yield and excellent stereocontrol.



Scheme 1 Cascade-based route to the B/C ring system of strigolactones.

Given that many strigolactones, such as orobranchol **2**,[8] fabacyl acetate **3**,[9] and solanacol **4**[10] are oxygenated at C4 (see Fig. 1 for numbering), we examined the reactivity of cations such as **5** (R = OH, Scheme 1) formed by protonation of an aldehyde in the precursor. Accordingly, the methyl esters **12**

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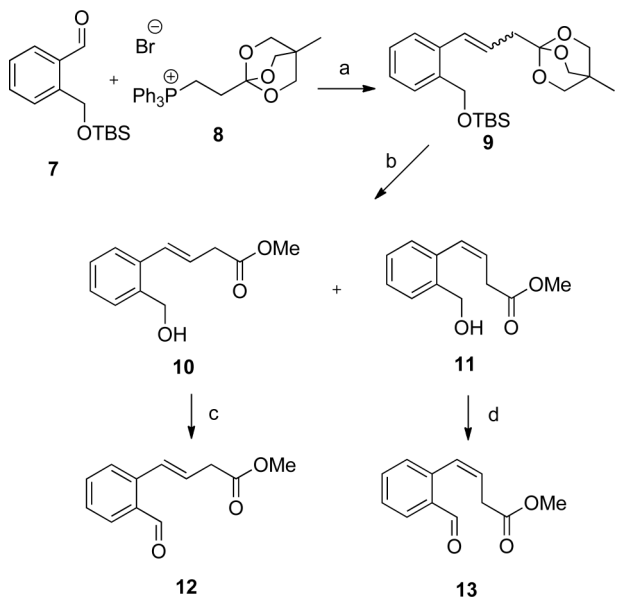
and **13** were prepared in three steps from known precursors (Scheme 2). Thus, the functionalized benzaldehyde **7** was prepared from phthalic anhydride by reduction with lithium aluminium hydride, monoprotection using sodium hydride and *tert*-butyldimethylsilyl chloride, and oxidation with manganese dioxide.[13] The linear cyclization precursors could then be obtained in a straightforward manner by introduction of the ester moiety using a Wittig reaction with **8**[14] followed by deprotection of both the *ortho*-ester and silylether with methanolic sulfuric acid.[14,15] This gave alcohols **10** and **11** as a 1 : 1 mixture, which were separated by flash column chromatography. Subsequent oxidation using pyridinium chlorochromate (PCC) then gave the desired aldehydes **12** and **13** in high yields.[16]



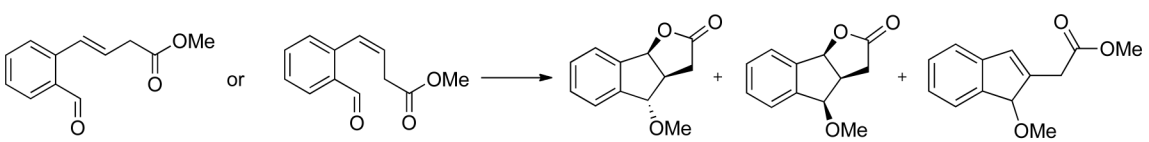
Scheme 2 Synthesis of cyclization precursors. Reagents: (a) LHMDS, THF, 97%, $E:Z = 1:1$; (b) 0.2 M H_2SO_4/MeOH, 66%; (c) PCC, CH_2Cl_2, 93%; (d) PCC, CH_2Cl_2, 93%.

With these two aldehydes in hand, we set out to test the cyclization hypothesis under chemical conditions using both Lewis and Brønsted acids to initiate the cyclization event. When the *trans*-olefin **12** was treated with catalytic Lewis acid, trimethylsilyltriflate (TMSOTf), in dichloromethane at 0 °C, the cyclized products **14** and **15** were produced in an 80 : 20 diastereomeric ratio (60% combined yield) together with 7% of **16**, which was presumably formed *via* a single cyclization event and subsequent deprotonation (entry 1, Table 1). Interestingly, these compounds were produced as methyl ethers by transfer of the methyl group to the C4 hydroxyl, presumably from the methyl ester moiety. The conditions were improved by using catalytic amounts of a protic acid. Thus, when **12** was treated with 0.1 equivalents of TfOH in dichloromethane, **14** and **15** were isolated as a 99 : 1 diastereomeric ratio in 68% combined yield (entry 2). This high ratio favoring the B-ring methyl ether *trans* to the C-ring initially suggested that the products might equilibrate to the most stable diastereomer under the reaction conditions. As a control experiment, diastereomers **14** and **15** were treated under the reaction conditions in both entries 1 and 2 to determine if epimerization of the C4 stereocenter was possible. Even with super-stoichiometric amounts of TMSOTf and TfOH, compounds **14** and **15** were recovered in high yield with no detectable interconversion. Interestingly, when stoichiometric amounts of TMSOTf or TfOH were used to catalyze the cyclization of **12**, the yields were lower than those observed in entries 1 and 2, likely due to decomposition of the substrate.

The *cis*-olefin **13** was also subjected to the cyclization conditions (Table 1, entries 3–5). The reaction was unexpectedly much slower than that of **12** requiring a minimum of 1 equivalent of catalyst to attain a reasonable reaction rate at 0 °C. While the reaction is slower, **13** exclusively gives the *cis*-diastereomer **15** when TMSOTf is employed, albeit in 46% yield along with 2% of **16** (entry 3). With TfOH (entry 4), a 48% yield of **14** and **15**, again favoring **15** in a 13 : 87 diastereomeric ratio, was obtained. When catalytic TMSOTf was used (entry 5), the reaction was slow, even at room temperature, but a mixture of **14** and **15** in a 30 : 70 ratio was obtained in a higher yield (68%).

A probable reaction mechanism is shown in Scheme 3. In this model, oxocarbenium ion **17** is formed by protonation of the aldehyde oxygen. At this stage, the substrate may form both the B- and C-rings in a single concerted step (**17**→**19**), but a stepwise mechanism is necessary to explain the formation of **16**. Cyclization of the olefin in **17** by addition to the C4 oxocarbenium ion produces the benzylic cation **18** which could further cyclize forming the C-ring (path a) or eliminate to form **20** (path b). Demethylation

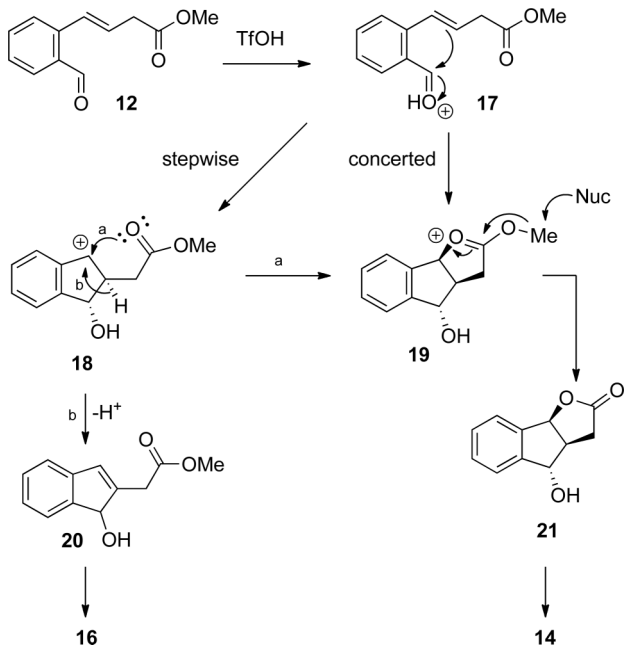
Table 1 Cyclization studies



12 **13** (±)-**14** (±)-**15** **16**

Entry	Substrate	Conditions	Yield[a] **14**+**15** (Ratio[b] **14** : **15**)	Yield **16**[a] (%)
1	**12**	TMSOTf (0.2 eq.), DCM, 0 °C, 2 h	60 (80 : 20)	7
2	**12**	TfOH (0.1 eq.), DCM, −78 °C, 1 h then 0 °C, 3 h	68 (99 : 1)	2
3	**13**	TMSOTf (1 eq.), DCM, 0 °C, 10 min then rt, 6.5 h	46 (0 : 100)	2
4	**13**	TfOH (1.1 eq.), DCM, −78 °C, 1 h then 0 °C, 2.5 h	48 (13 : 87)	0
5	**13**	TMSOTf (0.2 eq.), DCM, 0 °C, 3 h then rt 22h	68 (30 : 70)	3

[a] Isolated yield. [b] The ratio was determined by ^{1}H NMR.



Scheme 3 Mechanistic hypothesis for the cyclization reaction.

of **19** may occur by alkylation of a variety of nucleophilic species present in solution such as alcohols **20** or **21**. Under these catalytic conditions, the methylated tricyclic strigolactone core **14** is thus obtained and the acid catalyst regenerated.

Standard density functional theory (DFT) calculations using the B3LYP functional[17] as implemented in the *Gaussian03* software package[18] were employed to investigate the origin of the stereoselectivity observed in the acid-catalyzed cascade cyclization (see the ESI for computational details†). Transition states associated with attack of the double bond on the protonated aldehyde moiety were located as these define the relative stereochemistry of the product if the reaction is under kinetic control. It was found that for both *trans*-olefin **12** and *cis*-olefin **13** the cyclization could be either concerted (with the formation of both the B and the C rings at the same time) or stepwise. The difference in the energy between the two mechanisms is quite small.

The four lowest-lying transition states corresponding to those for cyclization of either the *trans*-olefin **12** or the *cis*-olefin **13** to each of the two possible diastereomeric products are shown in Fig. 2. The relative energies of these transition states provide a qualitative explanation of the observed cyclization stereoselectivity. The origin of the selectivity appears to arise from the degree of deviation of the protonated aldehyde moiety from co-planarity with the aromatic ring. In the energetically favored transition states ($TS_{12\rightarrow14}$ and $TS_{13\rightarrow15}$), small deviations from planarity are observed (~35°). On the other hand, in order to reduce steric repulsion between the protonated aldehyde oxygen and the attacking olefin, the formation of the *cis* isomer **15** from the *trans*-olefin **12** ($TS_{12\rightarrow15}$) and of the *trans* isomer **14** from the *cis*-olefin **13** ($TS_{13\rightarrow14}$) requires a higher deviation from co-planarity in the transition states with the aldehyde nearly perpendicular to the aromatic ring (~85° and ~75° dihedral angles, respectively).

In order to estimate the energetic contribution of this deviation to the increased activation energy barrier, the rotational barrier of protonated benzaldehyde was calculated (Fig. 3). Although previous computational work was reported by Setia and Formosinho in 1988,[19a] for consistency the barrier was calculated using identical methods to those used in locating the cyclization transition states. In this case, the barrier to rotation was found to be quite high (24 and 21 kcal mol^{-1} in gas phase and in dichloromethane, respectively), which is consistent with the differences in the energies obtained for the cyclization transition states.

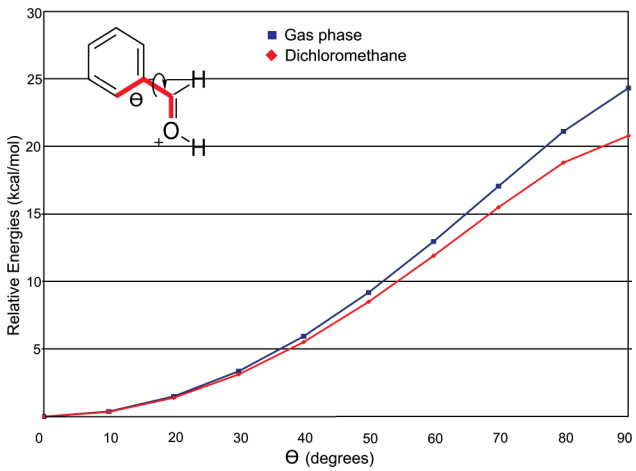


Fig. 3 Calculated rotational barriers for protonated benzaldehyde.

The successful demonstration of the cation-induced cascade cyclization outlined here not only represents a novel approach for constructing a similar ABC tricyclic ring system to that found in solanacol (**4**) from simple aldehyde precursors, but also raises the possibility that a similar reaction might be catalyzed by a single cyclase in the biosynthetic pathway leading to strigolactones. Indeed, such a hypothesis would greatly simplify literature proposals for the biosynthetic origins of strigolactones, which have invoked highly reactive intermediates or unusual chemical transformations in order to rationalize experimental observations.[6,20] Although

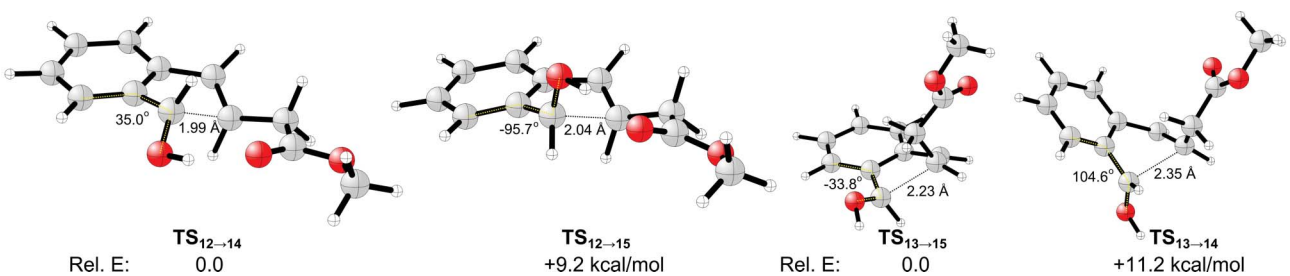


Fig. 2 Calculated transition states and relative energies for the cyclization of **12** and **13** initiated by protonation.

there is no direct evidence to rule out complicated chemical transformations in strigolactone biosynthesis, the chemical feasibility of constructing the ABC ring system from a linear aldehyde precursor makes new predictions for intermediates that might be tested in future feeding experiments and *in vitro* screening studies of recombinant enzymes that are implicated in strigolactone biosynthesis. Efforts to utilize this method in the synthesis of the ABC ring system of aliphatic strigolactones, such as orobanchol (**2**), are currently underway and will be reported in due course.

Acknowledgements

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