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Total Syntheses of the Phytotoxic Lactones Herbarumin I and II and a Synthesis-Based Solution of the Pinolidoxin Puzzle

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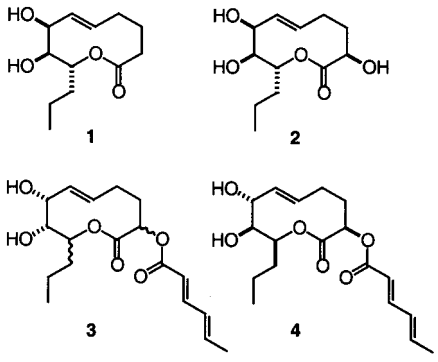
Abstract: A concise approach to a family of potent herbicidal 10-membered lactones is described on the basis of ring-closing metathesis (RCM) as the key step for the formation of the medium-sized ring. This includes the first total syntheses of herbarumin I (**1**) and II (**2**) as well as the synthesis of several possible macrolides of the pinolidoxin series. A comparison of their spectral and analytical data with those of the natural product allowed us to establish the stereostructure of pinolidoxin, a potent inhibitor of induced phenylalanine ammonia lyase (PAL) activity, as shown in **46**. This finding, however, makes clear that a previous study dealing with the relative and absolute stereochemistry of this phytotoxic agent cannot be correct. An important aspect from the preparative point of view is the fact that the stereochemical outcome of the RCM reaction can be controlled by the choice of the catalyst. Thus, use of the ruthenium indenylidene complex **16** always leads to the corresponding (*E*)-alkenes, whereas the second generation catalyst **17** bearing an *N*-heterocyclic carbene ligand affords the isomeric (*Z*)-olefin with good selectivity. This course is deemed to reflect kinetic versus thermodynamic control of the cyclization reaction and therefore has potentially broader ramifications for the synthesis of medium-sized rings in general. A further noteworthy design feature is the fact that D-ribose is used as a convenient starting material for the preparation of *both* enantiomers of the key building block **14** by means of a "head-to-tail" interconversion strategy.

Introduction

Bioassay guided fractionation of a culture broth of the fungus *Phoma herbarum* recently led to the discovery of the two novel nonenolides herbarumin I (**1**) and II (**2**). These lactones exhibit significant phytotoxic effects in an assay monitoring germination and growth of *Amaranthus hypochondriacus* seedlings, with IC_{50} values as low as 5.43×10^{-5} for compound **1**.[1] Not only is this level of activity interesting per se, but recent biochemical investigations hold even greater promise. Specifically, it has been found that pinolidoxin, a close relative of the herbarumins isolated from the phytopathogenic fungus *Ascochyta pinoides* Jones,[2] constitutes a potent inhibitor of induced phenylalanine ammonia lyase (PAL) activity. This enzyme plays a key role in the phenylpropanoid defense metabolism of higher plants.[3] While the constitution of pinolidoxin as shown in **3** is undisputed, studies concerning its relative and absolute stereochemistry remained inconclusive (see below). The published biological data, however, indicate that pinolidoxin is a potent inhibitor of induced PAL activity without any effect on the growth and viability of the cells.[3,4] The prospect of developing compounds that interfere with plant self-defense renders this class of compounds highly promising lead structures in the search for novel herbicidal agents. This notion is further corroborated by the significant phytotoxic activity reported for lethaloxin **4**, yet another member of this family of macrolides isolated from *Mycosphaerella lethalis*.[5,6]



The paucity of material available from the natural sources together with the lack of reliable information concerning the

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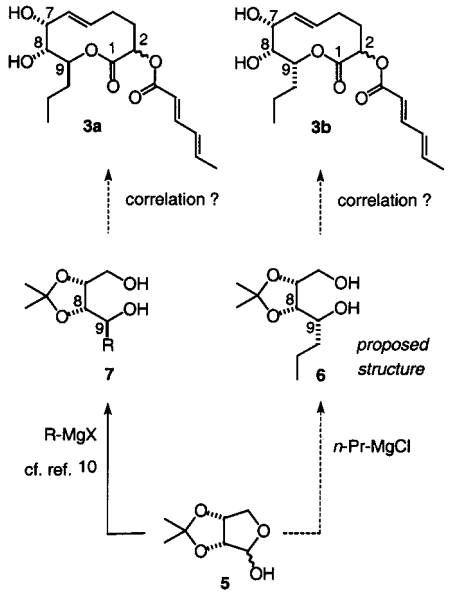
(1) Rivero-Cruz, J. F.; García-Aguirre, G.; Cerda-García-Rojas, C. M.; Mata, R. *Tetrahedron* **2000**, *56*, 5337.
(2) (a) Evidente, A.; Lanzetta, R.; Capasso, R.; Vurro, M.; Bottalico, A. *Phytochemistry* **1993**, *34*, 999. (b) Evidente, A.; Capasso, R.; Abouzeid, M. A.; Lanzetta, R.; Vurro, M.; Bottalico, A. *J. Nat. Prod.* **1993**, *54*, 1937.
(3) Vurro, M.; Ellis, B. E. *Plant Sci.* **1997**, *126*, 29.
(4) For a preliminary SAR study, see: Evidente, A.; Capasso, R.; Andolfi, A.; Vurro, M.; Zonno, M. C. *Nat. Toxins* **1998**, *6*, 183.
(5) Arnone, A.; Assante, G.; Montorsi, M.; Nasini, G.; Ragg, E. *Gazz. Chim. Ital.* **1993**, *123*, 71. Note that only the *relative* stereochemistry of compound **4** has been established so far.
(6) (a) For a review on 10-membered lactones, see: Dräger, G.; Kirschning, A.; Thiericke, R.; Zerlin, M. *Nat. Prod. Rep.* **1996**, *13*, 365. (b) For a general review on medium-sized rings, see: Yet, L. *Chem. Rev.* **2000**, *100*, 2963.

Scheme 1

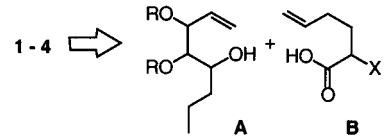


actual structures of **3** and **4**,[5] however, constitute major handicaps to a systematic evaluation of the structure/activity profile of these important leads.[4] A full account of our work in this area comprising the first total syntheses of herbarumin I[7] and II as well as a synthesis-driven solution of the puzzle concerning the stereostructure of pinolidoxin which ensued from the contradictory evidence in the literature is described below.

Results and Discussion

Structural Considerations and Strategy. A well-documented study of the herbarumins **1** and **2** leaves no doubt about the constitution, configuration, and conformation of these compounds.[1] Unfortunately, however, for pinolidoxin the situation is far from clear. Two preliminary reports suggested a 7/8-anti, 8/9-anti arrangement of the oxygen substituents at these three contiguous stereocenters as shown in **3a**.[8] However, one group later revised its conclusions and suggested a 7,8-anti but 8/9-syn relationship for this domain (**3b**).[9] This analysis was largely based on degradations of the natural product and comparison of the samples thus obtained with synthetic material prepared from either *rac*-tartaric acid or 2,3-*O*-isopropylidene-D-erythrose **5** (Scheme 1). Thereby, the addition of *n*-propylmagnesium chloride to **5** played a key role, which was assumed to provide alcohol **6** with a syn arrangement between C-8 and C-9 (pinolidoxin numbering).[9] This assignment, however, has not been rigorously proven and is inconsistent with previous reports demonstrating that Grignard additions to **5** (and related hemiacetals) follow the Felkin−Ahn model and uniformly deliver 8,9-anti configured products **7** with high selectivity.[10,11] The same authors also assigned the absolute stereochemistry at C-7 and C-8 of pinolidoxin as being opposite to the one found in herbarumin.[9] The fact, however, that pinolidoxin as well as the herbarumins all show positive $[\alpha]_D$ values together with the rather poor resolution of the relevant NMR spectra of the Mosher esters derivatives of **3** raises doubts as to the reliability of this conclusion. To complicate matters even further, no information concerning the stereochemistry at C-2 of pinolidoxin is presently available. Therefore, we reinvestigated this problem by synthesizing several possible candidates and comparing their analytical and spectroscopic data with those of the natural product.

Scheme 2



For this purpose, it was essential to develop a flexible yet stereochemically unambiguous approach (Scheme 2). Because all targets contain a double bond, ring-closing metathesis (RCM) seemed to be the method of choice for its inherently convergent character.[12,13] RCM allows the nonenolides to be deconvoluted into two rather simple fragments **A** and **B**. Importantly, as shown in Scheme 3, *all* possible cyclization precursors can be traced back to D-ribose as the ultimate source of chirality if required for structure elucidation purposes.

At the same time, however, one has to keep in mind that the formation of medium-sized rings by RCM still poses considerable challenges. Ring strain predisposes cycloalkenes of 8−11 ring atoms for the reverse process, that is, for ring-opening metathesis (ROM) or ring-opening metathesis polymerization (ROMP). Therefore, the number of successful applications of RCM to this series is still rather limited.[14−17]

One approach to circumvent this problem is to incorporate control elements that force the cyclization precursors to adopt conformations suitable for ring closure.[13] An isopropylidene protecting group spanning O-7 and O-8 should exert this function by aligning the olefinic side chains in a cyclization-

(7) For a preliminary communication on the total synthesis of herbarumin I, see: Fürstner, A.; Radkowski, K. *Chem. Commun.* **2001**, 671.
(8) (a) De Napoli, L.; Evidente, A.; Lasalvia, M.; Piccialli, G.; Piccialli, V. *Abstract of the 9th Int. Congress of Pesticide Chemistry*; London, United Kingdom, 1998 (http://www.chemsoc.org/chempest/html/3C-0007.html). (b) Pilli, R. A.; Sabino, A. A. *Abstract of the 22nd IUPAC Int. Symp. Chem. Nat. Prod.*; São Carlos, SP, Brazil, 2000.
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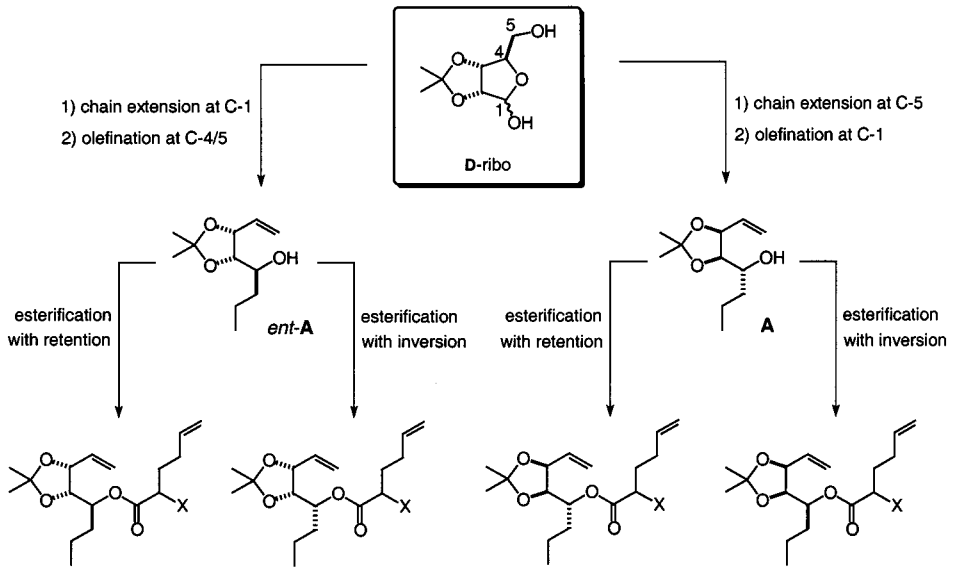
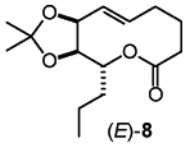
(10) (a) Mekki, B.; Singh, G.; Wightman, R. H. *Tetrahedron Lett.* **1991**, *32*, 5143. (b) Jiang, S.; Singh, G.; Wightman, R. H. *Chem. Lett.* **1996**, 67.
(11) For examples showing that Grignard additions to isopropylidene protected lactols of sugars other than erythrose also give anti-relationships, see: (a) Kinoshita, M.; Arai, M.; Tomooka, K.; Nakata, M. *Tetrahedron Lett.* **1986**, *27*, 1811. (b) Buchanan, J. G.; MacLean, K. A.; Wightman, R. H.; Paulsen, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1463. (c) Buchanan, J. G.; Dunn, A. D.; Edgar, A. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1191.
(12) For a discussion of strategic advantages related to RCM, see: Fürstner, A. *Synlett* **1999**, 1523.
(13) Reviews: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Fürstner, A. *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Fürstner, A. *Top. Catal.* **1997**, *4*, 285. (e) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, *109*, 2124; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037. (f) Schrock, R. R. *Top. Organomet. Chem.* **1998**, *1*, 1. (g) Maier, M. E. *Angew. Chem.* **2000**, *112*, 2153; *Angew. Chem., Int. Ed.* **2000**, *39*, 2073.
(14) For syntheses of 10-membered rings by RCM, see: (a) Fürstner, A.; Müller, T. *Synlett* **1997**, 1010. (b) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757. (c) Gerlach, K.; Quitschalle, M.; Kalesse, M. *Synlett* **1998**, 1108. (d) Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334. (e) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.* **1998**, 1041. (f) Quitschalle, M.; Kalesse, M. *Tetrahedron Lett.* **1999**, *40*, 7765. (g) Delgado, M.; Martin, J. D. *J. Org. Chem.* **1999**, *64*, 4798. (h) Bamford, S. J.; Goubitz, K.; van Lingen, H. L.; Luker, T.; Schenk, H.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 345. (i) Nakashima, K.; Ito, R.; Sono, M.; Tori, M. *Heterocycles* **2000**, *53*, 301. (j) Cho, S. C.; Dussault, P. H.; Lisec, A. D.; Jensen, E. C.; Nickerson, K. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 193. (k) Nevalainen, M.; Koskinen, A. M. P. *Angew. Chem.* **2001**, *113*, 4184; *Angew. Chem., Int. Ed.* **2001**, *40*, 4060. (l) Heinrich, M. R.; Steglich, W. *Tetrahedron Lett.* **2001**, *42*, 3287. (m) Banwell, M. G.; Bray, A. M.; Edwards, A. J.; Wong, D. J. *New J. Chem.* **2001**, *25*, 1347. (n) Telser, J.; Beumer, R.; Bell, A. A.; Ceccarelli, S. M.; Montio, D.; Gennari, C. *Tetrahedron Lett.* **2001**, *42*, 9187. (o) For an indirect approach, see: Méndez-Andino, J.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 1263.

Scheme 3



friendly conformation. The extent of bias, if any, conferred by such a group on the stereochemistry of the newly formed double bond is much less obvious and cannot be predicted with certainty. In general, RCM reactions in the macrocyclic series tend to give mixtures of the (*E*)- and (*Z*)-configured cyclic olefins, and a reliable and general method of controlling the geometry of the newly formed double bond has yet to be found.[18,19] Therefore, semiempirical calculations have been carried out for the acetal-protected herbarumin I which indicate



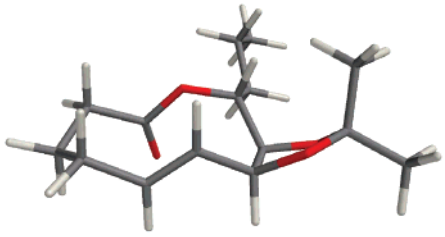


Figure 1. Calculated minimum energy conformation of compound (*E*)-**8**.

that lactone (*Z*)-**8** is ca. 3.5 kcal mol^{-1} more stable than the isomeric (*E*)-**8**.[20] This comparison of the minimum energy conformations[21] (Figures 1 and 2) suggests that *thermodynamic control during RCM will likely be counterproductive* en route to the targeted (*E*)-alkenes **1**−**3**; only under kinetic control might it be possible to obtain the desired products with reasonable selectivity. This, in turn, determines the choice of the metathesis catalyst because one should avoid those complexes that are known to favor the retro-reaction and hence lead to an equilibration of the products initially formed.[22−24]

(15) See ref 29 and the following for leading references on the RCM-based synthesis of natural products incorporating an eight-membered ring: (a) Martin, S. F.; Wagman, A. S. *Tetrahedron Lett*. **1995**, *36*, 1169. (b) Martin, S. F.; Liao, Y.; Wong, Y.; Rein, T. *Tetrahedron Lett*. **1994**, *35*, 691. (c) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc*. **1995**, *117*, 2108. (d) Fürstner, A.; Langemann, K. *J. Org. Chem*. **1996**, *61*, 8746. (e) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc*. **1998**, *120*, 7359. (f) Stefinovic, M.; Snieckus, V. *J. Org. Chem*. **1998**, *63*, 2808. (g) Joe, D.; Overman, L. E. *Tetrahedron Lett*. **1997**, *38*, 8635. (h) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett*. **1997**, 127. (i) Paquette, L. A.; Efremov, I. *J. Am. Chem. Soc*. **2001**, *123*, 4492. (j) Paquette, L. A.; Tae, J.; Arrington, M. P.; Sadoun, A. H. *J. Am. Chem. Soc*. **2000**, *122*, 2742. (k) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc*. **1999**, *121*, 5653. (l) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc*. **1999**, *121*, 866. (m) Krafft, M. E.; Cheung, Y. Y.; Abboud, K. A. *J. Org. Chem*. **2001**, *66*, 7443. (n) Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett*. **2001**, *3*, 3095. (o) Papaioannou, N.; Evans, C. A.; Blank, J. T.; Miller, S. J. *Org. Lett*. **2001**, *3*, 2879. (p) Harrison, B. A.; Verdine, G. L. *Org. Lett*. **2001**, *3*, 2157. (q) Codesido, E. M.; Castedo, L.; Granja, J. R. *Org. Lett*. **2001**, *3*, 1483. (r) Vo-Thanh, G.; Boucard, V.; Sauriat-Dorizon, H.; Guibé, F. *Synlett* **2001**, 37. (s) Creighton, C. J.; Reitz, A. B. *Org. Lett*. **2001**, *3*, 893. (t) Boiteau, J.-G.; van de Weghe, P.; Eustache, J. *Tetrahedron Lett*. **2001**, *42*, 239. (u) Fellows, I. M.; Kaelin, D. E.; Martin, S. F. *J. Am. Chem. Soc*. **2000**, *122*, 10781. (v) Hanna, I.; Ricard, L. *Org. Lett*. **2000**, *2*, 2651. (w) Krafft, M. E.; Cheung, Y. Y.; Juliano-Capucao, C. A. *Synthesis* **2000**, 1020. (x) Reichwein, J. F.; Liskamp, R. M. J. *Eur. J. Org. Chem*. **2000**, 2335. (y) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett*. **2000**, *41*, 4113. (z) Buszek, K. R.; Sato, N.; Jeong, Y. *Tetrahedron Lett*. **2002**, *43*, 181.

(16) For the synthesis of nine-membered rings by RCM see ref 29 and the following for leading references: (a) Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H.; Takemoto, Y. *J. Org. Chem*. **2001**, *66*, 81. (b) Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc*. **2001**, *123*, 1533. (c) Crimmins, M. T.; Emmitte, K. A. *Synthesis* **2000**, 899. (d) Clark, J. S.; Hamelin, O. *Angew. Chem*. **2000**, *112*, 380; *Angew. Chem., Int. Ed*. **2000**, *39*, 372. (e) Sasaki, M.; Noguchi, T.; Tachibana, K. *Tetrahedron Lett*. **1999**, *40*, 1337. (f) Crimmins, M. T.; Choy, A. L. *J. Org. Chem*. **1997**, *62*, 7548. (g) Barrett, A. G. M.; Baugh, S. P. D.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A. *Chem. Commun*. **1996**, 2231. (h) Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904.

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(18) The problem starts with eight-membered rings. For a pertinent example showing that RCM can lead to an (*E*)-configured cyclooctene, see: (a) Bourgeois, D.; Pancrazi, A.; Ricard, L.; Prunet, J. *Angew. Chem*. **2000**, *112*, 741; *Angew. Chem., Int. Ed*. **2000**, *39*, 725. (b) Bourgeois, D.; Mahuteau, J.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *Synthesis* **2000**, 869.

(19) Note that cycloalkenes of ≥12 ring atoms can be selectively formed by ring-closing alkyne metathesis followed by semi-reduction. Rings with 8−11 ring atoms, however, are hardly accessible by this method due to ring strain at the cycloalkyne stage, cf. the following references and literature cited therein: (a) Fürstner, A.; Seidel, G. *Angew. Chem*. **1998**, *110*, 1758; *Angew. Chem., Int. Ed*. **1998**, *37*, 1734. (b) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc*. **1999**, *121*, 11108. (c) Fürstner, A.; Mathes, C.; Lehmann, C. W. *Chem.-Eur. J*. **2001**, *7*, 5299.

(20) PC Spartan Pro 1.0.7, Wave function Inc.

(21) Although this comparison disregards the conformational space of the medium ring, it seems valid because in *both* series the next lowest conformers are uniformly 2−3 kcal mol^{-1} higher in energy than the most stable ones.

(22) Lee, C. W.; Grubbs, R. H. *Org. Lett*. **2000**, *2*, 2145.

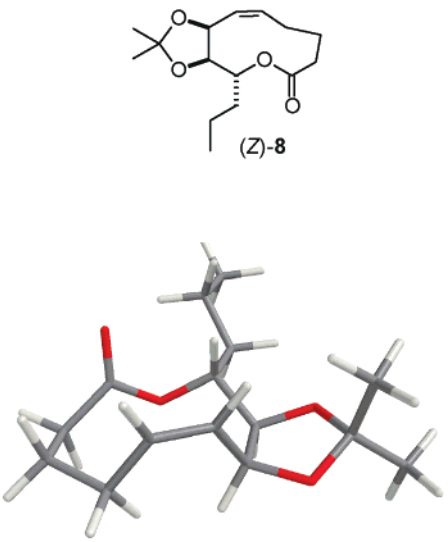


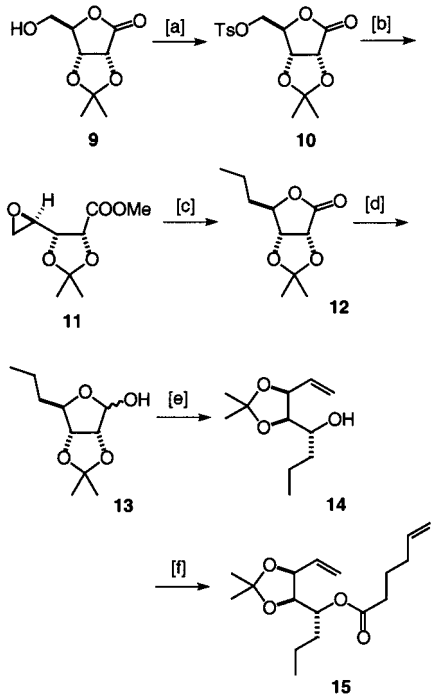
Figure 2. Conformation of lowest energy of compound (*Z*)-**8** which is ca. 3.5 kcal mol^{-1} more stable than the corresponding (*E*)-alkene shown in Figure 1.

Total Synthesis of Herbarumin I. Our approach to herbarumin I (**1**) as the biologically most active compound of this family of phytotoxins is based on the fact that the stereochemistry of its three contiguous chiral centers can be matched by the pattern displayed by D-ribose.[7] Therefore, the D-ribonolactone acetonide derivative **9** was chosen as a readily accessible starting material which is converted on a multigram scale into tosylate **10** (Scheme 4).[25] Subsequent treatment with NaOMe in THF leads to product **11** via transesterification followed by spontaneous closure of the epoxide ring once the alkoxide at O-4 is liberated.[26] This compound is then exposed to the cuprate reagent formed from EtMgBr and CuBr·Me_2S in THF,[27] providing lactone **12** in 60% yield. Attempts to prepare compound **12** more directly by reacting tosylate **10** with various ethyl donors invariably turned out to be low yielding and could not compete with the route depicted in Scheme 4.

Dibal-H reduction of **12** followed by reaction of the resulting lactol **13** with methylenetriphenylphosphorane in the presence of catalytic amounts of quinuclidine[28] delivers alcohol **14** in good yield, which is esterified with 5-hexenoic acid in the presence of DCC and DMAP to afford diene **15**. This sets the stage for the crucial macrocyclization reaction via RCM and allows the hypotheses concerning thermodynamic versus kinetic preferences of ring closure outlined above to be tested.

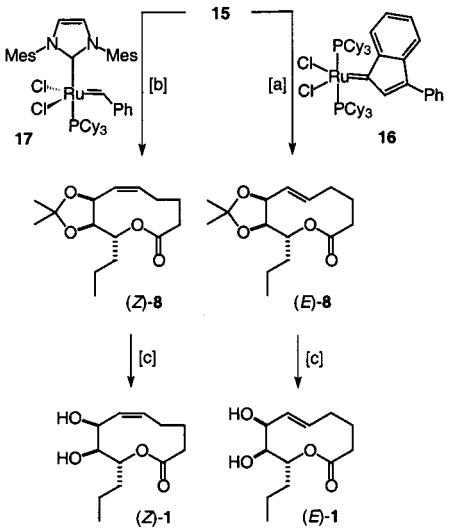
The preparative results obtained using two different metathesis catalysts turned out to be most gratifying and are fully consistent with the predictions made above (Scheme 5). Specifically, exposure of diene **15** to a catalytic amount of the ruthenium indenylidene complex **16**[29,30] in refluxing CH_2Cl_2 affords the desired lactone (*E*)-**8** as the major product, which is isolated in 69% yield (9% of the (*Z*)-isomer can also be detected). This example nicely features the excellent application profile of **16** which is equipotent with or even superior to the more popular Grubbs carbene $(Cy_3P)_2(Cl)_2Ru{=}CHPh$,[31] yet easier to make

Scheme 4 [a]



[a] [a] Tosyl chloride, pyridine, −25 °C, 77%; [b] NaOMe, THF, 0 °C → room temperature, 62%; [c] EtMgBr, CuBr·Me_2S, THF, −78 °C → room temperature, 60%; [d] Dibal-H, CH_2Cl_2, −78 °C, 97%; [e] $Ph_3P{=}CH_2$, quinuclidine cat., THF, reflux, 62−77%; [f] 5-hexenoic acid, DCC, DMAP, CH_2Cl_2, room temperature, 84%.

Scheme 5 [a]



[a] [a] Complex **16** cat., CH_2Cl_2, reflux, 69%; [b] complex **17** cat., CH_2Cl_2, reflux, 86%; [c] aqueous HCl, THF, 47% ((*Z*)-**1**), 90% ((*E*)-**1**).

(23) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990.
(24) For further examples illustrating how the reversible nature of RCM can be deliberately exploited in synthesis, see: (a) Smith, A. B.; Adams, C. M.; Kozmin, S. A. *J. Am. Chem. Soc.* **2001**, *123*, 990. (b) Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449. (c) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoyveda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302.
(25) Hough, L.; Jones, J. K. N.; Mitchell, D. L. *Can. J. Chem.* **1958**, *36*, 1720.
(26) (a) Hoffmann, R. W.; Ladner, W. *Chem. Ber.* **1983**, *116*, 1631. (b) Ortuño, R. M.; Merce, R.; Font, J. *Tetrahedron* **1987**, *43*, 4497.
(27) Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.* **1995**, *60*, 5628.
(28) Dahlhoff, W. V. *Liebigs Ann. Chem.* **1992**, 109.
(29) Fürstner, A.; Guth, O.; Düffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem.-Eur. J.* **2001**, *7*, 4811.
(30) (a) Fürstner, A.; Hill, A. F.; Liebl, M.; Wilton-Ely, J. D. E. T. *Chem. Commun.* **1999**, 601. (b) Fürstner, A.; Grabowski, J.; Lehmann, C. W. *J. Org. Chem.* **1999**, *64*, 8275. (c) Fürstner, A.; Thiel, O. R. *J. Org. Chem.* **2000**, *65*, 1738. (d) Fürstner, A.; Grabowski, J.; Lehmann, C. W.; Kataoka, T.; Nagai, K. *ChemBioChem* **2001**, *2*, 60. (e) Reetz, M. T.; Becker, M. H.; Liebl, M.; Fürstner, A. *Angew. Chem.* **2000**, *112*, 1294; *Angew. Chem., Int. Ed.* **2000**, *39*, 1236. (f) Schmidt, B.; Wildemann, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2916.

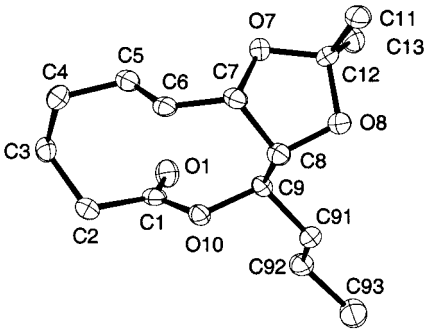


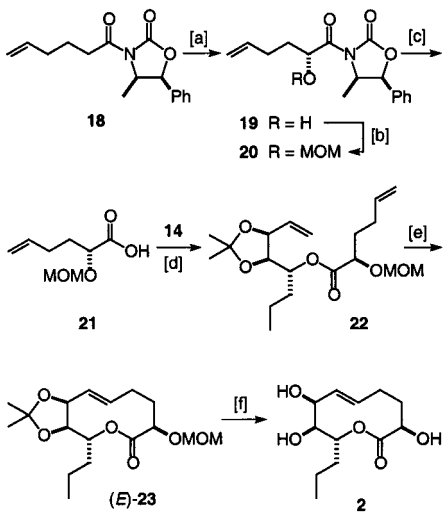
Figure 3. Molecular structure of compound (*E*)-**8** in the solid state. Anisotropic displacement parameters are shown at 50% probability level; hydrogen atoms are omitted for clarity.

from stable and commercially available precursors.[29] The (*E*/*Z*)-ratio does not evolve with time, indicating that the selective formation of this thermodynamically less stable (*E*)-isomer is likely the result of kinetic control. This is corroborated by the finding that the use of the "second generation" metathesis catalyst **17**[32] results in the selective formation of the diastereomeric product (*Z*)-**8** in 86% isolated yield. Complex **17** and congeners, due to their higher overall activity, are able to isomerize the cycloalkenes formed during the course of the reaction and hence enrich the mixture in the thermodynamically favored product.[22−24,33] These two particular applications may therefore be considered the first example of a rationally designed synthesis of either stereoisomer of a given olefinic target via RCM by tuning the activity of the catalyst.

The stereochemical assignment of the RCM products by NMR is hampered by the fact that compound (*E*)-**8** populates two slowly interconverting conformers in solution (ratio ≈ 3:1) as evident from 2D-NOESY spectra which contain exchange cross-peaks between the major and a minor component. Only after an unambiguous assignment of both sets of signals was it possible to extract from the high-resolution 2D-HSQC spectrum the indicative $^3J_{H-5,H-6} = 15.6 \pm 0.5$ Hz for the major conformer and the corresponding $^3J_{H-5,H-6} = 16.2 \pm 0.5$ Hz for the minor conformer, establishing that both are (*E*)-alkenes. Moreover, we were able to grow crystals of this key compound suitable for X-ray analysis. The structure in the solid state (Figure 3) confirms this assignment. The macrocycle adopts a conformation bringing the propyl side chain into an equatorial orientation, and the lactone has the expected *S*-cis conformation of the C−O bond (O1−C1−O10−C9 19.96°); for details, see the Supporting Information.

Cleavage of the acetal group in (*E*)-**8** with dilute aqueous HCl occurs uneventfully and provides herbarumin I (*E*)-**1** in 90% yield as a low melting solid (Scheme 5). Although the

Scheme 6 [a]



[a] [a] (i) $NaN(SiMe_3)_2$, THF, −78 °C; (ii) *trans*-3-phenyl-2-(phenylsulfonyl) oxaziridine, 89%; [b] $(MeO)_2CH_2$, P_4O_{10}, room temperature, 78%; [c] aqueous LiOH, aqueous H_2O_2 (30% w/w), THF/H_2O (4/1), 0 °C, 89%; [d] alcohol **14**, DCC, DMAP, CH_2Cl_2, room temperature, 67%; [e] complex **16** cat., CH_2Cl_2, reflux, 79%; [f] aqueous HCl, MeOH/H_2O (2/1), 60 °C, 84%.

$[\alpha]_D$ value of the synthetic sample deviates from the reported one to some extent, there is no doubt as to the constitution and configuration of this compound since the high-resolution NMR spectra (Bruker DMX 600) as well as the IR and MS data are in excellent agreement with the proposed structure and perfectly match those reported in the literature (cf. Supporting Information).[1,34]

Total Synthesis of Herbarumin II and Its C-2 Epimer. The ribose-derived alcohol **14** serves as a common platform, allowing the synthesis of herbarumin II **2** as well. The required carboxylic acid synthon **21** was prepared by exploiting the facial guidance exerted by an Evans auxiliary during the α-hydroxylation of the sodium enolate derivated from **18**,[35] followed by MOM-protection[36] of crude **19** and hydrolytic cleavage of the oxazolidinone in **20** under standard conditions (Scheme 6).[37] Esterification of the resulting acid **21** with alcohol **14** affords diene **22** which readily cyclizes on exposure to catalytic amounts of the ruthenium indenylidene complex **16**[29] in refluxing CH_2Cl_2. The desired 10-membered lactone (*E*)-**23** is obtained in 79% isolated yield, and only traces of the corresponding (*Z*)-isomer can be detected in the crude mixture (<5%). Treatment of **23** with aqueous HCl leads to the concomitant cleavage of the isopropylidene acetal and the MOM group, affording herbarumin II **2** in 84% yield.

Crystals of **2** suitable for X-ray analysis were grown from CH_2Cl_2. The molecular structure in the solid state (Figure 4) confirms unambiguously that the synthetic material is identical with the proposed structure for herbarumin II (for details, see the Supporting Information). Therefore, we were quite surprised to see that the NMR spectra recorded at 600 MHz only *partly*

(31) (a) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(32) (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (c) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787. (d) Weskamp, T.; Kohl, F. J.; Hieringer, W.; Gleich, D.; Herrmann, W. A. *Angew. Chem.* **1999**, *111*, 2573; *Angew. Chem., Int. Ed.* **1999**, *38*, 2416. (e) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (f) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204. (g) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem.-Eur. J.* **2001**, *7*, 3236.

(33) This interpretation is also supported by a control experiment showing that pure (*E*)-**8** is slowly isomerized to (*Z*)-**8** in the presence of catalyst **17** if the reaction is performed under an atmosphere of ethylene.

(34) For an alternative approach to **1**, see: Sabino, A. A.; Pilli, R. A. *Tetrahedron Lett.* **2002**, *43*, 2819.

(35) (a) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346. (b) Davis, F. A.; Chen, B.-C. In *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21e, p 4497.

(36) Xu, Z.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **1991**, *56*, 7183.

(37) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83.

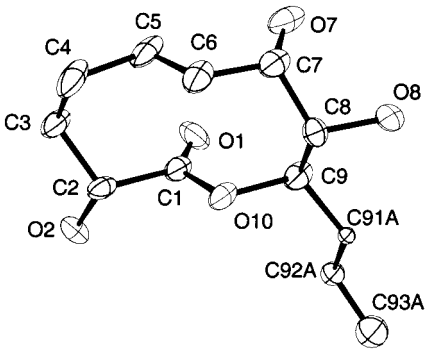
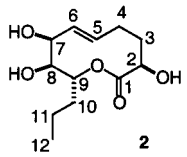


Figure 4. Molecular structure of herbarumin II (**2**) in the solid state (major component of the disordered *n*-propyl side chain shown). Anisotropic displacement parameters are shown at 50% probability level; solute $CDCl_3$ and hydrogen atoms are omitted for clarity.

Table 1. Correct Set of NMR Data of Herbarumin II (**2**) Recorded with a Bruker DMX-600 Spectrometer in Methanol-d_4 (Arbitrary Numbering as Shown)[a]



2

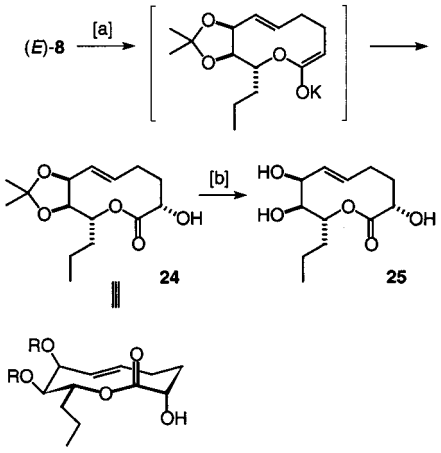
position	δ ^{1}H (ppm)	multiplicity	$J_{H,H}$ (Hz)	δ ^{13}C (ppm)
1				176.90 (s)
2	3.84	dd	J = 10.6, 3.0 Hz	73.56 (d)
3a	1.89	m		34.99 (t)
3b	1.79	m		
4a	2.29	dm	J = 13.1 Hz	29.71 (t)
4b	2.09	m		
5	5.49	dddd	J = 15.6, 10.3, 4.3, 2.2 Hz	123.47 (d)
6	5.55	ddd	J = 15.6, 2.1, 0.8 Hz	134.06 (d)
7	4.34	quint	J = 2.1 Hz	73.93 (d)
8	3.51	dd	J = 9.7, 2.5 Hz	74.11 (d)
9	5.15	td	J = 9.3, 2.8 Hz	71.90 (d)
10a	1.82	m		35.17 (t)
10b	1.52	m		
11a	1.41	m		18.66 (t)
11b	1.32	m		
12	0.92	t	J = 7.4 Hz	14.41 (q)

[a] All assignments are unambiguous and have been made using COSY, NOESY, and ^{13}C,^{1}H-chemical shift correlated spectra; for further information and the compilation of data in $CDCl_3$, see the Supporting Information.

matched the reported ones.[1] While some signals were in excellent agreement with the literature data, the resonances of H(C)-7, 8, and 9 clearly deviated from the reported values. Because our assignment of all signals is unambiguous (cf. the Supporting Information) and in view of the X-ray analysis described above, this partial mismatch could not be explained. Gratifyingly, however, copies of the original spectra of herbarumin II have been made available to us for comparison. *These original spectra and the spectra of our sample are superimposable*. The apparent discrepancies are due to some typographical errors in the original publication.[1] The correct set of spectral data of herbarumin II is now compiled in Table 1.

An even shorter entry into herbarumin II **2** might consist in the diastereoselective hydroxylation of herbarumin I **1** (Scheme 7). Not unexpectedly, however, this reaction affords the C-2 epimer **24** as the only product. This stereochemical course ensues from a trajectory in which the oxygen donor attacks the

Scheme 7 [a]



[a] [a] (i) $KN(SiMe_3)_2$, THF, −50 °C; (ii) *trans*-3-phenyl-2-(phenylsulfonyl) oxaziridine, −78 °C, 37% (+62% recovered substrate).

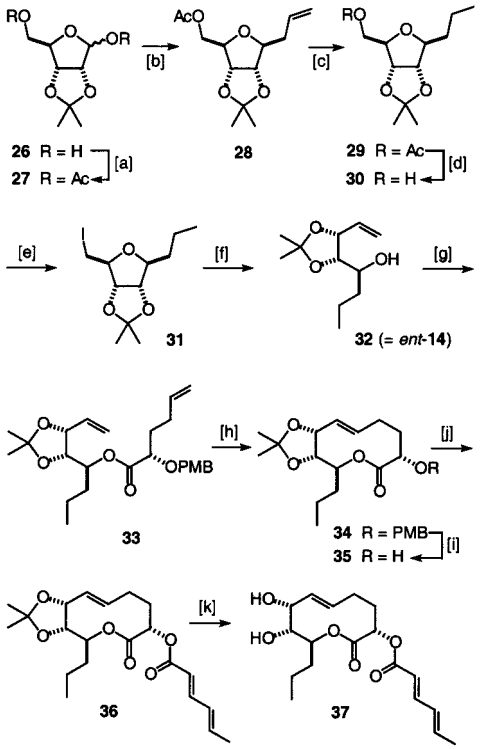
enolate from the α-face away from the dipoles and the sterically encumbering pseudoaxially oriented isopropylidene acetal. Deprotection of crude **24** with HCl provided the herbarumin II analogue **25**. An analysis of the NMR data shows that this compound − in contrast to **2** − exists as a single conformer in $CDCl_3$ solution in which the macrocycle adopts a chair-chair-chair conformation bringing the propyl side chain into a pseudoequatorial position, whereas all other substituents are pseudoaxially oriented. As it turned out later, this product represents the pinolidoxin core structure.

Pinolidoxin. As outlined above, the absolute and relative stereochemistry of pinolidoxin, a highly promising lead structure for the development of novel herbicidal agents, has not been rigorously assigned.[8,9] The available data suggest an absolute stereochemistry as depicted in **3a** or **3b**,[9] *opposite* to that found in the herbarumins. Hence, L-ribose would be required as the starting material if a route analogous to the one described above were pursued. The prohibitively high price of this substrate, however, forced us to devise an alternative entry. It is based on simple symmetry considerations which indicate that D-ribose can be used as substrate to enter into both enantiomeric series (cf. Scheme 3). While elaboration of the C-5 position into a propyl chain followed by olefination of the anomeric center are the key steps en route to synthon **A**, a "head-to-tail interchange"[38] should result in the formation of the enantiomeric product *ent*-**A**.

This plan was reduced to practice as depicted in Scheme 8. Protection of D-ribose as the isopropylidene acetal **26**[39] followed by acetylation under standard conditions afford compound **27** which is converted into C-glycoside **28** on treatment with allyltrimethylsilane and TMSOTf in acetonitrile as the solvent.[40] This reaction affords the desired product in respectable yield together with a trace amount of the corresponding α-anomer (α:$\beta \approx$ 1:10). The isopropylidene group in **27** which shields the α-side of the intermediate oxocarbenium cation at C-1 explains the observed stereochemical course which becomes apparent from an analysis of the pertinent coupling constants.

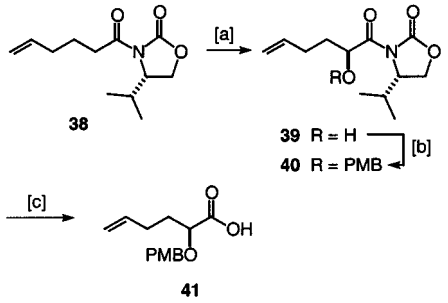
(38) (a) Fürstner, A.; Weidmann, H. *J. Org. Chem.* **1990**, *55*, 1363. (b) Fürstner, A. *Tetrahedron Lett.* **1990**, *31*, 3735. (c) Fürstner, A.; Baumgartner, J. *Tetrahedron* **1993**, *49*, 8541.
(39) Kaskar, B.; Heise, G. L.; Michalak, R. S.; Vishnuvajjala, B. R. *Synthesis* **1990**, 1031.
(40) (a) Takahashi, S.; Hirota, S.; Nakata, T. *Heterocycles* **2000**, *52*, 1079. (b) McDevitt, J. P.; Lansbury, P. T. *J. Am. Chem. Soc.* **1996**, *118*, 3818.

Scheme 8 [a]



[a] [a] Ac_2O, pyridine, room temperature, 97%; [b] allyltrimethylsilane, TMSOTf (0.3 equiv), 0 °C, 58% (β-anomer) + 5% (α-anomer); [c] H_2, Pd/C (5%), CH_2Cl_2, quant.; [d] NaOMe cat., MeOH, room temperature, 85%; [e] I_2, PPh_3, imidazole, CH_2Cl_2, room temperature, 89%; [f] Zn(Ag)-graphite, room temperature, 86%; [g] acid **41**, DCC, DMAP, CH_2Cl_2, room temperature, 87%; [h] complex **16** cat., CH_2Cl_2, reflux, 82%; [i] DDQ, CH_2Cl_2/H_2O (18/1), room temperature, 84%; [j] sorbic acid chloride, pyridine, CH_2Cl_2, 0 °C → room temperature, 84%; [k] aqueous HCl, MeOH/H_2O (2/1), 60 °C, 56%.

Scheme 9 [a]



[a] [a] (i) $NaN(SiMe_3)_2$, THF, −78 °C; (ii) *trans*-3-phenyl-2-(phenylsulfonyl) oxaziridine, 83%; [b] *p*-methoxybenzyl trichloroacetimidate, CF_3SO_2OH cat., Et_2O, room temperature, 48%; [c] aqueous LiOH, aqueous H_2O_2 (30% w/w), THF/H_2O (4/1), 0 °C, 94%.

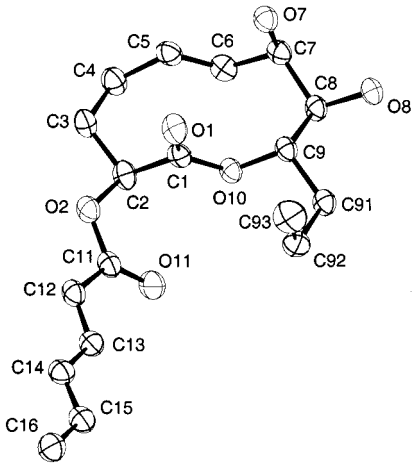


Figure 5. Molecular structure of compound **37** in the solid state. Anisotropic displacement parameters are shown at 50% probability level; solute water and hydrogen atoms are omitted for clarity.

Replacement of TMSOTf by $BF_3{\cdot}Et_2O$ as the promotor and/or the use of CH_2Cl_2 instead of MeCN led to inferior results in terms of yield and selectivity. Hydrogenation of the double bond of **28** followed by deprotection of the acetyl group in **29** proceed without incident. At this stage, the minor α-anomer produced in the C-glycosylation reaction can be conveniently separated on a preparative scale by routine flash chromatography. The hydroxyl group of **30** is then converted into the corresponding iodide **31**[41] which, on treatment with highly activated Zn(Ag)-graphite[42] according to a protocol previously described by our laboratory,[43] undergoes a smooth reductive elimination reaction delivering the desired product **32** (=*ent*-**14**) in 86% yield.

With this alcohol in hand, the completion of the synthesis of the proposed structure of pinolidoxin was straightforward. Esterification of **32** with acid **41** (prepared via the Evans α-hydroxylation protocol and PMB-protection as shown in Scheme 9)[35] affords the cyclization precursor **33** in excellent yield. In line with the results described above, treatment of the latter with catalytic amounts of the ruthenium indenylidene complex **16**[29] in refluxing CH_2Cl_2 effects a clean RCM reaction with formation of (*E*)-**34** in 82% yield together with small amounts of the (*Z*)-isomer (10%). Oxidative cleavage of the PMB group[44] liberates alcohol **35** which gives access to both possible C-2 epimers of pinolidoxin.

Specifically, esterification of **35** with sorbic acid chloride[45] under retention of configuration affords product **36** which is then deprotected to give compound **37** in good overall yield. Its structure in the solid state is depicted in Figure 5 (for details, see the Supporting Information). This analysis not only rigorously confirms the structural assigment but also reveals the highly conserved conformational preference of the nonenolide ring in all compounds of this series. This aspect is nicely featured by the overlap of the shapes of compounds **2**, (*E*)-**8**, and **37** displayed in Figure 6. The NMR data of **37**, however, clearly deviate from those published for pinolidoxin[2] and hence exclude that this compound represents the natural product (cf. Table 2 and the Supporting Information).

Therefore, we prepared the C-2 epimeric ester by converting the hydroxyl group of **35** into the corresponding triflate **42** which reacts with the potassium salt of sorbic acid to produce the targeted ester **43** (Scheme 10).[46] Deprotection with aqueous HCl then affords product **44**. As can be judged from Table 2, its

(41) (a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866. (b) Bennett, S. M.; Biboutou, R. K.; Zhihong, Z.; Pion, R. *Tetrahedron* **1998**, *54*, 4761.
(42) (a) Fürstner, A. *Angew. Chem.* **1993**, *105*, 171; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 164. (b) Fürstner, A.; Weidmann, H.; Hofer, F. *J. Chem. Soc., Dalton Trans.* **1988**, 2023.
(43) (a) Fürstner, A.; Weidmann, H. *J. Org. Chem.* **1989**, *54*, 2307. (b) Fürstner, A.; Jumbam, D.; Teslic, J.; Weidmann, H. *J. Org. Chem.* **1991**, *56*, 2213.
(44) (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885. (b) Fürstner, A.; Radkowski, K.; Grabowski, J.; Wirtz, C.; Mynott, R. *J. Org. Chem.* **2000**, *65*, 8758.
(45) Prepared as described in: Oppolzer, W.; Poli, G.; Kingma, A. J.; Starkemann, C.; Bernardinelli, G. *Helv. Chim. Acta* **1987**, *70*, 2201.
(46) For a related example of the preparation and nucleophilic substitution of an α-triflyloxyester, see: Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998**, *63*, 3072.

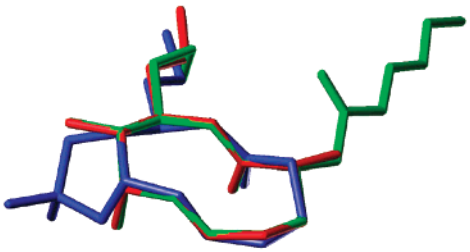
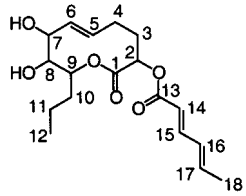


Figure 6. Overlap of the structures of **2** (red), (*E*)-**8** (blue), and **37** (green) revealing the highly conserved conformation of their 10-membered lactone core structures.

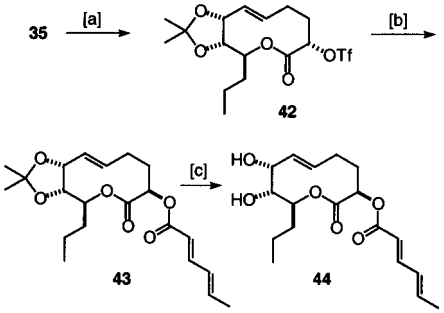
Table 2. Comparison of the ^{13}C NMR Data ($CDCl_3$) Reported for Pinolidoxin[2] with Those of Compounds **37**, **44**, and **46** Recorded with an Accuracy of ±0.1 ppm[a]



position	pinolidoxin[2]	**37**	**44**	**46** (=*ent*-**44**)
1	171.9	172.1	171.9	171.9
13	166.1	166.0	166.1	166.1
15	145.9	146.3	145.9	145.9
17	140.3	140.2	140.3	140.2
6	132.6	132.0	132.4	132.4
16	129.7	129.7	129.7	129.7
5	122.8	122.6	123.0	123.0
14	118.1	117.8	118.2	118.2
8	73.0	73.2	73.2	73.2
7	72.9	73.0	73.1	73.1
9	71.3	71.5	71.3	71.3
2	69.8	73.1	69.8	69.8
10	33.6	33.9	33.6	33.7
3	29.8	31.0	29.9	29.9
4	27.4	27.8	27.4	27.4
18	18.7	18.7	18.7	18.7
11	17.4	17.7	17.5	17.4
12	13.9	13.9	13.9	13.9

[a] These data exclude that pinolidoxin corresponds to compound **37**. Arbitrary numbering of the skeleton as shown in the insert. All assignments are unambiguous and have been made using COSY, NOESY, and ^{13}C,^{1}H-chemical shift correlated spectra as described in the Supporting Information.

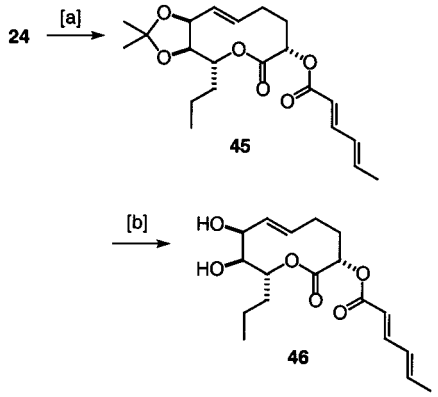
Scheme 10 [a]



[a] [a] Triflic anhydride, pyridine, CH_2Cl_2, 0 °C, 80%; [b] potassium sorbinate, DMF, room temperature, 63%; [c] aqueous HCl, MeOH/H_2O (2/1), 65 °C, 95%.

NMR spectra are not only fully consistent with the proposed structure but are also in excellent agreement with those of the natural product.[2] Importantly, however, the $[\alpha]_D$ values of our sample and of the natural product have opposite signs! Thus,

Scheme 11 [a]



[a] [a] Sorbic acid chloride, pyridine, CH_2Cl_2, 0 °C → room temperature, 76%; [b] aqueous HCl, MeOH/H_2O (2/1), 60 °C, 80%.

Table 3. Comparison of the ^{1}H NMR Data ($CDCl_3$) Reported for Pinolidoxin **3** (400 MHz)[2] with Those of Compound **46** Recorded on a Bruker AV 400 Spectrometer (400 MHz), Showing the Excellent Agreement of These Sets of Data[a]

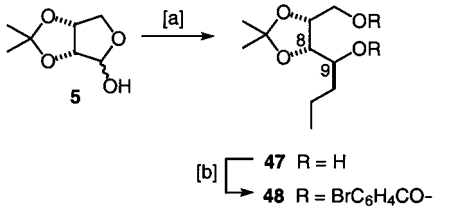
	pinolidoxin (**3**)[2]		compound **46**	
position	δ	multiplicity, *J*	δ	multiplicity, *J*
15	7.32	dd, *J* = 9.8, 15.4 Hz	7.32	dd, *J* = 9.8, 15.5 Hz
16	6.30	m	6.23	m
17	6.20	m		
14	5.87	d, *J* = 15.4 Hz	5.87	d, *J* = 15.5 Hz
6	5.66	dd, *J* = 1.4, 15.8 Hz	5.67	dd, *J* = 1.2, 15.8 Hz
5	5.53	m, *J* = 1.4, 15.8, 15.8 Hz	5.54	dddd, *J* = 2.3, 4.0, 10.6, 15.5 Hz
2	5.25	dd, *J* = 1.7, 5.6 Hz	5.27	dd, *J* = 1.9, 5.5 Hz
9	5.05	td, *J* = 2.6, 9.4 Hz	5.04	td, *J* = 2.7, 9.4 Hz
7	4.44	br s, *J* = 1.4, 2.5 Hz	4.44	br s
8	3.52	dd, *J* = 2.5, 9.4 Hz	3.52	br s
4a	2.41	m	2.44	m
3a/**4b**	2.20	m	2.23	m
3b	2.00	m	2.03	m
18	1.89	d, *J* = 5 Hz	1.89	d, *J* = 5.3 Hz
10a	1.78	m	1.77	m
10b	1.50	m	1.51	m
11a	1.33	m	1.31	m
11b	1.22	m	1.22	m
12	0.87	t, *J* = 7.3 Hz	0.87	t, *J* = 7.3 Hz

[a] Arbitrary numbering of the skeleton as shown in the insert in Table 2. All assignments are unambiguous and have been made using COSY, NOESY, and ^{13}C,^{1}H-chemical shift correlated spectra as described in the Supporting Information.

(i) the absolute stereochemistry of pinolidoxin as it appears in **3a**,**b** has previously been misassigned,[9] and (ii) the stereotriade from C-7 through C-9 is identical to that found in the herbarumins **1** and **2**.[1]

As a result, esterification of alcohol **24** prepared en route to **2** with sorbic acid must produce pinolidoxin (Scheme 11). The NMR data of **46** compiled in Tables 2 and 3 show that this is indeed the case. They are not only superimposable with those of the enantiomer **44** described above, but also match the spectra of the natural product in all regards.[2] An analysis of the coupling constants indicates that **46** exists as a single conformer in CH_2Cl_2 solution at ambient temperature, with the 10-membered ring adopting a chair-chair-chair conformation which must be similar to the one found in the solid state for its analogues **2**, (*E*)-**8**, and **37** (cf. Figure 6). The specific optical rotations of the synthetic sample **46** ($[\alpha]_D^{25} = +143.2$, $c = 0.25$, $CHCl_3$) and of the natural product ($[\alpha]_D^{25} = +142.9$, $c = 0.31$, $CHCl_3$) are also in excellent agreement. Taken together, this highly

Scheme 12 [a]



[a] [a] *n*-Propylmagnesium chloride, THF, 0 °C → room temperature, 82%; [b] *p*-bromobenzoyl chloride, pyridine, CH_2Cl_2, 76%.

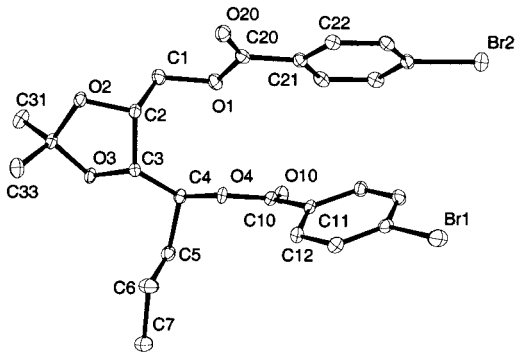


Figure 7. Molecular structure of the bis(*p*-bromobenzoyl) derivative **48** in the solid state. Anisotropic displacement parameters are shown at 50% probability level; hydrogen atoms are omitted for clarity.

consistent set of data obtained for the whole series of products described above leaves no doubt whatsoever as to the structure of pinolidoxin which is as it appears in **46** rather than in **3a**,**b**, although we were unable to examine a sample of the natural product ourselves. Hence, the assignments of the relative and absolute stereochemistry of this molecule previously made are incorrect.[9]

Identification of the Misleading Signpost. As outlined in the Introduction, the stereostructure of pinolidoxin had not been established at the outset of this investigation; in retrospect, however, it is clear that the *available pieces of information in ref 9 were misleading in terms of both relative and absolute stereochemistry*. Because we had speculated that the assumed stereochemical course of the addition of *n*-propylmagnesium chloride to the erythrose derivative **5** might have led to the erroneous assignments (vide supra), a rigorous proof of this aspect was called for. Therefore, this key experiment was repeated, and the resulting product **47** was converted into the crystalline bis(*p*-bromobenzoyl) derivative **48** (Scheme 12).

The structure of this compound in the solid state (Figure 7) unequivocally confirms the anti-orientation of the oxygen substituents at C-8/C-9 (pinolidoxin numbering) resulting from the attack of the nucleophile from the less hindered face of hemiacetal **5** opposite to the isopropylidene group, and disproves the syn relationship previously advocated in the literature.[9] Taken together, this information and the synthetic work described above result in a fully consistent and complete picture.

Conclusions

The first total syntheses of the potent phytotoxic lactones herbarumin I (**1**), herbarumin II (**2**), and pinolidoxin (**46**) are described. The latter rigorously establishes the previously elusive stereostructure of this promising herbicidal agent and corrects an earlier analysis published in the literature.[9] Thereby, a sound basis is set out for further studies on the structure/activity profile of this promising family of lead compounds. The flexibility of our synthesis route should be of great advantage in this respect.

Potentially broader ramifications for synthesis has the finding that the choice of the metathesis catalyst allows for the control of the stereochemistry of the resulting cycloalkene. This is illustrated by the RCM reaction of diene **15** which delivers the (*E*)-configured olefin (*E*)-**8** on exposure to the ruthenium indenylidene complex **16**, but the (*Z*)-configured product (*Z*)-**8** with the ruthenium-NHC catalyst **17**. The selectivity in either case is excellent, and the stereochemical course likely reflects kinetic versus thermodynamic control. Although the generality of this finding has yet to be shown by a larger set of substrates, this notion provides a first reasonable guideline on how to address the as yet unresolved problem of stereocontrol in RCM reactions furnishing medium-sized rings.[18,19] Studies along these lines and further applications of metathesis to the synthesis of bioactive target molecules are being actively pursued in this laboratory and will be reported soon.

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Supporting Information Available: Complete experimental section and information concerning the X-ray structures of compounds (*E*)-**8**, **2**, **37**, and **48** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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