Communications

Total Syntheses of (+)- and (−)-Syringolides 1 and 2

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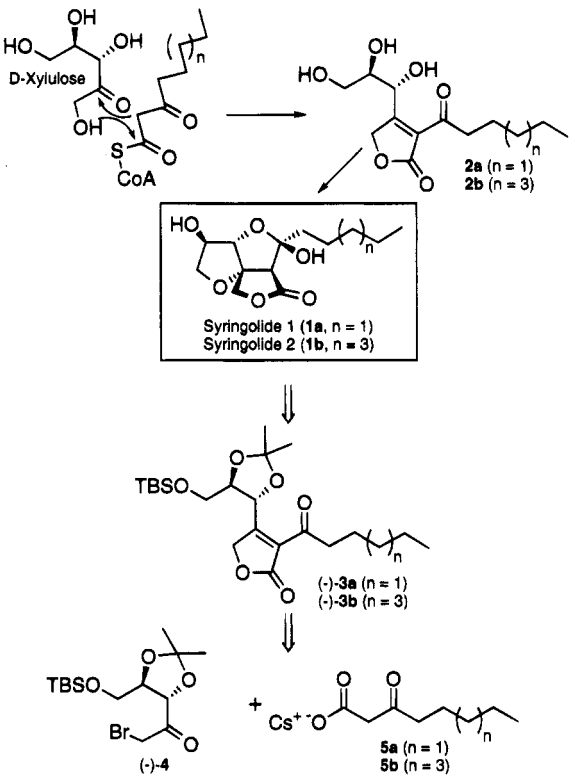
The identification of receptors for microbial signals, "the goal that looms largest" in plant molecular biology,[2] should lead to cloning of disease-resistance genes and the prospect of immunization through molecular genetic manipulation. Viable approaches to the cloning problem include gene tagging, shotgun cloning, chromosome walking, and the use of molecular probes to tag or immobilize the resistance gene product.[3] The latter strategy requires a ligand for the gene product (i.e., an elicitor) which can be converted to a probe molecule without loss of its binding affinity. In 1993, Keen and co-workers reported the structures of two small molecules which appear to be ideally suited for fashioning into such probes.[4]

Syringolides 1 and 2 (**1a** and **1b**), produced by *Pseudomonas syringae* pv. *tomato*, elicit a hypersensitive defense response (HR) in specific soybean cultivars.[5] The activity of both syringolides implicates the oxygen-rich tricyclic core as the recognition element and suggests that the aliphatic side chain could serve as a point of attachment to the polymer support in an affinity-matrix isolation procedure. Herein we report a concise biomimetic asymmetric synthesis of the syringolides which is readily amenable to the construction of analogs containing various aliphatic side chains.

The absolute stereochemistry illustrated in Scheme 1 was postulated by Smith and Mazzola, based upon an assumed biosynthetic pathway involving the condensation of an appropriate β-dicarbonyl unit with D-xylulose.[4] Intrigued by the possibility that the biosynthesis may require an avirulence gene product that simply mediates the condensation of two common bacterial metabolites, we designed an approach proceeding via cyclization of **2**. It was envisioned that this putative biosynthetic intermediate would derive from deprotection of butenolide **3** which, in turn, would arise via condensation of α-bromo ketone **4** with an appropriate β-keto carboxylate (**5**). In addition to establishing the ability of **2** to undergo cyclization to **1**, the successful implementation of this strategy would provide access to syringolides 1 and 2 and numerous analogs simply by altering the dicarbonyl reactant. All stereochemical information would be retained in the common advanced intermediate **4**, which would be generated from 2,3-*O*-isopropylidenethreitol.[6]

Scheme 1



Monoprotection of (+)-2,3-*O*-isopropylidene-L-threitol (**6**) under the conditions developed by McDougal (NaH, TBSCl, THF) furnished silyl ether (−)-**7**[7] in 65% yield (Scheme 2).[8] Conversion of (−)-**7** to α-diazo ketone (−)-**8**[7] was effected via a three-step sequence without purification of the intermediates.[9] Bromination of (−)-**8** with anhydrous ethereal HBr at −78 °C then provided (−)-**4**[7] in good yield. As the versatility of the scheme would rely upon the efficient conversion of **4** to various acyl butenolides, we were delighted to find that (−)-**3a**[7] and (−)-**3b**[7]

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(2) Long, S. R.; Staskawicz, B. J. *Cell* **1993**, *73*, 921.

(3) (a) Ellis, J. G.; Lawrence, G. J.; Peacock, W. J.; Pryor, A. J. *Ann. Rev. Phytopathol.* **1988**, *26*, 245. (b) For the successful isolation of a resistance gene from *Arabidopsis thaliana*, see: Bent, A. F.; Kunkel, B. N.; Dahlbeck, D.; Brown, K. L.; Schmidt, R.; Giraudat, J.; Leung, J.; Staskawicz, B. J. *Science* **1994**, *265*, 1856.

(4) (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. (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.

(5) (a) Keen, N. T.; Tamaki, S.; Kobayashi, D.; Stayton, M.; Gerhold, D.; Shen, H.; Gold, S.; Lorang, J.; Thordal-Christensen, H. In *Signal Molecules in Plants and Plant-Microbe Interactions*; Lugtenberg, B. J. J., Ed.; Springer-Verlag: Berlin, 1989; pp 183–188. (b) Keen, N. T.; Tamaki, S.; Kobayashi, D.; Gerhold, D.; Stayton, M.; Shen, H.; Gold, S.; Lorang, J.; Thordal-Christensen, H.; Dahlbeck, D.; Staskawicz, B. *Mol. Plant-Microbe Interact.* **1990**, *3*, 112. (c) Keen, N. T.; Buzzell, R. I. *Theor. Appl. Genet.* **1991**, *81*, 133. (d) Keen, N. T. *Plant Mol. Biol.* **1992**, *19*, 109.

(6) (a) Both antipodes of 2,3-*O*-isopropylidenethreitol are available commercially in enantiomerically pure form. The material used in these syntheses (98% ee)[6b] was prepared from (+)- and (−)-tartaric acid via a procedure reported by Mash.[6c] (b) Determined via 500 MHz ^{1}H NMR analysis of the (+)- and (−)-Mosher esters derived from **7**; see: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (c) Mash, E. A.; Nelson, K. A.; Van Deusen, S.; Hemperly, S. B. *Org. Synth.* **1989**, *68*, 92.

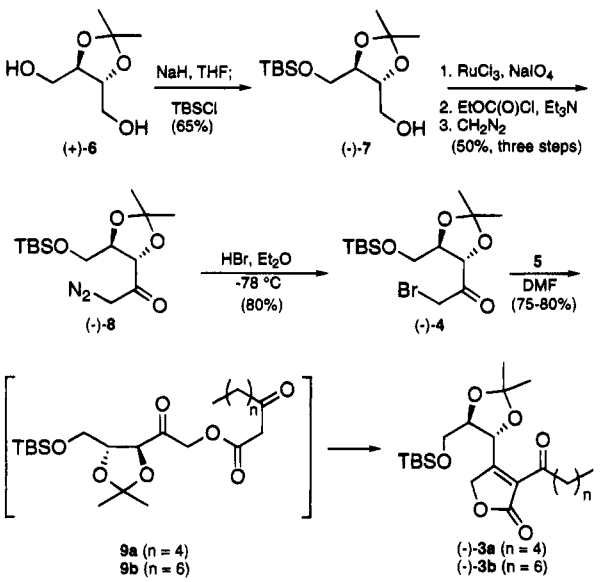
(7) The structure assigned to each new compound is in accord with its infrared and high-field ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry.

(8) McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.

(9) (a) Oxidation: Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) α-Diazo ketone: Coggins, J. R.; Kray, W.; Shaw, E. *Biochem. J.* **1974**, *138*, 579.

0022-3263/95/1960-0286$09.00/0

Scheme 2



could readily be assembled by treating (−)-**4** with the respective cesium carboxylates **5a**[10] and **5b**[10] in DMF (75−80% yields).[11] The intermediate esters **9a** and **9b** were not detected.

With **3** in hand the cyclization of the putative biosynthetic triol **2** to the natural product could be investigated. In the event, exposure of (−)-**3a** to HCl in THF (4 h, 25 °C) produced (−)-syringolide 1 in 15% yield, accompanied by three other products.[12,13] Analogous experiments employing (+)-**3a** and (+)- and (−)-**3b** produced (+)-syringolide 1 and (+)- and (−)-syringolide 2.[14] The known absolute stereochemistry of (+)-**6**, progenitor of the synthetic (−)-syringolides, confirms the absolute stereochemistry postulated by Smith and Mazzola.

To date, application of the described synthetic strategy has allowed incorporation of aliphatic chains suitable for both catalytic tritiation and attachment to a polymer support. These experiments, as well as detailed studies on the cyclization of **3** and our efforts to isolate the syringolide binding protein, will be reported in due course.

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Supplementary Material Available: Complete spectral data for compounds **3**, **4**, **7** and **8** and ^{1}H NMR comparison plot of natural and synthetic **1b** (16 pages).

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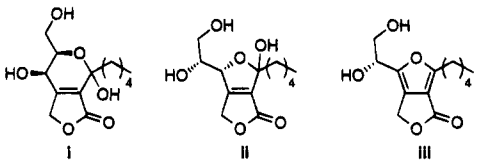
(10) (a) Prepared by treatment of the corresponding acid[10b] with 1.15 equiv of Cs_2CO_3. (b) Cook, L.; Ternai, B.; Ghosh, P. *J. Med. Chem.* **1987**, *30*, 1017.

(11) For butenolide formation employing a dihydroxyacetone derivative, see: Sakuda, S.; Tanaka, S.; Mizuno, K.; Sukcharoen, O.; Nihira, T.; Yamada, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2309.

(12) (+)-**3a** and (+)-**3b** were prepared as outlined in Scheme 2 employing (−)-2,3-*O*-isopropylidene-D-threitol[6] as the point of departure.

(13) The reaction mixture contained nearly equal amounts of four products. Whereas only 1 has been unambiguously characterized, spectral data also suggest the presence of hemiacetals **i** and **ii** and furan **iii**. Diastereomers of **1** were not detected.



(14) Synthetic (−)-syringolide 2 was identical in all respects with a sample derived from natural sources. The latter was kindly provided by Dr. Mitchell J. Smith (U.S. Food and Drug Administration).