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Spirolactone syntheses through a rhodium-catalyzed intramolecular C–H insertion reaction: model studies towards the synthesis of syringolides ☆

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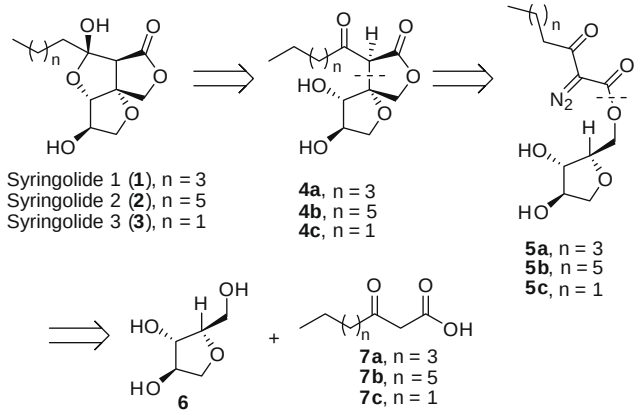
ABSTRACT

Model studies towards the total synthesis of syringolides using a rhodium-catalyzed intramolecular C–H insertion reaction as the key step are described. A highly stereospecific synthesis of spirolactones is achieved employing this methodology.

The syringolides are a family of nonproteinaceous specific elicitors of the hypersensitive response (HR) of plants, an active mechanism of defense that involves cell death in the site of infection, and a complex series of biochemical changes in the plant that restrict the pathogen's proliferation, allowing the plant to resist pathogen infection.[2] In 1993 Sims and co-workers[3] reported the isolation of syringolide 1 (**1**) and syringolide 2 (**2**), which are bacterial signal molecules (elicitors) produced by the avirulence gene D (*avrD*) of *Pseudomonas syringae* pv. *tomato*. The syringolides elicit a HR on soybean cultivars carrying the resistance gene *Rpg4*. Through a combination of NMR experiments and X-ray crystallography, Sims determined the structures of syringolides as illustrated in Scheme 1. Syringolides have attracted a great deal of attention from the synthetic community. Since Wood's first report[4], there have been ten total syntheses of syringolides 1 and 2[5] and two formal ones.[6] We recently reported the first synthesis of syringolide 3.[7]

In 1995, Doyle and Dyatkin[8] reported the use of a regioselective intramolecular carbon–hydrogen insertion reaction to access spirolactones akin to those found in the syringolide core. Thus, with an interest in improving the syringolide synthesis, a new approach using a C–H insertion as the key step was devised. Accordingly the retrosynthetic analysis shown in Scheme 1 was conceived. As illustrated, the hemiacetals of syringolides (**1–3**) were envisioned to arise via intramolecular ring closure from ketones **4a–c**. The spirolactone rings in **4a–c** would arise from an intramolecular C–H insertion reaction applied to the α-diazoesters **5a–c**. The requisite α-diazoesters **5a–c** would be synthesized by acylation of a primary alcohol such as **6** with the corresponding β-ketoacids **7a–c**, followed by a diazo transfer reaction.

Rather than synthesizing advanced intermediates **5a–c**, it was decided to first explore the C–H insertion key step with a series of model systems where the lateral chain and the *trans* diol would



Scheme 1. Syringolides retrosynthetic analysis.

☆ Portions of this work have appeared as a thesis dissertation.

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be masked with suitable precursors. When treated with a rhodium(II) catalyst such as $Rh_2(OAc)_4$, these precursors would be expected to undergo the desired intramolecular C–H insertion[8] producing the corresponding model spirolactones.

To fully explore how electronics, sterics, and substitution parameters impact the success of the C–H insertion we decided to investigate several classes of substituted diazo acetates: aryl (Table 1), vinyl (Table 2), H (Table 3), and β-carbonyl (Figure 2). Each one of the resulting C–H insertion products could be advanced to the target structures. Additionally, the diol-coupling partner was used as is or masked either as a protected *trans* diol or an olefin. To assess reactivity of the various side chains towards C–H insertion chemistry, the parent tetrahydrofuran was also included in our model studies.

Table 1
C–H insertions using aryl diazoacetates[9] (yield)

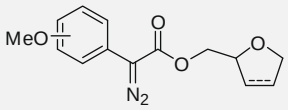
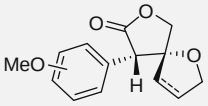
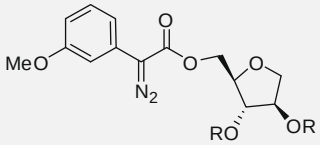
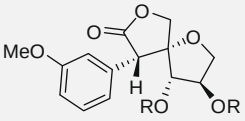
Diazo Compound	C-H insertion product
	
8 *meta*; tetrahydrofuranyl (81%) **9** *meta*; dihydrofuranyl (78%) **10** *para*; dihydrofuranyl (43%)	**15** *meta*; tetrahydrofuranyl (85%) **16** *meta*; dihydrofuranyl (73%) **17** *para*; dihydrofuranyl (63%)
	
11 R = TBS (67%) **(+)-12** R = Bn (79%) **13** R = Me (32%) **14** R = OH (44%)	**18** R = TBS (36%) **(-)-19** R = Bn (15%) **20** R = Me (0%) **21** R = OH (0%)

Table 2
C–H insertions using vinyl diazoacetates[9] (yield)

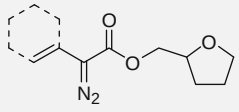
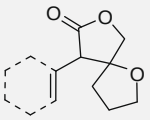
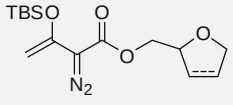
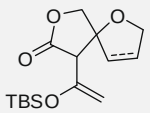
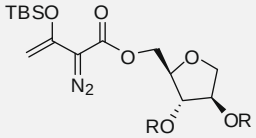
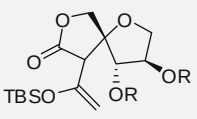
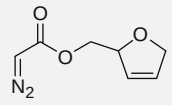
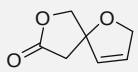
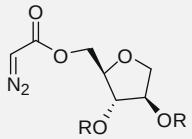
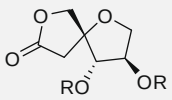
Diazo Compound	C-H insertion product
	
22 vinyl (34%) **23** cyclohexenyl (70%)	**29** vinyl (36%) **30** cyclohexenyl (51%)
	
24 tetrahydrofuranyl (100%) **25** dihydrofuranyl (98%)	**31** tetrahydrofuranyl (18%) **32** dihydrofuranyl (13%)
	
26 R = TBS (100%) **(+)-27** R = Bn (93%) **28** R = Me (87%)	**33** R = TBS (0%) **34** R = Bn (0%) **35** R = Me (0%)

Table 3
C–H insertions using diazoacetates[9] (yield)

Diazo Compound	C-H insertion product
	
36 (52%)	**40** (0%)
	
37 R = TBS (82%) **38** R = Me (68%) **(+)-39** R = Bn (84%)	**41** R = TBS (69%) **42** R = Me (54%) **(+)-43** R = Bn (7%)

Tables 1–3 and Figure 2 depict all the C–H insertion experiments performed.[9] In the cases where the reaction conditions failed to promote the formation of the desired spirolactone, an intractable mixture of compounds was produced instead. Whenever two diastereomers could be formed in the C–H insertion reaction, only one was observed by ^1H NMR.

Table 1 shows the C–H insertion results when aryl diazoacetates are employed. The α-diazoesters **8**–**13** required for the desired intramolecular C–H insertion reactions were synthesized by acylation of an alcohol[10] followed by a diazo transfer reaction.[11] For the synthesis of **14**, the parent ester of **11** was desilylated and then in one pot the corresponding diol underwent transient protection with 2-methoxypropene, diazo transfer, and finally diol deprotection. These electron-rich activated diazoacetates gave the best insertion results when tetrahydro and dihydrofuranyl rings were used (**8–10**). However, when either the protected or unprotected *trans*-diol substrates were used the reaction worked very poorly (**11–12**) or not at all (**13–14**). Interestingly, single-crystal X-ray analysis of C–H insertion products established that spirolactones **15–18**[12] all possessed the same relative stereochemistry (i.e., the tetrahydrofuranyl oxygen and the proton α to the lactone carbonyl were always oriented *anti* about the lactone ring, Fig. 1). This is the thermodynamically more favorable product, which positions the sterically hindered side chain on the same side as the tetrahydrofuranyl oxygen. By analogy, it is believed that **19** and **29–32** (Tables 1 and 2) also have the same relative stereochemical configuration. Although this relative configuration is opposite to that needed for the synthesis of the syringolides (cf. **3** to **18**), the potential epimerizability of the α-center renders the stereochemical outcome secondary in importance compared to the formation of the C–C bond.

Table 2 presents C–H insertion results using vinyl diazoacetates. Vinyldiazocarboxylate **22** was obtained as **8**–**13** while **23** was prepared from the corresponding diazoacetate[8] and cyclohexanone via the two-step condensation-dehydration procedure developed by Padwa and co-workers.[13] 2-Diazo-3-[(*t*-butyldimethylsilyl)oxy]-3-butenoates **24–28** were obtained by silylation of the corresponding diazoacetoacetates. In these experiments we observed the same trend as for Table 1, with the tetrahydro and dihydrofuranyl rings (**22–25**) producing the desired C–H insertion products while the more sterically demanding protected *trans*-diol moieties (**26–28**) failed to form the corresponding spirolactones. As for these electron-rich side chains, the vinylic diazoacetates did not work as well (**29–30**) as their methoxyphenyl counterparts of Table 1, and when a 2-diazo-3-[(*t*-butyl-dimethylsilyl)oxy]-3-butenoate was used instead of a simple alkene the yields of the C–H insertion product dramatically declined (**31–32**) or the reaction did not take place at all (**33–35**).

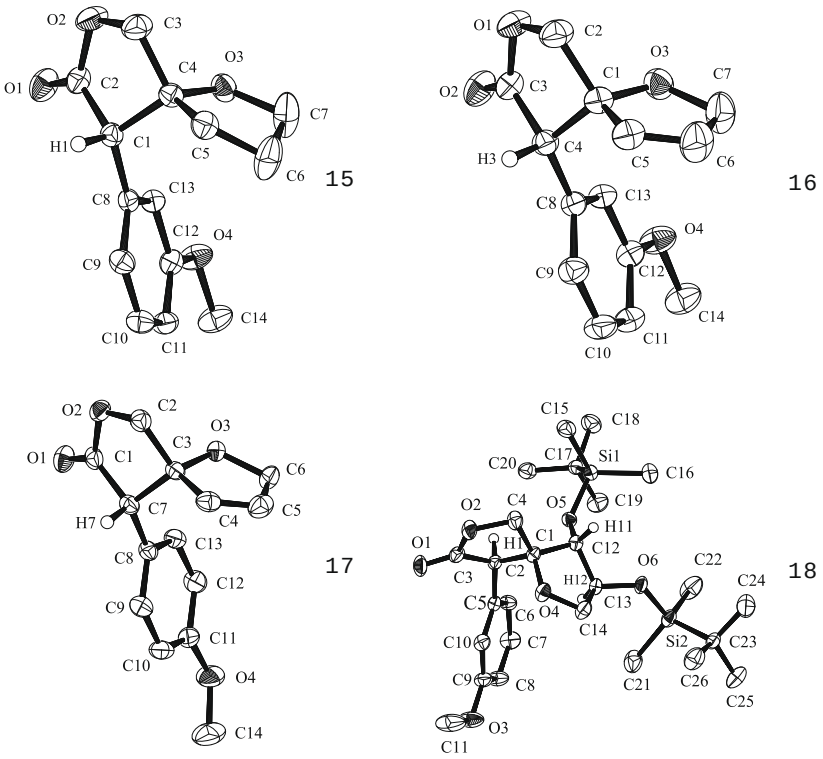


Figure 1. ORTEP plot of C–H insertion product.

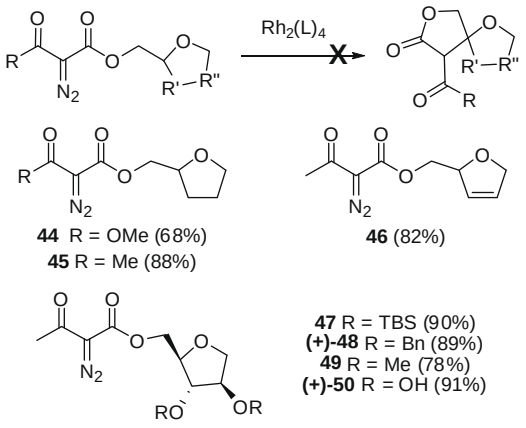


Figure 2. Unsuccessful β-oxo side-chain C–H insertions[9] (yield of diazotransfer).

Table 3 depicts C–H insertion results for diazoacetates. These diazoacetates **36–39** were obtained by deacylation of the corresponding diazoacetoacetates. This less sterically hindered side chain gave very different results than the vinyl and methoxyphenyldiazoacetates. Thus, the substrate with the dihydrofuranyl ring (**36**), unlike Doyle's tetrahydrofuranyl analog,[8] did not give the desired C–H insertion product probably due to competing detrimental reaction pathways such as dimerization of the substrate, cyclopropanation of the double bond, or the formation of an oxonium ylide. However this diazoacetate side chain allowed the expected spirolactones in good yields when the *trans*-diol group was TBS (**41**) or methyl (**42**) protected. Interestingly, when a benzyl-protecting group was employed the yield plumbeted [**(+)-43**].

Finally, Figure 2 shows substrates with a β-oxo side chain. Interestingly and regardless of the nature of the ring moiety, all substrates in this electron-withdrawing structure class fail in the C–H insertion reaction. Diazomalonate **44** was obtained by acylation of tetrahydrofurfuryl alcohol with methyl malonyl chloride in the presence of pyridine[14] followed by diazotransfer.[7,11] Diazoacetoacetates **45**–**50** were obtained by treating the corresponding alcohols with diketene in the presence of DMAP[15] followed by a diazotransfer reaction.[7,11,16] Unfortunately neither the diazomalonate nor the diazoacetoacetates showed the ability to yield the desired spirolactones.

Throughout these experiments we discovered that when a tetrahydrofuranyl ring moiety is used for the C–H insertion reaction the electron-rich 3-methoxyphenyl-acetate side chain gives the best results (**15**). The electronically similar vinyl diazoacetates **22–23** also produce the desired spirolactones but the yields are significantly lower. In contrast, when a side chain with an electron-withdrawing group was used, that is, diazomalonate **44** and diazoacetate **45**, the reaction did not take place. Doyle and Dyatkin had previously shown that the reaction works well with the unsubstituted diazoacetate.[8] A similar trend was observed when using the dihydrofuranyl ring moiety, with the best results obtained when using the electron-rich 3- and 4-methoxyphenylacetate side chains (**9** and **10**). Poor yields were obtained with vinyldiazoacetate **25** and no product was obtained when using the electron-withdrawing diazoacetate **46**. The unsubstituted diazoacetate **36** also failed to give the desired C–H insertion product as previously discussed.

Interestingly, when using the protected or unprotected *trans*-diol ring moieties sterics seemed to play a more important role than electronics in the C–H insertion reaction, with the most sterically hindered rings giving better yields in combination with the least sterically hindered side chains. Thus, the best results were observed when an unsubstituted diazoacetate was used with a TBS- or methyl-protected diol (**37** and **38**) although the benzyl analog **(+)-39** gave poor yields probably due to side reactions between the diazo functionality and the benzylic or aromatic positions of

the protecting group. The electron-rich 3-methoxyphenylacetate side chains also gave the best results with the TBS-protected diol (**11**) than with the benzyl-protected one [**(+)-12**] although the yields were significantly lower than those for the unsubstituted diazoacetate. In these cases the methyl-protected diol **13** and the transiently protected diol **14** failed to give the desired spirolactones. Vinyldiazoacetate side chains **26–28** and the electron-withdrawing acetoacetates **47–50** similarly failed to produce the expected C–H insertion product.

It is worthy of notice that a highly stereospecific synthesis of spirolactones was achieved since in all the cases where two diastereomers could be obtained we only produced one and we believe this methodology could potentially be employed in the assembly of other synthetically useful compounds.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.126.

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9. C–H insertion reaction conditions for all diazo compounds: To a suspension of $Rh_2(OAc)_4$ (1.2–0.5% equiv) in CH_2Cl_2 at reflux was added dropwise (over a 10 h period via syringe pump) a solution of the diazo compound in CH_2Cl_2. $Rh_2(TFA)_4$ was also tried with **14** and $Rh_2(cap)_4$ with **36**.
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12. The atomic coordinates for structures **3** and **15**–**18** have been deposited with the Cambridge Crystallographic Data Centre: Navarro Villalobos, Mauricio. Thesis[1] deposition to the Cambridge Structural Database; (a) **3**, deposition number CCDC 150205; (b) **15**, CCDC 150207; (c) **16**, CCDC 150206; (d) **17**, CCDC 150209; (e) **18**, CCDC 150208.
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