Tetrahedron Letters 50 (2009) 6450-6453

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet



Mauricio Navarro Villalobos *, John L. Wood †

Sterling Chemistry Laboratory, Yale University, New Haven, CT 06520-8107, USA

ARTICLE INFO

ABSTRACT

achieved employing this methodology.

Article history: Received 31 July 2009 Revised 26 August 2009 Accepted 27 August 2009 Available online 2 September 2009

Keywords: Syringolides Spirolactones C-H insertion Rhodium(II) stabilized carbene Stereospecific

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-workers³ 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 report⁴, there have been ten total syntheses of syringolides 1 and 2⁵ and two formal ones.⁶ We recently reported the first synthesis of syringolide 3.7

In 1995, Doyle and Dyatkin⁸ 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.

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

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.





© 2009 Elsevier Ltd. All rights reserved.

 $^{^{\}star}$ Portions of this work have appeared as a thesis dissertation.

^{*} Corresponding author at present address: Cornell University, Department of Chemistry & Chemical Biology, Baker Laboratory, Ithaca, NY 14853, USA. Tel.: +1 607 255 3001; fax: +1 607 255 4137.

E-mail addresses: navarro@aya.yale.edu, mn382@cornell.edu, mnavarrovillalobos@gmail.com (M. Navarro Villalobos).

 $^{^\}dagger$ Present address: Chemistry Department, Colorado State University, Fort Collins, CO 80523, USA.

^{0040-4039/\$ -} see front matter \odot 2009 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2009.08.126

be masked with suitable precursors. When treated with a rhodium(II) catalyst such as Rh₂(OAc)₄, these precursors would be expected to undergo the desired intramolecular C–H insertion⁸ 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 diazoacetates⁹ (yield)



Table 2C-H insertions using vinyl diazoacetates9 (yield)



Table 3

C-H insertions using diazoacetates⁹ (yield)



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 alcohol¹⁰ 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 15-18¹² 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 diazoacetate⁸ 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-I(tbutyl-dimethylsilyl)oxyl-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 insertions⁹ (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 pyridine¹⁴ followed by diazotransfer.^{7,11} Diazoacetoacetates **45–50** were obtained by treating the corresponding alcohols with diketene in the presence of DMAP¹⁵ 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 electronwithdrawing 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 TBSor 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

This work was supported by Yale University and was performed in the W6 laboratories of Professor John L. Wood under his leadership. The Camille and Henry Dreyfus Foundation (NF-93-0) and the American Cancer Society (JFRA-523) provided additional support through their Junior Faculty Award programs. Dr. Navarro would like to thank Professor Jón T. Njarðarson for useful comments when preparing this Letter.

Supplementary data

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

References and notes

- 1. Navarro Villalobos, M. Ph.D. Dissertation, Yale University, 2000.
- (a) Keen, N. T. Adv. Bot. Res. 1999, 30, 291–328; (b) Strange, R. N. Sci. Prog. 1998, 81, 35–68; (c) Heath, M. C. Eur. J. Plant. Pathol. 1998, 104, 117–124; (d) Staskawicz, B. J.; Ausubel, F. M.; Baker, B. J.; Ellis, J. G.; Jones, J. D. G. Science 1995, 268, 661–667; (e) Keen, N. T. In Mechanisms of Plant Defense Responses; Fritig, B., Legrand, M., Eds.; Kluwer Academic: Boston, 1993; pp 3–11; (f) Keen, N. T. Plant Mol. Biol. 1992, 19, 109–122; (g) Keen, N. T. Annu. Rev. Genet. 1990,

24, 447–463; (h) Lamb, C. J.; Lawton, M. A.; Dron, M.; Dixon, R. A. *Cell* **1989**, *56*, 215–224; (i) Gianinazzi, S.. In *Plant–Microbe Interactions*; Kosuge, T., Nester, E. W., Eds.; Macmillan: New York, 1984; Vol. 1, Chapter 13,.

- (a) Smith, M. J.; Mazzola, E. P.; Sims, J. J.; Midland, S. L.; Keen, N. T.; Burton, V.; Stayton, M. M. *Tetrahedron Lett.* **1993**, *34*, 223–226; (b) Midland, S. L.; Keen, N. T.; Sims, J. J.; Midland, M. M.; Stayton, M. M.; Burton, V.; Smith, M. J.; Mazzola, E. P.; Graham, K. J.; Clardy, J. J. Org. Chem. **1993**, *58*, 2940–2945.
 - Wood, J. L.; Jeong, S.; Salcedo, A.; Jenkins, J. J. Org. Chem. 1995, 60, 286-287.
- (a) Kuwahara, S.; Moriguchi, M.; Miyagawa, K.; Konno, M.; Kodama, O. *Tetrahedron Lett.* **1995**, *36*, 3201–3202; (b) Kuwahara, S.; Moriguchi, M.; Miyagawa, K.; Konno, M.; Kodama, O. *Tetrahedron* **1995**, *51*, 8809–8814; (c) Ishihara, I.; Sugimoto, T.; Murai, A. *Synlett* **1996**, 335–336; (d) Ishihara, I.; Sugimoto, T.; Murai, A. *Tetrahedron* **1997**, *53*, 16029–16040; (e) Henschke, J. P.; Rickards, R. W. *Tetrahedron Lett.* **1996**, *37*, 3557–3560; (f) Henschke, J.; Rickards, R. W. *Labelled Cpd. Radiopharm.* **1998**, *41*, 211–220; (g) Honda, T.; Mizutani, H.; Kanai, K. J. Org. Chem. **1996**, *61*, 9374–9378; (h) Zeng, C-M.; Midland, S. L.; Keen, N. T.; Sims, J. J. J. Org. Chem. **1997**, *62*, 4780–4784; (i) Yu, P.; Wang, Q.-G.; Mak, T. C. W.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1783–1788; (j) Wong, H. N. C. Chin. J. Chem. **2005**, *23*, 1106–1108; (k) Chênevert, R.; Dasser, M. Can. J. Chem. **2000**, *78*, 275–279; (l) Chênevert, R; Dasser, M. J. Org. Chem. **2000**, *65*, 4529–4531; (m) Varvogli, A.-A. C.; Karagiannis, I. N.; Koumbis, A. E. Tetrahedron **2009**, *65*, 1048–1058.
- (a) Yoda, H.; Kawauchi, M.; Takabe, K.; Hosoya, K. Heterocycles **1997**, 45, 1895– 1898; (b) Di Florio, R.; Rizzacasa, M. A. Aust. J. Chem. **2000**, 53, 327–331.
- Navarro Villalobos, M.; Wood, J. L.; Jeong, S.; Benson, C. L.; Zeman, Z. L.; McCarty, C.; Weiss, M. M.; Salcedo, A.; Jenkins, J. *Tetrahedron* 2009, 65, 8091– 8098.
- 8. Doyle, M. P.; Dyatkin, A. B. J. Org. Chem. 1995, 60, 3035-3038.
- C-H insertion reaction conditions for all diazo compounds: To a suspension of Rh₂(OAc)₄ (1.2–0.5% equiv) in CH₂Cl₂ at reflux was added dropwise (over a 10 h period via syringe pump) a solution of the diazo compound in CH₂Cl₂. Rh₂(TFA)₄ was also tried with 14 and Rh₂(cap)₄ with 36.
- (a) Neises, B.; Steglich, W. Angew. Chem., Int. Ed. Engl. 1978, 7, 522–523; (b) Hassner, A.; Alexanian, V. Tetrahedron Lett. 1978, 19, 4475–4478.
- 11. Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. Synth. Commun. 1987, 17, 1709–1716.
- The atomic coordinates for structures 3 and 15–18 have been deposited with the Cambridge Crystallographic Data Centre: Navarro Villalobos, Mauricio. Thesis¹ 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.
- (a) Padwa, A.; Kulkarni, Y. S.; Zhang, Z. J. Org. Chem. **1990**, 55, 4144–4153; (b) Pelliciari, R.; Natalini, B.; Sadeghpour, B. M.; Marinozzi, M.; Snyder, J. P.; Williamson, B. L.; Kuethe, J. T.; Padwa, A. J. Am. Chem. Soc. **1996**, *118*, 1–12.
- 14. Box, V. G. S.; Marinovic, N.; Yiannikouros, G. P. Heterocycles 1991, 32, 245–251.
- Nudelman, A.; Kelner, R.; Broida, N.; Gottlieb, H. E. Synthesis **1989**, 387–388.
 Taber, D. F.; Ruckle, R. E., Ir.; Hennessy, M. I. J. Org. Chem. **1986**, 51, 4077–4078
- 16. Taber, D. F.; Ruckle, R. E., Jr.; Hennessy, M. J. J. Org. Chem. 1986, 51, 4077–4078. Caution: These authors mention MsN₃ is potentially explosive. For safety reasons most diazo transfers were performed using p-ABSA.¹¹.